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# Daphlongeramine A, novel *Daphniphyllum* alkaloid from *Daphniphyllum longeracemosum*

Chunshun Li,[a,b] Hongping He,[a] Yingtong Di,[a] Yuehu Wang,[a] Shuzhen Mu,[c] Shunlin Li,[a] Suo Gao,[a] Zhulin Gao[a] and Xiaojiang Hao[a,*]

[a]*State Key Laboratory of Phytochemistry and Plant Resources in West China, Kunming Institute of Botany, Chinese Academy of Sciences, Kunming 650204, PR China*
[b]*Graduated School of Chinese Academy of Sciences, Beijing 100039, PR China*
[c]*Institute of Geochemistry, Chinese Academy of Sciences, Guiyang 550002, PR China*

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**Abstract**—A novel *Daphyniphyllum* alkaloid, Daphlongeramine A (**1**) with a unique fused octacyclic skeleton, together with a quite recently reported alkaloid Paxdaphnine A (**2**), were isolated from the fruits of *Daphniphyllum longeracemosum*. The structures were elucidated on the basis of spectroscopic data.


*Daphniphyllum* alkaloids, with structurally diversified and complex polycyclic skeletons,[1,2] have been a challenging target for total synthesis[3] as well as biosynthesis.[4] Heathcock and his co-workers proposed a biosynthetic pathway for *Daphniphyllum* alkaloids and demonstrated a biomimetic total synthesis of several *Daphniphyllum* alkaloids.[3] Although a series of *Daphniphyllum* alkaloids have been isolated by Kobayashi,[2d–o] Jossang,[5] Yue,[6] Bodo,[7] Hao[2b,c,8] and their co-workers, it is still meaningful to find unique skeleton alkaloids for the investigation of biogenetic pathway.

Recently, several new *Daphniphyllum* alkaloids have been isolated from *Daphniphyllum longeracemosum* by Yue[6a] and Hao.[2b,8b] In our continuing search for structurally and biogenetically interesting *Daphniphyllum* alkaloids, a new *Daphniphyllum* alkaloid with novel ring system together with a very recently published one were isolated from the fruits of *D. longeracemosum* Rosenth. In this Letter, we describe the isolation and structure elucidation of **1** and **2**.

The fruits of *D. longeracemosum* were extracted with 95% EtOH, and the crude extract was adjusted at pH2 with 2% HCl. The acidic mixture was defatted with petroleum ether (PE), followed by extraction with $CHCl_3$. Water-soluble materials, which were roughly alkalinized to pH10 with 3% NaOH, were exhaustively extracted with $CHCl_3$. $CHCl_3$-soluble materials were subjected to a silica gel column ($CHCl_3$/MeOH, 1:0→0:1), from which a fraction eluted with $CHCl_3$/MeOH (20:1) was chromatographed over a series of silica gel (PE/$Et_2NH$ and $CHCl_3$/MeOH) to afford Daphlongeramine A (**1**, 0.00012%) and Paxdaphnine A (**2**, 0.00036%).

Daphlongeramine A (**1**) was isolated as an optically active, $[\alpha]_D^{25}$ −39.4 (*c* 0.14, $CHCl_3$), colourless solid. The molecular formula was established as $C_{27}H_{35}NO_5$ by HR-ESI-MS (*m*/*z* 454.2586, $[M+H]^+$, calcd 454.2593), with 11 degrees of unsaturation. The IR spectrum implied the presence of hydroxyl (3423 $cm^{-1}$) and carbonyl (1735 $cm^{-1}$) functionalities, and UV absorption band was observed at 240.8 nm (log ε 3.56). Comprehensive analysis of $^1H$ and $^{13}C$ NMR data suggested 27 carbon signals, which were classified into 8 quaternary carbons ($5sp^3$, $3sp^2$), 6 methines, 11 methylenes and 2 methyls. Among them, one methylene ($\delta_C$ 50.1), one methylene ($\delta_C$ 71.8), and one quarternary carbon ($\delta_C$ 77.0) were supposedly ascribed to those attaching to a nitrogen atom. Moreover, one methine ($\delta_C$ 68.5) and one quarternary carbon ($\delta_C$ 86.1) were connected to an oxygen atom. In addition, two methines ($\delta_C$ 107.3 and 108.1) and two quarternary ($\delta_C$ 153.9 and 154.7) indi-

* Corresponding author. Tel.: +86 871 5223236; fax: +86 871 5219684; e-mail: haoxj@mail.kib.ac.cn

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cated the existence of two olefins. Besides 3 degrees of unsaturation were ascribed to one carbonyl group and two olefins, 8 degrees of unsaturation could only be assigned to the presence of an octacyclic skeleton.

The $^1$H–$^1$H COSY and TOCSY spectra of **1** indicated connectivity of 5 protonated fragment: **a** (C-3 to C-4), **b** (C-18 to C-20), **c** (C-6 to C-7 and C-12, C-11 to C-12), **d** (C-13 to C-17) and **e** (C-25 to C-26) drawn with bold bonds in Figure 1. HMBC correlations of $H_2$-7 to C-2 ($\delta_C$ 77.0) and C-23 ($\delta_C$ 71.8) indicated that C-2, C-7 and C-23 all connected to the nitrogen atom. The connection of fragments **a** and **b** was proved by the HMBC correlations (Fig. 1) of H-18a to C-3 and C-2, and H-3β to C-2. In HMBC spectrum, correlations observed between $H_2$-4, H-6 and $H_2$-21 to C-5 suggested the connections among C-4, C-6 and C-21 via C-5. Meanwhile, connections between C-2 and C-5 via C-8 were indicated by the correlations of H-3β to C-2 and C-8, H-4α and $H_2$-21 to C-5 and C-8. In addition, HMBC cross-peaks of $H_2$-11 and H-17β to C-9 and C-10 implied the connection of fragments **c** and **d** via C-10, and C-9 directly connected with C-10 was also deduced. The connections between C-13 and C-9 via C-8 were inferred from HMBC cross-peaks of H-13β and H-15 to C-8 and C-9. The proton signals observed at $\delta_H$ 3.99 (1H, d, 9.5, H-21a) and 3.88 (1H, d, 9.5, H-21b) showed clear correlations with C-10, which indicated the connection of C-10 with C-21 via one oxygen atom. From the HMBC correlation of H-23b to C-9 and C-15, the connection of C-9 with C-23 was deduced. The connection of a methoxycarbonyl group to C-14 was revealed by HMBC correlations of $H_3$-22′ and H-14 to C-22. Additionally, extensive analysis of positive HRESIMS, 1D and 2D NMR spectrum indicated the presence of a 2,5-disubstituted furan ring,[9] which was verified by the $^1$H NMR spectrum data of furan protons (6.44 ppm, 1H, d, $J = 3.1$ Hz; 6.38 ppm, 1H, br s), $^1$H–$^1$H COSY correlations of H-23 to H-25 and H-25

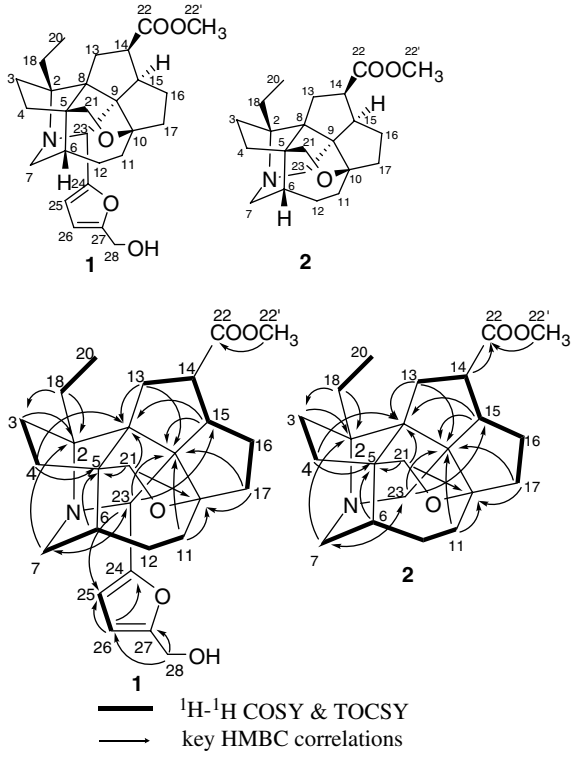



**Figure 1.** Selected 2D NMR correlations for **1** and **2.**

**Table 1.** $^1$H and $^{13}$C NMR data of Daphlongeramine A (**1**) in $C_5D_5N$ at 400 MHz

| No. | $\delta_H$ | $\delta_C$ |
|---|---|---|
| 2 | — | 77.0 s |
| 3α | 1.65 (1H, m) | 31.2 t |
| 3β | 2.45 (1H, m) | |
| 4α | 1.38 (1H, m) | 36.8 t |
| 4β | 1.49 (1H, m) | |
| 5 | — | 49.2 s |
| 6 | 1.54 (1H, m) | 42.8 d |
| 7α | 3.37 (1H, d, 15.3) | 50.1 t |
| 7β | 3.68 (1H, m) | |
| 8 | — | 64.1 s |
| 9 | — | 68.8 s |
| 10 | — | 86.1 s |
| 11α | 1.46 (1H, m) | 31.9 t |
| 11β | 1.69 (1H, m) | |
| 12 | 1.97 (2H, m) | 29.1 t |
| 13α | 1.62 (1H, m) | 28.2 |
| 13β | 2.51 (1H, t, 13.0) | |
| 14 | 3.28 (1H, m) | 46.9 d |
| 15 | 3.13 (1H, dd, 18.4, 9.2) | 55.3 d |
| 16α | 1.67 (1H, m) | 27.0 t |
| 16β | 1.85 (1H, m) | |
| 17α | 2.42 (1H, m) | 42.6 t |
| 17β | 1.75 (1H, m) | |
| 18a | 1.77 (1H, m) | 28.0 t |
| 18b | 1.25 (1H, m) | |
| 20 | 1.06 (3H, t, 7) | 10.2 q |
| 21a | 3.99 (1H, d, 9.5) | 68.5 t |
| 21b | 3.88 (1H, d, 9.5) | |
| 22 | — | 174.2 s |
| 23 | 4.61 (1H, s) | 71.8 d |
| 24 | — | 153.9 s |
| 25 | 6.44 (1H, d, 3.1) | 107.3 d |
| 26 | 6.38 (1H, br s) | 108.1 d |
| 27 | — | 154.7 s |
| 28 | 4.89 (2H, s) | 56.9 t |
| 22′ | 3.72 (3H, s) | 51.3 q |

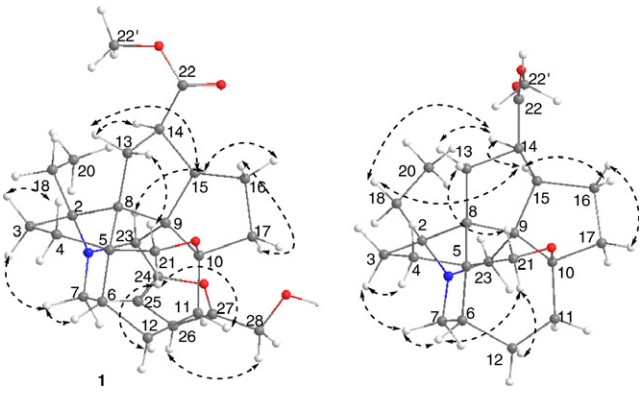



**Figure 2.** Key ROESY correlations and relative stereochemistry of **1** and **2**.

to H-26, and HMBC correlation of H-23 to C-25. The HMBC cross-peaks of H-28 to C-26 and C-27, and the TOCSY correlations of H-26 to H-28 implied the presence of hydroxymethyl at the C-27 position. Thus, the combinational structure of Daphlongeramine A (**1**), possessing a 5-hydroxymethyl furan moiety was undoubtedly established (Table 1).

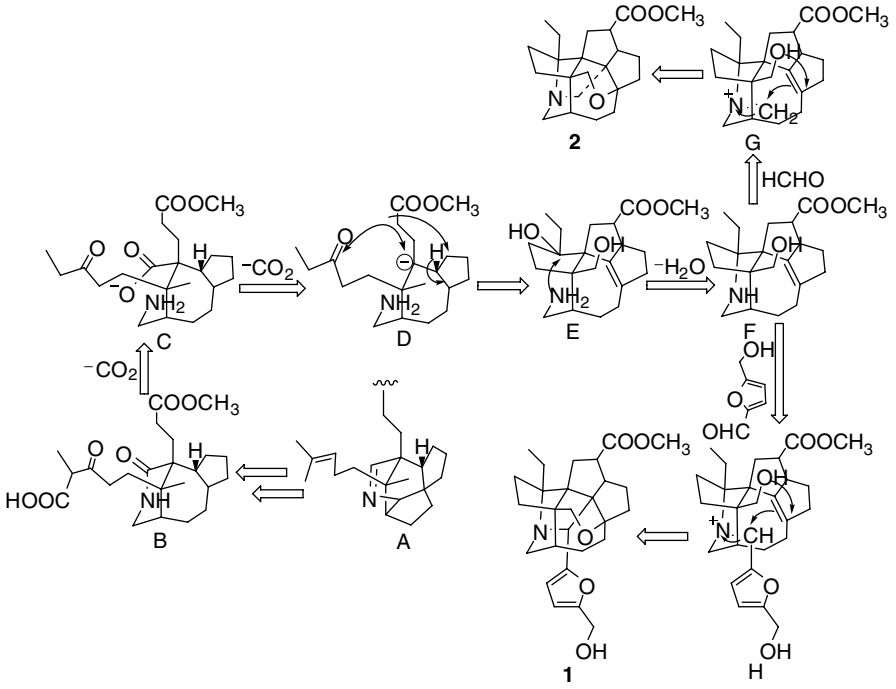
The relative stereochemistry of **1** was constructed by analysis of key correlations as shown in computer-generated 3D drawing (Fig. 2). ROESY correlations observed among H-13α/H-14, H-14/H-15, H-15/H-23 implied that H-14, H-15 and H-23 took α configuration. The correlations of H-7β/H-6 implied that H-6 was β configuration. The cycloheptane (C-5 to C-6 and C-8 to C-12) taking a chair form was suggested by the correlations between $H_2$-21 and H-12β. Thus, the relative stereostructure of Daphlongeramine A (**1**) was concluded as shown in Figure 2.

Compound **2** was determined to be a quite recently isolated alkaloid Paxdaphnine A[10] by extensive analysis of 1D and 2D NMR spectra. Although different solvent was used in NMR experiments, the data of compound **2** (Table 2) were consistent with Paxdaphnine A.

The possible biogenetic pathway for compounds **1** and **2** was proposed in Scheme 1. The biogenetic precursor of them seems to be a general imine intermediate A, which was proposed as a precursor of the secodaphniphylline-type skeleton by Heathcock and Joe.[3b] Intermediate B might be generated by possible oxidation of C-1, C-2 and C-19, as well as hydrolysis of lactam, which was followed by the decarboxylation of C-19 (intermediate C) and subsequent decarboxylatioin of C-1 (intermediate D). The formation of C-2–C-8 bond through aldol condensation reaction (intermediate E) followed by intramolecular nucleophilic substitution might form

**Table 2.** $^{1}H$ and $^{13}C$ NMR data of Paxdaphnine A (**2**) in $CDCl_3$ at 500 MHz

| No. | $\delta_H$ | $\delta_C$ |
|---|---|---|
| 2 | — | 77.5 s |
| 3α | 1.67 (1H, m) | 30.5 t |
| 3β | 2.36 (1H, m) | |
| 4α | 1.50 (1H, m) | 36.7 t |
| 4β | 1.62 (1H, m) | |
| 5 | — | 48.9 s |
| 6 | 1.68 (1H, m) | 43.1 d |
| 7α | 2.47 (1H, d, 15.0) | 57.5 t |
| 7β | 3.73 (1H, dd, 15.0, 10.0) | |
| 8 | — | 63.5 s |
| 9 | — | 65.6 s |
| 10 | — | 85.7 s |
| 11 | 2.02–1.91 (2H, m) | 32.1 t |
| 12α | 1.24 (1H, m) | 28.9 t |
| 12β | 2.14 (1H, m) | |
| 13α | 1.52 (1H, m) | 27.7 t |
| 13β | 2.32 (1H, m) | |
| 14 | 3.18 (1H, m) | 46.9 d |
| 15 | 2.54 (1H, dd, 18.0, 9.0) | 54.7 d |
| 16α | 1.57 (1H, m) | 26.6 t |
| 16β | 1.46 (1H, m) | |
| 17α | 1.43 (1H, m) | 42.2 t |
| 17β | 1.69 (1H, m) | |
| 18a | 1.57 (1H, m) | 27.9 t |
| 18b | 1.23 (1H, m) | |
| 20 | 0.93 (3H, t, 7.2) | 9.6 q |
| 21a | 4.08 (1H, d, 9.6) | 69.2 t |
| 21b | 3.96 (1H, d, 9.6) | |
| 22 | — | 174.2 s |
| 23a | 3.26 (1H, d, 14.1) | 67.3 t |
| 23b | 3.16 (1H, d, 14.1) | |
| 22′ | 3.63 (3H, s) | 51.4 q |




**Scheme 1.** Plausible biogenetic pathway for Daphlongeramine A (**1**) and B (**2**).

intermediate F. The condensation of formaldehyde or 5-hydroxymethyl-2-furancarboxaldehyde[9] to nitrogen atom of intermediate F might produce intermediate G and H, which were converted to compounds **1** and **2** by the subsequent cyclization, respectively. The results suggested that the 'extra' carbon (C-23) might be provided by formaldehyde, which undoubtedly proved Heathcock's hypothesis on the biosynthetic link between methyl homodaphniphyllate and daphnilactone skeletons.[3b] The 5-hydroxymethyl furan moiety of Daphlongeramine A (**1**) is the first example in all of the *Daphniphyllum* alkaloids reported up to date.

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