ORGANIC LETTERS

2006
Vol. 8, No. 16
3465−3467

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

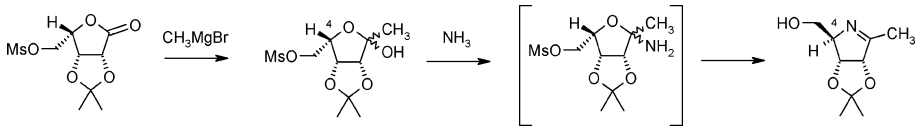
Robert M. Moriarty,*,† Carmen I. Mitan,† Norica Branză-Nichita,‡ Kenneth R. Phares,§ and Damon Parrish||

University of Illinois at Chicago, Department of Chemistry, Chicago, Illinois 60607, Institute of Biochemistry of the Romanian Academy, Splaiul Independentei 296, 77700 Bucharest, Romania, United Therapeutics Corporation Research, Triangle Park, North Carolina 27709, and Laboratory for the Structure of Matter, Department of the Navy, Naval Research Laboratory, Washington, D.C. 20375

moriarty@uic.edu

Received May 2, 2006

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.

† University of Illinois at Chicago.
‡ Institute of Biochemistry of the Romanian Academy.
§ United Therapeutics Corporation.
|| Laboratory for the Structure of Matter.

(1) (a) Winchester, B.; Fleet, G. W. J. *Glycobiology* **1992**, *2*, 199. (b) Look, G. C.; Fotsch, C. H.; Wong, C. H. *Acc. Chem. Res.* **1993**, *26*, 182. (c) Pearson, M. S. M.; Mathé-Allainmat, M.; Fargeas, V.; Lebreton, J. *Eur. J. Org. Chem.* **2005**, *11*, 2159.

(2) Mehta, A.; Ouzounov, S.; Jordan, R.; Simsek, E.; Lu, X.; Moriarty, R. M.; Jacob, G.; Dwek, R. A.; Block, T. M. *Antiviral Chem. Chemother.* **2002**, *13*, 299.

(3) Mehta, A.; Conyers, B.; Tyrrell, D. L. J.; Walters, K.-A.; Tipples, G. A.; Dwek, R. A.; Block, T. M. *Antimicrob. Agents Chemother.* **2002**, *46*, 4004.

(4) Saotome, C.; Wong, C.-H.; Kanie, O. *Chem. Biol.* **2001**, *8*, 1061.

(5) Mehta, A.; Carrouee, S.; Conyers, B.; Jordan, R.; Butters, T.; Dwek, R. A.; Block, T. M. *Hepatology* **2001**, *33*, 1488.

(6) (a) Zitzmann, N.; Mehta, A. S.; Carrouée, S.; Butters, T. D.; Platt, F. M.; McCauley, J.; Blumberg, B. S.; Dwek, R. A.; Block, T. M. *Proc. Natl. Acad. Sci. U.S.A.* **1999**, *96*, 11878. (b) Durantel, D.; Carrouée-Durantel, S.; Branza-Nichita, N.; Dwek, R. A.; Zitzmann, N. *Antimicrob. Agents Chemother.* **2004**, *48*, 497.

(7) Karpas, A.; Fleet, G. W. J.; Dwek, R. A.; Petursson, S.; Namgoong, S. K.; Ramsden, N. G.; Jacob, G. S.; Rademacher, T. W. *Proc. Natl. Acad. Sci. U.S.A.* **1988**, *85*, 9229.

(8) Behling, J. R.; Campbell, A. L.; Babiak, K. A.; Ng, J. S.; Medich, J.; Farid, P.; Fleet, G. W. J. *Tetrahedron* **1993**, *49*, 3359.

10.1021/ol061071r CCC: $33.50
Published on Web 07/15/2006

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]

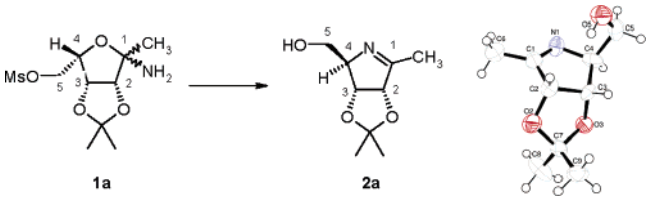
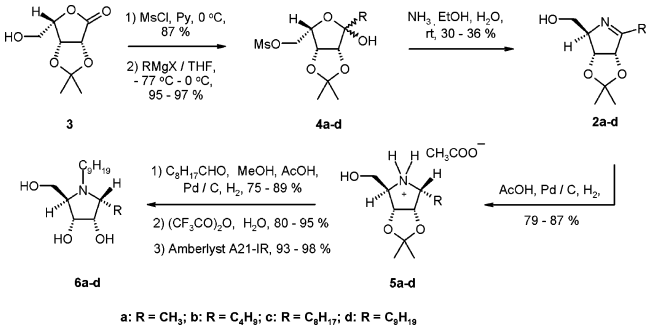


Figure 1. Basic reaction and X-ray structure of **2a**.

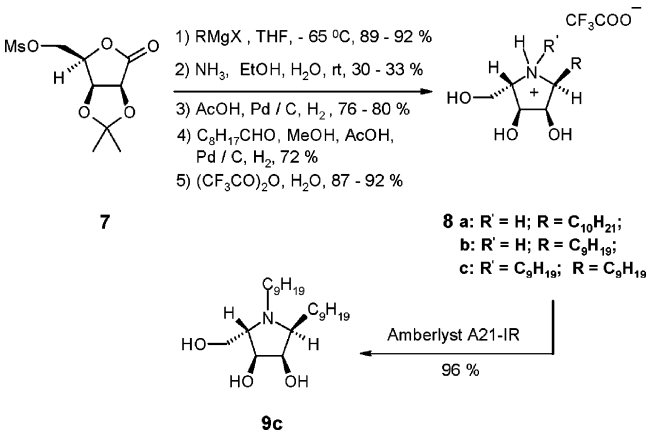
Figure 1 exemplifies the key step in the *exo*-imino to *endo*-iminocyclitol rearrangement in which the L-lyxo sugar (**1a**) is converted to the D-ribo iminocyclitol (**2a**). The X-ray structure of the D-ribo iminocyclitol (**2a**) is as shown. The reaction was generalized in the L-lyxo → D-ribo series (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



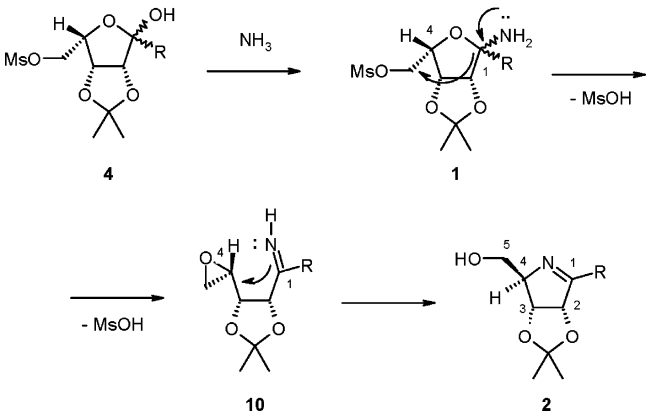
Members of the enantiomeric series of compounds have been made in the D-lyxo → L-ribo series (Scheme 2).[12] This is important because the C_4 (*S*) stereochemistry is the same as that for the C_2 amino carbon of α- and *β*-galactosyl ceramide as well as that for the C_3 and C_4 hydroxyl groups of α-galactosyl ceramide. α-Galactosyl ceramide is a potent

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



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 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]

(9) (a) Block, T. M.; Lu, X.; Platt, F. M.; Foster, G. R.; Gerlich, W. H.; Blumberg, B. S.; Dwek, R. A. *Proc. Natl. Acad. Sci. U.S.A.* **1994**, *91*, 2235. (b) Branza-Nichita, N.; Durantel, D.; Carrouée-Durantel, S.; Dwek, R. A.; Zitzmann, N. *J. Virol.* **2001**, *75*, 3527. (c) Durantel, D.; Branza-Nichita, N.; Carrouée-Durantel, S.; Butters, T. D.; Dwek, R. A.; Zitzmann, N. *J. Virol.* **2001**, *75*, 8987.

(10) (a) Lu, X.; Mehta, A.; Dwek, R.; Butters, T.; Block, T. *Virology* **1995**, *213*, 660. (b) Lu, X.; Mehta, A.; Dadmarz, M.; Dwek, R.; Blumberg, B. S.; Block, T. M. *Proc. Natl. Acad. Sci. U.S.A.* **1997**, *94*, 2380.

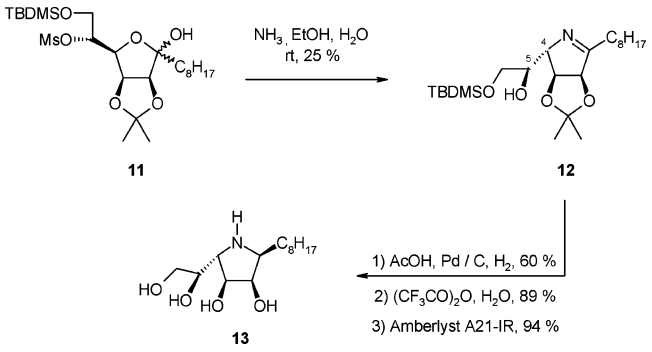
(11) For other recent combinatorial approaches, see: Chapman, T. M.; Davies, I. G.; Gu, B.; Block, T. M.; Scopes, D. I. C.; Hay, P. A.; Courtney, S. M.; McNeill, L. A.; Schofield, C. J.; Davis, B. G. *J. Am. Chem. Soc.* **2005**, *127*, 506.

(12) For related iminocyclitols, see: (a) Sifferlen, Th.; Defoin, A.; Streith, J.; Le Nouën, D.; Tarnus, C.; Dosbaâ, I.; Foglietti, M.-J. *Tetrahedron* **2000**, *56*, 971. (b) Wang, Y.-F.; Dumas, D. P.; Wong, C.-H. *Tetrahedron Lett.* **1993**, *34*, 403.

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

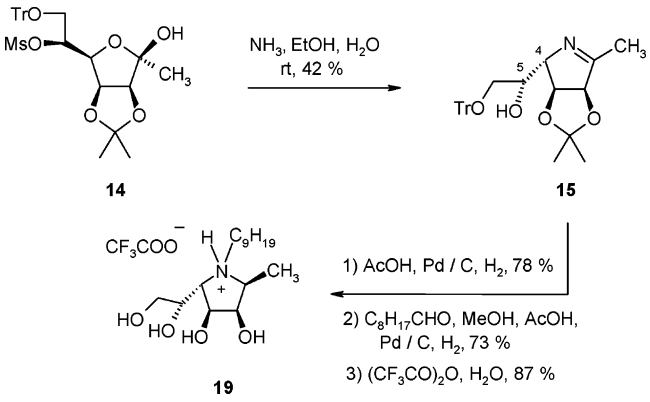
Scheme 4. Synthesis of C_1-Octyl-1,4-imino-1,4-dideoxy-D-talitol



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.

Acknowledgment. We thank the United Therapeutics Corporation (UTC) for support of this work under an unrestricted gift to the University of Illinois at Chicago. We are also grateful for valuable discussions of the biological results with scientists at UTC, Raymond A. Dwek and Terry D. Butters at the Department of Biochemistry, Oxford University, as well as insightful discussions of the chemistry with George Fleet of the Chemistry Department, Oxford University.

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

OL061071R

(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.

(14) (a) Mehta, A. S.; Gu, B.; Conyers, B.; Ouzounov, S.; Wang, L.; Moriarty, R. M.; Dwek, R. A.; Block, T. M. *Antimicrob. Agents Chemother.* **2004**, *48*, 2085. (b) Boucheron, C.; Desvergnes, V.; Compain, P.; Martin, O. R.; Lavi, A.; Mackeen, M.; Wormald, M.; Dwek, R.; Butters, T. D. *Tetrahedron: Asymmetry* **2005**, *16*, 1747.

(15) (a) Tenud, L.; Farooq, S.; Seibl, J.; Eschenmoser, A. *Helv. Chim. Acta* **1970**, *53*, 2059. (b) Baldwin, J. E. *J. Chem. Soc., Chem. Commun.* **1976**, *18*, 734. (c) A similar epoxide intermediate has been observed in the base hydrolysis of **7**. Treatment of **7** with aqueous ammonia takes a different pathway yielding the six-membered lactam, 5-amino-7-deoxy-2,3-*O*-isopropylidene, 1,5-lactam. See: Godskesen, M.; Lundt, I.; Madsen, R.; Winchester, B. *Bioorg. Med. Chem.* **1996**, *4*, 1857. (d) In the case of hydroxylamine, a five-membered nitrone is formed. See: Duff, F. J.; Vivien, V.; Wightman, R. H. *J. Chem. Soc., Chem. Commun.* **2000**, *21*, 2127. (e) Wasserman, H. H.; Thyes, M.; Wolff, S.; Rusiecki, V. *Tetrahedron Lett.* **1988**, *29*, 4973. Wasserman, H. H.; Rusiecki, V. *Tetrahedron Lett.* **1988**, *29*, 4977.

(16) (a) Cenci di Bello, I.; Fleet, G. W. J.; Namgoong, S. K.; Tadano, K.; Winchester, B. *Biochem. J.* **1989**, *259*, 855. (b) Al Daher, S.; Fleet, G.; Nagmoong, S. K.; Winchester, B. *Biochem. J.* **1989**, *258*, 613. (c) Lundt, I.; Madsen, R.; Al Daher, S.; Winchester, B. *Tetrahedron* **1994**, *50*, 7513.

(17) For a review of polyhydroxylated pyrrolidine cyclic imines, see: Chapman, T. M.; Davies, I. G.; Gu, B.; Block, T. M.; Scopes, D. I. C.; Hay, P. A.; Courtney, S. M.; McNeill, L. A.; Schofield, C. J.; Davis, B. G. *J. Am. Chem. Soc.* **2005**, *127*, 506.

(18) (a) Horenstein, B. A.; Zabinski, R. F.; Schramm, V. L. *Tetrahedron Lett.* **1993**, *34*, 7213. (b) Furneaux, R. H.; Limberg, G.; Tyler, P. C.; Schramm, V. L. *Tetrahedron* **1997**, *53*, 2915.

(19) (a) Evans, G. B.; Furneaux, R. H.; Gainsford, G. J.; Schramm, V. L.; Tyler, P. C. *Tetrahedron* **2000**, *56*, 3053. (b) Evans, G. B.; Furneaux, R. H.; Hutchison, T. L.; Kezar, H. S.; Morris, P. E., Jr.; Schramm, V. L.; Tyler, P. C. *J. Org. Chem.* **2001**, *66*, 5723. (c) Ting, L.-M.; Shi, W.; Lewandowicz, A.; Singh, V.; Mwakingwe, A.; Birck, Ma, R.; Ringia, E. A. T.; Bench, G.; Madrid, D. C.; Tyler, P. C.; Evans, G. B.; Furneaux, R. H.; Schramm, V. L.; Kim, K. *J. Biol. Chem.* **2005**, *280*, 9547.