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A New Method for the Formation of the α-Glycoside Bond of Sialyl Conjugates Based on Long-Range Participation

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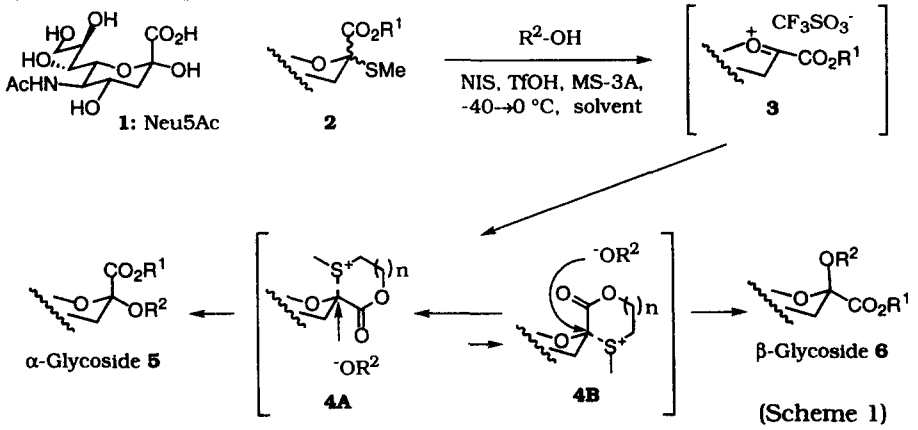
Abstract: Glycosidation of *N*-acetylneuraminic acid with primary and secondary alcohols in acetonitrile or DME utilizing "long range participation" produced the α-glycosyl linkages with high stereoselectivity. © 1997 Elsevier Science Ltd.

N-Acetylneuraminic acid (Neu5Ac; sialic acid (**1**) in scheme 1) is located at the nonreducing terminal position of glycoproteins, gangliosides and oligosaccharides, which are found on cell membranes and in the nervous systems of various living organisms.[1] These sialyl conjugates play an essential role in biological molecular recognition processes, such as cell adhesion and differentiation phenomena.[2] Recently, syntheses of sialyl conjugates have been undertaken to elucidate their biological properties and functions. One of the most difficult problems in the synthesis of sialyl conjugates is the stereoselective glycosidation of sialic acid to afford the α-glycosidic linkage. We report here a new method for α-glycoside formation of sialyl conjugates utilizing the concept of "long-range participation".

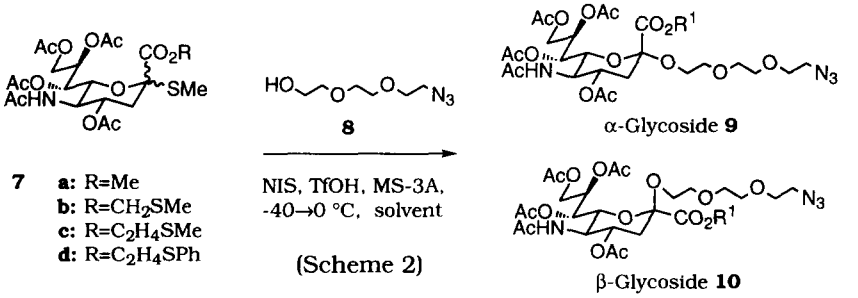


(Scheme 1)

The complexities associated with the glycoside formation of sialyl conjugates include the following three factors. First, the carboxyl group at C2 electronically disfavors the formation of an oxonium ion such as **3** (Scheme 1). Secondly, the carboxyl group sterically restricts glycoside formation. Thirdly, the lack of a substituent at C3 precludes the possible assisting and/or directing effect of an adjacent functional group. These factors disfavor glycoside formation and promote an elimination pathway to produce the 2,3-dehydro derivative. To solve these problems, many synthetic methods have been developed.[3] The most successful reports of using directing auxiliary groups (-OH, -SePh, -SPh) in the 3β-position of Neu5Ac have been published independently by Goto[4] and Ogawa[5]. In our method, an anomeric mixture (α : β = 1 : 1) of 2-

thioglycoside **2** was used as a glycosyl donor, whose ester side chain R^1 was designed to stabilize the newly formed oxonium intermediate **3** via long range participation as shown in **4A** and **4B**. Glycosidation from the thermodynamically stable β-sulfonium intermediate **4A** would give the α-glycoside **5**, whereas reaction from the unstable α-sulfonium intermediate **4B** would afford the β-glycoside **6**.[6)]

To find a suitable ester side chain R in **7** for the stabilization of the oxonium intermediate, we examined the glycosidation of 2-thioglycosides **7a-7d**[7)] with 2-[2-(2-azidoethoxy)ethoxy] ethanol (**8**) as a glycosyl acceptor upon activation with N-iodosuccinimide / trifluoromethanesulfonic acid[3a)] (NIS / TfOH) at -40 → 0 °C for 3 h in acetonitrile (Scheme 2, Table 1). Glycosidation of methyl ester **7a** with the primary alcohol **8** gave a 38 : 62 mixture of α- and β-glycosides **9a** and **10a** in 62% yield (entry 1). Reaction of methylthiomethyl ester **7b** with **8** also afforded a similar ratio of α- and β-glycosides **9b** and **10b** in 65% yield (entry 2). However, glycosidation of 2-methylthioethyl ester **7c** and 2-phenylthioethyl ester **7d**, possessing the same length on the ester side chain, produced predominantly the α-glycosides **9c**[8)] and **9d** in moderate yield and the β-glycosides **10c** and **10d** being obtained as the minor products, respectively (entry 3, 4). The ratio of the α- and β-glycosides in the reaction of **7c** and **7d** was 80 : 20 and 78 : 22, respectively. Glycosidations of **7a** and **7c** with **8** (entry 5, 6) in dichloromethane predominantly gave the β-glycoside **10a** and the α-glycoside **9c**, respectively. Thus, if the glycosidation reaction is of the S_N2 type as shown in scheme 1, these results clearly show the long range participation effect of $MeSC_2H_4$ and/or $PhSC_2H_4$ groups to stereochemically control the formation of the α-glycoside via the sulfonium intermediate **4A**. Moreover, solvent effects can raise the α-selectivity (entries 3, 6, 7). To increase the α-selectivity in the glycosidation of 2-methylthioethyl ester **7c** with **8**, reactions were carried out in both polar and non-poplar solvents such as DME and CH_2Cl_2. Glycosidation of **7c** in CH_2Cl_2 were less α-selective (α : β = 68 : 32) (entry 6), whereas reaction in DME afforded a higher α-selectivity (α : β = 95 : 5) (entry 7).

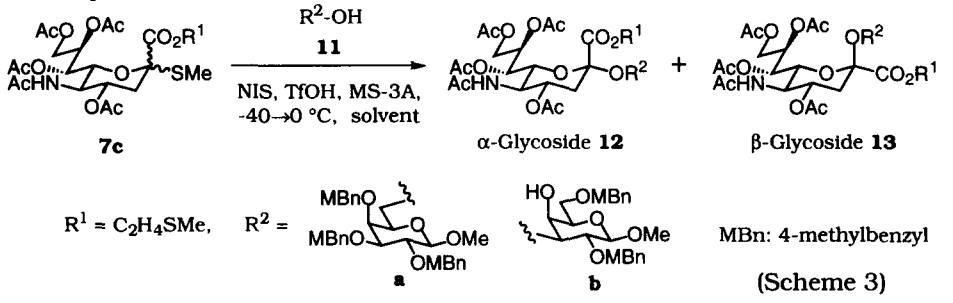


(Scheme 2)

(Table 1)

Entry	Donor	Acceptor	Solvent	Glycoside	Yield(%)
1	**7a**	**8**	CH_3CN	**9a** : **10a** (38 : 62)	62
2	**7b**	**8**	CH_3CN	**9b** : **10b** (38 : 62)	65
3	**7c**	**8**	CH_3CN	**9c** : **10c** (80 : 20)	50
4	**7d**	**8**	CH_3CN	**9d** : **10d** (78 : 22)	46
5	**7a**	**8**	CH_2Cl_2	**9a** : **10a** (38 : 62)	70
6	**7c**	**8**	CH_2Cl_2	**9c** : **10c** (68 : 32)	65
7	**7c**	**8**	DME	**9c** : **10c** (95 : 5)	45

Based on these results, we examined α- and β-selectivity in the glycosidation of 2-methylthioethyl ester **7c** with the primary and secondary alcohols of D-galactose derivatives **11a** and **11b** (Scheme 3 and Table 2) as glycosyl acceptors, since naturally occurring sialyl conjugates contain the α-glycosyl linkage. (see Figure 1) Glycosidation of **7c** with **11a** was proceeded in 3 h upon treatment with NIS and TfOH in acetonitrile and DME at -40 → 0 °C to give a similar ratio (84 : 16) of α- and β-glycoside **12a**[9] and **13a** in a moderate yield. With the secondary dihydroxy derivative **11b**, glycosidation of **7c** in acetonitrile and DME afforded the α-glycoside **12b**[10] with 83% and 91% selectivity in 35 and 21% yield, respectively. In these reactions, none of the conjugate products with the C4 alcohol of **11b** were observed and the only other reaction products were the β-elimination products.



(Scheme 3)

(Table 2)

Entry	Donor	Acceptor	Solvent	Glycoside	yield(%)
1	**7c**	**11a**	CH_3CN	**12a** : **13a** (84 : 16)	51
2	**7c**	**11a**	DME	**12a** : **13a** (84 : 16)	39
3	**7c**	**11b**	CH_3CN	**12b** : **13b** (83 : 17)	35
4	**7c**	**11b**	DME	**12b** : **13b** (91 : 9)	21

Thus the 2-methylthioethyl ester group of Neu5Ac is useful to construct the α-glycosyl linkage with primary alcohols of non-sugars as well as the primary and secondary alcohols of sugar. Further studies on the syntheses of N-acetylneuraminic acid conjugates utilizing "long range participation" of 2-methylthioethyl ester of N-acetylneuraminic acid are underway in our laboratory.

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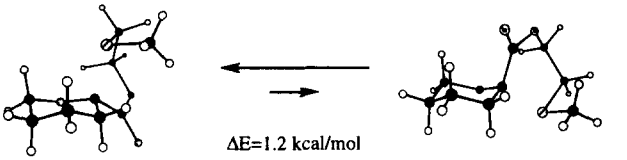
6) Application of PM3 calculations to the α- and β-sulfonium intermediates (all hydroxy groups and side chain at C5 in sialic acid were replaced by hydrogens for simplicity of calculations) revealed that the energy of β-sulfonium intermediate **14A** was calculated to be 1.2 kcal/mol more stable than that of α-sulfonium intermediate **14B**.



β-sulfonium intermediate **14A** α-sulfonium intermediate **14B**

7) The preparation of 2-methylthioethyl ester was carried out from sialic acid by 1) acetylation of hydroxy groups (Ac_2O/Py./DMAP), 2) esterification of the carboxylic acid with 2-chloroethyl methyl sulfide (Ag_2O/DMF), and 3) conversion of anomeric acetate to methylthio glycoside (TMS-SMe, TMS-OTf, $ClCH_2CH_2Cl$[11]) in 61% overall yield.

8) ^1H NMR (270 MHz, $CDCl_3$) data of **9c** δ 1.89, 2.03, 2.04, 2.14, 2.15, 2.16 (6s, 18H, NAc,OAc,SMe), 1.98 (dd, 1H, J_{gem}=12.6,$J_{3ax.,4}$=12.3Hz, H-3ax.), 2.65 (dd, 1H, $J_{3eq.,4}$=4.6Hz, H-3eq.), 2.79 (dd, 2H, $J_{a,b}$=6.5,$J_{a',b}$=6.7Hz, H-b in $CO_2CH_aH_{a'}CH_{b2}SMe$), 3.40 (t, 2H, $J_{g,h}$=5.1Hz, N_3CH_2-), 3.51-3.93 (m, 10H, TEG), 4.02-4.13 (m, 3H, H-5,6,9), 4.31 (dd, 1H, $J_{8,9'}$=2.6,J_{gem}=11.2Hz, H-9'), 4.31 (dt, 1H, J_{gem}=10.5Hz, H-a), 4.47 (dt, 1H, H-a'), 4.95 (ddd, 1H, $J_{4,5}$=9.9Hz, H-4), 5.12 (d, 1H, $J_{5,NH}$=9.6Hz, NH), 5.32 (dd, 1H, $J_{6,7}$=1.3,$J_{7,8}$=8.4Hz, H-7), 5.39 (ddd, 1H, $J_{8,9}$=5.6Hz, H-8).

9) ^1H NMR (270 MHz, $CDCl_3$) data of **12a** (Gal moiety) δ 2.32, 2.34, 2.35 (3s, 9H, MBn), 3.49 (dd, 1H, $J_{2,3}$=9.8,$J_{3,4}$=2.8Hz, H-3), 3.56 (s, 3H, OMe), 3.52-3.60 (m, 2H, H-5,6), 3.75 (dd, 1H, $J_{1,2}$=7.7Hz, H-2), 3.85-3.93 (m, 2H, H-4,6'), 4.27 (d, 1H, H-1), 4.59-4.92 (m, 6H, MBn), 7.07-7.26 (m, 12H, MBn), (Neu5Ac moiety) 1.89, 2.01, 2.03, 2.08, 2.12x2 (6s, 18H, NAc,OAc,SMe), 1.92 (dd, 1H, J_{gem}=12.6,$J_{3ax.,4}$=12.4Hz, H-3ax.), 2.61 (dd, 1H, $J_{3eq.,4}$=4.6Hz, H-3eq.), 2.65 (dd, 2H, $J_{a,b}$=$J_{a',b}$=6.9Hz, H-b), 4.01-4.12 (m, 4H, H-5,6,9,a), 4.32 (dd, 1H, $J_{8,9'}$=2.3Hz, H-9'), 4.36 (dt, 1H, J_{gem}=11.2Hz, H-a'), 4.90-5.00 (m, 1H, H-4), 5.13 (d, 1H, $J_{5,NH}$=9.6Hz, NH), 5.31 (dd, 1H, $J_{6,7}$<1,$J_{7,8}$=7.4Hz, H-7), 5.35 (ddd, 1H, $J_{8,9}$=7.6Hz, H-8).

10) ^1H NMR (270 MHz, $CDCl_3$) data of **12b** (Gal moiety) δ 2.33x2 (2s, 6H, MBn), 2.70 (br-s, 1H, OH), 3.50 (dd, 1H, $J_{1,2}$=7.7,$J_{2,3}$=9.7Hz, H-2), 3.56 (s, 3H, OMe), 3.61-3.80 (m, 4H, H-4,5,6,6'), 4.16 (dd, 1H, $J_{3,4}$=3.3Hz, H-3), 4.33 (d, 1H, H-1), 4.53 (s, 2H, MBn), 4.64, 4.78 (2d, 2H, J_{gem}=11.6Hz, MBn), 7.12-7.30 (m, 8H, MBn), (Neu5Ac moiety) 1.88, 1.98, 2.00, 2.03, 2.09, 2.11 (6s, 18H, NAc,OAc,SMe), 1.89 (dd, 1H, J_{gem}=12.0,$J_{3ax.,4}$=11.4Hz, H-3ax.), 2.56 (dd, 1H, $J_{3eq.,4}$=4.7Hz, H-3eq.), 2.77 (dd, 1H, $J_{a,b}$=6.4,$J_{a',b}$=5.9Hz, H-b), 3.99 (dd, 1H, $J_{8,9}$=5.6,J_{gem}=12.3Hz, H-9), 4.03 (dd, 1H, $J_{5,6}$=10.2,$J_{6,7}$=1.8Hz, H-6), 4.10 (ddd, 1H, $J_{4,5}$=10.5, $J_{5,NH}$=9.6Hz, H-5), 4.23 (dt, 1H, J_{gem}=11.3Hz, H-a), 4.35 (dd, 1H, $J_{8,9'}$=2.4Hz, H-9'), 4.44 (dt, 1H, H-a'), 4.93 (ddd, 1H, H-4), 5.09 (d, 1H, NH), 5.32 (dd, 1H, $J_{7,8}$=7.8Hz, H-7), 5.41 (ddd, 1H, H-8).

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