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Sialylation reactions with *N*,*N*-acetyl, benzoyl-*O*-perbenzoyl-protected sialyl donor

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ABSTRACT

A new sialyl donor, *N*,*N*-acetyl, benzoyl-O-perbenzoyl-protected *p*-toluenethiosialoside, was synthesized and its sialylation reaction was investigated. This reaction proceeded in dichloromethane and β anomeric selectivity was achieved when NIS–TfOH was used as promoter. This method may be employed to construct the unnatural β -linked sialosides.

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Sialic acid residues, found at the non-reducing terminus of many glycolipids and glycoproteins, are involved in a wide range of biological processes such as cell-cell interactions, cell differentiation, tumor metastasis, and pathogen-host recognition. The most common member of sialic acid family, N-acetylneuraminic acid (Neu5Ac), is often $\alpha(2,3)$ - and/or $\alpha(2,6)$ -linked to galactose or galactosamine residues.¹ However, to accomplish sialylation reactions in high yields with excellent stereoselectivities is still a challenge due to the peculiar structure of sialic acid: (i) no neighboring C-3 functionality that can direct the stereochemical outcome of glycosylations; (ii) the electron-withdrawing carboxylic acid at the anomeric center, which makes glycal prone to be formed; and (iii) the sterically hindered C-2 position that blocks the approach to the hydroxyl group of an acceptor.² To solve these problems, alternative chemical methodologies and strategies focusing on the structure of sialyl donor have been developed in addition to focusing on the nature of the leaving group and/or promoter, for example, modifications of the C-1 carboxylic group,^{3,4} introductions of participating aux-iliaries at the C-3 positions,⁵⁻⁷ and modifications of the C-5 acetamido group.⁸⁻¹⁰ These glycosyl donors have been outlined very well in several recent reviews.^{2,11,12}

Among the various sialyl donors, thiosialosides are one of the most widely used donors due to their stability, accessibility, and compatibility.^{13,14} It was reported that O-benzoylated and O-chloroacetylated thiosialosides **2** and **3** were more efficient donors toward sialylation than the corresponding O-acetylated donors, ^{15,16} and *N*,*N*-diacetyl, *N*-trifluoroacetyl, and *N*,*N*-acetyl, *tert*-butoxycarbonyl-substituted sialic acid derivatives **4**, **5**, and **6** as sialyl donors displayed an improvement of yields and/or stereoselectivities (Fig. 1).^{8,17,18} So we assumed that electron-withdrawing protective groups may avail sialylation reactions and the sialyl donor **1**, in which both N and O atoms were benzoylated, may also bring about an improved sialylation result. Herein, we wish to report the results of sialylation reactions using *N*,*N*-acetyl, benzoyl-*O*-perbenzoyl-protected thiosialoside **1** as the donor.

Donor 1^{19} was prepared by straightforward benzoylation of the known thiosialoside derivative 7^4 in the presence of *N*,*N*-dimethylaminopyridine (DMAP) in 98% isolated yield as described in Scheme 1.

Interestingly, the ¹H NMR spectrum of compound **1** at room temperature showed two groups of signals, whereas the variable temperature NMR experiment showed the coalescence of these happened at 80 °C. This phenomenon indicated that a pair of atropisomers **1a** and **1b** might exist, resulting from the hindered rotation around C5–N bond in which the steric strain barrier to rotation was high enough to be observed (Scheme 2).

To explore the potential of thiosialoside **1** as a sialyl donor, the glycosyl coupling reaction of **1** and methyl 2,3,4-tri-O-benzyl- α -p-galactopyranoside (**8**)²⁰ using NIS-TfOH as the promoter system was investigated. Solvents played an important role in





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Figure 1. Structures of thiosialoside donors 1-6.



this reaction. Under the influence of additional *N*-benzoyl group, donor **1** was not activated in the mixed solvent of acetonitriledichloromethane (v/v 1:10), and the same phenomenon was also observed in dichloromethane when a small amount of Et_2O (10 µL) was used to dilute TfOH. But the reaction proceeded smoothly when pure dichloromethane was used as the reaction solvent. In addition, molecular sieves also affected the reproducibility of sialylation reaction, and it was found that using





Scheme 2. Equilibrium between 1a and 1b.

Table 1 Sialylation reactions of donor 1 with acceptors $8\mathchar`-10$



^a A: NIS-TfOH, dichloromethane, AW-300 molecular sieves, −72 °C, donor and acceptor (1.5 equiv) were pre-mixed; B: Ph₂SO-Tf₂O, dichloromethane, 4 Å molecular sieves, −72 °C → room temperature, donor was pre-activated before acceptor (1.5 equiv) was added.

^b Anomeric ratios were determined by ¹H NMR analysis.

 $^{\rm c}~$ 2.0 equiv of acceptor was used.



Scheme 3. Reagents and conditions: (i) NaOMe, MeOH, room temperature, 2 h, 84% (14: 15 = 2.7: 1); (ii) Ba(OH)₂·8H₂O, EtOH-H₂O (v/v 1:1), reflux, 18 h; (iii) Ac₂O, MeOH, NaOH, room temperature, 12 h, 54% over two steps.

AW-300 molecular sieves for the reaction was more efficient than using 4 Å molecular sieves.²¹ Thus, in the absence of participant solvents, coupling product disaccharide 11^{22} was obtained as an unnatural β anomer in 90% isolated yield (Table 1, entry 1). To gain the α -selectivity, Ph₂SO-Tf₂O promoter system reported by Crich²³ was attempted. Unfortunately, unnatural β anomer was still a dominant product though an excess of Ph₂SO stabilized the intermediate oxacarbenium ion efficiently and the coupling reaction occurred under the donor pre-activation conditions^{24,25} (Table 1, entry 2). Coupling with another C-6 hydroxyl-exposed acceptor $\boldsymbol{9}^{26}$ afforded a similar result: higher β anomeric selectivity was also achieved when NIS-TfOH instead of Ph₂SO-Tf₂O system was used as promoter (Table 1, entries 3 and 4). To apply donor 1 to the construction of 2,3-sialyl linkages, partially protected galactoside acceptor 10²⁷ was selected. As expected, the coupling product 13 was obtained in 53% isolated yield. It was noteworthy that the good β selectivity was kept although the secondary hydroxyl acceptor was employed (Table 1, entry 5).

As an example, deprotection of disaccharide 11β is illustrated in Scheme 3. Fully protected disaccharide 11β was treated with NaOMe to provide separable compound 14 containing the acetamino group and compound 15 containing the benzamido group in 62% and 22% yields, respectively. Compound 15 was further treated with Ba(OH)₂ followed by selective N-reacetylation to give product 16 in acceptable yield.

All structures of new compounds were identified by their NMR and mass spectroscopic analyses. The ¹H NMR spectra of compounds **11**, **12**, and **13** at room temperature showed two groups of signals due to the hindrance of bond rotation around C5–N, so clear spectra were recorded at 80 °C. The stereochemistry of newly formed glycosidic linkages in **11** and **12** was assigned on the basis of the chemical shifts of sialic acid *H*-3 equiv as both anomers were obtained. However, the anomeric configuration of disaccharide **13** had to be determined based on its deprotected product. In addition, the $J_{C-1,H-3a}$ coupling constants were also used to confirm the glycosidic bond configurations of deprotected products of disaccharides **11** β and **13**.² The regioselectivity to form disaccharide **13** was confirmed by heteronuclear multiple-bond correlation (HMBC) experiment of its deprotected product.

In conclusion, *N*,*N*-acetyl, benzoyl-*O*-perbenzoyl-protected sialyl donor was prepared and its sialylation reactions with three acceptors using NIS–TfOH and Ph₂SO–Tf₂O as promotor systems were investigated. The new sialyl donor showed good β -anomeric selectivity by using NIS–TfOH as promotor and dichloromethane as solvent. The *N*,*N*-acetyl, benzoyl protective group was deprotected under basic conditions. The disclosed sialyl donor may find applications in the construction of unnatural β -linked sialosides with potential biological importance.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.04.034.

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- Methyl [p-methylphenyl 5-acetamido-4,7,8,9-tetra-O-benzoyl-5-N-benzoyl-3,5dideoxy-2-thio-D-glycero- β -D-galacto-non-2-ulopyranoside]-onate (1): ¹H NMR $(500 \text{ MHz}, \text{DMSO-}d_6, 80 \degree \text{C}) \delta 8.01 (d, J = 8.0 \text{ Hz}, 2\text{H}; \text{Ar}), 7.84-7.79 (m, 6\text{H}; \text{Ar}),$ $7.68 (t, J_1 = 7.5 \text{ Hz}, J_2 = 7.0 \text{ Hz}, 1\text{H}; \text{Ar}), 7.60-7.50 (m, 8\text{H}; \text{Ar}), 7.44-7.40 (m, 8\text{H}; \text{H}; \text{$ Ar), 7.29 (t, J₁ = 8.0 Hz, J₂ = 7.5 Hz, 2H; Ar), 7.15 (d, J = 7.5 Hz, 2H; Ar), 6.15 (dt, $J_{3e,4} = 5.0$ Hz, $J_{3a,4} = J_{4,5} = 10.0$ Hz, 1H; H-4), 5.89 (dd, $J_{6,7} = 1.5$ Hz, $J_{7,8} = 3.0$ Hz, 1H; H-7), 5.76 (dd, J_{5,6} = 10.0 Hz, J_{6,7} = 1.5 Hz, 1H; H-6), 5.50 (m, 1H; H-8), 4.91 $(t, J_{4.5} = J_{5.6} = 10.0 \text{ Hz}, 1\text{H}; \text{H-5}), 4.82 \text{ (dd}, J_{8.9a} = 3.0 \text{ Hz}, J_{9a.9b} = 12.5 \text{ Hz}, 1\text{H}; \text{H-}$ 9a), 4.55 (dd, J_{8,9b} = 7.0 Hz, J_{9a,9b} = 12.5 Hz, 1H; H-9b), 3.62 (s, 3H; OMe), 2.91 $(dd, J_{3a,3e} = 14.0 \text{ Hz}, J_{3e,4} = 4.5 \text{ Hz}, 1\text{H}; \text{H-3e}), 2.43 (dd, J_{3a,3e} = 14.0 \text{ Hz}, J_{3a,4} = 10.5 \text{$ Hz, 1H; H-3a), 2.13 (s, 3H; PhMe), 1.71 (s, 3H; Ac). 13C NMR (125 MHz, DMSOd₆, 80 °C) δ 173.38, 172.59, 167.26, 164.82, 164.72, 164.69, 164.30, 139.32, 135.25, 135.14, 133.10, 132.91, 132.69, 132.51, 129.36, 129.05, 128.98, 128.94, 128.74, 128.66, 128.53, 128.30, 128.27, 128.15, 128.04, 127.95, 124.89, 88.31, 72.07, 69.73, 69.10, 67.96, 61.76, 55.80, 51.97, 37.45, 26.84, 20.08. HRMS (ESI) calcd for C₅₄H₄₇NO₁₃S [M+Na]⁺ 972.2660; found: 972.2663
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H-9a), 4.90 (t, $J_{4,5} = J_{5,6} = 10.0$ Hz, 1H; H-5), 4.81 (d, $J_{1'2'} = 3.5$ Hz, 1H; H-1'), 4.77 (d, J = 11.5 Hz, 1H; PhCH₂), 4.70 (s, 2H; PhCH₂), 4.67 (d, J = 12.0 Hz, 1H; PhCH₂), 4.63 (d, J = 12.0 Hz, 1H; PhCH₂), 4.59–4.53 (m, 1H; H-9b), 4.54 (d, J = 11.5 Hz, 1H; PhCH₂), 3.97 (br s, 1H), 3.88–3.85 (m, 2H), 3.81–3.70 (m, 3H), 3.75 (s, 3H; OMe), 3.35 (s, 3H; OMe), 2.75 (dd, $J_{3a,3e} = 13.0$ Hz, $J_{3e,4} = 5.0$ Hz, 1H; H-3e), 2.11 (dd, $J_{3a,3e} = 13.0$ Hz, $J_{3a,4} = 10.5$ Hz, 1H; H-3a), 1.70 (s, 3H; Ac). HRMS (ESI) calcd for C₇₅H₇₁NO₁₉ [M+K]⁺ 1328.4246; found: 1328.4235.

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