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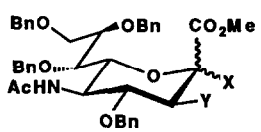
HIGHLY STEREOSELECTIVE GLYCOSYLATION OF N-ACETYLNEURAMINIC ACID AIDED BY A PHENYLTHIO SUBSTITUENT AS A STEREOCONTROLLING AUXILIARY

Yukishige Ito and Tomoya Ogawa*
RIKEN (The Institute of Physical and Chemical Research)
Wako-shi, Saitama, 351-01 Japan

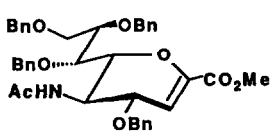
Abstract: The 2-halo-3β-phenylthio derivatives of N-acetylneuraminic acid afforded 2α-glycosides in a high stereoselectivity.

Among numerous unsolved problems in oligosaccharide synthesis, the introduction of a sialic acid residue is undoutedly one of the most challenging tasks. Although considerable efforts have been devoted to achieve this crucial transformation[1], reasonable yields were obtained only for highly reactive primary alcohols. Furthermore, a serious obstacle has been caused by the lack of stereoselectivity which makes a tedious isomer separation unavoidable.

As part of our project on complex glycolipid synthesis, we recently reported the stereoselective synthesis of 2α-glycosides of N-acetylneuraminic acid (NeuAc), the most representative of the sialic acid family, using the fluoride 1 which carries C-3 phenylselenyl group as a stereocontrolling auxiliary[2]. This approach presented, for the first time, the avenue to the construction of the α-D-NeuAc linkage predictably in a high selectivity. However, the efficiency was rather deteriorated, when a secondary alcohol was used as a substrate, because of the predominant formation of the 2,3-dehydro derivative 2 as a result of the elimination of a cationic selenium species. From a comparison of the polarizability of sulfur with that of selenium it was expected this tendency to be attenuated by changing the C-3 substituent to a sulfide group. We report herein a highly efficient synthesis of 2α-glycosides of NeuAc by use of 2-halo-3β-phenylthio derivatives 3, 4 and 5. As a common precursor of these compounds, the hemiketal 6 was chosen and synthesized from 2 in a following manner. At first, 2 was converted to a mixture of bromohydrins 7, $[\alpha]_D$ +15.1° (c 0.8)[3] and 8, m.p. 148-150°C, $[\alpha]_D$ -52.8° (c 0.8) [NBS[4], MeCN, 60°C; 97%, 7:8=4.1:1]. The axial isomer 7 was treated with thiophenol (2.0 equiv) [t-BuOK (1.5 equiv), t-BuOH-THF (1:1), 20°C] to afford 3α-sulfide 9 presumably as a result of an anchimeric



1 X = F, Y=SePh
3 X = F, Y=SPh
4 X = Cl, Y=SPh
5 X = Br, Y=SPh
6 X = OH, Y=SPh



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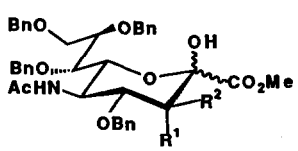
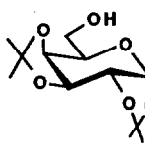


7 R^1=Br, R^2=H
8 R^1=H, R^2=Br
9 R^1=SPh, R^2=H

assistance of the C-2 OH substituent. Compound **9** could be epimerized with remarkable ease [DBU(0.1 equiv), toluene, 20°C] to give 3β-sulfide **6**[5] in an 83% yield from **7**. On the other hand, the equatorial isomer **8** directly afforded **6** in a 45% yield on treatment with thiophenol under a similar condition as above. In consequence, the hemiketal with the desired C-3 configuration **6** was obtained in a 73% overall yield from **2**. **6** was then transformed into halides **3** [DAST, $(ClCH_2)_2$-toluene (1:2), -40~0°C; 96%, α:β=2:1], **4**[6] [$(Me_2N)_3P$, CCl_4, THF, -78~20°C; 99%], and **5**[6] [$(Me_2N)_3P$, CBr_4, THF, -78~20°C; 97%].

The reactions of **3**, **4** and **5** with glycosyl acceptors **10**[7], **11**[8], **12**[1b,9] and **13**[10] were examined under various conditions. As shown in table 1, all reactions proceeded stereoselectively, giving α-isomers **14**[11], **15**[12], **16**[13] and **18**[14] as major products. The bromide **5** served best with respect to both the yield and the selectivity. Particularly noteworthy is the reaction with the lactose derivative **12**, which enabled the introduction of a NeuAc unit to C-3 OH the galactose residue in an unprecedentedly high yield. The product **16** represents a common trisaccharide part of various gangliosides[15]. Even a severely congested galactose derivative **13**



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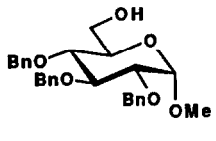

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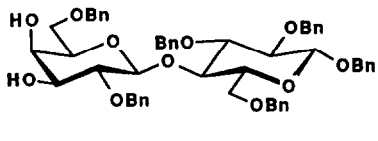

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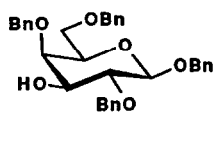

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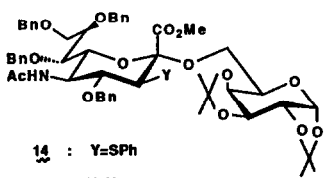
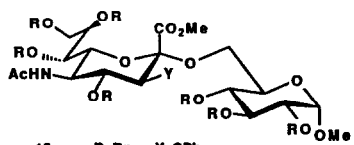


14 : Y=SPh

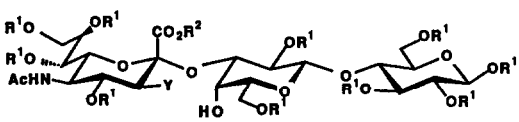
19 : Y=H



15 : R=Bn, Y=SPh

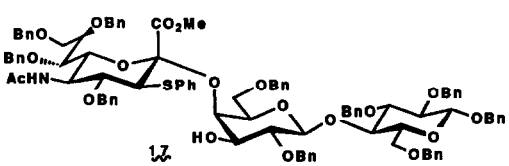
20 : R=Bn, Y=H

23 : R=Ac, Y=H



16 : R^1=Bn, R^2=Me, Y=SPh

24 : R^1=R^2=Y=H



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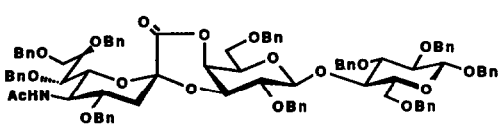

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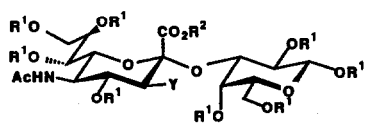

18 : R^1=Bn, R^2=Me, Y=SPh

22 : R^1=Bn, R^2=Me, Y=H

25 : R^1=R^2=Y=H

Table 1 Results of glycosylation reactions

entry[a]	halide[b]	acceptor[b]	promoter[e]	solvent	temp(°C)	time(h)	product	yield[f]	α : β[h]
1	3[c]	10	A	Et_2O	20	18	14	56%[g]	7 : 1
2	3[c]	10	A	$(ClCH_2)_2$	20	18	14	58%[g]	20 : 1
3	3[c]	10	A	CCl_4	20	18	14	72%[g]	20 : 1
4	3[d]	12	A	CCl_4	20	18	16 17	45% 5%	3.5: 1 i)
5	4	10	B	CCl_4	20	18	14	52%	i)
6	4	10	C	CCl_4	30	72	14	46%	i)
7	4	11	C	CCl_4	40	40	15	71%	i)
8	4	12	C	CCl_4	40	40	16 17	64% 2%	30 : 1 i)
9	5	10	C	CCl_4	20	18	14	72%	i)
10	5	12	C	CCl_4	20	18	16 17	78% 2%	i) i)
11	5	13	C	CCl_4	20	18	18	24%	i)

a) All reactions were carried out under atmosphere of dry nitrogen in the presence of molecular sieves 4A. b) Molar ratio of halide: acceptor was 1:1.6. c) An anomeric mixture (α:β=2:1) was used. d) Pure α-anomer was used. e) A: AgOTf (2.0 equiv)-$SnCl_2$ (2.0 equiv). B: AgOTf (2.0 equiv). C: $Hg(CN)_2$(1.6 equiv)-$HgBr_2$(0.5 equiv). f) Based on used halides except in entry 1~3. g) Yields were based on consumed **3**. h) Determined by individual isomer separation. i) Corresponding β-isomers could not be detected.

afforded the product **18** stereoselectively. Although the yield was only modest, this result is remarkable since none of previous studies succeeded in attaching an α-NeuAc residue to 2,4,6-triprotected-D-galactopyranosides[1c)16)].

Sulfide groups of these products could be removed by tin hydride reduction and the stereochemistry was confirmed as follows. Thus, **14** was treated with Ph_3SnH [AIBN, toluene, 100°C] to afford **19** (97% based on 79% conversion) which was reported previously[2)]. Similarly, **15**, **16** and **18** gave **20**[17)], **21**[18)] and **22**[19)], respectively. These were further transformed into the heptaacctate **23**[2)] and fully deprotected compounds **24**[1b)2)] and **25**[1b)] in a straightforward manner.

The results obtained here clearly demonstrates the highly expedient nature of the halides **3**, **4** and **5** as NeuAc synthons. Further application of this method to the synthesis of sialic acid containing glycolipids is under current investigations.

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Reference and Notes

1) a) H. Paulsen and U. von Deessen, *Carbohydr. Res.*, **146**, 147 (1986) and references cited therein. b) T. Ogawa and M. Sugimoto, *Carbohydr. Res.*, **135**, C5 (1985). c) K. Okamoto, T. Kondo and T. Goto, *Tetrahedron*, **43**, 5909, 5919 (1987).

2) Y. Ito and T. Ogawa, *Tetrahedron Lett.*, **28**, 6221 (1987).

3) All values of $[\alpha]_D$ were measured for $CHCl_3$ solutions at 20±3°C.

4) K. Okamoto, T. Kondo and T. Goto, *Bull. Chem. Soc. Jpn.*, **60**, 631 (1987).

5) m.p. 97~99°C, $[\alpha]_D$ +9.4 ° (c 0.9), δ_H($CDCl_3$, 400 MHz) 4.875 (d, 9.7 Hz, NH), 4.396 (d, 10.8 Hz, H-6), 4.205 (ddd, 10.8, 9.7, 9.5 Hz, H-5), 3.943 (dd, 10.8, 9.5 Hz, H-4), 3.645 (d, 10.8 Hz, H-3), 3.559 (s, CO_2Me), 1.722 (s, Ac).

6) Although the anomeric configurations are yet to be determined, 500 MHz ^1H NMR analysis revealed these compounds to be single isomers.

7) O. T. Schmidt, *Methods Carbohydr. Chem.*, **2**, 318 (1963).

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10) A. Liptak, *Tetrahedron Lett.*, **1976**, 3551.

11) $[\alpha]_D$ -4.5° (c 1.0), δ_H($CDCl_3$, 500 MHz), 5.460 (d, 4.9 Hz, H-1a), 4.466 (dd, 7.9, 2.1 Hz, H-3a), 4.337 (dd, 10.7, 1.5 Hz, H-6b), 4.256 (t, 10.1 Hz, H-4b), 4.229 (dd, 4.9, 2.4 Hz, H-2a), 4.059 (dd, 7.9, 1.8 Hz, H-4a), 3.975 (dd, 9.5, 6.7 Hz, H-6a), 3.658 (s, CO_2Me), 3.274 (d, 10.1 Hz, H-3b), 1.639 (s, Ac), δ_C($CDCl_3$, 22.5 MHz), 101.32 (C-2b), 98.28 (C-1a).

12) $[\alpha]_D$ +19.5° (c 0.9), δ_H($CDCl_3$, 500 MHz), 4.307 (dd, 11.3, 1.0 Hz, H-6b), 4.196 (dd, 9.2, 8.2 Hz, H-4b), 4.027 (dd, 10.7, 2.0 Hz, H-6a), 3.986 (dd, 10.7, 4.9 Hz, H-6a'), 3.623 (s, CO_2Me), 3.329 (d, 8.2 Hz, H-3b), 3.270 (s, OMe), 1.613 (s, Ac), δ_C($CDCl_3$, 22.5 MHz) 100.78 (C-2b), 97.52 (C-1a).

13) $[\alpha]_D$ +12.3° (c 1.8), δ_H($CDCl_3$, 500 MHz), 4.760 (d, 9.2 Hz, NH), 4.161 (d, 7.6 Hz, H-1a), 3.865 (dd, 9.5, 3.1 Hz, H-3b), 3.831 (d, 3.1 Hz, H-4b), 3.619 (s, CO_2Me), 3.390 (d, 9.5 Hz, H-3c), 1.668 (s, Ac), δ_C($CDCl_3$, 22.5 MHz) 102.40 and 102.29 (C-1a and C-1b), 101.15 (C-2c).

14) $[\alpha]_D$ -9.2° (c 1.0), δ_H($CDCl_3$, 500 MHz) 4.184 (d, 7.3 Hz, H-1a), 4.154 (dd, 10.7, 1.8 Hz, H-6b), 3.728 (dd, 9.8, 7.3 Hz, H-2a), 3.696 (dd, 5.5, 1.8 Hz, H-7b), 3.626 (s, CO_2Me), 3.381 (d, 10.7 Hz, H-3b), 1.522 (s, Ac).

15) M. Sugimoto, M. Numata, K. Koike, Y. Nakahara and T. Ogawa, *Carbohydr. Res.*, **156**, C1 (1986).

16) M. Sugimoto and T. Ogawa, unpublished results.

17) $[\alpha]_D$ +2.2° (c 1.0), δ_H($CDCl_3$, 400 MHz) 4.565 (d, 3.7 Hz, H-1a), 4.074 (dd, 10.5, 1.5 Hz, H-6b), 3.642 (s, CO_2Me), 3.500 (dd, 9.3, 3.7 Hz, H-2a), 3.336 (s, OMe), 2.835 (dd, 12.5, 4.2 Hz, H-3beq), 1.771 (s, Ac), 1.758 (dd, 12.5, 12.0 Hz, H-3bax).

18) $[\alpha]_D$ +2.3° (c 0.7), δ_H($CDCl_3$, 400 MHz) 5.139 (d, 3.9 Hz, H-4b), 4.804 (d, 9.8 Hz, NH), 4.492 (d, 7.8 Hz, H-1b or H-1a), 4.353 (d, 7.8 Hz, H-1a or H-1b), 2.285 (dd, 13.4, 5.4 Hz, H-3beq), 1.780 (dd, 13.4, 10.9 Hz, H-3bax), 1.771 (s, Ac).

19) δ_H($CDCl_3$, 500 MHz) 4.768 (d, 9.8 Hz, NH), 4.185 (d, 7.6 Hz, H-1a), 4.138 (ddd, 10.4, 9.8, 9.4 Hz, H-5b), 3.896 (dd, 9.8, 3.1 Hz, H-3a), 3.817 (d, 3.1 Hz, H-4a), 3.763 (m, H-8b), 3.657 (dd, 10.1, 7.6 Hz, H-2a), 3.596 (s, CO_2Me), 3.379 (ddd, 11.9, 9.4, 4.6 Hz, H-4b), 2.507 (dd, 13.4, 4.6 Hz, H-3beq), 2.011 (dd, 13.4, 11.9 Hz, H-3bax), 1.902 (s, Ac).

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