Asymmetric Total Synthesis of (*R*)-(−)-Cryptopleurine and (*R*)-(−)-Julandine via Highly Enantioselective Amidoalkylations with *N*-Acylhydrazonium Salts

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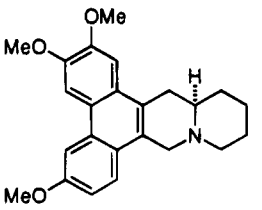
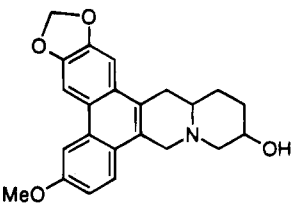
The first enantioselective total syntheses of the phenanthroquinolizidine alkaloid (−)-cryptopleurine (**1**) and its seco base (−)-julandine [(*R*)-**3**] are described. The synthesis of (*R*)-**3** allowed the 9a*S* configuration to be assigned to natural dextrorotatory julandine as shown by structure (*S*)-**3**. Both synthetic approaches are based on the high degree of 1,3-asymmetric induction achieved using an *N*-acylhydrazonium salt, which belongs to a new structural class of activated azomethines. Upon exposure of methoxy lactam **9**, with a chiral 2-substituted pyrrolidine auxiliary, to $BF_3{\cdot}Et_2O$ and a silyl enol ether the in situ generated *N*-acylhydrazonium intermediate **10** underwent asymmetric nucleophilic addition to give the (6*R*)-keto lactams **13** and **14** with complete diastereoselectivity. On the other hand, nucleophilic addition to the *N*-acylhydrazonium ion **25**, with an acyclic chiral auxiliary, showed poor diastereoselectivity. From these results, the high degree of diastereoselection observed for the *N*-acylhydrazonium ion **10** can be rationalized in terms of the pyramidal stability of the trivalent nitrogen in the chiral pyrrolidine auxiliary. Removal of the chiral auxiliary from **13** and **14** was achieved by reductive N−N bond cleavage using $BH_3{\cdot}THF$, affording (2*S*)-piperidine derivatives **15** and **31**, respectively, which were transformed into quinolizidinones **30** and **35**, respectively, via intramolecular aldol condensation. Reduction of **30** with alane provided (−)-julandine [(*R*)-**3**]. In addition, **35** was converted to (−)-cryptopleurine (**1**) in two steps, by radical cyclization with Bu_3SnH and AIBN, followed by $LiAlH_4$ reduction.

Introduction

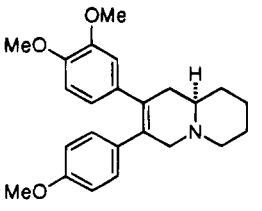
Cryptopleurine (**1**),[1] and cryptopleuridine (**2**),[2] members of a rare group of alkaloids with the phenanthro-[9,10-*b*]quinolizidine skeleton, have been shown to possess unique and interesting biological properties including vesicant,[3] antimicrobial,[4] and antiviral activities.[5] Cryptopleurine has also been shown to be cytotoxic in cancer cell test systems.[6] The absolute configuration of naturally occurring (−)-cryptopleurine has been reported[7] to be *R* as depicted in structure **1**, based on its ORD and CD spectra in which a positive Cotton effect was seen. While numerous research groups have been involved in developing synthetic approaches[8] to cryptopleurine over the last two decades, only one example of a chiral approach[9] to the unnatural antipode (i.e., (*S*)-(+)-cryptopleurine) which starts from (*S*)-α-aminoadipic acid has been published. This chiral synthesis confirmed the *R* configuration for natural cryptopleurine. However, the synthetic material was found to exhibit a positive CD spectrum in disagreement with the previous report[7] on the natural levorotatory alkaloid. No rational explanation has been given for this discrepancy.



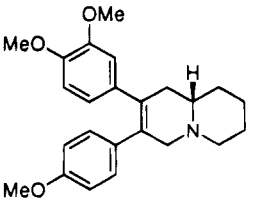
(−)-Cryptopleurine (**1**)



(+)-Cryptopleuridine (**2**)



(−)-Julandine [(*R*)-**3**]



(+)-Julandine [(*S*)-**3**]

(+)-Julandine (**3**), isolated from *Boehmeria platyphylla* along with cryptopleurine as a minor component, is closely related in structure to cryptopleurine and has been assigned as the seco base of cryptopleurine.[10] When this seco base was first reported, it was not given a name.

⊗ Abstract published in *Advance ACS Abstracts,* August 15, 1995.

(1) (a) Gellert, E.; Riggs, N. V. *Aust. J. Chem.* **1954**, *7*, 113. (b) Gellert, E. *Ibid.* **1956**, *9*, 489.

(2) Johns, S. R.; Lamberton, J. A.; Sioumis, A. A.; Willing, R. I. *Ibid.* **1970**, *23*, 353.

(3) de la Lande, I. S. *Aust. J. Exp. Biol. Med. Sci.* **1948**, *26*, 181.

(4) Al-Shamma, A.; Drake, S. D.; Guagliardi, L. E.; Mitscher, L. A.; Swayze, J. K. *Phytochemistry* **1982**, *21*, 485.

(5) Krmpotic, E.; Farnsworth, N. R.; Messmer, W. M. *J. Pharm. Sci.* **1972**, *61*, 1508.

(6) (a) Hoffman, J. J.; Luzbetak, D. J.; Torrance, S. J.; Cole, J. R. *Phytochemistry* **1978**, *17*, 1448. (b) Farnsworth, N. R.; Hart, N. K.; Johns, S. R.; Lamberton, J. A.; Messer, W. *Ibid.* **1969**, *22*, 1805. (c) Donaldson, G. R.; Atkinson, M. R.; Murray, A. W. *Biochem. Biophys. Res. Commun.* **1968**, *31*, 104.

(7) Gellert, E.; Rudzats, R.; Craig, J. C.; Roy, S. K.; Woodard, R. W. *Aust. J. Chem.* **1978**, *31*, 2095.

(8) For syntheses of (±)-cryptopleurine, see: (a) Paton, J. M.; Pauson, P. L.; Stevens, T. S. *J. Chem. Soc. C* **1969**, 1309. (b) Kotani, E.; Kitazawa, M.; Tobinaga, S. *Tetrahedron* **1974**, *30*, 3027. (c) Herbert, R. B. *J. Chem. Soc., Chem. Commun.* **1978**, 794. Crag, J. E.; Herbert, R. B. *J. Chem. Soc., Perkin Trans. 1* **1982**, 2487. (d) Iida, H.; Kibayashi, C. *Tetrahedron Lett.* **1981**, *22*, 2913. Iida, H.; Watanabe, Y.; Tanaka, M.; Kibayashi, C. *J. Org. Chem.* **1984**, *49*, 2412. (e) Bremmer, M. L.; Khatri, N. A.; Weinreb, S. M. *J. Org. Chem.* **1983**, *48*, 3661. (f) Iwao, M.; Mahalanabis, K. K.; Watanabe, M.; de Silva, S. O.; Snieckus, V. *Tetrahedron* **1983**, *39*, 1955. (g) Grieco, P. A.; Parker, D. *J. Org. Chem.* **1988**, *53*, 3325.

(9) Buckley, T. F., III; Rapoport, H. *J. Org. Chem.* **1983**, *48*, 4222.

(10) Hart, N. K.; Johns, S. R.; Lamberton, J. A. *Aust. J. Chem.* **1968**, *21*, 2579.

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After the first synthesis of this alkaloid in racemic form,[8a] which confirmed the originally proposed structure, it was named julandine by Herbert.[8c,11] The small value of the optical rotation ($[\alpha]_D$ +4.6° (*c* 0.5, $CHCl_3$)) reported[10] for natural julandine has been claimed to be due to its being largely racemic.[12] Although several syntheses of racemic julandine have been reported,[13] no work toward a chiral synthesis or the determination of the absolute configuration of julandine has appeared.

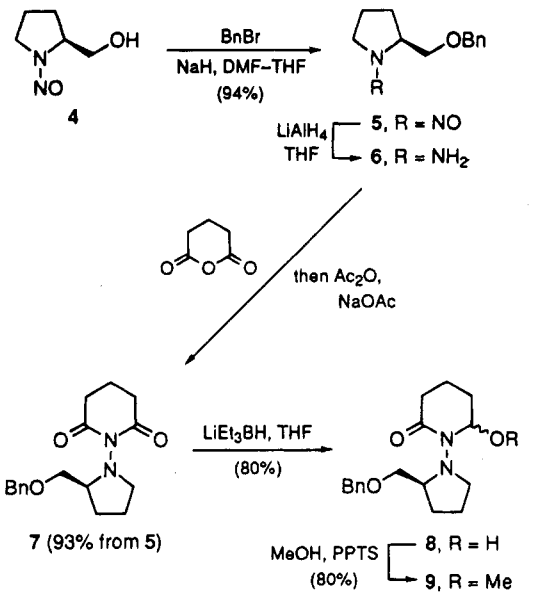
We have recently developed[14] a protocol of asymmetric induction resulting from the addition of carbon nucleophiles to "*N*-acylhydrazonium salts" which belong to a new structural class of activated azomethines.[15] This methodology has been utilized in a general procedure for preparing enantiomerically pure derivatives of pyrrolidine and piperidine that might find application to the synthesis of chiral heterocyclic natural products. Herein, we report the first enantioselective total syntheses of (*R*)-(−)-cryptopleurine (**1**)[16] and (*R*)-(−)-julandine [(*R*)-**3**] based on a highly efficient asymmetric amidoalkylation step using an *N*-acylhydrazonium intermediate. The synthesis of alkaloid (*R*)-**3** allowed the 9a*S* configuration to be assigned to natural dextrorotatory julandine as shown by structure (*S*)-**3**.

Results and Discussion

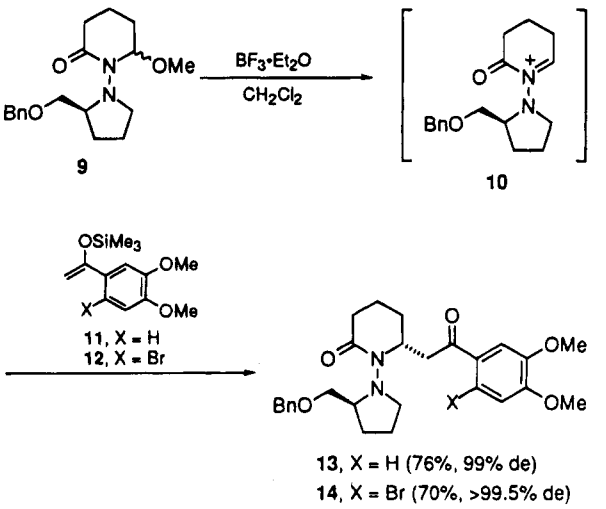
Enantioselective Synthesis of 2-Substituted Piperidine Intermediates via Asymmetric Amidoalkylation of *N*-Acylhydrazonium Ions. Our previous work[14] revealed that higher levels of asymmetric induction in nucleophilic additions to *N*-acylhydrazonium ions are obtained when 2-substituted pyrrolidines are used as chiral auxiliaries rather than C_2-symmetric 2,5-disubstituted pyrrolidines. Accordingly, we decided to employ cyclic imide **7**, bearing (*S*)-2-[(benzyloxy)methyl]-pyrrolidine, to give rise to the desired chirality in the reaction process. Thus, (*S*)-*N*-nitrosoprolinol (**4**)[17] was converted to the (*S*)-*N*-aminopyrrolidine **6** via O-benzylation followed by $LiAlH_4$ reduction (Scheme 1). The chiral *N*-pyrrolidinylimide **7** was prepared in 93% yield by treatment of **6** with glutaric anhydride at room temperature followed by condensation of the resulting ring-opened product (amidocarboxylic acid) by using Ac_2O and AcONa at reflux. Reduction of **7** with $LiBEt_3H$ afforded alcohol **8** as a *ca.* 4:1 diastereomeric mixture, which was converted to methoxy lactam **9** by treatment with a catalytic amount of pyridinium *p*-toluenesulfonate in methanol in 64% yield from **7**.

Upon exposure of **9** to $BF_3{\cdot}Et_2O$ followed by silyl enol ether **11** in CH_2Cl_2 at room temperature, the in situ generated *N*-acylhydrazonium ion **10** underwent asymmetric addition of the silyl enol ether to furnish (6*R*)-keto lactam **13** in 76% yield with excellent diastereoselectivity: based on the ^1H NMR spectrum only a trace amount (0.5%) of the C-6 epimeric keto lactam was present in the product (Scheme 2). Similarly, exposure of **9** to amidoalkylation with bromo silyl enol ether **12** gave (6*R*)-keto lactam **14** in 70% yield, and no trace of the (6*S*)-epimer could be detected by ^1H NMR analysis indicating a diastereo excess of >99.5%. The nature of the asymmetric induction was determined by the correlation of **13** with known *N*-Cbz-(*R*)-pipecolinic acid (**18**)[18] based on the following sequence (Scheme 3). After chromatographic separation of the diastereomerically pure keto lactam **13**, treatment with the borane–THF complex and subsequent aqueous alkaline workup effected reductive N–N bond cleavage and concomitant reduction of the lactam and ketone carbonyl groups. This procedure thus resulted in the formation of an 8:1 diastereomeric mixture (by ^1H NMR) of hydroxy piperidine **15** in 64% yield as well as recovery (66%) of the chiral auxiliary (*S*)-2-[(benzyloxy)methyl]pyrrolidine (**16**).[19] Compound **15** was converted in 52% yield to (*E*)-

Scheme 1

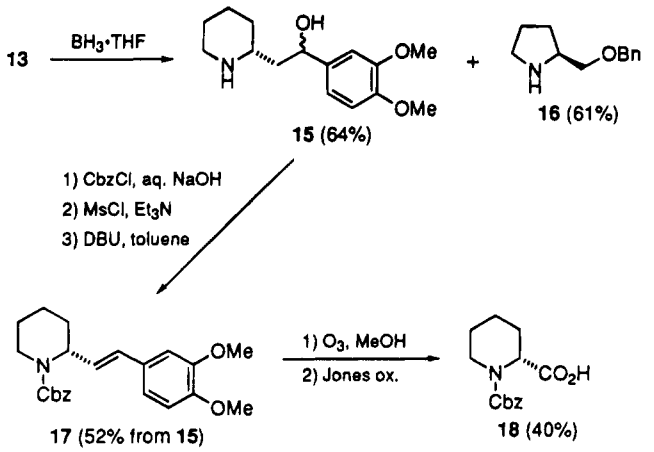


Scheme 2



(11) Herbert, R. B. In *Alkaloids: Chemical and Biological Perspectives*; Pelletier, S. W., Ed.; Wiley-Interscience: New York, 1985; Vol. 3, Chapter 6, p 256.
(12) Howard, A. S.; Michael, J. P. In *The Alkaloids*; Brossi, A., Ed.; Academic Press: Orlando, 1986; Vol. 28, Chapter 3, p 238.
(13) For syntheses of (±)-julandine, see ref 8a,c,d,g.
(14) Suzuki, H.; Aoyagi, S.; Kibayashi, C. *Tetrahedron Lett.* **1994**, *35*, 6119.
(15) The following classes have been known as "activated azomethines" containing the iminium structure: iminium salts and *N*-acyliminium salts and also some 1,3-dipoles (azomethine ylides, azomethine imines, and nitrones).
(16) For a preliminary account for the synthesis of (−)-cryptopleurine, see: Suzuki, H.; Aoyagi, S.; Kibayashi, C. *Tetrahedron Lett.* **1995**, *36*, 935.
(17) Enders, D.; Eichenauer, H. *Chem. Ber.* **1979**, *112*, 2933.
(18) Baláspiri, L.; Penke, B.; Petres, J.; Kovács, K. *Monatsh. Chem.* **1970**, *101*, 1177.
(19) For recycling the chiral pyrrolidine auxiliary, **16** was converted to (*S*)-*N*-nitroso-2-[(benzyloxy)methyl]pyrrolidine (**5**) in 80% yield by treatment with 2 equiv of *t*-BuONO in THF at reflux for 1 h.

Scheme 3



alkene **17** via a three-step sequence: protection of the secondary amine by treatment with benzyl chloroformate, mesylation of the hydroxyl group, and elimination by treatment with DBU. Ozonolysis of **17** followed by Jones oxidation of the resulting crude aldehyde led to **18** in 40% overall yield. The synthetic **18** we prepared showed mp 111–113 °C and $[\alpha]^{27}_D$ +56.5° (*c* 0.55, AcOH) in agreement with the previous reports[18] for *N*-Cbz-(*R*)-pipecolinic acid [mp 112–113 °C; $[\alpha]^{27}_D$ +57.2° (*c* 5.3, AcOH)] and, therefore, was confirmed to possess the *R* configuration.

The facial selectivity observed in the nucleophilic addition to the prochiral group C=N of the *N*-acylhydrazonium ion **10** may be attributed to the pyramidal stability of the adjacent trivalent nitrogen which thus constitutes a chiral center.[20] If we assume that the largest *N*-substituent (2-C of the pyrrolidine ring) adopts the perpendicular position to the plane of the C=N bond due to a destabilizing $A^{1,3}$ type interaction[21] and the ring methylene group (5-C of the pyrrolidine ring) is placed syn to the sterically less demanding amide carbonyl group, two conformers **10A** and **10B** would be possible as shown in Figure 1. Since maximum orbital overlap between the approaching nucleophile and the developing lone-electron pair on nitrogen can be achieved via chair-like transition states,[22] **10B** is disfavored relative to **10A** because of steric repulsion between the α-oriented (benzyloxy)methyl group and the ring methylene group. The approach of the nucleophile to the azomethine group therefore should preferably occur from the sterically less hindered *si* face, in agreement with the prediction based on the energetically favored conformer **10A** leading to the (6*R*)-isomers **13** and **14**.

To confirm that the facial selectivity resulted from the pyramidal stability of the chiral pyrrolidine auxiliary, we investigated nucleophilic addition to an *N*-acylhydrazonium ion with an acyclic amino chiral auxiliary. Thus, as outlined in Scheme 4, methoxy lactam **24** was synthesized from (*S*)-α-methylbenzylamine (**19**) according to the procedure described above for the preparation of **9** in 28% overall yield. Subsequent amidoalkylation was carried out by treatment with $BF_3{\cdot}Et_2O$ followed by allyltrimethylsilane to afford an inseparable mixture of

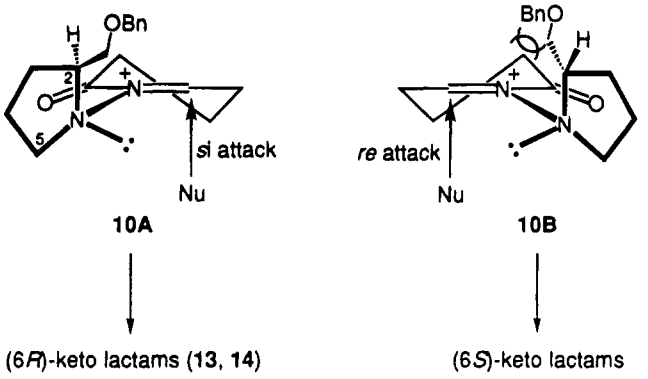
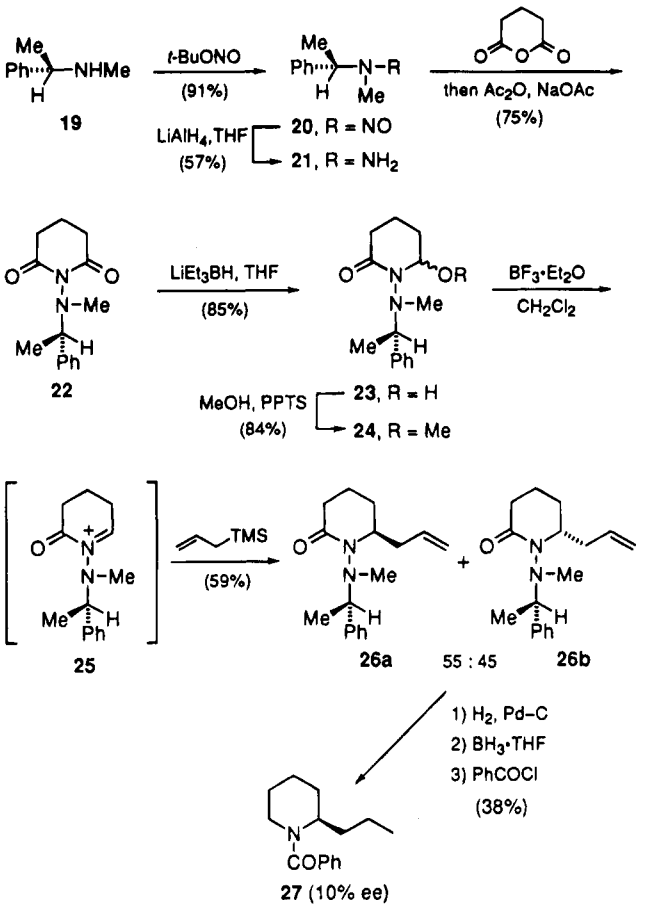


Figure 1. Two possible conformers in nucleophilic addition to the *N*-acylhydrazonium ion **10**.

Scheme 4

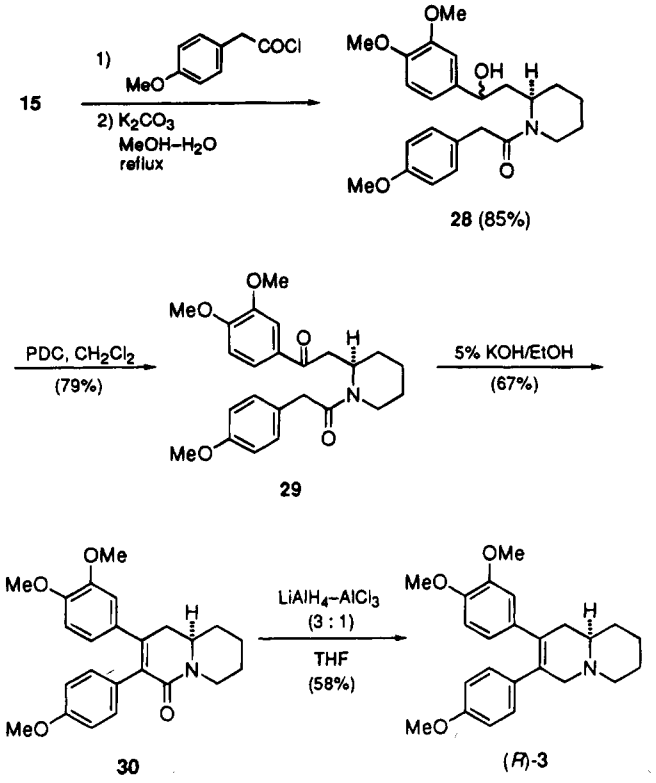


two diastereomeric compounds, **26a** and **26b**, with a very poor selectivity of 55:45 (59% combined yield). The stereochemical assignment for **26a** and **26b** was performed by conversion of the mixture in three steps to *N*-benzoylconiine (**27**), which when analyzed by HPLC on a Chiralcel OD column (eluent: hexane–*i*-PrOH, 95:5) was shown to be 10% enantiomeric excess in favor of the (*R*)-isomer, corresponding to major diastereomer **26a**. These results imply that pyramidal inversion at the nitrogen in the acyclic chiral auxiliary occurs so rapidly that diastereoselectivity was scarcely apparent in contrast to the case employing the pyrrolidine auxiliary.

Synthesis of (*R*)-(−)-Julandine. With the chiral amino alcohol **15** in hand, we envisioned the enantioselective approach to the synthesis of (*R*)-julandine [(*R*)-**3**] as outlined in Scheme 5. Treatment of **15** with (4-methoxyphenyl)acetyl chloride (CH_2Cl_2, 5% NaOH, 0 °C)

(20) Davis, F. A.; Jenkins, R. H., Jr. In *Asymmetric Synthesis*; Morrison, J. D., Scott, J. W., Eds.; Academic Press: Orlando, 1984; Vol. 4, Chapter 4.
(21) Hoffmann, R. W. *Chem. Rev.* **1989**, *89*, 1841.
(22) Stevens, R. V.; Lee, A. W. M. *J. Am. Chem. Soc.* **1979**, *101*, 7032. Stevens, R. V. In *Strategies and Tactics in Organic Synthesis*; Lindberg, T., Ed.; Academic Press: Orlando, 1984; Chapter 10, pp 275–298.

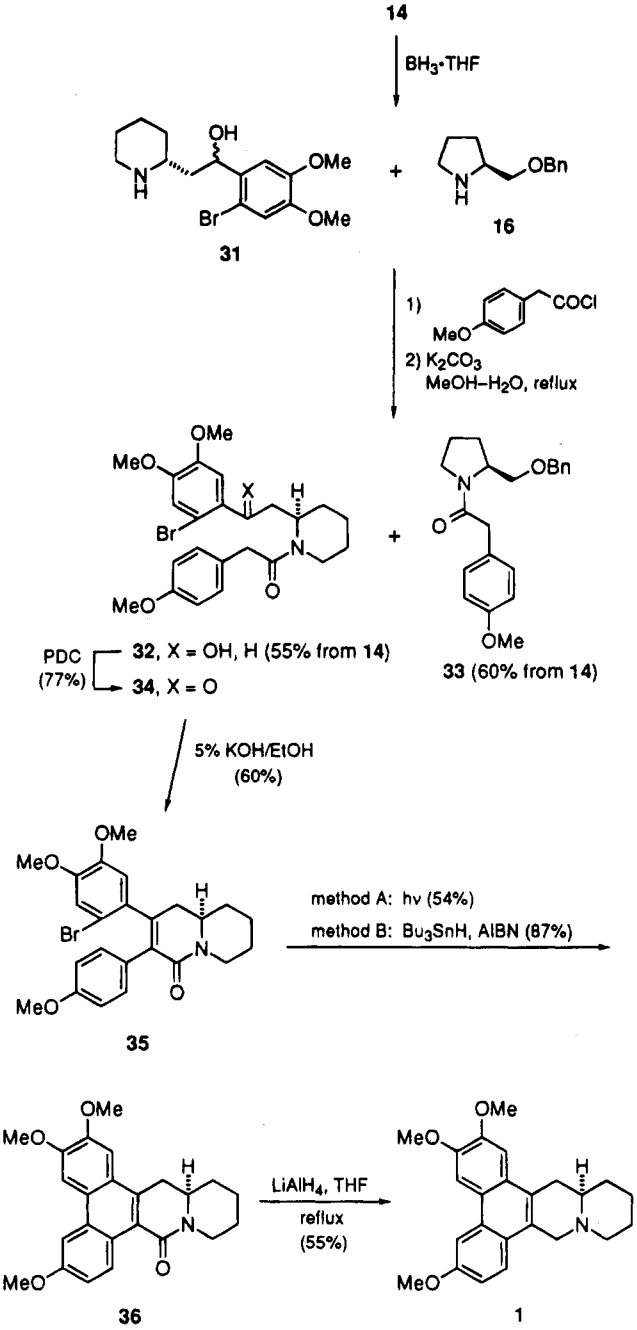
Scheme 5



followed by brief hydrolysis (aqueous K_2CO_3, MeOH, reflux, 30 min) of the concomitantly formed *N,O*-bis(phenylacetyl) derivative led to hydroxy amide **28** (85%). Oxidation of **28** with pyridinium dichromate gave keto amide **29** (79%), which underwent intramolecular aldol type condensation[23] under basic conditions (5% ethanolic KOH, reflux) to form the quinolizidinone **30** in 67% yield. Subsequent reduction of **30** with alane (3:1 $LiAlH_4$–$AlCl_3$) and recrystallization from ethyl acetate–hexane provided (*R*)-(−)-julandine [(*R*)-**3**], mp 138.5–140 °C (lit.[10] mp 134.5–135.5 °C), in 58% yield. The spectral data (^1H NMR) for synthetic (*R*)-**3** were identical to those reported for both the natural[10] and racemic substance.[8d,24] The synthetic material showed $[\alpha]^{26}_D$ −71.6° (*c* 0.34, $CHCl_3$) while the natural product is reported[10] to be dextrorotatory [$[\alpha]_D$ +4.6° (*c* 0.5, $CHCl_3$)]. Although the magnitude of the optical rotation of our synthetic sample is quite different from that reported for the natural product, the above observations indicate that naturally occurring julandine has the 9a*S* absolute configuration as depicted by structure (*S*)-**3**, which is opposite to that of natural cryptopleurine. The discrepancy in the reported absolute value for the natural product may arise from racemization in the isolated sample and/or decomposition in solution accompanied by decreasing rotatory strength as previously observed for optically active tylophorine.[25]

Synthesis of (*R*)-(−)-Cryptopleurine. We next focused our attention on the enantioselective synthesis of (*R*)-cryptopleurine (**1**) starting from the (6*R*)-keto lactam **14** as outlined in Scheme 6. Treatment of **14** with BH_3–THF and subsequent aqueous alkaline workup afforded a *ca.* 1:1 diastereomeric mixture (by ^1H NMR) of alcohol **31** and the chiral pyrrolidine auxiliary **16** via a simultaneous process involving reduction of both the carbonyl groups as well as reductive cleavage of the auxiliary bridge. Since products **31** and **16** were difficult to separate, the mixture was subjected to acylation followed by brief saponification of the ester to give a chromatographically separable mixture of hydroxy amide **32** (55% from **14**) and an *N*-acyl derivative of the pyrrolidine auxiliary **33** (60%). Oxidation of **32** with pyridinium dichromate gave keto amide **34** (77%), which underwent intramolecular aldol-type condensation under basic conditions (5% ethanolic KOH, reflux) to form quinolizidinone **35** in 60% yield. Construction of the phenanthrene nucleus was achieved through photocyclization (method A in Scheme 6) of **35**, affording 9-oxocryptopleurine (**36**) in 54% yield. Alternatively, treatment of **35** with Bu_3SnH and AIBN (method B in Scheme 6) effect intramolecular radical cyclization, leading to a significantly higher yield (87%) of **36**. Finally, reduction of **36** with $LiAlH_4$ provided (*R*)-(−)-cryptopleurine (**1**): mp 196–197

Scheme 6



(23) This step for aldol cyclization was carried out according to the procedure previously reported[8d] from this laboratory.

(24) Trigo, G. G.; Gálvez, E.; Söllhuber, M. M. *J. Heterocycl. Chem.* **1979**, *16*, 1625.

(25) Nordlander, J. E.; Njoroge, F. G. *J. Org. Chem.* **1987**, *52*, 1627.

°C (lit.[1a] mp 197–198 °C); $[\alpha]^{25}_D$ −96.7° (*c* 0.40, $CHCl_3$) [lit.[1a] $[\alpha]^{18}_D$ −106° (*c* 1.52, $CHCl_3$)]. The spectral data (^1H NMR) were identical to those of the authentic racemate.[8d]

Conclusion

In conclusion, the chiral *N*-acylhydrazonium ion is an efficient means of producing a high degree of 1,3-asymmetric induction in which the nitrogen adjacent to the imino group behaves as an asymmetric center. Addition of silyl enol ethers provides keto lactams with complete diastereoselectivity via amidoalkylation. Removal of the chiral auxiliary is accomplished by reductive cleavage of the N–N bond using BH_3–THF. This asymmetric strategy has allowed us to develop a highly enantioselective entry to the total syntheses of (*R*)-(−)-cryptopleurine (**1**) and (*R*)-(−)-julandine [(*R*)-**3**] and permitted the 9a*S* configuration to be assigned to natural (+)-julandine.

Experimental Section

General Procedures. Melting points are uncorrected. Optical rotations were recorded in a 1-dm cell. ^1H and ^1C NMR spectra were measured at 300 or 400 MHz in $CDCl_3$ solution. Mass spectra were determined at 70 eV. TLC was performed on precoated silica gel 60 F 254 plates (Merck), and silica gel 60 (230–400 mesh) (Merck) was used for column chromatography. Microanalyses were carried out by the Microanalytical Laboratory at Tokyo University of Pharmacy & Life Science.

(*S*)-2-[(Benzyloxy)methyl]-*N*-nitrosopyrrolidine (5). A solution of **4**[17] (3.73 g, 0.287 mol) in THF (10 mL) was added dropwise to a stirred suspension of NaH (60% in paraffin, 1.72 g, 0.430 mol) in DMF (10 mL) at rt. After the mixture was stirred for 30 min, benzyl bromide (5.88 g, 0.344 mol) was added dropwise and stirring was continued at rt for 3 h. The mixture was cooled in an ice bath and quenched with water (20 mL). The organic solvent of the solution was evaporated, and the resulting mixture was extracted with CH_2Cl_2 (3 × 30 mL). The combined extracts were washed with brine, dried ($MgSO_4$), and concentrated in vacuo. The residue was purified by chromatography on silica gel (hexane–EtOAc, 5:1) to give **5** (4.01 g, 94%) as a pale yellow oil: $[\alpha]^{28}_D$ −103° (*c* 1.7, $CHCl_3$); IR (neat) 2953, 2878, 1455, 1417, 1304, 1109, 741, 700 cm^{-1}; ^1H NMR (major rotamer) δ 1.91 (1 H, m), 1.99–2.27 (3 H, m), 3.52–3.74 (2 H, m), 3.82 (1 H, dd, *J* = 9.7, 5.8 Hz), 3.90 (1 H, dd, *J* = 9.7, 4.1 Hz), 4.55 (2 H, s), 4.68 (1 H, m, 7.21–7.41 (5 H, m); ^{13}C NMR (major geometrical isomer) δ 20.9, 27.3, 45.8, 60.4, 71.5, 73.3, 127.4, 127.6 (2 carbons), 128.3 (2 carbons), 137.7; EIMS *m/z* (rel intensity) 219 (M^+ − 1, 1), 203 (7), 189 (5), 160 (10), 91 (100), 65 (32); CIMS (isobutane) *m/z* 221 (MH^+). Anal. Calcd for $C_{12}H_{16}N_2O_2$: C, 65.43; H, 7.32; N, 12.72. Found: C, 65.68; H, 7.37; N, 12.39.

(*S*)-2-[(Benzyloxy)methyl]-*N*-glutarimidopyrrolidine (7). A solution of **5** (2.00 g, 9.08 mmol) in THF (5 mL) was added dropwise to an ice-cooled, stirred suspension of $LiAlH_4$ (0.689 g, 18.2 mmol) in THF (15 mL), and the suspension was stirred at rt for 15 min and then refluxed for 2 h and cooled to 0 °C. To this suspension was added 10% aqueous KOH (2 mL), and the mixture was refluxed for 30 min, filtered through a Celite pad, and concentrated in vacuo to leave (*R*)-1-amino-2-[(benzyloxy)methyl]pyrrolidine (**6**) as a pale yellow oil, which was subjected to the following reaction without purification: ^1H NMR δ 1.54 (1 H, m), 1.68–1.84 (2 H, m), 1.95 (1 H, m), 2.35 (1 H, q, *J* = 9.0 Hz), 2.47 (1 H, m), 3.15 (1 H, m), 3,26 (1 H, ddd, *J* = 9.0, 6.7, 2.5 Hz), 3.56 (1 H, dd, *J* = 9.4, 4.8 Hz), 3.59 (1 H, dd, *J* = 9.4, 6.1 Hz), 4.54 and 4.56 (2 H, AB q, *J* = 12.1 Hz), 7.26–7.39 (5 H, m); ^{13}C NMR δ 21.0, 26.6, 60.1, 68.6, 73.5, 73.7, 127.6, 127.7 (2 carbons), 128.4 (2 carbons), 138.4.

The above crude product of **6** was dissolved in CH_2Cl_2 (10 mL), and glutaric anhydride (1.24 g, 10.9 mmol) was added to this solution. After the mixture was stirred at rt for 1 h, acetic anhydride (1.11 g, 10.9 mmol) and a catalytic amount of sodium acetate (30 mg) were added and the mixture was refluxed for 1 h. The reaction mixture was cooled to 0 °C, and 5% aqueous $NaHCO_3$ (10 mL) was added. After being stirred for 30 min, the mixture was extracted with $CHCl_3$ (3 × 10 mL). The combined extracts were washed with brine, dried ($MgSO_4$), and concentrated in vacuo. The residue was purified by chromatography on silica gel (hexane–EtOAc, 2:1) to afford **7** (2.55 g, 93%) as a colorless oil: $[\alpha]^{28}_D$ −20.5° (*c* 1.7, $CHCl_3$); IR (neat) 2965, 2874, 1739, 1692, 1455, 1346, 1247, 1170, 1129, 996, 741, 700 cm^{-1}; ^1H NMR δ 1.50–2.08 (6 H, m), 2.31–2.58 (4 H, m), 3.20 (1 H, td, *J* = 7.9, 4.7 Hz), 3.28 (1 H, q, *J* = 7.9 Hz), 3.43 (1 H, dd, *J* = 9.1, 7.4 Hz), 3.47 (1 H, dd, *J* = 9.1, 4.6 Hz), 3.78 (1 H, dd, *J* = 7.4, 4.6 Hz), 4.37 (2 H, s), 7.36–7.90 (5 H, m); ^{13}C NMR δ 16.1, 22.6, 27.3, 33.5, 34.5, 51.4, 59.7, 73.4, 75.0, 127.5, 127.9 (2 carbons), 128.2 (2 carbons), 138.4, 171.7, 172.7; EIMS *m/z* (rel intensity) 302 (M^+ + 1, 0.5), 181 (100), 111 (6), 91 (36), 68 (26); HRMS (EI) calcd for $C_{17}H_{22}N_2O_3$ (M^+ + 1) 302.1630, found 302.1651. Anal. Calcd for $C_{17}H_{22}N_2O_3$: C, 67.53; H, 7.33; N, 9.26. Found: C, 67.45; H, 7.33; N, 9.31.

(6*RS*)-*N*-[(2*S*)-2-[(Benzyloxy)methyl]pyrrolidino]-6-hydroxy-2-piperidinone (8). To a cold (−78 °C) solution of **7** (292 mg, 0.966 mmol) in THF (10 mL) was added lithium triethylborohydride (1 M solution in THF, 1.16 mL, 1.16 mmol), and the reaction mixture was stirred at −78 °C for 2 h. To this was added 5% aqueous $NaHCO_3$ (5 mL), and the mixture was allowed to warm to rt and extracted with EtOAc (2 × 20 mL). The combined organic layers were washed with brine, dried ($MgSO_4$), and concentrated. The residual oil was purified by chromatography on silica gel (hexane–EtOAc, 1:1) to afford **8** (236 mg, 80%) as a colorless oil, which was a 4:1 mixture of the diastereomers: IR (neat) 3384, 2952, 2873, 1659, 1305, 1088 cm^{-1}; ^1H NMR δ 1.47 (1 H, m), 1.55–1.84 (4 H, m), 1.86–2.13 (3 H, m), 2.19–2.39 (2 H, m), 2.40–2.47 (1 H, m), 3.17 (1 H, td, *J* = 7.8, 2.5 Hz), 3.30–3.36 (2 H, m), 3.42 (1 H, dd, *J* = 9.6, 3.1 Hz), 3.87 (1 H, m), 4.48 (0.4 H, s, minor diastereomer), 4.56 and 4.58 (1.6 H, AB q, *J* = 12.3 Hz, major diastereomer), 5.03 and 5.09 (total 1 H in 1:4 ratio, t, *J* = 3.2 Hz, and m, respectively), 5.89 (1 H, m), 7.27–7.38 (5 H, m); ^{13}C NMR (major diastereomer) δ 15.7, 23.6, 27.1, 30.2, 34.0, 51.9, 60.1, 73.1, 73.4, 83.3, 127.8, 127.9 (2 carbons), 128.4 (2 carbons), 137.1, 169.1; EIMS *m/z* (rel intensity) 305 (M^+ + 1, 0.3), 286 (0.4), 205 (0.5), 183 (100), 165 (27), 91 (61); HRMS (EI) calcd for $C_{17}H_{24}N_2O_3$ (M^+) 304.1786, found 304.1799.

(6*RS*)-*N*-[(2*S*)-2-[(Benzyloxy)methyl]pyrrolidino]-6-methoxy-2-piperidinone (9). A mixture of **8** (363 mg, 1.19 mmol) and a catalytic amount of pyridinium *p*-toluenesulfonate (30 mg) in MeOH (2 mL) was stirred at rt for 3 h. The reaction mixture was concentrated in vacuo to leave the residual oil, which was dissolved in $CHCl_3$ (30 mL), washed with 5% aqueous $NaHCO_3$ (2 mL) and then brine, and dried ($MgSO_4$). Concentration in vacuo followed by chromatography on silica gel (hexane–EtOAc, 3:1) afforded **9** (304 mg, 80%) as a colorless oil: IR (neat) 2951, 2878, 1661, 1455, 1406, 1077 cm^{-1}; ^1H NMR δ 1.38–1.57 (3 H, m), 1.61–2.13 (5 H, m), 2.22 (1 H, m), 2.40 (1 H, m), 3.21 (1 H, ddd, *J* = 8.0, 7.4, 4.4 Hz), 3.34–3.41 (2 H, m), 3.44 (3 H, s), 3.52 (1 H, q, *J* = 8.0 Hz), 3.86 (1 H, quintet, *J* = 6.5 Hz), 4.49 (2 H, s), 4.64 (1 H, m), 7.27–7.38 (5 H, m); ^{13}C NMR δ 15.5, 23.2, 27.4, 27.9, 33.7, 52.6, 56.9, 60.0, 73.0, 74.8, 93.6, 127.5, 127.7 (2 carbons), 128.2 (2 carbons), 138.3, 169.1; CIMS (isobutane) 319 (MH^+), 287; HRMS (EI) calcd for $C_{18}H_{26}N_2O_3$ (M^+) 318.1943, found 318.1960.

(6*R*)-*N*-[(2*S*)-2-[(Benzyloxy)methyl]pyrrolidino]-6-[(3,4-dimethoxybenzoyl)methyl]-2-piperidinone (13). To a stirred solution of **9** (198 mg, 0.622 mmol) and 1-(3,4-dimethoxyphenyl)-1-(trimethylsiloxy)ethylene (**11**) (471 mg, 1.87 mmol) in CH_2Cl_2 (3 mL) was added $BF_3{\cdot}Et_2O$ (176 mg, 1.24 mmol) at rt. After the mixture was stirred at rt for 1 h, 5% aqueous $NaHCO_3$ (10 mL) was added and the mixture was extracted with CH_2Cl_2 (3 × 20 mL). The combined extracts were washed with brine, dried ($MgSO_4$), and concentrated in vacuo to give a brownish yellow oil, which was chromatographed on silica gel (hexane–EtOAc, 1:2) to afford 221 mg (76%) of the product as a colorless oil that was found to consist of the 99.5:0.5 mixture of **13** and the 6*S* epimer according to ^1H NMR (400 MHz). Careful chromatography on silica gel (hexane–EtOAc, 1:1) provided **13** in pure form: $[\alpha]^{26}_D$ +14.0°

(*c* 1.6, $CHCl_3$); IR (neat) 2940, 2875, 1668, 1645, 1595, 1515, 1417, 1264, 1154, 1025 cm^{-1}; ^1H NMR δ 1.36−1.70 (5 H, m), 1.78 (1 H, m), 1.88−2.07 (2 H, m), 2.23−2.37 (2 H, m), 2.84 (1 H, dd, J = 15.1, 9.0 Hz), 3.04 (1 H, td, J = 7.7, 4.7 Hz), 3.38 (2 H, d, J = 5.9 Hz), 3.58 (1 H, q, J = 7.7 Hz), 3.63 (1 H, dd, J = 15.1, 4.1 Hz), 3.88−3.96 (1 H, m), 3.93 (6 H, s), 4.30 (1 H, m), 4.43 and 4.45 (2 H, AB q, J = 11.8 Hz), 6.85 (1 H, d, J = 8.4 Hz), 7.20−7.30 (5 H, m), 7.53 (1 H, d, J = 2.0 Hz), 7.64 (1 H, dd, J = 8.4, 2.0 Hz); ^{13}C NMR δ 17.6, 22.8, 27.6, 28.5, 34.2, 42.4, 53.2, 56.0, 56.1, 60.1 (2 carbons), 73.2, 74.3, 110.1, 110.3, 123.0, 127.4, 127.7 (2 carbons), 128.2 (2 carbons), 130.4, 138.4, 149.2, 153.4, 169.2, 169.9; EIMS *m/z* (rel intensity) 345 (M^+ − CH_2OCH_2Ph, 100), 277 (10), 249 (6), 190 (8), 165 (62), 112 (27); HRMS (EI) calcd for $C_{19}H_{25}N_2O_4$ (M^+ − CH_2OCH_2Ph) 345.1855, found 345.1828.

(6*R*)-*N*-[(2*S*)-2-[(Benzyloxy)methyl]pyrrolidino]-6-[(2-bromo-3,4-dimethoxybenzoyl)methyl]-2-piperidinone (14). Following the procedure given above for the formation of **13**, **9** (202 mg, 0.634 mmol) was treated with 1-(2-bromo-4,5-dimethoxyphenyl)-1-(trimethylsiloxy)ethylene (**12**) (480 mg, 1.90 mmol), prepared from 2′-bromo-4′,5′-dimethoxyacetophenone[26] by treatment with LDA and Me_3SiCl, providing **14** (242 mg, 70%) as a colorless oil; no 6*S* epimer was detected in ^1H NMR (400 MHz): $[\alpha]^{26}_D$ +9.6° (*c* 0.73, $CHCl_3$); IR (neat) 2945, 2874, 1684, 1646, 1594, 1566, 1455, 1374, 1332, 1260, 1213, 1170, 1026, 791, 737 cm^{-1}; ^1H NMR δ 1.36−1.70 (5 H, m), 1.81−2.08 (3 H, m), 2.30 (2 H, t, J = 6.1 Hz), 2.96 (1 H, td, J = 8.2, 4.9 Hz), 3.11 (1 H, dd, J = 16.4, 8.0 Hz), 3.31 (1 H, dd, J = 9.4, 7.0 Hz), 3.36 (1 H, dd, J = 9.4, 4.7 Hz), 3.52, (1 H, q, J = 8.2 Hz), 3.63 (1 H, dd, J = 16.4, 4.8 Hz), 3.87 (3 H, s), 3.89−3.95 (1 H, m), 3.92 (3 H, s), 4.42 and 4.44 (2 H, AB q, J = 11.6 Hz), 7.05 (1 H, s), 7.11 (1 H, s), 7.23−7.34 (5 H, m); ^{13}C NMR δ 17.7, 22.8, 27.5, 28.9, 34.1, 46.9, 52.9, 56.0, 56.3, 59.7, 59.9, 73.1, 74.2, 111.3, 112.7, 116.3, 127.4, 127.7 (2 carbons), 128.1 (2 carbons), 132.4, 138.2, 148.1, 151.4, 169.0, 199.8.

(2*S*)-2-[(2*RS*)-2-(3,4-Dimethoxyphenyl)-2-hydroxyethyl]piperidine (15). To an ice-cold, stirred solution of **13** (395 mg, 0.847 mmol) in THF (10 mL) was added the borane−THF complex (1.0 M solution in THF, 15.6 mL, 15.6 mmol), and the solution was stirred at rt for 15 min and then refluxed for 24 h. After the mixture was cooled in an ice bath, 10% aqueous NaOH (10 mL) was added and the mixture was briefly stirred. The mixture was concentrated to one-third in volume, refluxed for 5 h, and then extracted with Et_2O (3 × 10 mL). The combined extracts were washed with brine, dried ($MgSO_4$), and concentrated in vacuo. Chromatography of the residue on silica gel ($CHCl_3$−MeOH−concentrated NH_4OH, 50:9:1) gave two fractions. The first fraction gave (*S*)-[(benzyloxy)methyl]-pyrrolidine (**16**) (106 mg, 66%). The second fraction gave **15** (143 mg, 64%) as a pale yellow oil, which was an 8:1 mixture of the diastereomers according to ^1H NMR: IR (neat) 3432, 3306, 1591, 1520, 1448, 1265, 1137, 1029, 808 cm^{-1}; ^1H NMR δ 1.12 (1 H, m), 1.22−1.42 (2 H, m), 1.46−1.75 (4 H, m), 1.78−1.88 (2 H, m), 2.64 (1 H, ddd, J = 13.7, 11.9, 2.8 Hz), 2.87 (1 H, tt, J = 10.7, 2.5 Hz), 3.08 (1 H, m), 3.85 (3 H, s), 3.89 (3 H, s), 4.88 and 4.98 (total 1 H in 8:1 ratio, dd, J = 10.5, 2.8 Hz, and dd, J = 7.5, 3.6 Hz), 6.79−6.87 (2 H, m), 6.96 (1 H, d, J = 1.7 Hz); ^{13}C NMR (major diasteromer) δ 24.5, 27.3, 34.3, 45.2, 46.0, 55.8, 55.9, 58.3, 75.3, 108.8, 110.9, 117.6, 138.1, 147.9, 148.9; EIMS *m/z* (rel intensity) 265 (M^+, 18), 247 (4), 180 (5), 164 (13), 139 (13), 127 (11), 98 (30), 84 (100); HRMS (EI) calcd for $C_{15}H_{23}NO_3$ (M^+) 265.1678, found 265.1682.

(2*S*)-*N*-(Carbobenzyloxy)-2-[2(*E*)-(3,4-dimethoxyphenyl)-ethenyl]piperidine (17). To an ice-cooled, stirred mixture of **15** (123 mg, 0.480 mmol) and 5% aqueous NaOH (1.5 mL) in CH_2Cl_2 (1.5 mL) was added dropwise benzyl chloroformate (82.0 mg, 0.480 mmol) via syringe. After being stirred at rt for 1 h, the mixture was diluted with CH_2Cl_2 (30 mL), washed with water, dried ($MgSO_4$), and concentrated. The residue was purified by chromatography on silica gel (hexane−EtOAc, 1:1) to give (2*R*)-*N*-(carbobenzyloxy)-2-[(2*RS*)-2-(3,4-dimethoxyphenyl)-2-hydroxyethyl]piperidine (153 mg, 80%) as a colorless oil. A part of this product (51.7 mg, 0.129 mmol) was then dissolved in CH_2Cl_2 (1.5 mL) and cooled to 0 °C. To this solution were added Et_3N (28 mg, 0.26 mmol) and then methanesulfonyl chloride (22.0 mg, 0.194 mmol), and the mixture was stirred at rt for 1 h. The mixture was diluted with CH_2Cl_2 (30 mL), washed with brine, dried ($MgSO_4$), and concentrated in vacuo. The resulting residue was dissolved in toluene (1.5 mL), and 1,8-diazabicyclo[5.4.0]undec-7-ene (98.5 mg, 0.647 mmol) was added. After heating at 100 °C for 1 h, the mixture was diluted with benzene (30 mL), washed with 5% HCl and brine, and dried ($MgSO_4$). Concentration followed by purification by chromatography on silica gel (hexane−EtOAc, 3:1) gave a colorless solid, which was recrystallized from AcOH−hexane to afford **17** (25.6 mg, 52%) as colorless needles: mp 111.5−112.5 °C; IR (neat) 2937, 2859, 1695, 1515, 1464, 1445, 1421, 1264, 1139, 1028 cm^{-1}; ^1H NMR δ 1.39−1.91 (6 H, m), 3.00 (1 H, m), 3.88 (3 H, s), 3.90 (3 H, s), 4.09 (1 H, m), 5.06 (1 H, br s), 5.15 and 5.19 (2 H, AB q, J = 12.5 Hz), 6.05 (1 H, dd, J = 16.0, 4.8 Hz), 6.33 (1 H, d, J = 16.0 Hz), 6.79−6.92 (3 H, m), 7.27−7.39 (5 H, m); ^{13}C NMR δ 19.6, 25.6, 29.5, 40.2, 52.4, 55.9, 56.0, 67.0, 108.8, 111.1, 119.3, 126.2, 127.80 (2 carbons), 127.81, 128.5 (2 carbons), 130.0, 130.9, 137.0, 148.7, 149.0, 155.8; EIMS *m/z* (rel intensity) 381 (M^+, 3), 290 (25), 246 (45), 152 (83), 91 (100); HRMS (EI) calcd for $C_{23}H_{27}NO_4$ (M^+) 381.1940, found 381.1957. Anal. Calcd for $C_{23}H_{27}NO_4$: C, 72.42; H, 7.13; N, 3.67. Found: C, 72.50; H, 7.17; N, 3.66.

(*R*)-(Carbobenzyloxy)pipecolinic Acid (18). Ozone was bubbled through a solution of **17** (25.0 mg, 0.0655 mmol) in MeOH (10 mL) at −78 °C until the color of the solution remained light blue. Dimethyl sulfide (0.5 mL) was added, and the solution was slowly warmed to rt. The mixture was diluted with CH_2Cl_2 (30 mL), washed with brine, and dried ($MgSO_4$). Concentration in vacuo resulted in the oil, which was dissolved in acetone (1 mL), cooled to 0 °C, and oxidized at 0 °C for 2 h with Jones reagent prepared according to the standard method. The mixture was diluted with CH_2Cl_2 (30 mL), washed with brine, and dried ($MgSO_4$). Evaporation followed by chromatography on silica gel ($CHCl_3$−MeOH, 100:1) gave **15** (7.1 mg, 40%) as a pale yellow oil which was crystallized upon standing. Recrystallization from Et_2O afforded colorless needles: mp 111−113 °C (lit.[18] 112−113 °C); $[\alpha]_D$ +56.5° (*c* 0.55, AcOH) [lit.[18] $[\alpha]_D$ +57.2° (*c* 5.3, AcOH)].

***N*-Methyl-*N*-nitroso-1(*S*)-phenylethylamine (20).** To a solution of (*S*)-α-methylbenzylamine (**19**) 1.11 g, 8.21 mmol) in THF (10 mL) was added *tert*-butyl nitrite (1.27 g, 12.3 mmol), and the mixture was heated under reflux for 3 h and concentrated in vacuo. The residue was purified by chromatography on silica gel (hexane−EtOAc, 3:1) to give **20** (1.23 g, 91%) as a colorless oil: $[\alpha]^{28}_D$ −31.2° (*c* 1.4, $CHCl_3$); IR (neat) 2983, 1496, 1435, 1342, 1278, 1233, 1195, 1069, 1051, 1031 cm^{-1}; ^1H NMR δ 1.81 (3 H, d, J = 7.1 Hz), 2.80 (3 H, s), 5.77 (1 H, q, J = 7.1 Hz), 7.20−7.42 (5 H, m); ^{13}C NMR δ 18.3, 29.1, 62.0, 126.7 (2 carbons), 128.2, 128.8 (2 carbons), 138.7; EIMS *m/z* (rel intensity) 164 (M^+, 13), 118 (10), 105 (100), 77 (16), 49 (7); HRMS (EI) calcd for $C_9H_{12}N_2O$ (M^+) 164.0950, found 164.0940.

1-Methyl-1-[1(*S*)-phenylethyl]hydrazine (21). A solution of **20** (506 mg, 3.08 mmol) in THF (5 mL) was added dropwise to an ice-cooled, stirred suspension of $LiAlH_4$ (3.50 g, 18.2 mmol) in THF (15 mL), and the suspension was stirred at rt for 15 min and then refluxed for 1 h and cooled to 0 °C. To this suspension was added dropwise 10% aqueous KOH (1 mL), and the mixture was refluxed for 1 h, filtered through a Celite pad, and concentrated in vacuo to give **21** (265 mg, 57%) as a pale yellow oil, which was subjected to the following reaction without purification: NMR δ 1.42 (3 H, d, J = 6.6 Hz), 2.42 (3 H, s), 2.80−3.10 (2 H, br s), 3.37 (1 H, q, J = 6.6 MHz), 7.16−7.46 (5 H, m); ^{13}C NMR δ 20.2, 46.2, 69.6, 127.3, 127.7 (2 carbons), 128.4 (2 carbons), 142.3.

***N*-Glutarimido-*N*-methyl-1(*S*)-phenylethylamine (22).** Following the procedure given above for the formation of **7**, **21** (715 mg, 4.76 mmol) was treated with glutaric anhydride (1.24 g, 10.9 mmol) followed by acetic anhydride (583 mg, 5.71 mmol) and a catalytic amount of sodium acetate (40 mg). The product was purified by chromatography on silica gel (hexane−EtOAc, 1:1) to give **22** (880 mg, 75%) as a colorless solid which

(26) Kimoto, S.; Sakai, S.; Ohkuma, K. *Yakugaku Zasshi* **1949**, *69*, 155.

was recrystallized from EtOAc–hexane to provide colorless plates: mp 110–110.5 °C; $[\alpha]^{25}_D$ −5.82° (*c* 4.26, $CHCl_3$); IR (KBr) 2977, 2954, 1741, 1692, 1346, 1244, 1171, 1132, 1113, 1088 cm^{-1}; ^1H NMR δ 1.22–1.36 (1 H, m), 1.30 (3 H, d, *J* = 6.5 Hz), 1.68 (1 H, m), 2.29–2.58 (4 H, m), 2.81 (3 H, s), 4.56 (1 H, q, *J* = 6.5 Hz), 7.17–7.36 (5 H, m); ^{13}C NMR δ 16.7, 21.6, 33.7, 34.0, 40.3, 63.0, 127.4 (3 carbons), 128.2 (2 carbons), 143.5, 172.2, 172.4; EIMS *m/z* (rel intensity) 246 (M^+, 0.3), 245 ($M^+ - 1$, 1.1), 231 (3), 134 (77), 118 (57), 105 (100). Anal. Calcd for $C_{14}H_{18}N_2O_2$: C, 68.27; H, 7.37; N, 11.37. Found: C, 68.02; H, 7.37; N, 11.36.

(6*RS*)-6-Hydroxy-*N*-[*N*-methyl-*N*-[1(*S*)-phenylethyl]amino]-2-pyrrolidinone (23). Following the procedure given above for the formation of **8**, **22** (289 mg, 1.17 mmol) was treated with lithium triethylborohydride (1 M solution in THF, 1.29 mL, 1.29 mmol) and the product was purified by chromatography on silica gel (hexane–EtOAc, 1:1) to give **23** (248 mg, 85%) as a colorless oil: IR (neat) 3369, 2959, 2883, 1631, 1443, 1409, 1328, 1290, 1086, 1005 cm^{-1}; ^1H NMR δ 0.99 (1 H, m), 1.18 and 1.36 (total 1 H in 1:1 ratio, each d, *J* = 6.6 Hz), 1.64 (1 H, m), 1.86–2.06 (2 H, m), 2.20–2.62 (2 H, m), 2.70 and 3.06 (total 3 H in 1:1 ratio, each s), 4.10–4.23 (1 H, m), 4.52 and 5.13 (total 1 H in 1:1 ratio, each d, *J* = 3.6 Hz), 4.63 and 4.74 (total 1 H in 1:1 ratio, each q, *J* = 6.6 Hz), 7.15–7.38 (5 H, m); EIMS *m/z* (rel intensity) 249 ($M^+ + 1$, 1), 248 (M^+, 0.6), 247 ($M^+ - 1$, 0.7), 233 (53), 134 (91), 105 (100), 77 (18); HRMS (EI) calcd for $C_{14}H_{20}N_2O_2$ (M^+) 248.1525, found 248.1529.

(6*RS*)-6-Methoxy-*N*-[*N*-methyl-*N*-[(1*S*)-phenylethyl]amino]-2-pyrrolidinone (24). Following the procedure given above for the formation of **9**, **23** (57.0 mg, 0.230 mmol) was treated with a catalytic amount of pyridinium *p*-toluenesulfonate (5 mg) in MeOH (0.5 mL), and the product was purified by chromatography on silica gel (hexane–EtOAc, 1:1) to give **24** (50.5 mg, 84%) as a colorless oil: IR (neat) 2954, 2885, 1664, 1456, 1364, 1328, 1293, 1196, 1079 cm^{-1}; ^1H NMR δ 1.20 and 1.39 (total 3 H in 1:1 ratio, each d, *J* = 6.6 Hz), 1.44–2.06 (4 H, m), 2.22–2.56 (2 H, m), 2.71 and 3.08 (total 3 H in 1:1 ratio, each s), 3.41 and 3.59 (total 3 H in 1:1 ratio, each s), 3.97 and 4.52 (total 1 H in 1:1 ratio, t, *J* = 3.2 Hz and m, respectively), 4.65 and 4.73 (total 1 H in 1:1 ratio, each q, *J* = 6.7 Hz), 7.20–7.41 (5 H, m); EIMS *m/z* (rel intensity) 263 ($M^+ + 1$, 0.5), 247 (2.8), 231 (2.5), 215 (0.4), 157 (2.9), 134 (85), 118 (45), 105 (100), 71 (32); HRMS (EI) calcd for $C_{14}H_{19}N_2O_2$ (M^+ − Me) 247.1465, found 247.1487.

(6*S*)- and (6*R*)-*N*-[*N*-Methyl-*N*-[1(*S*)-phenylethyl]amino]-6-allyl-2-piperidinone (26a and 26b). To a stirred solution of **24** (198 mg, 0.622 mmol) and allyltrimethylsilane (26.1 mg, 0.229 mmol) in CH_2Cl_2 (2 mL) was added $BF_3{\cdot}Et_2O$ (21.6 mg, 0.229 mmol) at rt, and the mixture was stirred for 30 min. To this mixture was added 5% aqueous $NaHCO_3$ (5 mL), and the mixture was extracted with CH_2Cl_2 (3 × 10 mL). The combined extracts were washed with brine, dried ($MgSO_4$), and concentrated in vacuo to give a brownish yellow oil, which was chromatographed on silica gel (hexane–EtOAc, 2:1) to afford 12.3 mg (59%) of the product as a colorless oil that was found to consist of a 55:45 mixture of **26a** and **26b** according to ^1H NMR (400 MHz): IR (neat) 2975, 2948, 1886, 1651, 1585, 1493, 1454, 1428, 1403, 1369, 1331, 1304, 1267, 1203, 1170, 1156, 1116, 1077, 1028 cm^{-1}; ^1H NMR δ 0.74–1.01 (1 H, m), 1.12–1.28 and 1.37 (total 3 H in 55:45 ratio, m and d, *J* = 6.6 Hz, respectively), 1.55–1.88 (3 H, m), 1.96–2.42 (4 H, m), 2.49, 2.62 and 2.99 (total 3 H, each s), 3.17–3.62 (1 H, m), 4.63–4.82 (1 H, m), 4.98–5.20 (2 H, m), 5.51–5.86 (1 H, m), 7.18–7.39 (5 H, m); EIMS *m/z* (rel intensity) 273 ($M^+ + 1$, 1.3), 272 (M^+, 0.6), 271 ($M^+ - 1$, 1) 257 (4.5), 231 (3), 195 (1.3), 137 (30), 134 (100), 118 (68), 105 (81); HRMS (EI) calcd for $C_{17}H_{25}N_2O$ ($M^+ + 1$) 273.1951, found 273.1967.

Preparation of (*R*)-*N*-Benzoylconiine (27) from 26. A solution of the 55:45 mixture (84 mg, 0.31 mmol) of **26a** and **26b** was hydrogenated over 10% palladium on carbon (5 mg) at atmospheric pressure for 10 min. Filtration and evaporation of the solvent afforded a crude product of *N*-[*N*-methyl-*N*-[1(*S*)-phenylethyl]amino]-6-propyl-2-piperidinone as a pale yellow oil which was, without purification, dissolved in THF (3 mL). In a manner similar to that described for the preparation of **15**, the THF solution of the above product was treated with the borane–THF complex (1.0 M solution in THF, 6.12 mL, 6.12 mmol). After the termination of the reaction, the mixture was extracted with Et_2O (3 × 10 mL), saturated methanolic HCl (0.5 mL) was added, and the mixture was concentrated in vacuo. The residue was then dissolved in a mixture of 5% NaOH solution (0.5 mL) and CH_2Cl_2 (0.5 mL) and cooled to 0 °C. To the mixture was added dropwise with stirring a solution of benzoyl chloride (129 mg, 0.918 mmol) in CH_2Cl_2 (0.5 mL). The mixture was stirred for another 1 h and extracted with CH_2Cl_2 (2 × 10 mL). The combined extracts were washed with water, dried ($MgSO_4$), and concentrated. Purification of the residue by chromatography on silica gel (hexane–EtOAc, 10:1) gave **27** (27 mg, 38% from **26**) as a colorless oil, which was analyzed by HPLC on a Chiralcel OD column (eluent: hexane–*i*-PrOH, 95:5) to be 10% ee: IR (neat) 2932, 2865, 1629, 1426, 1272, 1117, 1207 cm^{-1}; ^1H NMR δ 0.65–1.87 (10 H, m), 2.70–3.12 (2 H, m), 3.38–3.92 (2 H, m), 4.40–5.10 (2 H, m); EIMS *m/z* (rel intensity) 231 (M^+, 3), 181 (31), 105 (100), 77 (30); HRMS (EI) calcd for $C_{15}H_{21}NO$ (M^+) 231.1623, found 231.1616.

(2*S*)-2-[(2*RS*)-2-(3,4-Dimethoxyphenyl)-2-hydroxyethyl]-*N*-[(4-methoxyphenyl)acetyl]piperidine (28). To an ice-cold, stirred solution of **15** (8:1 diastereomeric mixture) (143 mg, 0.539 mmol) in CH_2Cl_2 (1.5 mL) were added 5% aqueous NaOH (1.5 mL) and then a solution of (4-methoxyphenyl)acetyl chloride (129 mg, 0.701 mmol) in CH_2Cl_2 (0.5 mL) and stirring was continued under cooling. After 40 min, the mixture was extracted with CH_2Cl_2 (3 × 10 mL) and the combined extracts were washed with brine and dried ($MgSO_4$). Concentration in vacuo gave the residual oil, which was dissolved in a 2:1 mixture (6 mL) of MeOH and water. To this was added K_2CO_3 (223 mg, 1.62 mmol), and the mixture was refluxed for 1 h. After being condensed to half volume under reduced pressure, the mixture was extracted with CH_2Cl_2 (10 mL) and the extract was successively washed with 5% aqueous NaOH, 5% HCl, and brine and then dried ($MgSO_4$). Evaporation of the solvent and purification by chromatography on silica gel ($CHCl_3$–MeOH, 200:1) gave **28** (189 mg, 85%) as a pale yellow oil: IR (neat) 3369, 2937, 1615, 1515, 1456, 1249, 1030 cm^{-1}; ^1H NMR (diastereomers) δ 1.24 (1 H, m), 1.46–1.64 (3 H, m), 1.80–1.94 (2 H, m), 2.02–2.14 (2 H, m), 2.59 and 2.92 (total 1 H, each m), 3.44–3.59 (1 H, m), 3.53 (2 H, s), 3.77 (3 H, s), 3.85 (3 H, s), 3.88 (3 H, s), 4.18 and 4.52 (total 1H, each m), 4.73 and 4.86 (total 1 H, each m), 6.80–7.13 (7 H, m); ^{13}C NMR (major diastereomer) δ 19.1, 25.6, 29.6, 40.6, 40.8, 42.1, 46.7, 55.2, 55.99, 56.01, 72.1, 109.1, 111.2, 114.1, 117.7, 127.1, 129.6, 137.6, 148.1, 149.0, 158.5, 171.3; EIMS *m/z* (rel intensity) 413 (M^+, 2), 411 (6), 274 (12), 233 (40), 121 (100); HRMS (EI) calcd for $C_{24}H_{31}NO_5$ (M^+) 413.2202, found 413.2222.

(2*R*)-2-[(3,4-Dimethoxybenzoyl)methyl]-*N*-[(4-methoxyphenyl)acetyl]piperidine (29). To a solution of **28** (183 mg, 0.443 mmol) in CH_2Cl_2 (3 mL) was added PDC (1.66 g, 4.43 mmol) and powdered molecular sieves 4 Å (0.83 g), and the resulting mixture was stirred for 5 h at rt. The mixture was diluted with Et_2O (15 mL), filtered through a Celite pad, washed with brine, and dried ($MgSO_4$). Evaporation of the solvent and purification by chromatography on silica gel ($CHCl_3$) gave **29** (144 mg, 79%) as a colorless oil: $[\alpha]^{27}_D$ −59.6° (*c* 2.3, $CHCl_3$); IR (neat) 2937, 1670, 1634, 1595, 1514, 1418, 1265, 1247, 1024, 808, 758 cm^{-1}; ^1H NMR (amide rotamers) δ 1.19–1.71 (6 H, m), 2.60 (0.5 H, td, *J* = 13.3, 2.6 Hz), 2.90 (0.5 H, dd, *J* = 16.8, 5.2 Hz), 2.99–3.25 (2 H, m), 3.64–3.83 (5.5 H, m), 3.92, 3.93, and 3.94 (total 6 H, each s), 4.60 (0.5 H, br d, *J* = 14.2 Hz), 4.75 (0.5 H, m), 5.25 (0.5 H, m), 6.75 (1 H, d, *J* = 8.5 Hz), 6.82–6.92 (2 H, m), 7.13 (1 H, d, *J* = 8.7 Hz), 7.17 (1 H, d, *J* = 8.7 Hz), 7.44 (1 H, m), 7.58 (0.5 H, d, *J* = 1.7 Hz), 7.80 (0.5 H, dd, *J* = 8.5, 1.9 Hz); EIMS *m/z* (rel intensity) 411 (M^+, 5), 410 ($M^+ - 1$, 16), 290 (5), 262 (29), 231 (10), 165 (100), 148 (45), 121 (95); HRMS (EI) calcd for $C_{24}H_{28}NO_5$ ($M^+ - 1$) 410.1967, found 410.1993.

(9a*R*)-8-(3,4-Dimethoxyphenyl)-1,3,4,6,9,9a-hexahydro-7-(4-methoxyphenyl)-2*H*-quinolizin-6-one (30). The ketone **29** (60.3 mg, 0.147 mmol) was dissolved in 5% ethanolic KOH (12 mL), and the solution was stirred under refluxing for 1 h. The solution was concentrated in vacuo, and the

residue was partitioned between water (5 mL) and CH_2Cl_2 (5 mL) and extracted with CH_2Cl_2 (3 × 10 mL). After two further extractions with CH_2Cl_2 (each 5 mL), the combined extracts were washed with brine, dried ($MgSO_4$), and concentrated in vacuo. The resulting crude solid was recrystallized from EtOAc–hexane to give **30** (38.8 mg, 67%) as colorless needles: mp 144–146 °C; $[\alpha]^{27}_D$ −10.7° (*c* 0.53, $CHCl_3$); IR (KBr) 2932, 2839, 1641, 1618, 1514, 1240, 1174, 1146, 1022 cm^{-1}; ^1H NMR δ 1.40–1.60 (3 H, m), 1.76–1.91 (3 H, m), 2.65 (1 H, td, *J* = 13.0, 3.2 Hz), 2.73 (1 H, dd, *J* = 17.2, 10.8 Hz), 2.86 (1 H, dd, *J* = 17.2, 5.6 Hz), 3.48 (3 H, s), 3.58 (1 H, m), 3.74 (3 H, s), 3.83 (3 H, s), 4.55 (1 H, m), 6.41 (1 H, d, *J* = 1.9 Hz), 6.70–6.76 (4 H, m), 6.98–7.01 (2 H, m); ^{13}C NMR δ 23.6, 24.8, 33.4, 43.3, 53.9, 55.2, 55.5, 55.8, 110.4, 112.8, 113.3 (2 carbons), 120.7, 129.4, 130.4, 132.2 (2 carbons), 132.5, 144.3, 147.9, 148.5, 158.4, 166.9; EIMS *m/z* (rel intensity) 393 (M^+, 88), 310 (100), 279 (44), 251 (22), 224 (9), 197 (8), 165 (54), 145 (9), 121 (8), 84 (26). Anal. Calcd for $C_{24}H_{27}NO_4$: C, 73.26; H, 6.92; N, 3.56. Found: C, 73.23; H, 6.64; N, 3.59.

(−)-(*R*)-Julandine [(*R*)-3]. To an ice-cold, stirred suspension of $LiAlH_4$ (21.0 mg, 0.564 mmol) in THF (3 mL) was added a solution of $AlCl_3$ (25.0 mg, 0.188 mmol) in THF (4 mL). After being stirred for 10 min at 0 °C, a solution of **30** (37.0 mg, 0.0940 mmol) in THF (3 mL) was added dropwise and stirring was continued at rt for 2 h. The reaction was quenched with 30% aqueous KOH (7 mL). The organic layer was separated, and the aqueous layer was extracted with Et_2O (2 × 20 mL). The combined organic layers were washed with brine, dried ($MgSO_4$), and concentrated in vacuo. The residue was purified by chromatography on silica gel ($CHCl_3$) to give (*R*)-**3** (20.7 mg, 58%) as a pale yellow oil which crystallized upon standing. A sample was recrystallized from EtOAc–hexane to afford colorless needles: mp 138.5–140 °C (lit.[10] mp 134.5–135.5 °C); $[\alpha]^{26}_D$ −71.6° (*c* 0.33, $CHCl_3$); ^1H NMR δ 1.29–1.43 (2 H, m), 1.58–1.91 (4 H, m), 2.12 (1 H, m), 2.27–2.46 (2 H, m), 2.53 (1 h, br d, *J* = 17.1 Hz), 3.02–3.13 (2 H, m), 3.54 (3 H, s), 3.62 (1 H, d, *J* = 16.9 Hz), 3.73 (3 H, s), 3.80 (3 H, s), 6.47 (1 H, d, *J* = 1.4 Hz), 6.64–6.71 (4 H, m), 6.96–6.99 (2 H, m); ^{13}C NMR δ 24.4, 25.9, 33.4, 39.6, 55.2, 55.5, 55.6, 55.7, 58.0, 60.4, 110.5, 113.1, 113.5 (2 carbons), 120.6, 130.2 (2 carbons), 131.3, 131.5, 133.3, 134.5, 147.3, 148.0, 158.1; CIMS (isobutane) 380 (MH^+), 296, 265; HRMS (EI) calcd for $C_{24}H_{29}NO_3$ (M^+) 379.2147, found 379.2146.

(2*R*)-2-[(2*RS*)-2-(2-Bromo-4,5-dimethoxyphenyl)-2-hydroxyethyl]-*N*-[(4-methoxyphenyl)acetyl]piperidine (32). To an ice-cold, stirred solution of **14** (375 mg, 0.687 mmol) in THF (20 mL) was added the borane–THF complex (1.0 M solution in THF, 13.7 mL, 13.7 mmol), and the mixture was stirred at rt for 15 min and then refluxed for 24 h. After the mixture was cooled in an ice bath, 10% aqueous NaOH (10 mL) was added and briefly stirred. The mixture was concentrated to one-quarter in volume, and the residual mixture was refluxed for 5 h. The product was taken up with Et_2O (3 × 20 mL), and the combined extracts were washed with brine, dried ($MgSO_4$), and concentrated. The residue was dissolved in CH_2Cl_2 (1 mL), and 5% aqueous NaOH (1 mL) was added. To this mixture was added slowly a solution of (4-methoxyphenyl)-acetyl chloride (317 mg, 1.72 mmol) in CH_2Cl_2 (0.5 mL) at 0 °C with stirring. After being stirred at 0 °C for 30 min then at rt for 30 min, the mixture was extracted with CH_2Cl_2 (3 × 10 mL). The combined extracts were washed with brine and concentrated in vacuo to give a residual oil, which was dissolved in a 2:1 mixture (6 mL) of MeOH and water. To this was added K_2CO_3 (300 mg, 2.17 mmol), and the mixture was refluxed for 1 h. After most of the organic solvent was evaporated under reduced pressure, the resulting mixture was extracted with CH_2Cl_2 (10 mL). The extract was successively washed with 5% aqueous NaOH, 5% HCl, and brine and then dried ($MgSO_4$). Evaporation followed by chromatography on silica gel (hexane–AcOEt–MeOH), 30:10:1) provided two fractions. The first fraction gave 2-[(benzyloxy)methyl]-*N*-[(4-methoxyphenyl)acetyl]pyrrolidine (**33**) (140 mg, 60%). The second fraction gave **32** (187 mg, 55%) as a pale yellow oil: IR (neat) 3369, 3003, 2937, 1614, 1511, 1441, 1250, 1210, 1162, 1030, 754 cm^{-1}; ^1H NMR δ 1.13–1.86 (7 H, m), 2.01–2.26 (1 H, m), 2.52 and 2.91 (total 1 H, each m), 3.63 and 3.67 (total 2 H, each br s), 3.75 (3 H, s), 3.82 (3 H, s), 3.85 (3 H, s), 4.29–4.52 (1 H, m), 4.82–4.96 (2 H, m), 6.80–7.20 (6 H, m); EIMS *m/z* (rel intensity) 412 (M^+ − Br, 10), 411 (20), 274 (8), 233 (58), 149 (18), 121 (100); HRMS (EI) calcd for $C_{24}H_{30}NO_5$ (M^+ − Br) 412.2124, found 412.2139.

(2*R*)-2-[(2-Bromo-4,5-dimethoxybenzoyl)methyl]-*N*-[(4-methoxyphenyl)acetyl]piperidine (34). Following the procedure given above for the formation of **29**, **32** (100 mg, 0.203 mmol) was treated with PDC (382 mg, 1.02 mmol) to give **34** as a colorless oil (76.5 mg, 77%): IR (neat) 2937, 1683, 1635, 1595, 1511, 1441, 1373, 1334, 1261, 1214, 1169, 1027, 755 cm^{-1}; ^1H NMR (amide rotamers) δ 1.10–1.70 (6 H, m), 2.50 (0.5 H, td, *J* = 13.4, 2.5 Hz), 2.93–3.34 (2.5 H, m), 3.61–3.80 (5.5 H, m), 3.86, 3.87, 3.88 and 3.89 (total 6 H, each s), 4.55 (0.5 H, br d, *J* = 13.5 Hz), 4.71 (0.5 H, m), 5.22 (0.5 H, m), 6.77–6.84 (2.5 H, m), 7.01 (1 H, m), 7.08–7.22 (2.5 H, m); EIMS *m/z* 410 (rel intensity) 491 (M^+ + 2, 7), 489 (M^+, 8), 342 (5), 340 (12), 245 (49), 243 (52), 149 (50), 121 (100); HRMS (EI) calcd for $C_{24}H_{28}NO_5{}^{79}Br$ (M^+) 489.1151, found 489.1128.

(9a*R*)-8-(2-Bromo-4,5-dimethoxyphenyl)-1,3,4,6,9,9a-hexahydro-7-(4-methoxyphenyl)-2*H*-quinolizin-6-one (35). The ketone **34** (76.5 mg, 0.156 mmol) was dissolved in 5% ethanolic KOH (12 mL), and the solution was refluxed for 1 h. The residue obtained by concentration was partitioned between water (5 mL) and CH_2Cl_2 (5 mL) and extracted with CH_2Cl_2 (3 × 5 mL). After two further extractions with CH_2Cl_2 (each 5 mL), the combined extracts were washed wtih brine, dried ($MgSO_4$), and concentrated. The residue was purified by chromatography on silica gel (hexane–EtOAc, 2:1) to afford **35** (44 mg, 60%) as a colorless oil: IR (neat) 3001, 2936, 2839, 1651, 1624, 1511, 1504, 1249, 1209, 1175, 1035, 832, 754 cm^{-1}; ^1H NMR δ 1.40–1.97 (6 H, m), 2.41–2.97 (3 H, m), 3.57 (3 H, s), 3.64–3.75 (1 H, m), 3.71 (3 H, s), 3.81 (3 H, s), 4.58 (1 H, m), 6.27 (1 H, br s), 6.66 (2 H, d, *J* = 8.8 Hz), 6.94 (1 H, br s), 7.03 (2 H, d, *J* = 8.8 Hz); EIMS *m/z* (rel intensity) 473 (M^+ + 2, 21), 471 (M^+, 23), 392 (42), 309 (100), 281 (11), 196 (20), 118 (28); HRMS (EI) calcd for $C_{24}H_{26}NO_4{}^{79}Br$ (M^+) 471.1046, found 471.1028.

11,12,13,14,14a,15-Hexahydro-2,3,6-trimethoxy-9*H*-phenanthro[9,10-*b*]quinolizin-9-one (36). Method A. A solution of **35** (13.5 mg, 0.0286 mmol) and Et_3N (10 mg, 0.099 mmol) in dioxane (90 mL) was irradiated with a 100 W high-pressure Hg lamp at ambient temoperature. After irradiation for 8 min, the solution was concentrated in vacuo to afford the residue, which was dissolved in CH_2Cl_2 (20 mL), washed with 5% aqueous $NaHCO_3$ and brine, and dried ($MgSO_4$). Evaporation of the solvent and purification of the residue by chromatography on silica gel (hexane–EtOAc, 1:1) afforded **36** (6 mg, 54%) as a colorless solid. Recrystallization from EtOAc–hexane afforded colorless needles: mp 194–195.5 °C; ^1H NMR δ 1.43–1.70 (4 H, m), 1.91 (2 H, m), 2.02 (1 H, m), 2.89 (1 H, td, *J* = 12.9, 3.1 Hz), 2.98 (1 H, dd, *J* = 16.3, 11.0 Hz), 3.39 (1 H, dd, *J* = 16.3, 4.7 Hz), 3.57 (1 H, m), 4.01 (3 H, s), 4.06 (3 H, s), 4.12 (3 H, s), 4.73 (1 H, br d, *J* = 13.5 Hz), 7.25 (1 H, dd, *J* = 9.5, 2.6 Hz), 7.31 (1 H, s), 7.85 (1 H, d, *J* = 2.6 Hz), 7.89 (1 H, s), 9.60 (1 H, d, *J* = 9.5 Hz); ^{13}C NMR δ 23.0, 24.8, 33.0 (2 carbons), 42.7, 52.8, 55.5, 56.07, 56.09, 104.0, 104.5, 104.9, 115.2, 121.3, 124.0, 124.2, 126.8, 130.2, 131.2, 132.7, 149.7, 150.5, 157.7, 167.2; EIMS *m/z* (rel intensity) 391 (M^+, 100), 308 (96), 280 (78), 237 (12), 195 (17); HRMS (EI) calcd for $C_{24}H_{25}NO_4$ (M^+) 391.1784, found 391.1780.

Method B. To a solution of **35** (10.4 mg, 0.0220 mmol) in benzene (5 mL) a catalytic amount of AIBN (1 mg, 0.006 mmol) and Bu_3SnH (128 mg, 0.0440 mmol) were added, and the mixture was heated under refluxing for 3 h. The reaction mixture was concentrated in vacuo, and the residue was dissolved in Et_2O (1 mL). To this was added 1,8-diazabicyclo-[5.4.0]undec-7-ene (13 mg, 0.085 mmol), and the resulting mixture was passed through a short column of silica gel eluting with Et_2O and concentrated. The residue was purified by chromatography on silica gel (hexane–EtOAc, 1:1) to give **36** (7.5 mg, 87%) as a colorless solid.

(−)-Cryptopleurine (1). To a stirred cold suspension of $LiAlH_4$ (5.1 mg, 0.135 mmol) in THF (1 mL) was added dropwise a solution of **36** (17.6 mg, 0.0450 mmol) in THF (1 mL), stirring was continued at rt for 1 h, and the mixture was

heated at reflux for 1 h. After being cooled to 0 °C, the mixture was quenched by the addition of $Na_2SO_4 \cdot 10H_2O$ (50 mg), the insoluble material was removed by filtration through a Celite pad, and the filtrate was concentrated in vacuo. The residue was purified by chromatography on silica gel ($CHCl_3$) to give **1** (9.4 mg, 55%) as a colorless solid, which was recrystallized from benzene to provide colorless needles: mp 196–197 °C (lit.[1a] mp 195–197 °C); $[\alpha]^{25}_D$ −96.7° (*c* 0.40, $CHCl_3$) [lit.[1a] $[\alpha]^{18}_D$ −106° (*c* 1.52, $CHCl_3$)]; ^{1}H NMR δ 1.40–1.61 (2 H, m), 1.76–1.93 (2 H, m), 2.05 (1 H, m), 2.32 (1 H, m), 2.41 (1 H, m), 2.92 (1 H, dd, *J* = 16.4, 10.5 Hz), 3.11 (1 H, dd, *J* = 16.4, 2.8 Hz), 3.28 (1 H, d, *J* = 11.4 Hz), 3.65 (1 H, 1/2 AB q, *J* = 15.5 Hz), 4.01 (3 H, s), 4.06 (3 H, s), 4.10 (3 H, s), 4.45 (1H, 1/2 AB q, *J* = 15.5 Hz), 7.20 (1 H, dd, *J* = 9.0, 2.6 Hz), 7.27 (1 H, s), 7.80 (1 H, d, *J* = 9.0 Hz), 7.90 (1 H, d, *J* = 2.6 Hz), 7.92 (1 H, s); ^{13}C NMR δ 24.4, 26.0, 33.9, 34.8, 55.6, 56.0, 56.1, 56.2, 56.3, 57.7, 104.1, 104.2, 104.9, 114.9, 123.6, 123.8, 124.1, 124.6, 125.7, 126.6, 130.2, 148.5, 149.6, 157.6; EIMS *m/z* (rel intensity) 377 (M^+, 30), 294 (100), 251 (4), 188 (5), 165 (3); HRMS (EI) calcd for $C_{24}H_{27}NO_3$ (M^+) 377.1991, found 377.1987.

Supporting Information Available: Copies of ^{1}H NMR spectra for compounds **1**, **3**, **6**, **8**, **9**, **13**–**15**, **20**, **21**, **23**, **24**, **26**–**29**, **32**, and **34**–**36** (20 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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