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Communications

Rational Design of Aza Sugars via Biocatalysis: Mannojirimycin and Other Glycosidase Inhibitors

Tomas Hudlicky,*,† Jacques Rouden, and Hector Luna

Chemistry Department, Virginia Polytechnic Institute and State University, Blacksburg, Virginia 24061

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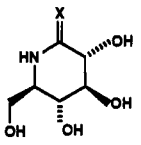
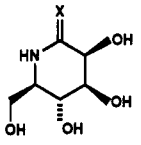
Summary: Mannojirymicin **2a**, its C-5 epimer **13**, and mannosidase inhibitor **3a** have been synthesized from chlorobenzene via enzymatic hydroxylation followed by stereoselective amination and oxidative cleavage of the 1-chlorocyclohexa-4,5-diene-2,3-diol.

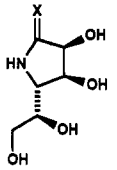
Compounds that selectively inhibit glycosidases have attracted interest because of the significance of such inhibition to both viral expression[1] and tumor growth.[2] The synthesis of nojirimycin derivatives **1**, mannojirimycins **2**, and the five-membered aza sugars **3** have been



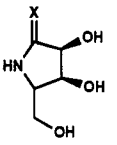
1a X = O
1b X = H_2



2a X = O
2b X = H_2

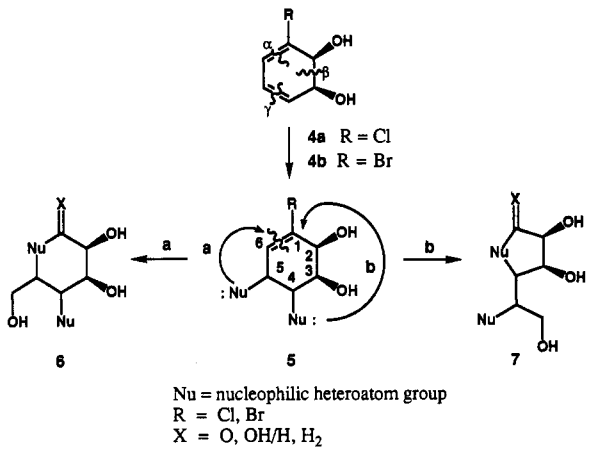


3a X = O
3b X = H_2



3c X = O
3d X = H_2

accomplished by numerous approaches from either carbohydrates or other naturally occurring compounds[3] by employing aldolases[4] or by combination of microbial oxidation with chemical synthesis.[5] As a part of a biocatalysis program directed at an exhaustive and general synthesis of monosaccharides of any stereomeric or enantiomeric constitution,[6a,b] we became interested in a similar general approach to aza sugars of type **6** and **7** (Nu = NR), Figure 1, by taking advantage of the immense



6 5 7

Figure 1. Design of heterosubstituted five- and six-membered sugar derivatives.

versatility of halocyclohexadiene-*cis*-diols such as **4** in enantiocontrolled synthesis.

Whereas the efficiency of the aldolase approaches is exemplary, for example, the development of a divergent

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(2) Bernacki, R. J.; Korytnyk, W. *Cancer Metastasis Rev.* **1985**, *4*, 81.

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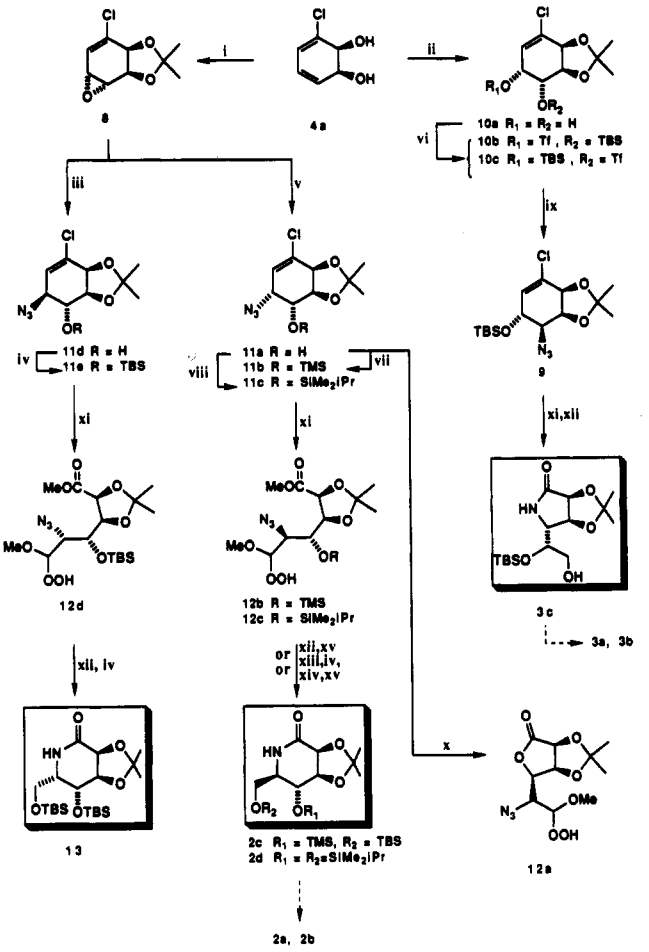
0022-3263/93/1958-0985$04.00/0

approach that addresses the preparation of any stereoisomer from a single starting material would be equally beneficial. Recent commercial availability of cyclohexadiene-*cis*-diols[7] and the demonstrated availability of a protocol for the exhaustive control of further peripheral oxygenation of diols 4 to carbohydrate derivatives and cyclitols of both enantiomeric series[6a,b,f] bode well for an approach to aza sugars where the peripheral substitution as well as the placement of the heteroatom would be similarly controlled. The preparation of biologically important compounds by methods based on the combination of biotransformations with organic synthesis[8] is rapidly gaining dominance in the pharmaceutical industry, where the use of efficient and environmentally benign procedures is important.

Our strategy, described in Figure 1, relies on the stereocontrolled introduction of heteroatoms at either C-4 or C-5 and subsequent oxidative cleavage of the vinyl halide with concomitant closure of the peripheral heteroatom onto the latent carboxylate at C-1 (at the stage of ozonide reduction) to yield either five- or six-membered heterosugars as defined by the placement of the heteroatom. Furthermore, all three sites (α, β, and γ) in diols 4 are susceptible to oxidative cleavage at any stage of functionalization; thus, the preparation of any heteroatom-substituted sugar can simply be reduced to precise design and planning of the order of reaction steps that are to be executed along the periphery of the diol such as 4. In this manuscript we describe the successful implementation of this strategy to the synthesis of several aza sugar derivatives.

Diol **4a**[6a,c] was protected as an acetonide (DMP, *p*-TSOH, quant.) and converted to epoxide **8** with *m*-CPBA (80%), Scheme I. Stereoselective generation of azido alcohol **11d** (this compound was originally reported in the literature[6a] as **9** due to an erroneous structure assignment)[9] was accomplished with NaN_3/NH_4Cl (88%), whereas the diastereoisomeric syn azido alcohol **11a** was attained by LiCl/ethyl acetoacetate[10] opening of the epoxide followed by inversion of the chloro alcohol with NaN_3 in DMF (83%). The details of the stereoelectronic parameters associated with the opening of epoxides such as **8** have been reported by our group,[6a] as well others,[6f,l-n] and as evidenced by the structure misassignment, are not easily

Scheme I[a]



[a] Reagents: (i) dimethoxypropane, H^+, *m*-CPBA/phosphate buffer; (ii) dimethoxypropane, H^+; OsO_4, NMO; (iii) NaN_3, NH_4Cl; (iv) TBSCl, DiPEA; (v) LiCl, ethyl acetoacetate; NaN_3; (vi) TBSCl, imidazole; Tf_2O, pyridine; (vii) HMDS/TMSCl; (viii) iPrMe$_2$SiCl, imidazole; (ix) NaN_3, DMF; (x) O_3, MeOH, $NaHCO_3$, −78 °C; (xi) O_3, MeOH–H_2O, $NaHCO_3$, −78 °C; (xii) $NaBH_4$, $CeCl_3$, −20 °C; H_2, Pd–C; (xiii) $NaBH_4$, THF–MeOH, 0 °C, H_2, Pd–C; (xiv) DMS, $Zn(BH_4)_2$, −78 °C; H_2, Pd–C; (xv) iPrMe$_2$SiCl, DBU.

(4) (a) Ziegler, T.; Straub, A.; Effenberger, F. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 716. (b) von der Osten, C. H.; Sinskey, A. J.; Barbas, D. F., III; Pederson, R. L.; Wang, Y.-F.; Wong, C.-H. *J. Am. Chem. Soc.* **1989**, *111*, 3924. (c) Kajimoto, T.; Chen, L.; Liu, K. K.-C.; Wong, C.-H. *J. Am. Chem. Soc.* **1991**, *113*, 6678. (d) Pederson, R. L.; Kim, M.-J.; Wong, C.-H. *Tetrahedron Lett.* **1988**, *29*, 4645.

(5) Kinast, G.; Schedel, M. *Angew. Chem., Int. Ed. Engl.* **1981**, *20*, 805.

(6) For other applications of this strategy see: (a) Hudlicky, T.; Luna, H.; Olivo, H. F.; Andersen, C.; Nugent, T.; Price, J. D. *J. Chem. Soc., Perkin Trans. 1* **1991**, 2907. (b) Hudlicky, T.; Fan, R.; Tsunoda, T.; Luna, H.; Andersen, C.; Price, J. D. *Isr. J. Chem.* **1991**, *30*, 229. (c) Hudlicky, T.; Price, J. D.; Fan, R.; Tsunoda, T. *J. Am. Chem. Soc.* **1990**, *112*, 9439. (d) Hudlicky, T.; Olivo, H. F. *Tetrahedron Lett.* **1991**, *32*, 6077; *J. Am. Chem. Soc.* **1992**, *114*, 9694. For recent examples of the applications of arene diols to synthesis by other leading authors see: (e) Ley, S. V.; Yeung, L. L. *Synlett* **1992**, *291*, 997. (f) Carless, H. A. J. *Tetrahedron Lett.* **1992**, 6379. Carless, H. A. J.; Busia, K. *Carbohydr. Res.* **1992**. *234*, 207. (g) Roberts, S. M.; Downing, W.; Latouche, R.; Pitoll, C. A.; Pryce, R. J.; Ryback, G.; Williams, J. *J. Chem. Soc., Perkin Trans. 1* **1990**, 2613. (h) Boyd, D. R.; Dorrity, R. M. J.; Hand, M. V.; Malone, J. F.; Sharma, N. D.; Dalton, H.; Gray, D. J.; Sheldrake, G. N. *J. Am. Chem. Soc.* **1991**, *113*, 666. Boyd, D. R.; Sharma, N. D.; Boyle, R.; McMordie, A. S.; Chima, J.; Dalton, H. *Tetrahedron Lett.* **1992**. 1241. Boyd, D. R.; Davies, J. H.; Hamilton, L.; McCullough, J. J. *J. Chem. Soc., Perkin Trans. 1* **1992**, 31. (i) Banwell, M. G.; Corbett, M.; Mackay, M. F. *J. Chem. Soc., Perkin Trans. 1* **1992**, 1. (j) Johnson, C. R.; Ple, P. A.; Su, L.; Heeg, M. J.; Adams, J. P. *Synlett* **1992**, 388. (k) Schurle, K.; Beier, B.; Piepersberg, W. *J. Chem. Soc., Perkin Trans. 1* **1991**, 2407. For studies of nucleophilic opening of cyclohexene oxide see: (l) Chini, M.; Crotti, P.; Flippin, L. A.; Macchia, F.; Pineschi, M. *J. Org. Chem.* **1992**, *57*, 1405. (m) Chini, M.; Crotti, P.; Flippin, L. A.; Gardelli, C.; Macchia, F. *J. Org. Chem.* **1992**, *57*, 1713. (n) Carless, H. A. J.; Malik, S. S. *Tetrahedron: Asymmetry* **1992**, *3*, 1135. See also ref 6f above. For the preparation of diol **4a** on a laboratory scale see: (o) Hudlicky, T.; Boros, C. H.; Boros, E. E. *Synthesis* **1992**, 174.

(7) The diols derived from chloro- and bromobenzene are now prepared crystalline and on a multikilogram scale by Genencor International, Inc.; over 20 other diols derived from substituted aromatics compounds are commercially available from the following sources: Genencor International, Inc., Rochester, NY; ICI Fine Chemicals, Manchester, U.K.; Enzymatix, Cambridge, U.K.; Janssen Chimica, Geel, Belgium.

(8) For reviews on enzymatic methods of synthesis, see: (a) Drueckhammer, D. G.; Hennen, W. J.; Pederson, R. L.; Barbas, C. F., III; Gautheron, C. M.; Krach, T.; Wong, C.-H. *Synthesis* **1991**, 499. (b) Klibanov, A. M. *Acc. Chem. Res.* **1990**, *23*, 114. (c) Pratt, A. J. *Chem. Brit.* **1989**, *25*, 282. (d) Turner, N. J. *Nat. Prod. Rep.* **1989**, 625. (e) Yamada, H.; Shimizu, S. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 622. (f) Roberts, S. M. *Chem. Ind.* **1988**, 384. For comprehensive reviews of cyclohexadiene-*cis*-diol chemistry see: (g) Brown, S. M. In *Organic Synthesis: Theory and Practice*; Hudlicky, T., Ed.; JAI Press: Greenwich, CT, 1992; Vol. 2, in press. (h) Widdowson, D. A.; Ribbons, D. A.; Thomas, S. D. *Janssen Chim. Acta* **1990**, *8*, 3. (i) Carless, H. A. J. *Tetrahedron: Asymmetry* **1992**, *3*, 795.

(9) The structure of azide **9** was originally incorrectly assigned during studies reported in ref 6a above. Subsequent structure proof showed that **11d** rather than **9** is the product in the reaction of epoxide **8** with azide. This opening is fully regiospecific, and only a trace of **9** can be detected in the reaction mixtures. Details of the discrepancies that led to errors in the structure elucidations of **9** and **11d** will be published in *J. Chem. Soc., Perkin Trans. 1* in the near future.

(10) Bajwa, J. S.; Anderson, R. C. *Tetrahedron Lett.* **1991**, 3021.

understood. The regioisomeric azide **9** was thus prepared by inversion via triflate **10c** derived from diol **10a**[6a] using a published procedure[3j,11] rather than by the opening of epoxide **8**.[9]

The crucial ozonolysis of **9** and **11** was investigated in detail because the ozonolysis of vinyl halides, especially those flanked by oxygen functionalities, constitutes a nontrivial problem.[12] Ozonides of these systems frequently rearrange, undergo further oxidation, or self-reduce[12l] and the workup sequences must be carefully monitored in order to control the oxidation state of the carboxylate (i.e., lactone, lactol, or hydroxymethylene). With a free hydroxyl group, ozonolysis of **11a** in methanol gave the stable azido hydroperoxide **12a** (quantitative), whereas for protected compounds **11b**, **11c**, and **11e**, the same oxidative cleavage in methanol–water led primarily to the ester azido hydroperoxides **12b**, **12c**, and **12d**, respectively (92–100%). Hydroperoxide **12b** was titrated with $NaBH_4$ in THF–MeOH to reduce the hydroperoxyacetal to a hydroxymethylene group (44% from **11b**), whereas the peroxide **12c** was subjected to initial reduction with dimethyl sulfide providing an unstable azido aldehyde that was reduced to an azido hydroxymethylene product with $Zn(BH_4)_2$ in Et_2O (59% from **11c**). An improved reductive workup of the ozonolysis of **9** and the reduction of **12c** and **12d** involved the treatment of the ozonide or the hydroperoxides with $NaBH_4/CeCl_3$ in $MeOH/H_2O$ at −20 °C. Subsequent hydrogenation of the azido group (and protection of the hydroxyls)[13] afforded cleanly the lactams **2d**, **3c**, and **13**, which can be easily converted through deprotection and/or reduction to five- or six-membered aza sugars such as **3a** and **3b** or mannojirimycin (**2a**) and deoxymannojirimycin (**2b**), according to known procedures.[14]

With the synthesis of **2a**, **3a**, **12a**, and **13** from diol **4** in only a few steps, it appears that many aza sugars of this type are readily accessible, as it is possible to prepare all eight possible isomers of azido or amino alcohols derived from **8** or **10a** by carefully controlled and stereospecific introduction of other functionalities. All compounds are derived from a single enantiomer of the starting material in synthetic sequences far shorter than any corresponding manipulations of known carbohydrates, which generally necessitate protective manipulations or inversions of stereocenters and become quite arduous and lengthy. We will report on further application of cyclohexadiene-*cis*-diols in enantioselective synthesis in due course.

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Supplementary Material Available: ^1H and ^{13}C NMR spectra for compounds described in Scheme I and full characterization data and experimental details (47 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

Registry No. **2a**, 62362-63-4; **2c**, 144303-23-1; **2d**, 144303-24-2; **3a**, 144303-17-3; **3c**, 144303-19-5; **4a**, 86992-79-2; **8**, 138913-30-1; **8** *trans*-chlorohydrin derivative, 139559-62-9; **9**, 139432-84-1; **9** TBS derivative, 144303-27-5; **10**, 144303-18-4; **10** 6-alcohol derivative, 144303-28-6; **11a**, 139432-85-2; **11b**, 144303-20-8; **11c**, 144303-21-9; **12a**, 144303-22-0; **12b**, 144303-25-3; **12b** 6-alcohol derivative, 144303-29-7; **12c**, 144303-26-4; **12c** 6-aldehyde derivative, 144303-30-0; **12c** 6-alcohol derivative, 144303-31-1; **12c** silylated 6-alcohol derivative, 144303-32-2.

(11) The allylic triflate **10b** is also produced during the reaction sequence but, because of its high reactivity, is conveniently removed during workup as a pyridinium salt.

(12) (a) Bailey, P. S. In *Ozonation in Organic Chemistry*; Bloomquist, A. T., Wasserman, H. H., Eds.; Academic Press: New York, 1978; Vol. 1. (b) Bailey, P. S. In *Ozonation in Organic Chemistry*; Bloomquist, A. T.; Wasserman, H. H., Eds.; Academic Press: New York, 1982; Vol. 2. (c) Griesbaum, K.; Hofmann, P. *J. Am. Chem. Soc.* **1976**, *98*, 2877. (d) Griesbaum, K.; Keul, H. *Can. J. Chem.* **1980**, *58*, 2049. (e) Griesbaum, K.; Neumeistert, J.; Huh, T.-S. *Can. J. Chem.* **1981**, *59*, 3188. (f) Gab, S.; Turner, W. V. *J. Org. Chem.* **1984**, *49*, 2711. (g) Griesbaum, K.; Bandyopadhyay, A. R.; Meister, M. *Can. J. Chem.* **1984**, *64*, 1553. (h) Griesbaum, K.; Bandyopadhyay, A. R. *Can. J. Chem.* **1987**, *65*, 487. (i) Griesbaum, K.; Meister, M. *Chem. Ber.* **1987**, *120*, 1573. (j) Dillen, J. L. M.; Meth-Cohn, O.; Moore, C.; van Rooyen, P. H. *Tetrahedron* **1988**, *44*, 3127. (k) Griesbaum, K.; Greinert, R. *Chem. Ber.* **1990**, *123*, 391. (l) Griesbaum, K.; Krieger-Beck, P.; Beck, J. *J. Org. Chem.* **1991**, *56*, 4005. (m) Turner, W. V.; Gab, S. *J. Org. Chem.* **1992**, *57*, 1610.

(13) TBS group for **2c**, **3c**, and **13** and $iPr(Me)_2Si$ group for **2d**. This protection is not necessary for the azidohydrogenation to obtain the lactam ring, but it is indispensable for further synthetic steps with those compounds.

(14) (a) Fleet, G. W. J.; Ramdsen, N. G.; Molyneux, R. J.; Jacob, G. S. *Tetrahedron Lett.* **1988**, 3603. (b) Fleet, G. W. J.; Ramdsen, N. G.; Witty, D. R. *Tetrahedron Lett.* **1988**, *29*, 2871.