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exo-Imino to *endo*-Iminocyclitol Rearrangement. A General Route to Five-Membered Antiviral Azasugars

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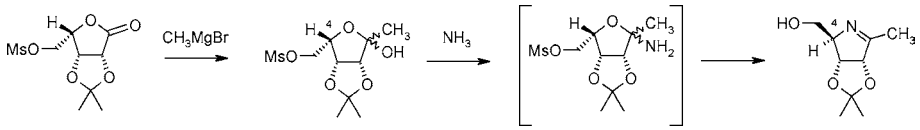
ABSTRACT



A facile synthesis is reported for five-membered iminocyclitols which allows for variation in stereochemistry at all the chiral centers, diverse C_1- and N-substitution, and the potential for a three-component combinatorial process. The key step is inversion at the C_4 stereocenter (L-lyxo sugar → D-ribono azasugar). The *exo*-imino to *endo*-iminocyclitol process was extended to the D-lyxo and the D- and L-hexose series. Some analogues were found to be more potent than *N*-butyl DNJ and *N*-nonyl DNJ in antiviral activity.

Azasugars are of considerable interest in modern glycobiology.[1] Recently, five-membered azasugars have assumed high biological significance, even eclipsing that of the better known six-membered deoxynojirimycin (DNJ)[2] and deoxygalactojirimycin (DGJ).[3] This is largely due to the work of Wong et al. who reported that members of this class of compounds were inhibitors of glycosidases and glycosyltransferases.[4] These workers showed, using a small library of five-membered C_1 alkyl-substituted analogues made using a Strecker synthesis, that selective inhibition of α-Glc-ase, α-Man-ase, α-Gal-ase, and β-Gal-ase could be effected.[4] The pyrrolidine ring system had 2(*R*), 3(*R*), 4(*S*), and 5(*R*) stereochemistries, and the ring could adopt either a galacto or a manno conformation. Our interest is in azasugars as antiviral compounds, e.g., hepatitis B virus (HBV),[5] hepatitis C virus (HCV),[6] and human immunodeficiency virus (HIV).[7] Among pyrrolidine azasugars, LAB1 (1,4-dideoxy-1,4-imino-L-arabinitol) was shown to inhibit both the cytopathic effect of HIV and the yield of infectious viruses.[8] A priori, one would expect that interference with the host cellular processing of carbohydrates by glucosidase inhibition could affect the infectivity of the virus by producing defective envelope glycoproteins.

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The mechanism of action of α-glucosidase inhibitors such as *N*-butyl and *N*-nonyl-DNJ upon HBV and bovine viral diarrhea virus (BVDV, a surrogate for HCV which causes human hepatitis C) is known in detail.[9] All of these flaviviridaes gain their glycoprotein envelope in the endoplasmic reticulum (ER). An obligate step is cleavage of the terminal glucose from oligosaccharide $(Gla)_3(Man)_9(GlcNAc)_2$ from an N-linked glycoprotein.[10]

We report now a general synthesis of five-membered iminocyclitols which allows for variation in the stereochemistry at all the chiral centers, diverse C_1- and N-substitution, and the potential for a three-component combinatorial process.[11]

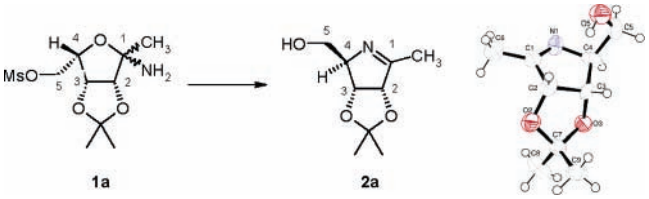
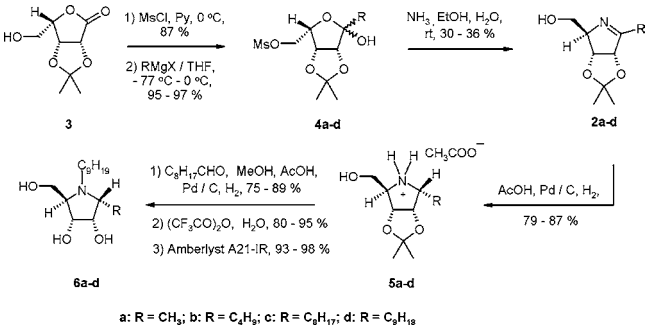


Figure 1. Basic reaction and X-ray structure of **2a**.

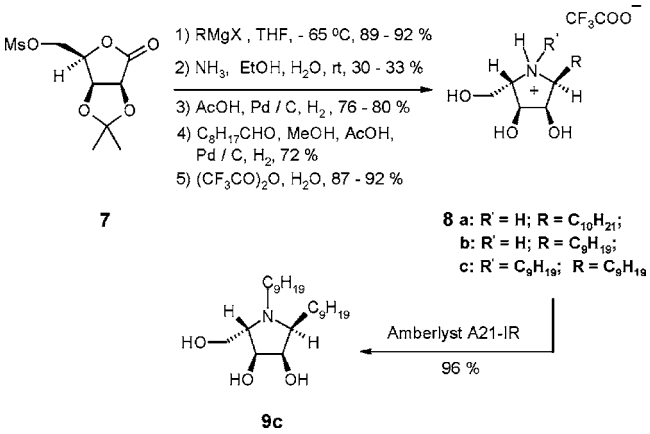
Figure 1 exemplifies the key step in the *exo*-imino to *endo*-iminocyclitol rearrangement in which the L-lyxo sugar (**1a**) is converted to the D-ribo iminocyclitol (**2a**). The X-ray structure of the D-ribo iminocyclitol (**2a**) is as shown. The reaction was generalized in the L-lyxo → D-ribo series (Scheme 1) with diversity in the C_1 alkyl substituent eventuating in the series of analogues **6a**−**d**.[12] The *N*-alkyl substituent is constant, C_9H_{19}, but this is independently variable based on the aldehyde used in the reductive amination step (**5** → **6**).[13]

Scheme 1. Synthesis of *N*-*n*-Nonyl-C_1-alkyl-1,4-imino-1,4-dideoxy-D-ribitols

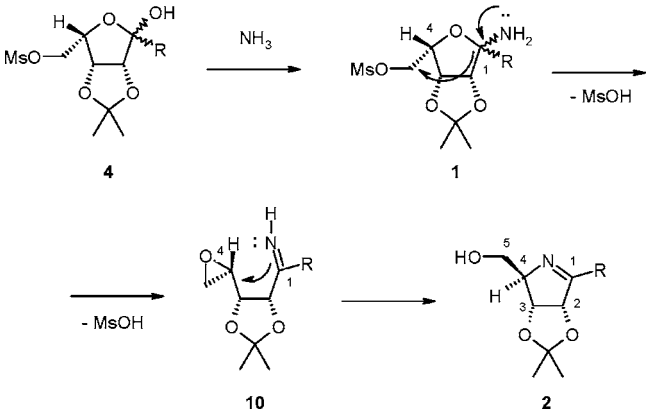


Members of the enantiomeric series of compounds have been made in the D-lyxo → L-ribo series (Scheme 2).[12] This is important because the C_4 (*S*) stereochemistry is the same as that for the C_2 amino carbon of α- and *β*-galactosyl ceramide as well as that for the C_3 and C_4 hydroxyl groups of α-galactosyl ceramide. α-Galactosyl ceramide is a potent anti hepatitis B agent, and the relationship between the linear acyclic ceramide structure and the cyclic azasugars has been pursued with respect to antiviral activity and glucosidase inhibitors.[14]

Scheme 2. Synthesis of *N*-*n*-Nonyl-C_1-alkyl-1,4-imino-1,4-dideoxy-L-ribitols



Scheme 3. Mechanism of *exo*-Imino to *endo*-Imino Rearrangement



The mechanism of **4** → **2** is shown in Scheme 3 with the key step being the intramolecular 5-exo-tet ring opening of the epoxide with inversion of configuration at C_4.[15a−d]

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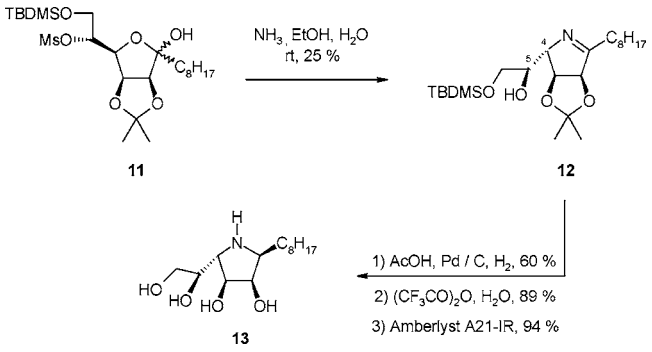
Wasserman et al. have shown that δ,ϵ-epoxyimines undergo intramolecular cyclization. Thus, 6,7-epoxy-2-heptanone upon treatment with benzylamine yielded *N*-benzyl-6-oxa-8-azabicyclo[3.2.1]octane. In contrast to **10** → **2**, in the epoxy heptanone system, the hydroxymethyl group adds intramolecularly to the imino double bond to yield the oxatropane.[15e] No evidence of such an intramolecular addition in the present epoxy imine system (**10**) was observed.

The *exo*-imino to *endo*-iminocyclitol process works equally efficiently in the D- and L-hexose series with the interesting consequence that a double inversion occurs at two carbon atoms, namely, C_4 and C_5. This process is illustrated by the conversion of the L-gulono analogue (**11**) to the 1,4-imino-1,4-dideoxy-D-talitol (**13**) (Scheme 4) and of the D-mannono

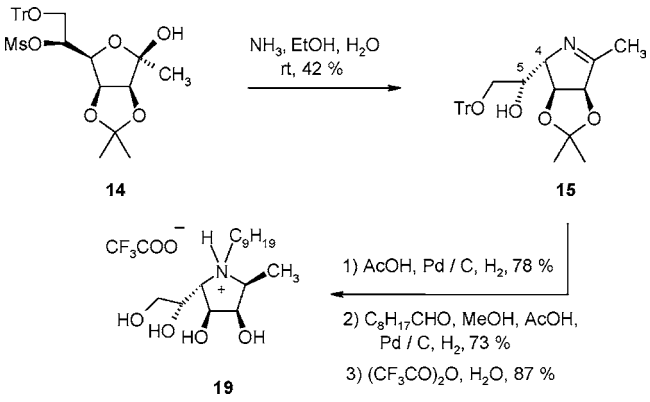
Scheme 4. Synthesis of C_1-Octyl-1,4-imino-1,4-dideoxy-D-talitol



analogue (**14**) to the 1,4-imino-1,4-dideoxy-L-allitol (**16**) (Scheme 5).[16]

The antiviral activity of selected C_1 monoalkyl and N,C_1 dialkyl analogues was evaluated in the bovine viral diarrhea virus assay (BVDV).[2] Compound **8b** having no alkyl group on nitrogen possesses an IC_{50} value of 1.5 μM. This value is superior to that for *N*-*n*-butyl DNJ (IC_{50} = 125 μM) and *N*-*n*-nonyl DNJ (IC_{50} = 10 μM).[9] The *N*-C_1-Dialkyl ana-

Scheme 5. Synthesis of *N*-*n*-Nonyl-C_1-methyl-1,4-imino-1,4-dideoxy L-allitol



logues **6d** (IC_{50} = 4.6 μM) and **9c** (IC_{50} = 8.2 μM) in the D-ribo and L-ribitol series, respectively, were less active relative to the *N*-desalkyl (NH) compound **8b**.

The general route to azasugars disclosed in this report fits within the context of other methods for their synthesis. For example, a number of C_1-substituted iminocyclitols have been synthesized from 5-*O*-TBDMS-1-*N*-dehydro-1,4-imino-2,3-*O*-isopropylidene-D-ribitol, which is formed by dehydrochlorination of the *N*-chloroamine and subsequent nucleophilic addition of lithium alkyls, aryls, and heteroaryls.[17−19]

The C_1 aryl compounds are powerful inhibitors for the nonspecific nucleoside *N*-ribohydrolases.[18] The C_1 nucleosides are called immucillins and are important PNP inhibitors.[19] In the present synthesis, the C_1 substituent is installed at an earlier stage and the troublesome dimerization and trimerization of the C_1-unsubstituted 1-*N*-pyrrolidines, used as starting materials, are avoided.

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Supporting Information Available: Experimental procedures and compound characterization data are available in a PDF file, and X-ray crystallographic data are available in a CIF for **2a**. This material is available free of charge via the Internet at http://pubs.acs.org

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(13) N-Alkylation, preferably C_8−C_9 is a requisite for BVDV and HCV activity. See: Mellor, H. R.; Nolan, J.; Pickering, L.; Wormald, M. R.; Platt, R. A.; Dwek, R. A.; Fleet, G. J.; Butters, T. D. *Biochem. J.* **2002** *366*, 225. $(CF_3CO)_2O/H_2O$ acts as a solvent for the substrate. The water affords a slow release of CF_3COOH necessary for hydrolysis.

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