

Daphniphyllum and Diterpenoid Alkaloids from *Daphniphyllum longeracemosum*

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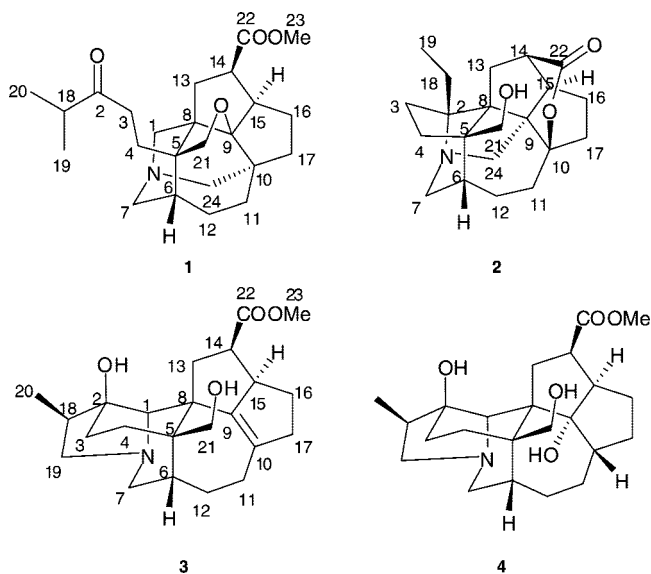
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Received March 3, 2008

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**.



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Results and Discussion

Daphlongamine A (**1**) was obtained as a white solid, and its molecular formula, C₂₄H₃₅NO₄, 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. ¹³C NMR and DEPT spectra (Table 2) revealed 24 carbon signals including two carbonyl carbons, four sp³ quaternary carbons, four sp³ methines, 11 sp³ 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 sp³ quaternary 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-1 α to C-7 (δ_C 55.6), H-1 β to C-24 (δ_C 64.9), and H-7 α 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 H₂-3 and H-18 with the ketone carbon (C-2, δ_C 213.5). Correlations of H₂-13 to C-1 and of H-1 α 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 H₂-21 to C-9 and of H₂-24 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-13 α /H-14, H-14/H-15, and H-15/H-16 α .

Daphlongamine B (**2**) showed a molecular formula of C₂₁H₂₉NO₃, as determined by HRESIMS 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

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

	1 ^a	2 ^a	3 ^b	4 ^b
1 α	3.27 (1H, d, 11.0)		2.45 (1H, m)	3.07 (1H, m)
1 β	2.89 (1H, d, 11.0)			
3 α	2.36 (2H, m)	1.50 (2H, m)	1.72 (1H, m)	1.50 (2H, m)
3 β			1.42 (1H, m)	
4 α	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)
7 α	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)
11 α	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)
12 α	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)
13 α	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)
16 α	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)
17 α	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)
18 α	2.60 (1H, m)	1.42 (1H, m)	1.87 (1H, m)	1.98 (1H, m)
18 β		1.81 (1H, m)		
19 α	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 $\text{CDCl}_3/\text{CD}_3\text{OD}$ (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 $\text{CDCl}_3/\text{CD}_3\text{OD}$ (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**.

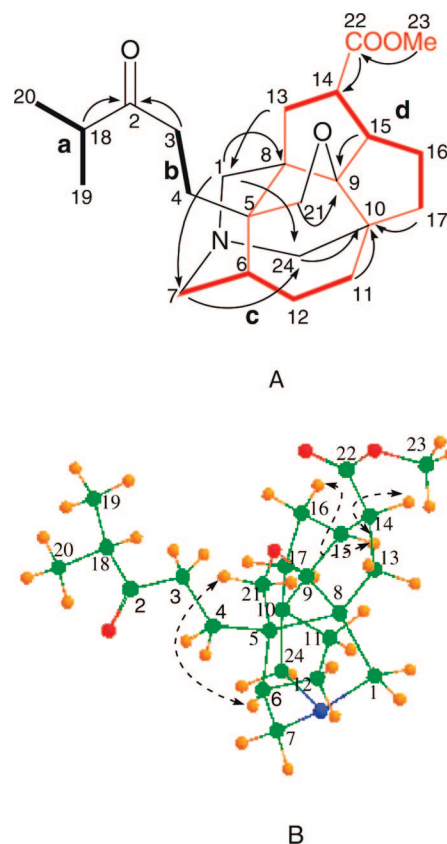


Figure 1. (A) ^1H – ^1H COSY (bold) and HMBC (arrow, $\text{H}\rightarrow\text{C}$) correlations of **1**. (B) NOESY (dashed) correlations of **1**.

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

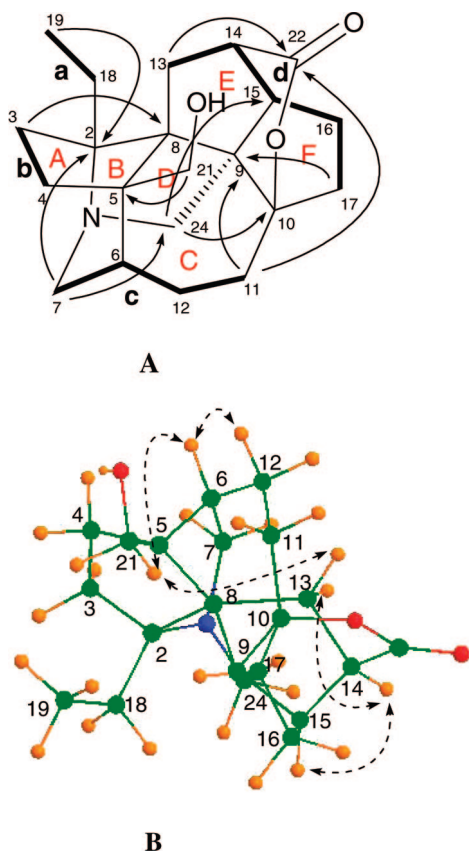


Figure 2. (A) ^1H – ^1H COSY (bold) and HMBC (arrow, H \rightarrow C) correlations of **2**. (B) NOESY (dashed) correlations of **2**.

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 (^1H – ^1H 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-11 β 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 $[\alpha]_D^{24} -27.27$ (c 0.17 $\text{CHCl}_3/\text{CH}_3\text{OH}$, 1:1). Its molecular formula was determined to be $\text{C}_{23}\text{H}_{33}\text{NO}_4$ 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 (^1H , ^{13}C , DEPT, HSQC, and HMBC) suggested that alkaloid **3** had 23 carbons, corresponding to six quaternary carbons ($\text{sp}^3 \times 3$ and $\text{sp}^2 \times 3$), 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 substituted by a hydroxy group. The structure and relative configuration of **3**

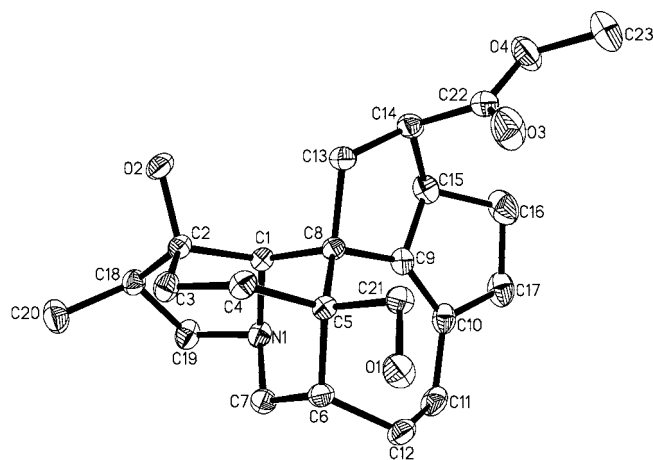


Figure 3. ORTEP drawing of the X-ray structure of **3**.

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 $\text{C}_{23}\text{H}_{35}\text{NO}_5$ by HRESIMS at m/z 406.2574 (calcd 406.2593). The ^1H 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 zwitterionic alkaloid,¹¹ oxodaphnigraciline,¹² daphnigraciline,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.

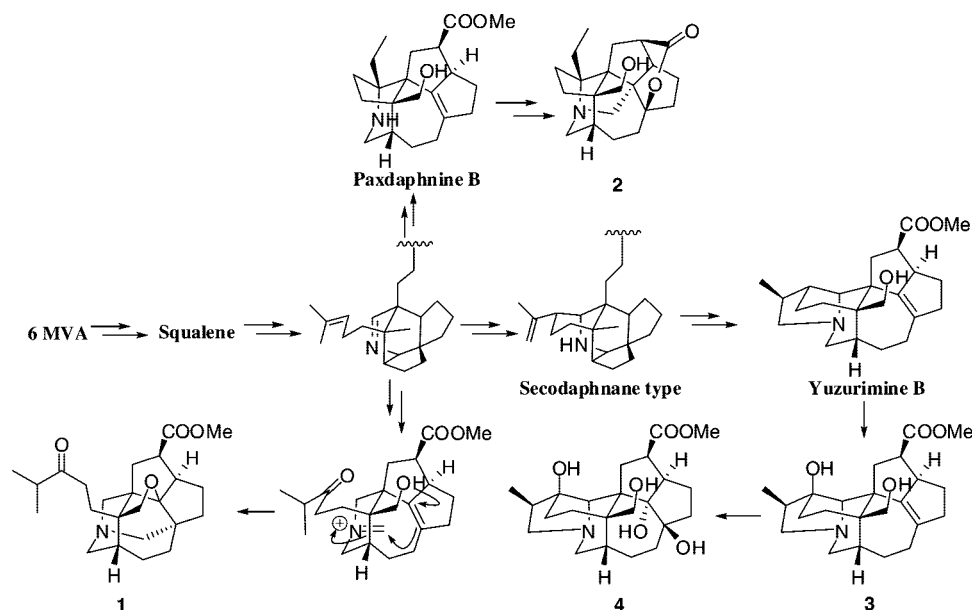
The proposed biogenetic pathways of *Daphniphyllum* alkaloids are different from those of diterpenoid alkaloids. The former originate from six molecules of mevalonic acid via a squalene-like intermediate;^{5b} the latter are derived from tetracyclic or pentacyclic diterpenes. The biogenetic pathways 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. longercemosum* were collected in Hekou of Yunnan Province, People's Republic of 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

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 CHCl₃. The pH of the aqueous layer was adjusted to pH 10 with 3% NaOH and then exhaustively extracted with CHCl₃ to give the crude alkaloid. The crude extracts were subjected to a Si gel column (CHCl₃/MeOH, 1:0 → 0:1) to obtain six major fractions (F₁–F₆). Fraction 3 (F₃) was further chromatographed over a Si gel (200–300 mesh) column (petroleum ether/Et₂NH, 50:1 → 10:1) followed by Sephadex LH-20 CC eluted with CH₃OH to afford daphlongamine A (1, 12 mg). Fraction 4 (F₄) was subjected to a RP-18 Si gel column (MeOH/H₂O) to give four fractions (P₁–P₄). Fraction 1 (P₁) was subjected to Si gel (EtOAc/MeOH, 8:1) followed by Sephadex LH-20 CC eluted with CH₃OH to yield daphlongamines C (3, 7 mg) and D (4, 17 mg). Fraction 3 (P₃) was chromatographed on Si gel (petroleum ether/Et₂NH, 50:1 → 10:1) to obtain daphlongamine B (2, 20 mg).

Daphlongamine A (1): white solid; $[\alpha]_D^{25} +5.08$ (c 0.29, CHCl₃); IR (KBr) ν_{\max} 3432, 2955, 2925, 1728, 1711, 1468, and 1199 cm⁻¹; ¹H and ¹³C NMR data, see Tables 1 and 2; ESIMS 402 [M + H]⁺; HRESIMS *m/z* 402.2652 (calcd for C₂₄H₃₆NO₄⁺, 402.2644).

Daphlongamine B (2): white solid; $[\alpha]_D^{25} -107.25$ (c 0.23, CHCl₃); IR (KBr) ν_{\max} 3239, 2961, 2934, and 1724 cm⁻¹; ¹H and ¹³C NMR data, see Tables 1 and 2; ESIMS 344 [M + H]⁺; HRESIMS *m/z* 344.2227 (calcd for C₂₁H₃₀NO₃⁺, 344.2225).

Daphlongamine C (3): block crystal (CH₃OH); mp 153–155 °C; $[\alpha]_D^{25} -27.27$ (c 0.17, CHCl₃/CH₃OH, 1:1); IR (KBr) ν_{\max} 3425, 2951, 2924, 2869, and 1736 cm⁻¹; ¹H and ¹³C NMR data, see Tables 1 and 2; ESIMS 388 [M + H]⁺; HRESIMS *m/z* 388.2492 (calcd for C₂₃H₃₄NO₄⁺, 388.2487).

Daphlongamine D (4): white solid; $[\alpha]_D^{25} -16.28$ (c 0.22, CHCl₃/CH₃OH 1:1); IR (KBr) ν_{\max} 3420, 2951, 2868, and 1733 cm⁻¹; ¹H and ¹³C NMR data, see Tables 1 and 2; ESIMS 406 [M + H]⁺; HRESIMS *m/z* 406.2574 (calcd for C₂₃H₃₆NO₅⁺, 406.2593).

Acknowledgment. Financial support by the National Natural Science Foundation (20672120) of PRC is acknowledged. The authors thank Prof. X. Gong, Kunming Institute of Botany, Chinese Academy of Sciences (CAS), for the identification of the plant material and also Dr. S. Haynes, Department of Chemistry, University of Warwick, for initial proofreading of the document.

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): C₂₃H₃₃NO₄, MW = 387.52, dimensions 0.20 × 0.30 × 0.50 mm; orthorhombic system, space group *P2₁2₁2₁*, crystal cell parameters: *a* = 8.799(1) Å, *b* = 14.981(1) Å, *c* = 15.655(1) Å, *V* = 2063.6(3) Å³, *Z* = 4, *d* = 1.305 g/cm³. A crystal was used for measurements on a MAC DIP-2030K diffractometer with a graphite monochromator (ω scans, $2\theta_{\max} = 50.0^\circ$), Mo K α radiation. The total number of independent reflections measured was 4651, of which 4339 were observed ($|I| \geq 2\sigma(I)$). The crystal structure of 3 was solved by direct methods using SHELXS-97 (Sheldrick, 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 ore-mail: deposit@ccdc.cam.ac.uk).
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NP8001332