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A New Synthesis of 3-Deoxy-D-Manno-2-Octulosonic Acid (KDO)

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Abstract : A KDO synthesis is described using in the key step a potassic anion derived from isopropyl dichloro or dibromoacetate, as an efficient equivalent to install an α-ketoester unit onto a conveniently protected D-mannose.

Chemical synthese of KDO and analogs have been intensively studied in view to obtain efficient inhibitors of the KDO biosynthetic pathway as potential, new antibacterial agents specific against Gram-negative bacteria. This clinical interest in combination with the synthetically challenging structure characterized by the presence of a pyruvic acid moiety joined to a pentitol part in the acylic form of the KDO molecule, has stimulated various routes to KDO. These include the introduction of the pyruvic acid part on the arabinose via a C3-C5 fragment connection using different anionic equivalents of the unstable pyruvic acid enolate[1] and a mimic of the natural reaction between D-arabinose-5-phosphate and enolpyruvate phosphate, catalyzed by 3-deoxy-8-0-phosphono-octulosonate synthetase.[2]

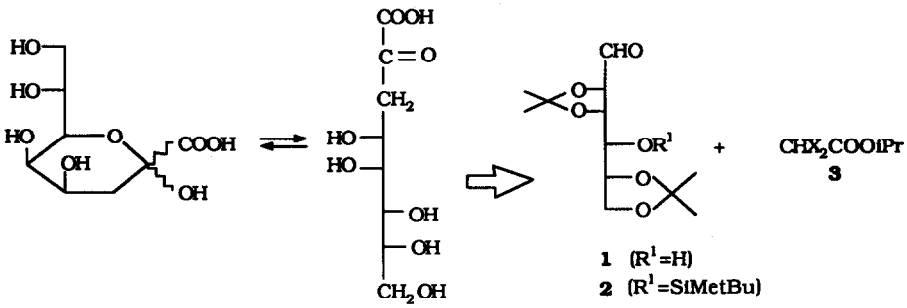
A second important strategy involves the coupling between C2 and C6 fragments based on the introduction of an α-keto carboxylic acid synthon on a conveniently protected D-mannose.[1,3]

As we have previously described the usefulness of the dihalogeno ester carbanions methodology to introduce directly an α-keto ester moiety on a substrate having a carbonyl group,[4] we report now this approach to the synthesis of the ketoside carboxylic acid KDO.

We attempted first the Darzens chain elongation reaction directly on the 2,3:5,6-di-O-isopropylidene-D-mannose hemiacetalic form of **1** (R^1=H), using different metallated anions of isopropyl dichloro- or dibromoacetate **3** (cation : Li+, Na+, K+, MgCl+) in various conditions (protic alcoolic solvent or aprotic THF solvent), in the presence or not of Lewis acids such as magnesium chloride or aluminum isopropoxide to confer the correct softness at the anionic center, allowing it to react on the masked aldehydic form. Unfortunately, these reactions did not succeed, the sole result being partial anomerisation of the isopropylidene α-D mannose.

To overcome the problem, the reaction was studied on the protected aldehyde **2** (R^1=$SiMe_2tBu$) readily prepared from 2,3:5,6-di-O-isopropylidene-D-mannose[5]. In a typical procedure, a solution of aldose **2** (4.25 mmol) and isopropyl dihalogenoacetate **3** [**3a** X=Cl or **3b** X=Br] (18.5 mmol) in ether (10 ml) was added

dropwise at 0°C to a solution of potassium isopropoxide (18.5 mmol) in isopropanol / ether (40ml : 10ml). After stirring 1h30 at 0°C the reaction mixture was neutralised with a saturated HCl ether solution. The potassium halide suspension was centrifugated and separated.The organic layer was concentrated under reduced pressure to give in high yields (92 and 85 % respectively) diastereomeric mixtures of α-halogenoglycidic esters **4** and **5** (**4a**:**5a** = 75:25 ; **4b**:**5b** = 63:37).



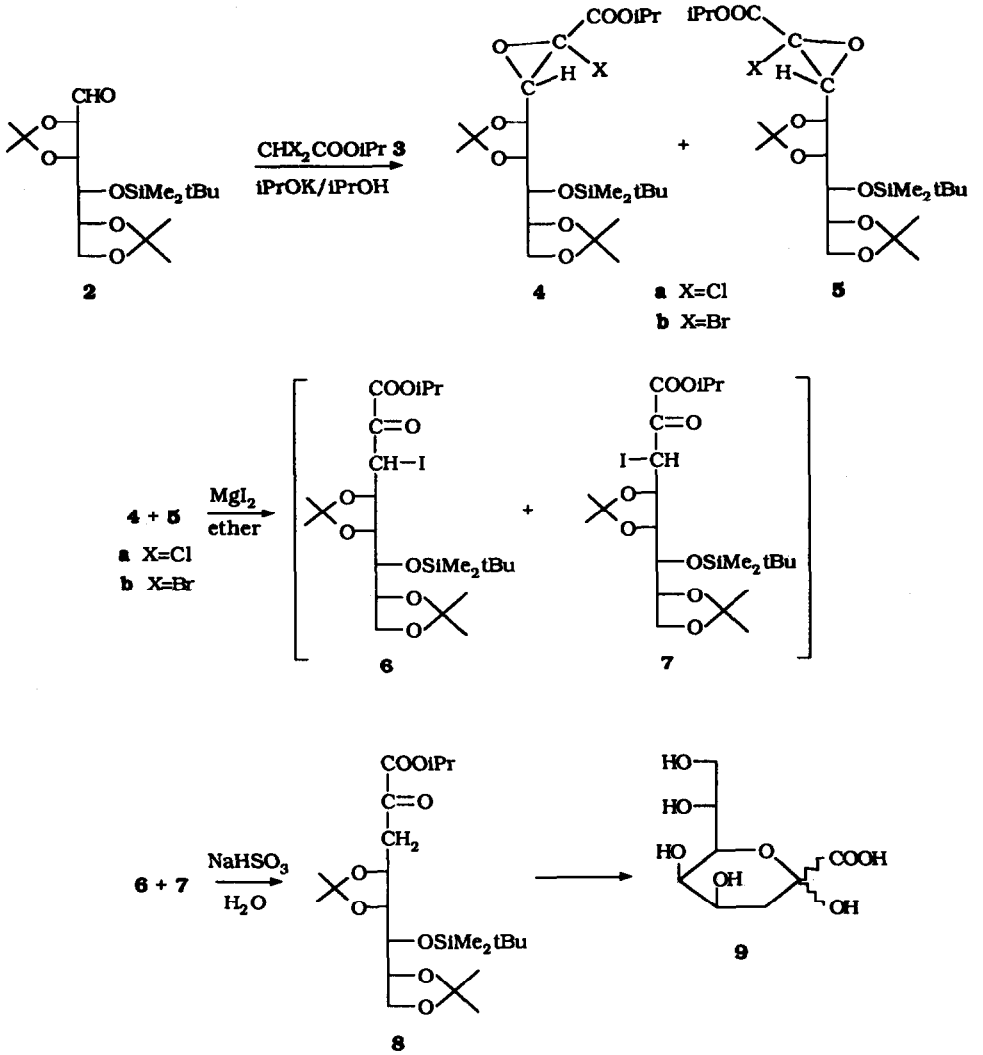
Subsequent treatment of the mixtures **4** and **5** (a or b) with magnesium iodide leads to the rearrangement of the halogenoepoxy ring to give a diastereomeric mixture of the α-iodoketoesters **6** and **7**. Because the ratio **6**:**7** was dependent of the reaction time and because this source of isomerism was going to be removed in the next stage of the synthesis, the mixture of the α-iodoketoesters **6** and **7** was carried on as such and no attempt was made to control this ratio.

The crude mixture of the α-iodoketoesters **6** and **7** was then reduced by a saturated aqueous solution of sodium hydrogen sulfite and yielded the α-ketoester **8** (80 % yield from **4a-5a** ; 70 % yield from **4b-5b**).[4b,6]

Removal of the isopropylidene groups simultaneously, with the t-butyldimethylsilyl group (90 % AcOH at 90°C for 15 min) followed by alkaline hydrolysis of the isopropyl ester (K_2CO_3/H_2O at 60°C for 15 min) gave free KDO **9** which was isolated as the crystalline ammonium salt (86 % yield from **8**) ; mp 122-124°C ; $[\alpha]^D_{20}$ = +39° (c=1.1, H_2O); lit.[3a] mp 120-122°C; $[\alpha]^D_{20}$ = +38,7° (c=1, H_2O) ; lit.[1a] mp 123-126°C ; $[\alpha]^D_{20}$ = +40.9 (c=1,05, H_2O). The ammonium salt thus obtained showed TLC behavior[2] ($MeOH/CHCl_3/H_2O$ 10:10:3, Rf=0.55) and ^1H and ^{13}C NMR spectra identical with a commercially available sample of KDO.[7]

The results described here illustrate the great utility of the alkyldichloro or dibromoacetate anion for the synthesis of the ketoside carboxylic acid KDO. This methodology advantageously compares with any reported chemical synthesis of KDO since the overall yield of the (+) KDO ammonium salt (63%) here reported, starting from the protected D-mannose **2**, can be compared with the best ones existing for a chemical

synthesis, according to Dondoni (6.8%)[1a] and Shing (37%).[1c] Furthermore, this methodology to install a pyruvic acid unit onto a glucidic aldehyde is very convenient from the double point of view of the availability of the key α-ketoacid synthon (alkyl dihalogenoacetates are commercially available) and of the ready access to the desired ketoside carboxylic acid in four steps from the protected D-mannose 2.



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6. The reaction conditions are crucial and require an exact temperature control. In a typical experiment, MgI_2 (786 mmol, 3 ml ether) was dropwise added, at -60°C with stirring, to the diastereomeric mixture of α-chloroglycidic ester **4** and **5** (393 mmol) at the concentration of 0.02 M in a mixture ether / toluene 4:2. The mixture was allowed to warm up to -30°C. After stirring at -30°C during 90 mn, the reaction mixture was treated with a freshly aqueous concentrated $NaHSO_3$ solution (5ml) and allowed to warm to room temperature. After 45mn stirring, the usual work up gave the syrup **8** (314 mmol). ^1H NMR (250MHz, $CDCl_3$) δ 0.10 (s, 3H) ; 0.12 (s, 3H), 0.90 (s, 9H) ; 1.20-1.40 (m, 18H) ; 3.10 (dd, J=8, 17Hz, 1H) ; 3.22 (dd, J=4, 17Hz, 1H) ; 3.73-3.89 (m, 3H) ; 4.05 (m, 2H) ; 4.45 (ddd, J=4, 8, 8Hz, 1H) ; 5.14 (m, J=6.5Hz, 1H).
7. Purchased from Sigma Chemical Co.

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