Total Syntheses of (+)-Australine and (−)-7-Epialexine

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Three approaches were examined for the synthesis of 3-(hydroxymethyl)pyrrolizidines, a class of compounds that includes the polyhydroxylated pyrrolizidine alkaloids alexine (**1**), australine (**2**), and various stereoisomers of thereof. In the first approach, the intramolecular cycloaddition of an azide onto an electron-rich 1,3-diene bearing a terminal alkoxymethyl substituent (i.e., **21**) afforded the dehydropyrrolizidines **22a** and **22b**, with **22a** predominating. A rationale for this stereoselectivity was proposed. Transformation of the major diastereomer **22a** into a natural 3-(hydroxymethyl)-pyrrolizidine was not possible due to difficulties encountered in transforming the phenyl vinyl sulfide functionality into other useful functional groups. A second approach was examined, wherein the intramolecular cycloaddition of an azide with an optically pure S-*t*-Bu-substituted diene (i.e., **30**) was found to produce the pyrrolizidine **31**. In this case, the alkoxymethyl substituent was incorporated into the tether between the azide and the diene, rather than on the diene itself. A key transformation in the synthesis of the diene **30** was the use of the allylic borane $R_2BCH_2CH{=}C(TMS)(S\mathit{t}Bu)$ for the stereoselective conversion of the D-arabinose-derived azido aldehyde **28** to the *E*-isomer of **30**. The cyclization of **30** to **31** also produced the bicyclic triazene **32**, the result of 1,3-dipolar cycloaddition of the azide onto the distal double bond of the diene. Again, difficulties in transformation of the vinyl sulfide functionality of **31** into useful oxygen functionality limited this approach to naturally occurring 3-(hydroxymethyl)pyrrolizidines. A third approach to these compounds was successful. The transformation of L-xylose into the azido epoxy tosylate **46** was accomplished using two Wittig reactions and an epoxidation, in addition to other standard functional group manipulations. Reductive double-cyclization of **46** afforded the pyrrolizidines **47a** and **47b**, which were debenzylated to afford (+)-australine **2** and (−)-7-epialexine **4**, respectively. In the preliminary report of this work, erroneous spectroscopic data in the original literature on the structural assignment of australine led to the conclusion that the synthetic material obtained herein was actually (+)-7-epiaustraline. Recently corrected spectroscopic data have appeared which verify that (+)-australine **2** was indeed synthesized for the first time.

Introduction

The legumes *Alexa leiopetala* and *Castanospermum australe* have yielded a small class of pyrrolizidine alkaloids bearing a C3 hydroxymethyl group,[2] represented by alexine (**1**)[3,4] and australine (**2**), Figure 1.[5−7] Several other stereoisomers of alexine and australine, e.g., 7-epiaustraline (**3**)[8] and 7-epialexine (**4**),[4,6a] have been obtained from nature or by synthesis.[2] The potential of the polyhydroxylated pyrrolizidine alkaloids as selec-

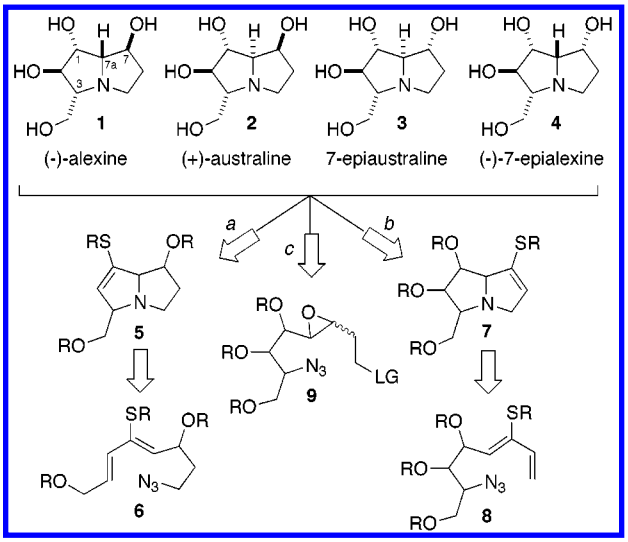

Figure 1.

(1) Current address: Department of Chemistry, Ohio University, Athens, OH 45701.

(2) (a) Fellows, L. E.; Fleet, G. W. In *Natural Products Isolation*; Wagman, G. H., Copper, R., Eds.; Elsevier: Amsterdam, 1988; p 540. (b) Nash, R. J.; Watson, A. A.; Asano, N. In *Alkaloids: Chemical and Biological Perspectives*; Pelletier, S. W, Ed.; Elsevier: Oxford, 1996; Vol. 11; pp 345−376. (c) Liddell, J. R. *Nat. Prod. Rep.* **1996**, 187−193.

(3) Isolation of alexine: Nash, R. J.; Fellows, L. E.; Dring, J. V.; Fleet, G. W. J.; Derome, A. E.; Hamor, T. A.; Scofield, A. M.; Watkin, D. J. *Tetrahedron Lett.* **1988**, *29*, 2487−2490.

(4) Synthesis of alexine: Fleet, G. W. J.; Haraldsson, M.; Nash, R. J.; Fellows, L. E. *Tetrahedron Lett.* **1988**, *29*, 5441−5444. The syntheses of 3-epi- and 7-epialexine are also reported.

(5) Isolation of australine: Molyneux, R. J.; Benson, M.; Wong, R. Y.; Tropea, J. E.; Elbein, A. D. *J. Nat. Prod.* **1988**, *51*, 1198−1206.

(6) Syntheses of australine: (a) Pearson, W. H.; Hines, J. V. *Tetrahedron Lett.* **1991**, *32*, 5513−5516 (the synthesis of 7-epiaustraline reported in this paper was actually a synthesis of australine; see text for explanation). (b) White, J. D.; Hrnciar, P.; Yokochi, A. F. T. *J. Am. Chem. Soc.* **1998**, *120*, 7359−7360. (c) Denmark, S. E.; Martinborough, E. A. *J. Am. Chem. Soc.* **1999**, *121*, 3046−3056. For a synthesis of australine from castanospermine, see: (d) Furneaux, R. H.; Gainsford, G. J.; Mason, J. M.; Tyler, P. C. *Tetrahedron* **1994**, *50*, 2131−2160.

(7) For the synthesis of ring-expanded analogues of australine and alexine, see: Pearson, W. H.; Hembre, E. J. *J. Org. Chem.* **1996**, *61*, 5545−5556.

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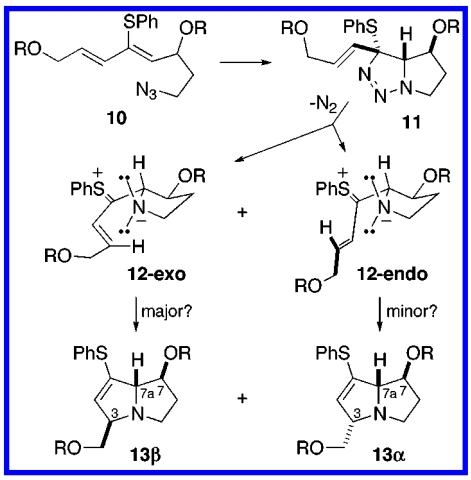
tive glycosidase inhibitors and as antiviral and antiretroviral agents makes them attractive targets for synthesis.[9] Alexine (**1**) is an inhibitor of α-glucosidase, trehalase, amyloglucosidase, fungal glucan 1,4-α-glucosidase,[8a] and thioglucosidase.[10] Australine (**2**) is an inhibitor of amyloglucosidase[8a,5,11] and the glycoprotein processing enzyme glucosidase I[11] and displays antiviral[12] and anti-HIV activity.[13] We wish to report our efforts to synthesize 3-(hydroxymethyl)pyrrolizidines, ultimately culminating in a synthesis of (+)-australine (**2**) and (−)-7-epialexine (**4**).[14]

A retrosynthetic analysis of the 3-(hydroxymethyl)-pyrrolizidines is shown in Figure 1. Our initial efforts centered on the synthesis of the pyrrolines **5** and **7** by a [4 + 1] cycloadditive approach[15,16] involving the cyclization of the azidodienes **6** and **8**, respectively (routes *a* and *b*). A second approach involving the reductive double-cyclization of azidoepoxides such as **9** proved to be most practical for the total synthesis of **2** and **4** (route *c*).[17]

Results and Discussion

Intramolecular Dipolar Cycloaddition of an Azide with an Alkoxymethyl-Substituted Diene. Our initial approach to 3-(alkoxymethyl)pyrrolizidines was based on our work on the intramolecular 1,3-dipolar cycloaddition of azides with electron-rich dienes, a method that produces bicyclic pyrrolines.[15] Two disconnections of the pyrrolizidine nucleus were explored, the first of which is outlined in Schemes 1 and 2. We planned to study a precursor such as **10**, which bears an alkoxymethyl group at the terminus of the diene (Scheme 1). Heating **10** should produce the bicyclic pyrroline **13** with an alkoxymethyl group in the desired C(3) position (australine/alexine numbering). We were confident that the relative stereochemistry at C(7) and C(7a) would result based on our prior work with dienes bearing an allylic alkoxy group.[15] However, since our prior work generally involved azido dienes with no substituent at the diene terminus, we were interested in the outcome of these cyclizations with respect to the relative configuration at C(3) vs C(7a). It is believed that the reaction proceeds via the triazoline **11**, which should fragment with loss of nitrogen to the zwitterion **12**, which is probably in equilibrium with a vinylaziridine (not shown). A 5-*endo*-*trig* closure of **12** would then produce **13**. Examination of models suggested that the zwitterion with the alkoxymethyl group exo to the newly forming ring (**12-exo**) would be preferred to the alternative zwitterion **12-endo** based on steric grounds, although the preference might not be high. Thus, we expected that pyrroline **13***β* would be produced predominantly over **13**α, potentially allowing access to C(3)-epi analogues of alexine, for example, the known synthetic compound 3-epialexine.[18]

Scheme 1



The synthesis of an appropriate alkoxymethyl-substituted azido diene (i.e., **21**) and its cyclization is shown in Scheme 2. The enyne **14**[19] was protected as its *tert*-butyldiphenylsilyl ether **15**, then metalated and added to the aldehyde **16**.[20] RedAl reduction of the resultant propargyl alcohol **17** using Marshall's method[21] followed by quenching of the aluminum intermediate with phenylsulfenyl chloride according to our prior work[15] gave the phenylthiodiene **18**. Protection of the secondary alcohol followed by removal of the *tert*-butyldimethylsilyl group gave the primary alcohol **20**, which was converted to the key azide **21** by a Mitsunobu reaction.[22] Heating **21** at 90 °C in THF in a sealed tube followed by purification and separation gave **22a** and **22b** in 35% and 15% yields, respectively. In both compounds, no NOE was detected between the protons at C(7) and C(7a), consistent with a trans relationship, as precedented by our prior work on the cyclization of dienes bearing an allylic alkoxy group.[15] The relative configuration at C(3) rested

(8) For a report of the isolation of 7-epiaustraline, later found to be australine, see: (a) Nash, R. J.; Fellows, L. E.; Dring, J. V.; Fleet, G. W. J.; Girdhar, A.; Ramsden, N. G.; Peach, J. M.; Hegarty, M. P.; Scofield, A. M. *Phytochemistry* **1990**, *29*, 111−114. For a report of the synthesis of 7-epiaustraline, later found to be australine, see ref 6a. For an unambiguous synthesis of 7-epiaustraline, see: (b) Denmark, S. E.; Herbert, B. *J. Am. Chem. Soc.* **1998**, *120*, 7357−7358. (c) Denmark, S. E.; Herbert, B. *J. Org. Chem.* **2000**, *65*, 2887−2896. See the text for a full explanation.

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(13) Fellows, L.; Nash, R. *PCT Int. Appl. WO* GB Appl. 89/7,951; *Chem. Abstr.* **1990**, *114*, 143777f.

(14) For a preliminary report of this work, see ref 6a.

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(17) For related one-pot double cyclizations using azido epoxides or amino epoxides, see refs 6a, 7, and: (a) Setoi, H.; Takeno, H.; Hashimoto, M. *J. Org. Chem.* **1985**, *50*, 3948−3950. (b) Setoi, H.; Takeno, H.; Hashimoto, M. *Tetrahedron Lett.* **1985**, *26*, 4617−4620. (c) Kim, Y. G.; Cha, J. K. *Tetrahedron Lett.* **1989**, *30*, 5721−5724. (d) Pearson, W. H.; Bergmeier, S. C.; Williams, J. P. *J. Org. Chem.* **1992**, *57*, 3977−3987. (e) Ina, H.; Kibayashi, C. *J. Org. Chem.* **1993**, *58*, 52−61. (f) Jirousek, M. R.; Cheung, A. W.-H.; Babine, R. E.; Sass, P. M.; Schow, S. R.; Wick, M. M. *Tetrahedron Lett.* **1993**, *34*, 3671−3674. (g) Kim, N.-S.; Choi, J.-R.; Cha, J. K. *J. Org. Chem* **1993**, *58*, 7096−7099. (h) Poitout, L.; Le Merrer, Y.; Depezay, J.-C. *Tetrahedron Lett.* **1994**, *35*, 3293−3296. (i) Lohray, B. B.; Jayamma, Y. and Chatterjee, M. *J. Org. Chem.* **1995**, *60*, 5958−5960. (j) Pearson, W. H.; Hembre, E. J. *J. Org. Chem.* **1996**, *61*, 5537−5545. (k) Hembre, E. J.; Pearson, W. H. *Tetrahedron* **1997**, *53*, 11021−11032.

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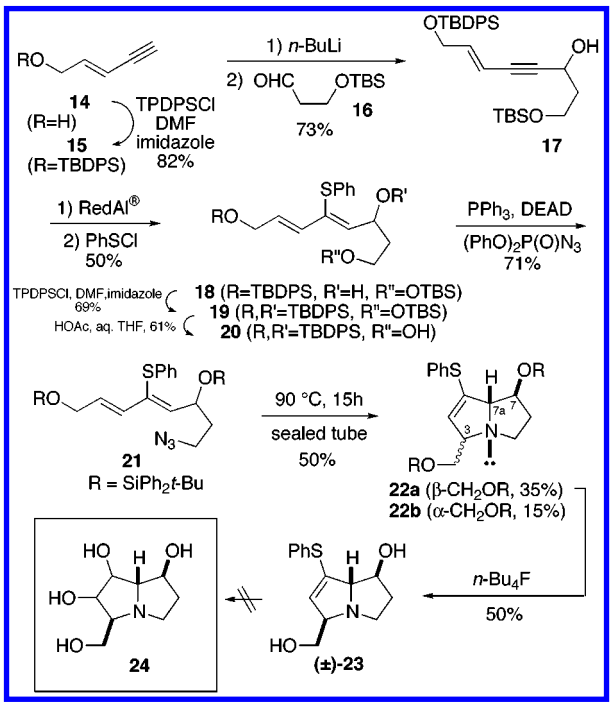
(19) Brandsma, L.; Verkuijsse, H. D. *Synthesis of Acetylenes, Allenes, and Cumulenes*; Elsevier: Amsterdam, 1981; Vol. 8.

(20) Pirrung, M. C.; Webster, N. J. G. *J. Org. Chem.* **1987**, *52*, 3603−3613.

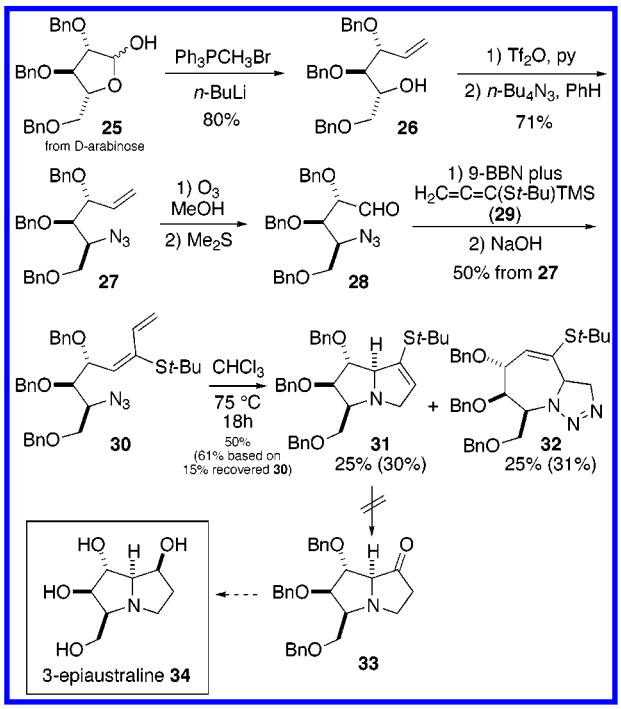
(21) Marshall, J. A.; Shearer, B. G.; Crooks, S. L. *J. Org. Chem.* **1987**, *52*, 1236−1245.

(22) Lal, B.; Pramanick, B. M.; Manhas, M. S.; Bose, A. K. *Tetrahedron Lett.* **1977**, 1977−1980.

Scheme 2



Scheme 3



upon the well-known deshielding of protons syn to nitrogen lone pairs.[23] Thus, the methine hydrogen at C(3) in **22b** appeared at δ 4.13, vs 3.43 for **22a**. Our expectations about the stereoselectivity of this cyclization were confirmed, although the level of selectivity was low. Attempts to improve the yield and stereoselectivity of the cyclization using different solvents and other alcohol protecting groups (acetate, benzyl, tetrahydropyranyl) were unsuccessful, generally resulting in lower yields with similar stereoselectivities. Cyclization of *O*-benzyl versions of **21** resulted in the formation of benzyl alcohol by loss of the terminal benzyloxy group. Accepting **21** as an optimized substrate for cyclization, we then proceeded to examine the transformation of the major cycloadduct into 3-epi analogues of alexine, e.g., **24**. Desilylation of **22a** afforded the diol **23**, but all attempts to use the vinyl sulfide functionality in **23**, **22a**, or **22b** for the introduction of the remaining two hydroxyl groups of **24** failed. Faced with the low selectivity and moderate yield of the cycloaddition of **21** and the difficulty in transforming the vinyl sulfide into the desired diol functionality, we embarked on an alternative cycloaddition strategy involving the assembly of the less hydroxylated ring of these pyrrolizidines.

Intramolecular Dipolar Cycloaddition of an Azide with a Simplified Diene. The studies outlined above showed that a diene bearing a terminal alkoxymethyl group was not an effective choice for the azide/diene cycloaddition. Further, the vinyl sulfide produced in the cycloadduct was difficult to use. We chose next to attempt to generate the desired pyrrolizidines by construction of the less-oxygenated ring by the cycloaddition of an azide with a less complex diene, e.g., **30** in Scheme 3. Further, since we had previously found that the use of a *tert*-butylthio group instead of a phenylthio group allowed hydrolysis of the vinyl sulfide cycloadducts to ketones,[24] we incorporated this design modification into our substrate. An attempted synthesis of 3-epiaustraline (**34**)[6c,25] is shown in Scheme 3. The lactol **25** was synthesized from D-arabinose by the literature procedure[26] and then subjected to a Wittig reaction to produce the alkene **26**. Formation of the triflate of **26** followed by displacement with azide ion gave the alkene **27**, which was best used without manipulation because of its propensity to undergo an intramolecular dipolar cycloaddition to give the corresponding triazoline. Ozonolysis of **27** followed by reductive workup gave the aldehyde **28**, which was found to decompose and/or epimerize upon attempted purification. Thus, the crude aldehyde was subjected to olefination with the allylic borane reagent derived from the hydroboration of the allene **29** by 9-BBN, producing the diene **30** in 50% overall yield from the alkene **27** after sodium hydroxide deoxysilylation of the intermediate β-hydroxysilane. We had previously reported this method for the stereocontrolled formation of either *E*- or *Z*-2-arylthio- or alkylthio-1,3-butadienes, depending on whether the intermediate β-hydroxysilane was decomposed by base or acid, respectively.[24,27] Heating the azido diene **30** in chloroform at 75 °C produced two cyclized products in equal amounts. The first, isolated in 25% yield (30% based on recovered **30**), was found to be a single stereoisomer of the desired pyrrolizidine **31**. The diastereoselectivity was found to be consistent with our earlier studies on the cyclization of azido dienes bearing allylic oxygenation.[15] Elemental analysis of the other cyclization product showed that it was isomeric with the starting diene **30**, still containing three nitrogen atoms.

(23) For studies on the deshielding effect in pyrrolizidine rings, see: (a) Skvortsov, I. M.; Elvidge, J. A. *J. Chem. Soc. B* **1968**, 1589−1595. (b) Jones, T. H.; Blum, M. S. *J. Org. Chem.* **1980**, *45*, 4778−4780.

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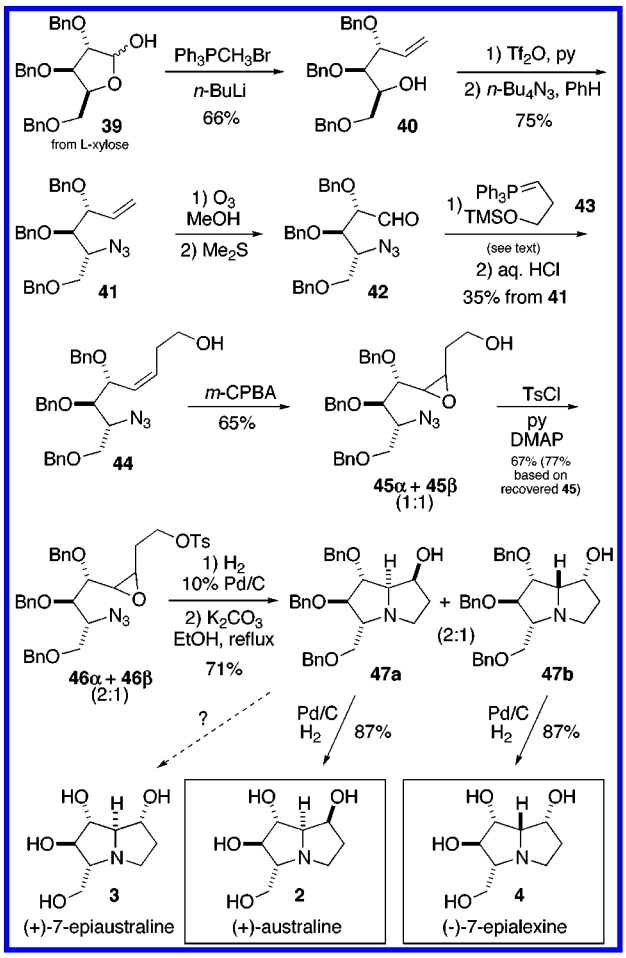
(27) Pearson, W. H.; Lin, K.-C.; Poon, Y.-F. *J. Org. Chem.* **1989**, *54*, 5814−5819.

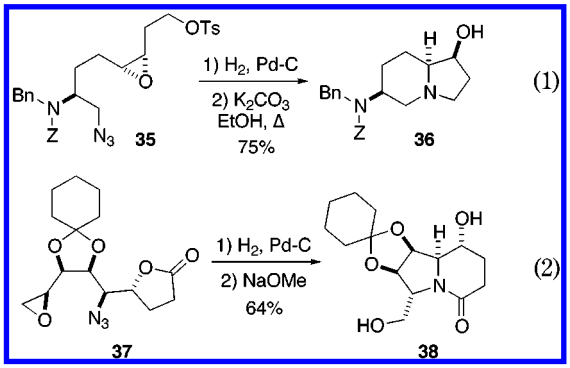
Scheme 4



The IR spectrum showed no azide stretch. The single vinylic hydrogen appeared as a clean doublet in the ^{1}H NMR spectrum, rather than the expected doublet of doublets. These data led us to propose that dipolar cycloaddition had taken place at the distal double bond of the diene **30**, producing the bicyclic triazoline **32**. We had previously found such materials in the cyclizations of similar azido dienes bearing oxygen rather than sulfur substituents.[15] To avoid this problem, we attempted to prepare the *Z*-isomer of **30** using the aforementioned acidic workup of the allylboration/desilylation reaction. Unfortunately, the acid sensitivity of these materials thwarted these efforts. Nonetheless, we had the desired cycloadduct **31** in hand. To complete a synthesis of 3-epiaustraline **34**, we attempted to hydrolyze the vinyl sulfide to the ketone **33**. A survey of many different hydrolysis conditions failed to produce more than a trace of the desired ketone, leading mainly to decomposition. Other strategies for transforming the vinyl sulfide into the required functionality were also found to be unsuccessful.

While the intramolecular cycloadditions of azides with sulfur-substituted dienes was useful for the generation of the late-stage pyrrolizidines **23** and **31** bearing the crucial hydroxy- or alkoxymethyl substituent (Schemes 2 and 3), functional group manipulation issues and low-yielding steps thwarted our efforts to complete the syntheses of the target pyrrolizidines. We also studied other diene substituents in an attempt to solve the functional group problems (e.g., S-*t*-Bu, OCON-*i*-Pr$_2$), but these materials were found to be difficult to employ for a variety of reasons. Thus, we sought to use a more conventional strategy to reach our objectives.

Reductive Double-Cyclization of Azidoepoxides. Synthesis of (+)-Australine (2) and (−)-7-Epialexine (4). We and others have found that the reductive double-cyclization of azides bearing an epoxide and one additional electrophile (e.g., an alkylating or acylating agent) is an effective way to generate the two rings of the pyrrolizidine, indolizidine, and quinolizidine alkaloids.[17] For example, the reductive double-cyclization of the azido epoxy tosylate **35** gave the indolizidine **36**, a precursor of slaframine, in good yield (eq 1).[17d] An internal azide was used in a double cyclization involving an epoxide and an acylating agent in the conversion of **37** to the indolizidine **38**, a precursor of (3*R*)-3-(hydroxymethyl)swainsonine (eq 2).[17k] Ring expanded analogues of alexine, australine, and swainsonine have also been prepared by reductive double-cyclizations of azido epoxides bearing internal acylating agents and alkylating agents, respectively.[7,17j] This strategy has now proven useful for the completion of the synthesis of australine (**2**) and 7-epialexine (**4**), as shown in Scheme 4.



Our synthesis began with 2,3,5-tri-*O*-benzyl-L-xylofuranose **39**,[28] which was prepared from L-xylose in three steps.[26] Wittig olefination produced **40**, which was converted to the azide **41** via the triflate. The azide **41** was relatively unstable, undergoing an intramolecular 1,3-dipolar cycloaddition upon standing at room temperature. Hence, it was best to carry **41** to the next step without delay. Ozonolysis of **41** afforded the aldehyde **42**, which was not purified due to its sensitivity and was directly converted to the *Z*-alkene **44** by a stereoselective Wittig reaction with the silyloxy-substituted ylide **43**.[29−31] Again, intramolecular 1,3-dipolar cycloaddition was observed if this azidoalkene was allowed to stand at room temperature. Epoxidation of **44** with *m*-CPBA produced a 1:1 mixture of epoxides **45**α and **45***β*, which were not separated.[32] Tosylation of **45**α/*β* gave **46**α/*β* as a 2:1 mixture of isomers, since one of the isomers of **45** underwent tosylation faster than the other and the reaction could not be driven to completion. Reduction of **46**α/*β* without debenzylation was possible by hydro-

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(32) For reports of similar epoxidations of allylic ethers, see: (a) Wang, Z.; Schreiber, S. L. *Tetrahedron Lett.* **1990**, *31*, 31−34. (b) Erickson, S. D.; Still, W. C. *Tetrahedron Lett.* **1990**, *31*, 4253−4256. (c) Coutts, S. J.; Wittman, M. D.; Kallmerten, J. *Tetrahedron Lett.* **1990**, *31*, 4301−4304.

genolysis. The resultant amine was not isolated but was directly heated in refluxing EtOH containing K_2CO_3, affording a 2:1 mixture of two pyrrolizidines **47a** and **47b** which were easily separated by flash chromatography. At this point, the configurations of **47a** and **47b** at C(7) and C(7a) were unknown, but it was assumed that the methine hydrogens at these positions were cis in both isomers due to their cis relationship in alkene **44** and epoxides **45** and **46**. Hydrogenolytic debenzylation of **47b** using a larger amount of palladium catalyst afforded (−)-7-epialexine **4**, as expected. However, a similar debenzylation of **47a** gave a pyrrolizidine that did not match the literature data for (+)-australine **2** as expected, but rather matched the literature data for (+)-7-epiaustraline **3**.[18,33] Since the structures of alexine **1**, australine **2**, and 7-epialexine **4** (three of the four possible diastereomers at C-7 and C-7a) had been established by X-ray crystallography[3,18,34] and since our data for the debenzylation product from **47a** were not consistent with these structures, it appeared initially that this material was 7-epiaustraline **3**.[6a] The literature assignment of **3** rested on NOE experiments and comparison with known structures.[33] The absolute stereochemistry was not determined, but was proposed to be as shown. The apparent formation of **3** was unexpected, since the methine hydrogens at C-7 and C-7a were trans rather than cis. Although we were confident that our chemistry would give australine **2**, the fact that our data did not match the literature values for australine, the structure of which was based on X-ray crystallography, led us to conclude that an unusual epimerization had occurred at some point. After extensive experimentation, we were not able to find evidence for such an epimerization. Fortunately, recent publications have allowed a resolution of this problem. Denmark and co-workers synthesized 7-epiaustraline **3** and proved its structure by X-ray crystallography.[8b,c] The properties of synthetic **3** did not match those of natural **3**, leading to a reevaluation of the assignments of the various naturally occurring pyrrolizidines. It was determined by Wormald et al. that the spectra for australine **2** were incorrectly reported in the original work.[35] We now find that our data for the debenzylation product of **47a** match the revised data for (+)-australine **2**. Thus, as we had originally intended, we were successful in our attempt to prepare **2**. In retrospect, our work represents the first total synthesis of (+)-australine.[6]

Conclusion

Three synthetic strategies for the assembly of 1,2,7-trihydroxy-3-(hydroxymethyl)pyrrolizidines were examined. The cyclization of the azido diene **21** gave the 3-(hydroxymethyl)pyrrolizidine **22** in reasonable yield as one major stereoisomer of four possibilities, although further transformations to naturally occurring pyrrolizidines was not possible. The cyclization of the azido diene **30** produced the 3-(hydroxymethyl)pyrrolizidine **31** as a single stereoisomer, but further transformation of the vinyl sulfide functionality was not possible. The novel byproduct **32**, the result of cyclization of the azide onto the distal double bond of the diene, was formed in the cyclization reaction. Finally, a successful route to (+)-australine (**2**) and (−)-7-epiaustraline (**4**) was developed, relying on the reductive double cyclization of the azido epoxy tosylate **46** to the pyrrolizidines **47**. Originally, it was thought that an unusual epimerization had occurred in the reductive cyclization, resulting in the eventual production of 7-epiaustraline **3** rather than australine **2**. Due to recent work by Denmark, an error in the original structural work on australine was found, allowing us to now conclude that australine **2** had been synthesized as was originally expected, resulting in what is, in retrospect, the first total synthesis of this alkaloid.

Experimental Section

(*E*)-5-(*tert*-Butyldiphenylsilyl)oxypent-3-en-1-yne (15). Imidazole (7.6 g, 112 mmol), *tert*-butyldiphenylsilyl chloride (15.2 g, 55.4 mmol), and *E*-5-hydroxypent-3-en-1-yne **14** (4.14 g, 50.5 mmol),[19] were stirred in dimethylformamide (90 mL) at room temperature for 8 h. The mixture was then diluted with ether and washed with saturated aqueous NH_4Cl (150 mL). The aqueous wash was extracted with ether, and the combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated in vacuo. Chromatography (5% ethyl acetate/hexane) gave 13.28 g (82%) of the title compound as a clear oil: R_f 0.62 (10% ethyl acetate/hexane); IR (neat) 3293 (s) cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.7−7.3 (m, 10 H), 6.28 (dt, 1 H, J = 15.5, 3.5 Hz), 5.92 (app dq, 1 H, J = 15.5, 1.8 Hz), 4.3−4.2 (m, 2 H), 2.85 (m, 1H), 1.2−1.0 (m, 9 H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 143.8, 135.45, 135.4, 129.8 127.8, 107.7, 82.1, 77.5, 63.4, 26.7, 19.2; MS (CI, CH_4), *m*/*e* 321 (MH^+, 48.9), 303 (10.6), 280 (14.9), 178 (100.0); HRMS (CI, CH_4) Calcd for $C_{21}H_{24}OSiH$ (MH^+) 321.1675 found 321.1678. Anal. Calcd for $C_{21}H_{24}OSi$: C, 78.69; H, 7.55. Found: C, 78.71; H, 7.88.

(*E*)-1-(*tert*-Butyldimethyllsilyl)oxy-3-hydroxy-8-(*tert*-butyldiphenylsilyl)oxyoct-6-en-4-yne (17). *n*-Butyllithium (6.1 mL of a 2.5 M solution in hexane, 15.3 mmol) was added in a dropwise fashion over 5 min to a solution of the enyne **15** (4.65 g, 14.5 mmol) in THF (200 mL) at −78 °C. After 10 min, 3-(*tert*-butyldimethylsilyl)oxypropanal **16** (3.28 g, 17.4 mmol)[20] in THF (10 mL) was over a 50 min period. After an additional 40 min, saturated aqueous NH_4Cl (2 mL) was added, and the mixture was warmed to room temperature and poured into saturated aqueous NH_4Cl. The layers were separated, and the aqueous layer was extracted three times with ether. The organic layers were combined and washed with brine, dried over Na_2SO_4, and concentrated in vacuo to give 7.3 g of crude oil. Chromatography (10% ethyl acetate/hexane) gave 5.4 g (73%) of the title compound as a clear oil: R_f 0.15 (10% ethyl acetate/hexane); IR (neat) 3420 (br) cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.7−7.4 (m, 10 H), 6.21 (dt, 1 H, J = 15.5, 4.0 Hz), 5.94 (app dq, 1 H, J = 15.5, 2.0 Hz), 4.75 (m, 1 H), 4.24 (dd, 2 H, J = 4.0, 2.0 Hz), 4.05 (m, 1 H), 3.86 (m, 1 H), 3.45 (d, 1 H, J = 6.0 Hz, −OH), 1.06 (s, 9 H), 0.91 (s, 9 H), 0.10 (s, 3 H), 0.09 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 142.1, 135.6, 133.4, 129.8, 127.8, 108.5, 90.1, 83.3, 63.6, 62.3, 61.2, 38.9, 26.8, 25.9, 19.3, 18.2, −5.5; MS (CI, CH_4), *m*/*e* 509 ($M + H^+$, 5.1), 507 ($M - H^+$, 5.2), 493 (25.8), 491 (100.0); HRMS (CI, CH_4) calcd for $C_{30}H_{43}O_3Si_2$ ($M - H^+$) 507.2750. Found: 507.2751. Anal. Calcd for $C_{30}H_{44}O_3Si_2$: C, 70.81; H, 8.72. Found: C, 70.50; H, 8.78.

(4*Z*,6*E*)-1-(*tert*-Butyldimethylsilyl)oxy-8-(*tert*-butyldiphenylsilyl)oxy-5-phenylthio-4,6-octadiene-3-ol (18). A solution of the enyne **17** (4.5 g, 8.8 mmol) in ether (10 mL) was added over 5 min dropwise to a solution of sodium bis(2-methoxyethoxy)aluminum hydride (Red-Al) (4.21 g of a 70% solution in toluene, 14.58 mmol) in ether (45 mL) at 0 °C. After 40 min, dry ethyl acetate (0.56 mL, 5.7 mmol) was added. After 5 min, the mixture was cooled to −78 °C and phenylsulfenyl chloride (1.8 g, 12 mmol) in ether (10 mL) was added over 5

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min. The solution was warmed to room temperature over 1 h and then poured into saturated aqueous NH_4Cl. The layers were separated and the aqueous layer was extracted with ether (6×). The combined organic layers were dried over Na_2SO_4 and concentrated in vacuo to give 7.35 g crude oil. Chromatography (10% ethyl acetate/hexane) gave 2.7 g (50%) of the title compound as a pale yellow oil. In earlier runs, this compound was found to decompose upon standing at room temperature and was thus used immediately in the next step: R_f 0.29 (10% ethyl acetate/hexane); IR (neat) 3421(br) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.8−7.0 (m, 15 H), 6.40 (bd, 1 H, J = 15.1 Hz), 6.28 (d, 1 H, J = 7.7 Hz), 6.10 (dt, 1 H, J = 15.1, 4.2 Hz), 5.09 (m, 1 H), 4.19 (bd, 2 H, J = 4.2 Hz), 3.9−3.8 (m, 2 H), 3.63 (d, 1 H, J = 2.9 Hz, OH), 2.0−1.7 (m, 2 H), 1.02 (s, 9 H), 0.89 (s, 9 H), 0.07 (s, 6 H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 143.7, 136.5, 135.8, 135.4, 134.8, 133.5, 133.4, 132.8, 131.3, 130.9, 129.6, 129.4, 128.8, 128.7, 127.64, 127.58, 127.53, 125.4, 70.3, 63.7, 62.1, 38.3, 26.8, 26.6, 25.8, 19.2, 18.1; MS (CI, CH_4), *m/e* 635 (3.5), 601 (100.0).

(4*Z*,6*E*)-1-(*tert*-Butyldimethylsilyl)oxy-3,8-di-[(*tert*-butyldiphenylsilyl)oxy]-5-phenylthio-4,6-octadiene (19). The alcohol **18** (1.8 g, 2.9 mmol) was added to a mixture of imidazole (0.43 g, 6.3 mmol) and *tert*-butyldimethylsilyl chloride (1.1 g, 3.8 mmol) in dimethylformamide (8 mL) at room temperature. After 15 h, the mixture was diluted with ether and washed with saturated aqueous NH_4Cl. The aqueous washes were then extracted with ether and the combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated in vacuo to give 4.3 g of a crude oil. Chromatography (5% ethyl acetate/hexane) gave 1.7 g (69%) of the title compound: R_f 0.5 (10% ethyl acetate/hexane); IR (neat) 2929-(s), 1472(s) cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.7−6.8 (m, 25 H), 6.27 (d, 2 H, J = 7.5 Hz), 6.25 (bd, 1 H, J_{app}= 14.5 Hz), 5.95 (dt, 1 H, J = 14.5, 4.5 Hz), 5.19 (m, 1 H), 4.2−4.1 (m, 2 H), 3.8−3.5 (m, 2 H), 2.0−1.7 (m, 2 H), 1.12 (s, 9 H), 1.08 (s, 9 H), 0.89 (s, 9 H), 0.08 (s, 6 H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 144.0, 136.1, 135.6, 134.5, 133.7, 132.4, 129.7, 129.5, 129.3, 128.6, 127.7, 127.6, 127.4, 125.1, 69.6, 63.8, 59.6, 41.4, 27.1, 27.0, 26.9, 25.9, 19.4, 19.3, 18.3; MS (CI, CH_4), *m/e* 857.4 (7.8, M + H^+), 856.4 (7.3, M^+), 601.2 (100.0); HRMS (CI, CH_4) calcd for $C_{52}H_{68}O_3SSi_3$ (M^+) 856.4197, found 856.4168.

(4*Z*,6*E*)-3,8-Di[(*tert*-butyldiphenylsilyl)oxy]-5-phenylthio-4,6-octadien-1-ol (20). Diene **19** (1.32 g, 1.54 mmol) was stirred in acetic acid/THF/water (20 mL of a 3:1:1 mixture) at 50 °C for 6h. The solution was then poured into a mixture of ether and brine. The layers were separated, the aqueous layer was extracted with ether, and the combined organic extracts were washed with saturated aqueous $NaHCO_3$ and brine, dried over Na_2SO_4, and concentrated in vacuo. Chromatography (7% ethyl acetate/hexane) gave 0.69 g (61%) of the title compound as a thick oil. In earlier experiments, it was found that this material decomposed upon standing at room temperature and was thus used immediately in the next step: R_f 0.55 (25% ethyl acetate/hexane); ^1H NMR (300 MHz, $CDCl_3$) δ 7.7−6.7 (m, 25 H), 6.26 (d, 1 H, J = 14), 6.22 (d, 1 H, J = 8.8 Hz), 5.90 (dt, 1 H, J = 14, 6 Hz), 5.15 (m, 1 H), 4.2−4.0 (m, 2 H), 3.8−3.5 (m, 3 H, CH_2 and OH), 2.0−1.7 (m, 2 H), 1.2−1.0 (m, 18 H).

(4*Z*,6*E*)-1-Azido-3,8-di[(*tert*-butyldiphenylsilyl)oxy]-5-phenylthio-4,6-octadiene (21). The alcohol **20** (0.61 g, 0.82 mmol) was added to a solution of triphenylphosphine (0.24 g, 0.92 mmol) in THF (8 mL) at 0 °C. Diethyl azodicarboxylate (0.16 g, 0.92 mmol) was added in a dropwise fashion. After 5 min, diphenylphosphoryl azide (0.31 g, 1.1 mmol) was added and the mixture was warmed to room temperature and stirred for 48 h in the dark. The mixture was then concentrated in vacuo and the resultant oil was purified by chromatography (3% ethyl acetate/hexane) to give 0.5 g (71%) of the title compound as an oil. Repeated attempts to obtain analytically pure material were unsuccessful: R_f 0.69 (10% ethyl acetate/hexane); ^1H NMR (300 MHz, $CDCl_3$) δ 7.7−6.8 (m, 25 H), 6.3−6.1 (m, 2 H), 5.91 (dt, 1 H,J = 15.2, 5.0 Hz), 5.03 (m, 1 H), 4.12 (bs, 2 H), 3.25 (m, 2 H), 1.9−1.6 (m, 2 H), 1.04 (s, 9H), 1.08 (s, 9 H).

(1*R,5*S**,7a*R**)-1-(*tert*-Butyldiphenylsilyl)oxy-5-(*tert*-butyldiphenylsilyl)oxymethyl-7-phenylthio-2,3,5,7a-tetrahydro-1*H*-pyrrolizine (22a) and (1*R**,5*R**,7a*R**)-1-(*tert*-Butyldiphenylsilyl)oxy-5-(*tert*-butyldiphenylsilyl)oxymethyl-7-phenylthio-2,3,5,7a-tetrahydro-1*H*-pyrrolizine (22b).** The azide **21** (0.36 g, 0.487 mmol) in THF (4.8 mL) was degassed by four freeze−thaw cycles, and the glass tube was sealed and heated behind a blast shield for 15 h at 90 °C. The vessel was then cooled to room temperature and opened, and the contents were concentrated in vacuo. Chromatography (5% ethyl acetate/hexane to elute **22a** and 25% ethyl acetate/hexane to elute **22b**) yielded 120 mg (35%) of **22a** and 51 mg (15%) of **22b** (50% overall yield). Data for **22a:** R_f 0.6 (20% ethyl acetate/hexane); ^1H NMR (360 MHz, $CDCl_3$) δ 7.7−7.1 (m, 25 H), 5.47 (app t, 1 H, J = 1.5 Hz), 4.29 (m, 1 H), 4.22 (m, 1 H), 3.69 (A), 3.50 (B) (AB of ABX, 2 H, J_{AB} = 8.5 Hz, J_{AX} = 6.0 Hz, J_{BX} = 16.0 Hz), 3.43 (m, 1 H, X of ABX), 3.25 (td, 1 H, J = 10.5, 4.5 Hz), 2.68 (m, 1 H), 1.52 (m, 1 H), 1.39 (m, 1 H), 1.02 (s, 9 H), 0.98 (s, 9 H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 136.1, 135.9, 135.7, 131.8, 129.6, 129.1, 128.8, 127.6, 127.5, 127.3, 82.3, 75.5, 68.8, 54.2, 33.4, 26.9, 19.2, 19.1 Data for **22b:** R_f 0.55 (25% ethyl acetate/hexane); ^1H NMR (360 MHz, $CDCl_3$) δ 7.8−7.2 (m, 25 H), 5.12 (appt, 1 H, J = 1.5 Hz), 4.39 (m, 1H), 4.32 (m, 1 H), 4.13 (m, 1 H, X of ABX), 3.66, 3.64 (ABof ABX, 2 H, J_{AB} = 10.0 Hz, J_{AX} = 4.5 Hz, J_{BX} = 5.5 Hz), 3.02 (t, 2 H, J = 6.0 Hz), 1.66 (m, 1 H), 1.57 (m, 1 H), 1.05 (s, 9 H), 0.97 (s, 9 H). Proton NMR assignments were made by COSY and NOE experiements. For both **22a/b**, no NOE was observed between the methine hydrogens at C-1 and C-7a, implying a trans relationship between these two protons. [In the earlier text, alexine/australine numbering was used instead, i.e., the phenylthio group is at C(1), the silyloxymethyl group at C(3), etc.] The relative configuration at C-5 vs C-7a was assigned based on the chemical shifts of the C-5 methine protons in **22a** (δ 3.43) and **22b** (δ 4.13), since methine hydrogens syn to lone pairs on nitrogen appear further downfield than those that are anti.[23]

(1*R,5*S**,7a*R**)-5-Hydroxymethyl-7-phenylthio-2,3,5,-7a-tetrahydro-1*H*-pyrrolizin-1-ol (23).** Tetra-*n*-butylammonium fluoride (320 μL of a 1 M solution in THF, 0.32 mmol) was added to a solution of the tetrahydropyrrolizine **22a** (40 mg, 0.054 mmol) in THF (2 mL) at room temperature. After 24 h, the mixture was concentrated in vacuo and the resultant oil was purified by chromatography (95/4.5/0.5 $CHCl_3$/MeOH/NH_4OH). The eluate was dissolved in $CHCl_3$ and washed with 4% NaOH and concentrated to give 7.0 mg (50%) of the title compound as a white solid, which was recrystallized from ether: R_f 0.28 (90/9/1 $CHCl_3$/MeOH/NH_4OH); mp 97−102 °C; IR ($CHCl_3$) 3690 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.5−7.3 (m, 5 H), 5.35 (appt, 1 H, J_{app}= 2.0 Hz), 4.29 (ddd, 1 H, J = 8.0, 4.9, 2.5 Hz), 4.1 (m, 1 H), 3.61 (m, 1 H, X of ABX), 3.58 (A), 3.38 (B) (AB of ABX, 1 H, J_{AB} = 10.5 Hz, J_{AX} = 4.5 Hz, J_{BX} = 5.5 Hz), 3.31 (ddd, 1 H, J = 10.5, 9.0, 5.5 Hz), 2.80 (ddd, 1 H, J = 11.5, 6.5, 4.5 Hz), 2.55 (bs, 2 H, OH), 1.90 (m, 1 H), 1.79 (m, 1 H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 136.9, 132.7, 131.7, 129.4, 128.3, 125.7, 81.3, 75.8, 74.9, 64.7, 54.0, 33.4; MS (70 eV) *m/e* 263 (5), 232 (100); HRMS calcd for $C_{14}H_{17}NO_2S$ (M^+) 263.0980, found 263.0966.

(3*R*,4*R*,5*R*)-5-Hydroxy-3,4,6-tribenzyloxy-1-hexene (26). *n*-Butyllithium (25.6 mL of a 1.87 M solution in hexanes, 49.6 mmol) was added to a solution of methyltriphenylphosphonium bromide (16.3 g, 45.5 mmol) in THF (71 mL) at 0 °C. After 0.5 h, the solution was cooled to −78 °C for 15 min, and then 2,3,5-tri-*O*-benzyl-D-arabinose **25** (7.8 g, 18 mmol)[26] in THF (31 mL) was added dropwise in a dropwise fashion. The resulting slurry was warmed to −25 °C over 1 h and then to room temperature. After 24 h, the reaction was quenched by the addition of water (1.5 mL), and the mixture was poured into cold ether and filtered. Concentration of the filtrate in vacuo followed by chromatography of the residue (10% ethyl acetate/hexane) gave 6.16 g (80%) of the title compound as an oil: R_f 0.41 (25% ethyl acetate/hexane); $[\alpha]^{25}_D$ −11.9 (c = 1.26, $CHCl_3$); IR (neat) 3480-(br) cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.4−7.2 (m, 15 H), 5.96 (ddd, 1 H J = 16.7, 11.0, 7.5 Hz), 5.34 (bs, 1 H), 5.30 (bd, 1 H, J = 7.5 Hz), 4.63, 4.35 (AB, 2 H, J_{AB} = 11.9 Hz), 4.62, 4.55 (AB, 2 H, J_{AB} = 11.4 Hz), 4.50 (s, 2 H), 4.07 (dd, 1 H, J = 7.5, 3.9 Hz), 4.01 (m, 1 H), 3.62 (dd, 1 H, J = 6.9, 3.9 Hz), 3.59

(bd, 2 H, J = 4.5 Hz), 2.83 (d, 1 H, J = 5.0 Hz, OH); ^{13}C NMR (90 MHz, $CDCl_3$) δ 138.3, 138.2, 137.9, 135.2, 128.4, 128.3, 128.1, 127.8, 127.7, 127.6, 118.8, 80.7, 80.3, 74.1, 73.4, 71.0, 70.7, 70.4; MS (CI, CH_4), *m/e* 436 (50.3, M + NH_4^+), 419 (49.1, M + H^+), 91 (100.0); HRMS (CI, CH_4) calcd for $C_{27}H_{31}O_4$ (M + H^+) 419.2222, found 419.2216. Anal. Calcd for $C_{27}H_{30}O_4$: C, 77.48; H, 7.22. Found: C, 77.33; H, 7.12.

(3*R*,4*S*,5*R*)-5-Trifluoromethanesulfonyloxy-3,4,6-tribenzyloxy-1-hexene. Trifluoromethanesulfonic anhydride (1.5 mL, 2.5 g, 8.9 mmol) in CH_2Cl_2 (9 mL) was added to a solution of pyridine (0.8 mL, 9.9 mmol) in CH_2Cl_2 (9 mL) at −40 °C. After 10 min, **26** in CH_2Cl_2 (39 mL) was added over 5 min. The slurry was warmed slowly to room temperature over 30 min and stirred at 0 °C for 2.5 h. The resulting mixture was filtered through Celite, washing with cold CH_2Cl_2, and the filtrate was concentrated in vacuo to give 5.6 g of the title compound as a crude pale yellow oil. Because of its instability, this crude material was used immediately without further purification for the synthesis of **27.** For characterization purposes, a small portion was purified by chromatography (10% ethyl acetate/hexane): R_f 0.29 (10% ethyl acetate/hexane); IR ($CHCl_3$) 1410(s) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.4−7.2 (m, 15 H), 5.80 (ddd, 1 H, J = 17.4, 10.3, 7.4 Hz), 5.32 (m, 2 H), 5.22 (m, 1 H), 4.70, 4.65 (AB, 2 H, J_{AB} = 11.3 Hz), 4.56, 4.34 (AB, 2 H, J_{AB} = 11.6 Hz), 4.47 (bs, 2 H), 3.95−3.91 (m, 2 H), 3.83 (bd, 2 H, J = 4.9 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 137.7, 137.4, 137.3, 134.1, 128.4, 128.3, 128.0, 127.9, 127.85, 127.8, 127.7, 120.2, 88.6, 81.2, 80.5, 75.2, 73.4, 70.8, 67.6.

(3*R*,4*R*,5*S*)-5-Azido-3,4,6-tribenzyloxy-1-hexene (27). Tetra-*n*-butylammonium azide (10.1 g, 35.5 mmol) was dissolved in benzene (65 mL) and the solution was cooled to −10 °C with rapid stirring. A solution of the crude triflate from above in benzene (30 mL) was added and the mixture was warmed to 0 °C over 30 min, then warmed to room temperature for 1 h and concentrated in vacuo to approximately 10 mL. The resulting red-orange oil was extracted with ether and the ether extracts were concentrated in vacuo to give 5.8 g of a yellow oil. This procedure separated the product from most of the tetra-*n*-butylammonium azide. Chromatography (6% ethyl acetate/hexane) gave 2.27 g (71% from **26**) of the title compound. This material proved to be unstable at room temperature, and was therefore used as soon as possible for the synthesis of **28**: R_f 0.24 (10% ethyl acetate/hexane); IR (neat) 2096(s), cm^{-1}; ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.4−7.1 (m, 15 H), 5.82 (ddd, 1 H, J = 17.4, 10.3, 7.8 Hz), 5.5−5.3 (m, 2 H), 4.84, 4.63 (AB, 2 H, J_{AB}= 11.5 Hz), 4.59, 4.33 (AB, 2 H, J_{AB}= 11.7 Hz), 4.41 (s, 2 H), 4.08 (bt, 1 H, J = 7.6 Hz), 3.7−3.6 (m, 2 H), 3.6−3.4 (m, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.4, 137.9, 135.1, 128.5, 128.4, 128.3, 128.1, 127.9, 127.8, 127.7, 119.5, 82.1, 80.7, 74.9, 73.5, 70.9, 69.8, 61.7.

(2*S*,3*R*,4*S*)-4-Azido-2,3,5-tribenzyloxy-1-pentanal (28). Azidoalkene **27** (2.3 g, 5.1 mmol) in CH_2Cl_2 (27 mL) and methanol (5.3 mL) was cooled to −78 °C, and one drop of Sudan III (0.1% in CH_2Cl_2) was added. The mixture was purged with argon, and then ozone was bubbled into the cooled mixture for 17 min until the pink color disappeared. The reaction mixture was then purged with argon for 15 min and treated with dimethyl sulfide (0.93 g, 14.9 mmol). After 45 min at −78 °C, 1 h at 0 °C, and 1.5 h room temperature, the yellow solution was concentrated in vacuo to give 2.3 g of a golden brown oil which was found to be pure aldehyde by ^{1}H NMR. This material was unstable to purification and was thus used immediately in the following reaction: R_f 0.3 (25% ethyl acetate/hexane); IR (neat) 2866(s), 2099(s), 1729(s) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.74 (d, 1 H, J = 1.0 Hz), 7.4−7.1 (m, 15 H), 4.72, 4.45 (AB, 2 H, J_{AB} = 11.8 Hz), 4.57 (s, 2 H), 4.44 (s, 2 H), 4.0−3.7 (M, 2 H), 3.6−3.4 (m, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 201.3, 137.6, 137.2, 136.9, 128.5, 128.4, 128.2, 128.1, 128.0, 127.8, 81.9, 78.7, 74.2, 73.46, 73.41, 69.1, 60.8.

1-Trimethylsilyl-1-*tert*-butylthio-1,2-propadiene (29).[24] A solution of lithium diisopropylamide (66 mmol) in THF (300 mL) was cooled to −78 °C and treated with 1-*tert*-butylthiopropyne (8.37 g, 65.3 mmol).[19] After 30 min, chlorotrimethylsilane (7.17 g, 66 mmol) was added rapidly, and the mixture was allowed to warm to room temperature and treated with saturated aqueous ammonium chloride. The mixture was extracted twice with petroleum ether, and the organic extracts were combined, dried ($MgSO_4$), and concentrated. Distillation gave 8.4 g (64%) of the title compound, 89% pure by GLC analysis: bp 69−72 °C at 4 mmHg; IR (neat) 2960 (s), 1920 (s) cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.58 (s, 2H), 1.42 (s, 9H), 0.15 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 208.0, 89.9, 72.5, 47.1, 30.1, −1.7.

(3*E*,5*R*,6*R*,7*S*)-7-Azido-5,6,8-tribenzyloxy-3-*tert*-butylthio-1,3-octadiene (30). Allene **29** (1.05 g, 5.20 mmol) and 9-borabicyclo[3.3.1]nonane (10.5 mL of a 0.5 M solution in THF, 5.3 mmol) were combined and heated at 70 °C for 24 h. The solution was then cooled to room temperature and the entire crude aldehyde **28** from the above experiment (5.1 mmol theoretically) in THF (5 mL) was added via a cannula. The mixture was stirred for 20 h, then 20% aqueous NaOH (25 drops) was added. After 48 h, the mixture was poured into ether/petroleum ether (1:1, 300 mL), the resultant mixture was filtered through Celite, and the filtrate was concentrated in vacuo. Chromatography (2.5% ethyl acetate/hexane) gave 1.4 g (50% from **27**) of the title compound: R_f 0.4 (10% ethyl acetate/hexane); $[\alpha]^{25}_D$ −8.86 (c = 1.14, abs EtOH); IR (neat) 2096(s) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.4−7.1 (m, 15 H), 6.73 (dd, 1 H, J = 16.6, 10.3 Hz), 6.06 (bd, 1 H, J = 9.6 Hz), 5.97 (dd, 1 H, J = 16.6, 1.8 Hz), 5.34 (dt, 1 H, J = 10.3, 1.8 Hz), 4.86 (d, 1 H, J = 11.4 Hz), 4.7−4.6 (m, 3 H), 4.39 (s, 2 H), 4.38 (d, 1 H, J = 11.4 Hz), 3.65 (dd, 1 H, J = 9.6, 2.9 Hz), 3.6−3.4 (m, 3 H), 1.42 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 139.7, 138.1, 137.9, 137.6, 136.8, 133.0, 128.4, 128.3, 128.2, 128.1, 127.7, 127.6, 121.3, 80.2, 75.3, 73.3, 71.1, 69.6, 61.4, 46.4, 31.7; MS (CI, NH_4), *m/e* 575 ((M + NH_4)$^+$, 25), 530 (100), 91 (45); HRMS (CI, NH_4) calcd for $C_{33}H_{39}N_3O_3SNH_4$ (M + NH_4^+) 575.3056, found 575.3052.

(1*R*,2*R*,3*S*,7a*S*)-1,2-Dibenzyloxy-3-benzyloxymethyl-7-*tert*-butylthio-2,3,5,7a-tetrahydro-1*H*-pyrrolizine (31) and (6*R*,7*R*,8*S*)-6,7-Dibenzyloxy-8-benzyloxymethyl-4-*tert*-butylthio-3a,6,7,8-tetrahydro-3*H*-[1,2,3]triazolo[1,5-*a*]-azepine (32). A solution of the azidodiene **30** (0.5 g, 0.9 mmol) in $CHCl_3$ (4 mL) was degassed with 5 freeze/thaw cycles and sealed in a thick-walled glass reaction tube fitted with a Teflon sealing valve. The solution was then heated at 75 °C for 18 h behind a blast shield and then cooled, removed from the tube, and concentrated in vacuo. Chromatography (1.5% MeOH/$CHCl_3$) gave 120 mg of **31** (35%; 30% based on recovered starting material), 124.6 mg of **32** (25%; 31% based on recovered starting material), and 76 mg (15%) of starting azidodiene **30**. For **31**: R_f 0.43 (4% MeOH/$CHCl_3$); $[\alpha]^{25}_D$ +1.74 (c = 1.18, abs EtOH), −5.3 (c 1.6 $CHCl_3$); IR ($CHCl_3$) 1496(s) cm^{-1}; ^{1}H NMR (360 MHz, $CHCl_3$) δ 7.5−7.1 (m, 15 H), 5.85 (bs, 1 H), 4.68, 4.57 (AB, 2 H, J_{AB} = 11.9 Hz), 4.60, 4.56 (AB, 2 H, J_{AB} = 12.1 Hz), 4.45, 4.28 (AB, 2 H, J_{AB} = 11.9 Hz), 4.24 (m, 1 H), 4.10 (ddd, 1 H, J = 14.9, 5.7, 2.1 Hz), 4.0−3.93 (m, 2 H), 3.87 (A), 3.84 (B), (AB of ABX system, 2 H, J_{AB} = 9.5, J_{AX} = 7.3, J_{BX} = 6.4 Hz), 3.7−3.6 (m, 2 H), 1.42 (s, 9 H); ^{13}C NMR (90 MHz, $CHCl_3$) δ 138.3, 138.2, 133.9, 131.7, 128.3, 128.2, 127.8, 127.7, 127.6, 127.5, 127.4, 127.2, 85.6, 84.9, 82.2, 73.3, 71.4, 71.2, 66.1, 64.2, 55.3, 46.2, 31.5; MS (70 eV), *m/e* 529 (M$^+$, 38), 91 (100); HRMS calcd for $C_{33}H_{39}NO_3S$ (M$^+$) 529.2650, found 529.2626. The structural assignment of **31** was based on COSY and NOESY spectroscopic studies. No NOE was detected between the methine hydrogens at C-7 and C-7a, indicating a trans relationship. For **32**: R_f 0.75 (4% MeOH/$CHCl_3$); $[\alpha]^{25}_D$ −35.7 (c = 1.56, $CHCl_3$); IR (neat) 1454(s) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.4−7.1 (m, 15 H), 6.20 (dd, 1 H, J = 6.0, 2.5 Hz), 5.05 (ddd, 1 H,J = 8.0, 6.0, 4.5 Hz), 4.7−4.5 (m, 7 H), 4.5−4.2 (m, 3 H), 4.15 (dd, 1 H, J = 6.5, 4.5 Hz), 3.84 (A), 3.78 (B) (AB of ABX, 2 H, J_{AB}= 9.0, J_{Ax}= 8.5, J_{BX} = 6.0 Hz), 1.16 (s, 9 H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 138.9, 138.2, 137.9, 128.5, 128.4, 128.1, 127.9, 127.8, 127.7, 75.4, 73.8, 73.4, 71.96, 71.90, 67.7, 59.0, 57.3, 47.2, 31.3; MS (70 eV), *m/e* 529 (M$^+$, 6), 91 (100). Anal. Calcd for $C_{33}H_{39}N_3O_3S$: C, 70.31; H, 6.60; N, 7.62. Found: C, 70.68; H, 6.62; N, 7.25. The structural assignment of **32** was based on elemental analysis (three nitrogens), the absence of an azide stretch in the IR spectrum,

and the fact that COSY and decoupling studies showed that the vinyl hydrogen appeared as a clean doublet, coupled only to the methine hydrogen at C-6. The configuration at C-3a was not assigned, but only one stereoisomer was observed by ^{1}H NMR.

(3*R*,4*R*,5*S*)-5-Hydroxy-3,4,6-tribenzyloxy-1-hexene (40). *n*-Butyllithium (9.5 mL of 2.5 M solution in hexane, 23.7 mmol) was added to a solution of methyltriphenylphosphonium bromide (7.8 g, 22 mmol) in THF (50 mL) at 0 °C. After 15 min, the solution was cooled to −78 °C, and 2,3,5-tri-*O*-benzyl-L-xylose **39** (4.14 g, 9.90 mmol) in THF (20 mL) was added in a dropwise fashion. (The procedure used for the synthesis of 2,3,5-tri-*O*-benzyl-L-xylofuranose[28] was the same as that reported for the synthesis of 2,3,5-tri-*O*-benzyl-D-arabinofuranose used in the synthesis of **26**.[26]) The resultant slurry was warmed slowly to room temperature over 3 h. After 24 h, water (0.5 mL) was added and the mixture was poured into cold ether and filtered, washing with cold ether. The combined filtrates were concentrated in vacuo. Chromatography (10% ethyl acetate/hexane) gave 2.72 g (66%) of the title compound: R_f 0.34 (25% ethyl acetate/hexane); $[\alpha]^{25}_D$ +5.8 (c = 1.6, $CHCl_3$); IR (neat) 3449(br) cm^{-1}; ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.4−7.1 (m, 15 H), 5.86 (m, 1 H), 5.4−5.3 (m, 2 H), 4.85, 4.55 (AB q, 2 H, J = 11.2 Hz), 4.62, 4.37 (AB q, 2 H, J = 11.8 Hz), 4.46, 4.41 (AB q, 2 H, J = 11.9 Hz), 4.10 (appt, 1 H, J = 7.2 Hz), 3.93 (m, 1 H), 3.61 (dd, 1 H, J = 6.5, 2.7 Hz), 3.45 (A), 3.41 (B) (ABq of ABX system, 2 H, J_{AB} = 9.4, J_{AX} = 6.0, J_{BX} = 6.3 Hz), 2.45 (d, 1 H, J = 6.9 Hz, OH); ^{13}C NMR (90 MHz, $CDCl_3$) δ 138.4, 138.3, 138.1, 135.3, 128.3, 128.26, 128.24, 128.1, 127.79, 127.77, 127.6, 127.5, 119.1, 82.1, 80.4, 74.9, 73.3, 71.3, 70.7, 69.9; MS (CI, NH_3), *m/e* 436 (M + NH_4^+, 100), 419 (M + H^+, 2). Anal. Calcd for $C_{27}H_{30}O_4$: C, 77.48; H, 7.22. Found: C, 77.59; H, 6.96.

(3*R*,4*R*,5*R*)-5-Azido-3,4,6-tribenzyloxy-1-hexene (41). Trifluoromethanesulfonic anhydride (1.5 mL, 2.5 g, 8.9 mmol) in CH_2Cl_2 (9 mL) was added to a solution of pyridine (0.85 mL, 9.9 mmol) in CH_2Cl_2 (9 mL) at −40 °C. After 10 min, the alcohol **40** (3.03 g, 7.24 mmol) in CH_2Cl_2 (39 mL) was added over 5 min. The resultant slurry was warmed slowly to room temperature over 30 min cooled to 0 °C. After 2.5 h, the mixture was filtered through Celite, washing with cold CH_2Cl_2, and the filtrate was concentrated in vacuo to give the crude triflate. This material was diluted with benzene (65 mL) and added to a cold (0 °C) solution of tetra-*n*-butylammonium azide (10.2 g, 36 mmol) in benzene (35 mL). The mixture was then warmed to room temperature for 1 h and then concentrated in vacuo to approximately 10 mL. The resulting red-orange oil was extracted with ether. Without concentration, the combined ethereal extracts were passed through a short column of silica gel and concentrated without warming to give 2.4 g (75%) of the title compound. Due to the instability of this material to cyclization, it was used immediately in the next step: R_f 0.25 (10% ethyl acetat/hexane); IR (neat) 2864(s) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.97 (m, 1 H), 5.5−5.3 (m, 2 H), 4.77, 4.64 (AB q, 2 H, J = 11.2 Hz), 4.61, 4.58 (AB q, 2 H, J = 9.4 Hz), 4.71, 4.45 (ABq, 2 H, J = 11.8 Hz), 4.21 (m, 1 H), 4.08 (m, 1 H), 3.9−3.8 (m, 2 H), 3.8−3.4 (m, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.2, 138.0, 137.9, 135.3, 128.6, 128.4, 128.3, 128.1, 128.0, 127.7, 119.2, 81.1, 80.6, 75.0, 73.3, 70.7, 69.4, 61.5.

(2*S*,3*R*,4*R*)-4-Azido-2,3,5-tribenzyloxy-1-pentanal (42). Azidoalkene **41** (2.4 g, 5.4 mmol) in CH_2Cl_2 (30 mL) and methanol (5.6 mL) was cooled to −78 °C and one drop of Sudan III (0.1% in CH_2Cl_2) was added. The mixture was purged with argon and then ozone was bubbled in for 17 min until the pink color disappeared. After the mixture was purged with with argon for 15 min, dimethyl sulfide was (1.0 g, 16 mmol) added. After 45 min at −78 °C, 1 h at 0 °C, and 1.5 h at room temperature, the yellow solution was concentrated in vacuo to give 2.5 g golden brown oil which was found to be nearly pure aldehyde by proton NMR. Due to its instability to purification procedures, the entire productc was used immediately in the next reaction: R_f 0.53 (30% ethyl acetate/hexane); IR (neat) 2864(s), 2098(s), 1729(m) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.65 (d, 1 H, J = 1 Hz), 7.4−7.0 (m, 15 H), 4.8−4.4 (m, 6 H), 4.01 (m, 1 H), 3.9−3.4 (m, 2 H), 3.5−3.3 (m, 2 H).

(2*R*,3*R*,4*R*,5*Z*)-2-Azido-8-hydroxy-1,3,4-tribenzyloxyoct-5-ene (44). A solution of 3-hydroxypropyltriphenylphosphonium bromide (2.31 g, 5.76 mmol)[29−31] in THF (30 mL) was cooled to 0 °C and treated with potassium hexamethyldisilazide (23 mL of a 0.5 M solution in toluene, 11.5 mmol). The solution was warmed to room temperature over 1 h, kept at that temperature for another 1 h, and then cooled to 0 °C and treated with freshly distilled chlorotrimethylsilane (0.74 mL, 5.83 mmol). After 10 min, the solution of the ylide **43** was cooled to −78 °C and treated with a solution of the entire quantity of aldehyde **42** prepared above (2.5 g, 5.4 mmol theoretical) in THF (10 mL). After 1 h, the mixture was warmed to room temperature. After 1 h, 1 M HCl (20 mL) was added, and the mixture was concentrated in vacuo. The residue was then taken up in THF (50 mL) and 1 M HCl (10 mL) and stirred vigorously for 1 h. The layers were then separated and the aqueous layer was extracted with ethyl acetate. The combined organic extracts were dried over $MgSO_4$ and concentrated in vacuo. Chromatography (25% ethyl acetate/hexane) gave 0.92 g (35% from the alkene **41**) of the title compound: R_f 0.17 (25% ethyl acetate/hexane); $[\alpha]^{25}_D$ −10.8 (c = 1.6, $CDCl_3$); IR (neat) 2097(s) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.5−7.2 (m, 15 H), 5.8−5.5 (m, 2 H), 4.75, 4.60 (AB q, 2 H, J = 11.2 Hz), 4.66, 4.39 (AB q, 2 H, J = 11.9 Hz), 4.57, 4.52 (AB q, 2 H, J = 12.4 Hz), 4.40 (m, 1 H), 3.9−3.8 (m, 2 H), 3.70 (m, 1 H), 3.65−3.50 (m, 3 H), 2.3−2.1 (m, 2 H), 1.98 (bs, 1 H, OH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.3, 137.9, 137.8, 131.5, 129.6, 128.3, 128.2, 127.9, 127.8, 127.6, 81.3, 75.0, 74.5, 73.4, 70.3, 69.7, 61.8, 61.6, 31.4; MS (CI, NH_3), *m/e* 460 ((M − N_2)$^+$, 100); HRMS (CI, NH_3) calcd for $C_{29}H_{33}NO_4H$ ((M − N_2) + H)$^+$) 460.2488, found 460.2466. Decoupling of the methylene protons at δ 2.3−2.1 allowed the determination of the coupling constant between the vinyl protons as J = 11.5 Hz, indicating a cis relationship. No trans isomer was detected by ^{1}H NMR.

(2*R*,3*R*,4*S*,5*S*,6*S*)-2-Azido-8-hydroxy-1,3,4-tribenzyloxy-5,6-epoxyoctane (45α) and (2*R*,3*R*,4*S*,5*R*,6*R*)-2-Azido-8-hydroxy-1,3,4-tribenzyloxy-5,6-epoxyoctane (45*β*). A solution of alkene **44** (0.61 g, 1.3 mmol) in CH_2Cl_2 (5 mL) was cooled to 0 °C and treated with *m*-chloroperbenzoic acid (0.33 g, 1.9 mmol). After being warmed to room temperature for 24 h, the mixture was diluted with CH_2Cl_2 and washed with 1 M NaOH and water. The organic layer was dried over $MgSO_4$ and concentrated. Chromatography (40% ethyl acetate/hexane) gave 0.41 g (65%) of an inseparable 1:1 mixture of **45**α and **45***β* as determined by ^{1}H NMR and HPLC: R_f 0.13 (25% ethyl acetate/hexane); $[\alpha]^{25}_D$ −36.9 (c = 2.3, $CHCl_3$); IR ($CHCl_3$) 3481(br), 2099(s) cm^{-1}; ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.4−7.1 (m, 15 H), 4.87, 4.48 (AB q, 1 H, J = 11.5 Hz), 4.76 (1/2 of AB q, 0.5 H, J = 11 Hz), 4.7−4.4 (m, 5.5 H), 4.0−3.8 (m, 3 H), 3.8−3.7 (m, 3 H), 3.63 (dd, 0.5 H, J = 8, 2 Hz), 3.55 (dd, 0.5 H, J = 8, 2.5 Hz), 3.41 (dd, 0.5 H, J = 8, 2 Hz), 3.3−3.2 (m, 1 H), 3.17 (dd, 0.5 H, J = 8, 4.5 Hz), 2.69 (app q, 0.5 H, J = 4 Hz), 2.0−1.4 (m, 4 H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 138.0, 137.9, 137.8, 137.4, 137.3, 128.6, 128.5, 128.47, 128.41, 128.33, 128.30, 128.1, 128.0, 127.9, 127.8, 127.7, 79.3, 77.8, 75.0, 74.7, 74.1, 73.5, 73.4, 72.5, 72.3, 69.7, 69.6, 61.0, 60.9, 60.5, 57.6, 56.4, 55.1, 52.8, 31.3, 31.2; MS (CI, NH_3), *m/e* 521 ((M + NH_4)$^+$, 100); HRMS (CI, NH_3) calcd for $C_{29}H_{33}N_3O_5NH_4$ (M + NH_4)$^+$ 521.2763, found 521.2747.

(2*R*,3*R*,4*S*,5*S*,6*S*)-2-Azido-8-(*p*-toluenesulfonyl)oxy-1,3,4-tribenzyloxy-5,6-epoxyoctane (46α) and (2*R*,3*R*,4*S*,5*R*,6*R*)-2-Azido-8-(*p*-toluenesulfonyl)oxy-1,3,4-tribenzyloxy-5,6-epoxyoctane (46*β*). A solution of the epoxides **45**α and **45***β* (0.34 g, 0.68 mmol) in CH_2Cl_2 (2 mL) was cooled to −15 °C and treated with pyridine (0.17 mL, 2.1 mmol), (dimethylamino)pyridine (10 mg, 0.08 mmol), and *p*-toluenesulfonyl chloride (0.27 g, 1.4 mmol). After 24 h at −15 °C and 24 h at −10 °C, the solution was diluted with ether (150 mL) and washed with water, 1 M HCl, saturated $NaHCO_3$, and water. The organic phase was dried over $MgSO_4$ and concentrated in vacuo. Chromatography (20% ethyl acetate/hexane) gave 40 mg (12%) of starting material and 0.3 g (67%, 77% based on recovered

starting material) of an inseparable 2:1 mixture of **46**α and **46***β* as determined by ^{1}H NMR and HPLC: R_f 0.27 (20% ethyl acetate/hexane); $[\alpha]^{25}_D$ −39.5 (*c* = 1.1, $CHCl_3$); IR ($CHCl_3$) 2099-(s), 1656(s) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) *δ* 7.78 (d, 2 H, *J* = 8 Hz), 7.5−7.1 (m, 17 H), 4.82, 4.43 (AB q, 1.4 H, *J* = 11.5 Hz), 4.7−4.5 (m, 4.6 H), 4.2−4.0 (m, 2 H), 3.9−3.6 (m, 4 H), 3.51 (d, 0.66 H, *J* = 5 Hz), 3.45 (d, 0.33 H, *J* = 5 Hz), 2.29 (d, 0.66 H, *J* = 5 Hz), 3.20 (m, 0.33 H), 3.1−3.0 (m, 1 H), 2.52 (m, 0.66 H), 2.43 (s, 3 H), 2.0−1.4 (m, 2 H); ^{13}C NMR (90 MHz, $CDCl_3$) *δ* 144.9, 137.9, 137.8, 137.2, 129.8, 128.6, 128.5, 128.47, 128.41, 128.3, 128.2, 128.0, 127.9, 127.8, 127.79, 127.74, 79.1, 77.7, 75.0, 74.5, 74.0, 73.5, 73.4, 72.7, 72.2, 69.6, 69.5, 67.5, 67.4, 61.0, 60.9, 57.8, 55.5, 54.8, 51.0, 28.6, 28.3, 21.5; MS (CI, NH_3), *m*/*e* 675 ((M + NH_4^+, 31), 246 (100); HRMS (CI, NH_3) calcd for $C_{36}H_{39}N_3O_7SNH_4$ (M + NH_4^+) 675.2852, found 675.2842.

(1*R*,2*R*,3*R*,7*S*,7a*R*)-1,2-Dibenzyloxy-3-benzyloxymethyl-7-hydroxy-2,3,5,6,7,7a-hexahydro-1*H*-pyrrolizine (47a) and (1*R*,2*R*,3*R*,7*R*,7a*S*)-1,2-Dibenzyloxy-3-benzyloxymethyl-7-hydroxy-2,3,5,6,7,7a-hexahydro-1*H*-pyrrolizine (47b). A mixture of the epoxides **46**α and **46***β* (240 mg, 0.36 mmol), ether (2 mL), and EtOH (1 mL) was stirred with 10% palladium on carbon (17 mg, 5 wt %) under a balloon of hydrogen for 15 h at room temperature. The hydrogen was evacuated and replaced by nitrogen, and then the catalyst was removed by filtration through a short column of Celite. The filtrate was diluted with EtOH (35 mL), and K_2CO_3 (0.30 g, 2.2 mmol) was added. The mixture was heated at reflux for 20 h and then filtered and concentrated. This residue was taken up in $CHCl_3$ and filtered. After concentration of the filtrate, chromatography (5% MeOH/$CHCl_3$) of the residue gave 116 mg (71%) of a 2:1 mixture of **47a** and **47b**. A second chromatographic separation (20% *i*-PrOH/hexane followed by 7% MeOH/$CHCl_3$) give 69 mg of **47a** and 29 mg **47b** as thick oils. Data for **47a**: R_f 0.66 (20% *i*-PrOH/hexane); $[\alpha]^{25}_D$ +8.4 (*c* = 1.6, EtOH); IR ($CHCl_3$) 3438(br) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) *δ* 7.4−7.1 (m, 15 H), 4.65, 4.57 (AB q, 2 H, *J* = 11.5 Hz), 4.55−4.45 (m, 4 H), 4.29 (t, 1 H, *J* = 4 Hz), 4.17 (t, 1 H, *J* = 4.5 Hz), 4.12 (m, 1 H), 3.6−3.4 (m, 3 H), 3.22 (m, 1 H), 3.39 (app q, 1 H, 1 H, *J* = 4.5 Hz), 2.8−2.7 (m, 1H), 2.22 (bs, 1 H), 2.1−1.8 (m, 2 H); ^{13}C NMR (90 MHz, $CDCl_3$) *δ* 138.6, 138.4, 137.9, 128.4, 128.3, 127.9, 127.72, 127.70, 127.6, 127.4, 85.9, 81.7, 73.4, 73.3, 72.3, 72.1, 71.9, 71.8, 69.9, 52.7, 36.9; MS (70 eV), *m*/*e* (%) 459 (M^+, 1), 338 (100), 91 (95); HRMS Calcd for $C_{29}H_{33}NO_4$ (M^+): 459.2409. Found: 459.2404. Data for **47b**: R_f 0.07 (20% *i*-PrOH/hexane); $[\alpha]^{25}_D$ +8.2 (*c* = 0.62, EtOH); IR ($CHCl_3$) 3488 (br) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) *δ* 7.4−7.1 (m, 15 H), 4.7−4.5 (m, 6 H), 4.3−4.2 (m, 2 H), 4.0−3.9 (m, 2 H), 3.8−3.6 (m, 2 H), 3.38 (dd, 1 H, *J* = 7.5, 3.5 Hz), 3.28 (app q, 1 H, *J* = 7.5 Hz), 3.19 (m, 1 H), 2.80 (m, 1 H), 2.0−1.7 (m, 2 H); ^{13}C NMR (90 MHz, $CDCl_3$) *δ* 138.3, 138.2, 137.2, 128.7, 128.4, 128.3, 128.2, 127.9, 127.8, 127.7, 127.6, 85.8, 84.7, 73.3, 73.1, 72.5, 71.8, 68.9, 68.2, 62.9, 46.5, 35.7; MS (CI, NH_3), *m*/*e* 460 ((M + H)$^+$, 100), 91 (30); HRMS (CI, NH_3) calcd for $C_{29}H_{33}NO_4H$ (M + H^+) 460.2488, found 460.2490.

(1*R*,2*R*,3*R*,7*S*,7a*R*)-3-Hydroxymethyl-2,3,5,6,7,7a-hexahydro-1*H*-pyrrolizine-1,2,7-triol [2, (+)-Australine]. Pyrrolizine **47a** (12 mg, 0.03 mmol) in EtOH (1 mL) was stirred vigorously with 10% Pd on carbon (30 mg, 300 wt %) under a balloon of hydrogen for 48 h at room temperature. The hydrogen was evacuated and replaced by nitrogen, the mixture was filtered through Celite, and the filtrate was concentrated in vacuo to give 4.3 mg (88%) of the title compound, which was found to be pure by ^{1}H NMR: $[\alpha]^{25}_D$ +8.0 (*c* = 0.35, H_2O); ^{1}H NMR (360 MHz, D_2O) *δ* 4.21 (m, 1 H), 4.08 (t, 1 H, *J* = 7.5 Hz), 3.73 (t, 1 H, *J* = 8.5 Hz), 3.63 (dd, 1 H, *J* = 11, 3 Hz), 3.45 (dd, 1 H, *J* = 11, 6.5 Hz), 3.1−2.9 (m, 2 H), 2.7−2.5 (m, 2 H), 1.9−1.7 (m, 2 H); ^{13}C NMR [90 MHz, D_2O with dioxane as an internal standard (*δ* 67.4)] *δ* 79.5, 73.9, 71.7, 71.4, 70.3, 63.1, 52.7, 35.9. These values were in good agreement with literature data.[6b,c]

(1*R*,2*R*,3*R*,7*R*,7a*S*)-3-Hydroxymethyl-2,3,5,6,7,7a-hexahydro-1*H*-pyrrolizine-1,2,7-triol [4, (−)-7-Epialexine]. Pyrrolizine **47b** (12 mg, 0.03 mmol) in EtOH (1.2 mL) was stirred vigorously with 10% Pd on carbon (32 mg, 300 wt %) under a balloon of hydrogen for 48 h at room temperature. The hydrogen was evacuated and replaced by nitrogen, the mixture was filtered through Celite, and the filtrate was concentrated in vacuo to give 4.4 mg (87%) of the title compound, which was found to be pure by ^{1}H NMR: $[\alpha]^{25}_D$ −8.9 (*c* 0.42, H_2O); ^{1}H NMR (360 MHz, D_2O) *δ* 4.32 (bt, 1 H, *J* = 3 Hz), 4.09 (t, 1 H, *J* = 8 Hz), 3.8−3.7 (m, 3 H), 3.39 (dd, 1 H, *J* = 8, 4 Hz), 3.08 (m, 1 H), 2.85 (m, 2 H), 1.71 (m, 2 H); ^{13}C NMR [(90 MHz, D_2O with dioxane as an internal standard (*δ* 67.4)] *δ* 78.3, 76.2, 72.8, 67.0, 64.5, 59.9, 46.6, 34.6. These values were in good agreement with literature data.[18]

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Supporting Information Available: Copies of ^{1}H NMR spectra for all new, stable compounds without elemental analysis. This material is available free of charge via the Internet at http://pubs.acs.org.

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