Further Alkaloids from the Fruits of *Daphniphyllum longeracemosum*

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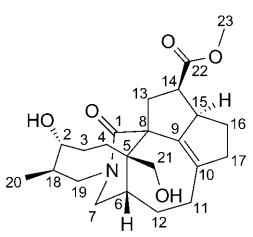
Three new *Daphniphyllum* alkaloids, daphlongeranines C–E (**1**–**3**), along with 13 known ones, were isolated from the fruits of *Daphniphyllum longeracemosum*. Their structures were elucidated on the basis of extensive spectroscopic analyses, especially 2D-NMR experiments.

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].

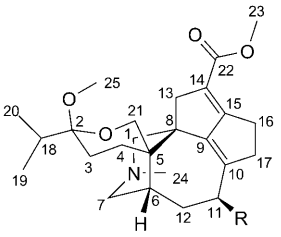
Plants of the genus *Daphniphyllum* comprise 30 species, of which ten grow in China [1]. *Daphniphyllum longeracemosum* ROSENTH. is an evergreen tree distributed in Yunnan Province, P. R. China [4d]. Our previous studies on this plant have resulted in the isolation of a series of novel alkaloids, such 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–E[1]) (**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 $C_{23}H_{33}NO_5$ 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 ^{13}C-NMR (*Table 1*), DEPT, and HSQC spectra showed 23 C-atom signals due to two C=O groups, one tetrasubstituted olefin moiety (δ(C) 135.7 and 139.6), two sp^3

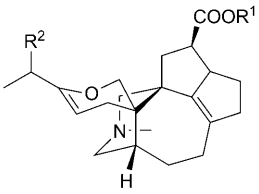
[1]) Trivial atom numbering; for systematic names, see *Exper. Part.*



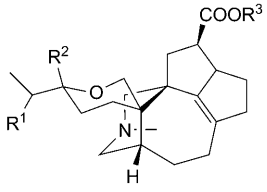
1[1])



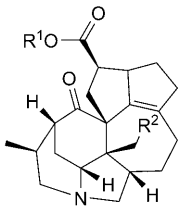
2[1]) R = OH
3[1]) R = H



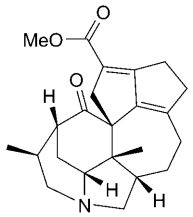
4 R^1 = H, R^2 = Me
5 R^1 = Me, R^2 = H



	R^1	R^2	R^3
6	Me	OH	Me
7	Me	MeO	H
8	Me	MeO	Me
9	H	OH	Me
10	H	MeO	Me



	R^1	R^2
11	H	H
12	Me	H
13	Me	OH



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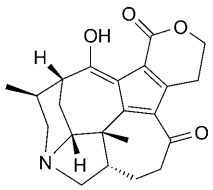

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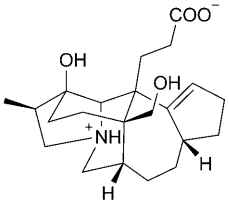

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quaternary C-atoms, and five sp^3 CH, ten sp^3 CH_2, one Me, and one MeO group. Among them, two CH_2 (δ(C) 54.7 and 51.5) and one C=O group (δ(C) 176.3) were ascribed to moieties bearing an N-atom, while one CH (δ(C) 74.3) and one CH_2 group (δ(C) 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, ^{1}H,^{1}H-COSY, TOCSY, and HMBC experiments) studies revealed the molecular framework of **1**. The ^{1}H,^{1}H-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 HMBCs CH_2(13)/C(8) and C(9), CH_2(16)/C(9) and C(10), H–C(15)/C(9), and CH_2(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 HMBCs CH_2(11)/C(10) and CH_2(12)/C(10). The connectivity from C(6) to C(8) *via* a quaternary C-atom, C(5), was suggested by the HMBCs CH_2(21)/C(5), CH_2(21)/

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

	δ(H)	δ(C)		δ(H)	δ(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*)				

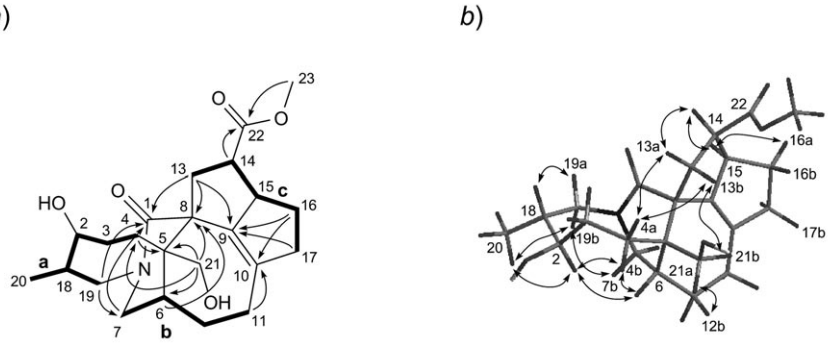

Fig. 1. a) *^{1}H,^{1}H-COSY and TOCSY* (—) *as well as key HMBC data* (H → C) *of* **1**[1]*;* b) *key ROESY correlations* (H ↔ H) *of* **1**[1])

C(6), CH_2(21)/C(8), and H–C(6)/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 CH_2(19)/C(1) (δ(C) 176.3) and C(7) and CH_2(7)/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 CH_2(13)/C(1), CH_2(4)/C(5), and CH_2(21)/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 H_b–C(21)/H_b–C(13), H_a–C(13)/H–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 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 $C_{25}H_{37}NO_5$ 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 ($\log \varepsilon = 4.1$) 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 ^{13}C-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*,4*S*,6′*R*,10a*R*)-2,3,4,5,5′,6,6′,7,8,10-decahydro-6′-hydroxy-2-methyl-6′-(1-methylethyl)spiro[1*H*-4,10a-methanopentaleno[1,6-*cd*]azonine-11,3′(4′*H*)-[2*H*]pyran]-9-carboxylic acid methyl ester) [7] as judged from the presence of an O-bearing CH_2 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-

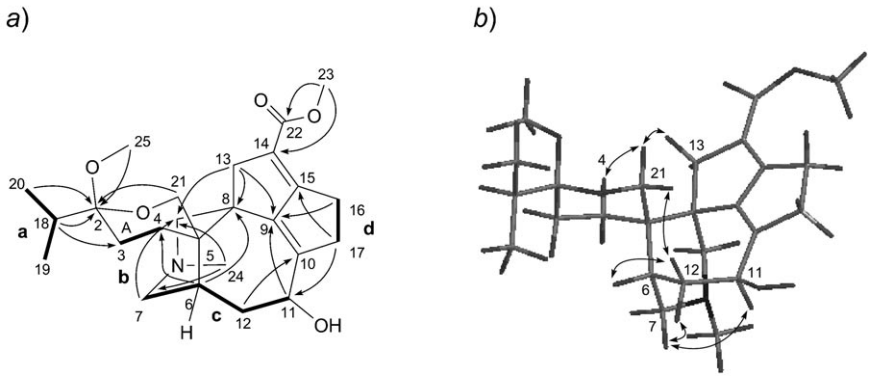

Fig. 2. a) *^{1}H,^{1}H-COSY* (—) *and key HMBC data* (H → C) *of* **2**[1]). b) *Key ROESY correlations* (H ↔ H) *of* **2**[1])

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

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

[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], daphniglaucine 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.

The financial support of the *Chinese Academy of Sciences* (2907024412P1) and the State Key Laboratory of Phytochemistry and Plant Resources in West China, Kunming Institute of Botany (52O807E11211) of PRC is acknowledged. We are grateful to Prof. *Xun Gong*, Kunming Institute of Botany, Chinese Academy of Sciences (CAS), for the identification of the plant material.

Experimental Part

General. TLC: silica-gel (SiO_2) plates; visualization by *Dragendorff*'s reagent. Column chromatography (CC): SiO_2 *H* (10–40 μm; *Qingdao Marine Chemical Co., Ltd.*), amino SiO_2 (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}. ^{1}H- and ^{13}C-NMR Spectra: *Bruker-AM-400* instrument (400 and 100 MHz) and *Bruker-DRX-500* instrument (500 and 125 MHz); δ in ppm rel. to Me_4Si 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 ($CHCl_3$/MeOH 100:0 → 0:1): *Fractions A–F. Fr. C* (6.2 g) was further subjected to CC (SiO_2, petroleum ether/Et_2NH 50:1 → 20:1, $CHCl_3$/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*, $CHCl_3$/MeOH 1:1; then SiO_2, 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 (C_{18} SiO_2 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*.

Daphlongeranine C (= rel-(*4*R,*5*R,*7a*R,*8*S,*12a*R,*13*R,*14a*S)-*3,4,5,6,7,7a,8,9,10,11,12,12a,13,14-Tetradecahydro-5-hydroxy-7a-(hydroxymethyl)-4-methyl-1-oxo-1*H-*2,8-methanocyclopent[1,8]azuleno[3a,4-c]azonine-13-carboxylic Acid Methyl Ester*; **1**): White amorphous powder. $[\alpha]_D^{23.4} = -47.07$ ($c = 0.52$, MeOH). IR (KBr): 3436, 2931, 1731, 1665, 1246. ^{1}H- and ^{13}C-NMR: *Table 1*. ESI-MS: 426 ($[M+Na]^+$). HR-ESI-MS: 426.2259 ($[M+Na]^+$; $C_{23}H_{33}NNaO_5^+$; calc. 426.2256).

Daphlongeranine D (=*(3′*R,*4*S,*6′*R,*10a*R*)-2,3,4,5,5′,6,6′,7,8,10-Decahydro-6-hydroxy-(6′-methoxy-2-methyl-6′-(1-methylethyl)spiro[1*H*-4,10a-methanopentaleno[1,6-*cd*]azonine-11,3′(4′*H*)-[2*H*]pyran]-9-carboxylic Acid Methyl Ester*; **2**): Colorless solid. $[\alpha]_D^{23.5} = -38.01$ ($c = 0.40$, MeOH). UV (MeOH): 296 (4.1). IR (KBr): 3430, 2925, 1696, 1655, 1630, 1456, 1167, 1018. ^{1}H- and ^{13}C-NMR: *Table 2*. ESI-MS: 432 ($[M+H]^+$). HR-ESI-MS: 432.2744 ($[M+H]^+$, $C_{25}H_{38}NO_5^+$; calc. 432.2749).

Daphlongeranine E (=*(3′*R,*4*S,*6′*R,*10a*R*)-2,3,4,5,5′,6,6′,7,8,10-Decahydro-(6′-methoxy-2-methyl-6′-(1-methylethyl)spiro[1*H*-4,10a-methanopentaleno[1,6-*cd*]azonine-11,3′(4′*H*)-[2*H*]pyran]-9-carboxylic Acid Methyl Ester*; **3**): White solid. $[\alpha]_D^{23.5} = -21.04$ ($c = 0.26$, MeOH). UV (MeOH): 298 (3.9). IR (KBr): 2956, 1690, 1660, 1625, 1460, 1350, 1248, 1067. ^{1}H- and ^{13}C-NMR: *Table 2*. ESI-MS: 416 ($[M+H]^+$). HR-ESI-MS: 416.2805 ($[M+H]^+$, $C_{25}H_{38}NO_4^+$; calc. 416.2800).

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Received April 28, 2010