Microbial Oxidation of Aromatics in Enantiocontrolled Synthesis. 2.[1] Rational Design of Aza Sugars (*endo*-Nitrogenous). Total Synthesis of (+)-Kifunensine, Mannojirimycin, and Other Glycosidase Inhibitors[2]

Tomas Hudlicky,*,† Jacques Rouden, Hector Luna, and Scott Allen‡

Contribution from the Department of Chemistry, Virginia Polytechnic Institute and State University, Blacksburg, Virginia 24061-0212

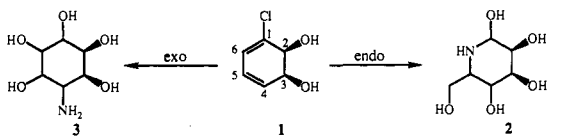
Received October 27, 1993⊛

Abstract: A general method of synthesis for lactones and lactams related to carbohydrates has been developed that relies on the biocatalytic generation of 1-chloro-2,3-dihydroxycyclohexa-4,6-diene (**1**), obtained in excellent yield by fermentation of chlorobenzene with *Pseudomonas putida* 39D, followed by further functionalization to nitrogen-substituted cyclitols. These amino or azido cyclitols of type **15** are then subjected to controlled ozonolysis, which yields either lactones such as **27** or lactams containing five-membered (**28**) or six-membered (**20** and **23**) rings. Such compounds are useful intermediates for the preparation of aza sugars. Mannojirimycin (**8a**) has been synthesized in seven steps from chlorobenzene. Kifunensine (**7**) has been prepared in 11 steps from chlorobenzene following an intersection with Hashimoto's procedure. Full experimental and spectral details are provided for all compounds. The potential of this general method and implications of the disclosed design features in the field of amino sugar and aza sugar synthesis are indicated.

Introduction

Carbohydrates, amino sugars, and their carbocyclic analogs (conduramines) account for diverse classes of compounds with a fascinating spectrum of biological activities,[3] including the inhibition of glycosidic enzymes[4] and tumor metastasis.[5] Nitrogenous carbohydrate derivatives find utility as antiobesity drugs,[6] fungistatic compounds,[7] insect antifeedants,[8] and antivirals,[9] including substances active against the human immunodeficiency virus (HIV).[10] In addition, these compounds provide challenging targets in organic synthesis,[11] which requires judicious method development in order to depart from the classical carbohydrate-to-carbohydrate conversions, which are tedious and impractical.

In a related paper,[1] we have described a divergent strategy for the design of carbohydrates and cyclitols by rational manipulation of cyclohexadiene-*cis*-diols such as **1**. Because the oxidative cleavage of C1–C6 olefin provides carbonyl termini differentiated by their relative oxidation states, it seemed plausible that any heteroatom previously appended to the periphery of cyclohexadiene-*cis*-diol could cyclize onto the carboxylate carbon and thus lead, in the case of nitrogen substitution, to aza sugar nucleus **2**, eq 1. Under thermodynamic conditions, the competition of



3 1 2 (1)

heteroatoms at C4 and C5 for the carboxylate generated at C1 upon ozonolysis should ultimately lead to the six-membered mannolactams, unless steps are taken to produce five-membered lactones or lactams instead.

Ideally, the functionalities in **1** permit a flexible design of either *endo*-nitrogenous carbohydrates or aza sugars such as **2** or *exo*-nitrogenous amino cyclitols such as **3**. The latter compounds

† Recipient of the American Cyanamid Faculty Research Award, 1992.
‡ Undergraduate research participant, 1991–93.
⊛ Abstract published in *Advance ACS Abstracts*, April 1, 1994.

(1) (a) For the first partof this series, see: Hudlicky, T.; Mandel, M.; Rouden, J.; Lee, R. S.; Bachmann, B.; Dudding, T.; Yost, K. J.; Merola, J. S. *J. Chem. Soc., Perkin Trans. 1* **1994**, 1553–1568. (b) For the third part, see: Hudlicky, T.; Olivo, H. F.; McKibben, B. *J. Am. Chem. Soc.*, following paper in this issue.

(2) Preliminary accounts of this work have been published: (a) Hudlicky, T.; Rouden, J. *J. Chem. Soc., Perkin Trans. 1* **1993**, 1095. (b) Hudlicky, T.; Rouden, J.; Luna, H. *J. Org. Chem.* **1993**, *58*, 985.

(3) For general references, see: *The Amino Sugars; the Chemistry and Biology of Compounds Containing Aminosugars*; Jeanloz, R. W., Balazs, E. A., Eds.; Academic Press: New York, 1965–1966; Vols. IA, IB, IIA, IIB.

(4) (a) Nishimura, Y. In *Studies in Natural Products Chemistry*; Atta-Ur-Rahman, ed.; Elsevier: Amsterdam, 1992; Part F, p 495. (b) Legler, G. *Adv. Carbohydr. Chem. Biochem.* **1990**, *28*, 319. (c) Sinnott, M. L. *Chem. Rev.* **1990**, *90*, 1171.

(5) Humphries, M. J.; Matsumoto, K.; White, S. L.; Olden, K. *Cancer Res.* **1986**, *46*, 5215.

(6) (a) Hanozet, G.; Pircher, H.-P.; Vanni, P.; Oesch, B.; Semenza, G. *J. Biol. Chem.* **1981**, *256*, 3703. (b) Truscheit, E.; Frommer, W.; Junge, B.; Muller, L.; Schmidt, D. D.; Wingender, W. *Angew. Chem., Int. Ed. Engl.* **1981**, *20*, 744.

(7) Nash, R. J.; Evans, S. V.; Fellows, L. E.; Bell, E. A. *Plant Toxicol., Proc. Aust.-U.S.A. Poisonous Plant Symp. 1984* **1985**, 309.

(8) (a) Nash, R. J.; Fenton, K. A.; Gatehouse, A. M. R.; Bell, E. A. *Entomol. Exp. Appl.* **1986**, *42*, 71. (b) Evans, S. V.; Gatehouse, A. M. R.; Fellows, L. E. *Entomol. Exp. Appl.* **1985**, *37*, 257. (c) Blaney, W. M.; Simmons, M. S. J.; Evans, S. V.; Fellows, L. E. *Entomol. Exp. Appl.* **1984**, *36*, 209.

(9) (a) Gruters, R. A.; Neefjes, J. J.; Tersmette, M.; de Goede, R. E. Y.; Tulp, A.; Huisman, H. G.; Miedema, F.; Ploegh, H. L. *Nature* **1987**, *330*, 74. (b) Fellows, L. E. *Chem. Br.* **1987**, 842. (c) Blough, H. A.; Pauwels, R.; de Clercq, E.; Cogniaux, J.; Sprecher-Goldberger, S.; Thiry, L. *Biochem. Biophys. Res. Commun.* **1986**, *141*, 33. (d) Schlesinger, S.; Koyama, A. H.; Malfer, C.; Gee, S. L.; Schlesinger, M. J. *Virus Res.* **1985**, *2*, 139.

(10) (a) Jones, I. M.; Jacob, G. S. *Nature* **1991**, *352*, 198. (b) Liu, P. S.; Hoekstra, W. J.; King, C.-H. R. *Tetrahedron Lett.* **1990**, *31*, 2829. (c) Winker, D. A.; Holan, G. J. *J. Med. Chem.* **1989**, *32*, 2084. (d) 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. (e) Fleet, G. W. J.; Karpas, A.; Dwek, R. A.; Fellows, L. E.; Tyms, A. S.; Petursson, S.; Namgoong, S. K.; Ramsden, N. G.; Smith, P. W.; Son, J. C.; Wilson, F.; Witty, D. R.; Jacob, G. S.; Rademacher, T. W. *FEBS Lett.* **1988**, *237*, 128. (f) Montefiori, D. C.; Robinson, W. E., Jr.; Mitchell, W. M. *Proc. Natl. Acad. Sci. U.S.A.* **1988**, *85*, 9248. (g) Walker, B. D.; Kowalski, M.; Goh, W. C.; Kozarsky, K.; Krieger, M.; Rosen, C.; Rohrschneider, L.; Hasletine, W. A.; Sodroski, J. *Proc. Natl. Acad. Sci. U.S.A.* **1987**, *84*, 8120.

(11) Recent reviews on amino sugars and aza sugars synthesis: Look, G. C.; Fotsch, C. H.; Wong, C.-H. *Acc. Chem. Res.* **1993**, *26*, 182. Golebiowski, A.; Jurczak, J. *Synlett* **1993**, 241. Fleet, G. W. J. *Chem. Br.* **1989**, 287. Recent review on amino cyclitol synthesis: Suami, T.; Ogawa, S. *Adv. Carbohydr. Chem. Biochem.* **1990**, *28*, 52; 64.

0002-7863/94/1516-5099$04.50/0

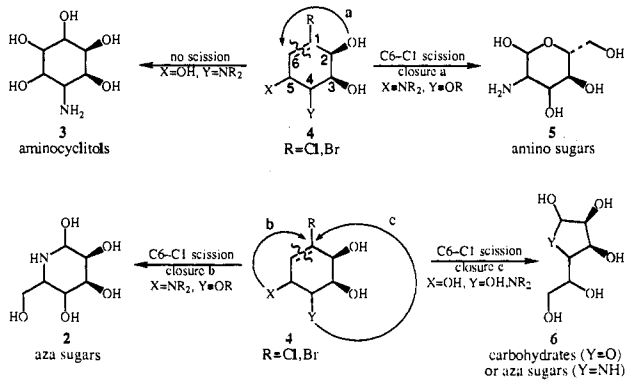
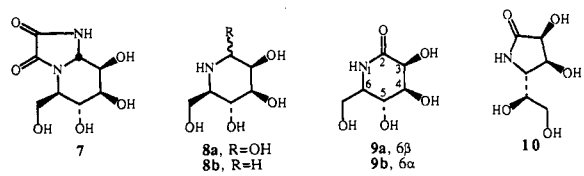


Figure 1. Divergent design of carbohydrate derivatives from peripherally functionalized diols.

could potentially be converted to amino carbohydrates, a ubiquitous group of naturally occurring saccharides, by controlling the stereochemistry and order of introduction of substituents in addition to the final oxidative cleavage and cyclization of the C2 hydroxyl to the C5 aldehyde, as shown in Figure 1. Judicious selection of methods should make it possible to prepare any stereoisomer of any of the major classes of carbohydrates from **1** with full control over the number and position of heteroatoms in the general intermediate **4**, Figure 1. For example, functionalization of the C4–C5 olefin with an amino alcohol unit allows for the choice between amino and aza sugars simply by deciding which nucleophilic entity will cyclize onto a specific electrophilic terminus obtained from oxidative cleavage of the C1–C6 double bond or, for that matter, any of the six available bonds of the cyclohexane ring. Thus, the C2 hydroxyl group cyclizing onto the C5 aldehyde provides an amino sugar, whereas the C5 amino group cyclizing onto the C1 carboxylate leads to an aza sugar. The regio- and stereochemistry of the amino alcohol determine not only the topology of the resulting class of compounds but also their stereochemical constitution. The order of execution of protecting and functionalizing steps thus easily determines which class of compounds will result. A guide to planning these steps has been published during our earlier work on the functionalization of cyclohexadiene-*cis*-diols[12] and has recently been summarized.[12c]

Here we focus our efforts on the design of aza sugars **2** and **6** with application to the total synthesis of kifunensine (**7**), mannojirimycin (**8a**), mannolactams **9**, and their five-membered-ring isomers **10**. The third part of this series, the following paper in this issue, describes the application of the strategy shown in Figure 1 (e.g., preparation of **3** from **4**) to the preparation of amino cyclitols or alkaloids that contain an amino cyclitol unit within their skeletons.



Results and Discussion

The established virtues of cyclohexadiene-*cis*-diols in enantiocontrolled synthesis need not be described here. These remarkable compounds gained popularity following their initial application to synthesis of (±)-pinitol by Ley in 1987.[13] Since then, more than 100 papers have appeared describing their short and efficient synthetic transformations with applications to total synthesis.[12c,14] More importantly, interest has been revived in the biodegradation of aromatic compounds, a process discovered and developed by Gibson,[15] and a number of investigators are isolating new metabolites derived from heteroaromatics,[16] halogenated aromatics,[17] and more highly functionalized substrates.[18–20]

In order to achieve selective conversions of a simple cyclohexadienediol such as **1** to a wide variety of carbohydrates, selective methods of further peripheral functionalization had to be devised. These include stereoselective dihydroxylation of the C4–C5 olefin, subsequent reduction of the vinyl halide, and final dioxygenation to inositols, as has been described in some of our published syntheses[12] and summarized in the introductory paper in this series.[1a] The introduction of nitrogen is best accomplished either by [4 + 2] nitrosyl cycloaddition[21] or by nucleophilic operations on an epoxide derived from **1** or its protected derivative **11**.

Figure 2 shows the possible topographies of amino alcohols that can, in principle, be derived from **1** by manipulations of diol **14** or epoxides **12**[22] and **13**.[23] There are four possible diasteriomers for each series, and some of these isomers represent the known configurations of conduramines A and E (**15a**, X = H, N = NH_2). In these compounds there is a 1,2,3-trihydroxy-4-amino arrangement around the cyclohexane ring. The members of the other isomeric series, **15b**, with a 1,2,4-trihydroxy-3-amino arrangement, are unnatural and more difficult to obtain compared

(12) (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.; Rulin, F.; Tsunoda, T.; Luna, H.; Price, J. D. *J. Am. Chem. Soc.* **1990**, *112*, 9439. (c) Hudlicky, T.; Reed, J. W. In *Advances in Asymmetric Synthesis*; Hassner, A., Ed.; JAI Press: Greenwich, CT, 1994, Vol. 2.

(13) Ley, S. V.; Sternfeld, F.; Taylor, S. M. *Tetrahedron Lett.* **1987**, *28*, 225.

(14) (a) Brown, S. M.; Hudlicky, T. In *Organic Synthesis: Theory and practice*; Hudlicky, T., Ed.; JAI Press: Greenwich, CT, 1993; Vol. 2, p 113. (b) Carless, H. A. J. *Tetrahedron: Asymmetry* **1992**, *3*, 795. (c) Widdowson, D. A.; Ribbons, D. W.; Thomas, S. D. *Janssen Chim. Acta* **1990**, 3.

(15) (a) Gibson, D. T.; Koch, J. R.; Kallio, R. E. *Biochemistry* **1968**, *7*, 2653. (b) Gibson, D. T.; Hensley, M.; Yoshioka, H.; Mabry, J. J. *Biochemistry* **1970**, *9*, 1626. (c) Gibson, D. T.; Zylstra, G. J.; Chauhan, S. In *Pseudomonas: Biotransformations, Pathenogenesis, and Evolving Biochemistry*; Silver, S., Chakrabarty, A. M., Iglewski, B., Kaplan, S., Eds.; American Society for Microbiology: Washington, DC, 1990; Chapter 13, p 121. (d) Zylstra, G. J.; Gibson, D. T. In *Genetic Engineering*; Setlow, J. A., Ed.; Pergamon: New York, 1991; Vol. 13, p 183. (e) Gibson, D. T. *Crit. Rev. Microbiol.* **1971**, *1*, 199. (f) Gibson, D. T. *Toxicol. Environ. Chem.* **1982**, *5*, 237. (g) Gibson, D. T.; Subramanian, V. In *Microbial Degradation of Organic Compounds*; Gibson, D. T., Ed.; Microbiology Series 13; Marcel Dekker: New York, 1984; Chapter 7.

(16) (a) Boyd, D. R.; Sharma, N. D.; Boyle, R.; Malone, J. F.; Chima, J.; Dalton, H. *Tetrahedron: Asymmetry* **1993**, *4*, 1307. (b) Boyd, D. F.; Sharma, N. D.; Dority, M. R. J.; Hand, M. V.; McMordie, R. A. S.; Malone, J. R.; Porter, H. P.; Dalton, H.; Chima, J.; Sheldrake, G. N. *J. Chem. Soc., Perkin Trans. 1* **1993**, 1065. (c) Boyd, D. R.; Sharma, N. D.; Stevenson, P. J.; Chima, J.; Gray, D. J.; Dalton, H. *Tetrahedron Lett.* **1991**, *32*, 3887. (d) Boyd, D. R.; Sharma, N. D.; Boyle, R.; McMurray, T. T.; Evans, T. A.; Malone, J. F.; Dalton, H.; Chima, J.; Sheldrake, G. N. *J. Chem. Soc., Chem. Commun.* **1993**, 49. (e) Boyd, D. R.; Sharma, N. D.; Boyle, R.; McMordie, R. A. S.; Chima, J.; Dalton, H. *Tetrahedron Lett.* **1992**, *33*, 1241.

(17) (a) Hudlicky, T.; Boros, E. E.; Boros, C. H. *Tetrahedron: Asymmetry* **1993**, *4*, 1365. (b) Hudlicky, T.; Boros, E. E.; Boros, C. H. *Synlett* **1992**, 391.

(18) (a) Taylor, S. J. C.; Ribbons, D. W.; Slawin, A. M. Z.; Widdowson, D. A.; Williams, D. J. *Tetrahedron Lett.* **1987**, *28*, 6391. (b) Rossiter, J. T.; Williams, S. R.; Cass, A. E. G.; Ribbons, D. W. *Tetrahedron Lett.* **1987**, *28*, 5173.

(19) (a) Whited, G. M.; Gibson, D. T. *J. Bacteriol.* **1991**, *173*, 3010. (b) Whited, G. M.; Gibson, D. T. *J. Bacteriol.* **1991**, *173*, 3017.

(20) For a recent compilation of known diol metabolites, see: (a) McMordie, R. A. S., Ph.D. Thesis, School of Chemistry, The Queen's University of Belfast, Belfast, BT9 5AG, U. K. (b) Stabile, M. M.S. Virginia Polytechnic Institute and State University, Blacksburg, VA, 1993.

(21) (a) Schurrle, K.; Beier, B.; Piepersberg, W. *J. Chem. Soc., Perkin Trans. 1* **1991**, 2407. (b) Dumortier, L.; Liu, P.; Dobbelaere, S; van der Eycken, J.; Vanderwalle, M. *Synlett* **1992**, 241. (c) Johnson, C. R.; Ple, P. A.; Su, L.; Heeg, M. S.; Adam, J. P. *Synlett* **1992**, 388. (d) Braun, H.; Burger, W.; Kresze, G.; Schmidtchen, F. P.; Vaerman, J. L.; Viehe, H. G. *Tetrahedron: Asymmetry* **1990**, *1*, 403. (e) For a review of nitrosyl cycloadditions, see: Boger, D. L.; Weineb, S. N. In *Hetero Diels–Alder Methodology in Organic Synthesis*; Academic Press: New York, 1987. (f) For applications of the nitrosyl cycloaddition in the synthesis of natural products, see: (g) Keck, G. E.; Nickell, D. G. *J. Am. Chem. Soc.* **1980**, *102*, 3632. (h) Keck, G. E. *Tetrahedron. Lett.* **1978**, *19*, 4767. (i) Burkholder, T. P.; Fuchs, P. L. *J. Am. Chem. Soc.* **1988**, *110*, 2431. (j) Iida, H.; Watanabe, Y.; Kibayashi, C. *J. Am. Chem. Soc.* **1985**, *107*, 5535. (k) Kresze, G.; Dittel, W. *Liebigs Ann. Chem.* **1981**, 610. (l) Braun, H.; Burger, W.; Kresze, G.; Schmidtchen, F. P.; Vaerman, J. L.; Viehe, H. G. *Tetrahedron: Asymmetry* **1990**, *1*, 403. (m) Shishido, Y.; Kybayashi, C. *J. Org. Chem.* **1992**, *57*, 2876. (n) Hudlicky, T.; Olivo, H. F. *Tetrahedron Lett.* **1991**, *32*, 6077. (o) Hudlicky, T.; Olivo, H. F. *J. Am. Chem. Soc.* **1992**, *114*, 9694.

(22) Carless, H. A. J. *J. Chem. Soc., Chem. Commun.* **1992**, 234.

(23) Hudlicky, T.; Rulin, F.; Tsunoda, T.; Luna, H.; Andersen, C.; Price, J. *Isr. J. Chem.* **1991**, *31*, 229.

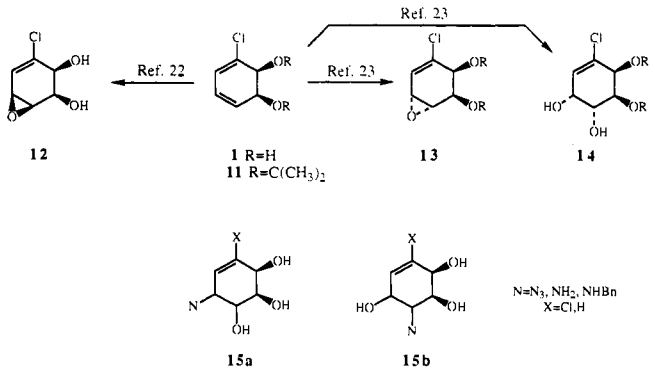


Figure 2. Conduramine topography accessible from derivaties of dienediol **1**.

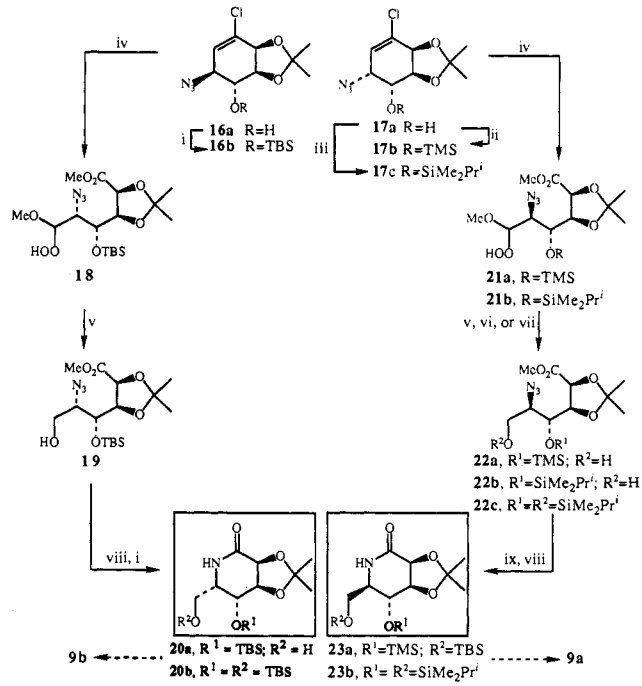
to the natural isomers, some of which are accessible by [4 + 2] cycloaddition of dienes with arylnitroso compounds (see the third paper in this series).[1b]

It is crucial to have in place a methodology that can generate *any* of the four isomers in each series (and/or any of the additional four enantiomers as well) in order to synthesize either the conduramines themselves or the aza sugars (and possibly amino sugars) by selective oxidative cleavage of appropriate faces of the cyclohexadienediols. Once these isomers are stereoselectively prepared with appropriately protected peripheral atoms, cleavage of the remaining C1–C6 olefin and recyclization can be considered in order to prepare the particular carbohydrate derivative desired (Figure 1). The ultimate goal of this method therefore is a generalized design for any carbohydrate isomer, natural or unnatural, containing oxygen, nitrogen, or other heteroatoms.

We began this general quest by the preparation of azido alcohols **16**, **17**, and **26**, because their configurations at C4 and C5 reflect those of both series of amino cyclitols and because their oxidative cleavage and recyclization would furnish previously synthesized lactams (for example, **23**) as well as their stereoisomers (for example, **20**).[10e,24]

Azido alcohol **16a** was prepared by opening the epoxide in **13** with NaN_3, Scheme 1. (The structure of **16a** was originally assigned as **26**;[12a] the correct structure was determined[25] by X-ray analysis, ^1H NMR decoupling work, and comparison of the NMR spectra of **16a** and **26**.) Azide **17a** was available by the opening of epoxide **13** with chloride according to the procedure of Bajwa,[26] followed by displacement of chloride with azide. The regioisomeric azide **26** was attained by monoprotection of diol **14** with TBSCl, conversion of this mixture to the corresponding triflates, and subsequent displacement of the C4 triflate with azide. Fortuitously, the more reactive C5 allylic triflate was eliminated during this reaction via its substitution by pyridine. An improved procedure using Bu_2SnO[27] allowed us to protect the alcohol group in the allylic position of diol **14** regioselectively and subsequently to achieve its conversion to triflate **24b** and then to **26**. Two of the three azido alcohols (**16** and **17**) possess configurations of known conduramines: the arrangement of nitrogen and alcohols found in **16** corresponds to a derivative reported by Piepersberg[28] and that in **17** to conduramine E1 reported by Johnson.[29] The

Scheme 1



[a] Reagents: (i) TBSCl, DiPEA; (ii) HMDS, TMSCl; (iii) Pr^iMe_2SiCl, imidazole; (iv) O_3, MeOH–H_2O, $NaHCO_3$, –78 °C; (v) $NaBH_4$, $CeCl_3$, –20 °C; (vi) $NaBH_4$, THF–MeOH, 0 °C; (vii) DMS, then $Zn(BH_4)_2$, –78 °C; (viii) H_2, Pd/C; (ix) R_2SiCl, DBU.

configuration of the "inside" position of nitrogen, as found in **26**, has not been reported.[30]

The ozonolysis of vinyl chlorides in azido alcohols or their protected derivatives is a sensitive reaction that requires careful adjustments from one case to the next. In some cases, the ozonolysis could be conveniently stopped at the stage of hydroperoxy acetals such as **18**, **21**, and **25**. These compounds were characterized and subjected to further reduction conditions in order to control the oxidation states of both the C1 carboxylate and the C6 aldehyde. The reduction of **21a** on a small scale by $NaBH_4$ in THF titrated with MeOH[31] furnished **22a** in moderate yield (44%). Other conditions for in situ reduction were developed that avoided the isolation and manipulation of these peroxides. The ozonolysis of **17c** was worked up with Me_2S to reduce the peroxide **21b** to an unstable azido aldehyde, which was further reduced with $Zn(BH_4)_2$ in Et_2O at –78 °C to afford **22b**. Subsequently an improved one-pot procedure was developed for the ozonolysis of **16b** and **21b** followed by reduction of **18** and **21b** with a large excess of $NaBH_4$ in the presence of $CeCl_3$.[32] The procedure afforded cleanly esters **19** and **22b**, which were protected and then hydrogenated, or reduced and then protected, to lactams **20** and **23**,[2b,33] fully protected except for the amide nitrogen. The reduction of **18** and **21** with $NaBH_4$ in MeOH *without* $CeCl_3$ never led cleanly to esters **19** and **22**. The synthesis of **20** and **23** in approximately seven synthetic operations from chlorobenzene constitutes a remarkably efficient pathway compared to those relying on carbohydrates. In carbohydrate-based syntheses, only known configurations can be achieved efficiently. Any changes in relative stereochemistry require protective and

(24) (a) Fleet, G. W. J.; Ramsden, N. G.; Witty, D. R. *Tetrahedron* **1989**, *45*, 319. (b) Fleet, G. W. J.; Ramsden, N. G.; Witty, D. R. *Tetrahedron Lett.* **1988**, *29*, 2871. (c) Shing, T. K. M. *J. Chem. Soc., Chem. Commun.* **1988**, 1221. (d) Niwa, T.; Tsuruoka, T.; Goi, H.; Kodama, Y.; Itoh, J.; Inouye, S.; Yamada, Y.; Niida, T.; Nobe, M.; Ogawa, Y. *J. Antibiot.* **1984**, *37*, 1579.

(25) See Corrigendum, *J. Chem. Soc., Perkin Trans. 1* **1993**, 535.

(26) Bajwa, J. S.; Anderson, R. C. *Tetrahedron Lett.* **1991**, *32*, 3021.

(27) (a) Wagner, D.; Verheyden, J. P. H.; Moffatt, J. G. *J. Org. Chem.* **1974**, *39*, 24. (b) David, S.; de Sennyey, G.; Sotta, B. *Tetrahedron Lett.* **1982**, *23*, 1817.

(28) Beier, B.; Schurrle, K.; Nerhitsky, O.; Piepersberg, W. *J. Chem. Soc., Perkin Trans. 1* **1991**, 2255.

(29) Johnson, C. R.; Ple, P. A.; Hey, M. J.; Adams, J. P. *Synlett* **1992**, 388.

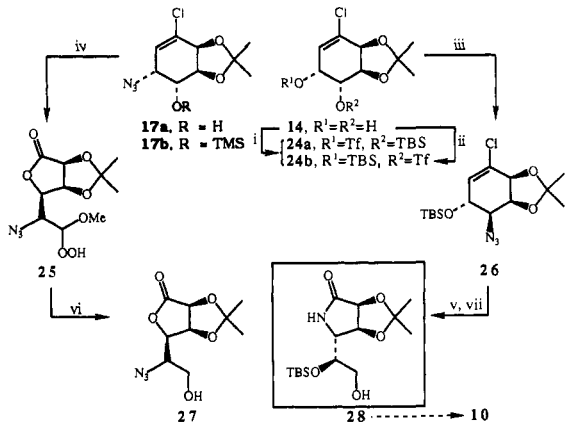
(30) For a recent compilation of spectral and physical data for amino cyclitols, see: Hudlicky, T.; Cebulak, M. *Cyclitols and Their Derivatives: A Handbook of Physical, Spectral, and Synthetic Data*; VCH: New York, 1993.

(31) Soai, K.; Yokoyama, S.; Ookawa, A. *Synthesis* **1987**, 48.

(32) Review on lanthanides: Molander, G. A. *Chem. Rev.* **1992**, *92*, 29–68.

(33) Synthesis of **20** and **23** allowed us to correct inadvertently a structure assignment of azido alcohol **16a** previously thought to have the configuration of **26** as described in ref 12a. Detailed NMR work followed by X-ray analysis, as well as the synthesis of the diastereomeric lactam, led to the corrected structure assignment. See Corrigendum to ref 12a: *J. Chem. Soc., Perkin Trans. 1* **1993**, 535.

Scheme 2



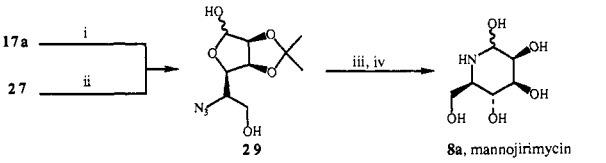
[a] Reagents: (i) TBSCl, imidazole; Tf_2O, pyridine; (ii) Bu_2SnO; TBSCl, Bu_4NBr; (iii) NaN_3, DMF; (iv) O_3, MeOH, $NaHCO_3$, −78 °C; (v) O_3, MeOH–H_2O, $NaHCO_3$, −78 °C; $NaBH_4$, $CeCl_3$, −20 °C; (vi) $NaBH_3CN$, pH 3; (vii) H_2, Pd/C.

deprotective steps as well as inversions, thereby leading to lengthy and arduous preparations. In contrast, the flexible introduction of substituents onto the periphery of dienediol **1** allows short and concise preparation of stereoisomeric aza sugars, as demonstrated by attaining **20** and **23**.

When the C4 hydroxyl is free during the ozonolysis (or when TMS derivative **17b** is used under unbuffered ozonolysis conditions), the in situ cyclization yields lactone **25**, which can be isolated or cleanly reduced with $NaBH_3CN$ at pH 3[34] directly to the azidomannolactone **27**. This is a convenient starting point for the synthesis of kifunensine, described later in this paper. Ozonolysis of azido alcohol **26**, prepared in the protected form from diol **14** via triflate displacement, and reductive workup with $NaBH_4/CeCl_3$ furnished directly the five-membered lactam **28**, Scheme 2, providing direct access to lactam **10**. Compounds that contain this structural unit have attracted immense attention because of their glycosidase inhibitory properties, and syntheses of many stereoisomers of this general type abound in the recent literature.[35]

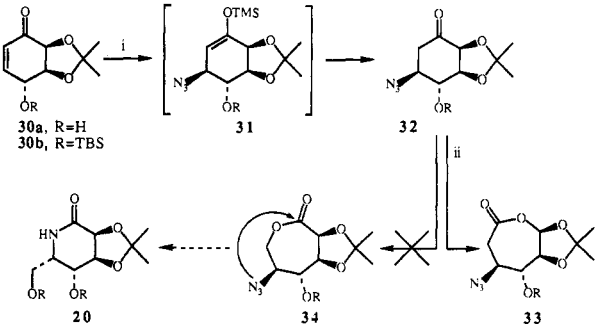
Synthesis of Mannojirimycin. When we discovered that the $NaBH_4$ workup of the ozonolysis mixture from **17a** led to the lactol **29** (presumably via reduction of the intermediate ozonide and not the resulting methyl ester or lactone), rapid access to mannojirimycin (**8a**) was at hand, Scheme 3. Sodium borohydride reduction of the carbonyl group in intermediate **25** seems to proceed faster than that of the peroxide group, whereas sodium

Scheme 3



[a] Reagents: (i) O_3, −78 °C, MeOH; $NaBH_4$; (ii) DIBAL-H, −78 °C; (iii) PMe_3, THF–H_2O; (iv) H^+.

Scheme 4



[a] Reagents: (i) $TMSN_3$, TMSOTf, Et_2O, room temperature, 43 h; (ii) *m*CPBA, CH_2Cl_2.

cyanoborohydride at a lower pH cleanly reduces the peroxy acetyl linkages to **27**. Interestingly, lactone **27** is reduced with $NaBH_4$ to lactol **29** as the major product.

Lactol **29** could also be obtained from lactone **27** by DIBAH reduction in quantitative yield. Reduction of azide with Me_3P in wet THF followed by acid-catalyzed deprotection gave mannojirimycin (**8a**) in a total of five synthetic operations from chlorobenzene—the shortest preparation of such a compound on record, Scheme 3.[36] This natural compound was characterized as its bisulfite derivative.[24a,36] According to literature,[37] a compound such as **29** should also provide direct access to deoxymannojirimycin (**8b**) simply by catalytic hydrogenation (and deprotection).

Kifunensine Synthesis. Our original synthetic plan was based on the oxidative cleavage of an appropriately functionalized cyclohexene such as **17** (or **31**) that would furnish lactam **23**, to which an oxalamido bridge could be appended. First we tried an approach to azido esters of type **18** and **21** via cleavage of an enol ether at C1–C6 or a Baeyer–Villiger oxidation of a ketone under either chemical or enzymatic conditions. Hydroxy enone **30b**,[23] available in our laboratory from cyclitol projects, served as a model substrate, and we expected it to yield the stereoisomeric lactam **20** (Scheme 4). However, under conditions described in the literature,[38] the only product isolated was ketone **32**; the intermediate enol ether **31** could not be isolated. An attempt to trap the enolate anion generated with LDA led only to elimination of the β-azido group to furnish the starting enone. Baeyer–Villiger oxidation of **32** gave exclusively lactone **33**, not **34**, which may be accessible via enzymatic Baeyer–Villiger oxidation, provided the enzyme would accept the substrate.[39]

We returned to our original plan utilizing protected lactam **23**, which was attained, as shown in Scheme 1, by ozonolysis of the vinyl halide. Treatment of this lactam with chlorosulfonyliso-

(34) Hutchins, R. O.; Kandasamy, D. *J. Org. Chem.* **1975**, *40*, 2530.

(35) (a) Wang, Y.-F.; Dumas, D. P.; Wong, C.-H. *Tetrahedron Lett.* **1993**, *34*, 403. (b) Behling, J. R.; Campbell, A. L.; Babiak, K. A.; Ng, J. S.; Medich, J.; Farid, P.; Fleet, G. W. J. *Tetrahedron* **1993**, *49*, 3359. (c) Thompson, D. K.; Hubert, C. N.; Wightman, R. H. *Tetrahedron* **1993**, *49*, 3827. (d) Lay, L.; Nicotra, F.; Paganini, A.; Pangrazio, C.; Panza, L. *Tetrahedron Lett.* **1993**, *34*, 4555. (e) Myerscough, P. M.; Fairbanks, A. J.; Jones, A. H.; Bruce, I.; Choi, S.-M. S.; Fleet, G. W. J.; Al-Daher, S. S.; Cenci di Bello, I.; Winchester, B. *Tetrahedron* **1992**, *48*, 10177. (f) Takano, S.; Moriya, M.; Ogasawara, K. *Tetrahedron: Asymmetry* **1992**, *3*, 681. (g) Kajimoto, T.; Chen, L.; Liu, K. K.-C.; Wong, C.-H. *J. Am. Chem. Soc.* **1991**, *113*, 6678. (h) Liu, K. K.-C.; Kajimoto, T.; Chen, L.; Zhong, Z.; Ichikawa, Y.; Wong, C.-H. *J. Org. Chem.* **1991**, *56*, 6280. (i) Hung, R. R.; Straub, J. A.; Whitesides, G. M. *J. Org. Chem.* **1991**, *56*, 595. (j) Wehner, V.; Jager, V. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 1169; 1171. (k) Buchanan, J. G.; Lumbard, K. W.; Sturgeon, R. J.; Thompson, D. K.; Wightman, R. H. *J. Chem. Soc., Perkin Trans. 1* **1990**, 699. (l) Reitz, A.; Baxter, E. W. *Tetrahedron Lett.* **1990**, *31*, 6777. (m) Robina, I.; Gearing, R. P.; Buchanan, J. G.; Wightman, R. H. *J. Chem. Soc., Perkin Trans. 1* **1990**, 2622. (n) Pederson, R. L.; Wong, C.-H. *Heterocycles* **1989**, *28*, 477. (o) Ziegler, T.; Straub, A.; Effenberger, F. *Angew. Chem. Int. Ed. Engl.* **1988**, *27*, 716. (p) Fleet, G. W. J.; Son, J. C.; Green, D. S.; Cenci di Bello, I.; Winchester, B. *Tetrahedron* **1988**, *44*, 2649. Fleet, G. W. J.; Son, J. C. *Tetrahedron* **1988**, *44*, 2637. (q) Austin, G. N.; Baird, P. D.; Fleet, G. W. J.; Peach, J. M.; Smith, P. W.; Watkin, D. J. *Tetrahedron* **1987**, *43*, 3095. (r) Bashyal, B. P.; Fleet, G. W. J.; Gough, M. J.; Smith, P. W. *Tetrahedron* **1987**, *43*, 3083. (s) Eis, M. J.; Rule, C. J.; Wurzburg, B. A.; Ganem, B. *Tetrahedron Lett.* **1985**, *26*, 5397. (t) Fleet, G. W. J.; Nicholas, S. J.; Smith, P. W.; Evans, S. V.; Fellows, L. E.; Nash, R. J. *Tetrahedron Lett.* **1985**, *26*, 3127. (u) Fleet, G. W. J.; Smith, P. W. *Tetrahedron Lett.* **1985**, *26*, 1469.

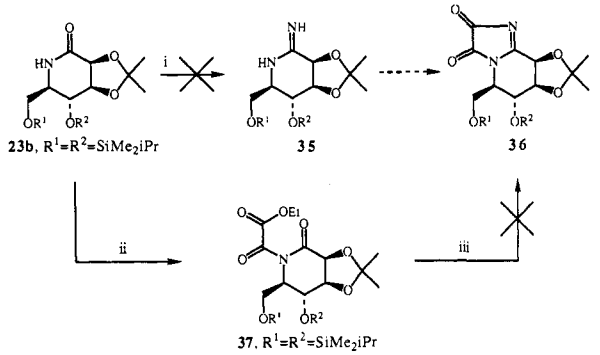
(36) (a) Dondoni, A.; Merino, P.; Perrone, D. *Tetrahedron* **1993**, *49*, 2939. (b) Legler, G.; Julich, E. *Carbohydr. Res.* **1984**, *128*, 61.

(37) Fleet, G. W. J.; Gough, M. J.; Shing, T. K. M. *Tetrahedron Lett.* **1984**, *25*, 4029.

(38) (a) d'Angelo, J.; Maddaluno, J. *J. Am. Chem. Soc.* **1986**, *108*, 8112. (b) Combret, J. C.; Klein, J. L.; Mouslouhoudine, M. *Synthesis* **1984**, 493. (c) Combret, J. C.; Klein, J. L.; Mouslouhoudine, M. *Tetrahedron Lett.* **1984**, *25*, 3449. (d) Ricci, A.; Degl'Innocenti, A.; Borselli, G.; Reginato, G. *Tetrahedron Lett.* **1987**, *28*, 4093.

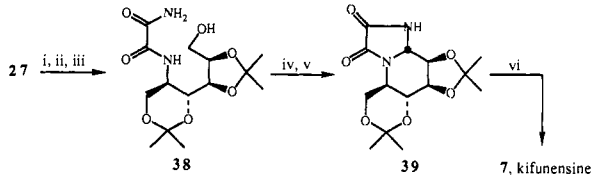
(39) Taschner, M. J.; Black, D. J. *J. Am. Chem. Soc.* **1988**, *110*, 6892.

Scheme 5



[a] Reagents: (i) CSI, then aqueous NaOH; (ii) BuLi, $ClCOCO_2Et$, THF, −78 °C to 0 °C; (iii) NH_3/MeOH.

Scheme 6



[a] Reagents: (i) DMP, DCE, CSA, cat.; (ii) $LiAlH_4$; (iii) $(MeO_2C)_2$, then NH_3; (iv) CrO_3·2py; (v) NH_3, MeOH; (vi) 75% aqueous CF_3CO_2H.

cyanide (CSI)[40] failed to give amidine **35**, Scheme 5, which would lead to amide **36**. Other attempts to produce amidine **35** (PPh_3, CCl_4, NH_3)[41] or compound **36** via the *N*-oxalyllactam **37** (BuLi, ClCOCOOEt)[42] followed by treatment with NH_3/MeOH failed. We did not attempt to prepare amidine **35** from the thiolactam derived from **23** by reaction with Lawesson's reagent[43] or to produce the 1,3-diamine from mannojirimycin following Ganem's procedure for nojirimycin,[44] as we turned instead to an intersection with Hashimoto's approach in which the oxalate is appended to an open and reduced form of the lactam.[45] A convenient precursor for this strategy was either mannojirimycin or lactone **27**. The latter was opened to an azido ester bisacetonide (DMP/$ClCH_2CH_2Cl$/CSA catalyst), reduced ($LiAlH_4$), and condensed with dimethyl oxalate followed by NH_3/MeOH workup[46] to furnish **38**. The known bisacetonide **39** and kifunensine **7** were attained in five and six steps, respectively, from **27**, Scheme 6, and found to be identical with the samples of **39** and **7**, respectively, kindly provided to us by Drs. Hashimoto (Nippon Glaxo, Ltd.), Kayakiri, and Shirahashi (Fujisawa Pharmaceutical Co., Ltd.).

Conclusion

The conversion of chlorodienediol **1** to the aza sugar nucleus **2** has been accomplished by selective functionalization and oxidative cleavage of the C1–C6 olefin. Short syntheses of mannojirimycin (**8a**) and kifunensine (**7**) attest to the general utility of this methodology in accessing aza sugar nuclei. The preparation of five-membered ring lactones and lactams provided further use in the design and synthesis of other known mannosidase inhibitors. Future endeavors will focus on the pursuit of other targets in the general class of aza sugars and also on the generation of amino sugars by investigations of other modes of oxidative cleavage and recyclization of intermediates of types **4**. We will report on these accomplishments in due course.

Experimental Section

General. All nonhydrolytic reactions were conducted in oven-dried or flame-dried glassware under atmospheres of dry argon. All solvents were reagent grade. Anhydrous solvents were dried immediately before use. Ether and THF were distilled from sodium benzophenone ketyl. Methylene chloride, 1,2-dichloroethane, diisopropylethylamine, pyridine, hexamethyldisilazane, chlorotrimethylsilane, triethylamine, dimethylformamide, and *tert*-butyldimethylsilyl chloride were distilled from CaH_2.

Ozonolyses were carried out with an OREC apparatus, Model 03V10-0. Dry oxygen containing about 2.5% ozone was introduced at a speed of 4 L/min into the solution of a substrate.

Analytical TLC was performed on silica gel Merck Kieselgel 60 F_{254} (0.25-mm thickness) plates. The plates were visualized by immersion in a *p*-anisaldehyde solution or phosphomolybdic acid solution (EtOH 95%) followed by warming on a hot plate. Flash chromatography was carried out on Merck Kieselgel 60 silica gel (230–400 mesh). Mass spectra were recorded on a Varian MAT-112 instrument (low resolution) or on a double-focusing VG 7070 E-HF instrument (exact mass). Infrared spectra were recorded on Perkin-Elmer 283B or 710B instruments. NMR spectra were recorded on a Bruker WP-270 instrument. Proton chemical shifts are reported in parts per million (ppm) relative to TMS, as are carbon chemical shifts. Rotations were recorded on a Perkin-Elmer 241 digital polarimeter. Melting points were obtained on a Thomas-Hoover melting point apparatus and are uncorrected. Elemental analyses were performed by Atlantic Microlab, Inc., P.O. Box 2288, Norcross, GA 30091.

(1*R*,4*S*,5*S*,6*R*)-3-Chloro-4,5-*O*-isopropylidene-7-oxabicyclo[4.1.0]hept-2-ene-4,5-diol (13).[23] To diene diol **1**[23,48] (2.93 g, 20 mmol) in dry CH_2Cl_2 (80 mL) were added 3.2 mL of 2,2-dimethoxypropane (26 mmol) and 57 mg (0.30 mmol) of *p*-TsOH. After the mixture was stirred for 20 min at room temperature, the reaction flask was placed into an ice bath, 80 mL of phosphate buffer (1.0 M, pH = 8) was poured into the mixture, and, at 0 °C, *m*CPBA (4.74 g, 22 mmol) was added in portions. The solution was allowed to warm to room temperature and was stirred for 8 h. The layers were separated, and the organic layer was washed with aqueous $NaHSO_3$ (10%, 20 mL), saturated aqueous $NaHCO_3$ (2 × 20 mL), and water (20 mL), dried over Na_2SO_4, and concentrated. Purification by flash chromatography (silica gel, hexane/ethyl acetate, 9:1) led to the epoxide **13** in 80% yield (3.25 g, 16 mmol) as a colorless solid. R_f: 0.34 (hexane/ethyl acetate, 92:8). Mp: 59–60 °C. $[\alpha]^{25}_D$: +40.2° (c = 0.21, $CHCl_3$). FTIR: (KBr) 2989, 2936, 1643, 1383, 1373 cm^{-1}. ^1H NMR: ($CDCl_3$) δ 6.19 (dd, J = 3.5, 1.0 Hz, 1H), 4.84 (d, J = 4.67 Hz, 1H), 4.34 (d, J = 6.7 Hz, 1H), 3.55 (dd, J = 3.5, 1.6 Hz, 1H), 3.36 (t, J = 5.4 Hz, 1H), 1.42 (s, 3H), 1.40 (s, 3H). ^{13}C NMR: ($CDCl_3$) δ 137.9, 122.2, 111.4, 73.1, 72.6, 49.6, 47.9, 27.4, 25.8. MS: (CI, 70 eV) m/z (relative intensity) 203 (M^+, 0.22), 187 (0.13), 145 (1.00), 109 (0.46). HRMS: calcd for $C_9H_{11}ClO_3$ 202.0485, found 202.0475, error 4.91 ppm.

(3*S*,4*R*,5*S*,6*S*)-3-Azido-1-chloro-4-hydroxy-5,6-*O*-isopropylidene-1-cyclohexene-5,6-diol (16a). Epoxide **13** (133 mg, 0.657 mmol), sodium azide (2.63 mmol, 171 mg), and dry ammonium chloride (2.63 mmol, 141 mg) were dissolved in a mixture of DME–EtOH–H_2O (1.5:1:1), and the solution was heated at 80 °C for 1 h. After the solution was cooled, brine (15 mL) and ethyl acetate (5 mL) were added, with stirring continued for 10 min. The layers were separated, and the aqueous layer was extracted with ethyl acetate (3 × 5 mL). The combined organic extracts were dried (Na_2SO_4) and evaporated to produce 192 mg of a slightly yellow solid, which was purified by flash chromatography (silica gel, hexanes/ethyl acetate, 7:3) to produce pure azido alcohol **16a** in 88% yield (141 mg, 0.574 mmol). An analytical sample was obtained by recrystallization from CH_2Cl_2–hexane. R_f: 0.09 (silica gel, hexanes/ethyl acetate, 8:2). Mp: 94–94.5 °C. $[\alpha]^{23}_D$: −10.2° (c = 0.96, MeOH). IR: (film) 3454, 2113, 1250, 1085, 1074, 869 cm^{-1}. ^1H NMR: ($CDCl_3$) δ 5.87 (d, J = 2.1 Hz, 1H), 4.6 (d, J = 6.4 Hz, 1H), 4.16 (dd, J = 8.7, 6.4 Hz, 1H), 3.96 (dd, J = 8.7, 1.4 Hz, 1H), 3.69 (td, J = 8.6, 3.0 Hz, 1H), 2.88 (d, J = 3.0 Hz, 1H), 1.53 (s, 3H), 1.40 (s, 3H). ^{13}C NMR: ($CDCl_3$) δ 131.0 (C), 126.6 (CH), 111.5 (C), 77.9 (CH), 75.6 (CH), 73.1 (CH), 61.3 (CH), 28.1 (CH_3), 25.9 (CH_3). MS: (CI) m/z (relative intensity) 246

(40) (a) Review on chlorosulfonylisocyanate (CSI): Dhar, D. N.; Murthy, K. S. K. *Synthesis* **1986**, 437. (b) Rama Rao, K.; Nageswar, Y. V. D.; Srinivasan, T. N.; Sattur, P. B. *Synth. Commun.* **1988**, *18*, 877.

(41) (a) Appel, R. *Angew. Chem., Int. Ed. Engl.* **1975**, *14*, 806. (b) Appel, R.; Warning, K.; Ziehn, K. D. *Chem. Ber.* **1973**, *106*, 3450.

(42) Evans, D. A. *J. Org. Chem.* **1985**, *50*, 1830.

(43) Tong, M. K.; Papandreou, G.; Ganem, B. *J. Am. Chem. Soc.* **1990**, *112*, 6137.

(44) Yoon, H.; King, S. B.; Ganem, B. *Tetrahedron Lett.* **1991**, *32*, 7199.

(45) (a) Kayakiri, H.; Kasahara, C.; Nakamura, K.; Oku, T.; Hashimoto, M. *Chem. Pharm. Bull.* **1991**, *39*, 1392. (b) Kayakiri, H.; Kasahara, C.; Oku, T.; Hashimoto, M. *Tetrahedron Lett.* **1990**, *31*, 225.

(46) This reaction sequence has not been optimized. For instance, the use of diisopropenyl oxalate[47] should improve the yield for the oxalate moiety addition.

(47) Neveux, M.; Bruneau, C.; Lecolier, S.; Dixneuf, P. H. *Tetrahedron* **1993**, *49*, 2629.

(48) Available from Genencor International, Inc., Rochester, NY. For a laboratory scale synthesis, see: Hudlicky, T.; Boros, C.; Boros, E. *Synthesis* **1992**, 174.

(M + 1) (40), 230 (100), 218 (20). Anal. Calcd for $C_9H_{12}N_3O_3Cl$: C, 44.0; H, 4.92; N, 17.10. Found: C, 44.11; H, 4.92; N, 17.07.

(3*S*,4*R*,5*S*,6*S*)-3-Azido-1-chloro-4-((*tert*-butyldimethylsilyl)oxy)-5,6-*O*-isopropylidene-1-cyclohexene-5,6-diol (16b). TBSCl (96.5 mg, 0.64 mmol) was dissolved in dry DMF (2 mL) under argon, and then diisopropylethylamine (0.81 mmol, 0.14 mL) was added, with HCl fumes removed by the flow of argon. A solution of azido alcohol **16a** (52.4 mg, 0.213 mmol) in dry DMF (0.5 mL) was added at room temperature. The reaction mixture was stirred at room temperature for 26 h, and then H_2O (3 mL) and Et_2O were added, and the mixture was stirred for 15 min, followed by separation of both layers. The aqueous layer was extracted with Et_2O (2 × 3 mL). The combined ethereal extract was washed with brine (2 × 5 mL) and then dried and evaporated. The product was purified by flash chromatography (silica gel, hexanes/ethyl acetate, 9:1) to give the protected azido alcohol **16b** in 52% yield (40 mg, 0.11 mmol). An analytical sample was obtained by preparative TLC. R_f: 0.69 (hexanes/ethyl acetate, 8:2). $[\alpha]^{23}_D$: +32.8° (c = 0.56, MeOH). IR: (neat) 2103 cm^{-1}. ^{1}H NMR: ($CDCl_3$) δ 5.88 (d, J = 2.73 Hz, 1H), 4.55 (d, J = 6.2 Hz, 1H), 4.14 (td, J = 6.2, 0.8 Hz, 1H), 3.75 (m, 2H), 1.49 (s, 3H), 1.38 (s, 3H), 0.88 (s, 9H), 0.13 (s, 3H), 0.11 (s, 3H). ^{13}C NMR: ($CDCl_3$) δ 133.0 (C), 124.6 (CH), 110.9 (C), 77.8 (CH), 75.2 (CH), 72.3 (CH), 27.8 (CH_3), 25.7 (CH_3), 18.1 (C), –4.4 (CH_3), –4.9 (CH_3). Anal. Calcd for $C_{15}H_{26}N_3O_3ClSi$: C, 50.05; H, 7.28; N, 11.67. Found: C, 50.18; H, 7.30; N, 11.60.

(3*R*,4*R*,5*S*,6*S*)-3-Azido-1-chloro-5,6-*O*-isopropylidene-1-cyclohexene-4,5,6-triol (17a) To a solution of epoxide **13** (615 mg, 3.04 mmol) in anhydrous THF (30 mL) were added ethyl acetoacetate (1.16 mL, 9.1 mmol) and lithium chloride (643 mg, 15.1 mmol) at room temperature. After the solution was stirred for 16 h at 45 °C, the reaction was quenched with saturated NH_4Cl (10 mL) and brine (10 mL). After separation, the aqueous layer was extracted with CH_2Cl_2 (2 × 20 mL). The organic extracts were washed with brine (1 × 15 mL) and dried with Na_2SO_4, and the solvent was evaporated. The crude product was purified by flash chromatography (silica gel, hexane/ethyl acetate, 3:1), producing the corresponding *trans*-chlorohydrin in 91% yield (664 mg, 2.78 mmol) and traces of the *cis*-chlorohydrin (2–3%). Data for the *trans*-chlorohydrin follow. R_f: 0.38 (hexane/ethyl acetate, 3:1). $[\alpha]^{26}_D$: –7.3° (c = 2.08, $CHCl_3$). IR: (neat) 3436, 2990, 1649, 1081 cm^{-1}. ^{1}H NMR: ($CDCl_3$) δ 6.04 (dd, J = 2.0, 1.0 Hz, 1H), 4.63 (d, J = 6.3 Hz, 1H), 4.38 (ddd, J = 8.4, 2.0, 1.0 Hz, 1H), 4.18 (dd, J = 8.4, 8.4 Hz, 1H), 3.81 (t, J = 8.4 Hz, 1H), 3.11 (br s, 1H), 1.56 (s, 3H), 1.43 (s, 3H). ^{13}C NMR: ($CDCl_3$) δ 130.5 (C), 128.7 (C), 111.6 (C), 77.5 (CH), 75.7 (CH), 74.3 (CH), 58.2 (CH), 28.0 (CH_3), 25.9 (CH_3). MS: (CI) m/z (relative intensity) 239 (M + 1, 100), 223 (20), 145 (20), 89 (18). HRMS: calcd for $C_9H_{13}Cl_2O_3$ 239.024 175, found 239.021 317.

To a solution of the *trans*-chlorohydrin (664 mg, 2.78 mmol) in dry DMF (30 mL) was added sodium azide (542 mg, 8.33 mmol) under argon atmosphere. The reaction mixture was stirred at room temperature for 24 h and then at 55 °C for 12 h. The reaction mixture was diluted with ether (30 mL) and washed with 10% $Na_2S_2O_3$ (20 mL). After separation, the aqueous layer was extracted with Et_2O (2 × 20 mL). The combined organic layer was washed with brine and dried (Na_2SO_4), and the solvent was evaporated. The resulting oil was purified by flash chromatography (silica gel, hexane/ethyl acetate, 3:1), producing the azido alcohol **17a** in 91% yield (621 mg, 2.53 mmol) and 2.7% (18 mg, 0.075 mmol) of the starting *trans*-chlorohydrin. Data for **17a** follows. R_f: 0.5 (hexane/ethyl acetate, 3:1). Mp: 93.5–94 °C (CH_2Cl_2/hexane). $[\alpha]^{27}_D$: –99° (c = 0.68, MeOH). IR: (KBr) 3884, 2115, 1651, 1383 cm^{-1}. ^{1}H NMR: ($CDCl_3$) δ 5.9 (dd, J = 3.6, 0.5 Hz, 1H), 4.58 (dd, J = 5.6, 1.1 Hz, 1H), 4.39 (t, J = 5.6 Hz, 1H), 4.23 (m, 1H), 4.19 (m, 1H), 2.49 (br s, 1H), 1.42 (s, 3H), 1.38 (s, 3H). ^{13}C NMR: ($CDCl_3$) δ 134.7 (C), 122.2 (CH), 110.9 (C), 75.9 (CH), 75.0 (CH), 69.4 (CH), 27.6 (CH_3), 26.0 (CH_3). MS: (CI) m/z (relative intensity) 246 (M^+, 100), 160 (35), 145 (60), 96 (100). Anal. Calcd for $C_9H_{12}ClN_3O_3$: C, 44.00; H, 4.92; N, 17.10. Found: C, 44.05; H, 4.95; N, 17.03.

(3*R*,4*R*,5*S*,6*S*)-3-Azido-1-chloro-5,6-*O*-isopropylidene-4-((trimethylsilyl)oxy)-1-cyclohexene-5,6-diol (17b). Azido alcohol **17a** (410 mg, 1.67 mmol) was dissolved in dry CH_2Cl_2 (10 mL) under anhydrous conditions, and then hexamethyldisilazane (HMDS) (0.455 mL, 2.17 mmol) was added, followed by trimethylchlorosilane (TMSCl) (0.276 mL, 2.17 mmol) at ice-bath temperature. The reaction mixture was stirred at room temperature for 12 h, and then 0.2 equiv of each reagent was added. After the mixture was stirred for 3 h more, the solvent was evaporated, and the residue was filtered through a small bed of silica gel with hexane/ethyl acetate, 9:1. The evaporation of the solvent afforded **17b** in 95% yield (506 mg, 1.59 mmol), of sufficient purity for further use. An analytical sample was purified by flash chromatography (silica gel, hexane/ethyl acetate, 9:1). R_f: 0.5 (hexane/ethyl acetate, 9:1). $[\alpha]^{27}_D$: –83.4° (c = 1.64, MeOH). IR: (film) 2940, 2095, 1380, 1230, 845 cm^{-1}. ^{1}H NMR: ($CDCl_3$) δ 5.87 (d, J = 3.2 Hz, 1H), 4.53 (m, 1H), 4.23 (m,1H), 3.85 (m, 1H), 1.40 (s, 3H), 1.38 (s, 3H), 0.22 (s, 9H). ^{13}C NMR: ($CDCl_3$) δ 134.4, 122.9, 110.4, 76.7, 75.2, 71.0, 58.1, 27.6, 26.6, –0.05.

(3*R*,4*R*,5*S*,6*S*)-3-Azido-1-chloro-5,6-*O*-((isopropyledene-4-isopropyldimethylsilyl)oxy)-1-cyclohexene-5,6-diol (17c). Azido alcohol **17a** (737 mg, 2.99 mmol) was dissolved in dry CH_2Cl_2 (30 mL) under anhydrous conditions, and then isopropyldimethylchlorosilane (0.564 mL, 3.59 mmol) was added, followed by imidazole (407 mg, 5.98 mmol). The reaction mixture was stirred at room temperature for 5 h, and then the solution was filtered, washed with water (10 mL) and brine (10 mL), and dried over Na_2SO_4. Purification by flash chromatography (silica gel, hexane/ethyl acetate, 95:5) afforded **17c** in 99% yield (1.02 g, 2.95 mmol). R_f: 0.45 (hexane/ethyl acetate, 95:5). $[\alpha]^{27}_D$: –76° (c = 1.24, $CHCl_3$). IR: (film) 2942, 2098, 1651, 1463, 1381, 1231, 1148, 1081 cm^{-1}. ^{1}H NMR: ($CDCl_3$) δ 5.90 (d, J = 3.1 Hz, 1H), 4.56 (dd, J = 5.3, 1.4 Hz, 1H), 4.29 (t, J = 5.3 Hz, 1H), 4.24 (dd, J = 5.3, 3.4 Hz, 1H), 3.92 (m, 1H), 1.41 (s, 3H), 1.39 (s, 3H), 0.97 (d, 6H), 0.93 (m, 1H), 0.16 (s, 3H), 0.15 (s, 3H). ^{13}C NMR: ($CDCl_3$) δ 134.5, 122.8, 110.5, 76.8, 75.4, 71.2, 58.5, 27.7, 26.2, 16.8, 14.8, –3.8, –3.9. MS: (CI) m/z (relative intensity) 346 (M + 1, 60), 303 (20), 260 (20), 245 (100), 217 (30), 201 (72), 159 (40), 119 (40), 109 (30). Anal. Calcd for $C_{24}H_{24}ClN_3O_3Si$: C, 48.61; H, 6.99; N, 12.14. Found: C, 48.48; H, 7.03; N, 12.21.

Methyl (2*S*,3*S*,4*R*,5*R*)-5-Azido-6-hydroperoxy-6-methoxy-4-((*tert*-butyldimethylsilyl)oxy)-2,3-(isopropylidenedioxy)hexanoate (18). To a solution of **16b** (631 mg, 1.76 mmol) in methanol (25 mL) was added sodium bicarbonate (933 mg, 11.1 mmol). The mixture was cooled to –78 °C, and a stream of O_3/O_2 was passed through until a blue color persisted for 5 min. After the excess of O_3 was removed at –78 °C, the temperature was raised to room temperature, and stirring was continued for 5 h. The solvent was evaporated, without heating, on a rotary evaporator. (***CAUTION**: The solution was peroxide active, iodostarch paper. Because of the presence of peroxides, all work must be performed in a hood, behind a shield. It is not recommended to increase the scale of this reaction without the appropriate reduction of all peroxides prior to handling*). The residue was taken up in ethyl acetate and filtered through Celite; the flask and solid were thoroughly washed with ethyl acetate. The combined filtrates were evaporated to give a viscous liquid (~100%). The crude material was homogeneous by TLC and could be used for the next reaction without purification. An analytical sample of **18** was obtained by flash chromatography (silica gel [dry pack], hexane/ethyl acetate, 7:3) and subsequent recrystallization from CH_2Cl_2/hexane. R_f: 0.5 (hexane/ethyl acetate, 7:3). Mp: 95.5–96 °C. $[\alpha]^{25}_D$: +38.31° (c = 0.35, MeOH). IR: (film) 3346, 2094, 1712, 1116, 837 cm^{-1}. ^{1}H NMR: ($CDCl_3$) δ 8.6 (br s, 1H), 4.9 (d, J =8.1 Hz, 1H), 4.5 (t, J = 5.8 Hz, 1H), 4.4 (t, J = 8.8 Hz, 1H), 4.0 (d, J = 8.8 Hz, 1H), 3.7 (s, 3H), 3.6 (s, 3H), 1.56 (s, 3H), 1.37 (s, 3H), 0.87 (s, 3H), 0.10 (s, 3H), 0.07 (s, 3H). ^{13}C NMR: ($CDCl_3$) δ 171.5, 110.9, 105.2, 79.2, 75.3, 61.3, 56.7, 26.6, 25.5, 18.5, –4.0, –4.8. Anal. Calcd for $C_{17}H_{33}N_3O_8Si$: C, 46.88; H, 7.63. Found: C, 46.99; H, 7.84.

(2*S*,3*S*)-2,3-*O*-Isopropylidene-4,6-bis((*tert*-butyldimethylsilyl)oxy)-D-(6-*epi*)-mannolactam (20b). Hydroperoxide **18**, prepared as described above on a scale of 0.235 mg (0.654 mmol) of the protected azido alcohol **16b**, was, without isolation, subjected to a reductive workup. After the excess O_3 was removed at –78 °C, the temperature was raised to –20 °C, and then 244 mg of $CeCl_3 \cdot 7H_2O$ (0.654 mmol) was added. $NaBH_4$ was then added in 25-mg portions (0.654 mmol) while the reaction was monitored by TLC (hexane/ethyl acetate, 8:2). Upon the completion of the reduction (as evidenced by a single sharp spot by TLC), the reaction was quenched with water and citric acid at pH 6 and stirred for 0.5 h at room temperature. The reaction mixture was extracted with Et_2O (3 times) and EtOAc (2 times). The combined organic phase was evaporated; the crude product was taken in CH_2Cl_2, washed with brine, and dried over Na_2SO_4. After filtration, the solvent was removed in vacuo, affording the crude azido ester alcohol **19**. An analytical sample was obtained by recrystallization from ethyl acetate/hexane. R_f: 0.5 (hexane/ethyl acetate, 1:1). Mp: 95.5–96.5 °C. $[\alpha]^{25}_D$: +56.7° (c = 0.49, MeOH). IR: (film) 3484, 2116, 1755, 1209 cm^{-1}. ^{1}H NMR: ($CDCl_3$) δ 4.50 (t, J = 6.0 Hz, 1H), 4.45 (t, J = 6.0 Hz, 1H), 3.93 (m, 2H), 3.81 (dd, J = 10.9, 6.7 Hz, 1H), 3.71 (m, 1H), 3.30 (td, J = 6.7, 1.5 Hz, 1H), 1.92 (br s, 1H), 1.56 (s, 3H), 1.37 (s, 1H), 0.87 (s, 3H), 0.09 (s, 3H), 0.06 (s, 3H). ^{13}C NMR: ($CDCl_3$) δ 170.0 (C), 110.9 (C), 78.9 (CH), 75.5 (CH), 71.4 (CH), 61.3 (CH2), 52.0 (CH), 26.5 (CH_3), 25.9 ($3CH_3$), 25.6 (CH_3), 18.4 (C), –4.1 (CH3), –4.8 (CH_3). Anal. Calcd for $C_{16}H_{31}N_3O_6Si$: C, 49.34; H, 8.02. Found: C, 49.58; H, 8.17.

The crude azido ester alcohol **19** (250 mg) was dissolved in MeOH (15 mL), and 10% Pd/C (50 mg) was added. The mixture was hydrogenated at 50 psi for 8 h. The mixture was filtered through Celite, the solvent was evaporated, and the crude material was purified by flash chromatography (silica gel, hexane/ethyl acetate, 1:1 + 6% MeOH) to give the pure hydroxylactam **20a** in 71% yield from **16b** (153 mg, 0.462 mmol). The material was used immediately in the next step.

To a solution of the hydroxylactam **20a** (99 mg, 0.30 mmol) in dry DMF (1.5 mL) were added TBSCl (134 mg, 0.886 mmol) and DIPEA (0.19 mL, 1.1 mmol) at room temperature under argon atmosphere. The mixture was stirred at room temperature for 19 h and then diluted with ether (10 mL) and brine (3 mL), and stirring was continued for 15 min. The layers were separated; the organic layer was washed with brine (2 × 3 mL) and dried (Na_2SO_4), and the solvent was evaporated to produce a yellow oil. The crude product was purified by flash chromatography (silica gel, ethyl acetate/hexane, 7:3), producing **20b** in 79% yield (105 mg, 0.235 mmol) as a colorless oil which crystallized on storage. R_f: 0.31 (hexane/ethyl acetate, 7:3). Mp: 147–148 °C. $[\alpha]^{24}_D$: −16.9° (*c* = 0.88, MeOH). IR: ($CHCl_3$) 3395, 3210, 3100, 2955, 2865, 1685, 1460, 1385, 1255, 1215, 1120, 1010, 910, 835, 755 cm^{-1}. ^1H NMR: ($CDCl_3$) δ 6.54 (br s, 1H), 4.46 (d, *J* = 6.7 Hz, 1H), 4.29 (dd, *J* = 6.7, 4.8 Hz, 1H), 3.95 (m, 1H), 3.73 (dd, *J* = 10.6, 8.1 Hz, 1H), 3.59 (m, 2H), 1.43 (s, 3H), 1.34 (s, 3H), 0.85 (s, 9H), 0.83 (s, 9H), 0.08 (s, 3H), 0.03 (s, 9H). ^{13}C NMR: ($CDCl_3$) δ 169.1, 110.4, 78.9, 76.5, 73.6, 68.3, 62.4, 54.3, 26.9, 25.8, 25.6, 24.9, 18.2, 17.9, −4.5. Anal. Calcd for $C_{21}H_{43}NO_5Si_2$: C, 56.58; H, 9.72; N, 3.14. Found: C, 56.30; H, 9.67; N, 3.10.

Methyl (2*S*,3*S*,4*R*,5*S*)-5-Azido-6-hydroperoxy-2,3-(isopropylidenedioxy)-4-((trimethylsilyl)oxy)-6-methoxyhexanoate (21a). The procedure above was repeated with (3*R*,4*R*,5*S*,6*S*)-3-Azido-1-chloro-5,6-*O*-isopropylidene-4-((trimethylsilyl)oxy)-1-cyclohexene-5,6-diol (**17b**) as starting material but with MeOH containing 10% water (*NOTE*: the reaction mixture did not turn blue). After workup, the crude product (92%) was isolated, which consisted of peroxide **21a** contaminated with traces of **25** and the starting material **17b**. Data for peroxide **21a** follow. R_f: 0.63 (hexane/ethyl acetate, 1:1). $[\alpha]^{22}_D$: +37.4° (*c* = 0.845, MeOH). IR: (neat) 3360, 2960, 2095, 1740, 1090 cm^{-1}. ^1H NMR: ($CDCl_3$) δ 8.81 (br s, 1H), 4.9 (d, *J* = 7.2 Hz, 1H), 4.64 (d, *J* = 6.0 Hz, 1H), 4.48 (dd, *J* = 9.0, 6.0 Hz, 1H), 3.82 (m, 2H), 3.74 (s, 3H), 1.56 (s, 3H), 1.36 (s, 3H). ^{13}C NMR: ($CDCl_3$) δ 170.8, 110.5, 106.5, 78.6, 75.8, 75.7, 73.2, 62.5, 56.9, 51.8, 26.5, 25.7.

Methyl (2*S*,3*S*,4*R*,5*S*)-5-Azido-6-hydroperoxy-2,3-(isopropylidenedioxy)-4-((isopropyldimethylsilyl)oxy)-6-methoxyhexanoate (21b). For comparison, the above procedure for ozonolysis was repeated with (3*R*,4*R*,5*S*,6*S*)-3-azido-1-chloro-5,6-*O*-isopropylidene-4-((isopropyldimethylsilyl)oxy)-1-cyclohexene-5,6-diol (**17c**) as starting material but in MeOH containing 7% water. After workup, a quantitative yield of crude peroxide **21b** was obtained. R_f: 0.52 (hexane/ethyl acetate, 7:3). IR: (film) 3352, 3021, 2954, 2886, 2111, 1756, 1462, 1438, 1383, 1253, 1216, 1091, 758 cm^{-1}. ^1H NMR: ($CDCl_3$) δ 8.4 (br s, 1H), 4,93 (d, *J* = 7.3 Hz, 1H), 4.66 (d, *J* = 5.9 Hz, 1H), 4.54 (dd, *J* = 9.5, 5.9 Hz, 1H), 3.92 (dd, *J* = 7.3, 1.7 Hz, 1H), 3.82 (dd, *J* = 9.5, 1.7 Hz, 1H), 3.77 (s, 3H), 3.6 (s, 3H), 1.59 (s, 3H), 1.38 (s, 3H), 0.95 (d, 6H), 0.9 (m, 1H), 0.11 (s, 6H). ^{13}C NMR: ($CDCl_3$) δ 171.1, 110.8, 106.8, 78.9, 75.8, 73.6, 63.0, 57.2, 52.0, 26.7, 25.9, 17.1, 15.3, −3.4, −3.7.

2,3-*O*-Isopropylidene-4-((trimethylsilyl)oxy)-6-((*tert*-butyldimethylsilyl)oxy)-D-mannolactam (23a). To a cooled (0 °C) solution of peroxide **21a** (114 mg, 0.286 mmol) in dry THF (10 mL) was added sodium borohydride (10.8 mg, 0.287 mmol). Next MeOH (0.035 mL, 0.858 mmol) was slowly added with efficient stirring. The reaction, monitored by TLC (silica gel, hexane/ethyl acetate, 1:1), was complete in 50 min. The reaction was quenched with saturated ammonium chloride solution (15 drops), brine (2 mL), and ethyl acetate (5 mL). After separation of layers, the organic layer was extracted with ethyl acetate (2 × 3 mL); the combined organic extracts were dried (Na_2SO_4), and the solvent was evaporated. The crude product was purified by flash chromatography (silica gel, hexane/ethyl acetete, 1:1) to produce the free alcohol **22a** in 44% yield (44.7 mg, 0.125 mmol). R_f: 0.27 (hexane/ethyl acetate, 1:1). $[\alpha]^{24}_D$: +45.7° (*c* = 0.155, MeOH). IR: (neat) 3480, 2940, 2080, 1740, 1375 cm^{-1}. ^1H NMR: ($CDCl_3$) δ 4.45 (d, *J* = 6.3 Hz, 1H), 4.30 (dd, *J* = 7.9, 6.3 Hz, 1H), 3.963.92 (m, 2H), 3.82 (m, 1H), 3.75 (s, 3H), 3.54 (m, 1H), 1.56 (s, 3H), 1.35 (s, 3H), 0.11 (s, 3H). ^{13}C NMR: ($CDCl_3$) δ 170, 110.8, 78.8, 75.8, 72.9, 64.2, 61.6, 26.4, 25.6, 0.3. HRMS: calcd for $C_{13}H_{26}O_6NSi$ 320.152 9413, found 320.152 995.

Palladium on carbon (10%) (7.1 mg) was added to the crude methyl (2*S*,3*S*,4*R*,5*R*)-5-azido-6-hydroxy-2,3-(sopropylidenedioxy)-4-((trimethylsilyl)oxy)hexanoate (**22a**) dissolved in MeOH (6 mL). The solution was hydrogenated at 44 psi for 7 h at room temperature. Filtration of the solution through Celite and evaporation of the solvent led to 92.8% yield of a practically pure (2*S*,3*S*,4*R*,5*R*)-2,3-*O*-isopropylidene-6-hydroxy-4-((trimethylsilyl)oxy)-1,5-mannolactam (34 mg, 0.12 mmol). This material was dissolved in dry CH_2Cl_2 (3 mL) with DBU (0.04 mL, 0.278 mmol) at room temperature under argon. TBDMSCl (34.8 mg, 0.232 mmol) was then added, and the reaction mixture was stirred for 72 h. The mixture was diluted with Et_2O (10 mL) and brine (3 mL). After separation of the layers, the aqueous layer was extracted with Et_2O (2 × 5 mL). The combined organic layers were washed with brine (5 mL), dried over Na_2SO_4, and evaporated. The crude product was purified by flash chromatography (silica gel, ethyl acetate/hexane, 1:1) producing **23a** in 41% yield (19.2 mg, 0.047 mmol). R_f: 0.42 (hexane/ethyl acetate, 1:1). $[\alpha]^{27}_D$: +16.4° (*c* = 1.43, MeOH). IR: (neat) 3300, 2910, 1660, 810 cm^{-1}. ^1H NMR: ($CDCl_3$) δ 6.17 (br s, 1H), 4.6 (d, *J* = 7.8 Hz, 1H), 4.27 (t, *J* = 7.8 Hz, 1H), 3.96 (dd, *J* = 8.7, 4.0 Hz, 1H), 3.57 (m, 2H), 3.4 (td, *J* = 8.7, 4.0 Hz, 1H), 1.48 (s, 3H), 1.37 (s, 3H), 0.86 (s, 9H), 0.05 (s, 9H), 0.03 (s, 6H). ^{13}C NMR: ($CDCl_3$) δ 168.0, 110.9, 78.9, 73.0, 71.4, 63.4, 54.7, 27.2, 25.8, 25.0, 18.2, 1.9, −4.2. **MS:** (CI) *m/z* (relative intensity) 446 (M + 1, 0.8), 332 (100), 274 (60), 89 (45).

2,3-*O*-Isopropylidene-4,6-bis((isopropyldimethylsilyl)oxy)-D-mannolactam (23b). To a solution of (3*R*,4*R*,5*S*,6*S*)-3-azido-1-chloro-5,6-*O*-isopropylidene-4-((isopropyldimethylsilyl)oxy)-1-cyclohexene-5,6-diol (**17c**) (215 mg, 0.621 mmol) in methanol containing 7% water (15 mL) was added sodium bicarbonate (261 mg, 3.1 mmol). The mixture was cooled to −78 °C and ozonized until a blue color persisted. Excess ozone was removed with a stream of argon at −78 °C. The mixture was then allowed to warm to room temperature over 3 h. Brine (15 mL) and water (5 mL) were added, and the solution was extracted with Et_2O (4 × 20 mL). The volume was reduced to 30 mL (on the rotary evaporator with a cold bath), and Me_2S (0.092 mL, 1.24 mmol) was added. After being stirred 3 h at room temperature, the solution was washed (brine, 2 × 5 mL), dried ($MgSO_4$), filtered, and concentrated (with cold temperature and high vacuum), leading to the azido aldehyde. The crude material (229 mg, 0.614 mmol, 99%) was subjected to analysis. IR: (film) 3453, 2953, 2865, 2111, 1761, 1734, 1462, 1438, 1382, 1253, 1118, 1091, 835 cm^{-1}. ^1H NMR: ($CDCl_3$) δ 9.62 (t, *J* = 1.1 Hz, 1H), 4.67 (d, *J* = 6.2 Hz, 1H), 4.41 (dd, *J* = 8.4, 6.2 Hz, 1H), 4.09 (t, *J* = 1.6 Hz, 1H), 4.03 (m, 1H), 3.78 (s, 3H), 1.58 (s, 3H), 1.38 (s, 3H), 0.93 (d, 6H), 0.87 (m, 1H), 0.10 (s, 3H), 0.08 (s, 3H). ^{13}C NMR: ($CDCl_3$) δ 197.9, 170.4, 111.2, 78.5, 75.5, 73.9, 69.4, 52.2, 26.5, 25.6, 16.8, 15.0, −3.6, −4.0.

The crude azido aldehyde (229 mg, 0.614 mmol) was dissolved in anhydrous Et_2O under argon. The temperature was cooled to −78 °C, and 4.9 mL of a freshly prepared $Zn(BH_4)_2$ solution (0.5 M in Et_2O) was slowly added over 20 min. The mixture was stirred 0.5 h more at −78 °C and quenched by NH_4Cl (saturated solution). After being stirred 1 h at room temperature, the solution was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were dried (Na_2SO_4) and concentrated. The crude product was purified by flash chromatography (silica gel, hexane/ethyl acetate, 3:1), producing the azido alcohol **22b** in 59% yield (36 mg, 0.362 mmol).

An alternative procedure for the reductive workup of the ozonolysis gave better results. After removal of excess of ozone, the temperature was raised to −20 °C, and 1 equiv of $CeCl_3 \cdot 7H_2O$ was added, followed by $NaBH_4$ added in 1-equiv portions. The reaction was monitored by TLC (hexane/ethyl acetate, 8:2); when the reduction was complete (single sharp spot by TLC), the reaction was quenched with water and citric acid (pH 6), followed by stirring 0.5 h at room temperature. The reaction mixture was extracted with Et_2O (3 times) and EtOAc (2 times). The combined organic phases were evaporated, and the residue was taken up in CH_2Cl_2, washed with brine, and dried over Na_2SO_4. After removal of the solvent in vacuo, reasonably pure azido alcohol **22b** (by ^1H NMR) was obtained [yield (crude) = 95%]. R_f: 0.375 (hexane/ethyl acetate, 3:1). $[\alpha]^{25}_D$: +33.6° (*c* = 1.43, $CHCl_3$). IR: (film) 3497, 2953, 2865, 2100, 1760, 1462, 1438, 1381, 1251, 1143, 1097, 834 cm^{-1}. ^1H NMR: ($CDCl_3$) δ 4.57 (d, *J* = 6.1 Hz, 1H), 4.31 (dd, *J* = 8.8, 6.1 Hz, 1H), 3.96 (dd, *J* = 8.8, 2.7 Hz, 1H), 3.9 (m, 2H), 3.78 (s, 3H), 3.63 (dt, *J* = 5.2, 2.7 Hz, 1H), 2.35 (t, *J* = 6 Hz, 1H), 1.59 (s, 3H), 1.38 (s, 3H), 0.96 (d, 6H), 0.89 (m, 1H), 0.11 (s, 3H), 0.10 (s, 3H). ^{13}C NMR: ($CDCl_3$) δ 170.4, 110.9, 79.0, 75.9, 73.2, 64.3, 61.7, 52.1, 26.6, 25.7, 16.9, 15.2, −3.4, −3.9. MS: (CI) *m/z* (relative intensity) 376 (M + 1, 10), 350 (100), 334 (20), 320 (50), 275 (20), 261 (25), 243 (30), 232 (40), 173 (70), 160 (80). Anal. Calcd for $C_{15}H_{29}N_3O_6Si$: C, 47.98; H, 7.78; N, 11.19. Found: C, 47.92; H, 7.82; N, 11.21.

To a solution of methyl (2*S*,3*S*,4*R*,5*R*)-5-azido-6-hydroxy-2,3-(isopropylidenedioxy)-4-((isopropyldimethylsilyl)oxy)hexanoate (**22b**) obtained above (308 mg, 0.821 mmol) in dry CH_2Cl_2 (20 mL) were added under argon isopropyldimethylchlorosilane (0.258 mL 1.64 mmol) and

DBU (0.295 mL, 1.97 mmol). The reaction was stirred 6 h at room temperature and quenched with brine (10 mL). After separation, the aqueous layer was extracted with Et_2O (2 × 15 mL). The combined organic layers were dried (Na_2SO_4) and concentrated. The crude material was purified by flash chromatography (silica gel, hexane/ethyl acetate, 95:5), leading to the protected azido alcohol **22c** in 75% yield (292 mg, 0.614 mmol). R_f: 0.38 (hexane/ethyl acetate, 95:5). $[\alpha]^{25}_D$: + 30.7° (c = 1.0, $CHCl_3$). IR: (film) 2953, 2865, 2101, 1762, 1734, 1463, 1437, 1381, 1371, 1251, 1098, 999, 832, 777 cm^{-1}. ^1H NMR: ($CDCl_3$) δ 4.55 (d, J = 6.0 Hz, 1H), 4.32 (dd, J = 9.0, 6.0 Hz, 1H), 3.98 (dd, J = 10.1, 5.5 Hz, 1H), 3.87 (dd, J = 9.0, 3.1 Hz, 1H), 3.76 (s, 3H), 3.69 (dd, J = 10.1, 6.6 Hz, 1H), 3.60 (m, 1H), 1.57 (s, 3H), 1.35 (s, 3H), 0.97 (m, 12H), 0.86 (m, 2H), 0.09 (s, 12H). ^{13}C NMR: ($CDCl_3$) δ 170.6, 110.6, 79.4, 76.0, 72.5, 64.8, 61.7, 51.9, 26.7, 25.8, 17.0, 15.3, 14.6, -3.3, -3.7, -4.4. MS: (CI) m/z (relative intensity) 460 (M - 15, 10), 448 (85), 432 (50), 418 (35), 404 (30), 390 (30), 374 (50). Anal. Calcd for $C_{20}H_{41}N_3O_6Si_2$: C, 50.49; H, 8.68; N, 8.83. Found: C, 50.55; H, 8.66; N, 8.76.

The above methyl (2*S*,3*S*,4*R*,5*R*)-5-azido-2,3-(isopropylidenedioxy)-4,6-bis((isopropyldimethylsilyl)oxy)hexanoate (**22c**) (290 mg, 0.61 mmol) was hydrogenated over Pd/C (10%) at 47 psi for 7.5 h in 25 mL of MeOH. The solution was filtered through Celite and concentrated. The crude was purified by flash chromatography (silica gel, hexane/ethyl acetate, 1:1), leading to the mannolactam **23b** in 90.5% yield (230 mg, 0.551 mmol). R_f: 0.43 (hexane/ethyl acetate, 1:1). $[\alpha]^{25}_D$: +30.3° (c = 0.6, $CHCl_3$). IR: (film) 3392, 3211, 3100, 2955, 2865, 1685, 1462, 1383, 1253, 1215, 1118, 999, 884, 834, 758 cm^{-1}. ^1H NMR: ($CDCl_3$) δ 6.08 (s, 1H), 4.60 (d, J = 7.9 Hz, 1H), 4.26 (dd, J = 7.9, 6.8 Hz, 1H), 3.91 (dd, J = 9.9, 3.6 Hz, 1H), 3.57 (dd, J = 8.7, 3.6 Hz, 1H), 3.48 (dd, J = 9.9, 8.7 Hz, 1H), 3.34 (m, 1H), 1.51 (s, 3H), 1.38 (s, 3H), 0.94 (m, 12H), 0.87 (m, 2H), 0.13 (s, 3H), 0.09 (s, 3H), 0.08 (s, 6H). ^{13}C NMR: ($CDCl_3$) δ 168.6, 110.6, 79.5, 73.1, 72.0, 63.0, 55.7, 27.0, 24.9, 16.9, 14.9, 14.5, -3.2, -4.0, -4.4. MS: (CI) m/z (relative intensity) 418 (M + 1, 100), 402 (10), 374 (55), 344 (15), 316 (20), 286 (15). Anal. Calcd for $C_{19}H_{39}NO_5Si_2$: C, 54.63; H, 9.41; N, 3.35. Found: C, 54.53; H, 9.43; N, 3.29.

(2*S*,3*S*)-2,3-*O*-Isopropylidene-4-(1(*S*)-azido-2-hydroperoxy-2-methoxyethyl)-γ-butyrolactone (25). To a solution of (3*R*,4*R*,5*S*,6*S*)-3-azido-1-chloro-5,6-*O*-isopropylidene-1-cyclohexene-4,5,6-diol (**17a**) (874 mg, 2.09 mmol) in methanol (20 mL) was added sodium bicarbonate (1.05 mg, 12.6 mmol). The mixture was cooled to -78 °C and ozonized until a blue color persisted. The excess ozone was removed with a stream of argon at -78 °C. The cooling bath was then substituted by an ice-water bath, and stirring was continued for 5.5 h. The solvent was evaporated under reduced pressure without heating. (*CAUTION: the solution gave a positive test for peroxides.*) The residue was taken up in ethyl acetate and filtered through Celite. Evaporation of the solvent gave peroxide **25** in nearly quantitative yield. An analytical sample was obtained by successive recrystallizations from ethyl acetate/hexane. R_f: 0.36 (hexane/ethyl acetate, 1:1). Mp: 101-102 °C dec. (gas evolution). $[\alpha]^{24}_D$: +28.3° (c = 0.925, MeOH). IR: (neat) 3250, 2900, 2045, 1755, 1160 cm^{-1}. ^1H NMR: ($CDCl_3$) δ 5.0 (d, J = 2.2 Hz, 1H), 4.84 (m, 2H), 4.39 (dd, J = 9.8, 3.2 Hz, 1H), 4.10 (ddd, J = 9.8, 3.2, 1.5 Hz, 1H), 3.64 (s, 3H), 1.46 (s, 3H), 1.40 (s, 3H). ^{13}C NMR: ($CDCl_3$) δ 172.9, 114.6, 106.4, 76.1, 75.8, 75.6, 60.5, 58.4, 26.7, 25.9. MS (CI) m/z (relative intensity) 272 (M - 17, 30), 244 (77), 184 (100), 142 (65), 128 (80), 85 (75). HRMS: calcd for $C_{10}H_{15}O_7N_3$ 272.088 2604, found 272.088 516.

(2*S*,3*S*)-2,3-*O*-Isopropylidene-4-(2-hydroxy-1(*R*)-azidoethyl)-γ-butyrolactone (27). A solution of (3*R*,4*R*,5*S*,6*S*)-3-azido-1-chloro-5,6-*O*-isopropylidene-1-cyclohexene-4,5,6-diol (**17a**) (370 mg, 1.507 mmol) in methanol (10 mL) was cooled to -78 °C and ozonized until a blue color persisted. Excess ozone was removed with a stream of argon at -78 °C. The mixture was then allowed to warm to room temperature over 3 h, and the volume was reduced to 5 mL by a stream of air, yielding a concentration of 0.3 M. The reduction was carried out, after addition one crystal of methyl orange (pH indicator), by addition of 2 equiv of $NaBH_3CN$ (190 mg, 3.014 mmol); the reaction was monitored by TLC (hexane/ethyl acetate, 1:1). HCl (2 N) was added dropwise continuously to maintain the pH ≈ 3 (pink color), and more $NaBH_3CN$ was added (6 equiv total). When the reduction was complete (single sharp spot by TLC), the reaction was quenched with acetone, with addition of 2 N HCl to maintain the pink color, followed by stirring for 1 h at room temperature. The reaction mixture was extracted with EtOAc (4 times). The combined organic phase was washed with brine and dried over Na_2SO_4. After removal of the solvent in vacuo, the crude material was purified by flash chromatography (silica gel, hexane/ethyl acetate, 1:1), affording the lactone **27** in 65% yield (239 mg, 0.983 mmol). R_f: 0.45 (hexane/ethyl acetate, 1:1). Mp: 115-116 °C (hexane, CH_2Cl_2). IR: ($CHCl_3$) 3500 (br), 2105, 1795 cm^{-1}. ^1H NMR: ($CDCl_3$) δ 4.91 (dd, J = 5.1, 3.3 Hz, 1 H), 4.86 (d, J = 5.1 Hz, 1H), 4.46 (dd, J = 9.7, 3.3 Hz, 1H), 4.04 (m, 1H), 3.90 (m, 2H), 1.94 (t, OH), 1.50 (s, 3H), 1.44 (s, 3H). ^{13}C NMR: ($CDCl_3$) δ 173.5, 114.5, 76.06, 75.9, 62.1, 61.3, 26.8, 25.9. MS: (CI) m/z (relative intensity) 244 (M + 1, 4), 228 (16), 216 (100), 186 (40), 174 (30). Anal. Calcd for $C_9H_{13}N_3O_5$: C, 44.44; H, 5.38; N, 17.27. Found: C, 44.53; H, 5.39; N, 17.34.

(3*R*,4*S*,5*S*,6*S*)-4-((Trifluoromethylsulfonyl)oxy)-1-chloro-3-((*tert*-butyldimethylsilyl)oxy)-5,6-*O*-isopropylidene-1-cyclohexene-5,6-diol (24b). TBSCl (2.1 g, 14 mmol) was added to a solution of diol **14**[12,23] (2.8 g, 13 mmol) in dry CH_2Cl_2 (40 mL), followed by imidazole (1.73 g, 25.39 mmol), and the reaction was stirred under argon at room temperature for 20 h. The reaction mixture was filtered, washed with water and brine, and dried over Na_2SO_4. The solvent was removed in vacuo, affording a crude product purified by flash chromatography (silica gel, hexane/ethyl acetate, 9:1) to give the monoprotected diol in 83% yield (3.53 g, 10.55 mmol) and 7.5% of the diprotected diol (426 mg). The fraction containing the monoprotected diol was shown to be a mixture (56/44 by ^1H NMR) of the two possible unseparable regioisomers. The major compound (56%) corresponded to the desired regioisomer with the TBSO group on the allylic position at C5.

The regioselective protection of diol **14** was performed as follows. The dibutylstannylene derivative of **14** was prepared according to Moffatt's procedure[27a] in MeOH or benzene under reflux until clarification of the reaction mixture. The reaction mixture was then evaporated to dryness and solubilized into dry CH_2Cl_2. Dry TBSCl (3 equiv) and Bu_4NBr (1 equiv) were added as well as molecular sieves, and the reaction mixture was stirred for 1 day, filtered through Celite, washed with H_2O and brine, and dried over Na_2SO_4. After evaporation, the crude product was purified as above, affording the single (by ^1H NMR) desired regioprotected monoalcohol in about 75% yield. (This procedure has not been optimized.) The same procedure carried out in benzene under reflux with a Dean-Stark trap afforded in less than 30 min a mixture of monoprotected alcohols in 88% yield containing 85% of the desired regioisomer.

The mixture of alcohols (448 mg, 1.339 mmol) was dissolved under argon in dry CH_2Cl_2 (20 mL) and cooled to -30 °C, whereupon 0.41 mL (5.0 mmol) of pyridine and then 0.34 mL (2 mmol) of triflic anhydride were added. The reaction mixture was stirred at -20 °C for 3 h, and the solvent was evaporated. The resulting gummy solid was triturated with hexane/ethyl acetate, 9:1 (50 mL), and the solution was filtered through a small bed of silica gel (2 cm). The solvent was removed in vacuo, affording quantitatively the pure triflate **24b**. R_f: 0.7 (hexane/ethyl acetate, 9:1). $[\alpha]^{25}_D$: -102.7° (c = 1.12, $CHCl_3$). IR: (film) 3000, 2970, 2950, 2900, 2870, 1650, 1470, 1415, 1385, 1245, 1210, 1140, 1085, 960 cm^{-1}. ^1H NMR: ($CDCl_3$) δ 5.97 (d, J = 5 Hz, 1H), 4.92 (dd, J = 7.3, 3.1 Hz, 1H), 4.74 (d, J = 6.1 Hz, 1H), 4.62 (dd, J = 6.3, 7.1 Hz, 1H), 4.51 (dd, J = 4.9, 3.2 Hz, 1H), 1.50 (s, 3H), 1.43 (s, 3H), 0.90 (s, 9H), 0.13 (s, 3H), 0.11 (s, 3H). ^{13}C NMR: ($CDCl_3$) δ 133.09, 127.34, 118.8 (quadruplet CF_3), 111.58, 88.93, 86.57, 76.09, 73.32, 66.34, 27.30, 25.70, 18.12, -4.23. MS: (CI) m/z (relative intensity) 467 (M + 1, 50), 451 (45), 427 (25), 419 (15), 409 (25), 393 (35), 351 (100), 333 (25), 317 (20), 259 (85). Anal. Calcd for $C_{16}H_{26}ClF_3O_6SSi$: C, 41.15; H, 5.61; S, 6.86. Found: C, 41.04; H, 5.64; S, 6.81.

(3*R*,4*R*,5*S*,6*S*)-4-Azido-1-chloro-3-((*tert*-butyldimethylsilyl)oxy)-5,6-*O*-isopropylidene-1-cyclohexene-5,6-diol (26). Freshly prepared triflate **24b** was dissolved in dry DMF (25 mL), and 195 mg (3 mmol) of NaN_3 was added. The reaction mixture was stirred at room temperature under argon overnight. The solution was diluted with Et_2O (25 mL), and 25 mL of 10% aqueous $Na_2S_2O_3$ solution was added. After separation, the aqueous layer was extracted with Et_2O (3 × 20 mL). The combined organic fractions were washed with brine, dried over Na_2SO_4, and evaporated. The crude product was purified by flash chromatography (hexane/ethyl acetate, 95:5), to produce pure **26** in 91% yield from the monoprotected diol mixture (245 mg, 0.68 mmol) based on the 56% content of the desired monoalcohol in the starting mixture. The other regioisomer was eliminated during the triflate formation. R_f: 0.5 (hexane/ethyl acetate, 9:1). $[\alpha]^{25}_D$: -92.7° (c = 1.0, $CHCl_3$). IR: ($CHCl_3$) 3020, 3000, 2960, 2940, 2900, 2870, 2105, 1475, 1385, 1375, 1260, 1215, 1100, 1050, 995, 900, 860, 835, 755 cm^{-1}. ^1H NMR: ($CDCl_3$) δ 5.78 (d, J = 2 Hz, 1H), 4.53 (m, 2H), 4.48 (dt, J = 8.3, 1.8-2.0 Hz, 1H), 3.53 (dd, J = 8.4, 2 Hz, 1H), 1.415 (s, 3H), 1.41 (s, 3H), 0.93 (s, 9H), 0.20 (s, 3H), 0.15 (s, 3H). ^{13}C NMR: ($CDCl_3$) δ 131.85, 129.56, 111.03, 76.44, 75.53, 68.74, 64.93, 27.31, 26.39, 25.72, 17.95, -4.7. MS: (CI) m/z (relative intensity) 360 (M + 1, 17), 332 (40), 417 (13), 304 (17), 302 (45), 274 (10), 261 (40), 259 (100). Anal. Calcd for $C_{15}H_{26}ClN_3O_3Si$: C, 50.05; H, 7.28; N, 11.67. Found: C, 49.87; H, 7.27; N, 11.63.

(2S,3S)-2,3-O-Isopropylidine-4-(2-hydroxy-1(S)-((*tert*-butyldimethylsilyl)oxy)-ethyl)-γ-butyrolactam (28). To a solution of (3*R*,4*R*,5*S*,6*S*)-4-azido-1-chloro-3-((*tert*-butyldimethylsilyl)oxy)-5,6-*O*-isopropylidene-1-cyclohexene-5,6-diol (**26**) (174 mg, 0.484 mmol) in methanol containing 7% water (15 mL) was added sodium bicarbonate (203 mg, 2.42 mmol). The mixture was cooled to −78 °C and ozonized until a blue color persisted. The excess of ozone was removed with a stream of argon at −78 °C. The temperature was raised to −20 °C, and then 180 mg of $CeCl_3 \cdot 7H_2O$ (0.484 mmol) was added, followed by $NaBH_4$ in 20-mg portions (0.484 mmol). The reaction was monitored by TLC (hexane/ethyl acetate, 8:2). When the reduction was complete (single sharp spot by TLC), the reaction was quenched with water and citric acid at pH 6, followed by stirring for 0.5 h at room temperature. The reaction mixture was extracted with Et_2O (3 times) and EtOAc (2 times). The combined organic phases were evaporated, and the crude product was taken up in CH_2Cl_2, washed with brine, and dried over Na_2SO_4. After removal of the solvent in vacuo, the crude azido alcohol was hydrogenated in the presence of 30 mg of Pd/C (10%) in EtOAc at 50 psi for 20 h. After filtration through Celite, the crude product was purified by flash chromatography (hexane/ethyl acetate, 1:1 + 5% MeOH) to give **28** in 69% yield (110 mg, 0.332 mmol). R_f: 0.35 (hexane/ethyl acetate, 1:1 + 5% MeOH). $[\alpha]^{25}_D$: +5.4° (*c* = 1.72, $CHCl_3$). IR: ($CHCl_3$) 3300 (br), 3020, 3000, 2960, 2940, 2900, 2870, 1710, 1465, 1385, 1375, 1255, 1215, 1155, 1125, 1090, 1050, 915, 835, 755 cm^{-1}. ^1H NMR: ($CDCl_3$) δ 7.56 (s, 1H), 4.55 (m, 2H), 4.0 (s, 1H), 3.90 (m, 1H), 3.64 (dd, *J* = 11.4, 4.7 Hz, 1H), 3.54 (dd, *J* = 11.5, 8.5 Hz, 1H), 3.25 (s, 1H), 1.44 (s, 3H), 1.36 (s, 3H), 0.86 (s, 9H), 0.09 (s, 6H). ^{13}C NMR: ($CDCl_3$) δ 175.5, 112.3, 78.8, 77.2, 72.6, 63.2, 60.3, 27.2, 25.9, 25.7, 18.1, −4.1, −4.5. MS: (CI) *m/z* (relative intensity) 332 (M + 1, 100), 316 (15), 274 (60), 258 (10), 246 (15), 216 (30). HRMS: (CI) calcd for $C_{15}H_{30}NO_5Si$ 332.189 326, found 332.187 393.

5-Amino-5-deoxy-D-mannopyranose ((+)-D-Mannojirimycin, 8a). To a solution of (3*R*,4*R*,5*S*,6*S*)-3-azido-1-chloro-5,6-*O*-isopropylidene-1-cyclohexene-4,5,6-triol (**17a**) (209 mg, 0.851 mmol) in methanol was added sodium bicarbonate (357 mg, 4.25 mmol). The mixture was cooled to −78 °C and ozonized until a blue color persisted. Excess ozone was removed with a stream of argon at −78 °C. The temperature was raised over 2 h to 0 °C, and then $NaBH_4$ was added in 1-equiv portions, and the reaction was monitored by TLC (hexane/ethyl acetate, 8:2). When the reduction was complete (single sharp spot by TLC), the reaction was quenched with water and citric acid at pH 6, followed by stirring for 0.5 at room temperature. The reaction mixture was extracted with Et_2O (3 times) and EtOAc (2 times). The combined organic phases were evaporated, and the crude product was taken up in CH_2Cl_2, washed with brine, and dried over Na_2SO_4. After removal of the solvent in vacuo, the crude was purified by flash chromatography (CH_2Cl_2/MeOH, 96:4) to give **29** in 58% yield (121 mg, 0.49 mmol).

From lactone **27**, **29** was synthesized as follows. To a cold (−78 °C) solution of **27** (185 mg, 7.61 mmol) in dry CH_2Cl_2 (15 mL) was added a DIBAL-H solution (1.0 M in CH_2Cl_2) (2.28 mL, 2.28 mmol). The mixture was stirred 3 h under anhydrous conditions and quenched at −78 °C with 1.1 mL of MeOH, 1.1 mL of H_2O, and 2.3 mL of saturated aqueous $NaHCO_3$. The reaction mixture was stirred 2 h until the solution was clear, and then the solvent was decanted. The remaining gummy solid was once again stirred with CH_2Cl_2/EtOAc (1:1) for 1 h, and then the decanted solvent was combined with the previous fraction to be dried over Na_2SO_4. Removal of the solvent in vacuo afforded the crude azido lactol **29** (188 mg, 7.61 mmol) in quantitative yield, shown to be greater than 95% pure by ^1H NMR. R_f: 0.38 (CH_2Cl_2/MeOH, 96:4). Mp: 92–93 °C (hexane/ethyl acetate). $[\alpha]^{25}_D$: −18.4° (*c* = 0.5, $CHCl_3$). IR: ($CHCl_3$) 3430 (br), 3025, 3000, 2950, 2110, 1385, 1375, 1215, 1070 cm^{-1}. ^1H NMR: ($CDCl_3$) δ 5.38 (d, *J* = 2.3 Hz, 1H), 4.85 (dd, *J* = 5.83, 3.66 Hz, 1H), 4.63 (d, *J* = 5.84 Hz, 1H), 4.14 (dd, *J* = 9.12, 3.6 Hz, 1H), 3.85 (m, 3H), 2.78 (d, *J* = 2.3 Hz, OH), 2.14 (br s, OH), 1.47 (s, 3H), 1.35 (s, 3H). ^{13}C NMR: ($CDCl_3$) δ 112.95 (C), 101.28 (CH), 88.78 (CH), 85.41 (CH), 79.81 (CH), 78.42 (CH), 62.87 (CH_2), 61.38 (CH), 26.01 (CH_3), 24.77 (CH_3). MS: (CI) *m/z* (relative intensity) 246 (M + 1, 10), 230 (58), 218 (60), 202 (20), 188 (100), 170 (45), 159 (70), 142 (85). Anal. Calcd for $C_9H_{15}N_3O_5$: C, 44.08; H, 6.16; N, 17.13. Found: C, 44.17; H, 6.21; N, 17.23.

To a solution of the azidolactol **29** (180 mg, 0.734 mmol) in dry THF (10 mL) was added at room temperature under argon a solution of trimethylphosphine (1.0 M in THF). After the mixture was stirred 1 h under anhydrous conditions, water (0.04 mL, 2.2 mmol) was added, and the reaction mixture was heated at reflux overnight. After removal of the solvent in vacuo, the compound slowly tautomerized at room temperature (over a few days). The trimethylphosphine oxide generated by the reaction process was removed by flash chromatography (silica gel, CH_2Cl_2/MeOH, 9:1), producing a 1/1 mixture of mannojirimycin monoacetonide, further deprotected in 90% aqueous CF_3COOH, affording crude mannojirimycin **8a**. The natural product was characterized as its bisulfite derivative following Dondoni's procedure.[36a]

(2S,3S,4R,5S)-5-Azido-2,3-(isopropylidenedioxy)-4-((*tert*-butyldimethylsilyl)oxy)cyclohexanone (32). To the dry enone **30b**[23] (259 mg, 0.87 mmol) was added trimethylsilyl azide ($TMSN_3$, 0.57 mL, 4.35 mmol) under argon. The reaction mixture was stirred at room temperature for 45 h. After evaporation of the reaction mixture under high vaccum, 307 mg of a liquid was obtained, containing the azido ketone **32** and some starting material. An analytical sample was purified by HPLC (reverse phase). R_f: 0.31 (CH_2Cl_2). $[\alpha]^{25}_D$: +15° (*c* = 0.6, MeOH). IR: (neat) 2954, 2858, 2102, 1736, 1254, 1064 cm^{-1}. ^1H NMR: ($CDCl_3$) δ 4.32 (m, 2H), 4.13 (dd, *J* = 2.9, 2.1 Hz, 1H), 3.95 (ddd, *J* = 8.9, 6.8, 2.1 Hz, 1H), 2.72 (d, *J* = 4.1 Hz, 1H), 2.69 (d, *J* = 1.88 Hz, 1H), 1.41 (s, 3H), 1.32 (s, 3H), 0.89 (s, 9H), 0.14 (s, 3H), 0.12 (s, 3H). ^{13}C NMR: ($CDCl_3$) δ 203.5 (C), 111.1 (C), 78.5 (CH), 77.1 (CH), 70.8 (CH), 57.4 (CH), 38.5 (CH_2), 26.7 (CH_3), 25.6 (CH_3), 24.9 (CH_3), 18 (C), −4.9 (CH_3), −5.1 (CH_3). Anal. Calcd for $C_{15}H_{27}N_3O_4Si$: C, 52.76; H, 7.97; N, 12.30. Found: C, 52.87; H, 8.01; N, 12.22.

(3S,4R,5R,6R)-3-Azido-6,5-O-isopropylidene-4-((*tert*-butyldimethylsilyl)oxy)-1,6-lactone (33). Ketone **32** (47.8 mg, 0.14 mmol) was dissolved in $CHCl_3$ (1 mL), and a solution of *m*CPBA (36 mg, 0.21 mmol) in $CHCl_3$ (2 mL) was added. The reaction mixture was stirred at room temperature for 7 h. A saturated solution of $NaHCO_3$ was added, and stirring was continued for 15 min. After separation, the organic layer was washed with a saturated $NaHCO_3$ solution and then brine and then dried over Na_2SO_4, and the solvent was evaporated to produce 55 mg. The crude product was purified by flash chromatography (silica gel, hexane/ethyl acetate, 8:2) leading to the lactone **33** in 71% yield (35.5 mg, 0.1 mmol). R_f: 0.3 (hexane/ethyl acetate, 8:2). IR: (film) 2930, 2900, 2130, 1720, 1250 cm^{-1}. ^1H NMR: ($CDCl_3$) δ 5.78 (d, *J* = 3 Hz, 1H), 4.36 (dd, *J* = 7.8, 3.0 Hz, 1H), 3.97 (m, 2H), 3.03 (dd, *J* = 14.8, 9.9 Hz, 1H), 2.30 (dd, *J* = 14.8, 7.0 Hz, 1H), 1.56 (s, 3H), 1.39 (s, 3H), 0.89 (s, 9H), 0.12 (s, 3H), 0.10 (s, 3H).

(+)-Kifunensine (7). To a solution of lactone **27** (140 mg, 0.576 mmol) in a mixture of dichloroethane/dimethoxypropane (4:1) was added a catalytic amount of camphorsulfonic acid. The reaction was stirred under anhydrous conditions for 2 days and then under reflux for 1 day. After removal of the solvent in vacuo, the crude material was purified by flash chromatograpy (silica gel, hexane/ethyl acetate, 1:1), yielding an azido ester diacetonide in 33% yield (60 mg, 0.19 mmol).

Reduction was carried out by adding 3 equiv of $LiAlH_4$ (22 mg, 0.57 mmol) to a solution of the above compound in dry Et_2O (10 mL) at room temperature. After being stirred 4 h, the reaction was quenched with 0.022 mL of H_2O, 0.022 mL of NaOH 10%, and 0.066 mL of H_2O. The solid was rinsed with EtOAc (2 times). The combined solvents were dried over Na_2SO_4, filtered, and evaporated to afford a colorless oil (pure by ^1H NMR) in 91% yield (45 mg, 0.173 mmol).

A solution of the above amino alcohol (60 mg, 0.23 mmol) in 15 mL of MeOH with dimethyl oxalate was heated at reflux for 4 days, and then the solvent was evaporated. The crude material was added to 10 mL of 20% (v/v) NH_3 in MeOH. After 15 min, the solvent was removed in vacuo, and the crude material was purified by flash chromatography (silica gel, CH_2Cl_2/ethyl acetate, 1:1 + 5% MeOH), affording the compound **38** in 53% yield (40 mg, 0.122 mmol), identical to Hashimoto's intermediate. The conversion of **38** to protected kifunensine **39** and then to (+)-kifunensine **7** has been previously reported.[45]

Acknowledgment. The authors are grateful to TDC Research, Inc., Jeffress Trust Fund, and Genecor International for support of this work. La Fondation pour la Recherche Therapeutique (France) and TDC Research Foundation are acknowledged for the provision of postdoctoral fellowships to J.R. We are also grateful to Professor David Gibson (University of Iowa) for his continuing interest and advice. We thank Drs. M. Hashimoto (now at Nippon Glaxo Ltd.), H. Kayakiri, and M. Shirahashi from Fujisawa Pharmaceutical Co., Ltd., for the provision of samples and spectra of kifunensine and its diacetonide.

Supplementary Material Available: ^1H and ^{13}C NMR spectra for compounds described in the experimental section (53 pages). This material is contained in many 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.