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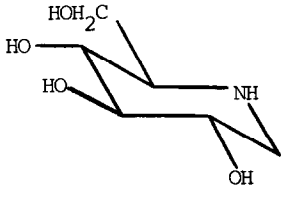
EFFICIENT PREPARATION OF ENANTIOMERICALLY PURE CYCLIC AMINOALDITOLS; TOTAL SYNTHESIS OF 1-DEOXYNOJIRIMYCIN AND 1-DEOXYMANNOJIRIMYCIN

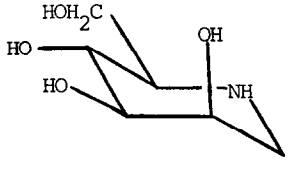
Ronald C. Bernotas and Bruce Ganem*
Department of Chemistry
Baker Laboratory
Cornell University
Ithaca, NY 14853

Summary: Expeditious new syntheses of the title compounds, which are potent glycosidase inhibitors, have been developed based on a high-yield, ring-forming aminomercuration.

Many polyhydroxylated alkaloids have been shown to affect the processing of biologically important carbohydrate chains.[1-4] The natural products 1-deoxynojirimycin (1)[5] and 1-deoxymannojirimycin (2)[6] represent a particularly interesting class of glycosidase inhibitors since they resemble azasugars having a basic nitrogen in place of the pyranose oxygen. The inhibition of specific intestinal glycosidases by such derivatives represents a promising approach to the treatment of carbohydrate-dependent metabolic disorders.[7] In addition, numerous reports have shown that 1 and 2 impair the normal biosynthesis of glycoproteins containing N-linked oligosaccharides of the complex type in animal cells.[8-9] In view of the heightened interest in (and demand for) these cyclic aminoalditols, we wish to report a general new synthesis of 1 and 2 by intramolecular aminomercuration.[10-11] Overall our method allows the direct conversion of a natural sugar into an aza-alditol having the same relative and absolute configuration.



1



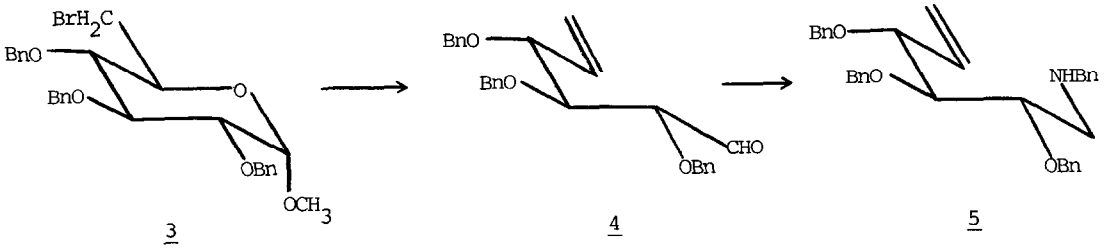
2

Tri-O-benzyl-6-bromopyranoside 3, the starting material for 1, was prepared in 73% overall yield from methyl-α -D-glucopyranoside after some improvements to the procedure of Vasella.[12] When bromoether 3 was heated at reflux (2h) in a mixture of HOAc-washed zinc dust (60 equiv) in 19:1 n-propyl alcohol:water containing benzylamine (16 equiv) and $NaBH_3CN$ (2 equiv), reductive ring opening occurred with concomitant reductive amination to afford aminoalkene 5 in 91% yield.[13] This yield was superior to a two-step process in which olefinic aldehyde 4 was isolated, then submitted to reductive amination (71% overall). The intramolecular aminomercuration of 5 was studied using a variety of mercuric salts in several different solvents. Under optimal conditions [mercuric trifluoroacetate (1.05 equiv), anhydrous THF], bromomercurials 6 and 7 could be isolated in 61% and 39% yield, respectively, after neutralization, ligand exchange and flash chromatography. Epimer 6 was converted to alcohol 9 by reductive oxygenation using $NaBH_4$-DMF-O_2 in 70% yield.[14] The overreduced by-product 10 could be minimized by presaturating the combination of $NaBH_4$-DMF with O_2, then adding a concentrated DMF solution of the mercurial over 1-2h while maintaining a vigorous O_2 flow. Hydrogenolysis of 9[10c] afforded pure (+)1-HCl in 28% overall yield, identical in every respect with an authentic sample.

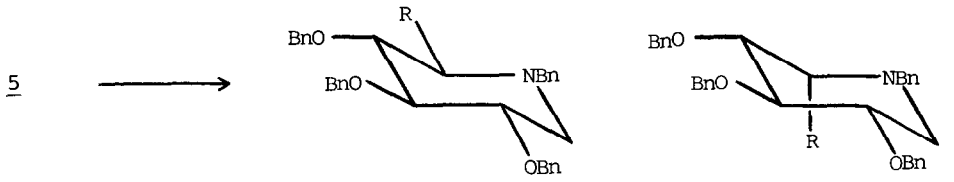
The yield of 1 could be increased by making use of the minor isomer 7 from the mercury—mediated cyclization of 5. Thus 8 could be oxidized using the method of Swern (DMSO, oxalyl chloride)[16] to aldehyde 11, whereupon epimerization (DBU, CH_2Cl_2) and reduction with $NaBH_4$ afforded additional 9. In this fashion 1-deoxynojirimycin could be obtained in 35% overall yield from methyl α -D-glucopyranoside, underscoring the efficiency of the approach.

By a parallel series of reactions, methyl-α -D-mannopyroside was transformed to aminoalkene 12 in high yield. Cyclization with $Hg(TFA)_2$ in THF and reductive oxygenation as described above afforded an 7:1 ratio of 13 and 14 in quantitative yield. The same ratio was also observed using I_2 as electrophile, thus ruling out any special mercury chelation effects. Swern oxidation of 13 followed by epimerization and reduction as previously described furnished 1-deoxymannojirimycin hydrochloride, mp 172.5-173.5°C; $[\alpha]_D$ -14.5° (c = .01, H_2O) in 13% overall yield from methyl-α-D-mannopyranoside.[13] Synthetic 1 and 2 were quantitatively indistinguishable from natural samples in bioassays with α and β-glucosidases and mannosidases.[15]

Several related cyclizations leading to other hexosidase inhibitors and factors controlling their stereoselectivity will be the subject of a future report.

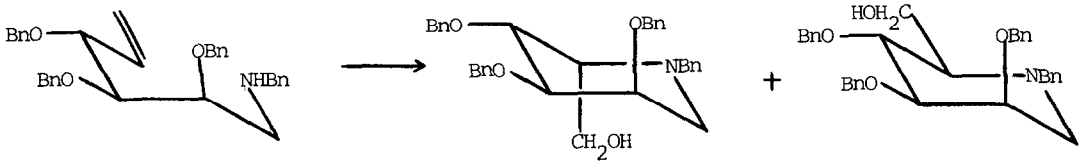


3 4 5



6 R= CH_2HgBr
9 R= CH_2OH
10 R= CH_3

7 R= CH_2HgBr
8 R= CH_2OH
11 R= CHO



12 13 14

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