Synthesis of Novel Glycosidase-Inhibitory Hydroxymethyl-Substituted Polyhydroxylated Indolizidines: Ring-Expanded Analogs of the Pyrrolizidine Alkaloids Alexine and Australine

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The pyrrolizidine azasugars alexine (**3**) and australine (**4**) and their stereoisomers are glycosidase inhibitors of potential therapeutic use. Since the glycosidase inhibitory activity of azasugars is profoundly effected by ring size modification, the ring-expanded indolizidine analogs **7** (homoalexine), **8** (8-epihomoaustraline), **9** (homoaustraline), and **10** (8-epihomoalexine) were prepared. L-Xylose was converted into the diols **16**, which were transformed into the nine-membered lactones **18** by Claisen rearrangment of the cyclic ketene acetal **17**. Transesterification of the lactones to the hydroxy esters **19** followed by azide displacement and epoxidation gave the epoxides **21** and **31**. Reductive double cyclization of these azido-epoxides followed by functional group adjustment provided the desired homologs **7**−**10**. An alternative route involving stereoselective epoxidation of the nine-membered lactones was also examined. The homologs **7**−**10** were found to be good inhibitors of amyloglucosidase (*Aspergillus niger*). The inhibitory activities of **8** and **10** are comparable to those exhibited by castanospermine (**5**) and the pyrrolizidines alexine (**3**), australine (**4**), and 7-epiaustraline. Indolizidines **7**−**10** do not inhibit β-glucosidase (almond) or α-glucosidase (bakers' yeast). This activity parallels that exhibited by the pyrrolizidine inhibitors alexine, australine, and 7-epiaustraline, which are generally good amyloglucosidase inhibitors but relatively weak inhibitors of α-glucosidase and β-glucosidase. However, in contrast to the pyrrolizidine inhibitors which have not been reported to possess mannosidase inhibitory activity, the indolizidines **7**−**10** were found to inhibit α-mannosidase (jack bean), albeit weakly.

Introduction

A number of naturally occurring polyhydroxylated pyrrolidine, piperidine, pyrrolizidine, and indolizidine alkaloids (often referred to as "amino-sugars" or "aza-sugars") exhibit glycosidase inhibitory activity.[1−5] Examples include the pyrrolidine (2*R*,5*R*,3*R*,4*R*)-2,5-bis-(hydroxymethyl)-3,4-dihydroxypyrrolidine (DMDP, **1**), the piperidine deoxynojirimycin (**2**), the pyrrolizidines alexine (**3**) and australine (**4**), and the indolizidines castanospermine (**5**) and swainsonine (**6**). At physiological pH, the protonated amino group may mimic the developing pyranosyl or furanosyl cation intermediate encountered in oligosaccharide cleavage. Due to their ability to inhibit glycoprotein processing enzymes, such alkaloids have been useful in studies on the effect of oligosaccharide structure on glycoprotein function.[3−6] Several of these alkaloids are also of interest for their activity against cancer, HIV, and other disorders. For example, DMDP (**1**), deoxynojirimycin (**2**) and certain stereoisomers of alexine (**3**) and australine (**4**) have shown anti-HIV activity *in vitro*.[7−9] The glucosidase inhibitor castanospermine (**5**) has shown anticancer[10] and antiviral activity,[11] including anti-HIV activity.[12] The mannosidase inhibitor swainsonine (**6**) inhibits tumor growth and metastasis[13] and exhibits immunomodulatory activity.[14] Structurally modified analogs of these naturally occurring compounds might provide more potent and selective glycosidase inhibitors or new therapeutic agents. We wish to report the synthesis and biological evaluation of the non-natural indolizidines **7**−**9**, com-

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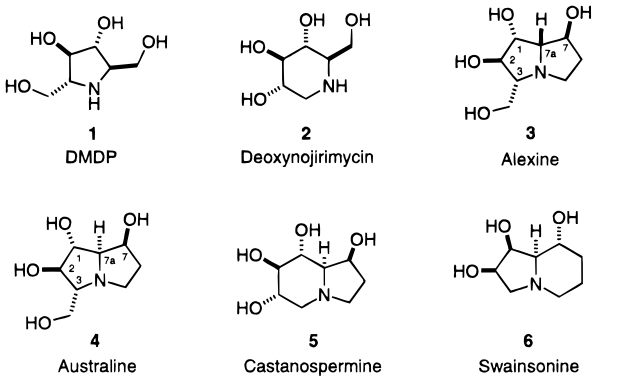
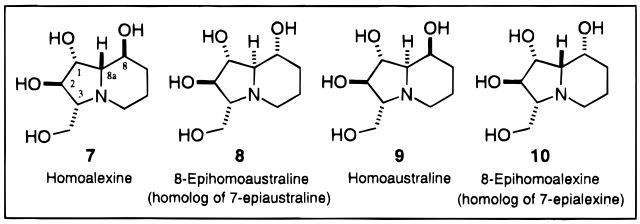
pounds which combine some of the structural features of the alkaloids **1**−**6**. These are the first examples of 3-(hydroxymethyl)indolizidines. From a nomenclature standpoint, **7**−**9** are considered to be ring-expanded analogs (homologs) of the alkaloids alexine (**3**) and australine (**4**).





The alkaloids **1**−**6** have been the subject of structure−activity relationship studies, primarily involving stereoisomeric analogs.[15−18] Another strategy involves the modification of ring sizes, where a profound effect on the glycosidase inhibitory activity of the polyhydroxylated alkaloids may be found. Ring-expanded quinolizidine analogs of castanospermine have been prepared and were found to retain inhibitory activity.[19] However, ring-expanded quinolizidine analogs of swainsonine were found to lack inhibitory activity (see preceding paper).[20] A ring-contracted pyrrolizidine analog of the indolizidine alkaloid swainsonine was found to be four orders of magnitude less effective as an α-mannosidase inhibitor.[21,22] This observation led us to propose that alexine and australine would gain a similar increase in activity if the less-oxygenated pyrrolidine ring were expanded to a piperidine ring, much like swainsonine. Hence, we set out to make the indolizidine analogs **7**−**10** of alexine and australine. We chose to attempt the preparation of all four of the C(8)/C(8a)diastereomers of these indolizidines, since variation of the C(7) and C(7a) stereochemistry in alexine and australine results in substantially different biological activity.[23] Indolizidine **7** is a homolog of alexine (**3**), a poor inhibitor of glucosidases and galactosidases,[24,25] but a good inhibitor of amyloglucosidase and thioglucosidase.[26,27] Analog **8** is a homolog of 7-epiaustraline,[9,26] a known alkaloid that is a good inhibitor of amyloglucosidase[26,28,29] and α-glucosidase[26,30] and shows anti-HIV activity.[30] Indolizidine **9** is a homolog of australine (**4**), an inhibitor of amyloglucosidase[26,28,29] and glucosidase I[29] that also shows antiviral and anti-HIV activity.[30] The analog **10** is a homolog of 7-epialexine, a known compound whose biological activity has not been determined.[9]

Results and Discussion

We envisaged preparing indolizidines **7**−**10** using a route analogous to that described in the preceding paper for the synthesis of polyhydroxylated quinolizidines.[31] The four diastereomers were thought to be readily available using an azido-epoxide reductive double cyclization approach.[20a,21,32] A retrosynthetic analysis of the indolizidines **7**−**10** is shown in Scheme 1. The lactam **11** may arise from a reductive double-cyclization of the azido-epoxide **12**, which should be available by epoxidation of **13**.[33] In order to prepare the four possible C(8)/C(8a) diastereomers of **7**−**10**, we would require a rela-

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(23) In general, it is often difficult to predict which stereoisomer of an azasugar will be an effective inhibitor of a certain glycosidase.[2,16]

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(31) See preceding paper in this journal. Although an azide−olefin cyclization approach to the indolizidine backbone would not suffer the undesired aromatization encountered in the quinolizidine work, this chemistry was not pursued since it would allow access to only one diastereomer of **7**−**10**.

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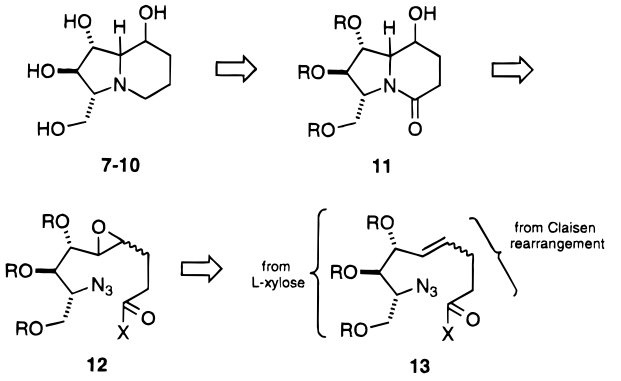
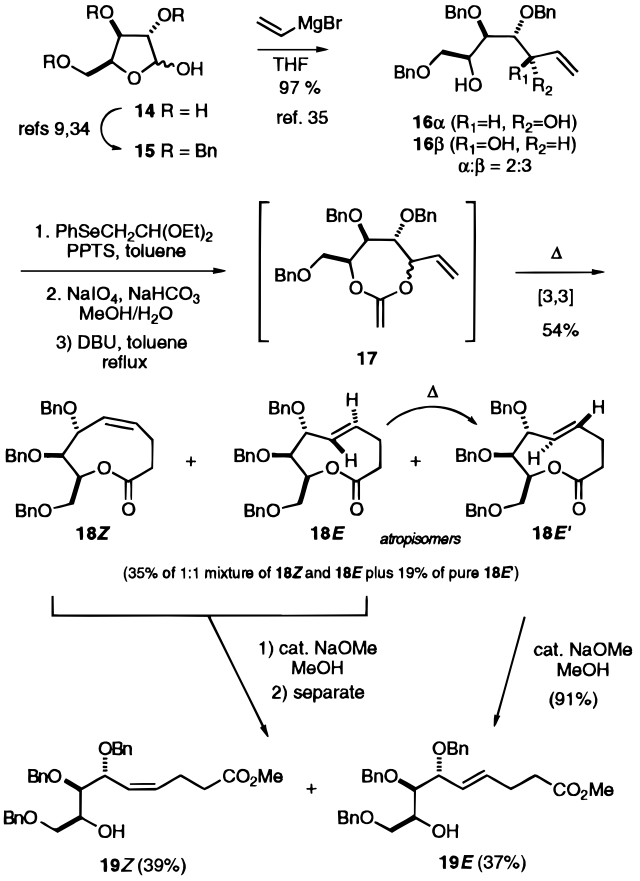
(33) We initially investigated the use of an azido-*chloro*-alkene epoxidation precursor similar to that used in the quinolizidine work (see preceding paper in this journal). However, the Wittig olefination of lactol **15** proved problematic, leading primarily to elimination products.

Scheme 1. Retrosynthesis: Reductive Cyclization of an Azide Bearing Two Remote Electrophilic Sites



Scheme 2. Use of a Claisen Rearrangement To Install the Alkene



tively nonstereoselective epoxidation of both geometric isomers of **13**. The γ,δ-unsaturated carboxylic acid derivative **13** was proposed to be available by a Claisen rearrangement of a carbohydrate-derived allylic alcohol.

The installation of the γ,δ-unsaturated carboxylic acid by a Claisen rearrangement is shown in Scheme 2. Commercially available L-xylose (**14**) was converted into tri-*O*-benzyl-L-xylofuranose (**15**) in three steps according to the literature procedure.[34] Addition of vinylmagnesium bromide to **15** provided a 2:3 mixture of diastereomeric allylic alcohols, **16**α and **16**β, consistent with the literature results in the enantiomeric D-series.[35] Our original plan was to carry out a Claisen rearrangement on **16** to produce the *E*-γ,δ-unsaturated ester **19*E***. Attempted orthoester-Claisen rearrangement of **16** failed due to the formation of a seven-membered cyclic orthoester which was resistant to further reaction even at high temperatures. Although we considered other options which would avoid the problem of the interfering hydroxyl group in **16**, a subsequent observation made these tactics unnecessary. Since we also required **19*Z***, we explored the use of Holmes's Claisen rearrangement method[36,37] for the synthesis of eight- and nine-membered lactones from cyclic ketene acetals, a method known to produce the *Z*-alkene isomer exclusively (i.e., **17** → **18*Z*** → **19*Z***). This strategy uses the extra hydroxyl present in **16** to our advantage. Acetal formation with (phenylseleno)acetaldehyde diethylacetal[38] followed by oxidation of the selenide afforded a complex mixture of diastereomeric selenoxide-bearing acetals. Heating this mixture in toluene-containing DBU caused selenoxide elimination to give the ketene acetal **17**, which suffered a Claisen rearrangement *in situ* to produce a mixture of three nine-membered lactones **18**. Chromatography afforded two fractions, the first containing the *Z*-alkene **18*Z*** and an *E*-alkene **18*E*** in a 1:1 ratio. The second fraction contained another *E*-alkene **18*E′***, presumably an atropisomer of **18*E***. Indeed, continued heating of the purified mixture of **18*Z*** and **18*E*** in refluxing toluene caused the slow conversion of **18*E*** to **18*E′***. In contrast to literature precedent[36,37] and predictions based on our examination of molecular models, the Claisen rearrangment of **17** proved to be moderately *E*-selective rather than highly *Z*-selective. The use of pure allylic alcohols **16**β resulted in a similar mixture of lactones. We have not been able to develop a convincing rationale for this result. The low stereoselectivity, while unexpected, was a welome turn of events, since we required both alkene stereoisomers. Methanolysis of the 1:1 mixture of **18*Z*** and **18*E*** produced the γ,δ-unsaturated esters **19*Z*** and **19*E*** in 39% and 37% yields, respectively, after separation by column chromatography. Methanolysis of the atropisomeric lactone **18*E′*** afforded 91% of **19*E***. With the two requisite alkenes **19*Z*** and **19*E*** in hand, we turned to completion of the synthesis of the indolizidines **7**−**10**.

The conversion of **19*E*** to homoalexine (**7**) and 8-epihomoaustraline (**8**) is shown in Scheme 3. A Mitsunobu reaction with hydrazoic acid[39] was found to be the best way to convert the alcohol **19*E*** into the azide **20**. Epoxidation of **20** afforded an inseparable 1:2 mixture of the diastereomeric *trans*-epoxides **21**α and **21**β.[40] Reduction of the azide to the primary amine resulted in intramolecular epoxide opening and partial acylation of the resultant pyrrolidine by the ester. To complete the acylation, the mixture was heated with methanolic sodium methoxide to afford the inseparable indolizidinones **22** and **23** in a ratio that reflected the relative

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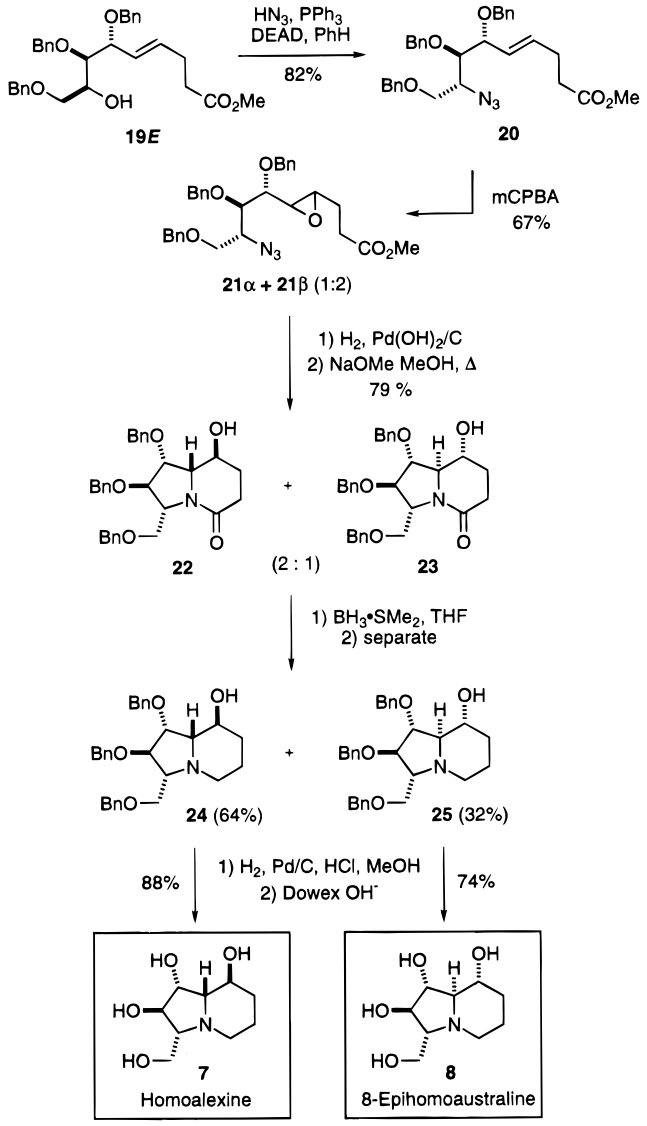
Scheme 3. Syntheses of Homoalexine (7) and 8-Epihomoaustraline (8)



amounts of the epoxides **21**β and **21**α. The lactams **22** and **23** were reduced with borane, producing the indolizidines **24** and **25** in good yield after separation by column chromatography. Hydrogenolysis of the benzyl protecting groups yielded the desired indolizidines homoalexine (**7**) and 8-epihomoaustraline (**8**).

While the low stereoselectivity in the epoxidation of **19*Z*** suited our purposes for the synthesis of both **7** and **8** for biological evaluation, we were curious about the stereoselectivity of the epoxidation of the pure nine-membered lactone **18*E′***, since models indicated that only one π-face of the alkene would be exposed to the oxidant (Scheme 4). Stereoselective functionalization of alkenes from the periphery of medium-ring alkenes has been explored by others.[41] Indeed, oxidation of **18*E′*** gave a single epoxide **26**. Mild transesterification with methanol yielded the alcohol **27**, which was converted to the azide **21**α, previously encountered as part of a mixture of stereoisomers in Scheme 3 above. Reductive double-cyclization of **21**α gave the indolizidinone **23** (see also Scheme 3) in good yield.

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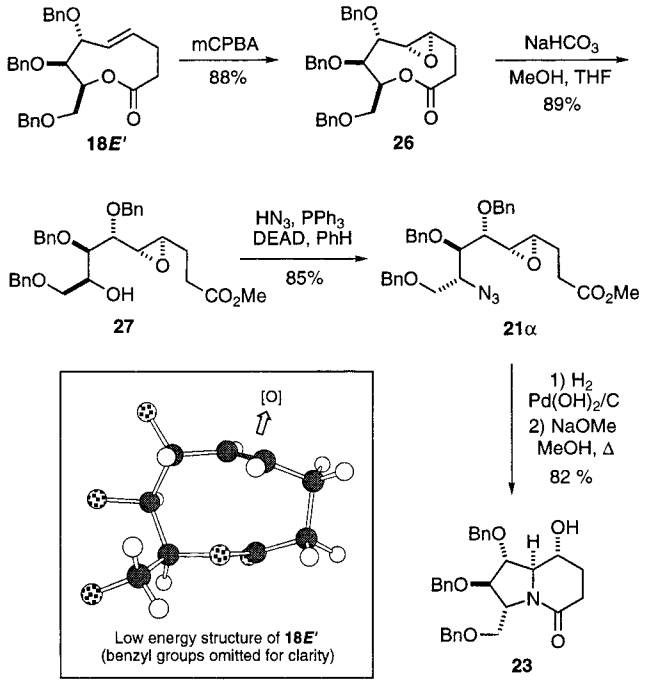
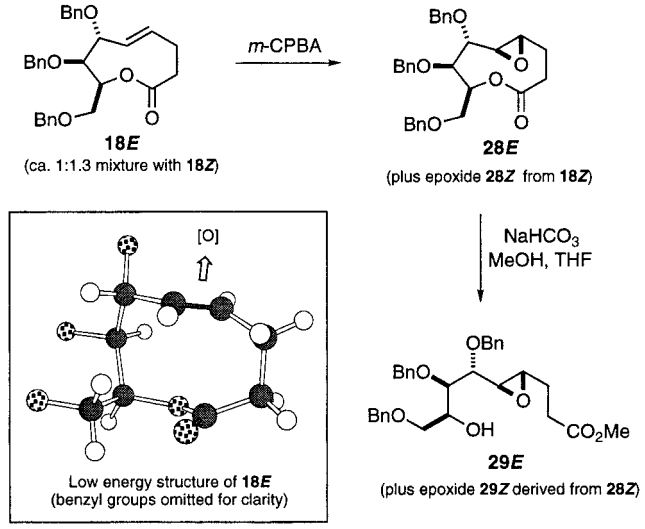
Scheme 4. An Alternative Route to the Indolizidine 23 Involving Epoxidation of the Lactone 18*E′*



Scheme 5. Lactone 18*E* Presents a Different π-Face to the Oxidant Than Its Atropisomer 18*E′*

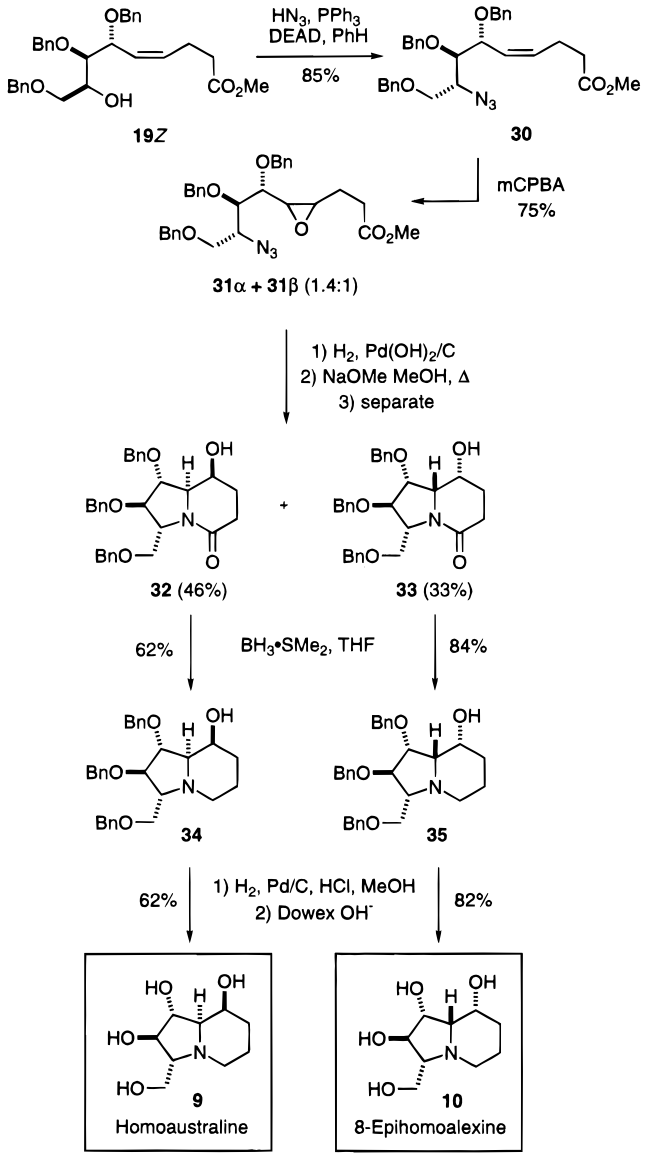


To provide evidence that **18*E*** and **18*E′*** are indeed atropisomers, we briefly studied the epoxidation of the kinetically-formed lactone 1**8*E*** (Scheme 5). An approximately equal mixture of **18*Z*** and **18*E*** was again prepared by the Claisen rearrangement route (see Scheme 2). Epoxidation of this mixture gave two epoxides **28*E*** and **28*Z*** which were found to be different from **26** (see Scheme 4). While it is likely that the difference between **26** and the **28*E*** is in the configuration of the epoxide, it could also be due to atropisomerism. Hence, we opened the epoxides **28*E*** and **28*Z*** to the hydroxy esters **29*E*** and **29*Z*** to remove the possibility of atropisomerism. It was found that the hydroxy ester **29*E*** was different from the hydroxy ester **27** in Scheme 4, proving that **18*E*** and **18*E′*** were indeed atropisomers, each presenting a different π-face to the oxidant. The lowest energy conformation of **18*E*** is shown in Scheme 5. The alkene π-system is essentially orthogonal to the mean plane of the nine-

membered ring, thus explaining the high stereoselectivity of the epoxidation.[42]

The conversion of **19*Z*** to homoaustraline (**9**) and 8-epihomoalexine (**10**) is shown in Scheme 6. A Mitsunobu reaction with hydrazoic acid[39] was used again to convert the alcohol **19*Z*** into the azide **30**. Epoxidation of **30** afforded an inseparable 1.4:1 mixture of the diastereomeric *cis*-epoxides **31**α and **31***β*.[40] Reduction of the azide followed by treatment with methanolic sodium methoxide caused double cyclization, producing the indolizidinones **32** and **33** in 45% and 33% isolated yields after separation by column chromatography. Reduction of **32** with borane gave the indolizidine **34**, which was deprotected by hydrogenolysis to afford homoaustraline (**9**). Similarly, reduction of **33** gave **35**, which was deprotected to produce 8-epihomoalexine (**10**).

Scheme 6. Synthesis of Homoaustraline (9) and 8-Epihomoalexine (10)



Biological Screening of the Indolizidines 7−10

The four hydroxymethyl substituted indolizidines were screened for inhibitory activity against a number of common glycosidases that accept *p*-nitrophenyl glycosides as substrates.[29] All four compounds were found to to be good inhibitors of amyloglucosidase (*Aspergillus niger*, *p*-nitrophenyl-α-glucopyranoside as substrate): $IC_{50} = 75$ μM (homoalexine **7**), 12 μM (8-epihomoaustraline **8**), 95 μM (homoaustraline **9**), 4.5 μM (8-epihomoalexine **10**). Inhibition of amyloglucosidase by the indolizidine homologs **7**−**9** is roughly tenfold weaker than that exhibited by the corresponding pyrrolizidines alexine (**3**) (IC_{50} = 11 μM[26]), 7-epiaustraline ($IC_{50} = 0.13$ μM[26]), and australine (**4**) ($IC_{50} = 5.8$ μM,[29] 1.5 μM[26]).[43] Indolizidines **7**−**10** do not inhibit *β*-glucosidase (almond) or α-glucosidase (bakers' yeast), exhibiting less than 50% inhibition at inhibitor concentrations of up to 2 mM. This activity parallels that exhibited by the pyrrolizidine inhibitors alexine, australine, and 7-epiaustraline, which are generally good amyloglucosidase inhibitors but relatively weak inhibitors of α-glucosidase and *β*-glucosidase.[26,29]

In contrast to the pyrrolizidine inhibitors, which do not possess mannosidase inhibitory activity,[28,29] the indolizidines **7**−**10** were found to inhibit α-mannosidase (jack bean) albeit weakly: $IC_{50} = 530$ μM (**7**), 150 μM (**8**), 190 μM (**9**), 480 μM (**10**). The fact that these compounds are mannosidase inhibitors at all is significant, since most good mannosidase inhibitors are epimeric to **7**−**10** at the carbon corresponding to C(1) (e.g. swainsonine (**6**)).[15,18] This suggests that a similar 3-(hydroxymethyl)-substituted swainsonine analog might provide a potent mannosidase inhibitor. Efforts to prepare such a compound are underway. More extensive biological testing of compounds **7**−**10**, including screening for anti-HIV activity, will be reported in due course.

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.[44] **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 via cannula, and any excess hydrazoic acid was quenched by the addition of 10% NaOH. Tetrahydrofuran was distilled from sodium/benzophenone ketyl. Toluene, 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. ^{1}H NMR spectral assignments and stereochemical determinations were made on the basis of two-dimensional correlated off resonance spectroscopy (COSY) experiments as well as two-dimensional nuclear Overhauser effect spectroscopy (NOESY). *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

(42) Note that the structure of **18*E*** shown in Scheme 5 differs from the structure of **18*E′*** in Scheme 4 in two ways. First, the alkene *π*-face exposed to oxidant is different for each. Second, each lactone has a different ester *π*-face on the periphery of the ring. Structures with the same orientation of the ester but with different alkene *π*-faces exposed were higher in energy.

(43) The biological activity of 7-epialexine has not been reported. The screens performed by Nash *et al.* used potato amylose as the substrate, rather than *p*-nitrophenyl-α-glucopyranoside.

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

(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[45] using flash grade Merck Silica Gel 60 (230−400 mesh). The enzymes α-mannosidase (from jack bean), α-glucosidase (from bakers' yeast), β-glucosidase (from almonds), amyloglucosidase (from *Aspergillus niger*), and the corresponding *p*-nitrophenyl glycoside substrates were obtained from Sigma Chemical Co. Enzyme inhibition was assayed colorimetrically by monitoring the release of *p*-nitrophenol from the appropriate *p*-nitrophenyl glycoside substrate according to the procedure described by Tropea *et al*.[29]

(2*S*,3*R*,4*R*,5*S*)-2,5-Dihydroxy-1,3,4-tris(benzyloxy)-6-heptene (16α) and (2*S*,3*R*,4*R*,5*R*)-2,5-Dihydroxy-1,3,4-tris(benzyloxy)-6-heptene (16*β*). Prepared according to the literature procedure for the enantiomeric series.[35] Vinyl magnesium bromide (15 mL of a 1 M solution in THF, 15 mmol) was added to a cold (0 °C) solution of 2,3,5-tri-*O*-benzyl-L-xylofuranose[9,34] (2.08 g, 4.94 mmol) in THF (25 mL). After 3 h, the reaction was quenched by the addition of saturated aqueous NH_4Cl (5 mL). The resulting mixture was diluted with water (50 mL) and extracted with ether (2 × 100 mL). The combined organic layers were washed with brine, dried ($MgSO_4$), and concentrated. Chromatography (3:1 to 2:1 hex/EtOAc gradient) provided 2.16 g (97%) of diols **16**α and **16***β* as a 3:2 mixture (not separated) based on ^{1}H NMR integration. R_f = 0.25 (2:1 hex/EtOAc); major isomer **16**α: ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.2−7.4 (m, 15H), 5.91 (ddd, *J* = 5.1, 10.5, 17.2 Hz, 1H), 5.35 (dt, *J* = 1.6, 17.2 Hz, 1H), 5.18 (dt, *J* = 1.6, 10.5 Hz, 1H), 4.38−4.85 (m, 7H), 4.10 (ddd, *J* = ∼1, 6.8, 12.2 Hz, 1H), 3.71 (dd, *J* = 1.6, 6.5 Hz, 1H), 3.57 (dd, *J* = 1.9, 6.5 Hz, 1H), 3.54 (dd, *J* = 6.3, 9.3 Hz, 1H), 3.42 (dd, *J* = 6.6, 9.3 Hz, 1H), 3.14 (d, *J*= 6.3 Hz, 1H), 3.05 (d, *J* = 7.4 Hz, 1H); ^{13}C NMR ($CDCl_3$, 90 MHz) δ 138.6, 138.0, 128.45, 128.40, 128.3, 128.2, 128.0, 127.9, 127.8, 127.7, 115.5, 80.2, 77.1, 74.40, 74.35, 73.2, 71.1, 70.5, 68.3; minor isomer **16***β*: ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.2−7.4 (m, 15H), 6.00 (ddd, *J* = 6.1, 10.5, 17.2 Hz, 1H), 5.37 (dt, *J* = 1.6, 17.2 Hz, 1H), 5.23 (dt, *J* = 1.6, 10.5 Hz, 1H), 4.38−4.75 (m, 7H), 4.06 (dt, *J* = 3.2, 6.2 Hz, 1H), 3.76 (dd, *J* = 2.9, 5.2 Hz, 1H), 3.64 (t, *J* = 5 Hz, 1H), 3.50 (dd, *J* = 6.1, 9.5 Hz, 1H), 3.42 (dd, *J* = 6.1, 9.5 Hz, 1H), 3.09 (br d, *J* = 5, 1H), 2.75 (br d, *J* = 6, 1H); IR (neat, mixture of isomers) 3410 (br m), 3030 (m), 2911 (m), 2864 (m), 1454 (m), 1092 (s), 1066 (s) cm^{-1}. The ^{1}H- and ^{13}C-NMR spectroscopic data reported above are consistent with those reported by Boschetti *et al*. for the enantiomers.[35]

(*Z*)-(7*R*,8*S*,9*S*)-7,8-Bis(benzyloxy)-9-[(benzyloxy)methyl]-1-oxa-2-oxocyclonon-5-ene (18*Z*) and (*E*)-(7*R*,8*S*,9*S*)-7,8-Bis(benzyloxy)-9-[(benzyloxy)methyl]-1-oxa-2-oxocyclonon-5-ene (18*E* and 18*E*′). (Phenylseleno)acetaldehyde diethyl acetal[37,38] (1.32 g, 4.82 mmol) and pyridinium *p*-toluenesulfonate (PPTS) (50 mg, 0.20 mmol) were added to a solution of diols **16**α/**16***β* (1.80 g, 4.01 mmol) in toluene (40 mL), and the resulting mixture was warmed to reflux. After 4.5 h, the mixture was poured into 10% $NaHCO_3$ (40 mL) and extracted with ether (3 × 50 mL). The combined organic layers were washed with brine, dried ($MgSO_4$), and concentrated to give a yellow oil that was found by ^{1}H- and ^{13}C-NMR spectroscopy to be a complex mixture of diastereomeric acetals, R_f = 0.38 (4:1 hex/EtOAc). The crude residue was dissolved in MeOH (330 mL) and water (50 mL), and then $NaHCO_3$ (0.45 g, 5.3 mmol) and sodium periodate ($NaIO_4$) (3.09 g, 14.4 mmol) were added. After 10 min at room temperature, a white precipitate formed. After 2 h, the mixture was poured into water (1.2 L) and extracted with EtOAc (3 × 400 mL). The combined organic layers were dried (Na_2SO_4) and concentrated. The residue was applied to a plug of silica gel (*ca*. 30 g) and was eluted with 5:1 hex/EtOAc (100 mL) followed by 20:1 $CHCl_3$/MeOH (200 mL). The selenoxide-containing fractions [R_f = 0.24 (20:1 $CHCl_3$/MeOH)] were then concentrated to give 1.5 g of a mixture of diastereomeric selenoxides as a pale yellow oil. This mixture was dissolved in toluene (400 mL) and treated with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) (1.80 mL, 1.83 g, 12.0 mmol). The resulting mixture was warmed to reflux for 24 h and then cooled to room temperature and concentrated. Chromatography (15:1 to 10:1 hex/EtOAc gradient) provided 660 mg (35%) of a mixture of **18*Z*** and **18*E*** (1:1 based on ^{1}H NMR integration) followed by 350 mg (19%) of pure **18*E*′**. Data for the **18*Z*/18*E*** mixture (see below for spectra of pure **18*Z***): R_f = 0.40 (4:1 hex/EtOAc); ^{1}H NMR ($CDCl_3$, 360 MHz) δ 7.2−7.4 (m, 30H), 5.84 (m, 2H), 5.70 (m, 1H), 5.55 (t, *J* = 10.4 Hz, 1H), 5.11 (dt, *J* = 1, 7.5 Hz, 1H), 4.95 (d, *J* = 10.7 Hz, 1H), 4.79 (m, 1H), 4.35−4.72 (m, 12H), 4.21 (m, 1H), 3.98 (dd, *J* = 3.4, 7.2 Hz, 1H), 3.79 (m, 2H), 3.71 (dd, *J* = 5.8, 9.4 Hz, 1H), 3.56 (m, 2H), 2.70 (m, 2H), 2.54 (m, 1H), 2.28−2.46 (m, 4H), 2.13 (dt, *J* = 5.8, 11.1 Hz, 1H); ^{13}C NMR ($CDCl_3$, 90 MHz) δ 174.2, 174.1, 138.6, 138.3, 138.2, 137.9, 137.6, 135.2, 132.4, 131.1, 128.4, 128.35, 128.30, 128.27, 128.1, 128.0, 127.8, 127.65, 127.60, 127.5, 127.3, 121.5, 82.5, 79.9, 79.1, 75.8, 75.6, 73.3, 73.0, 72.6, 71.2, 70.8, 68.0, 67.7, 33.9, 33.6, 23.9, 22.8; IR (neat) 3030 (w), 2933 (m), 2865 (m), 1742 (s), 1454 (m), 1094 (s), cm^{-1}; MS (CI, NH_3) *m*/*z* (rel intensity) 490 [$(M + NH_4)^+$, 100], 365 (38), 302 (29), 257 (30); HRMS (EI, 70 eV) calcd for $C_{30}H_{32}O_5$ 472.2250, found 472.2240. Anal. Calcd for $C_{30}H_{32}O_5$: C, 76.25; H, 6.83. Found: C, 76.32; H, 6.98.

Data for 18*E*′: R_f = 0.32 (4:1 hex/EtOAc); $[\alpha]^{23}_D$ = +63.1° (*c* = 1.27, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.2−7.4 (m, 15H), 5.88 (m, 1H), 5.46 (dd, *J* = 7.9, 16.7 Hz, 1H), 5.09 (t, *J* = 6.9 Hz, 1H), 4.51 (ABq, *J* = 12.0 Hz, Δν = 74.9 Hz, 2H), 4.48 (ABq, *J* = 12.1 Hz, Δν = 77.3 Hz, 2H), 4.42 (s, 2H), 4.19 (d, *J* = 7.8 Hz, 1H), 3.76 (s, 1H), 3.55 (dd, *J* = 6.8, 9.7 Hz, 1H), 3.44 (dd, *J* = 7.1, 9.7 Hz, 1H), 2.25−2.51 (m, 4H); ^{13}C NMR ($CDCl_3$, 90 MHz) δ 174.7, 137.95, 137.90, 137.5, 132.2, 130.1, 128.5, 128.4, 128.3, 127.9, 127.9, 127.8, 127.7, 127.6, 81.2, 79.3, 72.9, 72.7, 71.9, 70.1, 68.7, 35.7, 29.1; IR (neat) 3030 (w), 2922 (w), 2864 (m), 1738 (s), 1454 (m), 1116 (s) cm^{-1}; MS (CI, NH_3) *m*/*z* (rel intensity) 490 [$(M + NH_4)^+$, 70], 473 [$(M + H)^+$, 13], 365 (100), 275 (43), 257 (80), 198 (47), 181 (32), 108 (91), 91 (77); HRMS calcd for $C_{30}H_{32}O_5H$ [$(M + H)^+$] 473.2328, found 473.2309. Anal. Calcd for $C_{30}H_{32}O_5$: C, 76.25; H, 6.83. Found: C, 76.20; H, 7.11.

Conversion of 18*E* to 18*E*′. A mixture of **18*Z*** and **18*E*** (1.7:1, 45 mg, 0.095 mmol) was dissolved in toluene (2 mL) and warmed to reflux. After 24 h, the solution was cooled to room temperature and concentrated. ^{1}H NMR of the crude reaction mixture showed that peaks corresponding to **18*Z*** were still present, while peaks corresponding to **18*E*** had nearly dissappeared, being replaced by peaks corresponding to **18*E*′**. Chromatography (5:1 hex/EtOAc) provided 28 mg (62%) of a 10:1 mixture of **18*Z*/18*E*** followed by 16 mg (36%) of **18*E*′**. Data for **18*Z***: R_f = 0.40 (4:1 hex/EtOAc); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.2−7.4 (m, 15 H), 5.84 (m, 1H), 5.56 (t, *J* = 10.4 Hz, 1H), 4.94 (d, *J* = 10.8 Hz, 1H), 4.79 (ddd, *J* = 3.9, 5.8, 8.2 Hz, 1H), 4.69 (m, 1H), 4.67 (d, *J* = 10.8 Hz, 1H), 4.62 (d, *J* = 11.6 Hz, 1H), 4.52 (ABq, *J* = 11.8 Hz, Δν = 14.1 Hz, 2H), 4.40 (d, *J* = 11.6 Hz, 1H), 3.98 (dd, *J* = 3.7, 7.3 Hz, 1H), 3.80 (t, *J* = 9 Hz, 1H), 3.71 (dd, *J* = 5.8, 9.0 Hz, 1H), 2.70 (m, 2H), 2.33 (m, 1H), 2.14 (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 174.0, 138.7, 138.2, 138.0, 132.3, 131.1, 128.3, 128.2, 128.0, 127.9, 125.6, 127.5, 127.4, 127.3, 82.6, 79.1, 75.8, 75.6, 73.3, 70.8, 67.8, 34.0, 24.0. See above for **18*E*′** spectral data.

Methyl (*E*)-(6*R*,7*S*,8*S*)-8-Hydroxy-6,7,9-tris(benzyloxy)-4-nonenoate (19*E*) and Methyl (*Z*)-(6*R*,7*S*,8*S*)-8-Hydroxy-6,7,9-tris(benzyloxy)-4-nonenoate (19*Z*). Sodium methoxide (50 mg, 0.9 mmol) was added to a mixture of *cis* and *trans* lactones **18*Z*** and **18*E*** (1:1 mixture of isomers, 735 mg, 1.56 mmol) in CH_2Cl_2/MeOH (2:1, 12 mL) at room temperature. After 30 min, the mixture was poured into water (20 mL) and extracted with ether (2 × 40 mL). The combined organic layers were washed with brine (20 mL), dried ($MgSO_4$), and concentrated. Chromatography (4:1 hex/EtOAc) provided 310 mg (39%) of **19*Z*** as a pale yellow oil, followed by 290 mg (37%) of **19*E*** as a pale yellow oil. Data for **19*Z***: R_f = 0.21 (4:1 hex/EtOAc); $[\alpha]^{23}_D$ = +19.2° (*c* = 1.32, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 360 MHz) δ 7.2−7.4 (m, 15H, ArH), 5.69 (dt, *J* = 6.5, 11.0 Hz, 1H, H-4), 5.44 (dd, *J* = 9.7, 11.0 Hz, 1H, H-5), 4.73 (ABq, *J* =

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

11.2 Hz, $\Delta\nu$ = 130.4 Hz, 2H, OCH_2Ph), 4.52 (dd, J = 7.1, 9.7 Hz, 1H, H-6), 4.50 (ABq, J = 11.7 Hz, $\Delta\nu$ = 74.2 Hz, 2H, OCH_2-Ph), 4.44 (ABq, J = 11.9 Hz, $\Delta\nu$ = 20.4 Hz, 2H, -OCH_2Ph), 3.85 (ddd, J = 2.0, 6.3, 13.5 Hz, 1H, H-8), 3.66 (s, 3H, -OCH_3), 3.61 (dd, J = 2.0, 7.1 Hz, 1H, H-7), 3.45 (dd, J = 6.1, 9.3 Hz, 1H, H-9), 3.40 (dd, J = 6.5, 9.3 Hz, 1H, H-9), 2.51 (d, J = 7.4 Hz, 1H, -OH), 2.4 (m, 4H, H-2 and H-3); ^{13}C NMR ($CDCl_3$, 90 MHz) δ 173.4, 138.5, 138.0, 133.7, 128.4, 128.35, 128.30, 128.25, 127.9, 127.8, 127.7, 127.5, 80.4, 75.3, 73.3, 70.6, 70.0, 51.6, 33.6, 23.3; IR (neat) 3500 (br m), 3030 (m), 2919 (m), 2860 (m), 1738 (s), 1093 (s) cm $^{-1}$; MS (CI, NH_3) m/z (rel intensity) 522 [$(M + NH_4)^+$, 36], 414 (27), 289 (32), 247 (100), 108 (41), HRMS calcd. for $C_{31}H_{36}O_6NH_4$ [$(M + NH_4)^+$] 522.2856, found 522.2847. Anal. Calcd for $C_{31}H_{36}O_6$: C, 73.79; H, 7.19. Found: C, 73.66; H, 7.41.

Data for 19*E*: R_f = 0.15 (4:1 hex/EtOAc); $[\alpha]^{23}_D = -3.6°$ (c = 0.72, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 360 MHz) δ 7.19−7.36 (m, 15H, ArH), 5.75 (m, 1H, H-4), 5.50 (dd, J = 8.4, 15.7 Hz, 1H, H-5), 4.70 (ABq, J = 11.3 Hz, $\Delta\nu$ = 107 Hz, 2H, OCH_2Ph), 4.46 (ABq, J = 11.8 Hz, $\Delta\nu$ = 85.2 Hz, 2H, OCH_2Ph), 4.44 (ABq, J = 11.9 Hz, $\Delta\nu$ = 15.9 Hz, 2H, OCH_2Ph), 4.05 (dd, J = 7.0, 7.9 Hz, 1H, H-6), 3.88 (ddd, J = 2.4, 6.4, 12.9 Hz, 1H, H-8), 3.66 (s, 3H, OCH_3), 3.57 (dd, J = 2.5, 6.6 Hz, 1H, H-7), 3.42 (m, 2H, H-9), 2.45 (d, J = 6.9 Hz, 1H, OH), 2.35−2.42 (m, 4H, H-2 and H-3); ^{13}C NMR ($CDCl_3$, 90 MHz) δ 172.3, 138.4, 138.35, 138.0, 133.9, 128.4, 128.30, 128.28, 128.24, 127.8, 127.7, 127.5, 81.6, 80.3, 75.0, 73.3, 71.2, 70.3, 70.0, 51.6, 33.5, 27.6; IR (neat) 3470 (br m), 3030 (m), 2919 (m), 2860 (m), 1738 (s) cm^{-1}; MS (CI, NH_3) m/z (rel intensity) 522 [$(M + NH_4)^+$, 45], 414 (30), 289 (39), 247 (100), 168 (42), 106 (62); HRMS calcd for $C_{31}H_{36}O_6NH_4$ [$(M + NH_4)^+$] 522.2856, found 522.2859. Anal. Calcd for $C_{31}H_{36}O_6$: C, 73.79; H, 7.19. Found: C, 73.55; H, 7.40.

Methyl (*E*)-(6*R*,7*S*,8*S*)-8-Hydroxy-6,7,9-tris(benzyloxy)-4-nonenoate (19*E*) from Pure 18*E′*. Sodium methoxide (10 mg, 0.19 mmol) was added to a solution of lactone **18*E′*** (55 mg, 0.12 mmol) in CH_2Cl_2/MeOH (2:1, 1.5 mL) at room temperature. After 30 min, the mixture was poured into water (5 mL) and extracted with ether (2 × 10 mL). The combined organic layers were washed with brine (5 mL), dried ($MgSO_4$), and concentrated. Chromatography (3:1 hex/EtOAc) provided 53 mg (91%) of **19*E*** as a pale yellow oil. See above for spectral data.

Methyl (*E*)-(6*R*,7*R*,8*R*)-8-Azido-6,7,9-tris(benzyloxy)-4-nonenoate (20). Hydrazoic acid (HN_3)[44] (0.82 mL of a 1.2 M solution in benzene, 0.98 mmol) was added to a solution of the alcohol **19*E*** (248 mg, 0.491 mmol) and triphenylphosphine (PPh_3) (193 mg, 737 mmol) in benzene (2.5 mL). The resulting mixture was cooled to 5 °C and diethyl azodicarboxylate (DEAD) (128 mg, 0.737 mmol) was added in a dropwise fashion. The solution was allowed to warm slowly to room temperature. After 1.5 h, more HN_3 solution (0.40 mL, 0.48 mmol), PPh_3 (64 mg, 0.245 mmol), and DEAD (40 mg, 0.245 mmol) were added. After another 45 min, the solution was diluted with hexanes (10 mL), the resulting precipitate was filtered off, and the filtrate was concentrated without warming. [Heating or prolonged standing at room temperature resulted in an intramolecular 1,3-dipolar cycloaddition.] Chromatography (10:1 hex/EtOAc) provided 214 mg (82%) of the title compound as a colorless oil. R_f = 0.33 (5:1 hex/EtOAc); $[\alpha]^{23}_D = -24.6°$ (c = 0.24, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.2−7.4 (m, 15H), 5.69 (m, 1H), 5.50 (dd, J = 8.2, 15.5 Hz, 1H), 4.60 (ABq, J = 11.2 Hz, $\Delta\nu$ = 25.8 Hz, 2H), 4.52 (ABq, J = 11.9 Hz, $\Delta\nu$ = 13.9 Hz, 2H), 4.44 (ABq, J = 11.8 Hz, $\Delta\nu$ = 77.1 Hz, 2H), 3.92 (dd, J = 4.4, 8.1 Hz, 1H), 3.77 (m, 2H), 3.67 (dd, J = 7.3, 10.5 Hz, 1H), 3.65 (s, 3H), 3.54 (dd, J = 4.4, 6.5 Hz, 1H), 2.39 (m, 4H); ^{13}C NMR ($CDCl_3$, 90 MHz) δ 173.2, 138.2, 138.0, 137.8, 133.7, 128.4, 128.3, 128.2, 128.0, 127.7, 127.6, 81.1, 79.9, 75.0, 73.3, 70.3, 69.4, 61.5, 51.6, 33.4, 27.5; IR (neat) 3030 (m), 2920 (m), 2864 (m), 2096 (s), 1738 (s) cm^{-1}; MS (CI, NH_3) m/z (rel intensity) 502 [$(M - N_2+H)^+$, 100], 286 (15); HRMS calcd for $C_{31}H_{35}NO_5H$ [$(M - N_2+H)^+$] 502.2593, found 502.2571.

Methyl (4*R*,5*S*,6*S*,7*R*,8*R*)-8-Azido-4,5-epoxy-6,7,9-tris(benzyloxy)nonanoate (21α) and Methyl (4*S*,5*R*,6*S*,7*R*,8*R*)-8-Azido-4,5-epoxy-6,7,9-tris(benzyloxy)nonanoate (21*β*). See below for an alternate preparation of **21**α. *m*-Chloroperoxybenzoic acid (201 mg technical grade, 160 mg pure oxidant, 0.93 mmol) was added to a cold (0 °C) solution of the *trans*-azido-alkene **20** (197 mg, 0.371 mmol) in CH_2Cl_2 (1.9 mL), and the mixture was allowed to warm slowly to room temperature. After 24 h, the mixture was diluted with ether (10 mL) and washed with 1 M NaOH (2 × 5 mL), 10% $NaHCO_3$ (5 mL), and brine (5 mL) and then dried ($MgSO_4$) and concentrated. Chromatography (6:1 hex/EtOAc) provided 135 mg (67%) of an inseparable mixture of **21**α and **21***β* (1:2 based on ^{1}H and ^{13}C NMR integration) as a colorless oil. The stereochemical assignment of these epoxides was made by conversion to the indolizidines **24** and **25** (see below). R_f = 0.20 (5:1 hex/EtOAc); ^{1}H NMR ($CDCl_3$, 300 MHz, α indicates **21**α, *β* indicates **21***β*, integration α:*β* = 1:2) δ 7.2−7.4 (m, 15Hα and 15H*β*), 4.83 (d, J = 11.7 Hz, 1Hα), 4.68 (d, J = 11.2 Hz, 1H*β*) 4.5−4.65 (m, 5Hα and 5H*β*), 3.78−3.87 (m, 2Hα and 2H*β*), 3.6−3.75 (m, 2Hα and 2H*β*), 3.67 (s, 3H*β*), 3.66 (s, 3Hα), 3.31 (dd, J = 2.7, 6.8 Hz, 1H*β*), 3.26 (dd, J = 3.2, 7.1 Hz, 1Hα), 3.05 (dd, J = 2.2, 7.1 Hz, 1Hα), 2.86 (m, 1Hα and 1H*β*), 2.39 (t, J = 7.4 Hz, 2Hα), 2.38 (t, J = 7.4 Hz, 2H*β*), 1.85−2.02 (m, 1Hα and 1H*β*), 1.5−1.7 (m, 1Hα and 1H*β*); ^{13}C NMR ($CDCl_3$, 90 MHz, α indicates **21**α, *β* indicates **21***β*) δ 173.0, 137.9, 137.8, 137.7, 137.6, 137.4, 128.8, 128.41, 128.36, 128.32, 128.2, 128.1, 128.0, 127.9, 127.81, 127.78, 127.75, 127.66, 127.62, 79.6 (α), 78.9 (α), 78.2 (*β*), 78.2 (*β*), 74.9 (*β*), 74.2 (α), 73.4 (α), 73.2 (*β*), 73.0 (*β*), 72.3 (α), 69.6 (*β*), 69.3 (α), 61.1 (α), 60.6 (*β*), 59.2 (α), 58.3 (*β*), 56.3 (*β*), 53.3 (α), 51.7 (*β*), 29.9 (α), 29.8 (*β*), 26.6 (*β*), 26.5 (α); IR (neat) 3030 (m), 2920 (m), 2867 (m), 2098 (s), 1738 (s) cm^{-1}; MS (CI, NH_3) m/z (rel intensity) 563 [$(M + NH_4)^+$, 42], 518 (100), 488 (27), 402 (24), 108 (24); HRMS calcd for $C_{31}H_{35}N_3O_6$-NH_4 [$(M + NH_4)^+$] 563.2870, found 563.2889. Anal. Calcd for $C_{31}H_{35}N_3O_6$: C, 68.24; H, 6.47; N, 7.70. Found: C, 68.17; H, 6.47; N, 7.64. See below for the spectra of pure **21**α.

(1*R*,2*R*,3*R*,8*S*,8a*S*)-3-[(Benzyloxy)methyl]-1,2-bis(benzyloxy)-8-hydroxyindolizidin-5-one (22) and (1*R*,2*R*,3*R*,-8*R*,8a*R*)-3-[(Benzyloxy)methyl]-1,2-bis(benzyloxy)-8-hydroxyindolizidin-5-one (23). See below for an alternate preparation of **23**. Palladium hydroxide on carbon (25 mg) was added to a solution of the azido epoxides **21***β* and **21**α (2:1 mixture of diastereomers, 122 mg, 0.224 mmol) in MeOH/EtOAc (1:1, 5 mL). The flask was evacuated (aspirator) and purged with hydrogen three times. The mixture was stirred under a balloon of hydrogen for 4 h, and then the hydrogen was evacuated and the mixture was filtered, rinsing with MeOH (5 mL). The filtrate was concentrated, and the residue was redissolved in MeOH (15 mL). Sodium methoxide (15 mg, 0.48 mmol) was added, and the mixture was warmed to reflux. After 24 h, the mixture was cooled to room temperature and concentrated. Chromatography (100:1 $CHCl_3$/MeOH) provided 86 mg (79%) of the inseparable lactams **22** and **23** (2:1 mixture based on ^{1}H NMR integration) as an oil. The stereochemistry of these compounds was based on the analysis of indolizidines **24** and **25** (see below). R_f = 0.38 (20:1 $CHCl_3$/MeOH); ^{1}H NMR ($CDCl_3$, 300 MHz) (A indicates minor isomer **23**, B indicates major isomer **22**) δ 7.2−7.4 [m, (15 H_A + 15 H_B)], 4.69 (d, J = 11.8 Hz, 1H_A), 4.65 (d, J = 12.1 Hz, 1H_B), 4.63 (d, J = 11.9 Hz, 1H_B), 4.62 (d, J = 11.8 Hz, 1H_A), 4.59 (d, J = 11.6 Hz, 1H_A), 4.54 (s, 2H_A), 4.48 (d, J = 12.0 Hz, 1H_B), 4.46 (d, J = 11.9 Hz, 1H_B), 4.43 (d, J = 11.6 Hz, 1H_A), 4.33 (dt, J = 3.4, 6.0 Hz, 1H_A), 4.26 (m, 1H_B), 4.24 (d, J = 11.9 Hz, 1H_B), 4.23 (dd, J = 3.4, 4.8 Hz, 1H_A), 4.17 (dd, J = 4.4, 8.6 Hz, 1H_B), 4.16 (s, 1H_B), 4.05 (m, 1H_B), 4.00 (d, J = 3.8 Hz, 1H_B), 3.96 (dd, J = 4.8, 8.2 Hz, 1H_A), 3.72 (dd, J = 6.2, 9.4 Hz, 1H_A), 3.70−3.76 (m, 1H_A,), 3.64 (dd, J = 3.6, 9.4 Hz, 1H_A), 3.61 (dd, J = 3.8, 9.0 Hz, 1H_B), 3.45 (t, J = 8.3 Hz, 1H_A), 3.29 (dd, J = 8.7, 10.5 Hz, 1H_B), 2.67 (br d, J = 2.6 Hz, 1H_A) 2.48 (ddd, J = 2.5, 6.7, 18.3 Hz, 1H_A), 2.25−2.45 (m, 2H_A and 2H_B), 2.17 (br d, J = 3.0 Hz, 1H_B), 1.95−2.10 (m, 1H_A and 1H_B), 1.65−1.80 (m, 1H_A and 1H_B); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 169.3 (*A*), 167.8 (*B*), 138.3, 137.51, 137.47, 128.5, 128.4, 128.32, 128.28, 128.20, 128.0, 127.9, 127.8, 127.7, 127.63, 127.59, 127.44, 87.7 (*B*), 83.2 (*B*), 80.1 (*A*), 78.9 (*A*), 73.3 (*B*), 73.0 (*A*), 71.9 (*B*), 71.4 (*A*), 70.9 (*A*), 70.2 (*B*), 68.7 (*B*), 66.9 (*A*), 66.3 (*A*), 65.6 (*B*), 64.8 (*A*), 62.6 (*A*), 61.0 (*B*), 30.6 (*A*), 30.0 (*A*), 29.7 (*B*), 29.1 (*B*); IR (neat) 3362 (br m), 3031 (m), 2936 (m), 2867 (m), 1651 (s), 1621

(s), 1413 (s) cm^{-1}; MS (CI, NH_3) *m/z* (rel intensity) 488 [$(M + H)^+$, 100], 396 (2), 108 (2); HRMS (CI, CH_4 and NH_3) calcd for $C_{30}H_{33}NO_5H$ [$(M + H)^+$] 488.2437, found 488.2426. See below for spectra of pure **23**.

(1*R*,2*R*,3*R*,8*S*,8a*S*)-3-[(Benzyloxy)methyl]-1,2-bis(benzyloxy)-8-hydroxyindolizidine (24) and (1*R*,2*R*,3*R*,8*R*,8a*R*)-3-[(Benzyloxy)methyl]-1,2-bis(benzyloxy)-8-hydroxyindolizidine (25). Borane−methyl sulfide complex (0.31 mL of a 2 M solution in THF, 0.62 mmol) was added to a cool (0 °C) solution of the lactams **22** and **23** (2:1 mixture of diastereomers, 71 mg, 0.15 mmol) in THF (3.9 mL). After 30 min, the mixture was warmed to room temperature. After 6 h, the reaction was quenched by the slow addition of EtOH (2 mL). After 30 min, the mixture was concentrated, and the residue was redissolved in EtOH (4 mL) and warmed to reflux. After 2 h, the mixture was cooled to room temperature and concentrated. Chromatography (66:33:1 to 50:50:1 hex/EtOAc/MeOH) provided 44 mg (64%) of major diastereomer **24** as a pale yellow oil, followed by 22 mg (32%) of minor diastereomer **25** as a pale yellow oil. Data for **24**: $R_f = 0.46$ (1:1 hex/EtOAc); $[\alpha]^{23}_D = +46.9°$ ($c = 0.52$, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz) δ 7.2−7.4 (m, 15H, ArH), 4.52 (ABq, $J = 12.3$ Hz, $\Delta\nu = 78.5$ Hz, 2H, OCH_2Ph), 4.53 (ABq, $J = 12.0$ Hz, $\Delta\nu = 15.7$ Hz, 2H, -OCH_2Ph), 4.48 (s, 2H, OCH_2Ph), 3.92 (d, $J = 4.2$ Hz, 1H, H-1), 3.89 (m, 1H, H-8), 3.72 (d, $J = 4.0$ Hz, 1H, H-2), 3.64 (dd, $J = 5.3$, 9.7 Hz, 1H, H-9a), 3.52 (dd, $J = 6.4$, 9.7 Hz, 1H, H-9b), 3.13 (app dt, $J = \sim3$, 10.7 Hz, 1H, H-5eq), 2.64 (app dd, $J = 4$, 6 Hz, 1H, H-3), 2.17 (dd, $J = 4.2$, 9.0 Hz, 1H, H-8a), 2.03 (m, 1H, H-7eq), 1.96 (dd, $J = 3.8$, 10.9 Hz, 1H, H-5ax), 1.52−1.71 (m, 2H, H-6eq and H-6ax), 1.35 (d, $J = 4.0$ Hz, 1H, -OH), 1.18 (app qd, $J = 5.5$, 12 Hz, 1H, H-7ax); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 138.3, 138.1, 128.5, 128.3, 128.2, 128.0, 127.8, 127.7, 127.5, 127.4, 85.1, 80.2, 73.2, 72.8, 71.4, 71.3, 71.2, 70.8, 66.8, 51.8, 33.0, 24.2; IR (neat) 3440 (br m), 3029 (m), 2935 (s), 2856 (s), 2784 (m), 1605 (w) cm^{-1}; MS (CI, NH_3) *m/z* (rel intensity) 474 [$(M + H)^+$, 61], 352 (100), 91 (48); HRMS calcd for $C_{30}H_{35}NO_4H$ [$(M + H)^+$] 474.2644, found 474.2633.

Data for 25: $R_f = 0.23$ (1:1 hex/EtOAc); $[\alpha]^{23}_D = -19.2°$ ($c = 0.13$, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz) δ 7.2−7.4 (m, 15H, ArH), 4.52 (ABq, $J = 12.0$ Hz, $\Delta\nu = 50.7$ Hz, 2H, OCH_2Ph), 4.56 (ABq, $J = 11.9$ Hz, $\Delta\nu = 15.2$ Hz, 2H, OCH_2Ph), 4.55 (s, 2H, OCH_2Ph), 3.99 (dd, $J = 3.0$, 5.8 Hz, 1H, H-1), 3.92 (app t, $J = 2.7$ Hz, 1H, H-2), 3.64 (dd, $J = 5.0$, 9.4 Hz, 1H, H-9a), 3.52 (m, 2H, H-8 and H-9b), 3.39 (ddd, $J = 2.2$, 4.6, 4.8 Hz, 1H, H-3), 2.94 (dt, $J = \sim3$, 11.5 Hz, 1H, H-5eq), 2.63 (dd, $J = 3.9$, 8.8 Hz, 1H, H-8a), 2.51 (ddd, $J = 6.5$, 9.0, 11.6 Hz, 1H, H-5ax), 1.98−2.10 (m, 2H, -OH and H-7eq), 1.62 (m, 2H, H-6eq and H-6ax), 1.21 (m, 1H, H-7ax); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 138.10, 138.05, 138.00, 128.4, 128.3, 128.1, 127.9, 127.6, 87.9, 85.7, 73.4, 71.5, 71.3, 68.9, 68.6, 65.2, 46.2, 33.0, 22.8; IR (neat) 3440 (br w), 3029 (m), 2926 (s), 2856 (s), 1604 (w), 1454 (s) cm^{-1}; MS (CI, NH_3) *m/z* (rel intensity) 474 [$(M + H)^+$, 57], 352 (100), 91 (17); HRMS calcd for $C_{30}H_{35}NO_4H$ [$(M + H)^+$] 474.2644, found 474.2638.

(1*R*,2*R*,3*R*,8*S*,8a*S*)-3-(Hydroxymethyl)-1,2,8-trihydroxyindolizidine [Homoalexine, (7)]. Palladium on carbon (10%, 20 mg) and 6 N HCl (4 drops) were added to a solution of the indolizidine **24** (40 mg, 0.084 mmol) in MeOH (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 20 h, and then the hydrogen was evacuated and the mixture was filtered through a cotton plug, rinsing with MeOH (2 mL). The filtrate was concentrated, and the residue was dissolved in water and stirred with Dowex 1 × 8 200 $^-$OH ion exchange resin (0.5 g dry resin). After 30 min, the mixture was filtered and the filtrate was concentrated on a rotary evaporator. Chromatography (5:1 to 3:1 $CHCl_3$/MeOH gradient, SiO_2) provided 15 mg (88%) of the title compound as a colorless oil. $R_f = 0.42$ (2:1 $CHCl_3$/MeOH); $[\alpha]^{23}_D = +37.3°$ ($c = 0.79$, MeOH); ^1H NMR (D_2O, 300 MHz) δ 4.11 (d, $J = 3.8$ Hz, 1H), 3.87 (d, $J = 4.6$ Hz, 1H), 3.70−3.83 (m, 3H), 3.21 (br d, $J = 11.1$ Hz, 1H), 2.50 (br s, 1H), 2.34 (br d, $J = 5.8$ Hz, 1H), 2.04−2.21 (m, 2H), 1.79 (br d, $J = 14$ Hz, 1H), 1.56 (qt, $J = 4$, 13.2 Hz, 1H), 1.31 (qd, $J = 4.2$, 12.4 Hz, 1H); ^{13}C NMR (D_2O, CH_3OH int std, 75 MHz) δ 79.3, 75.4, 73.9, 72.2, 65.6, 60.9, 51.5, 32.3, 23.1; IR (neat) 3330 (br s), 2940 (m), 2858 (w), 2807 (w), 1650 (w) cm^{-1}; MS (CI, NH_3) *m/z* (rel intensity) 204 [$(M + H)^+$, 100], 172 (9); HRMS calcd for $C_9H_{17}NO_4$ [$(M + H)^+$] 204.1236, found 204.1238.

(1*R*,2*R*,3*R*,8*R*,8a*R*)-3-(Hydroxymethyl)-1,2,8-trihydroxyindolizidine [8-Epihomoaustraline, (8)]. Palladium on carbon (10%, 8 mg) and 6 N HCl (4 drops) were added to a solution of the indolizidine **25** (16.7 mg, 0.035 mmol) in MeOH (2 mL). The flask was evacuated (aspirator) and purged with hydrogen three times. The mixture was stirred under a balloon of hydrogen at room temperature for 20 h, and then the hydrogen was evacuated and the mixture was filtered through a cotton plug, rinsing with MeOH (2 mL). The filtrate was concentrated, and the residue was dissolved in water and stirred with Dowex 1 × 8 200 $^-$OH ion exchange resin (0.5 g dry resin). After 30 min, the mixture was filtered and the filtrate was concentrated on a rotary evaporator. Chromatography (5:1 to 3:1 $CHCl_3$/MeOH gradient, SiO_2) provided 5.3 mg (74%) of the title compound as a colorless oil. $R_f = 0.35$ (2:1 $CHCl_3$/MeOH); $[\alpha]^{23}_D = -25.2°$ ($c = 0.63$, MeOH); ^1H NMR (D_2O, 300 MHz) δ 4.03 (app t, $J = 4$ Hz, 1H), 3.96 (app t, $J = 4$ Hz, 1H), 3.80 (dd, $J = 4.9$, 12.0 Hz, 1H), 3.73 (dd, $J = 5.0$, 12.0 Hz, 1H), 3.62 (dt, $J = 4.5$, 10.8 Hz, 1H), 3.05 (dd, $J = 4.6$, 9.2 Hz, 1H), 2.97 (br d, $J = 12.9$ Hz, 1H), 2.56−2.74 (m, 2H), 2.02 (m, 1H), 1.55−1.70 (m, 2H), 1.32 (app qd, $J = 5.4$, 11.7 Hz, 1H); ^{13}C NMR (D_2O, CH_3OH int std, 75 MHz) δ 80.3, 79.9, 70.7, 68.6, 67.6, 60.1, 45.6, 32.3, 20.9; IR (neat) 3225 (br s), 2932 (m), 2863 (m), 1584 (w) cm^{-1}; MS (CI, NH_3) *m/z* (rel intensity) 204 [$(M + H)^+$,100], 172 (6); HRMS calcd for $C_9H_{17}NO_4H$ [$(M + H)^+$] 204.1236, found 204.1241.

(5*R*,6*S*,7*R*,8*S*,9*S*)-5,6-Epoxy-7,8-bis(benzyloxy)-9-[(benzyloxy)methyl]-1-oxa-2-oxocyclononane (26). *m*-Chloroperoxybenzoic acid (146 mg technical grade, 117 mg pure oxidant, 0.68 mmol) was added to a cold (0 °C) solution of ***18E′*** (160 mg, 0.339 mmol) in CH_2Cl_2 (1.7 mL), and the mixture was allowed to warm slowly to room temperature. After 12 h, the mixture was diluted with ether (10 mL) and washed with 1 M NaOH (2 × 5 mL), 10% $NaHCO_3$ (5 mL), and brine (5 mL) and then dried ($MgSO_4$) and concentrated. Chromatography (8:1 hex/EtOAc) provided 145 mg (88%) of the title compound as a colorless oil. $R_f = 0.47$ (2:1 hex/EtOAc); $[\alpha]^{23}_D = -13.5°$ ($c = 0.95$, $CHCl_3$); ^1H NMR ($CDCl_3$, 360 MHz) δ 7.2−7.4 (m, 15H), 5.22 (t, $J = 6.6$ Hz, 1H), 4.64 (ABq, $J = 12.0$ Hz, $\Delta\nu = 72.0$ Hz, 2H), 4.44 (s, 2H), 4.40 (ABq, $J = 11.8$ Hz, $\Delta\nu = 65.2$ Hz, 2H), 3.74 (app s, 1H), 3.59 (dd, $J = 6.4$, 9.7 Hz, 1H), 3.48 (dd, $J = 7.3$, 9.7 Hz, 1H), 3.33 (dd, $J = 1.4$, 6.7 Hz, 1H), 3.14 (dt, $J = 3$, 9.9 Hz, 1H), 2.68 (dd, $J = 2.6$, 6.7 Hz, 1H), 2.61 (ddd, $J = 6.0$, 11.2, 13.2 Hz, 1H), 2.51 (m, 1H), 2.43 (ddd, $J = 2$, 5.7, 11.2 Hz, 1H), 1.25 (ddt, $J = 4.5$, 8.4, 10.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 90 MHz) δ 172.9, 137.7, 127.6, 137.2, 128.3, 128.1, 128.0, 127.82, 127.79, 127.67, 79.7, 78.1, 73.0, 72.2, 71.9, 71.0, 68.2, 58.4, 51.7, 32.2, 28.7; IR (neat) 3030 (w), 2868 (m), 1741 (s), 1099 (s), 1059 (s) cm^{-1}; MS (CI, NH_3) *m/z* (rel intensity) 506 [$(M + NH_4)^+$, 100), 489 [$(M + H)^+$, 6], 397 (27), 181 (21), 108 (36), 91 (67); HRMS (CI, NH_3) calcd for $C_{30}H_{32}O_6NH_4$ [$(M + NH_4)^+$] 506.2543, found 506.2535. Anal. Calcd for $C_{30}H_{32}O_6$: C, 73.75; H, 6.60. Found: C, 73.72; H, 6.68.

Methyl (4*R*,5*S*,6*R*,7*R*,8*S*)-4,5-Epoxy-8-hydroxy-6,7,9-tris(benzyloxy)nonanoate (27). Sodium bicarbonate (36 mg, 0.43 mmol) was added to a solution of the epoxy-lactone **26** (105 mg, 0.215 mmol) in MeOH/THF (2:1, 6.5 mL). After 3 h at room temperature, the mixture was poured into water (10 mL) and extracted with ether (2 × 25 mL). The combined organic layers were washed brine (10 mL) and then dried ($MgSO_4$) and concentrated. Chromatography (4:1 to 3:1 hex/EtOAc gradient) provided 100 mg (89%) of the title compound as a colorless oil. $R_f = 0.27$ (2:1 hex/EtOAc); $[\alpha]^{23}_D = +14.6°$ ($c = 0.65$, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz) δ 7.2−7.4 (m, 15H), 4.68 (ABq, $J = 11.8$ Hz, $\Delta\nu = 69.8$ Hz, 2H), 4.58 (ABq, $J = 11.2$ Hz, $\Delta\nu = 40.8$ Hz, 2H), 4.46 (ABq, $J = 11.9$ Hz, $\Delta\nu = 14.8$ Hz, 2H), 4.04 (ddd, $J = 2.3$, 6.2, 13.4 Hz, 1H), 3.68 (dd, $J = 2.7$, 5.5 Hz, 1H), 3.64 (s, 3H), 3.44 (m, 2H), 3.37 (dd, $J = 5.3$, 6.8 Hz, 1H), 3.06 (dd, $J = 2.1$, 6.9 Hz, 1H), 2.91 (ddd, $J = 2.1$, 4.4, 6.5 Hz, 1H), 2.49 (d, $J = 7.4$ Hz, 1H), 2.42 (t, $J = 7.5$ Hz, 2H), 1.96 (ddt, $J = 4.5$, 7.6, 14.4 Hz, 1H), 1.74 (app sextet, $J = 7.2$ Hz, 1H); ^{13}C NMR ($CDCl_3$, 90 MHz) δ 173.2, 138.0,

137.9, 137.8, 128.4, 128.3, 128.2, 127.9, 127.8, 127.7, 127.6, 80.0, 78.4, 74.4, 73.2, 72.4, 71.1, 69.3, 58.8, 53.9, 51.7, 30.0, 26.6; IR (neat) 3500 (w), 3030 (m), 2922 (m), 2865 (m), 1738 (s) cm^{-1}; MS (CI, NH_3) *m/z* (rel intensity) 538 [$(M + NH_4)^+$, 35], 521 [$(M + H)^+$, 29], 506 (100), 397 (25), 181 (27), 108 (41), 91 (69); HRMS (CI, NH_3) calcd for $C_{31}H_{36}O_7H$ [$(M + H)^+$] 521.2539, found 521.2531. Anal. Calcd for $C_{31}H_{36}O_7$: C, 71.52; H, 6.97. Found: C, 71.62; H, 7.03.

Methyl (4*R*,5*S*,6*S*,7*R*,8*R*)-8-Azido-4,5-epoxy-6,7,9-tris(benzyloxy)nonanoate (21α). See above for an alternate preparation of **21**α. Hydrazoic acid (HN_3)[44] (0.29 mL of a 1.2 M solution in benzene, 0.35 mmol) was added to a solution of the epoxy alcohol **27** (90 mg, 0.17 mmol) and triphenylphosphine (PPh_3) (68 mg, 0.26 mmol) in benzene (0.5 mL). The resulting mixture was cooled to 5 °C, and diethyl azodicarboxylate (DEAD) (45 mg, 0.26 mmol) was added in a dropwise fashion. The solution was allowed to warm slowly to room temperature. After 1.5 h, the mixture was concentrated. Chromatography (10:1 hex/EtOAc) provided 78 mg (85%) of the title compound as a colorless oil. $R_f = 0.25$ (5:1 hex/EtOAc); $[\alpha]^{23}_D = -27.3°$ ($c = 0.97$, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz) δ 7.2−7.4 (m, 15H), 4.70 (ABq, $J = 11.7$ Hz, $\Delta\nu = 82.5$ Hz, 2H), 4.56 (ABq, $J = 11.3$ Hz, $\Delta\nu = 18.5$ Hz, 2H), 4.53 (s, 2H), 3.82 (m, 2H), 3.71 (m, 1H), 3.66 (s, 3H), 3.64 (m, 1H), 3.26 (dd, $J = 3.2$, 7.1 Hz, 1H), 3.05 (dd, $J = 2.2$, 7.1 Hz, 1H), 2.83 (ddd, $J = 2.3$, 3.8, 7.1 Hz, 1H), 2.39 (t, $J = 7.4$ Hz, 2H), 1.97 (ddt, $J = 3.7$, 7.7, 14.4 Hz, 1H), 1.56 (app sextet, $J = 7.2$ Hz, 1H); ^{13}C NMR ($CDCl_3$, 90 MHz) δ 173.1, 137.8, 137.6, 137.4, 128.5, 128.3, 128.2, 128.0, 127.8, 127.7, 79.6, 78.9, 74.2, 73.4, 72.4, 69.3, 61.1, 59.2, 53.3, 51.7, 30.0, 26.5; IR (neat) 3030 (m), 2950 (m), 2866 (m), 2099 (s), 1732 (s), 1092 (s) cm^{-1}; MS (CI, NH_3) *m/z* (rel intensity) 518 [$(M - N_2 + H)^+$, 37], 486 (67), 402 (88), 294 (40), 186 (100), 134 (71), 108 (77), 106 (73), 91 (74), 80 (41); HRMS (CI, NH_3) calcd for $C_{31}H_{35}NO_6$ [$(M - N_2 + H)^+$] 518.2543, found 518.2540. Anal. Calcd for $C_{31}H_{35}N_3O_6$: C, 68.24; H, 6.47; N, 7.70. Found: C, 68.26; H, 6.60; N, 7.69.

(1*R*,2*R*,3*R*,8*R*,8a*R*)-3-[(Benzyloxy)methyl]-1,2-bis(benzyloxy)-8-hydroxyindolizidin-5-one (23). See above for an alternate preparation of **23**. Palladium hydroxide on carbon (20 mg) was added to a solution of the azido epoxide **21**α (62 mg, 0.12 mmol) in MeOH/EtOAc (1:1, 4 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 4 h, and then the hydrogen was evacuated and the mixture was filtered, rinsing with MeOH (5 mL). The filtrate was concentrated, and the resulting residue was redissolved in methanol (10 mL). Sodium methoxide (10 mg, 0.18 mmol) was added, and the mixture was warmed to reflux. After 24 h, the mixture was cooled to room temperature and concentrated. Chromatography (25:25:1 hex/EtOAc/EtOH) provided 48 mg (82%) of the title compound as a colorless oil. $R_f = 0.10$ (25:25:1 hex/EtOAc/EtOH); $[\alpha]^{23}_D = -16.8°$ ($c = 1.12$, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz) δ 7.2−7.4 (m, 15H, ArH), 4.65 (ABq, $J = 11.8$ Hz, $\Delta\nu = 23.3$ Hz 2H, OCH_2Ph), 4.53 (s, 2H, OCH_2Ph), 4.51 (ABq, $J = 11.6$ Hz, $\Delta\nu = 46.9$ Hz, 2H, OCH_2Ph), 4.33 (app quintet, $J = 3$ Hz, 1H, H-3), 4.22 (t, $J = 4$ Hz, 1H, H-2), 3.96 (dd, $J = 4.8$, 8.1 Hz, 1H, H-1), 3.72 (m, 2H, H-8 and H-9a), 3.64 (dd, $J = 3.6$, 9.5 Hz, 1H, H-9b), 3.44 (t, $J = 8.2$ Hz, 1H, H-8a), 2.48 (ddd, $J = 2.3$, 6.3, 17.9 Hz, 1H, H-6eq), 2.38 (d, $J = 2.1$ Hz, 1H, -OH), 2.31 (ddd, $J = 6.3$, 11.6, 17.9 Hz, 1H, H-6ax), 2.03 (m, 1H, H-7eq), 1.75 (dt, $J = 6.4$, 12 Hz, 1H, H-7ax); ^{13}C NMR ($CDCl_3$, 90 MHz) δ 167.7, 138.0, 137.6, 137.4, 128.6, 128.45, 128.40, 128.1, 128.0, 127.9, 127.7, 87.7, 83.2, 73.3, 72.0, 71.9, 70.5, 68.8, 65.2, 61.0, 29.7, 28.9; IR (neat) 3360 (br m), 3030 (w), 2867 (m), 1621 (s), 1099 (s) cm^{-1}; MS (CI, NH_3) *m/z* (rel intensity) 488 [$(M + H)^+$, 100], 108 (6), 91 (8); HRMS (CI, CH_4 and NH_3) calcd for $C_{30}H_{33}NO_5H$ [$(M + H)^+$] 488.2437, found 488.2431.

Epoxy-Lactone 28 and Epoxy-Alcohol 29. To determine whether the atropisomerism of **18*E*** and **18*E*′** was due to rotation of the alkene or the ester faces of **18*E*** and **18*E*′**, the following study was carried out. First, the *trans*-hydroxyalkene **19*E*** was epoxidized: *m*-Chloroperoxybenzoic acid (68 mg technical grade, 54 mg pure oxidant, 0.32 mmol) and sodium bicarbonate (44 mg, 0.53 mmol) were added to a cold (0 °C) solution of **19*E*** (53 mg, 0.11 mmol) in CH_2Cl_2 (0.5 mL), and the mixture was allowed to warm slowly to room temperature. After 24 h, the mixture was diluted with ether (5 mL) and washed with 1 M NaOH (2 × 2 mL), 10% $NaHCO_3$ (2 mL), and brine (2 mL) and then dried ($MgSO_4$) and concentrated. Examination of the ^1H NMR spectra of the crude reaction mixture showed the presence of at least four compounds in roughly a 1:2:3:6 ratio based on integration of the methyl ester singlets. The two major compounds are believed to be the two diastereomeric *trans*-epoxides **27** and **29*E***, while the minor compounds are most likely cyclic ethers resulting from the intramolecular opening of the epoxide by the alcohol. Comparison of the ^1H NMR spectra of these epoxides with that of pure **27** (prepared above as shown in Scheme 4) showed that **27** was indeed present in the mixture as the minor epoxide product. Key resonances included δ 4.80 (d), 3.64 (s), 3.37 (dd), 3.06 (dd), 2.91 (ddd). The major component of the mixture was assumed to be the other diastereomeric *trans*-epoxide **29*E***. A mixture of **18*Z***/**18*E*** was then subjected to *m*-CPBA epoxidation followed by lactone-opening with methanol: *m*-Chloroperoxybenzoic acid (20 mg technical grade, 16 mg pure oxidant, 0.09 mmol) was added to a cold (0 °C) solution of a mixture of **18*Z*** and **18*E*** (1.3:1, 13 mg, 0.03 mmol) in CH_2Cl_2 (0.5 mL), and the mixture was allowed to warm slowly to room temperature. After 24 h, the mixture was diluted with ether (5 mL) and washed with 1 M NaOH (2 × 3 mL), 10% $NaHCO_3$ (2 mL), and brine (2 mL) and then dried ($MgSO_4$) and concentrated to give 13 mg of a colorless oil. The crude epoxy-lactones **28*E*** and **28*Z*** were dissolved in MeOH/CH_2Cl_2 (2:1, 2 mL) and treated with $NaHCO_3$. After 12 h, brine (5 mL) was added, and the mixture was extracted with ether (3 × 10 mL) and then dried ($MgSO_4$) and concentrated. Attempted silica gel chromatography led to significant decomposition in earlier runs. The ^1H NMR spectrum of the crude hydroxy ester mixture was compared to those of pure **27** and the epoxides **27** and **29*E*** obtained from epoxidation of **19*E*** (see above). No peaks corresponding to **27** could be identified in the spectrum, while peaks corresponding to the other *trans*-epoxide **29*E*** were present. Key resonances included δ 4.75 (d), 3.45 (m), 2.91 (m). These data indicate that the atropisomerism of **18*E***/**18*E*′** involves a conformational change of the molecule that results in the presentation of different faces of the alkene. An additional change in the ester configuration cannot be ruled out.

Methyl (*Z*)-(6*R*,7*R*,8*R*)-8-Azido-6,7,9-tris(benzyloxy)-4-nonenoate (30). Hydrazoic acid (HN_3)[44] (0.78 mL of a 1.2 M solution in benzene, 0.93 mmol) was added to a solution of the alcohol **19*Z*** (235 mg, 0.466 mmol) and triphenylphosphine (PPh_3) (183 mg, 0.698 mmol) in benzene (2.5 mL). The resulting mixture was cooled to 5 °C and diethyl azodicarboxylate (DEAD) (121 mg, 0.698 mmol) was added in a dropwise fashion. The solution was allowed to warm slowly to room temperature. After 1.5 h, more HN_3 solution (0.40 mL, 0.48 mmol), PPh_3 (64 mg, 0.245 mmol), and DEAD (40 mg, 0.245 mmol) were added. After another 45 min, the solution was diluted with hexanes (10 mL), the resulting precipitate was filtered off, and the filtrate was concentrated without warming. [Heating or prolonged standing at room temperature resulted in an intramolecular 1,3-dipolar cycloaddition.] Chromatography (10:1 hex/EtOAc) provided 210 mg (85%) of the title compound as a colorless oil. $R_f = 0.37$ (5:1 hex/EtOAc); $[\alpha]^{23}_D = -26.0°$ ($c = 0.30$, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz) δ 7.2−7.4 (m, 15H), 5.63 (m, 1H), 5.54 (dd, $J = 9.2$, 11.1 Hz, 1H), 4.62 (ABq, $J = 11.2$ Hz, $\Delta\nu = 42.2$ Hz, 2H), 4.52 (ABq, $J = 12.1$ Hz, $\Delta\nu = 13.4$ Hz, 2H), 4.48 (ABq, $J = 11.8$ Hz, $\Delta\nu = 90.4$ Hz, 2H), 4.38 (dd, $J = 4.3$, 9.1 Hz, 1H), 3.81 (m, 2H), 3.68 (dd, $J = 6.8$, 10.1 Hz, 1H), 3.66 (s, 3H), 3.55 (dd, $J = 4.2$, 6.8 Hz, 1H), 2.25−2.40 (m, 4H); ^{13}C NMR ($CDCl_3$, 90 MHz) δ 173.0, 138.2, 137.9, 137.8, 132.9, 128.5, 128.4, 128.3, 128.2, 128.0, 127.7, 127.6, 81.1, 75.1, 74.2, 73.4, 70.4, 69.7, 61.6, 51.6, 33.7, 23.3; IR (neat) 3030 (m), 2923 (m), 2864 (m), 2096 (s), 1738 (s), 1091 (s) cm^{-1}; MS (CI, NH_3) *m/z* (rel intensity) 502 [$(M - N_2 + H)^+$, 100], 286 (12); HRMS calcd for $C_{31}H_{35}NO_5H$ [$(M - N_2 + H)^+$] 502.2593, found 502.2593.

Methyl (4*S*,5*S*,6*S*,7*R*,8*S*)-8-Azido-4,5-epoxy-6,7,9-tris(benzyloxy)nonanoate (31α) and Methyl (4*R*,5*R*,6*S*,7*R*,8*S*)-8-Azido-4,5-epoxy-6,7,9-tris(benzyloxy)nonanoate (31*β*). *m*-Chloroperoxybenzoic acid (199 mg technical grade, 160 mg of pure oxidant, 0.92 mmol) was added to a cold (0 °C) solution of the *cis*-azido-alkene **30** (195 mg, 0.368 mmol) in CH_2Cl_2 (1.8 mL), and the mixture was allowed to warm slowly to room temperature. After 24 h, the mixture was diluted with ether (10 mL) and washed with 1 M NaOH (2 × 5 mL), 10% $NaHCO_3$ (5 mL), and brine (5 mL) and then dried ($MgSO_4$) and concentrated. Chromatography (10:1 hex/EtOAc) provided 150 mg (75%) of an inseparable mixture of **31**α and **31***β* (1.4:1 based on ^{1}H NMR integration) as a colorless oil. The stereochemical assignment of these epoxides was made by conversion to the indolizidines **34** and **35** (see below). R_f = 0.23 (5:1 hex/EtOAc); ^{1}H NMR ($CDCl_3$, 300 MHz, α indicates **31**α, *β* indicates **31***β*) *δ* 7.2−7.4 (m, 15Hα and 15H*β*), 4.86 (d, *J* = 11.7 Hz, 1Hα), 4.75 (d, *J* = 11.2 Hz, 1H*β*), 4.65 (d, *J* = 11.6 Hz, 1H*β*), 4.63 (d, *J* = 11.5 Hz, 1Hα), 4.45−4.58 (m, 4Hα and 4H*β*), 3.65−3.95 (m, 4Hα and 4H*β*), 3.71 (s, 3H*β*), 3.69 (s, 3Hα), 3.53 (m, 1Hα and 1H*β*), 3.41 (dd, *J* = 2.3, 8.0 Hz, 1Hα), 3.24 (dd, *J* = 3.9, 8.4 Hz, 1H*β*), 3.15 (m, 1H*β*), 3.13 (dd, *J* = 4.4, 8.0 Hz, 1Hα), 2.35−2.58 (m, 2Hα and 2H*β*), 1.98 (ddt, *J* = 3, 8, 14 Hz, 1H*β*), 1.8 (dddd, *J* = 3, 7, 8, 14 Hz, 1Hα), 1.6 (dddd, *J* = 6, 8, 9, 14 Hz, 1H*β*), 1.45 (dddd, *J* = 6, 8, 9, 14 Hz, 1Hα); ^{13}C NMR ($CDCl_3$, 90 MHz, α indicates **31**α, *β* indicates **31***β*) *δ* 173.0 (α), 172.9 (*β*), 137.9, 137.7, 137.6, 137.2, 128.8, 128.5, 128.5, 128.4, 128.4, 128.3, 128.3, 128.2, 128.2, 127.9, 127.8, 127.8, 127.7, 78.9 (α), 76.7 (*β*), 75.1 (α), 74.3 (α), 74.0 (*β*), 73.4 (*β*), 73.3 (α), 72.4 (α), 72.2 (*β*), 69.5 (α), 69.3 (*β*), 60.8 (*β*), 60.7 (α), 58.5 (*β*), 57.6 (α), 55.9 (α), 53.5 (*β*), 51.7 (α), 31.2 (*β*), 31.0 (α), 24.0 (*β*), 23.7 (α); IR (neat) 3030 (w), 2866 (w), 2097 (s), 1737 (s), 1092 (s) cm^{-1}; MS (CI, NH_3) *m*/*z* (rel intensity) 563 [(M + NH_4)$^+$, 49], 518 (100), 488 (26), 402 (43), 108 (16); HRMS calcd for $C_{31}H_{35}N_3O_6NH_4$ [(M + NH_4)$^+$] 563.2870, found 563.2893. Anal. Calcd for $C_{31}H_{35}N_3O_6$: C, 68.24; H, 6.47; N, 7.70. Found: C, 68.15; H, 6.47; N, 7.47.

(1*R*,2*R*,3*R*,8*S*,8a*R*)-3-[(Benzyloxy)methyl]-1,2-bis(benzyloxy)-8-hydroxyindolizidin-5-one (32) and (1*R*,2*R*,3*R*,-8*R*,8a*S*)-3-[(Benzyloxy)methyl]-1,2-bis(benzyloxy)-8-hydroxyindolizidin-5-one (33). Palladium hydroxide on carbon (25 mg) was added to a solution of the azido-epoxides **31**α and **31***β* (1.4:1 mixture of diastereomers, 131 mg, 0.24 mmol) in MeOH/EtOAc (1:1, 5 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 4 h, and then the hydrogen was evacuated and the mixture was filtered, rinsing with MeOH (5 mL). The filtrate was then concentrated, and the resulting residue was redissolved in methanol (15 mL). Sodium methoxide (15 mg, 0.48 mmol) was added, and the mixture was warmed to reflux. After 24 h, the mixture was cooled to room temperature and concentrated. Chromatography (100:1 $CHCl_3$/MeOH) provided 39 mg (33%) of the minor lactam **33** as a colorless oil, followed by 54 mg (46%) of the major lactam **32** as a colorless oil. The stereochemical assignment of these lactams was made by conversion to the indolizidines **34** and **35** (see below). Data for **33**: R_f = 0.45 (20:1 $CHCl_3$/MeOH); $[\alpha]^{23}_D$ = −17.5° (*c* = 0.08, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) *δ* 7.1−7.4 (m, 15H, ArH), 4.67 (d, *J* = 12.0 Hz, 1H, OCH_2Ph), 4.63 (d, *J* = 12.0 Hz, 1H, OCH_2Ph), 4.47 (d, *J* = 12.0 Hz, 1H, OCH_2Ph), 4.43 (d, *J* = 11.5 Hz, 1H, OCH_2Ph), 4.40 (d, *J* = 12.0 Hz, 1H, OCH_2Ph), 4.37 (m, 2H, H-8 and H-9a), 4.28 (dd, *J* = 4.5, 8.7 Hz, 1H, H-1), 4.22 (d, *J* = 11.6 Hz, 1H, OCH_2Ph), 4.15 (m, 2H, H-2 and H-9b), 3.99 (d, *J* = 2.2 Hz, 1H, OH), 3.77 (d, *J* = 4.0 Hz, 1H, H-3), 3.30 (dd, *J* = 8.8, 10.5 Hz, 1H, H-8a), 2.62 (ddd, *J* = 7.7, 11.8, 17.9 Hz, 1H, H-6ax), 2.30 (ddd, *J* = 1.0, 7.4, 17.8 Hz, 1H, H-6eq), 2.03 (dddd, *J* = 1.1, 3.7, 7.7, 14.0 Hz, 1H, H-7eq), 1.74 (dddt, *J* = 2, 7.4, 11.8, 14.0 Hz, 1H, H-7ax); ^{13}C NMR ($CDCl_3$, 75 MHz) *δ* 169.8, 138.3, 137.3, 135.9, 128.7, 128.4, 128.2, 127.9, 127.7, 127.5, 84.3, 77.6, 73.0, 71.5, 70.8, 66.7, 64.3, 62.4, 61.5, 28.4, 27.4, 13.8; IR (neat) 3500 (br m), 3030 (w), 2932 (m), 2872 (m), 1644 (s), 1454 (m), 1405 (m), 1074 (s) cm^{-1}; MS (CI, NH_3) *m*/*z* (rel intensity) 488 [(M + H)$^+$, 100], 108 (15); HRMS (CI, CH_4 and NH_3) calcd for $C_{30}H_{33}NO_5H$ [(M + H)$^+$] 488.2437, found 488.2419.

Data for 32: R_f = 0.30 (20:1 $CHCl_3$/MeOH); $[\alpha]^{23}_D$ = −15.9° (*c* = 0.39, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) *δ* 7.2−7.4 (m, 15H, ArH), 4.62 (ABq, *J* = 11.7 Hz, Δ*ν* = 25.5 Hz, 2H, OCH_2Ph), 4.57 (ABq, *J* = 11.7 Hz, Δ*ν* = 31.2 Hz, 2H, OCH_2Ph), 4.51 (s, 2H, OCH_2Ph), 4.40 (dt, *J* = 3.5, 6.1 Hz, 1H, H-3), 4.27 (dd, *J* = 3.6, 4.7 Hz, 1H, H-2), 4.19 (dd, *J* = 4.7, 7.7 Hz, 1H, H-1), 4.12 (br s, 1H, H-8), 3.78 (dd, *J* = 6.3, 9.4 Hz, 1H, H-9a), 3.65 (dd, *J* = 3.6, 9.4 Hz, 1H, H-9b), 3.62 (dd, *J* = 2.6, 7.5 Hz, 1H, H-8a), 2.61 (d, *J* = 3.5 Hz, 1H, -OH), 2.52 (ddd, *J* = 7.1, 12.0, 18.0 Hz, 1H, H-6ax), 2.30 (ddd, *J* = 1, 6.9, 18.0 Hz, 1H, H-6eq), 2.1 (dddd, *J* = 1.5, 4.1, 6.9, 14.0 Hz, 1H, H-7eq), 1.79 (dddd, *J* = 1.8, 7.1, 12.2, 14.0 Hz, 1H, H-7ax); ^{13}C NMR ($CDCl_3$, 75 MHz) *δ* 168.4, 138.1, 137.9, 137.6, 128.4, 128.3, 128.2, 127.8, 127.7, 127.5, 82.7, 82.2, 73.2, 72.3, 71.9, 68.6, 65.8, 62.3, 60.8, 27.6, 26.2; IR (neat) 3350 (br m), 3029 (m), 2923 (m), 2864 (m), 1618 (s), 1100 (s) cm^{-1}; MS (CI, NH_3) *m*/*z* (rel intensity) 488 [(M + H)$^+$, 100], 398 (5); HRMS calcd for $C_{30}H_{33}NO_5H$ [(M + H)$^+$] 488.2437, found 488.2434.

(1*R*,2*R*,3*R*,8*S*,8a*R*)-3-[(Benzyloxy)methyl]-1,2-bis(benzyloxy)-8-hydroxyindolizidine (34). Borane−methyl sulfide complex (0.29 mL of a 2 M solution in THF, 0.58 mmol) was added to a cool (0 °C) solution of the lactam **32** (67 mg, 0.14 mmol) in THF (3.7 mL). After 30 min, the mixture was warmed to room temperature. After 6 h, the reaction was quenched by the slow addition of EtOH (2 mL). After 30 min at room temperature, the mixture was concentrated and the residue was redissolved in EtOH (4 mL) and warmed to reflux. After 2 h, the mixture was cooled to room temperature and concentrated. Chromatography (66:33:1 to 50:50:1 hex/EtOAc/MeOH) provided 40 mg (62%) of the title compound as a pale yellow oil. R_f = 0.43 (1:1 hex/EtOAc); $[\alpha]^{23}_D$ = +3.7° (*c* = 0.38, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) *δ* 7.2−7.4 (m, 15H, ArH), 4.52 (ABq, *J* = 11.9 Hz, Δ*ν* = 29.5 Hz, 2H, OCH_2Ph), 4.52 (s, 2H, OCH_2Ph), 4.50 (s, 2H, OCH_2Ph), 4.13 (dd, *J* = 2.4, 6.5 Hz, 1H, H-1), 3.93 (br s, 1H, H-8), 3.90 (dd, *J* = 1.4, 2.4 Hz, 1H, H-2), 3.64 (dd, *J* = 4.8, 9.2 Hz, 1H, H-9a), 3.49 (dd, *J* = 6.7, 9.2 Hz, 1H, H-9b), 3.43 (app t, *J* = 5.6 Hz, 1H, H-3), 2.94 (br dd, *J* = 4, 10.8 Hz, 1H, H-5eq), 2.81 (dd, *J* = 1.5, 6.5 Hz, 1H, H-8a), 2.68 (br s, 1H, H-OH), 2.52 (app dt, *J* = 2.8, 11.5 Hz, 1H, H-5ax), 1.90 (br d, *J* = 13.5 Hz, 1H, H-7eq), 1.75 (app qt, *J* = 4.5, 13 Hz, 1H, H-6eq), 1.45 (m, *J* = 13.5 Hz, 1H, H-6ax), 1.35 (tdd, *J* = 2.2, 4.7, 13.5 Hz, 1H, H-7ax); ^{13}C NMR ($CDCl_3$, 75 MHz) *δ* 138.3, 138.1, 138.1, 128.3, 128.0, 127.6, 127.6, 127.5, 84.7, 84.5, 73.3, 72.1, 71.2, 69.3, 67.3, 66.3, 64.9, 47.6, 30.8, 19.4; IR (neat) 3475 (br m), 3029 (m), 2932 (s), 2857 (s), 1098 (s) cm^{-1}; MS (CI, NH_3) *m*/*z* (rel intensity) 474 [(M + H)$^+$, 62], 352 (100), 91 (55); HRMS (CI, CH_4) calcd for $C_{30}H_{35}NO_4H$ [(M + H)$^+$] 474.2644, found 474.2646.

(1*R*,2*R*,3*R*,8*R*,8a*S*)-3-[(Benzyloxy)methyl]-1,2-bis(benzyloxy)-8-hydroxyindolizidine (35). Borane−methyl sulfide complex (0.14 mL of a 2 M solution in THF, 0.28 mmol) was added to a cool (0 °C) solution of the lactam **33** (32 mg, 0.066 mmol). After 30 min, the mixture was warmed to room temperature. After 6 h, the reaction was quenched by slow addition of EtOH (1 mL). After 30 min at room temperature, the residue was redissolved in EtOH (2 mL) and warmed to reflux. After 2 h, the mixture was cooled to room temperature and concentrated. Chromatography (66:33:1 to 50:50:1 hex/EtOAc/MeOH gradient) provided 27 mg (84%) of the title compound as a pale yellow oil. R_f = 0.51 (1:1 hex/EtOAc); $[\alpha]^{23}_D$ = +10.7° (*c* = 0.14, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) *δ* 7.2−7.4 (m, 15H, ArH), 4.56 (ABq, *J* = 11.9 Hz, Δ*ν* = 22.3 Hz, 2H, OCH_2Ph), 4.53 (ABq, *J* = 11.9 Hz, Δ*ν* = 18.0 Hz, 2H, OCH_2Ph), 4.48 (ABq, *J* = 11.7 Hz, Δ*ν* = 22.3 Hz, 2H, OCH_2Ph), 4.23 (br s, 1H, H-8), 4.17 (s, 1H, -OH), 4.01 (d, *J* = 4.5 Hz, 1H, H-1), 3.73 (d, *J* = 3.8 Hz, 1H, H-2), 3.71 (dd, *J* = 5.1, 9.7 Hz, 1H, H-9a), 3.52 (dd, *J* = 7.0, 9.7 Hz, 1H, H-9b), 3.28 (m, 1H, H-5eq), 2.57 (ddd, *J* = 4.0, 5.0, 7.0 Hz, 1H, H-3), 2.39 (d, *J* = 4.4 Hz, 1H, H-8a), 1.92−3.2 (m, 2H, H-5ax and H-6eq), 1.87 (br d, *J* = 13.8 Hz, 1H, H-7eq), 1.25−1.48 (m, 2H, H-6ax and H-7ax); ^{13}C NMR ($CDCl_3$, 75 MHz) *δ* 138.30, 138.0, 137.0, 128.5, 128.3, 128.2, 127.9, 127.9, 127.7, 127.6, 127.5, 85.3, 84.3, 73.3, 71.4, 71.3, 71.3, 70.6, 67.8, 66.2, 53.5, 31.3, 20.0; IR (neat) 3515 (m), 3030 (m), 2937 (s), 2860 (s), 1454 (s), 1102 (s) cm^{-1}; MS (CI, NH_3) *m*/*z* (rel intensity) 474 [(M + H)$^+$, 100], 256 (9);

HRMS (CI, CH_4) calcd for $C_{30}H_{35}NO_4H$ [$(M + H)^+$] 474.2644, found 474.2657.

(1*R*,2*R*,3*R*,8*S*,8a*R*)-3-(Hydroxymethyl)-1,2,8-trihydroxyindolizidine [Homoaustraline, (9)]. Palladium on carbon (10%, 18 mg) and 6 N HCl (4 drops) were added to a solution of the indolizidine **34** (35.9 mg, 0.076 mmol) in MeOH (2 mL). The flask was evacuated (aspirator) and purged with hydrogen three times. The resulting mixture was stirred under a balloon of hydrogen at room temperature for 20 h, then the hydrogen was evacuated and the mixture was filtered through a cotton plug, rinsing with MeOH (2 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 (0.5 g dry resin). After 30 min, the mixture was filtered and the filtrate was concentrated on a rotary evaporator. Chromatography (5:1 to 3:1 $CHCl_3$/MeOH gradient, SiO_2) provided 9.5 mg (62%) of the title compound as a colorless oil. R_f = 0.37 (2:1 $CHCl_3$/MeOH); $[\alpha]^{23}_D = +16.9$ (c = 0.45, MeOH); ^{1}H NMR (D_2O, 300 MHz) δ 4.03−4.11 (m, 2H), 4.02 (dd, J = 5.3, 11.8 Hz, 1H), 3.88 (dd, J = 4.8, 12.4 Hz, 1H), 3.83 (dd, 4.6, 12.4 Hz, 1H), 3.16 (dd, J = 4.4, 8.7 Hz, 1H), 3.10 (m, 1H), 2.93 (d, J = 8.2 Hz, 1H), 2.80 (dt, J = 2.4, 11.5 Hz, 1H), 1.73−195 (m, 2H), 1.53−1.63 (m, 2H); ^{13}C NMR (D_2O, CH_3OH int std, 75 MHz) δ 78.1, 76.1, 68.4, 68.1, 63.4, 59.1, 47.1, 29.2, 18.2; IR (neat) 3332 (br s), 2936 (m), 1436 (m), 1057 (m) cm^{-1}; MS (CI, NH_3) m/z (rel intensity) 204 [$(M + H)^+$ 100], 186 (22), 172 (20); HRMS (CI, CH_4) calcd for $C_9H_{17}NO_4H$ [$(M + H)^+$] 204.1236, found 204.1234.

(1*R*,2*R*,3*R*,8*R*,8a*S*)-3-(Hydroxymethyl)-1,2,8-trihydroxyindolizidine [8-Epihomoalexine, 10]. Palladium on carbon (10%, 15 mg) and 6 N HCl (4 drops) were added to a solution of the indolizidine **35** (29.7 mg, 0.063 mmol) in MeOH (2 mL). The flask was evacuated (aspirator) and purged with hydrogen three times. The mixture was stirred under a balloon of hydrogen at room temperature for 20 h, and then the hydrogen was evacuated and the mixture was filtered through a cotton plug, rinsing with MeOH (2 mL). The filtrate was concentrated, and the residue was dissolved in a minimum amount of water and stirred with Dowex 1 × 8 200 $^-$OH ion exchange resin (0.5 g dry resin). After 30 min, the mixture was filtered and the filtrate was concentrated on a rotary evaporator. Chromatography (5:1 to 3:1 $CHCl_3$/MeOH gradient, SiO_2) provided 10.5 mg (82%) of the title compound as a colorless oil. R_f = 0.45 (2:1 $CHCl_3$/MeOH); $[\alpha]^{23}_D = -2.0°$ (c = 0.84, MeOH); ^{1}H NMR (D_2O, 300 MHz) δ 4.39 (br s, 1H), 4.20 (br d, J = 4.5 Hz, 1H), 3.78−3.86 (m, 3H), 3.35 (br d, J = 10.3 Hz, 1H), 2.61 (br s, 1H), 2.43 (m, 1H), 2.28 (br t, J = 11 Hz, 1H), 1.75−1.97 (m, 2H), 1.50−1.65 (m, 2H); ^{13}C NMR (D_2O, CH_3OH int std, 75 MHz) δ 79.1, 78.7, 73.1, 67.3, 66.4, 60.3, 52.6, 30.2, 18.9; IR (neat) 3288 (br s), 2934 (m), 1428 (m), 1069 (s) cm^{-1}; MS (EI, 70 eV) m/z (rel intensity) 204 [$(M + H)^+$, 2], 172 (100), 126 (23); HRMS (CI, CH_4) calcd for $C_9H_{17}NO_4H$ [$(M + H)^+$] 204.1236, found 204.1245.

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Supporting Information Available: Photocopies of ^{1}H-NMR, ^{13}C-NMR, COSY, and NOESY spectra for new compounds **7**−**10**, **18**−**27**, and **30**−**35** (59 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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