A Concise Chemical Synthesis of (+)-3-Deoxy-D-*glycero*-D-*galacto*-nonulosonic acid (KDN)

Tak-Hang Chan* and Chao-Jun Li

Department of Chemistry, McGill University, 801, Sherbrooke St. W., Montreal, Quebec, Canada H3A 2K6

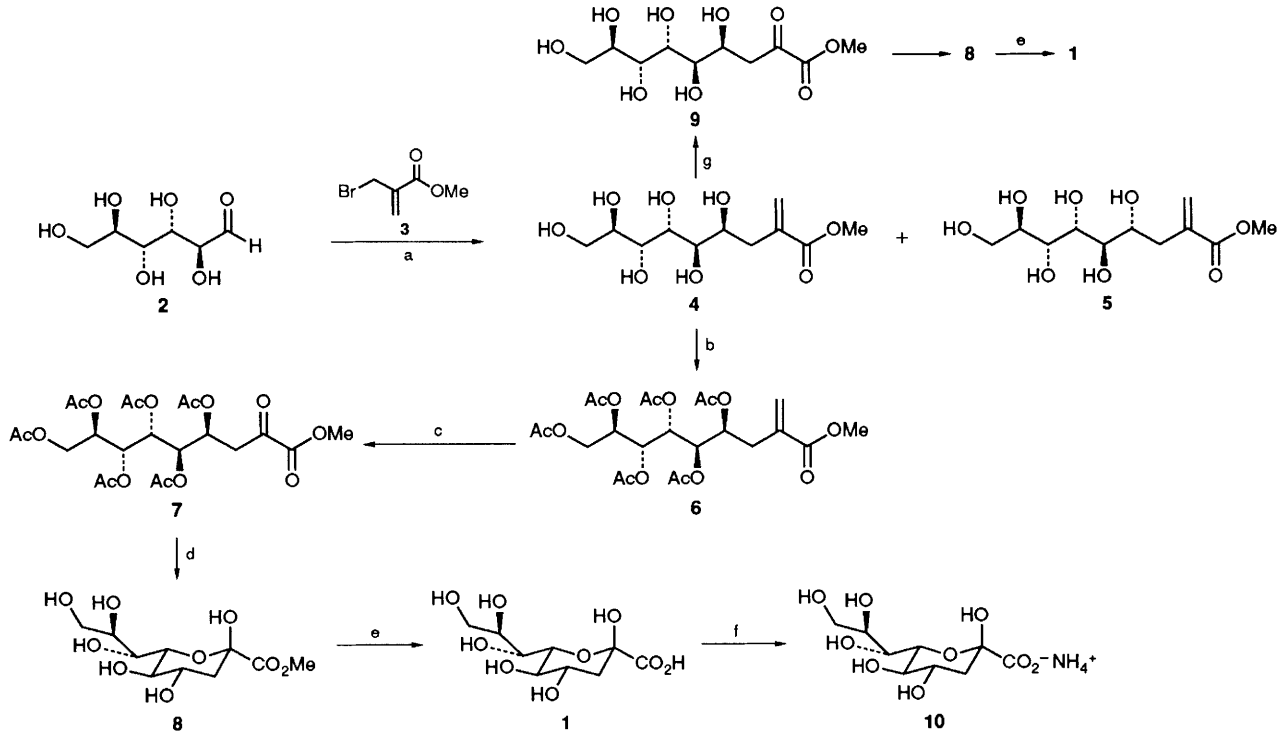
The sialic acid KDN is synthesized stereoselectively in three steps from D-mannose by taking advantage of an indium mediated coupling reaction in aqueous medium.

The sialic acids are a class of compounds of considerable importance in biological systems.[1,2] Recently, 3-deoxy-D-*glycero*-D-*galacto*-2-nonulosonic acid (KDN) **1** was isolated from the polysialoglycoprotein (PSGP) of rainbow trout eggs.[3] It has been shown that the KDN residues were located at the non-reducing termini in PSGP. It is believed that terminal capping of the oligo(poly)sialyl chains by the KDN residues protects these chains from exosialidases. As a consequence, it enables PSGP to perform some required function during egg activation or early development. The compound has been synthesized several times by using the aldolase enzymes[4–6] or by local modification of the corresponding neuraminic acid.[3,7] On the other hand, chemical synthesis of **1** has been reported only once as a mixture without isolation.[8] We report here a concise chemical synthesis of KDN based on an indium mediated coupling reaction in aqueous medium (Scheme 1)[9] recently developed by us.

D-(+)-Mannose **2** has the same absolute configurations as KDN at C-5, -6, -7 and -8 and is an ideal precursor for the synthesis of KDN. The remaining three-carbon fragment can be supplied by methyl 2-bromomethylacrylate **3**. Normal synthetic methodologies would have required the protection of the hydroxy groups in **2** in order to carry out the coupling reaction between **2** and **3** in organic solvents. Recently, we found that such coupling reactions can be carried out efficiently in aqueous medium with indium.[9] Obviously, hydroxy functions in the substrate need not be protected under such conditions. Indeed, when **2** and **3** were coupled with indium in water, the stereoisomeric compounds **4** and **5** in a ratio of 6:1 were obtained in good yield. The mixture was then peracetylated with acetic anhydride in pyridine and a catalytic amount of 4-dimethylaminopyridine (DMAP). The major diastereoisomer **6**, obtained pure by flash column chromatography, was found to have the same *syn*-stereochemsitry as KDN. Ozonolysis of **6** in CH_2Cl_2 at −78 °C gave the ketoester **7** which without purification was treated with dilute HCl in methanol to give the methyl ester **8**.[10] Transformation of **8** according to a literature procedure[11] gave (+)-KDN.

After the success of this synthesis, a more concise route was developed in which the acetylation–deacetylation steps can also be eliminated. It was found that **4** could be easily obtained pure in 62% yield by recrystallization from methanol–EtOAc. Direct ozonolysis of **4** in methanol afforded the corresponding ketoester **9** which immediately cyclised to give the (+)-KDN methyl ester **8**. The same procedure[11] of saponification and ion-exchange chromatography produced the (+)-KDN **1** (79% yield from **4**) which was also characterised as its ammonium salt **10**.

The relatively good *syn*-selectivity in the coupling step deserves some comments. In the reaction of α-hydroxyaldehydes with nucleophiles in organic solvents, diastereoselectivity is usually explained by the chelation-Cram model.[12] Felkin's model predicts the same stereochemical outcome if the hydroxy group is considered to be of medium size.[13] In either case, the *syn*-stereochemistry is expected. Since the present coupling reaction is carried out in aqueous solution, the water molecules are expected to solvate the metal ion and compete with the chelation complex. Yet the *syn*-selectivity (6:1) is even better than that normally encountered in organic solvents. The same preference for *syn*-selectivity was observed recently by Whitesides *et al.* in the allylation of sugars with tin in aqueous media.[14] At present, we explain this selectivity by the Felkin model. However, it is entirely possible that the stereoselectivity may be due to factors associated with the metal surface in such heterogeneous reactions.



Scheme 1 *Reagents and conditions*: a, In, H_2O, room temp.; b, Ac_2O, pyridine, DMAP, room temp.; c, O_3, CH_2Cl_2, −78 °C, then Me_2S, room temp.; d, HCl, MeOH, room temp.; e, KOH (0.1 mol dm^{-3}), aq. MeOH, room temp.; f, NH_4OH (0.1 mol dm^{-3}), room temp.; g, O_3, MeOH, −78 °C, then Na_2SO_3, room temp.

The present synthesis has the advantage that the normal protection–deprotection methodogy associated with carbohydrate synthesis is not required. In that sense, it mimics the enzymic process.[6] The coupling reaction can be applied to a variety of substrates.[9] The overall approach thus provides a general synthesis for other sialic acids.

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