Stereoselective Synthesis of N-Acetyl-α-neuraminosyl-galactose Disaccharide

Teruaki Mukaiyama, Takenori Sasaki, Eiichiro Iwashita, and Koki Matsubara

*Department of Applied Chemistry, Faculty of Science, Science University of Tokyo, Kagurazaka, Shinjuku-ku, Tokyo 162*

The glycosylation of N-acetylneuraminic acid (Neu5Ac) donor having an easily accessible acetoxy or phenoxycarbonyloxy leaving group at an anomeric position with the 6-OH position of D-galactose in propionitrile is effectively promoted by the catalyst generated from dichlorodimethylsilane and silver perchlorate to afford the corresponding α-sialosides in good yield with good stereoselectivity.

N-Acetyl-α-neuraminic acid (Neu5Ac), known to be involved in several biological phenomena,[1] is found at non-reducing ends of oligosaccharide chains of glycoproteins and glycolipids of cell membranes.[2] In order to clear the vital role of these glycoconjugates, the development of an efficient and selective α-sialylation method is strongly desired for the purpose of preparing pharmacological relevant compounds. To achieve this goal, a number of synthetic methods employing glycosyl donors having a substituent such as -OH,[3] -SPh,[4] or -SePh[5] at C-3 position have been reported. Although the use of these donors generally shows excellent α-selectivity owing to the neighboring participation and prevention of glycal formation, the total yield of the desired sialoside is decreased by the multiple steps required for introduction and removal of the C-3 substituent. In this communication, we would like to report a simple and effective method for the synthesis of α-sialoside using methyl (5-acetamido-2,4,7,8,9-penta-O-acetyl-3,5-dideoxy-β-D-glycero-D-galacto-2-nonulopyranosyl)onate (1), easily available in two steps from N-acetylneuraminic acid,[6] by the activation of combined promoter systems that were reported recently from our laboratory.[7] It also worked well in the case of using methyl [5-acetamido-4,7,8,9-tetra-O-acetyl-2-(phenoxycarbonyloxy)-3,5-dideoxy-β-D-glycero-D-galacto-2-nonulopyranosyl]onate (2) as a glycosyl donor.[8]

In the first place, the effect of leaving groups at C-2 position in the glycosylations with cyclohexylmethyl trimethylsilyl ether (3) as a model acceptor was examined in the presence of an equimolar amount of promoter generated from tetrachlorosilane and two-fold silver perchlorate (Table 1). The use of a glycosyl donor having acetoxy(1) or phenoxycarbonyloxy(2) group at an anomeric position gave good result with respect to the yield and the stereoselectivity. In this experiment, propionitrile was employed as a solvent based on the assumption that the intermediate oxocarbenium ion might be stabilized by forming the β-nitrilium complex.[9] The effect of promoters was screened by taking the reaction of 1 with 3 as a model, and the combination of dichlorodimethylsilane and two-fold silver perchlorate proved to be the most suitable promoter system (Table 2). Furthermore, when cyclohexylmethanol was employed in the above reaction instead of 3, almost the same result as the precedent one was obtained (84% yield, α / β = 85 / 15).

Next, the present procedure was further applied to the glycosylation reaction of 1 with methyl 2,3,4-tri-O-benzoyl-β-D-galactopyranoside (6) with a view to producing a disaccharide

Table 1. Effect of leaving groups
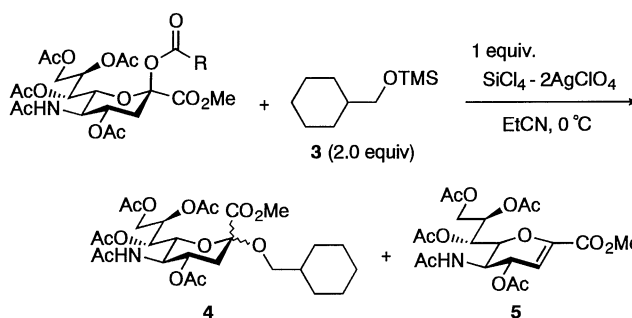
Entry	R	Time / h	4 : Yield / %	α / β	5 : Yield / %
1	Me (1)	4	74	87 / 13	23
2	(2-methoxy)ethoxy	2	45	87 / 13	39
3	2-methoxyphenyl	29	61	87 / 13	15
4	4-nitrophenyl	18	37	80 / 20	30
5	vinyl	2	40	89 / 11	45
6	OPh (2)	2	77	86 / 14	22

Table 2. Effect of promoters

Entry	Promoter	Time / h	4 : Yield / %	α / β	5 : Yield / %
1	SiCl₄ - 2AgClO₄	4	74	87 / 13	23
2	SiCl₄ - 2AgOTf	19	24	79 / 21	66
3	TiCl₄ - 2AgClO₄	24	67	80 / 20	20
4	SnCl₄ - 2AgClO₄	24	trace	—	trace
5	MeSiCl₃ - 2AgClO₄	7	67	86 / 14	25
6	Me₂SiCl₂ - 2AgClO₄	19	85	86 / 14	10
7	PhSiCl₃ - 2AgClO₄	6	72	87 / 13	25

derivative, a useful building block for the synthesis of sialyloligosaccharide.[10] However, both yield and stereoselectivity were found out to be lowered compared to the reaction with cyclohexylmethanol as mentioned above (Table 3; Entry 1). After examining the effects of reaction temperature and amount of promoter, it was found that the yield and the α-selectivity were considerably improved in the case of the reaction was carried out at -28 °C using 150 mol% of the activator (Table 3; Entry 4). Next, the reaction of the glycosyl donor 2 having phenoxycarbonyloxy group at an anomeric position with 6 was tried under the above reaction conditions and the yield increased up to 84% (Table 3; Entry 5). Further, as depicted in Entry 6, better yield and selectivity were achieved when the reaction was carried out at -35 °C.

A typical experimental procedure for the preparation of methyl

Table 3. Effects of reaction temperature and the amount
of promoter
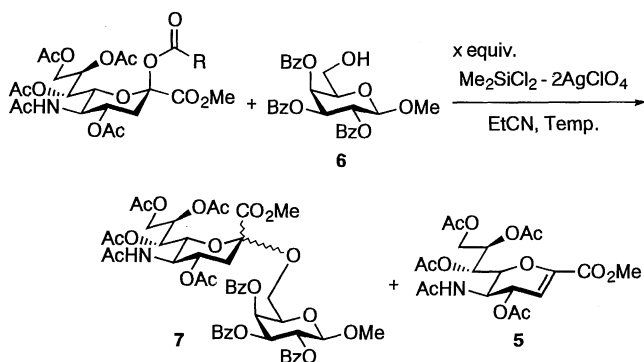
Entry	R	x	Time /h	Temp.[a] /°C	7 : Yield /%	α/β	5 : Yield /%
1[b]	Me	1.0	1	0	62	76 / 24	24
2[b]	Me	1.0	6	-10	74	79 / 21	17
3[b]	Me	1.5	9	-28	75	84 / 16	8
4[c]	Me	1.5	9	-28	76	83 / 17	5
5[c]	OPh	1.5	2	-28	84	85 / 15	9
6[c]	OPh	1.5	3	-35	86	86 / 14	6
7[c]	OPh	1.5	5	-48	70	90 / 10	6

[a] Glycosyl donor and acceptor were added at -78 °C, and then
the temperature was warmed up.

[b] The reaction was carried out with 2 equiv. of the nucleophile.

[c] The reaction was carried out with 1.5 equiv. of the nucleophile.

2,3,4-tri-O-benzoyl-6-O-[methyl   (5-acetamido-4,7,8,9-tetra-*O*-
acteyl-3,5-dideoxy-α-D-glycero-D-galacto-2-nonulopyranosyl)-
onate]-β-D-galactopyranoside (7α) is as follows; a solution of
Me₂SiCl₂ (0.15 mmol) in toluene (0.1 ml) was added to a
solution of AgClO₄ (0.3 mmol) in propionitrile (2 ml) at room
temperature, and the mixture was shielded from a light and stirred
for 1 h. To this mixture was added a solution of **1** (0.1 mmol)
and **6** (0.15 mmol) in propionitrile (1.3 ml) at -78 °C and the
mixture was then warmed up to -28 °C. After stirring for
additional 9 h, aqueous sodium hydrogen carbonate was added.
Usual work up and separation by TLC afforded the
corresponding α-sialoside (**7α**; 63%) and β-sialoside (**7β**;
13%)[11] along with 2-deoxy-2,3-dehydro-Neu5Ac methyl ester
(**5**; 5%). Determination of the anomeric configuration was

performed according to the general rule.[12]

Thus, facile and effective synthesis of sialoglycosides was
accomplished from easily available glycosyl donors such as sialyl
acetate or sialyl phenylcarbonate and alcohols using a combined
promoter system of Me₂SiCl₂ and two-fold AgClO₄.
Glycosylations with some other acceptors including secondary
alcohols are now in progress.

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References and Notes

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8   This compound was prepared according to the following
procedure; methyl (5-acetamido-4,7,8,9-tetra-*O*-acetyl-3,5-
dideoxy-β-D-glycero-D-galacto-2-nonulopyranosyl)onate[13]
was treated with phenyl chlorocarbonate (1.5 equiv.) and
pyridine (2 equiv.) in dichloromethane at 0 °C for 5 h. Usual
work   up   and   purification   by   silica   gel   column
chromatography gave **2** in 79% yield, $[\alpha]_D^{30}$ -35.2° (*c* 1.0,
CHCl₃); ¹H NMR (CDCl₃, 270 MHz) δ 2.70 (1H, dd, *J* =
13.9 and 5.0 Hz, H-3eq); ¹³C (CDCl₃, 67.8 MHz) δ 99.87
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11 Analytical data for α-anomer: $[\alpha]_D^{30}$ +59.2° (*c* 1.0, CHCl₃);
¹H NMR (CDCl₃, 270 MHz) δ 2.47 (1H, dd, *J* = 13.2 and
4.6 Hz, H-3eq); ¹³C (CDCl₃, 67.8 MHz) δ 98.76 (C-2),
β- anomer: $[\alpha]_D^{30}$ +59.8° (*c* 1.0, CHCl₃); ¹H NMR (CDCl₃,
270 MHz) δ 2.36 (1H, dd, *J* = 12.9 and 5.0 Hz, H-3eq);
¹³C (CDCl₃, 67.8 MHz) δ 98.61 (C-2).
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