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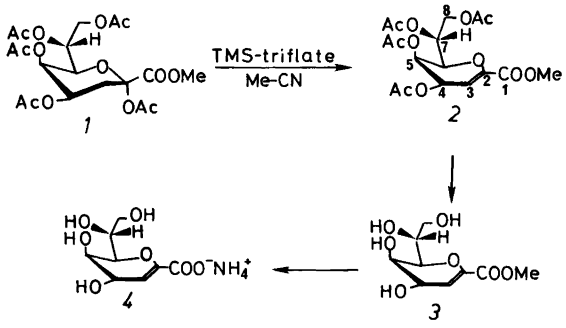
Short Communications

Synthesis of α,β-Unsaturated Analogues of KDO and *N*-Acetyl-neuraminic Acid by Trimethylsilyl Triflate-catalyzed Elimination Reactions

ALF CLAESSON and KRISTINA LUTHMAN

Department of Organic Pharmaceutical Chemistry, Biomedical Center, University of Uppsala, Box 574, S-751 23 Uppsala, Sweden



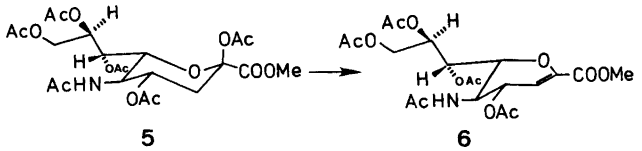
3-Deoxy-D-*manno*-2-octulosonic acid (KDO) is a unique constituent of the lipopolysaccharides of gram-negative bacteria. Very recently its chemistry and biological significance has been reviewed.[1] In a program aimed at synthesizing inhibitors of KDO metabolism we have discovered and report here a short synthesis of an unsaturated analogue (*4*), which might exhibit interesting biological properties. The synthesis, which brings a new facet to the already vivid chemistry of trimethylsilyl (TMS) sulfonates (review[2]), is simpler than one reported in a preliminary form.[3] We have also applied this method to the synthesis of the fully acetylated methyl ester of 2,3-dehydro-2-deoxy-*N*-acetylneuraminic acid. This acid and analogues are neuraminidase inhibitors of pharmaceutical interest.[5]

Treatment of the pentaacetate-methyl ester (*1*)[4] of KDO with catalytic amounts (0.1 mol equivalents) of TMS-trifluoromethanesulfonate gave after a few hours at room temperature the elimination product (*2*) in 91% yield. The solvent was acetonitrile. TLC data indicate that the reaction also goes to completion in nitromethane. Other solvents were not tested. A small amount of cyanotrimethylsilane was added as a scavenger of traces of acid in the catalyst. The omission of this reagent did not, however, seem to adversely affect the yield of the product (TLC data only). Deprotection of the unsaturated compound *2* by standard methods completed the synthesis of *4*.

The elimination of acetic acid from the neuraminic acid derivative *5* proceeded equally well by using 0.2 equivalents of TMS-triflate. The unsaturated compound *6* was isolated in 90% yield. The deprotection of this compound has already been described.[5]

The efficacy of TMS-triflate in catalytic amounts probably means that it is regenerated through the reaction of trifluoromethanesulfonic acid with the other reaction product *i.e.* TMS-acetate. The strong sulfonic acid might also in itself function as an efficient elimination catalyst.

Experimental. Melting points were determined in open capillary tubes and are uncorrected. NMR spectra were recorded on Jeol FX 90 Q or Jeol FX-200 spectrometers. TMS was used as internal standard in $CDCl_3$ and CD_3OD, and *t*-BuOH (^{13}C NMR δ 32.2, ^1H NMR δ 1.23) in D_2O. Optical rotations were determined with a Perkin-Elmer 241 polarimeter. Microanalyses were carried out at the Microanalytical Laboratory, Royal Agricultural College, Uppsala.



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Methyl 4,5,7,8-tetra-O-acetyl-2,6-anhydro-2,3-dideoxy-D-manno-2-octenoate (2). To a solution of KDO – pentaacetate – methyl ester (*1*)[4] (545 mg; 1.18 mmol) in 2 ml of dry acetonitrile was added 10 μl of cyanotrimethylsilane followed by trimethylsilyl trifluoromethanesulfonate (20 μl; 0.11 mmol). The mixture was left at room temperature for 4 h and then 0.5 g K_2CO_3 was added. After evaporation of solvent the residue was chromatographed on silica gel (60 ml) using ether – pentane, 3:1, as eluent. Pooling of the central fractions gave 350 mg of pure product, m.p. 132 – 133 °C (lit.[3] 129 – 132 °C), $[\alpha]_D^{23}$ −17.4° (*c* 1.42, $CHCl_3$) (lit.[3] $[\alpha]_D^{20}$ −14.8°). Altogether 429 mg (91 %) of crystalline product was obtained. Anal. $C_{17}H_{22}O_{11}$: C,H. ^{1}H NMR ($CDCl_3$): δ 5.89 (dd,H3), 5.71 (ddd,H4), 5.48 (ddd,H5), 5.19 – 5.36 and 4.13 – 4.72 (two m,H6-H8), 3.82 (s,OCH_3), 2.03 – 2.08 (Ac). ^{13}C NMR ($CDCl_3$): δ 169.1 – 170.1 (Ac), 161.2 (Cl), 144.3 (C2), 107.3 (C3), 73.2 (C6), 67.2 (C4), 64.6 (C7), 61.8 (C8), 60.6 (C5), 52.4 (OCH_3), 20.6 (Ac).

Methyl 2,6-anhydro-2,3-dideoxy-D-manno-2-octenoate (3). Compound *2* (400 mg) was treated with NaOMe (from 40 mg Na) in 5 ml MeOH for 1 h. Neutralization with MeOH-washed ion-exchange resin (H^+), filtration and evaporation gave 200 mg (~100 %) of crystalline residue. Recrystallization from MeOH-ether gave a product with m.p. 162 – 164 °C, $[\alpha]_D^{23}$ −31.9° (*c* 0.90, MeOH). Anal. $C_9H_{14}O_7$: C,H. ^{1}H NMR (CD_3OD): δ 5.45 (dd,H3), 4.08 (ddd,H4), 3.75 (ddd,H5), 3.6 – 3.2 (m,H6 – H8), 3.38 (s,OCH_3). ^{13}C NMR (CD_3OD): δ 164.0 (Cl), 145.0 (C2), 113.8 (C3), 78.9 (C6), 70.9 (C4), 66.7 (C7), 64.7 (C5), 64.5 (C8), 52.9 (OCH_3).

Ammonium 2,6-anhydro-2,3-dideoxy-D-manno-2-octenoate (4). Compound *3* (200 mg) was dissolved in 3 ml of water and 5 M NaOH was added dropwise until the mixture stayed alkaline (pH ~10) for 10 min. The reaction mixture was passed through an NH_4^+-saturated ion-exchange resin and the water was evaporated to almost dryness. The residue was treated with methanol, ethanol, and 2-propanol until no more crystals precipitated on placing the mixture in the refrigerator and then in the freezer. Yield = 76 %. M.p. 178 – 180 °C. $[\alpha]_D^{23}$ −15.8° (*c* 1.1 H_2O – MeOH 1:1). Anal. $C_8H_{15}NO_7$: C,H,N. ^{1}H NMR (D_2O): δ 5.56 (dd,H3), 4.57 (ddd,H4), 4.13 (ddd,H5), 3.97 – 3.74 (m,H6 – H8). ^{13}C NMR (D_2O): δ 171.7 (C1), 151.2 (C2), 110.1 (C3), 79.0 (C6), 71.7 (C4), 67.7 (C7), 65.5 (C5), 65.0 (C8).

Methyl 5-acetamido-4,7,8,9-tetra-O-acetyl-2,6-anhydro-2,3,5-trideoxy-D-glycero-D-galacto-2-nonenoate (6). Fully acetylated neuraminic acid methyl ester (5) (70 mg, 0.13 mmol) in 2 ml of acetonitrile was treated with 5 μl (0.027 mmol) TMS-triflate for 5 h. After addition of K_2CO_3 (0.1 g) and evaporation, the residue was filtered through a silica gel column with ethyl acetate as eluent. Yield: 56 mg (90 %). The ^{13}C and ^{1}H NMR data were in full agreement with those reported in the literature.[6]

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