A Rapid and Efficient Approach to Chiral, Nonracemic Aza Sugars from Nonsugars. A Formal Synthesis of 1,4-Dideoxy-1,4-imino-D-lyxitol

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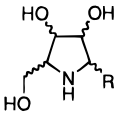
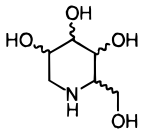
Azasugars **1** and **2** are particularly attractive synthetic targets because of their important biological properties which include glycosidase inhibition,[1] tumor growth inhibition,[2] and anti-HIV[3] behavior. The recent intense activity targeting the synthesis of azasugars has produced a large number of elegant and efficient routes based on carbohydrate[4] and noncarbohydrate[5] starting materials. Most of these routes, however, suffer from excessive length or from lack of selectivity.[4h,5e]

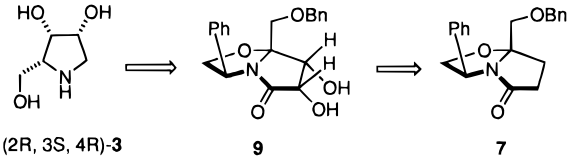


1 (R=H, Alkyl)



2

As a continuation of our studies describing stereoselective additions of heteroatoms to unsaturated chiral lactams,[6] we explored the diastereoselective dihydroxylation of **8** as a potential route to these important aza sugars, e.g., **3**. The implementation of this sequence



(2R, 3S, 4R)-**3** **9** **7**

required construction of the angularly substituted (benzyloxy)methylene lactam **7** followed by subsequent stereoselective steps leading to the appropriate diol **9**. The latter would then serve as the pivotal precursor, after removal of the chiral phenylglycinol moiety, to (2*R*,3*S*,4*R*)-1,4-dideoxy-1,4-imino-D-lyxitol, **3**, a known[1j,3,7] competitive inhibitor of α-galactosidase (green coffee beans).[1a] The synthetic route, depicted in Scheme 1, began with the alkylation of dihydrofuran **4** by treatment with *t*-BuLi in THF (0 °C) followed by benzyloxymethyl chloride (BOM-Cl, Fluka, 60% purity) to give crude furan derivative **5**. The crude substituted dihydrofuran **5** was then simultaneously hydrolyzed and oxidized[6d] by treatment with Jones reagent to furnish the keto acid **6**. Cyclodehydration of the latter with (*S*)-phenylglycinol[8] gave the chiral lactam **7** in 38% overall yield from dihydrofuran **4** without purification or isolation of any of the intermediates (**5** and **6**). Introduction of the unsaturation to produce **8** was accomplished in 85% yield by treatment with methyl phenylsulfinate and potassium hydride in THF, followed by thermal elimination of the intermediate sulfoxides in refluxing toluene.[9]

The key step to introduce the vicinal hydroxyl groups was accomplished with a catalytic quantity of osmium tetraoxide and stoichiometric *N*-methylmorpholine-*N* oxide (NMO) in aqueous acetone. An 80% yield of a 87:13 mixture of *endo*−*exo* diols **9** was obtained which was readily purified by chromatography and crystallization to provide the major component **9b** in 64% yield. The relative stereochemistry in **9b** was confirmed by X-ray crystallography which indicates preferential entry of the OsO_4 from the *endo* face. In preparation for the reductive cleavage of the C−O bond, the acetonide **10** was formed in 98% yield using dimethoxypropane and catalytic *p*-toluensulfonic acid in CH_2Cl_2.[10]

Reductive cleavage of the oxazolidine C−O bond in **10** was the final crucial step in the synthesis. This step had to proceed with high stereoselectivity to prevent the formation of **11** as an epimeric mixture at C-2 of the pyrrolidine ring. We have previously described related reductions of the fused aziridine[6c] lactam **13** and the fused cyclobutane[6d] lactam **14** which proceeded with a high degree of inversion of configuration at C-5 (Scheme 2). These results were interesting based on our previous observation of clean retention of configuration in reductions of simple unsubstituted bicyclic lactams.[11] By forming the acetonide in **10**, we had, in effect, added

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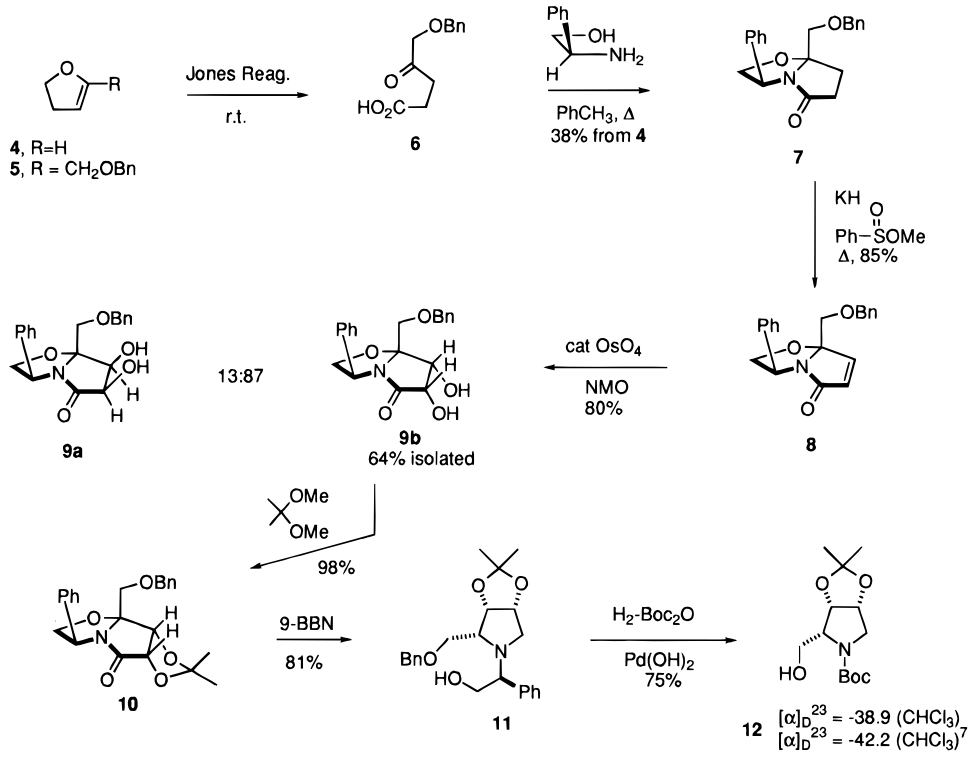
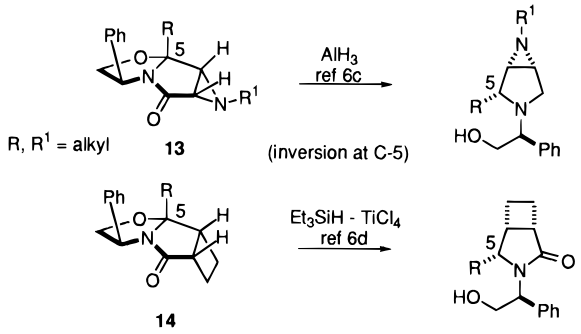
Scheme 1



Scheme 2



another "steric control element"[12] which was anticipated to also direct the reduction, *via* inversion of the benzyloxymethyl substituent, to the *all-cis* pyrrolidine, **11**. However, when the acetonide **10** was treated with alane under standard conditions,[11] the pyrrolidine **11** was formed in 85% yield but as a 2:1 mixture epimeric at C-2. A variety of conditions (solvents, temperature, different diol and angular protecting groups) failed to improve this disappointing ratio. Additional effort was directed at reducing the unmasked diol, **9b**, in the hope that the dialkoxyaluminum salt would itself serve as a bulky unit to enhance facial selectivity. However, the reaction proceeded poorly due to solubility problems associated with the alkoxide salts. Use of titanium-assisted silane reductions (Scheme 2) resulted in a variety of undesired side reactions including reduction of the acetonide ketal center. The problem of selectivity was finally overcome by reduction of the acetonide **10** with 9-BBN (THF, reflux, 10 equiv) which produced a single diastereomer of **11** in 81% yield. Subsequent hydrogenolysis of **11** with $Pd(OH)_2$ in the presence of di-*tert*-butyl dicarbonate (Boc_2O) gave, after chromatography, the *N*-Boc-lyxitol **12** in 75% yield, whose physical constants were identical to those previously reported.[7] The fact that (2*R*,3*S*,4*R*)-**12** was obtained confirmed that the 9-BBN reduction of the tricyclic intermediate **10** also proceeded with inversion at the angular benzyloxy group. Furthermore, the 9-BBN also conveniently reduced the lactam carbonyl, while the hydrogenation step (**11** → **12**) proceeded with simultaneous removal of the *N* and *O*-benzyl groups.

In summary, the asymmetric synthesis of **12**, well-known to be carried forward to **3**,[7] was accomplished in eight steps (12.3% from dihydrofuran) and in high enantiomeric purity from nonsugar precursors. Subsequent reports will describe synthetic routes to other members of these biologically important systems.

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Supporting Information Available: Experimental details and NMR spectra for **7**−**12** (11 pages).

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