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Application of 4,5-*O*,*N*-oxazolidinone protected thiophenyl sialosyl donor to the synthesis of α-sialosides

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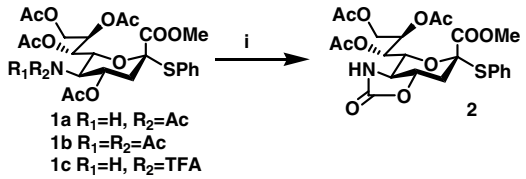
Abstract—The synthesis of a novel oxazolidinone sialosyl donor is reported. The introduction of a trans-fused ring enhances reactivity and stereoselectivity in glycosylation reactions for the synthesis of α-sialosides. The oxazolidinone ring can also be removed under basic conditions to afford the deprotected amine, which can be further functionalized.

Sialic acids are a family of 40 naturally occurring 2-keto-3-deoxy-nononic acids that are mainly found at the terminal position of glycolipids and glycoproteins. For this exposed position in the glycan chain, sialic acids are involved in a wide range of biological phenomena, such as cell–cell interactions, cell differentiation, tumor metastasis, and pathogen–host recognition.[1,2] The most widespread member of the sialic acid family, *N*-acetyl-neuraminic acid (Neu5Ac) is often linked to galactose or galactosamine via α(2,3) and α(2,6) glycosidic linkages. Although extensively explored, the chemical synthesis of sialosides in a high yield with a complete stereoselectivity is still a notable challenge.[3–5] The presence of a destabilizing electron-withdrawing carboxylic group together with a tertiary anomeric center and the lack of a participating auxiliary often drive glycosylation reactions toward competitive elimination reactions resulting in a poor stereoselectivity and in the formation of a 2,3-dehydro derivative. To address these problems, different strategies have been developed, primarily focusing on the nature of the leaving group or promoter. The introduction of participating auxiliaries at the C-3 positions (indirect methods) also have been investigated.[3,6–8] In addition, modifications of the C-1 carboxylic group[9,10] as well as 1,5-intramolecular lactamization[11] or modifications of the C-5 acetamido group[12] have been reported as alternative strategies to optimize glycosylation reactions.

Herein we report the application of 4,5-*O*,*N*-oxazolidinone protected sialosyl donor **2** as a versatile intermediate for the stereoselective synthesis of α(2,3) and α(2,6)-linked sialosides. Although the use of oxazolidinone protection for glucosamine has been described by Crich[13,14], Kerns,[15–17] and Oscarson[18] the effect of fused ring systems on neuraminic acid has not been fully investigated.[19]

Thus, compound **2**[20] was prepared in a straightforward manner starting from the known thioglycoside derivative **1a** as described in Scheme 1. Full deprotection of **1a** in the presence of methanesulfonic acid afforded the free amine intermediate, which was N-functionalized by treatment with *p*-nitro-phenyl chloroformate (NPCC) in an 80% yield, and then O-acetylated to afford **2**.

NMR comparison of **2** with **1a** showed a strong influence of the oxazolidinone fused ring on some signals. In particular, H-3eq is shifted downfield ($\delta = 3.07$ ppm) while H-4 and H-5 are shielded ($\delta = 3.86$ and 2.91 ppm, respectively). In the glycerol chain, H-9 is now magnetically equivalent, showing a singlet at 4.32 ppm.



Scheme 1. Reagents and conditions: (i) (a) MsOH, MeOH, 65 °C, 80%; (b) NPCC/$NaHCO_3$, MeCN–H_2O, 3 h, 80%; (c) Ac_2O/Py, 16 h, 90%.

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To explore the potential of a *trans*-4,5-cyclic carbamate as protecting/activating group in sialic acid moiety, sialosyl donor **2** was then coupled with 1,2:3,4-di-*O*-isopropylidene galactoside acceptor **3** and the results were compared with different C-5 protected sialyl donors **1a–c** (Table 1). All the reactions were performed using an equimolar amount of donor and acceptor in the presence of acetonitrile as stereocontrolling solvent, using NIS/TfOH as promoter. Interestingly, the introduction of the oxazolidinone ring increases yield and stereoselectivity of the glycosylation reaction (Table 1, entry 4, 90%, 10:1 α:β) when compared with the acetamido-bearing donor **1a** or the *N*-acetylacetamido compound **1b** (entries 1 and 2, respectively). In addition, sialyl donor **2** appears less reactive but more stereocontrolling than donor **1c** (entry 3).

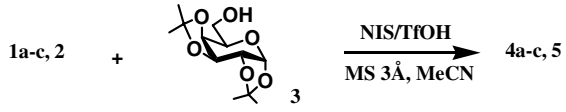
Encouraged by these preliminary results, we decided to investigate the glycosyl donor proprieties of **2** by coupling with different acceptors, ranging from simple alcohols (entries 1 and 2), to C-6 (entries 3 and 4) and C-3 acceptors (entries 5–7, Table 2).

Coupling with MeOH (entry 1, Table 2) gave a high yield of methyl glycoside **13** in the ratio 1.7:1. A complete stereoselectivity was observed when 2-trimethylsilyl ethanol **7** was used as the acceptor (entry 2).

In the series of C-6 acceptors (compounds **3**, **8**, and **9**) all the glycosylations proceeded with high yields and stereoselectivities. In particular, acceptor **9** gave the corresponding disaccharide **16** as 6:1 anomeric mixture in a 91% yield. The best result was obtained by using acceptor **3** as reported in Table 1.

To evaluate the glycosyl donor of **2** for the synthesis of α(2,3) linkages, three differently protected galactoside acceptors (**10**–**12**) were used. Unfortunately, glycosylation of diol **10** gave mainly the unnatural β anomer. However, Crich observed the same β-stereoselectivity in the coupling of donor **1b** with acceptor **10**.[21] Yet, a complete stereoselectivity was observed when triol **11** was used for the synthesis of sialoside **18** (entry 6); lower yield than expected (50%) was in part due to disialylation of **11** in positions 2 and 3, as confirmed by mass spectrometric analysis of the isolated trisaccharide

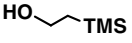
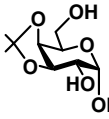
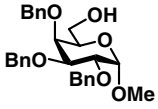
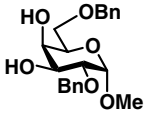
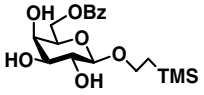
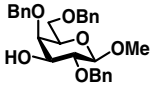
Table 1. Glycosylation of acceptor **3** with donor **1a–c**, **2**[a]



Entry	Donor	Product	Yield[b] (%)	Ratio (α:β)[c]	Reaction time
1	**1a**	**4a**	Trace[c]	—	16 h
2	**1b**	**4b**	89	2:1	16 h
3	**1c**	**4c**	88	5:1	10 min
4	**2**	**5**	90	10:1	30 min

[a] All glycosylations were performed in CH_3CN under argon at −40 °C.
[b] Isolated yields.
[c] Anomeric ratios were determined after column chromatography on Sephadex LH-20 by ^1H NMR analysis.[3]

Table 2. Glycosylation of donor **2** with acceptors **6–12**

Entry	Acceptor	Product	Yield[a] (%)	Ratio (α:β)[b]
1[c]	MeOH **6**	**13**	95	1.7:1
2	 **7**	**14**	82	α only
3	 **8**	**15**	90	2:1
4	 **9**	**16**	91	6:1
5	 **10**	**17**	80	1:1.5
6	 **11**	**18**	50	α only
7	 **12**	**19**	50	α only

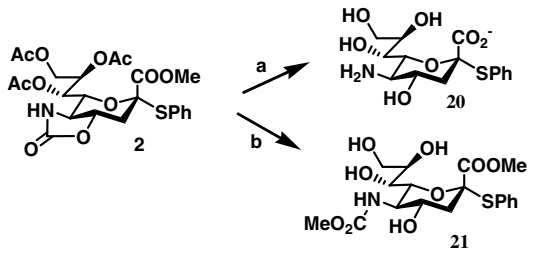
[a] Isolated yields after Sephadex LH-20.
[b] Anomeric ratios were determined by ^1H NMR analysis.[3]
[c] No molecular sieves were used, and 2 equiv of acceptor were required.

(10%). Similar results were previously reported for *N*-trifluoroacetyl 2-thiomethyl sialyl donor with the same acceptor.[22] To exclude the formation of regioisomers, we decided to use the sterically hindered, less reactive 2,4,6-substitued acceptor **12**. Remarkably, disaccharide **19** was isolated with a 50% yield as α-anomer only (Table 2, entry 7), whereas compound **1b** failed to give any glycosylation product,[21] while trifluroacetyl derivative **1c** gave it in an 84% yield.[22]

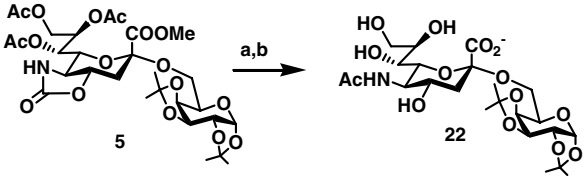
The versatility of oxazolidinone protecting group cannot be proved without a good deprotection method. In the glucosamine series different methods have been applied to the selective removal of the fused ring.[17,14] In the case of sialyl donor **2** complete deprotection to afford free amine **20** was achieved by treatment with barium hydroxide in ethanol, while sodium methoxide in methanol gave the corresponding *N*-methoxy carbonyl derivative **21**, as illustrated in Scheme 2.

Thus, disaccharide **5** was fully deprotected and then N-acetylated to obtain **22** (Scheme 3).

The structures of the disaccharides **5**, **13–18**, and **19** were confirmed by ^1H and COSY NMR experiments, and the



Scheme 2. Reagents and conditions: (a) $Ba(OH)_2$, EtOH, 65 °C, 16 h, 95%; (b) MeOH, MeONa, 2 h, 90%.



Scheme 3. Reagents and conditions: (a) $Ba(OH)_2$, EtOH, 65 °C, 16 h, 95%; (b) Ac_2O, MeOH, 5 h, 90%.

anomeric configurations were assigned using empirical rules.[3] Thus, the most useful characteristic parameters to undoubtedly assign anomeric configuration were the chemical shift of H-3′eq (α-glycosides: δ 3.10–2.78, β-glycosides: δ 2.60–2.50), the value $\Delta\delta$\{H-9′a-H-9′b\} (α-glycosides: δ 0.1–0.3 ppm, β-glycosides: δ 0.6–1.0 ppm) and the value of $J_{\text{H-7}',\text{H-8}'}$ coupling constant (α-glycosides: 6.2–9.6 Hz, β-glycosides: 1.6–3.0 Hz).[23]

In conclusion, the introduction of 4,5-*O*,*N*-oxazolidinone protecting group creates a donor whose reactivity can be in general considered higher than that of *N*-acetylacetamido but slightly lower than trifluroacetamido derivatives. It has also been demonstrated that the oxazolidinone fused ring enhances stereoselectivity in glycosylation reactions with a large number of glycosyl acceptors, although the anomeric selectivity is also dependent on the nature of acceptor. Thus, high yields and stereoselectivities can be achieved for the synthesis of α(2,6) linkages, while an excellent stereoselectivity in modest yields have been reported for the synthesis of α(2,3) linkages. The oxazolidinone ring can also be removed under basic conditions to afford the corresponding deprotected amine, which can be further functionalized.

Acknowledgment

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References and notes

1. Schauer, R. *Sialic Acids: Chemistry, Metabolism and Function*; Springer-Verlag: Wien–New York, 1982; Vol. 10.
2. *Biology of Sialic Acids*; Rosenberg, A., Ed.; Plenum Press: New York, London, 1995.
3. Boons, G. J.; Demchenko, A. V. *Chem. Rev.* **2000**, *100*, 4539–4565.
4. Boons, G. J.; Demchenko, A. V. In *Carbohydrate-Based Drug Discovery*; Wong, C.-H., Ed.; Wiley, 2003; pp 55–102.
5. Ress, D. K.; Linhardt, R. J. *Curr. Org. Synth.* **2004**, *1*, 31–46.
6. De Meo, C.; Parker, O. *Tetrahedron: Asymmetry* **2005**, *16*, 303–307.
7. Meijer, A.; Ellervik, U. *J. Org. Chem.* **2004**, *69*, 6249–6256.
8. Cai, S.; Biao, Y. *Org. Lett.* **2003**, *5*, 3827–3830.
9. Haberman, J. M.; Gin, D. Y. *Org. Lett.* **2001**, *3*, 1665–1668.
10. Ishiwata, A.; Ito, Y. *Synlett* **2003**, *9*, 1339–1343.
11. Ando, H.; Koike, Y.; Koizumi, S.; Ishida, H.; Kiso, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 2–7.
12. De Meo, C. *ACS Symp. Ser.*, in press.
13. Crich, D.; Vinod, A. U. *Org. Lett.* **2003**, *5*, 1297–1300.
14. Crich, D.; Vinod, A. U. *J. Org. Chem.* **2005**, *70*, 1291–1296.
15. Benakli, K.; Zha, C.; Kerns, R. J. *J. Am. Chem. Soc.* **2001**, *123*, 9461–9462.
16. Kerns, R. J.; Zha, C.; Benakli, K.; Liang, Y.-Z. *Tetrahedron Lett.* **2003**, *44*, 8069–8072.
17. Wei, P.; Kerns, R. J. *Tetrahedron Lett.* **2005**, *46*, 6901–6905; Wei, P.; Kerns, R. J. *J. Org. Chem.* **2005**, *70*, 4195.
18. Boysen, M.; Gemma, E.; Lahmann, M.; Oscarson, S. *Chem. Commun.* **2005**, 3044–3046.
19. During the preparation of this manuscript, Takahashi et al. reported the use of oxazolidinone donor and acceptor for the synthesis of α(2–8)-linked sialosides, see: Tanaka, H.; Nishiura, Y.; Takahashi, T. *J. Am. Chem. Soc.* **2006**, *128*, 7124–7125.
20. Methyl [2-thiophenyl 7,8,9-tri-*O*-acetyl-4,5-*O*,*N*-carbonyl-3,5-dideoxy-D-glycero-α-D-galacto-non-2-ulopyranoside]-onate (**2**): R_f 0.50 (ethyl acetate/toluene, 1/1 v/v); $[\alpha]_D^{26}$ −4.90 (*c* 1, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.11–7.43 (m, 5H, aromatic), 5.23–5.32 (m, 2H, H-8, NH), 5.03 (dd, 1H, $J_{7,8} = 9.6$ Hz, H-7), 4.33 (s, 2H, H-9), 3.97 (dd, 1H, $J_{6,7} = 1.5$ Hz, H-6), 3.8–3.90 (m, 1H, H-4), 3.47 (s, 3H, OCH_3), 3.08 (dd, 1H, $J_{3e,4} = 3.6$ Hz, $J_{3e,3a} = 10.4$ Hz, H-3e), 2.92 (t, 1H, $J_{5,6} = 9.9$ Hz, H-5), 2.08 (dd, 1H, H-3a), 2.13, 1.99, (2s, 6H, $OCOCH_3$). HR-FAB MS $[M+Na]^+$ calcd for $C_{23}H_{27}NaNO_{11}S$ 548.1203, found 548.1198.
21. Crich, D.; Wenju, L. *Org. Lett.* **2006**, *8*, 959–962.
22. De Meo, C.; Demchenko, A. V.; Boons, G. J. *Aust. J. Chem.* **2002**, *55*, 131–134.
23. Selected ^{1}H NMR data for compounds **5**α and **14**: *O*-[Methyl (7,8,9-tri-*O*-acetyl-4,5-*O*,*N*-carbonyl-3,5-dideoxy-D-glycero-α-D-galacto-non-2-ulopyranosyl)onate]-(2→6)-1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose (**5**α). ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.11 (dd, 1H, $J_{7',8'} = 9.7$ Hz, H-7′), 4.60 (dd, 1H, $J_{8',9'a} = 2.7$, $J_{9'a,9'b} = 9.5$ Hz, H-9′a), 4.35-4.23 (m, 4H, H-9′b), 2.89 (dd, 1H, $J_{3e,4} = 3.4$ Hz, $J_{3e,3a} = 12.8$ Hz, H-3′eq), 2.09 (dd, 1H, H-3′ax) ppm. Methyl [2-(trimethylsilyl)ethyl 7,8,9-tri-*O*-acetyl-4,5-*O*,*N*-carbonyl-3,5-dideoxy-D-glycero-α-D-galacto-non-2-ulopyranoside]onate (**14**). ^{1}H NMR (300 MHz, $CDCl_3$): 5.15 (dd, 1H, $J_{7,8} = 10.0$ Hz, H-7), 4.45–4.38 (m, 2H, H-9), 2.90 (dd, 1H, $J_{3e,4} = 3.6$ Hz, $J_{3e,3a} = 0.4$ Hz, H-3e), 2.05 (dd, 1H, H-3a) ppm.