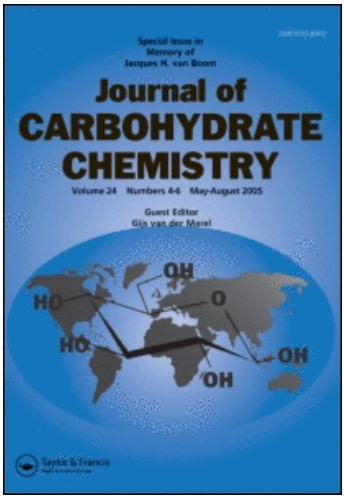

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Communication

GLYCOSYLATION USING METHYLTHIOGLYCOSIDES OF *N*-ACETYLNEURAMINIC ACID AND DIMETHYL(METHYLTHIO)SULFONIUM TRIFLATE[1]

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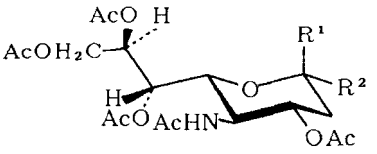
Recently, great interest has been focussed on the synthesis of oligosaccharides containing *N*-acetylneuraminic acid (Neu5Ac) because of its important roles in a variety of biological recognitions.[2] However, many difficulties in the synthesis of naturally occurring α-glycosides still remained.[3] We have recently reported the stereoselective synthesis of a series of α- and β-2-thio-neuraminyl glycosides.[1,4]

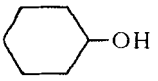
In the meantime, the utility of thioglycosides in oligosaccharide synthesis has been widely developed.[5] Particularly noteworthy is the dimethyl(methylthio)sulfonium triflate (DMTST) promoted glycosylation method[5k,l] because excellent yields are achieved due to the high thiophilicity of this reagent.

[1]Studies on the thioglycosides of *N*-acetylneuraminic acid, Part 5. For Part 4, see ref. 1. A part of this work was presented at the National Meeting of the Agricultural Chemical Society of Japan, Tokyo, Japan, April 1-4, 1987.



1 $R^1 = CO_2Me$, $R^2 = SMe$
2 $R^1 = SMe$, $R^2 = CO_2Me$

3 CH_3OH
4 $CH_3(CH_2)_3OH$
5 $CH_3(CH_2)_7OH$
6 $CH_3(CH_2)_{15}OH$



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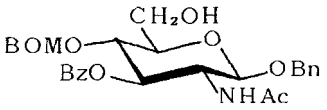

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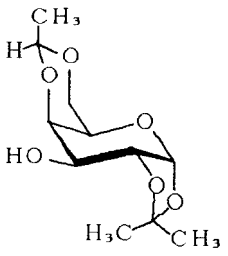

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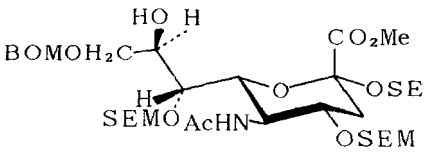

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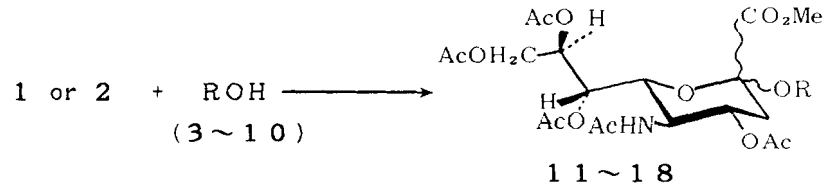
Bn : benzyl
BOM : benzyloxymethyl
Bz : benzoyl
SE : trimethylsilylethyl
SEM : trimethylsilylethoxymethyl

FIG.1. Glycosyl donors and acceptors.

TABLE 1. DMTST Promoted Glycosylation of Neu5Ac *via* its α- and β-Methylthioglycosides.



11～18

Entry	*Donor*	*Acceptor (ROH)*	*Acceptor /Donor*	*Solv*[a]	*Temp*	*Glycosides*	*Yield*	*(α/β)*[b]
1	1	3	10eq.	A	0°C	11	quant.	(5/2)
2	1	4	1.5eq.	A	0°C	12	84%	(1/4)
3	1	4	10eq.	A	0°C	12	quant.	(2/5)
4	1	5	10eq.	A	0°C	13	90%	(1/1)
5	1	6	1.5eq.	A	r.t.	14	78%	(2/5)
6	1	6	10eq.	A	r.t.	14	83%	(2/5)
7	1	7	10eq.	A	0°C	15	95%	(2/5)
8	2	3	10eq.	A	0°C	11	quant.	(1/10)
9	2	4	1.5eq.	A	0°C	12	95%	(1/20)
10	2	4	10eq.	A	0°C	12	quant.	(1/20)
11	2	5	10eq.	A	0°C	13	quant.	(1/20)
12	2	6	10eq.	A	r.t.	14	98%	(1/97)
13	2	7	10eq.	A	0°C	15	quant.	(1/20)
14	1	8	2eq.	A	0°C	16	58%	(1/2)[c,d]
15	1	8	10eq.	A	0°C	16	61%	(3/7)[c,d]
16	1	8	2eq.	B	0°C	16	51%	(7/4)[c,d]
17	1	8	2eq.	B	-40→0°C[e]	16	48%	(3/1)[c,d]
18	1	9	2eq.	B	-40→0°C[e]	17	50%	(6/5)[c,f]
19	1	10	0.9eq.	B	-40→0°C[e]	18	5.2%[c,g]	

a. A: CH_2Cl_2, B: CH_3CN. b. Anomeric ratio was determined by the intensity ratio of methyl ester protons in ^1H NMR. c. Each anomer was isolated by column chromatography. d. α-Anomer, syrup, $[\alpha]_D$ -44°(c 1.4, $CHCl_3$); β-anomer, syrup, $[\alpha]_D$ -26.8°(c 1.2, $CHCl_3$). e. The mixture was allowed to come to 0°C (ca.1h). f. α-Anomer, syrup, $[\alpha]_D$ +20°(c 1.1, $CHCl_3$); β-anomer, syrup, $[\alpha]_D$ 0°(c 1, $CHCl_3$). g. α-Anomer, syrup, $[\alpha]_D$ -1.7°(c 0.7, $CHCl_3$).

TABLE 2. The Selected ^1H NMR Spectral Data for Neu5Ac Moiety of the Glycosides.[a]

Glycosides	*H-3eq(ppm)*	*H-4(ppm)*	$J_{7,8}$*(Hz)*	$\Delta\delta$ |*H-9'-H-9*| *(ppm)*
1	2.73	4.83	8.3	0.21
2	2.54	5.27	2.2	0.65
11-α	2.58	4.87	8.3	0.25
11-β	2.44	5.25	2.4	0.69
12-α	2.58	4.86	-	0.19
12-β	2.46	5.27	3.5	0.68
13-α	2.59	4.86	-	ca. 0.20
13-β	2.48	5.24	2.4	0.67
14-α	2.58	4.85	9.8	0.20
14-β	2.46	5.26	3.9	0.66
15-α	2.60	4.83	-	0.18
15-β	2.53	5.26	2.4	0.79
16-α	2.72	4.89	8.3	ca. 0.22
16-β	2.49	5.28	2.4	0.72
17-α	2.71	4.91	8.8	0.23
17-β	2.70	5.31	1.8	0.71
18-α	2.62	4.87	6.8	ca. 0.23

a. ^1H NMR spectra were measured at 270 MHz in $CDCl_3$.

We now describe a novel DMTST promoted glycosylation using methyl (methyl 5-acetamido-4,7,8,9-tetra-*O*-acetyl-3,5-dideoxy-2-thio-D-*glycero*-α- and -β-D-*galacto*-2-nonulopyranosid)onates (1 and 2), and a series of alcohols as glycosyl donors and acceptors, respectively (FIG. 1). As summarized in TABLE 1, the reactions of donors (1 and 2) with alkyl alcohols (entry 1~13) were completed within several minutes, to give the corresponding *O*-glycosides in excellent yields. The anomeric ratio (α/β) of the glycosides was markedly affected by the anomeric configuration of the donors. The proportion of the α-glycosides was greater when donor 1 was employed. In contrast, the coupling with donor 2 (entry 8~13) gave a greater abundance of the β-glycosides. When the reaction of donor 1 with acceptor 8 was conducted in CH_3CN (entry 16 and 17), the α-glycoside was obtained in greater amount than when the reaction was performed in CH_2Cl_2 (entry 14 and 15). These results suggest that the glycosylation with 1 in

CH_3CN leads preferentially to the α-glycosides. Coupling of methyl (trimethylsilylethyl 5-acetamido-9-*O*-benzyloxymethyl-3,5-dideoxy-4,7-di-*O*-trimethylsilylethoxymethyl-D-*glycero*-α-D-*galacto*-2-nonulopyranosid)onate (**10**)[6] with **1** gave the corresponding α-(2→8)-linked disaccharide (entry 19). However, the yield was low because of the instability of trimethylsilylethoxymethyl (SEM) ether in the presence of the catalyst. The use of suitably protected acceptors may give better results.

In conclusion, a stereocontrolled sialylation was first achieved by using α- and β-methylthioglycosides of Neu5Ac (**1** and **2**) with DMTST. This procedure may become very useful for the synthesis of a variety of sialoglycoconjugates. The new compounds synthesized here gave elemental analyses, IR and NMR data in agreement with the structures assigned.

Preparation of the glycosyl donors (1 and 2): Freshly prepared sodium salt of methyl 5-acetamido-4,7,8,9-tetra-*O*-acetyl-3,5-dideoxy-2-thio-D-*glycero*-α- or -β-D-*galacto*-2-nonulopyranosonate[1,4] was methylated with methyl iodide in *N,N*-dimethylformamide, to give **1** and **2** in high yields, respectively: **1**, mp 80-82°C, $[\alpha]_D$ +26°(c 1, $CHCl_3$); **2**, mp 65-70°C, $[\alpha]_D$ -80.8°(c 0.64, $CHCl_3$); Some of the ^1H NMR data are given in TABLE 2.

General glycosylation procedure: To a stirred mixture of donor (**1** or **2**, 1 equiv), acceptor (ROH, 1.5~10 equiv), and molecular sieves 4Å in CH_2Cl_2 or CH_3CN (2 mL/100 mg of donor) was added DMTST (ca. 4 equiv) under nitrogen atmosphere at 0°C, room temperature, or -40°C. After completion of the reaction, the mixture was filtered, and washed with $CHCl_3$. The filtrate and washings were combined, and successively washed with M sodium carbonate and water, dried (Na_2SO_4), and concentrated. The products were purified by silica gel column chromatography.

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6. Compound **10** was prepared from methyl (5-acetamido-4,7,8,9-tetra-*O*-acetyl-3,5-dideoxy-D-*glycero*-β-D-*galacto*-nonulopyranosyl chlorid)onate, and will be described in a full paper.