Total Syntheses of (+)-Castanospermine and (+)-1-Epicastanospermine and Their 1-*O*-Acyl Derivatives from a Common Chiral Building Block

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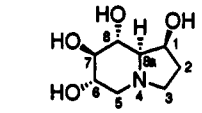
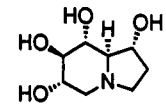
Stereoselective total syntheses of (+)-castanospermine (1) and (+)-1-epicastanospermine (2) and their 1-*O*-acyl derivatives 3-5 have been achieved via a noncarbohydrate-based approach utilizing allylic alcohol 9 as a common chiral building block. Epoxide 10, prepared from 9, underwent regio- and stereoselective ring opening with $Et_2AlN(CH_2Ph)_2$ to give amino alcohol 11, which was converted to aldehyde 15 in four steps. The aldol reaction of 15 with lithio ethyl acetate was predominantly anti selective and generated α-hydroxy ester 16 by a nonchelate Felkin-Anh pathway. Compound 16 was transformed into (+)-1-epicastanospermine (2) and its 1-*O*-acetyl and 1-*O*-butyryl derivatives (4 and 5) via the lactam intermediate 21. Alternatively, α-hydroxy ester 16 was converted to (+)-castanospermine (1) and its 1-*O*-acetyl derivative (3); these syntheses were achieved via reaction sequences involving the inversion of the C-3 configuration by the Mitsunobu process and 2-fold tandem cyclizations to form the indolizidine skeleton. The results of preliminary biological testing of compounds 2-5 for anti-HIV-1 activity in whole cells are presented.

Introduction

(+)-Castanospermine (1) is a polyhydroxylated indolizidine alkaloid isolated from *Castanospermum australe*[1] and *Alexa leiopetala*.[2] Compound 1 is a nitrogen-containing analogue of glucopyranoside and, thus, is a potent inhibitor of various α- and β-glucosidases[3] including glucosidases I of glycoprotein processing.[3c] In addition, 1 shows high anticancer,[4] antiviral,[5] and antiretroviral[6] activities. Compound 1 has been also shown to interfere with human immunodeficiency virus (HIV) syncytium formation[7] and has been of particular interest for its potential therapeutic usage as an anti-AIDS agent. 1-Epicastanospermine (2),[8] epimeric at C-1 with castanospermine, is the only isomer (of the 31 stereoisomers of castanospermine) in which the piperidine ring has the same configuration as D-glucose. These natural and unnatural tetrahydroxyindolizidines, 1 and 2, bearing close structural resemblance to D-glucose, are also structurally related to tetrahydroxypyrrolidine alkaloids such as australine[9] and 7-epiaustraline,[10] respectively, both recently reported to act as HIV inhibitors.[11] Although no report on the anti-HIV activity of 1-epicastanospermine (2) has been published in the literature, these facts suggest that 2 may also possess anti-HIV activity.



(+)-Castanospermine, 1



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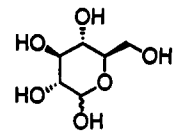
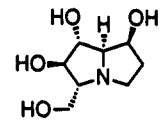
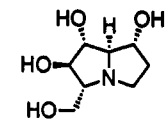


D-Glucose



(+)-Australine



(+)-7-Epiaustraline

Because of their significant biological activities, castanospermine[12-14] and its structural analogues[15] have been the subject of extensive synthetic efforts, which have culmi-

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(10) 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.
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(12) For syntheses of natural (+)-castanospermine, see refs 8a-c as well as the following: (a) Hamana, H.; Ikota, N.; Ganem, B. *J. Org. Chem.* **1987**, *52*, 5492. (b) Bhide, R.; Mortezaei, R.; Sih, C. J. *Tetrahedron Lett.* **1990**, *31*, 4827. (c) Miller, S. A.; Chamberlin, A. R. *J. Am. Chem. Soc.* **1990**, *112*, 8100. (d) Gerspacher, M.; Rapoport, H. *J. Org. Chem.* **1991**, *56*, 3700.
(13) For a synthesis of unnatural (-)-castanospermine, see ref 8d.
(14) For a synthesis of racemic castanospermine, see: Reymond, J.-L.; Vogel, P. *Tetrahedron Lett.* **1989**, *30*, 705.

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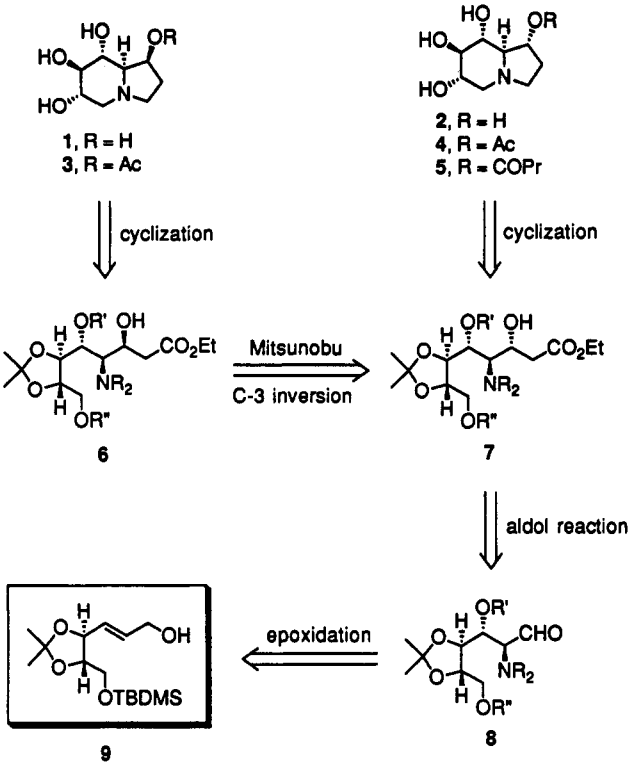
nated in several total syntheses of natural castanospermine[12] in recent years. With one exception,[12b] the reported chiral routes to natural castanospermine are based upon manipulation of natural hexoses as starting materials. Recent investigations in this laboratory have revealed that chiral allylic alcohol **9** serves as a versatile chiral building block in the preparation of several naturally occurring azasugars, e.g., nojirimycin,[16] 1-deoxynojirimycin,[16] galactostatin,[17] 1-deoxygalactostatin,[17] and α-homonojirimycin.[18] Because of our continuing interest in the chiral preparation of azasugars and to expand the synthetic utility of building block **9**, we undertook enantioselective syntheses of (+)-castanospermine (**1**) and (+)-1-epicastanospermine (**2**) and their 1-*O*-acyl derivatives **3–5** by means of a noncarbohydrate-based approach utilizing **9** as a *common* starting material.[19] Recent findings have revealed that several *O*-acylated derivatives of castanospermine are significantly better than castanospermine itself at inhibiting HIV replication because they are more lipophilic than the parent compound.[20] The higher anti-HIV activity has stimulated considerable interest in studies on the preparation of various *O*-acyl derivatives by means of chemical and enzymatic transformation of natural castanospermine in recent years.[21] In this paper, we describe the enantiocontrolled total syntheses of (+)-castanospermine (**1**) and (+)-1-epicastanospermine (**2**), their 1-*O*-acetyl derivatives **3** and **4**, and the 1-*O*-butyryl derivative of **2** (i.e., **5**), all starting from the *single chiral building block* **9**. We also report the preliminary evaluation of **2–5** for anti-HIV-1 activity in cells.

Retrosynthetic analysis of **1** and **2** and their 1-*O*-acyl derivatives **3–5** shows that a disconnection of the C-3–N and C-5–N bonds of the molecules would lead to acyclic amines **6** and **7** as summarized in Scheme I. Compound **6**, with the 3β-hydroxy group, could be obtained from 3α-alcohol **7** by Mitsunobu displacement. Alcohol **7** could arise from chiral building block **9** through epoxidation, ring opening, and stereocontrolled aldol reaction of an aldehyde **8**.

Scheme I



Results and Discussion

Syntheses of (+)-1-Epicastanospermine and 1-*O*-Acyl Derivatives. Allylic alcohol **9** was prepared in a straightforward manner from dimethyl L-tartrate in six steps.[16] With **9** in hand, we initially envisioned synthesizing (+)-1-epicastanospermine (**2**) according to the above-mentioned strategic planning (Scheme I). Thus, **9** was converted to epoxide **10** by Katsuki–Sharpless asymmetric epoxidation to set up the required stereochemistry.[16] Regio- and stereoselective cleavage of the oxirane ring was achieved by exposure of **10** to $Et_2AlN(CH_2Ph)_2$, prepared from Et_3Al and dibenzylamine,[22] to give amino alcohol **11** to 72% yield (Scheme II). After acetylation of primary alcohol **11** with 1.5 equiv of acetyl chloride, the remaining secondary alcohol was protected as the methoxymethyl ether to form **13** in 75% yield from **11**. Alcohol **14**, obtained from deacetylation of **13** with $LiAlH_4$, was converted to aldehyde **15** by Swern oxidation in 73% yield from **13**.

The aldol reaction of aldehyde **15** with lithio ethyl acetate, generated from ethyl acetate and $LiN(SiMe_3)_2$, in THF at −80 °C provided an inseparable mixture of diastereomeric α- and β-hydroxy esters **16** and **17**, epimeric at C-3, in a ratio of 89:11 in 92% yield. The ratio of **16** to **17** was calculated from the integrals of the ^1H NMR signals of the respective Si-methyl protons, which resonated at δ 0.03 and 0.05 in the case of **16** and at δ 0.12 and 0.13 in the case of **17**. When the reaction was conducted with lithio *tert*-butyl acetate under the same conditions, the α-hydroxy ester (*tert*-butyl ester analogue of **16**) was the major isomer formed; however, both the diastereoselectivity and yield are lower: 77:23 and 82% (for the mixture of diastereomers). An alternative way of introducing the acetic acid moiety into **15**, namely, a Lewis

(15) (a) Hendry, D.; Hough, L.; Richardson, A. C. *Tetrahedron Lett.* **1987**, *28*, 4597. (b) Hendry, D.; Hough, L.; Richardson, A. C. *Tetrahedron* **1988**, *44*, 6143, 6153. (c) Fleet, G. W. J.; Ramsden, N. G.; Molyneux, R. J.; Jacob, G. S. *Tetrahedron Lett.* **1988**, *29*, 3603. (d) Burgess, K.; Henderson, I. *Ibid.* **1990**, *31*, 6949. (e) Aamlid, K. H.; Hough, L.; Richardson, A. C. *Carbohydr. Res.* **1990**, *202*, 117. (f) Fleet, G. W.; Ramsden, N. G.; Nash, R. J.; Fellows, L. E.; Jacob, G. S.; Molyneux, R. J.; Cenci di Bello, I.; Winchester, B. *Ibid.* **1990**, *205*, 269. (g) Liu, P. S.; Kang, M. S.; Sunkara, P. S. *Tetrahedron Lett.* **1991**, *32*, 719. (h) Grandnig, G.; Berger, A.; Grassberger, V.; Stütz, A. E.; Legler, G. *Ibid.* **1991**, *32*, 4889. (i) St-Denis, Y.; Chan, T.-H. *J. Org. Chem.* **1992**, *57*, 3078.

(16) Iida, H.; Yamazaki, N.; Kibayashi, C. *J. Org. Chem.* **1987**, *52*, 3337.

(17) Aoyagi, S.; Fujimaki, S.; Yamazaki, N.; Kibayashi, C. *Heterocycles* **1990**, *30*, 783. Aoyagi, S.; Fujimaki, S.; Yamazaki, N.; Kibayashi, C. *J. Org. Chem.* **1991**, *56*, 815.

(18) Aoyagi, S.; Fujimaki, S.; Kibayashi, C. *J. Chem. Soc., Chem. Commun.* **1990**, 1485.

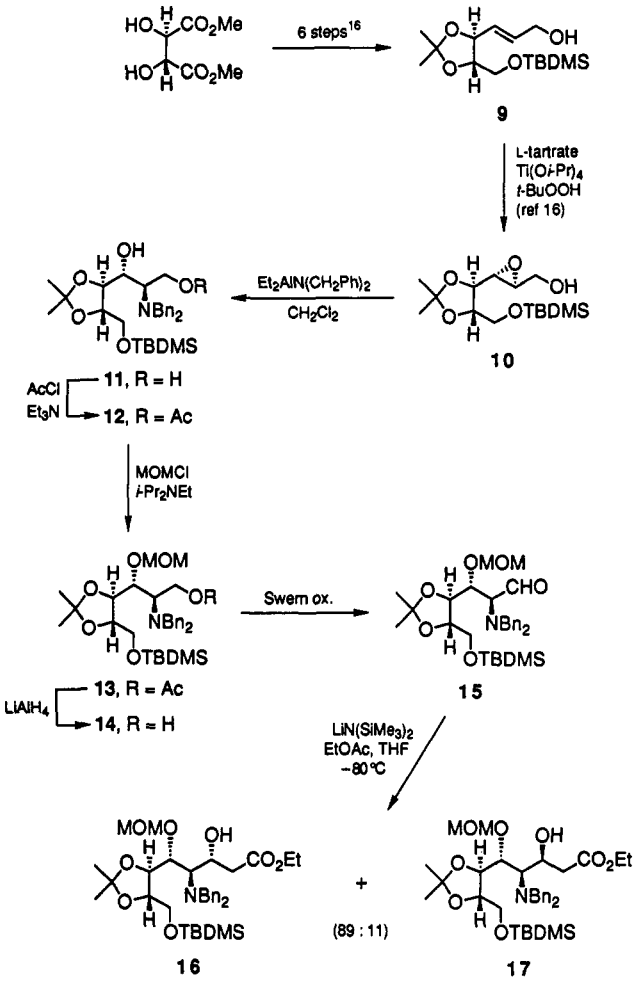
(19) For a preliminary account of a portion of this work, see: Ina, H.; Kibayashi, C. *Tetrahedron Lett.* **1991**, *32*, 4147.

(20) (a) Sunkara, P. S.; Taylor, D. L.; Kang, M. S.; Bowlin, T. L.; Liu, P. S.; Tyms, A. S.; Sjoerdsma, A. *Lancet* **1989**, *I*, 1206. (b) Taylor, D. L.; Sunkara, P. S.; Liu, P. S.; Kang, M. S.; Bowlin, T. L.; Tyms, A. S. *AIDS* **1991**, *5*, 693. (c) Ruprecht, R. M.; Bernard, L. D.; Bronson, R.; Gama Sosa, M. A.; Mullaney, S. *J. Acq. Immun. Def.* **1991**, *4*, 48.

(21) For preparations of *O*-acyl derivatives of castanospermine, see ref 20a as well as the following: (a) Margolin, A. L.; Delinck, D. L.; Whalon, M. R. *J. Am. Chem. Soc.* **1990**, *112*, 2849. (b) Anderson, W. K.; Coburn, R. A.; Gopalsamy, G.; Howe, T. J. *Tetrahedron Lett.* **1990**, *31*, 169. (c) Liu, P. S.; Hoekstra, W. J.; King, C.-H. R. *Ibid.* **1990**, *31*, 2829. (d) Delinck, D. L.; Margolin, A. L. *Ibid.* **1990**, *31*, 3093. (e) Gopalsamy, A.; Anderson, W. K. *Ibid.* **1991**, *32*, 4669.

(22) This procedure was based on: Overman, L. E.; Flippin, L. A. *Tetrahedron Lett.* **1981**, *22*, 195.

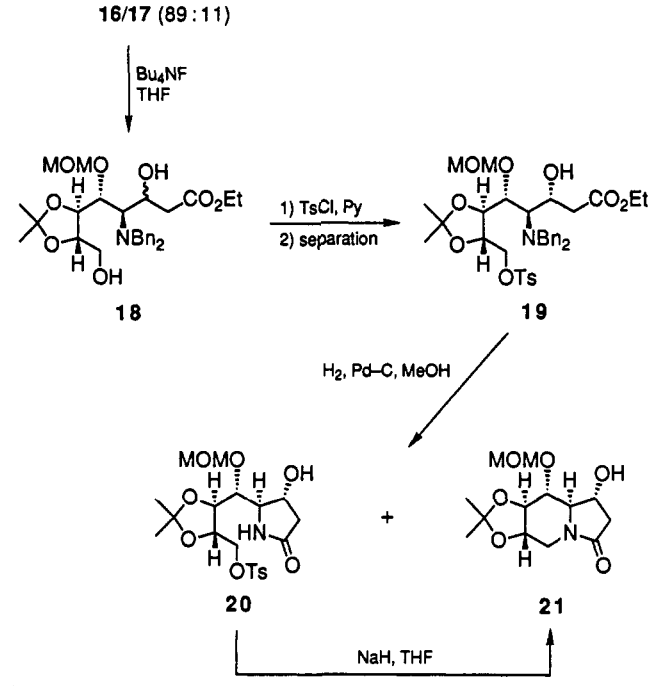
Scheme II



acid-mediated aldol-type reaction of **15** with ketene silyl acetal,[23] was then carried out. The reaction of *O*-ethyl-*O*-trimethylsilyl ketene acetal with **15** in the presence of various Lewis acids such as $TiCl_4$, $EtAlCl_2$, and $SnCl_4$ resulted in the formation of a mixture of **16** and **17**. These reactions with Lewis acids all exhibited anti diastereoselectivity, ranging from 82:18 to 90:10; however, the yields of adducts **16**/**17** were only 45%, 40%, and 10%, respectively. When *O*-benzyl-*O*-trimethylsilyl ketene acetal and $EtAlCl_2$ were used for this reaction, the anti/syn ratio increased to 93:7; however, the yield of the adducts (benzyl ester analogues of **16** and **17**) was very poor (23%). The decrease of the yields observed in these Lewis acid-prompted aldol reactions might be the result of the susceptibility of the protecting groups to acid. Another alternative, the Reformatsky reaction of **15** with ethyl bromoacetate (Zn, benzene, reflux), provided a mixture of **16** and **17** in 34% yield with lower anti selectivity (**16**:**17** = 67:33). The anti selectivity[24] observed in all cases is consistent with the prediction based on a nonchelate Felkin–Anh model.[25]

The 89:11 mixture of diastereomeric aldol adducts **16** and **17** obtained from the above aldol reaction with lithio

Scheme III



ethyl acetate was used as the material for the synthesis. The mixture was subjected to desilylation to give **18** as an inseparable mixture of diastereomers in 94% yield (Scheme III). After tosylation of the primary alcohol function, diastereomerically pure α-hydroxy tosylate **19** was separated as a crystalline product in 78% yield. Removal of the nitrogen protecting groups from **19** by catalytic hydrogenolysis over palladium on carbon in methanol led to in situ cyclization to lactams **20** and **21** in 49% and 20% yields, respectively. Major lactam **20** could be cyclized to **21** by further treatment with sodium hydride in THF in 71% yield; thus, the total yield of lactam **21** from **19** was 55%. The synthesis of 1-epicastanospermine (**2**) was accomplished as outlined in Scheme IV. Reduction of lactam **21** with borane afforded **22** in 66% yield. Subsequent removal of the alcohol protecting groups by heating **22** with concentrated HCl in methanol and applying the resulting oil to a column of ion-exchange resin (Dowex 1-X8, OH^- form) provided (+)-1-epicastanospermine (**2**) in 76% yield. Synthetic (+)-1-epicastanospermine showed an optical rotation in methanol,[26] $[\alpha]^{26}_D$ +3.8° (*c* 0.5), that was in accord with the published value for the opposite enantiomer $[[\alpha]^{20}_D$ −4° (*c* 1.2, MeOH)][8d] except for the sign and had ^1H NMR spectral data virtually in agreement with those reported[8b] for **2**.

The 1-*O*-acetyl and 1-*O*-butyryl derivatives of 1-epicastanospermine, i.e., **4** and **5**, were prepared from **22** in 55% and 58% yields, respectively, via acylation of the C-1 hydroxy group by standard methods and subsequent removal of the alcoholic protecting groups on the piperidine ring with anhydrous methanolic hydrochloric acid.

Synthesis of (+)-Castanospermine and Its 1-*O*-Acetyl Derivative. We next envisioned elaborating (+)-castanospermine (**1**) from aldol adducts **16** and **17**. Thus,

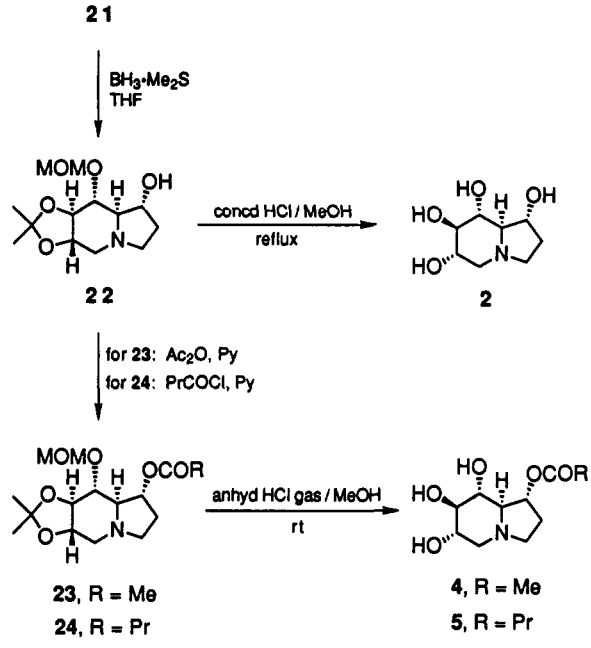
(23) For the Lewis acid-prompted aldol reaction of silyl ketene acetals with α-amino aldehydes, both chelation-controlled (Takemoto, Y.; Matsumoto, T.; Ito, Y.; Terashima, S. *Tetrahedron Lett.* **1990**, *31*, 217) and nonchelation-controlled (Mikami, K.; Kaneko, M.; Loh, T.-P.; Terada, M.; Nakai, T. *Ibid.* **1990**, *31*, 3909) mechanisms leading to syn and anti selectivities, respectively, have been reported.

(24) The discussion of the anti selectivity of the aldol reaction of **15** in the preliminary report[19] offered a misleading interpretation involving a chelate model.

(25) (a) Chérest, M.; Felkin, H.; Prudent, N. *Tetrahedron Lett.* **1968**, 2199. (b) Anh, N. Y.; Eisenstein, O. *Nouv. J. Chim.* **1977**, *1*, 61. (c) Anh, N. T. *Top. Curr. Chem.* **1980**, *88*, 145.

(26) For the optical rotation of 1-epicastanospermine in water, quite different values $[[\alpha]^{20}_D$ +6° (*c* 0.45)[8a] and $[\alpha]^{20}_D$ −39.1° (*c* 0.4)[8b]] have been reported. The discrepancy in these values has been suggested to be caused by a dependence of the optical rotation on the pH of the solvent.[8d]

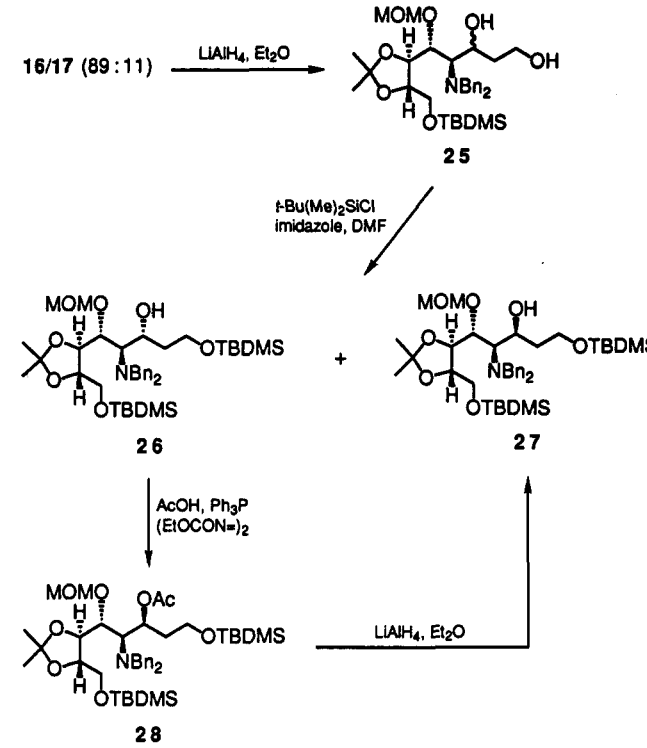
Scheme IV



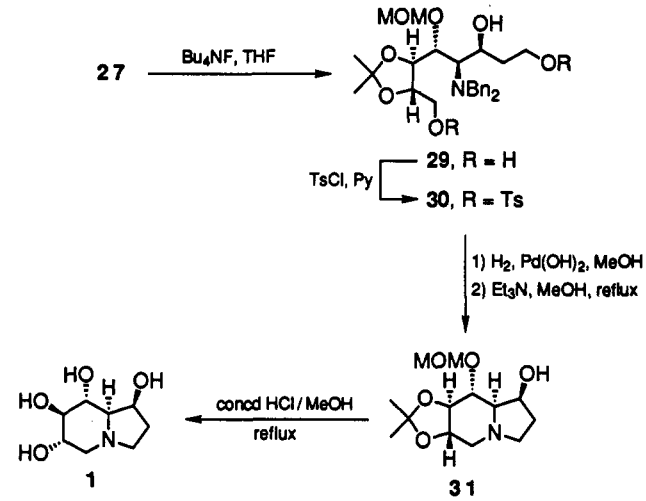
the 89:11 diastereomeric mixture of **16** and **17** underwent $LiAlH_4$ reduction to give **25** as an inseparable mixture of diastereomers. Chromatographic separation of the diastereomers was achieved after silylation of the primary alcohol with 1.2 equiv of *tert*-butyldimethylsilyl chloride in the presence of imidazole in DMF. Silylation afforded α- and β-epimers **26** and **27** in yields of 83% and 7%, respectively (Scheme V). Major product **26**, with the undesired configuration at C-3, was converted to requisite β-alcohol **27** in 46% yield by Mitsunobu displacement with acetic acid followed by deacetylation of resulting β-acetate **28** with $LiAlH_4$. β–Alcohol **27** thus obtained was used to complete the synthesis as outlined in Scheme VI. Silyl ether cleavage with Bu_4NF and subsequent tosylation of both the terminal hydroxy groups with 3 equiv of tosyl chloride gave bistosylate **30** in 60% overall yield from **27**. Upon N-deprotection via catalytic hydrogenolysis over palladium hydroxide in methanol followed by heating in the presence of triethylamine, a 2-fold tandem ring closure occurred to produce indolizidine **31** in 78% yield from **30**. Hydrolytic removal of the O-protecting groups under acidic conditions, application of the crude HCl salt to an ion-exchange column (Dowex 1-X8, OH^- form), and subsequent lyophilization provided (+)-castanospermine (**1**) in 71% yield. Physical and spectral data for the synthetic material were found to be consistent with those published[1] for the natural product.

α-Alcohol **26** described above is a key intermediate for the approach to (+)-1-*O*-acetylcastanospermine (**3**) as outlined in Scheme VII. Catalytic hydrogenolysis of **26** over palladium hydroxide cleaved the *N*,*N*-dibenzylamino group, and the primary amino group generated was protected with benzyl chloroformate. The inversion of the stereochemistry at C-3 of resulting carbamate **32** was accomplished by the Mitsunobu reaction with acetic acid to afford β-acetate **33** (70% yield), which was then desilylated to give **34** in 94% yield. After hydrogenolytic removal of the benzyloxycarbonyl group, resulting deprotected amino alcohol **35** was exposed at 0 °C to triphenylphosphine and carbon tetrabromide and then to triethylamine. This procedure led smoothly to double intramolecular cyclodehydration, resulting in the construction of indolizidine ring **36** in 66% yield from **34**. Finally, deblocking of the methoxymethyl and the isopropylidene groups with anhydrous methanolic hydrochloric acid generated (+)-1-*O*-acetylcastanospermine (**3**) in 69% yield. The melting point and spectral data of **3** were in accord with those reported[21a] for 1-*O*-acetylcastanospermine enzymatically derived from natural castanospermine.

Scheme V



Scheme VI



Preliminary Test for Anti-HIV Activity. Four of the target compounds, i.e., **2**–**5**, were preliminarily tested for anti-HIV activity in a whole cell assay. Compounds **2** and **3** were found to inhibit the cytopathic effect of acute HIV-1 infection against MT-4 cells at concentrations of more than 62.5 μg (0.33 μmol)/mL and 250 μg (1.08 μmol)/mL, respectively. The rest of the compounds were devoid of activity against HIV-1 in the same assay.

Conclusion

In conclusion, we have achieved the stereo- and enantioselective syntheses of (+)-castanospermine and (+)-1-

epicastanospermine, as well as their 1-*O*-acyl derivatives, via a noncarbohydrate-based strategy. That these syntheses were all accomplished from chiral allylic alcohol **9** has allowed us to demonstrate the marked versatility of **9** as a common chiral building block for the total syntheses of azasugars.

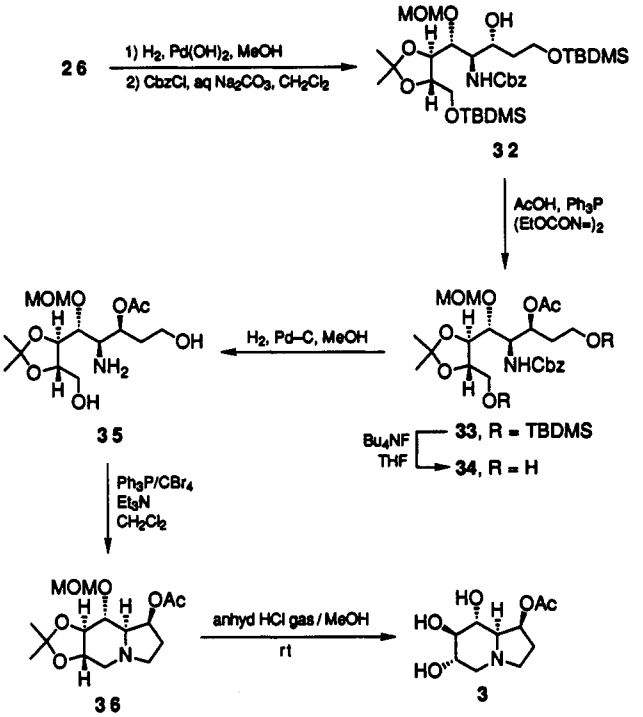
Experimental Section

General Procedures. Melting points are uncorrected. Optical rotations were measured on a digital polarimeter in a 1-dm cell. IR spectra were recorded on an FTIR instrument. ^{1}H NMR spectra were run at 300, 400, or 500 MHz. ^{13}C NMR spectra were determined at 75, 100, or 125 MHz. Chemical shifts were reported on the δ scale relative to $CHCl_3$ as an internal reference (7.26 ppm for ^{1}H and 77.0 ppm for ^{13}C), unless otherwise indicated. DMSO (2.50 ppm for ^{1}H and 39.5 ppm for ^{13}C), MeOH (3.35 ppm for ^{1}H and 49.0 ppm for ^{13}C), DOH (4.67 ppm for ^{1}H), and dioxane (67.4 ppm for ^{13}C) were occasionally used as internal references. ^{13}C NMR peak assignments were confirmed by DEPT experiments. Mass spectra were measured at 70 eV. TLC chromatography was performed on precoated silica gel 60 F 254 plates (Merck), and silica gel 60 (230–400 mesh) (Merck) was used for column chromatography. Microanalyses were carried out by the Microanalytical Laboratory at Tokyo College of Pharmacy.

(2*R*,3*R*,4*S*,5*S*)-6-[(*tert*-Butyldimethylsilyl)oxy]-2-(dibenzylamino)-4,5-(isopropylidenedioxy)hexane-1,3-diol (11). To a cooled (0 °C), stirred CH_2Cl_2 (65 mL) solution of dibenzylamine (2.84 g, 14.4 mmol) under Ar was added a 0.92 M solution of triethylaluminum (16.0 mL, 14.7 mmol) in hexane. After the reaction mixture was stirred for 30 min, a solution of **10** (4.60 g, 14.4 mmol) in CH_2Cl_2 (40 mL) was added, and stirring was continued for an additional 14 h at rt. The mixture was ice-cooled and quenched with water (20 mL). The resulting mixture was stirred for 2 h at rt and extracted with CH_2Cl_2 (3 × 50 mL). The combined extracts were washed with water and dried ($MgSO_4$). After removal of the solvent in vacuo, the residue was purified by column chromatography on silica gel (EtOAc–hexane (1:5)) to give **11** (5.81 g, 78%) as a colorless oil: $[\alpha]^{26}_D$ +5.3° (*c* 1.4, $CHCl_3$); IR (neat) 3442 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.06 (3 H s), 0.08 (3 H, s), 0.91 (9 H, s), 1.35 (3 H, s), 1.39 (3 H, s), 2.85 (1 H, dd, *J* = 12.6, 6.1 Hz), 3.72 (2 H $^1/_2$ AB q, *J* = 13.6 Hz), 3.75 (2 H, d, *J* = 4.5 Hz), 3.79 (2 H, $^1/_2$ AB q, *J* = 13.6 Hz), 3.88 (2 H, d, *J* = 6.1 Hz), 3.94–4.01 (2 H, m), 4.25 (1 H, dd, *J* = 8.1, 1.9 Hz), 7.23–7.30 (10 H, m); ^{13}C NMR ($CDCl_3$) δ -5.39 (CH_3), -5.35 (CH_3), 18.4 (C), 26.0 (CH_3, 3 carbons), 27.2 (CH_3, 2 carbons), 54.4 (CH_2, 2 carbons), 59.1 (CH_2), 60.7 (CH), 63.3 (CH_2), 68.6 (CH), 77.2 (CH), 78.8 (CH), 109.2 (C), 127.1 (CH, 2 carbons), 128.4 (CH, 4 carbons), 129.0 (CH, 4 carbons), 139.5 (C, 2 carbons); MS *m/z* (rel intensity) 500 (M^+ – CH_3, 2), 484 (7), 458 (5), 240 (100). Anal. Calcd for $C_{29}H_{45}NO_5Si$: C, 67.53; H, 8.79; N, 2.72. Found: C, 67.25; H, 8.91; N, 2.62.

(2*R*,3*R*,4*S*,5*S*)-1-Acetoxy-6-[(*tert*-butyldimethylsilyl)oxy]-2-(dibenzylamino)-4,5-(isopropylidenedioxy)hexan-3-ol (12). To a cooled (0 °C), stirred solution of **11** (2.40 g, 4.66 mmol) and triethylamine (1.41 g, 14.0 mmol) in CH_2Cl_2 (25 mL) was added dropwise a solution of acetyl chloride (548 mg, 6.99 mmol) in CH_2Cl_2 (3 mL). After the mixture was stirred at 0 °C for 30 min, it was poured into ice–water (60 mL). The organic phase was separated, and the aqueous phase was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic phases were washed with water, dried ($MgSO_4$), and concentrated in vacuo. Purification of the residue by column chromatography on silica gel (EtOAc–hexane (1:5)) gave **12** (2.28 g, 88%) as a colorless oil: $[\alpha]^{29}_D$ -20.8° (*c* 1.5, $CHCl_3$); IR (neat) 3522, 1742, 1250 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.01 (3 H, s), 0.04 (3 H, s), 0.87 (9 H, s), 1.32 (3 H, s), 1.34 (3 H, s), 2.10 (3 H, s), 3.01 (1 H, ddd, *J* = 7.4, 6.3, 3.4 Hz), 3.63 (2 H, $^1/_2$ AB q, *J* = 13.7 Hz), 3.65–3.82 (3 H, m), 3.86 (2 H, $^1/_2$ AB q, *J* = 13.7 Hz), 3.98 (1 H, ddd, *J* = 8.3, 6.0, 3.9 Hz), 4.41 (1 H, dd, *J* = 8.3, 1.4 Hz), 4.45 (1 H, dd, *J* = 11.9, 6.3 Hz), 4.55 (1 H, dd, *J* = 11.9, 3.4 Hz), 7.21–7.34 (10 H, m); ^{13}C NMR ($CDCl_3$) δ -5.42 (CH_3), -5.37 (CH_3), 18.4 (C), 21.3 (CH_3), 26.0 (CH_3, 3 carbons), 27.1 (CH_3), 27.2 (CH_3), 55.0 (CH_2, 2 carbons), 58.5 (CH), 61.7 (CH_2), 63.6 (CH_2), 67.9 (CH), 77.0 (CH), 78.0 (CH), 109.0 (C), 127.0 (CH, 2 carbons), 128.3 (CH, 4 carbons), 128.9 (CH, 4 carbons), 139.5 (C, 2 carbons), 171.0 (C); MS *m/z* (rel intensity) 557 (M^+, 1), 542 (2), 498 (8), 281 (100); HRMS calcd for $C_{31}H_{47}NO_6Si$ (M^+) 557.3173, found 557.3146.

Scheme VII



(2*R*,3*R*,4*S*,5*S*)-1-Acetoxy-6-[(*tert*-butyldimethylsilyl)oxy]-2-(dibenzylamino)-4,5-(isopropylidenedioxy)-3-(methoxymethoxy)hexane (13). A solution containing **12** (757 mg, 1.36 mmol), *N*,*N*-diisopropylethylamine (1.06 g, 8.16 mmol), and chloromethyl methyl ether (657 mg, 8.16 mmol) in $CHCl_3$ (10 mL) was refluxed for 1 h. The mixture was cooled to rt and diluted with $CHCl_3$ (10 mL), and the $CHCl_3$ solution was washed with water, dried ($MgSO_4$), and concentrated in vacuo. The residue was purified by column chromatography on silica gel (EtOAc–hexane (1:5)) to give **13** (694 mg, 85%) as a colorless oil: $[\alpha]^{26}_D$ -10.8° (*c* 2.3, $CHCl_3$); IR (neat) 1743, 1240 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ -0.02 (3 H, s), 0.02 (3 H, s), 0.85 (9 H, s) 1.35 (3 H, s), 1.36 (3 H, s), 2.10 (3 H, s), 3.21–3.30 (1 H, m), 3.36 (3 H, s), 3.61 (1 H, dd, *J* = 10.4, 6.5 Hz), 3.66 (2 H, $^1/_2$ AB q, *J* = 13.8 Hz), 3.72 (1 H, dd, *J* = 10.4, 3.9 Hz), 3.87 (2 H, $^1/_2$ AB q, *J* = 13.8 Hz), 3.90–3.93 (1 H, m), 3.95 (1 H, dd, *J* = 8.2, 2.4 Hz), 4.37 (1 H, dd, *J* = 12.0, 6.5 Hz), 4.41 (1 H, dd, *J* = 8.2, 2.1 Hz), 4.50 (1 H, dd, *J* = 12.0, 2.8 Hz), 4.65 and 4.74 (2 H, AB q, *J* = 6.6 Hz), 7.21–7.35 (10 H, m); ^{13}C NMR ($CDCl_3$) δ -5.6 (CH_3, 2 carbons), 18.3 (C), 21.18 (CH_3), 25.9 (CH_3, 3 carbons), 27.0 (CH_3), 27.2 (CH_3), 55.0 (CH_2, 2 carbons), 56.6 (CH_3), 57.0 (CH), 61.6 (CH_2), 64.0 (CH_2), 76.1 (CH), 77.1 (CH), 78.6 (CH), 98.9 (CH_2), 108.4 (C), 126.9 (CH, 2 carbons), 128.2 (CH, 4 carbons), 128.8 (CH, 4 carbons), 139.4 (C, 2 carbons), 170.8 (C); MS *m/z* (rel intensity) 587 (M^+ + 1 – CH_3, 17), 545 (48), 282 (100); HRMS calcd for $C_{32}H_{49}NO_7Si$ (M^+ + 1 – CH_3) 587.3278, found 587.3301.

(2*R*,3*R*,4*S*,5*S*)-6-[(*tert*-Butyldimethylsilyl)oxy]-2-(dibenzylamino)-4,5-(isopropylidenedioxy)-3-(methoxymethoxy)-hexan-1-ol (14). To a stirred, cooled (0 °C) slurry of $LiAlH_4$ (76 mg, 1.99 mmol) in Et_2O (5 mL) was added a solution of **13** (1.20 g, 1.99 mmol) in Et_2O (5 mL). After being stirred at rt for 2 h, the mixture was cooled and quenched with water (1 mL). The solid that separated was removed by filtration, and the filtrate was dried ($MgSO_4$). After removal of the solvent, the residue was purified by column chromatography on silica gel (EtOAc–hexane (1:5)) to give **14** (1.01 g, 91%) as a colorless oil: $[\alpha]^{24}_D$ +23.7° (*c* 1.9, $CHCl_3$); IR (neat) 3372 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.00 (3 H, s), 0.03 (3 H, s), 0.87 (9 H, s) 1.38 (6 H, s), 3.06 (1 H, ddd, *J* = 8.0, 5.6, 3.7 Hz), 3.43 (3 H, s), 3.66 (1 H, dd, *J* = 10.3, 6.7 Hz), 3.75 and 3.85 (4 H, AB q, *J* = 13.8 Hz), 3.80–3.92 (4 H, m), 4.05 (1 H, dd, *J* = 8.0, 2.2 Hz), 4.36 (1 H, dd, *J* = 8.3, 2.2 Hz), 4.71 and 4.84 (2 H, AB q, *J* = 6.6 Hz), 7.21–7.30 (10 H, m); ^{13}C NMR ($CDCl_3$) δ -5.6 (CH_3), -5.5 (CH_3), 18.3 (C), 25.9 (CH_3, 3

carbons), 27.1 (CH_3, 2 carbons), 54.7 (CH_2, 2 carbons), 56.7 (CH_3), 58.5, (CH_2), 59.6 (CH), 64.1 (CH_2), 76.1 (CH), 76.9 (CH), 79.6 (CH), 99.3 (CH_2), 108.5 (C), 127.0 (CH, 2 carbons), 128.4 (CH, 4 carbons), 129.0 (CH, 4 carbons), 139.7 (C, 2 carbons); MS *m/z* (rel intensity) 544 (M^+ - 15, 12), 528 (44), 502 (32), 284 (47), 240 (100). Anal. Calcd for $C_{31}H_{49}NO_6Si$: C, 66.51; H, 8.82; N, 2.50. Found: C, 66.30; H, 8.85; N, 2.55.

(2*R*,3*R*,4*S*,5*S*)-6-[(*tert*-Butyldimethylsilyl)oxy]-2-(dibenzylamino)-4,5-(isopropylidenedioxy)-3-(methoxymethoxy)hexanal (15). To a stirred, cold (-80 °C) solution of oxalyl chloride (1.31 g, 10.3 mmol) in CH_2Cl_2 (20 mL) was added dropwise a solution of dimethyl sulfoxide (1.61 g, 20.6 mmol) in CH_2Cl_2 (20 mL), and the mixture was stirred at -80 °C for 1 h. To this mixture was added dropwise a solution of 14 (2.88 g, 5.15 mmol) in CH_2Cl_2 (20 mL) over a period of 5 min, and stirring was continued at -80 °C. After 2 h, triethylamine (3.12 g, 30.9 mmol) was added to the reaction mixture, and the mixture was allowed to warm to rt. Addition of water (50 mL) and extraction with CH_2Cl_2 (4 × 30 mL) afforded a CH_2Cl_2 solution, which was washed with water, dried ($MgSO_4$), and concentrated. The residual oil was subjected to rapid chromatography on a short column of silica gel (EtOAc–hexane (1:20)) to give 15 (2.29 g, 80%) as a colorless oil: IR (neat) 1720 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.03 (3 H, s), 0.05 (3 H, s), 0.89 (9 H, s), 1.37 (3 H, s), 1.39 (3 H, s), 3.33 (3 H, s), 3.65–3.71 (2 H, m), 3.75–3.79 (1 H, m), 3.87 and 3.88 (4 H, AB q, J = 13.7 Hz), 4.04 (1 H, ddd, J = 8.2, 6.2, 3.8 Hz), 4.14 (1 H, dd, J = 8.3, 2.1 Hz), 4.34 (1 H, dd, J = 8.2, 2.1 Hz), 4.70 and 4.71 (2 H, AB q, J = 6.7 Hz), 7.22–7.38 (10 H, m), 9.80 (1 H, d, J = 1.8 Hz). This material is gradually decomposed in the air at rt, and hence, it was immediately used for further reactions.

Ethyl (3*R*,4*R*,5*R*,6*S*,7*S*)- and (3*S*,4*R*,5*R*,6*S*,7*S*)-8-[(*tert*-Butyldimethylsilyl)oxy]-4-(dibenzylamino)-3-hydroxy-6,7-(isopropylidenedioxy)-5-(methoxymethoxy)octanoate (16 and 17). Method A. To a stirred, cold (-80 °C) 1.0 M THF solution of lithium bis(trimethylsilyl)amide (1.54 mL, 1.54 mmol) was added EtOAc (150 μL, 1.54 mmol) via syringe under argon, and the mixture was stirred for 30 min at -80 °C. To this was then added a solution of 15 (690 mg, 1.23 mmol) in THF (3 mL), and stirring was continued at -80 °C. After 20 min, water (5 mL) was added, and the mixture was extracted with EtOAc (4 × 5 mL). The combined extracts were washed with water, dried ($MgSO_4$), and concentrated to give an oil, which was then purified by column chromatography on silica gel (EtOAc–hexane (1:10)) to furnish an inseparable mixture of 16 and 17 as a colorless oil (total: 735 mg, 92%) in a ratio of 89:11, respectively, according to ^1H NMR: IR (neat) 3418, 1733, 1255 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.03 and 0.12 (total 3 H with 89:11 ratio, s each), 0.05 and 0.12 (total 3 H with 89:11 ratio, s each), 0.89 and 0.94 (total 9 H with 89:11 ratio, s each), 1.28 and 1.23 (total 3 H with 89:11 ratio, t, J = 7.1 Hz, 6.8 Hz, each), 1.33 and 1.49 (total 3 H with 89:11 ratio, s each), 1.38 and 1.51 (total 3 H with 89:11 ratio, s each), 2.53 (1 H, dd, J = 15.6, 10.3 Hz), 2.83–2.87 (2 H, m), 3.45 and 3.46 (total 3 H with 89:11 ratio, s each), 3.65–3.70 (2 H, m), 3.70 and 3.82 (4 H, AB q, J = 13.8 Hz), 3.91–3.98 (1 H, m), 4.15–4.22 (3 H, m), 4.29 (1 H, dd, J = 8.1, 4.1 Hz), 4.61–4.68 (1 H, m), 4.85 and 4.82 (total 1 H with 89:11 ratio, 1/2 AB q, J = 6.3 Hz and 6.8 Hz, respectively), 4.95 and 4.86 (total 1 H with 89:11 ratio, 1/2 AB q, J = 6.3 Hz and 6.8 Hz, respectively), 7.22–7.35 (10 H, m). Anal. Calcd for $C_{35}H_{55}NO_6Si$: C, 65.08; H, 8.58; N, 2.17. Found: C, 65.28; H, 8.62; N, 2.15.

Method B. To a stirred, cold (-80 °C) mixture of 15 (111 mg, 0.200 mmol), *O*-ethyl-*O*-trimethylsilyl ketene acetal[27] (116 mg, 0.400 mmol), molecular sieves 4A (20 mg), and CH_2Cl_2 (4 mL) under argon was added via syringe a 1.0 M solution of $TiCl_4$ (300 μL, 0.300 mmol) in CH_2Cl_2. After the reaction mixture was stirred at -80 °C for 30 min, saturated aqueous $NaHCO_3$ (5 mL) was added, stirring was continued at rt for an additional 30 min, and the mixture was passed through a Celite pad. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (4 × 5 mL). The combined organic layers were washed with water, dried ($MgSO_4$), and concentrated. Column chromatography on silica gel (EtOAc–hexane (1:10)) gave an inseparable mixture of 16 and 17 (total: 58 mg, 45%) in a ratio of 82:18 (by ^1H NMR).

(27) Ainsworth, C.; Chen, F.; Kuo, Y. N. *J. Organomet. Chem.* **1972**, *46*, 59.

Method C. To a stirred, cold (-80 °C) mixture of 15 (111 mg, 0.200 mmol), *O*-ethyl-*O*-trimethylsilyl ketene acetal (116 mg, 0.400 mmol), molecular sieves 4A (20 mg), and CH_2Cl_2 (4 mL) under argon was added via syringe a 0.9 M solution of $EtAlCl_2$ (334 μL, 0.300 mmol) in hexane. The mixture was stirred at -80 °C for 1 h and worked up in a manner similar to that described above in method B. Purification of the crude product by silica gel chromatography (EtOAc–hexane (1:10)) gave an inseparable mixture of 16 and 17 (total: 52 mg, 40%) in a ratio of 90:10 (by ^1H NMR).

Method D. To a stirred, cold (-80 °C) mixture of 15 (111 mg, 0.200 mmol), *O*-ethyl-*O*-trimethylsilyl ketene acetal (116 mg, 0.400 mmol), molecular sieves 4A (20 mg), and CH_2Cl_2 (4 mL) under argon was added via syringe a 1.0 M solution of $SnCl_4$ (200 μL, 0.200 mmol) in CH_2Cl_2. The mixture was stirred at -80 °C for 2 h and worked up in a manner similar to that described above in method B. Purification of the crude product by silica gel chromatography (EtOAc–hexane (1:10)) gave an inseparable mixture of 16 and 17 (total: 13 mg, 10%) in a ratio of 89:11 (by ^1H NMR).

Method E. A mixture of 15 (557 mg, 1.00 mmol), Zn dust (98 mg, 1.5 mmol), ethyl bromoacetate (250 mg, 1.50 mmol), and benzene (10 mL) was refluxed for 14 h. The mixture was passed through a Celite pad, washed with water, and dried ($MgSO_4$). Evaporation of the solvent and purification of the residue by silica gel chromatography (EtOAc–hexane (1:10)) gave an inseparable 66:34 mixture (by ^1H NMR) of 16 and 17 (total: 219 mg, 34%).

Ethyl (3*R*/*S*,4*R*,5*R*,6*S*,7*S*)-4-(Dibenzylamino)-3,8-dihydroxy-6,7-(isopropylidenedioxy)-5-(methoxymethoxy)octanoate (18). To a THF (9 mL) solution of the 89:11 mixture of 16 and 17 (840 mg, 1.30 mmol), which had been obtained in the reaction described above in method A, was added a 1.0 M solution of tetrabutylammonium fluoride (2.61 mL, 2.61 mmol) in THF, and the mixture was stirred at rt. After 1 h, the mixture was diluted with EtOAc (30 mL), washed with water, and dried ($MgSO_4$). Evaporation of the solvent and purification of the residue by silica gel chromatography (EtOAc–hexane (1:2)) gave an inseparable 89:11 mixture of diastereomers 18 (650 mg, 94%) as a colorless oil: IR (neat) 3456, 1729, 1215 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.29 and 1.24 (total 3 H with 89:11 ratio, t, J = 7.1 Hz, each), 1.36 and 1.48 (total 3 H with 89:11 ratio, s each), 1.41 and 1.49 (total 3 H with 89:11 ratio, s each), 2.41 (1 H, dd, J = 16.0, 10.1 Hz), 2.75 and 2.68 (total 1 H with 89:11 ratio, dd, J = 6.2, 4.6 Hz, and m, respectively), 2.98 and 2.86 (total 1 H with 89:11 ratio, dd, J = 16.0, 2.6 Hz, and m, respectively), 3.30–3.42 (1 H, m), 3.45 and 3.46 (total 3 H with 89:11 ratio, s each), 3.50–3.70 (1 H, m), 3.60 (2 H, 1/2 AB q, J = 13.8 Hz), 3.80–3.86 (1 H, m), 3.90 (2 H, 1/2 AB q, J = 13.8 Hz), 4.08–4.15 (1 H, m), 4.17 (2 H, q, J = 7.1 Hz), 4.34 (1 H, dd, J = 8.0, 4.0 Hz), 4.60–4.70 (1 H, m), 4.90 and 4.78 (total 1 H with 89:11 ratio, 1/2 AB q, J = 6.3 Hz, each), 5.01 and 4.90 (total 1 H with 89:11 ratio, 1/2 AB q, J = 6.3 Hz, each), 7.23–7.31 (10 H, m). Anal. Calcd for $C_{29}H_{41}NO_8$: C, 65.52; H, 7.77; N, 2.63. Found: C, 65.63; H, 7.81; N, 2.61.

Ethyl (3*R*,4*R*,5*R*,6*S*,7*S*)-4-(Dibenzylamino)-3-hydroxy-6,7-(isopropylidenedioxy)-5-(methoxymethoxy)-8-[(*p*-toluenesulfonyl)oxy]octanoate (19). To a solution of 18 (1.40 g, 2.64 mmol) in pyridine (17 mL) was added *p*-toluenesulfonyl chloride (750 mg, 3.95 mmol). After being stirred at rt for 14 h, the mixture was poured into ice–water (50 mL) and extracted with EtOAc (4 × 40 mL). The combined organic layers were washed with water, dried ($MgSO_4$), and concentrated in vacuo. The residue was purified by column chromatography on silica gel (EtOAc–hexane (5:1)) and subsequent recrystallization from EtOAc–hexane to give 19 (1.41 g, 78%) as colorless plates: mp 95–96 °C; $[\alpha]^{24}_D$ -17.6° (c 2.5, $CHCl_3$); IR (KBr) 3570, 1718, 1356, 1180 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.24 (3 H, s), 1.30 (3 H, t, J = 7.1 Hz), 1.33 (3 H, s), 2.43 (3 H, s), 2.45 (1 H, dd, J = 16.1, 10.3 Hz), 2.74 (1 H, dd, J = 6.1, 4.7 Hz), 2.84 (1 H, dd, J = 16.1, 2.6 Hz), 3.31 (1 H, d, J = 4.5 Hz), 3.41 (3 H, s), 3.64 and 3.78 (4 H, AB q, J = 14.0 Hz), 3.92 (1 H, dd, J = 10.6, 5.1 Hz), 4.00 (1 H, dd, J = 10.6, 3.7 Hz), 4.04–4.09 (1 H, m), 4.19 (2 H, q, J = 7.1 Hz), 4.25 (1 H, dd, J = 8.0, 4.0 Hz), 4.59 (1 H, ddd, J = 13.6, 7.3, 2.6 Hz), 4.85 (2 H, br s), 7.20–7.32 (12 H, m), 7.73 (2 H, d, J = 8.3 Hz); ^{13}C NMR ($CDCl_3$) δ 14.3 (CH_3), 21.6 (CH_3), 26.9 (CH_3), 27.2 (CH_3), 40.8 (CH_2), 55.1 (CH_2, 2 carbons), 56.7 (CH_3), 60.6 (CH_2),

62.1 (CH), 66.5 (CH), 69.5 (CH_2), 74.6 (CH), 76.8 (CH), 79.1 (CH), 98.9 (CH_2), 109.5 (C), 127.2 (CH, 2 carbons), 128.1 (CH, 4 carbons), 128.5 (CH, 4 carbons), 129.0 (CH, 2 carbons), 129.6 (CH, 2 carbons), 133.0 (C), 139.3 (C, 2 carbons), 144.8 (C), 173.0 (C); MS *m/z* (rel intensity) 686 (M^+ + 1, 1), 671 (11), 640 (15), 568 (90), 370 (46), 326 (100). Anal. Calcd for $C_{36}H_{47}NO_{10}S$: C, 63.05; H, 6.91; N, 2.04. Found: C, 63.14; H, 6.96; N, 2.06.

[2*R*,2(1*R*),2(2*S*),2(3*S*),3*R*]-3-Hydroxy-2-[2,3-(isopropylidenedioxy)-1-(methoxymethoxy)-4-[(*p*-toluenesulfonyl)oxy]butyl]-5-oxopyrrolidine (20) and (1*R*,6*S*,7*S*,8*R*,8a*R*)-1-Hydroxy-6,7-(isopropylidenedioxy)-8-(methoxymethoxy)-3-oxoindolizidine (21). A solution of **19** (810 mg, 1.18 mmol) in MeOH (20 mL) was hydrogenated over 10% palladium on carbon (90 mg) at atmospheric pressure for 16 h. Filtration followed by evaporation of the solvent provided a solid, which was subjected to column chromatography on silica gel (EtOAc–hexane (10:1)) to give the two fractions. The first fraction furnished **21** (67 mg, 20%) as colorless crystals: mp 138–140 °C (EtOAc–hexane); $[\alpha]^{24}_D$ + 118° (*c* 0.7, MeOH); IR (neat) 3311, 2820–2740 (Bohlman bands), 1669 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.39 (3 H, s), 1.42 (3 H, s), 2.46 (1 H, dd, *J* = 17.8, 4.9 Hz), 2.73 (1 H, t, *J* = 11.8 Hz), 2.78 (1 H, dd, *J* = 17.8, 6.0 Hz), 3.20 (1 H, ddd, *J* = 11.8, 8.8, 4.8 Hz), 3.30 (1 H, dd, *J* = 9.8, 3.3 Hz), 3.42 (3 H, s), 3.50 (1 H, dd, *J* = 9.8, 8.8 Hz), 3.51 (1 H, t, *J* = 8.8 Hz), 4.40 (1 H, ddd, *J* = 6.0, 4.9, 3.3 Hz), 4.45 (1 H, dd, *J* = 11.8, 4.8 Hz), 4.71 and 4.94 (2 H, AB q, *J* = 6.4 Hz); ^{13}C NMR ($CDCl_3$) δ 29.7 (CH_3, 2 carbons), 39.4 (CH_2), 42.0 (CH_2), 56.2 (CH_3), 67.1 (CH), 68.6 (CH), 69.1 (CH), 77.3 (CH), 84.2 (CH), 98.1 (CH_2), 114.4 (C), 177.2 (C); MS *m/z* (rel intensity) 288 (M^+ + 1, 3), 269 (4), 242 (73), 225 (23), 184 (100), 168 (32), 142 (51), 112 (76). Anal. Calcd for $C_{13}H_{21}NO_6$: C, 54.34; H, 7.37; N, 4.88. Found: C, 54.51; H, 7.33; N, 4.72.

The second fraction furnished **20** (265 mg, 49%) as colorless crystals: mp 150–151 °C (AcOEt–hexane); $[\alpha]^{24}_D$ +21.9° (*c* 1.8, MeOH); IR (neat) 3370, 1735, 1680, 1599, 1370, 1178 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.33 (3 H, s), 1.39 (3 H, s), 2.38 (1 H, dd, *J* = 17.2, 6.4 Hz), 2.44 (3 H, s), 2.67 (1 H, dd, *J* = 17.2, 8.0 Hz), 3.34 (3 H, s), 3.57 (1 H, t, *J* = 3.8 Hz), 3.67 (1 H, t, *J* = 3.1 Hz), 4.02 (1 H, dd, *J* = 7.8, 2.3 Hz), 4.13–4.19 (2 H, unresolved), 4.24 (1 H, ddd, *J* = 12.3, 8.2, 4.2 Hz), 4.57–4.62 (1 H, m), 4.64 and 4.66 (2 H, AB q, *J* = 7.5 Hz), 6.51 (1 H, br s), 7.35 (2 H, d, *J* = 8.2 Hz), 7.78 (2 H, d, *J* = 8.2 Hz); ^{13}C NMR ($CDCl_3$) δ 21.7 (CH_3), 26.7 (CH_3), 27.0 (CH_3), 39.0 (CH_2), 56.4 (CH_3), 65.1 (CH), 67.9 (CH), 68.8 (CH_2), 74.5 (CH), 76.5 (CH), 78.4 (CH), 98.4 (CH_2), 110.6 (C), 128.1 (CH, 2 carbons), 130.1 (CH, 2 carbons), 132.8 (C), 145.4 (C), 175.4 (C); MS *m/z* (rel intensity) 272 (M^+ – CH_3 – TsOH, 5), 228 (45), 172 (100), 107 (80). Anal. Calcd for $C_{20}H_{29}NO_9S$: C, 52.28; H, 6.36; N, 3.05. Found: C, 52.33; H, 6.42; N, 2.81.

Cyclization of 20 to 21. To a stirred, ice-cold solution of **20** (183 mg, 0.399 mmol) in THF (5 mL) was added sodium hydride (40 mg of a 60% mineral oil dispersion, 1.00 mmol). After being stirred at 0 °C for 2 h, the mixture was poured into ice–water (10 mL) and extracted with EtOAc (4 × 5 mL). The extracts were washed with water, dried ($MgSO_4$), and concentrated in vacuo. The residue was chromatographed on silica gel (EtOAc–hexane (1:1)) to give **21** (77 mg, 71%) as colorless crystals, identical in all respects with an authentic sample of **21** directly derived from **19**.

(1*R*,6*S*,7*S*,8*R*,8a*R*)-1-Hydroxy-6,7-(isopropylidenedioxy)-8-(methoxymethoxy)indolizidine (22). To a solution of **21** (98 mg, 0.34 mmol) in THF (5 mL) was added a 2.0 M solution of borane–methyl sulfide complex (1.0 mL, 2.0 mmol) in THF. After the mixture was heated at 80 °C with stirring for 5 h, it was poured into brine (8 mL) and extracted with EtOAc (4 × 5 mL). The extracts were washed with water, dried ($MgSO_4$), and concentrated in vacuo. Purification of the residue by column chromatography on silica gel (EtOAc–hexane (1:1)) gave a colorless solid, which was recrystallized from EtOAc–hexane to provide **22** (61 mg, 66%) as colorless crystals: mp 90–91 °C; $[\alpha]^{28}_D$ +95.8° (*c* 0.7, $CHCl_3$); IR (neat) 3387, 2820–2700 (Bohlman bands) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.42 (3 H, s), 1.43 (3 H, s), 1.72 (1 H, dddd, *J* = 13.4, 9.0, 4.4, 2.4 Hz), 2.15 (1 H, dd, *J* = 9.0, 6.5 Hz), 2.32 (1 H, t, *J* = 9.8 Hz), 2.26–2.39 (1 H, m), 2.65 (1 H, q, *J* = 9.0 Hz), 2.96 (1 H, td, *J* = 9.0, 2.4 Hz), 3.22 (1 H, dd, *J* = 9.8, 4.1 Hz), 3.43 (3 H, s), 3.43 (1 H, t, *J* = 9.0 Hz), 3.58 (1 H, ddd, *J* = 9.8, 9.0, 4.1 Hz), 3.75 (1 H, t, *J* = 9.0 Hz), 4.24 (1 H, ddd, *J* = 9.0, 6.5, 4.4 Hz), 4.72 and 4.99 (2 H, AB q, *J* = 6.3 Hz); ^{13}C NMR ($CDCl_3$) δ 26.7 (CH_3), 26.9 (CH_3), 32.4 (CH_2), 50.8 (CH_2), 51.9 (CH_2), 55.7 (CH_3), 72.8 (CH), 74.5 (CH), 75.2 (CH), 77.3 (CH), 84.3 (CH), 96.4 (CH_2), 111.5 (C); MS *m/z* (rel intensity) 273 (M^+, 1), 258 (1), 228 (68), 155 (21), 154 (32), 100 (100), 86 (36), 82 (30). Anal. Calcd for $C_{13}H_{23}NO_5$: C, 57.13; H, 8.48; N, 5.12. Found: C, 56.97; H, 8.33; N, 4.96.

(1*R*,6*S*,7*R*,8*R*,8a*R*)-1,6,7,8-Tetrahydroxyindolizidine [(+)-1-Epicastanospermine] (2). A solution of **22** (104 mg, 0.381 mmol) in concd HCl–MeOH (1:2, 2 mL) was refluxed for 30 min. Concentration in vacuo gave an oil, which was subjected to ion-exchange chromatography (Dowex 1-X8, OH^- form, 100–200 mesh) with water. Evaporation of the water in vacuo left a colorless oil, which was dried in vacuo (50 °C, 0.2 mmHg) to give **2** (71 mg, 70%) as a hygroscopic, white amorphous powder: $[\alpha]^{28}_D$ +3.8° (*c* 0.5, MeOH) [for the opposite enantiomer: lit.[8d] $[\alpha]^{20}_D$ –4° (*c* 1.2, MeOH)]; IR (KBr) 3392 (br), 2918, 2828–2735 (sh) (Bohlman bands), 1648, 1159, 1119, 1088, 1065, 1005, 950, 581 cm^{-1}; ^1H NMR (D_2O) δ DOH 1.56 (1 H, dddd, *J* = 13.9, 9.0, 3.5, 1.8 Hz), 1.99 (1 H, dd, *J* = 9.0, 6.8 Hz), 2.11 (1 H, t, *J* = 10.8 Hz), 2.21–2.24 (1 H, m), 2.44 (1 H, q, *J* = 9.0 Hz), 2.82 (1 H, td, *J* = 9.0, 1.8 Hz), 3.02 (1 H, dd, *J* = 10.8, 5.2 Hz), 3.19 (1 H, t, *J* = 9.0 Hz), 3.25 (1 H, t, *J* = 9.0 Hz), 3.48 (1 H, ddd, *J* = 10.8, 9.0, 5.2 Hz), 4.10 (1 H, ddd, *J* = 9.0, 6.8, 3.5 Hz); ^1H NMR (CD_3OD) δ MeOH 1.63–1.71 (1 H, m), 1.98 (1 H, dd, *J* = 9.3, 6.3 Hz), 2.14 (1 H, t, *J* = 10.6 Hz), 2.23–2.34 (1 H, m), 2.52 (1 H, q, *J* = 8.8 Hz), 2.94 (1 H, br t), 3.11 (1 H, dd, *J* = 10.7, 5.2 Hz), 3.21 (1 H, t, *J* = 8.8 Hz), 3.32 (1 H, t, *J* = 9.0 Hz), 3.57 (1 H, ddd, *J* = 10.4, 8.8, 5.2 Hz), 4.19 (1 H, ddd, *J* = 8.8, 6.3, 3.6 Hz); ^{13}C NMR δ (D_2O) dioxane 33.3 (CH_2), 51.7 (CH_2), 55.7 (CH_2), 70.7 (CH), 73.7 (CH), 74.2 (CH), 74.5 (CH), 79.5 (CH); ^{13}C NMR (CD_3OD) δ CD_3OD 34.4 (CH_2), 52.5 (CH_2), 57.4 (CH_2), 71.8 (CH), 75.3 (CH), 75.49 (CH), 75.54 (CH), 81.0 (CH); MS *m/z* (rel intensity) 189 (M^+, 16), 172 (16), 145 (69), 128 (15), 100 (20), 98 (15), 86 (100), 82 (37); HRMS calcd for $C_8H_{15}NO_4$ (M^+) 189.1001, found 189.1018.

(1*R*,6*S*,7*S*,8*R*,8a*R*)-1-Acetoxy-6,7-(isopropylidenedioxy)-8-(methoxymethoxy)indolizidine (23). To a stirred solution of **22** (110 mg, 0.40 mmol) in pyridine (3 mL) was added acetic anhydride (1 mL). After being stirred at rt for 1 h, the mixture was poured into ice–water (30 mL) and extracted with EtOAc (3 × 15 mL). The combined organic layers were washed with water, dried ($MgSO_4$), and concentrated in vacuo. Chromatography of the residue on silica gel (EtOAc–hexane (1:5)) gave a colorless solid, which was recrystallized from EtOAc–hexane to give **23** (113 mg, 89%) as colorless crystals: mp 67–68 °C; $[\alpha]^{26}_D$ +59.3° (*c* 3.7, $CHCl_3$); IR (neat) 2820–2750 (Bohlman bands), 1739, 1250 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.43 (6 H, s) 1.63–1.67 (1 H, m), 2.07 (3 H, s), 2.37–2.56 (2 H, m), 2.50 (1 H, t, *J* = 10.2 Hz), 2.76 (1 H, q, *J* = 8.6 Hz), 2.94 (1 H, td, *J* = 8.6, 2.5 Hz), 3.29 (1 H, dd, *J* = 10.4, 4.2 Hz), 3.37 (3 H, s), 3.41 (1 H, t, *J* = 9.1 Hz), 3.58 (1 H, ddd, *J* = 10.2, 9.1, 4.2 Hz), 3.70 (1 H, t, *J* = 9.1 Hz), 4.61 and 4.96 (2 H, AB q, *J* = 6.6 Hz), 5.19 (1 H, ddd, *J* = 8.6, 4.8, 2.7 Hz); ^{13}C NMR ($CDCl_3$) δ 21.1 (CH_3), 26.6 (CH_3), 26.8 (CH_3), 32.2 (CH_2), 50.7 (CH_2), 50.9 (CH_2), 55.6 (CH_3), 69.8 (CH), 73.9 (CH), 75.7 (CH), 75.8 (CH), 84.5 (CH), 95.7 (CH_2), 111.0 (C), 170.3 (C); MS *m/z* (rel intensity) 316 (M^+ + 1, 1), 300 (14), 270 (100), 255 (21), 196 (39), 142 (47), 82 (90). Anal. Calcd for $C_{15}H_{25}NO_6$: C, 57.13; H, 7.99; N, 4.44. Found: C, 56.95; H, 7.98; N, 4.45.

(1*R*,6*S*,7*S*,8*R*,8a*R*)-1-(Butyryloxy)-6,7-(isopropylidenedioxy)-8-(methoxymethoxy)indolizidine (24). To a cooled (0 °C), stirred solution of **22** (196 mg, 0.718 mmol) in pyridine (3 mL) was added dropwise a solution of butyryl chloride (224 mg, 2.10 mmol) in CH_2Cl_2 (3 mL). After being stirred at rt for 2 h, the mixture was poured into ice–water (50 mL) and extracted with EtOAc (3 × 15 mL). The extracts were washed with water, dried ($MgSO_4$), and concentrated in vacuo. Silica gel chromatography (EtOAc–hexane (1:10–1:5)) gave **24** (220 mg, 90%) as a colorless oil: $[\alpha]^{28}_D$ +51.0° (*c* 3.6, $CHCl_3$); IR (neat) 2820–2750 (Bohlman bands), 1735, 1234 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.93 (3 H, t, *J* = 7.4 Hz), 1.41 (6 H, s), 1.57–1.71 (1 H, m), 1.64 (2 H, sext, *J* = 7.4 Hz), 2.28 (2 H, t, *J* = 7.4 Hz), 2.37–2.51 (2 H, m), 2.47 (1 H, t, *J* = 10.2 Hz), 2.72 (1 H, q, *J* = 8.6 Hz), 2.92 (1 H, td, *J* = 8.6, 2.5 Hz), 3.27 (1 H, dd, *J* = 10.6, 4.2 Hz), 3.35 (3 H, s), 3.39 (1 H, t, *J* = 9.1 Hz), 3.57 (1 H, ddd, *J* = 10.2, 9.1, 4.2 Hz), 3.70 (1 H, t, *J* = 9.1 Hz), 4.58 and 4.95 (2 H, AB q, *J* = 6.7 Hz), 5.18 (1 H, ddd, *J* = 8.6, 5.2, 2.7 Hz); ^{13}C NMR ($CDCl_3$) δ 13.5 (CH_3),

18.4 (CH_2), 26.6 (CH_3), 26.8 (CH_3), 32.4 (CH_2), 36.2 (CH_2), 50.8 (CH_2), 51.0 (CH_2), 55.6 (CH_3), 69.3 (CH), 74.1 (CH), 74.6 (CH), 75.5 (CH), 84.6 (CH), 95.6 (CH_2), 111.1 (C), 172.9 (C); MS *m/z* (rel intensity) 344 ($M^+ + 1$, 1), 328 (12), 298 (100), 255 (22), 224 (29), 210 (17), 170 (25), 82 (82). Anal. Calcd for $C_{17}H_{29}NO_6$: C, 59.46; H, 8.51; N, 4.08. Found: C, 59.63; H, 8.44; N, 4.13.

(1*R*,6*S*,7*R*,8*R*,8a*R*)-1-Acetoxy-6,7,8-trihydroxyindolizidine [(−)-1-*O*-Acetyl-1-epicastanospermine] (4). A solution of **23** (78 mg, 0.25 mmol) in an anhydrous 25% methanolic solution of HCl gas (4 mL) was stirred at rt for 30 min and then concentrated in vacuo. The residue was dissolved in MeOH (3 mL) and neutralized with methanolic NH_3. To the resulting mixture was added silica gel (300 mg), and the solvent was removed from the silica gel slurry by evaporation in vacuo. The remaining solid was loaded onto a silica gel column packed in CH_2Cl_2 and sequentially eluted with CH_2Cl_2 and then CH_2Cl_2–EtOH (23:2) to give a colorless solid, which was recrystallized from EtOAc to give **4** (35 mg, 61%) as colorless pillars: mp 151–153 °C $[\alpha]^{28}_D$ −17.9° (*c* 0.9, MeOH); IR (KBr) 3371, 3298, 2830–2710 (Bohlman bands), 1730, 1379, 1250, 1115, 1087, 1070, 1046, 899, 620 cm^{-1}; ^1H NMR (DMSO-d_6) δ DMSO 1.44–1.51 (1 H, m), 1.92–1.99 (1 H, unresolved), 1.96 (3 H, s), 2.01 (1 H, dd, *J* = 9.1, 6.1 Hz), 2.13–2.33 (1 H, m), 2.80 (1 H, t, *J* = 7.6 Hz), 2.90–2.98 (2 H, m), 3.06 (1 H, td, *J* = 8.9, 5.2 Hz), 3.30–3.39 (1 H, m), 4.80–4.89 (1 H, m); ^1H NMR (D_2O) δ DOH 1.65–1.71 (1 H, m), 1.99 (3 H, s), 2.18 (1 H, t, *J* = 11.0 Hz), 2.24–2.28 (1 H, m), 2.33 (1 H, dd, *J* = 9.0, 6.4 Hz), 2.50 (1 H, q, *J* = 9.1 Hz), 2.87 (1 H, t, *J* = 9.1 Hz), 3.07 (1 H, dd, *J* = 11.0, 5.2 Hz), 3.20 (1 H, t, *J* = 9.0 Hz), 3.28 (1 H, t, *J* = 9.0 Hz), 3.53 (1 H, ddd, *J* = 11.0, 9.0, 5.2 Hz), 4.92–4.97 (1 H, m); ^{13}C NMR (DMSO-d_6) δ DMSO-d_6 21.1 (CH_3), 31.9 (CH_2), 51.1 (CH_2), 56.1 (CH_2), 70.1 (CH), 70.8 (CH), 73.3 (CH), 76.3 (CH), 79.6 (CH), 169.9 (C); ^{13}C NMR (D_2O) δ dioxane 21.3 (CH_3), 31.1 (CH_2), 51.4 (CH_2), 55.0 (CH_2), 70.1 (CH), 70.5 (CH), 73.1 (CH), 77.1 (CH), 79.1 (CH), 174.5 (C); MS *m/z* (rel intensity) 232 ($M^+ + 1$, 0.7), 214 (3), 196 (2), 171 (100), 128 (22), 111 (22); HRMS calcd for $C_{10}H_{18}NO_5$ ($M^+ + 1$) 232.1185, found 232.1189.

(1*R*,6*S*,7*R*,8*R*,8a*R*)-1-(Butyryloxy)-6,7,8-trihydroxyindolizidine [(−)-1-*O*-Butyryl-1-epicastanospermine] (5). A solution of **24** (209 mg, 0.610 mmol) in an anhydrous 25% methanolic solution of HCl gas (4 mL) was stirred at rt for 30 min. The mixture was worked up in a manner similar to that described above for the preparation of **4**. Purification of the crude product by column chromatography on silica gel (CH_2Cl_2–EtOH (95:5)) gave a colorless solid, which was recrystallized from EtOAc to give **5** (104 mg, 64%) as colorless prisms: mp 183–184 °C; $[\alpha]^{26}_D$ −31.4° (*c* 1.7, MeOH); IR (KBr) 3365, 3272, 2830–2720 (Bohlman bands), 1722, 1368, 1355, 1268, 1204, 1096, 1008, 961, 887, 610 cm^{-1}; ^1H NMR (DMSO-d_6) δ DMSO 0.88 (3 H, t, *J* = 7.4 Hz), 1.42–1.48 (1 H, m), 1.53 (2 H, sext, *J* = 7.4 Hz), 1.96 (1 H, t, *J* = 10.5 Hz), 2.01 (1 H, dd, *J* = 9.2, 5.9 Hz), 2.21 (2 H, t, *J* = 7.4 Hz), 2.14–2.31 (2 H, m), 2.80 (1 H, t, *J* = 7.4 Hz), 2.90–2.98 (2 H, m), 3.05 (1 H, td, *J* = 8.9, 5.2 Hz), 3.28–3.32 (1 H, m), 4.74 (1 H, d, *J* = 5.0 Hz, disappeared upon addition of D_2O), 4.78 (2 H, d, *J* = 4.2 Hz, disappeared upon addition of D_2O), 4.86–4.91 (1 H, m); ^1H NMR (D_2O) δ DOH 0.79 (3 H, t, *J* = 7.4 Hz), 1.49 (2 H, sext, *J* = 7.4 Hz), 1.59–1.67 (1 H, m), 2.15 (1 H, t, *J* = 11.0 Hz), 2.22–2.26 (1 H, m), 2.24 (2 H, t, *J* = 7.4 Hz), 2.29 (1 H, dd, *J* = 9.0, 6.8 Hz), 2.47 (1 H, q, *J* = 9.0 Hz), 2.84 (1 H, t, *J* = 9.0 Hz), 3.05 (1 H, dd, *J* = 11.0, 5.2 Hz), 3.18 (1 H, t, *J* = 9.0 Hz), 3.25 (1 H, t, *J* = 9.0 Hz), 3.50 (1 H, ddd, *J* = 11.0, 9.0, 5.2 Hz), 4.90–4.96 (1 H, m); ^{13}C NMR (DMSO-d_6) δ DMSO-d_6 13.5 (CH_3), 18.0 (CH_2), 31.9 (CH_2), 35.6 (CH_2), 51.1 (CH_2), 56.1 (CH_2), 70.1 (CH), 70.9 (CH), 73.3 (CH), 76.1 (CH), 79.5 (CH), 172.4 (C); ^{13}C NMR (D_2O) δ dioxane 13.7 (CH_3), 18.8 (CH_2), 31.4 (CH_2), 36.7 (CH_2), 51.7 (CH_2), 55.1 (CH_2), 70.1 (CH), 70.7 (CH), 73.1 (CH), 76.8 (CH), 79.2 (CH), 176.9 (C); MS *m/z* (rel intensity) 258 ($M^+ - 1$, 0.2), 242 (1.5), 224 (1), 188 (1.4), 171 (100), 111 (24), 82 (40), 68 (32). Anal. Calcd for $C_{12}H_{21}NO_5$: C, 55.58; H, 8.16; N, 5.40. Found: C, 55.10; H, 8.07; N, 5.38.

(3*R*/*S*,4*R*,5*R*,6*S*,7*S*)-8-[(*tert*-Butyldimethylsilyl)oxy]-4-(dibenzylamino)-6,7-(isopropylidenedioxy)-5-(methoxymethoxy)octane-1,3-diol (25). To an ice-cooled, stirred slurry of $LiAlH_4$ (24 mg, 0.63 mmol) in Et_2O (4 mL) was added a solution of the 89:11 mixture of **16** and **17** (400 mg, 0.620 mmol), obtained from the aldol reaction of **15** according to method A, in Et_2O (4 mL). The mixture was stirred at rt for 2 h, cooled, and quenched with water (1 mL). After the mixture was filtered and rinsed with Et_2O (4 mL), the combined Et_2O solutions were dried ($MgSO_4$) and concentrated. The residue was purified by column chromatography on silica gel (EtOAc–hexane (1:5)) to give an inseparable 89:11 mixture of diastereomers **25** (303 mg, 81%) as a colorless oil: IR (neat) 3446, 1255 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.04 and 0.08 (total 3 H with 89:11 ratio, s each), 0.05 and 0.09 (total 3 H with 89:11 ratio, s each), 0.89 and 0.91 (total 9 H with 89:11 ratio, s each), 1.33 and 1.44 (total 3 H with 89:11 ratio, s each), 1.39 and 1.47 (total 3 H with 89:11 ratio, s each), 1.70–1.85 and 2.05–2.15 (total 1 H with 89:11 ratio, m each), 2.85 (1 H, dd, *J* = 8.6, 3.2 Hz), 3.45 and 3.44 (total 3 H with 89:11 ratio, s each), 3.60–3.75 (1 H, m), 3.61 (2 H, $^1/_2$ AB q, *J* = 13.8 Hz), 3.76–3.94 (3 H, m), 3.82 (2 H, $^1/_2$ AB q, *J* = 13.8 Hz), 4.20 (2 H, br d), 4.85 and 4.78 (total 1 H with 89:11 ratio, $^1/_2$ AB q, *J* = 6.4 Hz, each), 4.97 and 4.90 (total 1 H with 89:11 ratio, $^1/_2$ AB q, *J* = 6.4 Hz, each), 7.28–7.31 (10 H, m). Anal. Calcd for $C_{33}H_{53}NO_7Si$: C, 65.64; H, 8.85; N, 2.31. Found: C, 65.73; H, 8.90; N, 2.30.

(3*R*,4*R*,5*R*,6*S*,7*S*)- and (3*S*,4*R*,5*R*,6*S*,7*S*)-1,8-Bis[(*tert*-butyldimethylsilyl)oxy]-4-(dibenzylamino)-6,7-(isopropylidenedioxy)-5-(methoxymethoxy)octan-3-ol (26 and 27). To a solution of **25** (89:11 diastereomeric mixture) (310 mg, 0.52 mmol) in DMF (4 mL) were added successively imidazole (89 mg, 1.3 mmol) and *tert*-butyldimethylsilyl chloride (94 mg, 1.2 mmol). The mixture was stirred at rt for 14 h, diluted with water (10 mL), and extracted with EtOAc (4 × 8 mL). The extracts were washed with water, dried ($MgSO_4$), and concentrated. Column chromatography on silica gel (EtOAc–hexane (1:20)) provided two fractions. The first fraction gave **27** (24 mg, 7%) as a colorless oil: $[\alpha]^{26}_D$ +4.0° (*c* 3.7, $CHCl_3$); IR (neat) 3495, 1259 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.05 (3 H, s), 0.06 (3 H, s), 0.11 (3 H, s), 0.12 (3 H, s), 0.89 (9 H, s), 0.94 (9 H, s), 1.50 (3 H, s), 1.52 (3 H, s), 1.89–2.02 (1 H, m), 2.81 (1 H, dd, *J* = 8.8, 3.3 Hz), 3.44 (3 H, s), 3.61 (1 H, ddd, *J* = 9.9, 8.3, 4.4 Hz), 3.71–3.77 (4 H m), 3.82 (2 H, d, *J* = 4.4 Hz), 4.09–4.17 (5 H, m), 4.33 (1 H, dd, *J* = 8.0, 1.7 Hz), 4.83 and 4.90 (2 H, AB q, *J* = 6.6 Hz), 7.25–7.32 (10 H, m); ^{13}C NMR ($CDCl_3$) δ −5.5 (CH_3, 2 carbons), −5.4 (CH_3, 2 carbons), 18.2 (C), 18.3 (C), 25.9 (CH_3, 6 carbons), 27.2 (CH_3), 27.4 (CH_3), 36.6 (CH_2), 55.3 (CH_2, 2 carbons), 56.6 (CH_3), 61.1 (CH), 62.5 (CH_2), 63.2 (CH_2), 70.6 (CH), 76.0 (CH), 7.68 (CH), 79.2 (CH), 99.1 (CH_2), 108.5 (C), 126.8 (CH, 2 carbons), 128.0 (CH, 4 carbons), 129.6 (CH, 4 carbons); MS *m/z* (rel intensity) 718 ($M^+ + 1$, 2), 703 (5), 661 (6), 528 (32), 398 (100). Anal. Calcd for $C_{39}H_{67}NO_7Si_2$: C, 65.23; H, 9.40; N, 1.95. Found: C, 65.38; H, 9.17; N, 2.06.

The second fraction gave **26** (308 mg, 83%) as a colorless oil: $[\alpha]^{26}_D$ +3.1° (*c* 2.0, $CHCl_3$); IR (neat) 3491, 1255 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.00 (3 H, s), 0.01 (3 H, s), 0.08 (6 H, s), 0.86 (9 H, s), 0.89 (9 H, s), 1.34 (3 H, s), 1.38 (3 H, s), 1.60–1.75 (1 H, m), 2.80 (1 H, t, *J* = 5.5 Hz), 3.42 (3 H, s), 3.60 (1 H, br d), 3.70 and 3.77 (4 H, AB q, *J* = 14.1 Hz), 3.76–3.94 (5 H, m), 4.16 (1 H, dd, *J* = 5.3, 3.8 Hz), 4.28–4.32 (1 H, m), 4.35 (1 H, dd, *J* = 8.1, 3.8 Hz), 4.85 and 4.91 (2 H, AB q, *J* = 6.3 Hz), 7.25–7.34 (10 H, m); ^{13}C NMR ($CDCl_3$) δ −5.5 (CH_3, 2 carbons), −5.3 (CH_3, 2 carbons), 18.3 (C), 18.4 (C), 25.9 (CH_3, 6 carbons), 27.0 (CH_3), 27.2 (CH_3), 38.4 (CH_2), 54.7 (CH_2, 2 carbons), 56.4 (CH_3), 61.2 (CH), 62.2 (CH_2), 64.1 (CH_2), 67.2 (CH), 76.9 (CH), 77.6 (CH), 80.2 (CH), 99.0 (CH_2), 108.4 (C), 126.9 (CH, 2 carbons), 128.3 (CH, 4 carbons), 128.9 (CH, 4 carbons), 139.5 (C); MS *m/z* (rel intensity) 702 ($M^+ - 15$, 3), 660 (8), 528 (56), 398 (100). Anal. Calcd for $C_{39}H_{67}NO_7Si_2$: C, 65.23; H, 9.40; N, 1.95. Found: C, 65.48; H, 9.30; N, 2.07.

(3*S*,4*R*,5*R*,6*S*,7*S*)-3-Acetoxy-1,8-bis[(*tert*-butyldimethylsilyl)oxy]-4-(dibenzylamino)-6,7-(isopropylidenedioxy)-5-(methoxymethoxy)octane (28). To a benzene (2 mL) solution of **26** (72 mg, 0.10 mmol) and triphenylphosphine (53 mg, 0.20 mmol) were added successively a solution of acetic acid (12 mg, 0.20 mmol) in benzene (0.5 mL) and a solution of diethyl azodicarboxylate (35 mg, 0.20 mmol) in benzene (0.5 mL). The mixture was refluxed for 12 h, and the solid (Ph_3PO) that separated was removed by filtration. Concentration of the filtrate in vacuo and column chromatography of the residue on silica gel (EtOAc–hexane (5:1)) gave **28** (41 mg, 54%) as a colorless oil: $[\alpha]^{25}_D$ +4.8° (*c* 0.3, $CHCl_3$); IR (neat) 1742, 1245 cm^{-1}; ^1H NMR ($CDCl_3$) δ −0.05 (6 H, s), 0.10 (3 H, s), 0.12 (3 H, s), 0.84 (9 H,

s), 0.92 (9 H, s), 1.52 (6 H, s), 1.72–1.84 (1 H, m), 1.94 (3 H, s), 2.81 (1 H, dd, J = 7.0, 3.1 Hz), 3.04 (1 H, dd, J = 9.4, 2.2 Hz), 3.10(1 H, dd, J = 5.4, 1.7 Hz), 3.39 (3 H, s), 3.68 (2 H, dd, J = 13.0, 3.7 Hz), 3.78–3.82 (1 H, m), 3.87–3.92 (1 H, m), 3.99–4.16 (1 H, m), 4.25 (2 H, br s), 4.52 and 4.72 (2 H, AB q, J = 6.8 Hz), 5.22 (1 H, ddd, J = 6.4, 6.4, 2.2 Hz), 7.22–7.30 (10 H, m); ^{13}C NMR ($CDCl_3$) δ –5.44 (CH_3, 2 carbons), –5.40 (CH_3, 2 carbons), 18.25 (C, 2 carbons), 18.30 (C, 2 carbons), 21.4 (CH_3), 26.0 (CH_3, 6 carbons), 27.3 (CH_3), 27.4 (CH_3), 35.6 (CH_2), 55.7 (CH_2, 2 carbons), 56.6 (CH_3), 58.8 (CH), 59.5 (CH_2), 63.8 (CH_2), 72.3 (CH), 76.3 (CH), 77.0 (CH), 79.6 (CH), 99.6 (CH_2), 108.7 (C), 127.0 (CH, 2 carbons), 128.1 (CH, 4 carbons), 129.6 (CH, 4 carbons), 140.4 (C, 2 carbons), 170.1 (C); MS m/z (rel intensity) 744 (M^+ – 15, 1.5), 702 (6), 660 (4), 602 (1.5), 528 (7), 440 (100), 398 (70). Anal. Calcd for $C_{41}H_{69}NO_8Si_2$: C, 64.78; H, 9.15; N, 1.84. Found: C, 64.89; H, 9.21; N, 1.81.

$LiAlH_4$ Reduction of 28. To a stirred, cooled (0 °C) slurry of $LiAlH_4$ (24 mg, 0.63 mmol) in Et_2O (4 mL) was added a solution of **28** (471 mg, 0.630 mmol) in Et_2O (4 mL). After being stirred for 1 h at rt, the mixture was cooled and quenched with water (1 mL). The mixture was filtered and rinsed with Et_2O (4 mL), and the combined Et_2O solutions were dried ($MgSO_4$). Evaporation of the solvent and column chromatography of the residue on silica gel (EtOAc–hexane (1:20)) gave **27** (382 mg, 86%) as a colorless oil, identical in all respects with an authentic sample of **27** prepared from **25**.

(3*S*,4*R*,5*R*,6*S*,7*S*)-4-(Dibenzylamino)-6,7-(isopropylidenedioxy)-5-(methoxymethoxy)octane-1,3,8-triol (29). To a stirred solution of **27** (1.15 g, 1.60 mmol) in THF (15 mL) was added a 1.0 M solution of tetrabutylammonium fluoride (4.8 mL, 4.8 mmol) in THF at rt. After being stirred at rt for 1 h, the mixture was diluted with EtOAc (70 mL), washed with water, dried ($MgSO_4$), and concentrated in vacuo. The residue was purified by column chromatography on silica gel (EtOAc–hexane (1:1)) to give **29** (750 mg, 95%) as a colorless oil: $[\alpha]^{25}_D$ +28.1° (c 2.4, $CHCl_3$); IR (neat) 3426 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.43 (3 H, s), 1.46 (3 H, s), 1.85–1.98 (1 H, m), 2.00–2.18 (1 H, m), 2.78 (1 H, t, J = 5.2 Hz), 2.96–3.15 (1 H, m), 3.43 (3 H, s), 3.51 (1 H, dd, J = 11.9, 4.2 Hz), 3.63 (1 H, dd, J = 11.9, 4.2 Hz), 3.69 (2 H, $^1/_2$ AB q, J = 13.5 Hz), 3.73 (1 H, dd, J = 7.3, 4.6 Hz), 3.90 (1 H, dd, J = 8.3, 4.2 Hz), 3.92 (1 H, dd, J = 8.3, 4.2 Hz), 4.05 (1 H, dd, J = 5.7, 4.2 Hz), 4.11 (2 H, $^1/_2$ AB q, J = 13.5 Hz), 4.17 (1 H, dd, 8.3, 4.2 Hz), 4.20–4.25 (2 H, m), 4.83 (2 H, s), 7.23–3.30 (10 H, m); ^{13}C NMR ($CDCl_3$) δ 27.1 (CH_3, 2 carbons), 35.9 (CH_2), 55.1 (CH_2, 2 carbons), 56.8 (CH_3), 61.7 (CH), 62.1 (CH_2), 62.3 (CH_2), 71.1 (CH), 76.4 (CH), 77.1 (CH), 78.8 (CH), 99.1 (CH_2), 108.8 (C), 127.1 (CH, 2 carbons), 128.3 (CH, 4 carbons), 129.2 (CH, 4 carbons), 139.5 (C, 2 carbons); MS m/z (rel intensity) 474 (M^+ – 15, 1.5), 414 (4), 284 (100), 131 (35). Anal. Calcd for $C_{27}H_{39}NO_7$: C, 67.43; H, 7.74; N, 2.76. Found: C, 67.31; H, 7.82; N, 2.69.

(3*S*,4*R*,5*R*,6*S*,7*S*)-1,8-Bis[(*p*-toluenesulfonyl)oxy]-4-(dibenzylamino)-6,7-(isopropylidenedioxy)-5-(methoxymethoxy)-octane (30). A mixture of **29** (750 mg, 1.53 mmol), *p*-toluenesulfonyl chloride (876 mg, 4.59 mmol), and pyridine (12 mL) was stirred at rt for 14 h. The mixture was poured into ice–water (40 mL) and extracted with EtOAc. The combined organic layers were washed with water, dried ($MgSO_4$), and concentrated in vacuo. Column chromatography on silica gel ($CHCl_3$–MeOH (25:1)) gave **30** (978 mg, 80%) as a colorless oil: $[\alpha]^{27}_D$ +11.8° (c 0.5, $CHCl_3$); IR (neat) 3262, 1372, 1177 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.05–1.16 (1 H, m), 1.49 (3 H, s), 1.52 (3 H, s), 2.12–2.22 (1 H, m), 2.28 (3 H, s), 2.39 (3 H, s), 3.30–3.40 (1 H, m), 3.37 (3 H, s), 4.01 (1 H, dd, J = 6.8, 3.1 Hz), 4.38–4.53 (2 H, m), 4.59 (4 H, s), 4.70 (1 H, br s), 4.89 (1 H, $^1/_2$ AB q, J = 6.5 Hz), 4.93 (1 H, dd, J = 12.4, 9.2 Hz), 5.01 (1 H, J = 6.8 Hz), 5.13 (1 H, d, J = 12.4 Hz), 5.18 (1 H, $^1/_2$ AB q, J = 6.5 Hz), 7.07 (2 H, d, J = 8.5 Hz), 7.27 (2 H, d, J = 8.3 Hz), 7.37–7.50 (8 H, m), 7.76 (6 H, m); ^{13}C NMR ($CDCl_3$) δ 21.2 (CH_3), 21.6 (CH_3), 27.0 (CH_3), 27.2 (CH_3), 31.2 (CH_2), 56.7 (CH_3), 60.0 (CH_2), 63.5 (CH_2), 66.3 (CH_2), 68.3 (CH_2), 71.3 (CH), 72.5 (CH), 75.3 (CH), 75.6 (CH), 77.2 (CH), 99.7 (CH_2), 110.7 (C), 126.0 (CH, 2 carbons), 127.4 (C), 127.8 (CH, 2 carbons), 128.4 (CH, 2 carbons), 129.4 (CH, 2 carbons), 129.5 (CH, 2 carbons), 129.9 (CH, 2 carbons), 130.8 (CH), 130.9 (CH), 132.5 (C), 133.1 (CH, 2 carbons), 133.8 (CH, 2 carbons); MS m/z (rel intensity) 627 (M^+ – CH_3 – $C_7H_7SO_2$, 1), 580 (1.5), 504 (2), 363 (4), 302 (4), 220 (48), 159 (31), 107 (100). Anal. Calcd for $C_{41}H_{51}NO_{11}S_2$: C, 61.71; H, 6.44; N, 1.76. Found: C, 61.89; H, 6.51; N, 2.04.

(1*S*,6*S*,7*S*,8*R*,8a*R*)-1-Hydroxy-6,7-(isopropylidenedioxy)-8-(methoxymethoxy)indolizidine (31). A mixture of **30** (580 mg, 0.728 mmol), $Pd(OH)_2$ (120 mg), and MeOH (8 mL) was hydrogenated at atmospheric pressure for 1 h. After removal of the catalyst by filtration, triethylamine (787 mg, 7.87 mmol) was added to the filtrate, and then the mixture was refluxed for 1.5 h. Concentration in vacuo and silica gel chromatography of the residue (EtOAc–hexane (1:1)) gave **31** (167 mg, 84%) as a hygroscopic, white, amorphous powder: mp 79–80 °C; $[\alpha]^{26}_D$ +122° (c 1.6, $CHCl_3$); IR (neat) 3466, 2820–2710 (Bohlman bands) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.41 (3 H, s), 1.42 (3 H, s), 1.77–1.91 (1 H, m), 2.03 (1 H, dd, J = 9.0, 3.9 Hz), 2.18 (1 H, t, J = 9.7 Hz), 2.20–2.30 (2 H, m), 3.12 (1 H, dd, J = 7.5 Hz), 3.31 (1 H, dd, J = 9.7, 4.0 Hz), 3.43 (3 H, s), 3.46 (1 H, t, J = 9.1 Hz), 3.66 (1 H, ddd, J = 9.7, 9.1, 4.0 Hz), 3.88 (1 H, t, J = 9.1 Hz), 4.28–4.31 (1 H, m), 4.69 and 4.89 (2 H, AB q, J = 6.6 Hz); ^{13}C NMR ($CDCl_3$) δ 26.7 (CH_3), 26.8 (CH_3), 33.1 (CH_2), 50.9 (CH_2), 51.9 (CH_2), 55.8 (CH_3), 69.4 (CH), 71.9 (CH), 74.2 (CH), 75.2 (CH), 84.1 (CH), 97.2 (CH_2), 111.6 (C); MS m/z (rel intensity) 273 (M^+, 2), 258 (3), 228 (99), 154 (36), 100 (100), 86 (30). Anal. Calcd for $C_{13}H_{23}NO_5$: C, 57.13; H, 8.48; N, 5.12. Found: C, 56.84; H, 8.29; N, 5.17.

(1*S*,6*S*,7*R*,8*R*,8a*R*)-1,6,7,8-Tetrahydroxyindolizidine [(+)-Castanospermine] (1). A solution of **31** (25 mg, 0.092 mmol) in concd HCl–MeOH (1:2, 1 mL) was refluxed for 30 min. In vacuo concentration of the mixture, followed by coevaporation with benzene, left the crude HCl salt of **1**, which was subjected to ion-exchange chromatography (Dowex 1-X, OH^- form, 100–200 mesh) eluting with water. Subsequent lyophilization of the resulting aqueous solution provided **1** (12.3 mg, 71%) as a colorless solid: colorless pillars (aqueous EtOH); mp 208–211 °C dec (lit.[1] mp 212–215 °C dec); $[\alpha]^{25}_D$ +76.8° (c 0.1, H_2O) [lit.[1] $[\alpha]^{25}_D$ +79.7° (c 0.93, H_2O)]; IR (KBr) 3382 (br), 2923, 2826–2740 (sh) (Bohlman bands), 1646, 1159, 1118, 1092, 1065, 1005, 950, 581 cm^{-1}; ^{1}H NMR (D_2O) δ DOH 1.70 (1 H, dtd, J = 14.0, 9.1, 1.9 Hz), 2.02 (1 H, dd, J = 9.9, 4.4 Hz), 2.05 (1 H, t, J = 10.7 Hz), 2.20 (1 H, t, J = 9.1 Hz), 2.33 (1 H, ddd, J = 14.0, 7.0, 2.1 Hz), 3.07 (1 H, td, J = 9.1, 2.1 Hz), 3.17 (1 H, dd, J = 10.7, 5.0 Hz), 3.31 (1 H, t, J = 9.1 Hz), 3.58 (1 H, dd, J = 9.9, 9.1 Hz), 3.6 (1 H, ddd, J = 10.7, 9.1, 5.0 Hz), 4.40 (1 H, ddd, J = 7.0, 4.4, 1.9 Hz); ^{13}C NMR (D_2O) δ dioxane 32.5 (CH_2), 51.4 (CH_2), 55.2 (CH_2), 68.8 (CH), 69.4 (CH), 69.9 (CH), 71.3 (CH), 78.8 (CH); MS m/z (rel intensity) 189 (M^+, 18), 172 (20), 145 (72), 128 (15), 100 (19), 86 (100), 82 (31); HRMS calcd for $C_8H_{15}NO_4$ (M^+) 189.1001, found 189.1017.

(3*R*,4*R*,5*R*,6*S*,7*S*)-4-[[(Benzyloxy)carbonyl]amino]-1,8-bis[(*tert*-butyldimethylsilyl)oxy]-6,7-(isopropylidenedioxy)-5-(methoxymethoxy)octan-3-ol (32). A mixture of **26** (200 mg, 0.279 mmol), $Pd(OH)_2$ (140 mg), and MeOH (8 mL) was hydrogenated at atmospheric pressure for 1 h. After filtration of the catalyst, the solvent was evaporated in vacuo to give (3*R*,4*R*,5*R*,6*S*,7*S*)-4-amino-1,8-bis[(*tert*-butyldimethylsilyl)oxy]-6,7-(isopropylidenedioxy)-5-(methoxymethoxy)octan-3-ol (141 mg, 94%) as an oil, which was dissolved in CH_2Cl_2 (3 mL). A solution of Na_2CO_3 (55 mg, 0.52 mmol) in water (1.5 mL) was added. The mixture was stirred and cooled in an ice bath, and to the mixture was added dropwise a solution of benzyl chloroformate (49 mg, 0.29 mmol) in CH_2Cl_2 (2 mL). After the reaction mixture was stirred at 0 °C for 10 min, water (10 mL) was added, and the mixture was extracted with CH_2Cl_2 (4 × 10 mL). The combined organic layers were washed with water, dried ($MgSO_4$), and concentrated. The residue was purified by column chromatography on silica gel (EtOAc–hexane (1:8)) to yield **32** (160 mg, 86%) as a colorless oil: $[\alpha]^{25}_D$ –4.5° (c 6.9, $CHCl_3$); IR (neat) 3480, 3413, 1729, 1255 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.06 (6 H, s), 0.07 (3 H, s), 0.08 (3 H, s), 0.88 (9 H, s), 0.89 (9 H, s), 1.40 (3 H, s), 1.44 (3 H, s), 1.72–1.92 (1 H, m), 3.35 (3 H, s), 3.70 (1 H, dd, J = 10.4, 6.0 Hz), 3.76–3.85 (4 H, m), 4.00–4.11 (3 H, m), 4.22 (1 H, ddd, J = 7.8, 6.0, 4.1 Hz), 4.39 (1 H, dd, J = 7.9, 1.4 Hz), 4.58 and 4.73 (2 H, AB q, J = 6.8 Hz), 5.07 and 5.12 (2 H, AB q, J = 12.5 Hz), 6.05 (1 H, d, J = 9.1 Hz), 7.28–7.34 (5 H, m); ^{13}C NMR ($CDCl_3$) δ –5.7 (CH_3, 2 carbons), –5.6 (CH_3, 2 carbons), 18.0 (C), 18.3 (C), 25.78 (CH_3, 3 carbons), 25.84 (CH_3, 3 carbons), 26.6 (CH_3), 27.2 (CH_3), 34.9 (CH_2), 56.1 (CH_3), 56.7 (CH), 63.3 (CH_2), 63.6 (CH_2), 66.3 (CH_2), 71.6 (CH), 73.7 (CH), 76.6 (CH), 79.3

(CH), 96.0 (CH_2), 109.3 (C), 127.7 (CH, 2 carbons), 127.8 (CH), 128.3 (CH, 2 carbons), 137.0 (C), 157.2 (C); MS *m/z* (rel intensity) 656 ($M^+ - CH_3$, 1), 614 (7), 524 (10), 330 (65), 308 (35), 131 (100). Anal. Calcd for $C_{33}H_{61}NO_9Si_2$: C, 58.98; H, 9.15; N, 2.08. Found: C, 59.10; H, 9.19; N, 2.05.

(3*S*,4*R*,5*R*,6*S*,7*S*)-3-Acetoxy-4-[[(benzyloxy)carbonyl]amino]-1,8-bis[(*tert*-butyldimethylsilyl)oxy]-6,7-(isopropylidenedioxy)-5-(methoxymethoxy)octane (33). To a mixture of **32** (134 mg, 0.199 mmol), triphenylphosphine (105 mg, 0.401 mmol), and THF (4 mL) were added a solution of AcOH (24 mg, 0.40 mmol) in THF (1 mL) and then a solution of diethyl azodicarboxylate (70 mg, 0.40 mmol) in THF (1 mL). The mixture was stirred at rt for 14 h, and the solid (Ph_3PO) that separated was removed by filtration. Evaporation of the solvent followed by silica gel column chromatography (EtOAc–hexane (1:8)) of the residue gave **33** (99 mg, 70%) as a colorless oil: $[\alpha]^{27}_D$ −19.7° (*c* 5.5, $CHCl_3$); IR (neat) 1744, 1740, 1253 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.02 (6 H, s), 0.06 (6 H, s), 0.88 (9 H, s), 0.89 (9 H, s), 1.37 (3 H, s), 1.41 (3 H, s), 1.80 (2 H, q, *J* = 6.3 Hz), 3.38 (3 H, s), 3.56–3.67 (3 H, m), 3.72 (1 H, dd, *J* = 5.4, 2.0 Hz), 3.86 (1 H, dd, *J* = 10.2, 4.1 Hz), 4.04 (1 H, dd, *J* = 7.9, 1.9 Hz), 4.12–4.23 (2 H, m), 4.60 and 4.69 (2 H, AB q, *J* = 6.9 Hz), 5.04 and 5.15 (2 H, AB q, *J* = 12.5 Hz), 5.67 (1 H, d, *J* = 10.2 Hz), 7.30–7.36 (5 H, m); ^{13}C NMR ($CDCl_3$) δ −5.6 (CH_3, 4 carbons), 18.1 (C), 18.2 (C), 20.8 (CH_3), 25.8 (CH_3, 6 carbons), 26.6 (CH_3), 27.0 (CH_3), 34.8 (CH_2), 54.9 (CH), 56.3 (CH_3), 58.8 (CH_2), 64.1 (CH_2), 66.4 (CH_2), 77.0 (CH), 73.4 (CH), 75.9 (CH), 79.4 (CH), 96.5 (CH_2), 109.4 (C), 127.8 (CH), 127.9 (CH, 2 carbons), 128.4 (CH, 2 carbons), 136.9 (C), 156.7 (C), 170.0 (C); MS *m/z* (rel intensity) 714 ($M^+ + 1$, 2), 698 (5), 656 (21), 420 (18), 394 (61), 350 (22), 117 (100). Anal. Calcd for $C_{35}H_{63}NO_{10}Si_2$: C, 58.87; H, 8.89; N, 1.96. Found: C, 58.94; H, 8.85; N, 1.94.

(3*S*,4*R*,5*R*,6*S*,7*S*)-3-Acetoxy-4-[[(benzyloxy)carbonyl]amino]-6,7-(isopropylidenedioxy)-5-(methoxymethoxy)octane-1,8-diol (34). To a solution of **33** (118 mg, 0.165 mmol) in THF (2 mL) was added a 1.0 M solution of tetrabutylammonium fluoride (0.50 mL, 0.50 mmol) in THF. After 1 h of stirring at rt, the mixture was diluted with EtOAc (10 mL), washed with water, and dried ($MgSO_4$). Evaporation of the solvent and purification of the residue by silica gel column chromatography (EtOAc–hexane (1:1)) gave **34** (75 mg, 94%) as a colorless oil: $[\alpha]^{29}_D$ +5.9° (*c* 2.4, $CHCl_3$); IR (neat) 3424, 1730, 1245 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.37 (3 H, s), 1.41 (3 H, s), 1.72–1.80 (2 H, m), 2.03 (3 H, s), 2.27–2.30 (1 H, m), 3.32 (1 H, br s), 3.62–3.66 (1 H, m), 3.71 (1 H, dd, *J* = 11.5, 3.6 Hz), 3.77–3.81 (2 H, m), 4.04–4.08 (2 H, m), 4.11–4.23 (3 H, m), 4.70 and 4.75 (2 H, AB q, *J* = 6.7 Hz), 5.10 (2 H, s), 5.68 (1 H, d, *J* = 8.5 Hz), 7.28–7.34 (5 H, m); ^{13}C NMR ($CDCl_3$) δ 20.5 (CH_3), 26.4 (CH_3), 26.5 (CH_3), 32.4 (CH_2), 55.0 (CH), 56.0 (CH_3), 60.9 (CH_2), 61.7 (CH_2), 66.2 (CH), 66.4 (CH), 76.2 (CH), 76.6 (CH), 78.3 (CH), 98.1 (CH_2), 108.7 (C), 127.5 (CH), 127.6 (CH, 2 carbons), 128.0 (CH, 2 carbons), 136.0 (C), 156.2 (C), 170.9 (C); MS *m/z* (rel intensity) 486 ($M^+ + 1$, 14), 470 (8), 307 (43), 280 (49), 236 (100), 206 (97), 176 (95), 130 (88), 117 (93). Anal. Calcd for $C_{23}H_{35}NO_{10}$: C, 56.90; H, 7.27; N, 2.88. Found: C, 56.97; H, 7.29; N, 2.81.

(1*S*,6*S*,7*S*,8*R*,8a*R*)-1-Acetoxy-6,7-(isopropylidenedioxy)-8-(methoxymethoxy)indolizidine (36). A solution of **34** (50 mg, 0.103 mmol) in MeOH (2 mL) was hydrogenated over 10% palladium on carbon (15 mg) at atmospheric pressure for 20 min. Filtration of the catalyst and evaporation of the solvent in vacuo gave (3*S*,4*R*,5*R*,6*S*,7*S*)-3-acetoxy-4-amino-6,7-(isopropylidenedioxy)-5-(methoxymethoxy)octane-1,8-diol (**35**) (33 mg, 91%) as a colorless oil, which was, without purification, immediately dissolved in CH_2Cl_2 (3 mL). The solution containing **35** (33 mg, 0.094 mmol) was cooled to 0 °C, and then CBr_4 (75 mg, 0.22 mmol) and a solution of triphenylphosphine (57 mg, 0.22 mmol) in CH_2Cl_2 (1 mL) were successively added. The mixture was stirred at 0 °C for 15 min, and then triethylamine (27 mg, 0.22 mmol) was added. After being stirred for 0 °C for an additional 15 min, the mixture was filtered to remove precipitates and concentrated in vacuo. Subsequent column chromatography on silica gel (EtOAc–hexane (1:2)) gave **36** (21 mg, 70%) as a colorless oil: $[\alpha]^{25}_D$ +134° (*c* 1.3, $CHCl_3$); IR (neat) 2810–2700 (Bohlman bands), 1739, 1250 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.44 (6 H, s), 1.82–1.92 (1 H, m), 2.10 (3 H, s), 2.19–2.25 (2 H, m), 2.28–2.46 (2 H, m), 3.13–3.19 (1 H, m), 3.30 (3 H, s), 3.38 (1 H, dd, *J* = 9.6, 4.0 Hz), 3.44 (1 H, t, *J* = 9.2 Hz), 3.70 (1 H, ddd, *J* = 10.1, 9.2, 4.0 Hz), 4.03 (1 H, t, *J* = 9.2 Hz), 5.23–5.26 (1 H, m); ^{13}C NMR ($CDCl_3$) δ 21.0 (CH_3), 26.6 (CH_3), 26.8 (CH_3), 32.3 (CH_2), 50.9 (CH_2), 52.0 (CH_2), 55.6 (CH_3), 69.5 (CH), 71.5 (CH), 71.9 (CH), 74.9 (CH), 84.6 (CH), 95.9 (CH_2), 111.6 (C), 170.5 (C); MS *m/z* (rel intensity) 316 ($M^+ + 1$, 0.6), 300 (16), 270 (100), 255 (19), 196 (33), 170 (15), 142 (38), 82 (57). Anal. Calcd for $C_{15}H_{25}NO_6$: C, 57.13; H, 7.99; N, 4.44. Found: C, 56.93; H, 7.94; N, 4.38.

(1*S*,6*S*,7*R*,8*R*,8a*R*)-1-Acetoxy-6,7,8-trihydroxyindolizidine [(+)-1-*O*-Acetylcastanospermine] (3). A solution of **36** (140 mg, 0.444 mmol) in an anhydrous 25% methanolic solution of HCl gas (5 mL) was stirred at rt for 30 min. The mixture was worked up in a manner similar to that described for the preparation of **4**. Purification by column chromatography on silica gel (CH_2Cl_2–EtOH (23:2)) gave a white solid, which was recrystallized from EtOAc to give **3** (70 mg, 69%) as colorless cubics: mp 153–155 °C (lit.[21a] mp 151–153 °C); $[\alpha]^{26}_D$ +83.6° (*c* 1.5, MeOH); IR (KBr) 3378 (br), 2861, 2790–2730 (Bohlman bands), 1737, 1381, 1246, 1146, 1092, 1009, 937, 630 cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.48–1.59 (1 H, m), 1.74 (1 H, t, *J* = 10.4 Hz), 1.82 (1 H, dd, *J* = 9.3, 4.7 Hz), 1.97 (3 H, s), 1.98 (1 H, q, *J* = 8.6 Hz), 2.16–2.27 (1 H, m), 2.93–2.98 (3 H, m), 3.32 (1 H, t, *J* = 9.3 Hz), 3.34 (1 H, ddd, *J* = 10.4, 9.2, 4.4 Hz), 4.73 (1 H, d, *J* = 5.3 Hz, disappeared upon addition of D_2O), 4.76 (1 H, d, *J* = 4.9 Hz, disappeared upon addition of D_2O), 4.81 (1 H, d, *J* = 4.4 Hz, disappeared upon addition of D_2O), 5.07 (1 H, ddd, *J* = 7.0, 4.7, 1.7 Hz); ^{13}C NMR (DMSO-d_6) δ DMSO-d_6 21.1 (CH_3), 31.8 (CH_2), 51.9 (CH_2), 56.9 (CH_2), 68.7 (CH), 70.3 (CH), 70.6 (CH), 72.6 (CH), 79.5 (CH), 170.0 (C); MS *m/z* (rel intensity) 232 ($M^+ + 1$, 0.5), 214 (4), 171 (100), 128 (18), 111 (12); HRMS calcd for $C_{10}H_{18}NO_5$ ($M^+ + 1$) 232.1185, found 232.1180.

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