Regio- and Stereoselective Functionalization of an Optically Active Tetrahydroindolizine Derivative. Catalytic Asymmetric Syntheses of Lentiginosine, 1,2-Diepilentiginosine, and Gephyrotoxin 209D

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To demonstrate the usefulness of optically active 3,5,8,8a-tetrahydro-5-oxoindolizine (**9**) which is prepared by the catalytic asymmetric Heck-type cyclization, regio- and stereoselective functionalizations of (*S*)- and (*R*)-**9** have been examined. Stereoselective epoxidation of 3,5,6,7,8,8a-hexahydro-5-oxoindolizine (**10**) obtained by the regioselective reduction was examined, and it was found that electrophile (peracid or bromonium cation) reacted from the opposite side of C_{8a}-H in a highly stereoselective manner. The catalytic asymmetric syntheses of lentiginosine (**3**) and 1,2-diepilentiginosine (**4**) using these stereoselective epoxidations have been achieved. Dihydroxylation of (*S*)-**9** catalyzed by OsO_4 gave (6*R*,7*R*,8a*S*)-3,5,6,7,8,8a-hexahydro-6,7-dihydroxy-5-oxoindolizine (**16**) regio- and stereoselectively. Several other functionalizations and a synthesis of gephyrotoxin 209D (**6**) are also described. The origin of the high stereoselectivity observed in the functionalization of **9** is discussed based on the stereoelectronic principle such as the Cieplak model.

Introduction

A number of indolizidine alkaloids have been isolated from a variety of natural sources in recent years, and many of these compounds have proven to be biologically active, among which are castanospermine (**1**),[1] swainsonine (**2**),[2] lentiginosine (**3**),[3] slaframine (**5**),[4] and gephyrotoxin alkaloids (**6**, **7**)[5] (Figure 1). Polyhydroxyindolizidine derivatives such as **1**–**3** that have been isolated from plants or fungus are specific inhibitors of glycosidases,[6] and the discovery of the anti-HIV activity[7] of

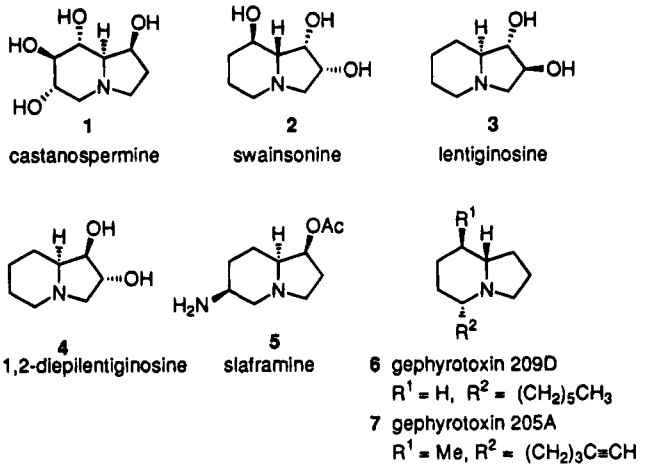

Figure 1.

castanospermine (**1**) and its derivatives has stimulated both medicinal and synthetic studies on these glycosidase inhibitors and their analogs. Slaframine (**5**) is a neurotoxic fungus metabolite that has potent use in the treatment of diseases involving cholinergic dysfunction.[4d] The indolizidine alkaloids having alkyl substituents that have been isolated from the secretions of frogs include the gephyrotoxin alkaloids **6** and **7** which inhibit neurotransmission and pumiliotoxin B[8] which shows cardiotonic activity.

[⊗] Abstract published in *Advance ACS Abstracts,* January 1, 1995.

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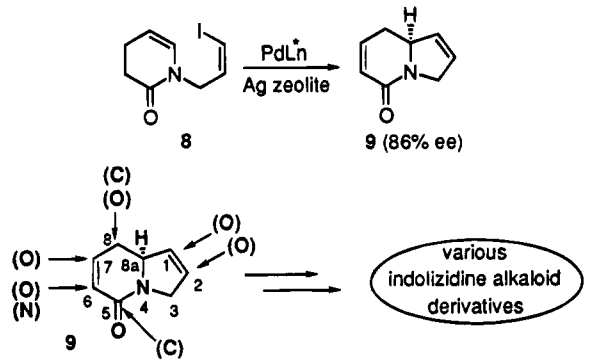
Scheme 1



Because of their varied and interesting biological activity, the indolizidine alkaloids have attracted much attention from synthetic chemists. Indeed many syntheses of these compounds have been reported,[9] but most of them have utilized naturally occurring chiral starting materials. In addition, each synthesis is useful for the preparation of a limited range of derivatives. It is therefore quite important to develop a synthetic route to the various indolizidine alkaloids and their non-natural derivatives, the latter which are expected to have interesting biological activity and to be candidates for novel therapeutic agents. Our basic plan for this goal is outlined in Scheme 1. We have selected optically active 3,5,8,8a-tetrahydro-5-oxoindolizine (**9**) as a key intermediate and have recently shown that both enantiomers of this compound can be prepared with high optical activity (up to 86% ee) using the catalytic, asymmetric Heck-type cyclization of **8**.[10]

The major challenge that remained in the preparation of these alkaloids involved functionalization of the simple indolizine derivative **9**, a compound that appears to have no facial bias (e.g. bulky substituent, convex conformation) for its stereoselective functionalization. Recently several interesting models regarding the stereoelectronic effects on the stereoselectivity of nucleophilic and electrophilic reactions have been reported,[11] and functionalization of **9** should allow further evaluation of the use of these models as predictive tools in synthesis. In this paper we describe the highly regio- and stereoselective introduction of hydroxy and alkyl groups to **9**, the origin of the high selectivities attained, and the synthesis of lentiginosine (**3**), 1,2-diepilentiginosine (**4**), and gephyrotoxin 209D (**6**).

Results

Stereoselective Epoxidation of the 1,2-Double Bond of 9. Functionalization of the C-1 and C-2 positions of **9** was examined first. Regioselective reduction of the 6,7-double bond was readily achieved on treatment of (*S*)-**9** with K-Selectride (−78−0 °C) and resulted in the sole formation of **10**. Because of its high volatility, however, the isolated yield of **10** was only 36%. Fortunately, direct addition of 30% aqueous hydrogen peroxide and formic acid to the reaction mixture containing **10** prior to isolation resulted in a 65% yield (two steps) of β-epoxide **11**. The yield of the minor α-isomer **12** was only 5.4% (two steps), and the α/β ratio was 1/12. Epoxidation of purified **10** with *m*-CPBA in methylene chloride also gave β-epoxide **11** as the major product (68% yield); however, use of *m*-CPBA in the "one-pot" procedure afforded a lower chemical yield of **11** (37%, two steps). In contrast, successive treatment of **9** with K-Selectride, NBS, and then potassium carbonate gave α-epoxide **12** in 43% yield (three steps in one pot), and no β-isomer **11** was detected. Thus both the β- and α-epoxides were obtained in a highly stereoselective manner (Scheme 2). Regioselective reduction of the epoxide moiety in **11** to 1β-hydroxyindolizidine (**13**),[12] a biosynthetic precursor of slaframine (**5**),[4] unequivocally established the stereochemistry of epoxidation (Scheme 3). These results indicate that electrophilic attack by both peracids and bromonium ion on the 1,2-double bond of **10** occurs from the β-side stereoselectively. The origin of this high stereoselectivity will be discussed later.

Synthesis of Lentiginosine (3) and 1,2-Diepilentiginosine (4). Regioselective opening of epoxides **11** and **12** at the less hindered C-2 position was achieved on treatment of either compound with 1% aq H_2SO_4–acetone (1:1) and the resulting diols were isolated as the dibenzoates **14** and **15** (Scheme 4). β-Epoxide **11** was converted predominantly to **14** (54% in two steps) with a small amount of stereoisomer **15** (10% in two steps) also being formed. In contrast, **15** was the major product (59% in two steps) formed from α-epoxide **12**, though **14** was also observed (29% in two steps). The stereochemistry of dibenzoates **14** and **15** was determined by NOE experiments and further confirmed by the conversion to the known natural product. Specifically, lentiginosine (**3**) was synthesized by the treatment of **15** with lithium aluminum hydride in ether in 98% yield. On comparison of the spectroscopic data with that reported, synthetic lentiginosine (**3**) was found to be identical with the natural compound.[3] Similar treatment of **14** resulted in quantitative formation of 1,2-diepilentiginosine (**4**), a novel dihydroxyindolizidine derivative which may be a glycosidase inhibitor.

Regio- and Stereoselective Dihydroxylation of the 6,7-Double Bond of 9. Next, functionalization of the C-6 and C-7 positions of **9** was investigated. Treatment of **9** with OsO_4 (4 mol %) and NMO (1 equiv) in acetonitrile at −20 °C for 2 days gave diol **16** regio- and stereoselectively in 60% yield on the basis of recovered diene **9** (Scheme 5). The stereochemistry of the diol was determined by NOE experiments on the dibenzoate **17**. Although the chemical yield of **16** is not satisfactory, the observed high regio- and stereoselectivity are remarkable. The osmium reagent attacked the electron poor 6,7-double bond from the α-side selectively.

Dihydroxylation of the 1,2-double bond in dibenzoate **17** was accomplished on treatment with OsO_4 (8 mol %)

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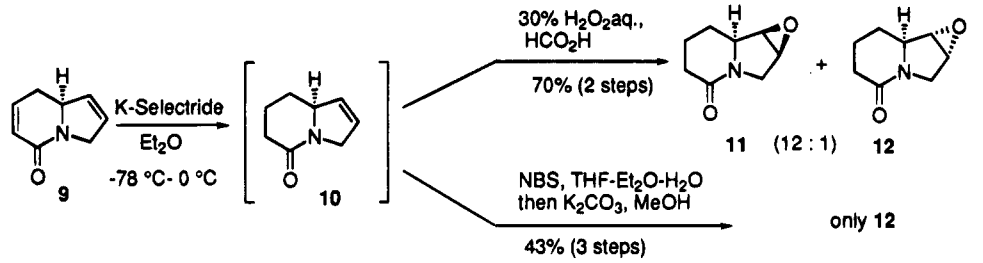
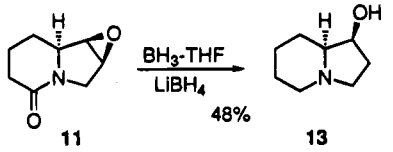
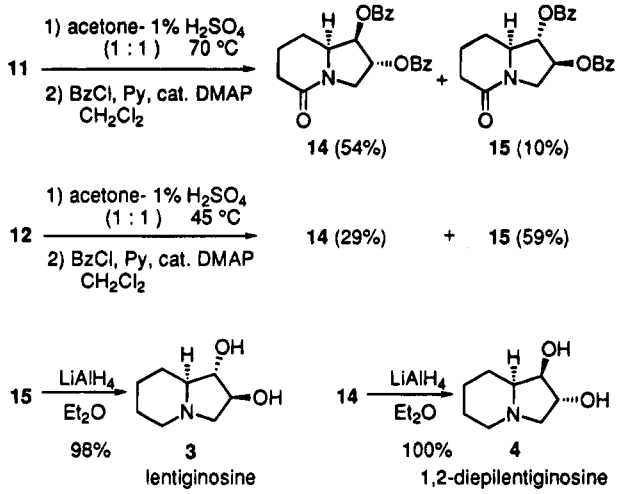
Scheme 2



Scheme 3



Scheme 4



and NMO (1 mol equiv) in acetone at 0 °C, and following protection of the resulting diol as an acetonide afforded **18** in 70% overall yield. NOE experiments on **18** indicated that dihydroxylation of the 1,2-double bond occurred from the β-side.[13] Epoxidation of acetonide **19** with *m*-CPBA also afforded β-isomer as a major stereoisomer (73% yield, β:α = 12:1). These polyoxygenated indolizidine derivatives, **18** and **20**, should be useful intermediates for the synthesis of a variety of polyhydroxy indolizidines.

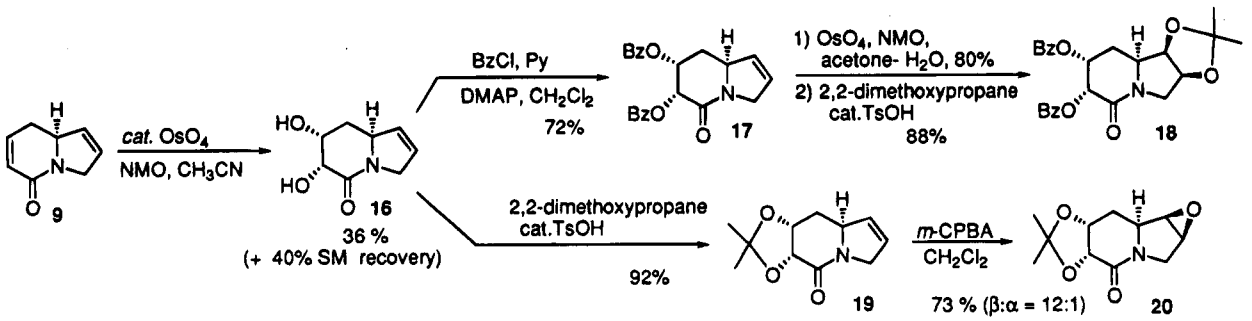
Synthesis of Gephyrotoxin 209D (6). To further demonstrate the synthetic utility of **9** as a chiral building block, we have also completed the synthesis of gephyrotoxin 209D. (*R*)-5-Oxoindolizine (**21**) was readily obtained on hydrogenation of (*R*)-**9**, though a small amount of racemization (86 to 81% ee) was observed (Scheme 6). Subsequent alkylation of amide **21** using alkyllithium or Grignard reagents was unsuccessful presumably because formation of the enolate was competitive. However, use of the cerium reagent[14] resulted in clean alkylation, and after reduction with sodium cyanoborohydride, **6** was obtained in 48% overall yield. No stereoisomer was isolated, and the spectral data for **6** were identical with that reported for gephyrotoxin 209D.[5d,e] Several groups have already reported a similar stereoselective reduction of the iminium ion in the indolizidine skeleton,[5d,15] and they have proposed that the high selectivity is a result of stereoelectronic effects. A similar explanation can be applied to the reduction of our iminium ion generated from **21** (Scheme 7).

Discussion

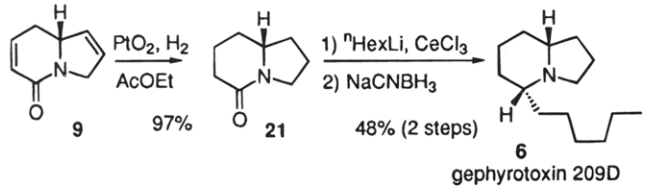
Many models for understanding the influence of stereoelectronic effects on π-facial diastereoselection have been proposed,[11] and the original models have focused primarily on the addition of nucleophile to carbonyl group. In attempting to understand the stereoselective epoxidation of **10**, we have found that the concepts put forth by Cieplak[11b] can be extended to explain the diastereoselection observed in electrophilic addition to olefins.[11c-f] Their basic concept invokes stabilization of the transition state by a two-electron interaction between the σ^* orbital of the newly formed bond ($\sigma_{\ddagger}^*$) and σ orbital of a bond antiperiplanar to it. In other words, the incoming electrophile will add to an olefin from the face that permits the best antiperiplanar hyperconjugative stabilization from an adjacent σ-bond (*i.e.*, the attack occurs antiperiplanar to the best donor bond).

Figure 2 illustrates the interactions believed to be involved in the epoxidation of **10**. This bicyclic amide should prefer a fairly flat conformation, and neither face of the olefin appears to be sufficiently biased sterically to explain the high selectivity observed. In the transition state for epoxidation of the β-face (A) the developing vacant orbital $\sigma_{\ddagger}^*$ at C-1 interacts with the filled σ orbital of the C_{8a}-H bond, but in the transition state for epoxi-

Scheme 5



Scheme 6



Scheme 7

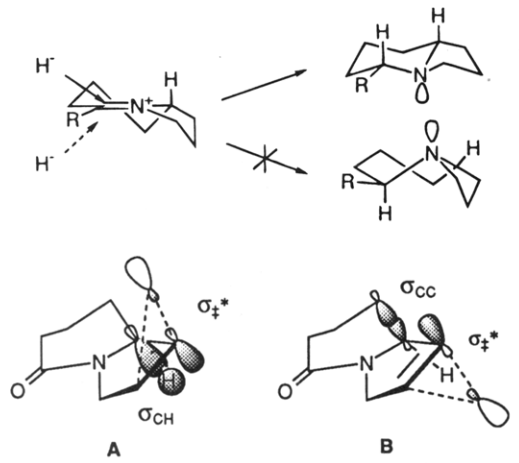


Figure 2.

dation of the α-face (B) the $\sigma_{\ddagger}^*$ orbital interacts with the σ orbital of the $C_{8a}-C_8$ bond. Since the C−H bond is a better donor than the C−C bond, and therefore the σ_{CH}, $\sigma_{\ddagger}^*$ stabilization energy is greater than the σ_{CC}, $\sigma_{\ddagger}^*$ stabilization energy, transition state A is more stabilized than B. The β-epoxide thus predominates. Similar arguments can be used to explain the stereoselectivity observed in the bromohydration of **10**, the dihydroxylation of **17**, and the epoxidation of **19**.

To understand the high stereoselectivity observed in the dihydroxylation of 6,7-double bond of **9**, more careful analysis is required, as both of the interactive σ bonds vicinal to the double bond are C−H bonds (or π orbital of the carbonyl group). Apparently the conformation of the substrate must be considered in this case. Stabilization by the $\sigma_{\ddagger}^*-\sigma_{CHa}$ interaction is optimum as shown in transition state C and leads to α-attack of the electrophile on the substrate as with conformation D (Figure 3). For the stabilization by the $\sigma_{\ddagger}^*-\sigma_{CHb}$ interaction (transition state E), the electrophile must attack the substrate in a conformation such as F. The most stable conformation predicted from calculations using PM3[16] is shown in

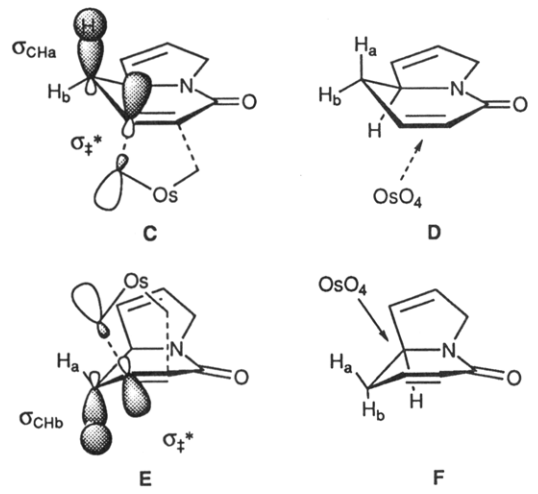


Figure 3.

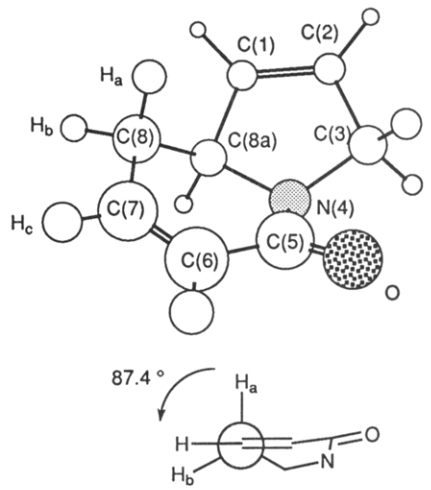


Figure 4.

Figure 4. Apparently it has type D, not type F, conformation. The $C-H_a$ bond is almost perpendicular to the 6,7-double bond (dihedral angle of $H_a-C(8)-C(7)-H_c$: 87.4°), and α-attack may be preferred, because large torsional energy would result on attack of the β-face of the conformer F. Since this molecule does not seem to have enough steric hindrance to prevent any β-attack (Figure 4), the stereoelectronic effects mentioned above would be a major factor for controlling stereoselectivity.

PM3 calculations have shown that **9** has large coefficients at C(7) and C(6) and negligible coefficients at C(1) and C(2) in its LUMO, whereas it has larger coefficients at C(1) and C(2) than at C(7) and C(6) in its HOMO. The observed high regioselectivity in the dihydroxylation of **9** suggests that LUMO(substrate)−HOMO(OsO_4) interactions dominate over other controlling elements in this regioselective dihydroxylation of **9**.[17]

Many rationales for the high diastereoselectivity observed in reactions of cyclic amide systems have been made,[18] and some of them have noted the importance of the stereoelectronic involvement of the lone pair of the pyramidalized nitrogen. Significant pyramidalization is expected in substrate **9** (Figure 4, dihedral angle of C(8a)−N(4)−C(5)−O: −166.2°, C(3)−N(4)−C(5)−O:

(13) Dihydroxylation of **10** have also been reported to be β-selective, see ref 12e.

(14) (a) Imamoto, T.; Kusumoto, T. Tawarayama, Y.; Sugiura, Y.; Mita, T.; Hatanaka, Y.; Yokoyama, M. *J. Org. Chem.* **1984**, *49*, 3904. (b) Imamoto, T.; Sugiura, Y.; Takiyama, N. *Tetrahedron Lett.* **1984**, *25*, 4233.

(15) (a) Stevens, R. V.; Lee, A. W. M. *J. Chem. Soc., Chem. Commun.* **1982**, 102. (b) Stevens, R. V. *Acc. Chem. Res.* **1984**, *17*, 289. (c) Polniaszek, R. P.; Belmont, S. E. *J. Org. Chem.* **1991**, *56*, 4868. (d) Satake, A.; Shimizu, I. *Tetrahedron: Asymmetry* **1993**, *4*, 1405. Reduction of the same iminium ion as shown in Scheme 7 generated from a different precursor has already been reported. See ref 5d.

(16) PM3 calculations were carried out using MOPAC (Ver. 6.0). For PM3, see: (a) Stewart, J. J. P. *J. Comput. Chem.* **1989**, *10*, 209. Conformation search using Monte Carlo method showed that the compound **9** had only one stable conformation similar to D. MacroModel molecular modeling program (Ver. 4.0), supplied by Department of Chemistry; Columbia University; New York, was used for this calculation. For Monte Carlo method, see: (b) Chang, G.; Guida, W. C.; Still, W. C. *J. Am. Chem. Soc.* **1989**, *111*, 4379.

(17) Both HOMO(substrate)−LUMO(OsO_4) and LUMO(substrate)−HOMO(OsO_4) interactions are suggested to be involved in the addition of OsO_4 to olefins, see: Jørgensen, K. A.; Hoffmann, R. *J. Am. Chem. Soc.* **1986**, *108*, 1867.

−28.8°), and it may be possible that such pyramidalization causes distortion of the olefinic π orbital. At this point, however, we can not find a rational explanation for such orbital distortion.

Conclusions

Highly regio- and stereoselective functionalizations of the optically active tetrahydroindolizine derivative (*S*)- and (*R*)-**9** have been achieved. The catalytic asymmetric syntheses of lentiginosine (**3**), 1,2-diepilentiginosine (**4**), and gephyrotoxin 209D (**6**) using these transformations effectively demonstrate the usefulness of optically active **9** as a chiral building block for the synthesis of various indolizidine alkaloids. We believe that the high stereoselectivity observed in the functionalization of **9** can be explained by the Cieplak model, and that these examples illustrate the potential importance of stereoelectronic effects in reaction selectivity. They should also encourage use of stereoelectronic principles in predicting reaction stereoselectivity for similar and more complex reactions.

Experimental Section

Infrared (IR) spectra were recorded on a JASCO A-300 diffraction grating infrared spectrophotometer. NMR spectra were measured on JEOL JNM-FX-270 spectrometer, operating at 270 MHz for ^{1}H and 68 MHz for ^{13}C NMR. Chemical shifts were reported on the δ scale relative to $CHCl_3$ as an internal reference (7.26 ppm for ^{1}H and 77.00 ppm for ^{13}C). DOH (4.75 ppm for ^{1}H) was also used as an internal reference. Mass spectra (MS) were measured on a JEOL JMS-DX303, JMS-SX102A instruments. Optical rotation was measured on a JASCO DIP-140 polarimeter. In general, reactions were carried out in dry solvents under an argon atmosphere, unless otherwise mentioned. IR, NMR and MS data were obtained on all intermediates described herein using chromatographically homogeneous samples.

Tetrahydrofuran (THF) and diethyl ether (Et_2O) were distilled from sodium benzophenone ketyl. Dichloromethane was distilled from calcium hydride.

(1*R*,2*S*,8a*S*)-1,2-Epoxy-5-oxoindolizidine (11). To a stirred solution of *(S)*-3,5,8,8a-tetrahydro-5-oxoindolizine (**9**) (86% ee, 42 mg, 0.31 mmol) in ether (3.1 mL) was added a solution of K-Selectride (1.0 M, in THF, 0.77 mL) at −78 °C. After gradual warming to 0 °C and further 15 min of stirring, formic acid (2.3 mL) and 30% aqueous hydrogen peroxide (1.8 mL) were added to this mixture at 0 °C. The whole reaction mixture was stirred at 23 °C for 2 days, quenched by the addition of saturated aqueous $NaHCO_3$, and extracted with methylene chloride. The organic layer was washed with brine, dried (Na_2SO_4), and concentrated under atmospheric pressure. The products were purified by preparative silica gel thin layer chromatography (ether−MeOH, 15:1) to give the β-epoxide **11** (31 mg, 65%) and the α-epoxide **12** (2.6 mg, 5.4%) as colorless oils: $[\alpha]^{23}_D$ −52.9° (*c* = 1.25, CH_2Cl_2) (86% ee); IR (neat) 2924, 1630, 1227, 860 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 4.25 (d, *J* = 13.5 Hz, 1H), 3.59 −3.68 (m, 3H), 3.21 (d, *J* = 13.5 Hz, 1H), 2.43 (dd, *J* = 18.0, 6.0 Hz, 1H), 2.26 (ddd, *J* = 18.0, 11.0, 7.0 Hz, 1H), 2.20−1.91 (m, 2H), 1.80−1.49 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 170.2, 58.5, 57.1, 52.4, 45.9, 30.7, 24.1, 20.3; MS *m*/*z* 154 (M^+ + 1), 153 (M^+), 136, 125, 124, 109, 108, 97, 69 (bp); HR-MS calcd for $C_8H_{11}NO_2$ 153.0790, found 153.0791.

(1*S*,2*R*,8a*S*)-1,2-Epoxy-5-oxoindolizidine (12). To a stirred solution of *(S)*-**9** (86% ee, 15.0 mg, 0.111 mmol) in ether (1.1 mL) was added a solution of K-Selectride (1.0 M, in THF, 0.37 mL) at −78 °C. After gradual warming to 0 °C and further 15 min of stirring, H_2O (1.8 mL), 3% aqueous H_3PO_4 (1.7 mL), THF (0.93 mL), and *N*-bromosuccinimide (593 mg, 3.33 mmol) were sequentially added to this mixture at 0 °C. The whole reaction mixture was stirred at 23 °C for 26 h, and K_2CO_3 (537 mg, 3.89 mmol) and MeOH (1.5 mL) were added at 0 °C. The mixture was stirred at 23 °C for 3 days, diluted with H_2O, and extracted with CH_2Cl_2. The organic layer was washed with brine, dried (Na_2SO_4), and concentrated under atmospheric pressure. The product was purified by preparative silica gel thin layer chromatography (ether−MeOH, 15:1) to give the α-epoxide **12** (7.3 mg, 43%) as a colorless oil. $[\alpha]^{24}_D$ +19.4° (*c* = 0.384, CH_2Cl_2) (86% ee); IR (neat) 2881, 1686, 1333, 869 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.90 (dd, *J* = 3.0, 14.0 Hz, 1H), 3.78 (dd, *J* = 3.0, 3.0 Hz, 1H), 3.70 (dd, *J* = 3.2, 12.5 Hz, 1H), 3.64 (d, *J* = 3.0 Hz, 1H), 3.57 (d, *J* = 14.0 Hz, 1H), 2.41−2.21 (m, 1H), 2.32 (ddd, *J* = 7.2, 6.5, 6.5 Hz, 1H), 2.10−1.76 (m, 3H), 1.42 (dddd, *J* = 12.5, 12.5, 10.0, 7.2 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 170.4, 60.7, 59.6, 56.3, 47.4, 29.9, 24.5, 19.8; MS *m*/*z* 154 (M^+ + H), 153 (M^+), 125, 124, 108, 98, 69 (bp); HR-MS calcd for $C_8H_{11}NO_2$ 153.0790, found 153.0793.

(1*S*,8a*S*)-1-Hydroxyindolizidine (13). To a stirred solution of lithium borohydride (23.5 mg, 1.08 mmol) in THF (0.5 mL) were added a solution of borane−THF complex (1.0 M in THF, 1.08 mL) and a solution of the epoxide **11** (11.0 mg, 0.0718 mmol) in THF (1.9 mL) at 0 °C. After stirring at 23 °C for 6 days, H_2O (0.44 mL) and 3N aqueous HCl (0.44 mL) were added to the reaction mixture at 0 °C, and the whole mixture was stirred at 60 °C for 4 h. The mixture was neutralized by the addition of saturated aqueous K_2CO_3 (0.55 mL), dried (Na_2SO_4), and concentrated under atmospheric pressure. The product was purified by silica gel column chromatography (CH_2Cl_2−pentane−NH_3 saturated MeOH, 5:5:1) to give the alcohol **13** (5.4 mg, 48%) as a colorless oil. The spectral data of **13** were identical with a literature sample.[12]

(1*R*,2*R*,8a*S*)-1,2-Bis(benzoyloxy)-5-oxoindolizidine (14) and (1*S*,2*S*,8a*S*)-1,2-bis(benzoyloxy)-5-oxoindolizidine (15). To a stirred solution of **11** (10.0 mg, 63.0 μmol) in acetone (0.6 mL) was added 1% aqueous H_2SO_4 (0.60 mL) at 23 °C. After stirring at 70 °C for 27 h, the reaction mixture was neutralized by the addition of saturated aqueous $NaHCO_3$ (0.67 mL) at 0 °C, diluted with CH_2Cl_2, dried (Na_2SO_4), and concentrated under atmospheric pressure to give the crude diol. To a stirred solution of this crude diol in CH_2Cl_2 (0.85 mL) were added pyridine (67.3 μL, 0.833 mmol), benzoyl chloride (64.4 μL, 0.555 mmol), and *N*,*N*-(dimethylamino)-pyridine (2.4 mg, 15 μmol) at 0 °C. After stirring at 23 °C for 2 days, MeOH (0.50 mL) was added at 0 °C and the reaction mixture was stirred for 30 min and concentrated under atmospheric pressure. The products were purified by preparative silica gel thin layer chromatography (Et_2O) to give the benzoate **14** (14.1 mg, 54%) and **15** (2.6 mg, 10%). **14:** $[\alpha]^{22}_D$ −52.7° (*c* = 0.900, $CHCl_3$) (86% ee); IR (neat) 1721, 1644, 1450, 710 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 8.07−7.98 (m, 4H), 7.66−7.56 (m, 2H), 7.52−7.43 (m, 4H), 5.65 (d, *J* = 3.8 Hz, 1H), 5.54 (d, *J* = 5.8 Hz, 1H), 4.27 (dd, *J* = 5.8 Hz, 14.3 Hz, 1H), 4.09 (ddd, *J* = 11.0, 3.8, 3.8 Hz, 1H), 3.73 (d, *J* = 14.3 Hz, 1H), 2.53 (dd, *J* = 19.0, 6.5 Hz, 1H), 2.34 (ddd, *J* = 19.0, 12.0, 6.0 Hz, 1H), 2.12−1.97 (m, 2H), 1.94−1.72 (m, 1H), 1.60−1.38 (m, 1H); ^{13}C-NMR ($CDCl_3$) δ 169.6, 165.0, 133.8, 133.6, 129.8, 129.8, 129.1, 128.7, 128.6, 128.5, 76.4, 73.2, 60.3, 50.2, 30.9, 23.1, 20.6; MS *m*/*z* 380 (M^+ + H), 379 (M^+), 275, 258, 257, 136 (bp); HR-MS calcd for $C_{22}H_{21}NO_5$ 379.1420, found 379.1408.

15: $[\alpha]^{22}_D$ +52.4° (*c* = 0.395, $CHCl_3$) (86% ee); IR (neat) 2950, 1723, 1644, 1450, 710 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 8.07−7.98 (m, 4H), 7.66−7.42 (m, 6H), 5.59 (ddd, *J* = 6.8, 4.3, 4.0 Hz, 1H), 5.48 (dd, *J* = 6.8, 4.3 Hz, 1H), 4.13 (dd, *J* = 4.0, 13.0 Hz, 1H), 3.91 (dd, *J* = 13.0, 6.8 Hz, 1H), 3.75−3.65 (m, 1H), 2.56−2.24 (m, 2H), 2.18−1.90 (m, 2H), 1.90−1.50 (m, 2H); ^{13}C-NMR ($CDCl_3$) δ 168.9, 165.8, 165.6, 133.6, 133.5, 129.8, 129.8, 129.1, 129.0, 128.5, 128.5, 80.4, 74.7, 61.7, 48.5, 30.9, 27.3, 20.5; MS *m*/*z* 380 (M^+ + H), 379 (M^+), 258, 257, 136, 135 (bp); HR-MS calcd for $C_{22}H_{22}NO_5$ 380.1529 (M + H), found 380.1499.

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14 and 15 from 12. The epoxide **12** (7.3 mg, 48 μL) was converted to **14** (5.2 mg, 29%) and **15** (10.7 mg, 59%) according to the same procedure described above except that the epoxide opening reaction was performed at 45 °C.

The stereochemistry of **14** and **15** was determined by the results of a NOE experiment. **14**: $H_{8a} \rightarrow H_1$, 17%; **15**: $H_{8a} \rightarrow H_2$, 5.2%.

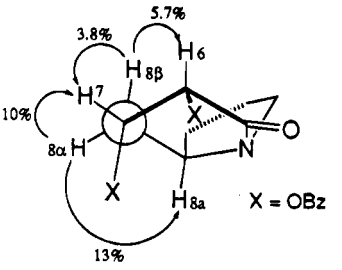
Lentiginosine [(1*S*,2*S*,8a*S*)-1,2-Dihydroxyindolizidine] (3). To a stirred solution of the dibenzoate **15** (8.2 mg, 22 μmol) in ether (0.76 mL) was added lithium aluminum hydride (10.0 mg, 0.26 mmol) at 0 °C. The reaction mixture was stirred at 23 °C for 9.5 h, diluted with ether, and quenched by the addition of $Na_2SO_4 \cdot (H_2O)_{10}$ at 0 °C. After stirring at 23 °C for 1 h, the insoluble salts were filtered off, and the resulting filtrate was concentrated under the atmospheric pressure. The product was purified by silica gel chromatography (CH_2Cl_2–MeOH–15% aqueous NH_3, 51:8:1) to give **3** (3.2 mg, 93%) as a colorless solid: $[\alpha]^{22}_D$ +0.55° (*c* = 0.16, MeOH) (86% ee); IR ($CHCl_3$) 3598, 2939, 1141 cm^{-1}; ^{1}H-NMR (D_2O) δ 4.10–4.02 (m, 1H), 3.64 (dd, *J* = 8.5, 4.5 Hz, 1H), 2.95 (brd, *J* = 11.0 Hz, 1H), 2.84 (d, *J* = 11.0 Hz, 1H), 2.66 (dd, *J* = 11.0, 7.7 Hz, 1H), 2.17–1.20 (m, 8H); ^{13}C-NMR ($CDCl_3$) δ 84.7, 77.6, 69.9, 61.6, 53.1, 28.5, 24.6, 23.8; MS *m*/*z* 158 (M^+ + H), 157 (M^+), 140 (M^+ − OH), 97 (bp), 84; HR-MS calcd for $C_8H_{15}O_2N$ 157.1103, found 157.1110.

1,2-Diepilentiginosine [(1*R*,2*R*,8a*S*)-1,2-Dihydroxyindolizidine] (4). The dibenzoate **14** (20 mg, 52 μmol) was reduced with lithium aluminum hydride (24 mg, 0.63 mmol) according to the similar manner to **15**. 1,2-Diepilentiginosine (**4**) (8.2 mg, 100%) was obtained as a colorless solid after silica gel chromatography (CH_2Cl_2–MeOH–15% aqueous NH_3, 41:8:1). $[\alpha]^{22}_D$ +3.44° (*c* = 0.414, MeOH) (86% ee); IR ($CHCl_3$) 3368, 2940, 1144 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 4.21 (dd, *J* = 6.9, 6.9 Hz, 1H), 3.83 (d, *J* = 4.7 Hz, 1H), 3.55 (dd, *J* = 10.7, 6.9 Hz, 1H), 3.20–2.95 (m, 3H), 2.26 (ddd, 11.2, 4.2, 4.2 Hz, 1H), 2.13–2.00 (m, 2H), 1.90–1.80 (m, 1H), 1.77–1.20 (m, 5H); ^{13}C-NMR ($CDCl_3$) δ 80.3, 77.3, 66.5, 61.5, 53.2, 24.9, 24.4, 23.7; MS *m*/*z* 158 (M^+ + 1), 157 (M^+), 140 (M^+ − OH), 98, 97 (bp), 84; HR-MS calcd for $C_8H_{15}O_2N$ 157.1103, found 157.1101.

(6*R*,7*R*,8a*S*)-3,5,6,7,8,8a-Hexahydro-6,7-dihydroxy-5-oxoindolizine (16). To a stirred solution of (*R*)-**9** (60 mg, 0.444 mmol) in CH_3CN (2.2 mL) were added H_2O (11.2 μL, 1.12 mmol), *N*-methylmorpholine *N*-oxide (52.0 mg, 0.444 mmol), and a solution of OsO_4 (39 mM in *t*-BuOH, 0.45 mL, 18 μmol) with CH_3CN (2.2 mL) at −20 °C. The reaction mixture was stirred at −20 °C for 48 h, and Na_2SO_3 (242 mg) was added. After stirring at −20 °C for 1 h, the reaction mixture was filtered through a short column (Na_2SO_3), and the filtrate was concentrated *in vacuo*. The residue was purified by silica gel column chromatography (pentane–acetone, 2:1 and then CH_2Cl_2–MeOH, 10:1) to give **16** (27 mg, 36%) as a colorless oil with recovery of the starting material **9** (24 mg, 40%): $[\alpha]^{26}_D$ +49.7° (*c* = 0.665, MeOH) (86% ee); IR (neat) 3394, 2922, 2860, 1634, 1606, 1463 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 5.94–5.87 (m, 1H), 5.85–5.79 (m, 1H), 4.89–4.78 (m, 1H), 4.48–4.26 (m, 3H), 4.10–3.99 (m, 2H), 3.21 (brs, 1H), 2.44 (ddd, *J* = 13.4, 4.4, 4.4 Hz, 1H), 1.64 (ddd, *J* = 13.4, 13.4, 1 Hz, 1H); ^{13}C-NMR ($CDCl_3$) δ 169.0, 130.1, 126.3, 70.2, 66.1, 58.9, 52.2, 32.4; MS *m*/*z* 169 (M^+), 167 (M^+ − 2H), 151 (M^+ − OH), 134, 122, 68 (bp); HR-MS calcd for $C_8H_{11}NO_3$ 169.0739, found 169.0738.

(6*R*,7*R*,8a*S*)-3,5,6,7,8,8a-Hexahydro-6,7-bis(benzoyloxy)-5-oxoindolizine (17). To a stirred solution of the diol **16** (12.0 mg, 70.9 μmol) in CH_2Cl_2 (0.4 mL) were added pyridine (28.7 μL, 0.355 mmol), benzoyl chloride (32.9 μL, 0.284 mmol), and *N*,*N*-(dimethylamino)pyridine (2.6 mg, 0.021 mmol) at 0 °C. After stirring at 23 °C for 24 h, MeOH (0.40 mL) was added at 0 °C, and the reaction mixture was stirred for 30 min and concentrated *in vacuo*. The product was purified by silica gel column chromatography (EtO_2–hexane = 4:1) to give the benzoate **17** (19 mg, 72%) as a colorless oil: $[\alpha]^{27}_D$ −107° (*c* = 0.965, $CHCl_3$) (86% ee); IR (neat) 1726, 1669, 1450, 709 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 8.23–7.92 (m, 4H), 7.78–7.27 (m, 6H), 6.04–5.97 (m, 1H), 5.92 (ddd, *J* = 4.2, 4.2, 1.7 Hz, 1H), 5.89–5.82 (m, 1H), 5.79 (d, *J* = 4.2 Hz, 1H), 4.95–4.82 (m, 1H), 4.62 (m, 1H), 4.17 (m, 1H), 2.69 (ddd, *J* = 13.5, 4.2, 4.2 Hz, 1H), 2.03 (ddd, *J* = 13.5, 11.5, 1.7 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 165.6, 165.6, 163.8, 133.5, 133.2, 130.0, 129.8, 129.5, 129.3, 129.2, 128.5, 128.2, 127.2, 69.1, 68.6, 59.1, 53.0, 31.9; MS *m*/*z* 378 (M^+ + 1), 287, 272, 150, 105 (bp), 77; HR-MS calcd for $C_{22}H_{20}NO_5$ (M + H) 378.1341, found 378.1339.

The stereochemistry of **17** was determined by ^{1}H NMR analysis: the results of the NOE experiment (%) and selected coupling constants.



$J_{8a,8\beta}$ = 11.5 Hz, $J_{7,8\alpha}$ = 4.2 Hz
$J_{7,8\beta}$ = 1.7 Hz, $J_{8\alpha,8\beta}$ = 13.5 Hz
$J_{8a,8\alpha}$ = 4.2 Hz

(1*R*,2*S*,6*R*,7*R*,8a*S*)-6,7-Bis(benzoyloxy)-1,2-(isopropylidenedioxy)-5-oxoindolizidine (18). To a stirred solution of the dibenzoate **17** (18.2 mg, 0.108 mmol), *N*-methylmorphorine *N*-oxide (6.3 mg, 54 μmol), and H_2O (8.8 μL, 0.490 mmol) in acetone (0.35 mL) was added a solution of OsO_4 (39.3 mM in *t*-BuOH, 0.10 mL, 39.3 mmol) in acetone (0.14 mL). After stirring at 0 °C for 2 h, $NaHSO_3$ (28.0 mg) was added, and the mixture was stirred for further 30 min. The reaction mixture was then filtered through a short column ($NaHSO_3$) and the filtrate was concentrated *in vacuo*. The residue was purified by preparative thin layer silica gel chromatography [CH_2Cl_2–MeOH (saturated with NH_3), 30:1] to give diol (16 mg, 80%). To a stirred solution of the diol in 2,2-dimethoxypropane (0.64 mL) was added $TsOH \cdot H_2O$ (0.61 mg, 3.2 μmol), and the mixture was stirred at 0 °C for 4 h. It was then diluted with AcOEt, neutralized by the addition of saturated aqueous $NaHCO_3$, and extracted with AcOEt. The organic extracts were washed with brine, dried (Na_2SO_4), and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (Et_2O) to give **18** (16 mg, 70%, two steps) as a colorless oil: $[\alpha]^{23}_D$ −92.9° (*c* = 0.640, $CHCl_3$) (86% ee); IR (neat) 2926, 2854, 1728, 1674, 1452, 1275 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 8.05–7.94 (m, 4H), 7.65–7.28 (m, 6H), 5.94 (ddd, *J* = 3.3, 3.3, 3.3 Hz, 1H), 5.82 (d, *J* = 3.3 Hz, 1H), 4.82 (dd, *J* = 5.3, 4.2 Hz, 1H), 4.63 (dd, *J* = 5.3, 4.2 Hz, 1H), 4.21 (d, *J* = 14.0 Hz, 1H), 3.80 (ddd, *J* = 8.0, 8.0, 4.2 Hz, 1H), 3.28 (dd, *J* = 14.0, 4.2 Hz, 1H), 2.53–2.46 (m, 2H), 1.48 (s, 3H), 1.35 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 165.6, 165.6, 164.3, 133.5, 133.2, 130.0, 129.7, 129.5, 129.3, 128.6, 128.2, 112.1, 80.3, 78.1, 69.7, 69.0, 57.5, 50.7, 26.5, 25.7, 24.6; MS *m*/*z* 452 (M^+ + H), 436, 208, 207, 167, 149, 105 (bp); HR-MS calcd for $C_{25}H_{25}NO_{10}$ (M + H) 452.1683, found 452.1717.

The stereochemistry of **18** was determined by the results of NOE experiment. **20**: $H_{8a} \rightarrow H_1$, 17%.

(6*R*,7*R*,8a*S*)-3,5,6,7,8,8a-Hexahydro-6,7-(isopropylidenedioxy)-5-oxoindolizine (19). To a stirred solution of diol **16** (18.2 mg, 0.108 mmol) in 2,2-dimethoxypropane (2.2 mL) was added $TsOH \cdot H_2O$ (2.1 mg, 11 μmol), and the mixture was stirred at 0 °C for 2 h. It was then diluted with AcOEt, neutralized by the addition of saturated aqueous $NaHCO_3$, and extracted with AcOEt. The organic extracts were washed with brine, dried (Na_2SO_4), and concentrated under atmospheric pressure. The residue was purified by silica gel column chromatography (CH_2Cl_2–MeOH, 30:1) to give **19** (21 mg, 92%) as a colorless oil: $[\alpha]^{24}_D$ +0.700° (*c* = 1.04, $CHCl_3$) (86% ee); IR (neat) 2889, 1654, 1402, 1195 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 5.95–5.89 (m, 1H), 5.81–5.75 (m, 1H), 5.53–4.46 (m, 4H), 4.14–4.03 (m, 1H), 2.27 (ddd, *J* = 14.0, 1.8, 1.8 Hz, 1H), 1.51–1.37 (m, 1H), 1.48 (s, 3H), 1.36 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 165.4, 129.1, 125.8, 109.3, 75.2, 72.7, 58.5, 52.6, 35.7, 25.8, 23.5; MS *m*/*z* 210 (M^+ + 1), 209 (M^+), 194, 167, 151 (bp), 134; HR-MS calcd for $C_{11}H_{15}NO_3$ 209.1052, found 209.1049.

(6*R*,7*R*,8a*S*)-1,2-Epoxy-3,5,6,7,8,8a-hexahydro-6,7-(isopropylidenedioxy)-5-oxoindolizine (20). To a stirred solution of **19** (5.8 mg, 28 μmol) in CH_2Cl_2 (0.55 mL) were added

m-CPBA (33.2 mg, 0.193 mmol) and NaH_2PO_4 (23.2 mg, 0.193 mmol) at 0 °C, and the mixture was stirred at 23 °C for 2 h. It was then diluted with AcOEt, quenched by the addition of saturated aqueous $Na_2S_2O_3$, and extracted with AcOEt. The organic extracts were washed with saturated aqueous $NaHCO_3$ and brine, dried (Na_2SO_4), and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (Et_2O–MeOH, 30:1) to give **20** and its stereoisomer as an inseparable mixture (4.5 mg, 73%, $\alpha:\beta$ = 1:12) as a colorless oil. IR (neat) 2987, 2934, 1652, 1456, 1071 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.66–4.59 (m, 1/13H), 4.64 (ddd, J = 6.5, 3.0, 3.0 Hz, 12/13H), 4.49 (d, J = 6.9 Hz, 1/13H), 4.43 (d, J = 6.5 Hz, 12/13H), 4.14 (d, J = 13.5 Hz, 12/13H), 4.03 (dd, J = 12.8, 2.5 Hz, 1/13H), 3.97–3.83 (m, 1H), 3.80 (dd, J = 2.7, 2.7 Hz, 1/13H), 3.74–3.59 (m, 2H), 3.35 (d, 13.5 Hz, 12/13H), 2.32 (ddd, J = 14.0, 3.0, 3.0 Hz, 12/13H), 2.14 (ddd, J = 10.0, 2.0, 2.0, 1/13H), 1.82 (ddd, J = 14.0, 11.5, 3.0 Hz, 12/13H), 1.65–1.53 (m, 1/13H), 1.44 (s, 36/13H), 1.44–1.33 (m, 6/13H), 1.38 (s, 36/13H); ^{13}C NMR ($CDCl_3$) (only the major peaks corresponding to the β epoxide **20** was shown) δ 166.9, 109.7, 74.5, 72.1, 57.8, 53.0, 52.5, 46.3, 29.4, 26.3, 24.2; MS m/z 225 (M^+); HR-MS calcd for $C_{11}H_{15}NO_4$ 225.1001, found 225.0996.

The epoxide stereochemistry of **20** was determined by the results of NOE experiment. **20**: $H_{8a} \rightarrow H_1$, 3.2%.

(5*R*,9*R*)-5-Hexylindolizidine (6) (Gephyrotoxin-209D). To a solution of $CeCl_3$ (177.0 mg, 0.718 mmol) in THF (5.9 mL) was added *n*-hexyllithium (2.5 M solution in hexane, 0.29 mL, 0.72 mmol) at −78 °C. After stirring at −78 °C for 1 h, a solution of **21**[10b] (20 mg, 0.144 mmol) in THF (5.9 mL) was added. The mixture was stirred at −78 °C for 10 h and then gradually warmed to −30 °C and quenched by the addition of 4 N HCl-dioxane in MeOH (4N HCl–dioxane:MeOH, 1:29, 12 mL). After addition of a trace of bromocresol green, the HCl–MeOH solution was added until the color turned yellow and excess $NaBH_3CN$ was added. The HCl–MeOH solution was added dropwise to maintain the yellow color during the reduction (at 0 °C for 3 h). Then 10% aqueous NaOH was added. The mixture was diluted with CH_2Cl_2 and extracted with CH_2Cl_2. The organic extracts were washed with brine, dried (Na_2SO_4), and concentrated *in vacuo*. The residue was purified by column chromatography over basic Al_2O_3 (hexane–Et_2O, 5:1) to give **6** (15 mg, 48%) as a colorless oil: $[\alpha]^{26}_D$ −58.7° (c = 0.360, CH_2Cl_2) (81% ee); IR (neat) 2927, 2856, 2781, 1457, 1374, 1127 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.26 (dt, J = 8.5, 2.2 Hz, 1H), 1.97 (q, J = 8.5 Hz, 1H), 1.92–1.10 (m, 22H), 0.88 (t, J = 6.7 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 65.1, 63.9, 51.5, 34.6, 31.8, 31.0, 30.8, 30.5, 29.7, 25.8, 24.7, 22.6, 20.4, 14.1; MS m/z 209 (M^+), 208, 149, 140, 124; HR-MS calcd for $C_{11}H_{14}O$ 209.2143 found 209.2128.

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Supplementary Material Available: Copies of ^1H- and ^{13}C-NMR spectra of all new compounds (24 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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