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AN EFFECTIVE SYNTHESIS OF α-GLYCOSIDES OF N-ACETYLNEURAMINIC ACID BY USE OF 2β-HALO-3β-HYDROXY-4,7,8,9-TETRA-O-ACETYL-N-ACETYLNEURAMINIC ACID METHYL ESTER[1]

Kaoru Okamoto,[†] Tadao Kondo,[††*] and Toshio Goto[*]
Laboratory of Organic Chemistry, Faculty of Agriculture; and
[††]Chemical Instrument Center; Nagoya University
Chikusa, Nagoya 464, Japan

Abstract: Glycosylations of 2β-chloro- and 2β-bromo-3β-hydroxy-N-acetylneuraminic acid derivatives with various acceptors such as 6-unprotected glucose, 3-unprotected galactose, and 3'-unprotected lactose derivatives (1.0 equiv) were carried out in the presence of silver triflate (1.0 equiv) to give 6-O-(3β-hydroxy-2α-neuraminyl)-glucoside, 3-O-(3β-hydroxy-2α-neuraminyl)galactoside, and 3'-O-(3β-hydroxy-2α-neuraminyl)lactoside in preference to the corresponding β-glycosides except for the lactoside. 3β-Hydroxy group in the products can be removed by reduction.

2α-Glycosylation of N-acetylneuraminic acid (NeuAc) is one of the most important steps in the synthesis of gangliosides. Condensation of the most common glycosyl donor, 4,7,8,9-tetra-O-acetyl-2-deoxy-2β-chloro-N-acetyl-neuraminic acid methyl ester with sugar derivatives, however, usually produces 2α-glycosides only in very low yields. We have reported that 2β,3α-dibromo-NeuAc and 2,3-epoxy-NeuAc derivatives prepared from 2-deoxy-2,3-dehydro-NeuAc derivative **1**[2] are useful glycosyl donors for the stereospecific syntheses of the β-glycosides such as NeuAc(β2-6)Glc, NeuAc(β2-3)Gal, and NeuAc(β2-8)NeuAc derivatives.[3,4] We report here an effective synthesis of 2α-glycosides of NeuAc by use of 2β-halo(Cl,Br)-3β-hydroxy-NeuAc derivatives **3b** and **3c**[3] prepared from the 2-deoxy-2,3-dehydro-NeuAc methyl ester **1** *via* the 2,3-epoxide **2** in high overall yield.

The acetyl protected 2-deoxy-2β-fluoro-3β-hydroxy-NeuAc methyl ester **3a** was unreactive to boron trifluoride etherate catalyst previously applied to the 2β-fluoro-tetra-O-acetyl-NeuAc methyl ester[5] and various other catalysts; thus the C-F bond being too strong for the glycosylation. The 2β-chloro-3β-hydroxy derivative **3b** could react with methyl 2,3,4-tri-O-benzyl-α-D-glucoside (**4**)[6] (1.0 equiv) in the presence of silver triflate (AgOTf) catalyst in benzene at

[†]Present address: Institute of Bio-Active Science (IBAS), Nippon Zoki Pharmaceutical Co., Ltd., Kinashi, Yashiro-cho, Kato-gun, Hyogo 673-14, Japan.

room temperature to give the 6-O-(3β-hydroxy-2α-neuraminyl)glucopyranoside **5**[7] (21% yield) and the 2β-neuraminyl isomer **8**[7] (18% yield); the latter being identified with the authentic sample.[4] The $J_{7,8}$ coupling constant and $\Delta\delta$|H-9'-H-9| value of the former compound **5** in ^{1}H-NMR spectrum showed 8.9Hz and 0.27ppm, respectively, suggesting the α configuration from empirical rule reported previously.[4] For confirmation of the anomeric configuration of **5**, the hydroxy group at C-3 was removed by phenoxythiocarbonylation [PhOC(=S)Cl and 4-dimethylaminopyridine (DMAP) in acetonitrile] to form **6** (95% yield) and reduction[8] [tri-n-butylstannane and azobisisobutyronitrile (AIBN) in toluene at 110 °C] to afford the glucoside **7** (97% yield), which was identical with the authentic (2α-neuraminyl)glucoside.[3] When this glycosylation was carried out by use of acetyl protected 2β-bromo-3β-hydroxy-NeuAc methyl ester **3c** in benzene at room temperature, the yields of **5** and **8** were 28 and 53%, respectively, whereas in toluene at -10 °C the yields of **5** and **8** were 64 and 15%, respectively. Interestingly, using $Hg(CN)_2$-$HgBr_2$ catalyst in 1,2-dichloroethane the 2β-isomer **8** was yielded in preference to the 2α-isomer **5** in the ratio of **5:8**= 6%:32%.

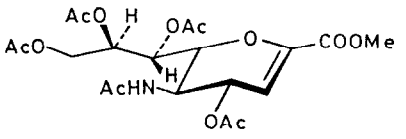
The glycosylation of methyl 2,6-di-O-benzyl-β-D-galactopyranoside (**9**) with the bromide **3c** in the presence of AgOTf (1.0 equiv) in benzene at room temperature gave in 71% yield a mixture of the 3-O-(3β-hydroxy-2α-neuraminyl)galactopyranoside **10**[7] and the corresponding 2β-neuraminyl isomer **11**;[7] These isomers being separated by preparative ODS HPLC (methanol-water, 70:30) in 23 and 48% yields, respectively. On the other hand, when the above reaction was carried out in toluene at -15 °C for 30 min, a mixture of **10** and **11** was obtanied in 52% yield in the ratio of **10:11**=37:15. The anomeric configuration was deduced from the $J_{7,8}$ coupling constant and $\Delta\delta$|H-9'-H-9| value in ^{1}H-NMR spectrum.[4] Incidentally, the chloride **3b** was unreactive to the sec-alcohol **9**.

Glycosylation of the benzyl protected lactoside derivative **17**[10] with the bromide **3c** in toluene-1,2-dichloroethane (1:1) in the presence of AgOTf at 15 °C[12] gave the 3'-O-(3β-hydroxy-2α-neuraminyl)lactoside **18**[7] (24% yield) and the corresponding (2β-neuraminyl)lactoside **19**[7] (28% yield), which were separated by preparative ODS HPLC (methanol-water, 88:12).

In conclusion, we found that the 2β-bromo-3β-hydroxy-NeuAc derivative **3c** is a prominent glycosyl donor to give 2α-glycosides of neuraminic acid in high yields in comparison with the previously reported procedures.[13] The hydroxy group remaining at 3 position in NeuAc unit can be removed by reduction.

REFERENCES AND FOOTNOTES

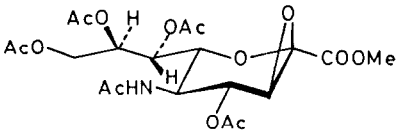
1. Synthetic Studies on Gangliosides 4.
2. "Functionalization of 2-deoxy-2,3-dehydro-N-acetylneuraminic acid methyl ester," K. Okamoto, T. Kondo, and T. Goto, Bull. Chem. Soc. Jpn., in contribution.



1

1) NBS, H_2O - CH_3CN
80°C, 0.2h, 73%

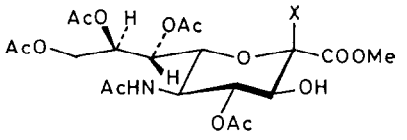
2) DBU, CH_3CN
rt, 10min, 92%



2

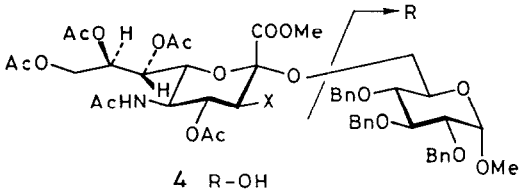
$BF_3 \cdot OEt_2$, $TiCl_4$, or

$TiBr_4$

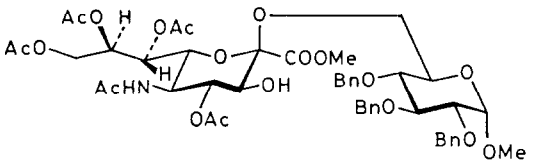


3a X = F (97%)
3b X = Cl (95%)
3c X = Br (98%)

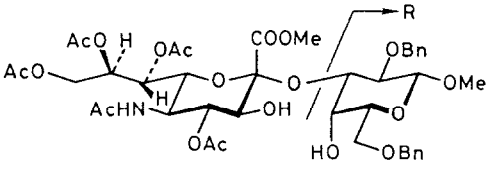
R - OH



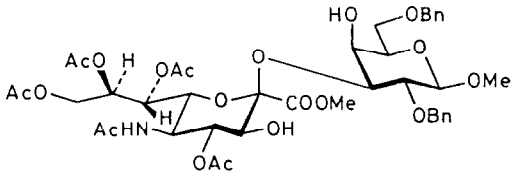
4 R-OH
5 X = OH (64%)
6 X = OC(=S)OPh (95%)
7 X = H (97%)



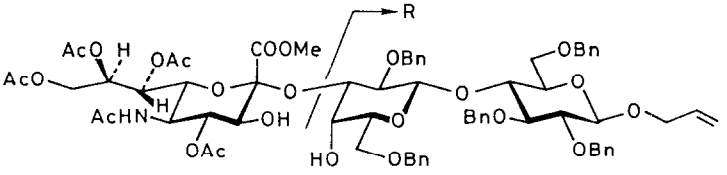
8 (15%)



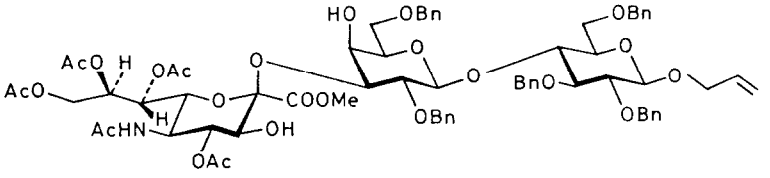
9 R-OH
10 (37%)



11 (15%)



17 R-OH
18 (24%)



19 (28%)

3. "A stereospecific synthesis of β-glycosides of N-acetylneuraminic acid and secondary alcohols," K. Okamoto, T. Kondo, and T. Goto, Chem. Lett., in press.
4. "Glycosylation of 4,7,8,9-tetra-O-acetyl-2-deoxy-2β,3β-epoxy-N-acetylneuraminic acid methyl ester," K. Okamoto, T. Kondo, and T. Goto, Bull. Chem. Soc. Jpn., in contribution; H. Paulsen and H. Tietz, Carbohydr. Res., **125**, 47 (1984). In ^{1}H-NMR spectra, $J_{7,8}$ coupling constants and $\Delta\delta|$H-9'-H-9$|$ values of NeuAc unit agreed with the empirical rule for the determination of the anomeric position, even if the 3 position of NeuAc unit is substituted with hydroxy group.
5. H. Kunz and H. Waldmann, J. Chem. Soc. Chem. Commun., 1985, 638.
6. P. Kovac, J. Alfödi, and B. Kosik, Che. Zveski, **28**, 820 (1974).
7. Satisfactory elemental analyses were obtained for these compounds. $[\alpha]_D$ and ^{1}H-NMR data (NeuAc unit in chloroform-d) are shown below.

Compound	$[\alpha]_D$[a]	Chemical shifts (δ) and $J_{7,8}$ coupling constants (Hz) in ^{1}H-NMR											
		H-3eq (dd)	H-3ax (dd)	H-4 (dd)	H-5 (ddd)	H-6 (dd)	H-7 (dd)	H-8 (ddd)	H-9 (dd)	H-9' (dd)	Me ester (s)	NH (d)	$J_{7,8}$
5	- 8.9°		3.82	5.12	4.15	4.56	5.21	5.33	3.85	4.12	3.73	5.38	8.9
6	- 4.9°		5.88[b]	5.43	4.41	4.64	5.28	5.37	3.98	4.22	3.65	5.40	8.9
7	+ 1.0°	2.65	1.97	4.85[c]	3.99	4.09	5.25	5.33	3.78	4.05	3.73	5.12	9.2
8	+11.5°		3.85	5.05	4.21	4.30	5.35	5.24	4.04	4.98	3.80	5.39	1.5
10	-19.7°		3.92	5.28	4.15	4.37	5.19	5.18	3.89	4.21	3.79	5.50	8.1
11	-23.3°		4.02	5.36	4.19	4.35	5.37	5.15	3.95	4.92	3.48	6.07	2.3
18	- 4.4°		3.90	5.30	4.19	4.38	5.21	5.18	3.88	4.19	3.78	5.54	7.9
19	- 5.8°		3.97	5.30	4.17	4.52	5.30	5.22	3.96	4.82	3.67	5.20	1.8

[a] Measured in chloroform. [b] Multiplicity: d. [c] Multiplicity: ddd.

8. M. J. Robins and J. S. Wilson, J. Am. Chem. Soc., **103**, 932 (1981).
9. H. M. Flowers, Carbohydr. Res., **39**, 245 (1975).
10. The lactoside acceptor **17** was prepared from peracetyl α-lactosyl bromide **12**[11] by the following five steps: (i) allyl alcohol-AgOTf in benzene at room temp for 0.5 h (1β-O-allyl **13**, 90%); (ii) t-BuOK in methanol at room temp for 1 h (2,3,6,2',3',4',6'-heptaol **14**, mp 168-170 °C, 77%); (iii) 2,2-dimethoxypropane-acetone-DMF and H_2SO_4 (cat.) with refluxing for 1.5 h (3',4'-acetonide **15**, mp 185-186 °C, 67%); (iv) NaH-BnBr in DMF at room temp for 6 h (2,3,6,2',6'-O-benzyllactoside **16**, 97%); (V) 80% AcOH at 70 °C for 1.5 h (3',4'-diol **17**, mp 110-111 °C, 92%).
11. C. S. Hudson and A. Kunz, J. Am. Chem. Soc., **47**, 2052 (1925).
12. Treatment at a lower temperature (-15 °C) resulted in a lower yield (23%).
13. T. Ogawa and M. Sugimoto, Carbohydr. Res., **135**, C5-C9 (1985); and the references cited therein.

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