Conjugate-Addition Reactions of α-Sulfinyl Ketimine Anions with a Methyl α-Amidoacrylate. Concise Asymmetric Total Syntheses of (−)-Slaframine and (−)-6-Epislaframine

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The in-situ 1,4-addition/ring-closure reactions of chiral α-sulfinyl ketimine anions with a methyl α-amidoacrylate provide a simple method for the construction of optically pure 6-aminoindolizidinones. This method afforded the syntheses of (−)-slaframine and (−)-6-epislaframine in six steps, respectively, from (±)-3-[(*tert*-butyldimethylsilyl)oxy]-4,5-dihydro-2-methyl-3*H*-pyrrole (**9**). Stereoselective reductions of α-sulfinyl ketimines (such as **10**) were also developed.

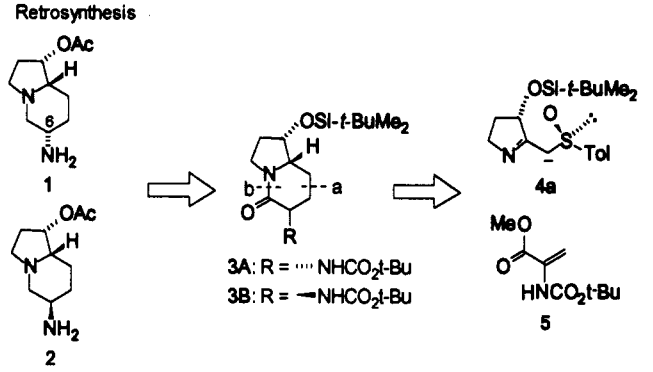
Introduction

1,4-Addition reactions of chiral α-sulfinyl ketimine anions with ene esters have been shown[1] to be a key step in a versatile method for the construction of alkaloids. In a continuation of these studies, we have investigated the conjugate addition with a methyl α-amidoacrylate possessing an acidic NH (e.g., **5**), a compound frequently used in the synthesis of α-amino acids[2] via various methods, although the 1,4-addition reaction with organocuprates reportedly failed.[3] We now report successful 1,4-addition reactions of α-sulfinyl ketimine anions with α-amidoacrylic ester and their application in concise asymmetric total syntheses of (−)-slaframine (**1**)[4] and (−)-6-epislaframine (**2**).[5]

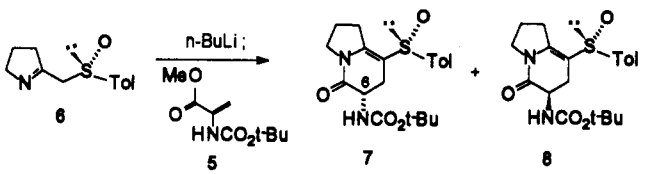
Results and Discussion

A major goal in our studies was the development of a concise asymmetric synthesis of biologically active aminoindolizidines (such as **1** and **2**) and aminonojirimycin derivatives.[6] Ideally, the amino group should be incorporated in the early stage of the synthesis in a protected form (e.g., amido group). This concept is incorporated in the relatively simple retrosynthesis shown in Scheme I for the assembly of the aminoindolizidine skeleton such as **3A** and **3B**. This synthesis could be carried out in one-pot reactions, 1,4-addition of α-sulfinyl ketimine anion **4a** to α-amidoacrylate **5** (formation of bond a) followed by ring closure (formation of bond b).

Scheme I



Scheme II



Despite the reports that **5** does not react with organocuprate reagents,[3] we decided to investigate first the addition reaction of **5** with an anion derived from the simpler α-sulfinyl ketimine **6**.[1] To our surprise, the anion of **6** underwent smooth conjugate addition followed by ring closure to give a 34.3% yield of a mixture of **7** and **8** in a ratio of 1.5:1 (Scheme II). Unequivocal assignment of the stereochemistry at C-6 of **7** and **8** could not be easily made without single-crystal X-ray analysis, and we are unable to obtain single crystals of either **7** or **8**. Tentative assignments were made on the basis of ^{1}H NMR chemical shifts of C-6 H (vide infra). The assignment of the stereochemistry at C-6 of **7** and **8** is not critical, however, since the stereochemistry of (−)-slaframine (**1**) is known.[4]

The required α-sulfinyl ketimine **4** for the synthesis of **1** and **2** and with its diastereomer **10** were prepared from

† Fellow of the Alfred P. Sloan Foundation, 1989–1993.

(1) Hua, D. H.; Bharathi, S. N.; Panagadan, J. A. K.; Tsujimoto, A. *J. Org. Chem.* **1991**, *56*, 6998–7007.

(2) Through hydroboration: (a) For review, see Koenig, K. E. *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: Orlando, FL, 1985; Vol. 5, p 71. (b) Knowles, W. S. *Acc. Chem. Res.* **1983**, *16*, 106–112. Preparation of α,β-diaminopropionic ester: (c) Labia, R.; Morin, C. *J. Org. Chem.* **1986**, *51*, 249–251. Preparation of α,β-didehydro amino acids via palladium-catalyzed coupling of aromatic halides and α-amidoacrylate: (d) Carlstroem, A. S.; Frejd, T. *Acta Chem. Scand.* **1992**, *46*, 163–171. Asymmetric hydroformylation with rhodium: (e) Gladiali, S.; Luigi, P. *Tetrahedron: Asymmetriy* **1991**, *2*, 623–632.

(3) α-Amidoacrylate **5** reportedly did not provide any 1,4-addition product with various organocuprates; it is likely that the acidic NH of **5** was deprotonated by the cuprate reagent and the resulting amide anion failed to react further: (a) Bajgrowicz, J. A.; El Hallaoui, A.; Jacquier, R.; Pigiere, Ch.; Viallefont, Ph. *Tetrahedron Lett.* **1984**, 2759–2762. (b) Bajgrowicz, J. A.; El Hallaoui, A.; Jacquier, R.; Pigiere, C.; Viallefont, P. *Tetrahedron* **1985**, *41*, 1833–1843.

(4) Synthesis of (−)-slaframine: (a) Sibi, M. P., Christensen, J. W.; Li, B.; Renhowe, P. A. *J. Org. Chem.* **1992**, *57*, 4329–4330. (b) Pearson, W. H.; Bergmeier, S. C. *J. Org. Chem.* **1992**, *57*, 3977–3987. (c) Knapp, S.; Gibson, F. S. *J. Org. Chem.* **1992**, *57*, 4802–4809. (d) Choi, J. R.; Han, S.; Cha, J. K. *Tetrahedron Lett.* **1991**, 6469–6472. For the synthesis of (±)-slaframine and biological activities, see refs 8–13, and 1 and 6, respectively, cited in ref 4b. For a recent review: (e) Molyneux, R. J.; James, L. F. *Mycotoxins and Phytoalexins*; Sharma, R. P.; Salunkhe, D. K., Eds.; CRC Press: Boca Raton, FL, 1991; pp 637–656.

(5) The enantiomer of **2**, (+)-1,8a-diepislaframine, has been synthesized by Pearson et al., ref 4b.

(6) For an example of aminonojirimycin, kifunensine: Kayakiri, H.; Takase, S.; Shibata, T.; Okanoto, M.; Terano, H.; Hashimoto, M. *J. Org. Chem.* **1989**, *54*, 4015–4016.

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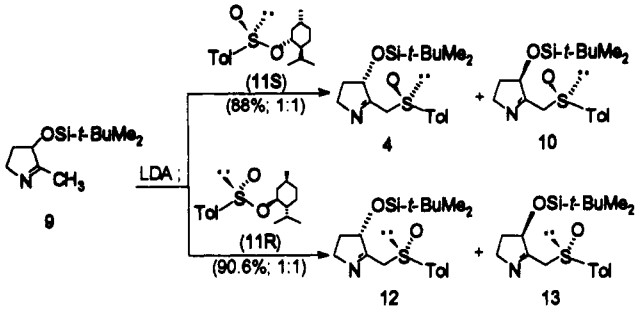
Scheme III

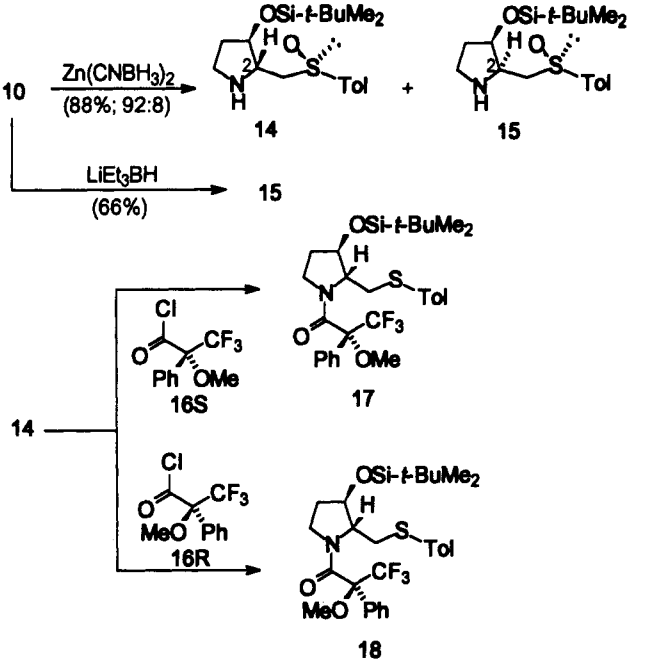


the displacement reaction of the anion of ketimine (±)-**9**[7] with *l*-(−)-(*SS*)-menthyl *p*-toluenesulfinate (**11S**) (Scheme III). A 1:1 mixture (88% yield) of **4** and **10** obtained from the reaction was readily separated by column chromatography. Since the chirality at the sulfur center of the sulfinyl ketimine may influence the selectivity at C-6 of the amino indolizidines, we also prepared the other two diastereomers emanating from the chiral sulfur, **12** and **13** (enantiomers of **10** and **4**, respectively), from the anion of (±)-**9** and *d*-(+)-(*SR*)-menthyl *p*-toluenesulfinate (**11R**) (90.6% yield; 1:1 mixture; separated by column chromatography). It should be noted that although **10** and **13** were not used in the synthesis of (−)-slaframine, they will be utilized in the asymmetric synthesis of (+)-retronecine.[8] The determination of the relative stereochemistry at C-3 and sulfur of **4** and **10** (or **12** and **13**) was based on a single-crystal X-ray analysis of a derivative of **13**, ethyl (2*R*,3*R*,*SR*)-3-[(ethoxycarbonyl)oxy]-2-[1-(*p*-tolylsulfinyl)cyclopropyl]-1-pyrrolidinecarboxylate.[9] The absolute *R*-configuration of sulfur of **4** and **10** was assigned because the displacement reaction **11S** → **4** proceeds with inversion of configuration.[1]

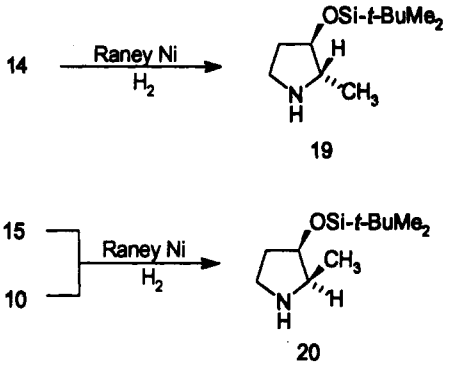
To determine the optical purity of α-sulfinyl ketimine **4** or **10**, ^{13}C NMR studies of Mosher's derivatives[10] of the reduced amine were carried out. Remarkably, reduction of **10** with 2 equiv of $Zn(CNBH_3)_2$[11] in MeOH stereoselectively gave an 81% yield of pyrrolidine **14** and 7% yield of its C-2 isomer **15** (Scheme IV). In contrast, reduction with 2 equiv of $LiEt_3BH$ in THF provided only **15** (66% yield); no **14** was detected. Treatment of pyrrolidine **14** with 2 equiv of (−)-(*S*)-α-methoxy-α-(trifluoromethyl)-phenylacetyl chloride (MTPAC) (**16S**) in pyridine at 50 °C for 20 h afforded amide **17**; similar treatment of **14** with (+)-(*R*)-MTPAC (**16R**) provided amide **18**. The ^{13}C NMR spectra of **17** and **18** are completely different and they indicate that **14** is optically pure (>99% ee), which implies that **10** is likewise optically pure. The sulfinyl group was reduced to sulfide in the presence of the acid chloride and pyridine;[12] therefore, more than 2 equiv of MTPAC was required for the reaction.

Assignment of absolute configuration to C-2 of **14** and **15** was based on the desulfurizations of **14** and **15** and

Scheme IV



Scheme V



desulfurization followed by hydrogenation of **10** with W-2 Raney nickel[13] under a hydrogen atmosphere (Scheme V), since hydrogenation of the imine (C=N) function of **10** would be expected to occur from the opposite face of the C-3 bulky (*tert*-butyldimethylsilyl)oxy group.[14]

Treatment of α-sulfinyl ketimine **4** with *n*-BuLi in THF at −78 °C followed by α-amidoacrylic ester **5** provided a 55% yield of indolizidinones **21** and **22** in a ratio of 3:2, they could be separated either at this stage or the next step (**3A** and **3B**; easier separation) (Scheme VI). It should be noted that C-6 H is epimerizable (vide infra). On the basis of the proposed transition states[1] as depicted in Figure 1, starting with the diastereomer of opposite configuration at sulfur (i.e., **12**) could provide different selectivity at C-6 of the indolizidinones. Indeed, the anion of **12** underwent conjugate addition followed by ring closure to give a 54.7% yield of **25** and **26** in a ratio of 1:2, which were separated by column chromatography. The assigned stereochemistry at C-6 of **21**, **22**, **25**, and **26** was based on their transformation to **1** and **2**. From the ^1H NMR chemical shifts of C-6 H of **25** (δ 4.97; α-epimer) and **26** (δ 5.04; β-epimer), the stereochemistry of adducts **7** and **8** derived from the addition of **6** to **5** was assigned. The

(7) Hua, D. H.; Miao, S.-W.; Bharathi, S. N.; Katsuhira, T.; Bravo, A. A. *J. Org. Chem.* **1990**, *55*, 3682–3684.

(8) For reviews of retronecine-related pyrrolizidine alkaloids: (a) Wrobel, J. T. *The Alkaloid*; Brossi, A., Ed.; Academic Press: New York, 1985; Vol. 26, p 327. (b) Reference 4e, pp 657–669.

(9) Robinson, P. D.; Hua, D. H.; Wu, X.; Miao, S. W.; Meled, M. *Acta Crystalogr., C.* **1992**, *C48*, 2088–90.

(10) Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* **1969**, *34*, 2543–2550.

(11) Kim, S.; Oh, C. H.; Ko, J. S.; Ahn, K. H.; Kim, K. J. *J. Org. Chem.* **1985**, *50*, 1927–1932.

(12) Hua, D. H.; Coulter, M. J.; Badejo, I. *Tetrahedron Lett.* **1987**, 5465–5468.

(13) Mozingo, R. *Organic Syntheses*; Wiley: New York, 1955; Collect. Vol. III, p 181.

(14) Meinwald, J.; Ottenheym, H. C. J. *Tetrahedron* **1971**, *27*, 3307–3315.

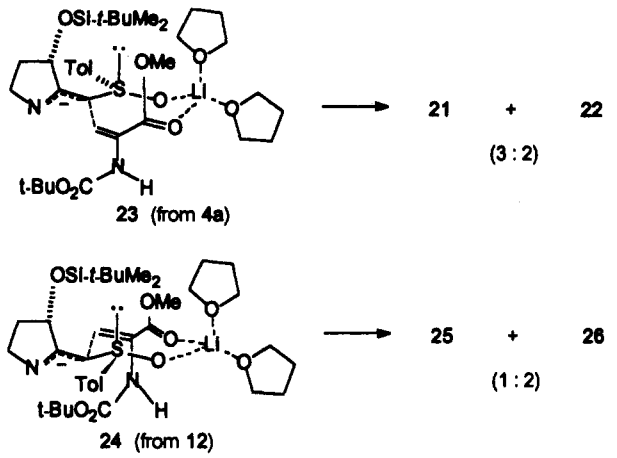
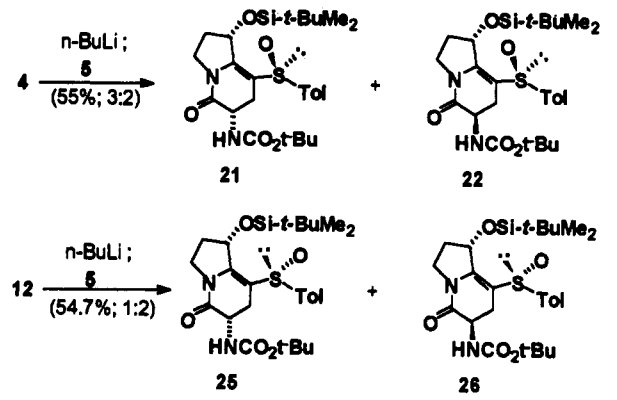
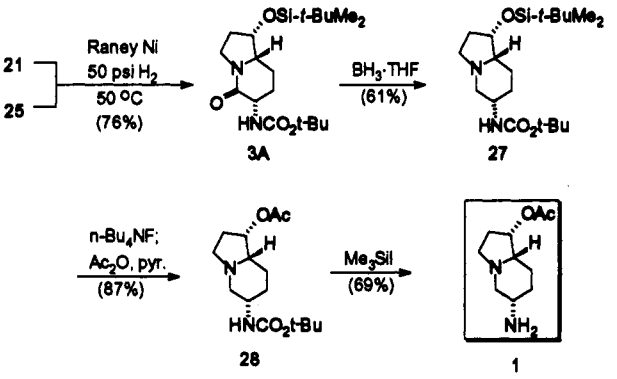


Figure 1.

Scheme VI



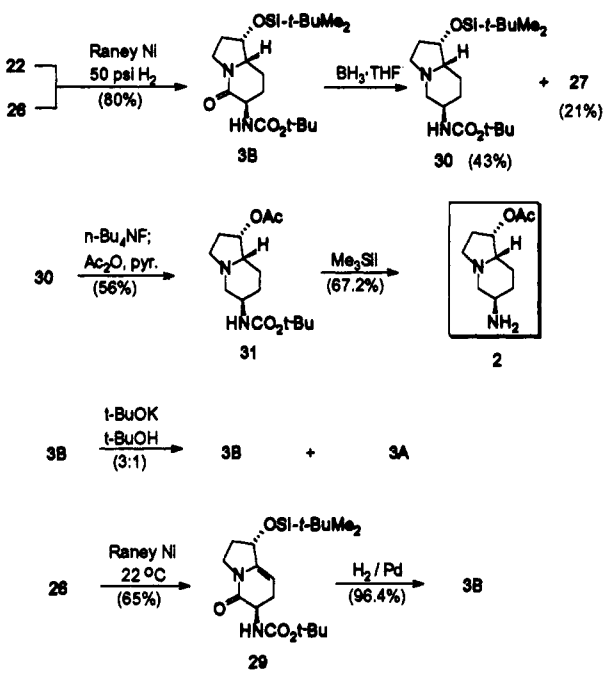
Scheme VII



isomer exhibiting the higher-field resonance (δ 5.04) was assigned with α-epimer, **7**, and that exhibiting the lower field resonance (δ 5.10) the β-epimer, **8**.

Conversions of **21** (or **25**) and **22** (or **26**) into (−)-slaframine (**1**) and (−)-6-epislaframine (**2**), respectively, were accomplished in four steps (Schemes VII and VIII). Yields of **3A** of ~76% from **21** as well as **25** were obtained from desulfurization–hydrogenation with W-2 Raney nickel in ethanol under 50 psi of hydrogen. Reduction of the amide function of **3A** with borane in THF provided a 61% yield of indolizidine **27**, which upon desilylation with *n*-Bu_4NF in THF followed by in situ acetylation with acetic anhydride and pyridine, afforded an 87% yield of carbamate **28**. Deprotection of **28** with Me_3SiI[15] furnished a 69% yield of (−)-slaframine (**1**) with physical properties identical to those reported.[4b]

Scheme VIII



Similar treatment of sulfoxides **22** and **26**, respectively, with W-2 Raney nickel under 50 psi of hydrogen at 50 °C gave an 80% yield of **3B**. Epimerization of **3B** (C-6 H) is effected by treatment with potassium *tert*-butoxide in *t*-BuOH, producing a mixture of 3:1 of **3B** and **3A**. The reduction of **26** to **3B** was also carried out in a stepwise manner. Desulfurization of **26** with W-2 Raney nickel under argon at 22 °C provided a 65% yield of the olefin intermediate **29**, which after treatment with Pd/C and 50 psi of hydrogen, afforded a 96.4% yield of **3B**. Although, the direct method (one-step conversion of **26** into **3B**) provided a higher yield, the stepwise method gave enamide **29**, which allows further functionalization at C-8 and -7 and hence can be used in the synthesis of 6-amino-6-deoxycastanospermines (derivatives of castanospermine[16]). The reduction of **3B** with borane·THF proceeded very slowly and required 3 equiv of BH_3; in addition to the expected product, **30** (43% yield), the C-6 epimer **27** (21% yield) was also formed. Undoubtedly, **3B** was slowly epimerized by BH_3 under the reaction conditions. The pure epimer **30** was transformed into (−)-6-epislaframine (**2**) in two steps (56% and 67.2% yields, respectively) as described above for the preparation of **1** using *n*-Bu_4NF and acetic anhydride followed by Me_3SiI.

Conclusions

α-Sulfinyl ketimine anions were shown to undergo conjugate addition with an α-amidoacrylic ester which failed to react with organocuprate reagents. This addition reaction and the accompanying ring closure provided concise syntheses of the parasympathomimetic alkaloids (−)-slaframine and (−)-6-epislaframine in six steps, respectively, from ketimine **9**. The method developed is general and should be applicable to the construction of other biologically important hydroxylated aminoindolizidine alkaloids such as aminonojirimycin and aminocastanospermine derivatives. The 1,4-addition reactions occurred readily with both diastereomers **4** and **12**

(15) Lott, R. S.; Chauhan, V. S.; Stammer, C. H. *J. Chem. Soc., Chem. Commun.* **1979**, 495–496.

(16) Hohenschutz, L. D.; Bell, E. A.; Jewess, P. J.; Leworthy, D. P.; Pryce, R. J.; Arnold, E.; Clardy, J. *Phytochem.* **1981**, *20*, 811–814.

further demonstrate the high utility of this method. Stereoselective reductions of α-sulfinyl ketimines (such as **10**) with $Zn(CNBH_3)_2$ and $LiEt_3BH$ provided useful chiral pyrrolidines (such as **14** and **15**) which can be utilized in other alkaloid syntheses.

Experimental Section

General Methods. Nuclear magnetic resonance spectra were obtained at 400 MHz for ^1H and 100 MHz for ^{13}C in deuteriochloroform, unless otherwise indicated. Infrared spectra are reported in wavenumbers (cm^{-1}). FAB MS were taken in Xe gas, 2 kV, using glycerol and *m*-nitrobenzyl alcohol as the matrix. Davisil silica gel, grade 643 (200–425 mesh), was used for the flash chromatographic separation. (−)-(S*S*)-4,5-Dihydro-2-[[(4-methylphenyl)sulfinyl]methyl]-3*H*-pyrrole (**6**)[17] and 3-[(*tert*-butyldimethylsilyl)oxy]-4,5-dihydro-2-methyl-3*H*-pyrrole (**9**)[7] were obtained as described. Methyl 2-[(*tert*-butoxycarbonyl)amino]-propanoate (**5**)[18] was prepared by following the reported procedure, kept in a dry benzene solution at 0 °C due to its instability in neat form, and used in the benzene solution.

(6*S*,S*R*)- and (6*R*,S*R*)-6-[(*tert*-Butoxycarbonyl)amino]-1,2,3,5,6,7-hexahydro-8-[(4-methylphenyl)sulfinyl]-5-indolizinone (7 and 8). To a cold (−78 °C) solution of 0.2 g (0.9 mmol) of sulfinyl ketimine **6** in 20 mL of THF under argon was added 0.67 mL (1.07 mmol) of *n*-BuLi (1.6 M in THF). After the solution was stirred at −78 °C for 0.5 h, 5.8 mL (0.9 mmol) of **5** in benzene (0.15 M solution) was added, the solution was stirred at −78 °C for 1 h and 22 °C for 12 h, diluted with 1 mL of H_2O and 10 mL of brine, and extracted three times with CH_2Cl_2 (20 mL each). The combined organic layer was dried ($MgSO_4$), concentrated, and column chromatographed on silica gel using a gradient mixture of MeOH in CH_2Cl_2 as eluant to give 0.1206 g (34.3% yield) of **7** and **8** in a ratio of 1.5:1 (determined by ^1H NMR). Recrystallization of this mixture in CH_2Cl_2–hexane (1:1) gave 47.6 mg (13.5% yield) of pure **7** and 73 mg of residue from the mother liquor (containing **7** and **8**). Pure indolizidine **7**: mp 200–202 °C dec; $[\alpha]^{22}_D$ = −21.6° (*c* 0.5, CH_2Cl_2); ^1H NMR δ 7.38 (d, *J* = 8 Hz, 2 H), 7.26 (d, *J* = 8 Hz, 2 H), 5.04 (m, 1 H, C-6 H), 4.3 (br s, 1 H, NH), 3.78 (dt, *J* = 11, 7 Hz, 1 H, C-3 H), 3.67 (dt, *J* = 11, 7 Hz, 1 H, C-3), 3.22–3.15 (m, 1 H), 3.05–2.98 (m, 2 H), 2.37 (s, 3 H, *p*-Me), 2.1–2.05 (m, 2 H), 1.8–1.7 (m, 1 H), 1.4 (s, 9 H, *t*-Bu); ^{13}C NMR δ 167.07 (s, C=O of lactam), 155.1 (s, C=O of carbamate), 147.34 (s, NC=), 140.81 (s, Ar), 138.67 (s, Ar), 129.78 (d, 2 C, Ar), 124.06 (d, 2 C, Ar), 111.72 (s, =CS), 79.89 (s, *t*-Bu), 50.94 (d, C-6), 46.44 (t, C-3), 29.02 (t), 28.15 (q, *t*-Bu), 23.07 (t), 21.94 (t), 21.43 (q, *p*-Me); MS, CI *m/z* 391 (M + 1), 363, 335 (100, M − C_4H_8), 291, 273, 195. Anal. Calcd for $C_{20}H_{26}N_2O_4S$: C, 61.54; H, 6.71. Found: C, 61.66; H, 6.43. Mixture of **7** and **8**: ^1H NMR δ 7.44 (d, *J* = 8 Hz, 2 H, Ar, **8**), 7.4 (d, *J* = 8 Hz, 2 H, Ar, **7**), 5.1 (m, 1 H, C-6 H, **8**), 5.05 (m, 1 H, C-6 H, **7**), 4.3 (br s, 1 H, NH), 3.85–3.8 (m, 1 H, C-3 H), 3.87–3.78 (m, 1 H, C-3 H), 3.32–3.18 (m, 1 H), 3.1–2.92 (m, 2 H), 2.59 (dd, *J* = 15, 7 Hz, 1 H, **8**), 2.44 (d, *J* = 15 Hz, 1 H, **8**), 2.41 (s, 3 H, *p*-Me, **8**), 2.39 (s, 3 H, *p*-Me, **7**), 2.15–2.05 (m, 2 H), 1.8–1.7 (m, 1 H), 1.41 (s, 9 H, *t*-Bu); ^{13}C NMR δ 167.15, 167.0 (s, C=O), 155.1 (s, C=O), 147.78, 147.53 (s, NC=), 141.04, 140.92 (s, Ar), 138.73 (s, Ar), 130.06, 129.88 (d, 2 C, Ar), 124.17 (d, 2 C, Ar), 111.7 (s, =CS), 79.9 (s, *t*-Bu), 51.09 (d, C-6), 46.5, 46.15 (t, C-3), 31.5, 29.08 (t), 28.22 (q, *t*-Bu), 24.48, 23.19 (t), 22.55, 21.97 (t), 21.85, 21.24 (q, *p*-Me); MS CI *m/z* 391 (M + 1), 335 (100, M − C_4H_8), 291, 193, 157.

(3*S*,S*R*)-3-[(*tert*-Butyldimethylsilyl)oxy]-4,5-dihydro-2-[[(4-methylphenyl)sulfinyl]methyl]-3*H*-pyrrole (4) and (3*R*,S*R*)-3-[(*tert*-Butyldimethylsilyl)oxy]-4,5-dihydro-2-[[(4-methylphenyl)sulfinyl]methyl]-3*H*-pyrrole (10). To a cold (−25 °C) solution of 0.0458 mol of lithium diisopropylamide (LDA) in 50 mL of THF under argon was added 4.89 g (0.0229 mol) of **9** in 45 mL of THF. The solution was stirred at −25 °C for 30 min and a solution of 6.73 g (0.0229 mol) of (−)-(*S*)-1-menthyl *p*-toluenesulfinate (**11S**)[19] in 45 mL of THF was added via cannula. After the dark red solution was stirred at −25 °C for 1.5 h, it was poured into 100 mL of H_2O and 200 mL of ether. The water layer was separated and extracted three times with CH_2Cl_2 (50 mL each). The combined organic layers were dried ($MgSO_4$), concentrated, and column chromatographed on silica gel (4.7 × 47 cm column), using a gradient mixture of hexane, toluene, and *tert*-butyl alcohol as eluant (products came out at hexane:toluene:*t*-BuOH = 20:70:5), to give pure **4** and **10** and a mixture of **4** and **10** (2.7466 g). The mixture was recolumned under the same conditions to give a total of 3.5204 g (44% yield) of **4** and 3.5136 g (~44% yield) of **10**.

Pure 4: mp 55–56 °C; $[\alpha]^{22}_D$ = +47.6° (*c* 1, CH_2Cl_2); IR (Nujol) ν 2910, 2840, 1630, 1450, 1390, 1356, 1243 (s), 1075 (s), 1035 (s); ^1H NMR δ 7.54 (d, *J* = 8 Hz, 2 H, Ar), 7.32 (d, *J* = 8 Hz, 2 H, Ar), 4.51 (t, *J* = 8 Hz, 1 H, CHO), 3.92 (d, *J* = 12 Hz, 1 H, CHS), 3.90 (m, overlap, 1 H, CHN), 3.85 (d, *J* = 12 Hz, 1 H, CHS), 3.59 (m, 1 H, CHN), 2.41 (s, 3 H , *p*-Me), 2.8 (m, 1 H), 1.6 (m, 1 H), 0.94 (s, 9 H, *t*-Bu), 0.14 (s, 3 H, MeSi), 0.10 (s, 3 H, MeSi); ^{13}C NMR δ 170.18 (s, C=N), 141.74 (s), 140.24 (s), 129.7 (d, 2 C), 124.23 (d, 2 C), 79.17 (d, CO), 58.27 (t, CN), 57.79 (t, CS), 33.41 (t), 25.58 (q, *t*-Bu), 21.27 (q, *p*-Me), 17.78 (s, *t*-Bu), −4.69 (q), −5.08 (q); MS EI *m/z* 351 (M^+), 303, 294, FAB 352 (M + 1), 334, 294. Anal. Calcd for $C_{18}H_{29}NO_2SSi$: C, 61.49; H, 8.31; N, 3.98. Found: C, 60.96; H, 8.00; N, 3.54.

Pure 10: oil, $[\alpha]^{22}_D$ = +143° (*c* 1.55, CH_2Cl_2); IR (neat) ν 2960, 2940, 2865, 1640, 1493, 1462, 1400, 1362, 1255 (s), 1115 (s), 1090 (s), 1050 (s); ^1H NMR δ 7.57 (d, *J* = 8 Hz, 2 H), 7.33 (d, *J* = 8 Hz, 2 H), 4.71 (t, *J* = 7.8 Hz, 1 H, CHO), 4.03 (dd, *J* = 16, 9 Hz, 1 H, CHN), 3.95 (d, *J* = 13 Hz, 1 H, CHS), 3.75 (dt, *J* = 16, 8 Hz, 1 H, CHN), 3.66 (d, *J* = 16 H, 1 H, CHS), 2.42 (s, 3 H, *p*-Me), 2.28 (m, 1 H, CH_2), 1.62 (ddt, *J* = 13, 8, 5 Hz, 1 H, CH_2), 0.88 (s, 9 H, *t*-Bu), 0.13 (s, 3 H, MeSi), 0.09 (s, 3 H, MeSi); ^{13}C NMR δ 171.15 (s, C=N), 141.7 (s, Ar), 141.08 (s, Ar), 129.84 (d, 2 C), 123.95 (d, 2 C), 79.74 (d, CO), 58.42 (t), 57.99 (t), 33.38 (t), 25.58 (q, *t*-Bu), 21.3 (q, *p*-Me), 17.78 (s, *t*-Bu), −4.7 (q), −4.99 (q); MS, EI *m/z* 351 (M^+).

(3*S*,S*S*)-3-[(*tert*-Butyldimethylsilyl)oxy]-4,5-dihydro-2-[[(4-methylphenyl)sulfinyl]methyl]-3*H*-pyrrole (12) and (3*R*,S*S*)-3-[(*tert*-Butyldimethylsilyl)oxy]-4,5-dihydro-2-[[(4-methylphenyl)sulfinyl]methyl]-3*H*-pyrrole (13). Similar reaction conditions to those described above were followed but using (+)-(*R*)-*d*-menthyl *p*-toluenesulfinate (**11R**). Starting with 3.84 mmol of **9** gave a 45.3% yield of **12** and a 45.3% yield of **13**. Pure **12**: oil, $[\alpha]^{22}_D$ = −151.7° (*c* 1.3, CH_2Cl_2); the ^1H and ^{13}C NMR spectra were identical to those of **10**. Pure **13**: mp 54.5–56 °C; $[\alpha]^{22}_D$ = −41.6° (*c* 1.4, CH_2Cl_2); the ^1H and ^{13}C NMR spectra were identical with those of **4**.

(2*R*,3*R*,S*R*)-3-[(*tert*-Butyldimethylsilyl)oxy]-2-[[(4-methylphenyl)sulfinyl]methyl]pyrrolidine (14) and (2*S*,3*R*,S*R*)-3-[(*tert*-Butyldimethylsilyl)oxy]-2-[[(4-methylphenyl)sulfinyl]methyl]pyrrolidine (15). To a cold (0 °C) solution of 57 mg (0.16 mmol) of **10** in 1 mL of MeOH (distilled over Mg) was added a solution of 0.32 mmol of $Zn(CNBH_3)_2$ in 1.6 mL of MeOH. After the solution was stirred at 0 °C for 2 h and 22 °C for 10 h, a few drops of 1 N NaOH and 10 mL of brine were added, and the solution was extracted three times with CH_2Cl_2 (25 mL each). The organic layer was dried ($MgSO_4$), concentrated, and column chromatographed on silica gel using a 98:2 mixture of CH_2Cl_2 and MeOH as eluant to give 45.7 mg (81% yield) of **14**, 4 mg (7% yield) of **15**, and 4 mg (7% recovery) of **10**. **14**: $[\alpha]^{22}_D$ = +63.6° (*c* 1.285, CH_2Cl_2); ^1H NMR δ 7.56 (d, *J* = 8 Hz, 2 H), 7.33 (d, *J* = 8 Hz, 2 H), 4.03 (q, *J* = 6 Hz, 1 H, CHO), 3.1–3.0 (m, 2 H, CHS), 3.02 (m, 1 H, CHN), 2.95–2.9 (m, 2 H, CH_2N), 2.42 (s, 3 H, *p*-Me), 2.17 (s, 1 H, NH), 2.08–1.98 (m, 1 H, CH_2), 1.7–1.65 (m, 1 H, CH_2), 0.85 (s, 9 H, *t*-Bu), 0.03 (s, 3 H, MeSi), 0.02 (s, 3 H, MeSi); ^{13}C NMR δ 141.62 (s), 141.05 (s), 129.99 (d, 2 C), 124.17 (d, 2 C), 77.0 (d, CO), 62.40 (CHN), 61.55 (CH_2N), 44.29 (t, CS), 33.73 (t), 25.72 (q, *t*-Bu), 21.37 (q, *p*-Me), 17.89 (s, *t*-Bu), −4.57 (q, MeSi), −4.84 (q, MeSi); MS, FAB *m/z* 354 (M + 1), 338, 185, 93. **15**: $[\alpha]^{22}_D$ = +106° (*c* 0.96, $CHCl_3$); IR (CCl_4) ν 2950, 2930, 2860, 1490, 1460, 1400, 1360, 1255 (s), 1100 (s), 1048 (s); ^1H NMR δ 7.51 (d, *J* = 8 Hz, 2 H), 7.29 (d, *J* = 8 Hz, 2 H), 4.23 (ddd, *J* = 8, 5,

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3 Hz, 1 H, CHO), 3.44 (dt, J = 9, 4 Hz, 1 H, CHN), 3.17 (dt, J = 11, 8 Hz, 1 H, CH_2N), 2.98–2.9 (m, 1 H, CH_2N), 2.89–2.85 (m, 2 H, CHS), 2.67 (br s, 1 H, NH), 2.38 (s, 3 H, p-Me), 2.0–1.93 (m, 1 H, CH_2), 1.77–1.7 (m, 1 H), 0.79 (s, 9 H, t-Bu), 0.00 (s, 3 H, MeSi), –0.04 (s, 3 H, MeSi); ^{13}C NMR δ 141.31 (s), 141.19 (s), 129.96 (d, 2 C), 123.92 (d, 2 C), 74.2 (d, CO), 59.12 (d, CN), 57.85 (t, CN), 44.32 (t, CS), 35.78 (t), 25.72 (q, t-Bu), 21.36 (q, p-Me), 17.97 (s, t-Bu), –4.59 (q, MeSi), –4.95 (q, MeSi); MS, FAB m/z 354 (M + 1).

Reduction of 10 with $LiEt_3BH$. Formation of 15. To a cold (0 °C) solution of 1.0433 g (2.97 mmol) of **10** in 50 mL of THF under argon was added 5.94 mL (5.94 mmol) of $LiEt_3BH$ in THF (1.0 M solution). After the solution was stirred at 22 °C for 29 h, 1 mL of water was added, and the THF was removed in vacuo. The residue was diluted with 150 mL of CH_2Cl_2, washed with $NaHCO_3$ solution and brine, dried ($MgSO_4$), concentrated, and column chromatographed on silica gel using a gradient mixture of ether and MeOH as eluant to give 0.6905 g (66% yield) of **15** and of 29 mg (3% recovery) of starting sulfoxide **10**.

(2*R*,3*R*,2′*R*)-3-[(*tert*-Butyldimethylsilyl)oxy]-2-[[(4-methylphenyl)sulfenyl]methyl]-1-[methoxy(trifluoromethyl)phenylacetyl]pyrrolidine (17). To a solution of 18 mg (0.05 mmol) of amine **14** in 0.1 mL of pyridine under argon was added 25.7 mg (0.1 mmol) of (–)-(*S*)-α-methoxy-α-(trifluoromethyl)-phenylacetyl chloride (MTPAC). After the solution was stirred at 50 °C for 20 h, it was diluted with 10 mL of brine and extracted three times with CH_2Cl_2 (20 mL each). The combined organic layer was dried ($MgSO_4$), concentrated, and column chromatographed on silica gel using a mixture of 9:1 of hexane and ether as eluant to give 12.4 mg (44% yield; only one diastereomer was detected) of **17**. Other unidentified byproducts were also isolated but the enantiomer of **18** was not detected. **17**: ^{1}H NMR δ 7.56 (m, 2 H, Ph), 7.41–7.39 (m, 5 H, Ph and Tol), 7.17 (d, J = 7 Hz, 2 H, Tol), 4.39 (s, 1 H, CHO), 4.27 (dd, J = 8, 2 Hz, 1 H, CHN), 3.73 (dd, J = 14, 2 Hz, 1 H, CH_2N), 3.68 (s, 3 H, OMe), 3.54 (dd, J = 14, 8 Hz, 1 H, CH_2N), 2.65 (td, J = 11, 2 Hz, 1 H, CS), 2.38 (t, J = 11 Hz, 1 H, CS), 2.34 (s, 3 H, p-Me), 1.74 (m, 1 H, CH_2), 1.66 (m, 1 H, CH_2), 0.83 (s, 9 H, t-Bu), 0.04 (s, 3 H, MeSi), 0.03 (s, 3 H, MeSi); ^{13}C NMR δ 165.14 (s, C=O), 136.13 (s), 133.68 (s), 131.63 (s), 129.92 (d), 129.2 (d), 128.23 (d), 126.91 (d), 123.72 (q, J = 290 Hz, CF_3), 84.78 (q, J = 26 Hz, CCF_3), 71.95 (d, CHO), 67.31 (q, OMe), 55.08 (d, CN), 44.54 (t, CN), 32.82 (t, CS), 32.47 (t), 25.60 (q, t-Bu), 20.98 (q, p-Me), 17.75 (s, t-Bu), –4.79 (q, MeSi), –5.02 (q, MeSi); MS, CI m/z 554 (M + 1), 498.

(2*R*,3*R*,2′*S*)-3-[(*tert*-Butyldimethylsilyl)oxy]-2-[[(4-methylphenyl)sulfenyl]methyl]-1-[methoxy(trifluoromethyl)phenylacetyl]pyrrolidine (18). Similar reaction conditions to those described for the preparation of **17** were followed, except using (+)-(*R*)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride. Only one diastereomer was detected; 60% yield. **18**: ^{1}H NMR δ 7.5 (m, 2 H, Ph), 7.38–7.33 (m, 5 H, Ph and Tol), 7.13 (d, J = 8 Hz, 2 H, Tol), 4.33–4.29 (m, 2 H, CHO, CHN), 3.68 (s, 3 H, OMe), 3.53 (dd, J = 13, 3 Hz, 1 H, CNH), 3.43 (dd, J = 10, 2.5 Hz, 1 H, CHS), 2.74 (dd, J = 13, 10 Hz, 1 H, CHN), 2.67 (dd, J = 10, 7 Hz, 1 H, CHS), 2.32 (s, 3 H, p-Me), 1.97–1.87 (m, 1 H, CH_2), 1.56–1.49 (m, 1 H, CH_2), 0.78 (s, 9 H, t-Bu), –0.02 (s, 3 H, MeSi), –0.06 (s, 3 H, MeSi); ^{13}C NMR δ 164.81 (s, C=O), 136.12 (s), 133.05 (s), 131.83 (s), 129.88 (d), 129.22 (d), 129.16 (d), 128.25 (d), 126.95 (d), 123.74 (q, J = 290 Hz, CF_3), 84.76 (q, J = 25 Hz, CCF_3), 71.93 (d, CHO), 67.11 (q, OMe), 55.12 (d, CN), 45.02 (t, CN), 34.01 (t, CS), 33.04 (t), 25.58 (q, t-Bu), 20.96 (q, p-Me), 17.70 (s, t-Bu), –4.86 (q, MeSi), –4.50 (q, MeSi); MS, CI m/z 554 (M + 1).

(2*R*,3*R*)-3-[(*tert*-Butyldimethylsilyl)oxy]-2-methylpyrrolidine (20). From Sulfoxide 15. A mixture of 75.2 mg (0.213 mmol) of **15** and 0.1 g of W-2 Raney nickel in 2 mL of EtOH was stirred under 1 atm of H_2 at 22 °C for 12 h. The mixture was filtered through Celite and washed thoroughly with a 5% NH_4OH–MeOH solution, and the filtrate was concentrated (^{1}H NMR spectrum of the crude product before separation indicated the absence of **19**) and column chromatographed on silica gel (14 × 0.75 cm) using a gradient mixture of CH_2Cl_2 and MeOH as eluant. The collected product was recrystallized from CH_2Cl_2–hexane (1:1) to give 29.2 mg (64% yield) of **20** as white needles: R_f = 0.15 (10% MeOH in CH_2Cl_2); mp 195–197 °C; $[\alpha]^{22}_D$ = –32° (c 2.03, $CHCl_3$); ^{1}H NMR δ 4.26 (dd, J = 3.5, 2 Hz, 1 H, C-3 H), 3.57 (qd, J = 6.7, 3.5 Hz, 1 H, C-2 H), 3.49 (dd, J = 11, 8 Hz, 1 H, C-5 H), 3.39 (ddd, J = 12, 9, 3 Hz, 1 H, C-5 H), 2.11–2.02 (m, 1 H, C-4 H), 1.99–1.93 (m, 1 H, C-4 H), 1.44 (d, J = 6.7 Hz, 3 H, Me), 0.91 (s, 9 H, t-Bu), 0.08 (s, 6 H, Me_2Si); ^{13}C NMR δ 72.51 (d, C-3), 59.65 (d, C-2), 42.36 (t, C-5), 33.74 (t, C-4), 25.62 (q, t-Bu), 17.97 (s, t-Bu), 12.45 (q, Me), –4.82 (q, MeSi), –5.08 (q, MeSi); MS, CI m/z 216 (100, M + 1), 200, 185, 158, 142, 112, 91, 71.

From α-Sulfinyl Ketimine 10. A mixture of 0.1135 g (0.323 mmol) of **10** and 0.2 g of W-2 Raney nickel in 5 mL of EtOH was stirred under 1 atm of H_2 at 22 °C for 6.5 h. The mixture was filtered through Celite and washed thoroughly with a 5% NH_4OH–MeOH solution, and the filtrate was concentrated to give 93.1 mg of a semisolid oil. ^{1}H NMR spectrum of this crude product indicated an about 1:1 mixture of **20** and 3-[(*tert*-butyldimethylsilyl)oxy]-2-pyrrolidinone and the absence of **19**. Recrystallization of this mixture from CH_2Cl_2–hexane (1:1) gave 24.1 mg (35% yield) of pure **20** as white needles; mp and ^{1}H and ^{13}C NMR spectra were identical with those obtained from **15**. The structure of the byproduct, 3-[(*tert*-butyldimethylsilyl)oxy]-2-pyrrolidinone was identified through TLC and NMR by comparison with the authentic sample.[7]

(2*S*,3*R*)-3-[(*tert*-Butyldimethylsilyl)oxy]-2-methylpyrrolidine (19). Similar reaction conditions to those described for the preparation of **20** were followed except that starting with 21.4 mg (0.06 mmol) of sulfoxide **14** gave 9.4 mg (72.3% yield) of **19**. The ^{1}H NMR spectrum of the crude product (before column separation) indicated the absence of **20**. **19**: $[\alpha]^{22}_D$ = –26° (c 0.94, MeOH); ^{1}H NMR δ 6.9 (br s, 1 H, NH), 4.05 (q, J = 5 Hz, 1 H, C-3 H), 3.5–3.4 (m, 3 H, C-2, C-5 H), 2.25–2.16 (m, 1 H, C-4 H), 1.89–1.82 (m, 1 H, C-4 H), 1.48 (d, J = 7 Hz, 3 H, Me), 0.87 (s, 9 H, t-Bu), 0.07 (s, 3 H, MeSi), 0.06 (s, 3 H, MeSi); ^{13}C NMR δ 76.3 (d, C-3), 61.71 (d, C-2), 42.39 (t, C-5), 32.38 (t, C-4), 25.61 (q, t-Bu), 17.84 (s, t-Bu), 15.6 (q, Me), –4.73 (q, MeSi), –4.88 (q, MeSi).

(1*S*,6*S*,S*S*)-6-[(*tert*-Butoxycarbonyl)amino]-1-[(*tert*-butyldimethylsilyl)oxy]-1,2,3,5,6,7-hexahydro-8-[(4-methylphenyl)sulfinyl]-5-indolizinone (21) and (1*S*,6*R*,S*S*)-6-[(*tert*-Butoxycarbonyl)amino]-1-[(*tert*-butyldimethylsilyl)oxy]-1,2,3,5,6,7-hexahydro-8-[(4-methylphenyl)sulfinyl]-5-indolizinone (22). To a cold (–78 °C) solution of 0.2 g (0.569 mmol) of **4** in 7 mL of THF under argon was added 0.5 mL (0.797 mmol) of n-BuLi (1.6 M in hexane). After the resulting deep red solution was stirred at –78 °C for 10 min, a solution of 0.114 g (0.569 mmol) of **5** in 4.3 mL of benzene was added via syringe. The resulting solution was warmed to 22 °C and stirred for 6 h. The reaction solution was diluted with CH_2Cl_2 and washed with water and brine. The organic layer was dried ($MgSO_4$), concentrated, and column chromatographed on silica gel (6.5 × 15 cm) using a 3% MeOH in CH_2Cl_2 as eluant to give 0.1634 g (55% yield) of a mixture of **21** and **22** in a ratio of 6:4. This mixture was used in the next step, since compounds **3A** and **3B** are easier to separate on silica gel column. For small amounts of samples, **21** and **22** were separated on a Chromatotron (Model 8924, Harrison Research, Palo Alto, CA) with a mixture of 1:1 hexane and ethyl acetate as eluant. **Pure 21**: mp 225–227 °C (white needles, recrystallized from 30% EtOAc in hexane); $[\alpha]^{22}_D$ = +25.1° (c 0.99, $CHCl_3$); IR ($CHCl_3$) δ 3400, 2980, 1680 (s), 1380, 1160 (s); ^{1}H NMR δ 7.35 (d, J = 8 Hz, 2 H), 7.25 (d, J = 8 Hz, 2 H), 5.38 (m, 1 H, C-1 H), 4.97 (m, 1 H, C-6 H), 4.27 (br s, 1 H, NH), 3.87 (ddd, J = 12, 8, 3 Hz, 1 H, C-3 H), 3.76 (td, J = 8, 7 Hz, 1 H, C-3 H), 3.03 (dd, J = 16, 8 Hz, 1 H, C-7 H), 2.4 (s, 3 H, p-Me), 2.15–1.95 (m, 2 H, C-2 H), 1.75–1.7 (m, 1 H, C-7 H), 1.4 (s, 9 H, O-t-Bu), 0.92 (s, 9 H, t-Bu), 0.2 (s, 3 H, MeSi), 0.13 (s, 3 H, MeSi); ^{13}C NMR δ 167 (s, C=O), 155.2 (s, C=O), 148.51 (s), 140.52 (s), 138.12 (s), 129.73 (d), 124.94 (d), 113.99 (s), 80.13 (s, O-t-Bu), 71.39 (d, C-1), 50.73 (d, C-6), 44.31 (t, C-3), 33.26 (t), 32.68 (t), 28.25 (q, t-Bu), 25.77 (q, t-Bu), 21.28 (q, p-Me), 17.95 (s, t-Bu), –4.16 (q, MeSi), –4.46 (q, MeSi); MS, FAB m/z 521 (M + 1), 465, 421, 407, 346, 332. Anal. Calcd for $C_{26}H_{40}N_2O_5SSi$: C, 59.97; H, 7.47. Found: C, 59.95; H, 7.54. **Pure 22**: $[\alpha]^{22}_D$ = +88.1° (c 0.99, $CHCl_3$); ^{1}H NMR δ 7.51 (d, J = 8 Hz, 2 H), 7.3 (d, J = 8 Hz, 2 H), 5.38 (dd, J = 5, 2 Hz, 1 H, C-1 H), 5.01 (m, 1 H, C-6 H), 4.1 (br s, 1 H, NH), 3.93 (ddd, J = 11, 8, 3 Hz, 1 H, C-3 H), 3.73 (td, J = 11, 7 Hz, 1 H, C-3 H), 2.48 (d, J = 14 Hz, 2 H, C-7 H), 2.40 (s, 3 H, p-Me), 2.31–2.05 (m, 2 H, C-2 H), 1.37 (br s, 9 H, O-t-Bu), 0.91 (s, 9 H, t-Bu), 0.17 (s, 3 H, MeSi), 0.11

(s, 3 H, MeSi); ^{13}C NMR δ 166.69 (s, C=O), 155.34 (s, C=O), 149.02 (s), 140.73 (s), 138.94 (s), 129.63 (d, 2 C), 124.63 (d, 2 C), 113.11 (s), 79.96 (s, O-*t*-Bu), 70.87 (d, C-1), 50.83 (d, C-6), 43.87 (t, C-3), 32.57 (t), 29.59 (t), 28.08 (q, *t*-Bu), 25.59 (q, *t*-Bu), 21.19 (q, *p*-Me), 17.79 (s), −4.43 (q, MeSi); MS, FAB *m/z* 521 (M + 1), 465, 421, 407, 346, 332.

(1*S*,6*S*,S*R*)-6-[(*tert*-Butoxycarbonyl)amino]-1-[(*tert*-butyldimethylsilyl)oxy]-1,2,3,5,6,7-hexahydro-8-[(4-methylphenyl)sulfinyl]-5-indolizinone (25) and (1*S*,6*R*,S*R*)-6-[(*tert*-Butoxycarbonyl)amino]-1-[(*tert*-butyldimethylsilyl)oxy]-1,2,3,5,6,7-hexahydro-8-[(4-methylphenyl)sulfinyl]-5-indolizinone (26). Similar reaction conditions to those described in the preparation of **21** and **22** were followed, except sulfinyl ketimine **12** (1.14 mmol) was used. Column chromatography separation of the crude product using 1% MeOH in CH_2Cl_2 as eluant gave 0.1041 g (17.6% yield) of **25**, 0.2202 g (37.1% yield) of **26**, and 78.4 mg (19.6% recovery) of ketimine **12**. Diastereomers **25** and **26** are easier to separate than **21** and **22**. **Compound 25**: R_f = 0.39 (5% MeOH in CH_2Cl_2); $[\alpha]^{22}_D$ = −23.0° (*c* 0.71, $CHCl_3$); IR ($CHCl_3$) ν 3400, 2980, 2940, 2860, 1680 (s), 1485, 1385, 1155 (s); ^{1}H NMR δ 7.43 (d, *J* = 8 Hz, 2 H), 7.3 (d, *J* = 8 Hz, 2 H), 5.38 (dd, *J* = 10, 5 Hz, 1 H, C-1 H), 4.97 (m, 1 H, C-6 H), 4.17 (br s, 1 H, NH), 3.81 (t, *J* = 7 Hz, 2 H, C-3 H), 2.52 (d, *J* = 11 Hz, 2 H, C-2 H), 2.40 (s, 3 H, *p*-Me), 2.09 (m, 2 H, C-7 H), 1.38 (br s, 9 H, *t*-Bu), 0.94 (s, 9 H, *t*-Bu), 0.26 (s, MeSi), 0.18 (s, MeSi); ^{13}C NMR δ 166.57 (s, C=O of lactam), 155.17 (s, C=O of carbamate), 148.29 (s), 140.84 (s), 139.78 (s), 129.95 (d, 2 C), 124.20 (d, 2 C), 113.02 (s), 79.94 (s, O-*t*-Bu), 71.68 (t, C-1), 50.31 (d, C-6), 44.1 (t, C-3), 33.2 (t), 29.68 (t), 28.2 (q, *t*-Bu), 25.73 (q, *t*-Bu), 21.33 (q, *p*-Me), 17.95 (s), −4.43 (q, MeSi), −4.5 (q, MeSi); MS, FAB *m/z* 521 (M + 1), 465 (M − *t*-Bu). **Compound 26**: R_f = 0.53 (5% MeOH in CH_2Cl_2); $[\alpha]^{22}_D$ = +53.5° (*c* 0.87, $CHCl_3$); IR ($CHCl_3$) ν 3400, 2980, 2940, 2860, 1680, 1485, 1385, 1160, 1110; ^{1}H NMR δ 7.35 (d, *J* = 8 Hz, 2 H), 7.25 (d, *J* = 8 Hz, 2 H), 5.36 (dd, *J* = 4, 2 Hz, 1 H, C-1 H), 5.04 (d, *J* = 6 Hz, 1 H, C-6 H), 4.37 (br s, 1 H, NH), 3.89 (ddd, *J* = 11, 9, 3 Hz, 1 H, C-3 H), 3.74 (td, *J* = 11, 7 Hz, 1 H, C-3 H), 3.07 (dd, *J* = 16, 8 Hz, 1 H, C-7 H), 2.39 (s, 3 H, *p*-Me), 2.07 (m, 2 H, C-2 H), 1.7 (m, 1 H, C-7 H), 1.41 (s, 9 H, *t*-Bu), 0.93 (s, 9 H, *t*-Bu), 0.26 (s, 3 H, MeSi), 0.22 (s, 3 H, MeSi); ^{13}C NMR δ 167.11 (s, C=O), 155.22 (s, C=O), 148.41 (s), 140.93 (s), 138.87 (s), 129.89 (d, 2 C), 124.26 (d, 2 C), 114.3 (s), 80.09 (s, O-*t*-Bu), 70.16 (d, C-1), 51.20 (d, C-6), 44.03 (t, C-3), 33.12 (t, C-7), 28.24 (q, *t*-Bu), 25.67 (q, *t*-Bu), 22.27 (t, C-2), 21.31 (q, *p*-Me), 17.93 (s), −4.44 (q), −4.66 (q); MS, FAB *m/z* 521 (M + 1), 465.

(1*S*,6*S*,8a*S*)-6-[(*tert*-Butoxycarbonyl)amino]-1-[(*tert*-butyldimethylsilyl)oxy]-1,2,3,5,6,7,8,8a-octahydro-5-indolizinone (3A). A mixture of 50 mg (0.096 mmol) of **21** and 0.1 g of freshly prepared Raney nickel in 11 mL of EtOH under 50 psi of hydrogen was heated at 50 °C for 2 h. The mixture was filtered through Celite, concentrated, and column chromatographed on silica gel using 1% MeOH in CH_2Cl_2 as eluant to give 28 mg (76% yield) of **3A**: R_f = 0.41 (5% MeOH–CH_2Cl_2); $[\alpha]^{22}_D$ = +53° (*c* 1.09, $CHCl_3$); IR (neat) ν 3400 (NH), 2950, 2885, 2860, 1705 (C=O), 1650, 1450; ^{1}H NMR δ 5.60 (br s, 1 H, NH), 4.22 (dd, *J* = 6, 3 Hz, 1 H, C-1 H), 3.97 (m, 1 H, C-6 H), 3.65 (q, *J* = 10 Hz, 1 H, C-8a-H), 3.56–3.46 (m, 2 H, C-3 H), 2.31 (sextet, *J* = 6 Hz, 1 H), 1.93–1.85 (m, 3 H), 1.75 (sextet, *J* = 7 Hz, 1 H), 1.59–1.5 (m, 1 H), 1.43 (s, 9 H, O-*t*-Bu), 0.86 (s, 9 H, *t*-Bu), 0.08 (s, 3 H, Me), 0.07 (s, 3 H, Me); ^{13}C NMR δ 169.17 (s, C=O), 155.82 (s, C=O), 79.41 (s, O-*t*-Bu), 73.14 (d, C-1), 60.3 (d, C-6), 50.58 (d, C-8a), 43.04 (t, C-3), 32.79 (t, C-2), 28.35 (q, O-*t*-Bu), 26.85 (t, C-8), 25.67 (q, *t*-Bu), 19.7 (t, C-7), 17.99 (s, *t*-Bu), −4.66 (q, MeSi), −5.02 (q, MeSi); MS, FAB *m/z* 385 (M + 1), 329, 285, 227, 196, 165, 89, 75. Anal. Calcd for $C_{19}H_{36}N_2O_4Si$: C, 59.34; H, 9.44. Found: C, 59.17; H, 9.39.

Reduction of **25** (91.1 mg; 0.175 mmol) under similar conditions also provided a 76% yield (50.9 mg) of **3A**; all physical data are identical with those obtained from the reduction of **21**.

(1*S*,6*R*,8a*S*)-6-[(*tert*-Butoxycarbonyl)amino]-1-[(*tert*-butyldimethylsilyl)oxy]-1,2,3,5,6,7,8,8a-octahydro-5-indolizinone (3B). Under the similar conditions to those described for the preparation of **3A**, except using sulfoxide **22** (50 mg; 0.096 mmol), an 80% yield (29.5 mg) of **3B** was obtained after column chromatographic separation. **3B**: R_f = 0.29 (40% EtOAc in hexane); $[\alpha]^{22}_D$ = +18.2° (*c* 0.9, CH_2Cl_2); IR (CH_2Cl_2) ν 3420 (NH), 2930, 2850, 1700 (C=O), 1630, 1450, 1360; ^{1}H NMR δ 5.29 (br s, 1 H, NH), 4.16 (s, 1 H, C-1 H), 3.91–3.89 (m, 1 H, C-6 H), 3.64 (q, *J* = 11 Hz, 1 H, C-8a H), 3.5–3.45 (m, 2 H, C-3 H), 2.5 (m, 1 H), 1.86–1.63 (m, 5 H), 1.43 (s, 9 H, O-*t*-Bu), 0.85 (s, 9 H, *t*-Bu), 0.05 (s, 3 H, Me), 0.04 (s, 3 H, Me); ^{13}C NMR δ 168.11 (s, C=O of lactam), 156.01 (s, C=O of carbamate), 79.2 (s, *t*-Bu), 72.44 (d, C-1), 63.8 (d, C-6), 51.96 (d, C-8a), 43.03 (t, C-3), 32.2 (t, C-2), 28.17 (q, O-*t*-Bu), 27.86 (t, C-8), 25.50 (q, *t*-Bu), 21.74 (t, C-7), 17.84 (s, *t*-Bu), −4.83 (q, MeSi), −5.17 (q, MeSi); MS, FAB *m/z* 385 (M + 1), 329 (M − *t*-Bu), 285.

Reduction of **26** under similar reaction conditions also provided a 79% yield of **3B**.

Epimerization of Lactam 3B with KO-*t*-Bu. A solution of 2.1 mg (0.0054 mmol) of **3B** and 1.8 mg (0.0162 mmol) of KO-*t*-Bu in 0.5 mL of *t*-BuOH was stirred at 50 °C for 33 h and 80 °C for 12 h. The ^{1}H NMR spectrum of the crude product indicated a 3:1 ratio of **3B** and **3A**. Column chromatographic separation of the crude product gave **3B** and **3A**.

Stepwise Reduction of 26 with Raney Nickel at 22 °C Followed by Hydrogen and Pd/C. Formation of 3B. A mixture of 0.1435 g (0.276 mmol) of **26** and 0.3 g of freshly prepared W-2 Raney nickel in 25 mL of EtOH under argon was stirred at 22 °C for 12 h. The mixture was filtered through Celite, concentrated, and column chromatographed on silica gel using 1% MeOH in CH_2Cl_2 as eluant to give 68.9 mg (65% yield) of olefin **29** as an oil: ^{1}H NMR δ 5.45 (br s, 1 H, NH), 5.09 (d, *J* = 6 Hz, 1 H, C-1 H), 4.6 (s, 1 H, C-8 H), 4.2 (m, 1 H, C-6 H), 3.71 (m, 2 H, C-3 H), 2.9 (m, 1 H), 2.15 (m, 1 H), 2.02 (m, 1 H), 1.9 (m, 1 H), 1.44 (s, 9 H, O-*t*-Bu), 0.87 (s, *t*-Bu), 0.09 (s, 3 H, MeSi), 0.07 (s, 3 H, MeSi). A mixture of 80.3 mg (0.21 mmol) of **29** and 10 mg of 10% Pd/C in 15 mL of EtOH under 50 psi of hydrogen was shaken for 17 h at 22 °C. The mixture was filtered through Celite, concentrated, and column chromatographed on silica gel using a gradient mixture of ethyl acetate and hexane as eluant to give 77.8 mg (96.4% yield) of **3B**.

Reduction of a 3:2 mixture of **21** and **22** (0.5488 g,; 1.05 mmol) under similar reaction conditions to those for **21** gave a 3:2 mixture of **3A** and **3B**. Chromatographic separation of this mixture on the Chromatotron using 30% EtOAc in hexane and then 50% EtOAc in hexane gave 0.1875 g (46.4% yield) of **3A** and 0.1216 g (30% yield) of **3B**.

(1*S*,6*S*,8a*S*)-6-[(*tert*-Butoxycarbonyl)amino]-1-[(*tert*-butyldimethylsilyl)oxy]-1,2,3,5,6,7,8,8a-octahydroindolizine (27). To a cold (0 °C) solution of 13.5 mg (0.0351 mmol) of **3A** in 0.5 mL of THF was added 38.6 μL (0.0386 mmol) of BH_3·THF (1 M solution in THF). After the solution was stirred at 0 °C for 45 min and at 22 °C for 4 h, it was diluted with 0.2 mL of water, the THF was removed in vacuo, and the residue was dissolved in 3 mL of CH_2Cl_2 and 0.2 mL of 1 N of NaOH. The mixture was stirred at 22 °C for 20 min, diluted with 10 mL of CH_2Cl_2, washed with water and brine, dried ($MgSO_4$), concentrated, and column chromatographed on silica gel using 10% ethyl acetate in hexane as eluant gave 7.9 mg (61% yield) of **27**: R_f = 0.47 (20% EtOAc in hexane); $[\alpha]^{22}_D$ = +5.2° (*c* 0.39, $CHCl_3$); IR ($CHCl_3$) ν 3430 (NH), 2940, 2850, 1690 (C=O), 1480, 1460, 1360; ^{1}H NMR δ 4.42 (ddd, *J* = 7.3, 6.7, 3.3 Hz, 1 H, C-1 H), 4.32 (m, 1 H, C-6 H), 4.17 (br s, NH), 3.23–3.11 (m, 3 H), 2.98 (m, 1 H), 2.57 (t, *J* = 10.5 Hz, 1 H), 2.33–2.21 (m, 2 H), 1.9–1.79 (m, 3 H), 1.61 (ddd, *J* = 24, 12, 4.5 Hz, 1 H), 1.43 (s, 9 H, O-*t*-Bu), 0.88 (s, 9 H, *t*-Bu), 0.06 (s, 3 H, MeSi), 0.05 (s, 3 H, MeSi); ^{13}C NMR δ 154.69 (s, C=O), 79.47 (s, O-*t*-Bu), 75.4 (d, C-1), 67.56 (d, C-6), 62.62 (t, C-3), 43.91 (d, C-8a), 32.83 (t, C-2), 29.59 (t, C-5), 28.27 (q, O-*t*-Bu), 26.82 (t, C-7), 25.76 (q, *t*-Bu), 20.13 (t, C-8), 17.83 (s, *t*-Bu), −4.87 (q, MeSi), −5.06 (q, MeSi); MS, FAB *m/z* 371 (M + 1, 100), 327, 315, 307, 297, 271, 253, 197, 165, 120. Anal. Calcd for $C_{19}H_{38}N_2O_3Si$: C, 61.58; H, 10.34. Found: C, 61.60; H, 10.63.

Reduction of 3B with Borane. Formation of 27 and (1*S*,6*R*,8a*S*)-6-[(*tert*-Butoxycarbonyl)amino]-1-[(*tert*-butyldimethylsilyl)oxy]-1,2,3,5,6,7,8,8a-octahydroindolizine (30). To a cold (0 °C) solution of 37.9 mg (0.0985 mmol) of **3B** in 2 mL of THF was added 110 μL (0.110 mmol) of BH_3·THF (1 M in THF). After the solution was stirred at 22 °C for 12 h, 197 μL (0.197 mmol) of the borane was added in a 20-h interval with 98.5 μL in each addition. The solution was diluted with 0.5 mL of water, THF was removed in vacuo, the residue was dissolved in 3 mL of CH_2Cl_2 and 0.5 mL of 1 N NaOH, and the solution was

stirred for 20 min. The mixture was washed with water and with brine, dried ($MgSO_4$), concentrated, and column chromatographed on silica gel (5.5 × 0.7 cm) using 5% EtOAc in hexane and the 20% EtOAc in hexane as eluant to give 7.7 mg (21% yield) of **27** and 15.6 mg (43% yield) of **30**. **Carbamate 30**: R_f = 0.56 (20% EtOAc in hexane); $[\alpha]^{22}_D$ = +18.8° (*c* 0.78, $CHCl_3$); IR ($CHCl_3$) ν 3425 (NH), 2950, 2860, 1690 (C=O), 1480; ^1H NMR δ 4.9 (dd, *J* = 12, 6 Hz, 1 H, C-1 H), 4.71 (m, 1 H, C-6 H), 3.8 (br s, 1 H, NH), 3.24–3.11 (m, 4 H, C-3, -5 H), 2.77 (dd, *J* = 15, 10 Hz, 1 H, C-8a H), 2.16–2.07 (m, 1 H), 1.84–1.79 (m, 1 H), 1.73–1.67 (m, 1 H), 1.65–1.54 (m, 1 H), 1.5–1.3 (m, 2 H), 1.43 (s, 9 H, O-*t*-Bu), 0.87 (s, 9 H, *t*-Bu), 0.06 (s, 3 H, Me), 0.05 (s, 3 H, Me); ^{13}C NMR δ 155.11 (s, C=O), 79.77 (s, O-*t*-Bu), 72.38 (d, C-1), 68.21 (d, C-6), 61.2 (t, C-3), 55.54 (t, C-2), 43.28 (d, C-8a), 31.10 (t, C-2), 28.32 (q, O-*t*-Bu), 28.15 (t, C-5), 25.72 (q, *t*-Bu), 21.06 (t, C-8), 17.9 (s, *t*-Bu), -4.84 (q), -5.45 (q); MS, FAB *m/z* 371 (M + 1).

(1*S*,6*S*,8a*S*)-1-Acetoxy-6-[(*tert*-butoxycarbonyl)amino]-1,2,3,5,6,7,8,8a-octahydroindolizine (28). To a cold (0 °C) solution of 57.4 mg (0.155 mmol) of **27** in 7 mL of THF under argon was added 0.23 mL (0.23 mmol) of *n*-Bu_4NF (1 M in THF). The reaction was completed within 5 min at 0 °C. To the solution were added 0.108 mL (0.775 mmol) of Et_3N and 30 μL (0.31 mmol) of acetic anhydride at 0 °C. After the solution was stirred at 22 °C for 1 h, THF was removed in vacuo, the residue was dissolved in 20 mL of CH_2Cl_2, and the solution was washed with $NaHCO_3$ and with brine. The organic layer was dried ($MgSO_4$), concentrated, and column chromatographed on silica gel (15 × 0.7 cm) using CH_2Cl_2 and then 1% MeOH in CH_2Cl_2 as eluant to give 40.2 mg (87% yield) of **28** as an oil: R_f = 0.4 (50% EtOAc in hexane); $[\alpha]^{22}_D$ = -26.9° (*c* 0.86, $CHCl_3$); IR ($CHCl_3$) ν 3430 (NH), 2960, 1725 (C=O), 1700 (C=O), 1485, 1360; ^1H NMR δ 5.44 (td, *J* = 7.5, 3.5 Hz, 1 H, C-1 H), 4.32 (m, 2 H, C-6 and NH), 3.35–3.09 (m, 4 H), 2.52 (m, 1 H), 2.50 (dtd, *J* = 14, 9, 3 Hz, 1 H), 2.33 (tdd, *J* = 13, 10, 6 Hz, 1 H), 2.1 (s, 3 H, Me) 1.97–1.79 (m, 4 H), 1.45 (s, 9 H, *t*-Bu); ^{13}C NMR δ 169.79 (s, C=O), 154.74 (s, C=O), 79.7 (s, *t*-Bu), 76.11 (d, C-1), 66.03 (d, C-6), 62.61 (d, C-8a), 57.64 (t, C-3), 44.56 (t, C-5), 29.63 (t, C-2), 28.33 (q, *t*-Bu), 26.61 (t, C-7), 21.27 (t, C-8), 19.83 (q, Me); MS, EI *m/z* 298 (M^+), 255 (M - Ac), 241, 237, 225 (100, M - *t*-BuO), 209, 194, 181, 165, 149. Anal. Calcd for $C_{15}H_{26}N_2O_4$: C, 60.38; H, 8.78. Found: C, 60.01; H, 9.05.

(1*S*,6*R*,8a*S*)-1-Acetoxy-6-[(*tert*-butoxycarbonyl)amino]-1,2,3,5,6,7,8,8a-octahydroindolizine (31). To a cold (0 °C) solution of 53.2 mg (0.144 mmol) of **30** in 3 mL of THF under argon was added 0.215 mL (0.215 mmol) of *n*-Bu_4NF in THF (1 M solution), and the solution was stirred at 0 °C for 30 min and at 22 °C for 1 h. To it were added 0.1 mL (0.72 mmol) of Et_3N and 60 μL (0.63 mmol) of acetic anhydride, and the solution was stirred at 22 °C for 12 h. The reaction was monitored by TLC and if the reaction was not completed at this time, a catalytic amount of 4-(dimethylamino)pyridine was added. The solvents were removed in vacuo, the residue was dissolved in 3 mL of CH_2Cl_2, and the solution washed with small amount of $NaHCO_3$ and with brine. The organic layer was dried ($MgSO_4$), concentrated, and column chromatographed on silica gel (7 × 0.7 cm) using 1% MeOH in CH_2Cl_2 and then 5% MeOH in CH_2Cl_2 as eluant to give 24.2 mg (56% yield) of **31** as white solids, mp 120–122 °C: R_f = 0.24 (40% EtOAc in hexane); $[\alpha]^{22}_D$ = +6.2° (*c* 0.61, CH_2Cl_2); IR (CH_2Cl_2) ν 3420, 2940, 1700, 1490, 1365; ^1H NMR δ 5.18 (ddd, *J* = 8, 5, 2 Hz, 1 H, C-1 H), 4.28 (br s, 1 H, NH), 3.66 (m, 1 H, C-6 H), 3.36 (m, 1 H), 3.18 (m, 1 H), 3.11 (td, *J* = 9, 2 Hz, 1 H), 2.25 (m, 1 H), 2.08–1.99 (m, 1 H), 2.03 (s, 3 H, Me), 1.83–1.75 (m, 2 H), 1.69–1.54 (m, 2 H), 1.5 (ddd, *J* = 24, 13, 4 Hz, 1 H), 1.4 (s, 9 H, O-*t*-Bu), 1.06 (ddd, *J* = 24, 13, 4 Hz, 1 H); ^{13}C NMR δ 170.88 (s, C=O), 155 (s, C=O), 79.23 (s, *t*-Bu), 74.25 (d, C-1), 66.69 (d, C-6), 58.72 (d, C-8a), 52.51 (t, C-3), 47.25 (t, C-5), 31.01 (t, C-2), 28.40 (q, *t*-Bu), 23.84 (t, C-7), 21.08 (t, C-8), 19.63 (q, Me).

(-)-Slaframine (1). To a solution of 24 mg (0.08 mmol) of **28** in 1.5 mL of $CDCl_3$ was added 30 μL (0.2 mmol) of trimethylsilyl iodide, and the solution was stirred at 22 °C for 10 min. To it was added 0.5 mL of MeOH, and the solvents were removed under vacuum. The residue was column chromatographed on silica gel (16 × 0.75 cm) using 5% MeOH (containing 5% of NH_4OH) in CH_2Cl_2 as eluant to give 11 mg (69% yield) of **1** as an oil: R_f = 0.44 (NH_4OH:MeOH:CH_2Cl_2 = 1:19:80); $[\alpha]^{22}_D$ = -38.5° (*c* 1.1, $CHCl_3$), lit.[4b] -33° (*c* 1.6, $CHCl_3$). IR (neat), MS, and ^1H and ^{13}C NMR spectra were identical to those reported.[4b]

(-)-6-Epislaframine (2). Similar reaction conditions to those described for the preparation of **1** were employed, starting with **31**, and the reaction provided a 67.2% yield of **2**: R_f = 0.42 (NH_4OH:MeOH:CH_2Cl_2 = 1:19:80); $[\alpha]^{22}_D$ = -11.6° (*c* 0.37, EtOH),[20] lit.[4b] for 1,8a-diepislaframine: +20° (*c* 0.5, EtOH). The ^1H NMR spectrum was identical with that reported by Pearson,[4b] but the ^{13}C NMR data were slightly different. ^{13}C NMR: δ 170.91 (s, C=O), 74.36 (d, C-1), 66.87 (d), 62.14 (t), 52.55 (t), 48.23 (d), 34.41 (t), 31.13 (t), 23.73 (t), 21.09 (q). MS, CI: *m/z* 199 (100, M + 1), 182 (M - 16), 139 (M - AcO).

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Supplementary Material Available: ^1H NMR spectra for compounds **10**, **13**, **14**, **15**, **17**, **18**, **19**, **20**, **22**, **25**, **26**, **3B**, **30**, and **31** (14 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.

(20) Our observed rotation is lower than that reported (ref 4b) probably because our concentration (*c* = 0.37) was lower.