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Efficient Synthesis of 2α-Glycoside of N-Acetylneuraminic Acid via Phenylsulfenyl Chloride Adduct of 2-Deoxy-2,3-dehydro-N-acetylneuraminic Acid Methyl Ester Tetra-O-acetate[1)]

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Phenylsulfenyl chloride adds to a 2-deoxy-2,3-dehydro-N-acetylneuraminic acid derivative to give predominantly the corresponding 2-chloro-3β-phenylthio derivative, which is an excellent glycosyl donor for the preparation of α-glycosides of sialic acid.

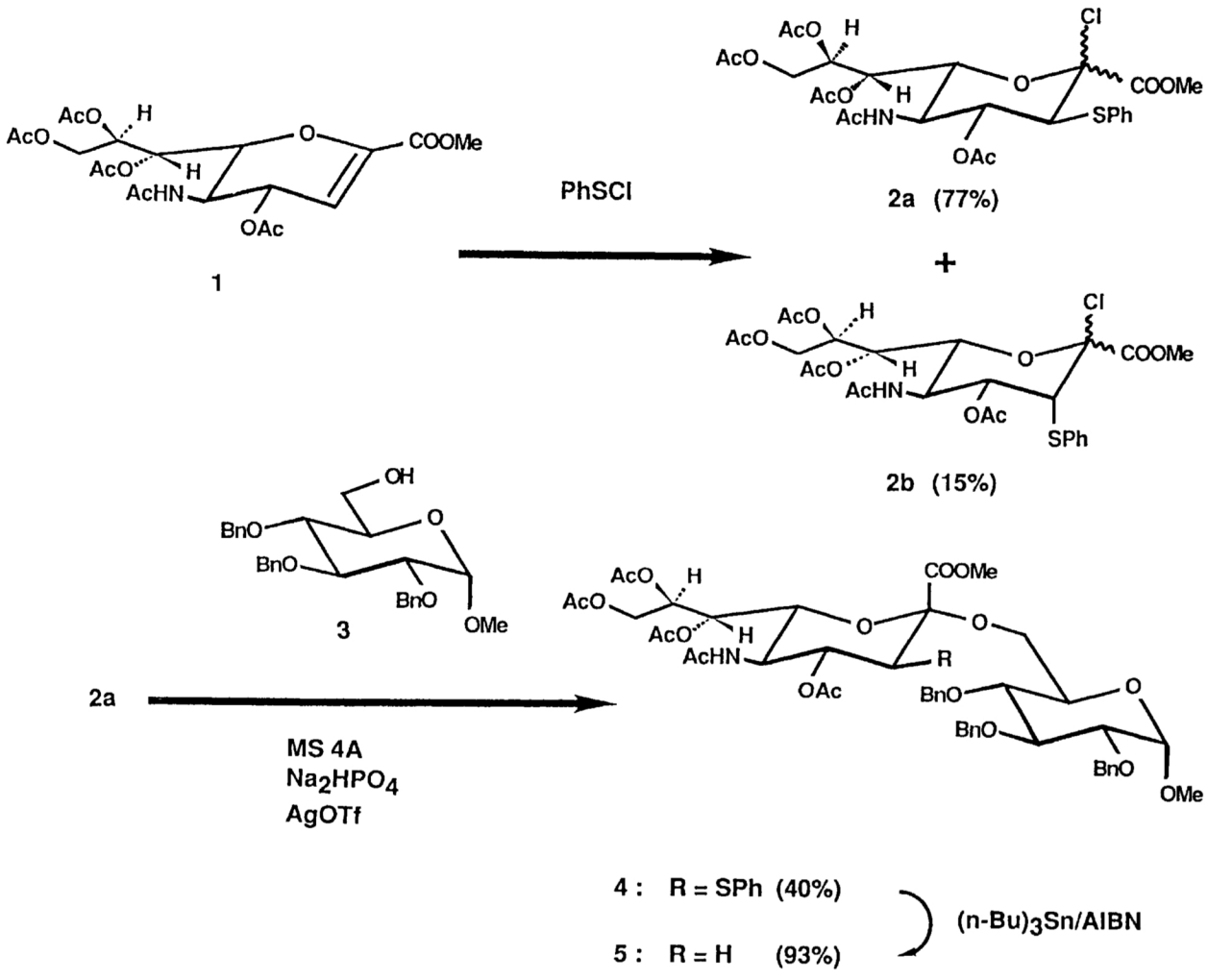
N-Acetylneuraminic acid (NeuAc) is widely found in glycoconjugate such as gangliosides and plays an important role on their biological activities. It exists exclusively as its 2α-glycosidic form in sugar chains. Synthesis of 2α-glycosides of NeuAc has been developed mainly by using 2β-chloro-2-deoxy-$NeuAc_5$ methyl ester ($NeuAc_5$: NeuAc tetra-O-acetate) as the glycosyl donor. The glycosidation is, however, always accompanied by a by-product, 2-deoxy-2,3-dehydro-$NeuAc_5$ methyl ester (**1**), by elimination of HCl.[2)] To prevent this side reaction, we introduced a substituent such as a bromine atom or a hydroxy group at 3-position of NeuAc.[3)] From these derivatives elimination of hydrogen halide did not occur and glycosides were obtained in good yields, but to obtain the 2α-glycosides the substituent must be 3β and not 3α; thus the 2α-glucoside was predominantly produced in the case of the 2β-bromo-3β-hydroxy derivative.[4)] Then removal of the 3β-hydroxy group was effected by derivation to its xanthate followed by reduction with tri-n-butyltin hydride.[4)] A difficulty was encountered to apply this method, however, in the case of oligosaccharides having free hydroxyl group(s) on other sugar moieties.[5)] Ogawa et al.[6)] have developed the synthesis of benzyl-protected NeuAc derivatives with 3β-phenylselenyl an 3β-phenylthio group as glycosyl donors for preparation of 2α-glycosides of NeuAc, in expectation of a neighboring group participation of the 3β-substituent. To synthesize the 3β-substituted NeuAc derivatives from the 2-deoxy-2,3-dehydro-NeuAc **1**, however, they needed several steps involving an isomerization of the initially formed 3α-substituent to 3β by equilibration of an intermediate, a 3α-substituted 2β-hydroxy derivative, with a base.

We have succeeded in one step synthesis of 2-chloro-2-deoxy-3β-phenylthio-$NeuAc_5$ **2a** from 2-deoxy-2,3-dehydro-$NeuAc_5$ **1** and phenylsulfenyl chloride in a good yield. The phenylthio-$NeuAc_5$ **2a** was an excellent glycosyl donor to produce a single product, 2α-glycoside of NeuAc. The phenylthio group was easily removed by reduction with tributyltin hydride. Thus, this method would be widely applicable

Table 1. Solvent effects on the yield of the adducts, **2a** and **2b**

Solvent	Reaction temp / °C	Time / day	Yield / % 2a	2b
Toluene	80	3	46	5
CH_2Cl_2	30	2	77	15
CH_3CN	30	2	35	60
CH_3NO_2	30	2	30	64
THF	30	2	no adduct[a)]	
Et_2O	30	2	no adduct[a)]	
DMSO	30	2	no adduct[a)]	

a) The starting material (**1**) was recovered.



for the synthesis of oligosaccharides containing 2α-glycoside of sialic acid.

Addition of phenylsulfenyl chloride to the 2-deoxy-2,3-dehydro-$NeuAc_5$ **1** was accomplished by addition of freshly prepared phenylsulfenyl chloride (0.7 g) to a solution of **1** (1.0 g) in dichloromethane (9 ml) at 30 °C and the mixture was allowed to stand for 2 days in the dark. After usual work-up, the product was chromatographed on a silica gel column to give two adducts. An adduct having a 3β-phenylthio group, 2-chloro-3β-phenylthio-$NeuAc_5$ methyl ester (**2a**),[7] was obtained in a 77% yield and its 3α-isomer (**2b**)[8] in a 15% yield (Table 1). Configuration of the 3-substituent was determined from $J_{3,4}$ (**2a**; 11 Hz; **2b**, 4 Hz).

Glycosidation of methyl 2,3,4-tri-O-benzyl-α-D-glucopyranoside (**3**) with the chloride **2a** was carried out as follows: to a suspension of molecular sieves 4A (250 mg) and Na_2HPO_4 (30 mg) in dichloroethane (0.9 ml) was added a solution of the tribenzylglucoside **3** (65 mg) and the chloride **2a** (60 mg) in dichloroethane (0.9 ml). After addition of silver triflate (50 mg) in toluene (0.6 ml) the mixture was allowed to stand at 70 °C for 18 h. The suspension was filtered by passing through a Celite 545 bed and the filtrate was diluted with ethyl acetate, washed with aq. sodium thiosulfate, aq disodium hydrogen phosphate, water and brine, and then dried over sodium sulfate. The solution was evaporated in vacuo and the residue was subjected to a silica gel TLC to give a crude product (90 mg), which was further purified by means of a preparative ODS-HPLC to afford a protected 3β-phenylthio-NeuAcα(2-6)Glc **4**[9] (41 mg, 40%). No 3β-isomer was detected.

Desulfidation of **4** was effected by addition of tributyltin hydride (30 μl) to a solution of **4** (40 mg) and AIBN (5 mg) in toluene (1.5 ml), followed by heating at 110 °C under stirring for 20 min. The solution was evaporated in vacuo and the residue subjected to a silica-gel chromatography to give protected NeuAcα(2-6)Glc **5**[10] (33 mg, 93%), physical data (mp, mixed mp, and ^1H NMR) of which were completely identical with those of an authentic sample prepared according to the method of Okamoto et al.[5]

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7) **2a**: mp 131 °C;[11] $[\alpha]_D$ -8.8° (c 0.4, $CHCl_3$); IR(KBr, cm^{-1}) 3398, 1750, 1665, 1539, 1438, 1370, 1219, 1124, 1034; UV λ_{max}^{MeOH} 253 nm(ε 4800): ^1H NMR(δ, J in Hz, $CDCl_3$) 1.87, 1.90, 2.05, 2.11, 2.12(3H each, s, CH_3CO); 3.82(3H, s, CH_3O), 3.99(1H, dd, J=5.0 & 12.5, H-9), 4.00(1H, d, J=11, H-3), 4.27(1H, dd, J=2.5 &

12.5, H-9), 4.34(1H, q, J=10, H-5), 4.40(1H, dd, J=2.5 & 10, H-6), 5.12(1H, ddd, J=2.5, 5.0 & 8.0, H-8), 5.36(1H, dd, J=10 & 11, H-4), 5.43 (1H, dd, J=2.0 & 8.0, H-7), 5.43(1H, dd, J=2.5 & 8, H-7), 5.44(1H, d, J=10, NH, exchangeable), 7.2-7.5(5H, arom.); FABMS (m-nitrobenzyl alcohol: NBA) m/z 618 and 620 (M^++1).

8) **2b:** amorphous powder; $[\alpha]_D$ -21.4 °(c 0.49, $CHCl_3$); IR(KBr, cm^{-1}) 3390, 1750, 1665, 1546, 1438, 1370, 1222, 1045, 748, 602: UV λ_{max}^{MeOH} 254 nm(ε 5200); ^1H NMR (δ, J in Hz, $CDCl_3$) 1.81, 1.95, 2.06, 2.07, 2.20(3H each, s, CH_3CO), 3.85(3H, s, CH_3O), 4.16(1H, dd, J=6 & 12.5, H-9), 4.18(1H, d, J=4, H-3), 4.44(1H, dd, J=2 & 11, H-6),4.49(1H, dd, J=2.5 & 12.5, H-9), 4.54(1H, br.dt, J=9.5 & 10.5, H-5), 5.27(1H, ddd, J=2.5, 6.0, & 7.0, H-8), 5.42(1H, dd, J=2.0 & 7.0, H-7), 5.45(1H, d, J=9.5, NH, exchangeable), 5.85(1H, dd, J=4 & 10.5, H-4), 7.2-7.6 (5H, arom.); FABMS (NBA) m/z 618 and 620 (M^++1).

9) **4:** mp 71-73 °C;[11] $[\alpha]_D$ +17.2° (c 0.47, $CHCl_3$); IR(KBr, cm^{-1}) 3434, 1749, 1665, 1369, 1219, 1047, 744, 699; UV λ_{max}^{MeOH} 255nm (ε 4800); ^1H NMR(δ, J in Hz, $CDCl_3$) 1.82, 1.86, 1.99, 2.01, 2.04(3H, each, s, CH_3CO), 3.26(1H, d, J=11, H-3'), 3.29(3H, s, CH_3O), 3.39(1H, dd, J=9 & 10.5, H-4), 3.45(1H, dd, J=3.5 & 10, H-2), 3.79(3H, s, CH_3O), 3.80(1H, m, H-5), 3.84(1H, dd, J=5.5 & 12.5, H-9'), 3.96(1H, t, J=9, H-3), 4.11(2H, br.d, J=3, H-6), 4.12(1H, dd, J=2.5 & 12.5, H-9'), 4.18(1H, q, J=10, H-5'), 4.25(1H, dd, J=2.5 & 10, H-6'), 4.63(1H, d, J=3.5, H-1), 4.70(1H, d, J=12, CH_2Ph), 4.71(2H, s, CH_2Ph), 4.78(1H, d, J=9, CH_2Ph), 4.79(1H, d, J=12, CH_2Ph), 4.95(1H, d, J=9, CH_2Ph), 5.25(1H, dd, J=2.5 & 9, H-7'), 5.30(1H, ddd, J=2.5, 5.5 & 9, H-8'), 5.32(1H, dd, J=10 & 11, H-4') 5.42(1H, br.d, NH), 7.1-7.5(20H, arom.); FABMS(NBA) m/z 1068 (M^++Na).

10) **5:** mp 104 °C(lit.[5] mp 104 °C); $[\alpha]_D$ -1.3° (c 0.44, $CHCl_3$): IR(KBr, cm^{-1}) 3394, 2928, 1746, 1665, 1539, 1454, 1369, 1219, 1044, 741, 699, 602; ^1H NMR(δ , J in Hz, $CDCl_3$)1.82, 1.86, 2.00, 2.02, 2.13, (3H, s, CH_3CO), 1.97(1H, t, J=12, H-3'a), 2.65 (1H, dd, J=5.0 & 12, H-3'b), 3.36(3H, s, CH_3O), 3.42(1H, dd, J=2 & 10.5, H-6), 3.51(1H, dd, J=3.5 & 9.5, H-2), 3.59(1H, t, J=9.5, H-4), 3.74(3H, s, CH_3O), 3.75(1H, ddd, J=2, 4 & 9.5, H-5), 3.77(1H, dd, 5 & 12.5, H-9'), 3.96(1H, t, J=9.5, H-3), 3.99(1H, q, J=9.5, H-5'), 4.05(1H, dd, J=2.5 & 13, H-9'), 4.09(1H, dd, J=2 & 10.5, H-6'), 4.21(1H, dd, J=4 & 10.5, H-6), 4.61(1H, d, J=3.5, H-1), 4.65(1H, d, J=12, CH_2Ph), 4.75(1H, d, J=11.5, CH_2Ph), 4.77(1H, d, J=10.5, CH_2Ph), 4.79(1H, d, J=10.5, CH_2Ph), 4.85(1H, dt, J=5 & 12, H-4'), 4.85 (1H, d, J=10.5, CH_2Ph), 4.91(1H, d, J=11.5, CH_2Ph), 5.06(1H, d, J=10, NH), 5.25(1H, dd, J=2 & 9, H-7'), 5.38(1H, ddd, J=2, 5 & 9.0, H-8'), 7.2-7.4(15H, arom.); FABMS(NBA) m/z 937(M^+).

11) Satisfactory elemental analysis was obtained.

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