Daphniphyllum and Diterpenoid Alkaloids from Daphniphyllum longeracemosum

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Daphniphyllum and Diterpenoid Alkaloids from *Daphniphyllum longeracemosum*

Chun-Shun Li,[†,‡] Ying-Tong Di,[†] Shu-Zhen Mu,[§] Hong-Ping He,[†] Qiang Zhang,[†] Xin Fang,[†] Yu Zhang,[†] Shun-Lin Li,[†] Yang Lu,[||] Yan-Qing Gong,[||] and Xiao-Jiang Hao*[,†]

State Key Laboratory of Phytochemistry and Plant Resources in West China, Kunming Institute of Botany, Chinese Academy of Sciences, Kunming 650204, People's Republic of China, Graduate School of Chinese Academy of Sciences, Beijing 100039, People's Republic of China, The Key Laboratory of Chemistry for Natural Product of Guizhou Province and Chinese Academy of Sciences, Guiyang 550002, People's Republic of China, and Institute of Materia Medica, Chinese Academy of Medical Sciences, Beijing 100050, People's Republic of China

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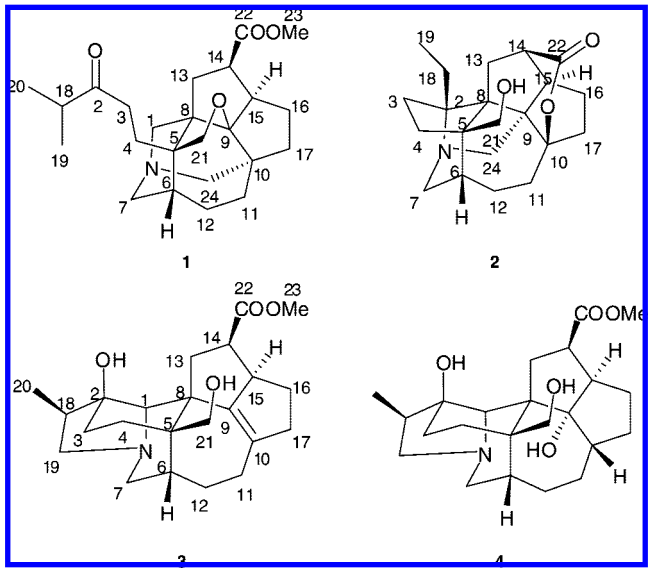
Four new *Daphniphyllum* alkaloids, daphlongamines A−D (**1**−**4**), were isolated from the fruits of *Daphniphyllum longeracemosum*. Their structures were characterized by spectroscopic methods, especially 2D NMR techniques. A single-crystal X-ray diffraction analysis was used to confirm the stereochemistry of **3**. Remarkably, this is the first report of aconitine- and veatchine-type diterpenoid alkaloids from the genus *Daphniphyllum*.

Daphniphyllum alkaloids are a family of alkaloids with structurally diverse and complex polycyclic skeletons,[1,2] which have attracted much attention regarding their total synthesis and biosynthesis.[3,4] The presence of many structurally unique *Daphniphyllum* alkaloids may be ascribed to their special biosynthetic pathways from key intermediates as proposed by Heathcock.[5]

In the past two years, we have isolated more than 30 structurally unique and biosynthetically meaningful *Daphniphyllum* alkaloids,[6,7] including some with novel skeletons from *Daphniphyllum longeracemosum* Rosenth.[7] In our continuing investigations of biogenetically and structurally interesting alkaloids from the fruits of *D. longeracemosum* Rosenth., four new *Daphniphyllum* alkaloids, daphlongamines A−D (**1**−**4**), as well as 22 known compounds, including 13 *Daphniphyllum* alkaloids and eight aconitine-type and one veatchine-type diterpenoid alkaloids, have been isolated. Herein, we present the isolation and structural elucidation of alkaloids **1**−**4**.



Results and Discussion

Daphlongamine A (**1**) was obtained as a white solid, and its molecular formula, $C_{24}H_{35}NO_4$, was established by HRESIMS (*m*/*z* 402.2652 $[M + H]^+$, calcd 402.2644), corresponding to eight degrees of unsaturation. IR absorption bands at 1728 and 1711 cm^{-1} implied the presence of two carbonyl groups. ^{13}C NMR and DEPT spectra (Table 2) revealed 24 carbon signals including two carbonyl carbons, four sp^3 quaternary carbons, four sp^3 methines, 11 sp^3 methylenes, and three methyl groups. Three methylenes (δ_C 53.1, δ_H 3.27 and 2.89; δ_C 55.6, δ_H 3.56 and 2.97; δ_C 64.9, δ_H 3.20 and 3.13) were ascribed to those attached to a nitrogen atom, while one methylene (δ_C 71.2, δ_H 3.88 and 3.62) and one sp^3 quarterary carbon (δ_C 99.9) were ascribed to those bearing oxygen atoms.

The structure of **1** was proposed to consist of two moieties (Figure 1A) by analyses of 2D NMR ($^1H-^1H$ COSY, HSQC, and HMBC). The $^1H-^1H$ COSY spectrum indicated the presence of four partial fragments: **a** (C-18 to C-19 and C-20), **b** (C-3 to C-4), **c** (C-6 to C-7 and C-12, and C-11 to C-12), and **d** (C-13 to C-17) drawn with bold bonds in Figure 1A. Furthermore, the HMBC spectrum suggested the presence of the right-hand moiety (in red) as shown in Figure 1A, containing three carbocyclic ring systems (two five-, one seven-membered), a carbomethoxy group at C-14, an oxymethylene at C-5, and a methylene at C-6, which are the usual structural components in yuzurine- and yuzurimine-type *Daphniphyllum* alkaloids. In addition, HMBC cross-peaks of H-1α to C-7 (δ_C 55.6), H-1β to C-24 (δ_C 64.9), and H-7α to C-24 (δ_C 64.9) imply that C-1, C-7, and C-24 are connected through a nitrogen atom. The connection of fragments **a** and **b** via C-2 was elucidated by correlations of H_2-3 and H-18 with the ketone carbon (C-2, δ_C 213.5). Correlations of H_2-13 to C-1 and of H-1α to C-8 implied that C-1 and C-13 were connected through C-8. Meanwhile, the formation of an ether linkage between C-21 and C-9 and connectivity of C-24 and C-10 were illustrated by HMBC correlations of H_2-21 to C-9 and of H_2-24 to C-10, respectively. Thus, the gross structure of daphlongamine A was assigned as **1** with a unique fused hexacyclic ring system as shown in Figure 1A. The relative configuration of **1** was elucidated by ROESY data, as shown in a computer-generated 3D drawing (Figure 1B). The ROESY cross-peak between the proton pair H-6/H-21b suggested that H-6 was in a β-orientation. H-14 and H-15 were established to be α-oriented by correlations of H-13α/H-14, H-14/H-15, and H-15/H-16α.

Daphlongamine B (**2**) showed a molecular formula of $C_{21}H_{29}NO_3$, as determined by HRESIMR at *m*/*z* 344.2227 (calcd 344.2225), with eight degrees of unsaturation. IR absorption bands at 1724 and 3239 cm^{-1} implied the presence of carbonyl and hydroxy

* To whom correspondence should be addressed. Tel: +86-871-5223263. Fax: +86-871-5219684. E-mail: haoxj@mail.kib.ac.cn.
[†] Kunming Institute of Botany.
[‡] Graduate School of Chinese Academy of Sciences.
[§] The Key Laboratory of Chemistry for Natural Product of Guizhou Province and Chinese Academy of Sciences.
[||] Institute of Materia Medica.

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Table 1. ^{1}H [δ_H (pattern, *J* (Hz))] NMR Data of Daphlongamines A−D (**1**−**4**)

	1[a]	**2**[a]	**3**[b]	**4**[b]
1α	3.27 (1H, d, 11.0)		2.45 (1H, m)	3.07 (1H, m)
1*β*	2.89 (1H, d, 11.0)			
3α	2.36 (2H, m)	1.50 (2H, m)	1.72 (1H, m)	1.50 (2H, m)
3*β*			1.42 (1H, m)	
4α	1.67 (1H, m)	1.92 (2H, m)	1.54 (1H, m)	1.94 (1H, m)
4*β*	1.86 (1H, m)		1.67 (1H, m)	1.69 (1H, m)
6	1.88 (1H, m)	2.11 (1H, m)	2.01 (1H, m)	2.26 (1H, t, 5.0)
7α	2.97 (1H, d, 11.4)	2.76 (1H, d, 6.5)	2.95 (1H, d, 16.0)	3.25 (1H, m)
7*β*	3.56 (1H, dd, 11.4, 4.4)	3.68 (1H, t, 6.5)	2.85 (1H, m)	2.89 (1H, t, 11.5)
10				2.12 (1H, m)
11α	1.58 (1H, m)	2.17 (1H, m)	1.88 (1H, m)	1.36 (1H, m)
11*β*	2.08 (1H, t, 10.0)	2.02 (2H, m)	2.10 (1H, m)	1.90 (1H, m)
12α	1.69 (1H, m)	1.47 (1H, m)	1.24 (1H, m)	1.27 (1H, m)
12*β*	2.19 (1H, t, 10.4)	2.06 (1H, m)	1.94 (1H, m)	1.80 (1H, m)
13α	1.62 (1H, m)	1.91 (1H, m)	2.80 (1H, m)	2.55 (1H, dd, 15.0, 7.5)
13*β*	2.80 (1H, m)	1.95 (1H, m)	2.24 (1H, dd, 17.0, 3.5)	2.11 (1H, m)
14	2.77 (1H, m)	3.04 (1H, t, 4.5)	2.75 (1H, s)	3.09 (1H, m)
15	2.63 (1H, m)	2.60 (1H, dd, 9.0, 5.0)	3.32 (1H, m)	2.61 (1H, dd, 19.0, 9.0)
16α	1.84 (1H, m)	1.81 (1H, m)	1.01 (1H, m)	1.60 (1H, m)
16*β*	1.94 (1H, m)	1.63 (1H, m)	1.69 (1H, m)	1.13 (1H, m)
17α	1.74 (1H, m)	1.72 (1H, m)	2.11 (1H, m)	1.36 (1H, m)
17*β*	1.81 (1H, m)	2.15 (1H, m)	2.45 (1H, m)	1.50 (1H, m)
18α	2.60 (1H, m)	1.42 (1H, m)	1.87 (1H, m)	1.98 (1H, m)
18*β*		1.81 (1H, m)		
19α	1.10 (3H, d, 1.5)	0.96 (3H, t, 7.3)	3.18 (1H, s)	3.47 (1H, t, 10.0)
19*β*			1.94 (1H, m)	2.14 (1H, d, 10.0)
20	1.07 (3H, d, 1.5)		0.88 (3H, d, 7.0)	0.93 (3H, d, 7)
21a	3.88 (1H, d, 6.8)	4.29 (1H, d, 10.3)	3.67 (1H, d, 11.5)	4.13 (1H, d, 10.9)
21b	3.62 (1H, d, 6.8)	3.64 (1H, d, 10.3)	3.62 (1H, d, 11.5)	3.67 (1H, d, 10.9)
23	3.66 (3H, s)		3.45 (3H, s)	3.75 (3H, s)
24a	3.20 (1H, d 11.0)	3.16 (1H, d, 13.6)		
24b	3.13 (1H, d, 11.0)	2.73 (1H, d, 13.6)		

[a] Measured in $CDCl_3$. [b] Measured in $CDCl_3/CD_3OD$ (4:1).

Table 2. ^{13}C [δ_C] NMR Data of Daphlongamines A−D (**1**−**4**)

	1[a]	**2**[a]	**3**[b]	**4**[b]
1	53.1		66.4	67.6
2	213.5	81.9	77.5	77.0
3	36.1	29.3	28.5	26.8
4	24.5	38.8	30.1	33.1
5	47.7	54.2	38.3	40.6
6	35.6	41.3	38.1	38.4
7	55.6	54.1	56.3	56.8
8	43.6	67.3[c]	44.5	48.2
9	99.9	67.3[c]	143.4	93.6
10	41.6	95.8	133.9	46.9
11	33.7	29.4	24.6	21.3
12	28.6	25.2	27.4	29.9
13	36.8	30.0	34.0	31.9
14	39.8	56.1	42.07	41.7
15	51.7	49.3	53.8	56.7
16	24.9	21.6	27.4	26.7
17	43.9	41.2	42.13	32.3
18	40.9	27.5	46.0	44.7
19	18.3[c]	9.0	60.9	60.5
20	18.3[c]		12.7	11.3
21	71.2	65.5	66.5	67.2
22	173.5	175.4	177.0	175.6
23	51.5		51.0	51.3
24	64.9	58.7		

[a] Measured in $CDCl_3$. [b] Measured in $CDCl_3/CD_3OD$ (4:1). [c] Overlapped.

functionalities, respectively. In its ^{13}C NMR spectrum, 21 carbon signals were revealed, including one sp^2 ester carbonyl group, five sp^3 quaternary carbons, three sp^3 methines, 11 sp^3 methylenes, and one methyl. Three carbons were inferred to bear a nitrogen (δ_C 81.9, s; 58.7, t; 54.1, t), and two carbons, an oxygen (δ_C 95.8, s; 65.5, t). Since the carbonyl group accounted for one out of the eight degrees of unsaturation, the remaining seven degrees of unsaturation were assumed to indicate the presence of a heptacyclic system in **2**.

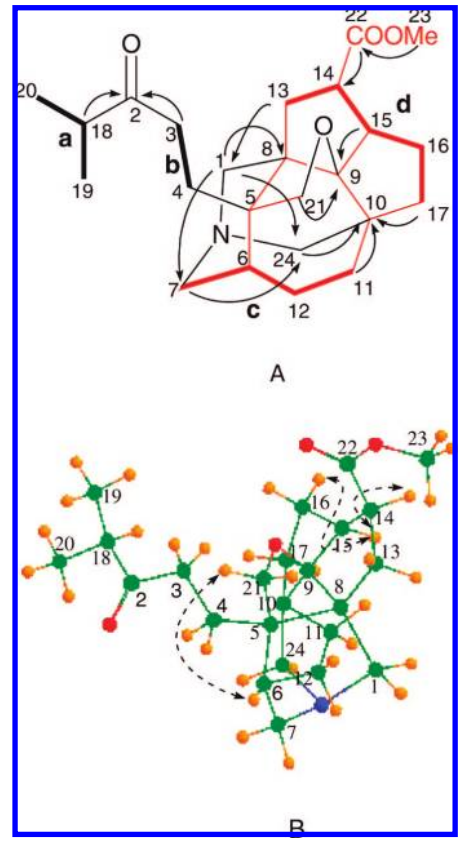


Figure 1. (A) ^{1}H−^{1}H COSY (bold) and HMBC (arrow, H→C) correlations of **1**. (B) NOESY (dashed) correlations of **1**.

By detailed comparison of the NMR data of **2** with those of paxdaphnine A,[2c] which had been previously isolated from this

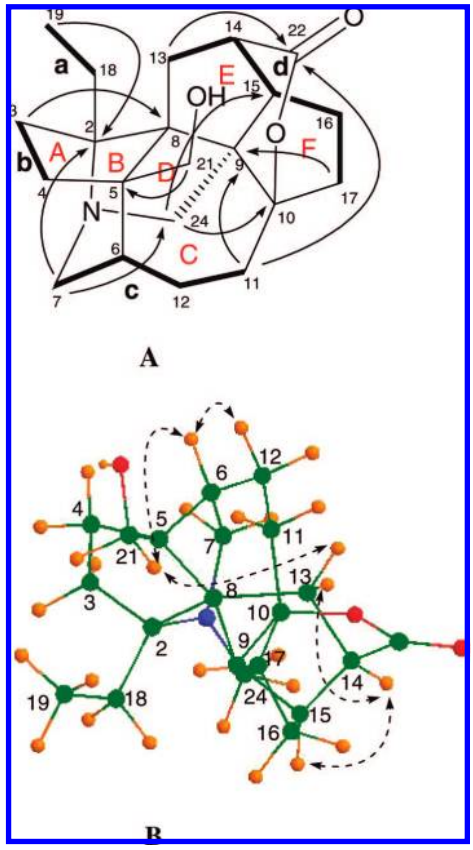


Figure 2. (A) ^{1}H−^{1}H COSY (bold) and HMBC (arrow, H→C) correlations of **2**. (B) NOESY (dashed) correlations of **2**.

genus,[7b] **2** was implied to possess a similar skeleton. The main difference was the absence of the ether linkage between C-10 and C-21 in **2**, which was suggested by the chemical shift of C-10 (upfield about 4 ppm) and C-21 (downfield about 10 ppm). When considering the heptacyclic system in **2**, a lactone ring was implied to exist between C-21 and C-22 or between C-10 and C-22. To further elucidate the structure of **2**, 2D NMR experiments were employed. 2D spectra (^{1}H−^{1}H COSY, HSQC, and HMBC) proved the presence of rings A−F, as shown in Figure 2, which were the same as those of paxdaphnine A. In addition, ^4J HMBC correlation from H-11β to C-22 indicated that C-10 and C-22 were linked, forming a six-membered lactone (C-14, C-15, C-9, C-10, oxygen atom, and C-22). Therefore, the planar structure of **2** was established. Furthermore, the relative configuration of **2** was the same as paxdaphnine A, which was verified by the NOESY spectrum, as shown in the computer-generated 3D drawing (Figure 2B).

Daphlongamine C (**3**) was isolated as block crystals (CH_3OH) with $[\alpha]^{24}_D$ −27.27 (*c* 0.17 $CHCl_3$/CH_3OH, 1:1). Its molecular formula was determined to be $C_{23}H_{33}NO_4$ by HRESIMS at *m*/*z* 388.2492 (calcd 388.2487), requiring eight degrees of unsaturation. IR absorption bands implied the presence of carbonyl (1736 cm^{-1}) and hydroxy (3425 cm^{-1}) functional groups. Analyses of the NMR spectra (^{1}H, ^{13}C, DEPT, HSQC, and HMBC) suggested that alkaloid **3** had 23 carbons, corresponding to six quaternary carbons (sp^3 × 3 and sp^2 × 3), five sp^3 methines, 10 sp^3 methylenes, and two methyl groups. Comparison of the NMR data of **3** with those of yuzurimine B indicated that both compounds were structurally similar, with the exception of the presence of a quaternary carbon at δ_C 77.5 (C-2) and the absence of a methine carbon at δ_C 37.9 in **3**. The HMBC correlation of H_3-20 (δ_H 0.88) with the quaternary carbon at δ_C 77.5 (C-2) suggested that C-2 should be substitued by a hydroxy group. The structure and relative configuration of **3**

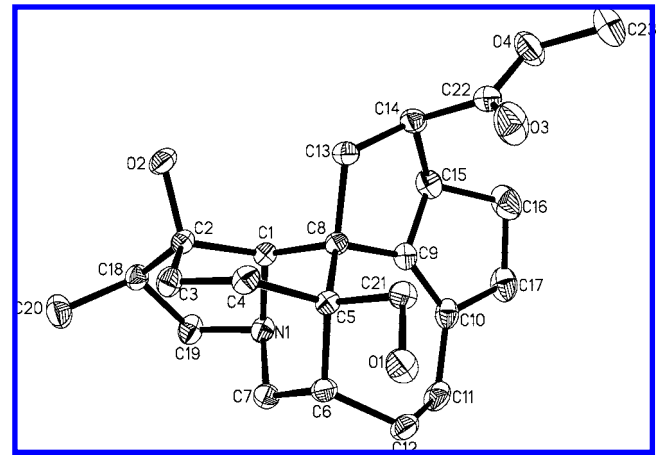


Figure 3. ORTEP drawing of the X-ray structure of **3**.

was further confirmed by an X-ray crystallographic study (Figure 3),[8] which was consistent with the ROESY data.

Daphlongamine D (**4**) was shown to have the molecular formula $C_{23}H_{35}NO_5$ by HRESIMS at *m*/*z* 406.2574 (cald 406.2593). The ^{1}H and ^{13}C NMR spectra were similar to those of compound **3** except for the absence of the double bond between C-9 and C-15 and the presence of an oxy-substituted quaternary carbon with a chemical shift of δ_C 93.6 in **4**. Long-range HMBC correlations of H-14 and H_2-11 with C-9 (δ_C 93.6) proved that C-9 was substituted by a hydroxy group. The planar structure of daphlongamine D was eventually established by the 2D experiments as **4**.

The relative configuration of daphlongamine D should be the same as alkaloid **3** on the basis of analysis of ROESY correlations and biogenetic considerations. Specifically, the observed NOE correlations of H_2-21 with H-10 indicated that H-10 was β-oriented, and the OH group at C-9 should take an α-orientation, which was compatible with the computer-optimized 3D structure of **4** using Hartree−Fock (HF) at the 3-21G(d) basis set level.

In addition to the four new alkaloids, the other 13 *Daphniphyllum* alkaloids, yuzurimine B,[9] daphnezomine S,[10] zwittenrionic alkaloid,[11] oxodaphnigraciline,[12] daphnigracine,[12] daphnigraciline,[12] methyl homodaphniphyllate,[13] daphniyunnines A, D, and E,[14] daphnipaxianines A and B,[6a] and longistylumphylline A,[15] together with eight aconitine-type C-19 diterpenoid alkaloids, condelphine,[16] neoline,[16] chasmanine,[16] talatisamine,[17] isotalatizidine,[17] nevadenine,[18] fuziline,[19] and beiwucine,[20] and one veatchine-type C-20 diterpenoid alkaloid, songorine,[21] were all identified by comparison of experimental and reported physical data.

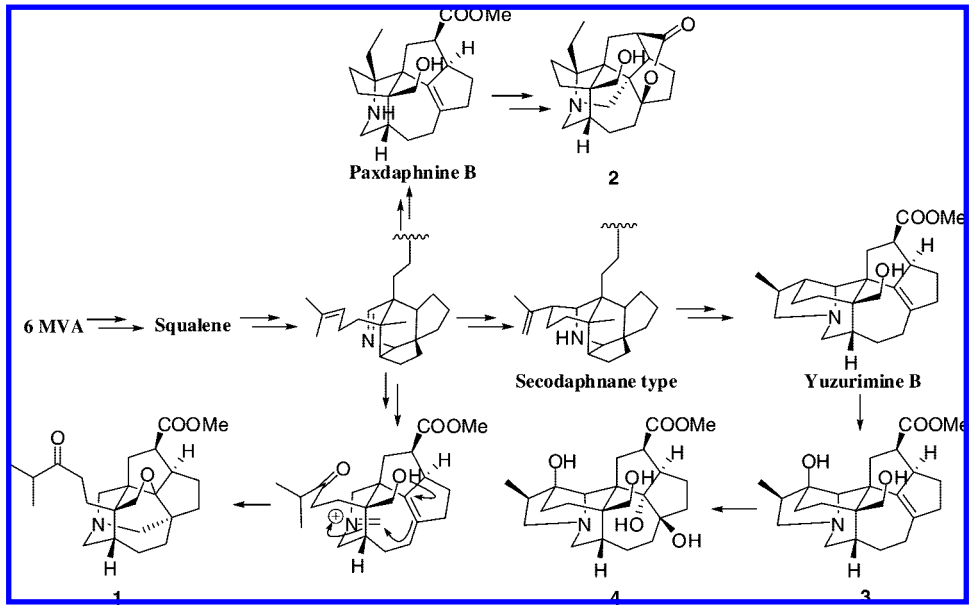
The proposed biogenetic pathways of *Daphniphyllum* alkaloids are different from those of diterpenoid alkaloids. The former originate from six molecules of mevalonic acid via a squalene-like intermediate;[5b] the latter are derived from tetracyclic or pentacyclic diterpenes. The biogenetic pathways of the four new *Daphniphyllum* alkaloids are proposed as shown in Scheme 1.

Experimental Section

General Experimental Procedures. Melting points were recorded on an X-4 apparatus without correction. IR spectra were measured in a Bio-Rad FTS-135 spectrometer with KBr pellets. Optical rotations were obtained on a Perkin-Elmer model 241 polarimeter. ESI and HRMS were measured on a Finnigan MAT 90 instrument and VG Auto Spec-3000 spectrometer, respectively. 1D and 2D NMR spectra were measured on a Bruker DRX-500 or AM-400 spectrometer. Column chromatography was performed on Si gel H (10−40 μm; Qingdao Marine Chemical Factory) and Sephadex LH-20 (40−70 μm, Amersham Pharmacia Biotech AB, Uppsala, Sweden).

Plant Material. The fruits of *D. longeracemosum* were collected in Hekou of Yunnan Province, People's Republic of China, in Octobor 2005. The sample was identified by Prof. Xun Gong, Kunming Institute of Botany, Chinese Academy of Sciences, and a voucher specimen (KIB

Scheme 1. Possible Biogenetic Pathways for Daphlongamines A−D (**1**−**4**)



05110021) was deposited at the State Key Laboratory of Phytochemistry and Plant Resources in West China, Kunming Institute of Botany, Chinese Academy of Sciences.

Extraction and Isolation. The fruits (60 kg) of *D. longeracemosum* were extracted with 95% EtOH, and the crude extract was adjusted to pH 2 with 2% HCl. The acidic mixture was defatted with petroleum ether (bp 60−90 °C), followed by extraction with $CHCl_3$. The pH of the aqueous layer was adjusted to pH 10 with 3% NaOH and then exhaustively extracted with $CHCl_3$ to give the crude alkaloid. The crude extracts were subjected to a Si gel column ($CHCl_3$/MeOH, 1:0 → 0:1) to obtain six major fractions (F_1−F_6). Fraction 3 (F_3) was further chromatographed over a Si gel (200−300 mesh) column (petroleum ether/Et_2NH, 50:1 → 10:1) followed by Sephadex LH-20 CC eluted with CH_3OH to afford daphlongamine A (**1**, 12 mg). Fraction 4 (F_4) was subjected to a RP-18 Si gel column (MeOH/H_2O) to give four fractions (P_1−P_4). Fraction 1 (P_1) was subjected to Si gel (EtOAc/MeOH, 8:1) followed by Sephadex LH-20 CC eluted with CH_3OH to yield daphlongamines C (**3**, 7 mg) and D (**4**, 17 mg). Fraction 3 (P_3) was chromatographed on Si gel (petroleum ether/Et_2NH, 50:1 → 10:1) to obtain daphlongamine B (**2**, 20 mg).

Daphlongamine A (1): white solid; $[\alpha]^{24}_D$ +5.08 (*c* 0.29, $CHCl_3$); IR (KBr) ν_{max} 3432, 2955, 2925, 1728, 1711, 1468, and 1199 cm^{-1}; ^1H and ^{13}C NMR data, see Tables 1 and 2; ESIMS 402 $[M + H]^+$; HRESIMS *m/z* 402.2652 (calcd for $C_{24}H_{36}NO_4^+$, 402.2644).

Daphlongamine B (2): white solid; $[\alpha]^{24}_D$ −107.25 (*c* 0.23, $CHCl_3$); IR (KBr) ν_{max} 3239, 2961, 2934, and 1724 cm^{-1}; ^1H and ^{13}C NMR data, see Tables 1 and 2; ESIMS 344 $[M + H]^+$; HRESIMS *m/z* 344.2227 (calcd for $C_{21}H_{30}NO_3^+$, 344.2225).

Daphlongamine C (3): block crystal (CH_3OH); mp 153−155 °C; $[\alpha]^{24}_D$ −27.27 (*c* 0.17, $CHCl_3$/CH_3OH, 1:1); IR (KBr) ν_{max} 3425, 2951, 2924, 2869, and 1736 cm^{-1}; ^1H and ^{13}C NMR data, see Tables 1 and 2; ESIMS 388 $[M + H]^+$; HRESIMS *m/z* 388.2492 (calcd for $C_{23}H_{34}NO_4^+$, 388.2487).

Daphlongamine D (4): white solid; $[\alpha]^{24}_D$ −16.28 (*c* 0.22, $CHCl_3$/CH_3OH 1:1); IR (KBr) ν_{max} 3420, 2951, 2868, and 1733 cm^{-1}; ^1H and ^{13}C NMR data, see Tables 1 and 2; ESIMS 406 $[M + H]^+$; HRESIMS *m/z* 406.2574 (calcd for $C_{23}H_{36}NO_5^+$, 406.2593).

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Supporting Information Available: 1D and 2D NMR spectra of daphlongamines A−D (**1**−**4**) are supplied, and this material is available free of charge via the Internet at http://pubs.acs.org.

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(8) Crystal data for daphlongamines A (**3**): $C_{23}H_{33}NO_4$, MW = 387.52, dimensions 0.20 × 0.30 × 0.50 mm; orthorhombic system, space group $P2_12_12_1$, crystal cell parameters: a = 8.799(1) Å, b = 14.981(1) Å, c = 15.655(1) Å, V = 2063.6(3) $Å^3$, Z = 4, d = 1.305 g/cm^3. A crystal was used for measurements on a MAC DIP-2030K diffractometer with a graphite monochromator (ω scans, $2\theta_{max}$ = 50.0°), Mo Kα radiation. The total number of independent reflections measured was 4651, of which 4339 were observed ($|F|^2 \geq 2\sigma|F|^2$). The crystal structure of **3** was solved by direct methods using SHELXS-97 (Sheldrich, G. M. University of Gottingen: Gottingen, Germany, 1997) and then expanded using full-matrix least-squares calculation and difference

Fourier techniques. H atoms were placed at geometrically idealized positions. The final indices were $R_1 = 0.0369$, $wR_2 = 0.1028$ ($w = 1/\sigma|F|^2$), $S = 1.055$. Crystallographic data for **3** reported in this paper have been deposited in the Cambridge Crystallographic Data Centre as CCDC 669445. Copies of the data can be obtained, free of charge, on application to the Director, CCDC, 12 Union Road, Cambridge CB21EZ, UK (fax: +44-(0)1223-336033 or e-mail: deposit@ccdc.cam.ac.uk).

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