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Note

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A Cyclopeptide and a Tetrahydroisoquinoline Alkaloid from *Ophiorrhiza nutans*

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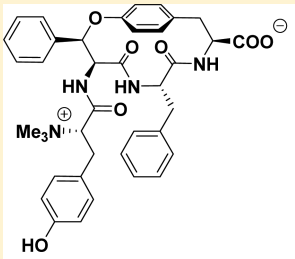
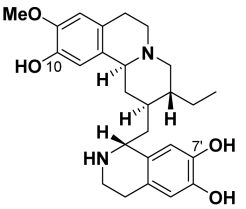
Supporting Information

ABSTRACT: A new cyclopeptide, ophiorrhisine A (**1**), a new tetrahydroisoquinoline alkaloid, 7′,10-dide-*O*-methylcephaeline (**2**), two known *β*-carboline alkaloids, and four known tetrahydroisoquinoline alkaloids were isolated from *Ophiorrhiza nutans* (Rubiaceae). Compound **1** is a tetrapeptide possessing a 14-membered paracyclophane ring and a novel *N,N,N*-trimethyltyrosine residue in the side chain. The stereochemistry at the aryl−alkyl ether bond was different from that of other known 14-membered paracyclophanes. The structure of **2** was established by spectroscopic analysis and semisynthesis.



Ophiorrhisine A (**1**)



7′,10-Dide-*O*-methylcephaeline (**2**)

Ophiorrhiza plants belonging to Rubiaceae are known to produce diverse monoterpenoid indole alkaloids such as camptothecins[1] having potent antitumor activity as well as *β*-carboline-type alkaloids.[2] Our studies on the constituents of *Ophiorrhiza* plants distributed in Japan[3] and Thailand[4] have resulted in the isolation of new camptothecin-related and/or *β*-carboline-type alkaloids. In the course of our studies of new biologically active natural products,[5] a chemical investigation of the alkaloids in *Ophiorrhiza nutans* collected in Thailand led to the isolation of a new cyclopeptide, ophiorrhisine A (**1**), and a new tetrahydroisoquinoline alkaloid, 7′,10-dide-*O*-methylcephaeline (**2**), together with two known indole alkaloids and four known tetrahydroisoquinoline alkaloids. Herein, the structure elucidation of these alkaloids is reported.

The dried whole plants of *O. nutans* were powdered and then extracted with MeOH. The MeOH-soluble part of the extract was separated by Sephadex LH-20 column chromatography with MeOH/H_2O. The 50% MeOH/H_2O-soluble fraction was purified by flash silica gel, reversed-phase, and amino-silica gel chromatography to afford **1** and **2**, together with the two known indole alkaloids and four known tetrahydoisoquinoline alkaloids: 5-carboxystrictosidine;[6] lyaloside;[7] demethylalangiside;[8] alangiside;[8] isoalangiside;[8] and 10-*O*-demethylprotoemetine.[9] This is only the second demonstration that monoterpenoid indole alkaloids and monoterpenoid isoquinoline alkaloids coexist in a plant species.[8] Furthermore, from a chemotaxonomical point of view, it is noteworthy that this is the first isolation of tetrahydroisoquinoline alkaloids from the genus *Ophiorrhiza*.

Compound **1**, named ophiorrhisine A, is a colorless solid having the molecular formula $C_{39}H_{42}N_4O_7$ based on its HRESIMS data (calcd 679.3132 $[M + H]^+$; found *m/z* 679.3131 $[M + H]^+$) (Figure 2). Its UV spectrum exhibited absorptions at 205, 228, and 278 nm, indicating the presence of phenyl and phenolic groups. The IR spectrum showed the presence of hydroxy [3380 (br) cm^{-1}], amine (3351 cm^{-1}), amide (1692 and 1656 cm^{-1}), and carboxylate[10] (1454 and 1387 cm^{-1}) functionalities. The ^1H NMR data acquired in methanol-d_4 (Table 1) showed signals for 18 aromatic protons [δ_H 7.61 (2H, d), 7.37 (2H, dd), 7.29 (dd), 7.24 (2H, dd), 7.20 (2H, d), 7.15 (dd), 7.11 (dd), 6.86 (dd), 6.79 (dd), 6.77 (2H, d), 6.75 (dd), 6.58 (2H, d)]; four *α*-amino methines [δ_H 5.03 (d), 4.67 (dd), 4.18 (dd), 3.95 (dd)]; one oxymethine [δ_H 5.77 (d)]; three methylenes [δ_H 3.45 (dd, J = 13.1, 6.2 Hz), 2.53 (dd, J = 13.1, 11.7 Hz); 3.07 (dd, J = 13.8, 3.4 Hz), 3.02 (dd, J = 13.8, 9.6 Hz); 2.93 (dd, J = 13.8, 4.8 Hz), 2.66 (dd, J = 13.8, 9.6 Hz)]; and three equivalent *N*-methyls [δ_H 2.70 (9H, s)]. The ^{13}C NMR data (Table 1) showed signals for four deshielded carbons assignable to amide or hydroxycarbonyl carbons (δ_C 178.4, 171.3, 167.0, 166.7); 24 aromatic carbons, that is, two oxygenated tertiary aromatic carbons (δ_C 159.4, 158.0), four quaternary carbons (δ_C 140.5, 138.7, 135.1, 125.5), and 18 tertiary carbons [δ_C 132.6, 131.5 (3C), 130.5 (2C), 129.4 (4C), 128.8, 127.6, 127.1 (2C), 122.5, 119.7, 117.0 (2C)]; eight tertiary carbons connected to oxygen or nitrogen

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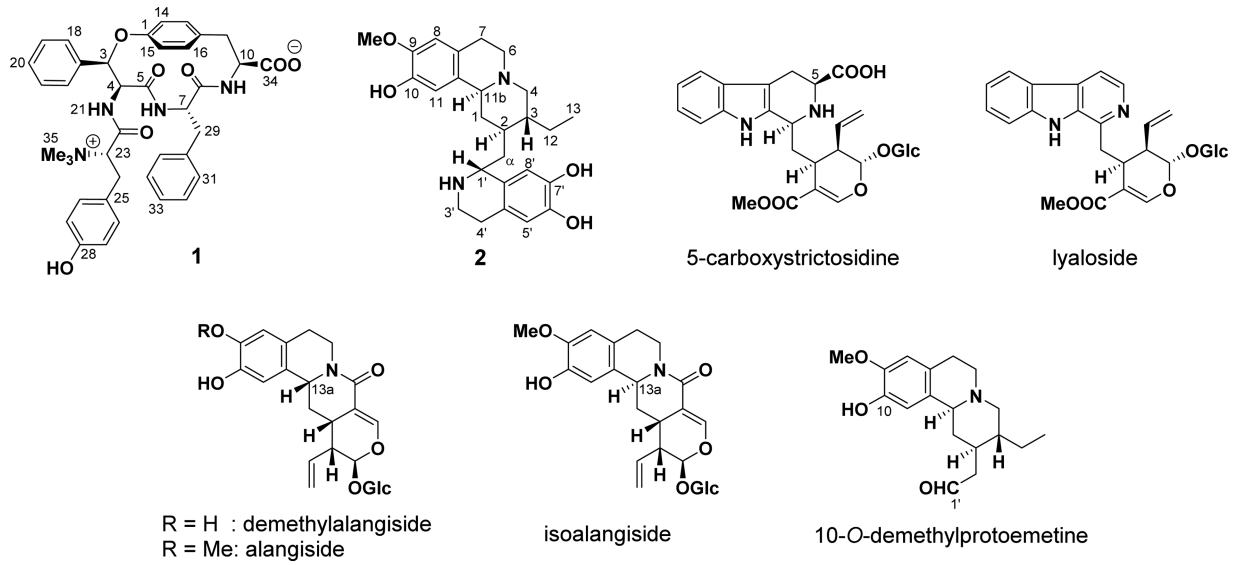

Figure 1. Structures of new compounds **1** and **2** and known alkaloids.

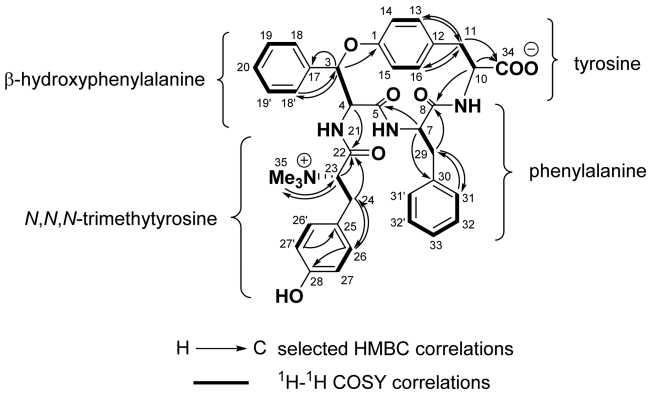

Figure 2. Structure and selected COSY and HMBC correlations of ophiorrhisine A (**1**).

[δ_C 86.4, 77.1, 57.9, 57.4, 55.5, 52.6 (3C)]; and three secondary carbons [δ_C 40.1 (2C), 33.1]. These NMR values indicated that **1** is an alkaloidal peptide possessing four amino acid units comprising two phenylalanine and two tyrosine residues. Further analysis of the 2D NMR spectroscopic data of **1** (Table 1 and Figure 2) revealed that **1** also contained a cyclopeptide consisting of a 14-membered cyclophane, a *β*-hydroxyphenylalanine connected to a tyrosine fragment via an aryl−alkyl ether bridge (vide infra), and an *N,N,N*-trimethyltyrosine residue.

In the ^{1}H−^{1}H COSY spectrum (Figure 2), correlations from H-18/18′ [δ_H 7.61 (2H, d, J = 8.3 Hz)] to H-20 [δ_H 7.29 (dd, J = 7.6, 7.6 Hz)] through H-19/19′ [δ_H 7.37 (2H, dd, J = 8.3, 7.6 Hz)] confirmed the presence of a phenyl moiety. H-3 [δ_H 5.77 (d, J = 2.1 Hz)] showed a cross-peak with H-4 [δ_H 5.03 (d, J = 2.1 Hz)] in the COSY spectrum, and HMBC correlations from H-3 to C-17 (δ_C 140.5) and C-18/18′ (δ_C 127.1) revealed the presence of the *β*-hydroxyphenylalanine unit. The HMBC correlation between H-3 [δ_H 5.77] and C-1 [δ_C 159.4] suggested that the hydroxy group in the *β*-hydroxyphenylalanine residue was connected to a tyrosine unit via an aryl−alkyl ether bond. The tyrosine moiety was identified from the ^{1}H−^{1}H COSY cross-peaks between H-13 at δ_H 7.15 (dd, J = 8.9, 2.1 Hz) and H-14 at δ_H 6.75 (dd, J = 8.9, 2.1 Hz), between H-15 at δ_H 6.79 (dd, J = 8.3, 2.1 Hz) and H-16 at δ_H 6.86 (dd, J = 8.3, 2.1 Hz), and between H-10 [δ_H 4.67 (dd, J = 11.7, 6.2 Hz)] and both H-11a [δ_H 3.45 (dd, J = 13.1, 6.2 Hz)] and H-11b [δ_H 2.53 (dd, J = 13.1, 11.7 Hz)], together with the HMBC correlations from both H-13 and H-16 to C-11 at δ_C 40.1. That H-10 and H$_2$-11 formed cross-peaks with the signal at δ_C 178.4 (C-34) indicated that this tyrosine unit possessed a carboxylic group. In addition, the HMBC correlation between H-10 and the amide carbonyl carbon at δ_C 171.3 (C-8) supported that the tyrosine moiety was connected to a phenylalanine unit via an amide linkage. The phenylalanine fragment was characterized from the ^{1}H−^{1}H COSY correlations between H-7 [δ_H 4.18 (dd, J = 9.6, 4.8 Hz)] and both H-29a [δ_H 2.93 (dd, J = 13.8, 4.8 Hz)] and H-29b [δ_H 2.66 (dd, J = 13.8, 9.6 Hz)] and from H-31/31′ [δ_H 7.20 (2H, d, J = 6.9 Hz)] to H-33 [δ_H 7.11 (dd, J = 7.6, 7.6 Hz)] through H-32/32′, together with the HMBC correlations from H-29 to both C-31/31′ [δ_C 130.5] and the amide carbonyl carbon [δ_C 171.3 (C-8)] of the phenylalanine unit. H-7 showed an HMBC cross-peak with the carbonyl carbon of the *β*-hydroxyphenylalanine unit [δ_C 167.0 (C-5)]. Thus, the 2D structure of the 14-membered cyclopeptide possessing a cyclophane architecture was clarified. The HMBC correlations also confirmed the presence of an *N,N,N*-trimethyltyrosine moiety. H-26/26′ [δ_H 6.77 (2H, d, J = 8.3 Hz)] showed COSY cross-peaks with H-27/27′ [δ_H 6.58 (2H, d, J = 8.3 Hz)], and the former protons showed HMBC correlations with the tertiary aromatic carbons at δ_C 131.5 (C-26/26′), the oxygenated tertiary carbon at δ_C 158.0 (C-28), and the secondary carbon at δ_C 33.1 (C-24), which indicated the presence of a tyrosine residue. H-24a [δ_H 3.07 (dd, J = 13.8, 3.4 Hz)] and H-24b [δ_H 3.02 (dd, J = 13.8, 9.6 Hz)] showed COSY cross-peaks with H-23 [δ_H 3.95 (dd, J = 9.6, 3.4 Hz)]. The noteworthy HMBC correlation between H-23 and the three equivalent *N*-methyls [δ_C 52.6 (C-35)] confirmed the presence of the *N,N,N*-trimethyltyrosine unit. HMBC correlations between C-22 [δ_C 166.7] and H-4, H-23, and H$_2$-24 showed that this tyrosine unit was attached to the macrocyclic ring via an amide linkage. From the above results, the 2D structure of **1** was determined.

The relative configuration was elucidated via NOESY experiments in DMSO-d_6 (Figure 3). NOESY correlations of

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Table 1. NMR Spectroscopic Data (600 MHz) of Ophiorrhisine A (1)

position	δ_C [a]	type	δ_H [a] (J in Hz)	δ_C [b]	δ_H [b] (J in Hz)
1	159.4,	C		157.7	
2					
3	86.4,	CH	5.77, d (2.1)	85.5	5.77, s
4	57.9,	CH	5.03, d (2.1)	56.6	4.96, d (9.6)
5	167.0,	C		164.8	
6		NH			8.15, br s
7	55.5,	CH	4.18, dd (9.6, 4.8)	52.7	4.27, m
8	171.3,	C		168.8	
9		NH			7.20, m
10	57.4,	CH	4.67, dd (11.7, 6.2)	56.2	4.28, m
11	40.1,	CH_2	3.45, dd (13.1, 6.2)	[c]	3.16, dd (12.4, 6.2)
			2.53, dd (13.1, 11.7)		2.42, dd (12.4, 11.7)
12	135.1,	C		134.4	
13	131.5,	CH	7.15, dd (8.9, 2.1)	130.6	6.96, br d (8.3)
14	119.7,	CH	6.75, dd (8.9, 2.1)	118.3	6.61, dd (8.3, 2.1)
15	122.5,	CH	6.79, dd (8.3, 2.1)	120.5	6.71, dd (8.3, 2.1)
16	132.6,	CH	6.86, dd (8.3, 2.1)	131.3	6.80, d (8.3)
17	140.5,	C		139.6	
18/18′	127.1,	CH	7.61, 2H, d (8.3)	125.8	7.61, 2H, d (8.3)
19/19′	129.4,	CH	7.37, 2H, dd (8.3, 7.6)	127.8	7.33, 2H, dd (8.3, 7.6)
20	128.8,	CH	7.29, dd (7.6, 7.6)	127.1	7.24, dd (7.6, 7.6)
21		NH			8.42, d (9.6)
22	166.7,	C		165.0	
23	77.1,	CH	3.95, dd (9.6, 3.4)	74.2	4.18, d (10.2)
24	33.1,	CH_2	3.07, dd (13.8, 3.4)	31.0	3.03, d (12.4)
			3.02, dd (13.8, 9.6)		2.85, dd (12.4, 10.2)
25	125.5,	C		124.1	
26/26′	131.5,	CH	6.77, 2H, d (8.3)	130.1	6.72, 2H, d (8.3)
27/27′	117.0,	CH	6.58, 2H, d (8.3)	115.6	6.57, 2H, d (8.3)
28	158.0,	C		156.6	
29	40.1,	CH_2	2.93, dd (13.8, 4.8)	[c]	2.93, dd (13.8, 4.8)
			2.66, dd (13.8, 9.6)		2.66, dd (13.8, 9.6)
30	138.7,	C		137.7	
31/31′	130.5,	CH	7.20, 2H, d (6.9)	127.8	7.18, 2H, m
32/32′	129.4,	CH	7.24, 2H, dd (7.6, 6.9)	129.1	7.24, 2H, m
33	127.6,	CH	7.11, dd (7.6, 7.6)	125.9	7.05, m
34	178.4,	C		172.8	
35	52.6,	CH_3	2.70, 9H, s	50.9	2.60, 9H, s

[a]Measured in methanol-d_4. [b]Measured in DMSO-d_6. [c]Overlapped with DMSO-d_6 signal.

H-3 [δ_H 5.77 (s)]/H-4 [δ_H 4.96 (d, J = 9.6 Hz)]/NH-6 [δ_H 8.15 (br s)]/H-14 [δ_H 6.61 (dd, J = 8.3, 2.1 Hz)], and of H-10 [δ_H 4.28 (m)]/H-11b [δ_H 2.42 (dd, J = 12.4, 11.7 Hz)]/H-13 [δ_H 6.96 (br d, J = 8.3 Hz)] revealed that these protons were on the same side of the 14-membered ring. The relative configuration of the β-hydroxyphenylalanine residue (H-3/H-4) was deduced from the ^{1}H−^{1}H NMR coupling constants and the ^{13}C NMR chemical shifts. H-3 was observed as a doublet in methanol-d_4 with a small coupling constant of $J_{3,4}$ = 2.1 Hz and as a singlet [δ_H 5.77 (s)] in DMSO-d_6, respectively, indicating that H-3 and H-4 were *syn*-oriented. In addition, the chemical shift of C-3 in **1** (δ_C 86.4 in methanol-d_4, δ_C 85.5 in DMSO-d_6) confirmed that compound **1** possessed an L-*threo* β-hydroxyphenylalanine residue[12] (3*R**, 4*S**). From these results and biosynthesis considerations, it was presumed that compound **1** consisted of L-amino acid moieties and its absolute configuration was 3*R*, 4*S*, 7*S*, 10*S*, and 23*S*. Compound **1** is an analogue of the known 14-membered paracyclophane xylopyrine C,[11] with the characteristic functions including a carboxylate group at C-10, an *N*,*N*,*N*-trimethylammonium group at C-23, and a hydroxy group at C-28.

Compound **2**, 7′,10-dide-*O*-methylcephaeline, is a colorless unstable solid, and in solution it darkened readily, indicating the presence of a catechol moiety. Compound **2** had a molecular formula of $C_{26}H_{34}N_2O_4$ from the HRESIMS data (calcd 439.2597 [M + H]$^+$; found m/z 439.2615 [M + H]$^+$) (Figure 4). Its UV spectrum exhibited absorptions at 207, 227 (sh), and 287 nm, which demonstrated the presence of tetrahydroisoquinoline moieties.

The ^{1}H NMR data acquired in methanol-d_4 (Table 2) showed signals for a methoxy group [δ_H 3.81 (3H, s)], an ethyl group [δ_H 0.93 (3H, dd, J = 7.6, 7.6 Hz), 1.70 (m), 1.13 (m)], and four one-proton aromatic singlets [δ_H 6.77 (s), 6.64 (s), 6.52 (s), 6.49 (s)]. The ^{13}C NMR data (Table 2) showed signals for 12 aromatic carbons, including four oxygenated tertiary aromatic carbons (δ_C 147.8, 145.8, 144.9, 144.7), four quaternary aromatic carbons (δ_C 131.2, 131.2, 126.8, 126.3), six carbons connected to oxygen or nitrogen (δ_C 63.7, 62.3, 56.3, 53.8, 53.0, 41.6), and eight aliphatic carbons (δ_C 42.9, 41.3,

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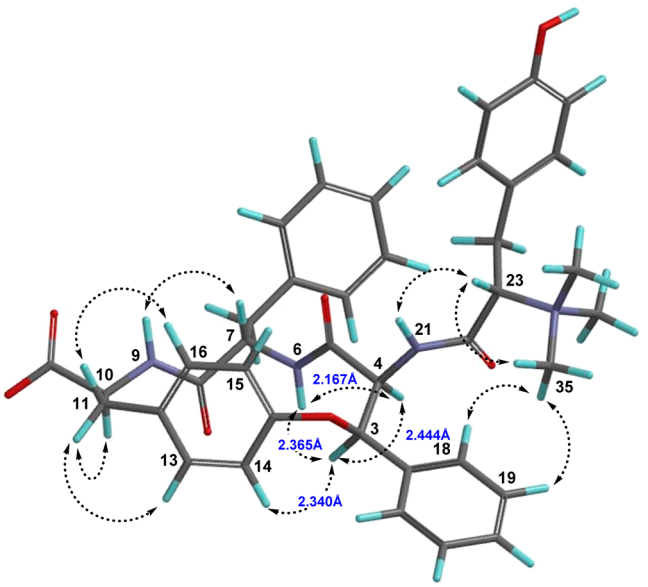

Figure 3. Key NOESY correlations of ophiorrhisine A (**1**) (DFT calcd structure, Spartan '16, B3LYP, 6-31*).

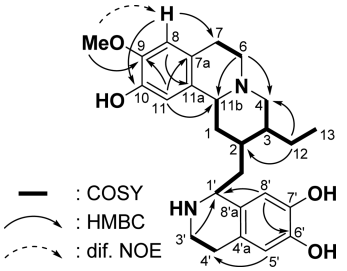

Figure 4. Structure, selected COSY and HMBC correlations, and differential NOE in 7′,10-dide-*O*-methylcephaeline (**2**).

37.7, 37.0, 29.5, 29.3, 24.5, 11.5). These spectroscopic data are similar to those of 10-*O*-demethylprotoemetine,[9] a coexisting alkaloid. The signal for the C-1′ formyl proton in the latter was absent, and instead, signals for an extra tetrahydroisoquinoline moiety was present in the spectrum of **2**. The 2D NMR spectroscopic data of **2** (Figure 4) indicated that the 2D structure should be similar to emetine,[13] but there were remarkable differences in the ^{1}H and ^{13}C NMR spectra. These spectra showed only one methoxy signal. The NOE correlation of OMe/H-8 suggested that the methoxy group was located at C-9. To establish the structure and the absolute configuration, **2** was treated with trimethylsilyldiazomethane $TMSCHN_2$ to afford a methylated compound whose ^{1}H NMR, ESIMS, and the specific rotation data were identical with those of emetine.[13] Accordingly, the structure of **2** was defined as 7′,10-dide-*O*-methylcephaeline.

Compound **1** was evaluated for cytotoxicity toward the human cancer cell lines A549, HT29, and HCT116, but no cytotoxicity was detected (IC_{50} > 15 μM).

EXPERIMENTAL SECTION

General Experimental Procedures. ^{1}H and ^{13}C NMR spectra: JEOL JNM ECZ at 600 MHz (^{1}H) or 150 MHz (^{13}C), respectively. UV: JASCO V-560. ESIMS: JEOL JMS T100GCV. HRESIMS: JEOL JMS-T100LP AccuTOF LC-plus. ECD: JASCO J-720WI. TLC: precoated silica gel 60 F_{254} plates (0.25 mm thick) and precoated RP-18 F_{254} plates (Merck, Tokyo, Japan); precoated amino-silica gel plates (Fuji Silysia Chemical, Tokyo, Japan). Column chromatography: silica gel 60 (70−230 mesh, Merck, Tokyo, Japan), silica gel 60N [40−50 mm (for flash chromatography), Kanto Chemical, Tokyo, Japan], Chromatorex NH (100−200 mesh, Fuji Silysia Chemical, Tokyo, Japan), Cosmosil 75C_{18}-OPN (Nacalai tesque, Kyoto, Japan), Sephadex LH-20 (GE Healthcare Japan, Tokyo, Japan), and DIAION HP20 (Mitsubishi Chemical, Tokyo, Japan). Medium-pressure liquid chromatography (MPLC): C.I.G. prepacked column CPS-HS-221-05 (silica gel, Kusano Kagakukikai, Tokyo, Japan), Ultra Pack NH-40A (amino-silica gel, Yamazen, Osaka, Japan), and Ultra Pack ODS-A-40A (ODS, Yamazen, Osaka, Japan).

Table 2. NMR Spectroscopic Data (600 MHz, Methanol-d_4) of 7′,10-Dide-*O*-methylcephaeline (2)

position	δ_C	type	δ_H (J in Hz)
1	37.0,	CH_2	2.62, m
			1.13, m
2	37.7,	CH	1.57, ddd (11.7, 11.0, 11.0)
3	42.9,	CH	1.39, m
4	62.3,	CH_2	3.07, dd (11.7, 3.4)
			2.10, dd (11.7, 11.7)
6	53.8,	CH_2	3.02, dd (11.0, 5.5)
			2.50, ddd (11.0, 11.0, 4.1)
7	29.5,	CH_2	3.07, m
			2.67, d (14.5)
7a	126.3,	C	
8	112.8,	CH	6.64, s
9	147.8,	C	
10	145.8,	C	
11	112.6,	CH	6.77, s
11a	131.2,	C	
11b	63.7,	CH	3.11, d (13.1)
12	24.5,	CH_2	1.70, m
			1.13, m
13	11.5,	CH_3	0.93, 3H, dd (7.6, 7.6)
α	41.3,	CH_2	2.06, dd (12.4, 11.0)
			1.45, dd (12.4, 11.7)
1′	53.0,	CH	4.03, d (11.0)
3′	41.6,	CH_2	3.18, ddd (11.7, 6.1, 5.5)
			2.92, m
4′	29.3,	CH_2	2.73, m
			2.62, m
4′a	126.8,	C	
5′	116.4,	CH	6.49, s
6′	144.9,	C	
7′	144.7,	C	
8′	113.8,	CH	6.52, s
8′a	131.2,	C	
-OMe	56.3,	CH_3	3.81, 3H, s

Plant Material. *Ophiorrhiza nutans* was collected from the northern part of Thailand (Queen Sirikit Botanic Garden, Chiang Mai, and Chiang Rai) in August to December 2007 and identified by one of the authors, D.S., on the basis of the specimens deposited in Queen Sirikit Botanic Garden and Chiang Mai University Herbarium. A voucher specimen (No. 2007003) was deposited in the Faculty of Pharmacy, Chiang Mai University.

The whole plants of *O. nutans* (321.9 g, dry weight) were powdered and then extracted with 90% MeOH (3 L, 2 × 2.5 L) to give a MeOH extract (49.9 g) after evaporation of the solvent. The MeOH-soluble part of the extract (26.4 g) was separated by Sephadex LH-20 column chromatography with a MeOH/H_2O gradient to give 12 fractions (fr. 1−4 were eluted with 50% MeOH/H_2O, fr. 5−7 with 75% MeOH/H_2O, fr. 8−11 with MeOH, and fr. 12 with acetone). Fr. 3 (11.72 g) was purified by silica gel chromatography with a MeOH/$CHCl_3$ gradient. Fr. 5 was separated by repeated chromatography, including

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silica gel flash column chromatography (MeOH/$CHCl_3$ gradient) or ODS open column chromatography, to afford demethylalangiside (179.6 mg), alangiside (183.3 mg), and isoalangiside (3.4 mg). Fr. 9 was purified by ODS chromatography (60% H_2O/MeOH) to give 5-carboxystrictosidine (922.2 mg). Fr. 4 (10.76 g) from Sephadex LH-20 column chromatography was purified by DIAION HP20 column chromatography with a H_2O/MeOH gradient. The fraction eluted with MeOH was separated by repeated chromatography, including amino-silica gel open column chromatography (MeOH/$CHCl_3$ gradient) or MPLC (ODS, 40% H_2O/MeOH), to afford ophiorrhisine A (**1**, 10.2 mg) and lyaloside (1.0 mg). The fraction eluted with MeOH was purified by repeated chromatography, including silica gel flash chromatography (NH_4OH/MeOH/$CHCl_3$ gradient) or amino-silica gel open column chromatography (15% MeOH/$CHCl_3$), to give 7′,10-dide-*O*-methylcephaeline (**2**, 7.5 mg) and 10-*O*-demethylprotoemetine (3.9 mg).

*Ophiorrhisine A (**1**):* colorless solid; $[\alpha]^{26}_D$ +1.8 (*c* 0.2, MeOH); UV (MeOH) λ_{max} (nm) 278, 228, 205; IR (ATR) 3380 (br), 3351, 3062, 1692, 1656, 1576, 1540, 1531, 1514, 1489, 1454, 1387, 1222, 1025, 1003, 822, 729, 632, 620 cm^{-1}; ^1H and ^{13}C NMR data, see Table 1; HRESIMS 679.3131 $[M + H]^+$ (calcd for $C_{39}H_{43}N_4O_7$, 679.3132).

*7′,10-Dide-O-methylcephaeline (**2**):* colorless solid; $[\alpha]^{25}_D$ +46.6 (*c* 0.03, MeOH); UV (MeOH) λ_{max} (nm) 287, 227 (sh), 207; ECD (*c* 0.2 mM, MeOH, 20 °C,) $\Delta\varepsilon$ (λ nm) −1.0 (291), +0.9 (237), +1.3 (219), −15.9 (204); ^1H and ^{13}C NMR data, see Table 2; HRESIMS 439.2615 $[M + H]^+$ (calcd for $C_{26}H_{35}N_2O_4$, 439.2597).

Methylation of 2. A methanolic solution (1.4 mL) of **2** (3.2 mg) was methylated with excess $TMSCHN_2$ [1 M in *n*-hexane/Et_2O (1:1)] and purified by SiO_2 column chromatography (MeOH/$CHCl_3$ = 1:9) to afford a white powder (0.7 mg). The product {$[\alpha]^{19}_D$ −44 (*c* 0.01, $CHCl_3$)} was identified as emetine[13] {^1H NMR, ESIMS, $[\alpha]_D$}.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.jnatprod.7b00290.

Photographs of *Ophiorrhiza* off. *nutans* Cl. *ex* Hk. f. and NMR spectra for ophiorrhisine A (**1**) and 7′,10-dide-*O*-methylcephaeline (**2**) (PDF)

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Notes

The authors declare no competing financial interest.

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