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REGIO- AND STEREOSELECTIVE SYNTHESIS OF THE CARBOCYCLIC ANALOGUE OF 3-DEOXY-β-D-MANNO-2-OCTULOPYRANOSONIC ACID (β-KDO) FROM (-)-QUINIC ACID.

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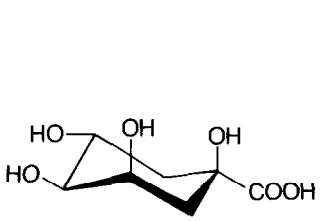
Abstract: The carbocyclic analogue of β-KDO has been synthesized from (-)-quinic acid.

Recent structural studies (1,2) on the 3-deoxy-D-manno-2-octulosonic acid (KDO) region of gram-negative bacterial lipopolysaccharide (LPS) have indicated that the KDO residues are present as α-glycosides, which suggests that it may be the β-anomer of KDO 2 which is being utilized by the bacterial enzymes involved in LPS biosynthesis. Therefore, we have synthesized a carbocyclic substrate analogue of β-KDO in order to investigate its effect on LPS biosynthesis.

Natural (-)-quinic acid, 1, was chosen as a starting material, because its functionality is obviously suitable for synthetic manipulation to give the required pseudo sugar, 3.



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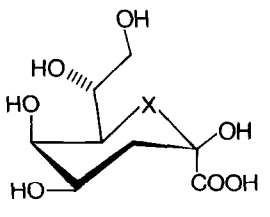
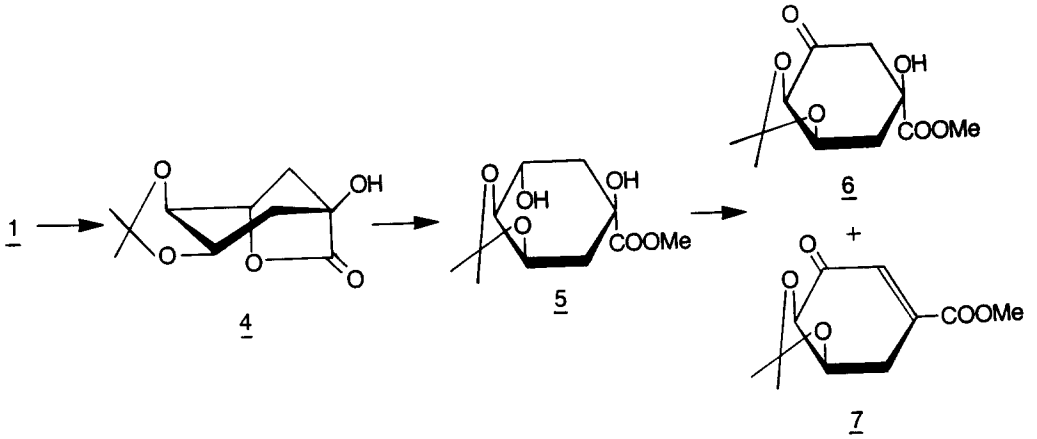
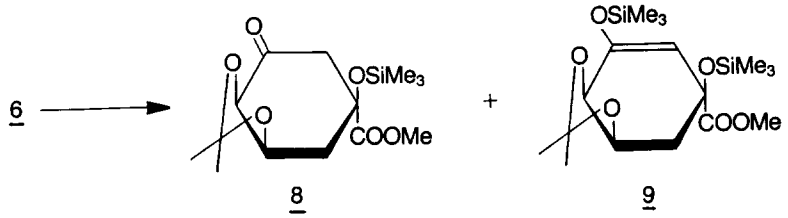


2; X=O
3; X=CH_2

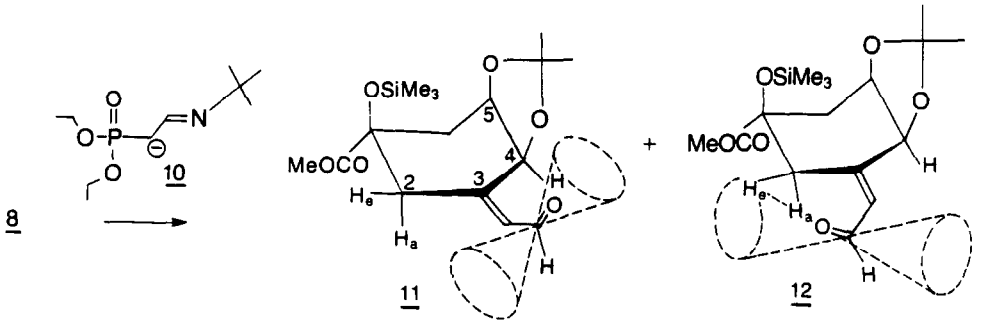
Thus, (-)-quinic acid was converted to the lactone derivative 4 in 85 % yield according to a literature method (3). Methanolysis (NaOMe, MeOH) of 4 gave methyl ester 5 {m.p. 59-60°C, $[\alpha]_D^{20}$ -30.4° (c 1 EtOH} which was oxidized (CrO_3 • 2 pyridine, CH_2Cl_2, 15 min, 25°C) to give ketone 6 {m.p. 70-1°C, $[\alpha]_D^{20}$ -5.2° (c 1 EtOH)} in 65 % yield from 4. A short (15 min.) reaction time in the oxidation step was found necessary in order to obtain a good yield of 6 and also minimize formation of the elimination product 7 {m.p. 96-97°, $[\alpha]_D^{20}$ -50.5° (c 1 EtOH), M^+ m/z 244}.



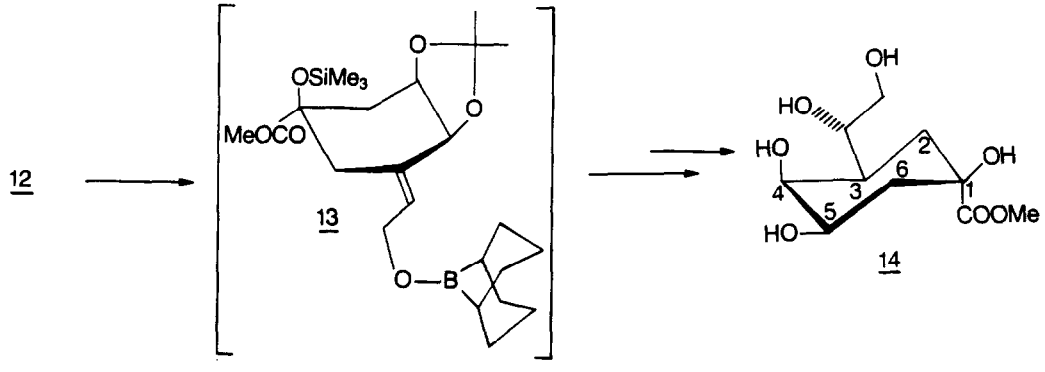
Attempts to silylate keto-alcohol 6 under standard conditions {pyridine, Me_3SiCl, $(Me_3Si)_2NH$} showed that the silyl derivative 8 was formed only very slowly. Reaction in the usual way with Me_3SiCl, DMAP, Et_3N was found to give mainly silyl enol ether 9 (57 %) together with the desired compound 8. However, by slow addition of a solution of DMAP (0.1 equiv.) followed by a solution of Et_3N (1.0 equiv.) to a mixture of Me_3SiCl and 6 in dichloromethane at 20°C an 80 % yield of 8 {m.p. 100-101°C, $[\alpha]_D^{20}$ +1.9° (c 1, EtOH)} could be obtained.



Next the side-chain was introduced via a modified Wittig reaction (4). Acetaldehyde-tert-butylimine was treated with lithium diisopropylamide in THF at -78°C and then with diethyl chlorophosphate at -10°C, to give the anion 10, which was then reacted with ketone 8 at -78°C to -10°C and the intermediate imine decomposed with oxalic acid/ water overnight. Work-up gave a 2:3 mixture of aldehydes 11 and 12 as an oil in 63 % yield. This mixture could be separated by liquid chromatography on silica gel (petroleum ether b.p. 40-60°C - isopropyl acetate, 80-20) to give 11 {m.p. 57-9°C $[\alpha]_D^{20}$ -12.4° (c 0.6 $CHCl_3$)} and 12 {m.p. 82-4°C $[\alpha]_D^{20}$ -37.1° (c 1 $CHCl_3$)}.
In the ^{1}H-nmr spectrum of 11 the shifts of 2He and 2Ha are centered at 2.7 ppm and the shifts of 4H and 5H are found at 5.2 and 4.5 ppm respectively, whereas in the spectrum of 12, 2He is found at 3.2 ppm. and 4H and 5H are centered at 4.5 ppm. These downfield shifts of 4H in 11 and 2He in 12 can be attributed to an anisotropy effect from the aldehyde carbonyl group (Figure) and implies that 11 has the Z-configuration and 12 the E-configuration. This was further established by a NOE-experiment on 12. Irridiation of 2He thus gave a 22 % signal increase for the aldehyde proton.



The transformation of aldehyde 11 or 12 to 14 was next considered. Inspection of models of 11 and 12 strongly suggested that hydroboration of the olefinic bond would take place from the exo face and 12 would thus give rise to the desired derivative of 14. A one step reduction-hydroboration with BH_3 · THF would be expected (5) to give elimination-rehydroboration of the intermediate borane-borate ester with reduction of both olefin and aldehyde as a net result, whereas substituted boranes (eg. 9-BBN) would be too unreactive to hydroborate this relatively hindered olefin. To avoid these complications a mixed borane procedure was applied. First aldehyde 12 was reduced with 9-BBN (THF, 0 °C) to give borinate ester 13, which was then directly subjected to hydroboration by BH_3 · THF (-30 °C - 10 °C) and oxidation (H_2O_2, NaOAc, +35 °C). Work-up and chromatography on silica gel gave an impure product, which was deprotected (pyridine · p-TsOH, EtOH, + 55 °C) (6) and chromatographed on silica gel to give pure 14 as an oil in 6 % yield from 12.

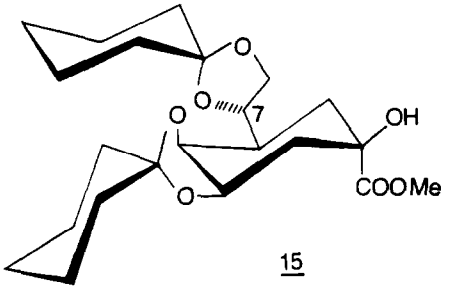


In order to establish the structure of 14 its 400 MHz ^{1}H-nmr-spectrum was analysed (Table). The vicinal couplings of the ring protons clearly showed that 14 has a $^4C_1$-conformation and that the side-chain is in the equatorial position (R-stereochemistry at C-3). Furthermore the coupling constants are in good agreement with those calculated for 14 in a $^4C_1$-conformation (see Table).

^{1}H-nmr data for 14

H	Shift (ppm)	Couplings (Hz)				Calculated ^{3}J couplings (7)		
2a	1.52	13	13			13.9		
2e	1.90	13	4	2.5		4.4		
3	1.67	13	8.5	4	2.5	4.4	13.9	2.6
4	4.08	-						
5	3.76	12.5	5	3.5		13.3	5.1	3.1
6a	1.77	12.5	12.5			13.3		
6e	2.19	12.5	5			5		

Since the configuration at C-7 was impossible to deduce from spectroscopic data, 14 was converted (ethoxycyclohexene, p-TsOH, DMF) to its dicyclohexylidene derivative 15 which could be crystallized from light petroleum {m.p. 95-7°C, $[\alpha]_D^{20}$ -10.5° (c 0.4 $CHCl_3$}. 15 was subjected to X-ray crystallography, which established the desired S-configuration at C-7.



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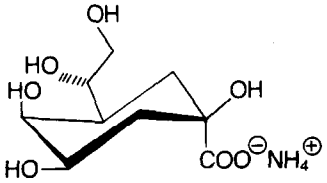

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Ester 14 was hydrolyzed and converted to the amorphorus ammonium salt 16 (aq. NaOH, then IR-120 NH_4^+) in quantitative yield.

Screening for potential inhibition of LPS-biosynthesis showed the carbocyclic β-KDO analogue 16 to have only moderate inhibitory properties.

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