α-Selective Sialylations with *N*-Acetyl-5-*N*,4-*O*-Oxazolidinone-Protected *p*-Toluenethiosialoside

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Abstract: A novel *N*-acetyl-5-*N*,4-*O*-oxazolidinone-protected *p*-toluenethiosialoside was readily prepared from sialic acid and *p*-toluenethiol. It was demonstrated that the *p*-toluenethiosialoside could be successfully applied to the α-selective sialylations with various glycosyl acceptors in good yields. In the coupling of *N*-acetyl-5-*N*,4-*O*-oxazolidinone-protected *p*-toluenethiosialoside and gluco alcohol, a quantitative reaction yield and high α-selectivity were obtained in dichloromethane–acetonitrile (2:1) at –40 °C.

Key words: *p*-toluenethiosialoside, oxazolidinone, sialic acid

N-Acetylneuraminic acid (Neu5Ac) is the best-known naturally occurring derivative of the sialic acid family, which is abundant on the mammalian cell surface. Many biological studies illustrate the significant importance of sialic acid in cell differentiation, charged molecules transportation, and pathogen-host recognition, which are involved in the numerous cellular events in high animals and human being. *N*-Acetylneuraminic acid frequently occupies the terminal position of glycan chains on glycoproteins and glycolipids via α-glycosidic linkage and is considered as the antennae of glycoconjugates.[1] Over the years, various sialylation strategies[2] were developed to construct the natural α-linkage, and mainly focused on the use of various leaving groups, such as sulfide,[3] xanthate,[4] phosphite,[5] and trifluoroacetimidate,[6] as well as promoters including NIS/TfOH,[7] NIS/TfOH/TMSOTf,[8] TBAOTf,[9] and Ph_2SO/Tf_2O.[10,11] In addition, some indirect chemical methods for sialylations such as participating auxiliaries at C-3[12,2b] and modifications of C-5[13] using *N*-Ac_2, *N*-TFA, *N*-Troc, etc. have also been investigated.

Recently, 5-*N*,4-*O*-oxazolidinone as a protective group of the sialyl donor was introduced by several research groups.[14–17] In particular, Crich et al. devised *N*-acetyl-5-*N*,4-*O*-carbonyl-protected phenylthiosialoside **2** (Figure 1),[14] and 1-adamantanylthiosialosides **3**.[15] These two novel sialyl donors were successfully used in the α-sialylation and a satisfactory reaction yield and α/β product ratio, respectively, were obtained. Unfortunately, it was noted that **2** failed in the glycosylation with secondary sugar acceptors promoted by NIS/TfOH in nitrile solvents at –40 °C in order to increase the α-selectivities of the sialylations by means of the nitrile effect.[15] Although **3** afforded a good α-selective sialylation at low temperature in nitrile solvent, it was synthesized via a comparatively longer synthetic route from pentaacetate derivative of Neu5Ac.[15]

p-Toluenethiosialoside (**4**) is a common donor for sialylation, which can be easily derivated to other kinds of useful sialyl donors.[18,20] Since *p*-methyl-phenyl group has a greater electron-donating property compared to phenyl group, toluenethioside should be more reactive than phenylthioside.[19] Furthermore, *p*-toluenethiol is a nonvolatile solid (mp 40–44 °C) instead of the liquid thiophenol (mp –15 °C), which can efficiently reduce the odor problem during its transformation into sulfide sialyl donor. Based on these facts, herein, we report the synthesis of a novel *N*-acetyl-5-*N*,4-*O*-oxazolidinone-protected *p*-toluenethiosialoside **1** and its application into sialylation with various sugar acceptors.

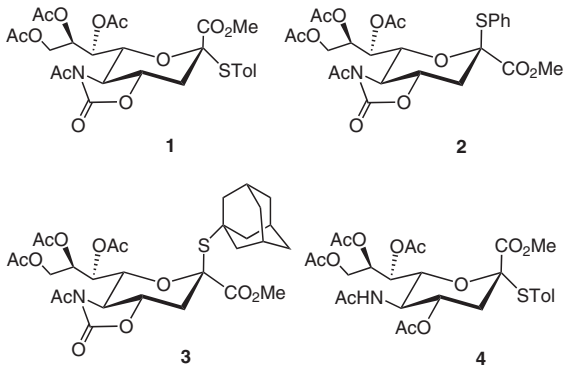

Figure 1

In order to prepare donor **1**, sialoside **4** was first prepared from Neu5Ac and *p*-toluenethiol as described in the literature.[20] Deacetylation of **4** with MsOH in MeOH under reflux afforded the free amine intermediate, which was then transformed into 5-*N*,4-*O*-carbonyl-protected derivative **5** by treatment with 4-nitrophenyl chloroformate in 60% yield (two steps). All the hydroxy groups in **5** and the amino nitrogen in the oxazolidinone were successively acetylated with acetic anhydride and pyridine then acetyl chloride and *N*,*N*-diisopropylethylamine to produce donor **1** in 80% yield (Scheme 1).[21] The solid-state structure of **1** has been confirmed by single-crystal X-ray diffraction (Figure 2).[24]

Initially, the donor **1** property was investigated with gluco alcohol **6** bearing a primary free 6-hydroxy group as the acceptor. To a stirring mixture of **1** and **6** (1.2 equiv), and

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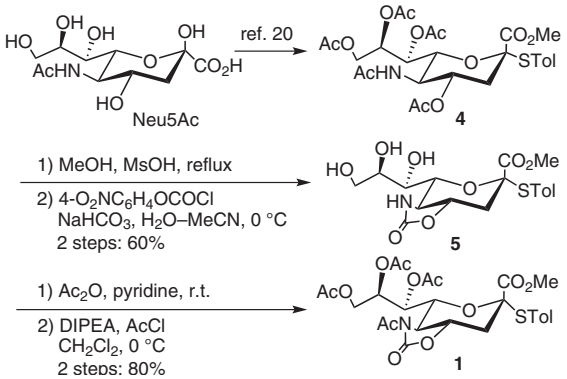


Scheme 1 Synthesis of donor **1**

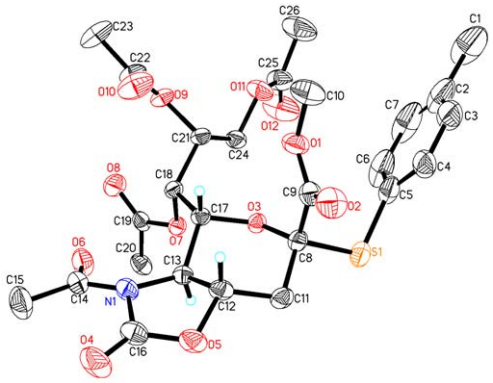
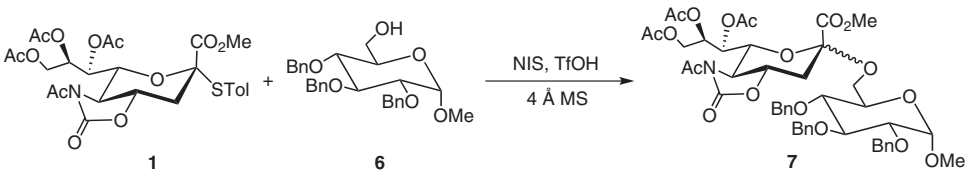


Figure 2 The X-ray crystallographic structure of **1**

4 Å molecular sieves in acetonitrile at –40 °C under argon was added trifluoromethanesulfonic acid and *N*-iodosuccinimide. Thin-layer chromatography indicated the reaction was finished in 20 minutes. The expected product **7** was achieved in high yield (93%) and an α/β ratio of 5.4:1 (Table 1, entry 1). We then further examined the solvent effect on the glycosylation. The results showed that using 2:1 CH_2Cl_2–MeCN as the solvent, the reaction went smoothly and a quantitative product yield and the highest α/β product ratio (6.5:1) were observed (Table 1, entry 3), suggesting that the best solvent to use was a CH_2Cl_2–MeCN mixture. In addition, decreasing the reaction temperature to –75 °C gave the α-anomer as the only product but in a lower reaction yield (63%, Table 1, entry 4). Higher temperature (–20 °C) was useful to improve the reaction yield (92%, Table 1, entry 6). However, the product yield was the highest when the reaction was carried out at –40 °C (Table 1, entry 5). Therefore we used the reaction conditions described in entry 5 of Table 1 for the following sialylations with various sugar acceptors.

Table 2 illustrates the results of our efforts to explore the sialylation reactions between donor **1** and various alcohol acceptors.[22] Besides methyl 2,3,4-tri-*O*-benzyl-α-D-glucopyranoside (**6**), it was found that excellent yields (>90%) and good α-selectivities (α/β >6:1) were obtained with other primary alcohols such as methyl 1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranoside (**8**) and 1-octanol (**9**, Table 2, entries 1–3). For secondary sugar acceptors, diosgenin (**10**) and 3β-cholestanol (**11**), both afforded the desired linkage types with α/β >10. In the case of 3β-cholestanol **11**, the product yield was low (51%) due to its poor solubility in the CH_2Cl_2–MeCN mixture used. In the regioselective 3-*O*-sialylation of methyl 2,6-di-*O*-benzyl-β-D-galactopyranoside (**12**), the α-anomer was the major product (α/β = 1.8:1). The ratio was much higher than in the case of donor **2** used for the sialylation (α/β = 1:1.3),[14] indicating that *p*-toluenethiosialoside **1** was a better sialyl donor than phenylthiosialoside **2**. Similarly, with 2,4,6-tri-*O*-benzyl-β-D-galactopyranoside (**13**) as the acceptor, compared with the unsatisfactory product α/β ratio (1:8)[14] of the known donor **2**, a much improved α-selectivity (α/β = 1.2:1) was obtained for the reaction. For the sterically hindered acceptor, coupling of **1** and 1-adamantanol (**14**) also gave the major α-anomer in 76% isolated yield.

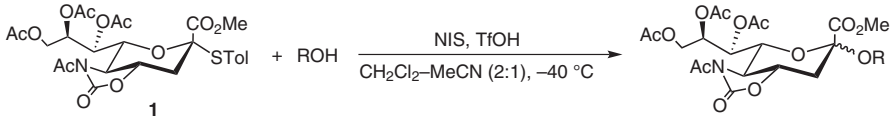
Table 1 The Effect of Solvent and Temperature on the Sialylation of Donor **1**



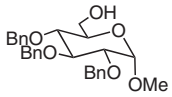
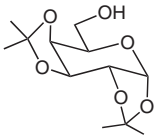
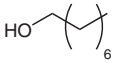
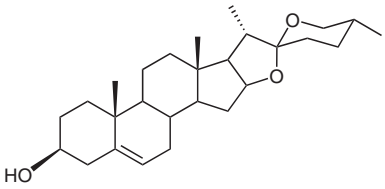
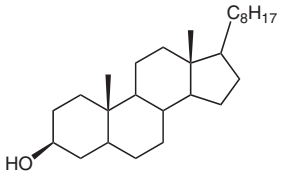
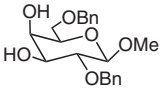
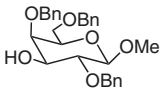
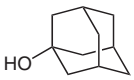
Entry	Solvent	Temp (°C)	Time (min)	Yield (%)[a]	α/β[b]
1	MeCN	–40	20	93	5.4:1
2	CH_2Cl_2	–40	20	90	3.9:1
3	CH_2Cl_2–MeCN (2:1)	–40	20	quant.	6.5:1
4	CH_2Cl_2–MeCN (2:1)	–75	60	63	α
5	CH_2Cl_2–MeCN (2:1)	–40	60	quant.	6.2:1
6	CH_2Cl_2–MeCN (2:1)	–20	60	92	6.3:1

[a] Isolated yields.
[b] Determined by ^{1}H NMR analysis.

Table 2 Sialylation of Various Alcohol Acceptors with Donor **1**



1

Entry	Acceptor	Product	Yield (%)[a]	α/β[b]
1	 **6**	**7**[d]	quant.	6.2:1
2	 **8**	**15**[d]	95	α
3	 **9**	**16**[d]	92	>10:1
4	 **10**	**17**[23]	80	>10:1
5	 **11**	**18**[d]	51	>10:1
6	 **12**	**19**[d]	72	1.8:1[c]
7	 **13**	**20**[d]	81	1.2:1
8	 **14**	**21**[d]	76	3.3:1

[a] Isolated yields.
[b] Determined by ^{1}H NMR analysis.
[c] Coupled to the 3-OH.
[d] The ^{1}H NMR data have good consistence with those reported in ref. [14].

In conclusion, *p*-toluenethiosialoside **1** was designed based on the known thioglycoside **2** and **4**. Since *p*-toluenethiol is a nonvolatile solid, donor **1** could be more readily prepared than phenylthiosialoside **2**. In the coupling of **1** and **6**, excellent product yield and α-selectivity were observed with CH_2Cl_2–MeCN (2:1) as reaction media at –40 °C. In this letter, the results also demonstrated that *N*-acetyl-5-*N*,4-*O*-oxazolidinone-protected *p*-toluenethiosialoside was successfully applied to the α-selective sialylations with various glycosyl acceptors in good yields. In some cases, *p*-toluenethiosialoside **1** proves to be a better sialyl donor than phenylthiosialoside **2**, especially in the regioselective 3-*O*-sialylation of galactopyranoside **12** and the glycosyaltion of tribenzyl galactopyranoside **13**.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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(21) Donor **1** was prepared similarly as literature described.[14] Compound characterization data for **5**: ^{1}H NMR (500 MHz, CD_3OD): δ = 7.47 (d, *J* = 7.7 Hz, 2 H), 7.22 (d, *J* = 7.7 Hz, 2 H), 4.06 (dt, *J* = 11.9, 3.3 Hz, 1 H), 3.83 (m, 3 H), 3.67–3.69 (m, 2 H), 3.67 (s, 3 H), 3.55 (d, *J* = 8.8 Hz, 1 H), 3.14 (dd, *J* = 11.7, 3.6 Hz, 1 H, H-3eq), 2.38 (s, 3 H), 2.21 (t, *J* = 12.2 Hz, 1 H, H-3ax). ^{13}C-APT NMR (125 MHz, CD_3OD): δ = 169.1, 160.9, 140.5, 136.3, 129.3, 125.1, 87.8, 78.3, 78.2, 71.5, 70.0, 63.1, 57.1, 52.2, 36.6, 19.9. HRMS: *m/z* calcd for $C_{18}H_{23}NO_8SNa$ [M + Na]$^+$: 436.10421; found. 436.10364.
Compound **1**: ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.45 (d, *J* = 7.9 Hz, 2 H), 7.18 (d, *J* = 7.9 Hz, 2 H), 5.55 (d, *J* = 5.8 Hz, 1 H), 5.38 (m, 1 H), 4.45 (dd, *J* = 12.2, 2.6 Hz, 1 H), 4.36 (d, *J* = 9.4 Hz, 1 H), 4.23 (m, 1 H), 3.98 (m, 1 H), 3.65 (s, 3 H), 3.63 (m, 1 H), 3.10 (dd, *J* = 12.1, 3.5 Hz, 1 H, H-3eq), 2.48 (s, 3 H), 2.39 (s, 3 H), 2.19 (s, 3 H), 2.14 (m, 1 H, H-3ax), 2.11 (s, 3 H), 2.10 (s, 3 H). ^{13}C-APT NMR (125 MHz, $CDCl_3$): δ = 171.9, 170.6, 170.3, 170.0, 168.2, 153.4, 140.6, 136.3, 129.7, 124.7, 87.8, 77.4, 75.7, 72.6, 70.7, 62.5, 59.1, 53.1, 36.5, 24.7, 21.3, 21.1, 20.9, 20.8. HRMS: *m/z* calcd for $C_{26}H_{31}NO_{12}SNa$ [M + Na]$^+$: 604.14647; found. 604.14590.

(22) **General Sialylation Procedure (with the Coupling Between 1 and 6 as Example)**
To a mixture of donor **1** (40.0 mg, 0.07 mmol, 1.0 equiv), acceptor **6** (38.4 mg, 0.08 mmol, 1.2 equiv), and activated 4 Å powdered MS, was added anhyd CH_2Cl_2–MeCN (2:1, 3 mL). The resulted solution was stirred for 0.5 h at r.t. under Ar, and then cooled to –40 °C followed by addition of NIS (37.7 mg, 0.17 mmol, 2.4 equiv) and TfOH (6.0 μL, 0.07 mmol, 1.0 equiv). The reaction was stirred at –40 °C for 1 h. After quenched with Et_3N (0.1 mL), the mixture was diluted with CH_2Cl_2, filtered through Celite, washed with 20% aq $Na_2S_2O_3$ solution, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography on SiO_2 eluting with hexane–EtOAc system to give the coupling product.

(23) Compound **17**: ^{1}H NMR (500 MHz, $CDCl_3$): δ = 5.60 (d, *J* = 7.2 Hz, 1 H), 5.40 (dt, *J* = 6.9, 2.8 Hz, 1 H), 5.34 (d, *J* = 3.1 Hz, 1 H), 5.12 (m, 1 H), 4.55 (d, *J* = 9.4 Hz, 1 H), 4.42–4.33 (m, 2 H), 4.13 (m, 1 H), 4.01 (m, 1 H), 3.79 (s, 3 H), 3.71 (t, *J* = 9.8 Hz, 1 H), 3.62 (m, 1 H), 3.48–3.35 (m, 2 H), 2.90 (dd, *J* = 12.0, 3.2 Hz, 1 H, H-3eq), 2.49 (s, 3 H), 2.15 (s, 3 H), 2.12 (s, 3 H), 2.03 (s, 3 H), 1.01 (s, 3 H), 0.96 (d, *J* = 6.9 Hz, 3 H), 0.79 (s, 3 H), 0.78 (d, *J* = 5.7 Hz, 3 H).

(24) CCDC 693369 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.