Daphnezomines F and G: Novel Alkaloids with 1-Azabicyclo[5.2.2]undecane Moiety from *Daphniphyllum humile*

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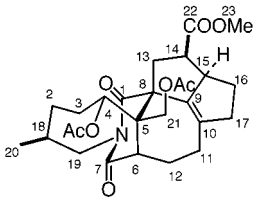
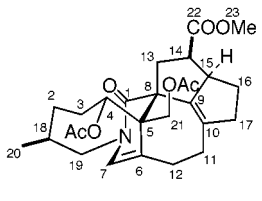
Daphniphyllum alkaloids are a group of highly complex polycyclic alkaloids which have attracted great interest from a biogenetic point of view.[1,2] Heathcock and coworkers have demonstrated a one-pot synthesis of a dialdehyde to a pentacyclic unsaturated amine, which turned out to be an exceptionally efficient way to construct the pentacyclic nucleus of the *Daphniphyllum* alkaloids, based on the hypothesis of their biosynthesis.[3] Recently we have isolated daphnezomines A and B,[4] which are novel alkaloids with a unique aza-adamantane core, and daphnezomines C, D, and E,[5] with an *N*-oxide moiety, from the leaves or stems of *Daphniphyllum humile*, respectively. A further search for biogenetically interesting alkaloids from the same plant resulted in the isolation of daphnezomines F (**1**) and G (**2**). Two novel alkaloids obtained from the stems possessed the 1-azabicyclo[5.2.2]undecane ring system. In this paper we describe the isolation and structure elucidation of **1** and **2**.



1



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The stems of *D. humile* collected in Sapporo were extracted with MeOH, which was partitioned between EtOAc and 3% tartaric acid. Water-soluble materials, which were adjusted at pH 9 with sat. Na_2CO_3, were partitioned with $CHCl_3$. $CHCl_3$-soluble materials were subjected to a C_{18} column (CH_3CN/0.1% TFA, 1:4 → 1:1), in which a fraction eluted with CH_3CN/0.1% TFA (1:1) was purified by a silica gel column (Hex/EtOAc, 7:3) followed by C_{18} HPLC (75% CH_3CN) to afford daphnezomines F (**1**, 0.0002% yield) and G (**2**, 0.0001%) as colorless solids. In addition, a known alkaloid, yuzurimine (**3**, 0.01%) was isolated from the alkaloidal fraction previously obtained from the leaves of *D. humile*.[6]

Table 1. ^{1}H and ^{13}C NMR Data of Daphnezomine F (1) in $CDCl_3$ at 300 K

	δ_H	δ_C	HMBC (^{1}H)
1		173.75	19, 13b
2	1.12 (2H, m)	26.32	3a, 4, 19b, 20
3a	2.35 (1H, m)	30.16	4
3b	1.20 (1H, m)		
4	5.35 (1H, d, 6.4)	74.28	6, 21
5		53.86	6, 13b, 21
6	3.75 (1H, d, 6.4)	43.52	4, 11, 21
7		175.54	6, 12, 19
8		45.48	4, 6, 17, 21
9		140.74	11, 13b, 14, 17
10		136.08	11, 12, 16b, 17
11	2.08 (2H, m)	25.50	6
12a	2.06 (1H, m)	25.15	
12b	2.42 (1H, m)		
13a	2.97 (1H, dd, 9.3, 14.4)	37.16	
13b	2.82 (1H, dd, 2.6, 14.4)		
14	3.11 (1H, dt, 2.6, 9.5)	42.90	13b
15	3.39 (1H, m)	54.52	14, 16a, 17
16a	1.34 (1H, m)	26.91	17
16b	1.88 (1H, dt, 11.9, 7.1)		
17a	2.41 (1H, m)	43.06	16a
17b	2.56 (1H, m)		
18	2.04 (1H, m)	32.51	19, 20
19a	3.96 (1H, dd, 9.9, 13.1)	45.01	2, 20
19b	4.00 (1H, dd, 7.8, 13.1)		
20	0.93 (3H, d, 6.8)	20.92	19a
21	4.44 (2H, s)	67.28	4
22		174.82	13, 14, 23
23	3.66 (3H, s)	51.41	
24		170.45	21, 25
25	2.02 (3H, s)	21.11	
26		169.23	4, 27
27	2.04 (3H, s)	20.96	

Daphnezomine F (**1**) showed the pseudomolecular ion at *m*/*z* 502 $(M + H)^+$ in the FABMS and the molecular formula, $C_{27}H_{35}NO_8$, was established by HRFABMS [*m*/*z* 502.2450, $(M + H)^+$, Δ +0.9 mmu]. ^{1}H and ^{13}C NMR data are presented in Table 1. The ^{13}C NMR spectrum revealed a total of 27 carbon signals including nine quaternary carbons ($sp^2 \times 7$ and $sp^3 \times 2$), 5 sp^3 methines, 9 methylenes, and 4 methyls including one methoxycarbonyl and two acetoxy groups which also were indicated by IR absorption due to the ester carbonyl (1740 cm^{-1}). Since 6 out of 11 unsaturations were accounted for, **1** was inferred to possess five rings. The presence and connection of four partial structures **a** (C-13 to C-17), **b** (C-6, C-12, and C-11), **c** (C-21 and 21-OAc), and **d** (C-4, C-3, C-2, C-18, C-19, C-20, and 4-OAc) were demonstrated by

(1) For reviews of the *Daphniphyllum* alkaloids, see: (a) Yamamura, S.; Hirata, Y. In *The Alkaloids*; Manske, R. H. F., Ed., Academic Press: New York, 1975; Vol. 15, p 41. (b) Yamamura, S. In *The Alkaloids*; Brossi, A., Ed.; Academic Press: New York, 1986; Vol. 29, p 265.

(2) (a) Hao, X.; Zhou, J.; Node, M.; Fuji, K. *Yunnan Zhiwu Yanjiu* **1993**, *15*, 205−207. (b) Arbain, D.; Byrne, L. T.; Cannon, J. R.; Patrick, V. A.; White, A. H. *Aust. J. Chem.* **1990**, *43*, 185−190. (c) Yamamura, S.; Lamberton, J. A.; Niwa, M., Endo, K.; Hirata, Y. *Chem. Lett.* **1980**, 393−396. (d) Yamamura, S.; Toda, M.; Hirata, Y. *Bull. Chem. Soc. Jpn.* **1976**, *49*, 839. (e) Yamamura, S.; Lamberton, J. A.; Irikawa, H.; Okumura, Y.; Hirata, Y. *Chem. Lett.* **1975**, 923−926. (f) Yamamura, S.; Irikawa, H.; Okumura, Y.; Hirata, Y. *Bull. Chem. Soc. Jpn.* **1975**, *48*, 2120−2123. (g) Yamamura, S.; Hirata, Y. *Tetrahedron Lett.* **1974**, *42*, 3673−3676. (h) Yamamura, S.; Sasaki, K.; Toka, M.; Hirata, Y. *Tetrahedron Lett.* **1974**, 2023−2026, and references therein.

(3) (a) Heathcock, C. H. *Proc. Natl. Acad. Sci. U.S.A.* **1996**, *93*, 14323−14327. (b) Heathcock, C. H.; Joe, D. *J. Org. Chem.* **1995**, *60*, 1131−1142. (c) Heathcock, C. H.; Kath, J. C.; Ruggeri, R. B. *J. Org. Chem.* **1995**, *60*, 1120−1130. (d) Heathcock, C. H. *Angew. Chem.* **1992**, *104*, 675−691. (e) Heathcock, C. H. *Angew. Chem., Int. Ed. Engl.* **1992**, *31*, 665−681, and references therein.

(4) Morita, H.; Yoshida, N.; Kobayashi, J. *J. Org. Chem.* **1999**, *64*, 7208−7212.

(5) Morita, H.; Yoshida, N.; Kobayashi, J. *Tetrahedron* **1999**, *55*, 12549−12556.

(6) In the previous study, yuzurimine as a major alkaloid, and secodaphniphylline, daphniteijsmine, deoxyyuzurimine, and isodaphnilactone-B as minor ones have been isolated from *D. humile*: Yamamura, S.; Terada, Y. *Chem. Lett.* **1976**, 1381−1382.

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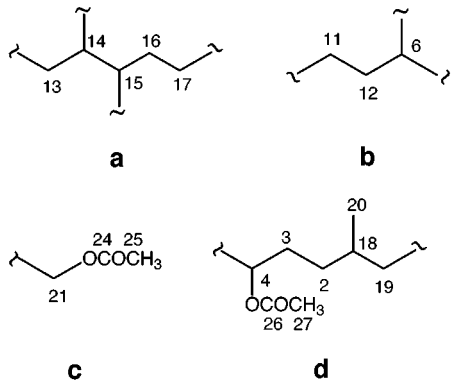
detailed analyses of 2D NMR data (^{1}H−^{1}H COSY, HOHAHA, HMQC, and HMBC) of **1** as follows.



For partial structure **a**, connectivities from C-13 to C-17 were clearly revealed by the COSY and HOHAHA spectra. The methoxycarbonyl group at C-14 was elucidated by HMBC correlations for H_2-13/C-22, H-14/C-22, and H_3-23/C-22. HMBC cross-peaks for H_2-13/C-8, H-13b/C-9, H-14/C-9, H_2-17/C-9, and H_2-17/C-10 indicated that partial structure **a** together with three quaternary carbons at δ_C 45.48 (C-8), 140.74 (C-9), and 136.08 (C-10) formed a bicyclo[3.3.0]octane ring system.

In partial structure **b** revealed by the COSY spectra, C-11 was connected to C-10 from HMBC correlations for H-11/C-10 and H-12/C-10. The connectivity from C-6 to C-8 through a quaternary carbon at C-5 was implied by long-rang correlations for H-6/C-5 and H-13b/C-5. The unit **c** consisting of an acetoxy methylene group was shown by HMBC cross-peaks for H_2-21/C-24 and H_3-25/C-24.

Partial structure **d** was revealed by the COSY, HOHAHA, and HMBC correlations as follows. The acetoxy group at C-4 was inferred by HMBC correlations for H-4/C-26 and H_3-27/C-26. The connections between C-4 and C-5 and between C-5 and C-21 were deduced from HMBC correlations of H-6/C-4, H_2-21/C-4, H-4/C-21, and H-4/C-8. On the other hand, the C-19 methylene (δ_C 45.01; δ_H 3.96 and 4.00) was attached to a nitrogen atom (1-N) to form the 1-azabicyclo[5.2.2]undecane ring system, since HMBC correlations of H_2-19 to two imide carbonyl carbons at δ_C 173.75 (C-1) and 175.54 (C-7) were observed. The position of the imide carbonyl groups at C-1 and C-7[7] was revealed by HMBC correlations for H-13b/C-1, H-6/C-7, and H_2-12/C-7. This glutarimide functionality[7] was also supported by the IR (1670 cm^{-1}) and UV (260 nm) spectral data.[8] Thus, the gross structure of daphnezomine F was assigned as **1**.

The relative stereostructure of **1** was elucidated by NOESY cross-peaks as depicted in the computer-generated 3D drawing as shown in Figure 1.[9] NOESY correlations of H-14/H-15, H_a-13/H-14, H-15/H_a-16, and H-15/H_a-17 indicated that both H-14 and H-15 were α-oriented. The stereochemistry of C-4 was deduced from NOESY correlations of H-4/H_b-13 and H-4/H-21. The NOEs of H_b-3/H_a-13, H_b-3/H-18, and H_a-2/H_a-19 argued well for the β-orientation of H-18 together with a stable conformation of the 1-azabicyclo[5.2.2]undecane ring, which was consistent with the calculated lowest energy conformation as shown in Figure 1.[9] The relative configuration at C-4, the ring junction at C-5 and C-6, and that at C-5 and C-8 were based on NOESY correlations of H_3-27/H-6, H-4/H_2-21, H_a-2/H-6, and H_2-21/H_b-11. Thus, the relative stereostructure of daphnezomine F (**1**) was assigned as shown in Figure 1.

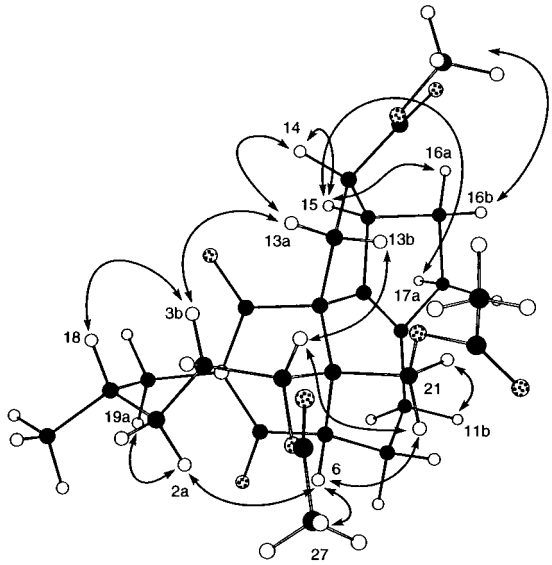


Figure 1. NOESY correlations (arrows) for daphnezomine F (**1**) and relative configurations.

HRFABMS data [*m*/*z* 486.2477, (M + H)$^+$, Δ −1.5 mmu] of daphnezomine G (**2**) established the molecular formula, $C_{27}H_{35}NO_7$, which was smaller than that of **1** by one oxygen. The UV absorption at 255 nm was similar to that of **1** with glutarimide functionality. The ^{1}H and ^{13}C NMR spectra of **2** at 300 K and even at 330 K in $CDCl_3$ or benzene-d_6 gave broad signals for a part of the molecule, which might be due to conformational exchange. The broadening observed for the ^{1}H NMR spectrum of **2** was overcome by measuring the NMR spectra at low temperature (Figure 2).[10] The low-temperature ^{1}H and ^{13}C NMR data are shown in Table 2.[11] The ^{13}C NMR spectrum at 250 K gave sharp signals including 9 quaternary carbons ($sp^2 \times 7$ and $sp^3 \times 2$), 5 methines ($sp^3 \times 4$ and $sp^2 \times 1$), 9 methylenes, and 4 methyls, suggesting that **2** had the same fused cyclic backbone skeleton as that of **1**. ^{1}H and ^{13}C NMR data of **2** at low temperature were analogous to those of **1** at 300 K except for the 1-azabicyclo[5.2.2]undecane moiety. In

(7) (a) Xiao, P.; Kubo, H.; Komiya, H.; Higashiyama, K.; Yan, Y.; Li, J.-S.; Ohmiya, S. *Chem. Pharm. Bull.* **1999**, *47*, 448−450. (b) Rudi, A.; Kashman, Y., *J. Org. Chem.* **1989**, *54*, 5331−5337. (c) Tempesta, M. S.; Corley, D. G.; Beutler, J. A.; Metral, C. J.; Yunes, R. A.; Giacomozzi, C. A.; Calixto, J. B. *J. Nat. Prod.* **1988**, *51*, 617−618. (d) Murakoshi, I.; Kidoguchi, E.; Nakamura, M.; Haginiwa, J.; Ohmiya, S.; Higashiyama, K.; Otomasu, H. *Phytochemistry* **1981**, *20*, 1725−1730. (e) Hart, N. K.; Johns, S. R.; Lamberton, J. A. *Aust. J. Chem.* **1968**, *21*, 1619−1624.

(8) The IR absorption for glutarimide carbonyl functionality was observed at 1679 cm^{-1}: Hall, H. K.; Zbinden, R. *J. Am. Chem. Soc.* **1958**, *80*, 6428−6432.

(9) Monte Carlo simulation and molecular mechanics calculations were conducted by Macromodel program: Mohamadi, F.; Richards, N. G. J.; Guida, W. C.; Liskamp, R.; Lipton, M.; Caufield, C.; Chang, G.; Hendrickson, T.; Still, W. C. *J. Comput. Chem.* **1990**, *11*, 440−467.

(10) Broad signals of H-2b, H-3a, H-4, H-19, and H-21 located at or near the 1-azabicyclo[5.2.2]undecane ring at 300 K were changed to fairly sharp ones at 250 K.

(11) The methylene signals of C-19 in **1** resonated at δ_H 3.96 and 4.00, whereas H_2-19 in **2** resonated at δ_H 2.34 and 4.26; this difference may be due to the presence of the carbonyl group at C-7.

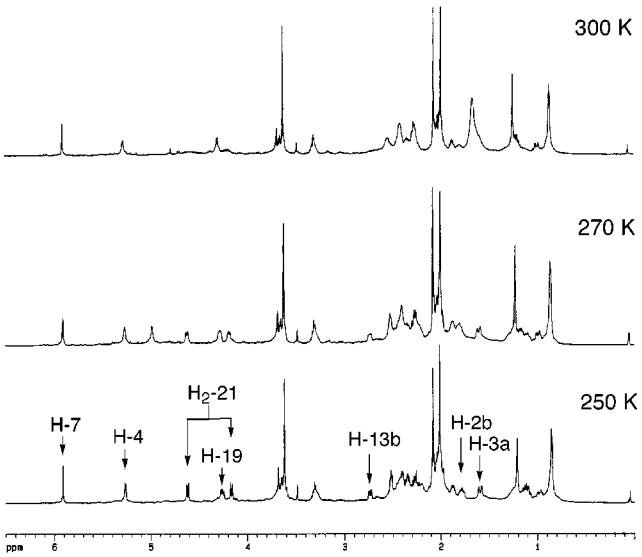


Figure 2. ^{1}H NMR spectra of daphnezomine G (**2**) at different low temperatures.

Table 2. ^{1}H and ^{13}C NMR Data of Daphnezomine G (2) in $CDCl_3$ at 250 K

	δ_H	δ_C	HMBC (^{1}H)
1		172.81	7, 13, 19a
2a	1.09 (1H, m)	24.56	4, 19b, 20
2b	1.78 (1H, m)		
3a	1.59 (1H, d, 17.2)	29.76	4
3b	2.45 (1H, m)		
4	5.26 (1H, d, 6.5)	70.21	21a
5		57.85	21b
6		125.05	4, 7, 12, 21b
7	5.91 (1H, s)	129.93	12
8		46.27	4, 7
9		141.36	
10		134.39	12
11	2.41 (2H, m)	32.28	17a
12	2.52 (2H, m)	26.47	7
13a	2.40 (1H, m)	33.25	
13b	2.74 (1H, dd, 6.6, 13.3)		
14	3.32 (1H, m)	43.51	13b
15	3.28 (1H, m)	50.25	14, 17
16a	1.13 (1H, m)	28.10	
16b	1.87 (1H, m)		
17a	2.26 (1H, m)	41.31	
17b	2.42 (1H, m)		
18	2.20 (1H, m)	31.68	
19a	2.34 (1H, m)	51.45	
19b	4.26 (1H, dd, 7.1, 12.9)		
20	0.85 (3H, d, 6.3)	20.80	
21a	4.16 (1H, d, 11.4)	62.73	
21b	4.62 (1H, d, 11.4)		
22		175.49	13b, 14, 23
23	3.62 (3H, s)	51.61	
24		171.28	21, 25
25	2.08 (3H, s)	21.30	
26		170.41	4, 27
27	2.01 (3H, s)	21.22	

the ^{13}C NMR spectrum of **2** signals due to the 3-substituted olefin at δ_C 125.05 (s) and 129.93 (d) appeared instead of those due to one (δ 175.54) of the imide carbonyl carbons and one sp^3 methine (δ 43.52) in **1**. The structure of **2** was elucidated by 2D NMR (^{1}H−^{1}H COSY, HOHAHA, HMQC, and HMBC) data at 250 K. HMBC correlations for H-4/C-6, H-7/C-6, H-12/C-6, H-21b/C-6, and H-12/C-7 indicated the position of the olefin at C-6. The presence of the 1-azabicyclo[5.2.2]undecane ring encompassing a carbonyl at C-1, an acetoxy at C-4, and a methyl at C-18 was revealed by HMBC correlations for

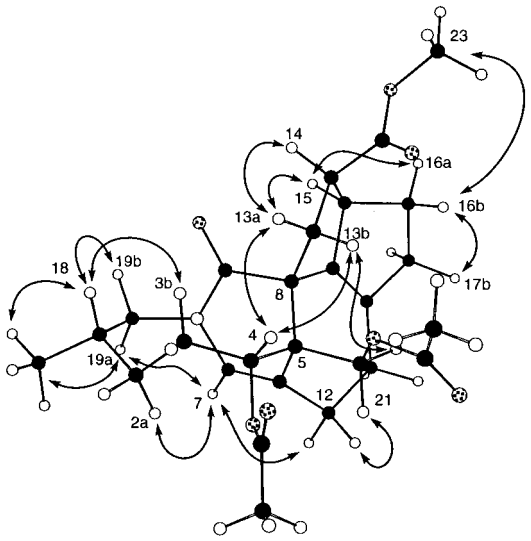


Figure 3. NOESY correlations (arrows) for daphnezomine G (**2**) at 250 K and relative configurations.

H-7/C-1, H-13/C-1, H-19a/C-1, H-27/C-26, and H-20/C-2. Thus the gross structure of daphnezomine G was assigned as **2**.

The relative stereochemistry of **2** was elucidated from NOESY correlations at 250 K (Figure 3). NOESY cross-peaks due to H-13a/H-14, H-13a/H-15, and H-15/H-16a suggested that these hydrogens were oriented to the same α face of the molecule.[12] The relative configuration at C-14 was verified by the NOESY correlation of H_3-23/H_b-16. The relative configurations at C-4, C-5, and C-8 were revealed by NOESY correlations of H-4/H-13a, H-4/H-13b, and H-21/H-13b. NOESY correlations of H-3b/H-18, H-2a/H-7, H-7/H-19a, and H-7/H-12a, implied the relative configurations at C-4 and C-18 together with the conformation of the 1-azabicyclo[5.2.2]undecane ring.

The conformational space for **2** was searched using MMFF force field[13] implemented in the Macromodel program,[9] and the results of the low-temperature NMR study described above were considered in terms of these calculations. Each of the lowest energy conformers belonging to four separate clusters are represented as **2a** (436.1 kJ/mol), **2b** (450.4 kJ/mol), **2c** (455.3 kJ/mol), and **2d** (476.3 kJ/mol). Conformers **2a** and **2b** possessed a twist chair conformation in the 1-azabicyclo[5.2.2]undecane part, while conformers **2c** and **2d** adopted a twist boat conformation (Figure 4). The populations calculated for these four clusters were 99.7, 0.2, 0.02, and 0.000006%, implying that **2a** was abundant. This result was consistent with the NOESY data and proton vicinal coupling constants obtained.[14] Furthermore, the conformational change among these conformers was simulated by molecular dynamics calculation.[16] The results of these

(12) The NOESY correlation of H-14/H-15 was not detected, since the chemical shifts (δ_H 3.32 and 3.28, respectively) were very close to each other.

(13) Halgren, T. *J. Am. Chem. Soc.* **1990**, *112*, 4710−4723.

(14) The calculated distances of H-18/H-3b (2.297 Å) and H-3b/H-13a (2.751 Å), and the coupling constant of H-4/H-3a (6.2 Hz)[15] for **2a** belonging to the major cluster, were consistent with the NOESY data and the proton coupling (6.4 Hz) observed.

(15) The *J*-values were calculated according to the equation for H−C(sp^3)−C(sp^3)−H system in the Macromodel program: Haasnoot, C. A. G.; de Leeuw, F. A. A. M.; Altona, C. *Tetrahedron* **1980**, *36*, 2783−2792.

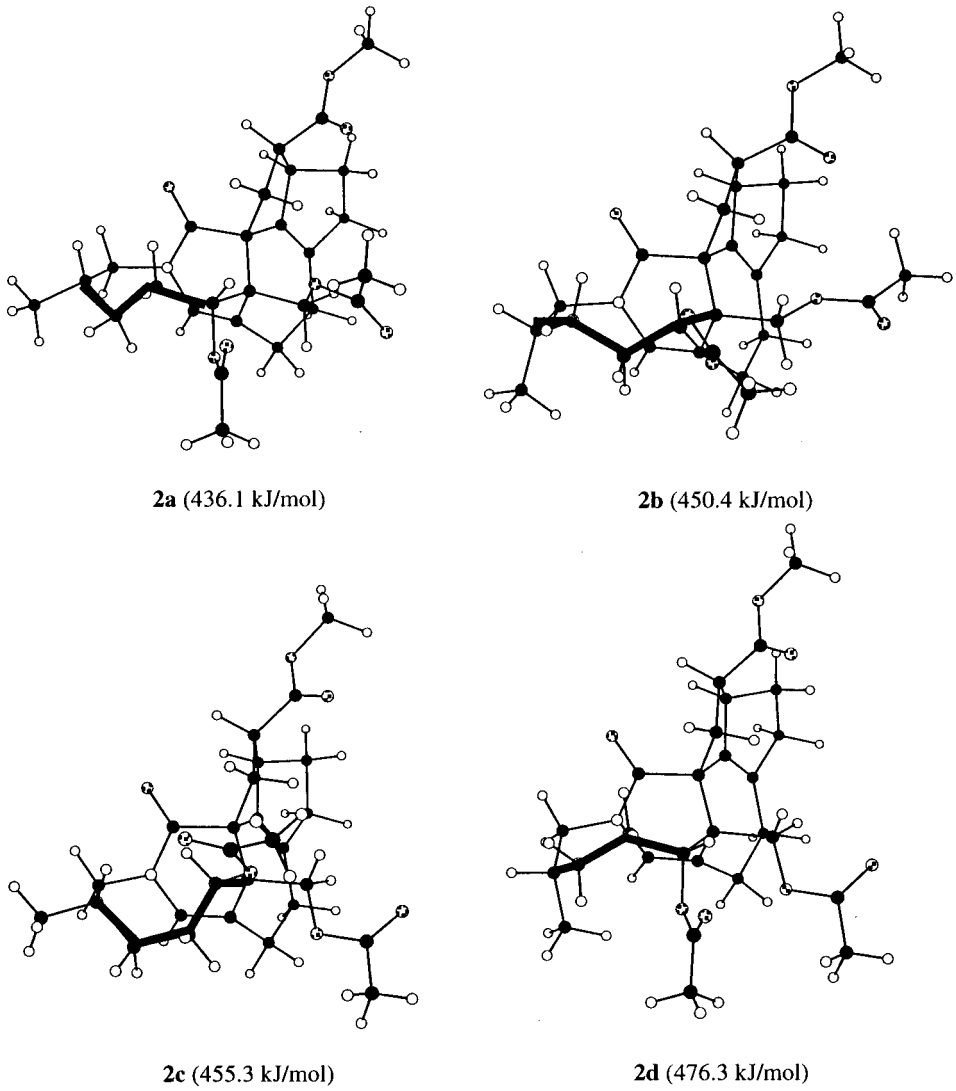


Figure 4. Four representative stable conformers (**2a**−**d**) of daphnezomine G (**2**) analyzed by Monte Carlo simulation followed by minimization and clustering analysis.

simulations are consistent with the relative stereochemistry of **2** and the shift of the equilibrium to the more stable conformer **2a** in $CDCl_3$ at 250 K inferred on the basis of the NMR data.

Daphnezomines F (**1**) and G (**2**) are novel alkaloids containing the 1-azabicyclo[5.2.2]undecane ring system. The structures of **1** and **2** are similar to that of yuzurimine (**3**) but they lack the C-1−C-2 bond. A biogenetic pathway for daphnezomines F (**1**) and G (**2**) is proposed as shown in Scheme 1. Daphnezomine G (**2**) might be generated through oxidation of a common imine intermediate **A** (proposed as a precursor of the secodaphniphylline-type skeleton by Heathcock et al.),[3] and subsequent cleavage of the C-7−C-10 bond followed by formation of the C-19−N-1 and C-14−C-15 bonds to give daphnezomine G (**2**). Daphnezomine F (**1**) may be derived from daphnezomine G (**2**) through oxidation of the C-7−C-6 bond. On the other hand, yuzurimine (**3**) might be generated from the intermediate **A** through the secodaphniphylline-type skeleton, although an alternative path through **2** is also possible.

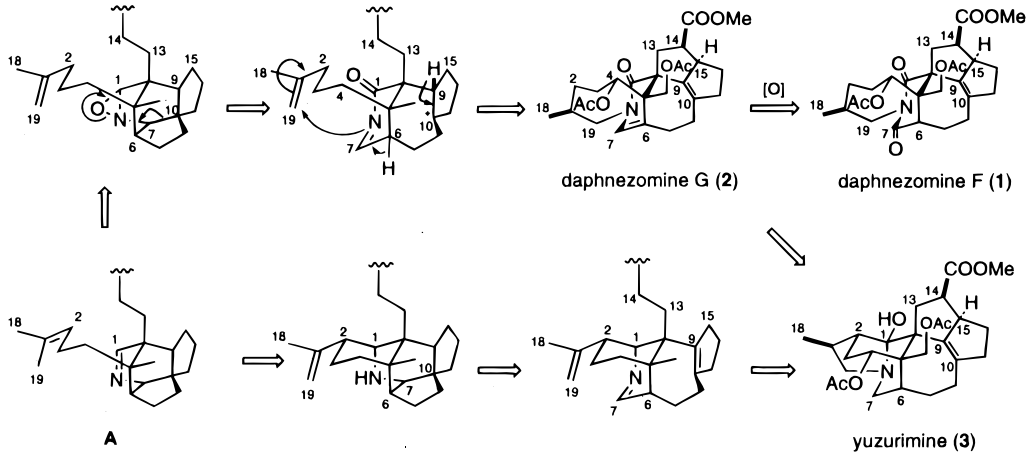
Daphnezomines F (**1**) and G (**2**) exhibited cytotoxicity against murine lymphoma L1210 cells (IC_{50}, 8.4 and 5.3 μg/mL, respectively) and human epidermoid carcinoma KB cells (IC_{50}, >10 and 7.3 μg/mL, respectively) in vitro.

(16) During 100 ps, starting conformer **2a** was converted into **2b** and then **2a** again by way of twist boat conformers such as **2c** and **2d**. On the other hand, the stable conformer of **1** obtained by essentially the same procedure, which corresponds to the conformer **2a**, was not converted into the other conformers during 100 ps simulation at 800 K.

Experimental Section

General Procedures. ^1H and ^{13}C NMR spectra were recorded at 330 K to 250 K on 600 and 500 MHz spectrometers equipped with an ×32 computer and an Eurotherm temperature control unit. 1D NMR spectra were measured at different temperatures between 330 K to 250 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 300K and 250K. 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 400, 600, and 800 ms. Since NOESY spectra gave no indications of spin diffusion at 600 ms, NOE intensities at this mixing time were used in the calculations. Typically 256 FIDs of 2K data points, and 32 scans each, were employed. Chemical shifts were measured using residual $CDCl_3$ (δ_H 7.26 and δ_C 77.03) as internal standards. Standard pulse sequences were employed for 2D NMR experiments. HMBC spectra were

Scheme 1



recorded using a 50 ms delay time for long-range C−H coupling with *Z*-axis PFG. FABMS was measured by using glycerol as matrix.

Material. The stems and leaves of *Daphniphyllum humile* were collected in Sapporo in 1998. The botanical identification was made by Mr. N. Yoshida, Faculty of Pharmaceutical Sciences, Hokkaido University. A voucher specimen has been deposited in the herbarium of Hokkaido University.

Isolation. The stems of *Daphniphyllum humile* (7.5 kg) were crushed and extracted with MeOH (10 L) three times. The MeOH extract (477 g) was treated with 3% tartaric acid (pH 2) and then partitioned with EtOAc. The aqueous layer was treated with sat. aq Na_2CO_3 to pH 9 and extracted with $CHCl_3$ to give a crude alkaloidal fraction (14.5 g). A portion (2 g) was subjected to C_{18} column chromatography (CH_3CN/0.1% TFA, 1:4 → 1:1), in which a fraction eluted with CH_3CN/0.1% TFA (1:1) was purified by a silica gel column (Hex/EtOAc 7:3) followed by C_{18} HPLC (75% CH_3CN) to afford daphnezomines F (**1**, 0.0002% yield) and G (**2**, 0.0001% yield) as colorless solids. The $CHCl_3$ extract (7.6 g) from the leaves of *D. humile* (4.0 kg) was subjected to C_{18} column chromatography (CH_3CN/0.1% TFA, 3:7) to give yuzurimine (**3**, 400 mg, 0.01% yield) as a colorless solid.

Daphnezomine F (1): colorless solid; $[\alpha]_D$ −29° (*c* 0.5, $CHCl_3$); IR (neat) ν_{max} 2960, 1740, 1670, and 1240 cm^{-1}; UV (MeOH) λ_{max} 215 (ϵ 3700), 260 nm (700); ^1H and ^{13}C NMR data (Table 1); FABMS *m*/*z* 502 $(M + H)^+$; HRFABMS *m*/*z* 502.2450 (M + H; calcd for $C_{27}H_{36}NO_8$, 502.2441).

Daphnezomine G (2): colorless solid; $[\alpha]_D$ −93° (*c* 0.4, $CHCl_3$); IR (neat) ν_{max} 2950, 1735, and 1245 cm^{-1}; UV (MeOH) λ_{max} 215 (ϵ 5600), 255 (2000); ^1H and ^{13}C NMR data (Table 2); FABMS *m*/*z* 486 $(M + H)^+$; HRFABMS *m*/*z* 486.2477 (M + H; calcd for $C_{27}H_{36}NO_7$, 486.2492).

Computational Methods. Conformational searching was carried out using Pseudo Monte Carlo simulation in Macromodel program for **2**. The closure bonds for the 1-azabicyclo[5.2.2]-undecane moiety were chosen at C-2−C-3 and C-1−N with the closure limit from 1 to 4 Å, while the other closure bond was chosen at C-11−C-12. Five thousand Monte Carlo steps were performed, yielding 71 unique conformations in the energy region of 0−10 kcal/mol, which could be classified into four clusters. Each conformer was finally minimized by molecular mechanics calculation of MMFF force field.[13] Conformers belonging to the different cluster possessed approximately identical conformations to each other as to 1-azabicyclo[5.2.2]undecane part. Conformational searching for **1** was performed by the same procedure as **2**, and the lowest energy conformation was depicted in Figure 1.

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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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