First total synthesis of (+)-3-deoxy-D-*glycero*-D-*galacto*-2-nonulosonic acid (KDN) from a non-carbohydrate source

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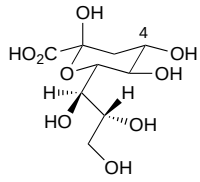
Enantiopure *cis*-1,2-dihydrocatechol 2, a product obtained by microbial oxidation of chlorobenzene, has been converted into KDN 1 *via* a ten step reaction sequence.

In 1986 Inoue isolated the deaminated sialic acid (+)-3-deoxy-D-*glycero*-D-*galacto*-2-nonulosonic acid (KDN, **1**) from the



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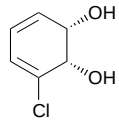

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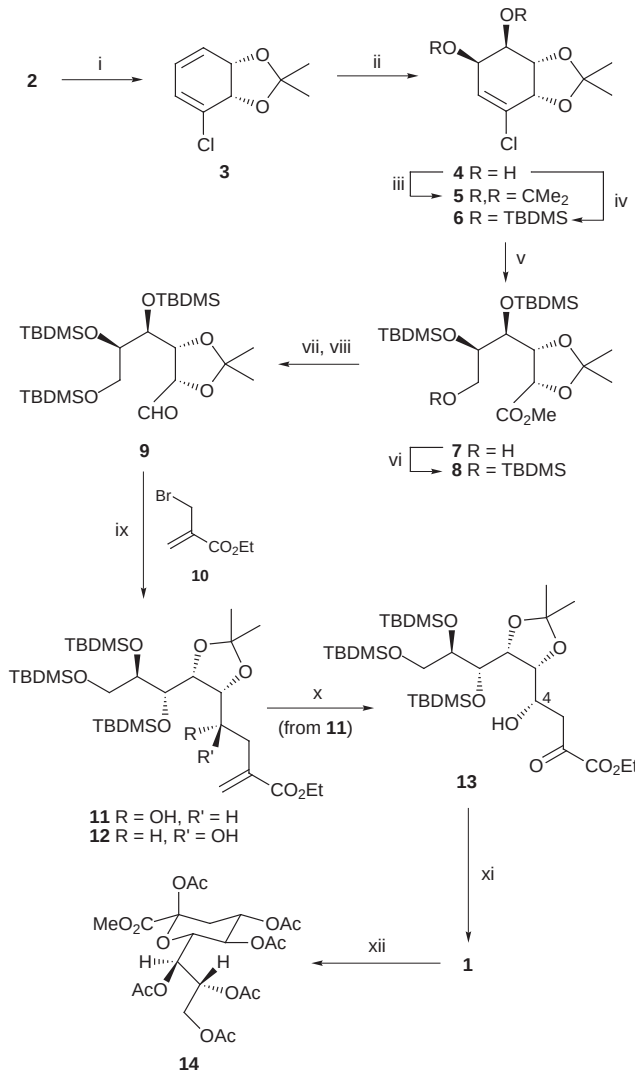
membrane polysialoglycoproteins of rainbow trout eggs.[1] Since KDN is likely responsible for protection of the egg membrane from attack by bacterial sialidases,[2] this compound is of interest as a sialic acid analogue that could be incorporated into other biologically relevant glycoproteins in order to protect them against sialidase activation by certain bacteria.[3] Such possibilities have sparked considerable interest in KDN glycoscience with the result that several syntheses of the title compound have now been reported.[1,4] All of these involve elaboration of carbohydrate-based starting materials. We now describe the first total synthesis of KDN from a non-carbohydrate source. The reaction sequence used will enable the preparation of novel analogues including those which incorporate ^{17}O-, ^{13}C- and/or ^{2}H-labels in various combinations. Such analogues[5] should be useful for probing the biological role(s) of KDN and related carbohydrate natural products.

The reaction sequence leading to compound **1** was inspired by the seminal work of Hudlicky and co-workers who have demonstrated the value of *cis*-1,2-dihydrocatechols as starting materials for the synthesis of various pentoses and hexoses.[6,7] In the present work (Scheme 1) the *cis*-1,2-dihydrocatechol **2**, which is obtained in >99% ee *via* microbial oxidation of chlorobenzene, was used. Thus, the acetonide derivative, **3**,[8] of compound **2** underwent regioselective and diastereofacially-selective *cis*-dihydroxylation on reaction with osmium tetraoxide and the resulting diol **4**[8] was reacted with 2,2-dimethoxypropane in the presence of toluene-*p*-sulfonic acid (TsOH) to give the *bis*-acetonide **5**‡ {99%, $[\alpha]_D$ + 68 (*c* 3.4)§}. Surprisingly, this last compound failed to react with ozone, perhaps because both faces of the π-bond are hindered by the *endo*-methyl groups associated with the adjacent 1,3-dioxolane rings. To circumvent such difficulties, diol **4** was converted into the corresponding bis(*tert*-butyldimethylsilyl ether) **6**[9] {83%, mp <25 °C, $[\alpha]_D$ − 56 (*c* 6.4)} which underwent smooth ozonolytic cleavage to give, after a reductive work-up with $NaBH_4$, the ester alcohol **7** {99%, $[\alpha]_D$ + 12 (*c* 6.8)}. The *tert*-butyldimethylsilyl ether derivative, **8** {100%, $[\alpha]_D$ + 2 (*c* 1.5)}, of the latter compound was then prepared in quantitative yield by standard methods. This compound was converted, over two conventional steps, into the unstable D-mannose derivative **9** {87% from **8**, $[\alpha]_D$ + 14 (*c* 5.8)}. Reaction of compound **9** with Vasella's pyruvate anion equivalent **10**,[10,11] under conditions we have used previously,[12] gave a *ca.* 2 : 3 mixture of the *syn*- and *anti*-addition products, **11** {37%, $[\alpha]_D$ + 10 (*c* 1.9)} and **12**



Scheme 1 *Reagents and conditions*: i, see ref. 8; ii, see ref. 8; iii, $Me_2C(OMe)_2$, TsOH (cat.), 18 °C, 1.0 h; iv, TBDMSCl (4 equiv.), imidazole (5 equiv.), DMF, 18 °C, 16 h; v, O_3, MeOH, −78 to 0 °C, 0.1 h, then $NaBH_4$ (4 equiv.), 18 °C, 2 h; vi, TBDMSOTf (1.5 equiv.), 2,6-lutidine (3 equiv.), CH_2Cl_2, 0 to 18 °C, 16 h; vii, LAH (1.5 equiv.), THF, −10 °C, 2 h; viii, $(COCl)_2$ (1.2 equiv.), DMSO, CH_2Cl_2, −78 to 0 °C, 1 h, then Et_3N (2.6 equiv.); ix, Zn dust (4.0 equiv.), sat. aq. NH_4Cl, THF, 0 to 18 °C, 1.5 h; x, O_3, MeOH, −78 °C, 0.033 h, then Me_2S (5 equiv.), −78 to 18 °C, 2 h; xi, 4 : 1 TFA–H_2O, 18 °C, 18 h; xii, Dowex 50W resin (H^+ form), MeOH, 6 h, 18 °C, then Ac_2O (10 equiv.), DMAP (trace), pyridine, 18 °C, 20 h

{52%, $[\alpha]_D$ + 16 (*c* 1.6)}, respectively. The components of this mixture were readily separated from one another by semi-preparative HPLC and compound **11** was then subjected to reaction with ozone. In this way the α-keto ester **13** {98%, $[\alpha]_D$ + 5 (*c* 2.2)} was obtained. Treatment of compound **13** with 4 : 1 TFA–water at 18 °C for 16 h resulted in deprotection of all the hydroxy groups as well as cyclisation to give KDN which was identical, as judged by ^{1}H NMR analysis, with an authentic sample prepared by enzymatic methods.[4g] For the purposes of further spectroscopic characterisation, KDN was esterified using MeOH and the intermediate methyl ester subjected to exhaustive acetylation. In this way the KDN derivative **14**[13] {68% from **13**, mp 100–104 °C; lit.,[13] 104–105 °C; $[\alpha]_D$ − 17 (*c* 1.9); lit.,[13] − 20 (*c* 0.7)} was obtained and the structure of this compound follows from spectroscopic data.¶ In addition, this material proved identical with a sample {$[\alpha]_D$ − 17 (*c* 1.2)} prepared from authentic KDN. Interestingly, while ozonylitic cleavage of compound **12** gave 4-*epi*-**13** {98%, $[\alpha]_D$ + 17 (*c* 5.0)}, sequential treatment of the latter compound with TFA–water, acidic MeOH then Ac_2O–pyridine only gave a complex mixture of uncharacterisable products.

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Notes and References

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‡ All new and stable compounds had spectroscopic data [IR, UV, NMR, mass spectrum] consistent with the assigned structure. Satisfactory combustion and/or high resolution mass spectral analytical data were obtained for new compounds and/or suitable derivatives.

§ All optical rotations were determined in $CHCl_3$ at 20 °C.

¶ *Selected data* for **14**: δ_H(300 MHz, $CDCl_3$) 5.40 (dd, *J* 6.4 and 2.3, 1 H), 5.27 (m, 1 H), 5.15 (dt, *J* 6.0 and 2.5, 1 H), 4.97 (t, *J* 9.7, 1 H), 4.43 (dd, *J* 12.2 and 2.2, 1 H), 4.19 (dd, *J* 10.1 and 2.4 Hz, 1 H), 4.14 (dd, *J* 12.2 and 5.8, 1 H), 3.78 (s, 3 H), 2.63 (dd, *J* 13.7 and 5.3, 1 H), 2.08 (obscured multiplet, 1 H), 2.16 (s, 3 H), 2.12 (s, 3 H), 2.07 (s, 3 H), 2.04 (s, 3 H), 2.02 (s, 3 H), 2.01 (s, 3 H); δ_C (75 MHz, $CDCl_3$) 170.6, 170.1, 170.0, 169.7, 169.6, 168.2, 166.0, 97.2, 71.4, 70.1, 68.7, 67.3, 66.8, 61.8, 53.2, 35.4, 20.8, 20.7, 20.6 (3 methyl carbon resonances obscured or overlapping); ν_{max}(KBr)/cm^{-1} 2961, 1750, 1437, 1372, 1233, 1169, 1114, 1055, 1013, 946; *m/z* (EI, 70 eV) 534 ($M^{+\cdot}$, < 1%), 433 (100), 373 (100) [HRMS: Calc. for $C_{22}H_{30}O_{15}$ ($M^{+\cdot}$), 534.1585. Found: 534.1583].

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