Directed Stereoselective Synthesis of α- and β-*N*-Acetyl Neuraminic Acid–Galactose Disaccharides Using 2-Chloro and 2-Fluoro Derivatives of Neuraminic Acid Allyl Ester

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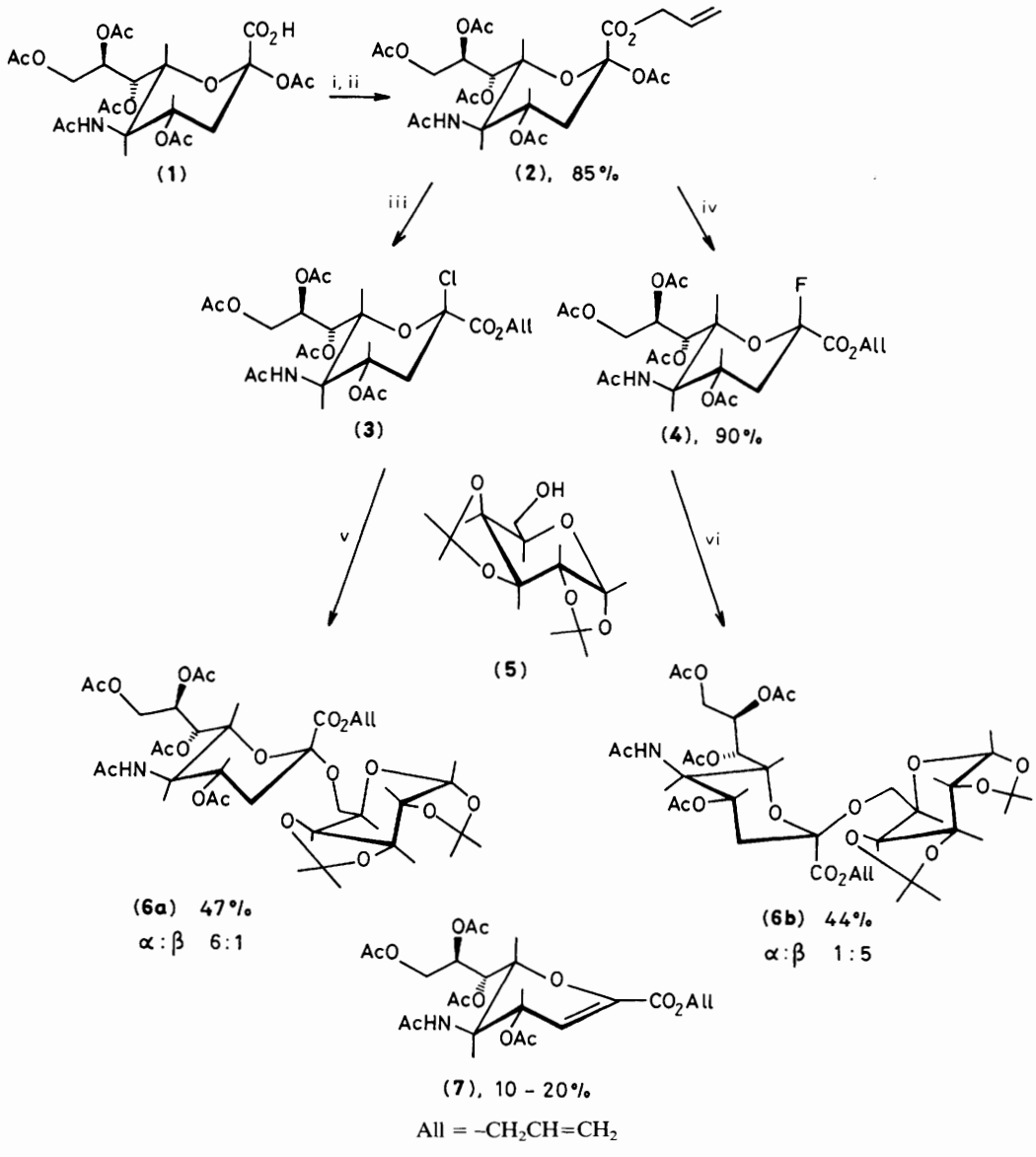
N-Acetyl neuraminic acid (carboxy-protected as the allyl ester) is converted stereoselectively into the 2,6-disaccharide with the α- or β-configuration with 1,2 : 3,4-di-isopropylidenegalactose starting from its acetyl-protected 2-chloro or 2-fluoro derivative; the advantages of the allyl protecting function are briefly discussed.

Sialic acids frequently terminate oligosaccharide side chains of glycoproteins and glycolipids. In this position they have been found to mask recognition structures of the glycoconjugates.[1] Therefore, synthetic glycosides and saccharides of neuraminic acid are of outstanding immunological interest since they offer possibilities of model studies of biological recognition and of processes of infection.[2]

The difficulties in stereoselective synthesis of neuraminic acid glycosides arise from the polyfunctional structure, the carboxylic function adjacent to the anomeric C-2, and the failure of neighbouring group support. Thus, it is only recently that neuraminic acid glycoside and disaccharide syntheses have been successfully carried out generally starting from the unstable 2-chloro or 2-bromo derivative of the peracetylated neuraminic acid methyl ester.[3] The use of the methyl ester, which is only cleavable under basic conditions, seems to be unsuitable, owing to the particular base sensitivity of the *O*-glycoproteins.[4] We therefore now report the carboxy



Scheme 1. *Reagents:* i, Cs_2-CO_3; ii, allyl bromide, dimethylformamide, room temp., 24 h; iii, HCl, AcCl, room temp., 24 h; iv, HF, pyridine, 0 °C, 1 h; v, Ag_2CO_3, Drierite, − 40 °C; vi, 6 equiv. BF_3–Et_2O, molecular sieve 4Å, room temp., 1 h.

protection of the neuraminic acid using the allyl ester which is quantitatively removable under mild and almost neutral conditions.[5] Peracetylated neuraminic acid caesium salt is allylated (see Scheme 1) in high yield, forming the 2,4,7,8,9-penta-*O*-acetyl-*N*-acetyl-neuraminic acid allyl ester (**2**). As shown in Scheme 1, (**2**) can be converted into the rather unstable β-2-chloro derivative (**3**) (which was not isolated) using acetyl chloride–hydrogen chloride, or alternatively in high yield into the stable β-2-fluoro-neuraminic acid allyl ester derivative (**4**),† by treatment with hydrogen fluoride–pyridine.[6] Both these reactions illustrate the stability to acid of the allyl ester protection.

The neuraminyl halides (**3**) and (**4**) open up synthetic routes to disaccharides involving acetal protected galactose (**5**) in a directed manner with respect to anomeric preference. Thus, using silver carbonate–Drierite in dichloromethane–toluene[3c] at low temperature the 2-chloro derivative yields the disaccharide (**6a**) with the α-configuration with high selectivity (α:β 6:1), while, in contrast, the 2-fluoro derivative (**4**) activated by boron trifluoride–diethyl ether in dichloromethane[7] reacts with (**5**) to form preferentially (α:β 1:5) the disaccharide (**6b**) with the β-configuration. As demonstrated earlier, this glycosylation conserves the acetal protection.[7a] The structural assignments and the composition of the anomeric mixtures (**6a**)–(**6b**) were determined by high-field n.m.r. spectroscopy‡ with reference to the corresponding data

† 84.67 MHz ^{19}F n.m.r. spectrum ($CDCl_3$, reference PhF): δ 3.26 p.p.m. [dd, J(F,3-H_{ax}) 33.82, J(F,3-H_{eq} 6.62 Hz]; $[\alpha]_D^{22}$ −21.4° (*c* 0.25, $CHCl_3$).

‡ 400 MHz ^1H n.m.r. spectra (C_6D_6): α-anomer (**6a**) δ 5.51 (d, J 5 Hz, 1-H), 4.88 [ddd, J(4′, 3*ax*) 12.5, J(4′, 3*eq*) 4.9, J(4′, 5′) 10.2 Hz, 4′-H], and 2.85 [dd, J(3′*eq*, 3′*ax*) 12.8 Hz, 3′-H_{eq}]; β-anomer (**6b**): δ 5.45 (d, J 5 Hz, 1-H), 5.40 [ddd, J(4′, 3′*ax*) 12.0, J (4′, 3′*eq*) 4.9, J(4′, 5′) 10.2 Hz, 4′-H], and 2.65 [dd, J(3′*eq*, 3′*ax*) 12.8 Hz, 3′-*eq*]; 100.6 MHz ^{13}C n.m.r. (C_6D_6): α-anomer: δ 118.8 (CH=*C*H_2), 109.3, 108.4 (*C*Me_2), 99.5 (C-2′), and 49.4 (C-5′); β-anomer: δ 118.9 (CH=*C*H_2), 109.7, 108.5 (*C*Me_2), 99.7 (C-2′), and 49.5 (C-5′).

of the analogous methyl ester derivatives described in the literature.[3] As is always observed in syntheses of neuraminic acid glycosides,[3] in both reactions the elimination product (**7**) is formed to an extent of 10—20%.

After chromatography on silica using light petroleum–acetone (2.2 : 1) as eluant the neuraminic acid disaccharides (**6**) were isolated in the overall yields from (**2**) or (**4**) respectively quoted in Scheme 1. The separated compound (**7**) was identified by its ^{1}H n.m.r. spectrum. By treatment of both anomeric mixtures (**6**) with tetrakis(triphenylphosphine)palladium(0) in tetrahydrofuran–morpholine[5] at room temperature for ~30 min the allyl ester protection is quantitatively removed without any side reaction. Furthermore, under the same conditions the peracetylated neuraminic acid allyl ester (**2**) having the better leaving group at the anomeric carbon atom quantitatively gives the carboxy deblocked compound (**1**) which is identical with the starting material in its physical data.

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