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# Highly Stereoselective Synthesis of β-Glycosides of 3-Deoxy-2-Hexulosonates[1]†

Ioncho R. Vlahov, Petinka I. Vlahova, and Richard R. Schmidt*

Fakultät Chemie, Universität Konstanz, Postfach 5560

D-7750 Konstanz, Germany

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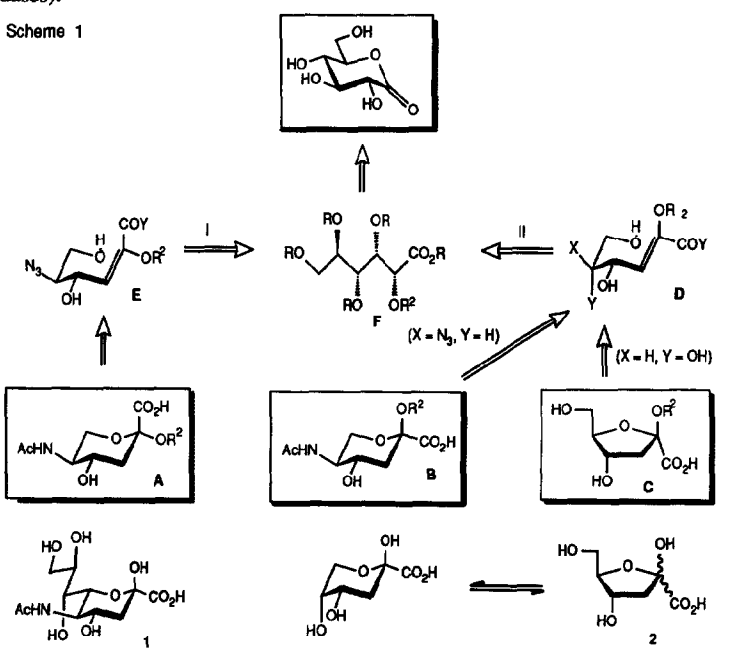
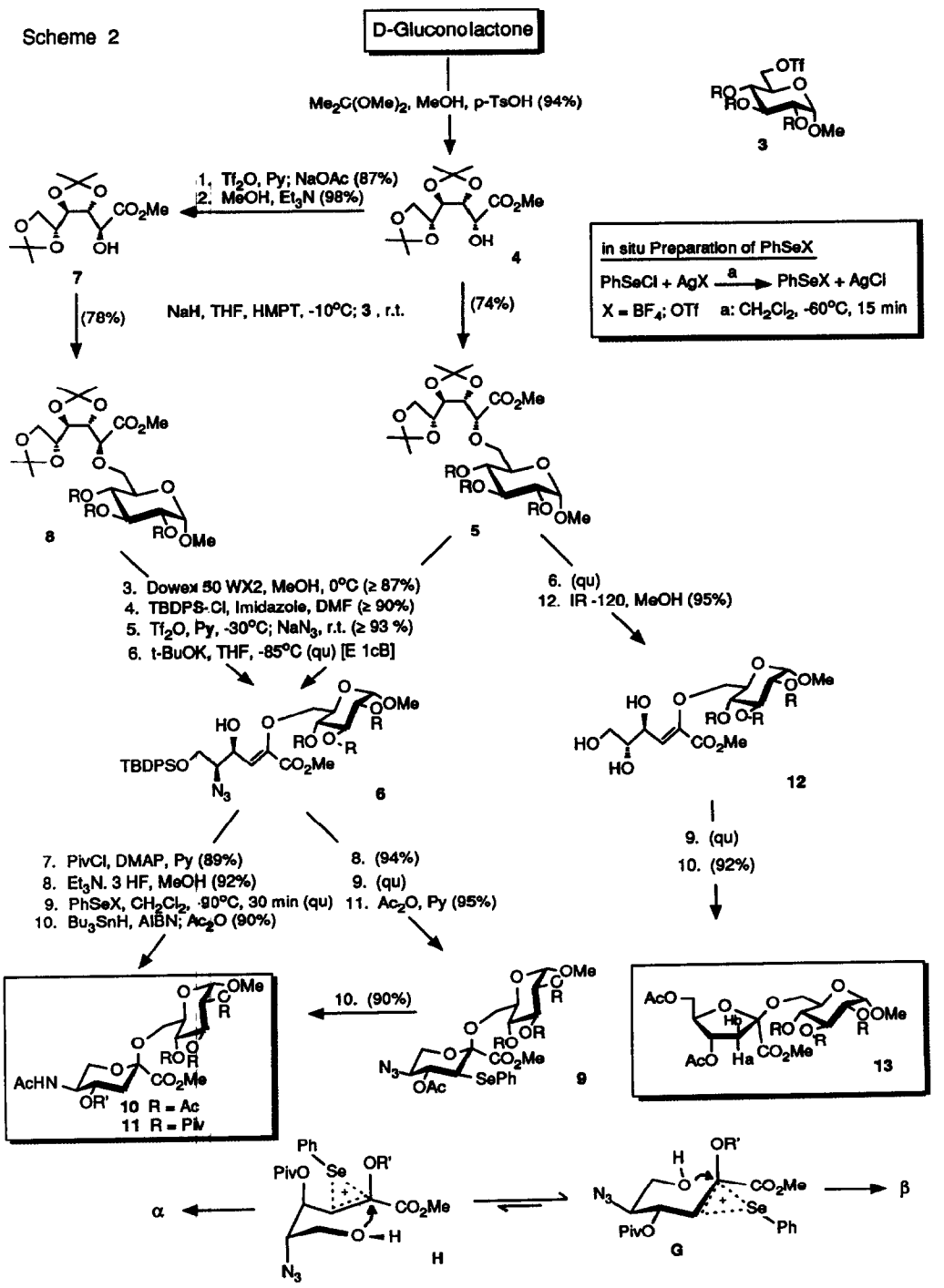
***Abstract***: ε-Hydroxy (Z)-enol ethers **6** and **12** were readily prepared from D-glucono-1,5-lactone by ring opening, 2-O-alkylation with triflate **3**, and Z-specific β-elimination. Cyclization of **6** and **12** induced by $PhSeBF_4$ or by PhSeOTf provided exclusively β-connected disaccharides, which were converted into neuraminic acid analogues **10** and **11** or 3-deoxy-2-glycosyl-D-2-hexulofuranosylonate **13**, respectively.

N-Acetylneuraminic acid (Neu5Ac, **1**, Scheme 1) occupies the nonreducing ends of the oligosaccharide chains in many glycoconjugates, which are constituents of the outer layer of plasma membranes; Neu5Ac is of considerable importance for a great number of biological functions.[2] Analogues and their glycosides are required for understanding the interactions with the enzymes involved in its metabolism (especially sialyltransferases and sialidases).[3]

Scheme 1




†In memory of our friend, Ph. D. supervisor (I.V.) and colleague Prof. Dr. Dr. h.c. (H) Günther Snatzke


Scheme 2
D-Gluconolactone
Me2C(OMe)2, MeOH, p-TsOH (94%)
1. Tf2O, Py; NaOAc (87%)
2. MeOH, Et3N (98%)
7
4
3
in situ Preparation of PhSeX
PhSeCl + AgX —a→ PhSeX + AgCl
X = BF4; OTf a: CH2Cl2, -60°C, 15 min
(78%)
NaH, THF, HMPT, -10°C; 3 , r.t.
(74%)
8
5
3. Dowex 50 WX2, MeOH, 0°C (≥ 87%)
4. TBDPS-Cl, Imidazole, DMF (≥ 90%)
5. Tf2O, Py, -30°C; NaN3, r.t. (≥ 93 %)
6. t-BuOK, THF, -85°C (qu) [E 1cB]
6. (qu)
12. IR -120, MeOH (95%)
6
12
7. PivCl, DMAP, Py (89%)
8. Et3N. 3 HF, MeOH (92%)
9. PhSeX, CH2Cl2, -90°C, 30 min (qu)
10. Bu3SnH, AIBN; Ac2O (90%)
8. (94%)
9. (qu)
11. Ac2O, Py (95%)
9. (qu)
10. (92%)
10. (90%)
10 R = Ac
11 R = Piv
9
13
α
H
G
β

In this context we recently reported[4a] a highly stereoselective disaccharide synthesis of α-glycosidically linked Neu5Ac-analogues of type **A**, lacking the D-*erythro*-trihydroxypropyl-side chain; this method is based on a cyclization of ε-hydroxy (E)-enol ether intermediate **E** (route I)[4b], initiated by N-iodosuccinimide.

In this paper we describe the cyclization of the alternative (Z)-enol ether **D** (route II) which depending on the substituent X at C-5 results in the formation of β-glycosidic Neu5Ac-analogues **B** or in newly prepared β-glycosides **C** of 3-deoxy-D-*erythro*-2-hexulosonic acid (KDG, **2**); **2** is an important metabolite of bacterial polysaccharide degradation.[5]

The starting material of type **F** (Scheme 2; **5**, *gluco*-series) could be easily obtained from D-glucono-1,5-lactone via regioselective di-O-isopropylidenation with simultaneous methyl ester formation (→ **4**)[6] and then alkylation of the OH-group at C-2 with freshly prepared methyl 2,3,4-tri-O-benzyl-6-O-trifluoromethansulfonyl-α-D-glucopyranoside **3**[7]. Acid catalyzed selective 5',6'-de-O-isopropylidenation, selective 6'-O-silylation with t-butyldiphenylsilyl chloride (TBDPS-Cl)[8], and azido group introduction at the C-5' atom afforded the intermediate desired for β-elimination. Thus, treatment of this base sensitive molecule with t-BuOK at -78°C led to abstraction of the acidic proton at C-2' and concomitant 3'-O-elimination providing the (Z)-enol ether **6** in quantitative yield.

Epimerization of the OH-group at C-2 in **4** to the *manno*-derivative **7** (Scheme 2, *manno*-series) and applying the same reagents and reaction conditions as described above resulted also in (Z)-enol ether **6**, thus evidencing the E1cB mechanism of this C-2'/C-3' β-elimination.

Compound **6** possesses the desired (Z)-configuration[9] required for the ensuing highly regio- and β-stereoselective cyclization which could be induced at low temperature by the new reagent $PhSeBF_4$ or also by PhSeOTf[10] as highly electrophilic promotors in a quantitative reaction. The $^2C_5$ conformation of the β-glycosides, obtained via **G** as intermediate, was derived from the $^1$H-NMR data of **9** ($J_{3',4'} = J_{4',5'} = 10.1$ Hz; *trans*-diaxial relationships between H-3', H-4', H-5'). The introduction of the bulky pivaloyl group (route to **11**) indicated, that the stereochemical course of the reaction depends mainly on two factors: i) the conformation of the two possible intermediates **G** and **H** after the addition of the $PhSe^+$-species favoring the chair-like form **G**, and ii) the cooperative anomeric effect in the nascent (Z)-enol ether product. Reduction of the azido and the phenylselenyl groups with $Bu_3SnH$ in the presence of catalytic amounts of AIBN (toluene, 90 °C, 30 min) and acetylation gave compounds **10** and **11**, respectively. On the other hand, O-unprotected (Z)-enol ether **12** gave after the same procedure the 3-deoxy-D-*erythro*-2-hexulofuranosylonate **13** in high yield. The observed regiochemistry accords with the kinetically preferred formation of five-membered rings in carbohydrate ring closure reactions. The compounds were characterized by their $^1$H-NMR data[11].

## References and Notes

1. This work was supported bei the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie. - I.V. is grateful for an Alexander von Humboldt Fellowship.

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11. Selected physiscal data for compounds **6** and **9-13**. [Values of $[\alpha]_D$ and $\delta_H$ (only the signals of the hexulosonate part of the molecules) were measusred for solutions in $CHCl_3$ and $CDCl_3$]: **6** $[\alpha]_D^{22}$ + 41.8 (c 1); $\delta_H$ = 3.69-3.77 (m, 6 H, H-5', 2 x H-6', $CO_2CH_3$), 4.62 (dd, $J_{3',4'}$ = 6.7 Hz, $J_{4',5}$ = 4.7 Hz, 1 H, H-4'), 6.30 (d, 1 H, H-3'). **9**: $[\alpha]_D^{22}$ + 46.0 (c 3.4); $\delta_H$ = 3.44 (ddd, $J_{4',5'} = J_{5',6'a}$ = 10.1 Hz, $J_{5',6'e}$ = 5.4 Hz, 1 H, H-5'), 3.55 (d, $J_{3',4'}$ = 10.1 Hz, 1 H, H-3'), 3.76 (dd, $J_{6'a,6'e}$ = 10.5 Hz, 1 H, 6'a), 4.05 (dd, 1 H, 6'e), 5.54 (dd, 1 H, H-4'). **10**: $[\alpha]_D^{23}$ - 4.6 (c 2); $\delta_H$ = 1.90 (dd, $J_{3'a,3'e} = J_{3a',4'}$ = 13.0 Hz, 1 H, H-3'a), 2.39 (dd, $J_{3'e,4'}$ = 5.0 Hz, 1 H, H-3'e), 3.95-4.05 (m, 2 H, H-6'a and H-6'e), 4.10 (m, 1 H, H-5'), 5.15 (ddd, $J_{4',5'}$ = 13.0 Hz, 1 H, H-4'), 5.77 (d, J = 7.5 Hz, 1 H, N*H*). **11**: $[\alpha]_D^{22}$ - 5.6 (c 2.5); $\delta_H$ = 1.91 (dd, $J_{3'a,3'e}$ = $J_{3'a,4'}$ = 12.9 Hz, 1 H, H-3'a), 2.41 (dd, $J_{3'e,4'}$ = 5.0 Hz, 1 H, H-3'e), 3.90-4.05 (m, 2 H, H-6'a and H-6'e), 4.12 (m, 1 H, H-5'), 5.16 (ddd, $J_{4',5'}$ = 12.9 Hz, 1 H, H-4'), 5.66 (d, J = 7.9 Hz, 1 H, N*H*). **12**: $[\alpha]_D^{21}$ + 17.6 (c 3.3); $\delta_H$ = 3.60-3.88 (m, 3 H, H-5', 2 x H-6'), 3.73 (s, 3 H, $CO_2CH_3$), 4.65 (m, 1 H, H-4'), 6.26 (d, $J_{3',4'}$ = 7.5 Hz, H-3'). **13**: $[\alpha]_D^{22}$ + 19.7 (c 2); $\delta_H$ = 2.40 (dd, $J_{3'a,3'b}$ = 14.2 Hz, $J_{3'a,4'}$ = 5.5 Hz, 1 H, H-3'a), 2.73 (dd, $J_{3'b,4}$ = 7.4 Hz, 1 H, H-3'b), 4.22 (dd, $J_{5',6'a}$ = 7.3 Hz, $J_{6'a,6'b}$ = 11.9 Hz, 1 H, H-6'a), 4.30 (dd, $J_{5',6'b}$ = 4.9 Hz, 1 H, H-6'b), 4.45 (ddd, $J_{4'5'}$ = 3.9 Hz, 1 H, H-5'), 5.21 (ddd, 1 H, H-4'); for this interpretation see also McNicholas; Batley and Redmond, J., *Carbohydr. Res.* **1986,** *146,* 219-231.