Synthesis of Tetrahydroxyquinolizidines: Ring-Expanded Analogs of the Mannosidase Inhibitor Swainsonine

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The indolizidine azasugar swainsonine (**1**) is an important inhibitor of mannosidase II and has shown antitumor and immunomodulatory activity. A comparison of the structure of swainsonine and D-mannopyranose shows that swainsonine lacks the C(4) hydroxymethine group of mannose. Ring-expanded quinolizidine analogs **4** of swainsonine were prepared where the "missing" hydroxymethine group was incorporated into the pyrrolidine ring of swainsonine between C(1) and C(8a). The quinolizidine analogs **4** resemble both D-mannopyranose and the related azasugar deoxymannojirimycin, a selective inhibitor of the glycoprotein processing enzyme mannosidase I. D-Arabinose was converted into the ω-halo azidoalkene **13**, which was subjected to thermolysis, a strategy which had been successful in an earlier synthesis of swainsonine itself. Rather than the desired quinolizidine **4**, the pyridinium ion **16** was produced. An alternate synthesis of all four C(9)/C(9a) diastereomers of **4** was developed which relied on the reductive double-alkylation of epoxides bearing remote azido and chloro groups. Thus, reduction of compounds **21**α, **21**β, **26**, and **27** resulted in the formation of the quinolizidines **22**, **23**, **28**, and **29**, which were deprotected to give the quinolizidine analogs of swainsonine (9*S*,9a*R*)-**4**, (9*R*,9a*S*)-**4**, (9*S*,9a*S*)-**4**, and (9*R*,9a*R*)-**4**, respectively. An alternate synthesis of (9*R*,9a*R*)-**4** involving the reductive *N*-alkylation of a cyclic imine was also developed. None of the quinolizidines showed significant glycosidase activity in screens against mannosidases, glucosidases, or fucosidases. Speculation on the significance of these findings is presented.

Introduction

A number of naturally occuring polyhydroxylated indolizidine, pyrrolizidine, pyrrolidine, and piperidine alkaloids (often referred to as "amino-sugars" or "azasugars") exhibit glycosidase inhibitory activity.[1−5] At physiological pH, the protonated amino group may mimic the developing pyranosyl or furanosyl cation intermediate encountered in oligosaccharide cleavage. Several of these alkaloids are of interest for their activity against cancer, HIV, and other disorders. Due to their ability to inhibit glycoprotein processing enzymes, such alkaloids have also been useful in studies on the effect of oligosaccharide structure on glycoprotein function.[3−6] Swainsonine (**1**) and deoxymannojirimycin (**2**) are azasugar analogs of mannose (**3**) and are indeed inhibitors of various mannosidases.[4,6−10] Swainsonine is an inhibitor of lysosomal α-mannosidases and the glycoprocessing enzyme mannosidase II, while deoxymannojirimycin selectively inhibits mannosidase I. Swainsonine inhibits tumor growth and metastasis[11] and exhibits immunomodulatory activity.[12] Structurally modified analogs of swainsonine might provide more potent and selective mannosidase inhibitors. We wish to report our findings on the synthesis and biological evaluation of ring-expanded analogs of swainsonine.[13]

Swainsonine has been the subject of structure−activity relationship studies, primarily involving examination of the activity of its stereoisomers.[8,14,15] Another strategy involves the synthesis of ring-expanded or ring-contracted analogs of swainsonine. Carpenter *et al.*[16] and Burgess and Henderson[17] have prepared ring-contracted analogs of swainsonine where one methylene group is missing from the piperidine ring, i.e., pyrrolizidine analogs of swainsonine. This modification resulted in diminished mannosidase activity.[16] A comparison of the structures of swainsonine (**1**), deoxymannojirimycin (**2**), and D-mannopyranose (**3**) shows that swainsonine lacks the C(4) hydroxymethine group of D-mannose and deoxynojirimycin. This led us to consider synthesizing the ring-expanded swainsonine analog **4** where the "missing"

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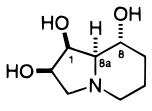
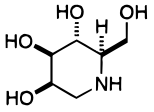
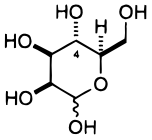
hydroxymethine group has been inserted into the pyrrolidine ring of swainsonine between C(1) and C(8a).



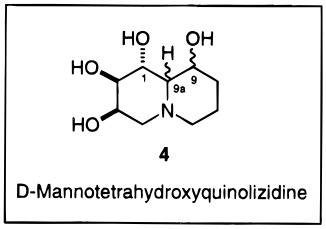
1
Swainsonine



2
Deoxymannojirimycin



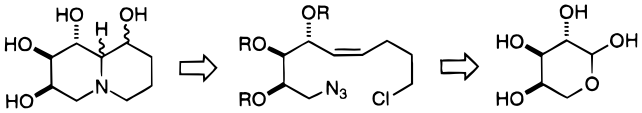
3
D-Mannopyranose



4
D-Mannotetrahydroxyquinolizidine

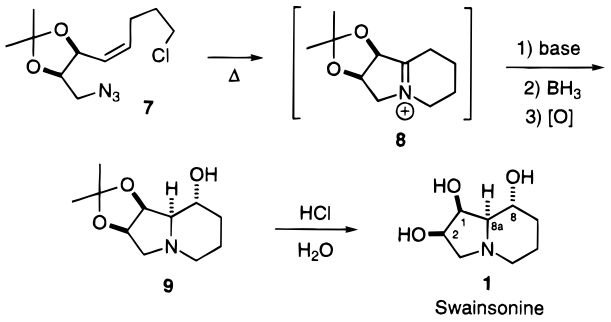
Ring-expanded analogs of castanospermine, a related indolizidine that shows glucosidase inhibitory activity, have been prepared and were found to retain inhibitory activity,[18] so we were optimistic that quinolizidine analogs of swainsonine would be reasonable targets. We were particularily interested to see if these quinolizidines would prove to be selective inhibitors of the glycoprotein processing enzyme mannosidase I. This enzyme appears to be inhibited by structures that more closely resemble the mannopyranose ground state conformation such as deoxymannojirimycin. Mannosidase II, on the other hand, appears to be inhibited by structures that mimic the proposed mannopyranosyl cation transition state.[14] Ganem and co-workers reported the preparation of (9*R*,-9a*R*)- and (9*S*,9a*R*)-**4** as part of a structure proof in a total synthesis of castanospermine, but no biological data were provided.[19] Concurrently with the publication of our preliminary work on the synthesis of two of the diastereomers of **4**,[13] Rassu, Casiraghi *et al.*, reported the synthesis of what were originally assigned as (9*R*,9a*R*)-**4** and its enantiomer,[20,21] but these structures have since been revised.[22] We now wish to provide a full report of the synthesis and glycosidase inhibitory activity of all four C(9)/C(9a) diastereomers of **4**. The following paper describes the synthesis and biological activity of another class of polyhydroxylated alkaloid analogs, namely the ring-expanded analogs of the pyrrolizidine alkaloids alexine and australine.

Scheme 1. Retrosynthetic Analysis of D-Mannotetrahydroxyquinolizidine Using the *ω*-Halo Azidoalkene Cyclization Strategy



4 **5** **6**
D-Arabinose

Scheme 2. Previous Use of the *ω*-Halo Azidoalkene Cyclization Strategy for the Synthesis of (−)-Swainsonine



7 **8** **9** **1**
Swainsonine

An Inital Synthetic Approach to the Quinolizidines 4 Using Azide Cycloaddition Methodology

Our initial synthetic strategy is shown in Scheme 1. Based on prior work from our group,[23−25] we proposed that the *ω*-halo azidoalkene **5** would undergo a thermal double-cyclization to produce **4** after suitable functional group manipulation. Wittig chemistry would be used to transform D-arabinose (**6**) into **5**. The closest analogy to the **5** → **4** transformation is our work on the synthesis of (−)-swainsonine (**1**), shown in Scheme 2, which involves a one-flask transformation of **7** to **9**.[23] Heating **7** caused (1) intramolecular 1,3-dipolar cycloaddition of the azide on to the alkene to afford a triazoline, (2) fragmentation of the triazoline with concomitant loss of nitrogen and 1,2-hydrogen shift to produce an imine, and (3) intramolecular *N*-alkylation of the imine to give the iminium ion **8**. Without isolation, **8** was deprotonated with base to generate an enamine which was subjected to hydroboration/oxidation *in situ* to produce **9** in good yield. Acidic hydrolysis of **9** gave swainsonine (**1**). Extension of the this methodology to the synthesis of **4** seemed to be a straightforward strategy, although the stereoselectivity of the hydroboration of the intermediate enamine was not certain.

Scheme 3 shows our attempted implementation of the *ω*-halo azidoalkene cyclization strategy. D-Arabinose (**6**) was converted into the 2,3,4-tri-*O*-benzyl-D-arabinose (**10**) by the literature procedure.[26] Wittig reaction with the known phosphonium salt **11**[23] gave the *Z*-alkene **12** with complete stereoselectivity. A Mitsunobu reaction with hydrazoic acid[27] proved to be the best way to convert the alcohol **12** into the azide **13** without interference from the primary chloride. With the key *ω*-halo azidoalkene **13** in hand, the double-cyclization was attempted. Heat-

(18) (a) Gradnig, G.; Berger, A.; Grassberger, V.; Stuetz, A. E.; Legler, G. *Tetrahedron Lett.* **1991**, *32*, 4889. (b) Liu, P. S.; Rogers, R. S.; Kang, M. S.; Sunkara, P. S. *Tetrahedron Lett.* **1991**, *32*, 5853. See also: (c) Herczegh, P.; Kovács, I.; Szilágyi, L.; Sztaricskai, F.; Berecibar, A.; Riche, C.; Chiaroni, A.; Olesker, A.; Lukacs, G. *Tetrahedron* **1995**, *51*, 2969. See also: (d) Marquart, A. L.; Podlogar, B. L.; Huber, E. W.; Demeter, D. A.; Peet, N. P.; Weintraub, H. J. R.; Angelastro, M. R. *J. Org. Chem* **1994**, *59*, 2092.

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(20) Rassu, G.; Casiraghi, G.; Pinna, L.; Spannu, P.; Ulgheri, F. *Tetrahedron* **1993**, *49*, 6627.

(21) Casiraghi, G.; Zanardi, F.; Rassu, G.; Spanu, P. *Chem. Rev.* **1995**, *95*, 1677.

(22) The data reported for (9*R*,9aR)-**4** by Rassu, Casiraghi *et al.* are not consistent with those obtained in our work (ref 13 and the current work) or in Ganem's work.[19] Upon subsequent investigation, Casiraghi *et al.* found that the critical annulation step in their work resulted in the formation of both a pyrrolizidine and a quinolizidine derivative. The quinolizidine reported in their paper as (9*R*,9a*R*)-**4** is probably a pyrrolizidine. The actual quinolizidine structure, not reported in their paper, is (9*S*,9a*S*)-**4**. The stereochemistry of an earlier compound in their sequence has now been reassigned based on X-ray crystallography, thus explaining the *S*- rather than *R*-configuration at C(9) and C(9a). We thank Professor Casiraghi for sharing this information with us prior to publication.

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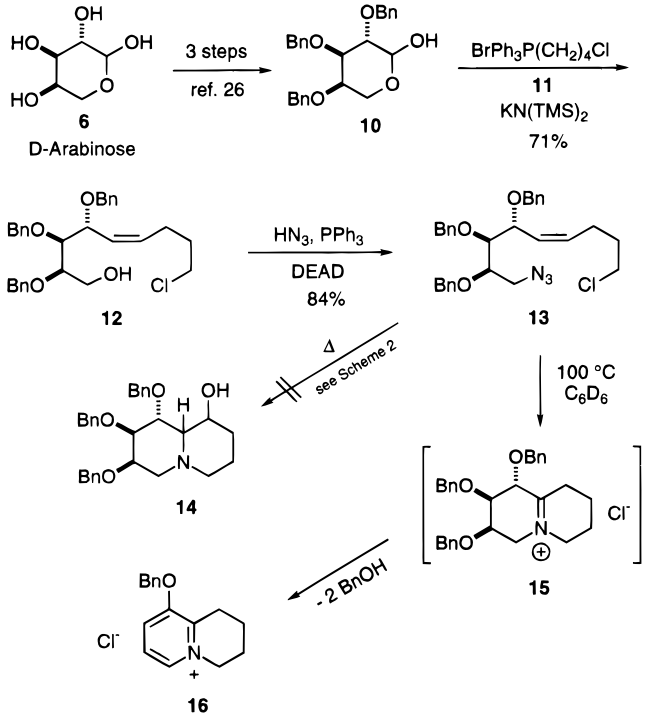
Scheme 3. Synthesis of the ω-Halo Azidoalkene 13 and Its Cyclization

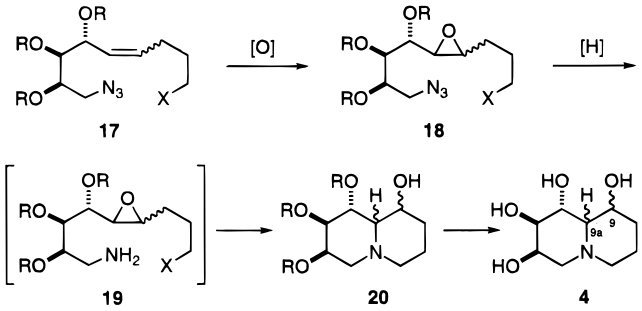


ing **13** followed by transformations similar to those shown in Scheme 2 failed to provide **14**, instead producing the pyridinium salt **16**. Apparently, cyclization to **15** proceeded as planned, but aromatization by loss of 2 equiv of benzyl alcohol rapidly ensued. A similar aromatization was observed in the Polonovski reaction of castanospermine tetraacetate *N*-oxide, where an iminium ion similar to **15** was generated.[28,29] All attempts at modifying the cyclization of **13** (e.g., presence of mild bases, use of different solvents, lower temperatures, or different protecting groups) failed to avoid the aromatization. Hence we were forced to examine a slightly longer, but ultimately practical alternative strategy.

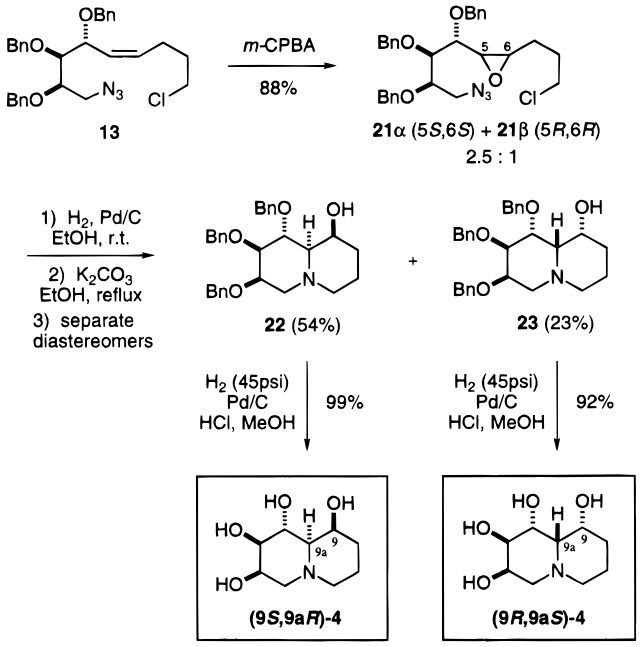
Alternate Synthetic Approach to the Quinolizidines 4 Using Epoxide Chemistry

While the ω-halo azidoalkene cyclization approach to polyhydroxylated quinolizidines had failed, an alternate plan using more traditional epoxide chemistry was examined, as outlined in Scheme 4. Oxidation of **17** (X = leaving group) to the epoxide **18** and reduction of the azide to the primary amine **19** should afford the quinolizidine **20** after an intramolecular double alkylation. We used such a reductive double-cyclization of an azido-epoxide bearing a remote leaving group in our syntheses of (−)-slaframine,[30] (+)-7-epiaustraline,[31] and (−)-7-epialexine.[31] Similar double-cyclizations have been reported by others.[16,32] The stereochemistry at C(9) and C(9a) of **4** will ultimately be determined by the geometry of the alkene **17** and the diastereoselectivity of its epoxidation. We hoped to synthesize the *E*- and *Z*-isomers of **17** in a

Scheme 4. Alternate Strategy Involving a Reductive Double-Alkylation



Scheme 5. Synthesis of Quinolizidines (9*S*,9a*R*)-4 and (9*R*,9a*S*)-4 Using the Reductive Double-Alkylation Method



stereoselective fashion. We recognized that the epoxidation of these two alkenes might not be very stereoselective,[33] but since it is not possible to predict which diastereomer will be the most biologically active, we felt this was not a disadvantage in this exploratory work.

Synthesis of Quinolizidines (9*S*,9a*R*)-4 and (9*R*,9a*S*)-4 from the *cis*-Epoxy Azides 21. Scheme 5 shows the synthesis of two of the four possible diastereomers of **4**, namely (9*S*,9a*R*)-**4** and (9*R*,9a*S*)-**4**. Epoxidation of the alkene **13** with *m*-chloroperbenzoic acid afforded a 2.5:1 mixture of the diastereomeric *cis*-epoxides **21**α and **21**β.[33,34] Without separation, the mixture of **21**α/**21**β was subjected to catalytic hydrogenolysis to generate the

(28) Brown, R. F. C.; Collins, D. J.; Lagniton, L. M.; Smith, R. J.; Wong, N. R. *Aust. J. Chem.* **1992**, *45*, 469.

(29) For the related aromatization of azasugars, see: Paulsen, H. *Angew. Chem., Int. Ed. Engl.* **1966**, *5*, 495.

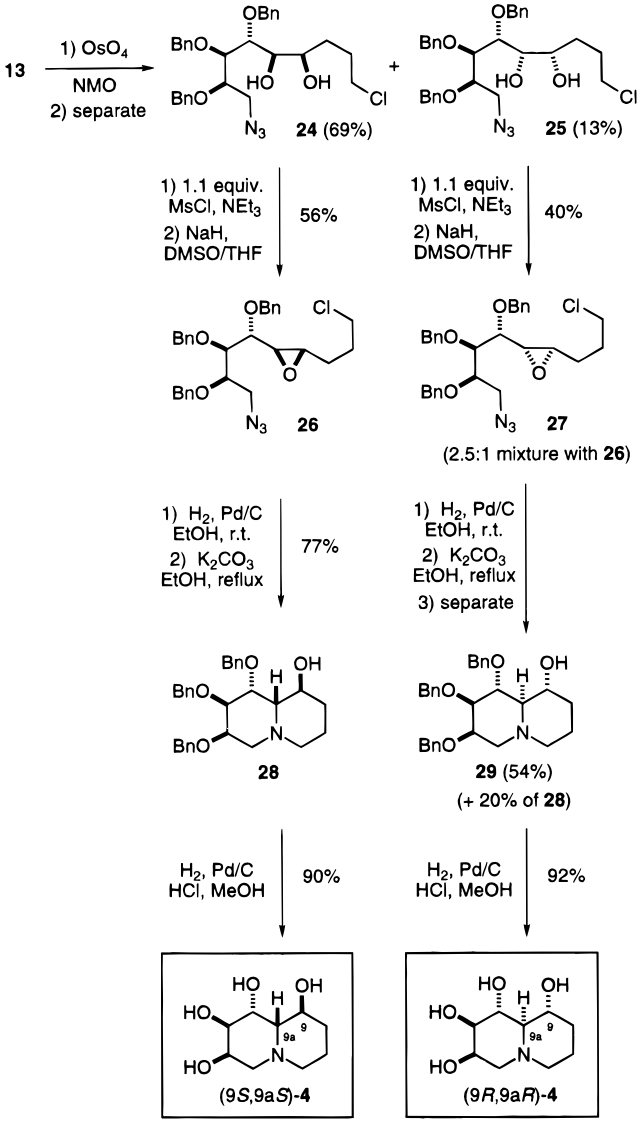
(30) (a) Pearson, W. H.; Bergmeier, S. C. *J. Org. Chem.* **1991**, *56*, 1976. (b) Pearson, W. H.; Bergmeier, S. C.; Williams, J. P. *J. Org. Chem.* **1992**, *57*, 3977.

(31) Pearson, W. H.; Hines, J. V. *Tetrahedron Lett.* **1991**, *32*, 5513.

(32) For related one-pot double cyclizations using amino epoxides, see: (a) Setoi, H.; Takeno, H.; Hashimoto, M. *J. Org. Chem.* **1985**, *50*, 3948. (b) Setoi, H.; Takeno, H.; Hashimoto, M. *Tetrahedron Lett.* **1985**, *26*, 4617. (c) Kim, Y. G.; Cha, J. K. *Tetrahedron Lett.* **1989**, *30*, 5721. (d) Kim, N.-S.; Choi, J.-R.; Cha, J. K. *J. Org. Chem* **1993**, *58*, 7096. (e) Lohray, B. B.; Jayamma, Y.; Chatterjee, M. *J. Org. Chem* **1995**, *60*, 5958. See also: (f) Poitout, L.; Le Merrer, Y.; Depezay, J.-C. *Tetrahedron Lett.* **1994**, *35*, 3293. For one-pot double cyclizations using amines with other electrophiles, see: (g) Ina, H.; Kibayashi, C. *J. Org. Chem.* **1993**, *58*, 52. (h) Jirousek, M. R.; Cheung, A. W.-H.; Babine, R. E.; Sass, P. M.; Schow, S. R.; Wick, M. M. *Tetrahedron Lett.* **1993**, *34*, 3671.

(33) For reports of similar epoxidations of allylic ethers, see: (a) Wang, Z.; Schreiber, S. L. *Tetrahedron Lett.* **1990**, *31*, 31. (b) Erickson, S. D.; Still, W. C. *Tetrahedron Lett.* **1990**, *31*, 4253. (c) Coutts, S. J.; Wittman, M. D.; Kallmerten, J. *Tetrahedron Lett.* **1990**, *31*, 4301.

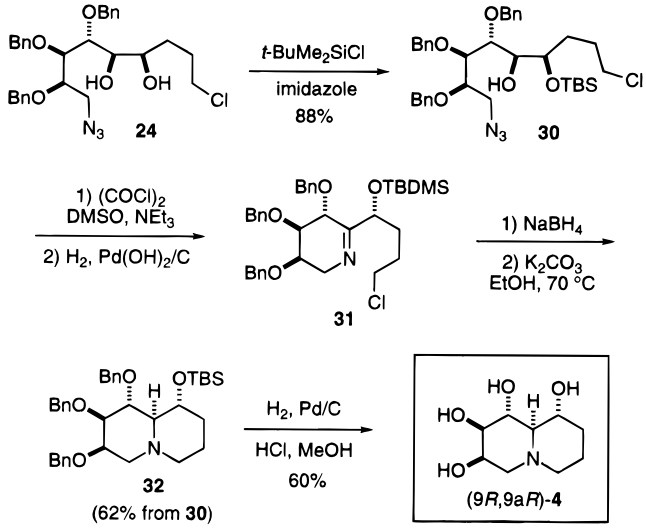
Scheme 6. Synthesis of Quinolizidines (9*S*,9a*S*)-4 and (9*R*,9a*R*)-4



primary amines, which were cyclized to the separable quinolizidines **22** and **23** upon heating. Hydrogenolysis of the benzyl protecting groups under acidic conditions afforded the desired quinolizidines (9*S*,9a*R*)-**4** and (9*R*,-9a*S*)-**4** in excellent yield after ion-exchange chromatography. The relative stereochemistries at C(9) and C(9a) in **22**, **23**, (9*S*,9a*R*)-**4**, and (9*R*,9a*S*)-**4** were easily assigned using ^{1}H-NMR coupling constants in these conformationally well-behaved *trans*-decalin-like structures.

Synthesis of Quinolizidines (9*S*,9a*S*)-4 and (9*R*,-9a*R*)-4 from the *trans*-Epoxy Azides 26 and 27. In order to prepare the remaining two C(9)/C(9a) diastereomers of **4**, we required the *trans*-epoxides **26** and **27**. Attempts to prepare *E*-**13** by other olefination methods or by isomerization of *Z*-**13** were unsuccessful, thus the alkene epoxidation route was abandoned.[35] Fortunately, we were able to transform *Z*-**13** into the desired *trans*-epoxides **26** and **27** by the alternative route shown in Scheme 6. Osmylation of **13** afforded the diols **24** and **25** in good yield after separation by column chromatography.[36] Selective monomesylation of the major diol **24** at the less-hindered secondary hydroxyl group was followed by sodium hydride treatment, affording the *trans*-epoxide **26** in moderate yield. The presence of DMSO was found to be crucial for the success of the NaH-promoted cyclization. A similar sequence on the minor diol **25** produced the alternate *trans*-epoxide **27** contaminated with some **26**, presumably due to a less regioselective mesylation. Subjection of **26** to the reductive cyclization conditions outlined above gave the quinolizidine **28**. Hydrogenolysis of the benzyl protecting groups of **28** under acidic conditions afforded (9*S*,9a*S*)-**4** after ion-exchange chromatography. Reductive cyclization of the mixture of **27** and **26** followed by separation gave the quinolizidine **29**. Deprotection as usual produced (9*R*,-9a*R*)-**4**. Again, the relative stereochemistries at C(9) and C(9a) in **28**, **29**, (9*S*,9a*S*)-**4**, and (9*R*,9a*R*)-**4** were easily assigned using ^{1}H-NMR coupling constants.

Scheme 7. Alternate Synthesis of Quinolizidine (9*R*,9a*R*)-4



A Selective Synthesis of Quinolizidine (9*R*,9a*R*)-4. from the Diol 24. Unfortunately, the route shown in Scheme 6 made it difficult to prepare significant quantities of (9*R*,9a*R*)-**4** for biological testing, since not only was **25** the minor product of the osmylation, but the closure of **25** to **27** was not very selective. Thus, we developed an efficient way to convert the *major* osmylation product **24** into the *minor* quinolizidine (9*R*,9a*R*)-**4** (Scheme 7). Selective monosilylation of **24** afforded **30**. Swern oxidation of **30** to the ketone followed by hydrogenolysis of the azide led to the formation of the labile cyclic imine **31**. Sodium borohydride reduction of **31** followed by heating afforded the quinolizidine **32** in good overall yield from **30**. Acidic hydrogenolysis of the benzyl groups of **32** also served to remove the silyl protecting group, affording (9*R*,9a*R*)-**4**.

(34) Attempted Jacobsen asymmetric epoxidation of **13** led to recovered starting material (Zhang, W.; Loebach, J. L.; Wilson, S. R.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1990**, *112*, 2801). Attempts to synthesize **13** with a free allylic hydroxyl group were made in order to attempt a Sharpless epoxidation, but the sequence became too cumbersome to be practical.

(35) We were able to prepare a related *trans* alkene, ethyl (*E*)-(6*R*,7*S*,8*R*)-9-azido-6,7,8-tris(benzyloxy)non-4-enoate, using an entirely different synthesis. Epoxidation gave a 2:1 ratio of epoxides. The major epoxide was transformed into (9*S*,9a*S*)-**4**, but this route offered no significant advantage over the route shown in Scheme 6.

(36) Attempts to increase the stereoselectivity of the osmylation in one direction or another using the Sharpless asymmetric dihydroxylation (Sharpless, K. B.; Amberg, W.; Bennani, Y. L.; Crispino, G. A.; Hartung, J.; Jeong, K.-S.; Kwong, H.-L.; Morikawa, K.; Wang, Z.-M.; Xu, D.; Zhang, X.-L. *J. Org. Chem.* **1992**, *57*, 2768) failed due to poor reactivity.

Biological Screening of the Quinolizidines 4

The four diastereomers of **4** were screened for inhibitory activity against a number of glycosidases.[37] With the exception of (9*R*,9a*S*)-**4**, which proved to be a relatively weak inhibitor of α-L-fucosidase (IC_{50} = 0.36 mM), the quinolizidines were found to have little or no glycosidase inhibitory activity. Less than 50% inhibition was observed against α-mannosidase (jack bean), α-glucosidase (bakers' yeast), *β*-glucosidase (almond), amyloglucosidase (*Aspergillus niger*), and α-L-fucosidase (bovine epididymis) at concentrations up to 2 mM. For comparison, swainsonine (**1**) has been reported to inhibit the α-mannosidase from jack bean by 50% at a concentration of 2 μM, and deoxymannonojirimycin **2** inhibits this enzyme by 50% at a concentration of 150 μM.[14] The quinolizidines **4** were also screened for inhibition of the glycoprocessing enzymes glucosidase I, glucosidase II, and mannosidase I,[38] and for anticancer and anti-HIV activity,[39] but no promising activity was found. These results contrast sharply with the glycosidase inhibitory activity of quinolizidine analogs of castanospermine.[18]

We had hoped that the quinolizidines **4** would selectively inhibit mannosidase I over mannosidase II, since mannosidase I is effectively inhibited by chairlike azasugars such as deoxymannojirimycin while mannosidase II is known to be most strongly inhibited by compounds that are able to adopt a ring-flattened conformation resembling the proposed mannopyranosyl cation intermediate which is encountered in the glycoside cleavage process.[14] While we were not able to test **4** against mannosidase II directly, jack bean α-mannosidase is usually a good indicator of mannosidase II activity.[3] Given the preference of mannosidase II and jack bean α-mannosidase for ring-flattened inhibitors, the failure of the quinolizidines **4** to inhibit jack bean α-mannosidase was not surprising due to their *trans*-decalin-like structures. Unfortunately, the quinolizidines **4** also failed to inhibit mannosidase I, despite the fact that the chair conformation of these structures mimics the mannopyranose ground state conformation which appears to be important for inhibition of this enzyme. This may indicate that the mannosidase I binding site does not tolerate the added steric bulk imposed by the second ring of **4**, or perhaps more likely, that mimicking the ground state conformation of mannose is not sufficient for mannosidase I inhibition. The greater conformational flexibility of deoxymannojirimycin as compared to **4** may explain the difference in the ability of these compounds to inhibit mannosidase I.

Experimental Section

General Methods. All commercial reagents (if liquid) were distilled prior to use. All other solid reagents were used as obtained. Hydrazoic acid solutions were prepared according to Wolff.[40] **Caution:** Hydrazoic acid should be handled with extreme care. All work involving hydrazoic acid solutions were carried out in an efficient fume hood. The solution was transferred vial cannula, and any excess hydrazoic acid was quenched by the addition of 10% NaOH. Tetrahydrofuran was distilled from sodium/benzophenone ketyl. Benzene, dichloromethane, dimethyl sulfoxide, and triethylamine were distilled from calcium hydride. Dimethylformamide was distilled from barium oxide at reduced pressure. Methanol and ethanol were distilled from calcium oxide. Analytical thin layer chromatography (TLC) was conducted on precoated silica gel plates (Kieselgel 60 F_{254}, 0.25 mm thickness, manufactured by E. Merck & Co., Germany). For visualization, TLC plates were either placed under ultraviolet light, or stained with iodine vapor or phosphomolybdic acid solution. Elemental analyses were performed by the University of Michigan Department of Chemistry CHN/AA Services Branch. Assignments in the ^{1}H NMR spectra were made on the basis of two-dimensional correlated off-resonance spectroscopy (COSY) experiments. *J*-Modulated spin echo Fourier transform (JMOD) ^{13}C NMR experiments are reported as (+) (for CH_3 and CH) or (−) (for CH_2 and C) and are used as an alternative to off-resonance decoupling experiments. High resolution mass spectrometric (HRMS) measurements are accurate to within 2.2 ppm (electron impact, EI), 3.9 ppm (chemical ionization, CI), or 3.3 ppm (fast-atom bombardment, FAB), based on measurement of the performance of the mass spectrometer on a standard organic sample. Flash column chromatography was performed according to the general procedure described by Still[41] using flash grade Merck silica gel 60 (230−400 mesh). Radial chromatography was performed on a Harrison Research Chromatotron, using glass plates coated with Merck silica gel 60. Solvent was delivered by an FMI Lab Pump solvent metering system. The enzymes α-mannosidase (from jack bean), α-glucosidase (from bakers' yeast), *β*-glucosidase (from almonds), amyloglucosidase (from *Aspergillus niger*), and α-L-fucosidase (from bovine epididymis), and the corresponding *p*-nitrophenyl glycoside substrates were obtained from Sigma Chemical Co. Enzyme inhibition was assayed colormetrically by monitoring the release of *p*-nitrophenol from the appropriate *p*-nitrophenyl glycoside substrate according to the procedure described by Tropea *et al*.[37]

(*Z*)-(2*R*,3*S*,4*R*)-2,3,4-Tris(benzyloxy)-9-chloro-5-nonen-1-ol (12). Potassium bis(trimethylsilyl)amide (13 mL of a 0.5 M solution in toluene, 6.5 mmol) was added to a suspension of $BrPh_3P(CH_2)_4Cl$ (**11**)[23] (2.802 g, 6.46 mmol) in THF (6.5 mL) at 0 °C. After 30 min, the dark red-orange solution was cooled to −78 °C, and 2,3,4-tri-*O*-benzyl-D-arabinopyranose (**10**)[26] (1.076 g, 2.55 mmol) in THF (5 mL) was added. The resulting yellow solution was allowed to warm slowly to room temperature. After 6 h, the reaction was quenched with excess acetone (5 mL) and diluted with ether (100 mL). The resulting precipitate was removed by filtration through a bed of Celite, rinsing with ether (50 mL). The filtrate was washed with water (50 mL), saturated aqueous $NaHCO_3$ (50 mL), and brine (50 mL) and then dried (Na_2SO_4), filtered, and concentrated. Chromatography (6:1 hex/EtOAc) gave 895 mg (71%) of the title compound as a pale yellow oil. R_f = 0.52 (2:1 hex/EtOAc): $[\alpha]^{23}_D = -14.0°$ (*c* 0.98, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) *δ* 7.4−7.2 (m, 15H), 5.58 (m, 2H), 4.73 (s, 2H), 4.47 (ABq, J = 11.9 Hz, $\Delta\nu$ = 91.1 Hz, 2H), 4.43 (ABq, J = 11.4 Hz, $\Delta\nu$ = 36.9 Hz, 2H), 4.42 (dd, J = 3.5, 8.2 Hz, 1H), 3.80 (broad s, 2H), 3.69 (m, 2H), 3.45 (t, J = 6.4 Hz, 2H) 2.30−2.00 (m, 3H), 1.84−1.74 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) *δ* 138.7, 138.5, 132.7, 129.5, 128.5, 128.4, 128.2, 128.0, 127.8, 127.8, 127.7, 127.6, 82.3, 79.6, 75.1, 74.8, 72.0, 70.5, 61.5, 44.2, 32.4, 25.3; IR ($CDCl_3$) 3580 (m), 3011 (s), 2873 (s), 1454 (s), 1062 (s) cm^{-1}; MS (CI NH_3) *m*/*z* (rel intensity) 512 [$(M + NH_4)^+$, 5], 495 [$(M + H)^+$, 3], 279 (21), 108 (43), 91 (100); HRMS calcd for $C_{30}H_{35}O_4ClH$ [$(M + H)^+$] 495.2302, found 495.2276. Anal. Calcd for $C_{30}H_{35}O_4Cl$: C, 72.79 H, 7.13. Found: C, 72.93; H, 7.36.

(*Z*)-(2*R*,3*S*,4*R*)-1-Azido-2,3,4-tris(benzyloxy)-9-chloro-5-nonene (13). Hydrazoic acid[40] (1.03 mL of a 1.2 M solution in benzene, 1.24 mmol) was added to a solution of **12** (558 mg, 1.13 mmol) and PPh_3 (325 mg, 1.24 mmol) in benzene (5 mL) at 5 °C. Diethyl azodicarboxylate (216 mg, 1.24 mmol) was added in a dropwise fashion, and the solution was allowed to warm to room temperature (Ph_3PO precipitation was ob-

(37) Tropea, J. E.; Molyneux, R. J.; Kaushal, G. P.; Pan, Y. T.; Mitchell, M.; Elbein, A. D. *Biochemistry* **1989**, *28*, 2027.

(38) We thank Prof. Alan D. Elbein (University of Arkansas) for the results of screening against the glucosidase I and II and mannosidase I.

(39) The results of anti-HIV and anticancer testing were provided by the National Cancer Institute Developmental Therapeutics Program. Only (9*S*,9a*R*)-**4** and (9*R*,9a*S*)-**4** were tested in these screens.

(40) Wolff, H. In *Organic Reactions*; Adams, R., Ed.; Wiley: New York, 1946; Vol. 3, pp 307−336.

(41) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem*. **1978**, *43*, 2923.

served). After 25 min, the solvent was removed and the product was separated from the Ph_3PO by washing the residue with hexane. Chromatography (20:1 hex/EtOAc) gave 490 mg of the title compound (84%) as a pale yellow oil. R_f = 0.32 (10:1 hex/EtOAc); $[\alpha]^{23}_D$ = −11.0° (*c* 1.51, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.2−7.5 (m, 15H), 5.58 (m, 2H), 4.69 (ABq, J = 11.4 Hz, $\Delta\nu$ = 13.5 Hz, 2H), 4.48 (ABq, J = 11.2 Hz, $\Delta\nu$ = 47.5 Hz, 2H), 4.46 (ABq, J = 11.8 Hz, $\Delta\nu$ = 91.4 Hz, 2H), 4.39 (m, 1H), 3.83 (dt, J = 3.0, 5.7 Hz, 1H), 3.64 (dd, J = 4.0, 5.5 Hz, 1H), 3.47 (m, 4 H), 2.0−2.3 (m, 2H), 1.80 (m, 2H); ^{13}C NMR ($CDCl_3$, 90 MHz) δ 138.3, 137.8, 132.9, 130.0, 129.1, 128.4, 128.3, 128.1, 127.9, 127.8, 127.7, 127.6, 126.1, 120.23, 120.2, 81.4, 78.7, 74.9, 73.9, 72.4, 70.2, 51.48, 44.2, 32.1, 25.1; IR (neat) 3062 (w), 3030 (m), 2866 (m), 2100 (s), 1454 (m) cm^{-1}; MS (CI NH_3) *m/z* (rel intensity) 537 [$(M + NH_4)^+$, 10], 492 (60), 384 (63), 348 (70), 240 (100), 150 (43), 108 (44), 91 (77); HRMS calcd for $C_{30}H_{34}N_3O_3Cl{\cdot}NH_4$ [$(M + NH_4)^+$] 537.2632, found 537.2632.

1-(Benzyloxy)-6,7,8,9-tetrahydroquinolizidinium Chloride (16). A degassed (three freeze-evacuate-thaw cycles) solution of **13** (30 mg, 0.08 mmol) in deuterated solvent ($CDCl_3$ or C_6D_6, 0.75 mL) was heated at 90 °C in a sealed NMR tube. The reaction progress was monitored periodically by ^{1}H NMR. After 12.5 h (C_6D_6) or 15 h ($CDCl_3$), the starting material resonances had disappeared and had been replaced by resonances for **16** and benzyl alcohol. This material was not purified. ^{1}H NMR ($CDCl_3$, 360 MHz) δ 8.95 (d, J = 5.9 Hz, 1H, H_4), 7.90 (d, J = 8.5 Hz, 1H, H_2), 7.75 (dd, J = 6.1, 8.6 Hz, 1H, H_3), 7.2−7.5 (m, 20 H), 5.23 (s, 2H, OCH_2Ph), 4.83 (t, J = 5.8 Hz, 2H, H_6), 4.68 (s, 6H, PhCH_2OH), 3.09 (t, J = 6.6 Hz, 2H, H_9), 2.08 (m, 2H), 1.95 (m, 2H); ^{13}C NMR ($CDCl_3$, 90 MHz) δ 141.3 ($PhCH_2OH$), 137.5, 134.1, 130.0, 128.9, 128.3 ($PhCH_2$-OH), 127.7, 127.3 ($PhCH_2OH$), 126.9 ($PhCH_2OH$), 126.0, 125.5, 124.9, 120.1, 72.0, 64.9 ($PhCH_2OH$), 56.4, 23.2, 21.0, 17.3.

(2*R*,3*R*,4*R*,5*S*,6*S*)-1-Azido-2,3,4-tris(benzyloxy)-9-chloro-5,6-epoxynonane (21α) and (2*R*,3*R*,4*R*,5*R*,6*R*)-1-Azido-2,3,4-tris(benzyloxy)-9-chloro-5,6-epoxynonane (21*β*). *m*-Chloroperbenzoic acid (1.160 g, technical grade, 0.928 g of pure oxidant, 5.38 mmol) was added to a cold (0 °C) solution of **13** (1.007 g, 1.94 mmol) in CH_2Cl_2 (8 mL), and the resulting mixture was allowed to warm slowly to room temperature. After 12 h, the solution was diluted with CH_2Cl_2 (15 mL), washed with 10% NaOH (2 × 20 mL), 15% NH_4OH (2 × 20 mL), and brine (20 mL), and then dried (Na_2SO_4) and concentrated. Chromatography (6:1 hex/EtOAc) gave 910 mg (88%) of an inseparable mixture of α and *β* isomers (2.5:1 based on ^{1}H NMR integration) as a colorless oil. The stereochemical assignment was made by conversion to the quinolizidines (9*S*,-9a*R*)-**4** and (9*R*,9a*S*)-**4** (see below). R_f = 0.22 (6:1 hex/EtOAc); ^{1}H NMR ($CDCl_3$, 300 MHz) major isomer (**21**α): δ 7.1−7.4 (m, 15H), 4.69 (ABq, J = 11.9 Hz, $\Delta\nu$ = 105.9 Hz, 2H), 4.65 (ABq, J = 11.6 Hz, $\Delta\nu$ = 54.0 Hz, 2H), 4.34 (ABq, J = 11.2 Hz, $\Delta\nu$ = 97.2 Hz, 2H), 3.81 (m, 1H), 3.3−3.7 (m, 6H), 3.10 (dd, J = 4.5, 8.0 Hz, 1H), 2.48 (ddd, J = 3.4, 4.4, 9.2 Hz, 1H), 1.7−2.1 (m, 2H), 1.5 (m, 1H), 1.22 (m, 1H); minor isomer (**21***β*): δ 7.1−7.4 (m, 15H), 4.76 (ABq, J = 11.2 Hz, $\Delta\nu$ = 27.1 Hz, 2H), 4.52 (ABq, J = 11.4 Hz, $\Delta\nu$ = 74.8 Hz, 2H), 4.49 (ABq, J 11.7 Hz, $\Delta\nu$ = 50.2 Hz, 2H), 3.92 (ddd, J = 2.7, 4.6, 7.5 Hz, 1H), 3.81 (m, 1H), 3.3−3.7 (m, 5H), 3.19 (dd, J = 3.9, 8.5 Hz, 1H), 3.06 (m, 1H), 1.7−2.1 (m, 3H), 1.4 (m, 1H); ^{13}C NMR ($CDCl_3$, 90 MHz) δ 138.0 (*β*), 138.0 (*β*), 137.9 (*β*), 137.7 (α), 137.5 (α), 137.3 (α), 128.9, 128.5, 128.9, 128.8, 128.2, 128.1, 127.9, 127.8, 127.8, 127.7, 127.6, 79.6 (*β*), 78.2 (α), 78.1 (α), 77.9 (*β*), 76.3 (α), 75.0 (*β*), 74.3 (*β*), 74.0 (α), 72.5 (α), 72.3 (*β*), 72.1 (*β*), 71.6 (α), 58.2 (α), 57.9 (*β*), 55.5 (*β*), 53.7 (α + *β*), 50.8 (α), 44.5 (*β*), 44.2 (α), 30.1 (α), 29.8 (*β*), 25.6 (α), 25.6 (*β*); IR ($CDCl_3$) 2928 (w), 2868 (w), 2104 (s), 1455 (m), 1293 (m) cm^{-1}; MS (CI with NH_3) *m/z* (rel int.) 553 ([$M + NH_4$]$^+$, 16), 508 (52), 474 (36), 384 (15), 120 (34), 108 (53), 91 (100); HRMS (CI with NH_3) calcd for $C_{30}H_{34}ClN_3O_4{\cdot}NH_4^+$: 553.2582, found 553.2559. Anal. Calcd for $C_{30}H_{34}ClN_3O_4$: C, 67.21, H, 6.39; N, 7.84. Found: C, 67.05; H, 6.60; N, 8.18.

(1*R*,2*R*,3*R*,9*S*,9a*R*)-1,2,3-Tri-*O*-benzyl-1,2,3,9-tetrahydroxyquinolizidine (22) and (1*R*,2*R*,3*R*,9*R*,9a*S*)-1,2,3-Tri-*O*-benzyl-1,2,3,9-tetrahydroxyquinolizidine (23). Palladium on carbon (10%, 130 mg) was added to a mixture of the azido-epoxides **21**α and **21***β* (2.5:1 mixture of diastereomers, 1.28 g, 2.38 mmol) in EtOH/EtOAc (1:1, 25 mL). The flask was evacuated (aspirator) and purged with hydrogen three times. The heterogeneous mixture was stirred at room temperature under a balloon of hydrogen for 12 h, and then the hydrogen was evacuated and the mixture was filtered through a plug of Celite, rinsing with EtOH (10 mL). The filtrate was transferred to a round bottom flask, K_2CO_3 (1.30 g) was added, and the solution was warmed to reflux. After 12 h, the mixture was cooled to room temperature, poured into brine, and extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were dried (Na_2SO_4) and concentrated. Radial chromatography (4 mm silica gel plate, 1:1 to 1:10 hex/EtOAc gradient) provided 612 mg (54%) of the quinolizidine **22** as a pale yellow oil, followed by 250 mg (23%) of the quinolizidine **23**, also as a pale yellow oil. The stereochemistry of each quinolizidine was assigned by ^{1}H NMR coupling constant analysis (see supporting information). Data for **22** (major): R_f = 0.18 (1:1 hex/EtOAc); $[\alpha]^{23}_D$ = −11.6° (*c* 1.09, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.2−7.5 (m, 15H), 4.90 (ABq, J = 10.6 Hz, $\Delta\nu$ = 75.5 Hz, 2H), 4.77 (s, 2H), 4.65 (ABq, J = 12.0 Hz, $\Delta\nu$ = 14.0 Hz, 2H), 4.17 (t, J =9.6 Hz, 1H, H_1), 4.10 (broad d, J =7.8 Hz, 1H, H_9), 3.79 (broad s, 1H, H_3), 3.43 (dd, J = 3.1, 9.8 Hz, 1H, H_2), 2.97 (dd, J = 3.2, 12.7 Hz, 1H, H_{4eq}), 2.72 (m, 1H, H_{6eq}), 2.67 (d, J = 10.7 Hz, 1H, D_2O exchangeable), 1.84−2.00 (m, 5H), 1.30−1.55 (m, 2H); ^{13}C NMR ($CDCl_3$, 90 MHz, JMOD) δ 138.9 (−), 138.8 (−), 138.6 (−), 128.3 (+), 128.1 (+), 128.1 (+), 127.8 (+), 127.6 (+), 127.5 (+), 83.7 (+), 75.7 (−), 75.3 (+), 71.8 (−), 71.4 (+), 71.3 (−), 69.2 (+), 63.7 (+), 56.7 (−), 55.6 (−), 30.7 (−), 19.4 (−); IR ($CDCl_3$) 3546 (w), 3066 (m), 3032 (m), 2946 (s), 2871 (s), 2813 (m) cm^{-1}; MS (EI, 70 eV) *m/z* (rel intensity) 474 (M^+, 2), 382 (28), 260 (24), 91 (100); HRMS calcd for $C_{30}H_{35}NO_4H$ 474.2644, found 474.2631. Data for **23** (minor): R_f = 0.53 (10:1 $CHCl_3$/MeOH); $[\alpha]^{23}_D$ = −3.5° (*c* 1.33, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.25−7.45 (m, 13 H), 7.05−7.20 (m, 2H), 4.70 (ABq, J = 12.4 Hz, $\Delta\nu$ =71.3 Hz, 2H), 4.52 (ABq, J = 12.3 Hz, $\Delta\nu$ =36.1 Hz, 2H), 4.40 (d, J = 1.8 Hz, 1H, D_2O exchangeable), 4.35 (ABq, J = 11.3 Hz, $\Delta\nu$ = 24.9 Hz, 2H), 3.98 (ddd, J = 2.7, 4.6, 11.4 Hz, 1H, H_3), 3.87 (m, 1H, H_9), 3.85 (broad t, J = 2.9 Hz, 1H, H_2), 3.67 (dd, J = 2.4, 3.4 Hz, 1H, H_1), 2.92 (m, 1H, H_{6eq}), 2.89 (dd, J = 4.5, 10.3 Hz, 1H, H_{4eq}), 2.48 (t, J = 10.8, 1H, H_{4ax}), 2.24 (broad s, 1H, H_{9a}), 2.05−2.19 (m, 2H, H_{6ax} and H_{7eq}), 1.75−1.87 (m, 1H, H_{8eq}), 1.30−1.45 (m, 2H, H_{7ax} and H_{8ax}); ^{13}C NMR ($CDCl_3$, 90 MHz, JMOD) δ 138.6 (−), 138.5 (−), 136.3 (−), 128.7 (+), 128.6 (+), 128.4 (+), 127.9 (+), 127.8 (+), 127.6 (+), 127.6 (+), 80.7 (+), 73.5 (+), 73.1 (−), 72.5 (−), 71.7 (+), 71.2 (−), 68.7 (+), 60.7 (+), 56.9 (−), 53.8 (−), 31.6 (−), 19.2 (−); IR ($CDCl_3$) 3477 (br m), 3032 (m), 2945 (s), 1454 (m) cm^{-1}; MS (CI, NH_3) *m/z* (rel intensity) 474 [$(M + H)^+$, 100], 382 (21), 260 (12), 91 (19); HRMS calcd for $C_{30}H_{35}NO_4H$ 474.2644, found 474.2627.

(1*R*,2*R*,3*R*,9*S*,9a*R*)-1,2,3,9-Tetrahydroxyquinolizidine [(9*S*,9a*R*)-4)]. Palladium on carbon (10%, 125 mg) was added to a solution of the quinolizidine **22** (277 mg, 0.586 mmol) in 1% methanolic HCl (25 mL), and the resulting heterogeneous mixture was shaken in a Paar hydrogenation apparatus under hydrogen (45 psi). After 48 h, the hydrogen was evacuated and the mixture was filtered through a bed of Celite, rinsing with methanol (10 mL). The filtrate was concentrated, and the residue was dissolved in water (1 mL) and applied to a Dowex 1 × 8 OH^- ion exchange column, eluting with water. The I_2-staining fractions were combined and concentrated. Chromatography (50:10:1 $CHCl_3$/MeOH/NH_4OH) provided 118 mg (99%) of the title compound as a pale yellow oil. The stereochemistry was assigned by ^{1}H NMR coupling constant analysis (see supporting information). R_f = 0.11 (4.5:1 $CHCl_3$/MeOH); $[\alpha]^{23}_D$ = −26.2° (*c* 1.07, EtOH); ^{1}H NMR (CD_3OD, 300 MHz) δ 4.09 (broad s, 1H, H_9), 3.81 (dt, J = 1.6, 3.3 Hz, 1H, H_3), 3.78 (t, J = 9.6 Hz, 1H, H_1), 2.87 (dd, J = 3.3, 12.3 Hz, 1H, H_{4eq}), 2.80 (broad d, J = 8.8 Hz, 1H, H_{6eq}), 2.24 (broad d, J = 12.1 Hz, 1H, H_{4ax}), 1.84−2.05 (m, 3H, H_{7eq}, H_{6ax} and H_{8eq}) 1.72 (broad d, J = 9.3 Hz, 1H, H_{9a}), 1.35−1.49 (m, 2H, H_{7ax} and H_{8ax}); ^{13}C NMR (CD_3OD, 90 MHz, JMOD) δ 76.8 (+), 70.4 (+), 69.9 (+), 69.0 (+), 64.6 (+), 61.0 (−), 56.8 (−), 32.2 (−), 20.5 (−); IR (KBr) 3501 (s), 3342 (s), 2926 (s), 2797 (m), 2757 (m), 1430 (m) cm^{-1}; MS (EI, 70eV) *m/z* (rel

intensity) 203 (M^+, 10), 186 (29), 185 (52), 146 (57), 113 (33), 99 (100), 96 (44), 72 (57); HRMS calcd for $C_9H_{17}NO_4$ 203.1158, found 203.1164. Anal. Calcd for $C_9H_{17}NO_4HCl$: C, 45.10; H, 7.58; N, 5.84. Found: C, 45.11; H, 7.44; N, 5.55.

(1*R*,2*R*,3*R*,9*R*,9a*S*)-1,2,3,9-Tetrahydroxyquinolizidine [(9*R*,9a*S*)-4)]. Palladium on carbon (10%, 55 mg) was added to a solution of the quinolizidine **23** (121 mg, 0.256 mmol) in 1% methanolic HCl (10 mL), and the resulting heterogeneous mixture was shaken in a Paar hydrogenation apparatus under hydrogen (45 psi). After 48 h, the hydrogen was evacuated, and the mixture was filtered through a bed of Celite, rinsing with methanol (10 mL). The filtrate was concentrated, and the residue was dissolved in water (1 mL) and applied to a Dowex 1 × 8 OH^- ion exchange column, eluting with water. The I_2-staining fractions were combined and concentrated, providing a white solid that was recrystallized from EtOH to afford 48 mg (92%) of the title compound. The stereochemistry was assigned by ^{1}H NMR coupling constant analysis (see supporting information). R_f = 0.15 (2:1 $CHCl_3$/MeOH); $[\alpha]^{23}_D$ = +22.7° (*c* 0.73, MeOH); mp 225−230 °C dec; ^{1}H NMR (CD_3OD, 300 MHz) δ 4.09 (broad s, 1H, H_9), 4.09 (ddd, J = 3.2, 4.9, 11.2 Hz, 1H, H_3), 3.95 (dd, J = 1.8, 3.7 Hz, 1H, H_1), 3.79 (t, J = 3.3 Hz, 1H, H_2), 2.85 (m, 1H, H_{6eq}), 2.61 (dd, J = 4.8, 10.5 Hz, 1H, H_{4eq}), 2.31 (t, J =11.0 Hz, 1H, H_{4ax}), 2.24 (t, J = 1.7 Hz, 1H, H_{9a}), 2.01−2.16 (m, 2H, H_{6ax} and H_{7eq}), 1.82 (m, 1H, H_{8eq}), 1.4−1.6 (m, 2H, H_{7ax} and H_{8ax}); ^{13}C NMR (CD_3OD, 90 MHz) δ 76.2, 71.9, 70.8, 66.2, 61.1, 57.7, 57.2, 33.1, 20.3; IR (KBr) 3507 (s), 3332 (s), 2941 (s), 2832 (m), 2668 (m), 1443 (m) cm^{-1}; MS (EI, 70 eV) *m*/*z* (rel intensity) 203 (M^+, 31), 185 (100), 168 (45), 146 (44), 113 (34), 99 (55), 96 (30), 72 (33); HRMS calcd for $C_9H_{17}NO_4$ 203.1158, found 203.1154. Anal. Calcd for $C_9H_{17}NO_4$: C, 53.20; H, 8.45; N, 6.89. Found: C, 52.95; H, 8.28; N, 6.62.

(2*R*,3*R*,4*R*,5*R*,6*R*)-1-Azido-2,3,4-tris(benzyloxy)-9-chloro-5,6-dihydroxynonane (24) and (2*R*,3*R*,4*R*,5*S*,6*S*)-1-Azido-2,3,4-tris(benzyloxy)-9-chloro-5,6-dihydroxynonane (25). Osmium tetraoxide (0.180 mL of a 4% w/w solution in water, 7 mg, 0.03 mmol) was added to a solution of the azido-alkene **13** (300 mg, 0.58 mmol) and *N*-methylmorpholine *N*-oxide (118 mg, 0.87 mmol) in THF/*t*-BuOH (5:2, 3 mL). After 72 h, sodium bisulfite (3 mL of a 10% solution) was added, and the mixture was stirred for an additional 30 min and then diluted with water (15 mL) and extracted with CH_2Cl_2 (3 × 25 mL). The combined organic layers were dried ($MgSO_4$) and concentrated. Chromatography (6:1 to 3:1 hex/EtOAc gradient) gave 40 mg (13%) of minor diastereomer **25** as a colorless oil followed by 220 mg (69%) of major diastereomer **24** as a colorless oil. Stereochemical assignments were made by conversion to the quinolizidines (9*S*,9a*S*)-**4** and (9*R*,9a*R*)-**4** (see below). Data for **25** (minor): R_f = 0.40 (3:1 hex/EtOAc): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.2−7.4 (m, 15 H), 4.65−4.78 (m, 4H), 4.57 (d, J =11.3 Hz, 1H), 4.52 (d, J = 11.3 Hz, 1H), 3.96 (dd, J = 6.0, 4.3 Hz, 1H), 3.83 (m, 2H), 3.50 (m, 6H), 2.78 (d, J = 7.7 Hz, 1H), 1.90 (m, 1H), 1.75 (m, 2H), 1.66 (d, J = 6.7 Hz, 1H), 1.39 (m, 1H); ^{13}C NMR ($CDCl_3$, 90 MHz, JMOD) δ 137.9 (−), 137.6 (−), 137.4 (−), 128.6 (+), 128.5 (+), 128.4 (+), 128.3 (+), 128.2 (+), 128.1 (+), 128.0 (+), 128.0 (+), 127.9 (+), 79.6 (+), 78.6 (+), 74.2 (−), 74.1 (−), 72.8 (+), 72.5 (−), 72.2 (+), 51.1 (−), 45.1 (−), 30.8 (−), 28.7 (−); IR (neat) 3462 (br, m), 3030 (m), 2923 (m), 2866 (m), 2100 (s), cm^{-1}; MS (CI, NH_3) *m*/*z* (rel int) 571 ([M + NH_4]$^+$, 16), 535 (59), 490 (100), 472 (24), 402 (25), 184 (23), 120 (20), 106 (82); HRMS calcd for $C_{30}H_{36}{}^{35}ClN_3O_5NH_4$ 571.2687, found 571.2674. Data for **24** (major): R_f = 0.30 (3:1 hex/EtOAc): $[\alpha]^{23}_D$ = +4.3° (*c* 1.17, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 360 MHz) δ 7.2−7.4 (m, 15 H), 4.70 (d, J = 11.3 Hz, 1H), 4.69 (ABq, J_{AB} = 11.3 Hz, 2H), 4.51 (ABq, J_{AB} = 11.4 Hz, 2H), 4.49 (d, J = 11.3 Hz, 1H), 4.01 (dd, J = 4.9, 3.3 Hz, 1H), 3.83 (dt, J = 5.7, 3.0 Hz, 1H), 3.70 (m, 3H), 3.5−3.6 (m, 4H), 2.98 (d, J = 4.7 Hz, 1H), 2.33 (br s, 1H), 1.9−2.0 (m, 1H), 1.65−1.8 (m, 2H), 1.4−1.5 (m, 1H); ^{13}C NMR ($CDCl_3$, 90 MHz) δ 137.3, 137.2, 137.2, 128.6, 128.5, 128.3, 128.2, 128.1, 128.1, 79.5, 78.4, 78.0, 73.9, 73.8, 72.8, 72.1, 51.2, 45.2, 29.7, 28.8; IR (neat) 3448 (br m), 3030 (w), 2922 (m), 2866 (m), 2100 (s) cm^{-1}; MS (DCI, NH_3) *m*/*z* (rel int) 571 ([M + NH_4]$^+$, 11), 535 (40), 490 (100), 402 (25), 106 (28); HRMS calcd for $C_{30}H_{36}N_3O_5{}^{35}ClNH_4$ 571.2687, found 571.2679.

(2*R*,3*R*,4*R*,5*R*,6*S*)-1-Azido-2,3,4-tris(benzyloxy)-9-chloro-5,6-epoxynonane (26). Methanesulfonyl chloride (26 mg, 18 μL, 0.23 mmol) was added to a cold (−50 °C) solution of the major diol **24** from above (115 mg, 0.21 mmol) and triethylamine (38 μL, 27 mg, 0.27 mmol) in CH_2Cl_2 (1.1 mL). The mixture was stirred for 1 h at −50 °C, then warmed slowly to 0 °C and quenched by the addition of water (5 mL). The resulting mixture was extracted with CH_2Cl_2 (3 × 5 mL), and the organic extracts were dried ($MgSO_4$) and concentrated to give 112 mg of the crude monomesylate. (^{1}H NMR of the crude residue shows the disappearance of the broad ^{1}H OH singlet at δ 2.32 and appearance of a sharp mesylate 3H methyl singlet at δ 2.89.) The crude monomesylate was dissolved in THF/DMSO (10:1, 5 mL) and cooled to 0 °C. Sodium hydride (17 mg of a 60% suspension in mineral oil, 10 mg of pure hydride, 0.42 mmol) was added, and the mixture was allowed to warm to room temperature. After 12 h the reaction was quenched by addition of saturated aqueous NH_4Cl (2 mL), and the mixture was diluted with water (10 mL) and extracted with Et_2O (2 × 15 mL). The combined organic layers were washed with brine (10 mL), dried ($MgSO_4$), and concentrated. Chromatography (10:1 to 6:1 hex/EtOAc gradient) afforded 63 mg (56%) of *trans* epoxide **26** as a pale yellow oil. R_f = 0.55 (4:1 hex/EtOAc): $[\alpha]^{23}_D$ = 0.0° (*c* 1.52, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.2−7.4 (m, 15 H), 4.72 (ABq, J_{AB} = 12.0 Hz, 2H), 4.63 (d, J = 11.3 Hz, 1H), 4.52 (ABq, J_{AB} = 11.9 Hz, 2H), 4.41 (d, J = 11.3 Hz, 1H), 3.8−3.9 (m, 2H), 3.64 (dd, J = 13.3, 2.3 Hz, 1H), 3.52 (dt, J = 6.5, 2.8 Hz, 2H), 3.41 (dd, J = 13.3, 4.5 Hz, 1H), 3.36 (dd, J = 6.9, 2.6 Hz, 1H), 2.84 (dd, J = 6.9, 2.2 Hz, 1H), 2.78 (ddd, J = 7.2, 3.7, 2.2 Hz, 1H), 1.83 (m, 2H), 1.68 (m, 1H), 1.39 (m, 1H); ^{13}C NMR ($CDCl_3$, 90 MHz) δ 138.2, 137.9, 137.6, 128.5, 128.4, 128.1, 127.9, 127.8, 79.0, 78.5, 78.1, 74.9, 73.0, 72.3, 58.5, 56.6, 50.7, 44.4, 28.8, 28.8; IR (neat) 3030 (m), 2914 (m), 2868 (m), 2100 (s), 1454 (m) cm^{-1}; MS (CI, NH_3) *m*/*z* (rel int) 553 ([M + NH_4]$^+$, 41), 508 (100), 474 (53), 472 (50), 400 (18), 108 (44), 91 (34); HRMS calcd for $C_{30}H_{34}{}^{35}ClN_3O_4NH_4$ 553.2582, found 553.2574. Anal. Calcd for $C_{30}H_{34}ClN_3O_4$: C, 67.22, H, 6.39; N, 7.84. Found: C, 67.13; H, 6.43; N, 7.88.

(1*R*,2*R*,3*R*,9*S*,9a*S*)-1,2,3-Tri-*O*-benzyl-1,2,3,9-tetrahydroxyquinolizidine (28). Palladium on carbon (10%, 5 mg) was added to a solution of the azido-epoxide **26** (30 mg, 0.06 mmol) in EtOH/EtOAc (1:1, 1 mL), and the flask was evacuated (aspirator) and purged with hydrogen three times. The resulting heterogeneous mixture was stirred under a balloon of hydrogen for 36 h, and then the hydrogen was evacuated and the mixture was passed through a plug of Celite, rinsing wth EtOH (3 mL). The filtrate was transferred to a round-bottom flask, potassium carbonate (45 mg) was added, and the resulting mixture was heated at reflux for 12 h, cooled, poured into water (10 mL), and extracted with CH_2Cl_2 (3 × 5 mL). The combined organic layers were dried (Na_2SO_4) and concentrated. Chromatography (50:1 $CHCl_3$/MeOH) provided 20.5 mg (77%) of the title compound as a pale yellow oil. The stereochemistry was assigned by ^{1}H NMR coupling constant analysis (see supporting information). R_f = 0.20 (50:1 $CHCl_3$/MeOH): $[\alpha]^{23}_D$ = +28.4° (*c* 1.41, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.25−7.45 (m, 13H), 7.2 (m, 2H), 4.72 (d, J = 12.4 Hz, 1H), 4.58 (d, J = 12.2 Hz, 1H), 4.56 (d, J = 12.4 Hz, 1H), 4.51 (d, J = 12.2 Hz, 1H), 4.51 (d, J = 12.2 Hz, 1H), 4.30 (d, J = 12.2 Hz, 1H), 3.94 (ddd, J = 12.0, 9.8, 4.4 Hz, 1H) 2.84 (dd, J = 4.5, 10.1, Hz, 1H), 2.78 (br d, J = 11.4 Hz, 1H), 2.51 (t, J = 10.7 Hz, 1H), 2.01 (m, 3H), 1.61 (m, 2H), 1.22 (m, 1H), 0.81 (m, 1H), 0.72 (br s, 1H, D_2O exchangeable); ^{1}H NMR (C_6D_6, 300 MHz) δ 7.0−7.5 (m, 15H), 4.75 (ABq, J_{AB}= 12.2 Hz, $\Delta\nu$ = 58.5 Hz, 2H), 4.48 (ABq, J_{AB}= 11.8 Hz, $\Delta\nu$ = 18.4 Hz, 2H), 4.38 (ABq, J_{AB}= 12.1 Hz, $\Delta\nu$ = 27.8 Hz, 2H), 4.19 (ddd, J = 2.4, 4.4, 10.9 Hz, 1H, H_3), 4.15 (t, J = 2.6 Hz, 1H, H_1), 3.98 (t, J = 2.9 Hz, 1H, H_2), 3.82 (ddd, J = 4.5, 9.0, 11.3 Hz, 1.H, H_9), 2.89 (dd, J = 4.6, 10.0 Hz, 1H, H_{4eq}), 2.80 (t, J = 10.5 Hz, 1H, H_{4ax}), 2.61 (br d, J = 11.0 Hz, 1H, H_{6eq}), 2.24 (dd, J = 2.0, 9.0 Hz, 1H, H_{9a}), 1.90 (dt, J = 2.5, 11.8 Hz, 1H, H_{6ax}), 1.76 (m, 1H, H_{8eq}), 1.52 (m, 1H, H_7), 1.28 (m, 1H, H_7), 1.06 (m, 1H, H_{8ax}); ^{13}C NMR ($CDCl_3$, 90 MHz) δ 138.8, 137.7, 138.1, 128.8, 128.6, 128.3, 128.3, 128.2, 127.9, 127.6, 74.0, 72.7, 72.6, 72.4, 71.1, 66.7, 65.6, 55.8, 53.3, 33.5, 23.2; IR (neat) 3420 (m),

3062 (m), 3029 (m), 2926 (s), 2857 (s), 1454 (s) cm^{-1}; MS (EI, 70 eV) *m/z* (rel int) 473 (M^+, 2), 382 (48), 260 (29), 149 (18), 91 (100), 57 (18); HRMS calcd for $C_{30}H_{35}NO_4$ 473.2566, found 473.2547.

(1*R*,2*R*,3*R*,9*S*,9a*S*)-1,2,3,9-Tetrahydroxyquinolizidine [(9*S*,9a*S*)-4]. Palladium on carbon (10%, 10 mg) was added to a solution of the quinolizidine **28** (22 mg, 0.047 mmol) in 1% methanolic HCl (2 mL) The flask was evacuated (aspirator) and purged with hydrogen three times. The resulting heterogeneous mixture was stirred under a balloon of hydrogen at room temperature for 48 h, and then the hydrogen was evacuated and the mixture was filtered, rinsing wth MeOH (3 mL). The filtrate was then concentrated, and the residue was dissolved in water (2 mL) and stirred with Dowex 1 × 8−200 $^-$OH ion exchange resin (200 mg). After 30 min, the mixture was filtered and the filtrate was concentrated. Chromatography (5:1:0.1 $CHCl_3$/MeOH/NH_4OH) gave 8.5 mg (90%) of the title compound as a white crystalline solid. The stereochemistry was assigned by ^{1}H NMR coupling constant analysis (see supporting information). R_f = 0.23 (2:1 $CHCl_3$/MeOH): mp 125−130 °C dec; $[\alpha]^{23}_D$ = +34.7° (*c* 0.79, MeOH); ^{1}H NMR (CD_3OD, 360 MHz) δ 4.09 (dd, *J* =1.8, 3.6 Hz, 1H, H_1), 4.03 (ddd, *J* = 3.3, 4.6, 11.3 Hz, 1H, H_3), 3.90 (t, *J* = 3.1 Hz, 1H, H_2), 3.68 (ddd, *J* = 4.6, 9.5, 11.5 Hz, 1H, H_9), 2.74 (br d, *J* = 11.3 Hz, 1H, H_{6eq}), 2.60 (dd, *J* = 4.9, 10.3 Hz, 1H, H_{4eq}), 2.34 (t, *J* = 10.8 Hz, 1H, H_{4ax}), 2.07 (dd, *J* = 3.1, 11.9 Hz, 1H, H_{6ax}), 2.0 (m, 2H, H_{8eq}+ H_{9a}), 1.5−1.7 (m, 2H, H_{7eq}+H_{7ax}), 1.32 (dq, *J* = 4.9, 11.9 Hz, 1H, H_{8ax}); ^{13}C NMR (CD_3-OD, 90 MHz) δ 72.4, 69.2, 67.2, 66.6, 66.5, 57.1, 56.7, 34.9, 24.3; IR (neat) 3334 (s), 2933 (m), 2854 (w), 2820 (w), 1598 (w), 1467 (w) cm^{-1}; MS (EI, 70 eV) *m/z* (rel int) 203 (M^+, 4), 185 (30), 146 (25), 99 (44), 72 (29), 36 (100); HRMS calcd for $C_9H_{17}NO_4$ 203.1158, found 203.1160.

(2*R*,3*R*,4*R*,5*S*,6*R*)-1-Azido-2,3,4-tris(benzyloxy)-9-chloro-5,6-epoxynonane (27). Methanesulfonyl chloride (50 mg, 34 μL, 0.43 mmol) was added to a cold (−50 °C) solution of the diol **25** (200 mg, 0.36 mmol) and triethylamine (65 μL, 48 mg, 0.47 mmol) in CH_2Cl_2 (2 mL). The mixture was stirred for 1 h at −50 °C and then warmed slowly to 0 °C and quenched by addition of water (5 mL). The resulting mixture was extracted with CH_2Cl_2 (3 × 5 mL), dried ($MgSO_4$), and concentrated to give 190 mg of the crude monomesylate, which was dissolved in THF/DMSO (10:1, 11 mL) and cooled to 0 °C. Sodium hydride (29 mg of a 60% suspension in mineral oil, 17 mg of pure hydride, 0.72 mmol) was added, and the mixture was warmed to room temperature. After 12 h, the reaction was quenched with aqueous NH_4Cl (2 mL), diluted with water (10 mL), and extracted with Et_2O (2 × 10 mL). The combined organic layers were washed with brine (10 mL), dried ($MgSO_4$), and concentrated. Chromatography (10:1 to 5:1 hex/EtOAc gradient) provided 75 mg (40%) of a 2.5:1 mixture of epoxides **27** and **26**. The stereochemical assignment of **27** was made by conversion to the quinolizidine (9*R*,9a*R*)-**4** (see below). Data for **27**: R_f = 0.55 (4:1 hex/EtOAc); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.15−7.40 (m, 15H), 4.86 (d, *J* = 11.8 Hz, 1H), 4.5−4.7 (m, 4H), 4.31 (d, *J* = 11.2 Hz, 1H), 3.84 (m, 1H), 3.68 (dd, *J* = 3.0, 6.0 Hz, 1H), 3.41−3.65 (m, 4H), 3.28 (dd, *J* = 2.7, 7.0 Hz, 1H), 3.05 (dd, *J* = 1.9, 7.2 Hz, 1H), 2.73 (dt, *J* = 2.8, 7.3 Hz, 1H), 1.7−1.9 (m, 3H), 1.37 (m, 1H); ^{13}C NMR ($CDCl_3$, 90 MHz) δ 138.0, 137.6, 137.5, 128.5, 128.4, 128.2, 128.0, 127.7, 79.7, 79.2, 78.5, 74.3, 72.6, 72.0, 59.3, 53.6, 51.0, 44.4, 29.0, 28.6; IR (neat) 3088 (w), 3063 (m), 3030 (m), 2918 (m), 2869 (m), 2101 (s), 1854 (w), 1878 (w), 1812 (w), 1727 (w), 1454 (m) cm^{-1}; MS (DCI, NH_3) *m/z* (rel int) 553 ([M + NH_4]$^+$, 15), 508 (59), 120 (19), 108 (21), 91 (100); HRMS calcd for $C_{30}H_{34}ClN_3O_4NH_4$ 553.2582, found 553.2555.

(1*R*,2*R*,3*R*,9*R*,9a*R*)-1,2,3-Tri-*O*-benzyl-1,2,3,9-tetrahydroxyquinolizidine (29). Palladium on carbon (10%, 10 mg) was added to a solution of the epoxides **26** and **27** (1:2.5 mixture of diastereomers, 59 mg, 0.11 mmol), in EtOH/EtOAc (1:1, 2 mL). The flask was evacuated (aspirator) and purged with hydrogen three times. The heterogeneous mixture was stirred under a balloon of hydrogen for 16 h, and then the hydrogen was evacuated and the mixture was filtered through a plug of Celite, rinsing wth EtOH (6 mL). Potassium carbonate (50 mg) was added to the filtrate, and the resulting mixture was heated at reflux for 12 h. The mixture was cooled, poured into brine (15 mL), and extracted with CH_2Cl_2 (3 × 10 mL). The resultant extracts were dried (Na_2SO_4) and concentrated. Chromatography (2:1 hex/EtOAc) provided 10 mg (20%) of the quinolizidine **28** (see above) as a pale yellow oil followed by 28 mg (54%) of the title compound **29** as a pale yellow oil. The stereochemistry of **29** was assigned by ^{1}H NMR coupling constant analysis (see supporting information). Data for **29**: R_f = 0.31 (1:1 hex/EtOAc); $[\alpha]^{23}_D$ = −6.3° (*c* 0.95, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.2−7.5 (m, 15H), 4.99 (ABq, *J* = 10.6 Hz, $\Delta\nu$ = 55.9 Hz, 2H), 4.86 (s, 1H, D_2O exchangeable), 4.79 (ABq, *J* = 13.0 Hz, $\Delta\nu$ = 19.1 Hz, 2H), 4.60 (ABq, *J* = 11.7 Hz, $\Delta\nu$ = 28.5 Hz, 2H), 4.16 (t, *J* = 9.2 Hz, 1H, H_1), 3.79 (m, *J* = 4.9, 8.5, 2.9 Hz, 2H, H_9 and H_3), 3.52 (dd, *J* = 3.2, 9.6 Hz, 1H, H_2), 2.95 (dd, *J* = 3.1, 12.7 Hz, 1H, H_{4eq}), 2.72 (broad d, *J* = 11.0 Hz, 1H, H_{6eq}), 2.06 (dd, *J* = 1.5, 12.7 Hz, 1H, H_{4ax}), 2.01 (m, 1H, H_{8eq}), 1.96 (dd, *J* = 2.7, 11.5 Hz, 1H, H_{6ax}), 1.79 (t, *J* = 8.5 Hz, 1H, H_{9a}), 1.71 (app qt, *J* = ∼3.5, ∼12 Hz, 1H, H_{7eq}), 1.59 (m, 1H, H_{7ax}), 1.21 (m, *J* = ∼4, ∼11 Hz, 1H, H_{8ax}); ^{13}C NMR ($CDCl_3$, 90 MHz, JMOD) δ 138.6 (−), 138.0 (−), 137.3 (−), 128.6 (+), 128.4 (+), 128.3 (+), 128.3 (+), 128.0 (+), 127.9 (+), 127.7 (+), 127.6 (+), 83.8 (+), 81.9 (+), 75.6 (−), 71.6 (−), 71.6 (+), 70.9 (+), 68.9 (+), 57.2 (−), 55.0 (−), 32.3 (−), 22.5 (−); IR (neat) 3472 (s), 3066 (m), 3029 (m), 2937 (s), 2862 (s), 2801 (m), 2734 (m), 1585 (w), 1453 (m), cm^{-1}; MS (EI, 70 eV) *m/z* (rel int) 473 (M^+, 1), 382 (45), 260 (29), 154 (19), 91 (100); HRMS calcd for $C_{30}H_{35}NO_4$ 473.2566, found 473.2548.

(1*R*,2*R*,3*R*,9*R*,9a*R*)-1,2,3,9-Tetrahydroxyquinolizidine [(9*R*,9a*R*)-4]. Palladium on carbon (10%, 15 mg) was added to a solution of the quinolizidine **29** (30 mg, 0.063 mmol) in 1% methanolic HCl (3 mL). The flask was evacuated (aspirator) and purged with hydrogen three times. The mixture was stirred at room temperature under a balloon of hydrogen for 48 h, and then the hydrogen was evacuated and the mixture was filtered, rinsing with MeOH (3 mL). The filtrate was concentrated, and the residue was dissolved in water (2 mL) and stirred with Dowex 1 × 8−200 $^-$OH ion exchange resin (50 mg). After 30 min, the mixture was filtered and the filtrate concentrated. Chromatography (8:1:0.1 $CHCl_3$/MeOH/NH_4OH) gave 12 mg (92%) of the title compound as a colorless oil that crystallized upon standing. The stereochemistry was assigned by ^{1}H NMR coupling constant analysis (see supporting information). R_f = 0.44 (5:1:0.1 $CHCl_3$/MeOH/NH_4-OH); mp = 150 °C; $[\alpha]^{23}_D$ = −64.6° (*c* 1.00, MeOH); ^{1}H NMR (CD_3OD, 300 MHz) δ 3.84 (dt, *J* = 1.7, 3.3 Hz, 1H, H_3), 3.82 (t, *J* = 9.1 hz, 1H, H_1), 3.69 (ddd, *J* = 4.6, 8.5, 11.1 Hz, 1H, H_9), 3.34 9dd, *J* = 3.5, 9.4 Hz, 1H, H_2), 2.89 (dd, *J* = 3.2, 12.5 Hz, 1H, H_{4eq}), 2.73 (br d, *J* = 11.6 Hz, 1H, H_{6eq}), 2.30 (dd, *J* = 1.7, 12.5 Hz, 1H, H_{4ax}), 2.04 (m, 1H, H_{6ax}), 1.94 (m, 1H, H_{8eq}), 1.66 (t, *J* = 8.5 Hz, 1H, H_{9a}), 1.64 (m, 2H, H_{7ax} and H_{7eq}), 1.29 (m, 1H, H_{8ax}); ^{13}C NMR (CD_3OD, 90 MHz, JMOD) δ 76.1 (+), 75.7 (+), 74.7 (+), 70.3 (+), 69.5 (+), 60.7 (−), 56.2 (−), 33.9 (−), 23.9 (−); IR (neat) 3332 (s), 2936 (m), 2801 (m), 2752 (m) cm^{-1}; MS (EI, 70 eV) *m/z* (rel int) 203 (M^+, 24), 185 (97), 168 (46), 146 (68), 128 (23), 113 (46), 99 (100), 72 (61); HRMS calcd for $C_9H_{17}NO_4$ 203.1158, found 203.1152. Anal. Calcd for $C_9H_{17}NO_4$: C, 53.20; H, 8.45; N, 6.89. Found: C, 53.19; H, 8.46; N, 6.80.

(2*R*,3*R*,4*R*,5*S*,6*R*)-1-Azido-2,3,4-tris(benzyloxy)-6-(*tert*-butyldimethylsilyl)oxy-9-chloro-5-hydroxynonane (30). *tert*-Butyldimethylsilyl chloride (TBDMSCl) (88 mg, 0.585 mmol) and imidazole (83 mg, 1.22 mmol) were added to a solution of the diol **24** (270 mg, 0.487 mmol) in THF/DMF (1:1, 3 mL) at room temperature. After 12 h, additional TBDMSCl (20 mg, 0.13 mmol) and imidazole (20 mg, 0.29 mmol) were added. After 8 h, the mixture was poured into aqueous NH_4-Cl (10 mL) and extracted with Et_2O (2 × 15 mL). The combined organic layers were washed with brine, dried ($MgSO_4$), and concentrated. Chromatography (20:1 to 10:1 hex/EtOAc gradient) gave 287 mg (88%) of the title compound as a colorless oil. R_f = 0.45 (6:1 hex/EtOAc); $[\alpha]^{23}_D$ = +10.8° (*c* 1.39, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.2−7.4 (m, 15H), 4.73 (ABq, *J* = 11.3 Hz, $\Delta\nu$ = 13.0 Hz, 2H), 4.60 (ABq, *J* = 11.2 Hz, $\Delta\nu$ = 62.0 Hz, 2H), 4.53 (ABq, *J* = 11.8 Hz, $\Delta\nu$ = 20.8 Hz, 2H), 4.07 (dd, *J* = 6.2, 2.6 Hz, 1H), 3.88 (m, 2H), 3.76

(m, 3H), 3.45 (m, 3H), 2.66 (d, J = 3.0 Hz, 1H), 1.85 (m, 1H), 1.4−1.7 (m, 3H), 0.86 (s, 9H), 0.08 (s, 6H); ^{13}C NMR ($CDCl_3$, 90 MHz) δ 138.2, 137.9, 137.6, 128.5, 128.4, 128.3, 127.9, 127.7, 127.7, 79.2, 78.5, 77.3, 74.4, 73.1, 72.6, 72.4, 72.2, 50.8, 45.3, 28.5, 28.3, 25.8, 18.0, −4.4; IR (neat) 3503 (br w), 3030 (w), 2942 (m), 2928 (m), 2848 (m), 2100 (s) cm^{-1}; MS (CI, NH_3) m/z (rel int) 685 ([M + NH_4]$^+$, 52), 640 (100), 604 (82), 516 (16), 106 (33); HRMS calcd for $C_{36}H_{50}{}^{35}ClN_3O_5SiNH_4$ 685.3552, found 685.3572.

(1*R*,2*R*,3*R*,9*R*,9a*S*)-1,2,3-Tri-*O*-benzyl-9-*O*-(*tert*-butyldimethylsilyl)-1,2,3,9-tetrahydroxyquinolizidine (32). A solution of dimethyl sulfoxide (80 mg, 1.0 mmol) in CH_2Cl_2 (1 mL) was added to a cooled (−60 °C) solution of oxalyl chloride (65 mg, 0.51 mmol) in CH_2Cl_2. After 5 min, the alcohol **30** (280 mg, 0.418 mmol) was added as a solution in CH_2Cl_2 (1 mL). After 10 min, triethylamine (216 mg, 2.14 mmol) was added as a solution in CH_2Cl_2 (1 mL). The resulting mixture was stirred at −60 °C for 15 min and then warmed to room temperature and quenched by the addition of water. The mixture was poured into Et_2O (15 mL) and washed with aqueous NH_4Cl (2 × 20 mL) and brine (15 mL). The organic layer was then dried ($MgSO_4$) and concentrated to give 240 mg of crude azido ketone as a colorless oil. R_f = 0.19 (10:1 hex/EtOAc); ^{1}H NMR ($CDCl_3$, 360 MHz) δ 7.2−7.4 (m, 15 H), 4.79 (d, J = 3.5 Hz, 1H), 4.63 (d, J = 11.4 Hz, 1H), 4.42 (d, J = 11.3 Hz, 1H), 4.36 (d, J = 11.4 Hz, 1H), 4.26 (dd, J = 7.1, 3.5 Hz, 1H), 4.08 (dd, J = 13.4, 2.9 Hz, 1H), 3.45 (m, 2H), 3.37 (dd, J = 13.4, 4.3 Hz, 1H), 1.6−1.9 (m, 4H), 0.88 (s, 9H), 0.09 (s, 3H), 0.06 (s, 3H); ^{13}C NMR ($CDCl_3$, 90 MHz) δ 208.9, 137.7, 137.6, 137.5, 128.4, 128.4, 128.3, 128.2, 127.9, 127.9, 127.8, 79.8, 78.0, 75.9, 73.4, 73.4, 72.3, 50.5, 44.9, 31.4, 27.3, 25.8, 18.0, −4.4, −4.6; IR (neat) 2953 (m), 2929 (m), 2857 (m), 2101 (s), 1727 (m) cm^{-1}. The crude ketone was dissolved in EtOAc/EtOH (1:1, 15 mL), and palladium hydroxide on carbon (80 mg) was added. The flask was evacuated (aspirator) and purged with hydrogen three times. The resulting heterogeneous mixture was stirred under a balloon of hydrogen for 1 h, and then the hydrogen was evacuated and the mixture was passed through a plug of Celite, rinsing with EtOH (10 mL). The filtrate was concentrated under reduced pressure without heating (to avoid cyclization) to give 205 mg of the crude imine **31**; R_f = 0.18 (5:1 hex/EtOAc); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.2−7.4 (m, 15H), 4.55−4.72 (m, 4H), 4.52 (ABq, J = 12.1 Hz, 2H), 4.34 (d, J = 4.1 Hz, 1H), 4.24 (dd, J = 8.0, 5.1 Hz, 1H), 3.82 (m, 4H), 3.44 (t, J = 6.3 Hz, 2H), 1.86 (m, 2H), 1.73 (m, 2H), 0.91 (s, 9H), 0.02 (s, 3H), 0.01 (s, 3H). The crude imine was then dissolved in methanol (15 mL), cooled to 0 °C, and treated with sodium borohydride (49 mg, 1.3 mmol). After 2 h, ethanol (20 mL) and potassium carbonate (180 mg, 1.3 mmol) were added, and the mixture was warmed to reflux (ca. 70 °C). After 3 h, the mixture was cooled to room temperature, poured into water (40 mL), and extracted with CH_2Cl_2 (3 × 30 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated. Chromatography (4:1 to 2:1 hex/EtOAc gradient) provided 152 mg (62%) of the title compound as a colorless oil. R_f = 0.44 (2:1 hex/EtOAc); $[\alpha]^{23}_D$ = −24.5° (*c* 1.11, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.2−7.4 (m, 15H), 4.45−4.67 (m, 6H), 4.20 (dt, J =4.3, 8.8 Hz, 1H, H_9), 4.02 (dd, J = 3.7, 4.3 Hz, 1H, H_1), 3.91 (ddd, J = 3.2, 4.2, 8.5 Hz, 1H, H_3), 3.75 (t, J = 3.7 Hz, 1H, H_2), 3.24 (dd, J = 9.2, 11.2 Hz, 1H, H_4), 2.97 (dt, J = 3.5, 13.4 Hz, 1H, H_6), 2.84 (ddd, J = 3.1, 11.1, 13.4 Hz, 1H, H_6), 2.71 (dd, J = 3.2, 8.8 Hz, 1H, H_{9a}), 2.63 (dd, J = 4.2, 11.3 Hz, 1H, H_4), 1.89 (m, 1H, H_8), 1.71 (m, 1H, H_7), 1.46 (m, 1H, H_7), 1.32 (m, 1H, H_8), 0.79 (s, 9H), −0.74 (s, 3H), −0.15 (s, 3H); ^{13}C NMR ($CDCl_3$, 90 MHz, JMOD) δ 138.6 (−), 138.5 (−), 138.5 (−), 128.2 (+), 128.2 (+), 128.1 (+), 127.9 (+), 127.8 (+), 127.4 (+), 127.3 (+), 76.2 (broad, +), 75.4 (+), 72.8 (+), 72.5 (−), 72.1 (−), 71.0 (−), 65.4 (+), 64.0 (+), 53.2 (−), 47.7 (broad, −), 34.7 (broad, −), 25.9 (+), 19.9 (−), 17.9 (−), −3.9 (+), −5.0 (+); IR (neat) 3204 (w), 2923 (s), 2850 (s), 2355 (m), 2326 (m), 1455 (m) cm^{-1}; MS (EI, 50eV) m/z (rel int) 587 (M^+, 3), 496 (100), 390 (20), 374 (18), 91 (71), 73 (29); HRMS calcd for $C_{36}H_{49}NO_4Si$ 587.3431, found 587.3439.

(1*R*,2*R*,3*R*,9*R*,9a*R*)-1,2,3,9-Tetrahydroxyquinolizidine [(9*R*,9a*R*)-4] from 32. Palladium on carbon (10%, 15 mg) was added to a solution of the quinolizidine **32** (30 mg, 0.063 mmol) in 1% methanolic HCl (3 mL). The flask was evacuated (aspirator) and purged with hydrogen three times. The mixture was stirred at room temperature under a balloon of hydrogen for 48 h, and then the hydrogen was evacuated and the mixture was filtered, rinsing with MeOH (3 mL). The filtrate was concentrated, and the residue was dissolved in water (2 mL) and stirred with Dowex 1 × 8−200 $^-$OH ion exchange resin (50 mg). After 30 min, the mixture was filtered and the filtrate concentrated. Chromatography (8:1:0.1 $CHCl_3$/MeOH/NH_4OH) gave 12 mg (92%) of the title compound as a colorless oil that crystallized upon standing. See above for characterization.

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Supporting Information Available: Discussion of the stereochemical assignments for all quinolizidines, ^{1}H and ^{13}C NMR spectra for compounds **4** (all four diastereomers), **12**, **13**, **21**−**30**, and **32**, and COSY spectra for all quinolizidines (52 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.

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