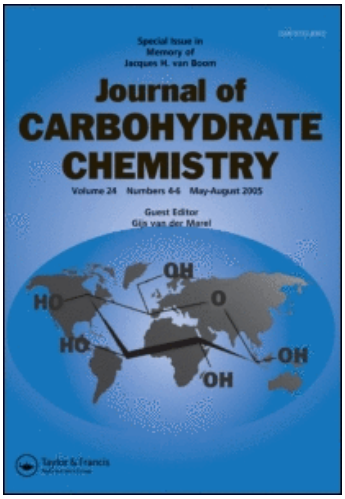

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A General Method for the Modification of the 9-Position of *N*-Acetyl-neuraminic Acid (NANA) and the Synthesis of Its 9-Fluoroanalogue

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Communication

A GENERAL METHOD FOR THE MODIFICATION OF THE 9-POSITION OF N-ACETYLNEURAMINIC ACID (NANA) AND THE SYNTHESIS OF ITS 9-FLUOROANALOGUE

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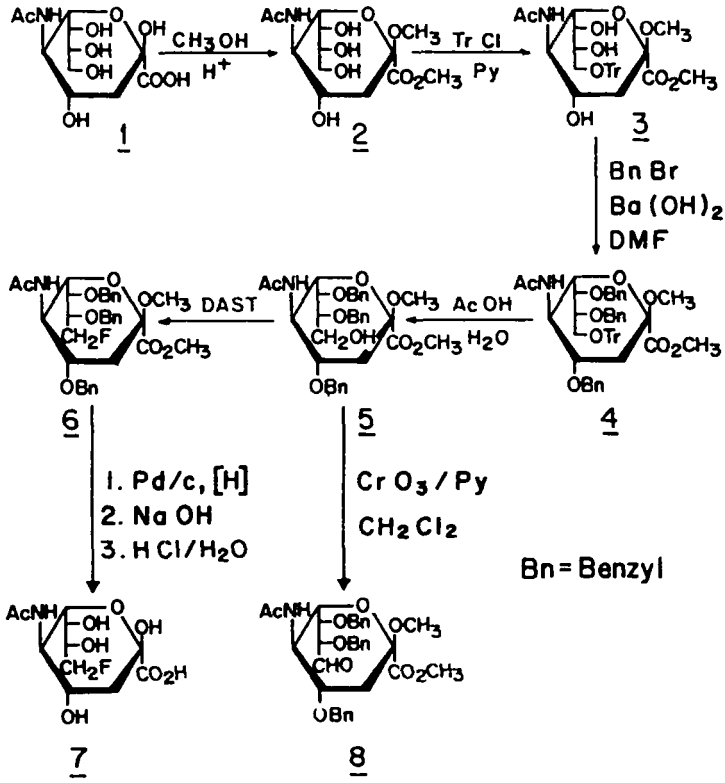
Analogs of N-acetylneuraminic acid (1, NANA) are of considerable interest as potential modifiers of cell surface sialic acid. NANA is greatly responsible for the negative charge on cell surface, and plays an important role in cell-to-cell interactions, immunogenic properties, and metastasis.[1] Considerable difficulty has been encountered in the development of approaches for the modification of this molecule.[2] The only fluorinated sialic acid which has been reported is N-acetyl-3-fluoro-neuraminic acid, a compound which was obtained in only 1% yield.[3] A systematic approach to the introduction of protecting groups into NANA, a process which would make specific groups amenable for modification, has not been explored. In this communication we

report a successful application of a protection-deprotection approach (Scheme 1) to the synthesis of N-acetyl-9-deoxy-9-fluoroneuraminic acid (7).

Esterification of the carboxylic acid group in 1 and simultaneous formation of the methyl glycoside (Scheme 1) were accomplished in one step by refluxing 1 with methanol in the presence of dry Dowex-50W(H^+) resin to give 2. Compound 2 was tritylated without further purification to give 3 (mp 138-140°C; 72% yield from 1). Benzylation of 3 in DMF with benzyl bromide in the presence of barium oxide and hydroxide was accompanied by some saponification of the methyl ester group; hence the crude



Scheme 1

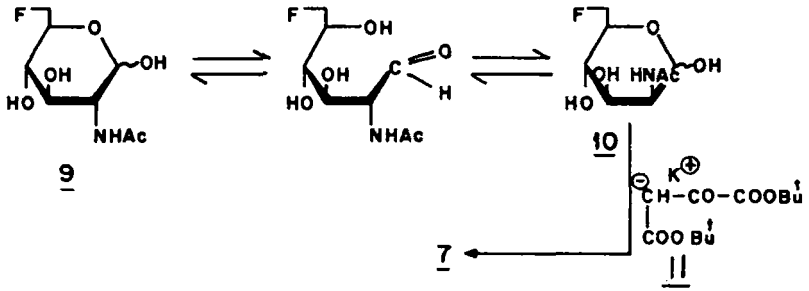
benzylation product was treated with diazomethane in ether to give 71% of 4 (mp 135-137°C). Detritylation was affected by heating 4 with aqueous acetic acid at 90-110°C (2 h) to provide the key intermediate 5 (mp 57°C).

Protection of 3 by acetyl groups also has been explored. Acetylation of 3 (Ac_2O/pyridine) gave the corresponding acetyl derivative; however, detritylation of the latter resulted in acetyl migration. Hence the acetyl group was not suitable as a protecting group.

Treatment of 5 with diethylaminosulfur trifluoride (DAST)[4] in methylene chloride at -10 to 0° for 3 h gave the fully protected 9-deoxy-9-fluoro derivative 6 (58.5%). Debenzylation of 6 was achieved by hydrogenolysis. Saponification (NaOH) and treatment with acid (HCl) gave the target compound 7 [mp 141°C, $[\alpha]^{25}$ - 47.6° (c1.0 H_2O)], which was characterized by ^{13}C and ^{19}F NMR spectroscopy: ^{13}C NMR (D_2O/TMS ext.): δ 23.34 (CH_3), 39.10 (C-3), 53.24 (C-5), 67.83 (C-4), 68.50 (C-7, $J_{C-7,F-9}$ = 7.20 Hz)69.90 (C-8, $J_{C-8,F-9}$ = 17.80 Hz), 71.47 (C-6), 86.40 (C-9, $J_{C-9,F-9}$ = 164.9 Hz), 96.42 (C-2), 174.18 (C=O), 175.50 (C-1); ^{19}F NMR (D_2O/$CFCl_3$ (Ext.)) δ-235.4 (Sextet, $J_{F-9,H-9'} = J_{F9,H-9}$ = 46.8 Hz, $J_{F-9,H-8}$ = 26.0 Hz)

Compound 5 has been oxidized to the aldehyde 8 (mp 64°C) using chromium oxide-pyridine complex. This aldehyde (8) is another key intermediate for further modifications.

An alternative method for the synthesis of 7, which is an adaptation of that developed by Kuhn and Baschang[5] for the synthesis of NANA (1), is shown in Scheme 2.[6] 2-Acetamido-2,6-dideoxy-6-fluoro-D-glucopyranose (9) was synthesized by an improved method[4b] and was shown by ^{13}C NMR spectroscopy to be converted at pH 11 to a mixture of the gluco (80%) 9 and manno (20%) 10 epimers. Condensation of 9 with 11 gave a condensation product from which 7 was obtained by hydrolysis (21% yield) and was shown to be identical to that obtained from the protection-de-



Scheme 2

protection method (Scheme 1). Compound 7 was a good substrate of cytidine monophosphate-sialic acid synthetase, giving rise to CMP-9-fluoro-NANA. Elemental analyses of all compounds reported in this communication were satisfactory.

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