Preparation of Sialyl Donors Carrying Functionalized Ester Substituents: Effects on the Selectivity of Glycosylation

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Dedicate to the memory of Professor Raymond U. Lemieux.

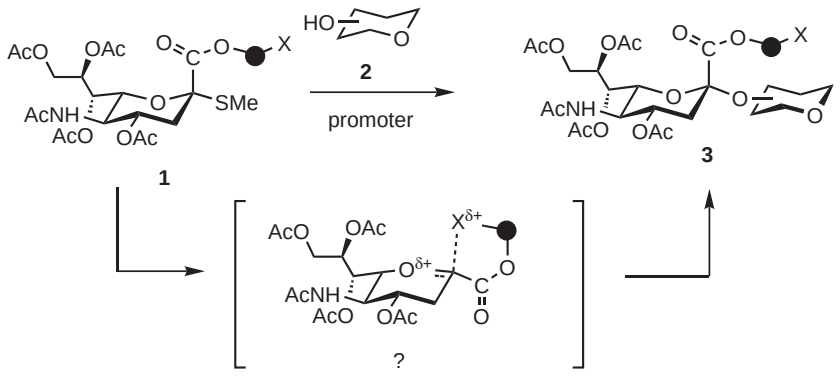
Abstract: Methylthio sialyl donors having various ester substituents were prepared systematically. Nucleophilic displacement of methyl ester with Ph_3SiSH and Cs_2CO_3 followed by in situ alkylation with RX or esterification with R-OH/DCC afforded these compounds in good yields. Glycosylations promoted by NIS–TfOH were examined in order to examine the effect of substituent of the ester portion. When conducted in CH_3CN, enhanced α-selectivities were observed for cyanomethyl, 2-cyanoethyl, 2-cyanobenzyl, and 2-nitrobenzyl esters, implying that these substituents are effective enhancing the solvent effect of acetonitrile, possibly by stabilizing the β-oriented nitrilium ion.

Key words: sialic acid, glycosylation, stereoselective, substituent effect, selective deprotection

Sialic acids, most typically *N*-acetylneuraminic acid (Neu5Ac), are important constituents of biologically important glycoconjugates,[1] and the chemical synthesis of Neu5Ac glycosides has been investigated with substantial success.[2] In order to overcome the difficulty inherent to the synthesis of Neu5Ac glycosides that solely exist with stereoelectronically disfavored α-configuration, various approaches have been reported. These exploits either 1) the solvent effect of CH_3CN,[3] 2) participation of the *C*-3 auxiliary,[4] or 3) fine-tuning the reactivity by changing NHAc to NAc_2,[5] N_3,[6] or NHTFA.[7]

Recently, substituent effects of the ester portion of Neu5Ac donors have been investigated by Takahashi[8] and Gin.[9] Such an approach is potentially attractive, because *C*-1 carboxylate should be masked in any event. Furthermore, Neu5Ac esters that can be detached under non-hydrolytic conditions would be valuable for the synthesis of complex oligosaccharides and glycopeptides. In this paper, we wish to report 1) the systematic preparation of various esters of Neu5Ac methylthio glycoside using Ph_3SiSH-Cs_2CO_3 mediated methyl ester cleavage as the key reaction, and 2) their use as glycosyl donors to explore the possibility to enhance the α-selectivity by peripheral participation (Scheme 1). In particular, nitrile-containing substituents are of primary interest, considering well-known solvent effect of acetonitrile,[3] posing that α-selective sialylation would be possible in a non-participating solvent.

In order to eliminate the complexity that may arise from the stereochemistry of Neu5Ac donors, known methyl ester **1a**[3a,10] was selected as the starting material, because this compound is obtainable in a pure α-form as a crystalline solid. For chemoselective cleavage of the methyl ester, S_N2 type reaction should be most appropriate.[11] For this purpose, the use of Ph_3SiSH attracted to our attention. This reagent, readily available from triphenylsilane and sulfur,[12] has been known as a powerful nucleophile,[13] yet being a stable solid. We expected that the thiolate derived from it might well have an enough reactivity to promote the methyl ester cleavage in an S_N2 fashion. Thus, **1a** was



Scheme 1

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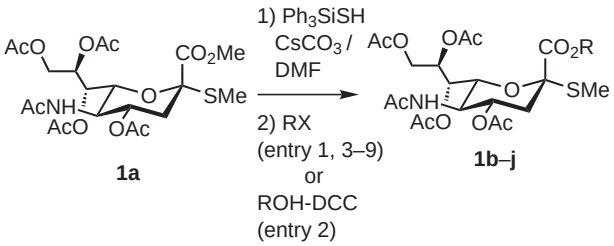
treated with Ph_3SiSH in DMF in the presence of Cs_2CO_3 and a catalytic amount of 2,6-di-*t*-butyl-4-cresol. In fact, smooth formation of carboxylate was observed under these conditions. Subsequent in situ alkylation cleanly gave esters **1b** and **1d**–**j** in high yield as summarized in Table 1. On the other hand, for the preparation of cyanoethyl ester **1c** (entry 2), reaction with 3-bromopropionitrile was not successful, presumably due to its base-sensitivity. In this case, an indirect route using DCC mediated esterification of carboxylic acid (**1k**, isolated in 96% yield) was adopted. (Scheme 2).[14]

With a series of Neu5Ac donors in hand, glycosylations with benzyl 2,3,4-tri-*O*-benzyl-β-D-glucopyranoside (**2A**)[15] and 1,2-4,5-di-*O*-isopropylidene-fructopyranose (**2B**)[16] were examined. The former was selected as a typical primary alcohol, while the latter was chosen because of its simple NMR pattern that allowed straightforward interpretations of spectra to assess α/β ratio of sialylated products.

Reactions with **2A** were first examined in non-participating medium CH_2Cl_2 using *N*-iodosuccinimide (NIS) and triflic acid (TfOH) (Table 2). Although it was initially hoped that α-selective glycosylation might be possible by the internal participation of functionalized ester substituents, beneficial substituent effect was observed in neither case, in terms of α-selectivity (entries 1–9) and β-isomers were obtained as the major products.

On the other hand, when CH_3CN was used as the solvent, increments of α-selectivity were observed in several cases. For instance, esters having nitrile (entries 12, 15) ester (entry 14), and nitro (entry 16) functionalities gave higher selectivity than methyl ester. In the cases of nitrile-containing substituents, the distances between anomeric carbon and nitrogen seemed to be important, implying that nitrile group participates the oxocarbenium ion, either directly or indirectly (vide infra). Namely, 2-cyanobenzyl carrying donor afforded highest selectivity (enry 15) and 2-cyanoethyl ester (entry 12) gave slightly higher selectivity than methyl (entry 10) and cyanomethyl (entry 11) counterparts. On the other hand, π-electornic (entry 18) and alkoxy (entry 17) groups were ineffective.

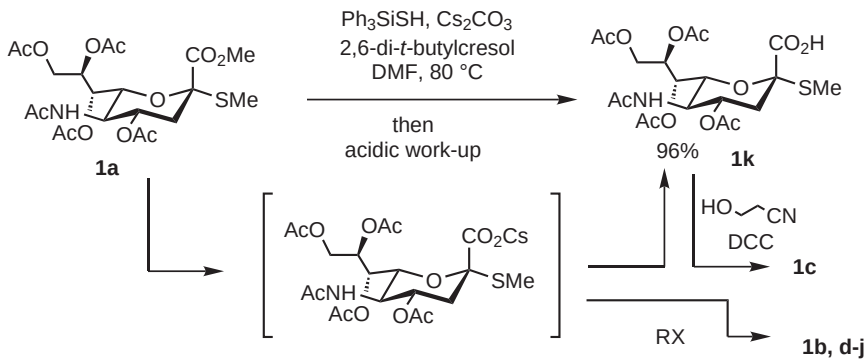
Table 1 Preparation of Various Esters



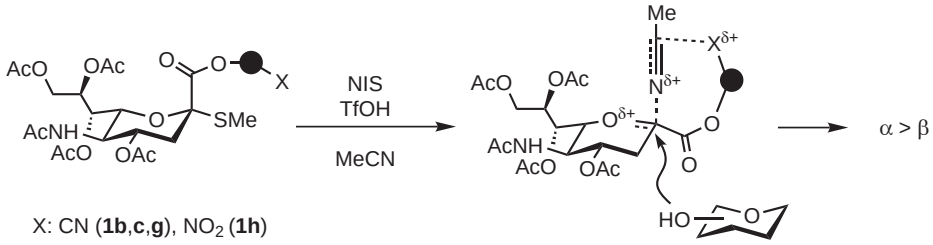
Entry	1	RX or ROH	Temp/Time	Yield (%)
1	**b**	$BrCH_2CN$	0 °C–r.t./3 h	85
2	**c**	$HOCH_2CH_2CN$	0 °C–r.t./12 h	84
3	**d**	$BrCH_2COPh$	0 °C/4 h	97
4	**e**	$BrCH_2CO_2Me$	0 °C/4 h	76
5	**f**	$BrCH_2CO_2$-*t*-Bu	0 °C/ 1 d	86
6	**g**	$BrCH_2C_6H_4CN$-(2-)	0 °C/4 h	77
7	**h**	$BrCH_2C_6H_4NO_2$-(2-)	0 °C/4 h	82
8	**i**	$ClCH_2C_6H_4OMe$-(2-)	40 °C/1 d	92
9	**j**	$ClCH_2C(Me)=CH_2$	40 °C/ 1 d	80

When secondary alcohol **2B** was used as the acceptor substrate, manifested effects were observed for cyanomethyl (entry 20) and cyanoethyl (entry 21) esters. Clearly, these results compare favorably with that obtained by standard methyl ester (entry 19).

For the present, straightforward interpretation of these results can not be provided. Obviously, results obtained in CH_2Cl_2 suggest that these substituents are not able to assist α-selective reaction through direct participation. To explain the enhanced selectivities observed in CH_3CN, more plausible would be the indirect participation, which stabilize the kinetically generated β-nitrilium ion,[17] thereby retarding its anomerization (Scheme 3).[18] Further participation of acetonitrile or succinimide (by-product accompanies NIS reaction) to these cyclic intermediates might be possible.



Scheme 2



Scheme 3

For the reaction with secondary alcohol, cyanoethyl ester seemed to be the best compromise between selectivity and yield and further investigations using more biologically relevant acceptors, **2C**[19] (Gal), **2D**[20] (βGal1→4Glc), and **2E**[21] (βGal1→4GlcN) were performed with this donor (Scheme 4). As expected, all reactions afforded α-glycosides as the major products in satisfactory yields (entries 1, 3, 5), and enhancement of selectivity was observed (entries 2, 4, 6) compared to methyl ester (Table 3).

Besides pronounced α-selectivity, the use of cyanoethyl ester would be attractive from practical point of view, because it is removable under non-hydrolytic conditions. This feature would be valuable for the synthesis of gangliosides, complex-type oligosaccharides, and glycopeptides, where methyl ester cleavage often complicates the synthetic scheme. In fact, removal of cyanoethyl ester proceeded smoothly in the presence of DBU in CH_2Cl_2 to give **4**,[22] with complete preservation of acetyl and phthalimide groups.

In conclusion, systematic preparations of methylthio Neu5Ac donors having modified esters were carried out and their effects on the selectivity of glcosylations with primary and secondary alcohols were examined. In CH_3CN, enhanced α-selectivities were observed for cyanomethyl, 2-cyanoethyl, 2-cyanobenzyl, and 2-nitrobenzyl esters, implying that these substituents are effective enhancing the solvent effect of acetonitrile, possibly by stabilizing the β-oriented nitrilium ion.

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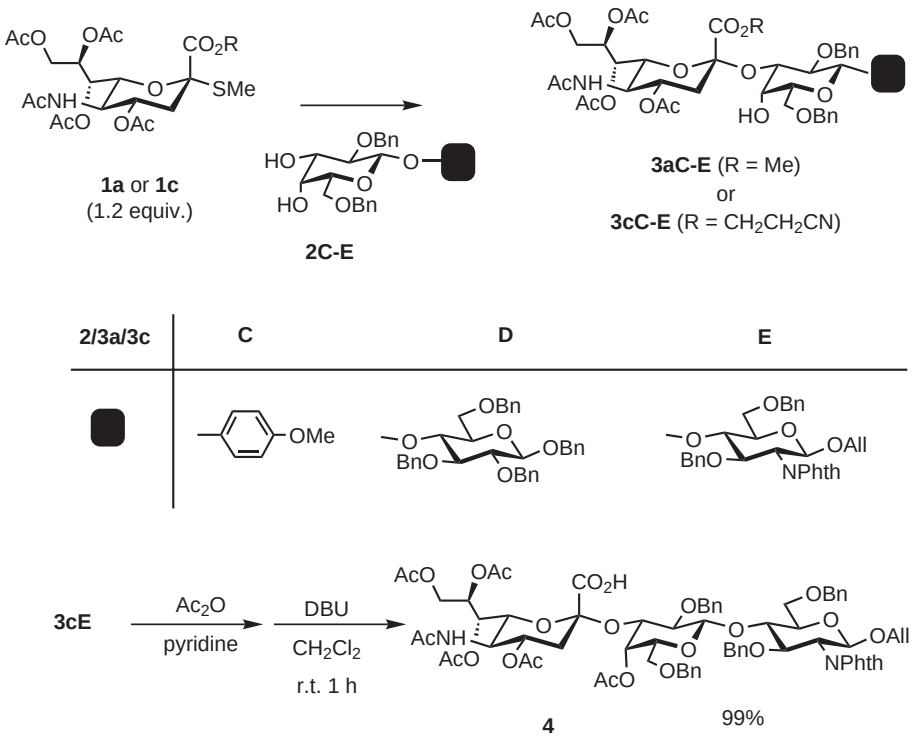
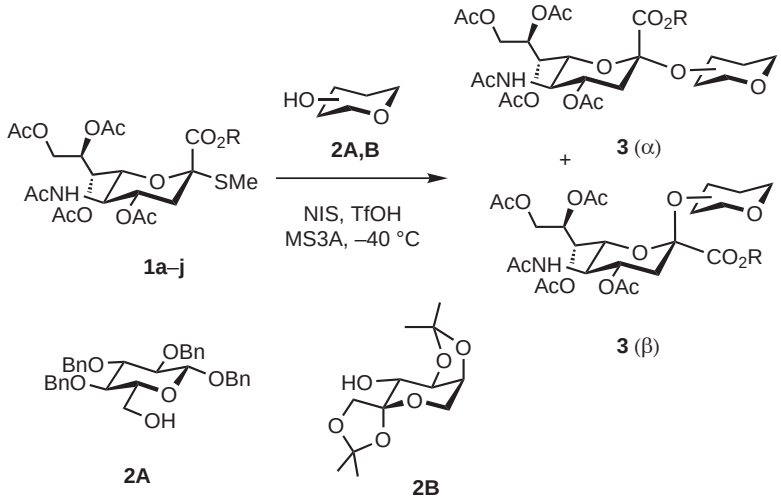


Scheme 4

Table 2 Glycosylation Reactions Using Neu5Ac Thioglycosides

1	R
a	Me
b	CH_2CN
c	CH_2CH_2CN
d	CH_2COPh
e	CH_2CO_2Me
f	CH_2CO_2t-Bu
g	$CH_2C_6H_4CN$-(2-)
h	$CH_2C_6H_4NO_2$-(2-)
i	$CH_2C_6H_4OMe$-(2-)
j	$CH_2C(Me)=CH_2$



Entry[a]	1	2	1:2	Solvent[b]	Time (h)	Yield (%)	Product	α:β[c]
1	**a**	**A**	1.2:1	D	8	77	**3aA**	1:9.6
2	**b**	**A**	1.3:1	D	1.5	90	**3bA**	1:5
3	**c**	**A**	1.2:1	D	8	85	**3cA**	β only
4	**e**	**A**	1.2:1	D	1.1	85	**3eA**	1:4
5	**f**	**A**	1.2:1	D	8	54	**3fA**	1:21
6	**g**	**A**	1.2:1	D	8	77	**3gA**	1:10
7	**h**	**A**	1.2:1	D	8	73	**3hA**	1:11
8	**i**	**A**	1.2:1	D	8	69	**3iA**	1:11
9	**j**	**A**	1.2:1	D	8	81	**3jA**	1:15
10	**a**	**A**	1.2:1	N	8	83	**3aA**	3:1
11	**b**	**A**	1.2:1	N	1.5	88	**3bA**	3:1
12	**c**	**A**	1.2:1	N	8	87	**3cA**	4:1
13	**e**	**A**	1.2:1	N	8	78	**3eA**	3.6:1
14	**f**	**A**	1.2:1	N	8	56	**3fA**	8.7:1
15	**g**	**A**	1.2:1	N	8	39	**3gA**	31:1
16	**h**	**A**	1.2:1	N	8	81	**3hA**	8.5:1
17	**i**	**A**	1.2:1	N	8	21	**3iA**	2.7:1
18	**j**	**A**	1.2:1	N	8	85	**3jA**	2.6:1
19	**a**	**B**	1:1.6	N	2	40	**3aB**	3.0:1
20	**b**	**B**	1:1.6	N	2	44	**3bB**	8.0:1
21	**c**	**B**	1.2:1	N	8	31	**3cB**	17:1
22	**d**	**B**	1:1.6	N	2.5	24	**3dB**	2.6:1
23	**e**	**B**	1:1.6	N	2	<5	**3eB**	2.4:1
24	**h**	**B**	1.2:1	N	8	15	**3bB**	14:1

[a] All reactions were performed in the presence of 1.5–1.7 equiv of NIS and 0.8–1.2 equiv of TfOH, except entries 18, 19, 21, and 22, where 0.3 equiv of TfOH was used.
[b] D: CH_2Cl_2, N; CH_3CN.
[c] Determined by 400 MHz ^1H NMR.

Table 3 Stereoselective Glycosylation; Comparison of Methyl (**1a**) and Cyanoethyl (**1c**) Esters

Entry[a]	1	2	Product	Yield (%)	α:β[b]
1	**a**	**C**	**3aC**	56	8.4:1
2	**c**	**C**	**3cC**	63	13:1
3	**a**	**D**	**3aD**	49	9.1:1
4	**c**	**D**	**3cD**	51	15:1
5	**a**	**E**	**3aE**	52	11:1
6	**c**	**E**	**3cE**	54	19:1

[a] All reactions were performed in the presence of 1.7 equiv of NIS and 1.0 equiv of TfOH.
[b] Determined by 400 MHz ^{1}H NMR.

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(14) Typical procedure (compound **1h**): To the solution of compound **1a** (209 mg, 0.401 mmol), 2,6-di-*t*-butyl-4-cresol (18 mg, 0.08 mmol) and Ph_3SiSH (352 mg, 1.20 mmol) in dry DMF (5 mL) was added Cs_2CO_3 (352 mg, 1.08 mmol) and the mixture was stirred at 80 °C for 8 h. After cooling down to ice-water temperature, 2-nitrobenzyl bromide (261 mg, 1.21 mmol) was added and stirring continued for 4 h at 0 °C. The reaction was saturated aq $KHSO_4$ and extracted with EtOAc. The organic layer was washed with brine, dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by flash chromatography (hexane–EtOAc, 10:1–1:2) to give compound **1h** (212 mg, 82%).
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(22) NMR (CD_3OD, 400 MHz) δ 1.72 (1 H, t, *J* = 12.0 Hz, H-3_{Neu5Ac}), 1.85, 1,86, 1.97, 1.98, 1.99, and 2.10 (each 3 H, s, 6Ac), 2.71 (1 H, dd, *J* = 12.0 Hz, 4.0 Hz, H-3_{Neu5Ac}), 3.37–3.42 (1 H, m, H-6_{Gal}), 3.52–3.60 (3 H, m, H-5_{Gal}, H-6_{Glc}, H-2_{Gal}), 3.83–3.88 (3 H, m, H-6_{Glc}, H-$6'_{Glc}$, H-5_{Gal}), 3.97–4.09 (3 H, m, H-4_{Glc}, CH_2=CHCH$_2$, H-5_{Neu5Ac}), 4.09 (1 H, dd, *J* = 11.2 Hz, 8.4 Hz, H-2_{Gal}), 4.14 (1 H, dd, *J* = 12.4 Hz, 5.2 Hz, H-9_{Neu5Ac}), 4.14 (1 H, dd, *J* = 12.4 Hz, 5.2 Hz, H-9_{Neu5Ac}), 4.17–4.25 (2 H, m, H-9_{Neu5Ac}, CH_2CH=CH$_2$), 4.28 (1 H, dd, *J* = 11.2 Hz, 8.4 Hz), 4.39 (1 H, d, *J* = 12.0 Hz, Bn), 4.41 (1 H, dd, *J* = 12.4 Hz, 3.2 Hz, H-9_{Neu5Ac}), 4.49 (1 H, d, *J* = 12.4 Hz, Bn), 4.54 (1 H, d, *J* = 12.0 Hz, Bn), 4.59 (1 H, d, *J* = 12.0 Hz, Bn), 4.69 (1 H, dd, *J* = 9.6 Hz, 2.4 Hz, H-3_{Gal}), 4.76 (1 H, d, *J* = 12. 0 Hz, Bn), 4.81 (1 H, d, *J* = 7.2 Hz, H-1_{Gal}), 4.88–4.96 (2 H, m, Bn), 4.98–5.03 (1 H, m, CH$_2$CH=CH_2), 5.03–5.23 (2 H, m, CH$_2$CH=CH_2, H-4_{Neu5Ac}), 5.16 (1 H, d, *J* = 8.4 Hz, H-1_{Gal}), 5.18 (1 H, d, *J* = 12.4 Hz, Bn), 5.38 (1 H, d, *J* = 2.4 Hz, H-4_{Gal}), 5.39 (1 H, dd, *J* = 8.0, 2.4 Hz, H-7_{Neu5Ac}), 5.66–5.77 (2 H, m, H-8_{Neu5Ac}, CH$_2$CH=CH$_2$), 6.82–7.90 (24 H, m, Ar).