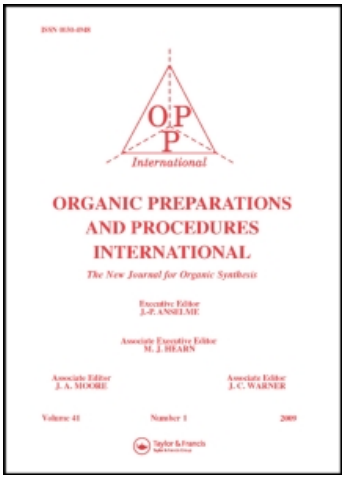

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A SYNTHESIS OF 4-α-GUANIDINO-2-DEOXY-2,3-DIDEHYDRO N-ACETYLNEURAMINIC ACID

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A SYNTHESIS OF 4-α-GUANIDINO-2-DEOXY-2,3-DIDEHYDRO N-ACETYLNEURAMINIC ACID

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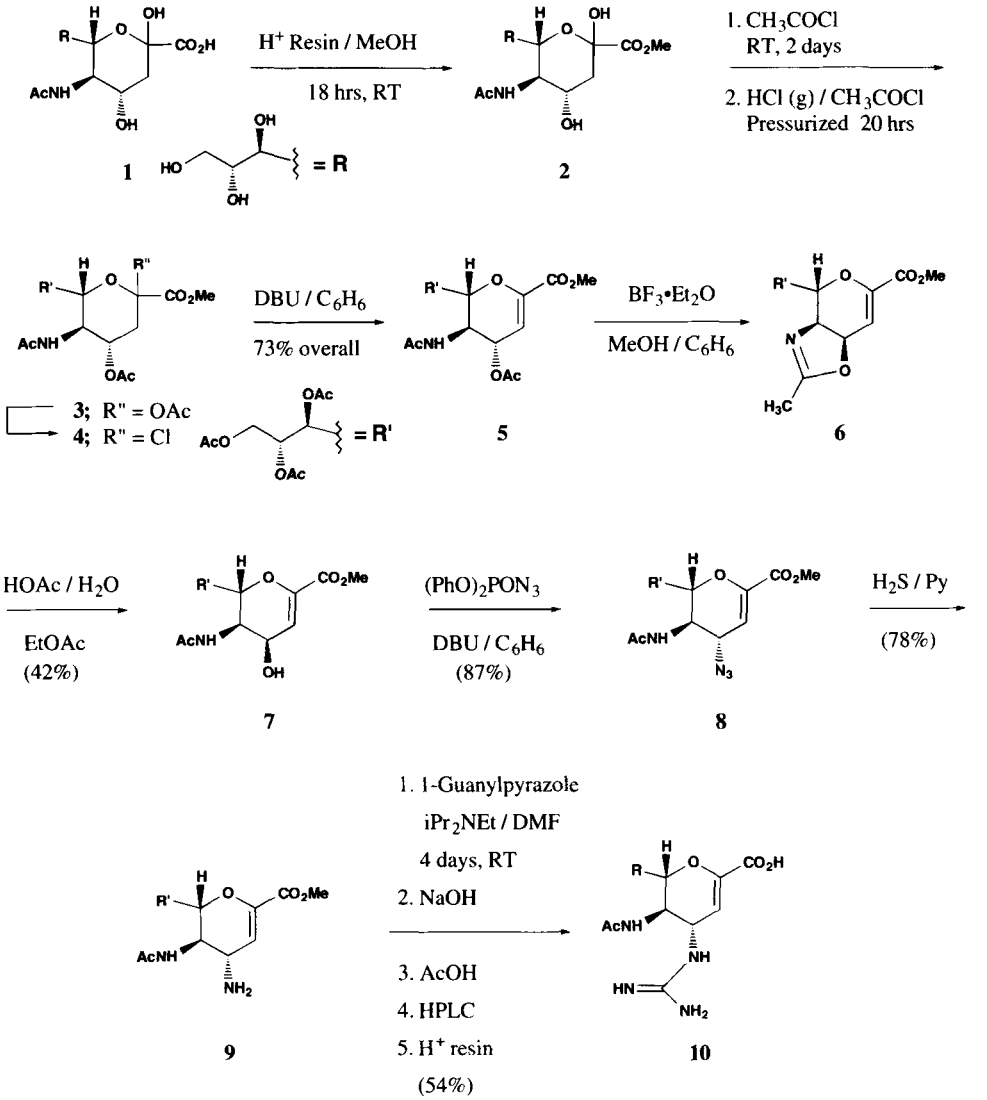
The 4-guanidino derivative **10** of N-acetylneuraminic acid has been shown to be a potent inhibitor of the sialidase derived from the influenza virus.[1] This activity has been demonstrated both *in vivo* and *in vitro* and therefore the compound is of considerable interest. All the routes[2,3] for the synthesis of **10** pass through the same intermediates; the major differences are the reproducibility of some steps, the reagents used and the yields. In our hands, the conversion of **2** to **5** was not reproducible. More recently, a short efficient method for the preparation of oxazolidine **6** from **3** in one step was reported by Zbiral.[4] Further into the synthesis, **6** was converted directly to **8** with high stereospecificity and yield[3] using azidotrimethylsilane to generate hydrazoic acid, a known explosive reagent that we wanted to avoid to use on a larger scale. The reduction of **8** to **9** is another "not easily reproducible" step and finally, the best deprotection and guanylation of **9** afforded **10** in 38% overall yield. We report here a more reproducible synthesis of intermediate **7**.

The sequence is not as concise as the method of Zbiral, but the intermediates are important for the synthesis of other compounds. We also report an alternative to the Mitsunobu reaction[5] which was used to introduce the 4α-azido group stereospecifically from the 4β-allylic alcohol derivative **7**. This is the first application of this methodology to glycals. Finally the C-4 amino sugar **9** was guanylated with 1-guanylpyrazole[6], and with subsequent hydrolysis improved the yield significantly over that reported.[2]

N-Acetylneuraminic acid **1** (NANA) was esterified[7] in dry methanol in the presence of a cation-exchange resin at room temperature. The 2-chloro derivative of acetylated NANA methyl ester **4** was synthesized by acetylating first using a modification of the method of Warner and O'Brien[8] and then displacing the 2-acetoxy substituent using chloride ion from HCl gas in a closed vessel under pressure by the method of Kuhn *et al.*[9]. Acetylation of the NANA methyl ester was carried out in acetyl chloride in a stoppered vessel for 2 days at room temperature. Analysis of the mixture by mass spectroscopy confirmed the presence of 2-chloro acetylated NANA methyl ester **4** with the major component being the intermediate pentaacetoxy compound **3**. Prolonging the reaction several more days did not change dramatically the amount of the pentaacetoxy intermediate remaining. To obtain a



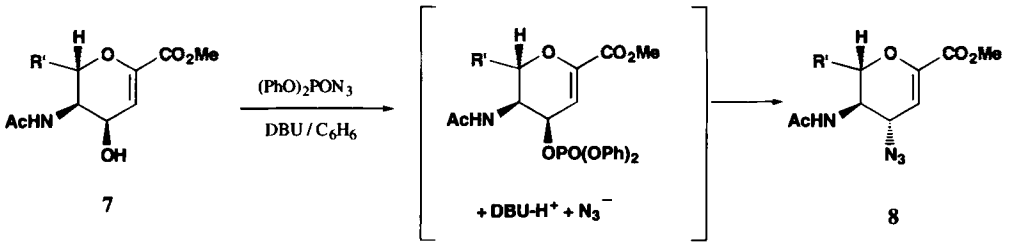
Scheme 1

high conversion to the 2-chloro compound **4** in a reasonable amount of time required saturating the acetylated mixture with HCl gas at -40° in acetyl chloride and reacting in a closed vessel at room temperature for 20 hours. Removal of the acetic acid generated in the chlorination step is crucial to obtain a good yield of the eliminated product methyl 4,7,8,9-tetra-O-acetyl-N-acetyl-2-deoxy-2,3-didehydro-D-neuraminate **5**. When compound **4** was treated under the elimination conditions in the presence of residual acetic acid, it underwent competitive displacement of chloride by acetate ion to give mixtures of acetate **3** and glycal **5**. The elimination reaction was carried out by treatment of **4** with 1,8-diazabicyclo[5.4.0]undecen-7-ene (DBU) in benzene[10] followed by a facile chromatography

on silica gel using ethyl acetate as eluent to obtain a 73% overall yield of α,β-unsaturated ester from NANA.

Epimerization of the 4α-center to the 4β-hydroxy compound **7** was effected through an oxazolidine intermediate.[2] Although the formation of the oxazolidine appeared to be clean by TLC using BF_3•Et_2O as the Lewis acid, the subsequent hydrolysis consistently gave only 40-45% yield after purification. The stereochemistry of the epimerized center was confirmed by acetylation of the 4β-hydroxy of compound **7** using acetic anhydride in pyridine and comparing the NMR spectrum to its epimer **5**.

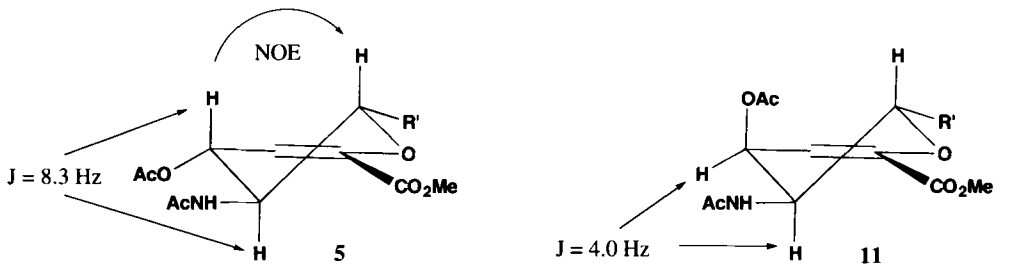
Our efforts to prepare the azide **8** from a sulfonate or mixed anhydride resulted mainly in decomposition. Applying a newly developed alternative[5] to the Mitsunobu type conditions, we successfully converted the optically active alcohol **7** to the inverted azide **8** in 87% yield, using diphenylphosphoryl azide (**Scheme 2**). This is the first time this method has been applied on a sugar and the reaction appears to be completely stereoselective. We could not detect the presence of the other isomer by examination of the reaction mixture by ^1H NMR after filtration through a silica plug. Reduction of the azide **8** with H_2S/pyridine[2] gave the amino compound **9** in 70-80% yields.



Scheme 2

Introduction of the guanidine to the 4-aminoneuraminate **9** required a guanylating reagent having a suitable reactivity. Initial studies with 3,5-dimethyl-1-guanylpyrazole nitrate or S-methylisothiouronium sulfate[11,2] were not very encouraging. The reported stability of the unsubstituted 1-guanylpyrazole[6] to self-condensation (57% in DMF after 64 hours at room temperature) and its apparent solubility made it attractive as a guanylating reagent. Reaction of 1-guanylpyrazole with compound **9** in DMF at room temperature for 4 days gave as determined by HPLC a ratio of 10/1 of product to starting material. Isolation including a HPLC purification gave 54% yield of compound **10**. As part of our overall scheme to optimize the reaction sequence, we attempted to guanylate the 4β-allylic alcohol **7** under Mitsunobu conditions using N,N^1-*bis*(*tert*-butyloxycarbonyl)guanidine[12] but were unsuccessful.

Vicinal coupling constants and NOEs confirmed the stereochemistry of some key intermediates (**Scheme 3**). In the case of the *trans* isomer **5**, a large J(4,5) = ca 8.3 Hz indicates a pseudo-*trans* relationship of these two protons and their substituents. Furthermore, NOE experiments clearly demonstrated that H-4 and H-6 share a 1,3-diaxial relationship. Irradiation of one resulted in a clear



Scheme 3

strong NOE in the other. In the case of the *trans* azide **8**, J(4,5) = 9.3 Hz. For the acetylated derivative of **7**, epimeric at C-4 compared with **5**, J(4,5)= 4.0 Hz and J(5,6) = 11.2 Hz.

EXPERIMENTAL SECTION

Melting points were measured in a Buchi 510 in open capillary tubes and are uncorrected. NMR spectra were obtained on Bruker ARX 400 or AMX 500 spectrometers using TMS as an internal standard. In the ^{13}C NMR a number in parenthesis after a chemical shift indicates the number of carbons at the same frequency. High resolution mass spectra were recorded in a VG Instruments ZAB-HF spectrometer at The Biomedical Mass Spectrometry Unit at McGill University, Montreal, Quebec. The samples were dissolved in glycerol and run using FAB mode. The masses of the ions of interest were manually peak matched against glycerol ion clusters whose exact masses were known and usually selected to be within 10% of the ions of interest. Analytical thin-layer chromatography (TLC) was routinely monitored on pre-coated Analtech glass sheets (Silica Gel GF, 0.25 mm thick) and detection was effected using an 8% cerium molybdate solution in 15% sulfuric acid. N-Acetyl neuraminic acid was purchased from Sigma Chemical Co and the cation resin Dowex 50W-X8 was obtained from Bio-Rad Laboratories.

Methyl N-Acetyl-4,7,8,9-tetra-O-acetyl-2-chloro-2-deoxy-D-neuraminate (4).- Compound **2**[7] (2.5 g, 7.7 mmol) was stirred with acetyl chloride (150 mL) in a stoppered flask at room temperature for 42 hrs. The solution was evaporated to dryness, the residue redissolved in acetyl chloride (40 mL) and transferred to a pressure tube. The contents were cooled to -42° using dry ice in acetonitrile and then saturated with HCl gas at that temperature. The tube was closed and maintained at room temperature for 20 hrs. After recooling to -42°, the tube was opened and the contents carefully transferred to a round bottom flask using some dichloromethane to rinse. The solution was evaporated to dryness and then the residue co-evaporated three times with *n*-heptane and once with toluene and benzene to completely drive off the acetic acid formed in the reaction. The crude weight of the yellow oil after pumping was 4.0g; it was used as such in the next step.

Methyl 4,7,8,9-Tetra-O-acetyl-N-acetyl-2-deoxy-2,3-didehydro-D-neuraminate (5).- To a stirred solution of compound **4** (4.0 g, 8.0 mmol) in benzene (50 mL) under nitrogen atmosphere and at room temperature was added 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) (0.7 mL, 4.7 mmol). After 1 hour, another 0.7 mL of DBU was added followed by a 0.3 mL portion after 2 hours for a total of 1.7 mL

(11.43 mmol) DBU. The reaction was followed by HPLC using a Zorbax Sil 21.2 mm x 25 cm column and eluting with ethyl acetate (the flow rate was 20 mL/min. and detection was done by refractive index). The starting chloro compound **4** eluted at 5.02 minutes and the eliminated product **5** at 5.31 minutes. The total mixture was chromatographed on a silica gel column and elution with ethyl acetate (R_f 0.5) yielded pure compound **5** as a foam (2.8g, 73% overall from N-acetylneuraminic acid) which was virtually identical by ^1H NMR spectroscopy to that previously reported.[10] ^1H NMR (500 MHz, $(CD_3)_2CO$): δ 7.39 (m, 1H), 6.08 (d, 1H, J = 5.6 Hz, H-3), 5.51 (dd, 1H, J = 2.0, 5.8 Hz, H-7), 5.32 (ddd, 1H, J = 12.3, 6.9, 5.8 Hz, H-8), 5.22 (dd, 1H, J = 4.0, 5.6 Hz, H-4), 4.60 (dd, 1H, J = 12.3, 12.3 Hz, H-9), 4.49 (ddd, 1H, J = 11.2, 4.0, 9.5, Hz, H-5), 4.37 (dd, 1H, J = 5.8, 2.0 Hz, H-6), 4.15 (dd, 1H, J = 12.3, 12.3 Hz, H-9^1), 3.76 (s, 3H, CO_2CH_3), 2.04, 2.02, 1.99, 198, 1.80 (s, 5 X 3 H, acetyl). ^{13}C NMR (500 MHz, $(CD_3)_2CO$): δ 170.6, 170.4, 170.3, 170.1, 170.0, 162.4, 147.2, 107.0, 74.4, 71.4, 68.5, 64.7, 62.7, 52.6, 45.6, 22.8, 20.7 (3), 20.6. HRMS: exact mass calcd for $C_{20}H_{28}NO_{12}$ 474.1611, found 474.1612.

Methyl 7,8,9-Tri-O-acetyl-N-acetyl-2-deoxy-2,3-didehydro-4ß-hydroxy-D-neuraminate (7).- A solution of compound **5** (2.0 g, 4.2 mmol) in benzene (80 mL) and methanol (0.5 mL) was cooled to 5° under nitrogen atmosphere. Boron trifluoride etherate (6.5 mL, 52 mmol) was added dropwise and the mixture stirred at room temperature for 18 hours. The reaction mixture was diluted with 250 mL of ethyl acetate and stirred to dissolve up all the gum which had formed on the side wall. The mixture was poured into excess 25% NH_4OAc solution. The layers were separated and the aqueous layer re-extracted with ethyl acetate (150 mL). The combined organic layers were evaporated and the intermediate oxazolidine compound **6** was observed on TLC at R_f 0.7 using ethyl acetate as the eluent. It was hydrolysed without purification. The crude material was redissolved in ethyl acetate (12 mL) and 50% acetic acid/H_2O (1 mL) added. After stirring at room temperature overnight two major, close eluting components were observed by TLC using ethyl acetate as the eluent of which the desired product was the more polar one at R_f 0.3. The less polar component was in fact a mixture of decomposition products. The mixture was diluted with more ethyl acetate (25 mL) and neutralized with $NaHCO_3$ solution. The organic layer was separated, dried (Na_2SO_4), filtered and evaporated. The product was purified by HPLC on a preparative Zorbax Sil column 21.2 mm x 25 cm eluting with ethyl acetate. The flow rate was 20 mL/min and detection was done by refractive index. Pure compound **7** (760 mg, 42%) was obtained as a foam which was virtually identical by ^1H NMR spectroscopy to that previously reported.[4] ^1H NMR (500 MHz, $(CD_3)_2CO$): δ 7.12 (m, 1H,HN), 6.08 (d, 1H, J = 5.9 Hz, H-3), 5.475 (dd, 1H, J = 1.5, 5.9 Hz, H-4), 5.325 (ddd, 1H, J = 2.9, 5.9, 8.8 Hz), 4.69 (d, 1H, J = 5.5 Hz), 4.57 (dd, 1H, J = 2.9, 12.1 Hz), 4.26 (m, 2H), 4.12 (m, 2H), 3.74 (s, 3H, CO_2CH_3), 2.02, 1.975, 1.97, 1.85 (s, 4x3H, acetyl). ^{13}C NMR (500 MHz, $(CD_3)_2CO$): δ 170.8, 170.4, 170.1, 170.0, 163.0, 145.4, 111.7, 73.7, 71.5, 69.0, 63.0, 61.8, 52.5, 47.8, 23.0, 20.9, 20.7, 20.6. HRMS: exact mass calcd for $C_{18}H_{26}NO_{11}$ 432.1505, found 432.1504.

Methyl 7,8,9-Tri-O-acetyl-N-acetyl-2-deoxy-2,3-didehydro-4α-azido-D-neuraminate (8).- A mixture of alcohol **7** (760 mg, 1.7 mmol) and diphenylphosphoryl azide (580 mg, 2.1 mmol) were

dissolved in dry benzene (20 mL). The mixture was cooled to 5° and DBU (320 mg, 2.1 mmol) was added under nitrogen. After stirring for 5 hours at room temperature, additonal amounts of diphenylphosphoryl azide (116 mg, 0.42 mmol) and DBU (64 mg, 0.42 mmol) were added and stirring was continued for 18 hrs. To the mixture was added ethyl acetate (20 mL) and 1N HCl (20 mL). After stirring for a few minutes, the organic layer was separated, rewashed with 1 N HCl (10 mL), dried (Na_2SO_4), filtered, evaporated to dryness and purified by silica gel chromatography using ethyl acetate (R_f 0.7) as the eluent to afford 700 mg (87%) of compound **8** as a white foam which was virtually identical by ^1H NMR spectroscopy to that previously reported.[4] ^1H NMR (500 MH_3, $(CD_3)_2CO$): δ 7.43 (d, 1H, HN), 5.90 (d, 1H, J = 2.5 Hz, H-3), 5.51 (dd, 1H, J = 5.9, 3.7 Hz, H-7), 5.29 (ddd, 1H, J = 6.9, 5.9, 2.9 Hz, H-8), 4.53 (dd, 1H, J = 12.3, 2.9 Hz, H-9), 4.47 (dd, 1H, J = 10.3, 3.7 Hz, H-6), 4.38 (dd, 1H, J = 9.3, 2.5 Hz, H-4), 4.25 ("q", 1H, H-5), 4.12 (dd, 1H, J = 6.9, 12.3 Hz, H-9^1), 3.75 (s, 3H, CO_2CH_3), 2.05, 1.975, 1.97, 1.86 (s, 4x3M, acetyl). ^{13}C NMR (500 MHz, $(CD_3)_2CO$): δ 170.6, 170.43, 170.40, 170.1, 162.2, 146.3, 108.9, 77.5, 71.1, 68.3, 62.7, 60.1, 52.6, 47.9, 23.0, 20.8, 20.7, 20.6. HRMS: exact mass calcd for $C_{18}H_{25}N_4O_{10}$ 457.1570, found 457.1571.

Methyl 7,8,9-Tri-O-acetyl-n-acetyl-2-deoxy-2,3-didehydro-4α-amino-D-neuraminate (9).- H_2S gas was gently bubbled into a stirred mixture of the azide compound **8** (530 mg, 1.1 mmol) in dry pyridine (20 mL) at room temperature for 1.5 hours. The mixture was flushed with nitrogen for 10 minutes and then evaporated to dryness keeping the bath temperature below 40°. The residue was purified by silica gel chromatography using ethyl acetate/methanol/triethylamine 25/10/1 as the eluent (R_f 0.5) to afford 390 mg (78%) of compound **9** mp. 137-139° which was virtually comparable by ^1H NMR and ^{13}C NMR spectroscopy to that previously reported.[2] ^1H NMR (500 MHz, Tol-d_8/DMSO-d_6 at 374°K): δ 5.92 (d, 1H, J = 2.5 Hz, H-3), 5.61 (dd, 1H, J = 2.4, 4.6 Hz, H-7), 5.51 (ddd, 1H, J = 3.0, 4.5, 7.4 Hz, H-8), 4.82 (dd, 1H, J = 3.0, 12.3 Hz, H-9), 4.33 (dd, 1H, J = 7.4, 12.2 Hz, H-9^1), 4.28 (dd, 1H, J = 2.4, 10.0 Hz, H-6), 3.96 ("q", 1H, J = 9.5 Hz, H-5; not fully coalesced at 374°K), 3.50 (s, 3H, OMe), 3.44 (dd, 1H, J = 2.5, 8.9 Hz, H-4), 1.93, 1.83, 1.77 (s, 4x3H, acetyl). ^{13}C NMR (500 MHz, Tol-d_8/DMSO-d_6 at 295°K): δ 170.2 (2), 170.0, 169.9, 162.4, 143.6, 115.8, 77.9, 72.6, 68.9, 63.0, 51.8, 51.6, 50.7, 23.3, 20.9, 20.8, 20.7. HRMS: exact mass calcd for $C_{18}H_{27}N_2O_{10}$ 431.1665, found 431.1663.

4-α-Guanidino-N-acetyl-2-deoxy-2,3-didehydro-D-neuraminic Acid (10).- To a mixture of compound **9** (150 mg, 0.34 mmol) and 1H-pyrazole-1-carboximidine hydrochloride[6](150 mg, 1.02 mmol) in DMF (0.75 mL) was added diisopropylethylamine (182 μL, 1.02 mmol). The mixture was stirred at room temperature for 2 days and then subsequent amounts of the 1-guanylpyrazole (50 mg, 0.34 mmol) in DMF (0.2 mL) and diisopropylethylamine (60 μL, 0.34 mmol) were added on the second and third days. The reaction was followed by HPLC with direct injections of the mixture onto an analytical Porasil column (3.9 mm x 300 mm) using 25% H_2O/iso-PrOH plus 0.3% AcOH as eluent (the flow rate was 2.0 mL/min and detection was done by refractive index). The starting amine **9** eluted at 8.1 minutes and the guanidino compound **10** at 9.2 minutes. After 2 days the ratio of product to starting material was 4/1 and after 4 days it was 10/1. The mixture gave a strong positive

Sakaguchi reaction[11] indicating the presence of a guanidine group. Hydrolyses of the O-acetyls and methyl ester were effected by adding H_2O (3 mL), methanol (7.5 mL) and 10% NaOH (1 mL). The mixture was stirred at room temperature overnight and then neutralized to pH 7.5 with acetic acid and evaporated to reduce the bulk of the volume. The crude material was partially purified by adsorbing on Dowex 50W-X8(H^+) resin, washing with H_2O until neutral and eluting with 1.5N NH_4OH. The eluate after evaporating gave compound **10** (150 mg) as a mixture. This mixture was purified on a preparative μ Porasil column (19 mm x 300 mm) eluting with 25% H_2O/iso-PrOH plus 0.3% AcOH to obtain pure compound **10** as the acetate salt. The acetate salt was removed by another pass on the Dowex 50W-X8(H^+) resin and washed with H_2O until neutral. Elution with 1.5 N NH_4OH gave, after concentrating the eluate *in vacuo* and freeze drying, a foam, compound **10** (63 mg, 54%) as the free base, mp. 235° (dec) was virtually comparable by ^1H NMR and ^{13}C NMR spectroscopy to that previously reported.[2] ^1H NMR (500 MHz, D_2O): δ 5.63 (d, 1H, J = 2.3 Hz), 4.45 (dd, 1H, J = 2.2, 9.2 Hz), 4.38 (dd, 1H, J = 1.5, 10.7 Hz), 4.22 ("t", 1H, J[a] 9.9 Hz), 3.95 (ddd, 1H, J = 2.6, 5.9, 9.2 Hz), 3.90 (dd, 1H, J = 2.6, 11.8 Hz), 3.66 (m, 2H, H-6), 2.03 (s, 3H, acetyl). ^{13}C NMR (500 MHz, D_2O): δ 177.0, 171.7, 159.8, 151.7, 106.5, 77.9, 72.4, 70.8, 65.7, 53.8, 50.4, 24.6. HRMS: exact mass calcd for $C_{12}H_{21}N_4O_7$ 333.1410, found 333.1410.

Methyl 4b-Acetoxy-7,8,9-tri-O-acetyl-N-acetyl-2-deoxy-2,3-didehydro-D-neuraminate (11).- A mixture of the b-alcohol **7** (11 mg, 0.025 mmol) and acetic anhydride (25 μL) in dry pyridine (0.5 mL) was stirred at room temperature for 18 hours, evaporated to dryness and purified by silica gel chromatography using ethyl acetate (R_f 0.8) as eluent to afford compound **11** (11 mg) as an oil.

^1H NMR [500 MHz, $(CD_3)_2CO$]: δ 5.88 (d, 1H, J = 2.8 Hz, H-3), 5.53 (dd, 1H, J = 8.3, 2.8 Hz, H-4), 5.50 (dd, 1H, J = 2.9, 5.9 Hz, H-7), 5.32 (ddd, 1H, J = 2.9, 6.9, 5.9 Hz, H-8), 4.50 (dd, 1H, J = 12.2, 2.9 Hz, H-9), 4.50 (dd, 1H, J = 6.0, 2.9 Hz, H-6), 4.33 (dd, 1H, J = 6.0, 8.3 Hz, H-5), 4.14 (dd, 1H, J = 12.2, 6.9 Hz, H-9[1]), 3.74 (s, 3H, CO_2CH_3), 2.05, 2.00, 1.99, 1.97, 1.80 (s, 5x3H, acetyl). ^{13}C NMR [500 MHz, $(CD_3)_2CO$]: δ 170.9, 170.6, 170.3, 170.2, 170.0, 162.3, 146.2, 109.2, 77.5, 70.8, 69.8, 68.3, 62.7, 52.5, 47.0, 22.9, 20.7 (3), 20.6.

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