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Alkaloids from *Daphniphyllum longeracemosum*

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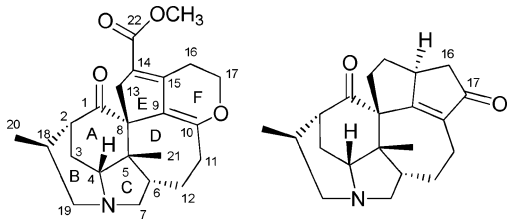
Four new *Daphniphyllum* alkaloids, daphnilongeranins A−D (**1**−**4**), along with four known ones, daphniphylline, longistylumphylline A, deoxyisocalyciphylline B, and daphnicyclidin D, were isolated from the leaves and stems of *Daphniphyllum longeracemosum*. Daphnilongeranin A (**1**) is the first *seco*-10,17-longistylumphylline A type *Daphniphyllum* alkaloid, and daphnilongeranin B (**2**) is a new C-22 nor-*Daphniphyllum* alkaloid based on a new C_{21} skeleton. Their structures and stereochemistry were determined using spectroscopic data and chemical methods.

The complex and structurally diversified *Daphniphyllum* alkaloids have been attractive projects for natural products and organic chemists.[1] Investigation of *Daphniphyllum* species has recently led to the isolation of a series of new *Daphniphyllum* alkaloids by Kobayashi,[2] Jossang,[3] Yue,[4] Bodo,[5] and their co-workers. Some of these alkaloids exhibited cytotoxic activities against several tumor cell lines.[2,3]

Daphniphyllum longeracemosum Rosenth. (Daphniphyllaceae), an evergreen tree, is distributed mainly in Yunnan Province of China.[6] Chemical constituents of *D. longeracemosum* have not previously been investigated. As part of our continuing investigations of *Daphniphyllum* alkaloids,[4] four new alkaloids (**1**−**4**), as well as daphniphylline,[7] longistylumphylline A,[4d] deoxyisocalyciphylline B,[4a] and daphnicyclidin D,[8] were isolated from the leaves and stems of this plant. Daphnilongeranin A (**1**) possesses an unprecedented *seco*-10,17-longistylumphylline A type skeleton, and daphnilongeranin B (**2**) is a nor-*Daphniphyllum* alkaloid based on a new C_{21} skeleton.



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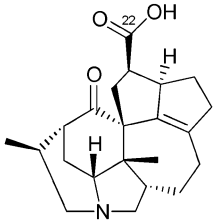

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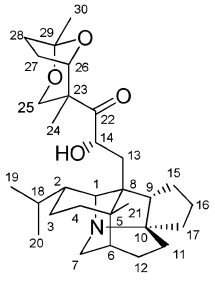

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Results and Discussion

The HREIMS ion at *m*/*z* 383.2088 enabled us to establish the molecular formula of daphnilongeranin A (**1**) as $C_{23}H_{29}NO_4$. IR absorptions suggested the presence of carbonyl functionalities (1701 and 1624 cm^{-1}). In accordance with the molecular formula, the presence of a ketone, an ester, two persubstituted double bonds, three methyls, eight methylenes, four methines, and two sp^3 quaternary carbons was revealed by analyses of its ^1H and ^{13}C NMR spectra (Table 1). The ^1H and ^{13}C NMR spectra also indicated that two methylenes (δ_C 55.7, δ_H 2.89; δ_C 51.0, δ_H 2.91 and 2.65) and one methine (δ_C 67.2, δ_H 3.51) were typical of nitrogenated groups, similar to those in the alkaloids longistylumphylline A[4d] and daphniglaucin D.[9]

Comparison of the NMR data of **1** with those of longistylumphylline A,[4d] which was also obtained from this plant, showed that both compounds were very similar, except for significant changes of some chemical shifts corresponding to protons and carbons near the conjugated system. The presence of one oxygenated methylene (δ_C 66.4, δ_H 4.15 and 3.94) and a likely oxygenated quaternary olefinic carbon (δ_C 164.4) in **1** implied that an oxygen atom was probably present between C-10 and C-11, or between C-10 and C-17, or between C-13 and C-14, or between C-15 and C-16. According to the molecular formula, alkaloid **1** contained one more oxygen atom than longistylumphylline A, supporting the above deduction. The gross structure of daphnilongeranin A (**1**) was finally established by 2D NMR (including HMQC, $^1H-^1H$ COSY, and HMBC) analyses. The linkages of proton-bearing structural fragments with quaternary carbons and heteroatoms were fixed by HMBC spectra. A ketone carbonyl at δ_C 216.2 was attributable to C-1 on the basis of its HMBC correlations with H-2, H_2-3, and H-18. The mutual HMBC correlations among CH_2-19, CH_2-7, and CH-4 established the key linkage of C-19, C-7, and C-4 via a nitrogen atom. The attachments of C-4, C-6, and C-21 to C-5 were established on the grounds of HMBC correlations of H-4/C-5, H-6/C-5, and H_3-21/C-5, respectively. The HMBC correlations from H_3-21 to C-8, from H-4 to C-8, and from H_2-13 to C-5 allowed the connection of C-5 to C-8. The C-8 bonding with C-13 and the C-1 ketone group was revealed by the HMBC correlations of H-13β/C-8 and H-13α/C-1. Both H_2-13 and H_2-16 correlated with C-14 and C-15 in HMBC and indicated the presence of a $\Delta^{14(15)}$ double bond. An olefinic carbon at δ 118.2 was assigned to C-9 on the basis of the HMBC correlations of H_2-11 and H-16α to C-9. In the HMBC, both olefinic carbons at δ_C 118.2 and 164.4 correlating with both H_2-11 indicated the presence of a $\Delta^{9(10)}$ double bond, and the latter one at δ_C 164.4 also correlating with H-12α was distinguished as C-10; correlations between the oxygenated methylene H_2-17 and C-10 clearly indicated the presence of an ether bond between C-10 and C-17. The linkage between C-9 and C-15 was tentatively assigned by the HMBC correlations of H_2-16/C-9 and H_2-17/C-15. The methoxyl (δ_C 51.7, δ_H 3.69) correlated with both C-22 and C-14 (J [4]), indicating that the only ester group was located at C-14. Although no direct HMBC correlation was available to link C-8 and C-9, from the degrees of unsaturation, the substitution patterns, and also the biogenetic view (Scheme 1), the

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Table 1. NMR Data of Daphnilongeranins A−D (**1**−**4**)

	1[a]		**2**[a]		**3**[b]		**4**[a]				
	δ_C	δ_H (pattern, *J* (Hz))	δ_C	δ_H (pattern, *J* (Hz))	δ_C	δ_H (pattern, *J* (Hz))	δ_C	δ_H (pattern, *J* (Hz))		δ_C	δ_H (pattern, *J* (Hz))
1	216.2		216.1		215.8		64.2	2.87 (d, 4.8)	21	26.2	0.93 (s, 3H)
2	45.5	2.31 (br d 3.9)	45.2	2.27 (br d, 1.3)	43.6	2.24 (m)	39.9	1.54 (m)	22	215.1	
3	20.9	*β* 2.33 (m) α 2.12 (dd, 15.4, 3.9)	20.5	*β* 2.28 (m) α 2.08 (m)	19.5	*β* 2.39 (m) α 2.06 (m)	28.4	1.90 (m) 1.54 (m)	23	50.8	
4	67.2	3.51 (m)	66.9	3.26 (br d, 4.9)	66.2	3.73 (br s)	43.3	1.72 (m) 1.35 (m)	24	19.8	0.90 (s, 3H)
5	51.2		52.7		51.5		38.4		25	66.6	4.53 (dd, 12.7, 1.8) 3.70 (d, 12.7)
6	51.7	2.29 (m)	53.3	2.24 (m)	49.7	2.35 (m)	43.2	1.33 (m)	26	83.2	4.78 (br d, 5.9)
7	55.7	2.89 (m, 2H)	55.4	α 2.89 (dd, 11.7, 9.9) *β* 2.86 (dd, 9.9, 8.8)	56.5	*β* 3.23 (dd, 10.6, 6.8) α 2.52 (br t, 11.4)	48.3	3.27 (br d, 14.2) 2.68 (dd, 15.7, 3.7)	27	25.4	2.00 (m, 2H)
8	65.0		65.2		63.0		49.5[c]		28	35.1	2.10 (m) 1.83 (m)
9	118.2		185.0		140.7		53.9	2.39 (dd, 10.3, 7.3)	29	106.7	
10	164.4		140.7		139.5		74.1		30	24.3	1.35 (s, 3H)
11	29.5	α 2.39 (m) *β* 1.96 (ddd, 16.3, 6.4, 2.0)	20.3	*β* 2.36 (ddd, 15.7, 5.6, 3.0) α 2.02 (m)	25.0	*β* 2.11 (m) α 1.94 (m)	30.3	1.80 (m) 1.50 (m)			
12	23.9	*β* 1.87 (m) α 1.79 (m)	25.2	*β* 1.85 (m) α 1.75 (m)	28.4	*β* 1.94 (m) α 1.55 (m)	23.9	1.92 (m) 1.59 (m)			
13	43.4	*β* 3.35 (d, 17.5) α 2.75 (d, 17.5)	39.4	*β* 2.77 (dd, 13.9, 7.8) α 1.00 (m)	41.1	*β* 2.73 (dd, 13.2, 9.1) α 2.25 (m)	34.6	2.71 (br d, 14.0) 1.07 (dd, 15.8, 7.2)			
14	117.5		32.6	α 2.13 (m) *β* 1.18 (m)	42.9	2.66 (m)	73.6	4.85 (dd, 7.2, 3.7)			
15	151.0		45.8	2.74 (m)	51.4	3.43 (m)	32.0	2.04 (m) 1.40 (m)			
16	26.5	α 3.07 (m) *β* 2.72 (m)	42.2	α 2.58 (dd, 18.0, 6.2) *β* 2.08 (m)	28.9	α 1.98 (m) *β* 1.47 (m)	26.2	1.70 (m) 1.39 (m)			
17	66.4	α 4.15 (ddd, 10.8, 5.0, 5.0) *β* 3.94 (ddd, 10.8, 10.8, 3.7)	212.1		40.5	*β* 2.68 (m) α 2.31 (m)	37.7	2.01 (m) 1.39 (dd, 14.4, 8.4)			
18	26.5	2.73 (m)	34.1	2.72 (m)	29.8	2.71 (m)	32.2	1.65 (m)			
19	51.0	*β* 2.91 (dd, 13.8, 6.9) α 2.65 (dd, 13.8, 10.9)	50.7	*β* 2.85 (dd, 14.2, 7.0) α 2.54 (dd, 14.2, 9.7)	48.2	α 2.87 (m) *β* 2.68 (m)	21.7	0.98 (d, 6.4, 3H)			
20	19.9	1.04 (d, 6.7, 3H)	19.2	1.02 (d, 6.8, 3H)	19.2	1.08 (d, 6.0, 3H)	22.4	0.99 (d, 6.3, 3H)			
21	24.0	1.26 (s, 3H)	22.9	1.24 (s, 3H)	25.7	1.42 (s, 3H)					
22	167.7				178.9						
OMe	51.7	3.69 (s, 3H)									

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

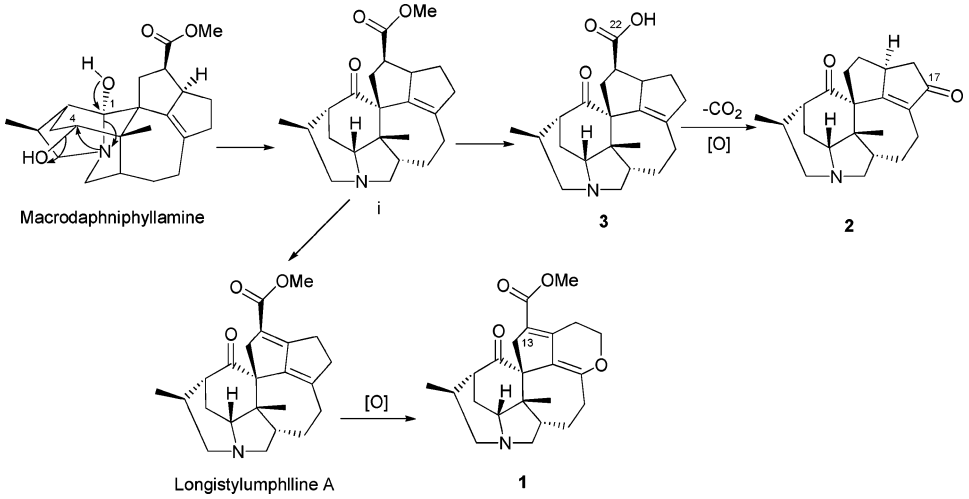
connection between C-8 and C-9 could be assumed. The planar structure of daphnilongeranin A (**1**) was thus elucidated as indicated.

The relative structural chemistry of **1** was fixed by NOESY experiments. The NOESY correlations of H_3-21/H-4, H_3-21/H-6, H_3-21/H-13*β*, H-6/H-4, and H_3-21/H-12*β* indicated that CH_3-21, H-4, and H-6 were all on the same side toward the *β*-face. As a consequence, the correlations between H-13α and H-2 indicated that H-2 had an α-orientation. H_3-20 correlated with one proton signal of *β*-oriented CH_2-3 at *δ* 2.12 and was assigned as having a *β*-configuration.

Daphnilongeranin B (**2**) had the molecular formula $C_{21}H_{27}NO_2$ as determined by HREIMS. The ^{13}C NMR spectrum of **2** (Table 1) displayed signals indicating two ketone groups, one persubstituted double bond, two methyls, eight methylenes, five methines, and two sp^3 quaternary carbons. The facts implied that alkaloid **2** was a C-22 nor-*Daphniphyllum* alkaloid based on a new C_{21} skeleton. Extensive analysis of the HMQC, $^1H-^1H$ COSY, and HMBC spectra of **2** enabled us to outline its planar structure, which had A- to D-rings identical with those of daphcalycinosidine C.[5b] The chemical shifts of both protons and carbons and the mutual HMBC correlations of CH-4, CH_2-7, and CH_2-19 revealed the attachment of C-4, C-7, and C-19 to the nitrogen atom. In the HMBC study, a ketone group was assigned to C-1 on the basis of the correlations of H-2, H-3α, and H-18 with C-1. The HMBC correlations of H_2-11/C-9, H_2-12/C-10, H-11*β*/C-10, and H-16α/C-9 (C-10) indicated the presence of a $\Delta^{9(10)}$ double bond, and the other ketone group was assigned to C-17 on the basis of correlations of H-11*β* and H_2-16 to C-17.

The relative stereochemistry of alkaloid **2** was demonstrated by the NOESY spectrum. The NOESY correlations of H_3-21/H-6, H_3-21/H-3*β*, H_3-21/H-13*β*, H-6/H-4, H-6/H-12*β*, H-6/H-7*β*, H-4/H-19*β*, and H-19*β*/H_3-20 indicated that CH_3-21, H-4, H-6, and CH_3-

Scheme 1. Biogenetic Pathway Proposed for Daphnilongeranins A−C (**1**−**3**).



20 were above the molecular plane and were assigned as having a β-configuration. The NOESY spectrum showed interaction of H-18 with H-7α, supporting the β-CH_3-20 assignment. NOESY correlations of H-15/H-13α and H-13α/H-2 suggested that H-15 and H-2 were α-oriented.

The molecular formula of daphnilongeranin C (**3**) was determined as $C_{22}H_{29}NO_3$ by HREIMS. The ^{13}C NMR data of daphnilongeranin C (**3**) (Table 1) were similar to those of the alkaloid moiety of daphcalycinosidine C,[5b] implying that daphnilongeranin C (**3**) was likely the alkaloid core of daphcalycinosidine C. Two-dimensional NMR experiments, including HMQC, $^1H-^1H$ COSY, and HMBC, finally revealed the backbone of **3**, which was consistent with the above deduction. In the HMBC spectrum, a ketone group at δ_C 215.8 was assigned to C-1 as judged from the HMBC correlations of H-2, H-18, and H-3α to C-1. The mutual HMBC correlations among CH-4, CH_2-7, and CH_2-19 showed the attachment of C-4, C-7, and C-19 to the nitrogen atom. The carboxyl was assigned to C-22 in view of the correlations of H_2-13/C-22 and H-14/C-22. The HMBC correlations of H-11α, H-13α, H-16α, and H_2-17 to the olefinic C-9 as well as HMBC correlations of H-11α, H_2-12, H_2-16, and H-17β to the olefinic C-10 indicated the presence of a Δ^9 double bond.

The ROESY spectrum of **3** showed the same relative stereochemistry as that of daphcalycinosidine C in the alkaloid moiety. CH_3-21 exhibited ROESY correlations with H-4 and H-6, indicating that they were on the same side of the molecular plane. The ROESY correlations of H-13α/H-14, H-13α/H-15, and H-7α/H-18 indicated that H-14, H-15, and H-18 were α-oriented. ROESY correlations between H_3-20 and H-2 indicated that H_3-20 and H-2 were on the same side.

Analysis of ^{13}C NMR data of daphnilongeranin D (**4**) showed that the structure of **4** was closely related to the known alkaloid daphniphylline,[7] also obtained from this plant. As judged from HREIMS ($C_{30}H_{47}NO_4$) and ^1H and ^{13}C NMR (Table 1), alkaloid **4** was proposed to be 14-deacetyldaphniphylline. The 2D NMR spectra, including HMQC, $^1H-^1H$ COSY, and HMBC, confirmed the proposed structure of **4** and placed the hydroxyl and ketone groups at C-14 and C-22, respectively. The relative configuration of HO-14 was finally resolved via hydrolysis of daphniphylline in basic MeOH to give an alkaloid, whose EIMS and ^1H NMR data were in good agreement with those of daphnilongeranin D (**4**).

Daphniphylline,[7] longistylumphylline A,[4d] deoxyisocalyciphylline B,[4a] and daphnicyclidin D [8] were identified by comparison of EIMS and ^1H and ^{13}C NMR data with data of authentic samples.

The biogenetic origin of daphnilongeranins A−C (**1**−**3**) may be visualized as originating with macrodaphniphyllamine (Scheme 1). Macrodaphniphyllamine could undergo a tandem rearrangement to form key intermediate **i**. Intermediate **i** could first be transformed into the known alkaloid longistylumphylline A and then form daphnilongeranin A (**1**) via insertion of an oxygen atom into the C-10−C-17 bond by oxidation. Hydrolysis of intermediate **i** would yield daphnilongeranin C (**3**), which could be further transformed into daphnilongeranin B (**2**) via the processes of degradation and oxidation.

Experimental Section

General Experimental Procedures. Optical rotations were measured on a Perkin-Elmer 341 polarimeter (Na filter, $\lambda = 589$ nm). UV spectra were measured on a Hitachi U-2010 spectrophotometer. IR spectra were recorded on a Perkin-Elmer 577 spectrometer with KBr disks. ^1H NMR, ^{13}C NMR, $^1H-^1H$ COSY, HMBC, HMQC, NOESY, and ROESY spectra were obtained on Bruker AM-500, Varian Mercury-400, and Varian Inova-600 spectrometers (CD_3OD at δ_H 3.30 and δ_C 49.3; TMS as internal standard). EIMS spectra (70 eV) were carried out on a Finnigan MAT 95 instrument. All solvents used were of analytical grade (Shanghai Chemical Plant). Silica gel (200−300 mesh), silica gel H_{60}, and amino silica gel (20−45 μM, Fuji Silysia Chemical LTD, Japan) were used for column chromatography, and precolated silica gel GF_{254} plates (Qingdao Haiyang Chemical Plant, Qingdao, People's Republic of China) were used for TLC.

Plant Material. Stems and leaves of *Daphniphyllum longeracemosum* Rosenth. were collected from Maguan County of Yunnan Province, People's Republic of China, in November 2004 and were identified by Dr. Qiang Fan of the Institute of Botany, School of Life Sciences, Zhongshan University. A voucher specimen was deposited in Shanghai Institute of Materia Medica (Accession number: DL-2004-1Y).

Extraction and Isolation. The dried and powdered of stems and leaves (5.2 kg) of *D. longeracemosum* were percolated three times with 95% EtOH. After removal of solvent under reduced pressure, the crude extract (0.8 kg) was dissolved in 1.5 L of H_2O to form a suspension and was adjusted with 10% H_2SO_4 to pH ~4. The acidic mixture was immediately defatted with EtOAc (1000 mL × 4), and the aqueous phase was basified with 30% Na_2CO_3 in H_2O to pH 10 and exacted with $CHCl_3$ (300 mL × 4) to obtain 3.20 g of crude alkaloids. The crude alkaloids were then subjected to silica gel column chromatography using a gradient solvent system of petroleum/EtOAc/Et_2NH (20:1:0.3 to 1:1:0.3, v/v/v) to give seven major fractions. Fraction 1 (1.3 g) was rechromatographed over a silica gel column (petroleum/2-propanol, 1:1) to give two major fractions. Each of them was then purified by silica gel (petroleum/EtOAc/ Et_2NH, 10:1:0.3) to yield **4** (0.10 g) and daphniphylline (0.05 g), respectively. Fraction 4 (0.39 g) was separated into four major parts with an amino silica gel column (petroleum/2-propanol, 20:1). Each part was then purified on a silica gel column (petroleum/EtOAc/Et_2NH, 6:1:0.3) to afford **1** (0.15 g), **2** (0.02 g), longistylumphylline A (0.11 g), and deoxyisocalyciphylline B (0.01 g), respectively. Fraction 5 (0.40 g) was chromatographed on a silica gel column eluted with mixture of $CHCl_3$/MeOH (10:1) to give daphnicyclidin D (0.30 g) and **3** (0.02 g).

Daphnilongeranin A (1): gum; $[\alpha]^{20}_D$ −52 (*c* 0.555, $CHCl_3$); UV (CH_3OH) λ_{max} (log ϵ) 291 (3.33); IR (KBr) λ_{max} cm^{-1} 3431 (H_2O), 2926, 1701, 1624, 1437, 1390, 1346, 1257, 1227, 1130, 1063, 762; ^1H and ^{13}C NMR, see Table 1; EIMS 70 eV *m*/*z* (rel int) 383 $[M]^+$ (13), 355 (6), 340 (5), 110 (100); HREIMS *m*/*z* 383.2088 ($C_{23}H_{29}NO_4$, calcd 383.2097).

Daphnilongeranin B (2): amorphous white powder; $[\alpha]^{20}_D$ −159 (*c* 0.101, CH_3OH); UV (CH_3OH) λ_{max} (log ϵ) 244 (3.32); IR (KBr) λ_{max} cm^{-1} 3423 (H_2O), 2916, 2864, 2812, 1703, 1689, 1668, 1479, 1448, 1377, 1261, 1107; ^1H and ^{13}C NMR, see Table 1; EIMS 70 eV *m*/*z* (rel int) 325 $[M]^+$ (100), 310 (13), 297 (10), 282 (10), 269 (15), 254 (10), 160 (19), 149 (16), 129 (13), 110 (86), 81 (24), 69 (40); HREIMS *m*/*z* 325.2025 ($C_{21}H_{27}NO_2$, calcd 325.2042).

Daphnilongeranin C (3): amorphous white powder; $[\alpha]^{20}_D$ −22 (*c* 0.081, CH_3OH); UV (CH_3OH) λ_{max} (log ϵ) 213 (3.08); IR (KBr) λ_{max} cm^{-1} 3666 (hydroxyl of C-22), 3421 (H_2O), 2929, 2835, 1697, 1622, 1462, 1436, 1391, 1320, 1264, 1088, 714; ^1H and ^{13}C NMR, see Table 1; EIMS 70 eV *m*/*z* (rel int) 355 $[M]^+$ (51), 340 (3), 326 (10), 310 (100), 292 (16), 161 (20), 110 (98); HREIMS *m*/*z* 355.2149 ($C_{22}H_{29}NO_3$, calcd 355.2147).

Daphnilongeranin D (4): amorphous white powder; $[\alpha]^{20}_D$ +50 (*c* 0.234, CH_3OH); UV (CH_3OH) λ_{max} (log ϵ) 202 (2.46); IR (KBr) λ_{max} cm^{-1} 3431 (H_2O), 2937, 2870, 1709, 1632, 1473, 1454, 1389, 1323, 1225, 1145, 1057, 829; ^1H and ^{13}C NMR, see Table 1; EIMS 70 eV *m*/*z* (rel int) 485 $[M]^+$ (39), 470 (20), 443 (9), 286 (100), 272 (39), 245 (20), 230 (8); HREIMS *m*/*z* 485.3504 ($C_{30}H_{47}NO_4$, calcd 485.3505).

Hydrolysis of Daphniphylline (5). Alkaloid **5** (20 mg) was dissolved in 5 mL of MeOH, and then 0.1 g of sodium hydroxide was added. The mixture was stirred at room temperature for 3 h. After removal of the MeOH under reduced pressure, the resulting alkaloid was subjected to a silica gel column eluted with petroleum/EtOAc/Et_2NH (6:1:0.3) to afford **4** (15 mg).

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Supporting Information Available: 1D, 2D NMR, EIMS, and IR spectra and figures of $^1H-^1H$ COSY, selected HMBC, and NOESY (ROESY) correlations for compounds **1**−**4**. This material is available free of charge via the Internet at http://pubs.acs.org.

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