# Enantiocontrolled Preparation of Indolizidines: Synthesis of (−)-2-Epilentiginosine and (+)-Lentiginosine

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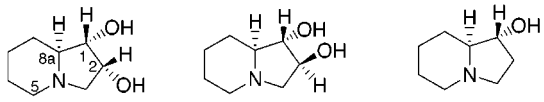
A highly stereoselective approach to (−)-2-epilentiginosine and (+)-lentiginosine has been developed based on a diastereofacially selective cycloaddition of dichloroketene with a chiral dienol ether. The two naturally occurring indolizidines are each obtained enantioselectively (≥99:1) in ca. 8.5% overall yield.

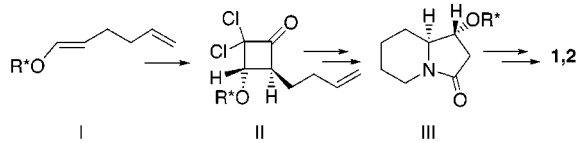
Hydroxylated indolizidines, several of which are potent inhibitors of glycosidases and of potential use in cancer chemotherapy, are widespread in nature and popular synthetic targets.[1,2] Somewhat surprisingly, in view of the present state of asymmetric synthesis, the vast majority of the reported enantioselective syntheses of these compounds rely on chiral pool material to secure the natural products in their native form. We have recently reported a dichloroketene−chiral enol ether based approach to indolizidines and demonstrated its effectiveness through the preparation of (−)-slaframine.[3] We now report an extension of this approach to provide ready access to the dihydroxylated indolizidines (−)-2-epilentiginosine (**1**)[4] and (+)-lentiginosine (**2**).[5]

(−)-2-Epilentiginosine, a metabolite of the fungus *Rhizoctonia leguminicola*[4b] and the locoweeds *Astragalus oxyphysus*[4d] and *A. lentiginosus*,[5a] has been postulated to arise biosynthetically from (1*R*,8a*S*)-1-hydroxyindolizidine (**3**),[6] itself produced from L-lysine via L-pipecolic acid, and engender swainsonine.[4b−d] (+)-Lentiginosine, a strong inhibitor of the fungal α-glucosidase amyloglucosidase, has as well been extracted from the leaves of *A. lentiginosus* and most likely also issues biosynthetically from (1*R*,8a*S*)-1-hydroxyindolizidine.[5a] While several syntheses of both of these dihydroxylated indolizidines have been reported,[4,5] they almost invariably involve elaboration of racemic or chiral pool starting material.



(−)-2-Epilentiginosine (**1**) (+)-Lentiginosine (**2**) (1*R*,8a*S*)-1-Hydroxyindolizidine (**3**)

It appeared that an effective enantioselective route to these natural products might be possible through regio- and diastereoselective cycloaddition of dichloroketene with an enantiopure enol ether **I** to provide cyclobutanone **II**, which through Beckmann ring expansion, dechlorination, and cyclization could be expected to produce indolizidinone **III**, an attractive platform for accessing (−)-2-epilentiginosine (**1**) and (+)-lentiginosine (**2**).



I II III

The synthesis of these indolizidines began with the conversion of the *S*-enantiomer of 1-(triisopropylphenyl)-

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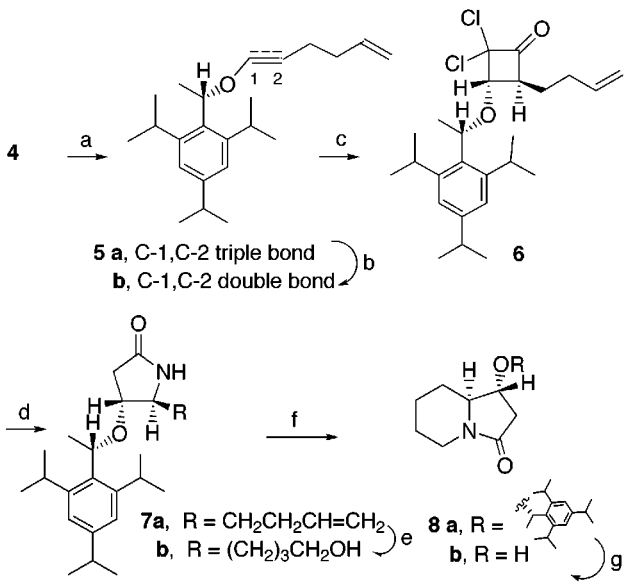
**Scheme 1**[a]




[a] Key: [a](i) KH, $Cl_2C{=}CHCl$. (ii) $C_4H_9Li$; 3-butenyl triflate. [b]$LiAlH_4$ (60%, 3 steps). [c]$Cl_3CCOCl$, Zn−Cu. [d](i) MSH; $Al_2O_3$. (ii) Zn−Cu, $NH_4Cl$ (82%, 3 steps). [e]$Sia_2BH$; $H_2O_2$, NaOH (84%). [f](i) $CH_3SO_2Cl$, $(C_2H_5)_3N$. (ii) NaH (88%, 70% after recryst., 2 steps). [g]$CF_3COOH$ (98%).

ethanol (**4**), a highly effective chiral controller developed for asymmetric dichloroketene-olefin cycloadditions,[7] into the *E*-enol ether **5b** via the corresponding ynol ether **5a** (Scheme 1).[8] This partial reduction of **5a** was efficiently accomplished with lithium aluminum hydride in ether, but a careful study of the reaction conditions was necessary in order to achieve the desired result.

On the basis of previous work from our laboratory[3,9] and molecular modeling studies[10] (Figure 1), it had appeared that enol ether **5b** would undergo cycloaddition with dichloroketene[11] largely on the $C_\alpha$-*re* face to generate cyclobutanone **6**. In the event, cycloaddition proceeded smoothly and, indeed, with high face selectivity to provide **6** (dr 95:5, $^1$H NMR). The depicted sense of the cycloaddition was subsequently confirmed by X-ray diffraction (see below). The cycloadduct was next transformed into pyrrolidinone **7a** through exposure to Tamura's Beckmann conditions,[12] followed by dechlorination[13] (82% yield from **5b**).

The indolizidine skeleton could be readily constructed from pyrrolidinone **7a** through sequential hydroboration−oxidation (84% yield), mesylate formation, and base-induced cyclization (88% yield). The resultant crystalline indolizidinone **8a** proved amenable to diastereomeric upgrading (≥99:1) through recrystallization from dichloromethane−hexane, which also provided crystals suitable for X-ray diffraction analysis.[14] Pleasingly, the expected formation of the required 1*R*,8a*S* stereoisomer was thus confirmed. Cleavage of the chiral controller in indolizidinone **8a** with neat trifluoroacetic acid at ambient temperature then gave the hydroxy indolizidinone **8b** in 98% yield.

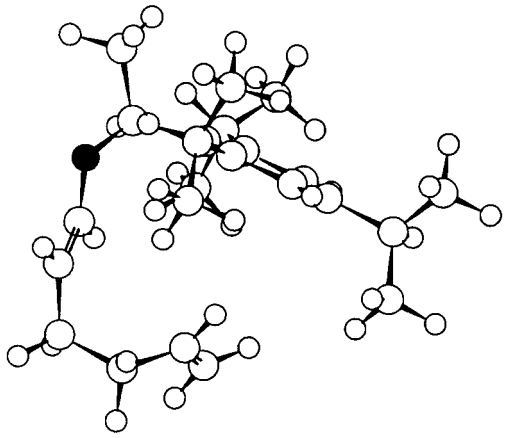
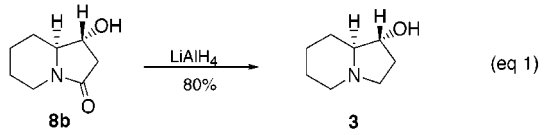


**Figure 1.** Lowest-energy conformation of enol ether **5b** (● = enol oxygen).

In the presence of lithium aluminum hydride in THF, **8b** gave rise in 80% yield to (1*R*,8a*S*)-1-hydroxyindolizidine (**3**) ($[\alpha]_D^{27}$ −51.0; lit.[6b,d] − 49, − 49.7), whose identity was verified through spectral comparison with an independently prepared[6b] sample (eq 1).




While direct α-hydroxylation of **8b** (or **8a**) proved unsatisfactory, the same end could be achieved through dehydration-dihydroxylation thanks to the C-8a stereochemical anchor, which allowed reintroduction of the C-1 hydroxyl group with the same stereogenicity. Dehydration of alcohol **8b** with the Martin sulfurane reagent[15] proceeded readily and reproducibly to provide the desired conjugated derivative; similar yields could occasionally be obtained with DCC in the presence of cuprous chloride,[16] but this method was less reliable and, thus, the former procedure was favored. $OsO_4$-catalyzed vicinal dihydroxylation then gave diol **9** as the major product

(7) Delair, P.; Kanazawa, A.; B. M. de Azevedo, M.; Greene, A. E. *Tetrahedron: Asymmetry* **1996**, *7*, 2707−2710.

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(10) Molecular modeling was performed on an IBM RS 6000 workstation running Insight II Discover 98.0 (MSI, San Diego). The structure was energy minimized with the force field cvff.frc. and the minimization algorithm VA09A. The molecular dynamics was performed at 500 K in a vacuum (dielectric constant fixed at 1; 200 000 steps of 1 fs) and consisted of generation of 400 structures.

(11) For reviews on ketene cycloadditions, see: Hyatt, J. A.; Raynolds, P. W. *Org. React.* **1994**, *45*, 159−646. Tidwell, T. T. *Ketenes*; Wiley: New York, 1995.

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(14) Crystal data for $C_{25}H_{39}N_1O_2$, orthorhombic $P2_12_12_1$ (N° 19), $a$ = 6.188(3), $b$ = 11.029(2), $c$ = 35.053(8) Å, $V$ = 2392(1) Å$^3$, $d_{calc}$ = 1.071 g/cm$^3$, $F(000)$ = 848, $\mu$ (Mo Kα) = 0.66 cm$^{-1}$, $2\theta$ range (Mo Kα) 4.36−59.94°, 4030 measured reflections. 1685 independent reflections, with $I > 2\sigma(I)$, $R$ = 0.069, $R_w$ = 0.069, GoF = 1.99. Full lists of atomic coordinates, bond lengths and angles, and anisotropic thermal parameters have been deposited as Supporting Material with the Cambridge Crystallographic Data Centre

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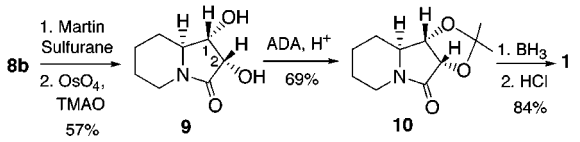
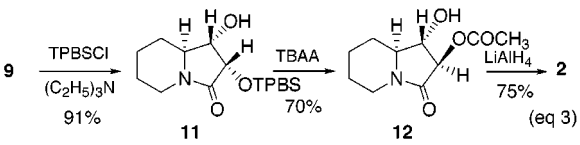
(4:1 ratio),[17] but this derivative could not be easily purified or, once purified, readily reduced (eq 2).




(eq 2)

Fortunately, however, the corresponding acetonide **10**,[4e] formed efficiently by acid-catalyzed exchange with acetone dimethyl acetal (ADA), could be easily purified by column chromatography. This derivative, whose stereochemistry was verified by X-ray crystallography,[18] could now be reduced in high yield to give, following hydrolysis, (−)-2-epilentiginosine (**1**) ($[\alpha]_D^{25}$ −39.3; lit.[4e,5a] −39.4, −32.5). The diacetate derivative of this material was found to be spectrally indistinguishable from that of the naturally derived substance.[4b]

Enantiopure (+)-lentiginosine (**2**) could also be secured from diol **9**. In the presence of a carefully controlled amount of 2,4,6-triisopropylbenzenesulfonyl chloride (TPBSCl) and triethylamine in dichloromethane at 0 °C, the cis diol underwent selective sulfonation of the α-hydroxyl group to give sulfonate **11** in high yield (eq 3).[17] Remark-




(eq 3)

ably, no *β*-sulfonated or disulfonated material could be detected in the crude reaction mixture.[19] The pure trans hydroxy acetate **12** was next efficiently obtained from the sulfonate by treatment with tetrabutylammonium acetate (TBAA) in toluene,[20,21] followed by recrystallization. In contrast to the cis diol **9**, trans hydroxy acetate **12** underwent smooth reduction on treatment with lithium aluminum hydride to yield (+)-lentiginosine (**2**) ($[\alpha]_D^{24}$ + 3.1, mp 108−109 °C; lit.[5f] +3.2, 106−107 °C), whose identity was confirmed through spectral comparison with independently synthesized material.[5d]

The nonchiral pool indolizidine approach presented in this paper is enantioselective (≥99:1), high-yielding (ca. 8.5% overall yields), and flexible and should be applicable to the preparation of pyrrolizidines, in addition to other indolizidines.

## Experimental Section

The reaction mixture was generally poured into water and the separated aqueous phase was then thoroughly extracted with the specified solvent. After being washed with 10% aqueous HCl and/or $NaHCO_3$ (if required), water, and saturated aqueous NaCl, the combined organic phases were dried over anhyd $Na_2SO_4$ or $MgSO_4$ and then filtered and concentrated under reduced pressure on a Büchi Rotovapor to yield the crude reaction product. Tetrahydrofuran and ether were distilled from sodium-benzophenone and dichloromethane; dimethylformamide and triethylamine were distilled from calcium hydride.

**2-[(*S*)-1-((*E*)-Hexa-1,5-dienyloxy)ethyl]-1,3,5-triisopropylbenzene (5b).** An argon-flushed flask was charged with 8.17 g (71.3 mmol) of a 35% suspension of potassium hydride in mineral oil. The mineral oil was removed by washing with pentane and the flask was capped with a rubber septum and connected to a Nujol-filled bubbler by means of a syringe needle. The potassium hydride was suspended in 115 mL of THF, and 8.00 g (32.2 mmol) of (*S*)-(+)-1-(2,4,6-triisopropylphenyl)ethanol (**4**) was added portionwise. The mixture was stirred until hydrogen evolution was complete (ca. 3 h), cooled to −50 °C, and treated dropwise with trichloroethylene (3.20 mL, 4.68 g, 35.6 mmol), after which the reaction mixture was allowed to warm to 15 °C over 4 h, whereupon a few drops of methanol were added. The crude product was isolated with pentane in the usual way and purified by filtration through silica gel (pretreated with 2.5% triethylamine, v/v) with pentane to afford 8.18 g (74%) of pure 2-((*S*)-1-((*E*)-1,2-dichloroethenyloxy)ethyl)-1,3,5-triisopropylbenzene:[3] mp 38−41 °C (pentane); $[\alpha]_D^{25}$ −15.5 (*c* 1.0, $CHCl_3$); IR 3086, 1623, 1609 $cm^{-1}$; $^1H$ NMR (200 MHz): *δ* 1.23−1.30 (m, 18 H), 1.67 (d, *J* = 6.9 Hz, 3 H), 2.85 (hept, *J* = 6.9 Hz, 1 H), 3.32−3.75 (m, 2 H), 5.57 (s, 1 H), 5.96 (q, *J* = 6.9 Hz, 1 H), 7.03 (s, 2 H); $^{13}C$ NMR (50.3 MHz) *δ* 21.0 ($CH_3$), 23.9 ($CH_3$), 24.5 ($CH_3$), 24.8 ($CH_3$), 29.4 (CH), 34.1 (CH), 76.5 (CH), 98.3 (CH), 122.1 (C), 131.3 (C), 143.0 (C), 148.5 (C); mass spectrum (EI), *m*/*z* 343 and 341 ($M^+$), 231 (100).

To a solution of 7.95 g (23.2 mmol) of the dichloro enol ether in 75 mL of THF at −78 °C was added dropwise 21.5 mL (51.6 mmol) of 2.4 M *n*-butyllithium in hexanes. The reaction mixture was allowed to warm to −40 °C and then treated dropwise over 10 min with 7.10 g (34.8 mmol) of 3-butenyl trifluoromethanesulfonate. The solution was stirred at −30 °C for 23 h, whereupon it was poured into cold saturated aqueous ammonium chloride. The product was isolated with pentane in the usual way to give 8.44 g of 2-[(*S*)-1-(hex-5-en-1-ynyloxy)ethyl]-1,3,5-triisopropylbenzene (**5a**), which was used below immediately: IR 3074, 2268, 1642, 1608 $cm^{-1}$; $^1H$ NMR (200 MHz) *δ* 1.20−1.30 (m, 18 H), 1.69 (d, *J* = 6.8 Hz, 3 H), 2.00−2.15 (m, 4 H), 2.86 (hept, *J* = 6.9 Hz, 1 H), 3.19−3.45 (m, 2 H), 4.85−4.96 (m, 2 H), 5.52−5.78 (m, 2 H), 7.01 (s, 2 H); $^{13}C$ NMR (50.3 MHz) *δ* 17.3 ($CH_2$), 21.6 ($CH_3$), 23.9 ($CH_3$), 24.1 ($CH_3$), 29.3 (CH), 34.0 ($CH_2$), 34.1 (CH), 37.7 (C), 82.8 (CH), 89.8 (C), 115.0 ($CH_2$), 120.3 (CH), 121.9 (C), 131.0 (C), 137.5 (CH), 148.4 (C).

A mixture of the above acetylenic ether **5a** and 4.40 g (115.9 mmol) of lithium aluminum hydride in 90 mL of ether was refluxed for 0.5 h. After being cooled to 5 °C, the mixture was carefully treated successively with 4.4 mL of water, 4.4 mL of 15% aqueous NaOH, and 13.2 mL of water and then stirred for 0.5 h. After the addition of sodium sulfate, the mixture was filtered and the filtrate was concentrated under reduced pressure to yield the crude product, which was purified by column chromatography on silica gel (pretreated with 2.5% triethylamine, v/v) with pentane to give 6.13 g (81%, 2 steps) of diene ether **5b**: $[\alpha]_D^{26}$ −50.2 (*c* 2.0, $CHCl_3$); IR 3075, 1670, 1655, 1609 $cm^{-1}$; $^1H$ NMR (200 MHz) *δ* 1.25−1.33 (m, 18 H), 1.64 (d, *J* = 6.9 Hz, 3 H), 1.90−2.12 (m, 4 H), 2.91 (hept, *J* = 6.9 Hz, 1 H), 3.41−3.65 (br m, 2 H), 4.85−5.02 (m, 3 H), 5.39

(17) For clarity, only the major cis diastereomer is shown.

(18) Crystal data for $C_{11}H_{17}N_1O_3$, orthorhombic $P2_12_12_1$ (N° 19), *a* = 6.787(2), *b* = 8.281(2), *c* = 19.914(6) Å, *V* = 1119.2(5) Å$^3$, $d_{calc}$ = 1.254 g/cm$^3$, *F*(000) = 456, *μ* (Mo Kα) = 0.91 $cm^{-1}$, 2*θ* range (Mo Kα) 4.10−59.96°, 1915 measured reflections. 1372 independent reflections, with $I > 1\sigma(I)$, *R* = 0.060, $R_w$ = 0.063, GoF = 1.97. Full lists of atomic coordinates, bonds lengths and angles, and anisotropic thermal parameters have been deposited as Supporting Material with the Cambridge Crystallographic Data Centre

(19) For other examples of this type of selectivity, see: Denis, J.-N.; Correa, A.; Greene, A. E. *J. Org. Chem.* **1990**, *55*, 1957−1959. Lee, Y. S.; Kang, D. W.; Lee, S. J.; Park, H. *J. Org. Chem.* **1995**, *60*, 7149−7152. Chun, J.; He, L.; Byun, H.-S.; Bittman, R. *J. Org. Chem.* **2000**, *65*, 7634−7640.

(20) Cf. Hawryluk, N. A.; Snider, B. B. *J. Org. Chem.* **2000**, *65*, 8379−8380.

(21) From the sulfonate the corresponding trans diol could also be obtained by using tetrabutylammonium nitrite, but the yield was lower. See: Binkley, R. W. *J. Org. Chem.* **1991**, *56*, 3892−3896. The endo sulfonate derived from the minor cis diol was considerably less reactive than **11** with both of these reagents, which permitted in both cases, through careful reaction monitoring, substantial diastereochemical enrichment to be achieved prior to recrystallization. Separation of the diastereomers by silica gel chromatography could not be readily accomplished.

(q, $J$ = 6.9 Hz, 1 H), 5.76 (dddd, $J$ = 6.5, 6.5, 10.3, 16.8 Hz, 1 H), 6.11 (dt, $J$ = 1.0, 11.3 Hz, 1 H), 7.05 (s, 2 H); $^{13}$C NMR (50.3 MHz) $\delta$ 22.5 ($CH_3$), 23.9 ($CH_3$), 24.6 ($CH_3$), 27.3 ($CH_2$), 29.0 (CH), 34.0 (CH), 34.9 ($CH_2$), 74.3 (CH), 105.5 (CH), 114.6 ($CH_2$), 121.9 (CH), 132.2 (C), 138.2 (CH), 145.4 (CH), 146.8 (C), 147.6 (C); mass spectrum (CI), $m/z$ 346 ($M + NH_4^+$, 0.9), 328 ($M^+$, 0.1), 231 (100). HRMS $m/e$ calcd for $C_{23}H_{36}O$ ($M^+$): 328.2766. Found: 328.2763.

**(3*S*,4*S*)-4-But-3-enyl-2,2-dichloro-3-[(*S*)-1-(2,4,6-triisopropylphenyl)ethoxy]cyclobutanone (6).** To a stirred mixture of 7.82 g (23.8 mmol) of enol ether **5b** and 3.7 g (ca. 57 mmol) of Zn−Cu couple in 260 mL of ether at 0 °C under argon was added over 1.75 h a solution of 3.20 mL (5.22 g, 28.7 mmol) of freshly distilled trichloroacetyl chloride in 60 mL of ether. The resulting mixture was stirred an additional 1 h at 0 °C and 2 h at 20 °C, after which the ether solution was separated from the excess couple and added to a large volume of pentane, and the resulting mixture was partially concentrated under reduced pressure in order to precipitate the zinc chloride. The supernatant was decanted and washed successively with a cold aqueous solution of sodium bicarbonate, water, and brine and then dried over anhydrous sodium sulfate. Evaporation of the solvent under reduced pressure left 10.60 g of cyclobutanone **6** (containing ca. 5% of its diastereomer ($\delta$ 4.49 ppm)), as an oil: IR 3077, 1808, 1643, 1608, 1573 cm$^{-1}$; $^1$H NMR (200 MHz) $\delta$ 1.29−1.38 (m, 18 H), 1.83 (d, $J$ = 6.8 Hz, 3 H), 1.77−1.87 (m, 1 H), 2.01−2.38 (m, 3 H), 2.99 (hept, $J$ = 6.9 Hz, 1 H), 3.32−3.52 (br m, 1 H), 3.59−3.67 (m, 1 H), 3.91 (br s, 1 H), 4.17 (d, $J$ = 7.6 Hz, 1 H), 4.95−5.06 (m, 2 H), 5.47 (q, $J$ = 6.8 Hz, 1 H), 5.72 (dddd, $J$ = 6.6, 6.7, 10.3, 17.0 Hz, 1 H), 7.12−7.19 (m, 2 H). HRMS $m/e$ calcd for $C_{25}H_{36}Cl_2O_2$ ($M^+$) + Li: 445.2252. Found: 445.2271.

**(4*R*,5*S*)-5-But-3-enyl-4-[(*S*)-1-(2,4,6-triisopropylphenyl)-ethoxy]pyrrolidin-2-one (7a).** A solution of 10.60 g of cyclobutanone **6** in 230 mL of dichloromethane was treated with 7.7 g (35.8 mmol) of *O*-mesitylenesulfonylhydroxylamine and a small amount of sodium sulfate and then stirred at 20 °C for 7 h, with additional 2.0-g (9.4 mmol) portions of *O*-mesitylenesulfonylhydroxylamine added after 2 and 4 h. After filtration of the mixture over Celite, the solvent was removed under reduced pressure, and the resulting material in 25 mL of toluene was placed on a column of basic alumina (220 g, Merck activity 1) and eluted rapidly with methanol. Evaporation of the solvents left a white solid, which was triturated with dichloromethane, which was then filtered over Celite and evaporated under reduced pressure to afford 11.62 g of (4*S*,5*S*)-5-but-3-enyl-3,3-dichloro-4-[(*S*)-1-(2,4,6-triisopropylphenyl)ethoxy]pyrrolidin-2-one, used directly below: IR 3407, 3226, 3053, 1736, 1641, 1607 cm$^{-1}$; $^1$H NMR (200 MHz) $\delta$ 1.20−1.27 (m, 18 H), 1.75 (d, $J$ = 6.9 Hz, 3 H), 1.85−1.99 (m, 1 H), 2.28−2.33 (m, 1 H), 2.58−2.64 (m, 1 H), 2.78−2.92 (m, 2 H), 3.11−3.28 (br m, 1 H), 3.30−3.40 (m, 1 H), 3.72−3.90 (m, 1 H), 3.93 (d, $J$ = 6.2 Hz, 1 H), 4.80−4.92 (m, 2 H), 5.38−5.65 (m, 2 H), 6.94−7.07 (br m, 3 H); mass spectrum (CI), $m/z$ 454 ($MH^+$, 31), 231 (100).

The above dichloro pyrrolidinone in 150 mL of methanol previously saturated with ammonium chloride was stirred with 6.0 g (ca. 92 mmol) of Zn−Cu couple at 20 °C for 11 h, whereupon the mixture was filtered to remove the excess couple. The filtrate was concentrated under reduced pressure and the residue was then processed with ethyl acetate in the usual way to give the crude product. Purification of this material by silica gel column chromatography with ethyl acetate in pentane (4:6) provided 7.52 g (82%, 3 steps) of pyrrolidinone **7a** as a foam: $[\alpha]_D^{25}$ −95.9 ($c$ 1.2, $CHCl_3$); IR 3216, 1697, 1640, 1607 cm$^{-1}$; $^1$H NMR (300 MHz) $\delta$ 1.13−1.40 (m, 20 H), 1.52 (d, $J$ = 6.9 Hz, 3 H), 1.87−2.07 (m, 2 H), 2.47 (AB of ABX, $\delta_a$ = 2.43, $\delta_b$ = 2.51, $J_{ab}$ = 17.2 Hz, $J_{ax}$ = 6.1 Hz, $J_{bx}$ = 3.0 Hz, 2 H), 2.83 (hept, $J$ = 6.9 Hz, 1 H), 2.99−3.24 (br s, 1 H), 3.44−3.51 (m, 1 H), 3.71 (m, 1 H), 3.76−3.94 (br s, 1 H), 4.90−4.98 (m, 2 H), 5.03 (q, $J$ = 6.9 Hz, 1 H), 5.64 (dddd, $J$ = 6.6, 6.7, 10.3, 17.0 Hz, 1 H), 6.66 (br s, N−H), 6.93 (br s, 1 H), 7.01 (br s, 1 H); $^{13}$C NMR (75.5 MHz) $\delta$ 23.1 ($CH_3$), 23.9 ($CH_3$), 24.6 ($CH_3$), 28.2 (CH), 29.1 (CH), 30.1 ($CH_2$), 33.5 ($CH_2$), 33.9(CH), 36.8 ($CH_2$), 61.1 (CH), 71.0 (CH), 77.3 (CH), 115.6 ($CH_2$), 120.5 (CH), 123.2 (CH), 132.5 (C), 137.1 (CH), 145.4 (C), 147.6 (C), 148.8 (C), 175.8 (C); mass spectrum (CI), $m/z$ 386 ($MH^+$, 100), 230 (61), 138 (24). HRMS $m/e$ calcd for $C_{25}H_{39}NO_2$ ($M^+$): 385.2981. Found: 385.2986.

**(4*R*,5*S*)-5-(4-Hydroxybutyl)-4-[(*S*)-1-(2,4,6-triisopropylphenyl)ethoxy]pyrrolidin-2-one (7b).** To a stirred solution of 7.32 g (19.0 mmol) of pyrrolidinone **7a** in 65 mL of THF at 0 °C was added 15.0 mL of a freshly prepared 2.6 M solution of disiamylborane in THF. After being stirred at 20 °C for 5 h, the solution was cooled to 0 °C and carefully treated with 13.0 mL of water, 13.0 mL of 3 M aqueous sodium hydroxide, and 13.0 mL of 35% aqueous hydrogen peroxide. The mixture was then vigorously stirred for 17 h at 20 °C, whereupon it was filtered through Celite with ethyl acetate. The crude product was isolated from the filtrate with ethyl acetate in the usual way and purified by silica gel chromatography with 0−10% methanol in ethyl acetate to give 6.42 g (84%) of alcohol **7b**: mp 108−109 °C (hexane); $[\alpha]_D^{25}$ −107.6 ($c$ 2.0, $CHCl_3$); IR 3410, 3222, 1693, 1608 cm$^{-1}$; $^1$H NMR (300 MHz) $\delta$ 1.15−1.23 (m, 19 H), 1.29−1.47 (m, 4 H), 1.51 (d, $J$ = 6.8 Hz, 3 H), 2.48 (AB of ABX, $\delta_a$ = 2.43, $\delta_b$ = 2.52, $J_{ab}$ = 17.4 Hz, $J_{ax}$ = 3.2 Hz, $J_{bx}$ = 6.2 Hz, 2 H), 2.83 (hept $J$ = 6.9 Hz, 1 H), 3.03−3.20 (m, 1 H), 3.44−3.65 (m, 4 H), 3.65−3.70 (m, 1 H), 3.75−3.93 (br s, 1 H), 5.02 (q, $J$ = 6.8 Hz, 2 H), 6.88−7.06, (br s, 2 H), 7.27 (s, 1 H); $^{13}$C NMR (75.5 MHz) $\delta$ 22.0 ($CH_2$), 23.1 ($CH_3$), 23.9 ($CH_3$), 24.7 ($CH_3$), 31.8, ($CH_2$), 33.9 ($CH_2$), 34.0 (CH), 37.0 ($CH_2$), 61.4 (CH), 62.1 ($CH_2$), 71.2 (CH), 77.4 (CH), 120.5 (CH), 123.2 (CH), 132.6 (C), 147.7 (C), 176.2 (C); mass spectrum (CI), $m/z$ 404 ($MH^+$, 100), 403 (2.9), 231 (32.8). Anal. Calcd for $C_{25}H_{41}NO_3$+0.5 $H_2O$: C, 72.78; H, 10.26; N, 3.39. Found: C, 72.79; H, 10.13; N, 3.42.

**(1*R*,8a*S*)-1-[(*S*)-1-(2,4,6-Triisopropylphenyl)ethoxy]-hexahydroindolizin-3-one (8a).** To a stirred solution of 6.30 g (15.6 mmol) of alcohol **7b** in 65 mL of dichloromethane and 4.30 mL (3.12 g, 30.9 mmol) of triethylamine at 0 °C was added 2.40 mL (3.55 g, 31.0 mmol) of methanesulfonyl chloride. The mixture was stirred at 20 °C for 1.5 h and then water was added. The crude product was isolated with dichloromethane in the usual way to give 7.67 g of crude methanesulfonic acid 4-{(2*S*,3*R*)-5-oxo-3-[(*S*)-1-(2,4,6-triisopropylphenyl)ethoxy]pyrrolidin-2-yl} butyl ester, which was used immediately below: IR 3429, 1696, 1606 cm$^{-1}$; $^1$H NMR (300 MHz) $\delta$ 1.15−1.24 (m, 22 H), 1.51 (d, $J$ = 6.9 Hz, 3 H), 1.63 (m, 2 H), 2.46 (AB of ABX, $\delta_a$ = 2.42, $\delta_b$ = 2.50, $J_{ab}$ = 17.3 Hz, $J_{ax}$ = 3.2 Hz, $J_{bx}$ = 6.0 Hz, 2 H), 2.83 (hept, $J$ = 6.8 Hz, 1 H), 2.95 (s, 3 H), 3.12 (m, 1 H), 3.46 (m, 1 H), 3.69 (m, 1 H), 3.84 (m, 1 H), 4.12 (t, $J$ = 6.5 Hz, 2 H), 5.03 (q, $J$ = 6.7 Hz, 1H), 6.95−7.10 (m, 3 H); $^{13}$C NMR (75.5 MHz) $\delta$ 21.8 ($CH_2$), 23.1 ($CH_3$), 23.9 ($CH_3$), 24.6 ($CH_3$), 28.7 ($CH_2$), 33.7 ($CH_2$), 33.9 (CH), 36.8 ($CH_2$), 37.3 ($CH_3$), 61.4 (CH), 69.3 ($CH_2$), 71.2 (CH), 77.3 (CH), 120.5 (CH), 123.2 (CH), 132.5 (C), 147.7 (C), 175.9 (C).

A solution of the above crude mesylate in 50 mL of THF and 11 mL of DMF was added dropwise to a stirred mixture of 3.11 g (77.8 mmol) of 60% sodium hydride (in mineral oil) in 75 mL of THF and 11 mL of DMF at 0 °C. The resulting mixture was stirred for 2 h at 20 °C, diluted with 50 mL of ether, and then carefully treated with water. The crude product was isolated with ether in the usual way and purified by silica gel column chromatography with 40−60% ethyl acetate in pentane to provide 5.32 g (88%, 2 steps) of indolizidinone **8a** as a white solid. Recrystallization of this material from hexane−dichloromethane gave 4.20 g (79% recovery) of stereochemically pure (de ≥ 98%, by NMR) indolizidinone **8a**: mp 194−195 °C (hexane−dichloromethane); $[\alpha]_D^{25}$ −105 ($c$ 2.0, $CHCl_3$); IR 1690, 1607 cm$^{-1}$; $^1$H NMR (300 MHz) $\delta$ 0.96 (m, 1 H), 1.16−1.34 (m, 20 H), 1.50 (d, $J$ = 7.0 Hz, 3 H), 1.57 (m, 1 H), 1.73−1.79 (m, 2 H), 2.47−2.56 (m, 2 H), 2.57−2.62 (m, 1 H), 2.82 (hept, $J$ = 7.0 Hz, 1 H), 3.12 (br s, 1 H), 3.30 (ddd, $J$ = 3.1, 3.1, 12.0 Hz, 1 H), 3.63 (m, 1 H), 3.85 (br s, 1 H), 4.09 (dd, $J$ = 4.8, 13.2 Hz, 1 H), 5.05 (q, $J$ = 6.7 Hz, 1 H), 6.92 (s, 1 H), 7.01 (s, 1 H); $^{13}$C NMR (75.5 MHz) $\delta$ 23.1 ($CH_3$), 23.6 ($CH_2$), 23.9 ($CH_3$), 24.4 ($CH_2$), 24.8 ($CH_3$), 30.7 (CH), 34.0 (CH), 37.6 ($CH_2$), 40.0 ($CH_2$), 64.2 (CH), 71.0 (CH), 74.9 (CH), 120.6 (CH), 123.2 (CH), 132.2 (C), 147.7 (C), 170.7 (C); mass spectrum (EI), $m/z$ 385 ($M^+$, 6.6), 342 (8.0), 230 (38). Anal.

Calcd for $C_{25}H_{39}NO_2$: C, 77.87; H, 10.19; N, 3.63. Found: C, 77.86; H, 10.25; N, 3.65.

**(1*R*,8a*S*)-1-Hydroxyhexahydroindolizin-3-one (8b).** A solution of the above indolizidinone **8a** (4.20 g,10.9 mmol) and 7.10 mL (10.5 g, 92.2 mmol) of trifluoroacetic acid in 55 mL of dichloromethane at 20 °C was stirred for 3 h, whereupon the reaction mixture was concentrated to dryness under reduced pressure. Purification of the resulting solid by silica gel column chromatography with 2−10% methanol in ethyl acetate gave 1.66 g (98%) of alcohol **8b**: mp 67−69 °C (dichloromethane−hexane); $[\alpha]_D^{25}$ +11 (*c* 1.0, acetone); IR 3381, 1666 cm$^{-1}$; $^1$H NMR (500 MHz, acetone-$d_6$) $\delta$ 1.10 (dddd, $J$ = 3.5, 12.4, 12.4, 12.8, 1 H), 1.20 (ddddd, $J$ = 3.7, 4.9, 13.0, 13.0, 13.0 Hz, 1 H), 1.44 (ddddd, $J$ = 3.4, 3.4, 13.2, 13.2, 13.2 Hz, 1 H), 1.62 (m, 1 H), 1.83 (m, 1 H), 1.96 (m, 1 H), 2.16 (ddd, $J$ = 1.6, 5.1, 17.1 Hz, 1 H), 2.56 (dd, $J$ = 7.7, 17.1 Hz, 1 H), 2.60 (dddd, $J$ = 1.5, 3.4, 12.9, 12.9 Hz, 1 H), 3.22 (ddd, $J$ = 3.6, 3.6, 7.8 Hz, 1 H), 3.99−4.02 (m, 2 H), 3.9−4.2 (br s, 1 H); $^{13}$C NMR (125 MHz) $\delta$ 24.0 ($CH_2$), 25.0 ($CH_2$), 30.8 ($CH_2$), 40.0 ($CH_2$), 40.3 ($CH_2$), 65.9 (CH), 70.7 (CH), 171.1 (C); mass spectrum (EI) *m*/*z* 155 ($M^+$, 25), 126 (42), 83 (100). Anal. Calcd for $C_8H_{13}NO_2$: C, 61.91; H, 8.44; N, 9.03. Found: C, 61.82; H, 8.49; N, 8.95.

**(1*R*,8a*S*)-Octahydroindolizin-1-ol (3).** A solution of alcohol **8b** (0.096 g, 0.62 mmol) in 1.7 mL of THF was added to a mixture of lithium aluminum hydride (0.073 g, 1.92 mmol) in 9 mL of THF at 20 °C, and the resulting mixture was stirred for 21 h. After being cooled to 0 °C, the mixture was carefully treated successively with 0.073 mL of water, 0.073 mL of 10% aqueous sodium hydroxide and 0.220 mL of water. The mixture was then stirred for 2 h, treated with anhydrous sodium sulfate, and filtered. The filtrate was concentrated under reduced pressure to give the crude product, which was purified by silica gel column chromatography with 0−10% methanol saturated with ammonia in ethyl acetate and evaporative distillation to afford 0.070 g (80%) of alcohol **3**: $[\alpha]_D^{27}$ −51.0 (*c* 0.7, ethanol) (lit.[6b,d] −49, −49.7); IR 3356, 2800 cm$^{-1}$; $^1$H NMR (300 MHz) $\delta$ 1.16 (m, 2 H), 1.44 (m, 2 H), 1.56 (m, 1 H), 1.68 (ddd, $J$ = 2.8, 7.6, 10.5 Hz, 1 H), 1.77 (m, 1 H), 1.95 (m, 2 H), 2.14 (m, 1 H), 2.28 (m, 1 H), 2.90 (ddd, $J$ = 2.4, 8.7, 8.7 Hz, 1 H), 2.94 (m, 1 H), 3.33 (br s, 1 H), 3.82 (ddd, $J$ = 4.7, 7.6, 10.0 Hz, 1 H); $^{13}$C NMR (75.5 MHz) $\delta$ 24.0 ($CH_2$), 24.9 ($CH_2$), 28.6 ($CH_2$), 31.7 ($CH_2$), 52.5 ($CH_2$), 53.3 ($CH_2$), 70.8 (CH), 75.7 (CH); mass spectrum (EI) *m*/*z* 141 ($M^+$, 6), 97 (100). The $^1$H NMR spectrum was in excellent agreement with that of an independently prepared[6b] sample (spectrum kindly provided by Professor C. Harris). HRMS *m*/*e* calcd for $C_8H_{15}NO$ ($M^+$): 141.1154. Found: 141.1149.

**(1*S*,2*S*,8a*S*)-1,2-Dihydroxyhexahydroindolizin-3-one (9) and 1*R*,2*R*,8a*S*-Isomer.** To a solution of 1.66 g (10.7 mmol) of alcohol **8b** in 60 mL of dichloromethane at 0 °C was added a solution of Martin sulfurane[15] (10.19 g, 15.15 mmol) in 45 mL of dichloromethane. The reaction mixture was stirred at 25 °C for 2 h and then concentrated under reduced pressure. Purification of the crude product by silica gel chromatography with 20−50% ethyl acetate in dichloromethane provided 1.21 g (82%) of (*S*)-6,7,8,8a-tetrahydro-5*H*-indolizin-3-one (ee ≥ 98%. HPLC: Chiralcel OD-H column, 5 mm, 2-propanol/hexane = 1:9, 0.5 mL/min, $t_R$ = 24.8 min (versus 31.4 min for the (*R*)-enantiomer)). $[\alpha]_D^{23}$ +23.9 (*c* 1.6, $CHCl_3$); IR 1674, 1581 cm$^{-1}$; $^1$H NMR (300 MHz) $\delta$ 0.96 (dddd, $J$ = 3.6, 12.5, 12.5, 12.6 Hz, 1 H), 1.23 (ddddd, $J$ = 3.5, 5.1, 12.9, 12.9, 12.9 Hz, 1 H), 1.46 (dddd, $J$ = 3.2, 3.2, 13.1, 13.1 Hz, 1 H), 1.69 (m, 1 H), 1.87 (m, 1 H), 2.05 (m, 1 H), 2.78 (ddd, $J$ = 3.6, 12.9, 12.9 Hz, 1 H), 3.81 (m, 1 H), 4.22 (dd, $J$ = 5.1, 13.2 Hz, 1 H), 6.09 (dd, $J$ = 1.5, 5.9 Hz, 1 H), 6.97 (dd, $J$ = 1.5, 5.9 Hz, 1 H); $^{13}$C NMR (75.5 MHz) $\delta$ 23.3 ($CH_2$), 25.2 ($CH_2$), 30.6 ($CH_2$), 39.1 ($CH_2$), 61.3 (CH), 127.3 (CH), 146.8 (CH), 168.7 (C); mass spectrum (EI) *m*/*z* 137 ($M^+$, 46), 108 (100), 81 (49). HRMS *m*/*e* calcd for $C_8H_{11}NO$ ($M^+$): 137.0841. Found:137.0839.

A 2.5% solution of osmium tetraoxide in *tert*-butyl alcohol (1.90 mL, 0.040 g, 0.15 mmol) was added to a solution of 0.407 g (2.97 mmol) of the above indolizidinone and 0.534 g (4.80 mmol) of trimethylamine *N*-oxide (TMAO) dihydrate in 12 mL of *tert*-butyl alcohol−water (3:1), and the resulting solution was stirred at 35−40 °C for 3.5 h. After being allowed to cool to 25 °C, the reaction mixture was treated with sodium bisulfite (1.0 g, 9.6 mmol), and the resulting mixture was stirred for 30 min, partially concentrated under reduced pressure, and then filtered through Celite with ethyl acetate. The filtrate was dried over sodium sulfate and concentrated under reduced pressure to afford the crude product, which was purified by silica gel column chromatography with 5% methanol in chloroform to afford 0.357 g (70%) of a 4:1 mixture of cis diol **9** and its 1*R*,2*R*,8a*S*-isomer, respectively: IR 3326, 1681, 1265 cm$^{-1}$; $^1$H NMR (300 MHz, acetone-$d_6$, major isomer) $\delta$ 1.13−1.33 (m, 2 H), 1.53 (ddddd, $J$ = 3.2, 3.2, 12.9, 12.9, 12.9 Hz, 1 H), 1.71 (m, 1 H), 1.90 (m, 1 H), 1.99 (m, 1 H), 2.71 (ddd, $J$ = 3.6, 12.9, 12.9 Hz, 1 H), 2.90−3.09 (br s, 1 H), 3.31 (ddd, $J$ = 3.1, 3.1, 12.2 Hz, 1 H), 3.94 (dd, $J$ = 2.9, 6.0 Hz, 1 H), 4.03 (m, 1 H), 4.17 (d, $J$ = 6.0 Hz, 1 H), 4.28−5.03 (br s, 1 H); $^{13}$C NMR (75 MHz, acetone-$d_6$, major isomer) $\delta$ 25.0 ($CH_2$), 26.0 ($CH_2$), 31.0 ($CH_2$), 41.4 ($CH_2$), 64.2 (CH), 71.5 (CH), 72.5 (CH), 172.1 (C); mass spectrum (EI) *m*/*z* 171 ($M^+$, 92), 84 (100). Anal. Calcd for $C_8H_{13}NO_3$: C, 56.13; H, 7.65; N, 8.18; $M_r$, 171.0896. Found: C, 55.74; H, 7.68; N, 8.12; $M_r$ (mass spectrum, EI), 171.0897.

**(1*S*,2*S*,8a*S*)-1,2-(Isopropylidenedioxy)hexahydroindolizin-3-one (10).** A mixture of 0.341 g (1.99 mmol) of the above cis diols and 1.0 g of Dowex 50W × 8 ($H^+$ form) in 50 mL of 2,2-dimethoxypropane (ADA) was stirred at 40 °C for 3.5 h, after which it was partially concentrated, filtered through Celite, and evaporated to dryness. Purification of the resulting crude product by silica gel column chromatography with 0−60% ethyl acetate in dichloromethane gave 0.039 g of the 1*R*,2*R*,8a*S*-acetonide and 0.291 g (69%) of acetonide **10**: mp 110−111 °C (hexane−dichloromethane); $[\alpha]_D^{25}$ +31.3 (*c* 1.0, $CHCl_3$); IR 1694 cm$^{-1}$; $^1$H NMR (500 MHz) $\delta$ 1.06 (dddd, $J$ = 3.5, 12.8, 12.8, 12.8 Hz, 1 H), 1.22−1.33 (m, 1 H), 1.35 (s, 3 H), 1.42 (s, 3 H), 1.50 (ddddd, $J$ = 3.5, 13.5, 13.5, 13.5, 13.5 Hz, 1 H), 1.64−1.67 (m, 1 H), 1.89−1.97 (m, 2 H), 2.69 (ddd, $J$ = 3.5, 13.0, 13.0 Hz, 1 H), 3.44 (dd, $J$ = 3.0, 12.5 Hz, 1 H), 4.16 (dd, $J$ = 4.8, 13.3 Hz, 1 H), 4.32 (d, $J$ = 6.5 Hz, 1 H), 4.61 (d, $J$ = 6.7 Hz, 1 H); $^{13}$C NMR (75.5 MHz) $\delta$ 23.8 ($CH_2$), 24.6 ($CH_2$), 25.4 ($CH_3$), 26.8 ($CH_3$), 30.8 ($CH_2$), 40.5 ($CH_2$), 62.2 (CH), 77.4 (2 × CH), 112.6 (C), 168.5 (C); mass spectrum (CI) *m*/*z* 212 ($MH^+$, 100), 211 (42), 171 (12), 124 (16). Anal. Calcd for $C_{11}H_{17}NO_3$: C, 62.54; H, 8.11; N, 6.63. Found: C, 62.38; H, 8.04; N, 6.44.

**(1*S*,2*R*,8a*S*)-Octahydroindolizin-1,2-diol ((−)-2-Epilentiginosine 1).** A stirred solution of 0.040 g (0.19 mmol) of acetonide **10** in 3 mL of THF was treated with 1.4 mL (1.4 mmol) of a 1 M solution of borane in THF. After being stirred at 55 °C for 12.5 h, the reaction mixture was allowed to cool to 20 °C, treated with ethanol, and evaporated to dryness. A solution of the resulting residue in 5 mL of ethanol was stirred at 60 °C for 2 h and then evaporated to dryness. The residue that resulted was stirred in 6 mL of 1 N HCl at reflux for 30 min, whereupon the reaction mixture was concentrated under reduced pressure, and the resulting residue was passed through a column of 6 g of Dowex 1 × 8−200 resin ($OH^-$ form) with water. The clear oil that was obtained on evaporation was purified by silica gel chromatography with 5−15% methanol saturated with ammonia in chloroform to give 0.025 g (84%, 2 steps) of pure **1**: $[\alpha]_D^{25}$ −39.3 (*c* 0.44, $CHCl_3$), (lit.[4e,5a] −39.4, −32.5); IR 3378, 2854, 2803 cm$^{-1}$; $^1$H NMR (300 MHz) $\delta$ 1.18−1.31 (m, 2 H), 1.40−1.55 (m, 1 H), 1.58−1.67 (m, 1 H), 1.78−1.89 (m, 2 H), 1.96−2.08 (m, 2 H), 2.15 (dd, $J$ = 5.3, 10.1 Hz, 1 H), 2.19−2.41 (br s, 2 H), 2.97 (dddd, $J$ = 1.4, 2.5, 4.7, 10.9 Hz, 1 H), 3.48 (ddd, $J$ = 0.4, 6.8, 10.1 Hz, 1 H), 3.63 (dd, $J$ = 7.7, 7.7 Hz, 1 H), 4.19 (ddd, $J$ = 5.3, 7.0, 7.0 Hz, 1 H); $^{13}$C NMR (75.5 MHz) $\delta$ 23.7 ($CH_2$), 24.9 ($CH_2$), 28.5 ($CH_2$), 52.7 ($CH_2$), 61.7 ($CH_2$), 67.3 (CH), 67.9 (CH), 75.0 (CH); mass spectrum (CI) *m*/*z* 158 ($MH^+$, 100), 157 (32). HRMS *m*/*e* calcd for $C_8H_{15}NO_2$ ($M^+$) + H: 158.1181. Found:158.1171.

The diacetate derivative of **1** ((1*S*,2*R*,8a*S*)-octahydro-1,2-diacetoxyindolizine)[4b,e] was prepared as previously described:[4b] $[\alpha]_D^{25}$ −67.4 (*c* 0.3, $CHCl_3$) (lit.[4e] −71.9); IR 2802, 1747 cm$^{-1}$; $^1$H NMR (300 MHz) $\delta$ 1.16−1.29 (m, 2 H), 1.41−1.65 (m, 2 H), 1.76−1.88 (m, 2 H), 2.02 (s, 3 H), 2.04 (s, 3 H), 2.05−2.15 (m, 2 H), 2.20 (dd, $J$ = 5.6, 10.1 Hz, 1 H), 2.98 (m, 1 H), 3.54 (dd,

$J$ = 7.0, 10.0 Hz, 1 H), 4.71 (dd, $J$ = 7.3, 8.7 Hz, 1 H), 5.19 (ddd, $J$ = 5.6, 7.1, 7.1 Hz, 1 H); $^{13}$C NMR (75.5 MHz) $\delta$ 20.5 ($CH_3$), 20.7 ($CH_3$), 23.6 ($CH_2$), 25.1 ($CH_2$), 28.7 ($CH_2$), 52.7 ($CH_2$), 59.4 ($CH_2$), 65.0 (CH), 68.4 (CH), 75.1 (CH), 170.0 (C); mass spectrum (CI) $m/z$ 242 ($MH^+$, 100), 180 (23). The $^1$H NMR spectrum was in excellent agreement with that of a sample prepared[4b] from the natural product (spectrum kindly provided by Professor C. Harris). HRMS $m/e$ calcd for $C_{12}H_{19}NO_4$ ($M^+$) + H: 242.1392. Found: 242.1404.

**2,4,6-Triisopropylbenzenesulfonic Acid (1*S*,2*S*,8a*S*)-1-Hydroxy-3-oxo-octahydroindolizin-2-yl Ester (11) and 1*R*,2*R*,8a*S*-isomer.** To a stirred solution of 0.161 g (0.94 mmol) of the above cis diols and 0.230 mL of triethylamine (0.167 g, 1.65 mmol) in 9.1 mL of dichloromethane at 0 °C was added 0.438 g (1.45 mmol) of 2,4,6-triisopropylbenzenesulfonyl chloride. The mixture was stirred at 20 °C for 20 h and then concentrated under reduced pressure. The resulting material was purified by silica gel chromatography with 10−40% ethyl acetate in cyclohexane to provide 0.373 g (91%) of sulfonate **11** and its 1*R*,2*R*,8a*S*-isomer as a white solid: IR 3384, 3054, 1710, 1599 cm$^{-1}$; $^1$H NMR (300 MHz, major isomer) $\delta$ 1.09 (dddd, $J$ = 3.6, 12.6, 12.6, 12.6 Hz, 1 H), 1.21−1.33 (m, 19 H), 1.38−1.53 (m, 1 H), 1.62−1.67 (m, 1 H), 1.86−1.92 (m, 1 H), 1.99−2.07 (m, 1 H), 2.70 (ddd, $J$ = 3.6, 12.9, 12.9 Hz, 1 H), 2.89 (hept, $J$ = 6.9 Hz, 1 H), 3.41 (ddd, $J$ = 2.9, 2.9, 12.3 Hz, 1 H), 4.03−4.16 (m, 3 H), 4.21 (dd, $J$ = 2.3, 5.8 Hz, 1 H), 4.92 (d, $J$ = 5.8 Hz, 1 H), 7.18 (s, 2 H); $^{13}$C NMR (75.5 MHz, major isomer) $\delta$ 23.8 ($CH_2$), 23.9 ($CH_3$), 24.7 ($CH_2$), 25.0 ($CH_3$), 25.1 ($CH_3$), 30.2 ($CH_2$), 30.4 (CH), 34.7 (CH), 41.1 ($CH_2$), 62.7 (CH), 70.6 (CH), 76.2 (CH), 124.4 (C), 128.9 (C), 151.7 (C), 154.9 (C), 164.3 (C); mass spectrum (FAB) $m/z$ 438 ($MH^+$, 100), 203 (11). Anal. Calcd for $C_{23}H_{35}NO_5S$: C, 63.13; H, 8.06; N, 3.20; S, 7.33; $M_r$ + H 438.2284. Found: C, 63.09; H, 8.04; N, 3.23; S, 7.38; $M_r$ (mass spectrum, FAB), 438.2314.

**Acetic Acid (1*S*,2*R*,8a*S*)-1-Hydroxy-3-oxo-octahydroindolizin-2-yl Ester (12).** To a stirred solution of 0.149 g (0.34 mmol) of the above sulfonates in 3.2 mL of toluene was added 0.244 g (0.81 mmol) of tetrabutylammonium acetate. The solution was stirred at 20 °C for 10 h and then concentrated under reduced pressure. The resulting material was purified by silica gel chromatography with 40−60% ethyl acetate in cyclohexane to provide 0.058 g of a mixture of acetates. Recrystallization of this material from dichloromethane-pentane gave 0.051 g (70%) of pure acetate **12**: mp 188−189 °C; $[\alpha]_D^{25}$ −51.9 ($c$ 1.0, $CHCl_3$); IR 3280, 1743, 1689 cm$^{-1}$; $^1$H NMR (300 MHz) $\delta$ 1.07−1.24 (m, 1 H), 1.25−1.33 (m, 2 H), 1.67−1.74 (m, 1 H), 1.86−1.92 (m, 1 H), 2.15 (s, 3 H), 2.11−2.19 (m, 1 H), 2.59−2.70 (m, 1 H), 3.22 (ddd, $J$ = 3.8, 6.0, 11.3 Hz, 1 H), 3.85−3.89 (m, 2 H), 4.07−4.14 (m, 1 H), 5.02 (dd, $J$ = 1.5, 6.4 Hz, 1 H); $^{13}$C NMR (75.5 MHz) $\delta$ 20.8 ($CH_3$), 22.9 ($CH_2$), 23.8 ($CH_2$), 30.8 ($CH_2$), 39.9 ($CH_2$), 59.5 (CH), 78.4 (CH), 80.0 (CH), 165.9 (C), 172.5 (C); mass spectrum (FAB) $m/z$ 214 ($MH^+$, 48), 73 (100). HRMS $m/e$ calcd for $C_{10}H_{15}NO_4$ ($M^+$) + H: 214.1081. Found: 214.1079.

**(1*S*,2*S*,8a*S*)-Octahydroindolizin-1,2-diol ((+)-Lentiginosine (2)).** To a stirred solution of 0.0227 g (0.106 mmol) of acetate **12** in 1.0 mL of THF at 0 °C was added 0.024 g (0.63 mmol) of lithium aluminum hydride. The mixture was stirred at 20 °C for 5 h, cooled to 5 °C, diluted with 1 mL of THF, and then carefully treated successively with 0.048 mL of water and 0.038 mL of 10% aqueous NaOH. The resulting mixture was stirred for 1 h, dried with sodium sulfate, and then processed with ethyl acetate to give, after recrystallization from dichloromethane−pentane, 0.0114 g of pure lentiginosine as a white solid. The residue obtained from the mother liquor on evaporation was reduced as above to provide an additional 0.0011 g (75% combined yield) of lentiginosine (**2**): mp 108−109 °C (lit.[5f] 106−107 °C); $[\alpha]_D^{24}$ +3.1 ($c$ 0.31, $CH_3OH$) (litt.[5f] +3.2); IR 3361 cm$^{-1}$; $^1$H NMR (300 MHz, $D_2O$) $\delta$ 1.18−1.35 (m, 2 H), 1.39−1.55 (m, 1 H), 1.61−1.70 (m, 1 H), 1.77−1.88 (m, 1 H), 1.93−2.00 (m, 2 H), 2.07 (ddd, $J$ = 2.9, 11.6, 11.7 Hz, 1 H), 2.74 (AB of ABX, $\delta_a$ = 2.64, $\delta_b$ = 2.84, $J_{ab}$ = 11.2 Hz, $J_{ax}$ = 7.3 Hz, $J_{bx}$ = 1.6 Hz, 2 H), 2.96 (br d, $J$ = 11.0 Hz, 1 H), 3.67 (dd, $J$ = 4.0, 8.7 Hz, 1 H), 4.08 (ddd, $J$ = 1.8, 3.9, 7.5 Hz, 1 H); $^{13}$C NMR (75.5 MHz, $D_2O$) $\delta$ 25.6 ($CH_2$), 26.5 ($CH_2$), 30.1 ($CH_2$), 55.5 ($CH_2$), 62.8 ($CH_2$), 71.1 (CH), 78.2 (CH), 85.5 (CH); mass spectrum (FAB) $m/z$ 158 ($MH^+$, 100%). The $^1$H NMR spectrum was in perfect agreement with that of an independently prepared[5d] sample (spectrum kindly provided by Professor M. Shibasaki). Anal. Calcd for $C_8H_{15}NO_2$: C, 61.12; H, 9.62; N, 8.91; $M_r$ + H 158.1180. Found: C, 60.75; H, 9.68; N, 8.75; $M_r$ (mass spectrum), 158.1181.

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**Supporting Information Available:** $^1$H and $^{13}$C NMR spectra of **1**, **2**, **3**, **5b**, **6**, **7a**, **12**, the olefin from **8b**, and the diacetate from **1** and ORTEP drawings for **8a** and **10**. This material is available free of charge via the Internet at http://pubs.acs.org.

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