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New Route to 3-Deoxy-2-Ulosonic Acids; Total Syntheses of KDO and KDN

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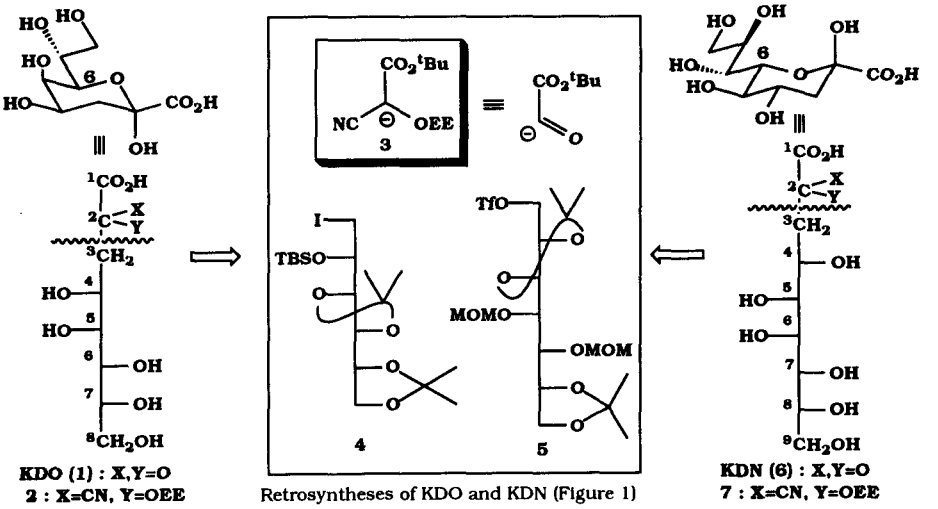
Abstract: Syntheses of KDO and KDN by alkylation of 2-alkoxy-2-cyanoacetate anion, an acyl anion equivalent of alkyl glyoxylate, with a sugar-derived iodide and triflate are described. © 1997 Elsevier Science Ltd.

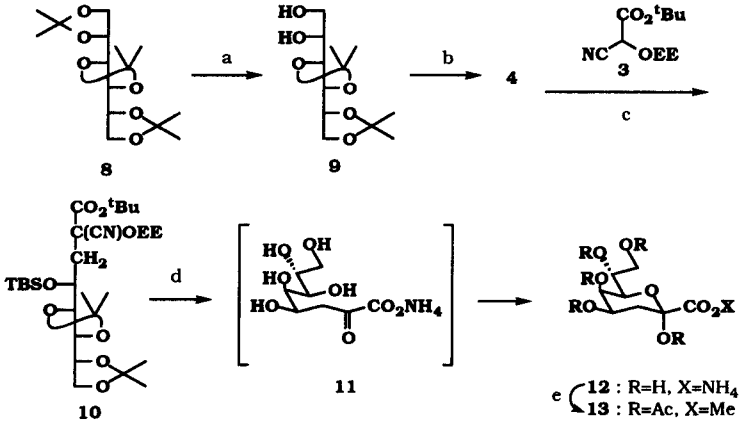
3-Deoxy-D-manno-2-octulosonic acid (KDO; **1**)[1] and 3-deoxy-D-glycero-D-galacto-2-nonulosonic acid (KDN; **6**)[2] possess a common synthetically challenging structure characterized by the presence of pyruvic acid moiety. KDO is found in the lipopolysaccharide region of the cell surface of all Gram-negative bacteria and is an essential component for their replication. KDN occurs in the nonreducing termini in polysialoglycoproteins (PSGP) and protects oligopolysialyl chains from exosialidase. These important findings have stimulated significant effort toward the syntheses of various 3-deoxy-2-ulosonic acid derivatives.[3] One of the problems in the syntheses of such molecules is the introduction of the α-ketoacid system. Among the reported enzymatic and chemical syntheses of 3-deoxy-2-ulosonic acids, the aldol reaction between C3 and C4 using pyruvic acid derivatives and sugar-derived aldehydes is the most simple and versatile.[4] This approach, however, leads to the formation of diastereomers at C4. To overcome this problem, synthesis of KDO via alkylation of dithioacetal of methyl glyoxylate with a sugar-derived triflate has been reported.[3d] Here we describe a new route to KDO **1** and KDN **6** based on alkylation of the protected cyanohydrin **3**, an acyl anion equivalent of alkyl glyoxylate[5] with the sugar-derived iodide **4** and triflate **5**.



Retrosyntheses of KDO and KDN (Figure 1)

The ketoacid moiety in **1** and **6** exists in a 6-membered cyclic acetal with the axial anomeric alcohol and the equatorial carboxylic acid (see Figure 1). Therefore the protected cyanohydrins **2** and **7** could serve as the advanced intermediates to the hemiacetals **1** and **6**, since the cyanohydrin ether in the alkylated products can be readily converted to the corresponding ketone.

Our synthesis of KDO **1** begins with the known 1,2:3,4:5,6-triisopropylidene derivative **8**, prepared from the C_2-symmetric D-mannitol[6] (Scheme1). Partial hydrolysis of the triacetonide **8** with conc. HCl in EtOH at 40 °C gave the 3,4:5,6-diisopropylidene compound **9** in 57% yield based on 56% conversion. Selective tosylation of the primary alcohol of **9**, protection of the secondary alcohol with *t*-butyldimethylsilyl chloride and iodination of the resulting tosylate gave the iodide **4** in 57% overall yield for the three steps. Alkylation of **4** with the protected cyanohydrin **3** using NaH in the presence of a catalytic amount of EtOH in DMF at 90 °C for 2 h gave the alkylated product **10** in 63% yield. The starting iodide **4** was also recovered in 20% yield. Acid treatment of **10** with 80% aq. trifluoroacetic acid in MeOH at room temperature for 3 days provided the free cyanohydrin, which was treated with 0.1 M aq. NH_4OH to afford the α-ketoacid **11** and spontaneous acetalization of the δ-hydroxy ketone moiety provided hemiacetal **12** as its ammonium salt. For further identification, the synthetic **12** was converted to the pentaacetylated methyl ester **13** according to Unger's procedure[7] in 36% overall yield from **10**. Physical constants of **13** (mp 154-155 °C, $[\alpha]_D$ +91° (c 0.5, MeOH); lit.[8] mp 155 °C, $[\alpha]_D$ +101° (c 1, MeOH)) were identical with those reported.[9]

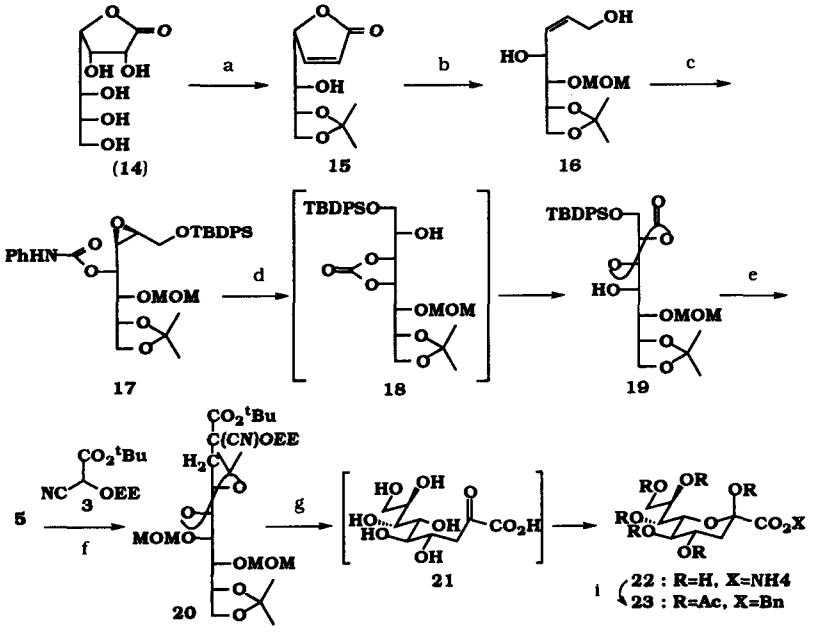


a) conc. HCl/60% aq. EtOH; 32% (recovery 44%) **b)** 1) TsCl/Py. 2) TBSCl/Imidazole 3) NaI/$NaHCO_3$; 3 steps 57% **c)** NaH/cat. EtOH/DMF at 90 °C for 2 h; 63% (recovery 20%) **d)** 1) 80% aq. TFA/MeOH at r.t. for 3 days 2) 0.1 M NH_4OH **e)** 1) Ac_2O/Py./cat. DMAP 2) CH_2N_2/MeOH; 4 steps 36%

Scheme 1

The synthesis of KDN **6** starts with the commercially available D-gylcero-D-guloheptose-1,4-lactone (**14**) (Scheme 2). The selective 6,7-O-isopropylidenation of **14** (99% yield) with acetone in the presence of $CuSO_4$, the 2,3-diacetylation of the resulting triol and SmI_2-promoted deacetoxylation of the resulting diacetate using Inanaga's procedure[10] provided the α,β-unsaturated lactone **15** in 30% overall yield over two steps. Protection of the secondary alcohol in **15** with chloromethyl methyl ether and reduction of the lactone in two steps (DIBAL, $LiAlH_4$) gave diol **16** in 67% overall yield from **15**. Selective protection of the primary alcohol in **15** with t-butyldiphenylsilyl chloride, stereoselective epoxidation of the Z-olefin using *m*-chloroperbenzoic

acid (83% overall yield for two steps) and protection of the C4-alcohol with phenyl isocyanate gave carbamate **17** in 89% yield. Regio- and stereoselective epoxide opening of **17** by a treatment with diethylaluminium chloride[11] followed by 1 M aq. H_2SO_4 afforded the more stable 2,3-cyclic carbonate **19** via the 3,4-cyclic carbonate **18** in 48% yield. Protection of the C4-hydroxy group in **19** with chloromethyl methyl ether, removal of the cyclic carbonate with NaH in ethylene glycol/THF (1/20) (78% yield over two steps), reprotection of the 2,3-diol as its acetonide and desilylation with tetrabutylammonium fluoride yielded the primary alcohol in 78% overall yield over two steps. Sulfonation of the primary alcohol with trifluoromethanesulfonic anhydride, followed by alkylation of the resulting triflate **5** with the protected cyanohydrin **3** with NaH in DMF at 0 °C for 2 h provided the protected cyanohydrin **20** in 71% yield for the two steps. Transformation of the alkylated product **20** to the target molecule were carried out essentially as same as above to provide the hemiacetal **22** as its ammonium salt. For further identification, the synthetic **22** was converted to the hexa-acetylated benzyl ester **23** in 31% overall yield from **20**. Physical constants of **23** ($[\alpha]_D$ -14.7° (c 1.1, $CHCl_3$); lit.[12] $[\alpha]_D$ -17.4° (c 1.0, $CHCl_3$)) were identical with those reported.[13]



a) 1) $CuSO_4$/acetone; 99% 2) AcCl/2,6-Lutidine/CH_2Cl_2 at -10 °C 3) SmI_2/AcOH/THF; 2 steps 30% **b)** 1) MOMCl/$PhNEt_2$ 2) DIBAL/CH_2Cl_2 3) $LiAlH_4/Et_2O$; 3 steps 67% **c)** 1) TBDPSCl/Et_3N/cat.DMAP 2) mCPBA/$Na_2HPO_4{\cdot}2H_2O$; 2 steps 83% 3) PhNCO/Py./cat. DMAP; 89% **d)** Et_2AlCl/Et_2O and then 1 M H_2SO_4; 48% **e)** 1) MOMCl/$^iPr_2EtN$ 2) NaH/ THF-ethylene glycol (20:1); 2 steps 78% 3) $Me_2C(OMe)_2$/PPTS 4) $^nBu_4NF$; 2 steps 78% 5) Tf_2O/2,6-Lutidine **f)** NaH/DMF at 0 °C for 2 h; 2 steps 71% **g)** 1) 80% aq.TFA/ MeOH at r.t. for 3 days 2) 0.6 M NH_4OH **h)** 1) BnBr/Cs_2CO_3/Drierite 2) Ac_2O/Py./cat. DMAP for 4 steps 31%

Scheme 2

Thus alkylation using the protected cyanohydrin and sugar-derived iodide or triflate is useful for constructing the α-ketoacid moiety in KDO and KDN. We also found that the protected cyanohydrin at C2 in the alkylated products, (i.e. **2** and **7**), undergoes ketalization via mild acid and base treatment. Further studies

on the synthesis of N-acetyl-5-amino-3,5-dideoxy-D-glycero-D-galacto-2-nonulosonic acid (N-acetyl-neuraminic acid) and its conjugates using the protected cyanohydrin alkylation are underway in our laboratory.

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9) NMR data of **13**: ^{1}H NMR (270MHz, $CDCl_3$) δ 1.99, 2.00, 2.05, 2.11, 2.14 (5s, 15H, Ac), 2.19 (dd, 1H, J=10.8, 13.5Hz), 2.24 (dd, 1H, J=6.3, 13.5Hz), 3.81 (s, 3H, OMe), 4.12 (dd, 1H, J=3.8, 12.5Hz), 4.18 (dd, 1H, J=1.2, 9.8Hz), 4.48 (dd, 1H, J=2.4, 12.5Hz), 5.22 (ddd, 1H, J=2.4, 3.8, 9.8Hz), 5.32 (ddd, 1H, J=2.9, 6.3, 10.8Hz), 5.39 (dd, 1H, J=1.2, 2.9Hz). ^{13}C NMR (67.8MHz, $CDCl_3$) δ 20.7x5, 31.0, 53.3, 62.2, 64.1, 66.0, 67.4, 69.9, 97.6, 166.7, 168.0, 169.6, 170.0, 170.3, 170.5.
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13) NMR data of **23**: ^{1}H NMR (270MHz, $CDCl_3$) δ 2.00, 2.01, 2.02x2, 2.10, 2.11 (6s, 18H, Ac), 2.02-2.10 (m, 1H), 2.62 (dd, 1H, J=5.4, 13.5Hz), 4.15 (dd, 1H, J=5.9, 12.5Hz), 4.19 (dd, 1H, J=2.2, 10.1Hz), 4.41 (dd, 1H, J=2.3, 12.5Hz), 4.97 (dd, 1H, J=9.9, 10.1Hz), 5.13-5.18 (m, 1H), 5.16 (d, 1H, J=12.4Hz, OBn), 5.23 (d, 1H, J=12.4Hz, OBn), 5.21-5.31 (m, 1H), 5.39 (dd, 1H, J=2.2, 6.4Hz), 7.35-7.36 (m, 5H, OBn). ^{13}C NMR (67.8MHz, $CDCl_3$) δ 20.6x2, 20.7x2, 20.8x2, 35.4, 61.8, 66.9, 67.5, 68.0, 68.7, 70.2, 71.6, 97.5, 128.3, 128.5, 128.6, 134.9, 165.3, 168.2, 169.6, 169.7, 170.0, 170.1, 170.5.

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