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Syntheses of G_{M4} and G_{M3} Intermediates via Alkylation and Subsequent Intramolecular Glycosidation of 2-Alkoxy-2-phenylthioacetate

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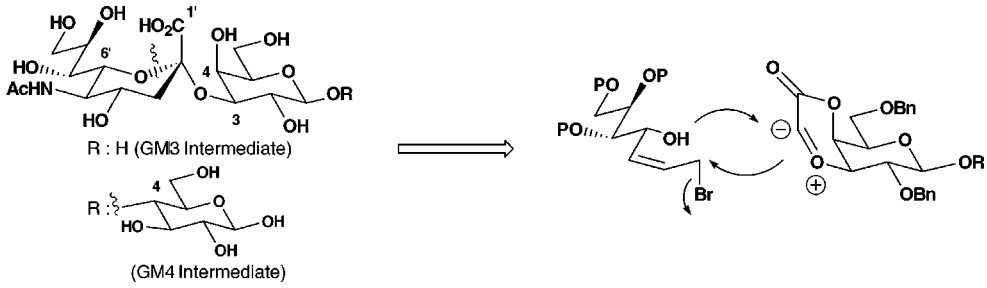
ABSTRACT



We developed a new method for α-glycoside formation of sialyl conjugates based on alkylation and subsequent intramolecular glycosidation of 2-alkoxy-2-phenylthioacetate. By this method we succeeded in the syntheses of G_{M4} and G_{M3} intermediates.

N-Acetylneuraminic acid (Neu5Ac; sialic acid) is located at the nonreducing terminal position of glycoproteins, gangliosides, and oligosaccharides, which are found on cell membranes and in the nervous systems of various living organisms.[1] These sialyl conjugates play an essential role in biological molecular recognition processes, such as cell adhesion and differentiation phenomena.[2] Recently, syntheses of sialyl conjugates have been undertaken to elucidate their biological properties and functions. One of the most difficult problems in the synthesis of sialyl conjugates is the stereoselective glycosidation of sialic acid to afford the α-glycosidic linkage.[3] Here we report a new method for α-glycoside formation of sialyl conjugates based on alkylation of sugar-derived 2-alkoxy-2-phenylthioacetate anion **3** with bromide **2**[4] and subsequent intramolecular glycosidation (Figure 1). We also demonstrate the usefulness of this method by the syntheses of G_{M4} and G_{M3} intermediates.

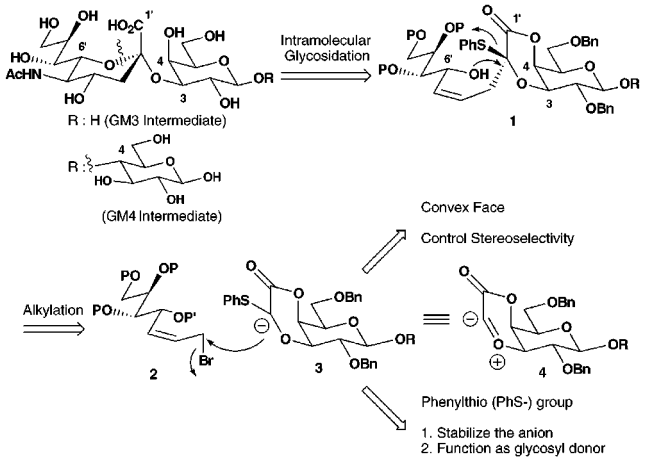


Figure 1. Retrosyntheses of G_{M4} and G_{M3} intermediates.

In our key intermediate, the anion **3** can be taken as "an anion equivalent of oxonium ion" as shown **4**. The phenylthio

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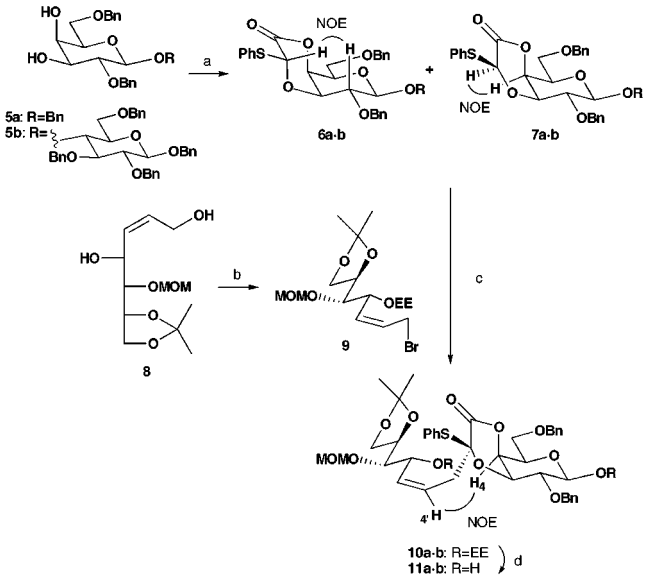
group in **3** serves as not only a stabilizer of an enolate in the alkylation but also as a leaving group in the glycosidation. Stereoselective formation of the α-glycosidic linkage in the sialic acid would result from the approach of bromide **2** from the convex face of cis-fused lactone **3** and subsequent attack of hydroxyl group at C-6′ via intramolecular S_N2-type substitution reaction.[5] The viability of the key intermediate **3** was first demonstrated in the synthesis of G_{M4} intermediate.

Treatment of the dibutylstannylene derivative of benzyl 2,6-di-*O*-benzyl-*β*-D-galactopyranoside[6] (**5a**) with tetrabutylammonium bromide and isopropyl 2-chloro-2-phenylthioacetate, prepared from isopropyl 2-phenylthioacetate and *N*-chlorosuccinimide, gave 2-alkoxy-2-phenylthioacetates **6a** and **7a** as a 5:1 mixture in 83% yield. After separation of the diastereoisomers on silica gel, their stereochemistry was determined by NOE experiments as shown in Scheme 1.[7]

Scheme 1. Preparation and Alkylation of 2-Alkoxy-2-phenylthioacetates[a]



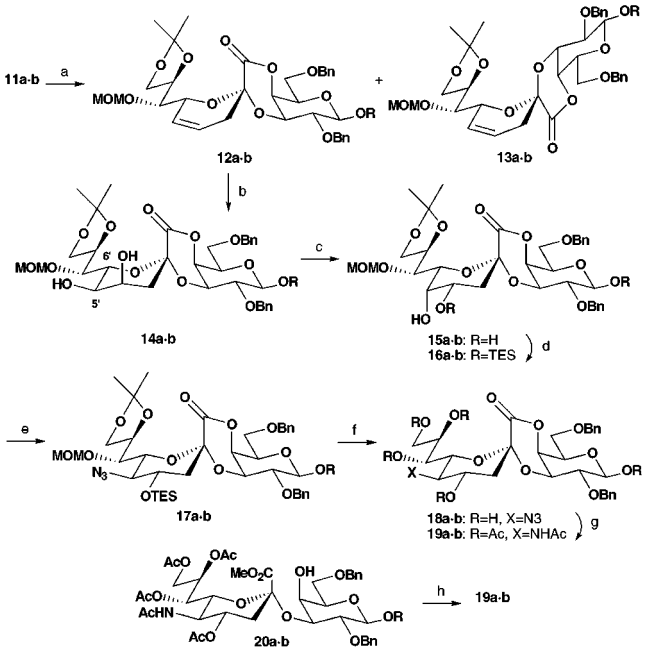
[a] (a) Bu_2SnO, PhMe, reflux, and then 3 equiv of (PhS)ClCHCO$_2$*i*Pr, Bu_4NBr, reflux, 83% for **6a** and **7a** (**6a**:**7a** = 5.0:1), 63% for **6b** and **7b** (**6b**:**7b** = 2.9:1); (b) CBr_4, PPh_3, CH_2Cl_2, and then ethyl vinyl ether, 80%; (c) **6a** or **6b**, LDA, THF−HMPA, 80% for **10a**, 68% for **10b**; (d) catalytic PPTS, EtOH, 76% for **11a**, 77% for **11b**.

Bromide **9** is obtained by selective bromination of the primary alcohol in **8**[4] and protection of the allylic alcohol with ethyl vinyl ether in 80% yield.

Alkylation of **9** with 2-alkoxy-2-phenylthioacetate **6a** was carried out as follows. After treatment of **6a** with LDA in THF at −78 °C followed by addition of bromide **9** and HMPA, the reaction mixture was stirred at −40 °C for 30 min to give alkylated product **10a** in 80% yield. Removal of the ethoxyethyl group gave alcohol **11a** as a single diastereomer whose stereogenic center was determined by NOE between the 4′-vinyl proton and the proton at C-4 of galactoside.[8] This showed that electrophile **9** was attacked from the convex face of **6a**.

Intramolecular glycosidation of **11a** was carried out with various reagents (MeSOTf/DTBP,[3i] DMTST,[3d] NIS/TfOH,[3d] and PhSOTf/DTBP[3j]) to give **12a** and **13a** in 66−89% combined yield (Scheme 2). The best stereoselectivity (4.0:1) was obtained when phenylsulfenyl triflate (PhSOTf) and 2,6-di-*tert*-butylpyridine (DTBP) were used as an activator for the phenylthio group. When only PhSOTf was used, the stereoselectivity was lowered to 2.0:1. However, the stereochemistry of each compound could not be determined at this stage, so the major compound **12a** was transformed into the acetyl derivative of *N*-acetylneuraminic acid **19a**.

Scheme 2. Intramolecular Glycosidation of 2-Alkoxy-2-phenylthioacetates **11a** and **11b** and Transformation of Glycosides **12a** and **12b** into Acetyl Derivatives of *N*-Acetylneuraminic Acid[a]



[a] (a) PhSOTf, DTBP, MS-4A, CH_2Cl_2, 79% for **12a** and **13a** (**12a**:**13a** = 4.0:1), 81% for **12b** and **13b** (**12b**:**13b** = 2.8:1); (b) catalytic $RuCl_3·H_2O$, $NaIO_4$, EtOAc−CH_3CN−H_2O (3:3:1), 87% for **14a**, 41% for **14b**; (c) (1) Tf_2O, Py, CH_2Cl_2, (2) $CsOCOCF_3$, 18-crown-6, PhMe-DMF (3:1) 80 °C and then aqueous $NaHCO_3$, MeOH, 2 steps, 70% for **15a**, 50% for **15b**; (d) TESCl, imidazole, CH_2Cl_2, 64% for **16a**, 36% for **16b**; (e) (1) Tf_2O, Py, CH_2Cl_2, (2) Bu_4NN_3, PhH, 2 steps, 80% for **17a**, 75% for **17b**; (f) CF_3CO_2H, MeOH, 68% for **18a**, 80% for **18b**; (g) (1) 5% Pd−$CaCO_3$, H_2, EtOH, (2) Ac_2O, Py, catalytic DMAP, CH_2Cl_2, 2 steps, 68% for **19a**, 83% for **19b**; (h) DBU, CH_2Cl_2, 50% for **19a** and 63% for **19b**.

Dihydroxylation of the olefin in **12a** with $RuCl_3·H_2O$−$NaIO_4$[9] afforded diol **14a** as a single diastereomer in 70% yield.[10] Inversion of configuration of the 4′,5′-diol in **14a**, according to Sato's procedure,[11] gave diol **15a** in 70% yield. Selective protection of an equatorial hydroxyl group with a triethylsilyl group afforded alcohol **16a** in 64% yield. Transformation of an axial hydroxyl group into triflate and subsequent treatment with tetrabutylammonium azide introduced an azido group at C-5′ with inversion of configuration.

Removal of the 8′,9′-*O*-isopropylidene protecting group, the 7′-*O*-methoxymethyl group, and the 4′-*O*-triethylsilyl group in **17a** was achieved with trifluoroacetic acid in methanol to give **18a** in 68% yield. Reduction of the azide group to amine followed by acetylation of the amine and all hydroxyl groups afforded **19a** in 68% yield from **18a**. Spectral data ($[\alpha]_D$, IR, ^{1}H NMR, ^{13}C NMR, and MS) of **19a** were in good agreement with those of an authentic sample obtained by DBU treatment of α-glycoside **20a**.[6b,c,1212−13] We confirmed that the major glycoside **12a** in the intramolecular glycosidation was the desired α-glycoside.

In addition, we applied this method to the synthesis of the G_{M3} intermediate by employing benzyl 2,3,6-tri-*O*-benzyl-*O*-[2,6-di-*O*-benzyl-*β*-D-galactopyranosyl]-*β*-D-glucopyranoside[13] (**5b**) as the starting compound.

Alkylation and subsequent intramolecular glycosidation of 2-alkoxy-2-phenylthioacetate are useful for construction of the α-glycoside linkage of *N*-acetylneuraminic acid. G_{M4} intermediate **19a** is an important compound for the synthesis of many gangliosides. Furthermore, the α-glycosides **12a** and **12b** are efficient intermediates for various derivatives of sialic acid. Further studies on the syntheses of *N*-acetylneuraminic acid conjugates utilizing 2-alkoxy-2-phenylthioacetate are underway in our laboratory.

Supporting Information Available: Experimental procedures for preparation of compounds **6**, **10**, **11**, and **12** and characterization data for **6**, **7**, **10**, **11**, **12**, **13**, and **19**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(7) 12% NOE for **6a**, 7% NOE for **7a**, 4% NOE for **6b**, and 6% NOE for **7b** were observed.

(8) 5% NOE for **11a** and 3% NOE for **11b** were observed.

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