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Use of Phenyl 2-α-Selenoglycosides of *N*-Acetylneuraminic Acid as a Glycosyl Donor for the Glycosylation Reactions

Kiyoshi Ikeda,* Yuji Sugiyama, Kiyoshi Tanaka and Masayuki Sato

School of Pharmaceutical Sciences, University of Shizuoka, Yada 52-1, Shizuoka 422-8526, Japan

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Abstract—Phenyl 2-α-selenoglycosides of Neu5Ac **2** were successfully prepared from the corresponding peracetylated chloro derivative of Neu5Ac **1** and phenylselenol in the presence of *N,N*-di-isopropylethylamine in excellent yields. The reaction of **2** with various alcohols was effectively catalyzed by NIS/TfOH or DMTST to produce a variety of glycosides in moderate yields. Selective activation of **2** over phenyl 2-α-thioglycoside of Neu5Ac **6** with $AgOTf/K_2CO_3$ was also achieved.

N-Acetylneuraminic acid (Neu5Ac), sialic acid and its various analogues play essential roles in a variety of biochemical and biological processes.[1] The development of an efficient method of *O*-sialylation has been a challenging task in the field of sialic acid chemistry.[2] Selenium-substituted carbohydrates are gaining increased attention with regard to the use of stereocontrolled glycosylations.[3] Many useful glycosylation reactions, originally developed using sulfur chemistry, may be carried out more selectively with the selenium analogues using appropriate thiophilic reagents. However, to the best of our knowledge, there has been only one report[4] of the synthesis of selenoglycosides of Neu5Ac to date, and no application to glycosylation reactions was described. Herein we report a novel procedure for the synthesis of phenyl 2-α-selenoglycosides of Neu5Ac **2** and their application to the glycosylation reaction.

Initially we focused on a search for an efficient method of synthesizing selenoglycosides **2**. Treatment of peracetylated chloro derivative of Neu5Ac **1a** with phenylselenol[5] in the presence of boron trifluoride etherate[6] resulted in the elimination of HCl to afford 2,3-dehydro derivative **5** in 56% yield (entry 1, Table 1). Next, reaction of **1b** with sodium phenylselenolate under Williamson reaction conditions[7] gave α-selenoglycoside of Neu5Ac **2a** in only 20% yield, together with **5** (entry 2).

Faillard and Rothermel reported the synthesis of **2a** using phase-transfer catalysis[4] from **1b** and phenylselenol in a moderate yield (entry 3). We succeeded in stereoselective preparation of α-glycosides **2a**,**b**[8] through S_N2 displacement of the chloro group in **1b**,**c** with phenylselenol in the presence of *N,N*-di-isopropylethylamine[6]

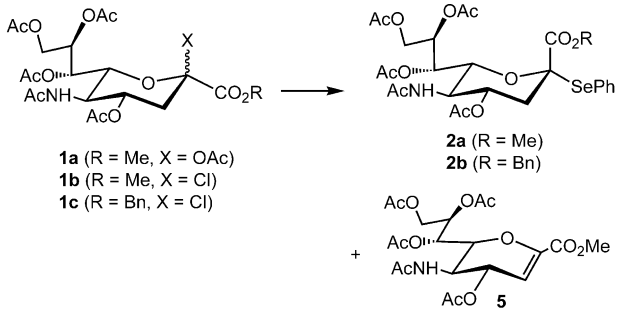

Table 1. Preparation of α-selenoglycosides of Neu5Ac

Entry	Glycosyl donor	Conditions	α-Selenoglycoside (%)
1	**1a**	PhSeH, BF_3OEt_2	**2a** (0)
2	**1b**	PhSeSePh, NaH	**2a** (20)
3	**1b**	PhSeH, $BnEt_3N^+Cl^-$	**2a** (60)
4	**1b**	PhSeH, $^iPr_2NEt$	**2a** (97)
5	**1c**	PhSeH, $^iPr_2NEt$	**2b** (92)

*Corresponding author. Tel.: +81-054-264-5108; fax: +81-054-264-5108; e-mail: ikeda@ys2.u-shizuoka-ken.ac.jp

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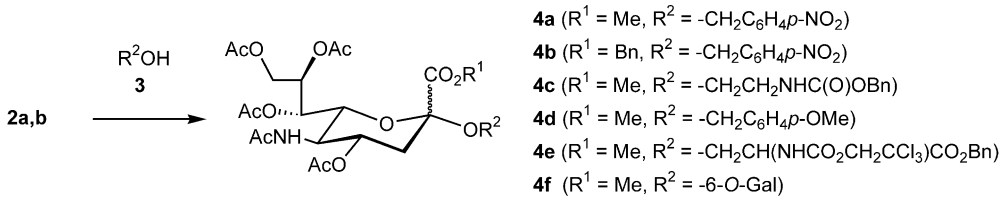
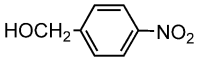
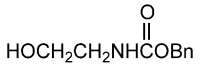
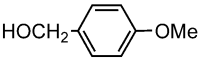
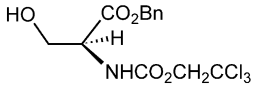
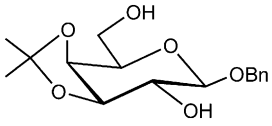


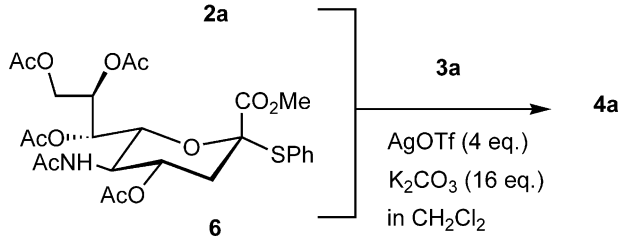
Table 2. NIS-TfOH or DMTST promoted glycosylations of selenoglycoside of Neu5Ac[a]

Entry	Donor **2**	Acceptor **3**	Promoters	Solvent/temp.	Products	Yield (%) (α/β)[b]
1	**2a**	 **3a**	NIS-TfOH	CH_3CN/−40 °C	**4a**	44 (3/1)
2	**2a**	**3a**	NIS-TfOH	CH_2Cl_2/−40 °C	**4a**	60 (1/4)
3	**2a**	**3a**	NIS-TfOH	Ether/−40 °C	**4a**	67 (1/1)
4	**2a**	**3a**	DMTST	CH_3CN/−40 °C	**4a**	80 (2/1)
5	**2b**	**3a**	NIS-TfOH	CH_3CN/−40 °C	**4b**	55 (2/1)
6	**2a**	 **3b**	NIS-TfOH	CH_3CN/−25 °C	**4c**	69 (2/1)
7	**2a**	**3b**	NIS-TfOH	CH_3CN/−40 °C	**4c**	42 (4/1)
8	**2a**	 **3c**	DMTST	CH_3CN/−40 °C	**4d**	50 (3/1)
9	**2a**	**3c**	NIS-TfOH	CH_3CN/−40 °C	**4d**	40 (4/1)
10	**2a**	 **3d**	NIS-TfOH	CH_3CN/−40 °C	**4e**	23 (7/1)
11	**2a**	 **3e**	NIS-TfOH	CH_3CN/−40 °C	**4f**	12 (3/1)

[a]With respect to **2**, 1.2 equiv of **3** and 3.0 equiv of promoter were used. Reaction time was 15 h.
[b]Isolated yields. The anomeric ratios were determined by comparison of the intensities of the H-3eq signals of the glycosides in ^1H NMR (270 MHz) spectroscopy.

in almost quantitative yields (entries 4 and 5). Next, glycosylations of **2** with alcohols were examined. As summarized in Table 2, the reactions of glycosyl donors **2** with alkyl alcohols **3a**–**e** were activated by *N*-iodosuccinimide (NIS)-TfOH[9] or dimethyl(methylthio)-sulfonium triflate (DMTST)[10] as promoters to give the corresponding *O*-glycosides (**4a**–**f**) in moderate yields. Anomeric stereochemistry of the resulting glycosides was markedly affected by the solvent and the reaction temperature. Thus, a relatively large amount of α-glycosides was obtained in acetonitrile, as expected from the more significant solvent participation of acetonitrile than dichloromethane or ether (entries 1, 2 and 3).[11] The ratio of α-glycosides at −40 °C was larger than that of the reaction at −25 °C (entries 6 and 7). The most promising yield was achieved when DMTST was used as a promoter in acetonitrile at −40 °C (entry 4).[12] For comparison of the donor **2a** with the corresponding sulfur analogue **6**, the competitive glycosylation was carried out using the reported conditions[13] of silver triflate as a promoter in the presence of potassium carbonate. This experiment resulted in recovery of 93% of compound **6** concomitant with the formation of **4a** (44%, α/β = 1:2) from **2a** (Scheme 1).

Thus, the efficient activation of selenoglycoside of Neu5Ac over the thioglycoside of Neu5Ac was achieved.



Scheme 1. Selective activation of selenolglycoside of Neu5Ac.

In summary, the selenoglycosides of Neu5Ac were efficiently prepared in this study, and these were shown to act as a versatile glycosyl donor.

Acknowledgements

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8. Spectral data and elemental analysis data of compounds **2a** and **2b** are shown below. Compound **2a** as a white amorphous powder: ^{1}H NMR ($CDCl_3$) δ 1.86 (s, 3H, NHAc), 2.01, 2.05, 2.06, 2.14 (s, each 3H, OAc), 2.85 (dd, 1H, $J_{3eq,3ax}=12.7$ Hz, $J_{3eq,4}=4.6$ Hz, H-3eq), 3.57 (s, 3H, CO_2Me), 3.88 (br d, 1H, $J_{6,5}=10.3$ Hz, H-6), 4.00 (q, 1H, $J_{5,4}=10.3$ Hz, H-5), 4.19 (dd, 1H, $J_{9a,8}=4.6$ Hz, $J_{9a,9b}=12.4$ Hz, H-9a), 4.39 (m, 1H, H-9b), 4.79 (m, 1H, H-4), 5.11 (br d, 1H, NH), 5.28 (br m, 2H, H-7,8), 7.31–7.36 (m, 2H, aromatic–H), 7.39–7.42 (m, 2H, aromatic–H), 7.62–7.64 (m, 1H, aromatic–H). FAB-MS *m*/*z* 632 $(M+H)^+$. Anal. calcd for $C_{26}H_{33}NO_{12}Se$: C, 49.53; H, 5.28; N, 2.22. Found: C, 49.43; H, 5.56; N, 2.22. Compound **2b** as a white amorphous powder: ^{1}H NMR ($CDCl_3$) δ 1.84 (s, 3H, NHAc), 1.94, 2.02, 2.05, 2.11 (s, each 3H, OAc), 2.87 (dd, 1H, $J_{3eq,3ax}=13.0$ Hz, $J_{3eq,4}=4.6$ Hz, H-3eq), 3.88 (dd, 1H, $J_{6,7}=2.2$ Hz, $J_{6,5}=10.3$ Hz, H-6), 3.97 (q, 1H, $J_{5,4}=10.3$ Hz, H-5), 4.17 (dd, 1H, $J_{9a,8}=5.9$ Hz, $J_{9a,9b}=12.4$ Hz, H-9a), 4.37 (dd, 1H, $J_{9b,8}=2.7$ Hz, H-9b), 4.78 (m, 1H, H-4), 5.01 (s, 2H, -OCH_2Ph), 5.19 (br s, 1H, H-8), 5.27 (dd, 1H, $J_{7,8}=6.5$ Hz, H-7), 7.27–7.39 (m, 9H, aromatic–H), 7.54–7.57 (m, 1H, aromatic–H). FAB-MS *m*/*z* 708 $(M+H)^+$. Anal. calcd for $C_{32}H_{37}NO_{12}Se$: C, 54.39; H, 5.28; N, 1.98. Found: C, 54.27; H, 5.18; N, 2.19.
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12. Typical procedure for α-glycoside of **4a**: To a stirred solution of compound **2a** (49 mg, 0.078 mmol) and *p*-nitrobenzyl alcohol (13 mg, 0.094 mmol) in CH_3CN (3 mL) in the presence of 4Å MS (0.3 g) was added DMTST (60 mg, 0.23 mmol) at −40 °C under Ar. After stirring for 15 h at the same temperature, the reaction mixture was filtered through a Celite 545 pad, and evaporated. Column chromatography on silica gel using CH_2Cl_2–methanol (10:1) gave compound **4a** (39 mg, 80%) as a white powder: IR (film) 1745, 1666, 1523 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.89 (s, 3H, NHAc), 2.03, 2.06, 2.12, 2.14 (s, each 3H, OAc), 2.70 (dd, 1H, $J_{3eq,3ax}=12.4$ Hz, $J_{3eq,4}=3.1$ Hz, H-3eq), 3.70 (s, 3H, CO_2Me), 4.01–4.08 (m, 2H, H-5,6), 4.55, 4.93 (d, each 1H, $J_{gem}=13.5$ Hz,–$CH_2C_6H_4$*p*-NO_2), 5.14 (br d, 1H, NH), 5.39 (m, 1H, H-8), 7.52 (d, 2H, $J=7.8$ Hz, aromatic–H), 8.20 (d, 2H, aromatic–H). FAB-MS *m*/*z* 627 $(M+H)^+$.
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