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Paxdaphnidines A and B, Novel Penta- and Tetracyclic Alkaloids from *Daphniphyllum paxianum*

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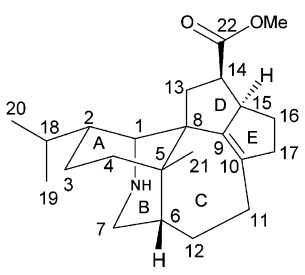
Abstract: Two novel alkaloids, paxdaphnidine A (**1**) with a unique pentacyclic skeleton and paxdaphnidine B (**2**) with an uncommon tetracyclic skeleton, were isolated from the stems and leaves of *Daphniphyllum paxianum*. Their structures were established by spectral methods, especially two-dimensional NMR techniques (^{1}H−^{1}H COSY, HSQC, HMBC, and NOESY).

Plants of the genus *Daphniphyllum* are known to produce highly complex polycyclic *Daphniphyllum* alkaloids.[1,2] *Daphniphyllum* alkaloids have been the challenging subject of natural products, biogenetic, and synthetic programs. Radioactive tracer experiments revealed that these alkaloids were generated from six molecules of mevalonic acid via a squalene-like intermediate.[3] In recent years, A number of the synthetic studies on *Daphniphyllum* alkaloids have been reported in which an exceptionally efficient route for biomimetic total synthesis of several polycyclic *Daphniphyllum* alkaloids was developed.[4] The genus of *Daphniphyllum* (Daphniphyllaceae), comprising about 30 species, is endemically distributed over southeast Asia, and 10 species grow in the southern China.[5] Some of the *Daphniphyllum* species such as *D. calycinum*, *D. macropodum*, and *D. oldhami* are used in traditional Chinese medicine for the treatment of asthma,[6] cough, rheumatism, inflammation, fever, and snakebites.[7]

Recently, a chemical investigation conducted in our laboratory led to the isolation of two novel alkaloids from *Daphniphyllum subverticillatum*.[8] In the continuation of our search for structurally unique and biogenetically interesting *Daphniphyllum* alkaloids, paxdaphnidines A (**1**) and B (**2**) were isolated from the stems and leaves of *Daphniphyllum paxianum* Rosenth. The structures of two alkaloids were elucidated by spectral methods, especially two-dimensional NMR techniques. The plausible origin of two alkaloids, paxdaphnidines A (**1**) and B (**2**), was rationalized biogenetically as shown in Scheme 1. We reported herein the isolation and structural elucidation of two novel alkaloids, paxdaphnidines A (**1**) and B (**2**).



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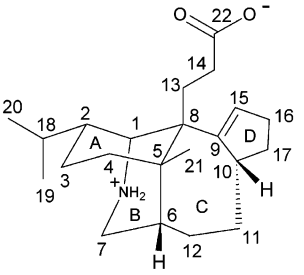

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Paxdaphnidine A (**1**) was obtained as an optically active ($[\alpha]^{20}_D$ −17.0°) colorless oil. Its molecular formula was established as $C_{23}H_{35}NO_2$ by HREIMS at *m*/*z* 357.2674 $[M]^+$ (calcd 357.2668), indicating the existence of seven degrees of unsaturation. The IR spectrum of **1** showed a strong absorption band at 1732 cm^{-1} for an ester carbonyl, which was confirmed by the carbon signal at δ 176.7 (in CD_3OD) in the ^{13}C NMR spectrum. A sharp IR absorption band at 3390 cm^{-1} was attributable to the presence of one NH group. The ^{1}H NMR spectrum (in CD_3OD, Table 1) of **1** displayed the presence of three methyls at δ 1.12 (3H, s), 1.03 (3H, d, J = 6.3 Hz), and 0.99 (3H, d, J = 6.3 Hz) and one methoxyl group at δ 3.63 (3H, s). ^{13}C NMR data (measured both in CD_3OD and $CDCl_3$, Table 1) revealed the presence of 23 carbon signals corresponding to 23 carbon atoms in the molecular formula, which included one carbonyl, two sp^2 quaternary carbons assignable to one tetrasubstituted double bond, two sp^3 quaternary carbons, six sp^3 tertiary carbons, eight sp^3 secondary carbons, three methyls, and one methoxyl. The carbonyl group and the only double bond accounted for two degrees of the unsaturation, and the remaining five degrees of unsaturation were assumed for the presence of a pentacyclic system in **1**.

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SCHEME 1. Biogenetic Pathway Proposed for Paxdaphnidines A (1) and B (2)

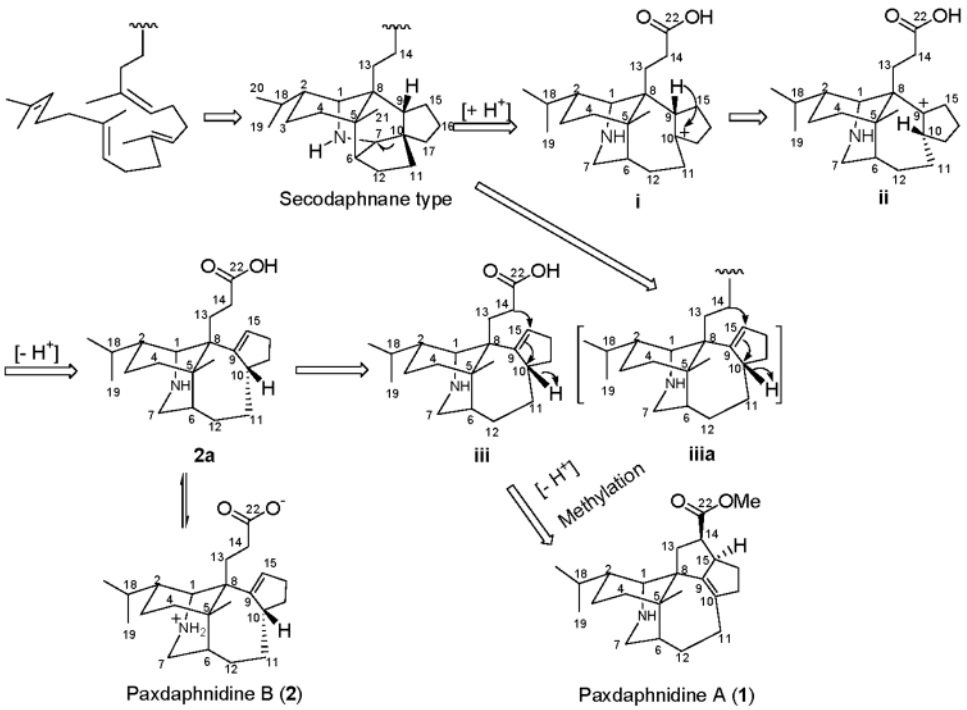

TABLE 1. ^{1}H and ^{13}C NMR Data and HMBC and NOESY Correlations of 1[a]

no.	δ_C[a]	δ_C[b]	δ_H, multi, J (Hz)[a]	HMBC[a] H→C	NOESY[a] H→H
1	56.6	54.1	3.18 (1H, d, 3.2)	2, 3, 5, 7, 8	2, 13a, 15, 20
2	40.9	40.0	1.74 (1H, m)	4	1, 3, 4b, 13a, 20
3	27.7	26.5	2.00 (2H, m)	4	2, 4b, 19
4	39.8	38.8	a: 1.67 (1H, m)	5, 6, 8	6, 7b, 21
			b: 1.70 (1H, m)	5, 6, 8	2, 3
5	36.3	35.2			
6	41.4	40.0	2.05 (1H, m)	4, 5, 7, 8, 12, 21	4a, 7b, 12b, 21
7	46.40	45.5	a: 3.21 (1H, d, 14.8)	1, 5, 6, 12	7b,
			b: 3.69 (1H, m)	6, 12	6, 4a, 7a,
8	49.0[c]	48.0			
9	144.6	142.4			
10	139.1	137.5			
11	26.1	25.3	2.29 (2H, m)	6, 9	17b
12	29.4	28.5	a: 1.62 (1H, m)	5, 6	
			b: 2.30 (1H, m)		6, 21
13	38.6	37.4	a: 2.17 (1H, dd, 9.3, 15.0)	5, 8, 14, 22	1, 2, 14, 13b
			b: 2.61 (1H, dd, 4.0, 15.0)	8, 9, 14, 22	13a, 21
14	43.8	42.2	2.98 (1H, dt, 4.0, 9.3)	9, 15, 22	13a, 15
15	55.3	54.1	3.57 (1H, m)		1, 14, 16a,
16	28.6	27.9	a: 1.94 (1H, m)	9, 10, 15	15, 16b, 17a
			b: 1.49 (1H, m)	15,	16a, 17b
17	44.3	43.5	a: 2.74 (1H, m)		16a, 17b
			b: 2.42 (1H, dd, 9.0, 15.5)	9, 10, 11, 15, 16	11, 16b
18	31.4	29.8	1.68 (1H, m)	2, 19, 20	19, 20
19	21.7	21.5	1.03 (3H, d, 6.3)	2, 19, 20	2, 3, 18
20	21.2	21.5	0.99 (3H, d, 6.3)	2, 18, 20	1, 2, 18
21	26.1	25.5	1.12 (3H, s)	4, 5, 6, 8	4a, 6, 12b, 13b
22	176.7	175.0			
OMe	52.0	51.3	3.63 (3H, s)	22	

[a] Measured in CD_3OD. [b] Measured in $CDCl_3$. [c] Overlapped with solvent CD_3OD.

Analysis of the ^{1}H NMR, ^{13}C NMR, and HSQC spectra of **1** enabled us to assign all the protons to their bonding carbons. The three partial structures **a** (C-1 to C-4 and C-18 to C-20), **b** (C-6 to C-7 and C-11 to C-12), and **c** (C-13 to C-17) drawn with bold bonds were established by using a combination of two-dimensional NMR spectra (HSQC, ^{1}H−^{1}HCOSY, and HMBC) measured in CD_3OD (Figure 1). The overlapping proton signals gave rise to some uncertainty in establishing the structural fragments **a**−**c** only from the HSQC and ^{1}H−^{1}HCOSY spectra, so the HMBC spectrum was further applied to confirm the structural fragments **a**−**c**. The linkage of three structural fragments **a**−**c** was finally made by the HMBC experiment (Figure 1), in which the "loose ends" resulting from the insertion of nitrogen and quaternary carbons of C-5, C-8, C-9, and C-10 into the molecule, could be fully connected. A methine assigned for the CH-1 (δ_C 56.6; δ_H 3.18) and a methylene assigned to the CH_2-7 (δ_C 46.4; δ_H 3.21, 3.69) were attributable to those attached to the nitrogen atom, indicating the connectivity of two partial structures **a** and **b** via the nitrogen atom, and this was confirmed by the HMBC cross-peaks of H-7/C-1 and H-1/C-7. In the HMBC, the quaternary carbon signal of C-8 (δ 49.0) was correlated with the H-1 (δ 3.18) and the H_2-13 (δ 2.17, 2.61) to connect fragments **a** and **c**; C-21 (the only methyl), C-4, and C-6 were attached to

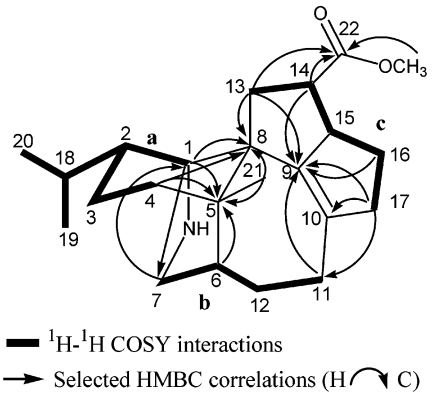

FIGURE 1. Selected two-dimensional NMR correlations for **1**.

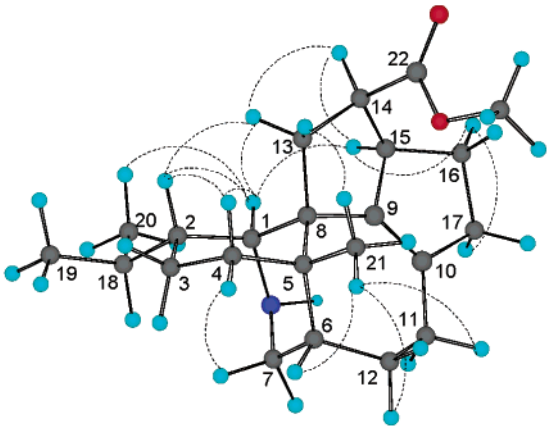

FIGURE 2. Key NOESY correlations and relative stereochemistry of **1**.

the C-5 by the strong HMBC correlations of H_3-21/C-5, H_2-4/C-5, and H-6/C-5, respectively; the connections of C-15 and C-8 to C-9 and of C-11 and C-17 to C-10 were also made by the corresponding HMBC correlations. Although the correlation between H-15 and C-9 (J^2) was not observed, the HMBC correlations between H_2-14 and C-9 (J^3) and the correlations between H_2-16 and C-9 (J^3) were still indicative of the linkage between C-9 and C-15. C-11 and C-17 were allocated to C-10, as deduced from the HMBC correlation pairs of H_2-11/C-9 (J^3) and H-17b/C-10 (J^2) and supported by the HMBC correlation between H-17b and C-11 (J^3). The linkage of two quaternary carbons C-8 and C-9 could be determined by the HMBC correlations between H_2-13 and C-9 (J^3). The connectivity of quaternary carbons C-5 and C-8 was tentatively linked by the HMBC cross-peaks of H-1/C-5 (J^3), H_2-4/C-8 (J^3), and H_3-21/C-8 (J^3). The quaternary carbon signal at δ 176.7 was allocated to C-22 by the strong correlations between C-22 and H-14 (δ 2.98 dt, 4.0, 9.3 Hz). The planar structure of **1** was thus outlined.

The relative stereochemistry of **1** was deduced from the NOESY correlations as depicted on a three-dimensional structure generated from the molecular modeling (CS Chem 3D Pro Version 6.0) using MM2 force field calculations for energy minimization (Figure 2). In the NOESY spectrum, the cross-peaks observed between the proton pairs of H-13a/H-14, H-14/H-15, H-15/H-16a, and H-16a/H-17a indicated that H-13a, H-14, H-15, H-16a, and H-17a were α-oriented. The H-6, H-12b, H-13b, and Me-21 were assigned β-configuration on the basis of the NOESY correlations of H_3-21 with H-6, H-12b, and H-13b. NOESY correlations between H-2 and H-4b and between H-2 and H-13a indicated that the A-ring took the chair conformation, and as a consequence, the B-ring definitely took the chair conformation. The NOESY correlation between H_3-21 and H-12b suggested that the seven-membered C-ring also took a chairlike-conformation. The five-membered D- and E-rings were tentatively furnished in the envelope conformation. The relative stereochemistry and a favorable conformation of **1** established by the NOESY experiment were in good agreement with those of **1** generated by the computer modeling (Figure 2). The structure of paxdaphnidine A was thereby elucidated as **1**.

In the ^{13}C NMR of **1**, the carbon signal of C-8 at δ 49.0 was overlapped with the solvent peaks (measured in CD_3OD), so chloroform-d_1 ($CDCl_3$) was also used as a solvent to record the ^{13}C NMR of **1** (Table 1 and Supporting Information). The complete assignments of the ^{1}H NMR and ^{13}C NMR data (Table 1) of **1** were achieved by using a combination of ^{1}H−^{1}H COSY, HSQC, HMBC, and NOESY spectra.

TABLE 2. ^{1}H and ^{13}C NMR Data and HMBC and NOESY Correlations of 2[a]

no.	δ_C	δ_H, multi, J (Hz)	HMBC H→C	NOESY H→H
1	61.9	3.59 (1H, brs)	2, 3, 5, 7, 8, 9, 18	6, 15, 18, 20
2	41.7	1.72 (1H, m)	3, 4,	4b, 13
3	27.2	2.00 (2H. m)	1, 2, 3, 4, 5	4a, 19, 20,
4	41.7	a: 1.45 (1H, m)	2, 3, 5, 6, 8 21	3, 7b
		b: 2.16 (1H, m)	3, 5, 6, 21	2
5	38.7			
6	43.4	2.05 (1H, m)	5, 12, 21	1, 7b, 11b, 21
7	46.4	a: 3.00 (1H, d, 14.6)	1, 5, 6, 12	7b
		b: 3.65 (1H, dd, 14.6, 9.2)	5, 6	4a, 6, 7a
8	45.5			
9	152.6			
10	48.6	3.12 (1H, brt, 10.0)		14b, 21
11	34.9	a: 1.55 (1H, m)	6, 12	14a
		b: 1.82 (1H, m)		6, 17b
12	32.9	1.54 (2H, m)	11	
13	33.7	2.04, (2H, m)	8, 9, 14, 22	2, 14b
14	34.8	a: 2.14 (1H, m)	8, 13, 22	11a
		b: 2.26 (1H, m)	8, 13, 22	13, 15
15	131.2	5.78 (1H, brs)	8, 9, 10, 16, 17	1, 14b
16	31.0	a: 2.38 (1H, m)	17	16b
		b: 2.57 (1H, m)		16a
17	34.0	1.60 (1H, m)	9, 11, 15	17b
		1.84 (1H, m)	9, 11	11b, 17a
18	31.4	1.70 (1H, m)	2, 19, 20,	1, 19, 20
19	22.0	0.99 (3H, d, 6.4)	2, 18	3, 18, 20
20	21.4	0.99 (3H, d, 6.4)	2, 18	1, 3, 18, 19
21	27.3	1.23 (3H, s)	4, 5, 6, 8,	6, 10
22	181.8			

[a] Measured in CD_3OD.

Paxdaphnidine B (**2**) was obtained as a tiny needle crystal (in CH_3OH). The HREIMS of **2** exhibiting the molecular ion at m/z 345.2679 established the molecular formula $C_{22}H_{35}NO_2$ (calcd 345.2688) with six degrees of unsaturation. The IR absorption bands indicated the presence of functionalities of carboxylate (1567 and 1402 cm^{-1}) and amine (3417 cm^{-1}). The existence of a carboxylate group was confirmed by the carbon signal at δ 181.8 in the ^{13}C NMR. One trisubstituted double bond was inferred by the proton signal at δ 5.78 (brs) in the ^{1}H NMR and the carbon signals at δ 152.6 and 131.2 in the ^{13}C NMR spectrum (Table 2). Three methyls at δ 0.99 (3H, d, J = 6.4 Hz), 0.99 (3H, d, J = 6.4 Hz), and 1.23 (3H, s) were observed in the ^{1}H NMR spectrum. Consistent with the molecular formula of **2**, 22 carbon signals comprising four quaternary carbons (two sp^3 and two sp^2), six tertiary carbons (five sp^3 and one sp^2), nine sp^3 secondary carbons, and three sp^3 methyls were observed in the ^{13}C NMR spectrum. Among them, one methylene (δ_C 46.4; δ_H 3.65, 3.00) and one methine (δ_C 61.9; δ_H 3.59) were ascribed to those bearing nitrogen. Besides the two degrees of unsaturation occupied by the double bond and the carboxylate group, the remaining four degrees of unsaturation were only ascribable to the occurrence of one tetracyclic ring system in **2**.

Three structural fragments **a** (C-1 to C-4 and C-18 to C-20), **b** (C-6−C-7, C-10−C-12, and C-15−C-17), and **c** (C-13 to C-14) drawn with bold bonds (Figure 3) in compound **2** were also figured out by using a combination of one-dimensional (^{1}H NMR and ^{13}C NMR) and two-dimensional NMR techniques (HSQC, ^{1}H−^{1}HCOSY, and HMBC). The connectivity of three structural fragments

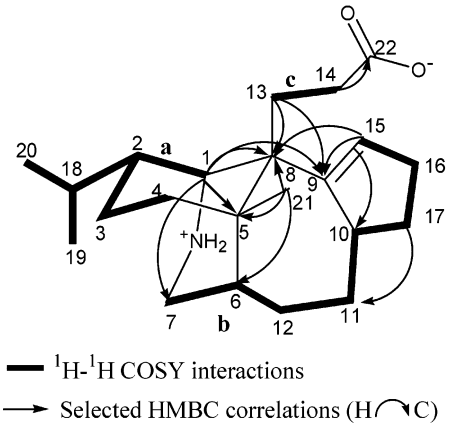

FIGURE 3. Selected two-dimensional NMR correlations of **2**.

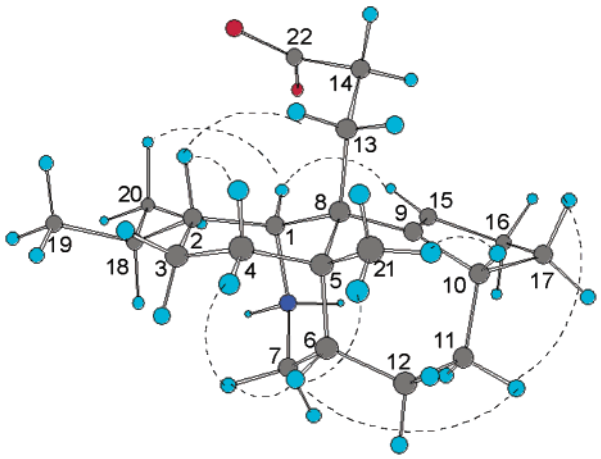

FIGURE 4. Key NOESY correlations and relative stereochemistry of **2**.

a−**c**, quaternary carbons, and the only nitrogen atom was achieved in a manner very similar to that of compound **1** due to the outstanding performance of HMBC experiment (Table 2 and Figure 3), in which both the J^2 and J^3 HMBC correlations were sufficient to finish the linkage. The planar structure of **2** was thus outlined as an intramolecular salt with a nitrogen-containing tetracyclic ring system.

The relative stereochemistry and conformation of **2** were established by NOESY experiment as demonstrated on the three-dimensional structure generated from the molecular modeling (CS Chem 3D Pro Version 6.0) using MM2 force field calculations for energy minimization (Figure 4). In the NOESY spectrum, the correlations of H_3-21/H-6, H_3-21/H-10, H-6/H-11b, and H-11b/H-17b indicated that the H-6, H-10, H-11b, H-17b, and Me-21 were in the β-configuration. The H-2 correlated with H-13 indicated that the carboxylate chain was β-orientated. The A-ring was assigned as a chair conformation on the basis of the NOESY correlations of H-2/H-4b and H-2/H-13, and as a consequence, the B-ring was also assigned the chair conformation. The NOESY correlations of H_3-21/H-10, H_3-21/H-6, and H-6/H-11b suggested that the seven-membered C-ring took a chairlike conformation. The five-membered D-ring was tentatively furnished in the envelope conformation. The structure of paxdaphnidine B was thus elucidated as **2**, and the ^{1}H NMR and ^{13}C NMR data of **2** were completely assigned by two-dimensional NMR spectra including the ^{1}H−^{1}H COSY, HSQC, HMBC, and NOESY spectra.

Plausible Biosynthetic Pathways Proposed for Paxdaphnidines A (1) and B (2). The possible biogenetic pathways for paxdaphnidines A (**1**) and B (**2**) were rationalized as shown in Scheme 1. The biogenetic precursor of these two alkaloids seems to be the secodaphniphylline-type alkaloids, which underwent a C-7−C-10 bond cleavage to give a key intermediate (**i**). The intermediate (**i**) was transformed to intermediate (**ii**) by a reasonable intramolecular rearrangement with the desired stereochemistry at C-10, followed by the C-9−C-15 double bond formation to yield the alkaloid **2a**, which then became an intramolecular salt **2**. Paxdaphnidine A (**1**) was assumed to be transformed from the alkaloid **2a** through a tandem intramolecular rearrangement (**iii**) and methylation or to be transformed from secodaphniphylline-type alkaloids directly via similar intermediates such as **i** and **ii** to form **iiia**, which underwent a tandem intramolecular rearrangement and was then methylated to produce the target alkaloid **1**.

Experimental Section

Plant Material. *Daphniphyllum paxianum* was collected from Guangdong Province of P. R. China and authenticated by Prof. Suhua Shi of Institute of Botany, School of Life Science, Zhongshan University of P. R. China. A voucher specimen has been deposited in the Herbarium of Institute of Materia Medica, SIBS, Chinese Academy of Sciences (Accession No. DS-2003-4Y).

Extraction and Isolation. The powder of dried stems and leaves (400 g) of *D. paxianum* was percolated with 95% ethanol to give a crude extract. The crude extract was dissolved in 1 L of water to form a suspension and then acidified with 0.5 N H_2SO_4 to pH ≈ 5. The acidic suspension was immediately partitioned with ethyl acetate (6 × 300 mL) to remove the nonalkaloid components. The acidic aqueous phase was adjusted with 2 N Na_2CO_3 to pH ≈ 10 and partitioned with chloroform (6 × 300 mL) to give the crude alkaloids (320 mg). The crude alkaloid fraction was then subjected to a silica gel column (2.0 × 50 cm) eluted with $CHCl_3$−MeOH (20:1−10:1) to give two major alkaloids A and B, and each of them was further purified on a flash column of Sephadex LH-20 eluted with ethanol to give 12 mg of paxdaphnidine A (**1**) (0.003%) and 53 mg of paxdaphnidine B (**2**) (0.012%), respectively.

Paxdaphnidine A (1): colorless oil; $[\alpha]^{20}_D$ −17.0°(*c* 0.27, CH_3OH); IR (KBr) ν_{max} cm^{-1} 3390, 2923, 2854, 1732, 1567, 1456, 1373, 1195, 1168, 1122, 1051; ^{1}H and ^{13}C NMR see Table 1; EIMS 70 eV *m*/*z* (rel intensity) 357 $[M]^+$ (100), 342 (18), 314 (33), 298 (20), 274 (24), 97 (12), 83 (15), 57(16); HREIMS at *m*/*z* 357.2674 ($C_{23}H_{35}NO_2$, calcd 357.2668).

Paxdaphnidine B (2): colorless needle crystal (MeOH); mp 121−122°; $[\alpha]^{20}_D$ −50.5° (*c* 0.58, CH_3OH); IR (KBr) ν_{max} cm^{-1} 3417, 2925, 2865, 1567, 1402, 1247, 655; ^{1}H and ^{13}C NMR see Table 2; EIMS 70 eV *m*/*z* (rel intensity) 345 $[M]^+$ (25), 330 (14), 302 (17), 300 (16), 284 (48), 260 (100), 192 (20), 91 (21), 55 (16); HREIMS at *m*/*z* 345.2679 ($C_{22}H_{35}NO_2$, calcd 345.2668).

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Supporting Information Available: General experimental procedures; EIMS, ^{1}H and ^{13}C NMR, and two-dimensional NMR of paxdaphnidines A (**1**) and B (**2**). This material is available free of charge via the Internet at http://pubs.acs.org.

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