New Morphinane and Hasubanane Alkaloids from *Stephania cepharantha*

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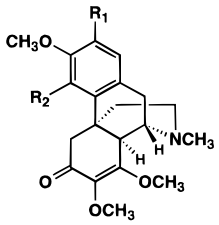
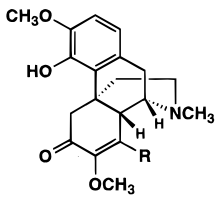
Six morphinane alkaloids, cephasamine (**3**), cephakicine (**4**), tannagine (**6**), 14-episinomenine (**7**), FK-3000 (**8**), and sinoacutine (**9**), and five hasubanane alkaloids, cephatonine (**5**), cepharamine (**10**), aknadinine (**11**), aknadicine (**12**), and aknadilactam (**13**), were isolated from the tuber of *Stephania cepharantha* Hayata (Menispermaceae) cultivated in Japan. Three of these (**3**−**5**) were new alkaloids. Structures were spectroscopically determined by comparison of their ^{1}H and ^{13}C NMR data with that of cephamonine (**1**), cephamuline (**2**), and other known alkaloids (**6**−**13**).

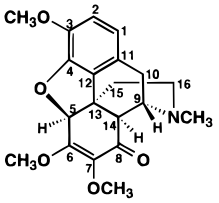
In a previous paper,[1] we have reported the isolation and structural determination of two new morphinane alkaloids, cephamonine (**1**) and cephamuline (**2**), from the tuber of *Stephania cepharantha* Hayata (Menispermaceae)[2] cultivated in Japan. In further investigation of the alkaloidal constituents of this plant, we have isolated two new morphinane alkaloids, cephasamine (**3**) and cephakicine (**4**), and one new husabanane alkaloid, cephatonine (**5**), together with four known morphinanes, tannagine (**6**),[3] 14-episinomenine (**7**),[4,5] FK-3000 (**8**),[6,7] and sinoacutine (**9**),[8,9] and four known hasubananes, cepharamine (**10**),[10,11] aknadinine (**11**),[12,13] aknadicine (**12**),[13] and aknadilactam (**13**).[13,14] This paper deals with the isolation and structural determination of **3**−**5**.



	R_1	R_2
1	H	OH
6	OCH_3	H



2 R = OCH_3
7 R = H



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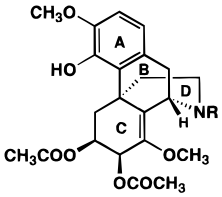
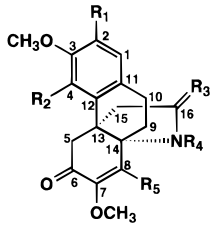
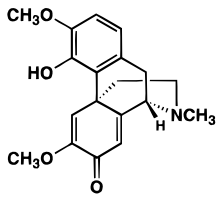


4 R = CH_3
8 R = H



	R_1	R_2	R_3	R_4	R_5
5	OH	H	H_2	CH_3	OCH_3
10	H	OH	H_2	CH_3	H
11	H	OH	H_2	CH_3	OCH_3
12	H	OH	H_2	H	OCH_3
13	H	OH	O	CH_3	OCH_3



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Results and Discussion

The alkaloidal fractions were repeatedly subjected to column chromatography on silica gel followed by preparative TLC to afford 11 alkaloids including three new alkaloids (**3**−**5**). Cephasamine (**3**) was obtained as colorless prisms from ether, and the molecular formula was assigned by the HRMS as $C_{20}H_{23}NO_5$. The IR (1667, 1611 cm^{-1}) and UV (229sh, 272 nm) spectra indicated the presence of an α,β-unsaturated carbonyl moiety which is present in morphinanes (**1**, **2**, **6**, **7**) and hasubananes (**10**−**13**). The structure of **3**, including stereochemistry, was clarified by the ^{1}H and ^{13}C NMR analysis. The assignments of signals were confirmed by comparison with reported data[1] of cephamonine (**1**) and cephamuline (**2**) and with the spectra of known alkaloids (**6**−**13**), whose signals were assigned using 1D and 2D NMR techniques (^{1}H−^{1}H COSY, ^{1}H−^{13}C COSY, NOESY, and COLOC).

The ^{1}H NMR spectrum of **3** showed signals of one *N*-methyl group (δ_H 2.44), three methoxy groups (δ_H 3.54, 3.84, 4.08), and a set of coupled aromatic protons (δ_H 6.60, 6.71) similar to those of **1** and **2**. In addition to these signals, **3** showed a methine proton (δ_H 5.40) signal as a singlet, instead of the signals due to the H-5 methylene protons of **1** and **2**, indicating that a >CHO− moiety is present at C-5.

The gross structure was obtained by COLOC experiments (Figure 1) in which the correlations were observed between the H-5 (δ_H 5.40) signal and the C-4 (δ_C 142.29), C-6 (δ_C 154.08), and C-7 (δ_C 139.40) signals, between the H-14 (δ_H 2.95) signal and the C-8 (δ_C 191.39) signal, and among two methoxy (δ_H 4.08, 3.54) signals and the C-6 and C-7 signals. These results indicated that **3** is a morphinane alkaloid bearing 4,5-epoxy, 6,7-dimethoxy, and 6,7-didehydro-8-oxo moieties.

The relative stereochemistry was determined by NOESY experiments (Figure 2). The cross peaks ob-

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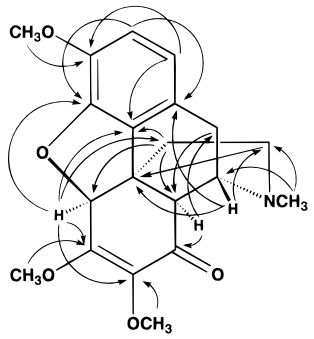

Figure 1. $^1H-^{13}C$ long range correlations of **3**.

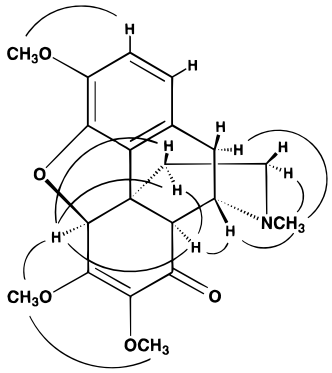

Figure 2. NOE correlations of **3**.

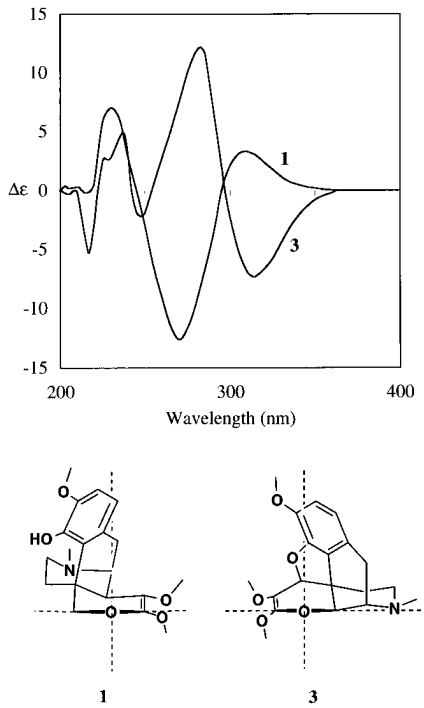

Figure 3. CD spectra and octant diagrams of **1** and **3**.

served mutually between the H-5, H-14, and H-15 (δ_H 1.84, 2.01) signals indicated that rings C and D have a *trans*-relationship like **1**. These experiments also indicated that a methoxy group is located at the C-6 position since the methoxy signal (δ_H 4.08) showed the correlation to the H-5 signal.

The absolute stereochemistry of **3** was deduced as follows: the CD spectrum (Figure 3) of **3** showed a negative ($\Delta\epsilon$ −7.2) Cotton effect at 315 nm arising from an n → π^* transition of an α,β-unsaturated carbonyl group. The enone system of **3** is nonplanar as shown in the stereostructure (Figure 3) of least energy which was obtained by calculation of Chem 3D Plus[15] with MM2 programs. On the basis of the experimental rule[16] in regard to the Cotton effect of nonplanar α,β-unsaturated ketone offered by Snatzke, the absolute stereochemistry was concluded to be 5*S*,9*S*,14*S* as shown by the octant diagram (Figure 3). This conclusion was supported by the fact that the Cotton effect was opposite to that ($\Delta\epsilon$ +3.3, 309 nm) of **1**, which has an opposite stereochemical relationship in respect to the enone moiety (7,8-dimethoxy and 7,8-didehydro-6-oxo) as shown by the octant diagram (Figure 3). Thus, the structure of cephasamine was elucidated as **3**.

Cephakicine (**4**) was obtained as an amorphous powder. The IR (1744 cm^{-1}) and UV (285 nm) spectra were very similar to those of FK-3000 (**8**). The molecular formula was established by the HRMS as $C_{23}H_{29}NO_7$, which has excess CH_2 compared to that of **8**. The ^1H and ^{13}C NMR spectra were also similar to those of **8**, except for the signal (δ_H 2.40, δ_C 42.15) assignable to the *N*-methyl group, indicating that **4** should be the *N*-methyl derivative of **8**. In fact, reductive *N*-methylation of **8** with HCHO−$NaBH_4$ in MeOH[17] gave the *N*-methyl derivative. The product was identical to an authentic sample of **4** by comparison of $[\alpha]_D$, IR, and ^1H NMR spectra. Thus, cephakicine was determined to be the *N*-methyl derivative of **8**.

Cephatonine (**5**) was isolated as an amorphous powder. The molecular formula, $C_{20}H_{25}NO_5$, determined by the HRMS was the same as that of aknadinine (**11**), and the fragmentation patterns in the EIMS were similar to those of **11**. Furthermore, the IR and ^1H and ^{13}C NMR spectra indicated the same functional groups as those of **11**, except that two aromatic proton (δ_H 6.56, 6.65) signals were observed as two singlets in the ^1H NMR spectrum. These data suggested that **5** was the regioisomer of **11**. The position of two aromatic protons was established by NOESY experiments, in which one aromatic proton (δ_H 6.56) signal showed a cross peak to the H-10 (δ_H 2.51) signal and the other aromatic proton (δ_H 6.65) signal was correlated to the H-5 (δ_H 3.01) and H-15 (δ_H 2.16) signals. Thus, two aromatic protons are located at the C-1 and C-4 positions. Furthermore, the position of the methoxy group on the aromatic ring was also elucidated by the NOESY experiments, in which the methoxy (δ_H 3.84) signal was correlated to the H-4 (δ_H 6.65) signal, indicating that the methoxy group is located at the C-3 position. Since the optical activity showed the same direction as that of **11**, the absolute stereochemistry was concluded to be 13*R* and 14*S*. Thus, the structure of cephatonine was determined to be **5**.

Experimental Section

General Experimental Procedures. Melting points were measured on a Yanagimoto hot-stage melting point apparatus without correction. NMR spectra were taken on a JNM-α500 (JEOL) (500 MHz for ^1H and 125 MHz for ^{13}C) spectrometer in $CDCl_3$ with TMS as an internal standard, and the chemical shifts are given in δ values. IR spectra were recorded on an FT/IR-5000 (JASCO) spectrometer as KBr pellets, and data are given in cm^{-1}. UV spectra were measured on a Ubest-35 (JASCO) spectrometer in MeOH, and data are given as λ_{max}nm (log ϵ). MS were taken on JMS-AX505H or JMS-D300

(JEOL) spectrometers at 30 eV, and EIMS data are given in *m/z* (rel int). Optical rotations were determined on a DIP-140 (JASCO) spectrometer in $CHCl_3$. CD spectra were measured on a J-600 (JASCO) spectrometer in MeOH, and data are given as $\Delta\epsilon$ (nm). Column chromatography was performed on Wakogel C-200 (Wako Pure Chemical Industries, Ltd.). Preparative TLC was done on precoated Silica gel 60 F_{254} (0.25 nm thick) plates (Merck).

Plant Material. *S. cepharantha* Hayata was cultivated at Yasato-machi, Ibaraki prefecture, Japan and collected in winter 1987.

Extraction and Isolation. Dry and cut tubers of *S. cepharantha* (37.4 kg) were extracted twice with hot MeOH. The extract was evaporated *in vacuo*, and the residue was treated with 5% HCl. The mixture was filtered, and the filtrate was extracted with Et_2O. The aqueous layer was adjusted to pH 7 with NH_4OH and extracted with Et_2O to yield fraction A (270.2 g). Then, the aqueous layer was basified with NH_4OH to pH 10 and extracted with Et_2O to yield fraction B (289.4 g). Fraction A was repeatedly subjected to silica gel column chromatography, using $CHCl_3$, 2%, 4%, and 8% MeOH−$CHCl_3$, and MeOH as eluents. The material eluted with 2% MeOH−$CHCl_3$ was further chromatographed, followed by preparative TLC, to afford cephasamine (**3**, 34 mg), cephakicine (**4**, 23 mg), cephatonine (**5**, 15 mg), 14-episinomenine (**7**, 46 mg), sinoacutine (**9**, 17 mg), cepharamine (**10**, 62 mg), aknadinine (**11**, 61 mg), aknadicine (**12**, 45 mg), and aknadilactam (**13**, 32 mg). Fraction B was repeatedly chromatographed on silica gel, using 2%, 4%, 6%, 8%, and 50% MeOH−$CHCl_3$ as eluents. Further chromatography of the fraction eluted with 2% MeOH−$CHCl_3$ gave FK-3000 (**8**, 8.5 g), and the mother liquor of **8** was repeatedly subjected to preparative TLC to afford tannagine (**6**, 38 mg).

Cephasamine (3): mp 142−144 °C (colorless prisms from ether); $[\alpha]^{28}_D$ +105° (*c* = 0.34); IR 3420, 1667, 1611, 1510, 1450, 1286, 1251; UV 229sh (4.04), 272 (4.02); EIMS 357 (M^+, 100), 342 (35), 326 (14), 314 (14), 300 (27), 285 (15), 190 (14); HRMS 357.1545 ($C_{20}H_{23}NO_5$ requires 357.1573); CD −7.2 (315), 12.0 (282), −2.2 (248), 4.9 (237), 2.6 (228), 2.6 (225), −5.3 (217); ^{1}H NMR 6.60 (d, *J* = 7.9 Hz, H-1), 6.71 (d, *J* = 7.9 Hz, H-2), 5.40 (s, H-5), 3.81 (dd, *J* = 5.8, 3.1 Hz, H-9), 2.52 (dd, *J* = 18.3, 5.8 Hz, H-10), 3.93 (d, *J* = 18.3 Hz, H-10), 2.95 (d, *J* = 3.1 Hz, H-14), 1.84 (ddd, *J* = 12.2, 3.6, 1.6 Hz, H-15), 2.01 (ddd, *J* = 12.2, 12.2, 4.9 Hz, H-15), 2.24 (ddd, *J* = 12.2, 12.2, 3.6 Hz, H-16), 2.54 (ddd, *J* = 12.2, 4.9, 1.6 Hz, H-16), 2.44 (s, NCH_3), 3.84 (s, 3-OCH_3), 4.08 (s, 6-OCH_3), 3.54 (s, 7-OCH_3); ^{13}C NMR 120.21 (C-1), 114.62 (C-2), 142.77 (C-3), 142.29 (C-4), 86.68 (C-5), 154.08 (C-6), 139.40 (C-7), 191.39 (C-8), 54.97 (C-9), 19.87 (C-10), 127.29 (C-11), 129.59 (C-12), 40.75 (C-13), 49.93 (C-14), 34.39 (C-15), 46.42 (C-16), 42.87 (NCH_3), 56.55 (3-OCH_3), 58.34 (6-OCH_3), 60.02 (7-OCH_3).

Cephakicine (4): amorphous powder; $[\alpha]^{28}_D$ −161° (*c* = 0.22); IR 3450, 1744, 1487, 1247; UV 283 (3.32); EIMS 431 (M^+, 5), 416 (17), 373 (43), 372 (100), 272 (18), 258 (11), 230 (10); HRMS 431.1919 ($C_{23}H_{29}NO_7$ requires 431.1942); ^{1}H NMR 6.62 (d, *J* = 8.2 Hz, H-1), 6.72 (d, *J* = 8.2 Hz, H-2), 2.35 (dd, *J* = 13.3, 12.8 Hz, H-5), 2.86 (dd, *J* = 12.8, 3.8 Hz, H-5), 5.24 (ddd, *J* = 13.3, 3.8, 3.8 Hz, H-6), 5.92 (dd, *J* = 3.8, 0.9 Hz, H-7), 4.15 (d, *J* = 5.2 Hz, H-9), 2.87 (ddd, *J* = 17.7, 5.8, 1.0 Hz, H-10), 3.14 (d, *J* = 17.7 Hz, H-10), 1.87 (ddd, *J* = 12.5, 3.1, 1.8 Hz, H-15), 2.10 (ddd, *J* = 12.5, 12.2, 4.6 Hz, H-15), 2.38 (ddd, *J* = 12.5, 12.2, 3.1 Hz, H-16), 2.55 (ddd, *J* = 12.5, 4.6, 1.8 Hz, H-16), 2.40 (s, NCH_3), 3.87 (s, 3-OCH_3), 2.01 (s, 6-$OCOCH_3$), 2.04 (s, 7-$OCOCH_3$) 3.55 (s, 8-OCH_3); ^{13}C NMR 118.38 (C-1), 108.81 (C-2), 145.03 (C-3), 143.40 (C-4), 32.75 (C-5), 68.40 (C-6), 64.37 (C-7), 141.18 (C-8), 52.06 (C-9), 29.92 (C-10), 130.63 (C-11), 128.01 (C-12), 38.12 (C-13), 125.78 (C-14), 35.06 (C-15), 48.05 (C-16), 42.15 (NCH_3), 56.26 (3-OCH_3), 170.29 (6-$OCOCH_3$), 21.03 (6-$OCOCH_3$), 170.64 (7-$OCOCH_3$), 21.04 (7-$OCOCH_3$), 56.98 (8-OCH_3).

Cephatonine (5): amorphous powder; $[\alpha]^{28}_D$ −264° (*c* = 0.13); IR 3420, 1665, 1601, 1514, 1243; UV 224sh (3.94), 270 (4.56); EIMS 359 (M^+, 46), 344 (12), 328 (11), 316 (13), 302 (22), 301 (100), 300 (40), 269 (11), 244 (24), 231 (23); HRMS 359.1769 ($C_{20}H_{25}NO_5$ requires 359.1733); ^{1}H NMR 6.56 (s, H-1), 6.65 (s, H-4), 2.63 (d, *J* = 15.9 Hz, H-5), 3.01 (d, *J* = 15.9 Hz, H-5), 1.98 (ddd, *J* = 13.7, 9.8, 4.9 Hz, H-10), 2.10 (ddd, *J* = 13.7, 5.5, 4.9 Hz, H-10), 2.51 (ddd, *J* = 16.5, 5.5, 4.9 Hz, H-11), 2.72 (ddd, *J* = 16.5, 9.8, 4.9 Hz, H-11), 2.03 (ddd, *J* = 13.1, 9.5, 4.6 Hz, H-15), 2.16 (ddd, *J* = 13.1, 9.8, 6.1 Hz, H-15), 2.78 (ddd, *J* = 9.5, 9.2, 6.1 Hz, H-16), 2.82 (ddd, *J* = 9.8, 9.2, 4.6 Hz, H-16), 2.52 (s, NCH_3), 3.84 (s, 3-OCH_3), 3.63 (s, 7-OCH_3), 4.08 (s, 8-OCH_3); ^{13}C NMR 113.81 (C-1), 143.60 (C-2), 145.43 (C-3), 109.57 (C-4), 48.56 (C-5), 193.94 (C-6), 137.96 (C-7), 165.38 (C-8), 22.72 (C-9), 25.10 (C-10), 127.79 (C-11), 133.90 (C-12), 48.06 (C-13), 67.24 (C-14), 37.37 (C-15), 51.34 (C-16), 36.21 (NCH_3), 56.07 (3-OCH_3), 60.72 (7-OCH_3), 60.63 (8-OCH_3).

Tannagine (6): amorphous powder; $[\alpha]^{24}_D$ +23° (*c* = 0.22); IR 3402, 1669, 1605, 1516, 1243; UV 223sh (4.04), 273 (4.01); EIMS 373 (M^+, 77), 359 (20), 358 (76), 343 (35), 342 (100), 330 (42), 285 (9), 222 (12); HRMS 373.1896 ($C_{21}H_{27}NO_5$ requires 373.1889); ^{1}H NMR 6.54 (s, H-1), 6.63 (s, H-4), 2.49 (d, *J* = 15.9 Hz, H-5), 3.17 (d, *J* = 15.9 Hz, H-5), 3.52 (dd, *J* = 5.3, 3.1 Hz, H-9), 2.65 (dd, *J* = 18.3, 5.8 Hz, H-10), 2.94 (d, *J* = 18.3 Hz, H-10), 3.06 (d, *J* = 3.1 Hz, H-14), 1.49 (ddd, *J* = 12.5, 3.4, 1.8 Hz, H-15), 1.90 (ddd, *J* = 12.5, 12.2, 4.9 Hz, H-15), 2.15 (ddd, *J* = 12.2, 11.9, 3.4 Hz, H-16), 2.48 (ddd, *J* = 11.9, 4.9, 1.8 Hz, H-16), 2.45 (s, NCH_3), 3.82 (s, 2-OCH_3), 3.81 (s, 3-OCH_3), 3.32 (s, 7-OCH_3), 4.01 (s, 8-OCH_3); ^{13}C NMR 110.48 (C-1), 147.48 (C-2), 147.36 (C-3), 108.08 (C-4), 49.36 (C-5), 193.43 (C-6), 137.82 (C-7), 162.64 (C-8), 53.23 (C-9), 23.90 (C-10), 129.34 (C-11), 129.25 (C-12), 37.20 (C-13), 48.51 (C-14), 39.20 (C-15), 46.52 (C-16), 42.94 (NCH_3), 56.03 (2-OCH_3), 55.76 (3-OCH_3), 60.69 (7-OCH_3), 60.71 (8-OCH_3).

14-Episinomenine (7): mp 101−103 °C (colorless prisms from acetone); $[\alpha]^{22}_D$ −55° (*c* = 0.36); IR 3400, 1682, 1630, 1611, 1487, 1284; UV 233sh (3.82), 270 (3.79); EIMS 329 (M^+, 75), 315 (21), 314 (100), 286 (13), 192 (22), 190 (10); HRMS 329.1683 ($C_{19}H_{23}NO_4$ requires 329.1627); ^{1}H NMR 6.66 (d, *J* = 8.6 Hz, H-1), 6.73 (d, *J* = 8.6 Hz, H-2), 2.67 (d, *J* = 17.6 Hz, H-5), 4.23 (d, *J* = 17.6 Hz, H-5), 5.76 (d, *J* = 2.1 Hz, H-8), 3.13 (dd, *J* = 6.1, 2.1 Hz, H-9), 2.84 (ddd, *J* = 18.0, 6.1, 0.9 Hz, H-10), 3.14 (d, *J* = 18.0 Hz, H-10), 2.97 (br s, H-14), 1.57 (ddd, *J* = 12.8, 3.1, 1.5 Hz, H-15), 2.19 (ddd, *J* = 12.8, 12.3, 4.8 Hz, H-15), 2.04 (ddd, *J* = 12.3, 11.9, 3.1 Hz, H-16), 2.41 (ddd, *J* = 11.9, 4.8, 1.5 Hz, Hz-16), 2.36 (s, NCH_3), 3.87 (s, 3-OCH_3), 3.71 (s, 7-OCH_3); ^{13}C NMR 118.67 (C-1), 109.01 (C-2), 144.70 (C-3), 143.77 (C-4), 48.30 (C-5),

194.74 (C-6), 151.11 (C-7), 119.81 (C-8), 57.99 (C-9), 27.50 (C-10), 130.65 (C-11), 127.04 (C-12), 38.20 (C-13), 42.03 (C-14), 28.18 (C-15), 47.15 (C-16), 43.20 (NCH_3), 56.21 (3-OCH_3), 54.86 (7-OCH_3).

FK-3000 (8): mp 160−161 °C (colorless needles from EtOAc); $[\alpha]^{22}_D$ −142° (*c* = 0.70); IR 3412, 1744, 1487, 1251; UV 285 (3.34); EIMS 417 (M^+, 7), 402 (10), 359 (27), 358 (100), 316 (7), 298 (10), 259 (14), 258 (37), 244 (11), 216 (10); HRMS 417.1772 ($C_{22}H_{27}NO_7$ requires 417.1784); ^{1}H NMR 6.62 (d, *J* = 8.3 Hz, H-1), 6.73 (d, *J* = 8.3 Hz, H-2), 2.35 (dd, *J* = 13.4, 13.4 Hz, H-5), 2.83 (dd, *J* = 13.4, 3.3 Hz, H-5), 5.20 (ddd, *J* = 13.4, 3.3, 3.3 Hz, H-6), 5.89 (dd, *J* = 3.3, 1.0 Hz, H-7), 4.38 (br d, *J* = 5.5 Hz, H-9), 2.96 (d, *J* = 17.4 Hz, H-10), 3.23 (ddd, *J* = 17.4, 6.4, 1.0 Hz, H-10), 1.91 (ddd, *J* = 12.2, 11.6, 4.8 Hz, H-15), 1.98 (ddd, *J* = 12.2, 3.5, 1.8 Hz, H-15), 2.69 (ddd, *J* = 13.9, 11.6, 3.5 Hz, H-16), 2.79 (ddd, *J* = 13.9, 4.8, 1.8 Hz, H-16), 3.87 (s, 3-OCH_3), 2.02 (s, 6-$OCOCH_3$), 2.04 (s, 7-$OCOCH_3$) 3.54 (s, 8-OCH_3); ^{13}C NMR 118.52 (C-1), 108.87 (C-2), 145.06 (C-3), 143.48 (C-4), 33.29 (C-5), 68.39 (C-6), 65.06 (C-7), 139.81 (C-8), 45.73 (C-9), 36.92 (C-10), 130.84 (C-11), 128.04 (C-12), 38.82 (C-13), 129.12 (C-14), 39.10 (C-15), 40.56 (C-16), 56.27 (3-OCH_3), 170.38 (6-O*C*OCH_3), 21.05 (6-OCO*C*H_3), 170.65 (7-O*C*OCH_3), 21.05 (7-OCO*C*H_3), 57.58 (8-OCH_3).

Sinoacutine (9): mp 190−192 °C (colorless needles from EtOAc); $[\alpha]^{22}_D$ −76° (*c* = 0.35); IR 3410, 1676, 1647, 1615, 1487, 1286; UV 241 (4.31), 278 (3.82); EIMS 327 (M^+, 100), 312 (57), 299 (29), 284 (34), 268 (11), 256 (10), 242 (11), 94 (16); HRMS 327.1473 ($C_{19}H_{21}NO_4$ requires 327.1470); ^{1}H NMR 6.67 (d, *J* = 8.2 Hz, H-1), 6.75 (d, *J* = 8.2 Hz, H-2), 7.55 (s, H-5), 6.33 (s, H-8), 3.69 (d, *J* = 5.8 Hz, H-9), 2.98 (ddd, *J* = 17.7, 5.8, 1.2 Hz, H-10), 3.33 (d, *J* = 17.7 Hz, H-10), 1.77 (ddd, *J* = 12.8, 3.1, 1.8 Hz, H-15), 2.37 (ddd, *J* = 12.8, 12.6, 4.6 Hz, H-15), 2.49 (ddd, *J* = 12.6, 12.5, 3.1 Hz, H-16), 2.61 (ddd, *J* = 12.5, 4.6, 1.8 Hz, H-16), 2.45 (s, NCH_3), 3.89 (s, 3-OCH_3), 3.75 (s, 6-OCH_3); ^{13}C NMR 118.84 (C-1), 109.47 (C-2), 145.35 (C-3), 143.33 (C-4), 120.46 (C-5), 150.99 (C-6), 181.49 (C-7), 122.19 (C-8), 61.05 (C-9), 32.64 (C-10), 129.80 (C-11), 123.98 (C-12), 43.68 (C-13), 161.63 (C-14), 37.76 (C-15), 47.03 (C-16), 41.69 (NCH_3), 56.30 (3-OCH_3), 54.86 (6-OCH_3).

Cepharamine (10): mp 187−188 °C (colorless prisms from ether); $[\alpha]^{22}_D$ −243° (*c* = 0.88); IR 3446, 1694, 1630, 1610, 1491, 1280; UV 258 (3.86); EIMS 329 (M^+, 41), 314 (26), 301 (18), 286 (42), 272 (21), 271 (24), 270 (100), 255 (28), 244 (23), 239 (22), 208 (30), 149 (17); HRMS 329.1633 ($C_{19}H_{23}NO_4$ requires 329.1627); ^{1}H NMR 6.59 (d, *J* = 8.2 Hz, H-1), 6.69 (d, *J* = 8.2 Hz, H-2), 2.49 (d, *J* = 16.8 Hz, H-5), 3.73 (d, *J* = 16.8 Hz, H-5), 5.62 (s, H-8), 1.78 (ddd, *J* = 14.0, 13.4, 4.7 Hz, H-10), 1.98 (ddd, *J* = 14.0, 5.0, 2.3 Hz, H-10), 2.58 (ddd, *J* = 16.2, 4.7, 2.3 Hz, H-11), 2.90 (ddd, *J* = 16.2, 13.4, 5.0 Hz, H-11), 2.00 (ddd, *J* = 13.7, 9.8, 3.1 Hz, H-15), 2.59 (ddd, *J* = 13.7, 9.1, 7.0 Hz, H-15), 2.36 (ddd, *J* = 9.8, 9.1, 7.0 Hz, H-16), 2.87 (ddd, *J* = 9.1, 9.1, 3.1 Hz, H-16), 2.41 (s, NCH_3), 3.85 (s, 3-OCH_3), 3.65 (s, 7-OCH_3); ^{13}C NMR 119.44 (C-1), 108.69 (C-2), 145.08 (C-3), 143.75 (C-4), 44.34 (C-5), 194.12 (C-6), 151.17 (C-7), 114.43 (C-8), 26.73 (C-9), 24.96 (C-10), 128.89 (C-11), 128.11 (C-12), 47.23 (C-13), 64.16 (C-14), 33.46 (C-15), 51.58 (C-16), 33.39 (NCH_3), 56.26 (3-OCH_3), 54.93 (7-OCH_3).

Aknadinine (11): amorphous powder; $[\alpha]^{22}_D$ −290° (*c* = 1.1); IR 3320, 1667, 1603, 1491, 1282; UV 232sh (3.92), 267 (4.02); EIMS 359 (M^+, 61), 344 (18), 328 (20), 316 (13), 302 (34), 301 (100), 300 (77), 285 (12), 270 (13), 269 (21), 259 (12), 244 (44), 231 (34), 230 (25), 229 (30); HRMS 359.1729 ($C_{20}H_{25}NO_5$ requires 359.1733); ^{1}H NMR 6.56 (d, *J* = 8.2 Hz, H-1), 6.66 (d, *J* = 8.2 Hz, H-2), 2.64 (d, *J* = 16.0 Hz, H-5), 3.50 (d, *J* = 16.0 Hz, H-5), 1.90 (ddd, *J* = 13.4, 11.3, 4.6 Hz, H-10), 2.15 (ddd, *J* = 13.4, 4.9, 4.9 Hz, H-10), 2.56 (ddd, *J* = 16.2, 4.9, 4.6 Hz, H-11), 2.79 (ddd, *J* = 16.2, 11.3, 4.9 Hz, H-11), 2.11 (ddd, *J* = 14.0, 9.5, 4.0 Hz, H-15), 2.47 (ddd, *J* = 14.0, 10.1, 6.4 Hz, H-15), 2.67 (ddd, *J* = 9.7, 9.5, 6.4 Hz, H-16), 2.83 (ddd, *J* = 10.1, 9.7, 4.0 Hz, H-16), 2.53 (s, NCH_3), 3.83 (s, 3-OCH_3), 3.65 (s, 7-OCH_3), 4.07 (s, 8-OCH_3); ^{13}C NMR 119.13 (C-1), 108.64 (C-2), 145.01 (C-3), 143.76 (C-4), 43.28 (C-5), 194.82 (C-6), 138.12 (C-7), 165.16 (C-8), 23.05 (C-9), 25.22 (C-10), 128.77 (C-11), 128.41 (C-12), 47.13 (C-13), 67.81 (C-14), 33.96 (C-15), 51.34 (C-16), 36.36 (NCH_3), 56.22 (3-OCH_3), 60.73 (7-OCH_3), 60.55 (8-OCH_3).

Aknadicine (12): mp 153−155 °C (colorless prisms from MeOH); $[\alpha]^{25}_D$ −231° (*c* = 0.70); IR 3420, 1661, 1607, 1487, 1280; UV 232sh (3.94), 268 (4.11); EIMS 345 (M^+, 41), 302 (21), 301 (100), 300 (59), 270 (28), 269 (42), 259 (11), 238 (10), 237 (31); HRMS 345.1609 ($C_{19}H_{23}NO_5$ requires 345.1576); ^{1}H NMR 6.59 (d, *J* = 8.2 Hz, H-1), 6.69 (d, *J* = 8.2 Hz, H-2), 2.50 (d, *J* = 16.8 Hz, H-5), 3.63 (d, *J* = 16.8 Hz, H-5), 1.82 (ddd, *J* = 13.4, 13.1, 5.2 Hz, H-10), 2.14 (ddd, *J* = 13.4, 4.9, 1.8 Hz, H-10), 2.61 (ddd, *J* = 17.0, 4.9, 1.8 Hz, H-11), 3.06 (ddd, *J* = 17.0, 13.1, 5.2 Hz, H-11), 2.17 (m, H-15), 2.64 (m, H-15), 2.84 (m, H-16), 2.86 (m, H-16), 3.85 (s, 3-OCH_3), 3.69 (s, 7-OCH_3), 4.13 (s, 8-OCH_3); ^{13}C NMR 119.48 (C-1), 108.82 (C-2), 144.99 (C-3), 143.69 (C-4), 42.86 (C-5), 194.42 (C-6), 136.92 (C-7), 164.96 (C-8), 26.63 (C-9), 24.96 (C-10), 128.23 (C-11), 128.12 (C-12), 45.36 (C-13), 66.97 (C-14), 34.52 (C-15), 42.21 (C-16), 56.22 (3-OCH_3), 60.61 (7-OCH_3), 61.25 (8-OCH_3).

Aknadilactam (13): amorphous powder; $[\alpha]^{28}_D$ −152° (*c* = 0.58); IR 3376, 1673, 1613, 1493, 1267; UV 268 (4.05); EIMS 373 (M^+, 100), 358 (31), 331 (15), 301 (32), 300 (35), 285 (22), 243 (11); HRMS 373.1522 ($C_{20}H_{23}NO_6$ requires 373.1523); ^{1}H NMR 6.57 (d, *J* = 8.2 Hz, H-1), 6.72 (d, *J* = 8.2 Hz, H-2), 2.79 (d, *J* = 16.8 Hz, H-5), 3.48 (d, *J* = 16.8 Hz, H-5), 2.17 (ddd, *J* = 14.1, 11.0, 5.4 Hz, H-10), 2.32 (ddd, *J* = 14.1, 5.1, 4.9 Hz, H-10), 2.64 (ddd, *J* = 16.8, 11.0, 4.9 Hz, H-11), 2.71 (ddd, *J* = 16.8, 5.1, 5.1 Hz, H-11), 2.76 (d, *J* = 17.1 Hz, H-15), 3.04 (d, *J* = 17.1 Hz, H-15), 2.96 (s, NCH_3), 3.85 (s, 3-OCH_3), 3.69 (s, 7-OCH_3), 4.11 (s, 8-OCH_3); ^{13}C NMR 119.36 (C-1), 109.66 (C-2), 145.24 (C-3), 143.90 (C-4), 41.52 (C-5), 192.86 (C-6), 137.15 (C-7), 160.76 (C-8), 25.01 (C-9), 25.06 (C-10), 127.83 (C-11), 123.90 (C-12), 42.70 (C-13), 67.90 (C-14), 40.47 (C-15), 174.42 (C-16), 28.16 (NCH_3), 56.22 (3-OCH_3), 60.64 (7-OCH_3), 60.95 (8-OCH_3).

***N*-Methylation of 8.** A solution of **8** (210 mg) and 35% aqueous HCHO (0.5 mL) in MeOH (5 mL) was stirred for 30 min at 60 °C, and $NaBH_4$ (100 mg) was added to the solution under ice cooling. After 30 min, the solution was diluted with H_2O and extracted with CH_2Cl_2. The extract was washed with H_2O, dried over Na_2SO_4, and evaporated *in vacuo*. The residue was subjected to preparative TLC [with EtOAc−Et_2NH (9:1)] to afford **4** (196 mg, 90.3%), which was found to be

identical with an authentic sample by comparison of TLC, HPLC, $[\alpha]_D$, IR, and ^{1}H NMR.

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