

Further Alkaloids from the Fruits of *Daphniphyllum longeracemosum*

by Ting-Quan Yang^{a) b)}, Ying-Tong Di^{a)}, Hong-Ping He^{a)}, Qiang Zhang^{a)}, Yu Zhang^{a)}, and Xiao-Jiang Hao^{*a)}

^{a)} State Key Laboratory of Phytochemistry and Plant Resources in West China, Kunming Institute of Botany, Chinese Academy of Sciences, Kunming 650204, P. R. China

(phone: +86-871-5223263; fax: +86-871-5219684; e-mail: haoxj@mail.kib.ac.cn)

^{b)} Graduate University of the Chinese Academy of Sciences, Beijing 100049, P. R. China

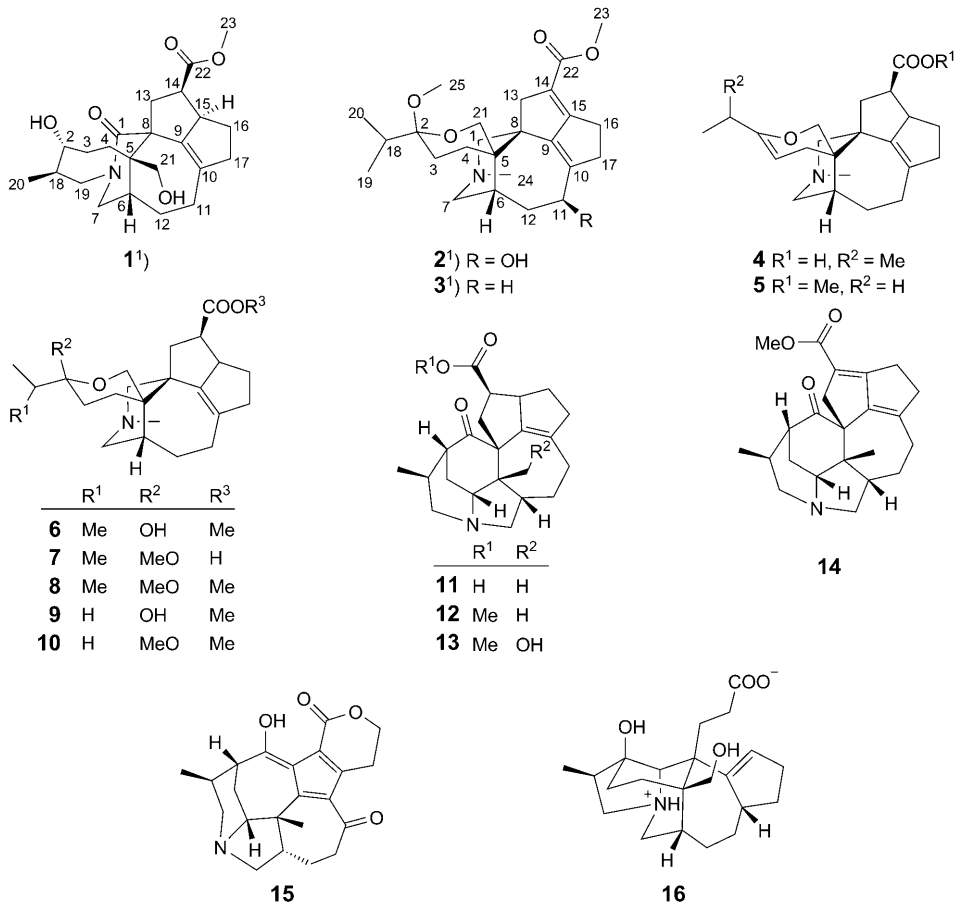
Three new *Daphniphyllum* alkaloids, daphlongeranines C–E (**1–3**), along with 13 known ones, were isolated from the fruits of *Daphniphyllum longeracemosum*. Their structures were elucidated on the basis of extensive spectroscopic analyses, especially 2D-NMR experiments.

Introduction. – *Daphniphyllum* alkaloids with complex polycyclic skeletons, as the characteristic constituent of the genus *Daphniphyllum*, are a group of structurally diverse natural products [1]. The structural diversity of them with unparalleled polycyclic ring systems may be explained by unique biogenetic processes, involving fission of C–C and/or C–N bonds followed by oxidation, methylation, rearrangements, cyclizations, and so on [1a]. Their fused heterocyclic systems have attracted great interest as challenging programs for total synthesis [2] as well as for biosynthetic research [3]. Until now, more than 220 alkaloids have been isolated from this genus [1–10].

Plants of the genus *Daphniphyllum* comprise 30 species, of which ten grow in China [1]. *Daphniphyllum longeracemosum* ROSENTH. is an evergreen tree distributed in Yunnan Province, P. R. China [4d]. Our previous studies on this plant have resulted in the isolation of a series of novel alkaloids, such as daphlongeranines A and B [4a], daphnilongerine [4b], and of the recently reported alkaloid daphenylline [4c] possessing a unique polycyclic system without O-atoms. In the present investigation on the fruits of *D. longeracemosum*, three new alkaloids, daphlongeranines C–E¹⁾ (**1–3**), were obtained, together with 13 known analogues. In this article, we present the isolation and structure elucidation of the three new compounds.

Results and Discussion. – Daphlongeranine C (**1**), isolated as a white amorphous powder, possesses the molecular formula C₂₃H₃₃NO₅ as determined by the HR-ESI-MS quasi-molecular-ion peak at *m/z* 426.2259 ($[M + Na]^+$), requiring eight degrees of unsaturation. The IR absorption bands at 3436, 1731, and 1665 cm⁻¹ suggested the presence of OH, ester C=O, and lactam functionalities, respectively [5]. Analysis of the ¹³C-NMR (Table 1), DEPT, and HSQC spectra showed 23 C-atom signals due to two C=O groups, one tetrasubstituted olefin moiety ($\delta(C)$ 135.7 and 139.6), two sp³

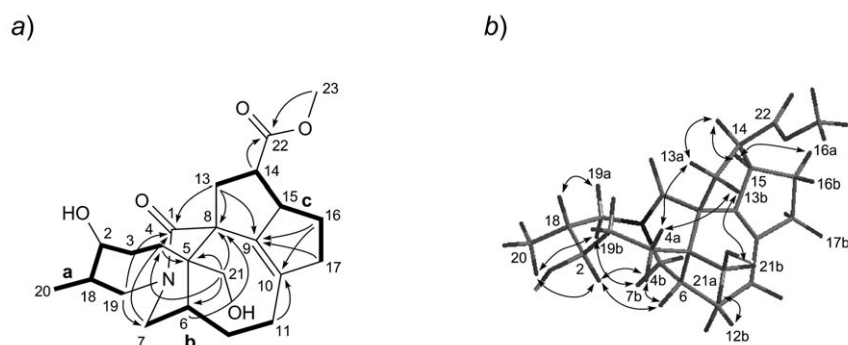
¹⁾ Trivial atom numbering; for systematic names, see *Exper. Part*.



quaternary C-atoms, and five sp^3 CH, ten sp^3 CH₂, one Me, and one MeO group. Among them, two CH₂ ($\delta(C)$ 54.7 and 51.5) and one C=O group ($\delta(C)$ 176.3) were ascribed to moieties bearing an N-atom, while one CH ($\delta(C)$ 74.3) and one CH₂ group ($\delta(C)$ 68.1) were bearing an O-substituent [4–6]. Since the ester C=O, lactam C=O, and C=C bond accounted for three out of eight degrees of unsaturation, the remaining were assumed to be due to the presence of a pentacyclic system in **1**. Detailed 2D-NMR (HSQC, ¹H,¹H-COSY, TOCSY, and HMBC experiments) studies revealed the molecular framework of **1**. The ¹H,¹H-COSY and TOCSY signals disclosed three substructures: **a** (C(2) to C(4), C(2) to C(18), and C(18) to C(19) and C(20)), **b** (C(6) to C(7), C(6) to C(12), and C(11) to C(12)) and **c** (C(13) to C(17)) as shown in Fig. 1, a. The HMBs CH₂(13)/C(8) and C(9), CH₂(16)/C(9) and C(10), H–C(15)/C(9), and CH₂(17)/C(9) suggested that substructure **c** was linked to three quaternary C-atoms, C(8), C(9), and C(10). For substructure **b**, C(11) was connected to C(10) as shown by the HMBs CH₂(11)/C(10) and CH₂(12)/C(10). The connectivity from C(6) to C(8) *via* a quaternary C-atom, C(5), was suggested by the HMBs CH₂(21)/C(5), CH₂(21)/

Table 1. ^1H - and ^{13}C -NMR Data (400 and 100 MHz, resp., CD_3OD) of **1**. δ in ppm, J in Hz.

	$\delta(\text{H})$	$\delta(\text{C})$		$\delta(\text{H})$	$\delta(\text{C})$
C(1)	–	176.3 (s)	H _a -C(13)	2.51 (dd, $J = 13.2, 8.8$)	35.7 (t)
H-C(2)	3.42–3.46 (m)	74.3 (d)	H _b -C(13)	2.18–2.21 (m)	
H _a -C(3)	1.63–1.67 (m)	37.6 (t)	H-C(14)	3.03–3.09 (m)	43.3 (d)
H _b -C(3)	1.78–1.82 (m)		H-C(15)	3.20–3.26 (m)	54.6 (d)
H _a -C(4)	1.52–1.58 (m)	37.2 (t)	H _a -C(16)	1.73–1.78 (m)	29.2 (t)
H _b -C(4)	1.92–1.98 (m)		H _b -C(16)	1.08–1.13 (m)	
C(5)	–	46.3 (s)	H _a -C(17)	2.13–2.19 (m)	43.0 (t)
H-C(6)	2.53–2.59 (m)	37.8 (d)	H _b -C(17)	2.39–2.45 (m)	
H _a -C(7)	3.37–3.42 (m)	51.5 (t)	H-C(18)	2.07–2.13 (m)	37.7 (d)
H _b -C(7)	3.64 (dd, $J = 14.0, 8.0$)		H _a -C(19)	4.10 (dd, $J = 14.0, 8.0$)	54.7 (t)
C(8)	–	57.5 (s)	H _b -C(19)	2.34 (dd, $J = 14.0, 6.8$)	
C(9)	–	139.6 (s)	Me(20)	0.86 (d, $J = 8.5$)	17.5 (q)
C(10)	–	135.7 (s)	H _a -C(21)	3.54 (br. d, $J = 10.8$)	68.1 (t)
H _a -C(11)	2.22–2.27 (m)	25.4 (t)	H _b -C(21)	3.91 (br. d, $J = 10.8$)	
H _b -C(11)	2.22–2.27 (m)		C(22)	–	177.4 (s)
H _a -C(12)	1.59–1.63 (m)	25.7 (t)	Me(23)O	3.55 (s)	51.8 (q)
H _b -C(12)	2.38–2.42 (m)				

Fig. 1. a) ^1H - ^1H -COSY and TOCSY (—) as well as key HMBC data ($\text{H} \rightarrow \text{C}$) of **1**¹; b) key ROESY correlations ($\text{H} \leftrightarrow \text{H}$) of **1**¹

C(6), $\text{CH}_2(21)/\text{C}(8)$, and $\text{H}-\text{C}(6)/\text{C}(8)$. Thus, substructures **b** and **c**, along with the quaternary C-atoms, established three fused rings (two five- and one seven-membered ring), a structural feature that is very common in *Daphniphyllum* alkaloids. The HMBCs $\text{CH}_2(19)/\text{C}(1)$ ($\delta(\text{C})$ 176.3) and C(7) and $\text{CH}_2(7)/\text{C}(1)$ indicated that C(1) represents the lactam C=O group. The two CH_2 groups assigned to C(7) and C(19) were attributable to those attached to an N-atom. Furthermore, the HMBCs $\text{CH}_2(13)/\text{C}(1)$, $\text{CH}_2(4)/\text{C}(5)$, and $\text{CH}_2(21)/\text{C}(4)$ suggested that the remaining moiety of **1** possesses a 1-azabicyclo[5.2.2]undecane ring system. Thus, the constitutional formula of **1** was elucidated as shown in Fig. 1, a. The relative configuration of **1** was subsequently elucidated by the NOESY data as shown in a computer-generated 3D drawing (Fig. 1, b). NOE Correlations $\text{H}_b-\text{C}(21)/\text{H}_b-\text{C}(13)$, $\text{H}_a-\text{C}(13)/\text{H}-\text{C}(14)$, and

H–C(14)/H–C(15) indicated that both H–C(14) and H–C(15) are on the same side, namely α -oriented. The correlations of H_b–C(4)/H–C(2), H_b–C(4)/H–C(6), H–C(2)/H–C(6), H_b–C(7)/H_b–C(19), Me(20)/H_b–C(19), and Me(20)/H–C(2) suggested that H–C(2), H–C(6), H_b–C(7), H_b–C(19), and Me(20) are all on the same side. Thus, the OH group at C(2) has α -orientation and Me(20) β -orientation.

Daphlongeranine D (**2**) exhibited the *pseudo*-molecular-ion peak at m/z 432 ($[M + H]^+$) in the FAB-MS, and the molecular formula C₂₅H₃₇NO₅ was established by HR-ESI-MR (m/z 432.2744 $[M + H]^+$) with eight degrees of unsaturation. The IR absorption band at 3430 cm⁻¹ suggested the presence of an OH group. The UV absorption at 296 nm (log ϵ = 4.1) and IR bands at 1696, 1655, and 1630 cm⁻¹ indicated the presence of an $\alpha\beta,\gamma\delta$ -unsaturated ester C=O group [7][8a], a presumption which was corroborated by the ¹³C-NMR data of the relevant C-atoms (Table 2) of **2** (δ (C) 117.7, 147.9, 152.7, 166.5, and 168.3) [7]. The NMR data of **2** displayed the characteristic features of a yuzurine-type *Daphniphyllum* alkaloid, and showed a high similarity with those of the alkaloid daphgracine (= (3'R,4S,6'R,10aR)-2,3,4,5,5',6,6',7,8,10-decahydro-6'-hydroxy-2-methyl-6'-(1-methylethyl)spiro[1H-4,10a-methanopentaleno[1,6-*cd*]azocine-11,3'(4'H)-[2H]pyran]-9-carboxylic acid methyl ester) [7] as judged from the presence of an O-bearing CH₂ group (δ (C) 62.5; δ (H) 3.41 (*dd*, J = 12.5, 3.0 Hz) and 3.92 (*d*, J = 12.5 Hz)), a MeN group (δ (C) 45.3; δ (H) 2.18 (*br. s*)), and of a quaternary C-atom (δ (C) 100.3) group. Compared to daphgracine, one hydroxylated CH group (δ (C) 64.1) was attributed to C(11) on the basis of the HMBCs H–C(11)/C(6), C(9), and C(17), at the same time, the downfield shift by *ca.* 3 ppm of the quaternary hemiacetal C-atom of daphgracine (δ (C) 97.8) implied that a MeO group (δ (C) 46.9; δ (H) 3.13 (*s*)) instead of an OH group was linked to C(2) of **2**, which was verified by the HMBC MeO/C(2). Thus, the gross structure of **2** was elucidated as shown in Fig. 2, *a*. The relative configuration of **2** was deduced from a ROESY experiment, as illustrated in a computer-generated 3D drawing (Fig. 2, *b*). The ROESY correlations H_a–C(21)/H_b–C(4) and H_a–C(21)/H_b–C(13) implied that the A-ring is present in a chair conformation. The correlations H_b–C(21)/H_b–C(12) and H_b–C(12)/H–C(6) inferred β -orientation for H–C(6). Subsequently, H–C(11) was assumed to be on the α -

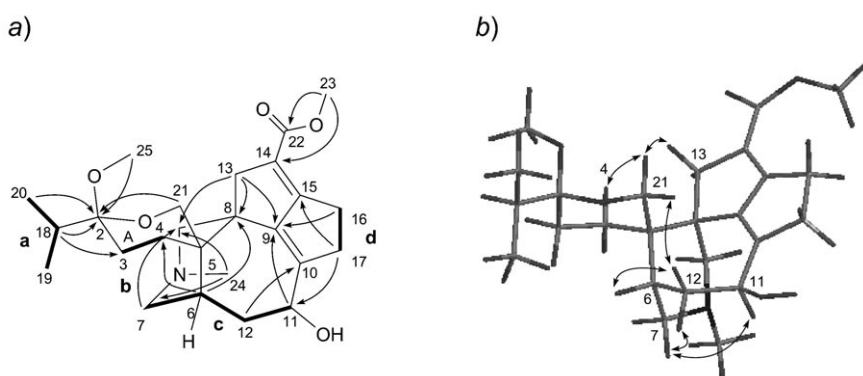


Fig. 2. a) ¹H,¹H-COSY (—) and key HMBC data (H → C) of **2**. b) Key ROESY correlations (H ↔ H) of **2**.

face on the basis of the correlations $H_a-C(7)/H_a-C(12)$ and $H_a-C(7)/H-C(11)$, as further supported by the corresponding NMR signal for $H-C(11)$ ($\delta(H)$ 4.17 (*dd*, $J = 10.2, 5.6$ Hz)) due to very different dihedral angles. Thus, $OH-C(11)$ was β -oriented.

Table 2. 1H - and ^{13}C -NMR Data (400 and 100 MHz, resp.) of **2** and **3**. δ in ppm, J in Hz

	2 ^{a)}		3 ^{b)}	
	$\delta(H)$	$\delta(C)$	$\delta(H)$	$\delta(C)$
$H_a-C(1)$	2.71–2.76 (<i>m</i>)	59.4 (<i>t</i>)	2.26–2.31 (<i>m</i>)	61.5 (<i>t</i>)
$H_b-C(1)$	2.39–2.44 (<i>m</i>)		2.22 (<i>d</i> , $J = 10.8$)	
C(2)	–	100.3 (<i>s</i>)	–	100.8 (<i>s</i>)
$H_a-C(3)$	1.53–1.59 (<i>m</i>)	24.3 (<i>t</i>)	1.32–1.39 (<i>m</i>)	21.4 (<i>t</i>)
$H_b-C(3)$	1.53–1.59 (<i>m</i>)		1.61–1.68 (<i>m</i>)	
$H_a-C(4)$	1.55–1.61 (<i>m</i>)	21.5 (<i>t</i>)	1.55–1.61 (<i>m</i>)	20.9 (<i>t</i>)
$H_b-C(4)$	1.68–1.73 (<i>m</i>)		1.90–1.97 (<i>m</i>)	
C(5)	–	35.1 (<i>s</i>)	–	35.6 (<i>s</i>)
$H-C(6)$	2.42–2.47 (<i>m</i>)	33.1 (<i>d</i>)	2.20–2.24 (<i>m</i>)	32.7 (<i>d</i>)
$H_a-C(7)$	2.93–2.98 (<i>m</i>)	54.6 (<i>t</i>)	2.52 (<i>dd</i> , $J = 11.6, 2.8$)	55.9 (<i>t</i>)
$H_b-C(7)$	2.73–2.79 (<i>m</i>)		2.68 (<i>d</i> , $J = 11.6$)	
C(8)	–	46.8 (<i>s</i>)	–	46.2 (<i>s</i>)
C(9)	–	147.9 (<i>s</i>)	–	149.8 (<i>s</i>)
C(10)	–	152.7 (<i>s</i>)	–	153.7 (<i>s</i>)
$H_a-C(11)$	4.17 (<i>dd</i> , $J = 10.2, 5.6$)	64.1 (<i>d</i>)	2.07–2.14 (<i>m</i>)	27.7 (<i>t</i>)
$H_b-C(11)$			2.90–2.96 (<i>m</i>)	
$H_a-C(12)$	2.04–2.08 (<i>m</i>)	33.9 (<i>t</i>)	1.69–1.74 (<i>m</i>)	27.4 (<i>t</i>)
$H_b-C(12)$	2.28–2.37 (<i>m</i>)		2.12–2.19 (<i>m</i>)	
$H_a-C(13)$	2.81–2.86 (<i>m</i>)	40.2 (<i>t</i>)	2.24–2.28 (<i>m</i>)	42.7 (<i>t</i>)
$H_b-C(13)$	3.19–3.26 (<i>m</i>)		3.07 (<i>br. d</i> , $J = 16.0$)	
C(14)	–	117.7 (<i>s</i>)	–	115.8 (<i>s</i>)
C(15)	–	168.3 (<i>s</i>)	–	169.1 (<i>s</i>)
$H_a-C(16)$	2.65–2.70 (<i>m</i>)	24.8 (<i>t</i>)	2.61–2.68 (<i>m</i>)	25.8 (<i>t</i>)
$H_b-C(16)$	2.65–2.70 (<i>m</i>)		2.61–2.68 (<i>m</i>)	
$H_a-C(17)$	2.35–2.38 (<i>m</i>)	42.2 (<i>t</i>)	2.78–2.84 (<i>m</i>)	41.9 (<i>t</i>)
$H_b-C(17)$	3.25–2.29 (<i>m</i>)		2.78–2.84 (<i>m</i>)	
$H-C(18)$	1.83–1.90 (<i>m</i>)	37.6 (<i>d</i>)	1.99–2.05 (<i>m</i>)	31.3 (<i>d</i>)
Me(19)	0.90 (<i>d</i> , $J = 8.0$)	16.8 (<i>q</i>)	0.91 (<i>d</i> , $J = 6.8$)	17.3 (<i>q</i>)
Me(20)	0.88 (<i>d</i> , $J = 8.0$)	16.1 (<i>q</i>)	0.82 (<i>d</i> , $J = 7.2$)	16.3 (<i>q</i>)
$H_a-C(21)$	3.92 (<i>d</i> , $J = 12.5$)	62.5 (<i>t</i>)	3.37 (<i>br. d</i> , $J = 11.6$)	62.9 (<i>t</i>)
$H_b-C(21)$	3.41 (<i>dd</i> , $J = 12.5, 3.0$)		3.56 (<i>dd</i> , $J = 11.6, 2.8$)	
C(22)	–	166.5 (<i>s</i>)	–	167.1 (<i>s</i>)
Me(23)O	3.71 (<i>s</i>)	52.1 (<i>q</i>)	3.70 (<i>s</i>)	50.8 (<i>q</i>)
Me(24)N	2.18 (<i>br. s</i>)	45.3 (<i>q</i>)	2.14 (<i>br. s</i>)	46.1 (<i>q</i>)
Me(25)O	3.13 (<i>s</i>)	46.9 (<i>q</i>)	3.09 (<i>s</i>)	46.3 (<i>q</i>)

^{a)} In CD_3OD . ^{b)} In $CDCl_3$.

Daphlongeranine E (**3**) showed the molecular formula $C_{25}H_{37}NO_4$ as established by HR-ESI-MS (m/z 416.2805 ($[M+H]^+$)). The presence of 25 C-atom signals was suggested by the ^{13}C -NMR and DEPT spectra. Extensive comparison of the relative molecular mass and the ^{13}C -NMR data of **3** with those of daphgracine revealed that they possess highly similar structures, except for the presence of a MeO group in **3**

instead of an OH group in daphgracine. The planar structure of **3** with a MeO group at C(2) was finally established by the HMBC Me(25)/C(2). Alkaloid **3** had the same relative configuration as daphgracine, which was further verified by the ROESY data.

In addition to the three new alkaloids, 13 known *Daphniphyllum* alkaloids, namely longistylumphylline B (**4**) [8a], dehydrodaphnigraciline (**5**) [9a], daphnigracine (**6**) [9a], daphnezomic acid (**7**) [8b], daphnezomine R (**8**) [5c], daphnigraciline (**9**) [9a], yuzurine (**10**) [9b], daphnilongeranin C (**11**) [10a], daphniyunnine A (**12**) [10b], daphniglaucaine D (**13**) [5d], longistylumphylline A (**14**) [8a], daphnicyclidin A (**15**) [5e], and daphnezomine S (**16**) [5c] were identified on the basis of reported physical, NMR, and ESI-MS data, some of which were also confirmed by co-TLC with authentic samples. Although the 16 *Daphniphyllum* alkaloids isolated from the fruits could be classified into five different C-atom skeletons, the yuzurine-type alkaloids are predominant. It may be worthy to point out that alkaloid **1** with a 1-azabicyclo[5.2.2]undecane ring system was obtained from *Daphniphyllum longeracemosum* for the first time.

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Experimental Part

General. TLC: silica-gel (SiO₂) plates; visualization by *Dragendorff's* reagent. Column chromatography (CC): SiO₂ H (10–40 μm; *Qingdao Marine Chemical Co., Ltd.*), amino SiO₂ (90–140 μm; *Fuji Silysia Chemical Ltd.*), *Sephadex LH-20* (40–70 μm; *Pharmacia*), and *Lichroprep RP-18* gel (40–63 μm; *Merk*). MPLC: instrument including a *Büchi* pump module C-605 and a *Büchi* pump manager C-615. Optical rotations: *Jasco-DIP-370* digital polarimeter. UV Spectra: *Shimadzu UV-2401PC*; λ_{max} (log ε) in nm. IR Spectra: *Bio-Rad-FTS-135* spectrometer; KBr discs; in cm⁻¹. ¹H- and ¹³C-NMR Spectra: *Bruker-AM-400* instrument (400 and 100 MHz) and *Bruker-DRX-500* instrument (500 and 125 MHz); δ in ppm rel. to Me₄Si as internal standard, *J* in Hz. ESI-MS: *Finnigan-MAT-90* instrument; in *m/z*. HR-ESI-MS: *API-Qstar-Pulsar* LC/TOF instrument; in *m/z*.

Plant Material. The fruits of *Daphniphyllum longeracemosum* were collected in Hekou of Yunnan Province, P. R. China, in October 2008. The material was identified by Prof. *Xun Gong*, and a specimen was deposited with the State Key Laboratory of Phytochemistry and Plant Resources in West China, Kunming Institute of Botany, Chinese Academy of Sciences.

Extraction and Isolation. The air-dried and powdered fruits of *D. longeracemosum* (13.0 kg) were extracted with MeOH, and the crude extract was adjusted to pH 3 with 2% HCl soln. The acidic mixture was defatted with petroleum ether and then subjected to cation-exchange resin to give the crude alkaloid (41 g). The material was subjected to CC (CHCl₃/MeOH 100:0 → 0:1): *Fractions A–F*. *Fr. C* (6.2 g) was further subjected to CC (SiO₂, petroleum ether/Et₂NH 50:1 → 20:1, CHCl₃/MeOH 60:1 → 10:1; followed by *Sephadex LH-20* CC, MeOH): **2** (3 mg), **3** (11 mg), **5** (13 mg), **6** (13 mg), **8** (17 mg), **9** (33 mg), and **10** (19 mg). *Fr. D* was subjected to CC (*Sephadex LH-20*, CHCl₃/MeOH 1:1; then SiO₂, petroleum ether/acetone 10:1): **1** (4 mg), **12** (44 mg), **13** (8 mg), and **14** (19 mg). *Fr. E* (23 g) was separated by CC (C₁₈ SiO₂ and then *Sephadex LH-20*, MeOH): **4** (21 mg) and **7** (38 mg). Compounds **11** (6.8 g), **15** (3.1 g), and **16** (29 mg) were crystallized from *Fr. E*.

Daphnilongeranin C (=rel-(4R,5R,7aR,8S,12aR,13R,14aS)-3,4,5,6,7,7a,8,9,10,11,12,12a,13,14-Tetra-decahydro-5-hydroxy-7a-(hydroxymethyl)-4-methyl-1-oxo-1H-2,8-methanocyclopent[1,8]azuleno[3a,4-c]azonine-13-carboxylic Acid Methyl Ester; **1**): White amorphous powder. [α]_D^{23.4} = –47.07 (c = 0.52, MeOH). IR (KBr): 3436, 2931, 1731, 1665, 1246. ¹H- and ¹³C-NMR: *Table 1*. ESI-MS: 426 ([M + Na]⁺). HR-ESI-MS: 426.2259 ([M + Na]⁺; C₂₃H₃₃NNaO₅⁺; calc. 426.2256).

Daphlongeranine D (= (3'R,4S,6S,6'R,10aR)-2,3,4,5,5',6,6',7,8,10-Decahydro-6-hydroxy-(6'-methoxy-2-methyl-6'-(1-methylethyl)spiro[1H-4,10a-methanopentaleno[1,6-cd]azonine-11,3' (4'H)-[2H]pyran]-9-carboxylic Acid Methyl Ester; **2**): Colorless solid. $[\alpha]_{\text{D}}^{23.5} = -38.01$ ($c = 0.40$, MeOH). UV (MeOH): 296 (4.1). IR (KBr): 3430, 2925, 1696, 1655, 1630, 1456, 1167, 1018. ¹H- and ¹³C-NMR: Table 2. ESI-MS: 432 ($[M + H]^+$). HR-ESI-MS: 432.2744 ($[M + H]^+$, C₂₅H₃₈NO₅⁺; calc. 432.2749).

Daphlongeranine E (= (3'R,4S,6'R,10aR)-2,3,4,5,5',6,6',7,8,10-Decahydro-(6'-methoxy-2-methyl-6'-(1-methylethyl)spiro[1H-4,10a-methanopentaleno[1,6-cd]azonine-11,3' (4'H)-[2H]pyran]-9-carboxylic Acid Methyl Ester; **3**): White solid. $[\alpha]_{\text{D}}^{23.5} = -21.04$ ($c = 0.26$, MeOH). UV (MeOH): 298 (3.9). IR (KBr): 2956, 1690, 1660, 1625, 1460, 1350, 1248, 1067. ¹H- and ¹³C-NMR: Table 2. ESI-MS: 416 ($[M + H]^+$). HR-ESI-MS: 416.2805 ($[M + H]^+$, C₂₅H₃₈NO₄⁺; calc. 416.2800).

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