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AN EFFICIENT APPROACH TO STEREOSELECTIVE GLYCOSYLATION OF N-ACETYLNEURAMINIC ACID: USE OF PHENYLSELENYL GROUP AS A STEREOCONTROLLING AUXILIARY

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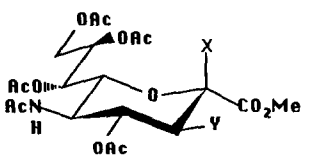
Abstract: α-Selective glycosylation of N-acetylneuraminic acid was achieved by use of the fluoride **3** which carries 3β-phenylselenyl substituent.

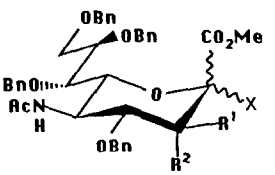
N-Acetylneuraminic acid (NeuAc) which is one of the principal constituents of glycoconjugate[1)2)3)] exists at the non-reducing ends of glycan chains solely as a 2α-glycoside. Hence α-selective glycoside formation of NeuAc is of definite significance. Commonly employed glycosyl donors, namely 2-chloro[4)] or -bromo[5)] derivatives **1** usually result in poor stereoselectivity and low yield of glycosylated products[6)]. A considerable improvement was made by Kondo et al.[7)], who employed the 2β-bromo-3β-hydroxy derivative **2** and succeeded in the first synthesis of α-NeuAc(2→8)NeuAc derivatives. However, the degree of α-selectivity was not predictable and α:β ratio ranges from 4.3:1 to 1:1.2 depending on the substrate. On the other hand, stereoselective syntheses of 2-deoxyglycosides aided by the neighbouring group participation of sulfide or selenide substituents are well precedented[8)]. Accordingly, it was expected 3β-thio or -seleno substituted donors derived from NeuAc to give α-glycosylated products via episulfonium or episelenonium ions in a predictable manner. We report here the highly stereoselective synthesis of 2α-glycosides of NeuAc by use of the 3β-selenyl fluoride **3**.

Obviously, the most crucial for the senario described above is the stereoselective introduction of 3β-selenyl substituent. This seemingly difficult problem could be simplified by choosing the hydroxy-selenide **5** as an intermediate, which is epimerizable to 3β (equatorial) configuration **5b**, irrespective of the original stereochemistry at C-2 and C-3.

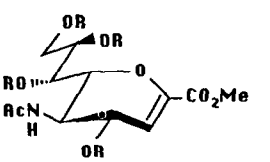
As a precursor of the hydroxy-selenide **5** 2,3-dehydro derivative **7**, $[\alpha]_D$ -3.3° (c 1.0)[9)] was chosen, which in turn was synthesized from tetraacetate **8**[4)10)] (1. NaOMe, MeOH, 2. $PhCH_2Br$, KOH, BaO, Bu_4NI, DMSO, 3. CH_2N_2, Et_2O-MeOH; 76% overall). A mixture of **7** and phenylselenenyl acetate[11)] (PhSeOAc; 2.0 equiv) in 1,2-dichloroethane was treated with trimethylsilyl triflate (TMSOTf; 0.1 equiv) at 0°C for 30 min to give acetoxy-selenide **6**[12)] (79%) together with hydroxy-selenides **5a** (11%) and **5b** (8%). Treatment of a mixture of **6**, **5a** and **5b** thus obtained with 0.1M methanolic sodium methoxide (room temp. 18h) caused deacetylation as well as epimerization at C-3 to give a 66:34 mixture of **5b** and **5a** in a 94% yield, which is readily separated by silica gel chromatography. After recycling of recovered **5a** twice, crystalline β-selenide **5b**[13)] was obtained in an 83% overall yield from **7**. Conversion of **5b** to the fluoride **3** was easily achieved by treatment with DAST[14)] (diethylaminosulfur trifluoride) in 2:1 toluene-1,2-dichloroethane at -40°C (88%; α:β≥20:1).



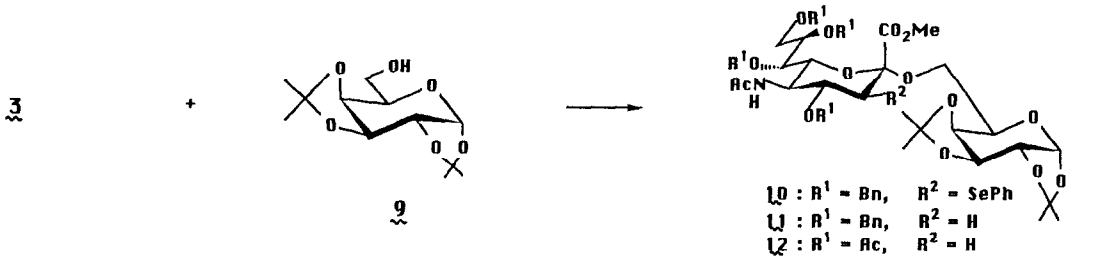
1 : X = Cl, Br, Y = H
2 : X = Br, Y = OH

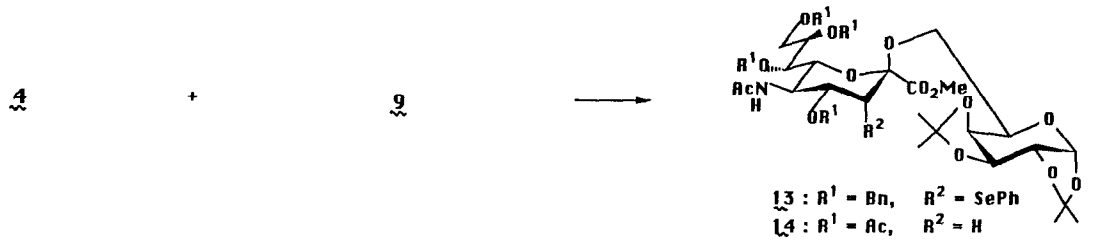


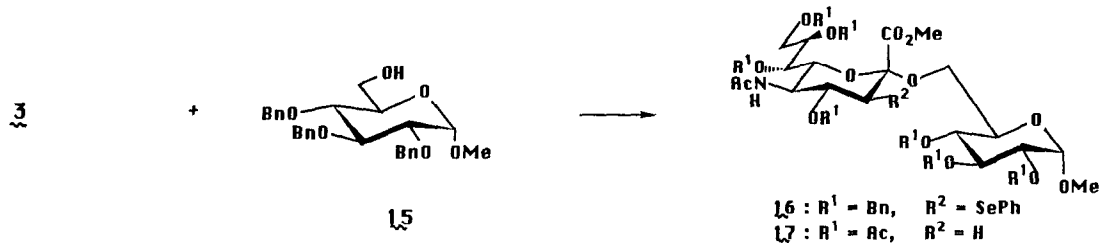
3 : X = F, R^1 = SePh, R^2 = H
4 : X = F, R^1 = H, R^2 = SePh
5 **a** : X = OH, R^1 = H, R^2 = SePh
b : X = OH, R^1 = SePh, R^2 = H
6 : X = OAc, R^1 = H, R^2 = SePh

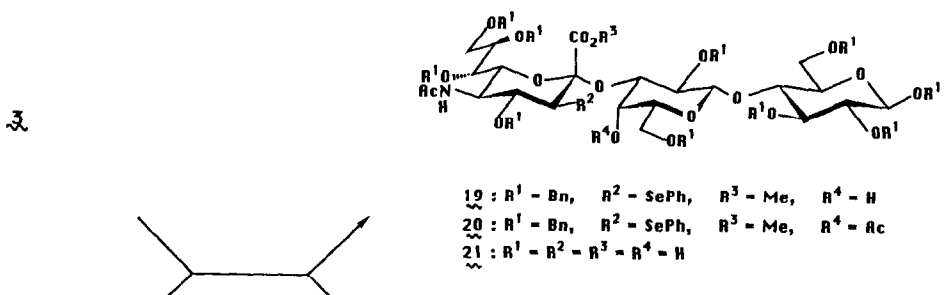


7 : R = Bn
8 : R = Ac


3
+
9
10 : R1 = Bn, R2 = SePh
11 : R1 = Bn, R2 = H
12 : R1 = Ac, R2 = H


4
+
9
13 : R1 = Bn, R2 = SePh
14 : R1 = Ac, R2 = H


3
+
15
16 : R1 = Bn, R2 = SePh
17 : R1 = Ac, R2 = H


3
19 : R1 = Bn, R2 = SePh, R3 = Me, R4 = H
20 : R1 = Bn, R2 = SePh, R3 = Me, R4 = Ac
21 : R1 = R2 = R3 = R4 = H

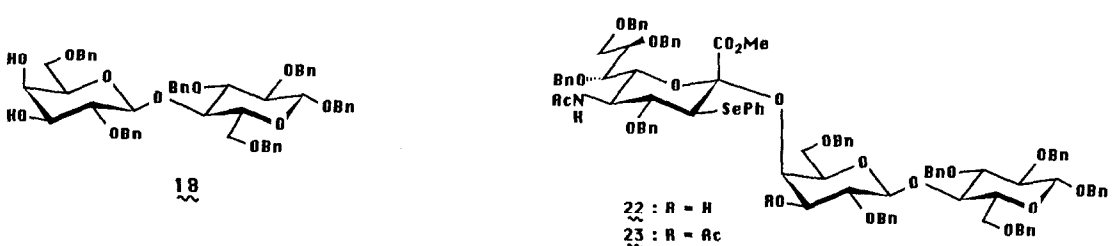

18
22 : R = H
23 : R = Ac

Table 1 Reactions of fluorides 3 and 4 with alcohols

entry[a]	fluoride	alcohol(equiv)	promoter[b]	solvent	temp,time	products yield(%)		
						10	**13**	**7**
1	3	**9** (1.5)	A	$(ClCH_2)_2$	r.t., 5h	18	_	69
2	3	**9** (1.5)	A	toluene	r.t., 18h	34	_	60
3	3	**9** (1.5)	A	CCl_4	r.t., 18h	46	_	33
4	3	**9** (1.5)	A	Et_2O	r.t., 18h	5	_	82
5	3	**9** (1.6)	B	CCl_4	r.t., 4h	45	5	43
6	3	**9** (1.6)	C	CCl_4	r.t., 16h	42	21	20
7	**4**	**9** (1.2)	A	$(ClCH_2)_2$	r.t., 1h	-	82	-
						16		**7**
8	3	**15**(2.0)	A	CCl_4	r.t., 3h	72		19
						19	**22**	**7**
9	3	**18**(2.1)	A	CCl_4	r.t., 18h	20	5	68

a) All reactions were carried out under atmosphere of dry nitrogen in the presence of molecular sieves 4A. b) A: AgOTf-$SnCl_2$, B: $Sn(OTf)_2$, C: n-Bu_3SnOTf.

The reaction of **3** with 1,2,3,4-di-O-isopropylidene-α-D-galactopyranose **9**[15] (1.6 equiv) was effected in the presence of silver triflate (2.0 equiv), tin(II)chloride[16] (2.0 equiv) and molecular sieves 4A to give the α-glycoside **10**[17] as an essentially single isomer. As shown in table 1, yields were highly dependent on the polarity of a solvent employed (entry 1~4). In every case the only isolable by-product was the 2,3-dehydro derivative **7** which can be recycled for the preparation of **3**. Tin(II)triflate[18] and tri-n-butyltin triflate[19] were also effective as the promoter, but the formation of β-glycoside **13** as a minor product was observed (entry 5,6). This was presumably derived from 3α-selenyl fluoride **4** or corresponding triflate, generated from **3** through the intermediacy of **7** by the addition of highly electrophilic phenylselenenyl triflate (PhSeOTf)[21]. Phenylselenyl group of **10** was removed (n-Bu_3SnH, AIBN, toluene; 82%) and **11**[22] thus obtained was converted to the known tetraacetate **12**[5] (1. H_2, Pd/C, MeOH, 2. Ac_2O, DMAP, pyridine; 92%). Also β-glycoside was synthesized stereoselectively by choosing **4** as a glycosyl donor which has 3α-configuration (entry 7). Thus, the fluoride **4** derived from α-selenide **5a** (DAST, THF, -20°C, 70%) was reacted with 1.2 equiv of **9** (AgOTf, $SnCl_2$, MS4A, $ClCH_2CH_2Cl$) to give an 82% yield of β-linked disaccharide **13**. The stereochemistry of **13** was confirmed by converting to the tetraacetate **14**[23].

Similarly, glucopyranoside **15**[24] (2.0 equiv) was reacted with **3** (1.6 equiv AgOTf, 1.6 equiv $SnCl_2$, MS4A, CCl_4, r.t. 3h) and the α-product **16**[25] was obtained in a 72% yield together with **7** (19%) (entry 8). **16** was then transformed into the heptaacetate **17** in three steps (1. n-Bu_3SnH, AIBN, toluene, 2. H_2, Pd/C, MeOH, 3. Ac_2O, DMAP pyridine), ^{1}H-NMR of which revealed the anomeric configuration unambiguously[26]. The present method could be applied to the reaction with secondary hydroxy group (entry 9). Thus the lactose derivative **18**[27][28] (2.1 equiv) was reacted with **3** to give α-glycosides **19** (20%) and **22** (5%) together with **7** (68%). Regiochemistry of **19** and **22** was determined by ^{1}H-NMR of corresponding acetates **20**[29] and **23**[30]. **19** was converted (1. Ph_3SnH, AIBN, toluene, 95%, 2. LiOH, aq. dioxane, 99%, 3. H_2, Pd/C, MeOH, 98%) to **21** which was reported previously[27].

In summary, stereoselective glycosylation of NeuAc was achieved by using rationally designed glycosyl donor **3**.

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Reference and Notes

1) A. Rosenberg and C.-L. Schengrund, "Biological Roles of Sialic Acid", Plenum Publishing Co., New York, 1976.

2) J. Montreuil, *Adv. Carbohydr. Chem. Biochem.*, 37, 157 (1980).

3) R. Schauer (ed.), "Sialic Acids. Chemistry, Metabolism and Function", *Cell Biology Monographs*, Vol.10 (1982).

4) R. Kuhn, P. Lutz and D. L. MacDonald, *Chem. Ber.*, **99**, 611 (1966).

5) H. Paulsen and H. Tietz, *Carbohydr. Res.*, **125**, 47 (1984).

6) For previous efforts, see: H. Paulsen and U. von Deessen, *Carbohydr. Res.*, **146**, 147 (1986) and references cited therein.

7) K. Okamoto, T. Kondo and T. Goto, *Tetrahedron Lett.*, **27**, 5229, 5233 (1986).

8) K. C. Nicolaou, T. Ladduwahett, J. L. Randall and A. Chucholowski, *J. Am. Chem. Soc.*, **108**, 2466 (1986); G. Jaurand, J.-M. Beau and P. Sinäy, *J. Chem. Soc. Chem.* Commun., **1981**, 572; Y. Ito and T. Ogawa, *Tetrahedron Lett.*, **28**, 2723 (1987).

9) Values of $[\alpha]_D$ were measured for $CHCl_3$ solutions at 20±3°C. Compounds having $[\alpha]_D$ recorded gave satisfactory elemental analysis.

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

11) Prepared in situ from phenylselenenyl chloride and silver acetate. H. J. Reich, *J. Org. Chem.*, **39**, 428 (1974), K. B. Sharpless and R. F. Lauer, *ibid.*, **39**, 429 (1974).

12) m.p. 104-106°C, $[\alpha]_D$ +7.1° (c 1.0), $\delta_H(CDCl_3)$ 4.770 (dd, 10.3, 4.2 Hz, H-4), 3.884 (d, 4.2 Hz, H-3), 3.785 (s, CO_2Me), 1.742 (s, OAc), 1.685 (s, NHAc).

13) m.p. 103-105°C, $[\alpha]_D$ -0.5° (c 0.5), $\delta_H(CDCl_3)$ 4.129 (d, 1.5 Hz, OH), 4.035 (dd, 10.7, 9.8 Hz, H-4), 3.629 (s, CO_2Me), 3.590 (dd, 10.7, 1.5 Hz, H-3), 1.723 (s, NHAc).

14) W. Rosenbrook, D. A. Riley and R. A. Lartey, *Tetrahedron Lett.*, **26**, 3 (1985); G. H. Posner and S. R. Haines, *ibid.*, **26**, 5 (1985).

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

16) T. Mukaiyama, Y. Murai and S. Shoda, *Chem. Lett.*, **1981**, 431.

17) $[\alpha]_D$ -2.6° (c 1.1), $\delta_H(CDCl_3)$ 5.480 (d, 4.9 Hz, H-1a), 4.318 (dd, 10.7, 9.8 Hz, H-4b), 3.632 (s, CO_2Me), 3.209 (d, 10.7 Hz, H-3b).

18) R. J. Batchelor, J. N. R. Ruddick, J. R. Sams and F. Aubke, *Inorg. Chem.*, **16**, 1414 (1977), T. Mukaiyama, N. Iwasawa, R. W. Stevens and T. Haga, *Tetrahedron*, **40**, 1381 (1984).

19) E. J. Corey and T. M. Eckrich, *Tetrahedron Lett.*, **25**, 2419 (1984).

20) $[\alpha]_D$ -22.4° (c 0.7), $\delta_H(CDCl_3)$ 5.449 (d, 4.9 Hz, H-1a), 4.001 (d, 3.9 Hz, H-3b), 3.750 (s, CO_2Me), 1.721 (s, NHAc).

21) S. Murata and T. Suzuki, *Chem. Lett.*, **1987**, 849.

22) $[\alpha]_D$ -29.8° (c 1.2), $\delta_H(CDCl_3)$ 5.479 (d, 4.9 Hz, H-1a), 4.122 (dd, 10.7, 1.7 Hz, H-6b), 3.955 (ddd, 7.0, 4.3, 1.7 Hz, H-8b), 3.803 (ddd, 10.5, 10.0, 8.8 Hz, H-5b), 3.642 (s, CO_2Me), 2.790 (dd, 12.5, 4.3 Hz, H-3beq), 1.760 (s, NHAc), 1.745 (dd, 12.5, 11.9 Hz, H-3bax).

23) $\delta_H(C_6D_6)$ 5.717 (dd, 3.5, 2.0 Hz, H-7b), 5.451 (d, 5.1 Hz, H-1a), 5.352 (ddd, 11.7, 10.0, 4.9 Hz, H-4b), 3.309 (s, CO_2Me), 2.559 (dd, 12.7, 4.9 Hz, H-3beq), 1.818 (dd, 12.7, 11.7 Hz, H-3bax).

24) J. M. Kuster and I. Dyong, *Liebigs Ann. Chem.*, **1975**, 2179.

25) $[\alpha]_D$ +21.1° (c 0.9), $\delta_H(CDCl_3)$ 4.577 (d, 3.7 Hz, H-1a), 4.230 (dd, 11.0, 2.0 Hz, H-6b), 3.884 (t, 9.3 Hz, H-4b), 3.817 (ddd, 7.6, 4.0, 2.0 Hz, H-8b), 3.662 (dd, 7.6, 2.0 Hz, H-7b), 3.605 (s, CO_2Me), 3.231 (d, 9.3 Hz, H-3b), 1.566 (s, NHAc).

26) $\delta_H(CDCl_3)$ 5.346 (ddd, 9.0, 5.6, 2.4 Hz, H-8b), 5.297 (dd, 9.0, 1.7 Hz, H-7b), 4.937 (d, 3.7 Hz, H-1a), 4.876 (ddd, 12.2, 9.5, 4.8 Hz, H-4b), 4.260 (dd, 12.5, 2.4 Hz, H-9b), 4.049 (dd, 12.5, 5.6 Hz, H-9b'), 3.807 (s, CO_2Me), 2.624 (dd, 12.8, 4.8 Hz, H-3beq), 1.978 (dd, 12.8, 12.2 Hz, H-3bax).

27) T. Ogawa and M. Sugimoto, *Carbohydr. Res.*, **135**, C5 (1985).

28) H. Paulsen, M. Paal, D. Hadamczyk and K.-M. Steiger, *Carbohydr. Res.*, **131**, C1 (1984); H. Paulsen, D. Hadamczyk, W. Kutschker and A. Bünsh, *Liebigs Ann. Chem.*, **1985**, 129.

29) $[\alpha]_D$ -6.6° (c 1.5), $\delta_H(CDCl_3)$, 5.453 (d, 3.4 Hz, H-4b), 4.093 (dd, 10.7, 2.0 Hz, H-6c), 3.720 (dd, 7.0, 2.0 Hz, H-7c), 3.666 (s, CO_2Me), 1.996 (s, OAc), 1.620 (s, NHAc).

30) $[\alpha]_D$ +17.3° (c 0.4), $\delta_H(CDCl_3)$ 4.462 (dd, 10.4, 3.7 Hz, H-3b), 4.001 (dd, 10.4, 1.5 Hz, H-6c), 3.428 (s, CO_2Me), 1.854 (s, OAc), 1.540 (s, NHAc).

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