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NEW INDOLE ALKALOIDS FROM *ERVATAMIA CUMINGIANA*

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Abstract – Two new *iboga*-vobasine-type bisindole alkaloids *N*-demethylervahanine A (**1**) and *N*-demethylervahanine B (**2**) and one new chippine-type alkaloid 3-*O*-methyl-10,11-demethoxychippine (**3**) were isolated from the roots of *Ervatamia cumingiana* collected in Thailand. Their chemical structures were determined by spectroscopic analyses. Compounds **1** and **2** are bisindole alkaloids having a linkage between C-3 in the vobasine unit and C-11' or C-10' in the *Iboga* unit, respectively.

INTRODUCTION

*Ervatamia cumingiana*¹ (*Tabernaemontana pandacaqui*)² is an apocynaceous plant that is widely distributed in Southeast Asia and Oceania. This plant has been used in folk medicine in Thailand for the treatment of toothache, pain, and inflammation. Plants belonging to genera *Ervatamia* and *Tabernaemontana* contain monoterpenoid indole and bisindole alkaloids.³ As part of our continuous

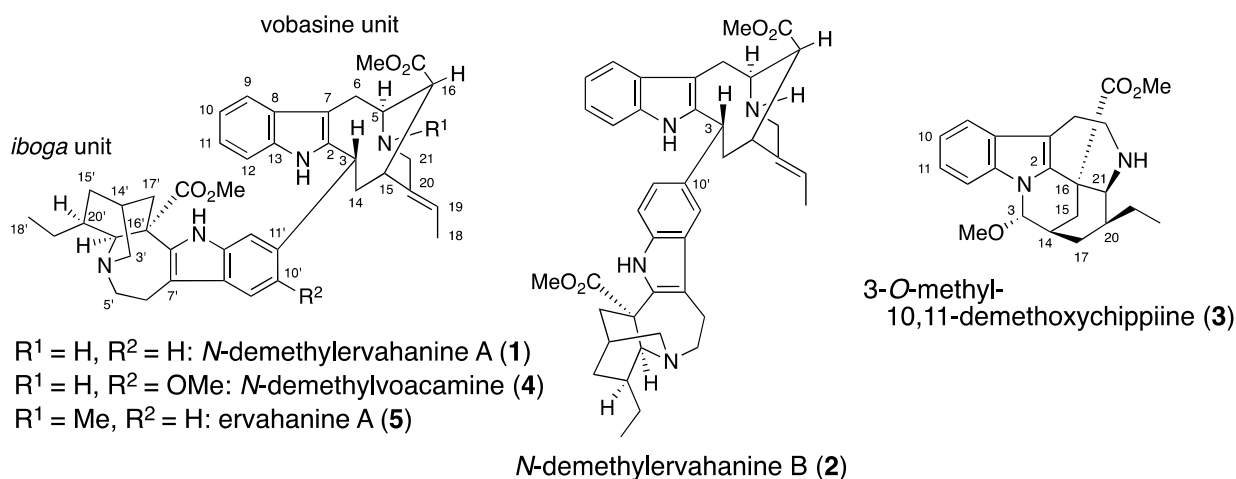


Figure 1. Structures of new (**1–3**) and known (**4, 5**) alkaloids isolated from *Ervatamia cumingiana*

chemical studies on new and bioactive alkaloids,⁴ we isolated two new *iboga-vobasine*-type bisindole alkaloids **1** and **2** and one new *chippiine*-type alkaloid **3** together with eleven known alkaloids from the roots of *E. cumingiana* collected in Thailand (Figure 1). The structure elucidation of new alkaloids **1–3** based on spectroscopic analyses and electronic circular dichroism (ECD) calculations is reported herein.

RESULTS AND DISCUSSION

Alkaloid **1** was found to have the molecular formula $C_{41}H_{48}N_4O_4$ from HRESIMS (m/z 661.3746 $[M+H]^+$), indicating that **1** was a bisindole alkaloid (Figure 2). Its UV spectrum exhibited absorption bands characteristic of an indole chromophore. Its 1H NMR spectrum (Table 1) showed signals for two indole NH protons [δ_H 7.68, 7.45 (each br s)], seven aromatic protons [δ_H 7.58 (br d, $J = 6.9$ Hz, H-9), 7.38 (d, $J = 7.5$ Hz, H-9'), 7.07–7.03 (3H, overlapped), 7.02 (s, H-12'), 6.98 (d, $J = 7.5$ Hz, H-10')], one ethylidene group [δ_H 5.29 (q, $J = 6.5$ Hz, H-19), 1.64 (3H, d, $J = 6.5$ Hz, H₃-18)], two carbomethoxy groups [δ_H 3.69, 2.47 (each 3H, s)], one ethyl group [δ_H 1.55 (m, H-19'), 1.42 (m, H-19'), 0.88 (3H, dd, $J = 6.2, 6.2$ Hz, H₃-18')], and a low-field shifted proton at δ_H 4.64 (br d, $J = 12.4$ Hz, H-3). One of the methyl esters was shielded (δ_H 2.47), suggesting that the ester was positioned above the aromatic ring. The ^{13}C NMR and HMQC spectral data revealed the presence of two ester carbonyl carbons (δ_C 175.4, 171.5), two indole systems, and one ethylidene group (δ_C 139.8, 117.7, 12.2). These spectral data were similar to those of *N*-demethylvobasine (**4**)⁵ and ervahanine A (**5**),⁶ two coexisting *iboga-vobasine*-type bisindole alkaloids with a linkage between C-3 in the vobasine unit and C-11' in the *iboga* unit. Differences included the absence of a methoxy group relative to **4** and the absence of an *N*-methyl group relative to **5**, respectively. HMBC correlations between the aromatic protons of H-10' (δ_H 6.98) and H-12' (δ_H 7.02) and C-3 (δ_C 45.3) and between H-3 (δ_H 4.64) and the aromatic carbons of C-10' (δ_C 119.5) and C-12' (δ_C 109.3) indicated the presence of a linkage between C-3 in the vobasine unit and C-11' in the *iboga* unit. The *E* configuration of the ethylidene group in the vobasine unit was confirmed by the NOE correlation of H-19 to H-21. The NOE correlations of H-3 to NH and H-15 suggested that H-3 was β -oriented. The

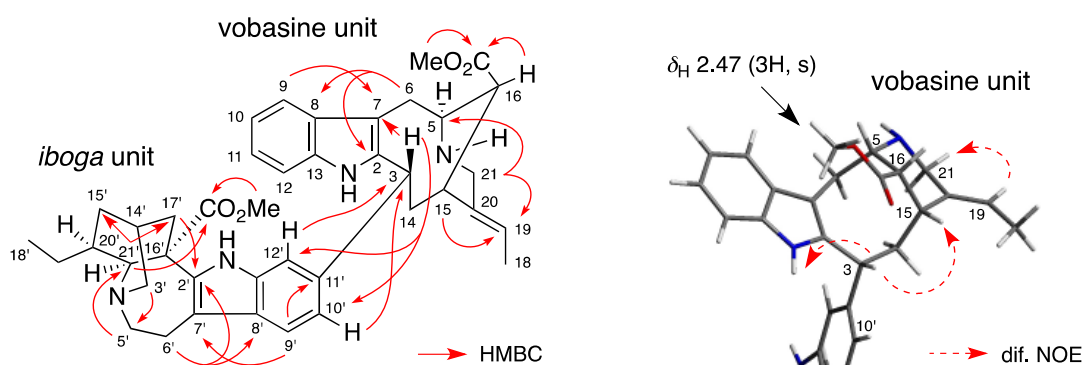


Figure 2. Selected HMBC and NOE correlations for *N*-demethylervahanine A (**1**)

configuration of C-20' in the *iboga* unit was confirmed by the NOE correlation of H-17' to H-20'. From these data, alkaloid **1** was deduced to be *N*-demethylervahanine A.

Table 1. ^1H and ^{13}C NMR data for **1** and **2** in CDCl_3

position	1		2	
	$\delta_{\text{H}}^{\text{a}}$	$\delta_{\text{C}}^{\text{b}}$	$\delta_{\text{H}}^{\text{a}}$	$\delta_{\text{C}}^{\text{b}}$
2		137.3		137.4
3	4.64 (br d, 12.4)	45.3	4.67 (dd, 13.1, 1.4)	45.4
5	4.24 (br dd, 9.6, 9.6)	53.3	4.21 (br dd, 8.3, 8.3)	53.4
6	3.66 (m)	24.6	3.70 (dd, 15.1, 11.0)	24.7
	3.36-3.33 (overlapped)		3.34-3.30 (overlapped)	
7		110.7		110.8
8		129.7		129.8
9	7.58 (br d, 6.9)	117.8	7.58 (d, 6.9)	117.7
10	7.07-7.03 (overlapped)	119.1	7.08-7.02 (overlapped)	119.0
11	7.07-7.03 (overlapped)	121.8	7.08-7.02 (overlapped)	121.6
12	7.07-7.03 (overlapped)	109.8	7.08-7.02 (overlapped)	110.0
13		135.9		135.9
14	2.77-2.73 (overlapped)	38.99	2.80-2.78 (overlapped)	39.2
	1.99 (m)		1.97 (ddd, 15.2, 6.9, 2.8)	
15	3.83 (br dd, 9.6, 9.6)	34.2	3.84 (m)	34.2
16	2.58 (br s)	50.0	2.56-2.55 (overlapped)	50.3
17				
18	1.64 (3H, d, 6.5)	12.2	1.63 (3H, dd, 6.4, 1.4)	12.1
19	5.29 (q, 6.5)	117.7	5.26 (q, 6.4)	117.3
20		139.8		140.2
21	4.05 (d, 14.5)	44.1	4.05 (d, 14.5)	44.3
	3.18-3.10 (overlapped)		3.20-3.11 (overlapped)	
CO ₂ Me	2.47 (3H, s)	50.0	2.46 (3H, s)	49.9
CO ₂ Me		171.5		171.7
NH	7.45 (br s)		7.45 (br s)	
2'		136.8		137.3
3'	2.87 (br d, 7.6)	51.7	2.96-2.90 (overlapped)	51.5
	2.77-2.73 (overlapped)		2.80-2.78 (overlapped)	
5'	3.36-3.33 (overlapped)	53.0	3.34-3.30 (overlapped)	53.1
	3.18-3.10 (overlapped)		3.20-3.11 (overlapped)	
6'	3.18-3.10 (overlapped)	22.1	3.20-3.11 (overlapped)	22.1
	2.97 (m)		2.96-2.90 (m)	
7'		110.3		110.3
8'		127.6		128.9
9'	7.38 (d, 7.5)	118.7	7.30 (br s)	117.1
10'	6.98 (d, 7.5)	119.5		136.9
11'		139.8	6.99 (dd, 8.3, 1.4)	122.1
12'	7.02 (s)	109.3	7.14 (d, 8.3)	110.8
13'		135.6		134.2
14'	1.83 (br s)	27.3	1.87-1.85 (overlapped)	27.3
15'	1.70 (br dd, 10.9, 10.9)	32.0	1.72 (br dd, 11.7, 11.7)	32.0
	1.10 (br dd, 10.9, 7.6)		1.12 (br dd, 11.7, 6.9)	
16'		55.0		55.1
17'	2.52 (br d, 11.7)	36.4	2.56-2.55 (overlapped)	36.5
	1.82 (br d, 11.7)		1.87-1.85 (overlapped)	
18'	0.88 (3H, dd, 6.2, 6.2)	11.6	0.88 (3H, dd, 6.9, 6.9)	11.6
19'	1.55 (m)	26.7	1.54 (m)	26.7
	1.42 (m)		1.43 (m)	
20'	1.30 (m)	39.04	1.30 (m)	39.1
21'	3.52 (s)	57.2	3.51 (s)	57.4
CO ₂ Me'	3.69 (3H, s)	52.5	3.67 (3H, s)	52.5
CO ₂ Me'		175.4		175.6
N'H	7.68 (br s)		7.72 (br s)	

^a 600 MHz, ^b 150 MHz.

Alkaloid **2** was found to have the same molecular formula $C_{41}H_{48}N_4O_4$ as **1** from HRESIMS (m/z 661.3747 $[M+H]^+$) (Figure 3). Its 1H NMR spectrum (Table 1) showed signals for two indole NH protons [δ_H 7.72, 7.45 (each br s)], seven aromatic protons, one ethylidene group [δ_H 5.26 (q, $J = 6.4$ Hz, H-19), 1.63 (3H, dd, $J = 6.4, 1.4$ Hz, H₃-18)], two carbomethoxy groups [δ_H 3.67, 2.46 (each 3H, s)], one ethyl group [δ_H 1.54 (m, H-19'), 1.43 (m, H-19'), 0.88 (3H, dd, $J = 6.9, 6.9$ Hz, H₃-18')], and a low-field shifted proton at δ_H 4.67 (dd, $J = 13.1, 1.4$ Hz, H-3). The ^{13}C NMR spectral data revealed the presence of two ester carbonyl carbons (δ_C 175.6, 171.7), two indole systems, and one ethylidene group (δ_C 140.2, 117.3, 12.1). The 1H and ^{13}C NMR data were similar to those of *N*-demethylervahanine A (**1**) and ervahanine B⁶ that had a C-3–C-10' linkage. Differences included the pattern of the aromatic region relative to **1** and the lack of an *N*-methyl signal in **2** relative to ervahanine B. HMBC correlations between the aromatic protons of H-9' (δ_H 7.30) and H-11' (δ_H 6.99) and C-3 (δ_C 45.4) and between H-3 (δ_H 4.67) and the carbons of C-9' (δ_C 117.1) and C-11' (δ_C 122.1) indicated the presence of a linkage between C-3 in the vobasine unit and C-10' in the *iboga* unit. The configuration of the *E*-ethylidene group and the β -oriented H-3 in the vobasine unit was confirmed by the NOE correlation of H-19 to H-21 and of H-3 to H-15. From these data, alkaloid **2** was deduced to be *N*-demethylervahanine B.

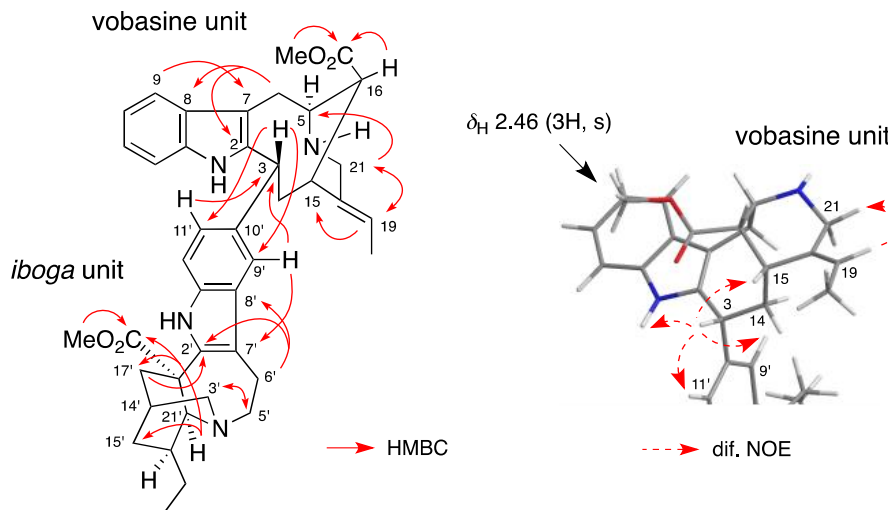


Figure 3. Selected HMBC and NOE correlations for *N*-demethylervahanine B (**2**)

The absolute configurations of **1** and **2** were deduced to be identical with those of ervahanines⁷ based on the similar CD spectra with a positive Cotton effect at around 240 nm and a negative Cotton effect at around 225 nm, respectively.

Alkaloid **3** was found to have the molecular formula $C_{22}H_{28}N_2O_3$ from HRESIMS (m/z 369.2161 $[M+H]^+$) (Figure 4). Its UV spectrum exhibited absorption bands characteristic of an indole chromophore. Its 1H NMR spectrum showed signals for four aromatic protons [δ_H 7.51 (d, $J = 7.5$ Hz, H-9), 7.41 (d, $J = 7.5$ Hz,

H-12), 7.22 (dd, $J = 7.5, 7.5$ Hz, H-11), 7.16 (dd, $J = 7.5, 7.5$ Hz, H-10)], one carbomethoxy group [δ_{H} 3.72 (3H, s)], one methoxy group [δ_{H} 3.62 (3H, s)], and one ethyl group [δ_{H} 1.38 (m, H-19), 0.94 (dq, $J = 13.9, 7.1$ Hz, H-19), 0.91 (3H, dd, $J = 7.1, 7.1$ Hz, H₃-18)]. In addition, a low-field shifted proton at δ_{H} 5.07 (d, $J = 2.3$ Hz, H-3) and a high-field shifted proton at δ_{H} 0.30 (ddd, $J = 14.2, 14.2, 7.2$ Hz, H-15) were observed. The ^{13}C NMR spectral data revealed the presence of an ester carbonyl carbon (δ_{C} 176.7) and a carbon that was expected to bear two heteroatoms at δ_{C} 86.9 (C-3). These data and the HMBC correlations between the methoxy protons and the carbon at δ_{C} 86.9 and between the proton at δ_{H} 5.07 and the carbons of C-2 (δ_{C} 132.0) and C-13 (δ_{C} 138.2) suggested that **3** was a 3-*O*-methyl derivative of a known chippiine-type alkaloid, 10,11-demethoxychippiine (**6**).⁸ The relative configuration at C-14, C-16, and C-21 was restricted as shown in Figure 4 because of the rigid character of the ring system. The relative configurations at C-3 and C-20 were deduced from the NOE correlations of H-3 to H-12 and H-15 and of H-20 (δ_{H} 1.85) to H-17 (δ_{H} 2.00), respectively. The absolute configuration of **3** was 3*S*, 14*R*, 16*S*, 20*S*, and 21*S* by comparison of the experimental and calculated ECD spectra. From these data, alkaloid **3** was deduced to be 3-*O*-methyl-10,11-demethoxychippiine.

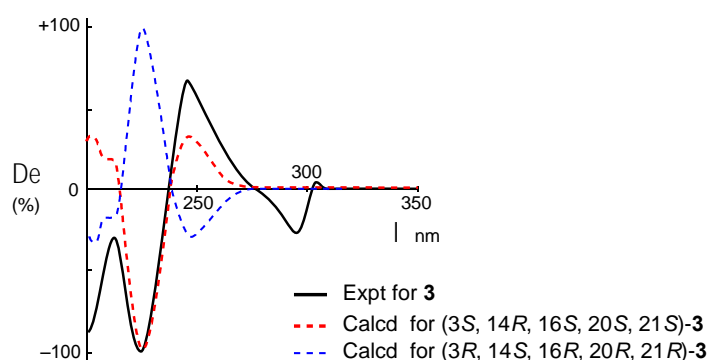
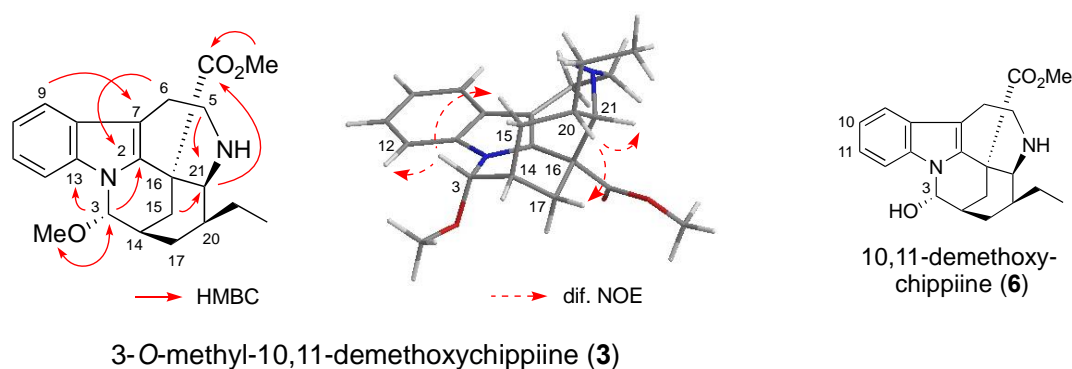


Figure 4. Selected HMBC and NOE correlations for 3-*O*-methyl-10,11-demethoxychippiine (**3**), experimental and calculated ECD spectra for **3**, and structure of 10,11-demethoxychippiine (**6**)

In conclusion, two new *iboga*-vobasine-type bisindole alkaloids *N*-demethylervahanine A (**1**) and *N*-demethylervahanine B (**2**) and one new chippiine-type alkaloid 3-*O*-methyl-10,11-demethoxychippiine

(3) were isolated from the roots of *Ervatamia cumingiana* collected in Thailand. Compounds **1** and **2** are bisindole alkaloids having a linkage between C-3 in the vobasine unit and C-11' or C-10' in the *iboga* unit, respectively. Biological evaluation of the alkaloids is underway.

EXPERIMENTAL

General. UV spectra were recorded in MeOH on a JASCO V-560 instrument. ^1H and ^{13}C NMR spectra were recorded on JEOL JNM ECZ600, JEOL JNM ECA600, and JEOL JNM ECP-600 at 600 MHz (^1H) or 150 MHz (^{13}C), respectively. ESIMS and HRESIMS spectra were recorded on JEOL JMS-T100GCV (AccuTOF GCv) or JEOL JMS-T100LP (AccuTOF LC-plus). Optical rotation was measured with a JASCO P-1020 or DIP-100 polarimeter. ECD was measured with JASCO J-1100 or JASCO J-720WI. TLC was performed on precoated silica gel 60 F254 plates (Merck, 0.25 mm thick) and precoated amino-silica gel plates (Fuji Silysia Chemical). Column chromatography was carried out on silica gel 60 [Kanto Chemical, 40–50 μm (for flash chromatography)] and Chromatorex NH [Fuji Silysia Chemical, 100–200 mesh (for amino-silica gel column chromatography)]. Medium pressure liquid chromatography (MPLC) was performed using C.I.G. prepacked column CPS-HS-221-05 (Kusano Kagakukikai, SiO_2).

Plant material. The roots of *Ervatamia cumingiana* were collected at Hat Yai district, Songkhla province in Thailand in 1992. A voucher specimen (No. 002-2535) was deposited at the Faculty of Traditional Thai Medicine, Prince of Songkla University, Thailand.

Extraction and Isolation. The roots (485 g, dry weight) of *E. cumingiana* were extracted with MeOH (3.5 L, twice at room temperature and twice under reflux) to give the extract (41.26 g). The MeOH extract was dissolved in H_2O and the whole was extracted with EtOAc (0.9 L) to give the EtOAc extract (7.13 g). The aqueous layer was extracted with 5% MeOH/ CHCl_3 (0.9 L) and *n*-BuOH (0.9 L) to afford the 5% MeOH/ CHCl_3 extract (1.14 g) and the *n*-BuOH extract (7.69 g), respectively. The EtOAc extract (7.13 g) was separated by silica gel flash column chromatography with an EtOAc/*n*-hexane gradient (frs. A1–4, 10% EtOAc/*n*-hexane; frs. A5–8, 30% EtOAc/*n*-hexane; frs. A9–12, 50% EtOAc/*n*-hexane; fr. 13, EtOAc) and MeOH (fr. 14) to give 14 fractions: frs. A1–2 (9.2 mg), fr. A3 (1465 mg), fr. A4 (533.5 mg), fr. A5 (22.6 mg), fr. A6 (12.6 mg), fr. A7 (604.4 mg), fr. A8 (281.4 mg), fr. A9 (374.5 mg), fr. A10 (247.1 mg), fr. A11 (269.0 mg), fr. A12 (207.7 mg), fr. A13 (1200 mg), and fr. A14 (1679 mg). The fractions were purified by repeated chromatography to afford two new alkaloids **1** and **2** along with eight known alkaloids. Fr. A14 was separated by silica gel flash column chromatography with a MeOH/ CHCl_3 gradient to give seven fractions (frs. A14A–G). The MeOH eluate (fr. A14G, 270.5 mg) was purified by silica gel flash column chromatography with a MeOH/ CHCl_3 gradient to yield three fractions (frs. A14G1–3). The 8–10% MeOH/ CHCl_3 eluate (fr. A14G2, 41.6 mg) was subjected to repeated

chromatography, including MPLC (SiO₂) with MeOH/EtOAc/*n*-hexane = 1:4:5 and 1:9:0 and amino-silica gel chromatography with 8–10% EtOH/*n*-hexane and MeOH, to yield *N*-demethylervahanine A (**1**, 2.5 mg). Separation of fr. A14G3 (MeOH eluate, 199.2 mg) by repeated chromatography, including silica gel flash column chromatography with MeOH/CHCl₃/*n*-hexane = 1:6:3~2:6:3 and amino-silica gel open column chromatography with EtOAc, gave *N*-demethylervahanine B (**2**, 7.3 mg). Additional *N*-demethylervahanine A (**1**, 4.5 mg) was obtained by purification of frs. A14F (20% MeOH/CHCl₃ eluate, 267.9 mg), A14G2, and A14G3. The known alkaloids isolated from the EtOAc extract were coronaridine (17.3 mg), voacangine (18.4 mg), 3-oxocoronaridine (35.9 mg), 5-oxocoronaridine (1.3 mg), coronaridine hydroxyindolenine (18.0 mg), sitsirikine (0.9 mg), *N*-demethylvoacamine (**4**, 29.6 mg), and ervahanine A (**5**, 1.2 mg). The MeOH/CHCl₃ extract (1.14 g) was separated by silica gel flash column chromatography with a MeOH/CHCl₃ gradient to give seven fractions: fr. B1, 1% MeOH/CHCl₃ (96.7 mg); fr. B2, 2% MeOH/CHCl₃ (105.8 mg); fr. B3, 3% MeOH/CHCl₃ (41.1 mg); fr. B4, 5% MeOH/CHCl₃ (280.6 mg); fr. B5, 10% MeOH/CHCl₃ (250.9 g); fr. B6, 20% MeOH/CHCl₃ (187.8 g); and fr. B7, MeOH (177.9 mg). The fractions were purified by repeated chromatography to afford new alkaloid **3** along with six known alkaloids. Fr. B5 was purified by silica gel flash column chromatography with a MeOH/EtOAc gradient to afford seven fractions (frs. B5A–G). The 5% MeOH/EtOAc eluate (fr. B5C, 14.2 mg) was separated by silica gel flash column chromatography with 5% MeOH/CHCl₃ and amino-silica gel open column chromatography with 20% EtOAc/*n*-hexane to yield 3-*O*-methyl-10,11-demethoxychippiine (**3**, 0.6 mg). The known alkaloids isolated from the MeOH/CHCl₃ extract were coronaridine (234.8 mg), ibogamine (2.4 mg), 3-oxocoronaridine (3.5 mg), coronaridine hydroxyindolenine (1.8 mg), pleiocarpamine (2.5 mg), and pandine (1.4 mg).

***N*-Demethylervahanine A (1):** Colorless amorphous solid; $[\alpha]_D^{24} -90.8$ (*c* 0.08, MeOH); UV (MeOH) λ_{\max} nm 293.5, 286.5, 232.5; ¹H and ¹³C NMR data, see Table 1; HRESIMS *m/z* 661.3746 [M+H]⁺ (calcd for C₄₁H₄₉N₄O₄ 661.3754); ECD (MeOH, 23 °C, *c* = 0.20 mmol/L) $\Delta\epsilon$ (λ nm) 0 (331), -13.8 (301), -1.8 (295), -7.6 (291), -4.6 (287), -6.6 (280), 0 (264), +51.3 (241), 0 (234), -78.9 (224), 0 (202).

***N*-Demethylervahanine B (2):** Colorless amorphous solid; $[\alpha]_D^{25} -122$ (*c* 0.1, MeOH); UV (MeOH) λ_{\max} nm 293.0, 287.5, 231.5; ¹H and ¹³C NMR data, see Table 1; HRESIMS *m/z* 661.3747 [M+H]⁺ (calcd for C₄₁H₄₉N₄O₄ 661.3754); ECD (MeOH, 24 °C, *c* = 0.20 mmol/L) $\Delta\epsilon$ (λ nm) 0 (327), -8.1 (301), 0 (268), +10.3 (242), 0 (234), -27.0 (224), 0 (202).

3-*O*-Methyl-10,11-demethoxychippiine (3): Colorless amorphous solid; $[\alpha]_D^{23} -7.9$ (*c* 0.07, CHCl₃); UV (MeOH) λ_{\max} nm 292.0 (sh), 282.5, 224.5; ¹H NMR (600 MHz, CDCl₃) δ ppm 7.51 (1H, d, *J* = 7.5 Hz,

H-9), 7.41 (1H, d, $J = 7.5$ Hz, H-12), 7.22 (1H, dd, $J = 7.5, 7.5$ Hz, H-11), 7.16 (1H, dd, $J = 7.5, 7.5$ Hz, H-10), 5.07 (1H, d, $J = 2.3$ Hz, H-3), 4.00 (1H, d, $J = 6.4$ Hz, H-21), 3.72 (3H, s, CO₂Me), 3.62 (3H, s, OMe), 3.20 (1H, m, H-5), 2.99 (1H, m, H-6), 2.73–2.65 (3H, overlapped, H-5, H-6, H-14), 2.48 (1H, d, $J = 13.0$ Hz, H-17), 2.00 (1H, dd, $J = 13.0, 5.0$ Hz, H-17), 1.85 (1H, m, H-20), 1.53 (1H, m, H-15), 1.38 (1H, m, H-19), 0.94 (1H, dq, $J = 13.9, 7.1$ Hz, H-19), 0.91 (3H, dd, $J = 7.1, 7.1$ Hz, H₃-18), 0.30 (1H, ddd, $J = 14.2, 14.2, 7.2$ Hz, H-15); ¹³C NMR (150 MHz, CDCl₃) δ ppm 176.7 (CO₂Me), 138.2 (C-13), 132.0 (C-2), 129.0 (C-8), 121.9 (C-11), 120.5 (C-10), 118.4 (C-9), 109.9 (C-7, C-12), 86.9 (C-3), 59.0 (C-21), 56.2 (OMe), 53.0 (CO₂Me), 49.1 (C-16), 40.5 (C-5), 36.1 (C-20), 31.6 (C-14), 24.4 (C-17, C-19), 24.1 (C-15), 22.8 (C-6), 12.5 (C-18); HRESIMS m/z 369.2161 [M+H]⁺ (calcd for C₂₂H₂₉N₂O₃ 369.2178); ECD (MeOH, 23 °C, $c = 0.03$ mmol/L) $\Delta\epsilon$ (λ nm) 0 (303), -0.7 (293), 0 (273), +1.6 (246), 0 (239), -2.4 (226), -0.8 (213).

ECD Computational Calculations for 3. A conformational search of (3*S*, 14*R*, 16*S*, 20*S*, 21*S*)-**3** was carried out by employing the procedure implemented in CONFLEX7 software⁹ under the MMFF94s force field (dielectric constant: 32.6).¹⁰ Fourteen low-energy conformers within 5 kcal/mol energy were selected from among 26 conformers. The selected conformers were optimized with DFT calculations at the CAM-B3LYP/6-31G (d, p) level with a CPCM solvent model in MeOH using the Gaussian 16 package.¹¹ TDDFT CD calculations for the optimized conformers were performed at the CAM-B3LYP/6-31G (d, p) level with a CPCM solvent model in MeOH. The calculated UV/ECD spectra were simulated and generated with a half-bandwidth δ/γ of 0.29 eV by SpecDis 1.63 software.¹² The ECD spectrum was weighted by using the Boltzmann distribution after UV correction (UV shift: +21 nm). The calculated ECD spectrum of (3*R*, 14*S*, 16*R*, 20*R*, 21*R*)-**3** was obtained in a similar way.

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