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Synthesis of Vinca Alkaloids and Related Compounds. 100. Stereoselective Oxidation Reactions of Compounds with the Aspidospermane and Quebrachamine Ring System. First Synthesis of Some Alkaloids Containing the Epoxy Ring[1a]

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The first syntheses of the alkaloids (−)-mehranine (**3**), (+)-voaphylline/conoflorine (**4**), (+)-N_a-methylvoaphylline/hecubine (**5**), and (−)-lochnericine (**2**) were achieved by stereoselective epoxidation starting from (−)-tabersonine (**1**), through intermediates with the aspidospermane and quebrachamine skeleton.

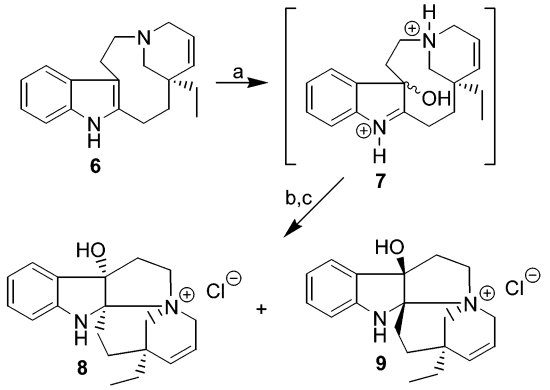
Introduction

In a previous publication[1b] we reported the oxidation of (−)-tabersonine (**1**) with dimethyldioxirane. In this reaction, instead of the expected oxidation of the C14−C15 double bond, ring transformation of the aspidospermane → eburnane skeleton[2] was only experienced. Similarly, no product with an epoxy ring was formed in the oxidation with dimethyldioxirane of (+)-14,15-didehydroquebrachamine (**6**),[3] obtainable from (−)-tabersonine (**1**). In our further experiments aimed at forming an epoxy ring the oxidizing agents *m*-chloroperoxy-benzoic acid (*m*-CPBA) and *tert*-butyl hydroperoxide were tried.

Results and Discussion

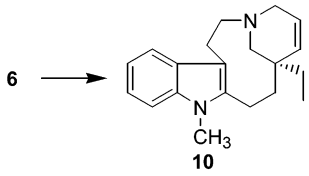
The forming of the epoxy ring on the (+)-14,15-didehydroquebrachamine (**6**) molecule was tried first with *m*-CPBA. However, instead of the expected reaction, a mixture of diastereomeric derivatives was obtained, presumably through the intermediates **7**;[1b] the isomers were isolated as their chlorides (**8** and **9**) (Scheme 1). The pure substances could not be isolated from the salt mixture. Then, to avoid the formation of the intermediate **7**, the nitrogen atom of the indole ring in molecule **6** was methylated. This was achieved with methyl iodide in dimethylformamide (DMF) in the presence of sodium hydride. The product was (+)-N_a-methyl-14,15-didehydroquebrachamine (**10**) in a fair yield (Scheme 2). The oxidation of **10** with *m*-CPBA did not give isolable product; therefore another oxidizing agent was tried. (+)-N_a-Methyl-14,15-didehydroquebrachamine (**10**) was made to react with *tert*-butyl-hydroperoxide in tetrahydrofuran in the presence of trifluoroacetic acid, resulting in the sole product (+)-N_a-methyl-(14*S*,15*R*)-epoxyquebrachamine (**12**). This reaction was also effected with the derivative

SCHEME 1[a]



[a] Reaction conditions: (a) *m*-CPBA, MeOH, 0 °C; (b) NaOH, H_2O; (c) HCl, MeOH, hexane.

SCHEME 2[a]



[a] Reaction condition: MeI, NaH, DMF.

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(1) (a) For part **99**, see: Csókási, P.; Baitz-Gács, E.; Szántay, Cs. Submitted for publication. (b) Éles, J.; Kalaus, Gy.; Lévai, A.; Greiner, I.; Kajtár-Peredy, M.; Szabó, P.; Szabó, L.; Szántay, Cs. *J. Heterocycl. Chem.* **2002**, *39*, 767.
(2) Aimi, N.; Asada, Y.; Sahaai, S.; Haginiwa, J. *J. Chem. Pharm. Bull. (Tokyo)* **1978**, *26*, 1182.
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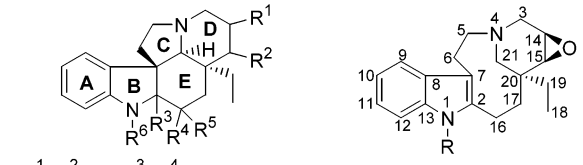
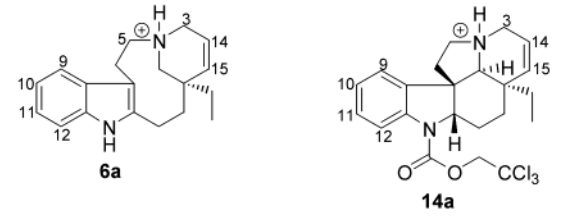


1 R^1, R^2 and R^3, R^4 = double bond, R^5 = $COOCH_3$, R^6 = H
2 R^1, R^2 = (α) -O-, R^3, R^4 = double bond, R^5 = $COOCH_3$, R^6 = H
3 R^1, R^2 = (β) -O-, R^3 = βH, R^4, R^5 = H, R^6 = CH_3

4 R = H
5 R = CH_3

FIGURE 1.



6a **14a**

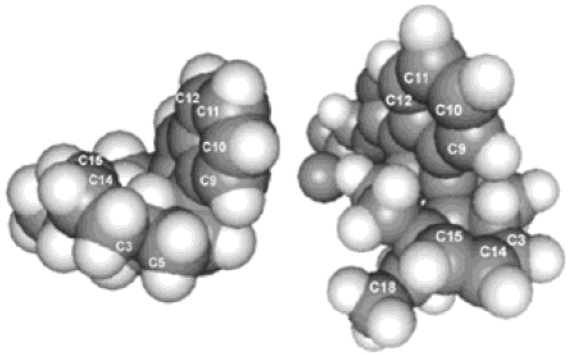
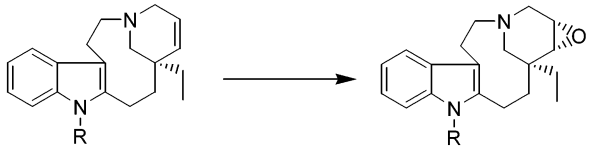


FIGURE 2.

SCHEME 3[a]



6 R = H
10 R = CH_3

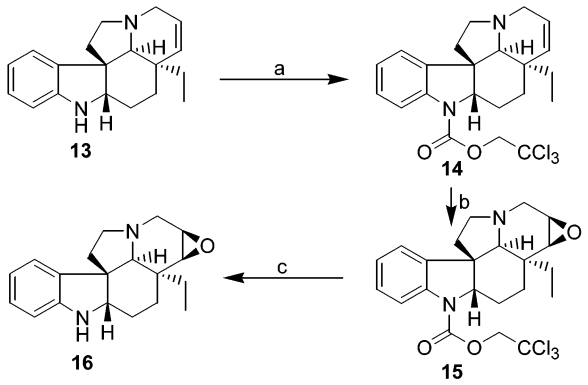
11 R = H
12 R = CH_3

[a] Reaction condition: *t*-BuOOH, THF, CF_3COOH.

6, which gave again only one product, (+)-(14*S*,15*R*)-epoxyquebrachamine (**11**) (Scheme 3). The stereoselectivity of the oxidation reaction is due to the geometry of the ring system, as was substantiated by molecular-mechanical computations.The conformation with the lowest energy of the molecule **6a**, protonated on the basic nitrogen atom, is shown in Figure 2. On the basis of the results it is concluded that owing to the orientation of the indole ring the bulky oxidizing agent can attack ring D from one side only, and consequently, solely a molecule (**11**) containing the carbon atoms in 14*S* and 15*R* configurations can be found.

In our further research we intended to form the epoxy ring in (−)-14,15-didehydroaspidospermidine (**13**), a compound readily obtained from (−)-tabersonine (**1**).

SCHEME 4[a]



13 **14** **15** **16**

[a] Reaction conditions: (a) $ClCOOCH_2CCl_3$, CH_2Cl_2; (b) *m*-CPBA, MeOH, $HClO_4$; (c) Zn, MeOH, Δ.

Compound **13** was prepared from (−)-tabersonine (**1**) as described in the literature[3] (hydrolysis with 1 M HCl, decarboxylation, and reduction by means of lithium aluminum hydride (LAH)). The secondary nitrogen atom of the molecule was protected with chlorotrichloroethyl formate. Surprisingly, the resulting compound (**14**) did not react with *tert*-butyl hydroperoxide. The oxidation was tried then with *m*-CPBA. The isolable product was molecule **15**, containing exclusively the epoxy ring with 14*R* and 15*S* configurations. The stereoselectivity of the reaction could be successfully explained also in this case by molecular-mechanical computations. The structure of the molecule containing the aspidospermane ring system in the conformation with the lowest energy (**14a**) shows (Figure 2) that the rings A and D are nearly planar. We presume that during the oxidation *m*-CPBA is inserted between rings A and D, parallel to ring A, and then the ensuing $\pi-\pi$ interaction will stabilize the transient state effected by the oxidation. In this way a molecule (**15**) containing the epoxy ring with 14*R* and 15*S* configurations is formed.

The protecting group of the intermediate **15** was removed with zinc dust in boiling methanol (Scheme 4). Methylation of the secondary nitrogen atom in (14*R*,15*S*)-epoxyaspidospermidine (**16**) with methyl iodide in dichloromethane in the presence of triethyl-amine resulted in the synthesis with a good yield of (−)-mehranine (**3**),[4] which was isolated from *Tabernaemontana bovina*. The molecule **16** was found suitable also for the syntheses of (+)-voaphylline/conoflorine (**4**),[5] occurring in *Stemmadenia grandiflora*, as well as of (+)-N_a-methylvoaphylline/hecubine (**5**).[5] First the secondary amine **16** was oxidized with potassium permanganate in the presence of 18-crown-6 ether phase transfer catalyst, and the reduction of the product (**17**) with sodium borohydride in boiling ethanol gave (+)-voaphylline (**4**) containing the epoxy ring. The synthesis of (+)-hecubine (**5**) was achieved from (+)-voaphylline (**4**), with methyl iodide in DMF by alkylation in the presence of sodium hydride (Scheme 5).

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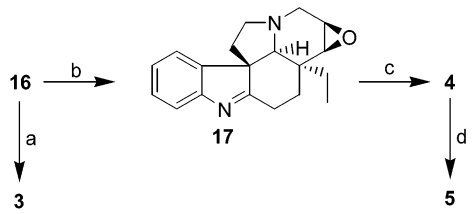
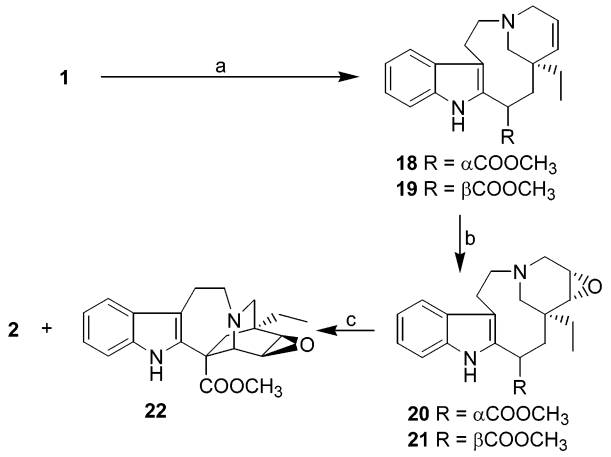
SCHEME 5[a]



[a] Reaction conditions: (a) MeI, Et_3N, CH_2Cl_2; (b) $KMnO_4$, 18crown6, benzene; (c) $NaBH_4$, EtOH, Δ; (d) MeI, NaH, DMF.

SCHEME 6[a]



[a] Reaction conditions: (a) $NaBH_4$, CH_3COOH, 90 °C; (b) *t*-BuOOH, THF, CF_3COOH; (c) $Hg(OAc)_2$, CH_3COOH.

On the basis of the above results, the synthesis of (−)-lochnericine (**2**),[6] isolated from *Catharanthus roseus*, was achieved by reacting (−)-tabersonine (**1**) with sodium borohydride in acetic acid at 90 °C. Next the mixture of the 14,15-didehydrocleavamine isomers (55% of **18** and 45% of **19**) was oxidized with *tert*-butyl hydroperoxide in THF in the presence of trifluoroacetic acid. According to previous experience, the reaction gave the mixture of 14,15-epoxycleavamine isomers (70% of **20** and 30% of **21**) containing the carbon atoms exclusively in 14*S*,15*R* configuration. Without separation this mixture was allowed to react with mercury(II) acetate in acetic acid. This transannular ring cyclization[7] gave the expected alkaloid (**2**) in a reasonable yield. A molecule with alloibogane skeleton (**22**) was also successfully isolated from the reaction mixture in a moderate yield (Scheme 6).

Conclusion

The first syntheses of the alkaloids (−)-mehranine (**3**), (+)-voaphylline (**4**), (+)-hecubine (**5**), and of (−)-lochnericine (**2**), all of them containing the epoxy ring, was achieved. The stereoselectivity of the oxidation reactions were rationalized by molecular-mechanical computations.

Experimental Section

Melting points are uncorrected. ^1H and ^{13}C NMR spectra chemical shifts (in ppm) are relative to Me_4Si. Mutual $^1H-^1H$ couplings are given only once, at their first occurrence. Mass spectra were obtained on a double focusing high-resolution mass spectrometer.

All molecular mechanics calculations were performed on a Silicon Graphics Indigo R10000. Calculations on the conformational space of **6a** and **14a** were carried out using the MacroModel 6.0 package.[8] The MM2* force field available in MacroModel was applied, which differs from the authentic MM2 force field only in that it employs the point charge Coulomb electrostatic equation. The electrostatic treatment of **6a** and **14a** was based on our positive experience of reproducing crystal structures by using calculations in vacuo with attenuated electrostatics. Therefore a distance-dependent dielectric constant was employed, which was further attenuated by a factor of 10. The conformational space of **6a** and **14a** was explored by the particularly efficient Monte Carlo Multiple Minimum (MCMM)[9] search available in MacroModel. Structures generated during the conformational search were minimized to yield unique conformers within an energy window of 50 kJ/mol above the global minimum. TNCG truncated Newton conjugate gradient technique (maximum iteration 150, convergence criterion in gradient 0.01) was used for all minimization.

(2*R*,7*S*,20*S*)-14,15-Didehydro-rhazidin (8) and (2*S*,7*R*,-20*S*)-14,15-Didehydro-rhazidin (9). To a stirred solution of **6** (200 mg, 0.7 mmol) in MeOH (10 mL) were added a few drops of $HClO_4$ and the mixture was cooled to −10 °C; 0.2 g (1.2 mmol) *m*-CPBA was added. The reaction mixture was maintained at 0 °C for 10 h, and then the solvent was evaporated. To the residue was added 10% Na_2CO_3 solution (5 mL) and the mixture was extracted with CH_2Cl_2. The combined organic layers were dried and evaporated in vacuo. The residue was dissolved in absolute MeOH (5 mL) and was acidified with methanolic HCl to pH value 4−5. Compounds **8** and **9** were crystallized from the reaction mixture. The crude product was filtered and recrystallized from absolute methanol to afford 131 mg (62%) as white crystals: mp 210−212 °C; IR (KBr) ν 3423, 2928, 1612, 1476, cm^{-1}; MS (FAB) *m*/*z* 297.1971 ($C_{19}H_{25}N_2O$ + H requires 297.1967).

Compound **8**: ^1H NMR (CD_3OD) δ 0.97(3H, t, J = 7.5 Hz; 18-H_3), 1.48−1.68(3H, m; 19-H_2 + 17-H_A), 1.98(1H, ddd, J_{gem} = 12.7, $J_{16,17B}$ = 12.3 + 4.2 Hz; 17-H_B), 2.06(1H, ddd, J_{gem} = 14.8, $J_{16A,17}$ = 12.3 + 5.5 Hz; 16-H_A), 2.33−2.45 (2H, m; 16-H_B + 6-H_A), 2.81(1H, ddd, J_{gem} = 14.5, $J_{5,6B}$ = 12.9 + 8.6 Hz; 6-H_B), 3.35−3.51(3H, m; 5-H_2 + 21-H_A), 3.69(1H, ddd, J_{gem} = 12.0, J_{lr} = 2.0 + 1.5 Hz; 21-H_B), 3.95 + 4.22(2 × 1H, 2 × dm, J_{gem} = 17.6 Hz; 3-H_2), 5.79(1H, dm; $J_{14,15}$ = 10.3 Hz; 15-H), 5.94(1H, m; 14-H), 6.70(1H, dm; 12-H), 6.89(1H, ddd; 10-H), 7.17(1H, ddd; 11-H), 7.28(1H, dm; 9-H); ^{13}C NMR (CD_3OD) δ 7.89(C18), 28.45(C16), 33.64(C17), 31.47(C19), 36.95(C20), 40.07(C6), 55.43(C3), 60.43(C5), 60.68 (C21), 90.59(C7), 103.37(C2), 111.47(C12), 122.18(C10), 122.60(C14), 124.28(C9), 131.11(C11), 133.07(C8), 133.09(C15), 147.08(C13).

Compound **9**: ^1H NMR (CD_3OD) δ 0.99(3H, t, J = 7.5 Hz; 18-H_3), 1.5−1.65(2H, m; 19-H_2), 1.70 + 2.08(2 × 1H, 2 × m; 17-H_2), 1.78 + 2.25(2 × 1H, 2 × ddd, J_{gem} = 14.3, $J_{16,17}$ = 4.0 + 2.0 and 13.0 and 4.6 Hz, respectively; 16-H_2), 2.41(1H, m; 6-H_A), 2.70(1H, ddd, J_{gem} = 14.4, $J_{5,6B}$ = 12.8 + 8.0 Hz, 6-H_B), 3.35−3.72(4H, m; 21-H_2 + 5-H_2), 4.04+4.84(2 × 1H, 2 × brd, J_{gem} = 18.0 Hz; 3-H_2), 5.90−5.98(2H, m; 14-H + 15-H), 6.80(1H, dm;12-H), 6.89(1H, ddd; 10-H), 7.17(1H, ddd; 11-H), 7.27(1H, dm; 9-H); ^{13}C NMR (CD_3OD) δ 7.89(C18), 23.04(C16), 29.98(C17), 31.19(C19), 36.54(C20), 41.97(C6), 58.68(C3), 59.03(C21), 62.85(C5), 87.09(C7), 104.23(C2), 112.08(C12), 122.13(C10), 123.09(C14), 123.16(C9), 130.82(C11), 133.32(C15), 133.61(C8), 145.97(C13).

(+)-N_a-Methyl-14,15-didehydro-quebrachamine (10). To a stirred solution of **6** (200 mg,0.7 mmol) in anhydrous DMF (5 mL) was added oil-free NaH (20 mg, 0.38 mmol). The

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(8) *MacroModel 6.0*; Schrödinger Inc.: U.S.

(9) Goodman, J. M.; Still, W. C. *J. Comput. Chem.* **1991**, *12*, 1110.

suspension was allowed to stir for 0.5 h. To the suspension was added CH_3I (0.045 mL, 0.7 mmol). After 0.5 h of stirring, the solvent was evaporated in vacuo (1 mmHg). To the residue was added 10% Na_2CO_3 solution (10 mL) and the mixture was extracted with CH_2Cl_2. The combined organic layers were dried ($MgSO_4$) and evaporated in vacuo. The residue was purified by preparative TLC (eluting with ether/hexane = 1/5, R_f = 0.79) to afford 73 mg (35%) of product **10** as yellow crystals mp 75−77 °C; IR (KBr) ν 2935, 2820, 1465, 1365, 1305 cm^{-1}; MS *m*/*z* (relative intensity) 294(100.0), 265(20.0), 199(20.0), 170(75.0), 158(39.0), 122(65.0), 79(39.0), 42(48.0); $[\alpha]_D$ = +107.1 (*c* 0.5, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 0.72(3H, t, J = 7.6 Hz; 18-H_3), 1.10 + 1.13(2 × 1H, 2 × dq, J_{gem} = 13.8 Hz; 19-H_2), 1.70 + 1.81(2 × 1H, 2 × ddd, J_{gem} = 14.0, $J_{16,17}$ = 10.2 + 1.3 and 8.8 + 1.2 Hz, respectively; 17-H_2), 2.29 + 2.52(2 × 1H, 2 × brd, J_{gem} = 11.5, J_{lr} = 1.7 and 1.5 + 1.5 Hz, respectively; 21-H_2), 2.40(1H, ddd, J_{gem} = 13.3, $J_{5,6}$ = 10.8 and 2.5 Hz; 5-H_A), 2.68 + 3.83(2 × 1H, 2 × ddd, J_{gem} = 14.5 Hz; 16-H_2), 2.70−2.90(3H, m; 5-H_B + 6-H_2), 3.07 + 3.25(2 × 1H, 2 × ddd, J_{gem} = 16.0, $J_{3,14}$ = 1.6 and 4.7, $J_{3,15}$ = 2.2 and 1.6 Hz, respectively; 3-H_2), 3.69(3H, s; N-Me), 5.37(1H, dddd, $J_{14,15}$ = 10.0, J_{lr} = 1.5 Hz; 15-H), 5.83(1H, ddd; 14-H), 7.07-(1H, ddd; 10-H), 7.14(1H, ddd; 11-H), 7.25(1H, dd; 12-H), 7.49-(1H, dd; 9-H); ^{13}C NMR ($CDCl_3$) δ 7.98(C18), 20.84(C16), 25.87(C6), 30.01(NMe), 33.22(C19), 38.74(C17), 40.01(C20), 51.83(C3), 54.26(C5), 58.52(C21), 108.41(C12), 109.59(C7), 117.71(C9), 118.43(C10), 120.22(C11), 126.61(C14), 127.92(C8), 134.00(C15), 136.67(C13), 141.05(C2). Anal. Calcd for $C_{20}H_{26}N_2$: C, 81.59; H, 8.90; N, 9.51. Found: C, 81.40; H, 8.87, N, 9.54.

Synthesis of Epoxy-Ring-Containing Compounds with Quebrachamine Skeleton (11, 12, 20, and 21). A 0.5 mmol portion of starting compound (**6**, **10**, **18**, and **19**) was stirred in anhydrous THF (15 mL). A few drops of TFAA were added and the mixture was cooled to 0 °C; 1.5 equiv of *t*-BuOOH (solution 80% in di-*tert*-buthylperoxide) was added dropwise. The reaction mixture was maintained at room temperature for 10 h, and then the solvent was evaporated. To the residue was added 10% Na_2CO_3 solution (5 mL) and the mixture was extracted with CH_2Cl_2. The combined organic layers were dried ($MgSO_4$) and evaporated in vacuo. The residue was purified by preparative TLC to afford **11** (82%) as white crystals; **12** (78%) as yellow crystals; and the mixture of **20** and **21** (62%) as brown oil.

(+)-(14*S*,15*R*)-Epoxy-quebrachamine (11): R_f = 0.52 (ether/hexane = 1/1); mp 86−88 °C; IR (KBr) ν 3400, 2950, 2750, 1460, 1338 cm^{-1}; MS *m*/*z* (relative intensity) 296(35.0), 267(9.0), 168(43.0), 156(100.0), 143(90.0), 77(55.0), 57(65.0); $[\alpha]_D$ = +87.0 (*c* 0.5, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 0.92(3H, t, J = 7.5 Hz; 18-H_3), 1.33 + 1.40(2 × 1H, 2 × dq, J_{gem} = 13.8 Hz; 19-H_2), 1.85(2H, m; 17-H_2), 1.87 + 2.64(2 × 1H, 2 × brd, J_{gem} = 12.2 Hz; 21-H_2), 2.31 + 2.42(2 × 1H, 2 × ddd, J_{gem} = 12.0, $J_{5,6}$ = 5.5 + 3.7 and 8.9 + 4.0 Hz, respectively; 5-H_2), 2.75 + 2.98(2 × 1H, 2 × ddd, J_{gem} = 12.8, $J_{3,14}$ < 1 and 5.2, J_{lr} < 1 and 1.8 Hz, respectively; 3-H_2), 2.75 + 3.06(2 × 1H, 2 × dm, J_{gem} = 15.0 Hz; 16-H_2), 2.78(1H, brd, $J_{14,15}$ = 4.1 Hz; 15-H), 2.78 + 2.88(2 × 1H, 2 × ddd, J_{gem} = 14.6 Hz; 6-H_2), 3.22(1H, dd; 14-H), 7.0−7.15(2H, m; 10-H + 11-H), 7.27(1H, dd; 12-H), 7.46(1H, ddd; 9-H), 8.00(1H, br; indole-NH); ^{13}C NMR ($CDCl_3$) δ 7.78(C18), 21.62(C16), 22.69(C6), 29.25(C19), 34.23(C17), 38.85(C20), 50.28(C21), 51.96(C3), 52.60(C5), 52.75-(C14), 58.49(C15), 108.92(C7), 110.13(C12), 117.47(C9), 118.76-(C10), 120.52(C11), 128.62(C8), 135.08(C13), 138.97(C2). Anal. Calcd for $C_{19}H_{24}N_2O$: C, 76.99; H, 8.16; N, 9.45. Found: C, 77.13; H, 8.12; N, 9.38.

(+)-N_a-Methyl-(14*S*,15*R*)-epoxy-quebrachamine (12): R_f = 0.71 (ether/hexane = 1/1); mp 105−107 °C; IR (KBr) ν 2910, 2790, 1470,1370 cm^{-1}; MS *m*/*z* (relative intensity) 310-(38.0), 226(30.0), 170(93.0), 158(100.0), 115(28.0) 77(24.0), 57(35.0); $[\alpha]_D$ = +80.2 (*c* 0.5, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 0.96-(3H, t, J = 7.5 Hz; 18-H_3), 1.40 + 1.44(2 × 1H, 2 × dq, J_{gem} = 13.8 Hz; 19-H_2), 1.71 + 1.87(2 × 1H, 2 × ddd, J_{gem} = 13.7, $J_{16,17}$ = 7.4 + 1.8 and 10.5 + 1.9 Hz, respectively; 17-H_2), 1.85 + 2.79(2 × 1H, 2 × d, J_{gem} = 12.2 Hz; 21-H_2), 2.34 + 2.37-(2 × 1H, 2 × ddd, J_{gem} = 11.8, $J_{5,6}$ = 5.6 + 4.2 and 8.7 + 4.2 Hz, respectively; 5-H_2), 2.70−2.80(3H, m; 3-H_A, 16-H_A, 15-H), 2.82 + 2.92(2 × 1H, 2 × ddd, J_{gem} = 14.8 Hz; 6-H_2), 2.89(1H, m; 3-H_B), 3.03(1H, ddd, J_{gem} = 15.5 Hz; 16-H_B), 3.15(1H, dd, $J_{3B,14}$ = 5.2, $J_{14,15}$ = 4.2 Hz; 14-H), 3.68(3H, s; N-Me), 7.06-(1H, ddd; 10-H), 7.14(1H, ddd; 11-H), 7.25(1H, dd;12-H), 7.46-(1H, dd; 9-H); ^{13}C NMR ($CDCl_3$) δ 8.03(C18), 18.71(C16), 22.49(C6), 29.07(C19), 29.57(NMe), 33.16(C17), 39.51(C20), 49.18(C21), 52.26(C3), 52.45(C14), 52.59(C5), 58.76(C15), 108.50-(C7), 108.58(C12), 117.46(C9), 118.52(C10), 120.23(C11), 127.53-(C8), 136.37(C13), 140.89(C2). Anal. Calcd for $C_{20}H_{26}N_2O$: C, 77.38; H, 8.44; N, 9.02. Found: C, 77.43; H, 8.40; N, 8.97.

(16*S*)-(14*S*,15*R*)-Epoxy-cleavamine (20) and (16*R*)-(14*S*,-15*R*)-Epoxy-cleavamine (21): R_f = 0.33 (ether/hexane = 1/1); IR (neat) ν 3300, 2928, 2832, 1728, 1696, 1608, 1464, 1432 cm^{-1}; MS *m*/*z* (relative intensity) 354(100.0), 295(11.0), 257-(17.0), 228(21.0), 215(47.0), 138(74.0), 97(34.0), 8339.0). The exact molecular mass for $C_{21}H_{26}N_2O_3$ *m*/*z* 354.1943 was confirmed by HRMS (EI, 70 eV). Compound **20**: ^{1}H NMR ($CHCl_3$) δ 0.78(3H, t, $J_{18,19}$ = 7.5 Hz; 18-H_3), 1.17 + 1.32(2 × 1H, 2 × dq, J_{gem} = 13.7 Hz; 19-H_2), 1.93 + 2.06(2 × 1H, 2 × brd, J_{gem} = 12.0 Hz; 21-H_2), 2.11 + 2.23(2 × 1H, 2 × dd, J_{gem} = 14.8, $J_{16,17}$ = 1.3 and 10.2 Hz, respectively; 17-H_2), 2.26 + 2.59(2 × 1H, 2 × ddd, J_{gem} = 13.9, $J_{5,6}$ = 9.0 + 5.2 and 3.3 + 3.2 Hz, respectively; 5-H_2), 2.81(2H, m; 6-H_2), 2.86(1H, brd, $J_{14,15}$ = 4.0 Hz; 15-H), 2.87 + 3.32(2 × 1H, 2 × ddd, J_{gem} = 13.0, $J_{3,14}$ = <1 and 5.2, J_{lr}∼1 and 1.7 Hz, respectively; 3-H_2), 3.52(1H, dd; 14-H), 3.70(3H, s; OMe), 5.25(1H, dd; 16-H), 7.08(1H, ddd; 10-H), 7.15(1H, ddd; 11-H), 7.33(1H, dm; 12-H), 7.48(1H, dm; 9-H), 8.55(1H, brs; NH); ^{13}C NMR ($CDCl_3$) δ 7.00(C18), 25.35(C6), 31.05(C19), 37.52(C20), 39.16(C16), 40.38-(C17), 50.86(C3), 52.28(OMe), 53.58(C5), 54.28(C14), 55.81-(C21), 57.75(C15), 110.75(C12), 111.87(C7), 118.22(C9), 119.12-(C10), 121.72(C11), 127.78(C8), 133.87(C13), 135.92(C2), 175.56(*C*OOMe). Compound **21**: ^{1}H NMR ($CHCl_3$) δ 1.00(3H, t, $J_{18,19}$ = 7.5 Hz; 18-H_3), 1.51(2H, q; 19-H_2), 1.86 + 2.85(2 × 1H, 2 × brd, J_{gem} = 12.7 Hz; 21-H_2), 2.03+2.15(2 × 1H, 2 × dd, J_{gem} = 14.0, $J_{16,17}$ = 2.4 and 5.3 Hz, respectively; 17-H_2), 2.31 + 2.39(2 × 1H, 2 × ddd, J_{gem} = 11.5, $J_{5,6}$ = 12.5 + 4.5 and 4.5 + 1.8 Hz, respectively; 5-H_2), 2.72 + 2.76(2 × 1H, 2 × ddd, J_{gem} = 12.8, $J_{3,14}$ = 1.0 and 4.4, J_{lr} = 1 and 1.9 Hz, respectively; 3-H_2), 2.75(1H, m; 15-H), 2.88 + 2.95(2 × 1H, 2 × ddd, J_{gem} = 15.0 Hz; 6-H_2), 3.03(1H, ddd, $J_{14,15}$ = 4.0 Hz; 14-H), 3.93(1H, dd; 16-H), 7.07(1H, ddd; 10-H), 7.13(1H, ddd; 11-H), 7.33(1H, dm; 12-H), 7.48(1H, dm; 9-H), 8.90(1H, brs; NH); ^{13}C NMR ($CDCl_3$) δ 7.96(C18), 21.27(C6), 27.43(C19), 37.21(C16), 38.74(C17), 40.61(C20), 47.34(C21), 51.40(C5), 51.68(C14), 52.47(OMe), 52.65(C3), 58.14(C15), 109.64(C7), 110.83(C12), 117.73(C9), 119.09(C10), 121.34(C11), 127.82(C8), 134.92(C13), 135.21(C2), 175.98(*C*OOMe).

(−)-N_a-(2,2,2-Trichloroethyloxycarbonyl)-14,15-dide-hydro-aspidospermidine (14). To a stirred solution of **13** (2 g, 7.1 mmol) in CH_2Cl_2 (40 mL) was added $ClCO_2CH_2CCl_3$ (1.3 mL, 9.4 mmol). The reaction mixture was allowed to stir for 24 h at room temperature; 10% Na_2CO_3 solution (20 mL) was added. After separation of the two phases, the aqueous layer was extraced with CH_2Cl_2. The combined organic layers were dried and evaporated in vacuo. The residue was purified by column chromatography (eluting with hexane/acetone = 2/1, R_f = 0.63) to afford 2.86 g (88%) of product **14** as brown oil: IR (neat) ν 2968, 2792, 1724, 1480, 1464, 1408 cm^{-1}; $[\alpha]_D$ = −2.4 (*c* 0.5, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 0.76(3H, t, $J_{18,19}$ = 7.5 Hz; 18-H_3), 1.21(2H, m; 19-H_2), 1.35 + 2.13(2 × 1H, 2 × dddd, J_{gem} = 13.0, $J_{2,16}$ = 11.0 and 6.0, $J_{16,17}$ = 13.0 + 3.3 and 3.0 + 4.0 Hz, respectively; 16-H_2), 1.40 + 1.75(2 × 1H, 2 × ddd, J_{gem} = 14.0 Hz; 17-H_2), 1.66 + 2.22(2 × 1H, 2 × ddd, J_{gem} = 13.2, $J_{5,6}$ = 10.2 + 3.4 and 8.5 + 8.0 Hz, respectively; 6-H_2), 2.36 + 3.32(2 × 1H, 2 × ddd, J_{gem} = 9.0 Hz; 5-H_2), 2.73(1H, brs; 21-H_α), 2.81 + 3.47(2 × 1H, 2 × ddd, J_{gem} = 16.0, $J_{3,14}$ = 1.5 and 4.8, $J_{3,15}$ = 2.0 and 1.5 Hz, respectively; 3-H_2), 4.37-

(1H, dd;2-H), 4.79 + 4.96(2 × 1H, 2 × d, J_{gem} = 11.7 Hz; OCH_2), 5.55(1H, ddd, $J_{14,15}$ = 10.0 Hz; 15-H), 5.69(1H, ddd; 14-H), 7.06-(1H, ddd; 10-H), 7.23(1H, brd; 9-H), 7.24(1H, brdd; 11-H), 7.85-(1H, brd; 12-H); ^{13}C NMR ($CDCl_3$) δ 7.76(C18), 24.20(C16), 27.57(C19), 29.02(C17), 38.65(C20), 40.96(C6), 51.87(C7), 52.98-(C5), 53.41(C3), 66.26(C21), 68.10(C2), 74.63(OCH_2), 95.47-(CCl_3), 115.90(C12), 122.00(C9), 122.78(C14), 124.00(C10), 127.89(C11), 134.02(C15), 138.37(C8), 139.76(C13), 151.07-(NCOO); MS *m/z* (relative intensity) 456(13.0), 446(19.0), 310-(100.0), 281(22.0), 199(23.0), 158(47), 144(62), 121(47.0), 108-(23.0). The exact molecular mass for $C_{22}H_{25}N_2O_2Cl_3$ *m/z* 454.0981 was confirmed by HRMS (EI, 70 eV).

(−)-*N*$_a$-(2,2,2-Trichloroethyloxycarbonyl)-(14*R*,15*S*)-epoxy-aspidospermidine (15). To a stirred solution of **14** (1 g, 2.2 mmol) in MeOH (30 mL) were added a few drops of $HClO_4$ and the mixutre was cooled to 0 °C. MCPBA (560 mg, 3.2 mmol) was added. The reaction mixture was stirred at room temperature for 18 h, and then the solvent was evaporated. To the residue was added 10% Na_2CO_3 solution (15 mL) and the mixture was extracted with CH_2Cl_2. The combined organic layers were dried and evaporated in vacuo. The residue was purified by column chromatography (eluting with hexane/acetone 2/1, R_f = 0.36) to afford 817 mg (79%) of product **15** as yellow oil: IR (neat) ν 2968, 2760, 1724, 1590, 1480, 1408 cm^{-1}; $[\alpha]_D$ = −15.9 (*c* 1, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 0.85(3H, t, $J_{18,19}$ = 7.5 Hz; 18-H_3), 1.20−1.37(3H, m; 19-H_2 + 16-H_A), 1.49 + 1.92(2 × 1H, 2 × ddd, J_{gem} = 14.5, $J_{16,17}$ = 3.8 + 3.5 and 14.0 + 3.0 Hz, respectively; 17-H_2), 1.63 + 2.19(2 × 1H, 2 × dm, J_{gem} = 12.5 Hz; 6-H_2), 2.18(1H, m; 16-H_B), 2.26 + 3.23-(2 × 1H, 2 × ddd, J_{gem} = 8.5, $J_{5,6}$ = 9.0 + 8.5 and 8.0 + 3.0 Hz, respectively; 5-H_2), 2.40(1H, brs; 21-H_α), 2.42 + 3.59(2 × 1H, 2 × dd, J_{gem} = 13.0, $J_{3,14}$ = 1.0 and 1.5 Hz, respectively; 3-H_2), 2.99(1H, d, $J_{14,15}$ = 4.0 Hz; 15-H), 3.37(1H, ddd; 14-H), 4.35-(1H, dd, $J_{2,16}$ = 10.8 + 5.8 Hz; 2-H), 4.82 + 4.90(2 × 1H, 2 × d, J_{gem} = 11.7 Hz; OCH_2), 7.06(1H, ddd; 10-H), 7.19(1H, dd; 9-H), 7.25(1H, ddd; 11-H), 7.84(1H, dd; 12-H); ^{13}C NMR ($CDCl_3$) δ 7.43(C18), 23.41(C17), 23.53(C16), 27.56(C19), 34.72-(C20), 41.86(C6), 51.31(C7), 52.94(C14), 53.24(C3+C5), 56.99-(C15), 67.46(C21), 68.30(C2), 74.65(OCH_2), 95.33(CCl_3), 115.93-(C12), 121.87(C9), 123.95(C10), 128.06(C11), 138.35(C8), 139.55(C13), 150.90(NCOO). MS *m/z* (relative intensity) 471-(100.0), 437(26.0), 296(30.0), 185(27.0), 93(41.0). The exact molecular mass for $C_{22}H_{25}N_2O_3Cl_3$ *m/z* 471.1009 was confirmed by HRMS (EI, 70 eV).

(−)-(14*R*,15*S*)-Epoxy-aspidospermidine (16). To a stirred solution of **15** (1 g, 2.1 mmol) in MeOH (30 mL) was added Zn dust (1.2 g) and the mixture was refluxed for 18 h. The reaction mixture was filtered. The filtrate was evaporated. The residue was purified by by column chromatography (eluting with hexane/acetone 1/1, R_f = 0.44) to afford 345 mg (55%) of product **16** as white crystals: mp 174−175 °C; IR (KBr) ν 2960, 2750, 1600, 1480, 1440 cm^{-1}; MS *m/z* (relative intensity) 296(100.0), 267(11), 204(15.0), 185(31), 156(22.0), 144(46.0), 130(49.0), 108(21.0); $[\alpha]_D$ = −71.1 (*c* 1, $CHCl_3$); ^{1}H NMR ($CDCl_3$ + DMSO-d_6) δ 0.84(3H, t, $J_{18,19}$ = 7.5 Hz; 18-H_3), 1.22−1.37(3H, m; 19-H_2 + 16-H_A), 1.40 + 1.82(2 × 1H, 2 × ddd, J_{gem} = 14.0, $J_{16,17}$ = 4.0 + 3.0 and 14.0 + 3.0 Hz, respectively; 17-H_2), 1.58(1H, m; 6-H_A), 1.65(1H, m; 16-H_B), 2.18−2.32(2H, m; 6-H_B + 5-H_A), 2.30(1H, brs; 21-H_α)2.40 + 3.56(2 × 1H, 2 × dd, J_{gem} = 13.0, $J_{3,14}$ = 1.0 and 1.6 Hz, respectively; 3-H_2), 2.95-(1H, d, $J_{14,15}$ = 4.0 Hz; 15-H), 3.18(1H, m; 5-H_B), 3.35(1H, dm; 12-H), 6.70(1H, ddd; 10-H), 7.01(1H, ddd; 11-H), 7.07(1H, dm; 9-H); ^{13}C NMR ($CDCl_3$ + DMSO-d_6) δ 7.49(C18), 23.48(C17), 26.04(C16), 27.50(C19), 34.80(C20), 40.79(C6), 52.16(C7), 52.89-(C14), 53.20(C5), 53.59(C3), 57.07(C15), 67.00(C2), 67.54(C21), 110.09(C12), 118.53(C10), 121.97(C9), 127.41(C11), 135.51(C8), 149.17(C13). Anal. Calcd for $C_{19}H_{24}N_2O$: C, 76.99; H, 8.16; N, 9.45. Found: C, 76.73; H, 8.06; N, 9.41.

(−)-Mehranine (3). To a stirred solution of (−)-(14*R*,15*S*)-epoxy-aspidospermidine (**16**) (150 mg, 0.5 mmol) in CH_2Cl_2 (10 mL) was added Et_3N (0.1 mL, 0.7 mmol). Then CH_3I (0.05 mL, 0.8 mmol) was added dropwise. The reaction mixture was maintained at room temperature for 10 h, abd then the solvent was evaporated. The residue was purified by preparative TLC (eluting with hexane/acetone 2/1, R_f = 0.46) to afford 108 mg (69%) of product **3** as white crystals: mp 105−106 °C (lit.[4c] mp 102−104 °C); IR (KBr) ν 2928, 2912, 2784, 1600, 1488, 1456, 1432, 1380 cm^{-1}; MS *m/z* (relative intensity) 310(100.0), 199(22.0), 170(18.0), 158(46.0), 144(60.0), 108(23.0); $[\alpha]_D$ = −48.1 (*c* 1, $CHCl_3$) (lit.[4b] $[\alpha]_D$ = −49 (*c* 0.831, $CHCl_3$)); ^{1}H NMR ($CDCl_3$) δ 0.82(3H, t, $J_{18,19}$ = 7.5 Hz; 18-H_3), 1.14(1H, m; 16-H_A), 1.25 + 1.30(2 × 1H, 2 × dq, J_{gem} = 14.2 Hz; 19-H_2), 1.47-(1H, m; 17-H_A), 1.63 + 2.27(2 × 1H, 2 × ddd, J_{gem} = 12.8, $J_{5,6}$ = 8.5 + 2.5 and 9.5 + 8.3 Hz, respectively; 6-H_2), 1.74−1.83(2H, m; 16-H_B + 17-H_B), 2.20 + 3.18(2 × H, 2 × ddd, J_{gem} = 8.5 Hz; 5-H_2), 2.25(1H, brs; 21-H_α), 2.36 + 3.57(2 × 1H, 2 × dd, J_{gem} = 13.0, $J_{3,14}$ = 1.0 and 1.8 Hz, respectively; 3-H_2), 2.75(3H, s; NMe), 2.96(1H, d, $J_{14,15}$ = 4.0 Hz; 15-H), 3.34(1H, ddd; 14-H), 3.36(1H, dd, $J_{2,16}$ = 10.8 + 5.2 Hz; 2-H), 6.39(1H, brd, $J_{11,12}$ = 7.8 Hz; 12-H), 6.63(1H, ddd, $J_{9,10}$ = 7.7, $J_{10,11}$ = 7.3, $J_{10,12}$ = 1.1 Hz; 10-H), 7.01(1H, dd, $J_{9,11}$ = 1.3 Hz; 9-H), 7.08(1H, ddd; 11-H); ^{13}C NMR ($CDCl_3$) δ 7.56(C18), 20.05(C16), 23.56(C17), 27.85(C19), 31.59(NMe), 34.74(C20), 41.24(C6), 51.43(C7), 53.09(C14), 53.25(C5), 53.79(C3), 57.37(C15), 67.80-(C21), 73.35(C2), 106.56(C12), 117.13(C10), 121.44(C9), 127.70-(C11), 136.84(C8), 150.21(C13). Anal. Calcd for $C_{20}H_{26}N_2O$: C, 77.38; H, 8.44; N, 9.02. Found: C, 77.40; H, 8.48; N, 8.99.

(−)-1,2-Didehydro-(14*R*,15*S*)-epoxy-aspidospermidine (17). A mixture of potassium permanganate (50 mg, 0.32 mmol) and 18-crown-6 ether (100 mg, 0.4 mmol) in anhydrous benzene (5 mL) was stirred at room temperature for 15 min. Then **16** (100 mg, 33 mmol) was added and the stirring was continued for 2 h. The mixture was filtered through a Whatman GF/A glass microfiber filter and the filtrate was washed with 10% Na_2CO_3 solution (5 mL). It was dried and evaporated in vacuo. The residue was purified by preparative TLC (eluting with hexane/acetone 1/1, R_f = 0.72) to afford 39 mg (39%) of product **17** as brown oil: IR (neat) ν 3312, 2968, 2750, 1700, 1576, 1450 cm^{-1}; $[\alpha]_D$ = −91.4 (*c* 1, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 0.78(1H, t, $J_{18,19}$ = 7.3 Hz; 18-H_3), 0.84−1.02(2H, m; 19-H_2), 1.62 + 2.30(2 × 1H, 2 × ddd, J_{gem} = 12.0, $J_{5,6}$ = 4.7 + ∼1 and 11.5 + 6.5 Hz, respectively; 6-H_2), 1.83 + 2.67(2 × 1H, 2 × dddd, J_{gem} = 14.3, $J_{16,17}$ = 9.2 + 2.0 and 10.8 + 9.2, J_{lr} = 1.8 and ∼0.6 Hz, respeectively; 17-H_2), 2.48(1H, d, J_{lr} = 1.8 Hz; 21-H_α), 2.81 + 3.62(2 × 1H, 2 × dd, J_{gem} = 12.8, $J_{3,14}$ = 1.2 and 1.3 Hz, respectively; 3-H_2), 2.85 + 3.25(2 × 1H, 2 × ddd, J_{gem} = 8.5 Hz; 5-H_2), 2.89 + 2.99(2 × 1H, 2 × ddd, J_{gem} = 17.2 Hz; 16-H_2), 2.92(1H, d, $J_{14,15}$ = 3.9 Hz; 15-H), 3.24(1H, ddd; 14-H), 7.16(1H, ddd; 10-H), 7.28−7.33(2H, m; 9-H + 11-H), 7.52(1H, dm; 12-H); ^{13}C NMR ($CDCl_3$) δ 7.76(C18), 23.21(C17), 24.26(C16), 26.67(C19), 35.97(C6), 36.18(C20), 50.47(C3), 52.66-(C14), 53.04(C5), 53.83(C7), 57.33(C15), 73.96(C21), 120.15-(C12), 121.10(C9), 125.28(C10), 127.80(C11), 147.32(C8), 154.21-(C13), 188.80(C2); MS *m/z* (relative intensity) 295.3(25.0), 287.2(100.0). The exact molecular mass for $C_{19}H_{22}N_2O$ *m/z* 294.1732 was confirmed by HRMS (EI, 70 eV).

(+)-Voaphylline (4). Compound **17** (100 mg, 0.34 mmol) was heated in ethanol (10 mL) at the boiling point and sodium borohydride (20 mg, 0.52 mmol) was added in portions. After addition of the reducing agent, the mixture was refluxed for 1 h. It was poured onto ice−water. The solution was extracted with CH_2Cl_2, and the combined organic layers were dried and evaporated in vacuo. The residue was purified by preparative TLC (eluting with ether/hexane 1/1, R_f = 0.52) to afford 80 mg (80%) of product **4** as white crystals: mp 166−167 °C (lit.[5b] mp 166−167 °C); IR (KBr) ν 3400, 2920, 2824, 1464, 1336 cm^{-1}; MS *m/z* (relative intensity) 297(100.0), 179.1(5.0), 101.1(10.0), 78.9(10.0); $[\alpha]_D$ = +27,1 (*c* 1, $CHCl_3$) (lit.[5b] $[\alpha]_D$ = +26 (*c* 0.64, $CHCl_3$)); ^{1}H NMR ($CDCl_3$) δ 0.74(3H, t, $J_{18,19}$ = 7.5 Hz; 18-H_3), 1.12(2H, m; 19-H_2), 1.71 + 2.37(2 × 1H, 2 × brd, J_{gem} = 12.2 Hz; 21-H_2), 1.73 + 2.23(2 × 1H, 2 × ddd, J_{gem} = 14.2, $J_{16,17}$ = 12.1 + 1.4 and 7.5 + 1.5 Hz, respectively; 17-H_2), 2.32 + 2.60(2 × 1H, 2 × ddd, J_{gem} = 13.3, $J_{5,6}$ = 9.5 + 4.0 and, 3.5 + 4.0 Hz, respectively; 5-H_2), 2.67 + 3.29(2 × 1H, 2 × dd,

J_{gem} = 12.5, $J_{3,14}$ = 1.0 and 1.5 Hz, respectively; 3-H_2), 2.72 + 4.17(2 × 1H, 2 × ddd, J_{gem} = 14.4 Hz; 16-H_2), 2.81 + 2.84(2 × 1H, 2 × ddd, J_{gem} = 13.8 Hz; 6-H_2), 2.92(1H, dd, $J_{14,15}$ = 4.0, J_{lr} = 1.5 Hz; 15-H), 3.13(1H, ddd; 14-H), 7.06(1H, ddd; 10-H), 7.09(1H, ddd; 11-H), 7.28(1H, dm; 12-H), 7.44(1H, dm; 9-H), 7.82(1H, brs; indole-NH); ^{13}C NMR ($CDCl_3$) δ 7.39(C18), 23.26-(C16), 26.04(C6), 32.33(C19), 33.64(C20), 36.54(C17), 52.32-(C14), 53.53(C5), 53.82(C3), 58.58(C21), 59.35(C15), 109.72-(C7), 110.06(C12), 117.72(C9), 118.78(C10), 120.61(C11), 128.57(C8), 135.59(C13), 139.36(C2). Anal. Calcd for $C_{19}H_{24}N_2O$: C, 76.99; H, 8.16; N, 9.45. Found: C, 76.90; H, 8,12; N, 9.40.

(+)-Hecubine (5). To a stirred solution of **6** (80 mg, 0.2 mmol) in anhydrous DMF (5 mL) was added oil-free NaH (10 mg, 0.19 mmol). The suspension was allowed to stir for 0.5 h at room temperature. To the suspension was added CH_3I (0.012 mL, 0.2 mmol). After 1.5 h of stirring, the solvent was evaporated in vacuo (1 mmHg). To the residue was added 10% Na_2CO_3 solution (10 mL) and the mixture was extracted with CH_2Cl_2. The combined organic layers were dried ($MgSO_4$) and evaporated in vacuo. The residue was purified by preparative TLC (eluting with ether/hexane 1/1, R_f = 0.71) to afford 29 mg (35%) of product **5** as amorphous crystals: IR (KBr) ν 2928, 2832, 1472, 1368 cm^{-1}; $[\alpha]_D$ = +22.2 (*c* 0.2, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 0.75(3H, t, $J_{18,19}$ = 7.5 Hz; 18-H_3), 1.15(2H, m; 19-H_2), 1.72 + 2.22(2 × 1H, 2 × ddd, J_{gem} = 14.2, $J_{16,17}$ = 12.1 + 1.4 and 7.5 + 1.5 Hz, respectively; 17-H_2), 1.75 + 2.51(2 × brd, J_{gem} = 12.2 Hz; 21-H_2), 2.37 + 2.60(2 × 1H, 2 × ddd, J_{gem} = 13.3, $J_{5,6}$ = 9.5 + 4.0 and 3.5 + 4.0 Hz, respectively; 5-H_2), 2.67 + 3.28(2 × 1H, 2 × dd, J_{gem} = 12.5, $J_{3,14}$ = 1.0 and 1.5 Hz, respectively; 3-H_2), 2.78 + 4.21(2 × 1H, 2 × ddd, J_{gem} = 14.4 Hz; 16-H_2), 2.87(2H, m; 6-H_2), 2.92(1H, dd, $J_{14,15}$ = 4.0, J_{lr} = 1.5 Hz; 15-H), 3.15(1H, ddd; 14-H), 3.70(3H, s; NMe), 7.06(1H, ddd; 10-H), 7.14(1H, ddd; 11-H), 7.25(1H, dm; 12-H), 7.45(1H, dm; 9-H); ^{13}C NMR ($CDCl_3$) δ 7.48(C18), 20.98(C16), 26.34(C6), 30.01(NMe), 32.46(C19), 33.82(C20), 35.26(C17), 52.41(C14), 53.57(C5), 53.82(C3), 58.10(C21), 59.39-(C15), 108.51(C12), 109.31(C7), 117.63(C9), 118.51(C10), 120.26-(C11), 127.79(C8), 136.94(C13), 140.84(C2); MS *m*/*z* (relative intensity) 311.2(100.0), 295.0(20.0). The exact molecular mass for $C_{20}H_{26}N_2O$ *m*/*z* 310.2045 was confirmed by HRMS (EI, 70 eV).

(16*S*)-14,15-Didehydro-cleavamine (18) and (16*R*)-14,-15-Didehydro-cleavamine (19). Compound **1** (3 g, 8.9 mmol) was heated in glacial acetic acid (5 mL) at 90 °C and sodium borohydride (2 g, 5.3 mmol) was added in portions. After addition of the reducing agent, the mixture was poured onto ice−water and neutralized with saturated Na_2CO_3 solution. The solution was extracted with CH_2Cl_2, and the combined organic layers were dried ($MgSO_4$) and evaporated in vacuo. The residue was purified by column chromatography (eluting with ether/hexane 1/5, R_f = 0.45) to afford 1.96 g (68%) the mixture of products **18** and **19** as brown oil: IR (neat) ν 3392, 2920, 2872, 1724, 1464 cm^{-1}; MS *m*/*z* (relative intensity) 339.1-(100.0), 299.2(5.0). The exact molecular mass for $C_{21}H_{26}N_2O_2$ *m*/*z* 338.1995 was confirmed by HRMS (EI, 70 eV). Compound **18**: ^{1}H NMR ($CHCl_3$) δ 0.70(3H, t, $J_{18,19}$ = 7.5 Hz; 18-H_3), 1.09 + 1.13(2 × 1H, 2 × dq, J_{gem} = 13.5 Hz; 19-H_2), 1.93 + 2.12(2 × 1H, 2 × dd, J_{gem} = 14.2, $J_{16,17}$ = 1.1 and 10.0 Hz, respectively; 17-H_2), 2.24(2H, brs; 21-H_2), 2.35 + 2.74(2 × 1H, 2 × ddd, J_{gem} = 13.5, $J_{5,6}$ = 10.6 + 3.6 and 3.5 + 3.0 Hz, respectively; 5-H_2), 2.8−2.9(2H, m; 6-H_2), 3.07 + 3.29(2 × 1H, 2 × ddd, J_{gem} = 16.0, $J_{3,14}$ = 1.7 and 4.8, J_{lr} = 2.3 and 1.7 Hz, respectively; 3-H_2), 3.65(3H, s; OMe), 5.28(1H, dd; 16-H_β), 5.35-(1H, ddd, $J_{14,15}$ = 9.8, J_{lr} = 2.3 + 2.0 Hz; 15-H), 5.89(1H, ddd; 14-H), 7.08(1H, ddd; 10-H), 7.14(1H, ddd; 11-H), 7.33(H, dm; 12-H), 7.50(1H, dm; 9-H), 8.58(1H, brs; NH); ^{13}C NMR ($CDCl_3$) δ 7.74(C18), 26.06(C6), 33.18(C19), 39.19(C16), 39.61(C20), 43.65(C17), 52.11(OMe), 51.90(C3), 53.75(C5), 58.83(C21), 110.65(C12), 111.81(C7), 118.21(C9), 118.94(C10), 121.50(C11), 127.26(C14), 127.97(C8), 133.10(C15), 134.58(C13), 135.81(C2), 175.96(*C*OOMe). Compound **19**: ^{1}H NMR ($CHCl_3$) δ 0.91(3H, t, $J_{18,19}$ = 7.5 Hz; 18-H_3), 1.39 + 1.46(2 × 1H, 2 × dq, J_{gem} = 14.0 Hz; 19-H_2), 1.94 + 3.42(2 × 1H, 2 × brd, J_{gem} = 12.0 Hz; 21-H_2), 1.98 + 22.27(2 × 1H, 2 × dd, J_{gem} = 14.2, $J_{16,17}$ = 2.4 and 5.5 Hz, respectively; 17-H_2), 2.44−2.55(2H, m; 5-H_2), 2.8−2.9(2H, m; 3-H_2), 2.9−3.0(2H, m; 6-H_2), 3.77(3H, s; OMe), 3.96-(1H, dd; 16-H), 5.37(1H, ddd, $J_{14,15}$ = 9.8, $J_{3,14}$ = 4.0+1.9 Hz; 14-H), 5.56(1H, dddd, J_{lr} = 2.2 + 2 + 2 Hz; 15-H), 7.06(1H, ddd; 10-H), 7.11(1H, ddd; 11-H), 7.31(1H, dm; 12-H), 7.49(1H, dm; 9-H), 8.96(1H, brs; NH); ^{13}C NMR ($CDCl_3$) δ 8.52(C18), 21.55(C6), 29.60(C19), 38.34(C16), 41.24(C20), 44.57(C17), 51.83(C21), 51.79(C5), 52.31(OMe), 54.72(C3), 109.54(C7), 110.77(C12), 117.66(C9), 118.90(C10), 121.09(C11), 125.03-(C14), 128.00(C8), 135.07(C13), 135.46(C2), 135.87(C15), 176.22-(*C*OOMe).

(−)-Lochnericine (2) and (+)-(14*S*,15*R*)-Epoxy-allocatharantine (22). To a stirred solution of **20** and **21** (1 g, 2.8 mmol) in glacial acetic acid (5 mL) was added mercury(II) acetate (3.3 g, 10.6 mmol). The reaction mixture was allowed to stir at room temperature for 2 h. The precipitated mercurous acetate was filtered off and the filtrate was treated with hydrogen sulfide gas. The resulting mixture was filtered through Celite, and the filtrate was poured onto ice−water and neutralized with saturated Na_2CO_3 solution. The solution was extracted with CH_2Cl_2, and the combined organic layers were dried ($MgSO_4$) and evaporated in vacuo. The residue was purified by preparative TLC (eluting with hexane/acetone 3/1). The less polar compound (**2**, R_f = 0.51), was obtained as white crystals (350 mg, 35%): mp 190−191 °C (lit.[6b] mp 193−195 °C); IR (KBr) ν 3360, 2992 1666, 1604, 1464 cm^{-1}; MS *m*/*z* (relative intensity) 353.2(100.0), 308.2(4.0); $[\alpha]_D$ = −498.5 (*c* 0.1, EtOH) (lit.[6b] $[\alpha]_D$ = −505 (*c* 0.1, EtOH)); ^{1}H NMR ($CDCl_3$) δ 0.74(3H, t, $J_{18,19}$ = 7.5 Hz; 18-H_3), 0.90 + 1.14(2 × 1H, 2 × dq, J_{gem} = 14.3 Hz; 19-H_2), 1.71 + 1.94(2 × 1H, 2 × ddd, J_{gem} = 11.5, $J_{5,6}$ = 4.5 + <1 and 12.0 + 6.4 Hz, respectively; 6-H_2), 2.47 + 2.87(2 × 1H, 2 × m; 5-H_2), 2.47(1H, brs; 21-H_α), 2.50 + 2.58(2 × 1H, 2 × d, J_{gem} = 14.8 Hz; 17-H_2), 2.89 + 3.51-(2 × 1H, 2 × m; 3-H_2), 3.11(1H, d, $J_{14,15}$ = 3.5 Hz; 15-H), 3.49-(1H, m; 14-H), 3.79(3H, s; OMe), 6.81(1H, dd; 12-H), 6.86(1H, ddd; 10-H), 7.13(1H, m; 11-H), 7.14(1H, m; 9-H), 8.95(1H, brs; NH); ^{13}C NMR ($CDCl_3$) δ 7.24(C18), 23.29(C17), 24.41(C19), 41.07(C20), 44.76(C6), 50.16(C3), 50.66(C5), 51.08(OMe) 53.96-(C14), 54.94(C7), 57.26(C15), 67.59(C21), 90.70(C16), 109.44-(C12), 120.72(C10), 121.43(C9), 127.78(C11), 137.56(C8), 143.03-(C13), 167.73(C2), 168.88(*C*OOMe). Anal. Calcd for $C_{21}H_{24}N_2O_3$: C, 71.57; H, 6.86; N, 7.95. Found: C, 71.70; H, 6.74; N, 7.91. The more polar compound (**22**, R_f = 0.3) was obtained as a yellow oil (80 mg, 8%): IR (neat) ν 3376, 2920, 1728, 1632, 1460 cm^{-1}; $[\alpha]_D$ = +48.0 (*c* 1, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 0.97-(3H, t, $J_{18,19}$ = 7.5 Hz; 18-H_3), 1.42 + 1.48(2H, 2 × dq, J_{gem} = 14.1 Hz; 19-H_2), 1.63 + 2.74(2 × 1H, d and dd, respectively, J_{gem} = 13.9, $J_{17,\ 21\beta}$ = 3.2 Hz; 17-H_2), 2.43 + 3.15(2 × 1H, brd and dd, respectively, J_{gem} = 9.0; 21-H_2), 2.85 + 3.23(2 × 1H, 2 × m; 6-H_2), 3.07(1H, dd, $J_{14,15}$ = 5.0, $J_{15,21\alpha}$ = 1.3 Hz; 15-H_α), 3.19 + 3.45((2 × 1H, 2 × m; 5-H_2), 3.33(1H, dd, $J_{3,14}$ = 3.9 Hz; 14-H_α), 3.83(3H, s; OMe), 4.26(1H, brd; 3-H_β0, 7.10(1H, ddd, $J_{9,10}$ = 7.7, $J_{10,11}$=7.1, $J_{10,12}$ = 1.2 Hz; 10-H), 7.16(1H, ddd, $J_{11,12}$ = 7.9, $J_{9,11}$ = 1.4 Hz; 11-H), 7.25(1H, brd; 12-H), 7.48-(1H, brd; 9-H), 7.72(1h, brs; NH); ^{13}C NMR ($CDCl_3$) δ 8.56-(C18), 20.94(C6), 29.29(C19), 37.44(C20), 41.74(C17), 51.40-(C14), 52.72(C21), 52.97(OMe), 53.59(C5), 54.04(C15), 54.30-(C16), 56.85(C3), 110.57(C12), 111.25(C7), 118.38(C9), 119.68-(C10), 122.27(C11), 128.95(C8), 134.91(C13), 136.16(C2), 174.52-(*C*OOMe). The exact molecular mass for $C_{21}H_{24}N_2O_3$ *m*/*z* 352.1796 was confirmed by HRMS (EI, 70 eV).

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