Chiral Total Synthesis of Indole Alkaloids of the *Aspidosperma* and *Hunteria* Types

Manabu Node, Hideko Nagasawa, and Kaoru Fuji*

Institute for Chemical Research, Kyoto University, Uji, Kyoto 611, Japan

Received June 9, 1989

Expeditious enantioselective syntheses of (+)-quebrachamine (**6**), (−)-aspidospermidine (**7**), (+)-demethoxyaspidospermine (**8**), and (−)-eburnamonine (**9**) were accomplished starting from (*S*)-lactone **1**. The syntheses also complete formal, total syntheses of 12 other indole alkaloids of the *Aspidosperma* and *Hunteria* types. The key step in the synthesis of (+)-quebrachamine (**6**) was the Pictet–Spengler condensation of chiral C_9 unit **10**, derived from **1**, with tryptamine. Another C_9 unit (**15**) was also prepared from **1** and utilized for the syntheses of three other alkaloids, **7**, **8**, and **9**.

Indole alkaloids play a central role in the biologically active alkaloids. A plethora of papers on the synthesis of *Aspidosperma* and *Hunteria* alkaloids reflect the continuing interests in these alkaloids.[1] The indole-2,3-quinodimethane strategy reported by Magnus et al.[2] is among the most elegant one from the chemical point of view. The Pictet–Spengler or the Bischler–Napieralsky condensation of tryptamine with the C_9 or C_{10} unit is one of the best methods of choice for the synthesis of these types of indole alkaloids because of the general applicability. However, this approach has seldom been applied for the synthesis of optically active alkaloids due to the lack of an efficient method for the synthesis of the chiral C_9 or C_{10} unit. We have developed a one-pot chiral synthesis of α,α-disubstituted δ-lactone **1** with a high enantiomeric excess (ee) in excellent yield through an addition–elimination process.[3] The lactone **1** has a C_9 unit in which each carbon is optimally arranged for the synthesis of the target alkaloids and possesses a different functional group feasible for the necessary transformations. Here, we report the full account[4] of efficient chiral synthesis of three *Aspidosperma* alkaloids, (+)-quebrachamine (**6**),[5] (−)-aspidospermidine (**7**),[6,7] and (+)-demethoxyaspidospermine (**8**),[7,8] and a *Hunteria* alkaloid, (−)-eburnamonine (**9**),[9] starting from (*S*)-(−)-**1**. These alkaloids contain a C_9 unit as a monoterpene part.

Scheme I shows our synthetic plan based on the Pictet–Spengler condensation. All four target alkaloids have a common structural feature involving a quaternary carbon bearing an ethyl group, C_1, C_2, and C_3 units. In the Pictet–Spengler approach, the aldehyde **2** is required for the construction of the key intermediate **4** in the synthesis of (+)-quebrachamine (**6**). While the key intermediate **5** for the syntheses of (−)-aspidospermidine (**7**) and (−)-eburnamonine (**9**) can be prepared from another aldehyde, **3**, in which, except for the ethyl group, each carbon unit on the chiral quaternary center has a different oxidation stage from **2**.

(1) (a) *Aspidosperma* alkaloids: Cordell, G. A. In *The Alkaloids*; Manske, R. H. F., Rodrigo, R. G. A., Ed.; Academic Press: New York, 1979; Vol. XVII, p 199. (b) *Hunteria* alkaloids: Döpke, W. In *The Alkaloid*; Manske, R. H. F., Rodrigo, R. G. A., Ed.; Academic Press: New York, 1981; Vol. XX, p 297. Atta-ur-Rahman, Sultana, M. *Heterocycles* **1984**, *22*, 841.

(2) (a) Magnus, P.; Gallagher, T.; Brown, P.; Pappalardo, P. *Acc. Chem. Res.* **1984**, *17*, 35. (b) Magnus, P.; Pappalardo, P.; Southwell, I. *Tetrahedron* **1986**, *42*, 3215. (c) Magnus, P.; Pappalardo, P. *J. Am. Chem. Soc.* **1986**, *108*, 212. (d) Cardwell, K.; Hewitt, B.; Ladlow, M.; Magnus, P. *J. Am. Chem. Soc.* **1988**, *110*, 2242 and references cited therein.

(3) Fuji, K.; Node, M.; Nagasawa, H.; Naniwa, Y.; Terada, S. *J. Am. Chem. Soc.* **1986**, *108*, 3855.

(4) A part of this work has been published in a preliminary form: Node, M.; Nagasawa, H.; Fuji, K. *J. Am. Chem. Soc.* **1987**, *109*, 7901.

(5) For the racemate, see: (a) Stork, G.; Dolfini, J. E. *J. Am. Chem. Soc.* **1963**, *85*, 2872. (b) Kuehne, M. E.; Bayha, C. *Tetrahedron Lett.* **1966**, 1311. (c) Kutney, J. P.; Abdurahman, N.; Le Quesne, P.; Piers, E.; Vlattas, I. *J. Am. Chem. Soc.* **1966**, *88*, 3656. Kutney, J. P.; Abdurahman, N.; Gletsos, C.; Le Quesne, P.; Piers, E.; Vlattas, I. *Ibid.* **1970**, *92*, 1727. (d) Ziegler, F. E.; Kloek, J. A.; Zoretic, P. A. *Ibid.* **1969**, *91*, 2342. (e) Takano, S.; Hatakeyama, S.; Ogasawara, K. *Ibid.* **1976**, *98*, 3022. (f) Takano, S.; Hirama, M.; Araki, T.; Ogasawara, K. *Ibid.* **1976**, *98*, 7084. (g) Takano, S.; Hatakeyama, S.; Ogasawara, K. *Ibid.* **1979**, *101*, 6414. (h) Giri, V. S.; Ali, E.; Pakrashi, S. C *J. Heterocycl. Chem.* **1980**, *17*, 1133. (i) Takano, S.; Murakata, C.; Ogasawara, K. *Heterocycles* **1981**, *16*, 247. (j) Wenkert, E.; Halls, T. D. J.; Kwart, L. D.; Magnusson, G.; Showalter, H. D. H. *Tetrahedron* **1981**, *37*, 4017. (k) Ban, Y.; Yoshida, K.; Goto, J.; Oishi, T. *J. Am. Chem. Soc.* **1981**, *103*, 6990. Ban, Y.; Yoshida, K. Goto, J.; Oishi, T.; Takeda, E. *Tetrahedron* **1983**, *39*, 3657. (l) Mandel, S. B.; Giri, V. S.; Sabeena, M. S.; Pakrashi, S. C. *J. Org. Chem.* **1988**, *53*, 4236. For the optically active form, see: (m) Takano, S.; Chiba, K.; Yonaga, M.; Ogasawara, K. *J. Chem. Soc., Chem. Commun.* **1980**, 616. (n) Takano, S.; Yonaga, M.; Ogasawara, K. *Ibid.* **1981**, 1153. (o) Asaoka, M.; Takei, H. *Heterocycles* **1989**, *29*, 243.

(6) For the racemate, see: (a) Harley-Mason, J.; Kaplan, M. *Chem. Commun.* **1967**, 915. (b) Laronze, J.-Y.; LaronzeFontaine, J.; Lévy, J.; Le Man, J. *Tetrahedron Lett.* **1974**, 491. (c) Gallagher, T.; Magnus, P.; Huffman, J. C. *J. Am. Chem. Soc.* **1982**, *104*, 1140. Gallagher, T.; Magnus, P.; Huffman, J. C. *Ibid.* **1983**, *105*, 4750. (d) *N*-Acetylaspidospermidine: Seki, K.; Ohnuma, T.; Oishi, T.; Ban, Y. *Tetrahedron Lett.* **1975**, 723. (e) Wenkert, E.; Hudlick, T. *J. Org. Chem.* **1988**, *53*, 1953. Reference 5c,k,l. No chiral synthesis has been reported.

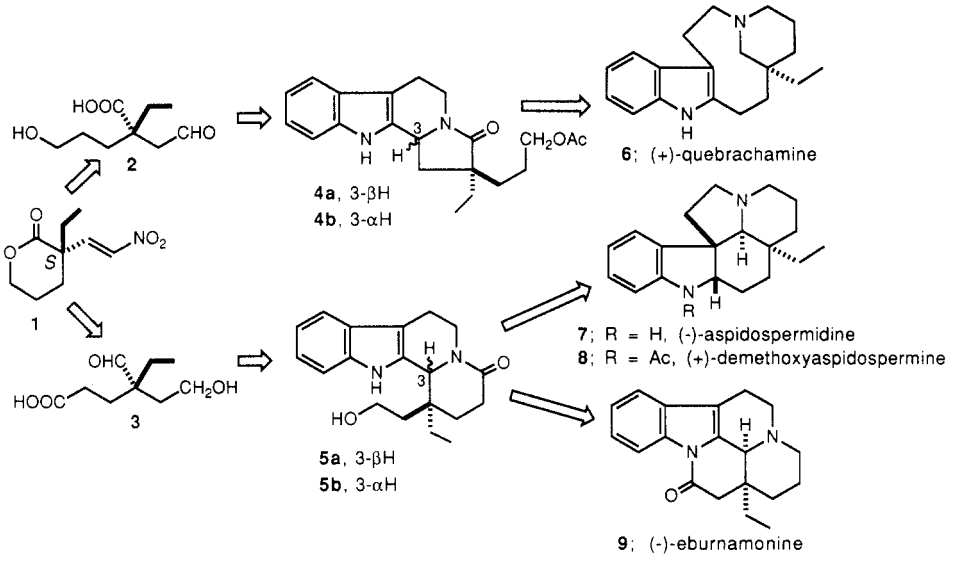
(7) The natural product is an enantiomer of this compound.

(8) Ferreira, J. M.; Gilbert, B.; Owellen, R. J.; Djerassi, C. *Experientia* **1963**, *19*, 585.

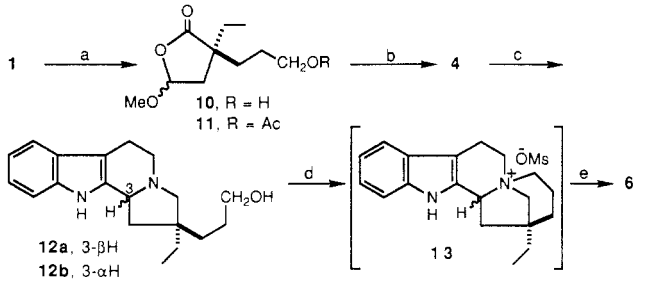
(9) For the racemate, see: (a) Bartlett, M. F.; Taylor, W. I. *J. Am. Chem. Soc.* **1960**, *82*, 5941. (b) Wenkert, E.; Wickberg, B. *Ibid.* **1965**, *87*, 1580. (c) Herrmann, J. L.; Kieczykowski, G. R.; Normandin, S. E.; Schlessinger, R. H. *Tetrahedron Lett.* **1976**, 801. (d) Buzas, A.; Harrison, C.; Lavielle, G. *C. R. Acad. Sci., Ser. C* **1976**, *283*, 763. (e) Klatte, F.; Rosentreter, U.; Winterfeldt, E. *Angew. Chem.* **1977**, *89*, 916; *Angew. Chem., Int. Ed. Engl.* **1977**, 878. (f) Wenkert, E.; Hudlicky, T.; Showalter, H. D. H. *J. Am. Chem. Soc.* **1978**, *100*, 4893. (g) Costerousse, G.; Buendia, J.; Toromanoff, E.; Martel, J. *Bull. Soc. Chem. Fr., Part 2* **1978**, 355. (h) Bölsing, E.; Klatte, F.; Rosentreter, U.; Winterfeldt, E. *Chem. Ber.* **1979**, *112*, 1902. (i) Herrmann, J. L.; Cregge, R. J.; Richman, J. E.; Kieczykowski, G. R.; Normandin, S. N.; Quesada, M. L.; Semmelhack, C. L.; Poss, A. J.; Shlessinger, R. H. *J. Am. Chem. Soc.* **1979**, *101*, 1540. (j) Buzas, A.; Jacquet, J. P.; Lavielle, G. *J. Org. Chem.* **1980**, *45*, 32. (k) Irie, K.; Okita, M.; Wakamatsu, T.; Ban, Y. *Nouv. J. Chem.* **1980**, *4*, 275. Irie, K.; Ban, Y. *Heterocycles* **1981**, *15*, 201. (l) Imanishi. T.; Miyashita, K.; Nakai, A.; Inoue, M.; Hanaoka, M. *Chem. Pharm. Bull.* **1982**, *30*, 1521. (m) Massiot, G.; Oliveira, F. S.; Lévy, J. *Tetrahedron Lett.* **1982**, *23*, 177. (n) Atta-ur-Rahman; Sultana, M. *Z. Naturforsch. B* **1982**, *37*, 793. (o) Imanishi, T.; Miyashita, K.; Nakai, A.; Inoue, M.; Hanaoka, M. *Chem. Pharm. Bull.* **1983**, *31*, 1191. (p) Atta-ur-Rahman; Sultana, M. *J. Chem. Soc. Pak.* **1984**, *6*, 49. (q) Kalaus, G.; Malkieh, N.; Katona, I.; Kajtar-Peredy, M.; Koritsanszky, T.; Kalman, A.; Szabo, L.; Szantay, C. *J. Org. Chem.* **1985**, *50*, 3760. (r) Shono, T.; Matsumura, H.; Ogaki, M.; Onomura, O. *Chem. Lett.* **1987**, 1447. References 2b, 5j, and 6e. For the optically active form, see: (s) Novak, L.; Rohaly, J.; Szantay, C. *Heterocycles* **1977**, *6*, 1149. (t) Cartier, D.; Lévy, J.; Le Man, J. *Bull. Soc. Chim. Fr.* **1976**, 1961. (u) Szabo, L.; Sapi, J.; Kalaus, G.; Argay, G.; Kalman, A.; Baitz-Gacs, E.; Tamas, J.; Szantay, C. *Tetrahedron* **1983**, *39*, 3737. (v) Takano, S.; Yonaga, M.; Ogasawara, K. *Heterocycles* **1982**, *19*, 1391. Takano, S.; Yonaga, M.; Morimoto, M.; Ogasawara, K. *J. Chem. Soc., Perkin Trans. I* **1985**, 305. (w) Magnus, P.; Brown, P. *J. Chem. Soc., Chem. Commun.* **1985**, 184. (x) Hakam, K.; Thielmann, M.; Thielmann, T.; Winterfeldt, E. *Tetrahedron* **1987**, *43*, 2035.

0022-3263/90/1955-0517$02.50/0

Scheme I

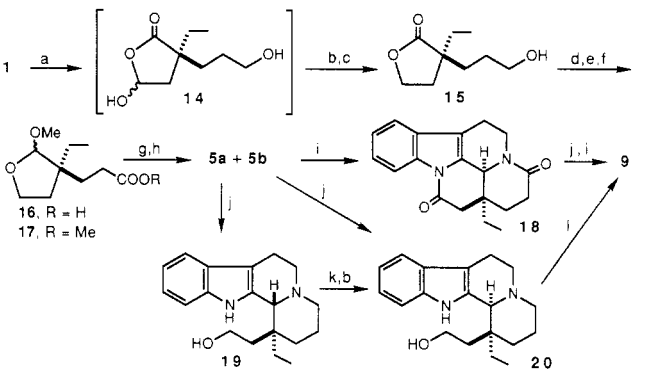


Scheme II[a]



[a] (a) $TiCl_3$/MeOH/pH 5; (b) tryptamine/AcOH; (c) $LiAlH_4$; (d) MsCl/Et_3N; (e) Na/liquid NH_3.

Scheme III[a]



[a] (a) $TiCl_3$/DME/pH 5; (b) $NaBH_4$; (c) HCl/MeOH/reflux; (d) Jones reagent (e) DIBAH; (f) *p*-TsOH/MeOH; (g) tryptamine/AcOH; (h) NaOH/MeOH; (i) CrO_3/pyridine; (j) $LiAlH_4$; (k) $Hg(OAc)_2$; (l) BF_3·OEt_2/PCC.

Chiral Synthesis of (+)-Quebrachamine (1). For preparation of aldehyde **2** or its equivalent, the necessary transformation is to convert the α,β-unsaturated nitro group into the $-CH_2CHO$ moiety. The McMurry modification[10] of the Nef reaction gave the best results. Thus, treatment of **1** of 85% ee with $TiCl_3$ in aqueous methanol at pH 5 provided the methyl acetal **10**, which is a chemical equivalent of the desired aldehyde **2** (Scheme II). It is worthy of note that the one-step conversion of an α,β-unsaturated nitro compound into an aldehyde has not been reported although a similar transformation giving a ketone is found in the literature.[10] The acetal **10** was characterized as acetate **11**. For the preparative purpose, crude acetal **10** was immediately subjected to the Pictet–Spengler condensation with tryptamine in acetic acid to yield **4** as an approximately 1:1 epimeric mixture at C-3 in 84% overall yield from **1**. Reduction of **4** with $LiAlH_4$ in tetrahydrofuran (THF) afforded **12a**[5m] and **12b**[5n] in 33% and 50% yield, respectively. A crude mixture of **12a** and **12b** was used for the synthesis of (+)-quebrachamine (**6**), since the chiral center at C-3 was destroyed at the later stage. According to Kutney's procedure,[5c] mesylation of a mixture of **12a** and **12b** gave **13**, which was directly reduced with Na–EtOH in liquid ammonia to furnish crude (+)-quebrachamine (**6**). A single recrystallization from MeOH yielded optically pure (+)-quebrachamine in 53% overall yield from the lactam **4**.

Synthesis of (−)-Eburnamonine (9). The reductive denitration of **1** in dimethoxyethane (DME) afforded the hemiacetal **14**. Reduction of **14** with $NaBH_4$, followed by refluxing in methanolic HCl, gave the γ-lactone alcohol **15** in 75% overall yield from **1** (Scheme III). No isomeric δ-lactone alcohol **21** was formed under these conditions. Transformation of **15** to the acetal **16**, which is an equivalent to the desired non-tryptamine unit **3**, was carried out in 75% yield through three steps involving Jones oxidation, reduction with diisobutylaluminum hydride (DIBAH), and acid treatment in methanol. A 6% yield of the lactone ester **17** was obtained along with **16**. The condensation of **16** with tryptamine in acetic acid proceeded smoothly to afford an approximately 1:1 mixture of **5a** and **5b** in 84% yield after basic hydrolysis. Enantiomeric enrichment of **5a** and **5b** by recrystallization was performed at this stage. The α-configuration of H-3 in **5b** was confirmed by the conversion to the known dilactam[9a] **18** on the Sarett oxidation. (−)-Eburnamonine (**9**) was obtained from **18** in 74% yield on reduction with $LiAlH_4$ followed by Sarett oxidation.[11] Another isomer **5a** formed from the Pictet–Spengler condensation could serve as an intermediate for the synthesis of (−)-eburnamonine (**9**) because **5a** and **5b** were shown to establish an equilibrium at an approximate ratio of 1:1 with boron trifluoride etherate at 35–40 °C after 10 h.

(10) McMurry, J. E.; Melton, J. *J. Org. Chem.* **1973**, *38*, 4367.

(11) (±)-Dilactam **18** was converted into (±)-eburnamonine previously: see ref 9a.

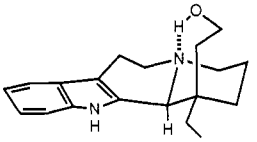
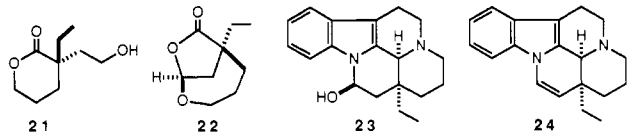


Figure 1. Conformation of **20**.

In an alternative synthesis of (−)-eburnamonine (**9**), a mixture of **5a** and **5b** was reduced with $LiAlH_4$ to give **19** and **20** in 48% and 47% yields, respectively. Attempted Sarett oxidation of pure **20** failed to provide (−)-eburnamonine (**9**) due to the strong intramolecular hydrogen bonding as shown in Figure 1. Sharp Wenkert–Bohlmann bands at 2750 and 2800 cm^{-1} support the *trans*-quinolizidine type C/D ring juncture in **19** and **20**.[12] Absorption for a free hydroxyl group at 3625 cm^{-1} in **19** was missing in **20**, but a broad absorption at 3100 cm^{-1} indicates the existence of the hydrogen-bonded hydroxyl group in **20**. Releasing the intramolecular hydrogen bonding by the addition of boron trifluoride etherate was followed by oxidation with pyridinium chlorochromate (PCC), giving (−)-eburnamonine (**9**) in 55% yield. Oxidation of **19** with $Hg(OAc)_2$ followed by reduction with $NaBH_4$ furnished an approximately 1:1 mixture of **19** and the desired C-3 epimer **20** in 80% yield. Thus, **19** can be utilized for the synthesis of (−)-eburnamonine (**9**).

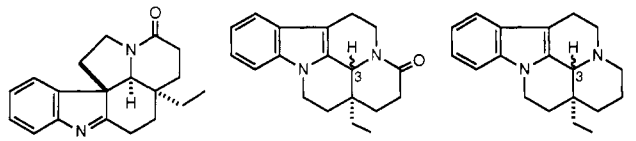
Recently, Takano and his co-workers[9v] reported the total syntheses of (−)-eburnamonine (**9**), (+)-eburnamine (**23**), and (−)-eburnamenine (**24**) through the optically active



21 **22** **23** **24**

bicyclic acetal **22** as the key intermediate, prepared from L-glutaric acid in more than 10 steps in a 13% overall yield. We prepared **22** from **1** in 74% yield in two steps involving the Nef reaction with $TiCl_3$ in DME followed by the treatment with *p*-toluenesulfonic acid (TsOH). This transformation constitutes an extremely short, formal synthesis of these alkaloids.

Syntheses of (−)-Aspidospermidine (7) and (+)-Demethoxyaspidospermine (8). The equilibrium between **5a** and **5b** with boron trifluoride etherate depends upon the reaction temperature. Thus, the 1:1 mixture of **5a** and **5b** was treated with boron trifluoride etherate at 100–110 °C for 1 h to afford **25** (47%) along with the eburnamonine-type lactams **26a** (17%) and **26b** (35%).[13]



25 **26a**, 3-βH **26b**, 3-αH **27a**, 3-βH **27b**, 3-αH

The structures of **26a** and **26b** were determined by the conversion into known compounds **27a**[12] and **27b**,[12] respectively. The combined yield (82%) of the product with a 3*S* configuration (**25** and **26b**) indicates that the fast isomerization from **5a** to **5b** takes place under these reaction conditions. On the other hand, the product distribution was quite different with triflic acid. Treatment of the same mixture of **5a** and **5b** with triflic acid at 100–110 °C for 45 min gave **25**, **26a**, and **26b** in 46%, 44%, and 10% yields, respectively. The products with a 3*S* configuration slightly exceeded 50%, indicating the slow equilibrium between **5a** and **5b** in triflic acid. In an attempt to increase the yield of the desired **25**, the single isomer **5b** was treated with triflic acid at 100–110 °C for 45 min. However, the isomerization was not completely suppressed. A 12% yield of **26a** was produced along with a 60% yield of the desired product **25** and undesired cyclization product **26b** in 20% yield. Exposure of **25** to $LiAlH_4$ in tetrahydrofuran (THF) gave (−)-aspidospermidine (**7**), acetylation of which gave (+)-demethoxyaspidospermine (**8**)[8] in 81% yield from **25**.

Conclusions

We have established a method for very short syntheses of (+)-quebrachamine (**6**), (−)-eburnamonine (**9**), (−)-aspidospermidine (**7**), and (+)-demethoxyaspidospermine (**8**) from **1**. The synthetic scheme described here introduces a general approach to a variety of optically active indole alkaloids. For instance, since vincadine,[14] *epi*-vincadine,[14] vincaminoreine,[15] vincaminorine,[14] vincadifformine,[14] minovine,[14] vincamine,[16] and apovincamine[17] were synthesized from quaternary salt **13**, synthesis of optically active **13** constitutes formal total synthesis of these alkaloids in optically active form. Total syntheses of optically active isoeburnamonine and 1,2-dehydroaspidospermidine have been completed though in formal sense, because these alkaloids have been prepared from dilactam **18**[9a] and quebrachamine (**6**),[18] respectively. Thus, lactone **1** bearing a quaternary center has been shown to be a versatile chiral building block for the synthesis of optically active indole alkaloids.

Experimental Section

General Method. Melting points were determined on a Yanagimoto micro melting point apparatus and are uncorrected. ^1H NMR and ^{13}C NMR spectra were recorded on a JOEL JMN-GX 400 or a JMN-FX 100 spectrometer. Optical rotations were measured with a Jasco DIP-181 polarimeter. IR spectra were measured with a Jasco IR-180 spectrophotometer. MS spectra were measured with a JEOL JMS-DX 300 mass spectrometer.

Cyclic Lactams 4a and 4b. A solution of **1**[19] (775 mg, 3.9 mmol) in MeOH (9 mL) was added to a mixture of NH_4OAc (10.7 g, 140 mmol), 20% aqueous $TiCl_3$ (18.6 mL, 23.3 mmol), MeOH (45 mL), and water (36 mL) under N_2 and stirred for 3 h at room temperature. The reaction mixture was then poured into ether and separated into phases. The aqueous phase was acidified with 10% HCl and extracted with AcOEt several times. The organic extracts were combined, washed with brine, dried ($MgSO_4$), and evaporated to give **10** as a colorless oil quantitatively, to which was added 7 mL of AcOH and tryptamine (625 mg, 3.9 mmol), and the mixture was refluxed overnight. After AcOH was removed under vacuum, 20% NaOH–ice water was added to the residue, and the solution was extracted with CH_2Cl_2. The organic layer was washed with brine, dried ($MgSO_4$), and evaporated to give a brown oil. Flash column chromatography (silica gel, AcOEt:hexane = 2:1) gave an approximately 1:1 mixture (1.16 g) of **4a** and **4b** in 84% overall yield from **1**.

(12) Coffen, D. L.; Katonak, D. A.; Wong, F. *J. Am. Chem. Soc.* **1974**, *96*, 3966.

(13) In ref 6a, it was reported that the racemate **5** afforded **25** on treatment with boron trifluoride etherate (neither the relative configuration of **5** nor the yield was reported).

(14) Kutney, J. P.; Chan, K. K.; Failli, A.; Fromson, J. M.; Gletsos, C.; Leutwiler, A.; Nelson, V. R.; de Souzu, J. P. *Helv. Chim. Acta* **1975**, *58*, 1648.

(15) Mokry, J.; Kompis, I. *Lloydia* **1964**, *27*, 428.

(16) Danieli, B.; Lesma, G.; Palmisano, G. *J. Chem. Soc., Chem. Commun.* **1981**, 908.

(17) Lewin, G.; Poisson, J. *Tetrahedron Lett.* **1984**, *25*, 3813.

(18) Bycroft, B. W.; Schumann, D.; Patel, M. B.; Schmid, H. *Helv. Chim. Acta* **1964**, *47*, 1147.

(19) Fuji, K.; Node, M.; Nagasawa, H.; Naniwa, Y.; Taga, T.; Machida, K.; Snatzke, G. *J. Am. Chem. Soc.* **1989**, *111*, 7921.

These epimers were separated by flash column chromatography over silica gel. Elution with AcOEt–hexane (2:1) afforded **4a** as a less polar fraction [^{1}H NMR ($CDCl_3$) δ 0.73 (t, 3 H, J = 7.6 Hz), 1.32–2.08 (m, 6 H), 2.05 (s, 3 H), 2.35 (dd, 1 H, J = 7.9, 12.8 Hz), 2.64–3.20 (m, 3 H), 3.88 (t, 1 H, J = 6.4 Hz), 4.08 (br t, 2 H, J = 5.9 Hz), 4.52 (m, 1 H), 4.88 (br t, 1 H, J = 7.9 Hz), 7.00–7.60 (m, 4 H), 8.11 (br s, 1 H); IR ($CHCl_3$) ν 3470, 1735, 1675 cm^{-1}; high resolution MS, calcd for $C_{21}H_{26}N_2O_3$ 354.1943, found 354.1914] and **4b** as a polar fraction [^{1}H NMR ($CDCl_3$) δ 0.99 (t, 3 H, J = 7.6 Hz), 1.35–2.08 (m, 6 H), 1.94 (s, 3 H), 2.40 (dd, 1 H, J = 7.9, 12.8 Hz), 2.68–3.20 (m, 3 H), 3.76–4.20 (m, 1 H), 3.95 (br t, 2 H, J = 5.4 Hz), 4.53 (m, 1 H), 4.87 (br t, 1 H, J = 7.9 Hz), 7.02–7.56 (m, 4 H), 8.04 (br s, 1 H); IR ($CHCl_3$) ν 3470, 1735, 1675 cm^{-1}; high resolution MS, calcd for $C_{21}H_{26}N_2O_3$ 354.1943, found 354.1962].

3-(3-Acetoxypropyl)-3-ethyl-5-methoxytetrahydrofuran-2-one (11). Crude **10** (14 mg) was acetylated with Ac_2O and pyridine to give crude **11** (14.5 mg), which was purified by PTLC (AcOEt:hexane = 5:1): ^{1}H NMR ($CDCl_3$) δ 0.90, 0.94 (2 t, 3 H, J = 7.4 Hz), 1.40–1.84 (m, 6 H), 1.84–2.46 (m, 2 H), 2.04 (s, 3 H), 3.51 (s, 3 H), 4.05 (m, 2 H), 5.33 (dd, 1 H, J = 3.5, 6.4 Hz); IR ($CHCl_3$) ν 1770, 1735, 1245, 1180 cm^{-1}; MS m/e 243 ($M^+ - 1$). Anal. Calcd for $C_{12}H_{20}O_5$: C, 59.00; H, 8.25. Found: C, 59.33; H, 8.14.

Alcohols 12a and 12b. To a refluxing suspension of $LiAlH_4$ (93 mg, 2.46 mmol) in THF (7 mL) was added dropwise a solution of **4** (145 mg, 0.4 mmol) in THF (3 mL) under N_2. After being refluxed for 5 h, the reaction mixture was cooled and stirred with 10% KOH (0.1 mL) for 30 min. The resulting mixture was filtered through a bed of Celite and the solid on the funnel was washed with CH_2Cl_2 several times. The organic layers were combined, dried with $MgSO_4$, and evaporated to give a light yellow powder, which can be used for the next step without purification.

Separation by column chromatography on neutral alumina (Woelm, activity II, benzene/CH_2Cl_2) afforded **12a** (40 mg, 33%) [mp 194.5–195.5 °C (from AcOEt) (lit.[5m] mp 193–194 °C); $[\alpha]^{22}_D$ +63.3° (c = 0.07, MeOH) (lit.[5m] $[\alpha]_D$ +61.14°); ^{1}H NMR ($CDCl_3$) δ 0.72 (t, 3 H, J = 7.0 Hz), 2.42–3.28 (m, 5 H), 3.66 (m, 2 H), 4.29 (br t, 1 H, J = 6.0 Hz), 6.96–7.53 (m, 4 H), 7.82 (br s, 1 H); IR (KBr) ν 3400, 3260, 1060, 740 cm^{-1}; MS m/e 298 (M^+)] and **12b** (62 mg, 50%) [mp 155–156 °C (from AcOEt–MeOH) (lit.[5n] mp 157–158 °C); $[\alpha]^{22}_D$ −70.4° (c = 0.25, MeOH) (lit.[5n] $[\alpha]_D$ −62.4°); ^{1}H NMR ($CDCl_3$) δ 0.85 (t, 3 H, J = 7.0 Hz), 1.08–1.92 (m, 9 H), 2.09 (dd, 1 H, J = 8.0, 13.0 Hz), 2.48–3.40 (m, 5 H), 3.45 (t, 2 H, J = 6.0 Hz), 4.14 (br t, 1 H, J = 6.0 Hz), 6.99–7.60 (m, 4 H), 7.70 (br s, 1 H); IR (KBr) ν 3400, 3260, 1060, 740 cm^{-1}; MS m/e 298 (M^+).

(+)-Quebrachamine (6). Crude alcohol **12** (1.0 g) obtained from the reduction of **4** (1.1 g, 3.1 mmol) was dissolved in a mixture of dry triethylamine (10 mL) and $CHCl_3$ (20 mL). Methanesulfonyl chloride (1.6 mL, 21 mmol) was added dropwise with vigorous stirring at −10 °C. The same workup as Kutney's procedure[5c] gave yellow amorphous mesylate **13** (1.3 g). The mesylate **13** (65 mg) was dissolved in anhydrous EtOH (1.5 mL) and subjected to reductive cleavage with sodium in liquid ammonia according to the method of Kutney[5c] to produce a colorless powder. Recrystallization from MeOH yielded (+)-quebrachamine (**6**: 24 mg, 53% from **4**) as colorless plates: mp 144–146 °C (lit.[20] mp 147–149 °C); $[\alpha]^{22}_D$ +117° (c = 0.18, $CHCl_3$) (lit.[20] $[\alpha]_D$ +111°); ^{1}H NMR ($CDCl_3$) δ 0.84 (t, 3 H, J = 6.8 Hz), 3.24 (dt, 1 H, J = 12.0, 2.5 Hz), 6.83–7.56 (m, 4 H), 7.68 (br s, 1 H); IR (Nujol) ν 3370 cm^{-1}; MS m/e 282 (M^+).

2-Ethyl-2-(3-hydroxypropyl)-4-butanolide (15). A solution of **1** (623 mg, 3.1 mmol) in 4 mL of DME was added to a mixture of 20% aqueous $TiCl_3$ (15 mL, 18.8 mmol), and NH_4OAc (8.7 g, 113 mmol) in water (29 mL), and DME (40 mL) under N_2 and the mixture was stirred for 10 h at room temperature. Workup as described in the procedure for **10** gave crude **14**, which was dissolved in MeOH (50 mL), and $NaBH_4$ (355 mg, 9.4 mmol) was added to the solution in small portions at 0 °C followed by the addition of another portion of $NaBH_4$ (118 mg, 3.1 mmol) after 30 min. The reaction mixture was stirred for 40 min at room temperature and then acidified with 9% HCl under ice cooling. After refluxing for 1 h, MeOH was removed, and the residue was partitioned with water and AcOEt with salting out. The extract was washed with brine, dried ($MgSO_4$), and evaporated to give an oily residue, which was purified by short column chromatography (silica gel, AcOEt:hexane = 4:5) to give **15** (403 mg) as a colorless oil, in 75% overall yield from **1**: ^{1}H NMR ($CDCl_3$) δ 0.95 (t, 3 H, J = 7.3 Hz), 1.62 (m, 6 H), 2.00 (s, 1 H), 2.15 (t, 2 H, J = 7.4 Hz), 3.64 (m, 2 H), 4.26 (t, 2 H, J = 7.4 Hz); IR ($CHCl_3$) ν 3620, 3600–3200, 1758 cm^{-1}; MS m/e 172 (M^+). Anal. Calcd for $C_9H_{16}O_3$: C, 62.76; H, 9.36. Found: C, 62.62; H, 9.36.

3-(3-Ethyl-2-methoxy-3-tetrahydrofuryl)propionic Acid (16). Jones reagent was added dropwise to a solution of butanolide **15** (367 mg, 2.1 mmol) in acetone (20 mL) at 0 °C until the orange color persisted. After a drop of 2-propanol and a small amount of water were added to the reaction mixture, acetone was removed under reduced pressure. The resulting mixture was saturated with NaCl and extracted with AcOEt. The extract was washed with brine, dried ($MgSO_4$), and evaporated to give a colorless oil (391 mg). This was dissolved in dry Et_2O (15 mL) and reduced with a 25% DIBAH solution in hexane (2.7 mL, 4.7 mmol) at −78 °C under N_2. After being stirred for 1 h, MeOH (10 mL) and p-TsOH (1.35 g, 7 mmol) were added to the mixture, and the resulting solution was refluxed for 40 min. Extractive workup with AcOEt followed by short column chromatography (AcOEt/hexane) gave epimeric acetal **16** (325 mg, 76%) and methyl ester **17** (25 mg, 6%). A part of epimeric mixture **16** was separated by preparative TLC (1:1 AcOEt:hexane) to provide the less polar one as a colorless oil [^{1}H NMR ($CDCl_3$) δ 0.87 (t, 3 H, J = 7.1 Hz), 1.10–2.00 (m, 6 H), 2.20–2.43 (m, 2 H), 3.32 (s, 3 H), 3.91 (dt, 2 H, J = 1.9, 7.5 Hz), 4.45 (s, 1 H), 6.80–7.80 (m, 1 H); IR ($CHCl_3$) ν 1715, 1100, 1045 cm^{-1}; high resolution MS, calcd for $C_{10}H_{18}O_4$ ($M^+ - 1$) 201.1127, found 201.1158] and the polar one as a colorless oil [^{1}H NMR ($CDCl_3$) δ 0.86 (t, 3 H, J = 7.6 Hz), 1.20–2.04 (m, 6 H), 2.20–2.45 (m, 2 H), 3.33 (s, 3 H), 3.92 (br t, 2 H, J = 7.8 Hz), 4.47 (s, 1 H), 6.80–7.80 (m, 1 H); IR ($CHCl_3$) ν 1715, 1100, 1030 cm^{-1}; high resolution MS, calcd for $C_{10}H_{18}O_4$ 202.1206, found 202.1216].

Methyl ester 17 (colorless oil): ^{1}H NMR ($CDCl_3$) δ 0.86 (t, 3 H, J = 7.2 Hz), 1.20–1.92 (m, 6 H), 2.12–2.36 (m, 2 H), 3.31, 3.32 (2 s, 3 H), 3.67 (s, 3 H), 3.91 (dt, 2 H, J = 7.2, 2.0 Hz), 4.44, 4.46 (2 s, 1 H); IR ($CDCl_3$) ν 1725, 1095, 1040 cm^{-1}; MS m/e 216 (M^+). Anal. Calcd for $C_{11}H_{20}O_4$: C, 61.09; H, 9.32. Found: C, 61.50; H, 9.44.

Cyclic Lactams 5a and 5b. A mixture of **16** (277 mg, 1.4 mmol) and tryptamine (263 mg, 1.6 mmol) in AcOH (3 mL) was refluxed for 6 days and then AcOH was removed under vacuum. The residue was dissolved in MeOH with 20% NaOH and stirred for 30 min at room temperature. After addition of water, MeOH was removed under vacuum and the resulting solution was extracted with CH_2Cl_2. The extract was washed with brine, dried ($MgSO_4$), and evaporated. The residue gave an approximately 1:1 mixture of **5a** and **5b** (357 mg, 84%) after short column chromatography over silica gel with AcOEt–hexane (5:1). These epimers were separated by short column chromatography twice. Repeated short column chromatography afforded pure **5a** [mp 107–108.5 °C (from aqueous MeOH); $[\alpha]^{22}_D$ +88.3° (c = 0.13, MeOH); ^{1}H NMR (DMSO-d_6) δ 0.63 (t, 3 H, J = 5.9 Hz), 0.81 (m, 1 H), 3.77 (m, 2 H), 4.58–5.14 (m, 3 H), 7.00 (m, 2 H), 7.38 (m, 2 H), 10.28 (br s, 1 H); ^{13}C NMR (DMSO-d_6) δ 13.8 (q), 17.5 (t), 19.9 (t), 21.9 (t), 31.3 (t), 31.8 (s), 33.2 (t), 33.5 (t), 49.7 (t), 53.3 (d), 104.0 (s), 104.4 (d), 110.3 (d), 111.5 (d), 113.9 (d), 119.1 (s), 125.0 (s), 129.1 (s), 162.1 (s); IR (KBr) ν 3400, 1595 cm^{-1}; MS m/e 312 (M^+). Anal. Calcd for $C_{19}H_{24}N_2O_2$ (+H_2O): C, 69.06; H, 7.93, N; 8.48. Found: C, 68.86; H, 7.88, N; 8.32] and **5b** [mp 263–265 °C dec (from aqueous MeOH); $[\alpha]^{22}_D$ −195.5° (c = 0.16, MeOH); ^{1}H NMR (DMSO-d_6) δ 1.06 (t, 3 H, J = 7.4 Hz), 3.17–3.30 (m, 2 H), 4.16 (t, 1 H, J = 5.0 Hz, O*H*), 4.83 (br s, 1 H), 4.76–5.00 (m, 1 H), 6.84–7.12 (m, 2 H), 7.24–7.50 (m, 2 H), 10.23 (br s, 1 H); IR (KBr) ν 3300, 1605 cm^{-1}; MS m/e 312 (M^+). Anal. Calcd for $C_{19}H_{24}N_2O_2$: C, 73.04; H, 7.74, N; 8.97. Found: C, 72.90; H, 7.81, N; 8.92.

19-Oxoeburnamonine (18). To a solution of **5b** (7.5 mg, 0.024 mmol) in dry pyridine (0.5 mL) was added a solution of CrO_3 (29 mg, 0.29 mmol) in dry pyridine (1 mL). After being stirred for 2 h at room temperature, the resulting mixture was passed through a column of silica gel with AcOEt. Evaporation of the solvent followed by preparative TLC (AcOEt) provided **18** (4 mg, 53%) as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 1.02 (t, 3 H, J = 7.6 Hz),

(20) Walls, F.; Collera, O.; Sandoval, A. *Tetrahedron* **1958**, *2*, 173.

2.80 (s, 2 H), 3.05 (br d, 2 H, J = 8.5 Hz), 4.50 (br s, 1 H), 4.98 (m, 1 H), 7.30 (m, 3 H), 8.34 (m, 1 H); IR ($CHCl_3$) ν 1705, 1635 cm^{-1}; MS m/e 308 (M^+).

(−)-Eburnamonine (9). To a solution of **18** (17 mg, 0.055 mmol) in anhydrous ether (12 mL) was added $LiAlH_4$ (76 mg, 2 mmol) at room temperature. After being refluxed for 2 h under N_2, water (1.5 mL) was added and the solution was filtered through a bed of Celite. The residue on the funnel was washed with $CHCl_3$ and the combined organic layer was evaporated to give a yellow oil (21 mg). It was dissolved in dry pyridine (ca. 1 mL) and CrO_3 (20 mg, 0.2 mmol) was added to the mixture in small portions under stirring at room temperature. After being stirred for 30 min, the resulting mixture was directly filtered through a column with neutral alumina, eluting with CH_2Cl_2 and then AcOEt. Combined fractions were evaporated and purified by preparative TLC (AcOEt) to afford **9** (12 mg, 74%): mp 171–172 °C (from MeOH) (lit.[21] mp 173–174 °C); $[\alpha]^{22}_D$ −88° (c = 0.09, $CHCl_3$) (lit.[21] $[\alpha]_D$ −85 °C); ^1H NMR ($CDCl_3$) δ 0.93 (t, 3 H, J = 7.6 Hz), 3.96 (br s, 1 H), 7.10–7.48 (m, 3 H), 8.20–8.50 (m, 1 H); IR (Nujol) ν 1700 cm^{-1}; MS m/e 294 (M^+). These spectroscopic data were identical with those of racemate.[9v]

Tetracyclic Alcohols 19 and 20. To a solution of a 1:1 mixture of **5a** and **5b** (94 mg, 0.3 mmol) in THF (10 mL) was added $LiAlH_4$ (69 mg, 1.8 mmol) and the mixture was refluxed for 30 min. Usual workup followed by short column chromatography over silica gel with AcOEt–hexanee (1:2) afforded **19** (43 mg, 48%) [mp 173.5–175 °C (from CH_2Cl_2–MeOH); ^1H NMR ($CDCl_3$) δ 0.65 (t, 3 H, J = 7.6 Hz), 3.34 (s, 3 H, CH_3 of MeOH) 3.49 (br s, 1 H), 4.00 (m, 2 H), 6.96–7.60 (m, 4 H), 9.23 (br s, 1 H); IR ($CHCl_3$) ν 3625, 3500, 3360, 2800, 2750 cm^{-1}. Anal. Calcd for $C_{19}H_{26}N_2O$ (+CH_3OH): C, 72.69; H, 9.15, N; 8.48. Found: C, 72.39; H, 8.78, N; 8.23] and **20** (42 mg, 47%) [mp 166–168 °C (from CH_2Cl_2–MeOH); ^1H NMR ($CDCl_3$) δ 1.08 (t, 3 H, J = 7.4 Hz), 3.33 (br s, 1 H), 3.35–3.57 (m, 1 H), 3.73 (dt, 1 H, J = 4.0, 12.0 Hz), 5.20–6.20 (br s, 1 H), 6.96–7.60 (m, 4 H), 7.90 (br s, 1 H); IR ($CHCl_3$) ν 3490, 3100 (br), 2960, 2920, 2800, 2750 cm^{-1}; high resolution MS, calcd for $C_{19}H_{26}N_2O$ 298.2050, found 298.2045].

Isomerization of 19 to 20. A mixture of **19** (7.6 mg, 0.026 mmol), $Hg(OAc)_2$ (24.4 mg, 0.077 mmol), and EDTA·Na_2 (28.5 mg, 0.077 mmol) in 1% aqueous AcOH (2 mL) was heated at 100 °C for 2 h. After cooling, the reaction mixture was filtered through a bed of Celite, which was washed with MeOH. The filtrate and the washings were combined, condensed to approximately 2 mL, and neutralized with 0.5 N $NaHCO_3$. Addition of EtOH (2 mL) and $NaBH_4$ (5.8 mg, 0.15 mmol) was followed by stirring for 1.5 h. The reaction mixture was filtered through a bed of Celite, acidified with HCl, concentrated to remove EtOH, and extracted with benzene. The aqueous layer was extracted with $CHCl_3$ after addition of NH_4OH. The extract was washed with brine, dried ($MgSO_4$), and evaporated to provide an approximately 1:1 mixture of **19** and **20** (6.1 mg, 80%).

(−)-Ebrunamonine (9) from 20. To a solution of **20** (10 mg, 0.034 mmol) in CH_2Cl_2 (0.5 mL) was added BF_3·OEt_2 (3.1 μL, 0.034 mmol) at 0 °C followed by addition of PCC (11 mg, 0.051 mmol), and the resulting mixture was stirred for 9 h. The reaction mixture was stirred for another 4 h after addition of the same amount of PCC, and then NH_4OH was added to it. Extractive workup with CH_2Cl_2 was followed by preparative TLC (AcOEt) to provide (−)-eburnamonine (**9**; 5.5 mg, 55%).

(+)-(1*S*,4*S*)-1-Ethyl-3,5-dioxabicyclo[4.2.1]nonan-2-one (22). A mixture of crude **14**, obtained from 100 mg of **1**, and p-TsOH (48 mg, 0.25 mmol) in benzene (50 mL) was refluxed, while water was separated azeotropically for 50 min. The reaction mixture was diluted with Et_2O, washed with water twice, dried ($MgSO_4$), and evaporated. Short column chromatography over silica gel with AcOEt:hexane (1:5) of the residue afforded **22** (63 mg, 74%): mp 89–90 °C (from Et_2O) (lit.[9v] mp 82–85 °C); $[\alpha]^{22}_D$ +5.4° (c = 1.47, CH_2Cl_2) (lit.[9v] $[\alpha]_D$ +6.7°); ^1H NMR ($CDCl_3$) δ 0.93 (t, 3 H, J = 7.0 Hz), 1.50–2.00 (m, 6 H), 2.33 (m, 2 H), 3.80–4.10 (m, 2 H), 5.83 (dd, 1 H, J = 4.9, 1.0 Hz); IR (Nujol) ν 1770 cm^{-1}. These NMR and IR spectral data and R_f value on silica gel TLC were identical with those of an authentic sample.

Rearrangement of 5. (a) A 1:1 mixture of **5a** and **5b** (11 mg, 0.035 mmol) was heated in 0.5 mL of BF_3·OEt_2 at 100–110 °C for 1 h. After the reaction mixture was cooled to 0 °C, it was poured into an ice-saturated $NaHCO_3$ solution. Extractive workup with $CHCl_3$ followed by preparative TLC with AcOEt–MeOH (10:1) afforded **25** (4.8 mg, 47%), **26a** (1.8 mg, 17%), and **26b** (3.6 mg, 35%). **25**: ^1H NMR ($CDCl_3$) δ 0.50–1.16 (m, 4 H), 1.92 (dd, 2 H, J = 6.0, 10.0 Hz), 3.53 (s, 1 H), 3.58 (dt, 1 H, J = 7.0, 13.0 Hz), 4.44 (dd, 1 H, J = 8.0, 13.0 Hz), 7.00–7.70 (m, 4 H); IR ($CHCl_3$) ν 1645, 1635 cm^{-1}. **26a**: ^1H NMR ($CDCl_3$) δ 0.72 (m, 4 H); 3.72 (dt, 1 H, J = 7.0, 12.0 Hz), 4.16 (m, 1 H), 4.22 (br s, 1 H), 4.90 (dt, 1 H, J = 14.0, 4.0 Hz), 7.04–7.60 (m, 4 H); IR ($CHCl_3$) ν 1635 cm^{-1}, which on reduction with $LiAlH_4$ in THF afforded epidihydroeburnamenine (**27a**) [^1H NMR ($CDCl_3$) δ 0.76 (unsym t, 3 H), 3.76 (dt, 1 H, J = 7.0, 12.0 Hz), 4.00–4.22 (m, 1 H), 7.00–7.60 (m, 4 H); IR ($CHCl_3$) ν 2800, 2750, 1625 (w), 1570 (w), 1185, 1120 cm^{-1}]. **26b**: ^1H NMR ($CDCl_3$) δ 1.00 (t, 3 H, J = 7.5 Hz), 3.68 (dt, 1 H, J = 7.0, 12.0 Hz), 4.21 (dt, 1 H, J = 12.0, 4.0 Hz), 4.34 (br s, 1 H), 4.95 (dd, 1 H, J = 6.0, 12.0 Hz), 7.04–7.58 (m, 4 H); IR ($CHCl_3$) ν 1630 cm^{-1}, which, on reduction with $LiAlH_4$ in THF afforded dihydroeburnamenine (**27b**) [^1H NMR ($CDCl_3$) δ 0.90 (t, 3 H, J = 7.0 Hz), 3.64–3.88 (m, 1 H), 3.88 (br s, 1 H), 4.15 (m, 1 H), 7.00–7.56 (m, 4 H); IR ($CHCl_3$) ν 1185, 1090 cm^{-1}]. (b) Treatment of the same mixture (20 mg, 0.064 mmol) with triflic acid (0.5 mL) at 100–110 °C for 45 min and usual workup described above provided **25** (8.6 mg, 46%), **26a** (8.3 mg, 44%), and **26b** (1.9 mg, 10%). (c) The cis isomer **5b** (11 mg, 0.035 mmol) yielded **25** (6.2 mg, 60%), **26a** (1.2 mg, 12%), and **26b** (2.1 mg, 20%) by the same treatment as described in b.

(−)-Aspidospermidine (7) and (+)-Demethoxyaspidospermine (8). To a refluxing suspension of $LiAlH_4$ (22 mg, 0.57 mmol) in anhydrous THF (3 mL) was added dropwise a solution of imine **25** (5.6 mg, 0.019 mmol) in anhydrous THF (2 mL) under N_2. After 20 min of reflux, to the reaction mixture were added several drops of 25% KOH and ether (2 mL) at room temperature. The resulting mixture was stirred for 30 min and filtered through a bed of Celite, eluting with CH_2Cl_2. The organic extract was washed with brine, dried ($MgSO_4$), and evaporated to afford (−)-aspidospermidine (**7**), which was immediately acetylated with Ac_2O and pyridine. The acetate was purified by preparative TLC with AcOEt–MeOH (5:1) to yield (+)-demethoxyaspidospermine (**8**) (5.0 mg, 81%) as a colorless oil: $[\alpha]^{22}_D$ +14.1° (c = 0.31, $CHCl_3$) (lit.[8] $[\alpha]_D$ −15°); ^1H NMR ($CDCl_3$) δ 0.64 (t, 3 H, J = 7.0 Hz), 2.26 (s, 3 H), 2.96–3.20 (m, 2 H), 4.09 (dd, 1 H, J = 6.0, 11.3 Hz), 6.96–7.45 (m, 3 H), 8.13 (br d, 1 H, J = 7.9 Hz); IR ($CHCl_3$) ν 1645, 1600 cm^{-1}; MS m/e 324 (M^+). These spectroscopic data were identical with those of the racemate.[5k]

Acknowledgment. We thank Professors Seiichi Takano (Tohoku University, Japan) and James P. Kutney (University of British Columbia, Canada) for providing us with an authentic sample and spectroscopic data. This work is supported by a grant from the Ministry of Education, Science, and Culture, Japan (No. 63430024 to K.F.).

(21) Döpke, W.; Meisel, H. *Pharmazie* **1966**, *21*, 444.