A Facile Synthesis of *N*-Acetylneuraminic Acid Glycal

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The paper is dedicated to the memory of Professor Nikolay K. Kochetkov and his outstanding contribution to carbohydrate chemistry.

Abstract: Treatment of the readily available peracetylated *N*-acetylneuraminic acid glycosyl chloride [methyl 5-acetamido-4,7,8,9-tetra-*O*-acetyl-2-chloro-2,3,5-trideoxy-β-D-glycero-D-galactononulopyranosonate)] with anhydrous Na_2HPO_4 in refluxing MeCN quantitatively affords the peracetylated *N*-acetylneuraminic acid glycal [methyl 5-acetamido-4,7,8,9-tetra-*O*-acetyl-3,5-dideoxy-2,6-anhydro-D-glycero-D-galacto-non-2-enonate], which can be isolated from the reaction mixture by simple filtration and subsequent evaporation of the solvent. No glycal formation was detected at room temperature even after prolonged treatment with Na_2HPO_4. The method proposed is experimentally simple and allows ready preparation of substantial amounts of the title compound, which is an important intermediate in sialic acid chemistry.

Key words: carbohydrates, halides, eliminations, alkenes, phosphates

Sialic acid containing oligosaccharides play many important roles in biological processes.[1] For this reason, tremendous efforts have been made in order to develop efficient methods for their synthesis.[2] The most reliable approaches for the construction of sialyl glycosidic bond make use of *N*-acetylneuraminic acid (Neu5Ac) derivatives with an auxiliary stereocontrolling group at the C-3 atom of sialic acid.[2] The key intermediate for the preparation of these 3-substituted derivatives is the Neu5Ac glycal **1**. This compound has also found application in the synthesis of inhibitors of influenza virus sialidase, two of which were commercialized recently as anti-influenza drugs (Relenza and Tamiflu).[3] Not surprisingly, several methods for the preparation of this important intermediate were developed (Figure 1).[4–6] Unfortunately, each has its own disadvantages.

The most widely used synthesis of Neu5Ac glycal **1** involves treatment of Neu5Ac glycosyl chloride **2**,[7] which can be prepared quantitatively[8a] from peracetylated Neu5Ac **3**,[9] with a base (initially Et_3N was used,[4a] later DBU was suggested[4b]) at room temperature. Although this method is fairly straightforward on low-to-medium scale (81% yield after chromatography and crystallization), it can lead to disappointing results on a large scale (20–50 g) due to partial hydrolysis of the methyl ester and concomitant de-O-acetylation of acetylated glycal **1** during workup procedure.[10] An alternative approach for the synthesis of glycal **1** is based on the trimethylsilyl trifluoromethanesulfonate (TMSOTf)-catalyzed elimination reaction from the peracetylated Neu5Ac methyl ester **3** in MeCN.[5] The use of 'fresh' TMSOTf was reported to be essential in order to reduce formation of the undesired 4,5-oxazoline.[5c] This reaction was studied in detail and shown to be highly 'sensitive to changes in solvent and temperature'.[5d] A recently described transformation of Neu5Ac thioglycosides **4a**,**b** to Neu5Ac glycal **1** under oxidative conditions (MCPBA, Py, CH_2Cl_2)[6a] or by treatment with DMTST and DBU[6b] albeit efficient require additional steps for the preparation of the starting thioglycoside. These limitations of the known methods call for search for new approaches for the preparation of Neu5Ac **1**, which would be experimentally simple, robust and efficient.

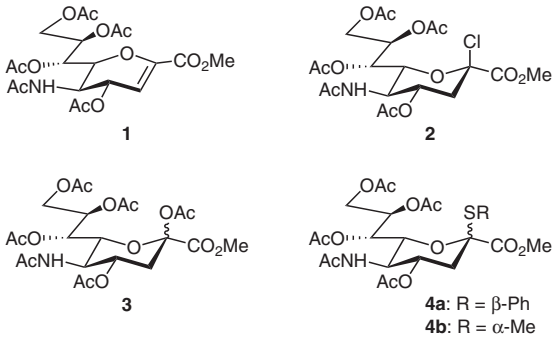

Figure 1 Neu5Ac derivatives

During the development of the synthesis of Neu5Ac glycosyl phosphates by reaction of Neu5Ac glycosyl chloride **2** with various phosphate nucleophiles,[8] we discovered that treatment of Neu5Ac glycosyl chloride **2** with anhydrous Na_2HPO_4 in refluxing MeCN for three hours quantitatively affords the peracetylated Neu5Ac glycal **1** (Scheme 1). The pure product can be isolated from the reaction mixture by simple filtration and subsequent evaporation of the solvent. No chromatography or crystallization is required thus making this approach potentially applicable to large-scale preparation of **1**. It is important to note that no glycal formation was detected at room temperature even after prolonged treatment with Na_2HPO_4. The latter observation may allow the use of Na_2HPO_4 as an acid scavenger in the reactions of Neu5Ac glycosyl chloride **2** (other bases are known to cause its elimination, leading to the formation of glycal **1**).

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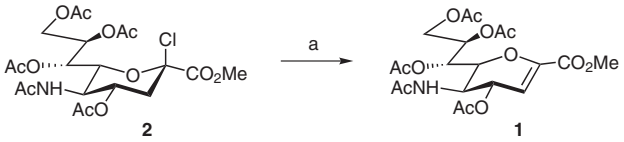

Scheme 1 *Reagents and conditions*: (*a*) Na_2HPO_4, MeCN, reflux, 3 h, 95%.

The proposed method for the synthesis of Neu5Ac glycal **1** is experimentally simple and allows ready preparation of substantial amounts of the title compound, which is an important intermediate in sialic acid chemistry.

The reactions were performed with the use of commercial reagents (Aldrich and Fluka) and distilled solvents purified according to standard procedures. MeCN was distilled over CaH_2 under argon prior to use. TLC was carried out on plates with silica gel 60 on aluminum foil (Merck). Spots of compounds were visualized with a solution of 85% H_3PO_4 in 96% EtOH (1:10) with subsequent heating (150 °C) and under UV light. The ^1H and ^{13}C NMR spectra of solutions in $CDCl_3$ were recorded on a Bruker AC-200 instrument (200.13, and 50.32, MHz, respectively). The ^1H chemical shifts are referred to the signal of the residual $CHCl_3$ (δ = 7.27), and the ^{13}C of the ^{13}C NMR, to the signal of $CDCl_3$ (δ = 77.0). All reactions were carried out with the use of glycosyl chloride **2**, which was freshly prepared from the fully acetylated neuraminic acid methyl ester **3** according to a modified procedure[8a] and dried for 3 h under vacuum (oil pump). The yield of glycal **1** was calculated with respect to the amount of **3** taken.

Methyl 5-Acetamido-4,7,8,9-tetra-*O*-acetyl-3,5-dideoxy-2,6-anhydro-D-glycero-D-galactonon-2-enonate (1)

Glycosyl chloride **2** [prepared from **3** (103.6 mg, 0.194 mmol)] was dissolved in MeCN (4 mL), then Na_2HPO_4 (33 mg, 0.23 mmol) was added and the suspension refluxed. The course of the reaction was monitored by TLC [R_f **1** = 0.48, R_f **2** = 0.50 (EtOAc)]. After 3 h, the mixture was cooled to the r.t., filtered through a Celite pad and the volatiles were evaporated. The residue was dried under vacuum (oil pump) to give crude glycal **1** (87.1 mg), which was pure according to NMR spectroscopy. The product was subjected to silica gel column chromatography (gradient from EtOAc–hexanes, 1:1 to EtOAc) to give glycal **1** (87.1 mg, 95%). The ^1H spectrum of the product was identical to that described in the literature;[4b] $[\alpha]_D^{20}$ +56.6 (*c* = 1.3, $CHCl_3$) {Lit.[6b] $[\alpha]_D^{20}$ +56.0 (*c* = 1.3, $CHCl_3$)}.

^{13}C NMR: δ = 20.6, 20.7, [C(O)*C*H_3], 22.9 [NHC(O)*C*H_3], 46.2 (C-5), 52.5 (CH_3), 61.9 (C-9), 67.5 (C-4), 68.1 (C-7), 70.9 (C-8), 76.5 (C-6), 108.0 (C-3), 145.0 (C-2), 161.5 (C-1), 170.1, 170.3 (2 C), 170.6, 170.8 (C=O).

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