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Highly Stereoselective Synthesis of α-Glycosides of Neuraminic Acid Analogues[1)]

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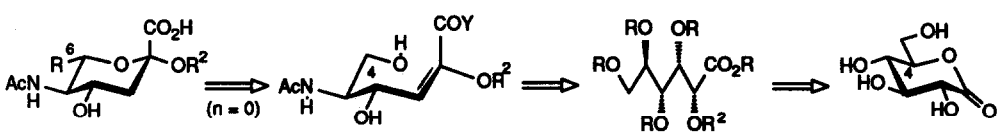
Abstract: ε-Hydroxy enol ether 6 was readily prepared from D-gluconolactone via ester formation and selective di-O-isopropylidenation, 2-O-alkylation with triflate 1. selective 5,6-de-O-isopropylidenation and 6-O-silylation, azide introduction, and subsequent E-specific β-elimination. NIS-induced cyclization of 6 at low temperature provided exclusively a-connected disaccharide 7, which was converted into neuraminic acid analogues 8, 10, and 11, respectively.

N-Acetylneuraminic acid (Neu5Ac, Scheme 1, A) is a constituent of many glycoconjugates, where it is found in a-connection at the nonreducing end of oligosaccharide chains. The great number of its biologically important function& is exhibited by interactions with the enzymes involved in its metabolism (especially sialyhransferases and sialidases). For understanding the structure-activity relationships of such substrate-enzyme complexes a series of Neu5Ac analogues has been recently prepared[3)]. In this paper we describe the highly stereoselective synthesis of a-glycosidically linked analogues, lacking the D-*erythro*-trihydroxypropyl-side chain (A, n = 0). which is based on an electrophile initiated cyclisation of ε-hydroxy enol ether intermediate B. Related approaches have been applied in the sugar series by Mukaiyama[4)] and by Sinaÿ[5)]; in these investigations the e-hydroxy enol ether precursors were obtained as E/Z-mixtures via a Wittig-Homer procedure, thus causing difficulties in the stereocontrol of glycoside bond formation.

Scheme 1

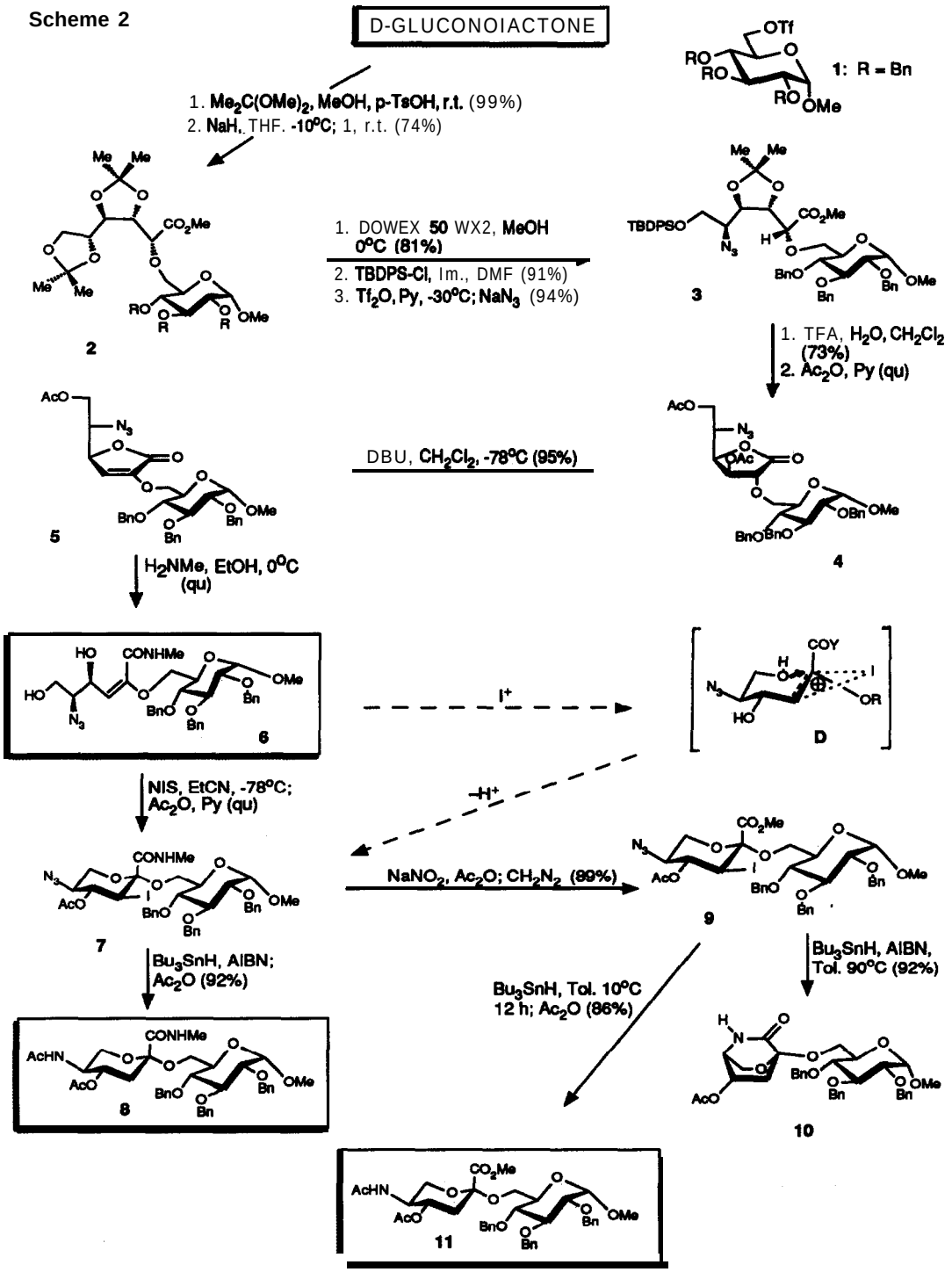


A [$R^6 = (CHOH)_nH$] B C (R = prot. group)

The efficiency of our strategy is based on the convenient formation of a 2-O-ether of gluconate (intermediate C), its efficent conversion to Ecnol ether B via E-specific g-elimination, and ensuing regio- and stereoselective ring closure resulting in the desired a-glycoside A.

The decisive starting material of type B could be readily obtained from Dgluconolactone (Scheme 2) via regioselective di-O-isopropylidenation with simultaneous methyl ester formation[6)], then alkylation of the OH-group at C-2 with the easily prepared methyl 2,3,4-tri-O-benzyl-6-O-trifluoromethansulfonyl-α-D-glucopyranoside[7)] (→2), acid catalyzed selective 5',6'-de-O-isopropylidenation, selective 6'-O-silylation with *tert*-butyldiphenyl chloride (TBDPS-Cl)[8)], and azido group introduction at the C-S atom, affording intermediate 3.

Scheme 2


D-GLUCONOIACTONE
1. $Me_2C(OMe)_2$, MeOH, p-TsOH, r.t. (99%)
2. NaH, THF. -10°C; 1, r.t. (74%)
1: R = Bn
1. DOWEX 50 WX2, MeOH 0°C (81%)
2. TBDPS-Cl, Im., DMF (91%)
3. Tf_2O, Py, -30°C; NaN_3 (94%)
1. TFA, H_2O, CH_2Cl_2 (73%)
2. Ac_2O, Py (qu)
DBU, CH_2Cl_2, -78°C (95%)
H_2NMe, EtOH, 0°C (qu)
I^+
$-H^+$
NIS, EtCN, -78°C; Ac_2O, Py (qu)
$NaNO_2$, Ac_2O; CH_2N_2 (89%)
Bu_3SnH, AIBN; Ac_2O (92%)
Bu_3SnH, AIBN, Tol. 90°C (92%)
Bu_3SnH, Tol. 10°C 12 h; Ac_2O (86%)
2
3
4
5
6
7
8
9
10
11
D

Treatment of3 with trifluoroacetic acid (TFA) in dichloromethane-water resulted in regioselective formation of *the* γ-lactone, *which upon* acetylation gave derivative 4. Treatment of 4 with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) as base led to abstraction of the proton at C-2' and concomitant 3'-O-elimination providing butenolide derivative 5. Removal of the acetyl protective group with methylamine resulted in simultaneous ring opening, thus affording the e-hydroxy enol ether 6 in quantitative yield

Compound 6 possesses the desired E-configuration[9] required for the ensuing highly regio- and a-stenoselective cyclization which could be induced by N-iodosuccinimlde (NIS) as electrophilic promoter at low temperature in a quantitative reaction. The $^2C_5$ conformation of a-glycoside 7 obtained via D as intermediate was derlved from the ^{1}H-NMR data ($J_{3',4'} = J_{4',5'}$ = 9.5 Hz; *trans*-diaxial relatlonships between H-3', H-4', H-S). Reduction of azido iodide 7 with Bu_3SnH in the presence of catalytic amounts of AIBN (toluene. 90°C, 30 min) and acetylation gave diamide 8. On the other hand, conversion of N-methyl amide 7 in methyl ester[10] 9 and subsequent treatment with Bu_3SnH/AIBN resulted in lactam 10, thus proofing the assignment of the a-configuration at C-2'[11]. Finally, when compound 9 was treated with Bu_3SnH at 10°C for 12 h and then with acetic anhydride the acetylated α-glycoside of D-hexulosonate 11 was isolated in high yield. The compounds were characterized by their ^{1}H-NMR data[12]. The results of a shnllar strategy for the highly stereoselective synthesis of β-glycosides will be reported[13].

REFERENCES AND NOTES

1. This work was support& by the Deutsche Forschungsgemeinsch and the Ponds der Chemischen Industrie. I.V. is grateful for an Alexander von Humboldt Fellowship.
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12. Selected physical data for compounds 2-11 [values of $[\alpha]_D$ and δ_H (250 MHz) were measured for solutions in $CHCl_3$ and $CDCl_3$]: 2 $[\alpha]_D^{22}$ +16.9 (c 4); δ_H 1.33, 1.35, 1.37, 1.39 [4s, 3 H each, 2 x $C(CH_3)_2$], 3.34 (s, 3 H, OCH_3), 3.47 (dd, $J_{1,2}$ = 3.4 Hz, $J_{2,3}$ = 9.8 Hz, 1 H, H-2), 3.64 (dd, $J_{3,4} = J_{4,5}$ = 9.9 Hz, 1 H, H-4), 3.73 (s, 3 H, CO_2CH_3), 3.90-4.34 (m, 10 H. H-3, H-5.2 x H-6, H-2'. H-3', H-4'. H-5' and 2 x H-6'). 4.60 (d. 1 H, H-l), 4.65-4.96 (m, 6 H, 3 x CH_2Ph), 7.25-7.36 (m, 15 H, aromatic H). 3: $[\alpha]_D^{22}$ +30.7 (c 2); δ_H 1.06 [s, 9 H, $SiC(CH_3)_3$], 1.31, 1.38 (2 s, 3 H each $(C(CH_3)_2$], 3.32 (s, 3 H, OCH_3), 3.48-3.58 (m, 4 H, H-2, H-4, H-5', 1 x H-6), 3.69 (s, 1 H, CO_2CH_3), 3.82-4.40 (m, 8 H, H-3, H-5, 1 x H-6, H-2'. H-3', H-4', 2 x H-6'). 4.53 (d, $J_{1,2}$ = 3.4 Hz, 1 H, H-l), 4.5G4.97 (m, 6 H, 3 x CH_2Ph), 7.23-7.70 (m, 25 H, aromatic H). 4: $[\alpha]_D^{22}$ +72.4 (c 2), δ_H 2.10, 2.11 (2 s, 3 H each 2 x Ac), 3.37 (s, 3 H, OCH_3), 3.51 (dd, $J_{1,2}$ = 3.5 Hz, $J_{2,3}$ = 9.6 Hz, 1 H, H-2). 3.57 (dd, $J_{3,4} = J_{4,5}$ = 9.5 Hz, 1 H, H-4), 3.71 (m, 2 H, H-5' and 1 x H-6') 3.89-4.28 (m, 5 H, H-3, H-5, 1 x H-6,2 x H-6'), 4.61-4.97 (m, 9 H, 3 x CH_2Ph, H-l, H-2' and H-4'), 5.40 (dd, $J_{2',3'} = J_{3',4'}$ = 7.2 Hz), 7.24-7.37 (m, 15 H, aromatic H). 5: $[\alpha]_D^{22}$ +28.9 (c 2.2); δ_H 2.11 (s, 3 H, Ac), 3.37 (s, 3 H, OCH_3), 3.53 (dd, $J_{1,2}$ = 2.0 Hz, $J_{2,3}$ = 9.6 Hz, 1 H, H-2), 3.57 (dd, $J_{3,4} = J_{4,5}$ = 9.6 Hz, 1 H, H-4), 3.76 (m, 1 H, H-f), 3.89 (m, 1 H, H-5). 3.96-4.35 (m, 3 H, H-3,2 x H-6), 4.15-4.29 (m, 2 H, 2 x H-6'), 4.52-5.03 (m, 8 H, 3 x CH_2Ph, H-l, H-4'), 5.91 (d, $J_{3',4'}$ = 2.0 Hz, 1 H, H-3'), 7.25-7.34 (m, 15 H, aromatic H). 6: Mp 105-108°C (PE/Et_2O); $[\alpha]_D^{22}$ +25.0 (c 2); δ_H 2.78 (d, J = 5.1 Hz, 3 H, $NHCH_3$), 3.36 (m. 1 H, H-4'). 3.38 (s, 3 H, OCH_3), 3.48 (dd, $J_{3,4} = J_{4,5}$ = 9.5 Hz, H-4), 3.54 (dd, $J_{1,2}$ = 3.6 Hz, $J_{2,3}$ = 9.6 Hz, H-2), 3.77-4.09 (m, 7 H, H-3, H-5, 2 x H-6, H-S, 2 x H-6'). 4.60 (d, 1 H, H-l), 4.55-5.03 (m, 6 H, 3 x CH_2Ph), 5.12 (d, $J_{3',4'}$ = 2.5 Hz, H-3'), 6.58 (d, 1 H, NH), 7.22-7.38 (m, 15 H, aromatic H). 7: $[\alpha]_{22}^{D}$ -11.5 (c 3); δ_H 2.07 (s, 3 H, Ac). 2.72 (d, J = 5.0 Hz, 3 H, $NHCH_3$), 3.32 (s, 3 H, OCH_3), 3.86 (d, $J_{2',3'}$ = 9.5 Hz, 1 H, H-3'), 3.51-4.30 (m. 9 H, H-2, H-3, H-4, H-5,2 x H-6, H-T, 2 x H-6'), 4.56 (d, $J_{1,2}$ = 3.2 Hz, 1 H, H-l), 4.60-4.96 (m, 6 H, 3 x CH_2Ph), 5.94 (dd, $J_{4',5'}$ = 9.5 Hz, 1 H, H-4), 6.75 (d, 1 H, NH), X18-7.30 (m, 15 H, aromatic H). 8: $[\alpha]_D^{22}$ +18.3 (c 2); δ_H 2.00 and 2.07 (2 s, 3 H each, 2 x Ac). 1.97-2.09 (2 H more, H-3'e and H-3'a), 2.75 (d, J = 4.9 Hz, 3 H, $NHCH_3$), 3.37 (s, 3 H, OCH_3), 3.48-3.62 (m, 4 H, H-2, H-4, H-5, H-6'a), 3.71-3.79 (m, 2 H, H-3, 1 x H-6), 3.92-4.12 (m, 3 H, H-5, 1 x H-6 and H-6'e), 4.60 (d, $J_{1,2}$ = 3.5 Hz, 1 H, H-1), 4.63-5.02 (m, 7 H, 3 x CH_2Ph, H-4'), 6.90 and 6.98 (2 d, 1 H each, 2 x NH), 7.18-7.30 (m, 15 H, aromatic H). 9: MP 132-134°C (MeOH); $[\alpha]_D^{22}$ -21.0 (c 3); δ_H 2.13 (s, 3 H, Ac), 3.40 (s, 3 H, OCH_3), 3.42-3.60 (m, 4 H, H-2, H-4, H-S, H-6'a), 3.78 (s, 3 H, CO_2CH_3), 3.79-3.97 (m, 6 H, H-3, H-5.2 x H-6, H-3', H-6'e), 4.61 (d, $J_{1,2}$ = 3.2 Hz, 1 H, H-l), 4.63-5.01 (m, 6 H, 3 x CH_2Ph), 5.66 (dd, $J_{3',4'} = J_{4',5'}$ = 8.8 Hz, 1 H, H-4'), 7.25-7.35 (m, 15 H, aromatic H). 10: $[\alpha]_D^{22}$ -32.2 (c 2.5); δ_H 1.99 (dd, $J_{3'a,4'}$ = 4.0 Hz, $J_{3'a,3'e}$ = 14.3 Hz, 1 H, H-3'a'), 2.08 (s, 3 H, Ac), 2.46 (dd, $J_{3'e,4'}$ = 11 Hz, 1 H, H-3'e'), 3.37 (s, 3 H, OCH_3), 3.55 (dd, $J_{1,2}$ = 3.5 Hz, $J_{2,3}$ = 9.7 Hz, 1 H, H-2), 3.64-3.81 (m, 4 H, H-4,2 x H-6, H-S), 3.99 (dd, $J_{3,4}$ = 9.7 Hz, 1 H, H-3). 4.16 (dd, $J_{5,6'a'}$ = 3.8 Hz, $J_{6'a',6'e'}$ = 10.6 Hz, 1 H, H-6'a), 4.27 (m, 1 H, H-5). 4.36 (dd, $J_{5',6'e'}$ = 2.1 Hz, 1 H, H-6'e'), 4.66 (d, 1 I-I, H-l), 4.63-5.01 (m, 7 H, H-4', 3 x CH_2Ph), 7.25-7.36 (m, 15 H, aromatic H), 7.61 (d, J = 5.8 Hz, 1 Ii, NH). 11: $[\alpha]_D^{22}$ +38.4 (c 2.9); δ_H 1.96, 2.03 (2 s, 3 H each, 2 x Ac), 2.12 (dd, $J_{3'a,3'e}$ = 14.9 Hz, $J_{3'a,4'}$ = 5.1 Hz, 1 H, H-3'a), 2.24 (dd, $J_{3'e,4'}$ = 4.1 Hz, 1 H, H-3'e), 3.38 (s, 3 H, OCH_3), 3.42-3.55 (m, 4 H, H-2, H-4.2 x H-6). 3.71 (s, 3 H, CO_2CH_3), 3.74-3.83 (m, 2 H, H-5, H-6'a), 3.95 (m, 1 H, H-5'), 4.04 (dd, $J_{2,3} = J_{3,4}$ = 9.3 Hz, 1 H, H-3), 4.22 (dd, $J_{5',6'e}$ = 2.9 Hz, $J_{6'a,6'e}$ = 12.1 Hz, 1 H, H-6'e), 4.58-5.03 (m, 8 H, H-l, H-4', 3 x CH_2Ph), 6.06 (d, J = 6.8 Hz, 1 H, NH), 7.21-7.33 (m, 15 H, aromatic H).

13. I.R. Vlahov, P.I. Vlahova, R.R. Schmidt publication in preparation.

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