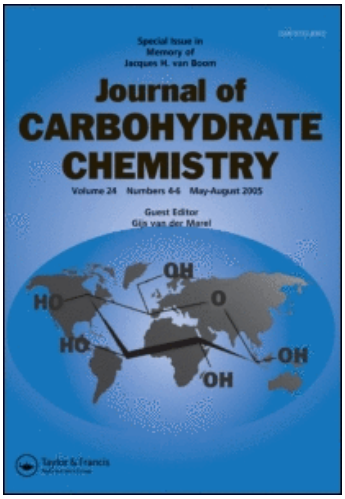

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STEREOSELECTIVE SYNTHESES OF ALKYL- and ALKYL-2-THIO-α-SIALOSIDES [1]

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ABSTRACT

Alkyl and thioalkyl α-glycosides of *N*-acetylneuraminic acid have been prepared in near quantitative yield and with complete stereoselectivity, under the Williamson reaction conditions using RONa or RSNa, respectively, in ROH or RSH as solvent.

INTRODUCTION

As *N*-acetylneuraminic acid (Neu5Ac) and analogs have always been found as α-linked glycosides (with the exception of CMP-Neu5Ac, the cofactor required for its enzymatic transfer), many efforts have been made to achieve stereoselective syntheses of α-sialosides. In general, alkyl α-glycosides of Neu5Ac were prepared from the chloro derivative 3 with alcohols under Koenigs-Knorr conditions in the presence of a heavy metal salt as catalyst.[3] As a general rule, a mixture of α and β anomers was

obtained, yields were moderate and long reaction times were required. Most of the time, under these conditions, the 2,3-dehydro derivative **8b** was obtained as by-product. In contrast, more recently,[4] silver salicylate has been shown to give alkyl α-sialosides in good yields without the formation of the unsaturated derivative. An alternative to the Koenigs-Knorr condensation from the chloro derivative **3**, would be the use of alcoholate under Williamson reaction conditions. Until now, this reaction has been carried out only with phenols leading to aryl glycosides under various conditions[5] including phase transfer catalysis.[6]

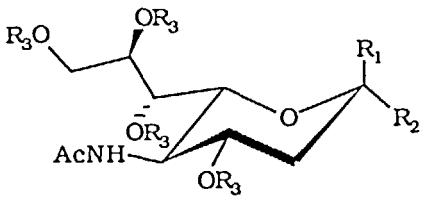
RESULTS AND DISCUSSION

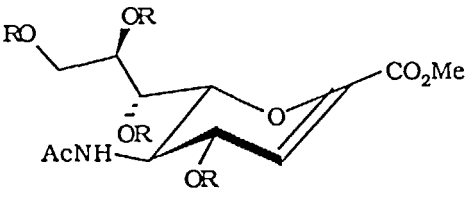
We disclose in this communication, that the above mentioned Williamson reaction could be done with primary alkyl alcoholates or alkyl thiolates to give in near quantitative isolated yields, the α anomer in a completly stereoselective way, *i.e.*, without the formation of the β anomer. It is quite noteworthy that under our conditions (RONa (2 eq.) in ROH as solvent), no elimination occurred and the 2,3-dehydro compounds **8a** or **8b** could not even be detected (by NMR analysis) in the crude mixture. Under these conditions, we were not able to avoid transesterification at position one or deacetylation, and as a result, the final product was the unprotected α-glycoside easily recovered after treatment with Dowex 50(H^+) followed by evaporation of solvent.

We must emphasize that the interest in this reaction lies not only in the fact that we obtained in a near quantitative yield, only the α-glycosides without the need of a tedious separation, but also, from a more fundamental point of view, that quite surprisingly no dehydrohalogenation occurred under these basic conditions, as it might be expected from the current literature of sialic acids derivatives. Due to its simplicity, this method should provide the basis for many applications when it is necessary to protect the anomeric position of sialic acids derivatives.

On the other hand, alkylthioglycosides of sialic acids have been shown[7] to be good precursors of α-glycosides and this brings us to the question of whether our method could be used for the preparation of alkylthio α-sialosides. Until now, these compounds were prepared from the glycosyl chloride **3** either in three steps, by the reaction with potassium thioacetate followed by *S*-deacetylation and alkylation in DMF in ca. 80% overall yield,[8] or in two steps involving first the reaction with *O*-ethyl *S*-

potassium dithiocarbonate followed by the decomposition of the resulting thiocarbonate in the presence of sodium iodide at 110 °C with an overall yield of ca. 45%.[9] When the chloro compound 3 was subjected to our reaction conditions (EtSNa (3 eq.) in EtSH as solvent), the peracetylated ethylthio α-sialoside 7 was obtained in 95% isolated yield.[10] As for alcoholate, neither the β anomer nor the unsaturated derivatives 8a or 8b were found even in trace amounts in the reaction mixture, and all the ester functions withstood the reaction conditions.





R_1	R_2	R_3	
OH	CO_2H	H	**1**
OH	CO_2Me	H	**2**
Cl	CO_2Me	Ac	**3**
OH	CO_2Me	Ac	**4**
CO_2Me	OMe	H	**5**
CO_2Et	OEt	H	**6**
CO_2Me	SEt	Ac	**7**

R=H **8a**

R=Ac **8b**

This method implies good availability of the starting compound 3. It has already been prepared in 80% yield[3b] from the 4,7,8,9 tetra-*O*-acetyl compound 4 by treatment with acetyl chloride saturated with HCl or directly from the methyl ester of *N*-acetylneuraminic acid 2 in neat acetyl chloride.[11] In the latter case the chloride 3 was obtained in 95% (crude) or 60% (crystalline) yield. In our hands, we found that the best results were obtained when the methyl ester 2 was treated with a mixture of AcCl-AcOH (1:1) saturated with HCl at 0 °C. Under these conditions, compound 3 was obtained in 96% isolated yield after silica gel chromatography, which ensured the absence of acidic impurities.

We are currently broadening the scope of this reaction by using other halogeno sugars along with more complex alcoholates.

EXPERIMENTAL

General methods. - Preparative separations were performed by flash chromatography with 6-35μ silica gel from S.D.S. company. Melting points were measured on a Reichert hot-stage apparatus and are uncorrected. Optical rotations were measured at 20 °C with a Roussel-Jouan electronic polarimeter. NMR spectra were recorded at 200 MHz with a Brucker AM200 spectrometer. Chemical shifts are expressed in ppm downfield from internal tetramethylsilane in the case of organic solvents or from a solution of tetramethylsilane (1%) in $CDCl_3$ as external standard in the case of deuterium oxide. Elemental analysis were performed by the Service Central de Microanalyse du CNRS.

Methyl 4,7,8,9-Tetra-*O*-acetyl-*N*-acetyl-2-chloro-2-deoxy-D-neuraminate (3). - A solution of compound 2[12] (3.6 g, 11.15 mmol) in a mixture of AcCl-AcOH (1:1, 60 mL) was saturated at 0 °C with anhydrous HCl. After 20 h at room temperature, the reaction mixture was concentrated several times with toluene. Flash chromatography (AcOEt) of the residue afforded compound **3** as a white solid foam (5.38 g, 96%), free of unsaturated derivative **8b** : $[\alpha]_D$ -66° (*c* 0.6, CH_2Cl_2) [lit.[11] $[\alpha]_D$ -68° (*c* 1, $CHCl_3$)]; ^1H NMR ($CDCl_3$) δ 1.9, 2.05, 2.08, 2.12 (4 s, 15 H, 4 OAc, 1 NHAc), 2.28 (dd, 1 H, $J_{3a,\,3e}$ = 14, $J_{3a,\,4}$ = 10 Hz, H_{3a}), 2.80 (dd, 1 H, $J_{3e,\,3a}$ = 14, $J_{3e,\,4}$ = 5 Hz, H_{3e}), 3.88 (s, 3 H, $COOCH_3$), 4.07 (dd, 1 H, $J_{9,8}$ = 6, $J_{9,9'}$ = 12.5 Hz, H_9), 4.24 (t, 1 H, $J_{5,6} = J_{5,4}$ = 10 HZ, H_5), 4.39 (dd, 1 H, $J_{6,5}$ = 10, $J_{6,7}$ = 2.5 Hz, H_6), 4.43 (dd, 1 H, $J_{9',8}$ = 3, $J_{9,9'}$ = 12.5 Hz, $H_{9'}$), 5.18 (dt, 1 H, $J_{8,9'}$ = 3, $J_{8,9}$ = 6, $J_{8,7}$ = 6 Hz, H_8), 5.41 (dt, 1 H, $J_{4,3a}$ = 10, $J_{4,3e}$ = 5, $J_{4,5}$ = 10 Hz, H_4), 5.49 (dd, 1 H, $J_{6,7}$ = 2.5, $J_{7,8}$ = 6 Hz, H_7), 5.53 (d, 1 H, $J_{5,NH}$ = 10 Hz, NH).

General procedures for the preparation of alkyl α-glycosides (5) and (6). - A solution of sodium alcoholate in the corresponding alcohol (3 mL, 0.2 M) was added to a stirred solution of compound **3** (156 mg, 0.3 mmol) in the same alcohol (3 mL). After 1 h at room temperature, the mixture was made neutral with Dowex 50(H^+), filtered and concentrated. Flash chromatography (AcOEt - MeOH, 8:2) afforded pure α- glycosides.

Methyl (Methyl 5-Acetamido-3,5-dideoxy-α-D-*glycero*-D-*galacto*-2-nonulopyranosid)onate (5). 152 mg (98%), mp 169 °C (MeOH-AcOEt-Et_2O), $[\alpha]_D$ -6.5° (*c* 0.4, MeOH). [lit.[4] mp 166-168 °C (MeOH-Et_2O), $[\alpha]_D$ -5.2° (*c* 0.52, MeOH)].

Ethyl (Ethyl 5-Acetamido-3,5-dideoxy-α-D-*glycero*-D-*galacto*-2-nonulopyranosid)onate (6). 138 mg (87%), mp 106 °C (MeOH-AcOEt-Et_2O), $[\alpha]_D$ -18° (*c* 0.52, H_2O); ^1H NMR (D_2O) δ 1.20 (t, 3 H, J = 8 Hz, OCH_2CH_3), 1.35 (t, 3 H, J = 8 Hz, $COOCH_2CH_3$), 1.81 (dd, 1 H, $J_{3a,4}$ = 11.5, $J_{3a,3e}$ = 12 Hz, H_{3a}), 2.05 (s, 3H, NHAc), 2.73 (dd, 1 H, $J_{3e,3a}$ = 12, $J_{3e,4}$ = 4.5 Hz, H_{3e}), 3.44-3.94 (m, 9 H), 4.37 (q, J = 8 Hz, $COOCH_2CH_3$).

Anal. Calcd for $C_{15}H_{27}NO_9$: C, 49.31; H, 7.45; N, 3.83; O, 39.41. Found : C, 49.11; H, 7.26; N, 3.72; O, 39.61.

Methyl (Ethyl 5-Acetamido-4,7,8,9-tetra-*O*-acetyl-3,5-dideoxy-2-thio-α-D-*glycero*-D-*galacto*-2-nonulopyranosid)onate (7). - A solution of sodium ethanethiolate in ethanethiol (3 mL, 0.26 M) was added to a stirred solution of compound **3** (130 mg, 0.255 mmol) in ethanethiol (3 mL). After 1 h at room temperature, the reaction mixture was treated with Dowex 50 (H^+), filtered and concentrated. Flash chromatography [hexane-AcOEt (1:9)] of the residue gave the thio-glycoside **7** (130 mg, 95%) : mp 70 °C (benzene) $[\alpha]_D$ +21° (*c* 1, $CHCl_3$); [lit.[9] mp 80 °C (softening at 65 °C) (benzene-hexane), $[\alpha]_D$ +21° (*c* 1, $CHCl_3$)]; ^1H NMR (C_6D_6) as described in ref. 9.

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1. This work was presented at the French Carbohydrate Group Meeting (the First Mediterranean Conference on Carbohydrates), May 21-23, 1990, Avignon, France.

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12. The compound **2** was prepared following literature procedure[3b] from *N*-Acetyl neuraminic acid **1** available in multigram scale quantity by the enzymatic method.[13]

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