Alkaloids from the Leaves of *Daphniphyllum longeracemosum* ROSENTH.

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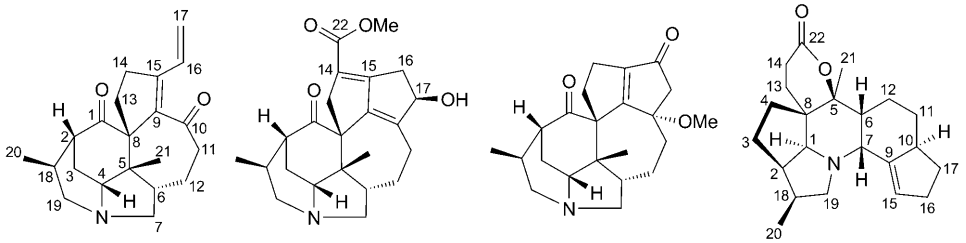
Four new *Daphniphyllum* alkaloids, daphlongamines E–H (**1**–**4**, resp.), along with 19 known alkaloids, were isolated from the leaves of *Daphniphyllum longeracemosum*. Their structures were characterized by spectroscopic methods, especially 2D-NMR techniques. It is noteworthy that aconitine- and veatchine-type diterpenoid alkaloids were also isolated from this species.

Introduction. – *Daphniphyllum* alkaloids, isolated from the genus *Daphniphyllum*, constitute a series of natural products with complex structurally diverse and polycyclic skeletons[1]). These unique compounds have been challenging targets for total syntheses [2] as well as biogenetic studies [3]. *Daphniphyllum longeracemosum* ROSENTH. is an evergreen tree mainly distributed in Yunnan Province, P. R. China. Our investigation on the chemical constituents of this species distributed in different areas of Yunnan Province led to the isolation of several new alkaloids [4]. In our continuing search for biogenetically and structurally interesting alkaloids [5] from leaves of *D. longeracemosum*, four new *Daphniphyllum* alkaloids, daphlongamines E–H (**1**–**4**, resp.), along with 19 known alkaloids, including 14 *Daphniphyllum* alkaloids, as well as four aconitine-type and one veatchine-type diterpenoid alkaloids, were isolated. Herein, we present the isolation and structural elucidation of the new compounds **1**–**4**.



1 **2** **3** **4**

[1]) For a review of *Daphniphyllum* alkaloids, see [1].

Results and Discussion. – Daphlongamine E (**1**) was obtained as an optically active, yellowish solid. Its molecular formula was determined as $C_{21}H_{27}NO_2$ by HR-ESI-MS (*m/z* 326.2114 ($[M+H]^+$), calc. 326.2120), requiring nine degrees of unsaturation. The IR absorption band at 1695 cm^{-1} implied the presence of an α,β-unsaturated ketone group. The ^{13}C-NMR spectrum displayed signals of 21 C-atoms, including those of two ketone C=O groups at δ(C) 218.1 and 205.2, and of two conjugated C=C bonds, which accounted for four degrees of unsaturation. The remaining five degrees of unsaturaton, thus, could only be attributed to the existence of a pentacyclic ring system. Extensive analysis of ^{1}H- and ^{13}C-NMR (*Tables 1* and *2*, resp.), HSQC, ^{1}H,^{1}H-COSY, and HMBC allowed us to establish the structure of **1** to daphlongamine E, a *seco*-10,17-daphnilongeranin B-type alkaloid.

Table 1. *^{1}H-NMR Data of* **1**–**4**. Measured in $CDCl_3$ at 500 MHz; δ in ppm, *J* in Hz.

	1	**2**	**3**	**4**
H–C(1)	–	–	–	3.90 (*d*, *J* = 4.0)
H–C(2)	1.98–2.02 (*m*)	2.14–2.18 (*m*)	2.08–2.14 (*m*)	2.92–2.96 (*m*)
H_α–C(3)	1.98–2.03 (*m*)	2.00 (*t*, *J* = 2.5)	1.99–2.02 (*m*)	1.74–1.77 (*m*)
H_β–C(3)	2.30–2.36 (*m*)	2.20–2.23 (*m*)	2.11–2.15 (*m*)	
H_α–C(4)	3.49 (*d*, *J* = 4.4)	3.29 (br. *s*)	3.48 (*d*, *J* = 6.0)	1.85–1.87 (*m*)
H_β–C(4)	–	–	–	2.14–2.19 (*m*)
H–C(6)	2.25–2.31 (*m*)	2.24–2.29 (*m*)	2.22–2.27 (*m*)	2.38–2.42 (*m*)
H_α–C(7)	2.80–2.85 (*m*)	2.78–2.85 (*m*)	2.89–2.91 (*m*)	–
H_β–C(7)	2.75 (*t*, *J* = 7.2)	2.78–2.85 (*m*)	2.96 (*dd*, *J* = 16.0, 11.5)	4.07 (*d*, *J* = 6.4)
H–C(10)	–	–	–	3.00–3.04 (*m*)
H_α–C(11)	2.48–2.55 (*m*)	2.18–2.22 (*m*)	1.94 (*td*, *J* = 8.0, 2.0)	2.04–2.08 (*m*)
H_β–C(11)	2.30–2.35 (*m*)	2.23–2.26 (*m*)	1.80 (*dd*, *J* = 8.0, 2.0)	0.98 (*qd*, *J* = 12.0, 2.4)
H_α–C(12)	1.73–1.78 (*m*)	1.80–1.85 (*m*)	1.81–1.86 (*m*)	2.16–2.18 (*m*)
H_β–C(12)	1.90 (*t*, *J* = 6.5)	1.75 (*tt*, *J* = 12.5, 6, 3)	1.42–1.45 (*m*)	1.88–1.91 (*m*)
H_a–C(13)	2.62–2.67 (*m*)	2.85 (*d*, *J* = 17.0)	2.24–2.26 (*m*)	1.67–1.69 (*m*)
H_b–C(13)	1.73–1.78 (*m*)	3.46 (*d*, *J* = 17.0)	2.88–2.92 (*m*)	2.10–2.13 (*m*)
H_α–C(14)	2.59–2.64 (*m*)	–	2.46–2.51 (*m*)	2.77–2.81 (*m*)
H_β–C(14)	2.50–2.53 (*m*)	–	2.38–2.42 (*m*)	2.73–2.76 (*m*)
C(15)	–	–	–	5.84 (*d*, *J* = 2.4)
H_α–C(16)	6.82 (*dd*, *J* = 17.5, 10.8)	3.13 (*dd*, *J* = 17.0, 6.5)	–	2.19–2.22 (*m*)
H_β–C(16)	–	2.48 (*dd*, *J* = 17.0, 2.5)	–	1.49–1.52 (*m*)
H_a–C(17)	5.36 (*d*, *J* = 1.0)	4.98 (*d*, *J* = 6.0)	2.67–2.71 (*m*)	2.36–2.39 (*m*)
H_b–C(17)	5.31 (*dd*, *J* = 12.5, 1.0)	–	2.85–2.89 (*m*)	2.36–2.39 (*m*)
H–C(18)	2.82–2.86 (*m*)	2.72–2.76 (*m*)	2.83–2.85 (*m*)	2.65–2.69 (*m*)
H_α–C(19)	2.74 (*t*, *J* = 7.2)	2.78 (*d*, *J* = 13.5)	2.86–2.88 (*m*)	3.68 (*dd*, *J* = 12.0, 8.8)
H_β–C(19)	2.45–2.52 (*m*)	2.51 (*d*, *J* = 13.5)	2.58–2.62 (*m*)	2.81–2.83 (*m*)
Me(20)	0.92 (*d*, *J* = 6.8)	0.96 (*d*, *J* = 6.5)	0.98 (*d*, *J* = 8.0)	1.07 (*d*, *J* = 6.8)
Me(21)	1.24 (*s*)	1.13 (*s*)	1.13 (*s*)	1.715 (*s*)
Me(23)	–	3.68 (*s*)	3.21 (*s*)	–

Table 2. *^{13}C-NRM Data of* **1**–**4**. Measured in $CDCl_3$ at 125 MHz; δ in ppm.

	1	**2**	**3**	**4**
C(1)	218.1 (*s*)	215.2 (*s*)	216.5 (*s*)	75.9 (*d*)
C(2)	44.0 (*d*)	43.8 (*d*)	44.4 (*d*)	47.7 (*d*)
C(3)	20.6 (*t*)	19.9 (*t*)	19.9 (*t*)	22.4 (*t*)
C(4)	65.5 (*d*)	64.1 (*d*)	64.6 (*d*)	33.8 (*t*)
C(5)	53.7 (*s*)	49.4 (*s*)	53.2 (*s*)	83.5 (*s*)
C(6)	49.0 (*d*)	51.5 (*d*)	49.5 (*d*)	43.8 (*d*)
C(7)	53.6 (*t*)	53.6 (*t*)	53.9 (*t*)	60.9 (*d*)
C(8)	71.7 (*s*)	60.8 (*s*)	69.4 (*s*)	50.7 (*s*)
C(9)	140.8 (*s*)	150.4 (*s*)	177.1 (*s*)	139.1 (*s*)
C(10)	205.2 (*s*)	152.1 (*s*)	82.3 (*s*)	41.2 (*d*)
C(11)	36.7 (*t*)	23.2 (*t*)	32.0 (*t*)	33.5 (*t*)
C(12)	19.3 (*t*)	24.1 (*t*)	19.5 (*t*)	24.9 (*t*)
C(13)	33.1 (*t*)	45.3 (*t*)	39.0 (*t*)	30.6 (*t*)
C(14)	31.8 (*t*)	116.6 (*s*)	24.4 (*t*)	25.7 (*t*)
C(15)	149.9 (*s*)	164.3 (*s*)	156.7 (*s*)	135.6 (*d*)
C(16)	131.3 (*d*)	36.4 (*t*)	201.6 (*s*)	29.0 (*t*)
C(17)	120.1 (*t*)	83.5 (*d*)	51.8 (*t*)	31.0 (*t*)
C(18)	32.5 (*d*)	33.4 (*d*)	32.8 (*d*)	34.0 (*d*)
C(19)	49.8 (*t*)	49.4 (*t*)	49.6 (*t*)	58.8 (*t*)
Me(20)	18.7 (*q*)	18.8 (*q*)	19.0 (*q*)	13.7 (*q*)
Me(21)	22.1 (*q*)	22.9 (*q*)	21.2 (*q*)	22.7 (*q*)
C(22)	–	165.9 (*s*)	–	170.1 (*s*)
Me(23)	–	51.2 (*q*)	50.8 (*q*)	–

^{1}H,^{1}H-COSY and HSQC data suggested the four structural fragments **a**–**d** (*Fig.*). The connection of these fragments through heteroatoms or quaternary C-atoms were established by an exhaustive analysis of the HMBC signals. In the HMBC spectrum, cross-peaks of CH_2(7)/C(19), H–C(4)/C(7), and CH_2(19)/C(4) implied that H–C(4) (δ(C) 65.5), CH_2(7) (δ(C) 53.6), and CH_2(19) (δ(C) 49.8) are connected to each other *via* an N-atom, which also established the connectivity of the sub-units **a** and **b**. The attachment of fragments **a** and **b**, and Me(21) to C(5) were established on the basis of

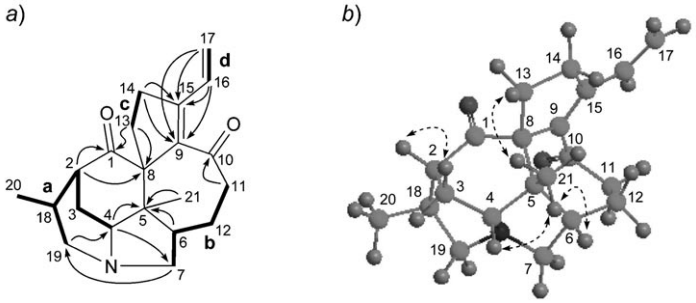


Figure. a) *^{1}H,^{1}H-COSY* (—) *and key HMBC* (H → C) *correlations of* **1**. b) *Key ROESY correlations* (H ←- - - → H) *of* **1**.

HMBC correlations between H–C(4)/C(5), CH_2(6)/C(5), and Me(21)/C(5), respectively. On the other hand, correlations of H–C(2)/C(1) and C(8), as well as CH_2(13)/C(8) and C(1), showed that C(2) and C(13) were connected through C(1) and C(8), which also suggested the connectivity of fragments **a** and **c**. The observed HMBC of the vinyl group CH_2(17)=CH(16) with C(15) and C(9), and CH_2(14)/C(15) and C(9) indicated the presence of a C(9)=C(15) bond. In addition, a C=O C-atom at δ(C) 205.2 was assigned to C(10) based on the HMBC of CH_2(11)/C(10). Thus, the constitutional formula of daphlongamine E (**1**) was established as indicated in the *Figure*, *a*.

The relative configuration of **1** was determined by ROESY data as shown in a computer-generated 3D drawing (*Fig.*, *b*). The NOE correlations between the H-atoms of Me(21)/H–C(4) and Me(21)/H–C(6) suggested that H–C(4) and H–C(6) are in β-orientation. The α-orientation of C(18) was determined by correlation of H–C(2) with H_β–C(3).

Daphlongamine F (**2**) was isolated as a white powder, and the molecular formula was determined as $C_{23}H_{29}NO_4$ by HR-ESI-MS (*m*/*z* 384.2171 ($[M+H]^+$), calc. 384.2174) with ten degrees of unsaturation. Its IR spectrum suggested the presence of an OH group (3431 cm^{-1}), a C=O group (1703 cm^{-1}), and of an α,β-unsaturated ester C=O group (1644 cm^{-1}). The ^{13}C-NMR spectrum revealed 23 C-atom signals, which were classified into one ketone C=O (δ(C) 215.2), one ester C=O (δ(C) 165.9), two tetrasubstituted C=C bonds (δ(C) 164.3, 152.1, 150.4, 116.6), two sp^3 quaternary C-atoms, five sp^3-CH, seven CH_2, and three Me groups. The NMR data of **2** (*Tables 1* and *2*) closely resembled those of the known compound longistylumphylline A [6], with the exception of the presence of a CH group δ(C) 83.5 in **2** instead of a CH_2 (δ(C) 42.2) in longistylumphylline A. Based on the molecular formula, **2** was assumed to be a hydroxylated longistylumphylline A. The structure of **2** was eventually established by 2D-NMR data. In the HMBC spectrum, a correlation of CH_2(16) with C(17) (δ(C) 83.5) implied that C(17) was substituted by the OH group, which was corroborated by the ^{1}H,^{1}H-COSY correlation of CH_2(16)/H–C(17). The relative configuration of **2** was identical with that of longistylumphylline A, as shown by ROESY spectroscopy. The observed ROESY cross-peaks of H–C(17)/H_α–C(11) implied that the OH group at C(17) has β-orientation. Thus, compound **2** was identified as 17-β-hydroxylongistylumphylline A, and named daphlongamine F.

Daphlongamine G (**3**) was shown to have the molecular formula $C_{22}H_{29}NO_3$ by HR-ESI-MS (*m*/*z* 356.2219 ($[M+H]^+$), calc. 356.2225). The IR absorption at 1710 cm^{-1} indicated the presence of a C=O group. Twenty-two C-atom signals were observed in the ^{13}C-NMR spectrum, which were assigned to two C=O groups, one tetrasubstitued C=C bond (δ(C) 177.1, 156.7), three sp^3 quaternary C-atoms, four CH, eight CH_2, and three Me groups (including one MeO group). Comparison of the molecular weights and ^{13}C-NMR data of **3** with those of daphnipaxianie A [5e] revealed that they share a similar structure; except for the presence of MeO in **3**, instead of an OH group in daphnipaxianine A. The constitution of **3** with a MeO group at C(17) was finally established by 2D-NMR data (^{1}H,^{1}H-COSY, HSQC, and HMBC). For biogenetic reasons, the relative configuration of **3** should be the same as in daphnipaxianine A, which was verified by a ROESY spectrum. The NOE correlation of H_β–C(17)/H_β–C(11) suggested that the MeO group could only be in α-configuration.

Daphlongamine H (**4**) was isolated as a white solid, and its molecular formula, $C_{22}H_{31}NO_2$, was suggested by HR-ESI-MS (*m/z* 342.2422 ($[M+H]^+$), calc. 342.2433). The IR absorption at 1710 cm^{-1} indicated the presence of a C=O group. Comparison of 1D- and 2D-NMR data with those of deoxyisocalyciphylline B [7] implied that they had the same constitutional formula. The relative configuration of **4** was determined by a ROESY spectrum. The NOE correlations of H–C(1)/Me(21), H–C(18), and H–C(2) suggested that H–C(1), H–C(21), and H–C(2) were co-facial. Cross-peaks of H_α–C(11) with H–C(10) implied that H–C(10) was in α-orientation. Correlations of H_β–C(19)/H–C(7), and H–C(7)/H–C(6) implied that H–C(6) and H–C(7) were β-oriented. Thus, compound **4** was determined to be the *C(6)*-epimer of deoxyisocalyciphylline B, and it was named daphlongamine H.

In addition to the four new alkaloids, the other 14 known *Daphniphyllum* alkaloids, longeracinphyllin B [4e], daphnipaxianines A and B [5e], daphniyunnines A, C, and E [8], deoxycalyciphylline B [7], deoxyisocalyciphylline B [7], longistylumphyllines A and C [6], daphnilongeranin B [9], yuzurine [10], codaphniphylline [11], daphniphylline [12], together with four aconitine-type C(19) diterpenoid alkaloids, neoline [13], talatisamine [14], isotalatizidine [14], and fuziline [15], and one veatchine-type C(20) diterpenoid alkaloid, songorine [16], were all identified by comparison of the experimental and reported physical data.

Experimental Part

General. Column chromatography (CC): silica gel (SiO_2; 300–400 mesh; *Qingdao Marine Chemical Ltd. Co.*), *Sephadex LH-20* (40–70 μm, *Amersham Pharmacia Biotech AB*, Uppsala, Sweden). Optical rotations: *JASCO DIP-370* Digital Polarimeter. IR Spectra: *Bio-Rad FTS-135* spectrometer, KBr pellets, in cm^{-1}. NMR Spectra: *Bruker DRX-500* or *AM-400* spectrometer; 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.

Plant Material. The leaves of *Daphniphyllum longeracemosum* were collected in Hekou of Yunnan Province, P. R. China, in October 2005. The sample was identified by Prof. *Xun Gong*, Kunming Institute of Botany, Chinese Academy of Sciences, and a voucher specimen (KIB 05110021) 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 leaves (60 kg) of *D. longeracemosum* were extracted with 95% EtOH, and the crude extract was adjusted to pH 2 with 2% HCl followed by extraction with $CHCl_3$. The pH of the aq. layer was adjusted to pH 10 with 3% NaOH, and then exhaustively extracted with AcOEt to give the crude alkaloid mixture (100 g). The crude extracts were subjected to a CC (SiO_2; petroleum ether (PE)/AcOEt/Et_2NH, 10:0:0.1 → 0:1:0.1) to obtain five major fractions (*Fr. A–E*). *Fr. C* was further chromatographed over SiO_2 (PE/Et_2NH, 50:1 → 10:1), followed by *Sephadex LH-20* CC eluted with MeOH to afford **1** (30 mg) and **4** (17 mg). *Fr. D* was subjected to *Sephadex LH-20* CC eluted with $CHCl_3$/MeOH 1:1, and then to SiO_2 CC ($CHCl_3$/acetone 2:1) to give **2** (21 mg) and **3** (8 mg).

Daphlongamine E (= rel-*(6a*S*,10*S*,11*R*,12a*R*,12b*S*,12c*S*)-3-Ethenyl-1,2,5,6,6a,7,9,10,11,12,12a,12b-dodecahydro-10,12b-dimethyl-4*H*-11,12c-methanoazuleno[4,5-a]indolizine-4,13-dione*; **1**). Light yellow solid. $[\alpha]_D^{23.4} = +42.31$ ($c = 0.52$, $CHCl_3$). UV ($CHCl_3$): 269 (3.94). IR (KBr): 2920, 1747, 1695, 1576. ^{1}H- and ^{13}C-NMR: *Tables 1* and *2*. ESI-MS: 326 ($[M+H]^+$). HR-ESI-MS: 326.2114 ($[M+H]^+$, $C_{21}H_{28}NO_2^+$; calc. 326.2120).

Daphlongamine F (= *Methyl* rel-*(2*R*,4a*S*,8*S*,9*R*,10a*R*,10b*S*,10c*R*)-2,3,4,4a,5,7,8,9,10,10a,10b,11-Dodecahydro-2-hydroxy-8,10b-dimethyl-13-oxo-1*H*-9,10c-methanocyclopenta[1,8]azuleno[4,5-a]indolizine-*

12-carboxylate; **2**). White solid. $[\alpha]_D^{23.5} = -113.75$ ($c = 0.40$, $CHCl_3$). UV ($CHCl_3$): 288 (4.15). IR (KBr): 3431, 2921, 1703, 1695, 1644, 1437. ^{1}H- and ^{13}C-NMR: *Tables 1* and *2*. ESI-MS: 384 ($[M+H]^+$). HR-ESI-MS: 384.2171 ($[M+H]^+$, $C_{23}H_{30}NO_4^+$; calc. 384.2174).

Daphlongamine G (= rel-*(2a*S*,4a*S*,8*S*,9*R*,10a*R*,10b*S*,10c*S*)-2,2a,3,4,4a,5,7,8,9,10,10a,10b,11,12-Tetradecahydro-2a-methoxy-8,10b-dimethyl-1*H*-9,10c-methanocyclopenta[1,8]azuleno[4,5-a]indolizine-1,13-dione*; **3**). White solid. $[\alpha]_D^{23.5} = +10.12$ ($c = 0.28$, $CHCl_3$). UV ($CHCl_3$): 244 (3.96). IR (KBr): 3392, 2925, 1710, 1454, 1378. ^{1}H- and ^{13}C-NMR: *Tables 1* and *2*. ESI-MS: 356 ($[M+H]^+$). HR-ESI-MS: 356.2219 ($[M+H]^+$, $C_{22}H_{30}NO_3^+$; calc. 356.2225).

Daphlongamine H (= rel-*(2*S*,2a*R*,4a*S*,8a*S*,8b*R*,10a*R*,13b*R*,13d*S*)-1,2,2a,3,4,5,6,8a,8b,9,10,10a,11,12,13b,13d-Hexadecahydro-2,8a-dimethyl-7*H*-8-oxa-13c-azacyclopenta[a]pentaleno[1,6-kl]phenanthren-7-one*; **4**). White solid. $[\alpha]_D^{27.3} = -33.70$ ($c = 0.46$, $CHCl_3$). IR (KBr): 3432, 2980, 1710, 1457, 1392. ^{1}H- and ^{13}C-NMR: *Tables 1* and *2*. ESI-MS: 342 ($[M+H]^+$). HR-ESI-MS: 342.2422 ($[M+H]^+$, $C_{22}H_{32}NO_2^+$; calc. 342.2433).

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