General Entry to the 3,5-Disubstituted Indolizidine Class of Dendrobatid Alkaloids. Total Syntheses of Both Enantiomers of Indolizidines 195B, 223AB, 239AB, and 239CD from a Common Chiral Synthon

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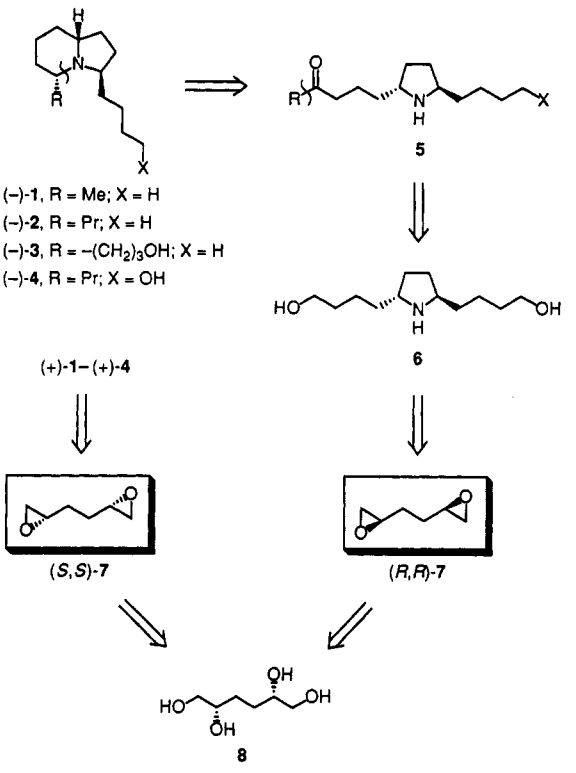
Received April 13, 1992

A general protocol for the total syntheses of both enantiomers of dendrobatid alkaloids, indolizidines **195B**, **223AB**, **239AB**, and **239CD**, belonging to the 3,5-disubstituted indolizidine subclass is described, in which 3,4-dideoxy-D-*threo*-hexitol (**8**) has been used as a single and common chiral synthon. The syntheses of the (+)- and (−)-enantiomers of these alkaloids begin with (*S,S*)- and (*R,R*)-1,2:5,6-diepoxyhexanes (**7**), respectively, both of which were derived from **8** in three steps and are carried out by way of pyrrolidine formation via the cyclic sulfates leading to the (2*R*,5*R*)- and (2*S*,5*S*)-*trans*-2,5-dialkylated pyrrolidines, which were converted to the (+)- and (−)-enantiomers, respectively, of the title indolizidine alkaloids. These syntheses involve the first chiral preparations of indolizidines **239AB** and **239CD** both in natural (−)- and unnatural (+)-enantiomeric forms, which confirm the absolute configurations of natural **239AB** and **239CD** as 3*R*,5*S*,8a*R* and 3*R*,5*R*,8a*R*, respectively.

The neotropical dart-poison frogs (family Dendrobatidae) have been a rich source of a variety of structurally unique and biologically significant alkaloids.[1] After the early discovery of indolizidine **223AB** (formerly referred to as "gephyrotoxin" **223AB**)[2] a series of the simple indolizidine class of dendrobatid alkaloids have been detected. Such compounds related to indolizidine are subdivided into three classes based on substitution pattern of the side chains on the indolizidine nucleus: 5-substituted,[3] 3,5-disubstituted, and 5,8-disubstituted[1] indolizidines. The 3,5-disubstituted indolizidines occur in a limited number of dendrobatid species, and all members of this subclass so far characterized are indolizidines **195B** (**1**),[4] **223AB** (**2**),[2,5] **239AB** (**3**),[4a,5] and **239CD** (**4**)[4a,5] (Figure 1). The latter three alkaloids **223AB** and its ω-hydroxy congeners **239AB** and **239CD** are all levorotatory. Although neither racemic nor chiral synthesis of **239AB** and **239CD** has been reported in the literature, the 3*R*,5*R*,8a*R* enantiomer of indolizidine **223AB** has been synthesized by Husson et al.[6] and shown to be levorotatory, which established the absolute stereochemistry of natural **223AB** given in (−)-**2**.[7,8] From this result, the absolute configurations of both the natural ω-hydroxy congeners **239AB** and **239CD** have been inferred to be 3*R*,5*S*,8a*R* [(−)-**3**] and 3*R*,5*R*,8a*R* [(−)-**4**], respectively, in analogy with that of **223AB**.

Another alkaloid **195B**, unlike **223AB**, **239AB**, and **239CD**, is dextrorotatory, which suggests that this alkaloid has the opposite, namely 3*S*,5*S*,8a*S*, configuration as shown in (+)-**1** compared to the other 3,5-disubstituted indolizidines. The proposed absolute stereochemistry of **195B** has currently been confirmed by the syntheses of both enantiomers of **195B** achieved in our laboratory.[4b]

Scheme I



For several years, research efforts in our laboratory have been directed toward the development of chiral methods for the synthesis of dendrobatid alkaloids.[4b,9] In this paper we report the enantioselective total syntheses of all four of these 3,5-disubstituted indolizidine alkaloids in both enantiomeric forms starting from *a single common chiral synthon*.[10]

Our synthetic strategy for a general approach to a series of the (−)-enantiomers of indolizidines **195B**, **223AB**, **239AB**, and **239CD** is illustrated in Scheme I. This scheme suggests 2-fold disconnection providing the (*R,R*)-2,5-dialkylated pyrrolidine **6** with C_2 symmetrical

(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) Isolation: (a) Daly, J. W.; Brown, G. B.; Mensah-Dwumah, M.; Myers, C. W. *Toxicon* **1978**, *16*, 163. (b) Spande, Th. F.; Daly, J. W.; Hart, D. J.; Tsai, Y.-M.; Macdonald, T. L. *Experientia* **1981**, *37*, 163.

(3) Daly, J. W. *Fortschr. Chem. Org. Naturst.* **1982**, *41*, 205.

(4) (a) Isolation: Tokuyama, T.; Nishimori, N.; Karle, I. L.; Edwards, M. W.; Daly, J. W. *Tetrahedron* **1986**, *42*, 3453. (b) For chiral synthesis of the both enantiomers of **195B**, see: Yamazaki, N.; Kibayashi, C. *J. Am. Chem. Soc.* **1989**, *111*, 1396.

(5) Isolation: 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.

(6) Royer, J.; Husson, H.-P. *Tetrahedron Lett.* **1985**, *26*, 1515.

(7) For the synthesis of stereoisomers of **223AB**, see: (a) Macdonald, T. L. *J. Org. Chem.* **1980**, *45*, 193. (b) Hart, D. J.; Tsai, Y.-M. *Ibid.* **1982**, *47*, 4403. (c) Stevens, R. V.; Lee, A. W. M. *J. Chem. Soc., Chem. Commun.* **1982**, 103.

(8) For the synthesis of racemic **223AB**, see: (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*, 4097. (b) Broka, C. A.; Eng, K. K. *J. Org. Chem.* **1986**, *51*, 5043.

(9) (a) Machinaga, N.; Kibayashi, C. *Tetrahedron Lett.* **1990**, *31*, 3637. (b) Machinaga, N.; Kibayashi, C. *J. Org. Chem.* **1991**, *56*, 1386. (c) Shishido, Y.; Kibayashi, C. *J. Chem. Soc., Chem. Commun.* **1991**, 1237. (d) Shishido, Y.; Kibayashi, C. *J. Org. Chem.*, in press.

(10) A preliminary report of part of this work has appeared. See: Machinaga, N.; Kibayashi, C. *J. Chem. Soc., Chem. Commun.* **1991**, 405.

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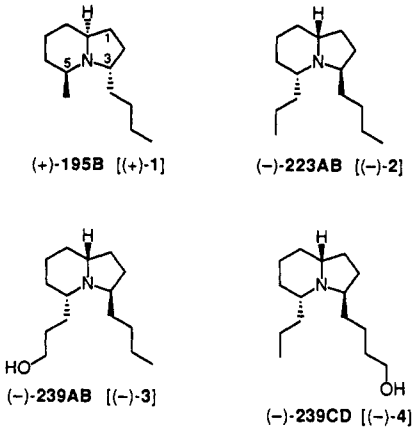


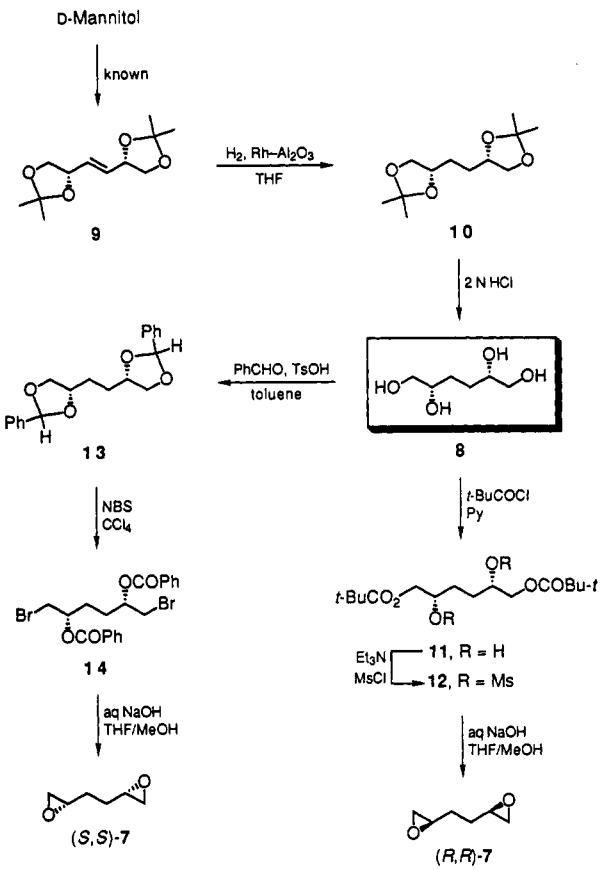
Figure 1. Naturally occurring 3,5-disubstituted indolizidine alkaloids from dendrobatid frogs.

structure as an advanced intermediate, which might be prepared from the C_2 symmetrical (*R,R*)-diepoxide building block **7**. This strategic approach is adaptable for the synthesis of a series of the (+)-enantiomers of these alkaloids by using the (*S,S*)-diepoxide **7**. Both enantiomers of the diepoxide, (*R,R*)-**7** and (*S,S*)-**7**, are available by utilizing 3,4-dideoxy-D-*threo*-hexitol (**8**) as a common chiral synthon.

Very recently, we have shown that both enantiomers of the diepoxide **7** can be used as versatile C_2 symmetric chiral building blocks in the enantiodivergent synthesis of natural products.[9a,b] Both the chiral diepoxides (*R,R*)-**7** and (*S,S*)-**7** were prepared from the tetrol **8**, available from D-mannitol, as a single common chiral synthon.[9b] These methods for the preparation of the diepoxides are however somewhat limited by the moderate overall yield and a high cost of the reagent. Thus we initially aimed to develop more efficient, practical procedures for the preparation of both enantiomers of diepoxide **7** starting from **8**.

For the preparation of (*R,R*)-**7**, the previously reported four-step procedure[7b] has employed the silyl group for the protection of the primary alcohol functions using expensive *tert*-butyldimethylsilyl chloride. In an attempt to obviate this problem and to shorten the reaction sequence, we employed the pivaloyl group as a protecting group of the primary alcohol as outlined in Scheme II. Thus, *trans*-3,4-didehydro-3,4-dideoxy-1,2:5,6-di-*O*-isopropylidene-D-*threo*-*hexitol* (**9**), prepared by the known procedure starting from D-mannitol,[11] was hydrogenated by using Rh–Al_2O_3 as the catalyst[12,13] in THF to give **10** in 95% yield. Deprotection of **10** by acid hydrolysis afforded the tetrol **8**, which can be used as a common chiral synthon for the preparation of both the enantiomers of the diepoxide **7**.[14] The selective protection was carried out by

Scheme II



treatment of **8** with 2 equiv of pivaloyl chloride in pyridine to give the 1,6-bispivalate **9** in 63% yield, which was very smoothly converted to (*R,R*)-**7** by mesylation followed by basic treatment (aqueous NaOH, THF–MeOH) in virtually quantitative yield.

Our next attempt to prepare (*S,S*)-**7** was aimed at the regioselective introduction of bromine at C-1 and C-6 for obtaining an efficient precursor for epoxidation. Thus, **8** was converted to the bis(benzylidene acetal) **13** (PhCHO, TsOH, toluene) in 98% yield. Exposing **13** to 2.2 molar equiv of *N*-bromosuccinimide in carbon tetrachloride led to regioselective ring opening (Hanessian–Hullar reaction[15]) furnishing the 1,6-dibromide **14** as a single product, which was then treated under basic conditions similar to those used for (*R,R*)-**7** to generate (*S,S*)-**7** in 93% yield from **13**.

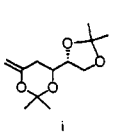
With the chiral building block (*R,R*)-**7** in hand, on the basis of the above strategic planning (Scheme I) we initially envisioned the synthesis of (−)-indolizidine **239CD** [(−)-**4**]. Indolizidine **239CD** has been characterized as 3-(4-hydroxybutyl)-5-propylindolizidine with the tentative absolute stereochemistry shown as (−)-**4**.[4a,5] It has been reported to cause long-lasting locomotor difficulties and prostration after subcutaneous administration to mice.[2a]

The diepoxide (*R,R*)-**7** was converted to the diol **15** via reported procedure[7b] using [3-(benzyloxy)propyl]magnesium bromide in the presence of catalytic amount of copper(I) iodide. Compound **15** was then converted to **16** by known method.[9b] As outlined in Scheme III, **16** was subjected to benzoylation followed by removal of the silyl protecting groups to give the diol **18** in 95% overall yield.

(11) Eastwood, F. W.; Harrington, K. J.; Josan, J. S.; Pura, J. L. *Tetrahedron Lett.* **1970**, 5223. Hanessian, S.; Bargiotti, A.; LaRue, M. *Ibid.* **1978**, 737. Cf.: Corey, E. J.; Hopkins, P. B. *Ibid.* **1982**, *23*, 1979. Damha, M.; Giannaris, P. A.; Marfey, P.; Reid, L. S. *Ibid.* **1991**, *32*, 2573.

(12) Marzi, M.; Mistiti, D. *Tetrahedron Lett.* **1989**, *30*, 6075.

(13) When hydrogenation of **9** was carried out by using 10% Pd–C as the catalyst in THF at 1 atm, a ca. 1:1 mixture of **10** and **i** was formed. Data for **i**: IR (neat) 2987, 2937, 2872, 1713, 1456, 1376, 1313, 1274, 1216, 1157, 1130, 1062, 975, 936, 849, 791 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.32, 1.39, 1.41, 1.42 (3 H, s, each), 2.34 (2 H, m), 3.56 (1 H, m), 3.98 (1 H, m), 4.09 (1 H, m), 4.18 (1 H, m), 4.42 (2 H, d, J = 1.4 Hz); ^{13}C NMR ($CDCl_3$) δ 25.17, 25.60, 26.86, 29.34, 66.09, 68.98, 75.78, 76.58, 88.45, 108.74, 111.53, 150.52.

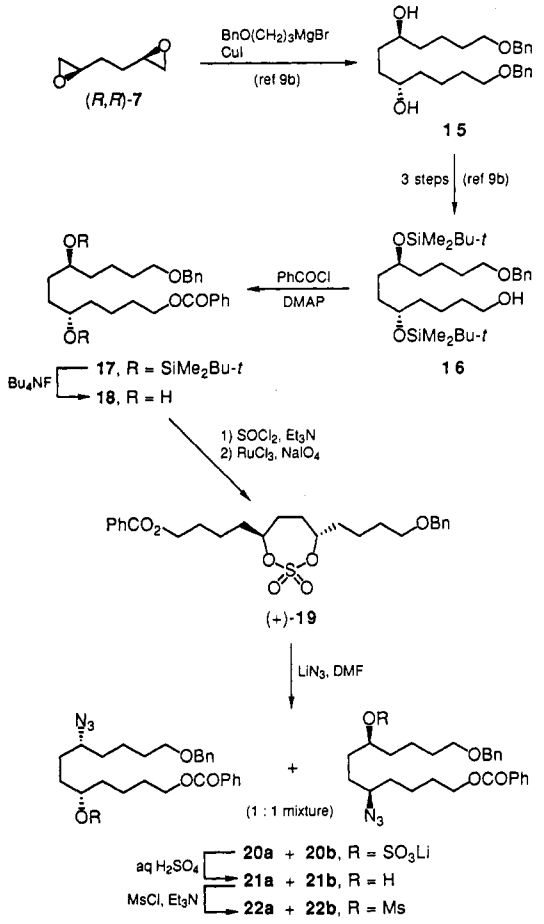


i

(14) Elaboration of the epoxides (*R,R*)-**7** and (*S,S*)-**7** utilizing several routes has been reported. See: Machinaga, N.; Kibayashi, C. *Synthesis*, in press.

(15) (a) Failla, D. L.; Hullar, T. L.; Siskin, S. B. *Chem. Commun.* **1966**, 716. (b) Hanessian, S. *Carbohydr. Res.* **1966**, *2*, 86. (c) Hanessian, S.; Plessas, N. R. *J. Org. Chem.* **1969**, *34*, 1035.

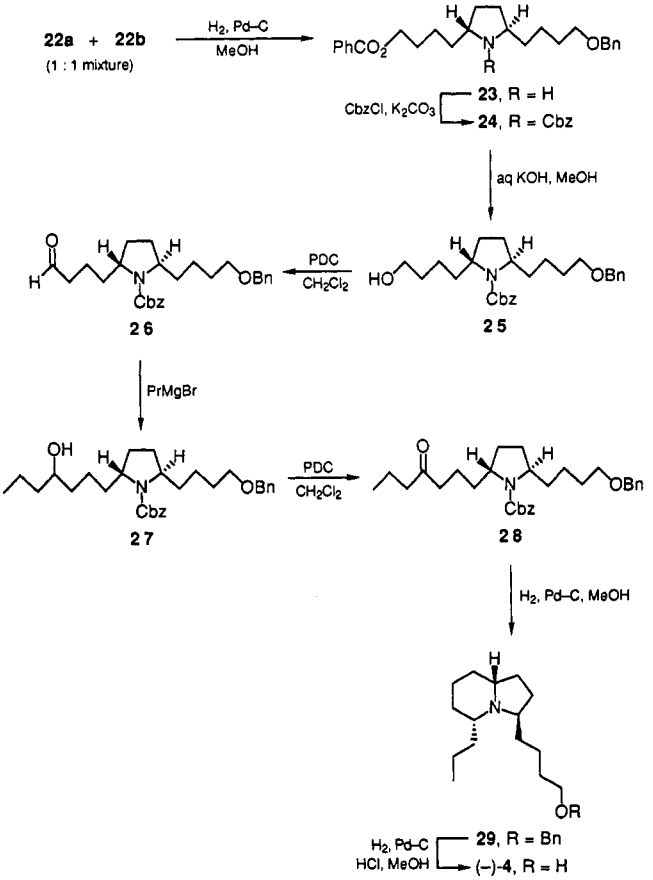
Scheme III



Conversion of **18** to the trans-2,5-dialkylated pyrrolidine was achieved by utilization of the sequence via a cyclic sulfonate previously reported by us.[9a,b] Accordingly, **18** was treated with thionyl chloride and triethylamine, followed by a catalytic amount of RuO_4 (prepared from $RuCl_3$ and $NaIO_4$) to afford the cyclic sulfate (+)-**19** in 82% yield. Subsequent nucleophilic ring opening of (+)-**19** with LiN_3 in DMF proceeded in a nonregioselective manner, providing an inseparable 1:1 mixture of structural isomers **20a** and **20b**, which, without separation, was immediately hydrolyzed (aqueous H_2SO_4 in THF) to yield a 1:1 mixture of **21a** and **21b** in quantitative yield from (+)-**19**. This mixture was then converted to a 1:1 mixture of the corresponding mesylates **22a** and **22b** (94% yield).

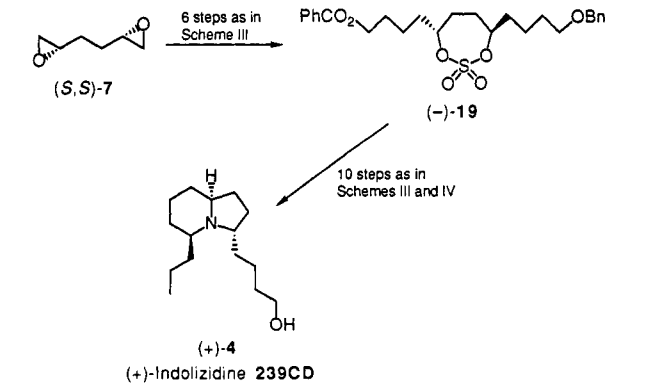
Thanks to being equally cyclized to the desired pyrrolidine, both isomers **22a** and **22b** were, without separation, subjected to hydrogenation of the azide function which led to in situ intramolecular cyclization via S_N2 displacement to give the *trans*-pyrrolidine **23** as a single product. The resulting *trans*-pyrrolidine **23** was immediately subjected to N-protection to provide **24** in 77% overall yield (Scheme IV). Alkaline hydrolysis followed by oxidation of the resulting primary alcohol **25** with pyridinium dichromate (PDC) afforded the aldehyde **26** in 71% yield from **24**. Homologation was performed by treatment of **26** with the Grignard reagent PrMgBr in THF followed by PDC oxidation to furnish the ketone **28** (71% yield). Hydrogenolysis over palladium on carbon in methanol resulted in the cyclization product **29**, which without isolation underwent further hydrogenolysis under acidic conditions (HCl/MeOH), leading to complete removal of the benzyl groups to provide (−)-indolizidine **239CD** [(−)-4] as a single isomer in 75% yield from **28**. The

Scheme IV



spectroscopic data (^{13}C NMR, MS, and IR) of our synthetic (−)-**4** were found to be identical with those for the natural alkaloid,[16] and its observed optical rotation $[\alpha]^{26}_D$ −58.6° (*c* 0.21, MeOH) was satisfyingly close to that reported[5] for the natural product, $[\alpha]^{16}_D$ −52° (*c* 0.19, MeOH). These results provide clear evidence for the gross structure and absolute configuration of natural indolizidine **239CD** to be 3*R*,5*R*,8a*R* as shown by formula (−)-**4** as tentatively proposed by Daly et al.[4a,5]

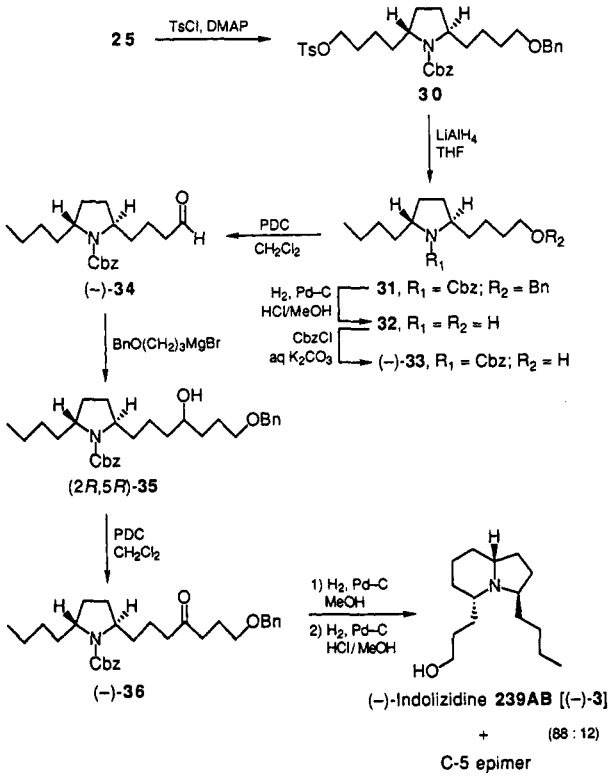
An identical strategy as that used for the synthesis of (−)-indolizidine **239CD** was then applied to the synthesis of (+)-indolizidine **239CD** [(+)-**4**] starting from the (*S*,*S*)-diepoxide **7** via the cyclic sulfate (−)-**19**. The product (+)-**4**, the unnatural enantiomer of indolizidine **239CD**, was identical in all respects except for the sign of optical rotation [$[\alpha]^{26}_D$ +58.6° (*c* 0.21, MeOH)].



Having established a route to both enantiomers of the 3,5-disubstituted indolizidine alkaloid in a stereodefined

(16) For ^{13}C NMR data for natural **239CD**, see ref 5.

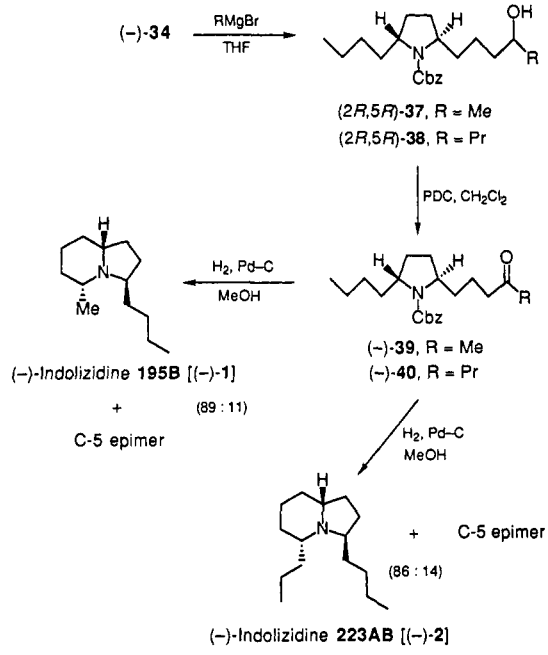
Scheme V



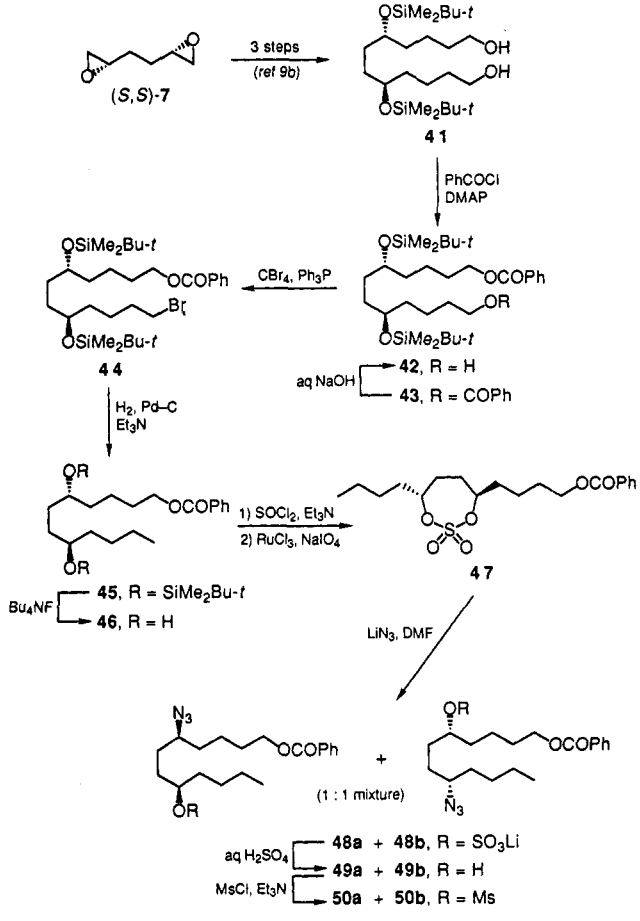
manner via the trans-2,5-dialkylated pyrrolidine intermediate prepared by utilizing the diepoxide building block **7**, we next envisaged that this synthetic methodology could provide an efficient, versatile entry into the other ω-hydroxy congener indolizidine **239AB**. The enantioselective synthesis of the (-)-enantiomer of **239AB** began with the (2*R*,5*R*)-pyrrolidine **25**, prepared from the diepoxide (*R*,*R*)-**7** in 13 steps via the above sequence (see Schemes II and III), which was deoxygenated by the procedure involving tosylation followed by $LiAlH_4$ reduction to produce **31** in 68% yield (Scheme V). Removal of the N- and O-protecting groups (benzyloxycarbonyl and benzyl, respectively) by hydrogenolysis, followed by N-protection afforded (-)-**33**, which underwent oxidation with pyridinium dichromate (PDC) to provide the aldehyde (-)-**34** (57% yield from **31**). Homologation of (-)-**34** was performed by the Grignard reaction [$BnO(CH_2)_3MgBr$] and subsequent oxidation with PDC, leading to the ketone (-)-**36** (81% yield). On catalytic hydrogenolysis of (-)-**36**, intramolecular cyclization occurred in situ to afford a chromatographically separable mixture of the levorotatory indolizidine **239AB** [(-)-**3**] and its C-5 epimer in an 88:12 ratio (96% total yield). The synthetic **239AB** exhibited ^{13}C NMR data virtually identical with that reported[5] for the natural product and the same sign of the optical rotation [$[\alpha]^{25}_D$ -87.5° (*c* 0.16, MeOH)] as that published[5] for the natural product [$[\alpha]^{16}_D$ -38° (*c* 1.0, MeOH)], indicating that (3*R*,5*R*,8a*R*)-**239AB** [(-)-**3**] represents the naturally occurring configuration.

In an analogous manner, the aldehyde (-)-**34** was readily converted to (-)-indolizidines **195B** and **223AB**. Thus, (-)-**34** was subjected to the Grignard reaction using MeMgBr and PrMgBr in THF to give the alcohols (2*R*,5*R*)-**37** and (2*R*,5*R*)-**38**, respectively, which were then converted to the corresponding ketones (-)-**39** and (-)-**40** (Scheme VI). Hydrogenation of (-)-**39** resulted in cyclization to produce the unnatural (-)-enantiomer of indolizidine **195B** [(-)-**1**] along with its C-5 epimer in a ratio of 89:11 (total yield: 89%). The synthetic material was

Scheme VI



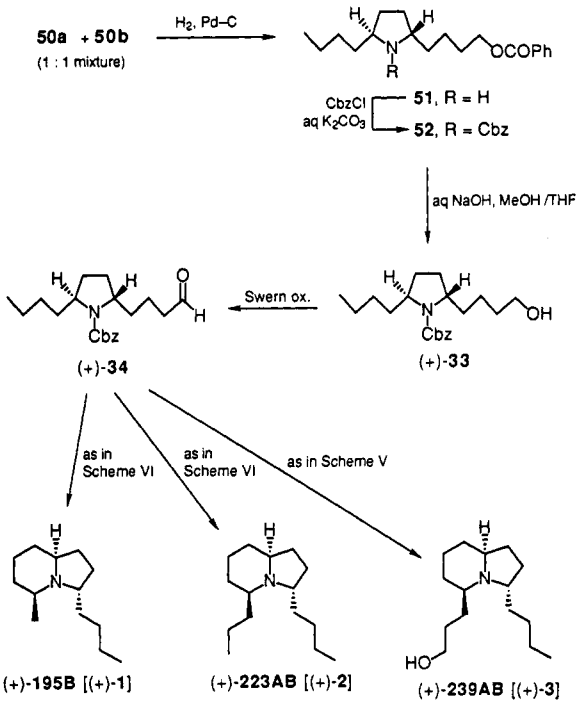
Scheme VII



identical in all respects with an authentic material of (-)-indolizidine **195B** previously prepared in this laboratory.[4a]

Similarly, the propyl ketone (-)-**40** was cyclized via hydrogenation to give (-)-indolizidine **223AB** [(-)-**2**] along with its C-5 epimer in an 86:14 ratio (total yield: 99%). The synthetic (-)-**223AB** had [$[\alpha]^{25}_D$ -97.7° (*c* 0.43, hexane) virtually identical with that published for the (-)-enantiomer of **223AB** [$[\alpha]^{20}_D$ -101° (*c* 2.3, hexane)][6] and ex-

Scheme VIII



hibited spectral data (^{1}H and ^{13}C NMR and MS) identical with those of (±)-**2** previously prepared in this laboratory.[8b]

We next focused on the preparation of the (+)-enantiomers of indolizidines **195B** [(+)-1], **223AB** [(+)-2], and **239AB** [(+)-3] employing a more convenient, shorter route starting with the (*S*,*S*)-diepoxide (*S*,*S*)-**7**. Thus, the diepoxide (*S*,*S*)-**7** was converted to the (5*R*,8*R*)-diol **41** in three steps by the method previously reported by us[9b] (Scheme VII). Benzoylation of **41** with 1.3 equiv of benzoyl chloride (DMAP, 0 °C) gave the mono- and dibenzoates **42** and **43** in 46% and 41% yields, respectively. The dibenzoate **43** was converted to the monobenzoate **42** by partial hydrolysis with 10% aqueous NaOH. Deoxygenation of **42** was employed by bromination (CBr_4, Ph_3P) followed by hydrogenolysis over Pd–C in the presence of triethylamine to furnish **45** in 77% overall yield. Removal of both the silyl groups (Bu_4NF, THF) gave the diol **46** (91% yield), which was then reacted with thionyl chloride and triethylamine followed by RuO_4 to afford the cyclic sulfate **47** in 96% yield. Nucleophilic displacement of **47** with lithium azide and subsequent acidic hydrolysis resulted in an inseparable 1:1 mixture of the two azides **49a** and **49b** (total yield: 92%), which was quantitively converted to the mesylate **50a** and **50b**.

The 1:1 mixture of **50a** and **50b** without separation was subjected to hydrogenation over palladium on carbon to produce the 2,5-*trans*-pyrrolidine **51** as a single isomer, the amino function of which was then protected to give **52** in 81% overall yield (Scheme VIII). The aldehyde (+)-**34** with the 2*S*,5*S* configuration was obtained from **52** by ester hydrolysis and Swern oxidation in 85% yield. Following the same procedure as described for the (−)-enantiomers of indolizidines **195B**, **223AB**, and **239AB** (Schemes V and VI), (+)-**34** was subjected to homologation of the alkyl side chain followed by cyclization of the resulting ketones (+)-**39**, (+)-**40**, and (+)-**36** to yield the natural (+)-enantiomer of indolizidine **195B** [(+)-1] and the unnatural (+)-enantiomers of **223AB** [(+)-2] and **239AB** [(+)-3], respectively.

In conclusion, these results established a general strategy for a successful approach to both enantiomers of all of four dendrobatid alkaloids, indolizidines **195B**, **223AB**, **239AB**, and **239CD**, belonging to the 3,5-disubstituted indolizidine subclass. These syntheses have been accomplished by a route starting from the 3,4-dideoxyhexitol **8** as a common chiral synthon and involve the first chiral preparations of indolizidines **239AB** and **293CD** both in natural (−)- and unnatural (+)-enatiomeric forms, which confirmed the absolute configurations of natural **239AB** and **239CD** as 3*R*,5*S*,8a*R* and 3*R*,5*R*,8a*R*, respectively.

Experimental Section

General Procedures. Optical rotations were measured on a digital polarimeter in a 1-dm cell. IR spectra were obtained on an FTIR instrument. ^{1}H and ^{13}C NMR spectra were taken at 300, 400, or 500 MHz and 75, 100, or 125 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. Mass spectra were obtained at 70 eV. Column chromatography was performed on silica gel 60 (230–400 mesh, E. Merck) and basic Al_2O_3 (activity I, 70–230 mesh, E. Merck). Microanalyses were carried out by the Microanalytical Laboratory at Tokyo College of Pharmacy.

3,4-Dideoxy-1,2:5,6-di-*O*-isopropylidene-D-*threo*-hexitol (10). A solution of **9** (20.0 g, 87.6 mmol) in THF (80 mL) was hydrogenated over 10% Rh–Al_2O_3 (4.00 g) at 1 atm for 1 h. Filtration of the mixture and concentration of the filtrate provided an oily residue, which was purified by flash column chromatography on silica gel (hexane–EtOAc, 6:1) and distillation to give **10** (19.2 g, 95%) as a colorless oil: bp 73 °C (0.6 mmHg); $[\alpha]^{23}_D$ +17.5° (*c* 5.78, $CHCl_3$) [lit.[12] $[\alpha]_D$ + 18.5° (CH_2Cl_2)]; IR (neat) 2986, 2937, 2872, 1456, 1379, 1370, 1251, 1216, 1159, 1061, 860 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.33 (6 H, s), 1.39 (6 H, s), 1.50–1.78 (4 H, series of m), 3.52 (2 H, t, *J* = 7.3 Hz), 4.03 (2 H, dd, *J* = 7.7, 6.0 Hz), 4.10 (2 H, m); ^{13}C NMR ($CDCl_3$) δ 25, 77, 27.01, 29.60, 69.35, 75.58, 108.91. Anal. Calcd for $C_{12}H_{22}O_4$: C, 62.58; H, 9.63. Found: C, 62.77; H, 9.58.

3,4-Dideoxy-D-*threo*-hexitol (8). A mixture of **10** (65.0 g, 0.282 mol) and 2 N HCl (30 mL) was stirred at 80 °C for 2 h. The mixture was concentrated in vacuo. Ethanol (100 mL) and toluene (50 mL) were added to the residue, and the mixture was further concentrated in vacuo to remove azeotropically the rest of water. The residue obtained as a pale yellow syrup was recrystallized from EtOH–$CHCl_3$ to give **8** (36.5 g, 86%) as colorless prisms: mp 93–94 °C (lit.[17] mp 92–94 °C); $[\alpha]^{26}_D$ −24.0° (*c* 1.69, MeOH) [lit.[17] $[\alpha]^{20}_D$ −24° (MeOH)]; ^{1}H NMR ($CDCl_3$) δ 1.69 (4 H, m), 3.62 (2 H, dd, *J* = 11.7, 6.8 Hz), 3.73 (2 H, dd, *J* = 11.7, 3.8 Hz), 3.84 (2 H, m); ^{13}C NMR (D_2O, MeCN) δ 29.21, 66.30, 72.50.

(2*S*,5*S*)-2,5-Dihydroxy-1,6-bis(pivaloyloxy)hexane (11). To a stirred solution of **8** (10.0 g, 66.6 mmol) in pyridine (250 mL) cooled to −10 °C was added a solution of pivaloyl chloride (2.41 g, 133 mmol) in CH_2Cl_2 (100 mL), and the mixture was stirred at rt for 3 h. The reaction mixture was poured into ice-cooled 10% aqueous HCl (300 mL) and extracted with Et_2O (3 × 300 mL). The ethereal solution was washed with water (300 mL), saturated aqueous $NaHCO_3$ (300 mL), and water (100 mL) and dried ($MgSO_4$). The solvent was evaporated, and the residue was purified by flash column chromatography on silica gel (hexane–EtOAc, 2:1) to give a colorless solid, which was recrystallized from Et_2O–hexane to give **11** (13.4 g, 63%) as colorless needles: mp 80.5–81.5 °C; $[\alpha]^{29}_D$ −1.0° (*c* 1.57, $CHCl_3$); IR (KBr) 3261, 2972, 2877, 1720, 1483, 1462, 1285, 1168, 1126, 1082, 936, 880, 772 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.19 (18 H, s), 1.62 (4 H, m), 3.18 (2 H, br s), 3.84 (2 H, m), 3.98 (2 H, dd, *J* = 11.3, 6.4 Hz), 4.07 (2 H, dd, *J* = 11.3, 4.2 Hz); ^{13}C NMR ($CDCl_3$) δ 27.09, 29.66, 38.76, 68.25, 69.77, 178.68; MS (CI, isobutane) *m*/*z* (relative intensity) 319 (M^+ + 1, 2), 302 (18), 301 (100), 217 (25), 199 (40), 185 (73), 115 (22), 101 (31), 85 (77). Anal. Calcd for $C_{16}H_{30}O_6$: C, 60.36; H, 9.50. Found: C, 60.49; H, 9.47.

(2*S*,5*S*)-2,5-Bis((methylsulfonyl)oxy)-1,6-bis(pivaloyloxy)hexane (12). To a stirred, ice-cooled solution of **11** (13.00 g, 40.8 mmol) and Et_3N (9.08 g, 89.8 mmol) in $CHCl_3$ (40 mL) was added a solution of methanesulfonyl chloride (10.30 g, 89.8 mmol) in $CHCl_3$ (20 mL), and stirring was continued for 15 min.

(17) Kuszmann, J.; Sohár, P. *Carbohydr. Res.* **1980**, *83*, 63.

The reaction mixture was diluted with $CHCl_3$ (300 mL) and washed with 10% aqueous HCl (100 mL) and water (100 mL). The solution was dried ($MgSO_4$) and concentrated to give **12** (19.36 g, 100%) as a colorless oil, which was solidified by cooling and sufficiently pure for further conversion. An analytical sample was obtained by recrystallization from Et_2O–hexane as colorless needles: mp 58–60 °C; $[\alpha]^{24}_D$ +11.34° (*c* 1.16, $CHCl_3$); IR (KBr) 3037, 3018, 2972, 2941, 2877, 1738, 1718, 1482, 1457, 1418, 1399, 1333, 1284, 1231, 1212, 1176, 1161, 1136, 1052, 994, 978, 899, 786, 770, 740, 715, 667 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.20 (18 H, s), 1.88 (4 H, m), 3.06 (6 H, s), 4.11 (2 H, dd, J = 12.4, 6.0 Hz), 4.32 (2 H, dd, J = 12.4, 3.5 Hz), 4.91 (2 H, m); ^{13}C NMR ($CDCl_3$) δ 26.91, 27.16, 38.75, 64.79, 78.46, 178.00; MS *m/z* (relative intensity) 459 (M^+ – 15, 0.3), 393 (0.2), 379 (10), 363 (6), 359 (11), 323 (10), 276 (32), 263 (24), 185 (58), 183 (27), 182 (100), 179 (35), 135 (5), 101 (5). Anal. Calcd for $C_{18}H_{34}O_{10}S_2$: C, 45.52; H, 7.22. Found: C, 45.50; H, 7.15.

(2*R*,5*R*)-1,2:5,6-Diepoxyhexane [(*R*,*R*)-7]. To a stirred, ice-cooled solution of **12** (19.00 g, 40.0 mmol) in 4:3 THF–MeOH (80 mL) was added 40% aqueous NaOH (25 mL), and the mixture was stirred at rt for 30 min. The mixture was diluted with water (150 mL) and extracted with Et_2O (2 × 200 mL and then 2 × 100 mL). The combined extracts were washed with brine (50 mL), dried ($MgSO_4$), and concentrated to give (*R*,*R*)-**7** (4.48 g, 98%) as a colorless oil, which was sufficiently pure for further reaction. An analytical sample was obtained by distillation: bp 76 °C (16 mmHg); $[\alpha]^{26}_D$ +26.8° (*c* 5.03, $CHCl_3$) [lit.[9b] $[\alpha]^{26}_D$ +18.5° (*c* 2.22, $CHCl_3$)]. Anal. Calcd for $C_6H_{10}O_2$: C, 63.12; H, 8.84. Found: C, 63.06; H, 8.89. The spectra (^1H and ^{13}C NMR) characteristics of this material were identical with those of a sample previously synthesized in our laboratory.[9b]

(4*S*)-1,2-Bis(2-phenyl-1,3-dioxolan-4-yl)ethane (13). A solution of **8** (36.5 g, 0.243 mol), benzaldehyde (64.5 g, 0.608 mol), and *p*-toluenesulfonic acid monohydrate (50 mg, 0.26 mmol) in toluene (250 mL) was refluxed for 5 h. The reaction mixture was diluted with Et_2O (250 mL) and washed with saturated aqueous $NaHCO_3$ (150 mL) and water (150 mL). The solution was dried ($MgSO_4$), and the solvent was evaporated to give a light brown oil, which was purified by a short column over silica gel (hexane–EtOAc, 6:1) to furnish **13** (77.7 g, 98%) as a pale yellow oil: IR (neat) 2756, 2360, 1495, 1456, 1403, 1311, 1294, 1220, 1175, 1067, 1027, 970, 916, 850, 758, 697, 639, 625 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.66–2.02 (4 H, m), 3.63–3.78 (2 H, m), 4.11–4.37 (4 H, m), 5.84, 5.95, 5.97 (2.6:1:1 ratio, total 2 H, s, each), 7.38–7.54 (10 H, m); MS *m/z* (relative intensity) 326 (M^+, 3), 325 (6), 220 (4), 219 (10), 205 (5), 203 (8), 149 (12), 114 (30), 105 (100). Anal. Calcd for $C_{20}H_{22}O_4$: C, 73.60; H, 6.79. Found: C, 73.40; H, 6.84.

(2*S*,5*S*)-1,2:5,6-Diepoxyhexane [(*S*,*S*)-7]. A solution of **13** (26.3 g, 80.6 mmol) and *N*-bromosuccimide (31.6 g, 177 mmol) in CCl_4 (270 mL) was stirred at rt for 20 h. The resulting suspension was filtered, and the filtrate was washed with saturated aqueous $NaHCO_3$ (100 mL) and brine (100 mL) and dried ($MgSO_4$). Evaporation of the solvent gave (2*S*,5*S*)-2,5-bis(benzoyloxy)-1,6-dibromohexane (**14**) as a pale yellow oil, which was used without further purification. Data for **14**: $[\alpha]^{27}_D$ –9.92° (*c* 1.19, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.98 (4 H, m), 3.61 (4 H, ddd, J = 16.2, 11.1, 4.9 Hz), 5.31 (2 H, m), 7.41–8.07 (10 H, m); ^{13}C NMR ($CDCl_3$) δ 28.19, 33.74, 72.02, 128.45, 129.67, 129.76, 133.31, 165.78.

The crude product of **14** obtained above was dissolved in 4:3 THF–MeOH (350 mL) and cooled to 0 °C. To this solution was added 40% aqueous NaOH (50 mL), and the mixture was stirred at rt for 30 min. The reaction mixture was diluted with water (700 mL) and extracted with Et_2O (2 × 500 mL and then 2 × 250 mL). The combined extracts were washed with brine (100 mL) and dried ($MgSO_4$). After evaporation of the solvent, the residue was purified by flash column chromatography on silica gel (hexane–EtOAc, 6:1) to give (*S*,*S*)-**7** (8.60 g, 93% from **13**) as a colorless oil: $[\alpha]^{26}_D$ –26.4° (*c* 1.86, $CHCl_3$) [lit.[9b] $[\alpha]^{26}_D$ –19.0° (*c* 1.26, $CHCl_3$)]. Anal. Calcd for $C_6H_{10}O_2$: C, 63.12; H, 8.84. Found: C, 63.25; H, 8.72. The spectra (^1H and ^{13}C NMR) characteristics of this material were identical with those of a sample previously synthesized in our laboratory.[9b]

(5*S*,8*S*)-1-(Benzoyloxy)-12-(benzyloxy)-5,8-bis[(*tert*-butyldimethylsilyl)oxy]dodecane (17). A solution of benzoyl chloride (1.50 g, 10.7 mmol) in CH_2Cl_2 (10 mL) was added dropwise to a stirred mixture of **16** (3.93 g, 7.11 mmol), 4-(dimethylamino)pyridine (1.71 g, 14.2 mmol) and CH_2Cl_2 (20 mL) at 0 °C. The mixture was stirred at rt for 1 h, after which the reaction was quenched with water (50 mL). The organic phase was separated, and the aqueous phase was extracted with CH_2Cl_2 (3 × 40 mL). The combined organic phases were washed with cold 5% aqueous HCl and then brine and dried ($MgSO_4$). Removal of the solvent and flash column chromatography on silica gel (hexane–EtOAc, 20:1) gave **17** (4.66 g, 100%) as a colorless oil: $[\alpha]^{28}_D$ –5.6° (*c* 1.95, $CHCl_3$); IR (neat) 2929, 2856, 2360, 2342, 1719, 1272, 1110, 1070, 834, 773, 710, 669 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.03 (6 H, s), 0.04 (6 H, s), 0.88 (18 H, s), 1.33–1.53 (12 H, m), 1.61 (2 H, quint, J = 6.6 Hz), 1.76 (2 H, quint, J = 6.5 Hz), 3.46 (2 H, t, J = 6.6 Hz), 3.63 (2 H, quint, J = 5.3 Hz), 4.32 (2 H, t, J = 6.6 Hz), 4.50 (2 H, s), 7.25–7.56 (8 H, m), 8.03–8.06 (2 H, m); ^{13}C NMR ($CDCl_3$) δ –4.34 (2 C), –4.29 (2 C), 18.21 (2 C), 21.96, 22.08, 26.02 (6 C), 29.12, 30.10, 32.78, 32.88, 36.81, 37.07, 65.12, 70.55, 72.37, 72.45, 72.99, 127.54, 127.68 (2 C), 128.39 (2 C), 128.42 (2 C), 129.65 (2 C), 130.64, 132.86, 138.84, 166.76; MS *m/z* (relative intensity) 657 (M^+ + 1, 0.1), 642 (0.3), 600 (0.4), 507 (1), 497 (4), 467 (0.9), 179 (50), 105 (100). Anal. Calcd for $C_{38}H_{64}O_5Si_2$: C, 69.46; H, 9.82. Found: C, 69.13; H, 9.87.

(5*S*,8*S*)-1-(Benzoyloxy)-12-(benzyloxy)-5,8-dodecanediol (18). A 1.0 M solution of tetrabutylammonium fluoride in THF (15 mL, 15.0 mmol) was added dropwise to a stirred solution of **17** (3.50 g, 5.40 mmol) in THF (30 mL) at rt. After 1 h of stirring at rt, water (10 mL) and then Et_2O (200 mL) was added to the mixture, and the mixture was washed with 1% HCl (10 mL) and then brine (10 mL). The organic phase was dried ($MgSO_4$) and concentrated to give a crude solid, which was purified by flash column chromatography on silica gel (hexane–EtOAc, 1:1) and recrystallization from CH_2Cl_2–hexane to give **18** (2.19 g, 95%) as colorless needles: mp 77–78 °C; $[\alpha]^{29}_D$ +2.69° (*c* 1.56, $CHCl_3$); IR (neat) 3272, 2941, 2861, 1723, 1275, 1070, 1028, 996, 976, 882, 857, 733 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.39–1.69 (14 H, m), 1.74–1.86 (2 H, m), 2.05 (2 H, br s), 3.48 (2 H, t, J = 6.4 Hz), 3.61–3.63 (2 H, m), 4.33 (2 H, t, J = 6.6 Hz), 4.48 (2 H, s), 7.25–7.61 (8 H, m), 8.03–8.05 (2 H, m); ^{13}C NMR ($CDCl_3$) δ 22.38, 22.49, 28.89, 29.72, 34.03, 34.20, 37.40, 37.58, 64.98, 70.36, 72.70, 73.30, 127.74 (2 C), 128.42 (2 C), 128.45 (2 C), 129.64 (2 C), 130.57, 132.92, 138.66, 166.56; MS (CI, isobutane) *m/z* (relative intensity) 429 (M^+ + 1, 6), 411 (6), 319 (6), 303 (40), 247 (12), 105 (100). Anal. Calcd for $C_{26}H_{36}O_5$: C, 72.87; H, 8.47. Found: C, 72.67; H, 8.46.

(5*S*,8*S*)-1-(Benzoyloxy)-12-(benzyloxy)-5,8-dodecanediol Cyclic Sulfate [(+)-19]. A solution of thionyl chloride (119 mg, 1.09 mmol) in CH_2Cl_2 (5 mL) was added dropwise to a stirred mixture of **18** (358 mg, 0.835 mmol), Et_3N (200 mg, 1.98 mol), and CH_2Cl_2 (5 mL) at 0 °C, after which stirring was continued for 5 min at rt. To this mixture was added water (5 mL), and the mixture was diluted with Et_2O (100 mL), washed with brine, and dried ($MgSO_4$). The solvent was evaporated to dryness, and the residual oil was dissolved in 2:2:3 CCl_4–MeCN–H_2O (7 mL). To this solution were added $RuCl_3 \cdot xH_2O$ (10 mg) and $NaIO_4$ (359 mg, 1.68 mmol), and the mixture was stirred at 0 °C. After 1 h of stirring, the mixture was diluted with Et_2O (50 mL) and water (50 mL) was added to the mixture. The organic phase was separated, and the aqueous phase was extracted with Et_2O (2 × 50 mL). The combined Et_2O solution was washed with brine (50 mL), dried ($MgSO_4$), and concentrated. Purification by flash column chromatography on silica gel (hexane–EtOAc, 4:1) followed by recrystallization from CH_2Cl_2–hexane gave (+)-**19** (337 mg, 82%) as colorless pillars: mp 73–74 °C; $[\alpha]^{27}_D$ +10.95° (*c* 1.32, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.48–1.97 (16 H, m), 3.48 (2 H, t, J = 6.1 Hz), 4.33 (2 H, dt, J = 6.4, 1.3 Hz), 4.49 (2 H, s), 4.64–4.66 (2 H, m), 7.26–7.58 (8 H, m), 8.04 (2 H, dd, J = 8.3, 1.3 Hz); ^{13}C NMR ($CDCl_3$) δ 21.77, 22.02, 28.25, 29.22, 32.94, 33.03, 35.04, 35.27, 64.51, 70.02, 73.04, 84.71, 85.11, 127.63, 127.75 (2 C), 128.45 (4 C), 129.66, 130.44, 132.98, 138.63, 166.71; MS *m/z* (relative intensity) 482 (M^+ – 8, 0.5), 450 (0.6), 392 (0.4), 360 (1), 301 (1), 269 (0.4), 242 (1), 205 (2), 179 (5), 129 (10), 105 (100); MS (CI, isobutane) *m/z* (relative intensity) 483 (M^+ – 7, 2), 462 (2), 450 (2), 403 (2), 303 (4), 261 (9), 197 (6), 163 (13), 123 (53), 105 (100). Anal. Calcd for $C_{26}H_{34}O_7S$: C, 63.65; H, 6.99. Found: C, 63.75; H, 7.01.

Reaction of (+)-19 with Lithium Azide. To a solution of (+)-**19** (1.93 g, 3.93 mmol) in DMF (5 mL) was added LiN_3 (289 mg, 5.90 mmol), and the mixture was stirred at rt. After being

stirred for 1 h, the solvent was removed under reduced pressure (0.01 mmHg) at 50 °C. The residue was suspended in THF (5 mL) and water (0.1 mL), and then concd H_2SO_4 (0.1 mL) was added to this at rt with stirring. After the mixture was stirred for 2 h, Et_2O (20 mL) was added, and the mixture was neutralized with Na_2CO_3. The insoluble inorganic material was removed by filtration, and the filtrate was dried ($MgSO_4$). Evaporation of the solvent followed by flash column chromatography on silica gel (hexane–EtOAc, 3:2) gave a 1:1 mixture of (5*S*,8*R*)-8-azido-1-(benzoyloxy)-12-(benzyloxy)-5-dodecanol (**21a**) and (5*S*,8*R*)-8-azido-12-(benzoyloxy)-1-(benzyloxy)-5-dodecanol (**21b**) (total: 1.78 g, 100%) as a colorless oil: IR (neat) 3475, 2939, 2862, 2097, 1718, 1453, 1315, 1275, 1177, 1113, 1071, 1027, 736, 713, 699 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.39–1.84 (total 34 H, m), 3.24–3.33 (total 2 H, m), 3.48 (total 4 H, dt, J = 6.3, 2.1 Hz), 3.60 (total 2 H, br s), 4.34 (total 4 H, dt, J = 6.5, 1.3 Hz), 4.50 (total 4 H, s), 7.26–7.37 (total 10 H, m), 7.42–7.46 (total 4 H, m), 7.53–7.58 (total 2 H, m), 8.03–8.06 (total 4 H, m); MS m/z (relative intensity) 408 (0.8), 316 (4), 286 (4), 259 (4), 220 (2), 195 (10), 105 (100); MS (CI, isobutane) m/z (relative intensity) 448 (4), 408 (22), 317 (8), 286 (12), 259 (7), 220 (6), 197 (49), 105 (100). Anal. Calcd for $C_{26}H_{35}N_3O_4$: C, 68.85; H, 7.78; N, 9.26. Found: C, 68.93; H, 7.80; N, 9.07.

Mesylation of 21a and 21b. To an ice-cooled, stirred solution of the 1:1 mixture (203 mg, 0.448 mmol) of **21a** and **21b**, obtained by the reaction described above, in CH_2Cl_2 (5 mL) including Et_3N (100 mg, 0.988 mmol) was added dropwise a solution of methanesulfonyl chloride (62 mg, 0.54 mmol) in CH_2Cl_2 (3 mL). After 15 min of stirring at 0 °C, the mixture was poured into water (10 mL) and extracted with Et_2O (2 × 50 mL). The extracts were washed with brine, dried ($MgSO_4$), and concentrated. The residual product was chromatographed on silica gel (hexane–EtOAc, 2:1) to give a 1:1 mixture of (5*S*,8*R*)-8-azido-1-(benzoyloxy)-12-(benzyloxy)-5-(methanesulfonyloxy)dodecane (**22a**) and (5*S*,8*R*)-8-azido-12-(benzoyloxy)-1-(benzyloxy)-5-(methanesulfonyloxy)dodecane (**22b**) (total: 224 mg, 94%) as a pale yellow oil: IR (neat) 2941, 2866, 2099, 1718, 1454, 1355, 1276, 1174, 1114, 1072, 1027, 906, 715 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.45–1.93 (total 32 H), 2.98 (3 H, s), 3.00 (3 H, s), 3.23–3.34 (total 2 H, m), 3.48 (total 4 H, dt, J = 6.3, 1.7 Hz), 4.34 (total 4 H, dt, J = 6.5, 1.9 Hz), 4.495 (2 H, s), 4.500 (2 H, s), 4.69–4.78 (2 H, m), 7.26–7.39 (total 10 H, m), 7.45 (total 4 H, t, J = 7.8 Hz), 7.52–7.58 (total 2 H, m), 8.03–8.05 (total 4H, m); MS m/z (relative intensity) 407 (0.2), 316 (12), 286 (8), 259 (6), 194 (5), 151 (4), 122 (12), 105 (97), 91 (100); MS (CI, isobutane) m/z (relative intensity) 408 (29), 316 (7), 286 (9), 259 (4), 196 (3), 123 (12), 105 (43), 97 (61), 91 (100). Anal. Calcd for $C_{27}H_{37}N_3O_6S$: C, 61.00; H, 7.01; N, 7.90. Found: C, 60.96; H, 7.02; N, 7.74.

(2*R*,5*R*)-2-[4-(Benzoyloxy)butyl]-5-[4-(benzyloxy)butyl]-*N*-[(benzyloxy)carbonyl]pyrrolidine (23). A solution of the 1:1 mixture (518 mg, 0.974 mmol) of **22a** and **22b**, obtained by the reaction described above, in MeOH (5 mL) was hydrogenated over 10% Pd–C (100 mg) for 1 h. Filtration and evaporation of the solvent afforded a crude product of (2*R*,5*R*)-2-[4-(benzoyloxy)butyl]-5-[4-(benzyloxy)butyl]pyrrolidine (**23**), which was, without purification, dissolved in CH_2Cl_2 (5 mL). To this solution was added 20% aqueous K_2CO_3 (3 mL), and the mixture was cooled and stirred in an ice bath. To this was added dropwise a solution of (benzyloxy)carbonyl chloride (332 mg, 1.95 mmol) in CH_2Cl_2 (3 mL). After the mixture was stirred for 15 min, Et_2O (100 mL) was added, and the organic phase that separated was washed with brine (50 mL) and dried ($MgSO_4$). The solvent was evaporated, and the residue was purified by flash column chromatography on silica gel (hexane–EtOAc, 5:1) to give **24** (405 mg, 77%) as a colorless oil: $[\alpha]^{27}_D$ −35.0° (*c* 1.06, $CHCl_3$); IR (neat) 3063, 3031, 2948, 2858, 1716, 1697, 1602, 1585, 1497, 1455, 1407, 1355, 1314, 1275, 1212, 1176, 1112, 1028, 771, 736, 713 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.17–1.94 (16 H, series of m), 3.39, 3.47 (1:1 ratio, total 2 H, t, J = 6.4 Hz, each, due to double bond character of the C(O)–N bond in amide), 3.77, 3.82 (1:1 ratio, total 2 H, br s, each, due to double bond character of the C(O)–N bond in amide), 4.23, 4.32 (1:1 ratio, total 2 H, t, J = 6.5 Hz, each, due to double bond character of the C(O)–N bond in amide), 4.45, 4.50 (1:1 ratio, total 2 H, s, each, due to double bond character of the C(O)–N bond in amide), 5.06, 5.18 (2 H, AB q, J = 12.4 Hz), 7.26–7.37 (10 H, m), 7.42–7.45 (2 H, m), 7.53–7.58 (1 H, m), 8.04 (2 H, t, J = 6.4 Hz); ^{13}C NMR ($CDCl_3$) δ 23.15, 23.22, 23.30, 26.69, 26.76, 27.66, 27.73, 28.60, 28.77, 29.62, 29.72, 32.38, 32.40, 33.72, 33.81, 57.49, 57.67, 58.03, 58.19, 64.75, 64.96, 66.46, 70.17, 70.33, 72.88, 127.48, 127.52, 127.62, 127.88, 127.92, 127.96, 128.04, 128.36, 128.45, 129.57, 130.54, 132.81, 132.86, 137.09, 138.68, 138.76, 154.25, 154.31, 166.58, 166.65; MS m/z (relative intensity) 503 (1), 452 (6), 408 (95), 380 (12), 336 (94), 321 (63), 302 (4), 232 (6), 181 (7), 150 (16), 105 (100); MS (CI, isobutane) m/z (relative intensity) 546 (M^+ + 3, 5), 545 (10), 544 (25), 543 (M^+, 6), 500 (16), 436 (46), 408 (86), 336 (55), 105 (100). Anal. Calcd for $C_{34}H_{41}NO_5$: C, 75.11; H, 7.60; N, 2.58. Found: C, 74.91; H, 7.71; N, 2.54.

(2*R*,5*R*)-5-[4-(Benzyloxy)butyl]-*N*-[(benzyloxy)carbonyl]-2-(4-hydroxybutyl)pyrrolidine (25). A solution of **24** (87 mg, 0.16 mmol) in MeOH (1 mL) was added to a 1% methanolic solution of KOH (5 mL), and the mixture was stirred at rt for 30 min. The reaction mixture was diluted with $CHCl_3$ (60 mL), and the solution was washed with water (2 × 10 mL). The $CHCl_3$ solution was dried ($MgSO_4$) and concentrated in vacuo to give an oily product, which was purified by flash column chromatography on silica gel (hexane–EtOAc, 2:1) to provide **25** (68 mg, 97%) as a pale yellow oil: $[\alpha]^{28}_D$ −46.2° (*c* 1.15, $CHCl_3$); IR (neat) 3455, 3088, 3063, 3031, 2937, 2860, 1695, 1497, 1455, 1408, 1356, 1309, 1210, 1104, 1029, 772, 736, 698 cm^{-1}; ^1H NMR ($CDCl_3$, 20 °C) δ 1.19–1.66 (13 H, series of m), 1.89–1.93 (4 H, m), 3.39, 3.47 (1:1 ratio, total 2 H, t, each, J = 6.4 and 6.7 Hz, respectively, due to double bond character of the C(O)–N bond in amide), 3.52, 3.64 (1:1 ratio, total 2 H, t, each, J = 6.5 and 6.3 Hz, respectively, due to double bond character of the C(O)–N bond in amide), 3.75, 3.81 (1:1 ratio, total 2 H, br s, each, due to double bond character of the C(O)–N bond in amide), 4.45, 4.50 (1:1 ratio, total 2 H, s, each, due to double bond character of the C(O)–N bond in amide), 5.05, 5.06 (1:1 ratio, total 1 H, $^1/_2$ AB q, J = 12.4 Hz, due to double bond character of the C(O)–N bond in amide), 5.18, 5.20 (1:1 ratio, total 1 H, $^1/_2$ AB q, J = 12.4 Hz, each, due to double bond character of the C(O)–N bond in amide), 7.28–7.36 (10 H, m); ^1H NMR ($CDCl_3$, 60 °C) δ 1.21–1.74 (13 H), 1.91–2.03 (4 H, m), 3.44 (2 H, br s), 3.59 (2 H, br s), 3.80 (2 H, br s), 4.48 (2 H, s), 5.07, 5.18 (2 H, AB q, J = 12.4 Hz), 7.26–7.37 (10 H, m); ^{13}C NMR ($CDCl_3$) δ 22.83, 23.34, 26.73, 26.82, 27.71, 29.66, 29.76, 32.34, 32.47, 33.77, 33.84, 57.64, 57.74, 58.06, 58.23, 62.71, 62.81, 66.51, 70.23, 70.38, 72.93, 127.58, 127.68, 127.94, 128.01, 128.13, 128.42, 128.50, 137.13, 138.70, 154.42; MS m/z (relative intensity) 437 (M^+ − 2, 0.3), 394 (0.6), 366 (6), 323 (15), 322 (55), 304 (100), 276 (17), 232 (86), 124 (29); MS (CI, isobutane) m/z (relative intensity) 441 (M^+ + 2, 6), 440 (22), 436 (5), 396 (31), 366 (8), 332 (43), 322 (35), 304 (100), 276 (17), 232 (62), 181 (14), 124 (27). Anal. Calcd for $C_{27}H_{37}NO_4$: C, 73.77; H, 8.48; N, 3.19. Found: C, 73.44; H, 8.53; N, 3.16.

(2*R*,5*R*)-5-[4-(Benzyloxy)butyl]-*N*-[(benzyloxy)carbonyl]-2-(4-oxobutyl)pyrrolidine (26). To a stirred suspension of pyridinium dichromate (135 mg, 0.359 mmol) in CH_2Cl_2 (6 mL) was added dropwise a solution of **25** (80 mg, 0.18 mmol) in CH_2Cl_2 (3 mL). The mixture was stirred at rt for 12 h. To the reaction mixture was added Et_2O (50 mL), and the dark solid that separated was filtered through a Celite pad and washed with Et_2O (50 mL). The combined filtrates were washed with brine (30 mL), dried ($MgSO_4$), and concentrated to give an oily residue, which was subjected to flash column chromatography on silica gel (hexane–EtOAc, 3:1) to afford **26** (58 mg, 73%) as a colorless oil: $[\alpha]^{27}_D$ −53.3° (*c* 0.97, $CHCl_3$); IR (neat) 3063, 3031, 2935, 2860, 2721, 1724, 1695, 1497, 1455, 1407, 1355, 1210, 1170, 1103, 1029, 913, 772, 737, 698, cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.27–1.99 (14 H, series of m), 2.29, 2.47 (1:1 ratio, total 2 H, ddd, each, J = 31.1, 17.8, 6.6 Hz and J = 25.8, 17.5, 7.7 Hz, respectively, due to double bond character of the C(O)–N bond in amide), 3.39, 3.47 (1:1 ratio, total 2 H, t, each, J = 6.4 and 6.2 Hz, respectively, due to double bond character of the C(O)–N bond in amide), 3.72–3.80 (2 H, m), 4.45, 4.50 (1:1 ratio, total 2 H, s, each, due to double bond character of the C(O)–N bond in amide), 5.06, 5.18 (2 H, AB q, J = 12.5 Hz), 7.26–7.36 (10 H, m), 9.63, 9.77 (1:1 ratio, total 1 H, s, each, due to double bond character of the C(O)–N bond in amide); ^{13}C NMR ($CDCl_3$) δ 19.06, 23.34, 26.74, 26.84, 27.72, 27.81, 29.66, 29.75, 32.25, 32.42, 33.65, 33.81, 43.58, 43.83, 57.30, 57.77, 57.84, 58.27, 66.53, 66.59, 70.21, 70.36, 72.94, 127.59, 127.68, 127.95, 128.00, 128.21, 128.42, 128.52, 137.06, 138.70, 154.21, 154.39, 202.04, 202.39;

MS m/z (relative intensity) 437 (M^+, 0.8), 392 (0.5), 366 (0.5), 322 (44), 302 (100), 274 (20), 230 (90), 181 (6), 150 (14), 124 (34). Anal. Calcd for $C_{27}H_{35}NO_4$: C, 74.11; H, 8.06; N, 3.20. Found: C, 73.88; H, 8.13; N, 3.19.

(2*R*,5*R*)-5-[4-(Benzyloxy)butyl]-*N*-[(benzyloxy)carbonyl]-2-(4-hydroxyheptyl)pyrrolidine (27). A 2 M solution of propylmagnesium bromide (0.41 mL, 0.82 mmol) in THF was added dropwise using a syringe to a stirred, ice-cooled solution of **26** (237 mg, 0.542 mmol) in THF (10 mL) under Ar. After the mixture was stirred for 1 h at 0 °C, the reaction was quenched with water (20 mL) and the product was extracted with Et_2O (3 × 50 mL). The extracts were washed with brine (50 mL) and dried ($MgSO_4$). Evaporation of the solvent and flash column chromatography on silica gel (hexane–EtOAc, 3:1) gave **27** (226 mg, 87%) as a colorless oil containing a mixture of diastereomers at C-4: IR (neat) 3456, 3063, 3031, 2927, 2863, 1696, 1455, 1408, 1356, 1100, 1028, 911, 772, 735, 698 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.92 (3 H, t, J = 6.8 Hz), 1.19–1.98 (21 H, m), 3.38, 3.47 (1:1 ratio, total 2 H, t, each, J = 6.5 and 6.8 Hz, respectively, due to double bond character of the C(O)–N bond in amide), 3.60 (1 H, br s), 3.75, 3.80 (1:1 ratio, total 2 H, br s, each, due to double bond character of the C(O)–N bond in amide), 4.45, 4.50 (1:1 ratio, total 2 H, s, each, due to double bond character of the C(O)–N bond in amide), 5.05 (1 H, dd, J = 12.3, 5.0 Hz), 5.15–5.21 (1 H, m), 7.27–7.35 (10 H, m); MS m/z (relative intensity) 439 (0.2), 438 (1), 394 (2), 346 (100), 322 (68), 274 (52), 166 (20), 124 (25); MS (CI, isobutane) m/z (relative intensity) 484 (M^+ + 3, 2), 483 (7), 482 (20), 438 (18), 374 (18), 346 (100), 322 (49), 274 (38), 166 (19), 124 (24). Anal. Calcd for $C_{30}H_{43}NO_4$: C, 74.81; H, 9.00; N, 2.91. Found: C, 74.61; H, 9.01; N, 2.87.

(2*R*,5*R*)-5-[4-(Benzyloxy)butyl]-*N*-[(benzyloxy)carbonyl]-2-(4-oxoheptyl)pyrrolidine (28). To a stirred solution of **27** (220 mg, 0.457 mmol) in CH_2Cl_2 (3 mL) was added pyridinium dichromate (344 mg, 0.914 mmol). After the mixture was stirred for 24 h at rt, Et_2O (50 mL) was added. The dark solid that separated was filtered through a Celite pad and washed with Et_2O (50 mL). The combined filtrates were washed with brine, dried ($MgSO_4$), and concentrated. Purification by flash column chromatography on silica gel (hexane–EtOAc, 5:1) gave **28** (179 mg, 82%) as a pale yellow oil: $[\alpha]^{26}_D$ –50.1° (*c* 0.99, $CHCl_3$); IR (neat) 2937, 2864, 1697, 1455, 1407, 1355, 1100, 771, 736, 698 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.89, 0.90 (1:1 ratio, total 3 H, t, J = 7.3 Hz, each, due to double bond character of the C(O)–N bond in amide), 1.21–1.95 (16 H, series of m), 2.18–2.51 (4 H, m), 3.38, 3.47 (1:1 ratio, total 2 H, t, J = 6.4 and 6.9 Hz, respectively, due to double bond character of the C(O)–N bond in amide), 3.70–3.80 (2 H, m), 4.45, 4.49 (1:1 ratio, total 2 H, s, each, due to double bond character of the C(O)–N bond in amide), 5.057, 5.064 (1:1 ratio, total 1 H, $^1/_2$ AB q, J = 12.4 Hz, each, due to double bond character of the C(O)–N bond in amide), 5.16, 5.17 (1:1 ratio, total 1 H, $^1/_2$ AB q, J = 12.4 Hz, each, due to double bond character of the C(O)–N bond in amide), 7.26–7.36 (10 H, m); ^{13}C NMR ($CDCl_3$) δ 13.80, 17.35, 20.63, 23.30, 26.71, 27.68, 29.63, 29.72, 32.16, 32.41, 33.65, 33.80, 42.34, 42.51, 44.78, 44.83, 57.40, 57.73, 57.90, 58.22, 66.45, 70.19, 70.34, 72.90, 127.50, 127.55, 127.64, 127.90, 128.08, 128.39, 128.47, 137.11, 138.68, 154.22, 154.33, 210.80, 211.18; MS m/z (relative intensity) 480 (M^+ + 1, 0.4), 479 (M^+, 0.4), 434 (0.6), 388 (1.5), 366 (4), 344 (100), 322 (42), 272 (78), 238 (2), 181 (5), 150 (15), 124 (17). Anal. Calcd for $C_{30}H_{41}NO_4$: C, 75.12; H, 8.62; N, 2.92. Found: C, 75.00; H, 8.65; N, 2.93.

(3*R*,5*R*,8a*R*)-4-(Hydroxybutyl)-5-propyloctahydroindolidine [(–)-Indolizidine 239CD, (–)-4]. A stirred slurry of **28** (24 mg, 0.050 mmol) and 10% Pd–C (20 mg) in MeOH (5 mL) was hydrogenated at 1 atm for 1 h. To this reaction mixture containing the cyclized product **29** was added concd HCl (0.1 mL), and the resulting mixture was further hydrogenated at 1 atm for 1 h. The mixture was basified with 10% aqueous NaOH, filtered, and washed with MeOH (5 mL). The combined filtrates were concentrated in vacuo. The residue was dissolved in CH_2Cl_2 (10 mL), washed with brine (5 mL), and dried ($MgSO_4$). The solvent was evaporated, and the resulting residue was purified by flash column chromatography on silica gel ($CHCl_3$–10% methanolic NH_3, 20:1) to give (–)-**4** (9 mg, 75%) as a colorless oil: $[\alpha]^{26}_D$ –58.6° (*c* 0.21, MeOH); IR (neat) 3313, 2931, 2861, 2800, 1458, 1380, 1274, 1177, 1073 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.92 (3 H, t, J = 7.2 Hz), 1.07–1.93 (21 H, m), 2.40 (2 H, br s), 3.34 (1 H, br s), 3.66 (2 H, t, J = 6.6 Hz); ^{13}C NMR ($CDCl_3$) δ 14.56, 19.00, 23.13, 24.64, 25.34, 26.36, 30.01, 30.84, 32.29, 33.04, 35.86, 56.76, 58.54, 59.20, 63.02; MS m/z (relative intensity) 293 (M^+, 2), 238 (3), 210 (3), 197 (12), 196 (81), 167 (12), 166 (100); MS (CI, isobutane) m/z (relative intensity) 240 (M^+ + 1, 11), 238 (9), 196 (15), 166 (20), 143 (12), 129 (19), 115 (20), 91 (48), 79 (87), 69 (100); HRMS calcd for $C_{15}H_{29}NO$ (M^+) 239.2249, found 239.2218.

(2*R*,5*R*)-5-[4-(Benzyloxy)butyl]-*N*-[(benzyloxy)carbonyl]-2-[4-(*p*-toluenesulfonyloxy)butyl]pyrrolidine (30). To an ice-cooled and stirred mixture of **25** (555 mg, 1.26 mmol), 4-(dimethylamino)pyridine (308 mg, 2.52 mmol), and CH_2Cl_2 (5 mL) was added a solution of *p*-toluenesulfonyl chloride (289 mg, 1.51 mmol) in CH_2Cl_2 (3 mL). The ice bath was removed, and the mixture was stirred for 2 h. After addition of water (20 mL), the mixture was extracted with Et_2O (2 × 40 mL). The extract was washed with brine (40 mL), dried ($MgSO_4$), and concentrated. The residue was purified by flash column chromatography on silica gel (hexane–AcOEt, 4:1) to give **30** (628 mg, 84%) as a colorless oil: $[\alpha]^{26}_D$ –37.1° (*c* 0.95, $CHCl_3$); IR (neat) 3064, 3031, 2939, 2862, 1693, 1599, 1496, 1453, 1408, 1358, 1308, 1189, 1177, 1099, 1020, 958, 931, 817, 771, 735 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.19–1.95 (16 H, series of m), 2.45 (3 H, s), 3.38, 3.47 (1:1 ratio, total 2 H, t, J = 6.4 Hz, each, due to double bond character of the C(O)–N bond in amide), 3.64–3.83 (2 H, m), 3.93, 4.02 (1:1 ratio, total 2 H, t, J = 6.3 Hz and dd, J = 11.0, 6.1 Hz, respectively, due to double bond character of the C(O)–N bond in amide), 4.45, 4.49 (1:1 ratio, total 2 H, s, each, due to double bond character of the C(O)–N bond in amide), 5.04, 5.15 (2 H, AB q, J = 12.5 Hz), 7.28–7.36 (12 H, m), 7.78 (2 H, t, J = 7.3 Hz). Anal. Calcd for $C_{34}H_{43}NO_6S$: C, 68.78; H, 7.30; N, 2.36. Found: C, 69.08; H, 7.42; N, 2.37.

(2*R*,5*R*)-*N*-[(Benzyloxy)carbonyl]-2-[4-(benzoyloxy)butyl]-5-butylpyrrolidine (31). To an ice-cold stirred suspension of $LiAlH_4$ (20 mg, 0.53 mmol) in THF (5 mL) was added dropwise a solution of **30** (104 mg, 0.175 mmol) in THF (2 mL) under Ar. After being stirred for 2 h at rt, the mixture was cooled in an ice bath and quenched with water (1 mL). The mixture was filtered through a Celite pad and washed with Et_2O (20 mL). The combined filtrates were dried ($MgSO_4$) and concentrated to leave a syrup, which was purified by flash column chromatography on silica gel (hexane–EtOAc, 8:1) to give **31** (60 mg, 81%) as a colorless oil: $[\alpha]^{28}_D$ –53.4° (*c* 1.10, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 0.83, 0.89 (1:1 ratio, total 3 H, t, J = 6.9 Hz, each, due to double bond character of the C(O)–N bond in amide), 1.14–1.98 (16 H, series of m), 3.39, 3.47 (1:1 ratio, total 2 H, t, J = 6.5 Hz, each, due to double bond character of the C(O)–N bond in amide), 3.75, 3.80 (1:1 ratio, total 2 H, br s, each, due to double bond character of the C(O)–N bond in amide), 5.0634, 5.0633 (1:1 ratio, total 1 H, $^1/_2$ AB q, J = 12.4 Hz, each, due to double bond character of the C(O)–N bond in amide), 5.18, 5.19 (1:1 ratio, total 1 H, $^1/_2$ AB q, J = 12.4 Hz, each, due to double bond character of the C(O)–N bond in amide), 7.28–7.36 (10 H, m); MS m/z (relative intensity) 366 ($M^+ - C_4H_9$, 6), 322 (61), 288 (90), 260 (28), 216 (86), 124 (21), 91 (100); MS (CI, isobutane) m/z (relative intensity) 424 (M^+ + 1, 7), 380 (5), 316 (14), 288 (28), 260 (8), 216 (16), 181 (5), 124 (7), 91 (100).

(2*R*,5*R*)-*N*-[(Benzyloxy)carbonyl]-5-butyl-2-(4-hydroxybutyl)pyrrolidine [(–)-33]. A stirred slurry of **31** (150 mg, 0.354 mmol) and 10% Pd–C (150 mg) in MeOH (6 mL) containing concd HCl (0.1 mL) was hydrogenated at 1 atm for 1 h. The mixture was basified with 20% aqueous KOH, filtered, and washed with MeOH (5 mL). The combined filtrates were concentrated in vacuo to give (2*R*,5*R*)-5-butyl-2-(4-hydroxybutyl)pyrrolidine (**32**) as a crude oil, which was without purification dissolved in $CHCl_3$ (6 mL). To this solution was added 20% aqueous KOH (3 mL), and the mixture was cooled in an ice bath. The mixture was stirred, and a solution of (benzyloxy)carbonyl chloride (242 mg, 1.42 mmol) in $CHCl_3$ (2 mL) was added dropwise to this mixture. After being stirred for 20 min at ice-cooling, the mixture was diluted with Et_2O (50 mL) and washed with water (2 × 20 mL). The aqueous phase was dried ($MgSO_4$) and concentrated, and the resulting residue was purified by flash column chromatography on silica gel (hexane–EtOAc, 3:1) to give (–)-**33** (110 mg, 93%) as a colorless oil, which crystallized on standing in the refrigerator: mp 28–29 °C; $[\alpha]^{26}_D$ –61.1° (*c* 1.15, $CHCl_3$); IR (neat) 3418, 2958, 2932, 2860, 1696, 1680, 1456, 1408, 1355, 1104, 771, 734, 698 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.82, 0.89 (1:1 ratio, total 3 H, t, J = 7.1 Hz, each, due

to double bond character of the C(O)–N bond in amide), 1.14–2.00 (17 H, series of m), 3.52, 3.64 (1:1 ratio, total 2 H, t, J = 6.3 Hz, each, due to double bond character of the C(O)–N bond in amide), 3.71–3.85 (2 H, m), 5.05, 5.06 (1:1 ratio, total 1 H, $^1/_2$ AB q, J = 12.4 Hz, each, due to double bond character of the C(O)–N bond in amide), 5.18, 5.20 (1:1 ratio, total 1 H, $^1/_2$ AB q, J = 12.4 Hz, each, due to double bond character of the C(O)–N bond in amide), 7.30–7.36 (5 H, m); MS m/z (relative intensity) 276 (M^+ – 57, 4), 260 (6), 232 (22), 216 (23), 198 (6), 91 (100); MS (CI, isobutane) m/z (relative intensity) 334 (M^+ + 1, 3), 332 (1), 290 (11), 276 (4), 260 (6), 232 (12), 226 (5), 216 (12), 198 (9), 91 (100). Anal. Calcd for $C_{20}H_{31}NO_3$: C, 72.04; H, 9.37; N, 4.20. Found: C, 71.72; H, 9.34; N, 4.19.

(2*R*,5*R*)-*N*-[(Benzyloxy)carbonyl]-5-butyl-2-(4-oxobutyl)pyrrolidine [(–)-34]. To a stirred suspension of pyridinium dichromate (113 mg, 0.300 mmol) in CH_2Cl_2 (5 mL) was added a solution of (–)-**33** (51 mg, 0.15 mmol) in CH_2Cl_2 (3 mL). The mixture was stirred at rt for 24 h. To the reaction mixture was added Et_2O (50 mL), and the dark solid that separated was filtered through a Celite pad and washed with Et_2O (50 mL). The combined filtrates were washed with brine (30 mL), dried ($MgSO_4$), and concentrated to give an oily residue, which was subjected to flash column chromatography on silica gel (hexane–EtOAc, 6:1) to give (–)-**34** (31 mg, 61%) as a colorless oil: $[\alpha]^{27}_D$ –65.0° (*c* 1.36, $CHCl_3$); IR (neat) 2954, 2930, 2861, 2835 (sh), 2719, 1725, 1694, 1455, 1408, 1355, 1102, 772, 749, 699, 669, cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.82, 0.89 (1:1 ratio, total 3 H, t, J = 6.9 Hz, each, due to double bond character of the C(O)–N bond in amide), 1.14–2.01 (14 H, series of m), 2.30, 2.47 (1:1 ratio, total 2 H, octet, J = 7.0 Hz, each, due to double bond character of the C(O)–N bond in amide), 3.67–3.86 (2 H, m), 5.051, 5.057 (1:1 ratio, total 1 H, $^1/_2$ AB q, J = 12.5 Hz, each, due to double bond character of the C(O)–N bond in amide), 5.1782, 5.1784 (1:1 ratio, total 1 H, $^1/_2$ AB q, J = 12.5 Hz, each, due to double bond character of the C(O)–N bond in amide), 7.28–7.35 (5 H, m), 9.63, 9.76 (1:1 ratio, total 1 H, s, each, due to double bond character of the C(O)–N bond in amide); ^{13}C NMR ($CDCl_3$) δ 14.03, 14.16, 19.06, 22.58, 22.73, 26.74, 26.85, 27.73, 27.80, 28.84, 32.27, 32.33, 33.67, 43.58, 43.83, 57.27, 57.81, 57.86, 58.32, 66.52, 127.91, 127.98, 128.21, 128.47, 137.08, 154.19, 154.42, 202.03, 202.37; MS m/z (relative intensity) 331 (M^+, 0.5), 274 (10), 260 (10), 230 (28), 217 (22), 124 (5), 91 (100); HRMS calcd for $C_{20}H_{29}NO_3$ (M^+) 331.2147, found 331.2168.

(2*R*,5*R*)-*N*-[(Benzyloxy)carbonyl]-2-(7-(benzyloxy)-4-hydroxyheptyl)-5-butylpyrrolidine [(2*R*,5*R*)-35]. The Grignard reagent prepared by a standard procedure from Mg (65 mg, 2.7 mmol) and 1-(benzyloxy)-3-bromopropane (619 mg, 2.70 mmol) in THF (1 mL) was added dropwise via syringe to a stirred solution of (–)-**34** (31 mg, 0.093 mmol) in THF (5 mL) at 0 °C under Ar. After 1 h, water (50 mL) was added, and the mixture was extracted with Et_2O (3 × 50 mL). The extracts were washed with brine (50 mL) and dried ($MgSO_4$). Evaporation of the solvent and flash column chromatography on silica gel (hexane–EtOAc, 4:1) afforded (2*R*,5*R*)-**35** (38 mg, 84%) as a colorless oil: IR (neat) 3430, 3070, 3050, 3008, 2925, 2847, 1690, 1663, 1440, 1395, 1341, 1318, 1295, 1082, 758, 720, 682 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.83, 0.90 (1:1 ratio, total 3 H, due to amide rotamers), 1.21–1.93 (21 H, m), 3.47–3.52 (2 H, m) 3.59 (1 H, br s), 3.75–3.80 (2 H, m), 4.52 (2 H, s), 5.04–5.08 (1 H, m), 5.19 (1 H, dd, J = 12.4, 1.8 Hz), 7.28–7.37 (10 H, m); MS (CI, isobutane) m/z (relative intensity) 482 (M^+ + 1, 5), 480 (M^+ – 1, 4), 478 (4), 464 (8), 438 (7), 420 (8), 380 (18), 346 (100), 260 (26), 238 (24), 216 (80), 181 (12), 107 (25). Anal. Calcd for $C_{25}H_{35}N$: C, 73.56; H, 9.93; N, 3.73. Found: C, 73.19; H, 9.87; N, 3.73.

(2*R*,5*R*)-*N*-[(Benzyloxy)carbonyl]-2-(7-(benzyloxy)-4-oxoheptyl)-5-butylpyrrolidine [(–)-36]. To a stirred suspension of pyridinium dichromate (68 mg, 0.18 mmol) in CH_2Cl_2 (3 mL) was added a solution of (2*R*,5*R*)-**35** (35 mg, 0.073 mmol) in CH_2Cl_2 (3 mL). The mixture was stirred at rt for 24 h. To the reaction mixture was added Et_2O (20 mL), and the dark solid that separated was filtered through a Celite pad and washed with Et_2O (20 mL). The combined filtrates were washed with brine (15 mL), dried ($MgSO_4$), and concentrated to give an oily residue, which was subjected to flash column chromatography on silica gel (hexane–EtOAc, 4:1) to give (–)-**36** (33 mg, 95%) as a colorless oil: $[\alpha]^{25}_D$ –52.7° (*c* 1.06, $CHCl_3$); IR (neat) 3070, 3035, 2960, 2925 (sh), 2838, 1715, 1690, 1492, 1450, 1356, 1325, 1304, 1300, 764, 750, 736, 698 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.83, 0.89 (1:1 ratio, total 3 H, t, J = 6.9 Hz, each, due to double bond character of the C(O)–N bond in amide), 1.14–1.99 (16 H, series of m), 2.26, 2.45 (1:1 ratio, total 2 H, m, each, due to double bond character of the C(O)–N bond in amide), 2.42, 2.50 (1:1 ratio, total 2 H, t, J = 7.2 Hz, each, due to double bond character of the C(O)–N bond in amide), 3.46 (2 H, dd, J = 10.8, 5.9 Hz), 3.69–3.83 (2 H, m), 4.47 (2 H, s), 5.06, 5.18 (2 H, AB q, J = 12.5 Hz), 7.26–7.37 (10 H, m); ^{13}C NMR ($CDCl_3$) δ 14.03, 14.16, 20.65, 22.58, 22.73, 23.95, 26.73, 27.70, 28.84, 32.17, 32.34, 33.67, 39.46, 42.44, 42.61, 57.37, 57.84, 58.29, 66.45, 69.42, 72.92, 127.62, 127.69, 127.87, 127.95, 128.09, 128.43, 137.13, 138.52, 154.22, 154.37, 210.32, 210.66; MS m/z (relative intensity) 479 (M^+, 0.3), 422 (1.6), 378 (50), 344 (100), 260 (14), 238 (21), 216 (71).

(3*R*,5*S*,8a*R*)-3-Butyl-5-(3-hydroxypropyl)octahydroindolidine [(–)-Indolizidine 239AB, (–)-3]. In a manner similar to that described for the cyclization of **28**, a solution of (–)-**36** (21 mg, 0.043 mmol) in MeOH (3 mL) was hydrogenated over 10% Pd–C (20 mg) at 1 atm for 1 h. To the mixture was added concd HCl (0.1 mL), and hydrogenation was continued for another 1 h. Workup and flash column chromatography on silica gel ($CHCl_3$–10% methanolic NH_3, 20:1) gave a mixture of (–)-**3** and the C-5 epimer as a pale yellow oil (10 mg, 96%) in a ratio of 88:12 (by ^{1}H NMR). Further chromatography of this mixture on silica gel ($CHCl_3$–10% methanolic NH_3, 20:1) provided (–)-**3** (8.0 mg, 78%) as a colorless oil: $[\alpha]^{25}_D$ –87.5° (*c* 0.16, MeOH) [lit.[6] $[\alpha]^{16}_D$ –38° (*c* 1.0, MeOH)]; IR (neat) 3364, 2928, 2859, 2819, 2720, 2600 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.91 (3 H, t, J = 7.1 Hz), 1.06–1.93 (21 H, series of m), 2.37–3.44 (1 H, m), 2.56 (1 H, sext, J = 4.5 Hz), 3.28 (1 H, br t, J = 8.9 Hz), 3.52 (1 H, dt, J = 11.2, 3.0 Hz), 3.68 (1 H, dt, J = 11.2, 4.5 Hz), 5.47 (1 H, br s); ^{13}C NMR ($CDCl_3$) δ 14.14, 22.93, 24.51, 24.86, 26.12, 27.89, 29.02, 29.30, 29.83, 30.96, 31.67, 54.85, 58.56, 59.03, 63.34; MS m/z (relative intensity) 239 (M^+, 1), 238 (2), 183 (12), 182 (100), 181 (12), 180 (90); HRMS calcd for $C_{15}H_{29}NO$ (M^+) 239.2249, found 239.2222.

(–)-**3**-HCl: $[\alpha]^{27}_D$ –72.0° (*c* 0.35, MeOH); ^{1}H NMR ($CDCl_3$) δ 0.92 (3 H, t, J = 6.4 Hz), 1.24–2.48 (20 H, m), 2.96 (2 H, br s), 3.65 (2 H, t, J = 5.4 Hz), 3.70 (1 H, m), 3.90 (1 H, br s); ^{13}C NMR ($CDCl_3$) δ 13.89, 22.40, 23.13, 25.05, 26.73, 27.30, 27.53, 27.63, 27.74, 28.11 (2 C), 59.89, 60.37, 61.67, 63.22.

(2*R*,5*R*)-*N*-[(Benzyloxy)carbonyl]-2-(4-hydroxypentyl)-5-butylpyrrolidine [(2*R*,5*R*)-37]. In a manner similar to that described for the preparation of **26**, a solution of (–)-**34** (46 mg, 0.14 mmol) in THF (5 mL) was allowed to react with a 0.95 M solution of methylmagnesium bromide (0.15 mL, 0.14 mmol) in THF. Workup and purification of the crude product by flash column chromatography on silica gel (hexane–EtOAc, 2:1) gave (2*R*,5*R*)-**37** (43 mg, 88%) as a colorless oil: IR (neat) 3407, 2955, 2931, 2862, 1698, 1682, 1457, 1408, 1356, 1101, 698, 673 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.82, 0.89 (1:1 ratio, total 3 H, t, J = 6.8 Hz, each, due to double bond character of the C(O)–N bond in amide), 1.10–1.94 (20 H, series of m), 3.68 (1 H, m), 3.75–3.80 (2 H, m), 5.06, 5.18 (2 H, AB q, J = 12.4 Hz), 7.26–7.35 (5 H, m); ^{13}C NMR ($CDCl_3$) δ 14.03, 14.16, 22.50, 22.60, 22.75, 22.91, 23.07, 23.59, 23.69, 26.76, 26.88, 27.75, 28.87, 32.39, 32.57, 32.70, 33.73, 33.97, 34.11, 39.01, 39.14, 57.59, 57.69, 57.84, 58.08, 58.29, 66.48, 67.85, 68.06, 127.90, 128.01, 128.12, 128.47, 137.20, 154.33, 154.46; MS m/z (relative intensity) 290 (M^+ – C_4H_9, 1), 260 (3), 246 (8), 212 (6), 138 (2), 91 (100); MS (CI, isobutane) m/z (relative intensity) 348 (M^+ + 1, 2), 330 (2), 304 (3), 290 (3), 260 (44), 246 (8), 216 (12), 212 (10), 194 (2), 170 (1), 138 (3), 91 (100). Anal. Calcd for $C_{21}H_{33}NO_3$: C, 72.59; H, 9.57; N, 4.03. Found: C, 72.21; H, 9.54; N, 4.01.

(2*R*,5*R*)-*N*-[(Benzyloxy)carbonyl]-5-butyl-2-(4-oxopentyl)pyrrolidine [(–)-39]. In a manner similar to that described for the preparation of (–)-**36**, (2*R*,5*R*)-**37** (42 mg, 0.12 mmol) was oxidized with pyridinium dichromate (113 mg, 0.300 mmol). Workup and flash column chromatography on silica gel (hexane–EtOAc, 2:1) gave (–)-**39** (38 mg, 92%) as a colorless oil: $[\alpha]^{23}_D$ –62.9° (*c* 0.94, $CHCl_3$); IR (neat) 2957, 2936, 2873, 1710 (sh), 1697, 1456, 1407, 1355, 1102, 911, 771, 749, 699 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.82, 0.89 (1:1 ratio, total 3 H, t, J = 6.7 Hz, each, due to double bond character of the C(O)–N bond in amide), 1.23–3.17 (total 19 H, series of m, including total 3 H, s, each, in 1:1 ratio, at δ 2.03, 2.12, due to double bond character of the C(O)–N bond in amide), 3.72–3.79 (2 H, m), 5.06, 5.17 (2 H, AB q, J = 12.4 Hz),

7.26–7.35 (5 H, m); ^{13}C NMR ($CDCl_3$) δ 14.04, 14.16, 20.71, 22.61, 22.75, 26.82, 27.76, 28.87, 32.20, 32.38, 33.65, 33.72, 43.34, 43.52, 57.40, 57.89, 58.34, 66.51, 127.91, 127.98, 128.17, 128.50, 137.18, 154.25, 154.43, 208.49, 208.89. Anal. Calcd for $C_{21}H_{31}NO_3$: C, 73.01; H, 9.04; N, 4.05. Found: C, 72.61; H, 9.00; N, 4.04.

(3*R*,5*R*,8a*R*)-3-Butyl-5-methyloctahydroindolidine [(−)-Indolizidine 195B, (−)-1]. A solution of (−)-**39** (38 mg, 0.11 mmol) in MeOH (10 mL) was hydrogenated over 10% Pd–C (40 mg) at 1 atm for 30 min. Filtration of the mixture and concentration of the filtrate provided an oily residue. This was purified by column chromatography of this mixture on Al_2O_3 (hexane–$CHCl_3$, 3:1) to give a mixture of (−)-1 and its C-5 epimer in an 89:11 ratio (by ^{1}H NMR) as a colorless oil (19 mg, 89%). Further column chromatography on Al_2O_3 (hexane–$CHCl_3$, 3:1) provided (−)-1 (17 mg, 79%) as a colorless oil: $[\alpha]^{24}_D$ −101.3° (*c* 0.15, MeOH) [lit.[4b] $[\alpha]^{22}_D$ −97.1° (*c* 0.12, MeOH)]; ^{1}H NMR ($CDCl_3$) δ 0.89 (3 H, t, *J* = 7.2 Hz), 0.98–1.92 (total 19 H, m, including 3 H, d, *J* = 6.2 Hz, at δ 1.08), 2.37 (1 H, m), 2.50 (1 H, m), 3.26 (1 H, br t, *J* = 8.0 Hz); ^{13}C NMR ($CDCl_3$) δ 14.26, 20.56, 23.09, 24.84, 24.96, 26.47, 29.28, 30.17, 32.56, 34.71, 52.02, 58.84, 59.03; MS *m*/*z* (relative intensity) 195 (M^+, 1), 194 (2), 180 (5), 139 (11), 138 (100), 124 (4); MS (CI, isobutane) *m*/*z* (relative intensity) 196 (M^+ + 1, 40), 195 (M^+, 12), 194 (20), 139 (16), 138 (100), 129 (16), 91 (52); HRMS calcd for $C_{12}H_{22}N$ ($M^+ - CH_3$) 180.1752, found 180.1735.

(2*R*,5*R*)-*N*-[(Benzyloxy)carbonyl]-2-(4-hydroxyheptyl)-5-butylpyrrolidine [(2*R*,5*R*)-38]. In a manner similar to that described for the preparation of **26**, a solution of (−)-**34** (25 mg, 0.075 mmol) in THF (3 mL) was allowed to react with a 0.48 M solution of propylmagnesium bromide (0.50 mL, 0.24 mmol). Workup and purification of the crude product by flash column chromatography on silica gel (hexane–EtOAc, 5.5:1) gave (2*R*,5*R*)-**38** (25 mg, 88%) as a colorless oil: IR (neat) 3360, 2955, 2931, 2871, 1698, 1682, 1456, 1409, 1356, 1102, 846, 772, 748, 698 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.72–0.93 (6 H, m), 1.14–2.09 (21 H, series of m), 3.49, 3.60 (1:1 ratio, total 1 H, br s, each, due to double bond character of the C(O)–N bond in amide), 3.74–3.81 (2 H, m), 5.05, 5.18 (1 H, $^1/_2$ AB q, *J* = 12.4 Hz), 5.06, 5.20 (1 H, $^1/_2$ AB q, *J* = 12.4 Hz), 7.28–7.35 (5 H, m); ^{13}C NMR ($CDCl_3$) δ 14.05, 14.19, 18.89, 22.40, 22.61, 22.67, 22.76, 22.87, 23.06, 26.75, 26.86, 27.73, 28.88, 32.39, 32.60, 32.77, 33.73, 34.03, 34.20, 37.18, 37.31, 39.82, 39.97, 57.61, 57.74, 57.84, 58.09, 58.29, 66.47, 71.49, 71.69, 127.90, 128.01, 128.08, 128.48, 137.16, 154.34, 154.47; MS *m*/*z* (relative intensity) 318 ($M^+ - C_4H_9$, 2), 274 (12), 260 (8), 241 (16), 216 (24), 166 (6), 91 (100); MS (CI, isobutane) *m*/*z* (relative intensity) 376 (M^+ + 1, 7), 358 (9), 332 (7), 318 (3), 274 (10), 268 (11), 260 (9), 240 (25), 216 (23), 166 (6), 91 (100); HRMS calcd for $C_{19}H_{28}NO_3$ ($M^+ - C_4H_9$) 318.2071, found 318.2054. Anal. Calcd for $C_{23}H_{37}NO_3$: C, 73.56; H, 9.93; N, 3.73. Found: C, 73.19; H, 9.87; N, 3.73.

(2*R*,5*R*)-*N*-[(Benzyloxy)carbonyl]-5-butyl-2-(4-oxoheptyl)pyrrolidine [(−)-40]. In a manner similar to that described for the preparation of (−)-**34**, (2*R*,5*R*)-**38** (25 mg, 0.067 mmol) was oxidized with pyridinium dichromate (66 mg, 0.17 mmol). Workup and flash column chromatography on silica gel (hexane–EtOAc, 7:1) gave (−)-**40** (20 mg, 80%) as a colorless oil: $[\alpha]^{26}_D$ −58.5° (*c* 1.00, $CHCl_3$); IR (neat) 2957, 2940, 2873, 1698, 1407, 1355, 1101, 834, 771, 734, 698 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.80–0.92 (6 H, m), 1.13–1.99 (16 H, m), 2.16–2.51 (2 H, m), 2.27, 2.36 (1:1 ratio, total 2 H, t, *J* = 7.3 Hz, each, due to double bond character of the C(O)–N bond in amide), 3.70–3.80 (2 H, m), 5.059, 5.065 (1:1 ratio, total 1 H, $^1/_2$ AB q, *J* = 12.5 Hz, each, due to double bond character of the C(O)–N bond in amide), 5.1718, 5.1719 (1:1 ratio, total 1 H, $^1/_2$ AB q, *J* = 12.5 Hz, each, due to double bond character of the C(O)–N bond in amide), 7.29–7.36 (5 H, m); ^{13}C NMR ($CDCl_3$) δ 13.83, 14.05, 14.18, 17.38, 20.68, 22.61, 22.75, 26.76, 27.72, 28.86, 32.22, 32.36, 33.71, 42.40, 42.57, 44.83, 44.87, 57.42, 57.88, 57.91, 58.32, 66.48, 127.90, 127.94, 127.97, 128.12, 128.48, 137.16, 154.26, 154.41, 210.86, 211.24; MS *m*/*z* (relative intensity) 316 ($M^+ - C_4H_9$, 1.3), 272 (21), 238 (26), 216 (16); MS (CI, isobutane) *m*/*z* (relative intensity) 374 (M^+ + 1, 12), 330 (9), 272 (17), 266 (26), 238 (41), 216 (15), 91 (100). Anal. Calcd for $C_{23}H_{35}NO_3$: C, 73.96; H, 9.44; N, 3.75. Found: C, 73.71; H, 9.45; N, 3.80.

(3*R*,5*R*,8a*R*)-3-Butyl-5-propyloctahydroindolidine [(−)-Indolizidine 223AB, (−)-2]. In a manner similar to that described for the preparation of (−)-1, a solution of (−)-**40** (20 mg, 0.054 mmol) in MeOH (5 mL) was hydrogenated over 10% Pd–C (20 mg). Workup and purification by flash column chromatography on Al_2O_3 (hexane–$CHCl_3$, 3:1) gave a mixture of (−)-**2** and the C-5 epimer in an 86:14 ratio (by ^{1}H NMR) as a pale yellow oil (17 mg, 99%). Further column chromatography of this mixture on Al_2O_3 (hexane–$CHCl_3$, 3:1) provided (−)-**2** (9.7 mg, 80%) as a colorless oil: $[\alpha]^{25}_D$ −97.7° (*c* 0.43, hexane) [lit.[4a] $[\alpha]^{27}_D$ −44° (*c* 1.0, hexane), lit.[6] $[\alpha]^{20}_D$ −101° (*c* 2.3, hexane)]; $[\alpha]^{28}_D$ −89.2° (*c* 0.25, MeOH) [lit.[5] $[\alpha]^{16}_D$ −35° (*c* 0.49, MeOH)]; ^{1}H NMR ($CDCl_3$) δ 0.88–0.93 (6 H, m), 0.99–1.92 (20 H, series of m), 2.34–2.40 (2 H, m), 3.30 (1 H, br t, *J* = 8.7 Hz); ^{13}C NMR ($CDCl_3$) δ 14.20, 14.57, 19.03, 23.00, 24.73, 25.03, 26.44, 29.19, 30.13, 31.04, 32.47, 35.95, 56.66, 58.57, 59.06; MS *m*/*z* (relative intensity) 223 (M^+, 2), 222 (3), 181 (12), 180 (93), 167 (12), 166 (100); MS (CI, isobutane) *m*/*z* (relative intensity) 224 (M^+ + 1, 16), 223 (M^+, 11), 222 (14), 181 (12), 180 (83), 167 (14), 166 (100).

(−)-**2**·HCl: ^{1}H NMR ($CDCl_3$) δ 0.93 (3 H, t, *J* = 7.0 Hz), 0.94 (3 H, t, *J* = 7.3 Hz), 1.18–2.22 (19 H, series of m), 2.51 (1 H, dt, *J* = 14.8, 7.0 Hz), 2.78–2.88 (1 H, m), 2.93 (1 H, quint, *J* = 9.5 Hz), 3.88 (1 H, br s); ^{13}C NMR ($CDCl_3$) δ 13.72, 13.84, 18.89, 22.39, 23.20, 25.09, 26.65, 27.46, 27.61, 27.70, 28.06, 32.69, 59.90, 60.07, 63.14.

(5*R*,8*R*)-12-(Benzoyloxy)-5,8-bis[(*tert*-butyldimethylsilyl)oxy]-1-dodecanol (42). To a cold (0 °C) stirred mixture of **41** (2.01 g, 4.34 mmol), 4-(dimethylamino)pyridine (1.06 g, 8.68 mmol), and CH_2Cl_2 (20 mL) was added a solution of benzoyl chloride (756 mg, 5.64 mmol) in CH_2Cl_2 (5 mL). The mixture was stirred at rt for 1.5 h and diluted with Et_2O (200 mL). This was washed with water (50 mL) and then brine (50 mL), dried ($MgSO_4$), and concentrated. The residue was purified by flash column chromatography on silica gel (hexane–EtOAc, 4:1) to give (5*R*,8*R*)-1,12-bis(benzoyloxy)-5,8-bis[(*tert*-butyldimethylsilyl)oxy]-1-dodecanol (**43**) (1.14 g, 41%) and **42** (1.14 g, 46%) both as colorless oil. Compound **43** (1.14 g, 1.78 mmol) thus obtained was dissolved in 6:1 THF–MeOH (20 mL). The solution was cooled to 0 °C and stirred. To this was added 10% aqueous NaOH (10 mL), and the mixture was stirred at 0 °C for 1.5 h. To the mixture was added Et_2O (100 mL) and brine (50 mL), and the two liquid phases of the mixture were separated. The aqueous phase was extracted with Et_2O (2 × 100 mL). The organic phase and the extracts were combined, and the solution was washed with brine (40 mL), dried ($MgSO_4$), and concentrated. The crude product was purified by flash column chromatography on silica gel (hexane–EtOAc, 4:1) to give **42** (0.45 g, 44%) as colorless oil. Thus, total yield of **42** was 1.59 g (65%). Data for **42**: $[\alpha]^{24}_D$ +6.43° (*c* 0.56, $CHCl_3$); IR (neat) 3427, 2958, 2930, 2857, 1723, 1463, 1453, 1275, 1256, 1113, 1070, 1006, 836, 774, 712 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.03 (12 H, s), 0.88 (18 H, s), 1.26–1.61 (15 H, m), 1.77 (2 H, quint, *J* = 6.2 Hz), 3.62–3.65 (2 H, m), 4.32 (2 H, t, *J* = 6.6 Hz), 7.43 (2 H, t, *J* = 7.7 Hz), 7.55 (1 H, t, *J* = 7.4 Hz), 8.04 (2 H, m); ^{13}C NMR ($CDCl_3$) δ −4.30, 18.20, 21.48, 21.92, 26.01, 29.12, 32.72, 32.85, 33.10, 36.78, 36.94, 63.06, 65.10, 72.34, 72.40, 128.39, 129.65, 130.65, 132.86, 166.76. Anal. Calcd for $C_{31}H_{58}O_5Si_2$: C, 65.67; H, 10.31. Found: C, 65.54; H, 10.31.

(5*R*,8*R*)-1-(Benzoyloxy)-12-bromo-5,8-bis[(*tert*-butyldimethylsilyl)oxy]dodecane (44). To a cold (0 °C) stirred mixture of **42** (1.59 g, 2.80 mmol), CBr_4 (2.32 g, 7.00 mmol), and CH_2Cl_2 (30 mL) was added triphenylphosphine (1.83 g, 7.00 mmol). After being stirred at 0 °C for 10 min, the mixture was condensed, and hexane (100 mL) was added to the oily residue. The solid (Ph_3PO) that separated was removed by filtration, and the filtrate was condensed to leave a crude oil, which was purified by flash column chromatography on silica gel (hexane–EtOAc, 20:1) to give **44** (1.62 g, 92%) as a pale yellow oil: $[\alpha]^{24}_D$ + 5.33° (*c* 1.67, $CHCl_3$); IR (neat) 2953, 2922, 2900 (sh), 2857, 1723, 1472, 1463, 1274, 1256, 1112, 1070, 1028, 1006, 836, 806, 774, 712 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.04 (12 H, s), 0.880 (9 H, s), 0.881 (9 H, s), 1.36–1.54 (12 H, series of m), 1.75–1.86 (4 H, m), 3.39 (2 H, t, *J* = 6.8 Hz), 3.64 (2 H, quint, *J* = 4.8 Hz), 4.32 (2 H, t, *J* = 6.6 Hz), 7.43 (2 H, m), 7.55 (1 H, tt, *J* = 7.4, 1.3 Hz), 8.05 (2 H, m); ^{13}C NMR ($CDCl_3$) δ −4.32, 18.19, 21.92, 24.02, 26.00, 29.13, 32.76, 32.81, 33.12, 33.77, 36.24, 36.82, 65.08, 72.22, 72.30, 128.39, 129.64, 130.65, 132.86, 166.73; MS *m*/*z* (relative intensity) 574 ($M^+ + 2 - C_4H_9$, 0.2), 573 (1, $M^+ + 1 - C_4H_9$), 572 ($M^+ - C_4H_9$, 0.2), 571 (0.8), 361 (6), 321 (8), 245 (12), 243 (13), 179 (100), 105 (98). Anal. Calcd for $C_{31}H_{57}BrO_4Si_2$: C, 59.11; H, 9.12. Found: C, 59.51; H, 9.20.

(5*R*,8*R*)-1-(Benzoyloxy)-5,8-bis[(*tert*-butyldimethylsilyl)oxy]dodecane (45). A mixture of **44** (131 mg, 0.21 mmol), Et_3N (42 mg, 0.42 mmol), and MeOH (5 mL) was hydrogenated over 10% Pd–C (100 mg) at 1 atm for 1 h. Filtration of the mixture and concentration of the filtrate provided an oily residue, which was dissolved in Et_2O (100 mL), washed with water (50 mL) and then brine (50 mL), and dried ($MgSO_4$). Evaporation of the solvent and purification of the residue by flash column chromatography on silica gel (hexane–EtOAc, 30:1) gave **45** (6 mg, 84%) as a colorless oil: $[\alpha]^{24}_D$ + 6.21° (*c* 1.68, $CHCl_3$); IR (neat) 2958, 2930, 2900 (sh), 2858, 1724, 1463, 1453, 1361, 1315, 1274, 1070, 1006, 939, 836, 774, 711 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.030 (3 H, s), 0.039 (6 H, s), 0.043 (6 H, s), 0.88 (18 H, s), 0.89 (3 H, t, *J* = 7.2 Hz), 1.29–1.57 (14 H, series of m), 1.77 (2 H, quint, *J* = 6.4 Hz), 3.58–3.67 (2 H, m), 4.33 (2 H, t, *J* = 6.6 Hz), 7.43 (2 H, m), 7.54 (1 H, tt, *J* = 7.4, 1.3 Hz), 8.05 (2 H, m); ^{13}C NMR ($CDCl_3$) δ −4.31, 14.17, 18.20, 21.96, 22.98, 26.01, 27.59, 29.14, 32.75, 32.88, 36.80, 36.94, 65.11, 72.39, 72.54, 128.38, 129.65, 130.67, 132.84, 166.73; MS *m/z* (relative intensity) 535 ($M^+ - CH_3$, 0.6), 493 ($M^+ - C_4H_9$, 3), 417 (0.5), 361 (10), 297 (8), 201 (15), 179 (100), 105 (98). Anal. Calcd for $C_{31}H_{58}O_4Si_2$: C, 67.58; H, 10.61. Found: C, 67.35; H, 10.58.

(5*R*,8*R*)-1-(Benzoyloxy)-5,8-dodecanediol (46). A mixture of **45** (340 mg, 0.62 mmol) and a 1 M solution of tetrabutylammonium fluoride (2.00 mL, 2.00 mmol) in THF was stirred at rt for 2 h. The mixture was diluted with Et_2O (150 mL), and the solution was washed with 1% HCl (50 mL) and then brine (50 mL) and dried ($MgSO_4$). Evaporation of the solvent and purification of flash column chromatography on silica gel (hexane–EtOAc, 1:1) gave colorless crystals, which were recrystallized from CH_2Cl_2–hexane to give **46** (182 m, 91%) as a colorless needles: mp 57–58 °C; $[\alpha]^{24}_D$ −3.96° (*c* 1.14, $CHCl_3$); IR (neat) 3263, 2960, 2942, 2905, 1721, 1451, 1314, 1275, 1122, 1069, 1029, 957, 855, 709 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.90 (3 H, t, *J* = 6.9 Hz), 1.30–1.70 (14 H, series of m), 1.79 (2 H, m), 2.19 (1 H, br s), 2.47 (1 H, br s), 3.62 (2 H, m), 4.33 (2 H, t, *J* = 6.6 Hz), 7.43 (2 H, t, *J* = 7.7 Hz), 7.55 (1 H, t, *J* = 7.4 Hz), 8.04 (2 H, m); ^{13}C NMR ($CDCl_3$) δ 14.11, 22.39, 22.81, 27.99, 28.90, 34.02, 34.22, 37.41, 37.61, 64.99, 72.08, 72.39, 128.42, 129.65, 130.59, 132.91, 166.78; MS *m/z* (relative intensity) 247 ($M^+ - 75$, 7), 207 (3), 127 (19), 123 (31), 105 (100); MS (CI, isobutane) *m/z* (relative intensity) 305 ($M^+ - OH$, 0.3), 303 (0.2), 247 (0.8), 207 (0.3), 183 (4.5), 165 (2.3), 127 (2), 123 (32), 109 (3.1), 105 (9.7), 58 (100). Anal. Calcd for $C_{19}H_{30}O_4$: C, 70.77; H, 9.38. Found: C, 70.62; H, 9.33.

(5*R*,8*R*)-1-(Benzoyloxy)-5,8-dodecanediol Cyclic Sulfate (47). In a manner similar to that described for the preparation of (+)-**19**, a mixture of **46** (158 mg, 0.490 mmol) and CH_2Cl_2 (2 mL) was treated with a solution of $SOCl_2$ (87 mg, 0.73 mmol). After workup the residue was dissolved in 2:1:1 CCl_4–MeCN–H_2O (8 mL), and the solution was treated with $RuCl_3 \cdot xH_2O$ (10 mg) and $NaIO_4$ (419 mg, 1.96 mmol) at 0 °C for 2 h. Workup and flash column chromatography on silica gel (hexane–EtOAc, 6:1) provided **47** (181 mg, 96%) as a colorless oil: $[\alpha]^{24}_D$ −11.7° (*c* 1.54, $CHCl_3$); IR (neat) 2957, 2940, 2871, 1718, 1453, 1387, 1315, 1275, 1196, 1114, 1071, 1027, 948, 899, 825, 714, 689, 676 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.91 (3 H, t, *J* = 7.2 Hz), 1.26–2.00 (16 H, m), 4.33 (2 H, dt, *J* = 6.4, 1.3 Hz), 4.64 (2 H, m), 7.44 (2 H, m), 7.56 (1 H, tt, *J* = 7.4, 1.3 Hz), 8.04 (2 H, m); ^{13}C NMR ($CDCl_3$) δ 13.89, 21.79, 22.28, 27.24, 28.27, 30.01, 33.08, 35.06, 35.21, 64.51, 84.67, 85.33, 128.45, 129.67, 130.47, 132.97, 166.70; MS *m/z* (relative intensity) 286 ($M^+ - H_2SO_4$, 0.6), 247 (2), 205 (0.7), 164 (22), 135 (11), 105 (100). Anal. Calcd for $C_{19}H_{28}O_6S$: C, 59.35; H, 7.34. Found: C, 59.56; H, 7.39.

Reaction of 47 with Lithium Azide. In a manner similar to that described for the preparation of **21a** and **21b**, a solution of **47** (180 mg, 0.47 mmol) in DMF (3 mL) was treated with LiN_3 (34 mg, 0.69 mmol) for 30 min. After workup the product was dissolved in THF (5 mL), and the solution was treated with water (0.1 mL) and then concd H_2SO_4 (0.1 mL) at rt for 30 min. Workup and flash column chromatography on silica gel (hexane–EtOAc, 4:1) gave a 1:1 mixture of (5*S*,8*R*)-8-azido-1-(benzoyloxy)-5-dodecanol (**49a**) and (5*S*,8*R*)-8-azido-12-(benzoyloxy)-5-dodecanol (**49b**) (total: 150 mg, 92%) as a pale yellow oil: IR (neat) 3426, 2966 (sh), 2934, 2861, 2098, 1721, 1452, 1315, 1276, 1177, 1116, 1071, 1027 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.91 (total 6 H, t, *J* = 7.0 Hz), 1.26–1.87 (total 34 H, m), 3.23–3.34 (total 2 H, m), 3.62 (total 2 H, m), 4.34 (total 4 H, t, *J* = 6.5 Hz), 7.44 (total 4 H, m), 7.56 (total 2 H, m), 8.05 (total 4 H, m); ^{13}C NMR ($CDCl_3$) δ 13.99, 14.07, 22.26, 22.57, 22.76, 27.84, 28.28, 28.63, 28.84, 30.81, 30.82, 33.97, 34.12, 34.21, 34.25, 37.28, 37.47, 63.22, 63.39, 64.70, 64.89, 71.67, 71.88, 128.41, 129.61, 130.47, 130.53, 132.91, 132.93, 166.68, 166.73; MS *m/z* (relative intensity) 302 ($M^+ - N_2 - OH$, 5), 273 (3), 258 (5), 180 (16), 142 (5), 123 (16), 105; MS (CI, isobutane) *m/z* (relative intensity) 344 ($M^+ - 3$ H, 5), 320 (9), 305 (10), 304 (35), 303 (34), 301, (6), 300 (8), 273 (5), 258 (4), 238 (4), 222 (5), 199 (6), 198 (22), 196 (10), 181 (38), 180 (34), 123 (88), 105 (100). Anal. Calcd for $C_{19}H_{29}N_3O_3$: C, 65.68; H, 8.41; N, 12.09. Found: C, 65.39; H, 8.36; N, 12.06.

Mesylation of 51a and 51b. In a manner similar to that described for the mesylation of **23a** and **23b**, a solution of the 1:1 mixture (140 mg, 0.40 mmol) of **49a** and **49b**, obtained by the reaction described above, in CH_2Cl_2 (5 mL) including Et_3N (81 mg, 0.80 mmol) was treated with methanesulfonyl chloride (69 mg, 0.60 mmol). Workup and flash column chromatography on silica gel (hexane–EtOAc, 2:1) gave a 1:1 mixture of (5*S*,8*R*)-8-azido-1-(benzoyloxy)-5-(methanesulfonyloxy)dodecane (**50a**) and (5*S*,8*R*)-8-azido-1-(benzyloxy)-5-(methanesulfonyloxy)dodecane (**50b**) (total: 170 mg, 100%) as a pale yellow oil: IR (neat) 2964, 2956, 2871, 2099, 1718, 1453, 1353, 1276, 1175, 1116, 906, 715 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.91 (total 6 H, m), 1.36 (total 8 H, m), 1.46–1.93 (total 24 H, m), 2.990, 2995 (1:1 ratio, total 6 H, s, each), 3.22–3.33 (total 2 H, series of m), 4.34 (total 4 H, dt, *J* = 6.5, 1.7 Hz), 4.73 (total 2 H, m), 7.43 (total 4 H, m), 7.55 (total 2 H, dt, *J* = 7.4, 1.2 Hz), 8.03 (total 4 H, m); ^{13}C NMR ($CDCl_3$) δ 13.88, 13.94, 21.60, 22.45, 22.49, 22.72, 27.10, 28.21, 28.50, 28.57, 29.91, 31.10, 31.15, 34.09, 34.12, 34.17, 34.27, 38.80, 62.65, 62.78, 64.45, 64.57, 82.74, 83.26, 128.40, 129.58, 130.39, 130.43, 132.93, 132.95, 166.60; MS *m/z* (relative intensity) 319 ($M^+ + 1 - CH_3SO_2 - N_2$, 0.3), 318 (2), 303 (0.7), 302 (3), 301 (2), 300 (1), 259 (5), 196 (10), 180 (25), 152 (10), 124 (23), 105 (100); MS (CI, isobutane) *m/z* (relative intensity) 344 ($M^+ - H_2 - CH_3SO_2$, 5), 342 (4), 305 (2), 304 (10), 303 (26), 302 (100), 301 (5), 300 (7), 259 (5), 206 (4), 180 (60), 152 (7), 123 (30), 105 (85). Anal. Calcd for $C_{20}H_{31}N_3O_5S$: C, 56.45; H, 7.34; N, 9.87. Found: C, 56.49; H, 7.40; N, 9.55.

(2*S*,5*S*)-*N*-[(Benzyloxy)carbonyl]-2-[4-(benzoyloxy)butyl]-5-butylpyrrolidine (52). A solution of the 1:1 mixture (170 mg, 0.399 mmol) of **50a** and **50b**, obtained by the reaction described above, in MeOH (10 mL) was hydrogenated over 10% Pd–C (170 mg) for 1 h. Filtration and evaporation of the solvent afforded a crude product of (2*S*,5*S*)-2-[4-(benzoyloxy)butyl]-5-butylpyrrolidine (**51**), which was, without purification, dissolved in CH_2Cl_2 (10 mL). In a manner similar to that described for the preparation of **25**, the solution was treated with 20% aqueous K_2CO_3 (10 mL) and a solution of (benzyloxy)carbonyl chloride (136 mg, 0.797 mmol) in CH_2Cl_2 (3 mL). Workup and purification by flash column chromatography on silica gel (hexane–EtOAc, 8:1) gave **52** (141 mg, 81%) as a colorless oil: $[\alpha]^{26}_D$ +45.8° (*c* 1.47, $CHCl_3$); IR (neat) 3100, 3075, 3040, 2957, 2930 (sh), 2860, 1720, 1698, 1602, 1586, 1498, 1453, 1407, 1354, 1274, 1194, 1176, 1111, 1028, 955, 910, 771, 676, 606 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.83, 0.90 (1:1 ratio, total 3 H, t, *J* = 6.7 Hz, each, due to double bond character of the C(O)–N bond in amide) 1.21–1.96 (16 H, series of m), 3.76–3.83 (2 H, m), 4.24, 4.32 (1:1 ratio, total 2 H, t, *J* = 6.5 Hz, and dt, *J* = 6.5, 4.7 Hz, respectively, due to double bond character of the C(O)–N bond in amide), 5.07, 5.19 (2 H, AB q, *J* = 12.4 Hz), 7.26–7.36 (5 H, m), 7.44 (2 H, t, *J* = 7.2 Hz), 7.54 (1 H, m), 8.04 (2 H, m); ^{13}C NMR ($CDCl_3$) δ 14.02, 14.14, 22.58, 22.72, 23.23, 26.75, 26.82, 27.73, 28.65, 28.84, 32.37, 32.43, 32.72, 33.78, 57.51, 57.81, 58.05, 58.28, 64.79, 65.00, 66.48, 127.88, 127.92, 128.00, 128.06, 128.38, 128.45, 129.60, 130.60, 132.82, 137.15, 154.28, 154.39, 166.68; MS *m/z* (relative intensity) 437 (M^+, 0.1), 381 (5), 380 (17), 337 (26), 336 (100), 303 (7), 302 (36), 260 (45), 217 (16), 216 (95), 180 (3), 124 (53), 105 (73); MS (CI, isobutane) *m/z* (relative intensity) 438 ($M^+ + 1$, 39), 437 (M^+, 3), 395 (7), 394 (21), 381 (7), 380 (22), 337 (16), 336 (65), 331 (23), 330 (100), 303 (15), 302 (61), 260 (64), 216 (97), 182 (33), 124 (70), 105 (88). Anal. Calcd for $C_{27}H_{35}NO_4$: C, 74.11; H, 8.06; N, 3.20. Found: C, 73.73; H, 8.06; N, 3.21.

(2*S*,5*S*)-*N*-[(Benzyloxy)carbonyl]-5-butyl-2-(4-hydroxybutyl)pyrrolidine [(+)-33]. A mixture of **52** (870 mg, 1.99 mmol), 1:2 MeOH–THF (6 mL), and 15% aqueous NaOH (1 mL) was stirred at rt for 2 h. The mixture was diluted with brine (50

mL) and extracted with EtOAc (3 × 50 mL). The extracts were dried ($MgSO_4$) and concentrated to give a pale yellow oil, which was purified by flash column chromatography on silica gel (hexane–EtOAc, 1:1) to give (+)-**33** (594 mg, 90%) as a colorless oil: $[\alpha]^{23}_D$ +60.4° (*c* 5.90, $CHCl_3$).

(2*S*,5*S*)-*N*-[(Benzyloxy)carbonyl]-5-butyl-2-(4-oxobutyl)pyrrolidine [(+)-34]. To a stirred solution of oxalyl chloride (227 mg, 1.79 mmol) in CH_2Cl_2 (3 mL) at −78 °C was added dropwise a solution of DMSO (211 mg, 2.70 mmol) in CH_2Cl_2 (3 mL), and the mixture was stirred for 30 min at −78 °C. To this mixture was added dropwise a solution of (+)-**33** (149 mg, 0.447 mmol) in CH_2Cl_2 (3 mL), and stirring was continued. After 1 h, a solution of Et_3N (364 mg, 3.60 mmol) in CH_2Cl_2 (3 mL) was added to the mixture, and the mixture was warmed to ambient temperature and stirred for 15 min. After addition of water (5 mL), the mixture was diluted with Et_2O (150 mL). The organic phase was separated, washed with water (50 mL) and then brine (50 mL), and dried ($MgSO_4$). Evaporation of the solvent and purification of flash column chromatography on silica gel (hexane–EtOAc, 4:1) gave (+)-**34** (140 mg, 94%) as a colorless oil: $[\alpha]^{23}_D$ +65.5° (*c* 1.52, $CHCl_3$).

(3*S*,5*S*,8a*S*)-3-Butyl-5-methyloctahydroindolidine [(+)-Indolizidine 195B, (+)-1]. Compound (+)-**34** was transformed into (+)-**1** in the same manner as described for the preparation of (−)-**1**: $[\alpha]^{24}_D$ +97.7° (*c* 0.18, MeOH) [lit[4a] $[\alpha]^{16}_D$ +65° (*c* 0.41, MeOH), lit.[4b] $[\alpha]^{24}_D$ +98.0° (*c* 0.30, MeOH)].

(3*S*,5*S*,8a*S*)-3-Butyl-5-propyloctahydroindolidine [(+)-Indolizidine 223AB, (+)-2]. Compound (+)-**34** was transformed into (+)-**2** in the same manner as described for the preparation of (−)-**2**: $[\alpha]^{24}_D$ +101.1° (*c* 0.36, hexane).

(3*S*,5*R*,8a*S*)-5-(3-Hydroxypropyl)-3-butyloctahydroindolidine [(+)-Indolizidine 239AB, (+)-3]. Compound (+)-**34** was transformed into (+)-**3** in the same manner as described for the preparation of (−)-**3**: $[\alpha]^{27}_D$ +82.7° (*c* 0.48, MeOH).

Acknowledgment. We are indebted to Dr. J. W. Daly, National Institutes of Health, for IR and MS spectra of natural indolizidine **239CD**.

Preparation of (2*S**,5*S**)-2,5-Dibenzylphospholanic Acid†

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Received June 12, 1992

The cheletropic cycloaddition of $[ClP(N\text{-}i\text{-}Pr_2)]^+AlCl_4^-$ with 1-substituted dienes at 0 °C afforded 1-(*N*,*N*-diisopropylamino)-1-chloro-2-alkyl-Δ^3-phospholenium tetrachloroaluminates. The stereoselectivity of these reactions ranged from 5:1 to 100:0. Hydrolysis of the cycloadducts afforded a diastereomeric mixture of 1-(*N*,*N*-diisopropylamino)-1-oxo-2-alkyl-Δ^3-phospholenes. The ratio of the Δ^3-phospholene amides differed significantly from the ratio of the intermediate Δ^3-phospholenium ions, implying that the hydrolysis reactions occurred via five-coordinate phosphoranes which underwent pseudorotation prior to elimination of HCl. Hydrogenation of the Δ^3-phospholene amides afforded saturated phospholane amides which underwent regioselective deprotonation and subsequent stereospecific alkylation reactions with alkyl halides. 1-(*N*,*N*-Diisopropylamino)-1-oxo-2,5-dimethyl- and -2,5-dibenzylphospholanes (**10a** and **10b**) were converted by acid-promoted hydrolysis to (2*R**,5*R**)-2,5-dimethyl- and (2*S**,5*S**)-2,5-dibenzylphospholanic acid (**12a** and **12b**), respectively.

Recently, the potential utility of trans-2,5-disubstituted derivatives of phospholane as chiral reagents in organic[1,2] and organometallic[3,4] chemical transformations has been recognized by ourselves[1] and three other groups.[2-4] We report herein an improved method for the preparation of (2*R**,5*R**)-2,5-dimethyl- and (2*S**,5*S**)-2,5-dibenzylphospholanic acids (**12a** and **12b**).

(*N*,*N*-Diisopropylamino)dichlorophosphine has been shown to undergo chloride ion abstraction by aluminum trichloride to form phosphenium ion[5] **1**. Cowley[6] and Baxter[7] have independently demonstrated that phosphenium ions undergo cycloaddition reactions with 1,3-dienes. We have found that cheletropic cycloaddition of the (*N*,*N*-diisopropylamino)chlorophosphenium ion **1** with *trans*-piperylene at 0 °C afforded a 5:1 mixture of diastereomeric *P*-chloro-*P*-(*N*,*N*-diisopropylamino)-Δ^3-phospholenium tetrachloroaluminates. Aqueous hydrolysis of the phospholenium ions at 0 °C afforded a 2:1 mixture of 1-(*N*,*N*-diisopropylamino)-1-oxo-Δ^3-phospholenes **5a** and **5b**. These compounds possess a phosphinic amide moiety, and such entities will hereafter be referred to as Δ^3-phospholene amides. In a similar fashion *trans*-1-benzyl-1,3-butadiene[8] reacted with phosphenium ion **1** at 0 °C to afford a 10:1 mixture of *P*-chloro-*P*-(*N*,*N*-diisopropylamino)-Δ^3-phospholenium ions which upon aqueous hydrolysis afforded a 3:1 mixture of Δ^3-phospholene amides **6a** and **6b**. (*E*)-1-*tert*-Butyl-1,3-butadiene[9] underwent cycloaddition with **1** to afford a single Δ^3-phospholenium ion. The Δ^3-phospholenium ion then underwent a stereospecific hydrolysis to afford 2-*tert*-butyl-Δ^3-phospholene amide **7a**.

The ratio of diastereomeric *P*-chloro-Δ^3-phospholenium tetrachloroaluminates **3** and **4** obtained in the cheletropic

† Dedicated to Professor David A. Evans.

‡ Recipient of a Junior Faculty Research Award of the American Cancer Society, 1990–1993.

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0022-3263/92/1957-5189$03.00/0