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SYNTHESIS OF 2S-CARBOXY-3R,4R,5S-TRIHYDROXYPIPERIDINE; A NATURALLY OCCURRING INHIBITOR OF β-D-GLUCURONIDASE

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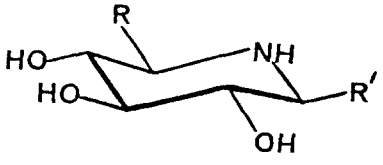
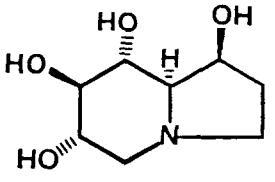
Summary: The glucuronic acid analog 5 of 1-deoxynojirimycin has been synthesized in good overall yield from D-glucose.

The study of specific glycosidase inhibitors represents a promising therapeutic approach to the regulation of such important metabolic processes as the breakdown of carbohydrate foodstuffs, the processing of eucaryotic glycoproteins and the catabolism of polysaccharides and other glycoconjugates.[1] Structures such as nojirimycin (1) and 1-deoxynojirimycin (2)[2] as well as the plant indolizidine alkaloid castanospermine (3)[3] alter the processing of N-linked glycans by inhibiting glucosidases. Other natural products such as 1-deoxymannojirimycin[4] and the indolizidine alkaloid swainsonine (4)[5] inhibit the action of mannosidases. Recently 5, the glucuronic acid analog of 1-deoxynojirimycin, was isolated from seeds of Baphia racemosa and shown to inhibit liver β-D-glucuronidase.[6] Such glucuronidases are involved in the degradation of mammalian glycosaminoglycans like hyaluronic acid, heparin sulfate and chondroitin sulfate which appear to play a central role in the development and differentiation of mammalian organisms. Here we report an expeditious synthesis of 2S-carboxy-3R,4R,5S-trihydroxypiperidine 5 from D-glucose.



1 R= CH_2OH, R'= OH
2 R= CH_2OH, R'= H
5 R= COOH, R'= H



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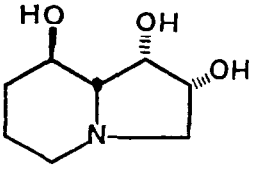

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Bromomercurial 7, the major product formed in the Hg^{++}-mediated cyclization of aminoalkene 6, was reductively oxygenated ($NaBH_4$-DMF-O_2) to alcohol 8 in 72% yield.[7-9] Oxidation of 8 to 10 was best accomplished in two stages. Using the Swern method (DMSO-oxalyl chloride), 8 furnished the sensitive aldehyde 9 (90%) which was immediately oxidized to acid 10 using $KMnO_4$ (acetone-H_2O, -10°C) in 40% yield. Exhaustive hydrogenolysis (Pd-C, EtOH, 96%) of 10 gave the title compound 5: mp 226-230°, $[\alpha]_D^{25}$ 22° (c= 0.3% w/w in H_2O); lit mp 228-230°, lit rotation[6] 18.5° (1% in H_2O).[9]

6

7 R= CH_2HgBr 9 R= CHO

8 R= CH_2OH 10 R= COOH

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9. Satisfactory 300MHz NMR, IR and mass spectral data (both EI and CI) were obtained for this and all other new compounds reported.

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