Daphnicyclidins J and K, Unique Polycyclic Alkaloids from *Daphniphyllum humile*

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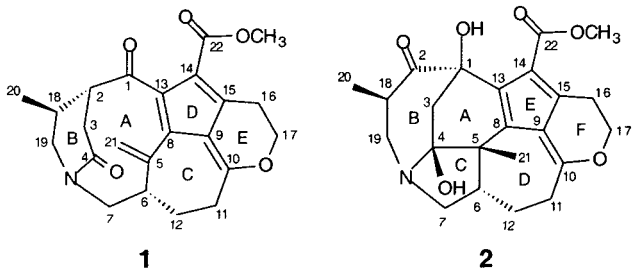
Two *Daphniphyllum* alkaloids with unprecedented polycyclic skeletons, daphnicyclidins J (**1**) and K (**2**), have been isolated from the stems of *Daphniphyllum humile*, and the structures and relative stereochemistry were elucidated on the basis of spectroscopic data. The absolute stereochemistry of **1** was established by chemical correlation with a known-related alkaloid, daphnicyclidin D (**3**), through a modified Polonovski reaction.

Introduction

Daphniphyllum alkaloids are a group of unique squalene-derived alkaloids, some of which are elaborated by an oriental tree "Yuzuriha" (*Daphniphyllum macropodum*; Daphniphyllaceae) in Japan and classified into six types of backbone skeletons.[1,2] These unusual ring systems have attracted great interest as challenging targets for total synthesis or biosynthetic studies.[3] Heathcock and co-workers have proposed a biogenetic pathway for *Daphniphyllum* alkaloids and reported a biomimetic total synthesis of (+)-methyl homodaphniphyllate.[4]

Recently, we have isolated some novel types of *Daphniphyllum* alkaloids[5−8] such as daphnezomines A and B[5] with a unique aza-adamantane core and daphnezomines F and G[6] with an 1-azabicyclo[5.2.2]undecane ring system as well as daphnicyclidins A−H[8] with a unique hexa- or pentacyclic ring system from the leaves and stems of *D. teijismanni* and/or *D. humile*. In our continuing search for structurally unique and biogenetically interesting *Daphniphyllum* alkaloids, daphnicyclidins J (**1**) and K (**2**), two novel alkaloids with unprecedented fused penta- or hexacyclic skeletons, respectively, were isolated from the stems of *D. humile*. This paper describes the isolation and structural elucidation of **1** and **2** and chemical correlation of **1** with a known-related alkaloid, daphnicyclidin D (**3**), through a modified Polonovski reaction.



1 **2**

Results and Discussion

Isolation of Daphnicyclidins J (1) and K (2). The stems of *D. humile* were extracted with MeOH, and the extract was partitioned between EtOAc and 3% tartaric acid. Water-soluble materials, which were adjusted at pH 9 with saturated Na_2CO_3, were extracted with $CHCl_3$. $CHCl_3$-soluble materials were subjected to an amino silica gel column (Hex/EtOAc, 9:1 → 1:1 and then $CHCl_3$/MeOH, 1:0 → 0:1) from which a fraction eluted with MeOH was purified by C_{18} HPLC (25% CH_3CN/0.1%TFA) followed by amino silica gel HPLC (15% CH_3CN) to afford daphnicyclidins J (**1**, 0.002% yield) and K (**2**, 0.002%) together with known related alkaloids, daphnicyclidins A−C, D (**3**), E (**4**), and F−H.[8]

Structure of Daphnicyclidin J (1). Daphnicyclidin J (**1**) showed the pseudomolecular ion peak at *m*/*z* 396 $(M + H)^+$ in the FABMS, and the molecular formula, $C_{23}H_{25}NO_5$, was established by HRFABMS [*m*/*z* 396.1797 $(M + H)^+$, Δ −1.4 mmu]. IR absorptions implied the presence of ketone and amide carbonyl (1690 and 1660 cm^{-1}, respectively) functionalities. ^1H and ^{13}C NMR data (Table 1) revealed 23 carbon signals due to one *exo*-methylene, three tetrasubstituted olefins, three carbonyls, three sp^3 methines, seven sp^3 methylenes, and two

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Table 1. ^{1}H and ^{13}C NMR Data of Daphnicyclidin J (1) in CD_3OD at 300 K

	δ_H	δ_C	HMBC (^{1}H)
1		212.1	2, 3a, 18
2	2.70 (1H, ddd, 1.1, 3.0, 5.0)		53.1
3a	2.49 (1H, dd, 5.0, 15.9)		33.9
3b	2.85 (1H, ddd, 1.9, 3.0, 15.9)		
4		174.0	2, 3, 7, 19a
5		141.1	6, 7a, 12b
6	2.99 (1H, m)	45.9	
7a	2.44 (1H, d, 13.9)	50.2	
7b	4.69 (1H, dd, 8.8, 13.9)		
8		129.1	6, 21
9		123.0	11a
10		182.3	11, 12, 17b
11a	2.56 (1H, ddd, 1.4, 7.0, 17.6)	32.6	
11b	2.62 (1H, dd, 10.2, 17.6)		
12a	1.76 (1H, m)	34.7	
12b	2.19 (1H, m)		
13		136.2	
14		119.3	
15		134.1	16, 17b
16a	3.05 (1H, ddd, 5.7, 15.5, 19.0)	25.3	
16b	3.30 (1H, ddd, 1.4, 4.4, 19.0)		
17a	4.22 (1H, ddd, 4.4, 11.1, 15.5)	71.3	
17b	4.74 (1H, ddd, 1.4, 5.7, 11.1)		
18	2.48 (1H, m)	28.3	
19a	3.32 (1H, dd, 9.4, 13.3)	54.4	
19b	2.94 (1H, dd, 6.0, 13.3)		
20	0.98 (3H, d, 7.1)	20.0	
21	4.99 (1H, d, 2.2)	122.7	6
	5.07 (1H, dd, 0.9, 2.2)		
22		166.6	OMe
22-OMe	3.75 (3H, s)	51.7	

methyls. Among them, two methylenes (δ_C 50.2; δ_H 2.44 and 2.69, δ_C 54.4; δ_H 2.94 and 3.32) were ascribed to those bearing a nitrogen, while one methylene (δ_C 71.3; δ_H 4.22 and 4.74) and one quaternary carbon (δ_C 182.3) were those bearing an oxygen.

The ^{1}H−^{1}H COSY and HOHAHA spectra revealed connectivities of three partial structures **a** (C-2 to C-3 and C-18, and C-18 to C-19 and C-20), **b** (C-6 to C-7 and C-12, and C-11 to C-12), and **c** (C-16 to C-17) as shown in Figure 1. HMBC correlations were observed for H-2 and H_a-3 to a conjugated ketone (C-1, δ_C 212.1) and H_2-3 to an amide carbonyl (C-4, δ_C 174.0), which was also correlated with H_2-7 and H_a-19 through a nitrogen atom, suggesting that C-2 and N-7 of a δ lactam ring (ring B) were connected to C-1 and C-7, respectively. HMBC cross-peaks for H_a-7, H-6, and H_b-12 to C-5 (δ_C 141.1), H-6 to C-21 (δ_C 122.7), and H-21 and H-6 to C-8 (δ_C 129.1) indicated that an *exo*-methylene unit (C-5 and C-21) was located between C-6 and C-8. The connectivity of C-11 and C-17 through C-10 and O-10 was implied by HMBC correlations for H_2-11, H_2-12, and H_b-17 to C-10 (δ_C 182.3). In addition, HMBC correlations for H_a-11 to C-9 (δ_C 123.0), H_2-16 to C-14 (δ_C 119.3), and H_2-16 and H_b-17 to C-15 (δ_C 134.1) indicated connectivities between C-9 and C-10 and between C-15 of an olefin (C-14 and C-15) and C-16. A methoxy group was attached to C-22 by the HMBC correlation for the methoxy protons to C-22 (δ_C 166.6). The presence of a fulvene functionality (C-8−C-10 and C-13−C-15), which was conjugated with two carbonyl groups (C-1 and C-22) and an *exo*-methylene group (C-5 and C-21), was elucidated by comparison of the carbon chemical shifts [129.1 (C-8), 123.0 (C-9), 182.3 (C-10), 136.2 (C-13), 119.3 (C-14), 134.1 (C-15)] with those [137.3 (C-8), 120.8 (C-9), 180.6 (C-10), 134.4 (C-13), 122.9 (C-14), 130.2 (C-15)] of daphnicyclidin D (**3**).[8] The presence of the methoxy carbonyl group (C-22) at C-14 was

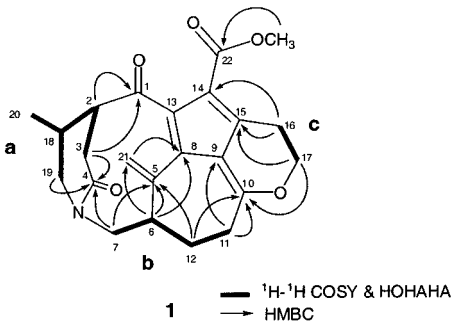

Figure 1. Selected 2D NMR correlations for daphnicyclidin J (**1**).

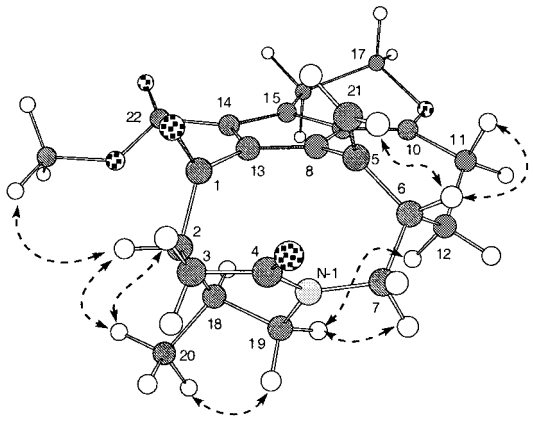

Figure 2. Selected NOESY correlations (dotted arrows) and relative configurations for daphnicyclidin J (**1**).

implied by the NOESY correlation between methoxy protons and H-2 (Figure 2). UV absorptions (245, 320, and 330 nm) also supported the existence of the conjugated fulvene functionality. Thus, the structure of daphnicyclidin J was assigned as **1** having a unique fused-pentacyclic ring system (one five-, two six-, one seven-, and one 10-membered ring) containing a δ-lactam and a pyran rings as shown in Figure 1.

The relative stereochemistry of H-2, H-6, and the methyl group at C-18 was deduced from the $^3J_{H2,\,H18}$ value (1.1 Hz)[9] and NOESY correlations as shown in Figure 2. Conformational space for **1** was searched using the MMFF force field[10] implemented in the Macromodel program,[11] and the lowest energy conformers belonging to two separate clusters were represented as **1a** (296.62 kJ/mol) and **1b** (351.76 kJ/mol) (Figure 3). In the energetically stable conformer **1a**, an *exo*-methylene and an amide ketone were faced to each other, which was consistent with the conformation of **1** deduced from the NOESY data (Figure 2).

Structure of Daphnicyclidin K (2). Daphnicyclidin K (**2**) was shown to have the molecular formula of $C_{23}H_{27}NO_6$ by HRFABMS [*m*/*z* 414.1907, $(M + H)^+$, Δ −1.0 mmu]. IR absorptions implied the presence of hydroxyl (3600 cm^{-1}), ester carbonyl (1700 cm^{-1}), and conjugated carbonyl (1650 cm^{-1}) functionalities. ^{1}H and

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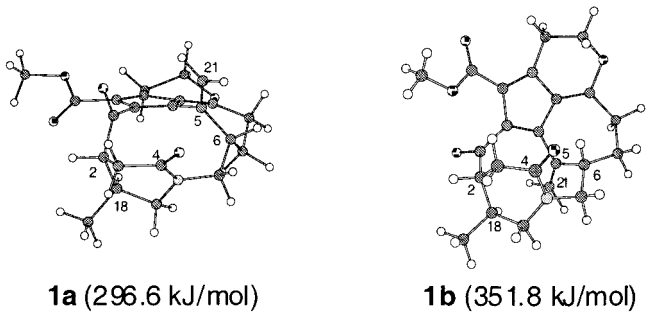

Figure 3. Two representative stable conformers (**1a** and **1b**) for daphnicyclidin J (**1**). The *exo*-methylene and the ketone groups in **1a** were faced toward each other, whereas the two functions were situated in the opposite direction in **1b**.

Table 2. ^{1}H and ^{13}C NMR Data of Daphnicyclidin K (2) in $CDCl_3/CD_3OD$ (1:1) at 300 K

	δ_H	δ_C	HMBC (^{1}H)
1		77.8	3
2		212.8	3, 18, 19, 20
3a	2.06 (1H, d, 14.8)	34.0	
3b	2.20 (1H, d, 14.8)		
4		97.2	3, 7b, 19a, 21
5		52.8	3, 6, 7, 12b, 21
6	2.68 (1H, m)	42.0	7b, 11b, 21
7a	2.48 (1H, dd, 8.3, 10.9)	58.5	6, 19b
7b	3.19 (1H, t, 7.6)		
8		133.9	6, 21
9		120.0	11, 16b
10		177.3	11, 17b
11a	2.51 (1H, ddd, 2.4, 6.7, 10.6)	31.3	
11b	3.00 (1H, ddd, 2.5, 12.2, 17.5)		
12a	1.58 (1H, m)	27.1	7a
12b	2.37 (1H, m)		
13		134.3	3b
14		128.1	
15		137.6	16, 17b
16a	2.96 (1H, ddd, 3.2, 5.7, 18.7)	25.7	
16b	3.27 (1H, ddd, 1.4, 4.1, 18.7)		
17a	4.16 (1H, ddd, 4.2, 11.0, 15.4)	69.9	
17b	4.62 (1H, ddd, 1.4, 4.2, 7.1)		
18	2.85 (1H, m)	38.4	20
19a	3.10 (1H, dd, 10.2, 15.5)	53.1	7, 20
19b	2.91 (1H, dd, 2.7, 15.5)		
20	0.88(3H, d, 6.8)	13.2	
21	1.33 (3H, s)	24.6	
22		167.7	OMe
22-OMe	3.69 (3H, s)	51.5	

^{13}C NMR data (Table 2) disclosed 23 carbon signals due to three tetrasubstituted olefins, two carbonyls, two sp^3 methines, seven sp^3 methylenes, three sp^3 quaternary carbons, and three methyls. Among them, two methylenes (δ_C 58.5; δ_H 2.48 and 3.19, δ_C 53.1; δ_H 2.91 and 3.10) were ascribed to those bearing a nitrogen, while one methylene (δ_C 69.9; δ_H 4.16 and 4.62), one olefin carbon (δ_C 177.3), and two sp^3 quaternary carbons (δ_C 77.8 and 97.2) were those bearing an oxygen. Since five out of 11 unsaturations were accounted for, **2** was inferred to possess six rings. The structure of **2** was elucidated by analyses of 2D NMR data including ^{1}H−^{1}H COSY, HOHAHA, HMQC, and HMBC spectra in CD_3OD. The ^{1}H−^{1}H COSY and HOHAHA spectra revealed connectivities of three partial structures **a** (C-18 to C-19 and C-20), **b** (C-6 to C-7 and C-12, and C-11 to C-12), and **c** (C-16 to C-17) as shown in Figure 4. The HMBC spectrum showed correlations for H_b-3 to C-13 (δ_C 134.3), H_2-3 to C-1 (δ_C 77.8) and C-2 (δ_C 212.8), and H-18 and H_3-20 to C-2, suggesting connectivities between C-18 and C-2, and bonding of C-2, C-3 and C-13 all to C-1 (Figure 4). HMBC

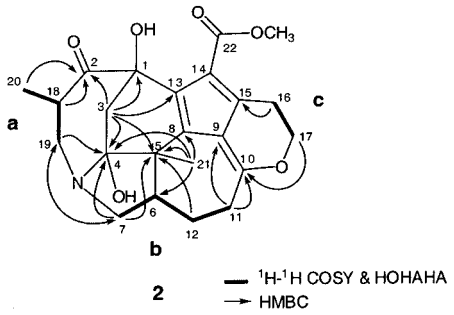

Figure 4. Selected 2D NMR correlations for daphnicyclidin K (**2**).

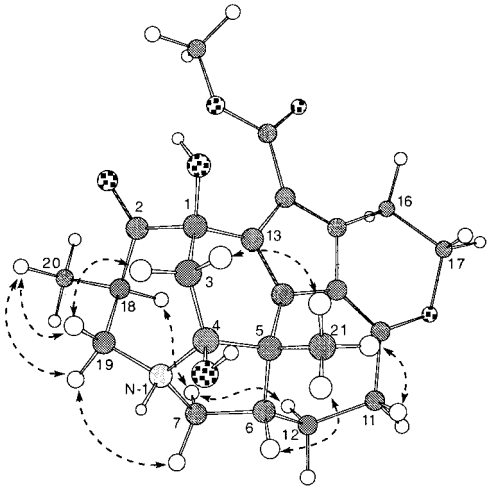

Figure 5. Selected NOESY correlations (dotted arrows) and relative configurations for daphnicyclidin K (**2**).

correlations for H-7 to C-19 (δ_C 53.1) and H-19 to C-7 (δ_C 58.5) gave rise to the connectivity of partial structures **a** and **b** through a nitrogen atom. HMBC correlations for H-3, H_a-19, and H_b-7 to C-4 (δ_C 97.2), and H-3, H-7, and H-12 to C-5 (δ_C 52.8) suggested the presence of a pyrrolo-[1,2-*a*]azepine ring (rings B and C). The presence of a methyl group (C-21) at C-5 was indicated by the HMBC correlation for H_3-21 to C-5. On the other hand, HMBC correlations for H_2-11 to C-9 (δ_C 120.0) and C-10 (δ_C 177.3) indicated connectivities of C-9 to C-11, while those for H_b-17 to C-10 and H_2-16 to C-15 suggested the presence of a pyrane ring (ring F). The fulvene function with a methoxy carbonyl group at C-14 was elucidated by comparison of carbon chemical shifts [δ_C 133.9 (C-8), 120.0 (C-9), 177.3 (C-10), 134.3 (C-13), 128.1 (C-14), 137.6 (C-15)] with those of daphnicyclidins J (**1**) and D (**3**), which was also supported by UV absorptions (245 and 320 nm). Thus, the structure of daphnicyclidin K was assigned as **2** having an unusual skeleton consisting of a 6/7/5/7/5/6 hexacyclic system.

The relative stereochemistry of the hydroxy groups at C-1 and C-4, the methyl groups at C-5 and C-18, and H-6 in **2** was elucidated from NOESY correlations as shown in Figure 5. Conformational calculations of daphnicyclidin K (**2**) by Monte Carlo simulation[12] suggested that the seven-membered ring (ring B) with a chair conformation

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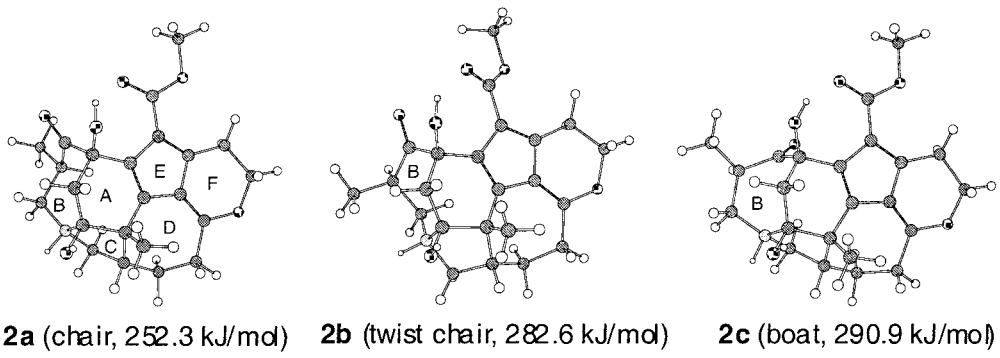
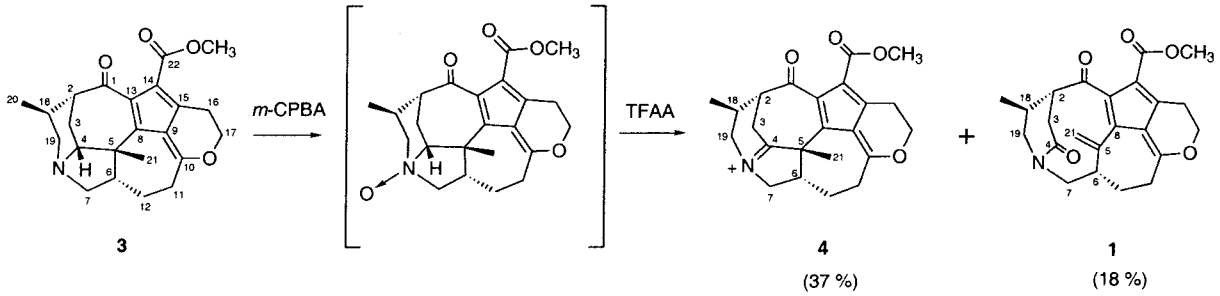
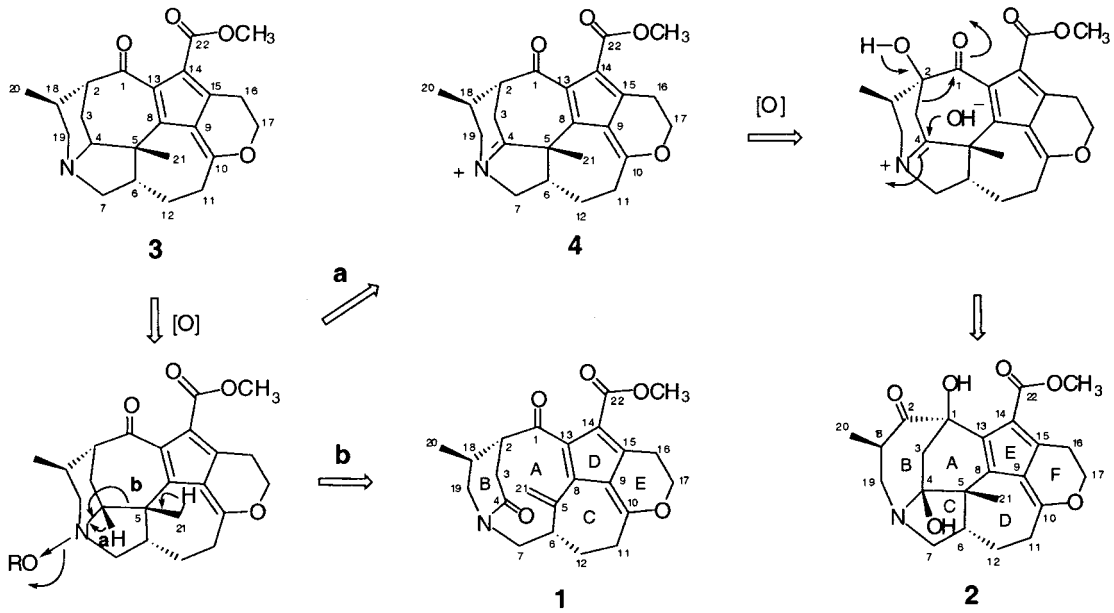


Figure 6. Three representative stable conformers (**2a**−**c**) for daphnicyclidin K (**2**) analyzed by Monte Carlo simulation followed by minimization and clustering analysis.

Scheme 1



Scheme 2



(**2a**) was most stable, whereas those with a twist-boat (**2b**) and a boat (**2c**) conformation had considerably higher energy (Figure 6). In addition, the NOESY correlation of H_b-11/H_3-21 (Figure 5) indicated that another seven-membered ring (ring D) took a twist-boat conformation similar to the crystal structure of daphnicyclidin A.[8]

Chemical Correlation for Daphnicyclidins J (1) and D (3) through Polonovski Reaction. Daphnicyclidin J (**1**) was obtained together with daphnicyclidin E (**4**) from daphnicyclidin D (**3**) through a modified Polonovski reaction[12] as follows (Scheme 1). Treatment of **3** with *m*-chloroperbenzoic acid (*m*-CPBA) followed by reaction[13] with trifluoroacetic anhydride (TFAA) gave two compounds in 37% and 18% yields, whose spectral data were identical with those of natural daphnicyclidins E (**4**) and J (**1**), respectively. This result indicated that the absolute stereochemistry of C-2, C-6, and C-18 in daphnicyclidin J (**1**) was the same as that of daphnicyclidin D (**3**).[8]

Plausible Biogenesis of Daphnicyclidins J (1) and K (2). A plausible biogenetic pathway for daphnicyclidins J (**1**) and K (**2**) is proposed as shown in Scheme 2. Daphnicyclidins J (**1**) and K (**2**) as well as daphnicyclidins A−H reported more recently[8] might be derived from

(13) The Polonovski reaction has been well-studied under various conditions, and trifluoroacetic anhydride (TFAA) has been frequently used as an efficient reagent for obtaining the desired fragmentation.

yuzurimine-type alkaloids such as yuzurimine A[14] and macrodaphniphyllamine.[15] Daphnicyclidin J (**1**) might be generated through N-oxidation of daphnicyclidin D (**3**), while daphnicyclidin K (**2**) might be derived from an imine form (**4**) of daphnicyclidin D (**3**) through introduction of hydroxy groups to C-2 and C-4 followed by acyloin rearrangement (Scheme 2). This proposed biogenesis seems to be supported by a biomimetic reaction as shown in Scheme 1.[16]

Cytotoxicity. Daphnicyclidins J (**1**) and K (**2**) exhibited cytotoxicity against murine lymphoma L1210 cells (IC_{50}, 1.9, and 4.7 μg/mL, respectively) and human epidermoid carcinoma KB cells (IC_{50}, 2.5, and 6.5 μg/mL, respectively) in vitro.

Experimental Section

General Procedures. ^{1}H and ^{13}C NMR spectra were recorded on 600 and 500 MHz spectrometers equipped with an ×32 computer and an Eurotherm temperature control unit. 1D NMR spectra were measured at 300 K with 16K data points, which were multiplied by a Gaussian filter and zero filled to 32K data points before Fourier transformation. 2D NMR spectra were measured at 300 K and NOESY and HOHAHA spectra in the phase-sensitive mode were recorded using the TPPI method. HOHAHA spectra were recorded by spin-lock field preceded and followed by 2.5 ms trim pulses. NOESY spectra were measured with mixing times of 800 ms. Typically, 256 FIDs of 2K data points and 32 scans each were employed. Chemical shifts were observed using residual $CDCl_3$ (δ_H 7.26 and δ_C 77.03) or CD_3OD (δ_H 3.31 and δ_C 49.0) as internal standards. Standard pulse sequences were employed for 2D NMR experiments. HMBC spectra were recorded using a 50 ms delay time for long-range C−H coupling with *Z*-axis PFG. FABMS was measured by using glycerol as a matrix.

Material. The stems of *D. humile* (Daphniphyllaceae) were collected in Sapporo in 1998. The botanical identification was made by Mr. N. Yoshida, Graduate School of Pharmaceutical Sciences, Hokkaido University. Voucher specimens (no. 980801) have been deposited in the herbarium of Hokkaido University.

Isolation. The stems of *D. humile* (7.5 kg) were extracted, and a crude alkaloidal fraction (14.5 g) was prepared as described in the previous paper.[5,6] A part (7.0 g) of the fraction was subjected to an amino silica gel column chromatography (hexane/EtOAc, 9:1 → 1:1 and then $CHCl_3$/MeOH, 1:0 → 0:1), in which a fraction eluted with MeOH was purified by C_{18} HPLC (25% CH_3CN/0.1%TFA) and amino silica gel HPLC (15% CH_3CN) to afford daphnicyclidins J (**1**, 0.002%) and K (**2**, 0.002%) as colorless solids together with daphnicyclidins A−C, D (**3**), E (**4**), and F−H.

Daphnicyclidin J (1): colorless solid; $[\alpha]_D$ −15° (*c* 0.3, CH_3OH); IR (neat) ν_{max} 3370, 2950, 1690, 1660, 1610, 1200 cm^{-1}; UV (MeOH) λ_{max} 206 (ϵ 15 600), 245 (6100), 320 (6300), 330 nm (6200); ^{1}H and ^{13}C NMR data (Table 1); FABMS *m*/*z* 396 (M + H)$^+$; HRFABMS *m*/*z* 396.1797 (M + H; calcd for $C_{23}H_{26}NO_5$, 396.1811).

Daphnicyclidin K (2): colorless solid; $[\alpha]_D$ −246° (*c* 0.3, CH_3OH); IR (KBr) ν_{max} 3600, 2930, 1700, 1650, 1610, 1540, 1455 cm^{-1}; UV (MeOH) λ_{max} 245 (ϵ 9500), 320 nm (11 500); ^{1}H and ^{13}C NMR data (Table 2); FABMS *m*/*z* 414 (M + H)$^+$; HRFABMS *m*/*z* 414.1907 (M + H; calcd for $C_{23}H_{28}NO_6$, 414.1917).

Modified Polonovski Reaction. *m*-Chloroperbenzoic acid (6 mg, 0.035 mmol) in 0.1 mL of CH_2Cl_2 was added to a stirred solution of daphnicyclidin D (**3**, 10 mg, 0.026 mmol) in 0.1 mL of CH_2Cl_2 at 0 °C for 1 h. After the reaction mixture was concentrated, trifluoroacetic anhydride (10 μL, 0.072 mmol) was added to a stirred solution of the residue in dry CH_2Cl_2 (0.2 mL) under N_2 at −20 °C for 1 h. After the solvent was evaporated, the residue was subjected to C_{18} HPLC (25% CH_3CN/0.1% TFA) to afford two compounds (3.7 and 1.8 mg), whose spectral data and $[\alpha]_D$ values were identical with those of daphnicyclidins E (**4**) and J (**1**), respectively.

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Supporting Information Available: 1D and 2D NMR spectra for compounds **1** and **2**. This material is available free of charge via the Internet at http://pubs.acs.org.

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