Notes

Daphnimacropodines A−D, Alkaloids from *Daphniphyllum macropodum*

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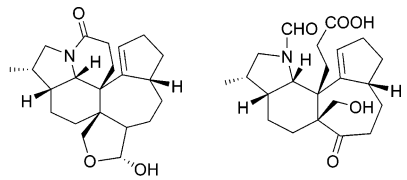
Four new *Daphniphyllum* alkaloids, daphnimacropodines A−D (**1**−**4**), together with three known ones, daphnilactone B and daphnezomines H and I, were isolated from the fruits of *Daphniphyllum macropodum*. Their structures were determined by spectroscopic methods, especially 2D NMR techniques.

Daphniphyllum alkaloids with highly complex polycyclic structures are the secondary metabolites elaborated by plants of the genus *Daphniphyllum*.[1] Radioactive tracer experiments revealed that they were generated from six molecules of mevalonic acid via a squalene-like intermediate.[2] Heathcock and co-workers performed biomimetic total syntheses of several *Daphniphyllum* alkaloids.[3] In recent years, more than 60 new *Daphniphyllum* alkaloids were isolated.[4−8] Some of these alkaloids showed cytotoxic activities against several tumor cell lines.

Daphniphyllum macropodum Miq., widely distributed in the south of China, is commonly used in Chinese traditional medicine to treat several symptoms, such as inflammation, pyreticosis, and influenza.[9] In the investigation of *Daphniphyllum* alkaloids, *D. macropodum* was the first species to be studied[10] and a series of *Daphniphyllum* alkaloids were discovered.[11] Recently, three new *Daphniphyllum* alkaloids, macropodumines A−C, were isolated from this species.[8] In our investigation of *D. macropodum*, four new *Daphniphyllum* alkaloids, daphnimacropodines A−D (**1**−**4**), as well as daphnilactone B[12] and daphnezomines H[12] and I[12] were isolated from the fruits of this plant. Daphnimacropodine A (**1**) is associated with daphniglaucin C[13] in biogenetic syntheses and possesses a new ring system.



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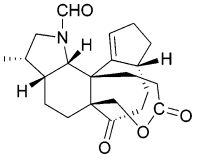

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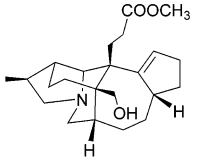

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Daphnimacropodine A (**1**) was obtained as colorless gum with $[\alpha]^{20}_{D}$ +50.5 (*c* 1.00, acetone). Its molecular formula was determined as $C_{22}H_{31}NO_3$ by HRESIMS at *m*/*z* 358.2368 [(M + H)$^+$, calcd for $C_{22}H_{32}NO_3$, 358.2382], corresponding to eight degrees of unsaturation. IR absorptions suggested the presence of hydroxy (3420 cm^{-1}) and carbonyl (1624 cm^{-1}) functional groups. The ^{13}C NMR data (Table 1) revealed 22 carbon resonances, which were classified into two sp^2 quaternary carbons, two sp^3 quaternary carbons, one sp^2 methine, six sp^3 methines, 10 sp^3 methylenes, and one methyl group. The ^{1}H and ^{13}C NMR spectra of **1** indicated that the sp^2 quaternary carbon (δ_C 168.8) was a lactam carbonyl and the sp^3 methine carbon (δ_C 104.3) was a hemiacetal carbon. One methine (δ_C 64.8; δ_H 3.68) and one methylene (δ_C 53.7; δ_H 3.79 and 3.18) were ascribed to carbons linked to a nitrogen atom. Since two degrees of unsaturation were attributable to the carbonyl and the trisubstituted double bond, **1** was inferred to possess six ring systems.

Three partial structures, **a** (C-1 to C-4, C-2 to C-18, C-18 to C-19 and C-20), **b** (C-6 to C-7, C-10 to C-12, C-10 to C-17, C-15 to C17), and **c** (C-13 to C-14), and an isolated CH_2 (δ_C 74.9; δ_H 4.13 and 3.53) were deduced from the ^{1}H−^{1}H COSY (including HMQC) data of **1**, as shown in Figure 2. The linkages of the three partial structures and the isolated methylene with quaternary carbons and heteroatoms were achieved by analysis of the HMBC spectum (Figure 2). The presence of a 2-hydroxytetrahydrofuran ring was suggested by the HMBC correlations of H-7 to C-5, C-6, and C-21, as well as H-21 to C-5, C-6, and C-7. The attachment of C-22 to the nitrogen atom was established by HMBC correlation of H_2-19 to C-22. An olefinic carbon at δ_C 147.0 was assigned to C-9 by HMBC correlations of H-15 and H_2-16 to C-9. The connectivity of C-9 to C-10 was supported by the HMBC correlations of H-15 to C-9 and C-10. The HMBC correlations from H-15 to C-8 and C-9, as well as H-1 to C-8 and C-9, allowed the connection of C-8 to C-9 and C-1 to C-8. The connection of C-5 to C-8 was indicated by the HMBC correlations of H-1 to C-5 and C-8. In the HMBC experiment, the correlations of H_2-13 to C-8 and C-9 established the attachment of C-13 to C-8.

The relative configuration of **1** was established by ROESY experiments (Figure 3). The ROESY correlations of H_2-21/H-1, H_2-21/H-2, H_2-21/H-4β, H_2-21/H-13β, and H_2-21/H-6 indicated that H-1, H-2, and H-6 were all β-cofacial with the B ring in a boat conformation. H-7 and H-10 were also β-oriented on the basis of the ROESY correlations of H-6/H-7 and H-6/H-10. The ROESY correlation of H-1/H-18 suggested that CH_3-20 was in the α-orientation. The structure of daphnimacropodine A (**1**) was thereby elucidated as **1**.

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Table 1. NMR Spectroscopic Data (400 MHz, $CDCl_3$) of Daphnimacropodine A (**1**)

position	δ_C, mult.	δ_H (J in Hz)	HMBC	ROESY
1	64.8, CH	3.68, d (10.2)	2, 3, 5, 8, 9, 13, 18, 19	H-2, H-13 β, H_2-21
2	38.5 CH	2.62, m	1, 3, 4, 8, 18, 19, 20	H-1, H-3 β
3	19.5, CH_2	α 1.96, m	1, 2, 4, 5, 18	H-3 β, H-15, H_3-20
		β 1.44, m	1, 2, 4, 5	H-2, H-3 α, H-18
4	25.6, CH_2	α 1.73, m	2, 3, 5, 6, 21	H_2-3
		β 1.54, m	3, 5, 8, 21	H-2 β, H-4 α
5	49.0, qC			
6	50.1, CH	2.19, m	4, 5, 7, 8, 12	H-7, H-10, H_2-13, H-21 b
7	104.3, CH	α 5.05, d (5.1)	5, 6, 12, 21	H-6, H_2-12
8	44.9, qC			
9	147.0, qC			
10	44.7, CH	2.64, m	8, 9, 11, 15	H-6, H-11 β, H-13 α, H-17 β
11	31.5, CH_2	β 1.76, m	6, 9, 10, 17	H-6, H-10, H-12 β
		α 1.70, m	6, 9, 10, 12, 17	H-11 β
12	23.0, CH_2	β 1.92, m	5, 6, 7, 10, 11	H-6, H-12 α
		α 1.58, m	6, 7, 10, 11	H-7, H-12 β
13	27.5, CH_2	α 2.02, m	1, 5, 9, 14, 22	H-6, H-10, H-13 β, H_2-14
		β 1.73, m	1, 5, 9, 14	H-1, H-6, H-13 α, H-21 a
14	30.4, CH_2	β 2.42, m	8, 13, 22	H_2-13, H-14 α
		α 2.18, m	8, 13, 22	H-10, H-13 α
15	128.2, CH	5.32, s	5, 9, 10, 14, 16,17	H_3-20, H-19 α
16	30.3, CH_2	α 2.29 (m)	9, 15, 17	H-16 β, H-17 α
		β 2.18, m	10, 9, 15	H-15, H-16 α
17	33.8, CH_2	β 1.90, m	9, 10, 11, 15, 16	H-10, H-16 β, H-17 α
		α 1.48, m	9, 10, 11, 15, 16	H-16α, H-17 β
18	32.5, CH	2.69, m	1, 3, 19, 20	H-1, H-3 β, H-19 β, H_3-20
19	53.7, CH_2	β 3.79, m	1, 2, 18, 20, 22	H-18, H-19 α
		α 3.18, dd (12.5, 7.0)	1, 2, 18, 20, 22	H-15, H-19 β, H_3-20
20	14.6, CH_3	1.03, d (7.0)	2, 18, 19	H_2-3, H-15, H-18, H-19 α
21	74.9, CH_2	b 4.13, d (7.8)	6, 12	H-1, H-2, H-4β, H-6, H-13 β
		a 3.53, d (7.8)	4, 5, 6, 7	H-1, H-2, H-4 β, H-6, H-13 β
22	168.8, qC			

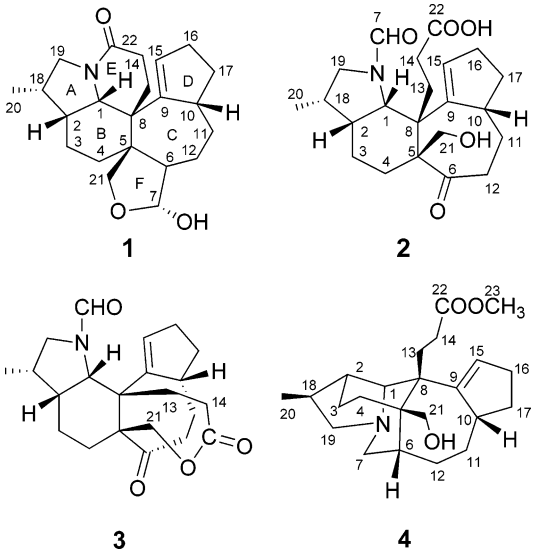


Figure 1. Structures of daphnimacropodines A−D (**1**−**4**).

A plausible biogenetic pathway for daphnimacropodine A (**1**) is proposed in Scheme 1. Daphnimacropodine A (**1**) might be generated from a common imino intermediate C, which has been proposed as a precursor of daphniglaucin C by Kobayashi et al.[13] The intermediate C could be transformed into intermediate D through Schiff base hydrolysis and then converted into intermediate E through a series of oxidation reactions. Oxidation of the C-7 hydroxy group would lead to the C-7−N bond cleavage and the C-22−N bond formation; consequently lactam intermediate F would

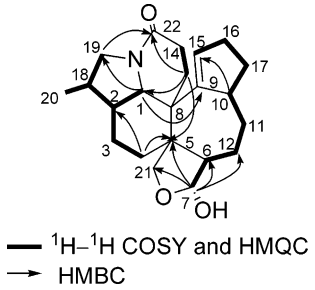


Figure 2. Selected 2D NMR correlations for daphnimacropodine A (**1**).

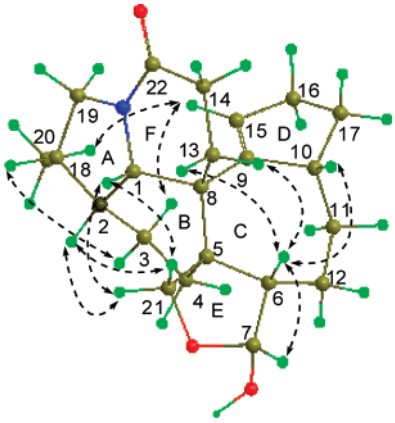
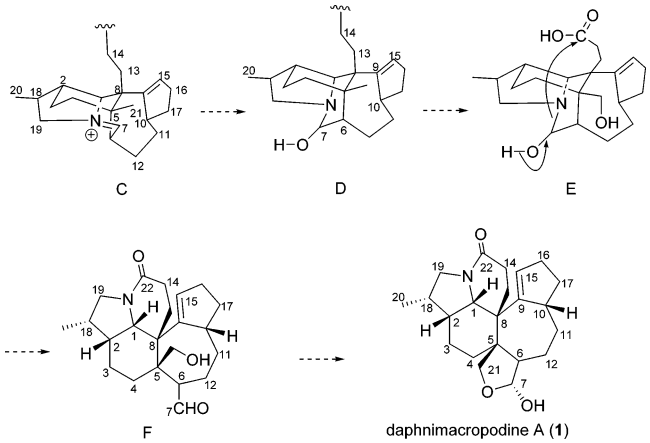


Figure 3. Selected ROESY correlations (dashed arrows) and relative configuration of daphnimacropodine A (**1**).

Scheme 1. Plausible Biogenetic Path for Daphnimacropodine A (**1**)



be formed. Daphnimacropodine A (**1**) would be finally produced from intermediate F through intramolecular hemiacetal formation.

Daphnimacropodine B (**2**) showed a molecular formula of $C_{22}H_{31}NO_5$ as determined by HRESIMS at m/z 390.2280 $(M + H)^+$ with eight degrees of unsaturation. The ^{13}C NMR spectrum displayed 22 carbon resonances attributed to three carbonyls, one trisubstituted double bond, two quaternary carbons, four methines, 10 methylenes, and one methyl. Comparing the ^{1}H and ^{13}C NMR chemical shifts (Table 2) with those of daphniglaucin C, the only difference was the absence of the C-22 *O*-methyl resonance in **2**. Therefore, daphnimacropodine B (**2**) was elucidated as de-*O*-methyldaphniglaucin C.

The ROESY spectrum of **2** showed the same relative configuration as that of daphniglaucin C. Correlations of H-21a (δ_H 4.49) to H-10 and H-21b (δ_H 3.82) to H_2-13 suggested that H_2-21, H-10, and CH_2-13 were β-cofacial. As a consequence, the correlations of H-1 to H_2-13 and of H-1 to H-2 and H-18 indicated that H-1, H-2, and H-18 were β-oriented.

Table 2. NMR Spectroscopic Data of Daphnimacropodines B−D (**2**−**4**)

position	**2**[a]		**3**[b]		**4**[a]	
	δ_C, mult.	δ_H (J In Hz)	δ_C	δ_H (J in Hz)	δ_C, mult.	δ_H (J in Hz)
1	65.5, CH	4.15, d (4.0)	71.1	3.79, d (5.5)	72.3, CH	3.62, d[c]
2	40.4, CH	2.26, m	37.8	2.42, m	37.8, CH	2.40 (m)
3	17.0, CH_2	α 1.73, m	18.3	α 2.01, m	20.0, CH_2	α 1.80, m
		β 1.66, m		β 1.63, m		β 1.39, m
4	26.9, CH_2	α 2.21, m	25.6	1.81, m	32.3, CH_2	β 2.20, m
		β 1.59, m		1.81, m		α 2.03, m
5	57.7, qC		55.1		41.1, qC	
6	216.3, qC		201.2		38.1, CH	2.49, m
7	165.4, CH	8.06, s	167.0	8.56, s	58.3, CH_2	α 3.79, m
						β 3.15, t (11.5)
8	46.9, qC		49.5		40.3, qC	
9	150.6, qC		148.5		146.7, qC	
10	47.2, CH	3.16, m	49.1	3.11, m	47.8, CH	2.87, m
11	32.3, CH_2	β 1.87, m	27.4	β 1,81, m	31.4, CH_2	α 2.05, m
		α, 1.53, m		α 1.47, m		β 1.64, m
12	42.9, CH_2	α 3.20, dt (5.8, 13.2)	43.4	α 2.64, dt (13.0, 5.0)	30.4, CH_2	β 2.00, m
		β 2.31, m		β 2.41, m		α 1.45, m
13	31.9, CH_2	1.98, t (7.8)	33.9	β 2.38, m	31.5, CH_2	2.07, m
		1.98, t (7.8)		α 2.07, dd (15.0, 7.5)		1.74, m
14	31.4, CH_2	2.15, t (7.8)	29.7	α 2.75, m	30.1, CH_2	2.24, m
		2.15, t (7.8)		β 2.50, t (7.5)		2.19, m
15	131.9, CH	5.72, s	134.7	5.93, d (2.0)	132.9, CH	5.80, s
16	30.1, CH_2	α 2.42, m	30.3	2.45, m	29.8, CH_2	β 2.87, m
		β 2.30, m		2.45, m		α 2.18, m
17	34.5, CH_2	β 2.18, m	32.8	β 2.36, m	32.4, CH_2	β 2.01, m
		α 1.73, m		α 1.63, m		α 1.68, m
18	34.9, CH	2.30, m	36.0	1.92, m	36.0, CH	2.53, m
19	51.7, CH_2	β 3.62, dd (11.5, 6.5)	49.5	β 3.95, dd (11.5, 6.9)	65.6, CH_2	α 4.46, brs
		α 2.96, t (11.5)		α 2.69, d (11.5)		β 2.52, m[c]
20	12.8, CH_3	1.08, d (6.5)	10.9	0.96, d (6.9)	13.3, CH_3	1.05, d (6.5)
21	66.5, CH_2	4.49, d (10.5)	70.8	4.61, d (13.0)	66.4, CH_2	4.28, d (10.0)
		3.82, d (10.5)		3.91, d (13.0)		3.65, d (10.0)
22	178.2, qC		173.7		173.6, qC	
23					51.7, CH_3	3.63, s

[a] 500 MHz, CD_3OD. [b] 500 MHz, $CDCl_3$. [c] Resonances partially obscured.

Daphnimacropodine C (**3**) had a molecular formula of $C_{22}H_{29}NO_4$ as shown by HRESIMS at m/z 394.1970 [$(M + Na)^+$, calcd for $C_{22}H_{29}NO_4Na$ 394.1994]. Its ^{13}C NMR and DEPT spectra (Table 2) revealed 22 carbon resonances, which were consistent with that of **2**, implying that the two alkaloids likely shared the same basic skeleton. Considering that the molecular weight of **3** is 18 less than those of **2**, **3** was inferred as the lactone derivative of **2**. Analysis of 2D NMR spectra (HMQC, $^1H-^1H$ COSY, HMBC) confirmed that **3** had the structure as inferred. The ROESY spectrum showed that daphnimacropodine C (**3**) and daphnimacropodine B (**2**) had the same relative configuration.

Daphnimacropodine D (**4**) showed a molecular formula of $C_{23}H_{35}NO_3$ as determined by HRESIMS at m/z 374.2695 [$(M + H)^+$, calcd for $C_{22}H_{36}NO_3$ 374.2695] with seven degrees of unsaturation. All 23 carbon resonances were displayed in its ^{13}C NMR spectrum (Table 2), which were assignable to one ester carbonyl, one trisubstituted double bond, two quaternary carbons, five sp^3 methines, 11 methylenes, one methyl, and one *O*-methyl. The methylene (δ_C 66.4, δ_H 4.28 and 3.65) had to be connected to a hydroxyl group. The carbonyl and the double bond accounted for two degrees of unsaturation; the remaining five degrees of unsaturation were assignable to the presence of a pentacyclic ring system in **4**.

The patterns and the chemical shifts of ^{13}C NMR data (Table 2) were similar to those of daphnilactone B,[12] except for the presence of an *O*-methyl resonance (δ_C 51.7) in **4**, suggesting that these two alkaloids shared the same basic skeleton. 2D NMR spectra (HMQC, $^1H-^1H$ COSY, and HMBC) showed that **4** was the methyl ester derivative of daphnilactone B.

The ROESY correlations of H-21a (δ_H 4.28) to H-10 and H-12β (δ_H 2.00) and of H-21b (δ_H 3.65) to H-4β (δ_H 2.20) and H-6 suggested that CH_2-21, H-10, H-4β, and H-6 were β-cofacial. The ROESY correlations of H-6 to H-7β (δ_H 3.15), H-7β to H-3β (δ_H 1.39) and H-19β (δ_H 2.52), and H-3β and H-19β to CH_3-20 indicated that CH_3-20 was β-oriented. On the other hand, the ROESY correlations of H-1 to H-2 and H-18, as well as H-2 to H-3α and H-4α, indicated that H-1, H-2, and H-18 were in the α-orientation.

Daphnilactone B and daphnezomines H and I were identified by comparison of ^1H and ^{13}C NMR data with those of authentic samples.

Daphnimacropodines A−D (**1**−**4**) showed no inhibition on in vitro platelet aggregation induced by PAF, ADP, and AA.

Experimental Section

General Experimental Procedures. Optical rotations were measured on a Jasco DIP-370 digital polarimeter. IR spectra were recorded on a BIO-Rad FTS spectrometer with KBr disks. ^1H NMR, ^{13}C NMR, $^1H-^1H$ COSY, HMBC, HMQC, and ROESY spectra were measured on DRX-500 or AV-400 spectrometers with TMS as internal standard. ESIMS were obtained on a Waters 2659 HPLC-Thermo Finnigan LCQ Advantage ion trap mass spectrometer. Column chromatography was carried out on silica gel (200−300 mesh; Qingdao Marine Chemical Factory, Qingdao, People's Republic of China) and Sephadex LH-20 (40−70 μm; Amersham Pharmacia Biotech AB, Uppsala, Sweden).

Plant Material. The fresh fruits of *D. macropodum* were collected in Jiangxi Province, People's Republic of China, in November 2005, and identified by Prof. Xun Gong of the Kunming Institute of Botany, CAS.

Extraction and Isolation. The fresh fruits of *D. macropodum* (20 kg) were percolated with 95% EtOH. After removal of solvent under reduced pressure, the crude extract (2.1 kg) was dissolved in H_2O (8 L) to form a suspension, which was adjusted with tartaric acid to pH ~3. The acidic mixture was defatted with $CHCl_3$ (2 L × 4), and the aqueous phase was basified with $NH_3 \cdot H_2O$ to pH 10 and extracted with $CHCl_3$ (2 L × 4) to obtained a crude alkaloid (47.0 g) fraction. The alkaloids were then subjected to column chromatography on silica gel eluted with a gradient solvent system of $CHCl_3$/MeOH (100:0 to 0:100) to give six fractions (F_1-F_6). Fraction F_3 (7.6 g) was rechromatographed over a silica column eluted with $CHCl_3$/MeOH (100:4−100:8) to give two major fractions, D_1 and D_2. Each of them was separated by silica gel column chromatography eluted with petroleum/acetone/Et_2NH (10:1:0.02 to 10:3:0.02) and then purified by Sephadex LH-20 column chromatography eluted with MeOH to afford **1** (20 mg), **2** (6 mg), **3** (7 mg), and **4** (120 mg), as well as daphnilactone B (320 mg), daphnezomine H (34 mg), and daphnezomine I (27 mg).

Daphnimacropodine A (1): colorless gum; $[\alpha]^{20}_D$ +50.5 (*c* 1.00, acetone); IR (KBr) λ_{max} 3420, 2931, 1624, 1465, 1408, 1037, 1011 cm^{-1}; ^1H and ^{13}C NMR, see Table 1; ESIMS m/z 358.5 $(M + H)^+$; HRESIMS m/z 358.2368 [$(M + H)^+$, calcd for $C_{22}H_{32}NO_3$ 358.2382].

Daphnimacropodine B (2): amorphous, white powder; $[\alpha]^{20}_D$ −30.1 (*c* 0.15, CH_3OH); IR (KBr) λ_{max} 3431, 2933, 1705, 1696, 1630, 1455, 1382, 1171 cm^{-1}; ^1H and ^{13}C NMR, see Table 1; ESIMS m/z 390.5 $(M + H)^+$; HRESIMS m/z 390.2282 [$(M + H)^+$, calcd for $C_{22}H_{32}NO_5$ 390.2280].

Daphnimacropodine C (3): amorphous, white powder; $[\alpha]^{20}_D$ −49.4 (*c* 0.30, acetone); IR (KBr) λ_{max} 3433 (H_2O), 2932, 1742, 1696, 1644, 1441, 1184, 1086 cm^{-1}; ^1H and ^{13}C NMR, see Table 1; ESIMS m/z 372.4 $(M + H)^+$; HRESIMS m/z 394.1970 [$(M + Na)^+$, calcd for $C_{22}H_{29}NO_4Na$ 394.1994].

Daphnimacropodine D (4): colorless gum; $[\alpha]^{20}_D$ −22.5 (*c* 0.20, CH_3OH); IR (KBr) λ_{max} 3431, 2924, 1738, 1456, 1169 cm^{-1}; ^1H and ^{13}C NMR, see Table 1; ESIMS m/z 374.6 $(M + H)^+$; HRESIMS m/z 374.2695 [$(M + H)^+$, calcd for $C_{23}H_{36}NO_3$ 374.2695].

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Supporting Information Available: This material is available free of charge via the Internet at http://pubs.acs.org.

References and Notes

(1) For a recent review of *Daphniphyllum* alkaloids, see: Kobayashi, J.; Morita, H. In *The Alkaloids*; Cordell, G. A., Ed.; Academic Press: New York, 2003; Vol. 60, pp 165−205, and references therein.

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