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Thiomidoyl approach to the synthesis of α-sialosides

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Abstract—Novel sialosyl donors, *S*-benzoxazolyl (SBox) and *S*-thiazolyl (STaz) sialosides, have been synthesized and applied to the stereoselective synthesis of α-sialosides. It was also demonstrated that it is possible to selectively activate SBox sialyl donor over ethyl thioglycoside, allowing the direct synthesis of disaccharide donors that could be used in subsequent glycosylations without further manipulations.

1. Introduction

Sialic acids are a family of about 50 naturally occurring 2-keto-3-deoxy-nononic acids involved in a wide range of biological processes.[1,2] Sialic acid-containing glycoconjugates are involved in a large number of biological phenomena such as cell–cell adhesion, cell growth regulation, immune response, and oncogenesis.[3,4] The C-5-amino derivative represents the long-known neuraminic acid, and its amino function can either be acetylated (Neu5Ac) or glycolylated. Sialic acids normally appear at the terminal positions of glycoproteins and glycolipids where they are α(2,3)- or α(2,6)- linked to galactosides or α(2,6)- linked to 2-acetamido-galactosyl residues. The disialosyl structures Neu5Acα(2,8)Neu5Ac and Neu5Acα(2,9)Neu5Ac have also been found as constituents of glycoproteins and glycolipids.

The appreciation of the biological importance and therapeutic potential of sialic acid and its derivatives has revealed certain drawbacks in the methods for chemical sialylation. Introduction of sialic acid residues with a high regio- and stereoselectivity is a challenging problem of the contemporary oligosaccharide synthesis. The use of sialyl donors is complicated by the lack of a participating substituent at C-3. In addition, the presence of the deoxy moiety in combination with the electron withdrawing carboxylate group at the anomeric center make these derivatives prone to elimination to give 2,3-dehydro derivatives. For these reasons, sialylation reactions are often plagued with lower yields and stereoselectivities in comparison with 'common' glycosylation reactions.[5] In order to cover these gaps, novel sialylation methods, indirect strategies, and enzymatic approaches emerged at the turn of the century.[5,6] Thus, thioglycosides[7] and phosphites[8,9] are examples of versatile sialyl donors that allow mild activation conditions, high stereoselectivity, and good yields. Further improvement came with the discovery of a rather unusual activating effect of the remote substituent at C-5, such as trifluoroacetamido.[10]

The last decade witnessed an improvement in the methods and strategies used for convergent oligosaccharide assembly. Approaches such as armed–disarmed,[11] orthogonal,[12] semi-orthogonal,[13] one-pot,[14] and active-latent,[15,16] allow, significantly, shortening of the oligosaccharide assembly. The majority of these approaches are based on selective activation of one donor over another.[17] Less attention in that respect has been given to the convergent synthesis of sialosides, as the number of approaches for their selective glycosidation is limited and the overall efficiency not so high.[18] For example, for the synthesis of sialosyl derivatives, multi-step transformations (removal of protecting group, introduction of a leaving group) are still required to obtain the disaccharide donor, decreasing the over-all efficiency (Scheme 1a).[10,19]

We reasoned that it would be beneficial to develop a new sialyl donor that could be selectively activated over the thioglycoside moiety of the glycosyl acceptor for the direct activation of the latter in the next glycosylation step (Scheme 1b).

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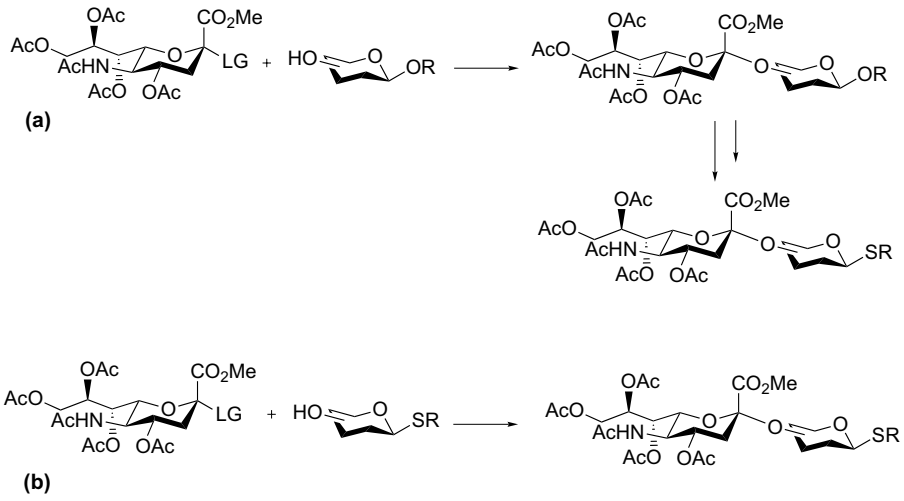


Scheme 1. (a) Linear approach to the synthesis of sialosides; (b) convergent approach to the synthesis of sialosides.

Recently, a number of new approaches for glycosylations have emerged.[20] Among these, glycosyl thioimidates, *S*-benzoxazolyl (SBox), and *S*-thiazolyl (STaz) were determined to be very stable and stereoselective donors for the D-*gluco*, D-*galacto*, and D-*manno* series.[21–23] They also could be activated under mild reaction conditions. Most importantly, they can be activated in the presence of silver triflate or cupper triflate, allowing the selective activation of the thioimidoyl glycosyl donors over *S*-ethyl and *O*-pentenyl moieties.

We were interested to find out whether the leaving groups of this class would be suitable for selective sialylation. This work describes the synthesis of SBox **1a**[24] and STaz **1b**[25] sialosides and their application to stereoselective sialylation and convergent oligosaccharide synthesis (Fig. 1).

2. Results and discussions

Synthesis of the SBox and STaz glycosides can be achieved by a variety of pathways from acetates, bromides, and by opening of 1,2-anhydro derivatives. Among these, chlorides received less attention. We were curious to find out whether the sialyl chloride could serve as a suitable precursor for the introduction of the *S*-imidoyl moiety. The synthesis of **1a** was straightforwardly achieved by the treatment of the β-chloro glycoside of Neu5Ac **2** with potassium 2-mercaptobenzoxazolate and [18]crown-6 in acetone to afford **1a** in 80% yield (Scheme 2). Similarly, sialosyl donor **1b** was synthesized from **2** in the presence of sodium 2-mercaptothiazolate and [15]crown-5 in 70% yield. The lower yield for the synthesis of **1b** is due to the formation of the N-linked side product **1c** (Fig. 2).

This side reaction is due to the high basicity and ambident reactivity of STaz anion.[23] In this context, the alternative method for the synthesis of **1b** by treatment of the anomeric acetate in the presence of the thiol and Lewis acid gave lower yield and stereoselectivity.

The glycosyl donor proprieties of **1a** and **1b** were initially evaluated by the coupling with the C3 and C6 hydroxyl of a series of D-galactosyl acceptors having different protecting group patterns (**3**–**5**, Scheme 3).

Coupling of the sialyl donor **1a** with acceptor **3** was first investigated. Thus, different reaction conditions includ-

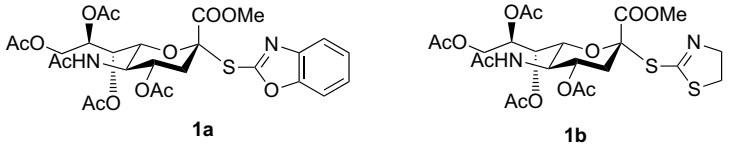
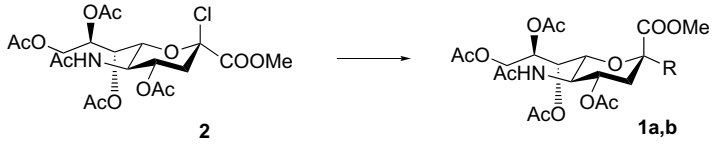


Figure 1.



Scheme 2. Reagents and conditions: (**1a**), KSBox, acetone, [18] crown-6, rt, 80%; (**1b**), NaSTaz, acetone, [15] crown-5, rt, 70%.

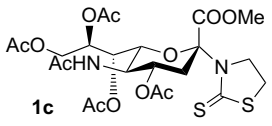


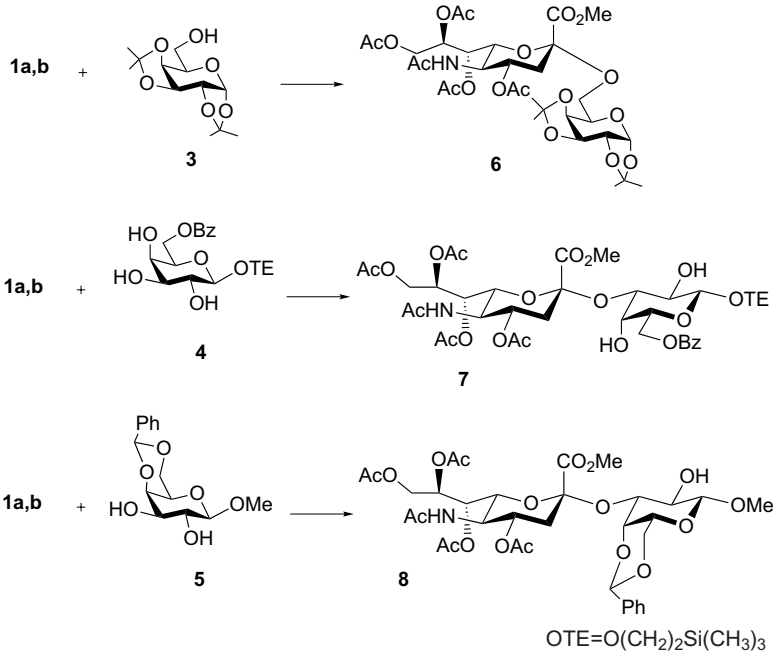
Figure 2.

ing temperature, promoter, and solvent were tested. These results are summarized in Table 1. It should be noted that sialylation of primary hydroxyls, for example **3**, often proceeds with low stereoselectivity, which is commonly credited to the high reactivity of the glycosyl acceptor. Thus, sialyl donor **1a** gave comparable results (yield and stereoselectivity) to those achieved by conventional donors, thioglycosides or phosphites. In particular, activation by MeOTf and NIS/TfOH (entries 1 and 2, respectively) gave the desired disaccharide **6** with high yields and good stereoselectivity. It is worthy to mention that no methylation at the acetamido group was detected when MeOTf was used as the promoter, a side reaction previously reported for thioglycosides.[19]

Promoters such as AgOTf, $Cu(OTf)_2$, and TfOH were deactivated by the presence of CH_3CN, and, therefore, no reaction was observed even at room temperature. Surprisingly, the same reactions performed in CH_2Cl_2 still gave good stereoselectivity and yield, (entries 6 and 7).

Encouraged by these results, attention was turned toward the synthesis of α(2,3) sialosides: in particular, reaction of **1a** with acceptor **4**[26] gave mainly the α-anomer in the presence of either MeOTf or NIS/TfOH (entries 1 and 2, Table 2). The lower stereoselectivity which was observed in the presence of AgOTf can be due to the use of CH_2Cl_2 as solvent (entry 3). Good stereoselectivities and moderate yields were also obtained with acceptor **5**[27] (entries 4–6). As evident from these results, in a number of cases excellent stereoselectivity was achieved. Although a number of reactions resulted in the disaccharide formation with moderate yield, these results still represent a creditable achievement, when compared to other direct sialylation procedures.[5]

Glycosylations using **1b** as sialosyl donor were marginally less efficient: although good yield and stereoselectivity were observed by reaction of **1b** with acceptors **3** and **4** in the presence of MeOTf (entries 7 and 9, Table 2),



Scheme 3. Synthesis of sialosides **6**–**8** from (**1a**) and (**1b**).

Table 1. Glycosylation reaction between **1a** and **3**

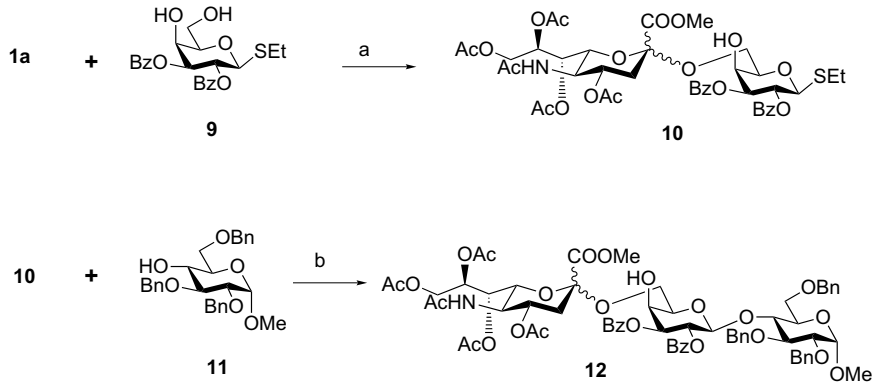
Entry[a]	Promoter	Solvent	Temp	Time (h)	Yield	α/β ratio[b]
1	MeOTf	MeCN	−40	16	90	2:1
2	NIS/TfOH	MeCN	−40	16	70	1.6:1
3	AgOTf	MeCN	−40 to rt	24	No rxn.	—
4	$Cu(OTf)_2$	MeCN	−40 to rt	24	No rxn.	—
5	TfOH	MeCN	−40 to rt	24	No rxn.	—
6	$Cu(OTf)_2$	DCM	−40 to 0	24	65	3:1
7	AgOTf	DCM	−40	16	55	2:1

[a] In a typical glycosylation procedure, 2 equiv of donor per acceptor were used in the presence of MS 3 Å.
[b] Anomeric ratios were obtained by comparison of the integral intensities of the corresponding signals in ^1H NMR spectra; conventional empirical NMR rules for the assignment of anomeric configurations of sialosides were applied.[5]

Table 2. Glycosylation reaction between **1a**, **1b**, and **3–5**

Entry[a]	Donor	Acceptor	Promoter	Product	Yield	α/β ratio
1	**1a**	**4**	MeOTf	**7**	75	19:1
2	**1a**	**4**	NIS/TfOH	**7**	60	20:1
3	**1a**	**4**	AgOTf	**7**	55	1.5:1
4	**1a**	**5**	MeOTf	**8**	65	1.5:1
5	**1a**	**5**	NIS/TfOH	**8**	60	2:1
6	**1a**	**5**	AgOTf	**8**	50	1.2:1
7	**1b**	**3**	MeOTf	**6**	70	2.3:1
8	**1b**	**3**	AgOTf	**6**	77	1:1.1
9	**1b**	**4**	MeOTf	**7**	79	17:1
10	**1b**	**4**	AgOTf	**7**	50	1:1
11	**1b**	**5**	MeOTf	**8**	—[b]	
12	**1b**	**5**	AgOTf	**8**	40	1:1

[a] All glycosylations were performed in the presence of MS 3 Å; glycosylations in the presence of AgOTf required the use of CH_2Cl_2 as solvent; MeCN was the solvent of choice for all the other glycosylations.
[b] No disaccharide was detected, methylated 2,3 dehydro derivate was isolated.



Scheme 4. Reagents and conditions: (a) AgOTf, MS 3 Å, DCN, −40 °C, 24 h, 89%, α/β = 1:1; (b) NIS/TfOH, MS 3 Å, DCM, −40 °C, 2 h, 70%, β only.

sialosyl donor **1b** gave mainly glycal and N-linked product when coupled to less reactive acceptor **5** (entries 11 and 2).

As previously mentioned, the possibility to activate thioimidoyl sialoside in the presence of thioglycosides was especially attractive. Indeed, this would allow the synthesis of disaccharides that can be directly used in subsequent glycosylation. Based on this concept, **1a** was coupled with galactoside acceptor **9**[28] bearing a thioethyl moiety as leaving group in the presence of AgOTf. In this case the reaction went to completion after 24 h. The disaccharide **10** was synthesized with a high yield of 89%. Subsequently, it was used without further manipulations as a donor by coupling with acceptor **11**[29] to obtain a GM3 derivative **12** in 70% yield (Scheme 4).

3. Conclusion

To summarize, two novel sialyl donor bearing a thioimidoyl moiety as leaving group have been synthesized and tested in the syntheses of sialosides. SBox and STaz sialosides proved to be excellent glycosyl donors when activated with MeOTf and AgOTf. In general, good yields and stereoselectivities were observed with a number of glycosyl acceptors, ranging from highly reactive primary to less reactive secondary acceptors. The most attractive feature of thiomidoyl moieties is that they can be selectively activated over thioglycosides in the presence of AgOTf as promoter. Based on this concept, we synthesized a disaccharide donor **10** that could be directly used for the synthesis of trisaccharide **12**. Further studies in order to improve the stereoselectivity of sialylations with thioimidoyl donors, by the introduction of a *N*-acetylacetamido and *N*-trifluroacetamido groups at C-5, are in progress.

Acknowledgements

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24. Experimental data for compound **1a**: crown ether (18-crown-6, 0.14 g, 0.4 mmol) and salt (KSBox, 0.7 g, 4.0 mmol) were added to a solution of **2** (2 g, 4.0 mmol) in dry acetone (8 mL) under an atmosphere of argon. The reaction mixture was stirred for 16 h at rt. Upon completion, the mixture was diluted with CH_2Cl_2 (30 mL) and washed with 1% aq NaOH (15 mL) and water (3 × 10 mL), the organic phase was separated, dried with $MgSO_4$ and concentrated in vacuo. The residue was purified by column chromatography on silica gel (10% gradient acetone in toluene) to afford **1a** (1.96 g, 80%): R_f 0.43 (acetone/toluene, 5:5, v/v); $[\alpha]_D^{29}$ = +15.2 (*c* 1, $CHCl_3$); ^{1}H NMR: δ; 7.72–7.20 (m, 4H, aromatic), 5.27 (d, 1H, $J_{NH,5}$ = 9.8 Hz, NH), 5.23–5.13 (m, 2H, $J_{7,8}$ = 6.9 Hz, $J_{8,9a}$ = 2.4 Hz, $J_{8,9b}$ = 5.6 Hz, H-7, 8), 4.92–4.80 (m, 1H, H-4), 4.26 (dd, 1H, $J_{9a,9b}$ = 12.2 Hz, H-9a), 4.12 (dd, 1H, $J_{6,7}$ = 3.0 Hz, H-6), 4.05 (dd, 1H, H-9b), 3.95 (dd, 1H, $J_{5,6}$ = 1.9 Hz, H-5), 3.72 (s, 3H, OCH_3), 2.86 (dd, 1H, $J_{3e,4}$ = 4.5 Hz, $J_{3e,3a}$ = 12.8 H-3e), 2.37 (t, 1H, H-3a), 1.97, 1.96, 1.88, 1.86, 1.80 (5s, 15H, NHCOCH_3, OCOCH_3); ^{13}C NMR: δ 171.3, 170.9, 170.6, 170.4, 168.3, 152.9, 142.0, 126.3, 125.1, 120.6, 111.3, 86.8, 75.9, 70.4, 69.5, 67.9, 62.2, 54.0, 49.5, 38.8, 23.5, 21.3, 21.2, 21.1, 20.8; HR-FAB MS $[M+H]^+$ calcd for $C_{27}H_{33}O_{13}N_2S$ 625.1703, found 625.1706.
25. Experimental data for compound **1b:** crown ether (15-crown-5, 0.04 g, 0.2 mmol) and NaSTaz (0.26 g, 2.0 mmol) were added to a stirred solution of **2** (1.0 mmol) in a dry acetone (2 mL) under an atmosphere of argon. The reaction mixture was stirred for 1.5 h at rt. Upon completion, the mixture was diluted with CH_2Cl_2 (20 mL) and washed with 1% aq NaOH (10 mL) and water (3 × 10 mL), the organic phase was separated, dried with $MgSO_4$, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (10% gradient acetone in hexane) to afford **1b** (415 mg, 70%): R_f 0.78 (acetone/toluene, 5:5, v/v); $[\alpha]_D^{29}$ = +7.1 (*c* 1, $CHCl_3$); ^{1}H NMR: δ; 5.43–5.27 (m, 2H, $J_{8,9b}$ = 8.5 Hz H-7, 8), 5.21 (d, 1H, $J_{NH,5}$ = 10.2 Hz, NH), 4.98–4.88 (m, 1H, H-4), 4.44–4.34 (m, 3H, $J_{9a,9b}$ = 11.5 Hz, H-9a, CH_2N), 4.26–4.08 (m, 3H, H-5, 6, 9b), 3.79 (s, 3H, OCH_3), 3.47–3.29 (m, 2H, CH_2S) 2.77 (dd, 1H, $J_{3e,4}$ = 4.9 Hz, $J_{3e,3a}$ = 12.4 Hz, H-3e), 2.22 (t, 1H, H-3a), 2.17, 2.13, 2.12, 2.04, 2.03 (5s, 15H, NHCOCH_3, OCOCH_3); ^{13}C NMR: δ 171.3, 171.2, 170.8, 170.7, 170.6, 168.5, 162.0, 159.3, 145.5, 129.4, 128.6, 125.7, 108.3, 95.2, 89.7, 74.0, 72.6, 71.2, 69.5, 64.6, 61.9, 53.3, 53.1, 38.2, 35.2, 23.2, 21.1, 21.0, 20.8; HR-FAB MS $[M+H]^+$ calcd for $C_{23}H_{33}O_{12}N_2S_2$ 593.1475, found 593.1474.
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