3.50 (br s, OH), 3.79 (s, 3 H), 4.93 (t, 1 H, J = 6.0 Hz), 6.90 (d, 2 H, J = 8.5 Hz), 7.33 (d, 2 H, J = 8.5 Hz); IR 3400 (vs), 2260 (w) cm^{-1}.

β-Hydroxy-β-(3,4-dimethoxyphenyl)propionitrile (10d): oil; ^1H NMR δ 2.65 (d, 2 H, J = 6 Hz), 3.30 (s, OH), 3.79 (s, 6 H), 4.86 (t, 1 H, J = 6 Hz), 6.83 (m, 3 H); IR 3410 (vs), 2250 (w) cm^{-1}. The dehydration of **10d** was shown to give **19d**.

β-Hydroxy-β-[3,4-(methylenedioxy)phenyl]propionitrile (10e): oil (lit.[38] mp 80.5–81.0 °C); ^1H NMR δ 2.67 (d, 2 H, J = 6 Hz), 3.65 (s, OH), 4.90 (t, 1 H, J = 6 Hz), 5.95 (s, 2 H), 6.80 (m, 2 H); IR 3400 (vs), 2260 (w) cm^{-1}.

***trans*-3-(3,4-Dimethoxyphenyl)propenenitrile (19d)**: mp 88–90 °C (lit.[37] mp 91–2 °C); ^1H NMR δ 3.76 (s, 6 H), 5.56 (d, 1 H, J = 16 Hz), 6.80 (m, 3 H, Ar H), 7.06 (d, 1 H, J = 16 Hz); IR (KCl) 2200 (m), 1615 (m) cm^{-1}.

The physical constants of authentic **19a–e** were in agreement with those reported in the literature.[36,38]

Acknowledgment. We are grateful for financial support provided by the National Natural Sciences Foundation of China and the Chinese Academy of Sciences. We also thank Dr. Chen Chen for helpful discussions and Mr. C. W. Xu for part-time participation in this work.

Enantioselective Total Synthesis of (+)- and (−)-Pyrrolidine 197B, a New Class of Alkaloid from the Dendrobatid Poison Frog: Assignment of the Absolute Configuration

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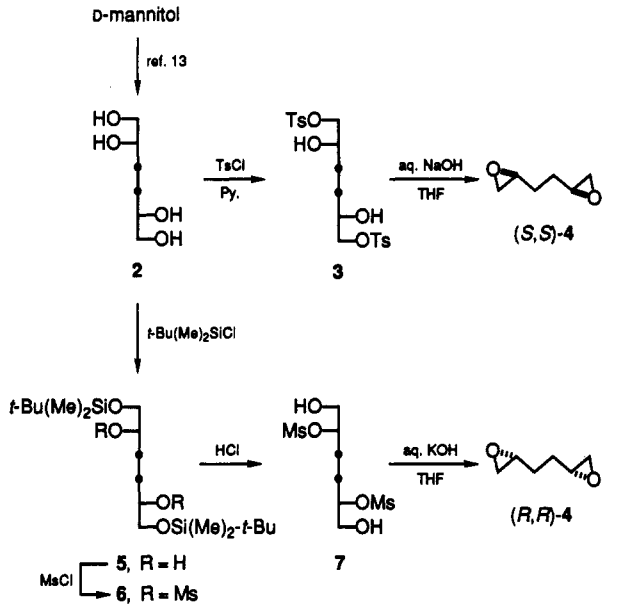
Enantioselective total synthesis of both enantiomers of pyrrolidine 197B (1), a new class of dendrobatid alkaloid, is described. The synthesis begins with the C_2 symmetric *S,S* or *R,R* diepoxides **4**, derived from (*S,S*)-1,2,5,6-hexanetetraol (**2**) as a single common chiral synthon, and involves pyrrolidine formation via the cyclic sulfonates to afford (+)- or (−)-**1**, respectively. The (+) and (−) enantiomers of **1** were converted to the corresponding *N*-benzoyl derivatives (+)-**27** and (−)-**27**, which were directly compared with **27** derived from natural **1** by HPLC using a Chiralcel column. This comparison established the absolute stereochemistry of the natural enantiomer of pyrrolidine 197B as 2*S*,5*S* [(+)-**1**].

Neotropical poison-dart frogs of the dendrobatid species have been shown to contain more than 200 alkaloids.[1] Many of these alkaloids occur in only trace amounts and have been characterized by gas chromatography–mass spectrometry techniques. Recently, such techniques led to the identification of a new class of dendrobatid alkaloid, *trans*-2-butyl-5-pentylpyrrolidine (**1**), named pyrrolidine 197B, in skin extracts of the Colombian populations of *Dendrobates histrionicus*.[2] Interestingly, **1** has also been detected in the alkaloidal venoms of fire ants of the genus *Solenopsis*[3] and the old world ants of *Monomorium*.[4,5] Owing to the minute quantities of **1** available, however, the absolute configuration has remained unknown, and no physical and detailed spectral characteristics have been reported.[6]

In continuation of our work on the synthesis of dendrobatid alkaloids,[7] we have now developed a general synthesis of optically active *trans*-2,5-dialkylated pyrrolidines and investigated its application to this alkaloid.[8-10]

Scheme I



In this paper we describe the enantioselective preparation of both enantiomers of **1**[11,12] based on a stereodefined

(1) Daly, J. W.; Spande, T. F. In *Alkaloids: Chemical and Biological Perspectives*; Pelletier, S. W., Ed.; Wiley-Interscience: New York, 1986; Vol. 4, Chapter 1.

(2) Daly, J. W.; Spande, T. F.; Whittaker, N.; Highet, R. J.; Feigl, D.; Nishimori, N.; Tokuyama, T.; Myers, C. W. *J. Nat. Prod.* **1986**, *49*, 265.

(3) Pedder, D. J.; Fales, H. M.; Jaouni, T.; Blum, M.; MacConnell, J.; Crewe, R. M. *Tetrahedron* **1976**, *32*, 2275.

(4) Ritter, F. J.; Persoons, C. J. *Neth. J. Zool.* **1975**, *25*, 261.

(5) Jones, T. H.; Blum, M. S.; Fales, H. M. *Tetrahedron* **1982**, *38*, 1949.

(6) For natural pyrrolidine 197B, only mass spectra have been reported in ref 2.

(7) (a) Iida, H.; Watanabe, Y.; Kibayashi, C. *J. Am. Chem. Soc.* **1985**, *107*, 5534. Watanabe, Y.; Iida, H.; Kibayashi, C. *J. Org. Chem.* **1989**, *54*, 4088. (b) Yamazaki, N.; Kibayashi, C. *J. Am. Chem. Soc.* **1989**, *111*, 1396.

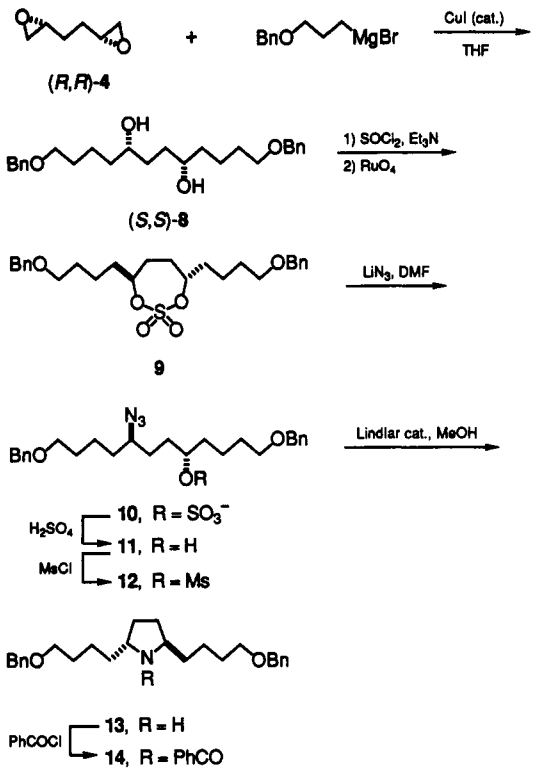
(8) For reviews of the synthesis of 2,5-dialkylpyrrolidine alkaloids, see: (a) Jones, T. H.; Blum, M. S. In *Alkaloids: Chemical and Biological Perspectives*; Pelletier, S. W., Ed; Wiley-Interscience: New York, 1983; Vol. 1, Chapter 2. (b) Attygalle, A. B.; Morgan, E. D. *Chem. Soc. Rev.* **1984**, *13*, 245. (c) Massiot, G.; Delaude, C. In *The Alkaloids*; Brossi, A., Ed.; Academic Press: New York, 1986; Vol. 27, Chapter 3. (d) Numata, A.; Ibuka, T. In *The Alkaloids*; Brossi, A., Ed; Academic Press: New York, 1987; Vol. 31, Chapter 6.

(9) For a recent synthesis of racemic *trans*-2,5-dialkylpyrrolidine alkaloids, see: (a) Gessner, W.; Takahashi, K.; Brossi, A.; Kowalski, M.; Kaliner, M. A. *Helv. Chim. Acta* **1987**, *70*, 2003. (b) Bacos, D.; Celerier, J. P.; Marx, E.; Saliou, C.; Lhommet, G. *Tetrahedron Lett.* **1989**, *30*, 1081. (c) Miyashita, M.; Awen, B. Z. E.; Yoshikoshi, A. *Chem. Lett.* **1990**, 239. (d) Backvall, J.-E.; Schink, H. E.; Renko, Z. D. *J. Org. Chem.* **1990**, *55*, 826.

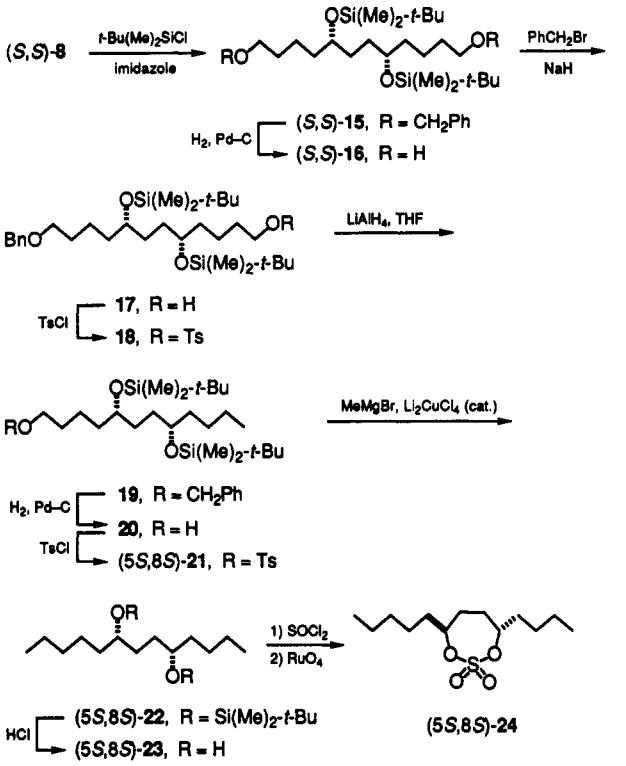
(10) For the synthesis of optically active *trans*-2,5-dialkylpyrrolidine alkaloids, see: (a) Shiosaki, K.; Rapoport, H. *J. Org. Chem.* **1985**, *50*, 1229. (b) Marco, J. L. *J. Heterocycl. Chem.* **1986**, *23*, 1059. (c) Huang, P. Q.; Arseniyadis, S.; Husson, H.-P. *Tetrahedron Lett.* **1987**, *28*, 547. (d) Jegham, S.; Das, B. C. *Tetrahedron Lett.* **1989**, *30*, 2801. (e) Skrinjar, M.; Wistrand, L.-G. *Tetrahedron Lett.* **1990**, *31*, 1775.

0022-3263/91/1956-1386$02.50/0

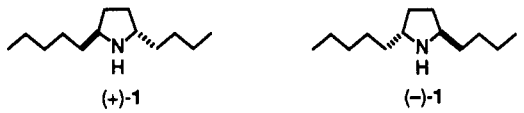
Scheme II



Scheme III



method using the optically active diepoxide **4** as a C_2 symmetrical building block. Compound **4** was synthesized in both enantiomeric forms from D-mannitol. Our results represent the first preparation of optically active 1[19] and establish that natural pyrrolidine 197B possesses the 2*S*,5*S* configuration shown in formula (+)-**1** by direct comparison with a natural sample of **1**.



Both the *S*,*S* and *R*,*R* diepoxides **4** were easily prepared in two and four steps, respectively, using (*S*,*S*)-1,2,5,6-hexanetetraol (**2**) from D-mannitol[13] as a single common chiral synthon (Scheme I). Thus tosylation of the primary alcohol functions of tetraol **2** followed by alkaline treatment of the ditosylate **3** provided (*S*,*S*)-**4** in 58% overall yield from **2**. On the other hand, **2** was converted to the dimesylate **6** by protection of the primary alcohol functions by silylation, followed by mesylation of **5**, in 77% yield. Removal of the silyl groups of **6** by acid, followed by alkaline treatment of the resultant diol **7**, led to (*R*,*R*)-**4** in 51% overall yield from **5**.

Our initial objective was to elaborate the *trans*-2,5-dialkylpyrrolidine ring system by utilization of **4** as a C_2 symmetrical chiral building block. Thus we first undertook a model study for the preparation of the symmetric *trans*-pyrrolidine **13** starting from (*R*,*R*)-**4** (Scheme II). Treatment of (*R*,*R*)-**4** with 2 equiv of [3-(benzyloxy)-propyl]magnesium bromide in the presence of a catalytic amount of copper(I) iodide (THF, −15 °C) resulted in epoxide ring opening to give the diol (*S*,*S*)-**8** in 62% yield.

When (*S*,*S*)-**8** was treated with thionyl chloride and triethylamine, followed by a catalytic amount of ruthenium tetraoxide (RuO_4),[14] the cyclic sulfate **9** was produced in 88% yield. Nucleophilic ring opening of **9** proceeded smoothly on treatment with lithium azide (DMF, room temperature) to afford the sulfate **10**, which was hydrolyzed by acid without isolation to give the inverted azide **11** as a single isomer in 99% yield. Mesylation of **11** gave **12**,[15] which was subjected to selective hydrogenation of the azide function using Lindlar's catalyst,[16] followed by intramolecular cyclization via S_N2 displacement with inversion of configuration at C-5 to furnish the *trans*-pyrrolidine **13** in 86% overall yield. This product was converted to the more stable *N*-benzoylpyrrolidine **14** (PhCOCl, K_2CO_3). Products **13** and **14** showed $[\alpha]^{26}_D$ −10.0° (*c* 1.07, $CHCl_3$) and $[\alpha]^{26}_D$ −65.9° (*c* 2.5, $CHCl_3$), respectively, which unambiguously indicates that pyrrolidine **13** possesses C_2 symmetrical C-2, C-5-trans stereochemistry rather than cis meso stereochemistry.

From these results, we envisioned that a reaction sequence involving an intramolecular cyclization via the cyclic sulfate starting with the diepoxides **2** could be utilized for the enantioselective preparation of unsym-

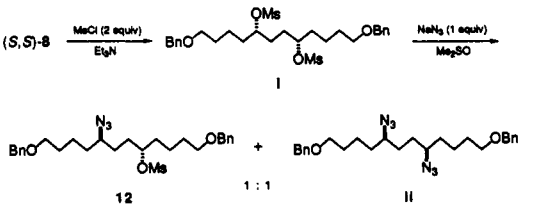
(11) The chiral synthesis of **1** has been reported in preliminary form: Machinaga, N.; Kibayashi, C. *Tetrahedron Lett.* **1990**, *31*, 3637.

(12) For a recent synthesis of racemic **1**, see: (a) Jones, T. H.; Blum, M. S.; Fales, H. M. *Tetrahedron* **1979**, 1031. (b) MacDonalds, T. L. *J. Org. Chem.* **1980**, *50*, 1229. See also ref 9a.

(13) Deane, C. C.; Inch, T. D. *J. Chem. Soc., Chem. Commun.* **1969**, 813.

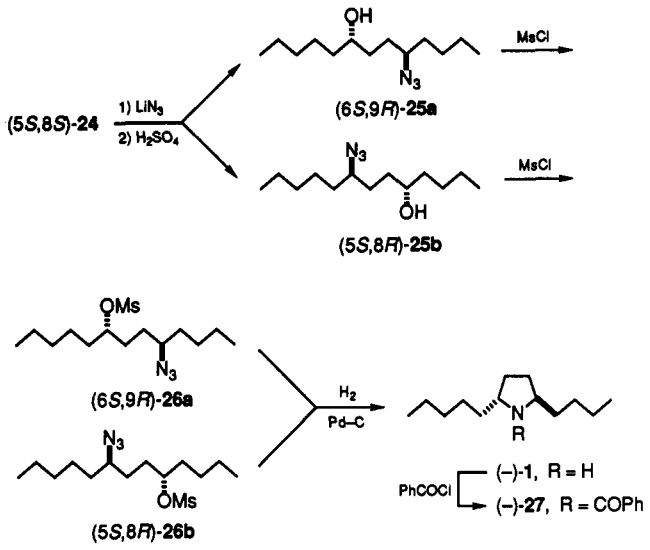
(14) (a) Gao, Y.; Sharpless, K. B. *J. Am. Chem. Soc.* **1988**, *110*, 7538. (b) Kim, B. M.; Sharpless, K. B. *Tetrahedron Lett.* **1989**, *30*, 655.

(15) For an alternative synthesis of the azide **12**, the dimesylate **i** prepared from (*S*,*S*)-**8** was treated with 1 equiv of NaN_3 (Me_2SO, room temperature); however, it resulted in the formation of a 1:1 mixture of **12** and the diazide **ii** (total yield: 40%).

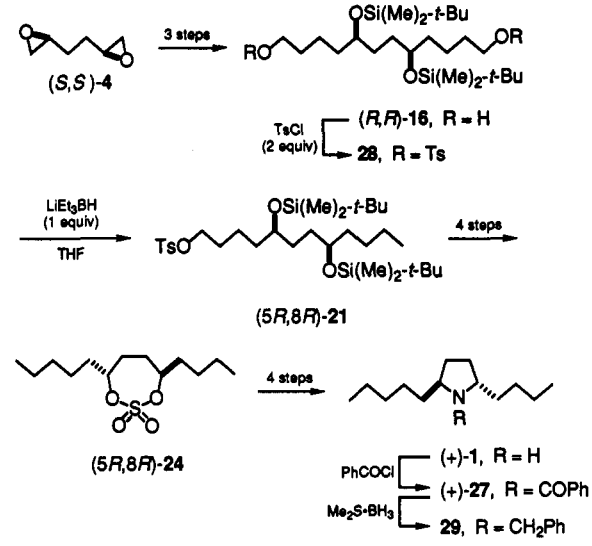


(16) Corey, E. J.; Nicolaou, K. C.; Balanson, R. D.; Machida, Y. *Synthesis* **1975**, 590.

Scheme IV



Scheme V



metrical *trans*-pyrrolidines, such as pyrrolidine 197B (1). Accordingly, with the 5*S*,8*S* diol (*S*,*S*)-8 in hand, we investigated the preparation of the 2*R*,5*R* enantiomer of pyrrolidine 197B [(−)-1]. Thus (*S*,*S*)-8 was converted to the diol (*S*,*S*)-**16** via silylation followed by debenzylation (H_2, Pd–C). Benzylation of (*S*,*S*)-**16** with 1 equiv of benzyl bromide and NaH in DMF afforded **17** (56% yield); the same monobenzylated product was formed by benzylation of either the C-1 or C-12 hydroxy group because of the C_2 symmetry of the molecule (Scheme III). Deoxygenation of **17** was achieved by tosylation followed by reduction with $LiAlH_4$ to provide **19** in 75% overall yield. Subsequent elongation of the left-hand alkyl side chain of **19** was effected by a sequential procedure involving hydrogenolytic debenzylation, tosylation, and coupling with methylmagnesium bromide catalyzed by Li_2CuCl_4 to yield (5*S*,8*S*)-**22** in 72% overall yield. Both silyl groups were removed by acid treatment to give the unsymmetrical diol (5*S*,8*S*)-**23**, which was then reacted with thionyl chloride and triethylamine followed by RuO_4, to afford the cyclic sulfate (5*S*,8*S*)-**24** in 77% overall yield from (5*S*,8*S*)-**22**.

Nucleophilic displacement of (5*S*,8*S*)-**24** with lithium azide and subsequent acidic hydrolysis resulted in an inseparable mixture of the two azides (6*S*,9*R*)-**25a** and (5*S*,8*R*)-**25b** (total yield: 91%) in a 1:1 ratio, which was treated with methanesulfonyl chloride to give a mixture of the corresponding mesylates (6*S*,9*R*)-**26a** and (5*S*,8*R*)-**26b** in 92% yield (Scheme IV). The 1:1 mixture of (6*S*,9*R*)-**26a** and (5*S*,8*R*)-**26b** without separation was subjected to hydrogenation over palladium on carbon to produce (2*R*,5*R*)-*trans*-2-butyl-5-pentylpyrrolidine [(−)-1], having $[\alpha]^{27}_D$ −5.8° (*c* 0.61, $CHCl_3$), as a *single product* in 90% yield. This compound had a CIMS spectrum identical with that reported[2] for natural pyrrolidine 197B, but assignment of the absolute configuration of natural pyrrolidine 197B could not be made at this stage for lack of data on the optical rotation of the natural material.

We next focused on the preparation of the (+) enantiomer of pyrrolidine 197B [(+)-1] employing a more convenient, shorter route starting with the *S*,*S* epoxide **4** as outlined in Scheme V. The epoxide (*S*,*S*)-**4** was converted to the C_2 symmetrical diol (*R*,*R*)-**16** in three steps as described for the preparation of (*S*,*S*)-**16**. Tosylation gave ditosylate **28**, which was treated with 1 equiv of Super-Hydride ($LiEt_3BH$) in THF at 0 °C. In this way, the requisite monotosylate (5*R*,8*R*)-**21** was obtained in 60% yield (98% based on recovered **28**). This product was converted to (+)-1, $[\alpha]^{27}_D$ +5.8° (*c* 0.79, $CHCl_3$), via the cyclic sulfate (5*S*,8*S*)-**24** by the same procedure as that used for the preparation of (−)-1. The trans stereochemistry of (+)-1 was verified by ^1H NMR spectroscopy[17] of the *N*-benzyl derivative **29**, prepared from (+)-1 via N-benzoylation (PhCOCl, K_2CO_3) and reduction of (+)-**27** ($Me_2S{\cdot}BH_3$, THF). The benzyl methylene protons appear as a well-resolved AB quartet, centered at δ 3.64 and 3.81 with a coupling constant of 13.9 Hz, consistent with a trans disposition of the two alkyl groups in which the methylene protons are nonequivalent.

The enantiodivergent synthesis of both enantiomers of pyrrolidine 197B [(+)- and (−)-1] has thus been achieved. This work constitutes the first chiral preparation of structure **1** assigned to the ant venom pyrrolidine alkaloid.[3-5] In order to assign an absolute configuration to natural pyrrolidine 197B, we determined the natural absolute stereochemistry by direct comparison of both the synthetic enantiomers of **1** with a sample of the natural material, supplied by Drs. Daly and Spande as a methanol (0.5 mL) extract of *D. histrionicus* from Al Valle, Colombia, which included pyrrolidine 197B as the major alkaloid component. The crude extract was concentrated and subjected to N-benzoylation by the same procedure used for the preparation of (+)-**27** from synthetic (+)-1. Synthetic (−)-1 was also converted to the *N*-benzoyl derivative (−)-**27**. The *N*-benzoyl derivative of natural pyrrolidine 197B thus obtained was compared with both the synthetic enantiomers (+)-**27** and (−)-**27** by HPLC using a Chiralcel OD column (Figure 1). The peaks for the synthetic (+) and (−) enantiomers of **27** were well separated from each other. The retention times (t_R) for (−)-**27** (A) and (+)-**27** (B) were 7.5 and 11.0 min (hexane/*i*-PrOH, 20:1), respectively, and that of naturally derived *N*-benzoylpyrrolidine 197B (C) was consistent with that of (+)-**27**. When a 1:1 mixture of (−)-**27** and (+)-**27** was coinjected with naturally derived *N*-benzoylpyrrolidine 197B, the peak corresponding to (+)-**27** (t_R = 11.0 min) was enhanced as shown in D. These observations confirm the structure of pyrrolidine 197B and prove that natural pyrrolidine 197B possesses the 2*S*,5*S* configuration (+)-1.

Experimental Section

General Procedures. Optical rotations were measured on a digital polarimeter in a 1-dm cell. ^1H and ^{13}C NMR spectra were

(17) Cf.: Hill, R. K.; Chan, T.-H. *Tetrahedron* **1965**, *21*, 2015.

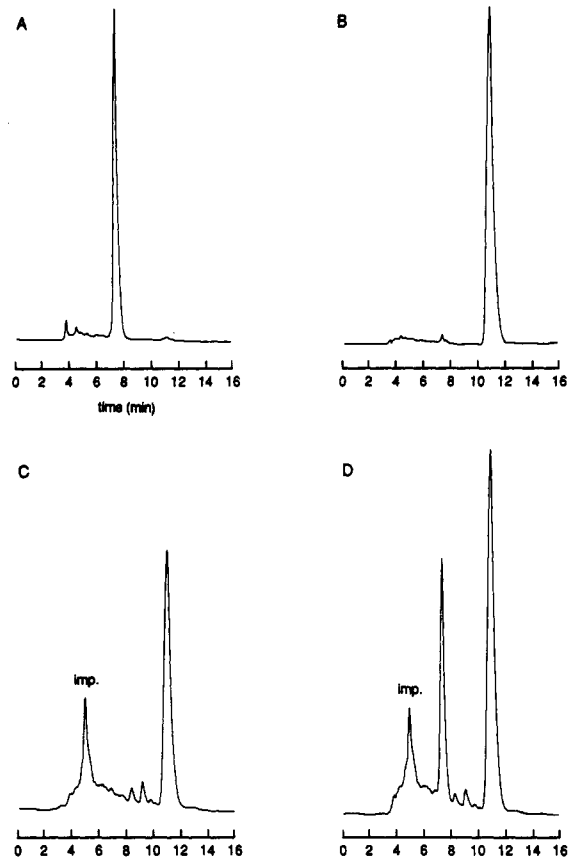


Figure 1. High-performance liquid chromatograms of (A) synthetic (−)-**27**, (B) synthetic (+)-**27**, (C) the *N*-benzoyl derivative of natural pyrrolidine 197B, and (D) a 1:1 mixture of synthetic (−)-**27** and (+)-**27**, coinjected with the *N*-benzoyl derivative of natural pyrrolidine 197B. HPLC was run on a Chiralcel OD column (0.46 × 25 cm) eluted with hexane–*i*-PrOH (20:1) and detected at 254 nm.

taken at 400 and 100.6 MHz, respectively. ^{1}H chemical shifts are expressed relative to $CHCl_3$ at δ 7.26 and ^{13}C chemical shifts relative to $CDCl_3$ at δ 77.1 unless otherwise indicated. Mass spectra were obtained at 70 eV for both EI and CI (NH_3 as a reagent gas). High-performance liquid chromatography (HPLC) was performed on a Chiralcel OD column (Daicel Chemical Industries) by using a Kusano KPW-10 micro pump and a JASCO UVIDEC-100-V detector at λ = 254 nm and flow rate = 0.8 mL/min. Analytical TLC was performed on Merck precoated silica gel 60 F254 plates. Merck silica gel 60 (230–400 mesh) was used for column chromatography. Microanalyses were carried out by the Microanalytical Laboratory at Tokyo College of Pharmacy.

(2*S*,5*S*)-1,2:5,6-Diepoxyhexane [(*S*,*S*)-4]. To an ice-cold solution of **2**[13] (5.00 g, 33.3 mmol) in pyridine (40 mL) was added *p*-toluenesulfonyl chloride (12.71 g, 66.6 mmol). The mixture was stirred in the ice bath for 30 min and then at room temperature for 1 h. The mixture was diluted with $CHCl_3$ (300 mL) and washed with water (50 mL), 5% HCl (200 mL), and water (50 mL). Drying ($MgSO_4$) followed by evaporation in vacuo gave the crude tosylate **3** as a white crystalline product, which was used in the next step without further purification. Thus it was dissolved in THF (100 mL) and cooled to 0 °C, and 15% NaOH (30 mL) was added dropwise over a period of 10 min with stirring. After being stirred at room temperature for 1.5 h, the mixture was diluted with Et_2O (200 mL), washed with brine (2 × 20 mL), and dried ($MgSO_4$). After evaporation of the solvent in vacuo, the residue was purified by silica gel chromatography on silica gel with hexane–acetone (4:1) as eluent to give **4** (2.20 g, 58%) as a colorless oil: bp 75–80 °C (42 mmHg)[18]; $[\alpha]^{26}_D$ −19.0° (*c* 1.26, $CHCl_3$)[18]; ^{1}H NMR ($CDCl_3$) δ 1.57–1.85 (4 H, s), 2.48 (2 H, *J* = 4.9, 2.7 Hz), 2.57 (2 H, dd, *J* = 4.9, 4.0 Hz), 2.89–3.00 (2 H, m); ^{13}C NMR ($CDCl_3$) δ 28.80, 47.09, 51.64.

(2*S*,5*S*)-1,6-Bis[(*tert*-butyldimethylsilyl)oxy]-2,5-hexanediol (5). To a stirred solution of **2** (3.00 g, 20.0 mmol) in DMF (20 mL) were added imidazole (5.44 g, 80.0 mmol) and *t*-Bu-$(Me)_2SiCl$ (6.60 g, 43.8 mmol), and the mixture was stirred at room temperature. After 1 h, the mixture was diluted with Et_2O (200 mL), washed with water, and dried ($MgSO_4$). The solvent was removed by evaporation, and the residue was purified by chromatography on silica gel with hexane–AcOEt (4:1) as eluent to give **5** (6.17 g, 82%) as a colorless oil, which crystallized on standing in the refrigerator: mp 78 °C; $[\alpha]^{26}_D$ +2.2° (*c* 1.11, $CHCl_3$); IR (neat) 3400 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.07, 0.08, 0.892, 0.899, 0.906 (6 H, s, each), 1.35–1.67 (4 H, m), 2.75–2.90 (2 H, br s), 3.44 (1 H, dd, *J* = 9.8, 7.2 Hz), 3.61 (1 H, dd, *J* = 9.8, 3.8 Hz), 3.66 (2 H, m); ^{13}C NMR ($CDCl_3$) δ −5.29 (2 C), −5.25 (2 C), 18.39 (2 C), 25.99 (6 C), 29.21 (2 C), 67.33 (2 C), 71.88 (2 C); MS *m*/*z* (relative intensity) 379 (M^+, 0.2), 215 (14), 171 (30), 75 (100), 73 (99).

Anal. Calcd for $C_{18}H_{42}O_4Si_2$: C, 57.09; H, 11.18. Found: C, 57.16; H, 11.31.

(2*S*,5*S*)-1,6-Bis[(*tert*-butyldimethylsilyl)oxy]-2,5-bis[(methylsulfonyl)oxy]hexane (6). To an ice-cold, stirred mixture of **5** (6.17 g, 16.3 mmol) and Et_3N (6.59 g, 65.3 mmol) in CH_2Cl_2 (20 mL) was added dropwise methanesulfonyl chloride (5.62 g, 48.9 mmol). The mixture was stirred in the ice bath for another 10 min and diluted with Et_2O (200 mL). The solution was washed with water (2 × 50 mL), dried ($MgSO_4$), and concentrated. The residue was purified by chromatography on silica gel with hexane–AcOEt (5:1) as eluent to give **6** (8.18 g, 94%) as a colorless oil, which crystallized on standing in the refrigerator: mp 74–76 °C; $[\alpha]^{27}_D$ −1.4° (*c* 0.56, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 0.07 (12 H, s), 0.89 (18 H, s), 1.76–1.82 (4 H, m), 3.06 (6 H, s), 3.74 (4 H, dd, *J* = 17.4, 6.3 Hz), 4.69–4.78 (2 H, m); ^{13}C NMR ($CDCl_3$) δ −5.65 (4 C), 18.45 (2 C), 25.97 (6 C), 26.49 (2 C), 38.72 (2 C), 65.18 (2 C), 83.34 (2 C); MS *m*/*z* (relative intensity) 439 (M^+ − OMs, 0.2), 211 (80), 171 (89), 153 (100), 115 (20).

Anal. Calcd for $C_{20}H_{46}O_8S_2Si_2$: C, 44.91; H, 8.67. Found: C, 44.51; H, 8.67.

(2*R*,5*R*)-1,2:5,6-Diepoxyhexane [(*R*,*R*)-4]. To an ice-cold solution of **6** (17.3 g, 32.3 mmol) in MeOH (20 mL) was added concentrated HCl (4 mL), and the mixture was stirred at room temperature for 1.5 h. The mixture containing the diol **3** was recooled in an ice bath, and 20% KOH (20 mL) was added dropwise with stirring. Stirring was continued for an additional 1 h, and the mixture was concentrated in vacuo to leave an oily product, which was dissolved in Et_2O (200 mL), washed with water (2 × 30 mL), and dried ($MgSO_4$). After removal of the solvent by evaporation, the residue was purified by chromatography on silica gel with hexane–AcOEt (5:1) as eluent to give (*R*,*R*)-**4** (2.3 g, 63%) as a colorless oil, $[\alpha]^{26}_D$ +18.5° (*c* 2.22, $CHCl_3$), which was identical with previously isolated (*S*,*S*)-**4** by ^{1}H and ^{13}C NMR and TLC.

(5*S*,8*S*)-1,12-Bis(benzyloxy)-5,8-dodecanediol [(*S*,*S*)-8]. The Grignard reagent prepared from Mg (131 mg, 5.41 mmol) and 1-(benzyloxy)-3-bromopropane (1.24 g, 5.41 mmol) in THF (10 mL) was added dropwise via syringe to a stirred suspension of CuI (10 mg, 0.53 mmol) in THF (1.0 mL) at −15 °C under an argon atmosphere. To the resulting dark suspension was added dropwise via syringe a solution of (*R*,*R*)-**4** (170 mg, 1.55 mmol) in THF (2 mL) at −15 °C, and the mixture was stirred at this temperature. After 1.5 h, the reaction was quenched by water (5 mL), and Et_2O (150 mL) was added to the mixture. The organic layer was separated, washed with brine (50 mL), dried ($MgSO_4$), and evaporated. The residue was chromatographed on silica gel with hexane–AcOEt (2:1 to 1:1) as eluent to give a white solid, which was recrystallized from hexane to give (*S*,*S*)-**8** (338 mg, 62%) as white needles: mp >300 °C; $[\alpha]^{26}_D$ +2.8° (*c* 2.03, $CHCl_3$); IR ($CHCl_3$) 3279 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.38–1.71 (16 H, m), 2.10–2.55 (2 H, br s), 3.48 (4 H, t, *J* = 6.4 Hz), 3.59–3.68 (2 H, m), 4.50 (4 H, s), 7.24–7.37 (10 H, m); ^{13}C NMR ($CDCl_3$) δ 22.50 (2 C), 29.75 (2 C), 34.08 (2 C), 37.57 (2 C), 70.38 (3 C), 72.19 (2

(18) The following values have been reported for **4**: bp 50–55 °C (0.01 mmHg); $[\alpha]^{20}_D$ −9° ($CHCl_3$) (Kuszmann, J.; Sohár, P. *Carbohydr. Res.* **1980**, *83*, 63).

(19) After submission of this paper, a chiral synthesis of (+)-**1** was reported: Takahata, H.; Takehara, H.; Ohkubo, N.; Momose, T. *Tetrahedron: Asymmetry* **1990**, *1*, 561.

C), 73.02 (2 C), 127.61 (4 C), 127.75 (4 C), 128.45 (2 C), 138.68 (2 C); MS m/z (relative intensity) 378 (M^+ - 36, 0.4), 305 (4), 286 (6), 233 (19), 199 (100), 197 (4), 143 (42), 107 (82); CI 415 (M^+ + 1, 0.4), 305 (3), 287 (4), 233 (16), 199 (100), 197 (46), 181 (18), 143 (41), 107 (80).

Anal. Calcd for $C_{26}H_{38}O_4$: C, 75.32; H, 9.42. Found: C, 75.04; H, 9.28.

(5*S*,8*S*)-1,12-Bis(benzyloxy)-5,8-dodecanediol Cyclic Sulfate (9). To an ice-cooled, stirred mixture of (*S*,*S*)-8 (4.82 g, 11.6 mmol), Et_3N (4.70 g, 46.6 mmol), and CH_2Cl_2 (10 mL) was added dropwise a solution of thionyl chloride (4.15 g, 34.92 mmol) in CH_2Cl_2 (5 mL). After being stirred for 30 min in the ice bath, the mixture was diluted with Et_2O (200 mL) and the ethereal solution was washed with brine (3 × 50 mL) and dried ($MgSO_4$). The solvent was evaporated, and the resulting dark brown residue was dissolved in a mixture of CCl_4 (60 mL), MeCN (60 mL), and water (90 mL). To this solution were added $NaIO_4$ (4.98 g, 23.3 mmol) and then $RuCl_3 \cdot xH_2O$ (20 mg) with stirring at 0 °C. After 2 h, the reaction mixture was extracted with Et_2O (3 × 100 mL), and the extract was washed with brine (50 mL), dried ($MgSO_4$), and concentrated. The residue was chromatographed on silica gel with hexane–AcOEt (4:1) as eluent to give **9** (4.87 g, 88%) as a crystalline product, which was recrystallized from hexane to give white needles: mp 83–84 °C; $[\alpha]^{26}_D$ +11.4° (*c* 2.14, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.46–1.81 (12 H, m), 1.84–1.96 (4 H, m), 3.48 (4 H, t, J = 6.1 Hz), 4.50 (4 H, s), 4.57–4.67 (2 H, m), 7.26–7.37 (10 H, m); ^{13}C NMR ($CDCl_3$) δ 30.59 (2 C), 37.81 (2 C), 41.54 (2 C), 43.85 (2 C), 78.60 (2 C), 81.61 (2 C), 93.62 (2 C), 136.20 (2 C), 136.33 (4 C), 137.04 (4 C), 147.20 (2 C).

Anal. Calcd for $C_{26}H_{36}O_6S$: C, 65.52; H, 7.61. Found: C, 65.53; H, 7.58.

(5*S*,8*S*)-8-Azido-1,12-bis(benzyloxy)-5-dodecanol (11). To a stirred solution of **9** (100 mg, 0.21 mmol) in DMF (3 mL) was added LiN_3 (16 mg, 0.33 mmol) at room temperature, and the mixture was stirred for 30 min. The mixture was concentrated in vacuo (0.02 mmHg, below 40 °C), and the residue containing the acyclic sulfate **10** was dissolved in THF (3 mL). To this solution was added a mixture of concentrated H_2SO_4 (25 μL) and water (9 μL), and the resulting mixture was stirred at room temperature. After being stirred for 1 h, the mixture was cooled in an ice bath and neutralized with Na_2CO_3. To this mixture was added Et_2O (100 mL), the separated solid was filtered, and the filtrate was concentrated. The residue was chromatographed on silica gel with hexane–AcOEt (2:1) as eluent to give **11** (92 mg, 99%) as a pale yellow oil: $[\alpha]^{26}_D$ +1.0° (*c* 1.47, $CHCl_3$); IR (neat) 3446 (OH), 2098 (N_3) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.35–1.77 (16 H, m), 3.23–3.31 (1 H, m), 3.45–3.51 (5 H, m), 3.58 (1 H, br s), 4.50 (4 H, s), 7.26–7.37 (10 H, m); ^{13}C NMR ($CDCl_3$) δ 22.41, 22.95, 29.62, 29.72, 30.82, 34.04, 34.41, 37.48, 63.37, 70.13, 70.30, 71.78, 73.03 (2 C), 127.62 (2 C), 127.73 (4 C), 128.45 (4 C), 138.64 (2 C); MS m/z (relative intensity) 394 (M^+ - 44, 3), 302 (60), 161 (68), 105 (100).

Anal. Calcd for $C_{26}H_{37}N_3O_3$: C, 71.04; H, 8.48; N, 9.56. Found: C, 70.75; H, 8.51; N, 9.46.

(5*S*,8*R*)-8-Azido-1,12-bis(benzyloxy)-5-[(methylsulfonyl)oxy]dodecane (12). In a similar manner to that described for the preparation of **6**, **11** (1.71 g, 3.90 mmol) was treated with methanesulfonyl chloride (537 mg, 4.69 mmol) and Et_3N (789 mg, 7.79 mmol) in CH_2Cl_2. The usual workup and chromatography of the crude product on silica gel with hexane–AcOEt (4:1) as eluent afforded **12** (1.84 g, 91%) as a pale yellow oil: $[\alpha]^{26}_D$ -5.1° (*c* 1.76, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.41–1.91 (16 H, m), 2.98 (3 H, s), 3.23–3.33 (1 H, br m), 3.48 (2 H, t, J = 6.3 Hz), 3.49 (2 H, t, J = 6.2 Hz), 4.498, 4.504 (2 H, s, each), 4.67–4.73 (1 H, m), 7.26–7.37 (10 H, m); ^{13}C NMR ($CDCl_3$) δ 21.88, 22.96, 29.47, 29.60, 29.94, 31.19, 34.32, 34.40, 38.84, 62.83, 69.96, 70.08, 73.06 (2 C), 83.17, 127.64 (2 C), 127.74 (4 C), 128.46 (4 C), 138.66 (2 C); MS m/z (relative intensity) 484 (M^+ - 34, 2), 394 (5), 302 (84), 196 (43), 161 (43), 107 (100).

Anal. Calcd for $C_{27}H_{39}N_3O_5S$: C, 62.64; H, 7.95; N, 8.12. Found: C, 62.40; H, 7.61; N, 8.10.

(2*R*,5*R*)-2,5-Bis[4-(benzyloxy)butyl]pyrrolidine (13). A solution of **12** (1.70 g, 3.29 mmol) in MeOH (10 mL) was hydrogenated over 5% palladium on $BaSO_4$ (1.0 g) for 8 h. Filtration and evaporation of the reaction mixture provided an oil, which was chromatographed on silica gel with $CHCl_3$–MeOH (5:1) as eluent to give **13** (1.29 g, 99%) as a pale yellow oil: $[\alpha]^{26}_D$ -10.0° (*c* 1.07, $CHCl_3$); IR (neat) 3435 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.22–1.69 (14 H, m), 1.89 (2 H, td, J = 13.7, 8.0 Hz), 2.10 (2 H, m), 3.40–3.49 (total 6 H, m, containing 4 H, t, J = 6.3 Hz at δ 3.45), 4.46 (4 H, s), 7.24–7.35 (10 H, m); ^{13}C NMR ($CDCl_3$) δ 23.60 (2 C), 29.45 (2 C), 30.80 (2 C), 33.36 (2 C), 59.22 (2 C), 70.11 (2 C), 72.98 (2 C), 127.59 (2 C), 127.73 (4 C), 128.43 (4 C), 138.63 (2 C); MS m/z (relative intensity) 395 (M^+, 0.3), 394 (M^+ - 1, 0.7), 304 (13), 232 (78), 91 (100).

(2*R*,5*R*)-*N*-Benzoyl-2,5-bis[4-(benzyloxy)butyl]pyrrolidine (14). To an ice-cold solution of **13** (1.47 g, 3.72 mmol) in CH_2Cl_2 (20 mL) was added 10% K_2CO_3 (20 mL). To this mixture was added dropwise a solution of benzoyl chloride (1.05 g, 7.44 mmol) in CH_2Cl_2 (10 mL) with vigorous stirring. After the mixture was stirred for 10 min, the organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (2 × 20 mL). The combined organic layers were washed with brine (40 mL), dried ($MgSO_4$), and concentrated in vacuo to give an oily product, which was purified by chromatography on silica gel, eluting with hexane–AcOEt (4:1), to yield **14** (1.36 g, 73%) as a pale yellow oil: $[\alpha]^{28}_D$ -65.9° (*c* 2.50, $CHCl_3$); IR (neat) 1625 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.88–0.91 (1 H, m), 1.10–1.29 (5 H, m), 1.38–1.49 (3 H, m), 1.62–1.75 (4 H, m), 1.91–2.13 (3 H, m), 3.18, 3.51 (ca. 1:1 ratio, total 4 H, t each, J = 6.0, 6.4 Hz, respectively, due to amide rotamers), 3.91–3.96, 4.25–4.27 (ca. 1:1 ratio, total 2 H, m, due to rotamers), 4.38, 4.51 (ca. 1:1 ratio, total 4 H, s each, due to rotamers), 7.26–7.36 (13 H, m), 7.43–7.74 (2 H, m); ^{13}C NMR ($CDCl_3$) δ 22.84, 23.21, 26.48, 28.25, 28.98, 29.76, 32.87, 34.39, 57.60, 59.45, 69.85, 70.39, 72.94, 127.00, 127.53, 127.64, 127.72, 128.35, 128.42, 129.56, 138.54; MS m/z (relative intensity) 500 (M^+, 1), 499 (M^+ - 1, 8), 408 (3), 336 (30), 149 (60), 105 (100).

Anal. Calcd for $C_{33}H_{41}NO_3$: C, 79.32; H, 8.27; N, 2.80. Found: C, 78.99; H, 8.36; N, 2.77.

(5*S*,8*S*)-1,12-Bis(benzyloxy)-5,8-bis[(*tert*-butyldimethylsilyl)oxy]dodecane [(*S*,*S*)-15]. To a stirred solution of (*S*,*S*)-8 (1.53 g, 3.70 mmol) in DMF (10 mL) were added imidazole (1.51 g, 22.2 mmol) and then *t*-Bu(Me)$_2$SiCl (3.35 g, 22.2 mmol), and the mixture was stirred at room temperature for 5 h. The mixture was diluted with Et_2O (200 mL) and washed with water (2 × 50 mL). Drying ($MgSO_4$) of the mixture and evaporation of the solvent gave an oil, which was chromatographed on silica gel with hexane–AcOEt (20:1) as eluent to afford (*S*,*S*)-**15** (2.19 g, 91%) as a colorless oil: $[\alpha]^{28}_D$ -6.9° (*c* 1.45, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 0.04, 0.05, 0.88, 0.89, 0.90 (6 H, s, each), 1.29–1.53 (12 H, m), 1.62 (4 H, dt, J = 13.1, 6.7 Hz), 3.47 (4 H, t, J = 6.6 Hz), 3.63 (2 H, m), 4.51 (4 H, s), 7.26–7.53 (10 H, m); ^{13}C NMR ($CDCl_3$) δ -4.31 (4 C), 18.22 (2 C), 22.09 (2 C), 26.04 (6 C), 30.10 (2 C), 32.80 (2 C), 37.04 (2 C), 70.55 (2 C), 72.50 (2 C), 72.98 (2 C), 127.52 (2 C), 128.20 (4 C), 128.41 (4 C), 138.86 (2 C).

Anal. Calcd for $C_{38}H_{66}O_4Si_2$: C, 70.97; H, 10.34. Found: C, 70.98; H, 10.29.

(5*S*,8*S*)-5,8-Bis[(*tert*-butyldimethylsilyl)oxy]-1,12-dodecanediol [(*S*,*S*)-16]. A solution of (*S*,*S*)-**15** (2.18 g, 3.39 mmol) in MeOH (20 mL) was hydrogenated over 10% palladium on carbon (200 mg) for 5 h. The catalyst was removed by filtration and washed with MeOH (20 mL), and the combined MeOH solution was concentrated in vacuo. The residual oil was chromatographed on silica gel with hexane–AcOEt (6:1) as eluent to give (*S*,*S*)-**16** (1.41 g, 90%) as a colorless oil: $[\alpha]^{28}_D$ -6.5° (*c* 1.39, $CHCl_3$); IR (neat) 3338 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.035, 0.042, 0.87, 0.88, 0.89 (6 H, s, each), 1.31–1.50 (12 H, m), 1.56 (4 H, dt, J = 13.1, 7.0 Hz), 3.58–3.60 (total 6 H, m, including 4 H, t, J = 6.6 Hz at δ 3.64); ^{13}C NMR ($CDCl_3$) δ -4.32 (4 C), 18.21 (2 C), 21.46 (2 C), 26.03 (6 C), 32.66 (2 C), 33.07 (2 C), 36.85 (2 C), 63.03 (2 C), 72.41 (2 C); MS m/z (relative intensity) 368 (M^+ - 95, 0.5), 315 (2), 273 (86), 181 (100), 159 (84), 125 (87), 121 (87).

Anal. Calcd for $C_{24}H_{54}O_4Si_2$: C, 62.28; H, 11.76. Found: C, 62.18; H, 11.60.

(5*S*,8*S*)-12-(Benzyloxy)-5,8-bis[(*tert*-butyldimethylsilyl)oxy]-1-dodecanol (17). To a stirred suspension of NaH (87 mg, 3.63 mmol) in dimethyl sulfoxide (10 mL) was added dropwise a solution of (*S*,*S*)-**16** (1.00 g, 2.16 mmol) in THF (5 mL) at room temperature. After the mixture was stirred for 1 h, a solution of benzyl bromide (370 mg, 2.16 mmol) in THF (5 mL) was added dropwise, and the mixture was heated at 70–80 °C with stirring for 1.5 h. After cooling of the mixture, followed by

quenching with water (10 mL), Et_2O (200 mL) was added. The organic layer was washed with water (2 × 50 mL) and dried ($MgSO_4$). The solvent was evaporated, and the residue was chromatographed on silica gel with hexane–AcOEt (4:1) as eluent to give **17** (672 mg, 56%) as a pale yellow oil: $[\alpha]^{27}_D$ −5.83° (*c* 1.44, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 0.037, 0.040 (6 H, s, each), 0.89 (18 H, s), 1.33–1.50 (12 H, m), 1.56 (2 H, dt *J* = 13.9, 7.0 Hz), 1.61 (1 H, dt, *J* = 13.7, 6.6 Hz), 3.47 (2 H, t, *J* = 6.6 Hz), 3.61–3.64 (total 5 H, m, including 2 H, t, *J* = 6.5 Hz at δ 3.62), 4.50 (2 H, s), 7.25–7.37 (5 H, m); ^{13}C NMR ($CDCl_3$) δ −4.31 (4 C), 18.20 (2 C), 21.47, 22.06, 26.02 (6 C), 30.08, 32.70, 32.72, 33.08, 36.87, 37.00, 63.02, 70.54, 72.43, 72.46, 72.97, 127.53, 127.67 (2 C), 128.41 (2 C), 138.82; MS *m/z* (relative intensity) 553 (M^+, 0.4), 551 (0.5), 479 (1.2), 419 (2.0), 363 (100), 301 (24), 271 (83), 215 (40).

Anal. Calcd for $C_{31}H_{60}O_4Si_2$: C, 67.33; H, 10.94. Found: C, 67.05; H, 10.97.

(5*S*,8*S*)-12-(Benzyloxy)-5,8-bis[(*tert*-butyldimethylsilyl)oxy]-1-[(*p*-tolylsulfonyl)oxy]dodecane (18). To a stirred mixture of **17** (40 mg, 0.072 mmol) and 4-(dimethylamino)pyridine (13 mg, 0.11 mmol) in CH_2Cl_2 (3 mL) was added a solution of *p*-toluenesulfonyl chloride (20 mg, 0.10 mmol) in CH_2Cl_2 (2 mL), and the resulting mixture was stirred at room temperature for 12 h. The mixture was quenched with water (20 mL) and extracted with CH_2Cl_2 (2 × 30 mL). The combined extracts were washed with brine, dried ($MgSO_4$), and concentrated in vacuo to give an oily residue, which was chromatographed on silica gel with hexane–AcOEt (8:1) as eluent to afford **18** (49 mg, 96%) as a colorless oil: $[\alpha]^{24}_D$ −5.1° (*c* 0.76, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 0.000, 0.017, 0.025, 0.030 (3 H, s, each), 0.86, 0.87 (9 H, s, each), 1.21–1.47 (12 H, m), 1.57–1.65 (4 H, m), 2.44 (3 H, s), 3.47 (2 H, t, *J* = 6.6 Hz), 3.60 (2 H, td, *J* = 10.0, 5.0 Hz), 4.02 (2 H, t, *J* = 6.6 Hz), 4.50 (2 H, s), 7.25–7.38 (7 H, m), 7.79 (2 H, d, *J* = 8.2 Hz); ^{13}C NMR ($CDCl_3$) δ −4.35 (2 C), −4.29 (2 C), 18.17, 18.21, 21.30, 21.69, 22.08, 26.00 (3 C), 26.02 (3 C), 29.23, 30.10, 32.71, 32.80, 36.44, 37.06, 70.54, 70.60, 72.19, 72.42, 72.99, 127.53, 127.67 (2 C), 127.97 (2 C), 128.41, 129.88 (2 C), 133.55, 138.85, 144.64; MS *m/z* (relative intensity) 557 (M^+ − 150, 0.7), 522 (0.5), 411 (6), 371 (4), 303 (11), 229 (100), 163 (24).

Anal. Calcd for $C_{38}H_{66}O_6SSi_2$: C, 64.54; H, 9.41. Found: C, 64.60; H, 9.50.

(5*S*,8*S*)-1-(Benzyloxy)-5,8-bis[(*tert*-butyldimethylsilyl)oxy]dodecane (19). To a stirred, ice-cooled suspension of $LiAlH_4$ (9 mg, 0.24 mmol) in THF (4 mL) was added dropwise a solution of **18** (52 mg, 0.074 mmol) in THF (2 mL) under an argon atmosphere. After being stirred for 3 h at room temperature, the mixture was cooled in an ice bath and quenched with water (1.5 mL). The mixture was filtered through a Celite pad, which was washed with Et_2O. The combined filtrate was dried ($MgSO_4$) and concentrated to leave a syrup, which was chromatographed on silica gel with hexane–AcOEt (20:1) as eluent to give **19** (31 mg, 78%) as a colorless oil: $[\alpha]^{24}_D$ −3.8° (*c* 0.98, MeOH); ^1H NMR ($CDCl_3$) δ 0.04 (12 H, s), 0.88–0.91 (21 H), 1.23–1.54 (14 H, m), 1.62 (2 H, dt, *J* = 13.5, 6.6 Hz), 3.47 (2 H, t, *J* = 6.6 Hz), 3.60–3.63 (2 H, m), 4.51 (2 H, s), 7.25–7.34 (5 H, m); ^{13}C NMR ($CDCl_3$) δ −4.29 (4 C), 14.19, 18.24 (2 C), 22.11, 23.00, 26.05 (6 C), 27.63, 30.12, 32.77, 32.82, 36.92, 37.04, 70.58, 72.54, 72.61, 73.00, 127.54, 127.67 (2 C), 128.43 (2 C), 138.88; MS *m/z* (relative intensity) 537 (M^+, 5), 536 (M^+ − 1, 5), 535 (9), 479 (10), 429 (6), 405 (33), 403 (35), 387 (30), 362 (22), 347 (56), 297 (33), 273 (9), 241 (99), 215 (48), 201 (9), 181 (99), 147 (98), 136 (100), 109 (99).

Anal. Calcd for $C_{31}H_{60}O_3Si_2$: C, 69.34; H, 11.26. Found: C, 69.24; H, 11.25.

(5*S*,8*S*)-5,8-Bis[(*tert*-butyldimethylsilyl)oxy]-1-dodecanol (20). A solution of **19** (248 mg, 0.46 mmol) in MeOH (5 mL) was hydrogenated over 10% palladium on carbon (100 mg) for 12 h. Filtration and evaporation afforded a syrup, which was chromatographed on silica gel with hexane–AcOEt (9:1) as eluent to give **20** (201 mg, 98%) as a colorless oil: $[\alpha]^{24}_D$ −7.6° (*c* 0.92, $CHCl_3$); IR (neat) 3338 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.03 (12 H, s), 0.87–0.90 (21 H), 1.24–1.34 (4 H, m), 1.36–1.50 (10 H, m), 1.56 (2 H, dt, *J* = 13.9, 7.0 Hz), 3.58–3.64 (total 5 H, m, including 2 H, t, *J* = 6.6 Hz at δ 3.63); ^{13}C NMR ($CDCl_3$) δ −4.31 (4 C), 14.17, 16.23 (2 C), 21.52, 22.99, 26.03 (6 C), 27.61, 32.76 (2 C), 33.12, 36.91 (2 C), 63.06, 72.49, 72.58; MS *m/z* (relative intensity) 374 (M^+ − 163, 0.1), 373 (0.6), 313 (1), 299 (2), 275 (4), 257 (44), 241 (17), 201 (22), 159 (35), 109 (100).

Anal. Calcd for $C_{24}H_{54}O_3Si_2$: C, 64.51; H, 12.18. Found: C, 64.42; H, 12.31.

(5*S*,8*S*)-5,8-Bis[(*tert*-butyldimethylsilyl)oxy]-1-[(*p*-tolylsulfonyl)oxy]dodecane [(5*S*,8*S*)-21]. In a similar manner to that described for the preparation of **18**, **20** (106 mg, 0.24 mmol) was treated with *p*-toluenesulfonyl chloride (54 mg, 0.28 mmol) and 4-(dimethylamino)pyridine (58 mg, 0.48 mmol). Workup provided the crude product, which was purified by chromatography on silica gel with hexane–AcOEt (30:1) as eluent to give (5*S*,8*S*)-**21** (139 mg, 96%) as a colorless oil: $[\alpha]^{27}_D$ −4.0° (*c* 1.28, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 0.000, 0.016, 0.022, 0.030 (3 H, s, each), 0.85–0.91 (total 21 H, m, including 9 H, s at δ 0.86, and 9 H, s at δ 0.88), 1.19–1.52 (14 H, m), 1.64 (2 H, dt, *J* = 12.5, 6.2 Hz), 2.45 (3 H, s), 3.55–3.62 (2 H, m), 4.02 (2 H, t, *J* = 6.6 Hz), 7.34 (2 H, d, *J* = 8.3 Hz), 7.79 (2 H, d, *J* = 8.3 Hz); ^{13}C NMR ($CDCl_3$) δ −4.30 (4 C), 14.18, 18.18, 18.23, 21.32, 21.70, 22.99, 26.01 (3 C), 26.04 (3 C), 27.60, 29.25, 32.69, 32.82, 36.44, 36.93, 70.62, 72.22, 72.52, 127.98 (2 C), 129.89 (2 C), 144.65.

Anal. Calcd for $C_{31}H_{60}O_5SSi_2$: C, 61.95; H, 10.06. Found: C, 62.00; H, 10.11.

(5*S*,8*S*)-5,8-Bis[(*tert*-butyldimethylsilyl)oxy]tridecane [(5*S*,8*S*)-22]. To a cooled (−78 °C), stirred solution of (5*S*,8*S*)-**21** (210 mg, 0.36 mmol) in THF (7 mL) was added dropwise 3.8 mL of a 0.94 M solution of methylmagnesium bromide (3.59 mmol) in THF via syringe under an argon atmosphere. To this mixture was added via syringe 36 μL of a 0.1 M solution of Li_2CuCl_4 (0.0036 mmol) in THF with stirring at −78 °C, and the resulting mixture was allowed to warm to room temperature with stirring for another 24 h. The reaction was quenched with water (2 mL), and Et_2O (100 mL) was added. The organic phase was separated, washed with brine (50 mL), and dried ($MgSO_4$). The solvent was evaporated, and the residue was chromatographed on silica gel with hexane–AcOEt (50:1) to give (5*S*,8*S*)-**22** (122 mg, 76%) as a colorless oil: $[\alpha]^{26}_D$ −4.9° (*c* 2.27, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 0.04 (12 H, s), 0.87–0.91 (total 24 H, m, including 18 H, s at δ 0.89), 1.27–1.51 (18 H, m), 3.60–3.62 (2 H, m); ^{13}C NMR ($CDCl_3$) δ −4.29 (4 C), 14.12, 14.19, 18.26 (2 C), 22.78, 23.01, 25.10, 26.07 (6 C), 27.64, 32.20, 32.79 (2 C), 36.92, 37.21, 72.64, 72.67; MS *m/z* (relative intensity) 387 (M^+ − 57, 10), 347 (2), 331 (2), 311 (12), 289 (5), 275 (56), 255 (44), 241 (51), 215 (28), 201 (29), 189 (95), 149 (100), 125 (55), 111 (99), 101 (20).

Anal. Calcd for $C_{25}H_{56}O_2Si_2$: C, 67.49; H, 12.69. Found: C, 67.20; H, 12.61.

(5*S*,8*S*)-5,8-Tridecanediol [(5*S*,8*S*)-23]. To an ice-cold stirred solution of (5*S*,8*S*)-**22** (148 mg, 0.33 mmol) in MeOH (5 mL) was added concentrated HCl (1 mL), and the mixture was stirred at room temperature. After 1 h, the reaction mixture was recooled, neutralized with 2 N K_2CO_3 (5 mL), and concentrated in vacuo. The residue was diluted with Et_2O (100 mL), and the resulting solution was washed with brine (20 mL), dried over $MgSO_4$, and concentrated. The residue was purified by chromatography on silica gel with hexane–AcOEt (2:1) as eluent to give a white solid, which was recrystallized from hexane, affording (5*S*,8*S*)-**23** (60 mg, 84%) as white needles: mp 78 °C; $[\alpha]^{26}_D$ +4.0° (*c* 0.99, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 0.89 (3 H, t, *J* = 6.7 Hz), 0.91 (3 H, t, *J* = 6.7 Hz), 1.25–1.68 (18 H, m), 2.21 (2 H, br s), 3.59–3.62 (2 H, m); ^{13}C NMR ($CDCl_3$) δ 14.10 (2 C), 22.72, 22.84, 25.50, 28.02, 32.00, 34.08 (2 C), 37.59, 37.88, 72.40 (2 C); MS *m/z* (relative intensity) 215 (M^+ − 1, 2), 189 (2), 141 (64), 127 (78), 123 (58), 109 (97), 83 (85), 71 (73), 57 (87), 55 (100).

Anal. Calcd for $C_{13}H_{28}O_2$: C, 71.17; H, 13.04. Found: C, 71.99; H, 13.01.

(5*S*,8*S*)-5,8-Tridecanediol Cyclic Sulfate [(5*S*,8*S*)-24]. In a similar manner to that described for the preparation of **9**, (5*S*,8*S*)-**23** (80 mg, 0.37 mmol) was treated with Et_3N (150 mg, 1.36 mmol) and thionyl chloride (132 mg, 1.11 mmol), followed by $NaIO_4$ (317 mg, 1.48 mmol) and $RuCl_3 \cdot xH_2O$ (5 mg). Workup and chromatography on silica gel with hexane–AcOEt (6:1) as eluent, followed by recrystallization from hexane, gave (5*S*,8*S*)-**24** (93 mg, 90%) as white needles: mp 42–44 °C; $[\alpha]^{26}_D$ +19.8° (*c* 1.36, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 0.89 (3 H, t, *J* = 7.1 Hz), 0.90 (3 H, t, *J* = 7.1 Hz), 1.22–1.97 (18 H, m), 4.59–4.63 (2 H, m); ^{13}C NMR ($CDCl_3$) δ 13.87, 13.98, 22.26, 22.46, 24.78, 27.24, 30.63, 33.04 (2 C), 35.21, 35.48, 85.23 (2 C); MS *m/z* (relative intensity) 180 (M^+ − 98, 18), 137 (4), 123 (12), 109 (18), 95 (27), 81 (61), 67 (100).

Anal. Calcd for $C_{13}H_{26}O_4S$: C, 56.08; H, 9.41. Found: C, 56.16; H, 9.38.

Reaction of (5*S*,8*S*)-24 with Lithium Azide. In a similar manner to that described for the preparation of 11, (5*S*,8*S*)-**24** (28 mg, 0.10 mmol) was treated with LiN_3 (8 mg, 0.16 mmol). Workup and purification by chromatography on silica gel, eluting with hexane–AcOEt (5:1), gave a chromatographically inseparable 1:1 mixture of (6*S*,9*R*)-9-azido-6-tridecanol [(6*S*,9*R*)-**25a**] and (5*S*,8*R*)-8-azido-5-tridecanol [(5*S*,8*R*)-**25b**] (total: 22 mg, 91%) as a colorless oil: IR (neat) 3344 (OH), 2099 (N_3) cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.89 (6 H, t, J = 6.9 Hz), 0.91 (6 H, t, J = 6.9 Hz), 1.26–1.78 (36 H, m), 3.23–3.29 (2 H, m), 3.59–3.62 (2 H, m); ^{13}C NMR ($CDCl_3$) δ 14.02, 14.08, 22.61, 22.69, 22.79, 25.36, 25.83, 27.87, 28.33, 30.87, 31.71, 31.94, 34.09, 34.30, 34.57, 37.50, 37.78, 63.49, 72.00; MS m/z (relative intensity) 214 (2), 196 (213), 167 (19), 156 (33), 142 (36), 126 (18), 112 (21), 98 (70), 84 (96), 69 (100).

Anal. Calcd for $C_{13}H_{27}N_3O$: C, 64.69; H, 11.27; N, 17.41. Found: C, 64.63; H, 11.17; N, 17.10.

Mesylation of (6*S*,9*R*)-25a and (5*S*,8*R*)-25b. In a similar manner to that described for the preparation of **12**, the 1:1 mixture of (6*S*,9*R*)-**25a** and (5*S*,8*R*)-**25b** (60 mg, 0.25 mmol), obtained by the reaction described above, was treated with methanesulfonyl chloride (57 mg, 0.50 mmol). Workup and purification by chromatography on silica gel, eluting with hexane–AcOEt (6:1), gave a chromatographically inseparable 1:1 mixture of (6*S*,9*R*)-6-azido-9-[(methylsulfonyl)oxy]tridecane [(6*S*,9*R*)-**26a**] and (5*S*,8*R*)-8-azido-5-[(methylsulfonyl)oxy]tridecane [(5*S*,8*R*)-**26b**] (total: 73 mg, 92%) as a colorless oil: IR (neat) 2099 cm^{-1} (N_3); ^1H NMR ($CDCl_3$) δ 0.89 (6 H, t, J = 7.0 Hz), 0.91 (6 H, t, J = 7.0 Hz), 1.25–1.89 (36 H, m), 3.01 (6 H, s), 3.23–3.29 (2 H, m), 4.68–4.74 (2 H, quint, J = 6.0 Hz); ^{13}C NMR ($CDCl_3$) δ 13.91, 13.98, 22.50, 22.55, 24.67, 25.78, 27.13, 28.26, 29.96, 31.17, 31.56, 31.63, 34.17, 34.31, 34.44, 34.58, 38.66, 62.89, 83.46; MS m/z (relative intensity) 262 (M^+ – 57, 0.8), 248 (0.9), 212 (12), 196 (40), 166 (23), 152 (23), 138 (29), 124 (27), 98 (38), 82 (76), 69 (100).

Anal. Calcd for $C_{14}H_{29}N_3O_3S$: C, 52.64; H, 9.15; N, 13.15. Found: C, 52.74; H, 9.12; N, 13.10.

(2*R*,5*R*)-*trans*-2-Butyl-5-pentylpyrrolidine [(–)-Pyrrolidine 197B] [(–)-1]. A solution of the 1:1 mixture of (6*S*,9*R*)-**26a** and (5*S*,8*R*)-**26b** (43 mg, 0.135 mmol), obtained by the reaction described above, in MeOH (3 mL) was hydrogenated over 10% palladium on carbon (30 mg) for 1 h. After filtration, the solution was concentrated in vacuo and the residue was chromatographed on silica gel with $CHCl_3$–5% methanolic NH_3 (10:1) to give (–)-**1** (24 mg, 90%) as a pale yellow oil: $[\alpha]^{27}_D$ –5.8° (*c* 0.61, $CHCl_3$); IR (neat) 3446 cm^{-1}; ^1H NMR ($CDCl_3$)[20] δ 0.88 (3 H, t, J = 6.8 Hz), 0.89 (3 H, t, J = 6.8 Hz), 1.18–1.67 (17 H, m), 1.88–1.96 (2 H, m), 3.06–3.12 (2 H, m); ^{13}C NMR ($CDCl_3$)[20] δ 14.04, 14.08, 22.65, 22.86, 27.00, 29.52, 32.03, 32.51 (2 C), 36.91, 37.18, 58.00, 58.03; MS m/z (relative intensity) 197 (M^+, 1), 196 (M^+ – 1, 1.9), 168 (1.8), 140 (82), 126 (100); CIMS (NH_3) m/z (relative intensity) 199 (M^+ + 2, 13), 198 (M^+ + 1, 84), 196 (M^+ – 1, 2), 141 (8), 140 (60), 127 (7), 126 (75), 58 (100); HRMS calcd for $C_{13}H_{27}N$ (M^+) 197.2142, found 197.2136.

(5*R*,8*R*)-1,12-Bis(benzyloxy)-5,8-dodecanediol [(*R*,*R*)-8]. This compound was prepared from (*S*,*S*)-**4** in 59% yield by following the same procedure used to obtain (*S*,*S*)-**8** from (*R*,*R*)-**4**: $[\alpha]^{24}_D$ –2.5° (*c* 1.49, $CHCl_3$). The product was identical with the previously isolated (*S*,*S*)-**8** by ^1H and ^{13}C NMR and TLC.

(5*R*,8*R*)-1,12-Bis(benzyloxy)-5,8-bis[(*tert*-butyldimethylsilyl)oxy]dodecane [(*R*,*R*)-15]. This compound was prepared from (*R*,*R*)-**8** in 88% yield via the same procedure used to obtain (*S*,*S*)-**15** from (*S*,*S*)-**8**: $[\alpha]^{26}_D$ +6.5° (*c* 1.93, $CHCl_3$). The product was identical with the previously isolated (*S*,*S*)-**15** by ^1H and ^{13}C NMR and TLC.

(5*R*,8*R*)-5,8-Bis[(*tert*-butyldimethylsilyl)oxy]-1,12-dodecanediol [(*R*,*R*)-16]. This compound was prepared from (*R*,*R*)-**15** in 90% yield via the same procedure used to obtain (*S*,*S*)-**16** from (*S*,*S*)-**15**: $[\alpha]^{25}_D$ +6.3° (*c* 1.00, $CHCl_3$). The product was identical with the previously isolated (*S*,*S*)-**16** by IR, ^1H and ^{13}C NMR, MS, and TLC.

(5*R*,8*R*)-5,8-Bis[(*tert*-butyldimethylsilyl)oxy]-1,12-bis[(*p*-tolylsulfonyl)oxy]dodecane (28). In a similar manner to that described for the preparation of **28**, (*R*,*R*)-**16** (1.00 g, 2.16 mmol) was treated with 4-(dimethylamino)pyridine (779 mg, 6.48 mmol) and *p*-toluenesulfonyl chloride (1.24 g, 6.48 mmol). Workup followed by chromatography on silica gel using hexane–AcOEt (6:1) afforded **28** (1.39 g, 83%) as a colorless oil: $[\alpha]^{26}_D$ +3.3° (*c* 1.30, $CHCl_3$); ^1H NMR ($CDCl_3$) δ –0.01, 0.01, 0.84, 0.85, 0.86 (6 H, s, each), 1.29–1.45 (12 H, m), 1.62–1.70 (4 H, m), 2.45 (6 H, s), 3.51–3.57 (2 H, m), 4.02 (4 H, t, J = 6.6 Hz), 7.34 (4 H, d, J = 8.0 Hz), 7.79 (4 H, d, J = 8.3 Hz); ^{13}C NMR ($CDCl_3$) δ –4.34 (4 C), 18.17 (2 C), 21.29 (2 C), 21.70 (2 C), 25.99 (6 C), 29.24 (2 C), 32.74 (2 C), 36.47 (2 C), 70.60 (2 C), 72.12 (2 C), 127.98 (4 C), 129.89 (4 C), 144.67 (2 C); MS m/z (relative intensity) 713 (M^+ – 58, 0.1), 541 (0.8), 467 (1.1), 427 (2), 229 (100), 163 (55).

Anal. Calcd for $C_{38}H_{66}O_8Si_2S_2$: C, 59.18; H, 8.63. Found: C, 58.97; H, 8.67.

(5*R*,8*R*)-5,8-Bis[(*tert*-butyldimethylsilyl)oxy]-1-[(*p*-tolylsulfonyl)oxy]dodecane [(5*R*,8*R*)-21]. To an ice-cold, stirred solution of **28** (1.06 g, 1.37 mmol) in THF (10 mL) was added dropwise via syringe 1.37 mL (1.37 mmol) of a 1 M solution of Super-Hydride in THF under an argon atmosphere. After stirring the mixture for 1.5 h in an ice bath, the reaction was quenched with water (5 mL) and additional water (50 mL) was added to the mixture to dissolve a slurry that precipitated. The resulting mixture was extracted with Et_2O (2 × 100 mL), washed with brine (2 × 25 mL), and dried ($MgSO_4$). Evaporation of the solvent left a syrup, which was chromatographed on silica gel with hexane–AcOEt (20:1) to give (5*R*,8*R*)-**21** (482 mg, 60%), $[\alpha]^{26}_D$ +4.3° (*c* 2.09, $CHCl_3$), along with recovered starting material (39%). The product was identical with the previously isolated (5*S*,8*S*)-**21** by ^1H and ^{13}C NMR and TLC.

(5*R*,8*R*)-5,8-Bis[(*tert*-butyldimethylsilyl)oxy]tridecane [(5*R*,8*R*)-22]. This compound was prepared from (5*R*,8*R*)-**21** in 79% yield via the same procedure used to obtain (5*S*,8*S*)-**22** from (5*S*,8*S*)-**21**: $[\alpha]^{28}_D$ +4.4° (*c* 2.31, $CHCl_3$). The product was identical with the previously isolated (5*S*,8*S*)-**22** by ^1H and ^{13}C NMR, MS, and TLC.

(5*R*,8*R*)-5,8-Tridecanediol [(5*R*,8*R*)-23]. This compound was prepared from (5*R*,8*R*)-**22** in 88% yield via the same procedure used to obtain (5*S*,8*S*)-**23** from (5*S*,8*S*)-**22**: $[\alpha]^{28}_D$ –4.5° (*c* 1.10, $CHCl_3$). The product was identical with the previously isolated (5*S*,8*S*)-**23** by ^1H and ^{13}C NMR, MS, and TLC.

(5*R*,8*R*)-5,8-Tridecanediol Cyclic Sulfate [(5*R*,8*R*)-24]. This compound was prepared from (5*R*,8*R*)-**23** in 91% yield via the same procedure used to obtain (5*S*,8*S*)-**24** from (5*S*,8*S*)-**23**: $[\alpha]^{22}_D$ –19.0° (*c* 1.00, $CHCl_3$). The product was identical with the previously isolated (5*S*,8*S*)-**24** by ^1H and ^{13}C NMR, MS, and TLC.

(2*S*,5*S*)-*trans*-2-Butyl-5-pentylpyrrolidine [(+)-Pyrrolidine 197B] [(+)-1]. This compound was prepared from (5*R*,8*R*)-**24** in 90% yield via the same procedure used to obtain (–)-**1** from (5*S*,8*S*)-**24**: $[\alpha]^{27}_D$ +5.8° (*c* 0.79, $CHCl_3$). The product was identical with the previously isolated (–)-**1** by IR, ^1H and ^{13}C NMR, MS, and TLC.

(2*S*,5*S*)-*N*-Benzoyl-2-butyl-5-pentylpyrrolidine [(+)-27]. To an ice-cold solution of (+)-**1** (20 mg, 0.10 mmol) in CH_2Cl_2 (2 mL) was added in one portion 2 mL of a 20% aqueous solution of K_2CO_3 (2.9 mmol). The mixture was stirred in an ice bath, and a solution of benzoyl chloride (29 mg, 0.20 mmol) in CH_2Cl_2 (1 mL) was added. After being stirred for 10 min, the reaction mixture was dissolved in Et_2O (100 mL) and the organic phase was washed with brine (2 × 25 mL), dried ($MgSO_4$), and concentrated. The product was purified by chromatography on silica gel with hexane–AcOEt (20:1) as eluent to give (+)-**27** (24 mg, 79%) as a colorless oil: $[\alpha]^{27}_D$ +125.5° (*c* 1.0, $CHCl_3$); IR (neat) 1626 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.61, 0.70 (1:1 ratio, total 6 H, t, J = 7.0 Hz, each, due to amide rotamers), 0.76–1.20 (9 H, m), 1.33–1.38 (3 H, m), 3.90–3.95, 4.23–4.27 (1:1 ratio, total 2 H, m, due to rotamers), 7.35–7.39 (3 H, m), 7.44–7.48 (2 H, m); ^{13}C NMR ($CDCl_3$) δ 13.74, 13.89, 14.12, 14.18, 21.94, 22.23, 22.79, 25.81, 26.25, 26.52, 28.30, 28.37, 28.80, 31.01, 31.88, 32.83, 33.07, 34.35, 34.58, 57.67, 59.55, 127.04, 128.29, 129.47, 138.67, 170.34; MS m/z (relative intensity) 301 (M^+, 5), 244 (72), 230 (88), 105 (100), 77 (74); HRMS calcd for $C_{20}H_{31}NO$ (M^+) 301.2404, found 301.2397.

(2*S*,5*S*)-*N*-Benzyl-2-butyl-5-pentylpyrrolidine (29). To an ice-cold, stirred solution of (+)-**27** (22 mg, 0.073 mmol) in THF (5 mL) was added dropwise via syringe a 2.0 M solution of

(20) ^1H and ^{13}C NMR spectral data previously reported[11] for (–)-**1** appear in considerable error due probably to the presence of a sufficient amount of HCl in $CDCl_3$ used to convert the sample of (–)-**1** to the salt.

BH_3·Me_2S complex in THF (0.37 mL, 0.74 mmol). The mixture was allowed to warm to room temperature and refluxed for 1 h. The reaction mixture was cooled in an ice bath, and 6 N HCl (5 mL) was added with stirring. After being stirred for 2 h at room temperature, the mixture was basified with 20% KOH, extracted with $CHCl_3$ (2 × 30 mL), and dried (Na_2CO_3). Evaporation of the solvent and chromatography on silica gel with $CHCl_3$–MeOH (50:1) as eluent afforded **29** (13 mg, 62%) as a pale yellow oil: ^1H NMR ($CDCl_3$) δ 0.85 (6 H, t, J = 6.4 Hz), 1.03–1.28 (12 H, m), 1.43–1.59 (4 H, m), 1.84–1.88 (2 H, m), 2.83 (2 H, br s), 3.64 and 3.81 (total 2 H, AB q, J = 13.9 Hz), 7.18–7.37 (5 H, m); ^{13}C NMR ($CDCl_3$) δ 14.11, 14.19, 22.75, 23.11, 25.73, 26.21, 28.50 (2 C), 28.79, 30.47, 30.73, 32.30, 51.47, 60.49 (2 C), 126.40, 128.09 (2 C), 128.53 (2 C), 141.24; MS m/z (relative intensity) 287 (M^+, 0.8), 286 (M^+ – 1, 0.6), 230 (57), 216 (67), 91 (100); HRMS calcd for $C_{20}H_{33}N$ (M^+) 287.2611, found 287.2586.

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Stereoselective Synthesis of (±)-Indolizidines 167B, 205A, and 207A. Enantioselective Synthesis of (–)-Indolizidine 209B[1]

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The first syntheses of the dendrobatid indolizidine alkaloids 167B (**3**), 205A (**4**), and 207A (**5**) are described using as a key step the highly stereoselective intramolecular nitrone cycloaddition of the (*Z*)-*N*-alkenylnitrone **10** to prepare the isoxazolidine **11**. Mesylate-promoted cyclization of the alcohol **12**, followed by reductive cleavage of the resulting mesylate salt, afforded the key axial hydroxymethyl compound **13**, which was epimerized via the aldehyde to the equatorial alcohol, and was subsequently reduced to the required 8-methyl-substituted indolizidine. The feasibility of extending this strategy to the enantioselective synthesis of such alkaloids was demonstrated in the first synthesis of (–)-indolizidine 209B (**6**), whose nitrone precursor **10d** was obtained from the (*S*)-glutamate-derived amine **40**.

A large number of alkaloids have been isolated in minute quantity from the skin extracts of neotropical poison-dart frogs family (Dendrobatidae).[2] The lack of availability of natural material and the fascinating biological activity of the compounds which have been studied[2] make these alkaloids ideal targets for total synthesis.[3,4] In recent years we have been interested in examining the intramolecular nitrone cycloaddition reaction[5] and its application to alkaloid synthesis. These studies have included a stereoselective synthesis of (±)-carpamic acid (**1**)[6] and a stereoselective approach to gephyrotoxin (**2**).[7] This report details these synthetic studies within the context of the previously unsynthesized dendrobatid alkaloids 167B (**3**), 205A (**4**), and 207A (**5**).[1] This intramolecular nitrone cycloaddition approach represents a new, highly efficient, and stereoselective strategy for the synthesis of 5,8-disubstituted indolizidines.[8] The method was further extended

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