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Assistance of the C-7,8-Picoloyl Moiety for Directing the Glycosyl Acceptors into the α-Orientation for the Glycosylation of Sialyl Donors

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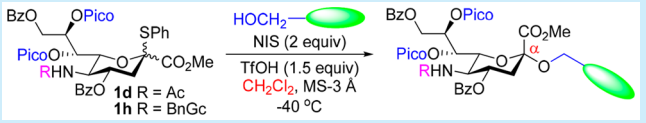
Supporting Information

ABSTRACT: An efficient α-sialylation method for many primary hydroxyl acceptors that include 6-OH glycosides has been developed. 7,8-Di-*O*-picoloyl sialyl glycoside was used as the glycosyl donor, and α-glycoconjugation was controlled by using the 7,8-di-*O*-picoloyl moiety in CH_2Cl_2. The methodology was successfully applied to the total synthesis of ganglioside Hp-s1 possessing neuritogenic activity.



Sialic acids are a diverse family of carboxylated sugars with a skeleton of nine carbon atoms.[1] As sialic acids are widely expressed on the cell surfaces of all animals and are frequently located at the terminal position of glycoconjugates on the cell surface,[1a,c,2] they can play important functional roles in various biological and pathological processes, such as cell−cell adhesion and recognition, cell differentiation, signal transduction, and tumor metastasis.[3] Hence, sialic acid glycosides and their oligomers have potential applications in medicine,[4] and the synthesis of glycoconjugates containing sialic acid is very important.

Natural sialosides have an α-anomeric structure. Because of the presence of the C-1 carboxyl group at the tertiary anomeric center and the lack of a stereocontrolling group at C-3 to direct α-stereoselective sialylation, achieving high α-stereoselectivity of the glycosylation of sialic acid donors with high product yield remains a challenge. Despite previously reported studies on elegant strategies and methodologies, such as the application of various leaving groups,[5] solvents,[6] and promoters[7] as well as structural modification at C-1,[8] C-3,[9] and C-5,[10] it is imperative to develop efficient strategies and methodologies for α-sialylation from the biological viewpoint as well as for potential applications in medicine.

Recently, Yasomanee and Demchenko[11] reported a novel methodology for stereodirected glycosylation. The stereoselectivity of glycosylation was controlled by the picolinyl (2-pyridylmethyl, Pic) and picoloyl (2-pyridinecarbonyl, Pico) substituents via intermolecular H-bond tethering between the glycosyl donor and glycosyl acceptor counterparts. However, to the best of our knowledge, no related studies describing the application of this method to the glycosylation of sialic acid have been reported apart from De Meo's results.[12] In that study, α-stereoselectivity for the sialylation of hydroxyl aglycone assisted by the Pico group was described.

To seek a potential glycosyl donor, the glycosylation of phenyl thiosialosides **1a−e** (see the Supporting Information for the corresponding preparation) with glycosyl acceptor **2** in the presence of NIS/TfOH in CH_2Cl_2 was explored (Table 1). The best result was obtained with the glycosylation of 7,8-di-*O*-picoloyl donor **1d** with acceptor **2** at −40 °C, in which the coupling product **3d** was obtained in 70% yield with excellent stereoselectivity (α only) along with glycal **4d** in 27% yield (entry 4). 8-*O*-Picoloyl donor **1b** also exhibited high α-stereoselectivity (α/β = 8:1) and moderate yield (62%) for disaccharide **3b**, with glycal **4b** observed in 24% yield (entry 2). 7-*O*-Picoloyl donor **1a** (entry 1) and 4,9-di-*O*-picoloyl donor **1c** (entry 3) showed no significant stereoselectivity for disaccharides **3a** (α/β = 1:1.2, 57% yield) and **3c** (α/β = 1.3:1, 43% yield), and glycals **4a** and **4c** were obtained in 40% and 49% yield, respectively. Per-*O*-benzoyl donor **1e** gave disaccharide **3e** in excellent yield (90%) but with poor α-stereoselectivity (α/β = 1:3.3) (entry 5).[13] We also explored the glycosylation of the 7,8-di-*O*-nicotinoyl (3-pyridinecarbonyl, Nico), and 7,8-di-*O*-isonicotinoyl (4-pyridinecarbonyl, iNico) sialyl donors with acceptor **2**. The results revealed excellent α-stereoselectivity (α only) for the corresponding disaccharides, albeit with very poor product yields (see Table S1 for the detailed results).

To optimize the conditions for glycosylation, the glycoconjugation of sialyl donor **1d** with acceptor **2** was conducted using various solvents and temperatures (Table 2). First, the effect of temperature was investigated. Using NIS/TfOH as the promoter and conducting the glycosylation in CH_2Cl_2 at −20 °C, we observed low stereoselectivity (α/β = 5.3:1) and poor product yield (24%) (entry 1). When the reaction temperature was decreased to −60 °C (entry 2), the yield (69%) and α-stereoselectivity (α only) of disaccharide **3d** were as good as those at −40 °C. Next, the effect of the solvent was examined. Using CH_3CN (entry 3) or $CHCl_3$ (entry 4), we got excellent α-stereoselectivity, but the yield of disaccharide **3d** was not satisfactory (56% or 20%, respectively). Interestingly, using toluene as the solvent (entry 5) did not result in the glycosylation of sialyl donor **1d** with acceptor **2**; **1d** was

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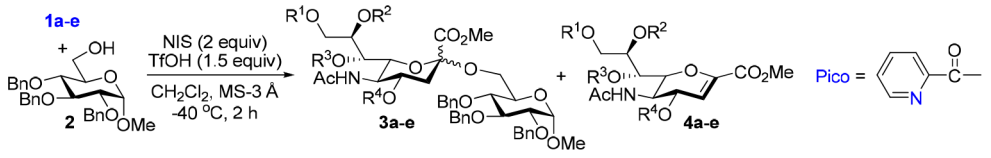
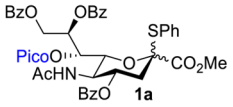
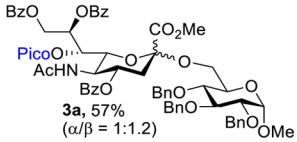
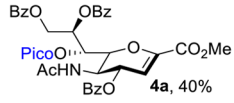
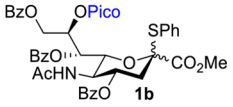
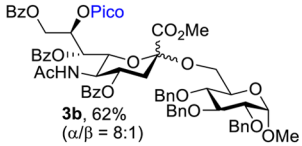
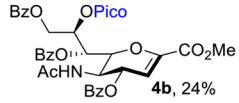
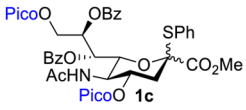
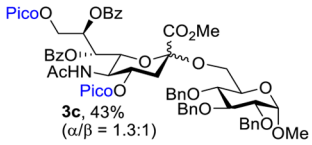
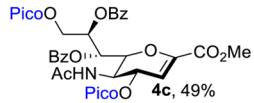
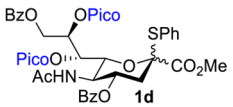
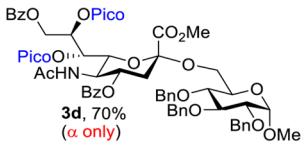
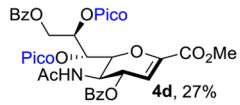
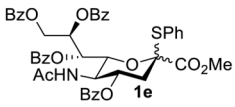
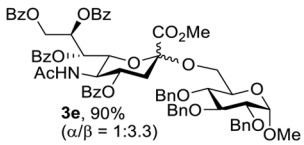
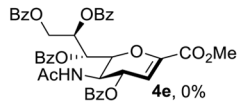
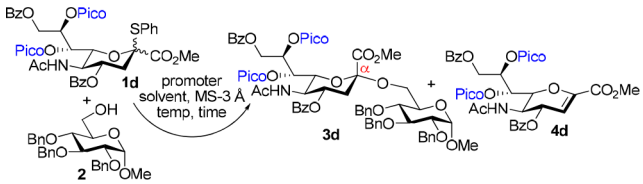
Table 1. Exploring the Glycosylation of Sialyl Donors 1a−e with Glucosyl Acceptor 2



entry	donor	yield[a] of **3a-e** (α/β)[b]	yield[a] of **4a-e**
1		 **3a**, 57% (α/β = 1:1.2)	 **4a**, 40%
2		 **3b**, 62% (α/β = 8:1)	 **4b**, 24%
3		 **3c**, 43% (α/β = 1.3:1)	 **4c**, 49%
4		 **3d**, 70% (α only)	 **4d**, 27%
5		 **3e**, 90% (α/β = 1:3.3)	 **4e**, 0%

[a]Isolated through chromatography. [b]Determined by ^{1}H NMR spectroscopy.

Table 2. Screening of the Optimized Conditions for the Glycosylation of Sialyl Donor 1d with Glucosyl Acceptor 2



entry[a]	solvent	temp (°C)	time (h)	yield (%)[b] of **3d** (α/β)[c]	yield (%)[b] of **4d**
1	CH_2Cl_2	−20	0.5	24 (5.3:1)	70
2	CH_2Cl_2	−60	5.0	69 (α only)	25
3	CH_3CN	−40	0.5	56 (α only)	44
4	$CHCl_3$	−40	0.5	20 (α only)	76
5	toluene	−40	2.0	−[d]	0

[a]Promoter: NIS (2 equiv)/TfOH (1.5 equiv). [b]Isolated through chromatography. [c]Determined by ^{1}H NMR spectroscopy. [d]The starting material was recovered.

recovered quantitatively after 2 h.[14] The reason for this result is not clear. As to the effects of promoters and some solvents, detailed results are shown in Table S2.

To understand the effects of the leaving group on the stereoselectivity of glycosylation and the yield of the final product, other leaving groups such as *S*-benzoxazolyl (SBox), $OP(OEt)_2$, $OP(O)(OPh)_2$, and OPico were examined under the optimal conditions (i.e., use of NIS/TfOH as the promoter in CH_2Cl_2 at −40 °C). However, the results (see Table S3) were not better than that for SPh as the leaving group.

To further evaluate the scope of glycosylation for sialyl donor **1d** under the optimized reaction conditions (Table 3), various glycosyl acceptors were prepared according to a previously reported method (see the Supporting Information). The glycoconjugation of sialyl donor **1d** with primary alcohol **5a** afforded the corresponding disaccharide **6a** in 97% yield as a single α-stereoisomer (entry 1). For the sialylation of primary alcohol **5b** with donor **1d**, the coupling product **6b** was obtained in excellent yield (98%), albeit with moderate α-stereoselectivity (α/β = 2.8:1) (entry 2). The coupling of primary alcohols **5c** and **5d** containing carbohydrates with **1d** also furnished the desired coupling products **6c** and **6d** in good yields (68% and 73%, respectively) with excellent stereoselectivity (α only) (entries 3 and 4). Using secondary sugars (e.g., **5e**) as acceptors, we did not obtain the corresponding disaccharides (e.g., **6e**) but obtained only the glycal side product **4d**, possibly because of the strong steric hindrance in these acceptors (entry 5). Detailed results for the glycosylation of **1d** with other acceptors are provided in Table S4. The stereochemistry of disaccharides **3d** and **6a−d** was determined by comparing the chemical shifts of the de-*O*-acylated

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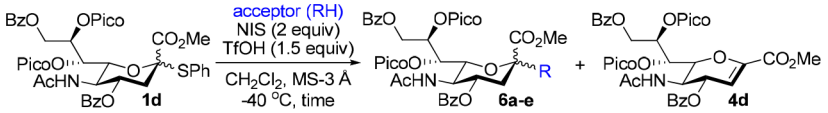
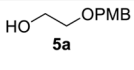
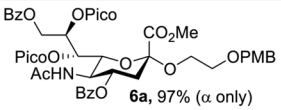
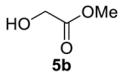
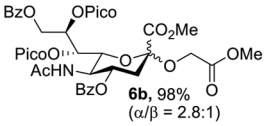
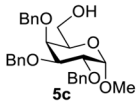
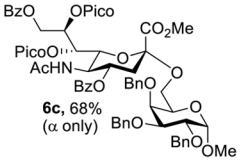
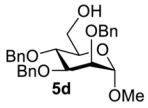
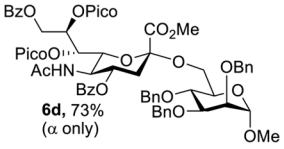
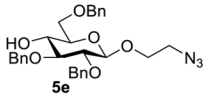
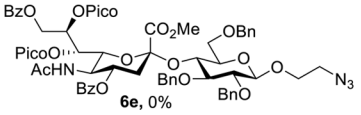
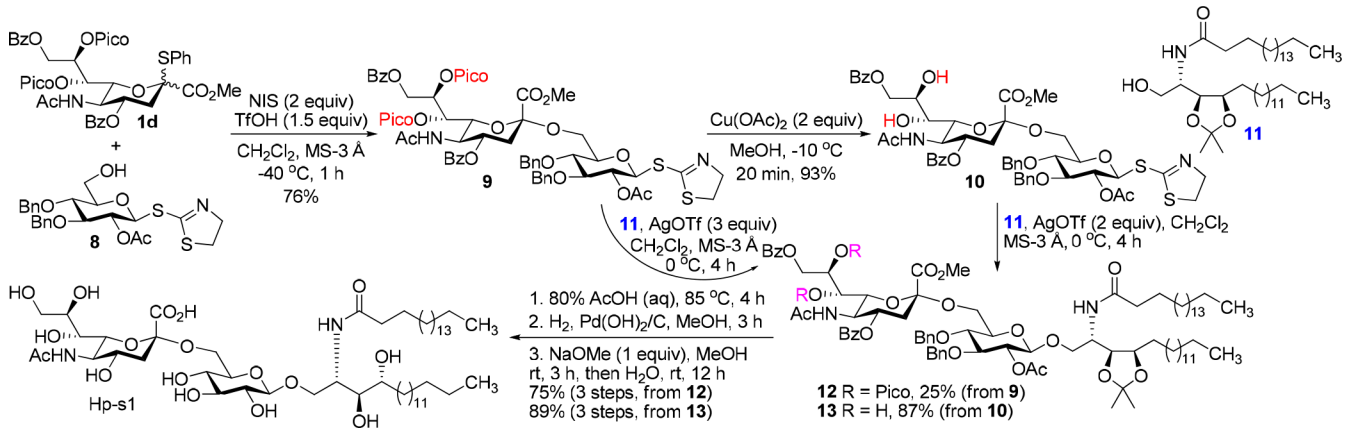
Table 3. Evaluation of the Glycosylation Scope of Sialyl Donor 1d with Various Acceptors[a]



entry	acceptor	time (h)	yield[b] of **6a-e** (α/β)[c]	yield (%)[b] of **4d**
1	 **5a**	0.5	 **6a**, 97% (α only)	0
3	 **5b**	0.5	 **6b**, 98% (α/β = 2.8:1)	0
4	 **5c**	0.5	 **6c**, 68% (α only)	25
5	 **5d**	0.5	 **6d**, 73% (α only)	20
6	 **5e**	1.0	 **6e**, 0%	99

[a]The reaction was carried out under the following conditions: NIS (2 equiv), TfOH (1.5 equiv), CH_2Cl_2, −40 °C. [b]Isolated by chromatography. [c]Determined by ^{1}H NMR spectroscopy.

Scheme 1. Total Synthesis of Ganglioside Hp-s1 Possessing Neuritogenic Activity



disaccharides with those of the corresponding compounds reported in the literature (see Tables S5−S7 for the detailed results). The sialylation of primary alcohols containing carbohydrates, e.g., **2** and **5c**, with 7,8-di-*O*-picoloyl-Neu5Gc as the donor was also investigated, and good yields of the corresponding disaccharides as single α-stereoisomers were observed (see Table S8 for the detailed results).

Finally, to confirm the utility of this aforementioned methodology, it was extended to the synthesis of the natural product ganglioside Hp-s1, which exhibits neuritogenic activity (Scheme 1).[15] The sialylation of *S*-thiazolyl (STaz) acceptor **8**[15b] with sialyl donor **1d** was performed using NIS/TfOH as the promoter in CH_2Cl_2 with powdered 3 Å molecular sieves at −40 °C to afford the α-stereoisomer disaccharide **9** in 76% yield. Compound **9** was coupled with protected phytoceramide **11** in the presence of a promoter such as AgOTf in anhydrous CH_2Cl_2 at 0 °C, and only the β-anomer was obtained for protected Hp-s1 **12**, albeit in poor yield (25%). Fortunately, when **9** was first treated with $Cu(OAc)_2$ in MeOH at −10 °C to selectively remove the picoloyl group[16] and then protected phytoceramide **11** was glycosylated with the resulting disaccharide **10** (93% yield) under the same conditions as those described for disaccharide **9**, the desired Hp-s1 analogue **13** was obtained in high yield (87%) with excellent stereoselectivity (β only). Finally, protected Hp-s1 analogues **12** and **13** were subjected to sequential deprotection reactions

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involving deisopropylidenenation, debenzylation, deacetylation, and saponification to furnish the desired ganglioside Hp-s1 in 75% and 89% yield, respectively, in three steps.

In summary, 7,8-di-*O*-picoloyl sialyl donors can be applied in the α-sialylation of most primary hydroxyl acceptors such as 6-OH glycosides. The α-stereocontrolled glycosylation was best achieved using the 7,8-di-*O*-picoloyl moiety in CH_2Cl_2. A further advantage of this method is the facile preparation of the 7,8-di-*O*-picoloyl sialyl donors. This methodology was successfully applied to the total synthesis of ganglioside Hp-s1 via chemoselective glycosylation. This developed method can be used to efficiently synthesize various glycoconjugates possessing an $\alpha(2-6)$ disaccharide segment. The investigation of the mechanism of glycosylation is also in progress, and the results will be reported in due course.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b01658.

Detailed experimental procedures for the preparation and characterization of all compounds (PDF)

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Notes

The authors declare no competing financial interest.

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