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A NEW APPROACH TO THE SYNTHESIS OF NEURAMINIC ACID ANALOGUES[1)]

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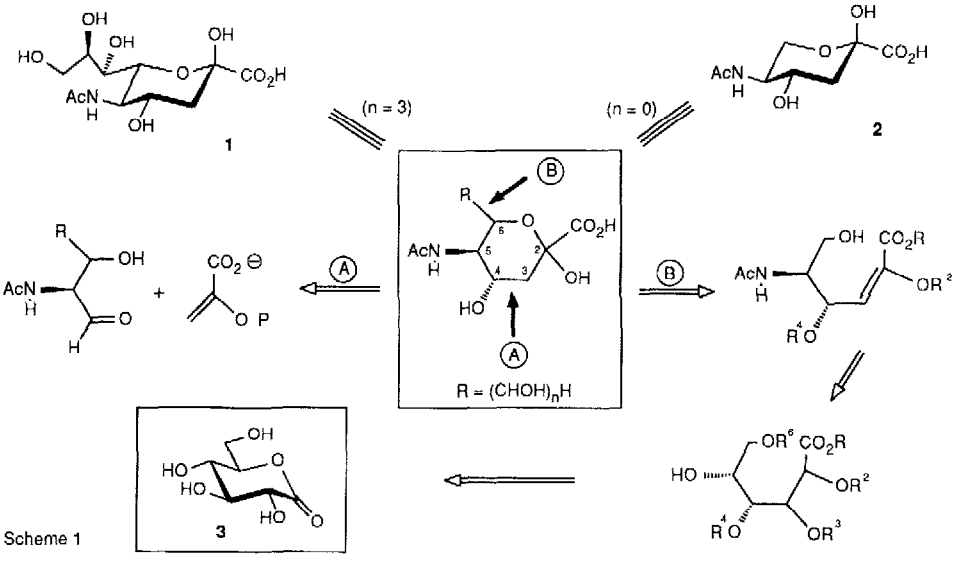
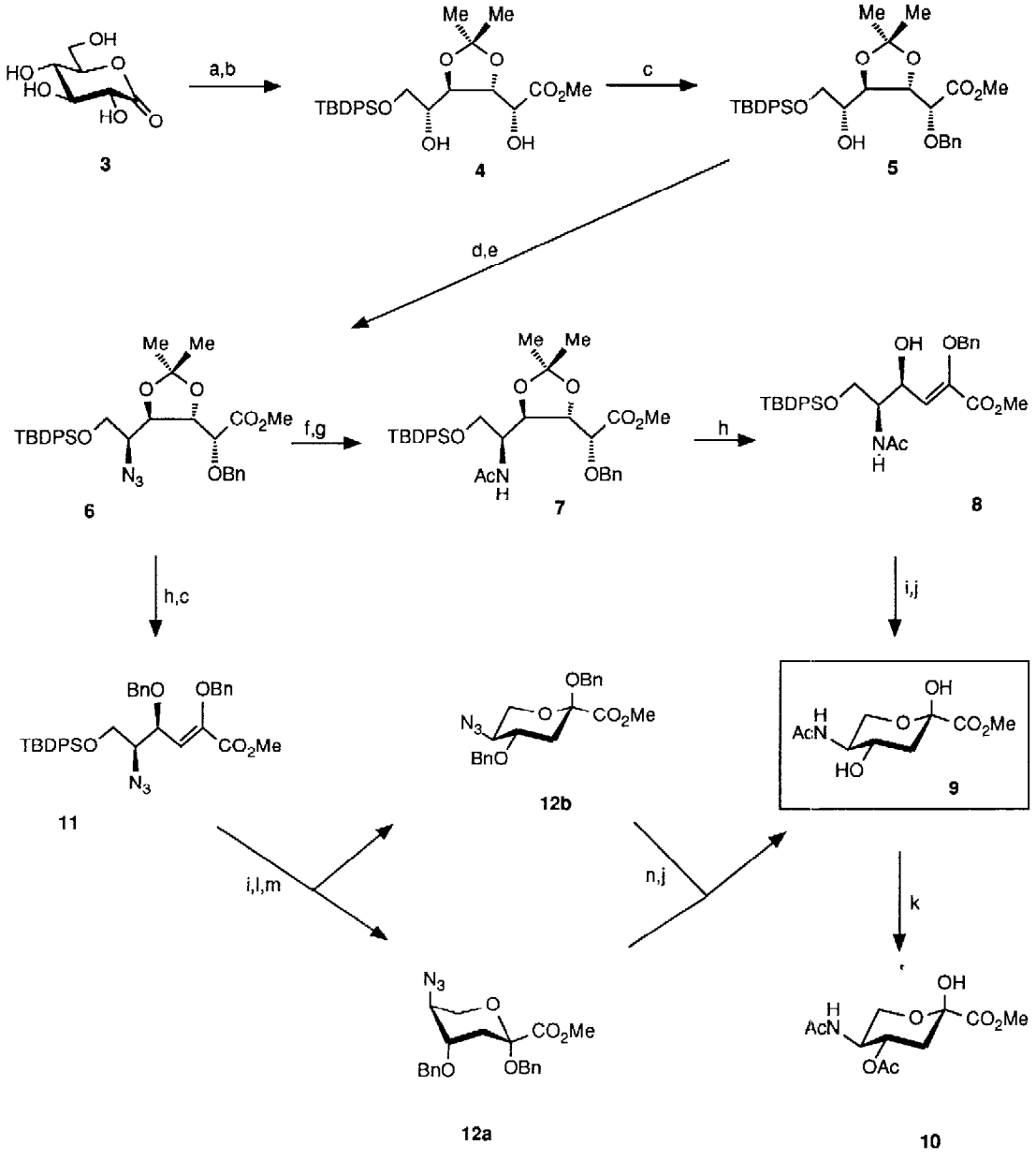
Abstract: 2-Alkoxy acrylate derivatives **8** and **11**, readily prepared from D-glucono-1,5-lactone by ring opening and β-elimination, are converted into neuraminic acid analogues **9** and **12** via debenzylation and spontaneous cyclization or ring closure via oxymercuration-demercuration, respectively.

N-Acetylneuraminic acid **1** (Scheme 1) is a constituent of many glycoconjugates, where it occupies the nonreducing ends of the oligosaccharide chains; it is involved in a great number of biologically important functions[2]. For gaining more insight into the structure-activity relationship of the enzymes involved in its metabolism (especially sialyltransferases and sialidases) various neuraminic acid analogues have been recently prepared[3]. Based on a versatile strategy the synthesis of analogues which lack the trihydroxypropyl-D-*erythro* side chain (N-acetyl-5-amino-3,5-dideoxy-L-*threo*-2-hexulosonates **2**) will be described in this paper.



Scheme 1



Scheme 2 (a) TBDPSCl, imidazole, DMF, RT (91 %); (b) 2,2-dimethoxypropane, MeCH, cat. p-TsOH·H_2O, RT (95 %); (c) BnBr, Ag_2O, MS 4Å, CH_2Cl_2, RT, (84 %); (d) trifluoromethanesulfonic anhydride, pyr., CH_2Cl_2, -30°C; (e) NaN_3, N,N,N'N'-tetramethylurea, DMF, RT (82 % from **5**); (f) 1,3-propanedithiol, Et_3N, MeOH, RT (92 %); (g) Ac_2O, Py, RT, quant.; (h) t-BuOK, THF, -78°C, (89 %); (i) $Et_3N \cdot 3HF$, MeOH; (j) H_2, 10 % Pd/C, EtOAc, RT; (k) Ac_2O, cat. $HClO_4$, (52 % from **9**); (l) $Hg(O_2CCF_3)_2$, THF, RT; (m) $NaBH_4$, pH = 8, (80 % from **11**); (n) AcSH, RT, 4 days (90 %).

The retrosynthetic scheme (Scheme 1) exhibits that in the cell (route A) a retroaldol reaction between C-3 and C-4 leads to the basic constituents, namely N-acetyl-D-mannosamine (C_6 unit) and the energyrich phosphoenol pyruvate (C_3 unit). Our strategy is based on a disconnection between C-6 and C-7 (route B); thus, for the basic frame commercially available D-glucono-1,5-lactone (or any other C-4/C-5-D-*erythro*-hexonolactone) is sufficient which necessitates only C-2/C-3 β-elimination and amino group introduction at the selectively accessible C-5 carbon atom. The side chain could be readily attached at the C-6 carbon atom.

The efficiency of this approach could be demonstrated in the selection and order of introduction of protective groups as well as in the convenient ring closure to the desired target molecule. Thus, the 2,5-O-unprotected ester **4** (Scheme 2) was obtained in high yield from lactone **3** via selective 6-O-silylation with *tert*-butyldiphenylsilyl chloride[4] (TBDPS-Cl) and subsequent 3,4-O-isopropylidenation with simultaneous ester formation. Treatment of a mixture of diol **4** (1 eq), Ag_2O (1.2 eq) and benzyl bromide (2.5 eq) in presence of M.S. (4 Å, 1 w eq) in anhydrous dichloromethane resulted in regioselective formation of 2-O-benzyl derivative **5** which was transformed via the trifluoromethanesulfonate with NaN_3 in presence of tetramethylurea[5] into azide **6**. Reduction of the azido group was performed with 1,3-propane-dithiol (6 eq) in presence of triethylamine (6 eq) and dry methanol[6]; N-acetylation with acetic anhydride/pyridine furnished in excellent yield the acetamido derivative **7**. The proton at C-2 of this compound is sufficiently acidic to undergo base abstraction and concomitant stereocontrolled 3-O-elimination with loss of the isopropylidene group[7]. Accordingly, when compound **7** was treated with t-BuOK (1.3 eq) in THF at -78°C for 30 min the 4-O-unprotected 2-benzyloxy-acrylate derivative **8** was isolated (which posseses according to ref.[7] Z-configuration). Removal of the silyl protective group in the presence of $Et_3N{\cdot}3HF$ (1 eq)[8] and subsequent hydrogenolytic debenzylation with palladium on carbon as catalyst in dry ethyl acetate led immediately to the desired ring closed 3-deoxy-2-hexulosonate derivative **9** which was transformed into the 4-O-acetyl compound **10** using the procedure of Kuhn et al.[9]. The ^{1}H-NMR data of **10** are in good agreement with related compounds[10].

Alternatively, azido derivative **6** was directly employed in base promoted 2,3-elimination reaction resulting in a 4-O-unprotected 2-benzyloxy-acrylate which gave upon O-benzylation compound **11** by applying the reagents and conditions as described above. After desilylation intramolecular oxymercuration with $Hg(O_2CCF_3)_2$[11] and *in situ* demercuration with $NaBH_4$ at pH 8 provided benzyl glycosides **12a/b** (82 %, 1:9). The $^5C_2$ and $^2C_5$ conformations are derived from the ^{1}H-NMR data (**12a**:$J_{3e,4}$ = 4.0, $J_{3a,4}$ = 6.2, $J_{4,5}$ = $J_{5,6e}$ = 5.0 Hz; **12b**: $J_{3e,4}$ = 4.8, $J_{3a,4}$ = 11.0, $J_{4,5}$ = 11.1 Hz). Thus, the preferred conformation is determined by the steric effect of the carboxylate group and the anomeric effect of the benzyloxy group. The mixture of **12a,b** was treated with thiolacetic acid[12] to provide the acetamido derivative which furnished upon hydrogenolytic debenzylation target molecule and upon O-acetylation **10**. The compounds were characterized by their ^{1}H-NMR data[13].

REFERENCES AND FOOTNOTES

1. This work was supported by the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie. I.V. is grateful for an Alexander von Humboldt Fellowship
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13. Selected physical data for compounds **4-12a,b** (Values of $[\alpha]_D$ and δ_H (250 MHz) were measured for solutions in $CHCl_3$ and $CDCl_3$ or * $CDCl_3$ and D_3COD): **4**: $[\alpha]_D^{22}$ + 2.1 (c 2.25); δ_H 1.08 [s, 9 H, $SiC(CH_3)_3$], 1.32, 1.37 [2s, 3 H each, $C(CH_3)_2$], 2.69 (d, $J_{5,OH}$ = 4.7 Hz, 1 H, O*H*), 3.09 (d, $J_{2,OH}$ = 9.2 Hz, 1 H, O*H*), 3.74-3.89 (m, 3 H, H-5, H-6', H-6''), 3.82 (s, 3 H, CO_2CH_3), 4.12 (d, $J_{3,4} = J_{4,5}$ = 7.9 Hz, 1 H, H-4), 4.29 (dd, $J_{2,3}$ = 1.6 Hz, 1 H, H-3), 4.30 (dd, 1 H, H-2), 7.26-7.68 (m, 10 H, aromatic H). **5**: $[\alpha]_D^{22}$ + 35.8 (c 3.3); δ_H 1.07 [s, 9 H, $SiC(CH_3)_3$], 1.30, 1.38 [2s, 3 H each, $C(CH_3)_2$], 2.41 (d, $J_{5,OH}$ = 6.6 IIz, 1 H, O*H*), 3.65 (m, 1 H, H-5), 3.69-3.85 (ABX, $J_{5,6A} = J_{6A,6B}$ = 5.3 Hz, $J_{5,6B}$ = 3.3 Hz, 2 H, H-6_A, H-6_B), 3.79 (s, 3 H, CO_2CH_3), 4.12 (dd, $J_{3,4} = J_{4,5}$ = 7.3 Hz, 1 H, H-4), 4.19 (d, $J_{2,3}$ = 2.8 Hz), 4.38 (dd, 1 H, H-3), 4.42-4.87 (AB, $J_{A,B}$ = 11.7 Hz, CH_2Ph), 7.22-7.69 (m, 15 H, aromatic H), **6**: $[\alpha]_D^{22}$ + 45.6 (c 1.95); δ_H 1.07 [s, 9 H, $SiC(CH_3)_3$], 1.33, 1.39 [2s, 3 H each, $C(CH_3)_2$], 3.31 (ddd, $J_{4,5}$ = 2.7 Hz, $J_{5,6A}$ = 8.3 Hz, $J_{5,6B}$ = 5.1 Hz, 1 H, H-5), 3.74-3.90 (ABX, $J_{6A,6B}$ = 10.3 Hz, 2 H, H-6_A, H-6_B), 3.76 (s, 3 H, CO_2CH_3), 4.03 (d, $J_{2,3}$ = 3.9 Hz, 1 H, H-2), 4.20 (dd, $J_{3,4}$ = 8.0 Hz, 1 H, H-4), 4.36 (dd, 1 H, H-3), 4.34-4.80 (AB, J_{AB} = 11.7 Hz, CH_2Ph), 7.25-7.70 (m, 15 H, aromatic H). **7**: Mp. 145-146°C (PE/Et_2O); $[\alpha]_D^{20}$ + 40.0 (c 1.80); δ_H 1.03 [s, 9 H, $SiC(CH_3)_3$], 1.39, 1.40 [2s, 3 H each, $C(CH_3)_2$], 1.92 (s, 3 H, Ac), 3.56-3.71 (ABX, $J_{6A,6B}$ = 9.8 Hz, $J_{5,6A}$ = 5.5 Hz, $J_{5,6B}$ = 7.7 Hz, 2 H, H-6_A, H-6_B), 3.78 (s, 3 H, CO_2CH_3), 4.06-4.16 (m, 3 H, H-2, H-3, H-5), 4.43-4.82 (AB, J_{AB} = 11.6 Hz, CH_2Ph), 4.57 (dd, $J_{2,3}$ = 1.2 Hz, $J_{3,4}$ = 8.7 Hz, 1 H, H-3), 5.70 (d, $J_{5,HN}$ = 9.4 Hz, 1 H, N*H*Ac), 7.24-7.69 (m, 15 H, aromatic H). **8**: Mp. 164-166°C (PE/Et_2O); $[\alpha]_{578}^{22}$ - 3.25 (c 2.4); δ_H 1.05 [s, 9 H, $SiC(CH_3)_3$], 1.89 (s, 3 H, Ac), 2.95 (broad. s, 1 H, O*H*), 3.62-3.75 (ABX, $J_{6A,6B}$ = 10.2 Hz, $J_{5,6A}$ = 4.3 Hz, $J_{5,6B}$ = 6.1 Hz, H-6_A, H-6_B), 3.80 (s, 3 H, CO_2CH_3), 3.91 (m, 1 H, H-5), 4.83 (dd, $J_{3,4}$ = 7.8 Hz, $J_{4,5}$ = 2.5 Hz, 1 H, H-4), 4.94 (s, 2 H, CH_2Ph), 5.92 (d, $J_{5,HN}$ = 8.8 Hz, 1 H, N*H*Ac), 6.22 (d, 1 H, H-3), 7.26-7.65 (m, 15 H, aromatic H). **10**: $[\alpha]_D^{25}$ -83.2 (c 2.1): δ^*_H 1.94 (s, 3 H, Ac), 2.06 (s, 3 H, Ac), 2.07 (dd, $J_{3a,3e}$ = 12.8 Hz, $J_{3a,4}$ = 10.8 Hz, 1 H, H-3a), 2.28 (dd, $J_{3e,4}$ = 5.0 Hz, H-3e), 3.70 (dd, $J_{5,6a} = J_{6a,6e}$ = 11.1 Hz, 1 H, H-6a), 3.82 (s, 3 H, CO_2CH_3), 3.89 (dd, $J_{5,6e}$ = 5.7 Hz, 1 H, H-6e), 4.11 (ddd, $J_{4,5}$ = 10.8 Hz, 1 H, H-5), 5.18 (ddd, 1 H, H-4). **12a**: $[\alpha]_D^{25}$ + 52.5 (c 1.0); δ_H: 2.20 (dd, $J_{3a,3e}$ = 14.3 Hz, $J_{3a,4}$ = 6.2 Hz), 2.37 (dd, $J_{3e,4}$ = 4.0 Hz), 3.56-3.71 (m, $J_{4,5} = J_{5,6e}$ = 5.0 Hz, 3 H, H-4, H-5, H-6a), 3.77 (s, 3 H, CO_2CH_3), 4.20 (dd, $J_{6a,6e}$ = 12.3 Hz, $J_{5,6e}$ = 3.0 Hz), 4.43-4.75 (2 AB, 4 H, 2 x CH_2Ph), 7.24-7.35 (m, 10 H, aromatic H). **12b**: $[\alpha]_D^{25}$ - 96.5 (c 2.45); δ_H 1.65 (dd, $J_{3a,3e}$ = 13.0 Hz, $J_{3a,4}$ = 11.0 Hz, 1 H, H-3a), 2.61 (dd, $J_{3e,4}$ = 4.8 Hz, 1 H, H-3e), 3.34 (dd, $J_{5,6a} = J_{6a,6e}$ = 11.1 Hz, 1 H, H-6a), 3.54 (ddd, $J_{5,6e}$ = 4.3 Hz, $J_{4,5}$ = 11.1 Hz, 1 H, H-5), 3.70 (s, 3 H, CO_2CH_3), 3.79-3.90 (m, 2 H, H-4, H-6e), 4.34-4.47 (AB, J_{AB} = 11.4 Hz, CH_2Ph), 4.49-4.60 (AB, J_{AB} = 11.2 Hz, CH_2Ph), 7.17-7.29 (m, 10 H, aromatic H).

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