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

Yue Wang, Xin-Shan Ye *

State Key Laboratory of Natural and Biomimetic Drugs, Peking University, and School of Pharmaceutical Sciences, Peking University, Xue Yuan Road #38, Beijing 100191, China

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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.

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 α(2,3)- and/or α(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 auxiliaries 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 ^{1}H 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-D-galactopyranoside (**8**)[20] using NIS–TfOH as the promoter system was investigated. Solvents played an important role in

* Corresponding author. Tel.: +86 10 8280 1570; fax: +86 10 6201 4949.
E-mail address: xinshan@bjmu.edu.cn (X.-S. Ye).

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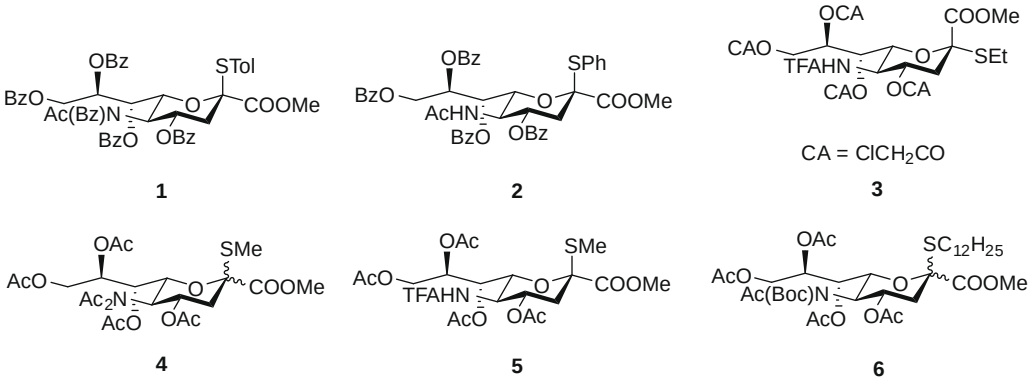
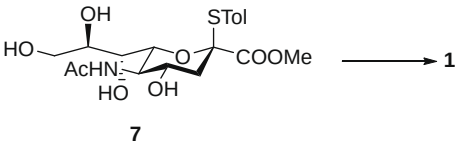
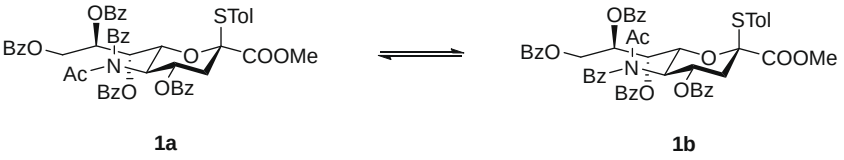


Figure 1. Structures of thiosialoside donors **1–6**.



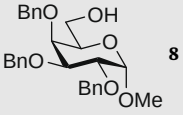
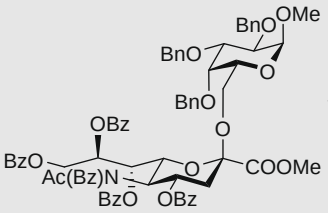
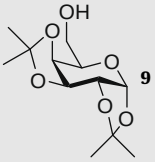
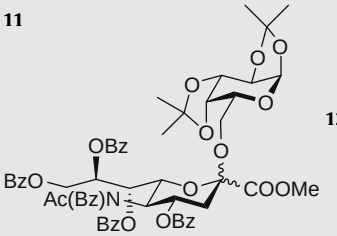
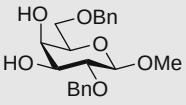
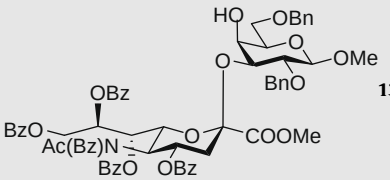
Scheme 1. Reagents and conditions: benzoyl chloride, dry pyridine, DMAP, room temperature, 24 h, 98%.

this reaction. Under the influence of additional *N*-benzoyl group, donor **1** was not activated in the mixed solvent of acetonitrile-dichloromethane (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

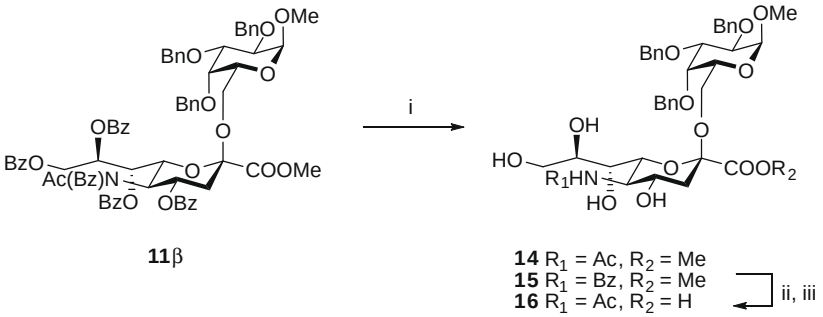


Scheme 2. Equilibrium between **1a** and **1b**.

Table 1
Sialylation reactions of donor **1** with acceptors **8–10**

Entry	Acceptor	Conditions[a]	Product	Yield (%)	Ratio (α/β)[b]
1	 **8**	A	 **11**	90	β
2	**8**	B	**11**	70	1:2.2
3	 **9**	A	 **12**	86	1:6.7
4	**9**	B	**12**	63	1:1.8
5	 **10**	A	 **13**	53[c]	β

[a] A: NIS–TfOH, dichloromethane, AW-300 molecular sieves, −72 °C, donor and acceptor (1.5 equiv) were pre-mixed; B: Ph_2SO–Tf_2O, 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.
[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) $Ba(OH)_2{\cdot}8H_2O$, EtOH–H_2O (v/v 1:1), reflux, 18 h; (iii) Ac_2O, 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, Ph_2SO–Tf_2O promoter system reported by Crich[23] was attempted. Unfortunately, unnatural β anomer was still a dominant product though an excess of Ph_2SO 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 **9**[26] afforded a similar result: higher β anomeric selectivity was also achieved when NIS–TfOH instead of Ph_2SO–Tf_2O 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 **10**[27] 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 ^{1}H 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 $J_{C\text{-}1,H\text{-}3a}$ coupling constants were also used to confirm the glycosidic bond configurations of deprotected products of disaccharides **11β** 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 Ph_2SO–Tf_2O 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.

Acknowledgments

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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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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; $PhCH_2$), 4.70 (s, 2H; $PhCH_2$), 4.67 (d, J = 12.0 Hz, 1H; $PhCH_2$), 4.63 (d, J = 12.0 Hz, 1H; $PhCH_2$), 4.59–4.53 (m, 1H; H-9b), 4.54 (d, J = 11.5 Hz, 1H; $PhCH_2$), 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 $C_{75}H_{71}NO_{19}$ $[M+K]^+$ 1328.4246; found: 1328.4235.

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