Pergamon

Tetrahedron 55 (1999) 12549–12556

TETRAHEDRON

Daphnezomines C, D, and E, New Alkaloids with an N-Oxide Moiety from *Daphniphyllum humile*

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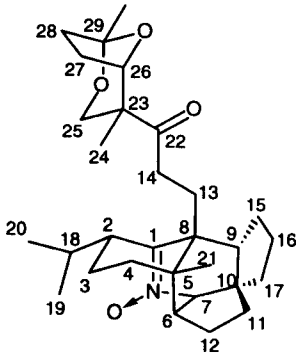
Received 6 August 1999; accepted 30 August 1999

Abstract: Three new alkaloids containing an N-oxide moiety, daphnezomines C (**1**), D (**2**), and E (**3**), have been isolated from the stems of *Daphniphyllum humile*, and the structures including relative stereochemistry were elucidated on the basis of spectroscopic data.

Daphniphyllum alkaloids with unique polycyclic nitrogen-containing ring systems have attracted great interests from a biogenetic point of view.[1] Recently two novel alkaloids with a unique aza-adamantane core, daphnezomines A and B, have been isolated from the leaves of *D. humile*.[2] Our continuing search for biogenetic intermediates of *Daphniphyllum* alkaloids resulted in the isolation of three new alkaloids with an N-oxide moiety, daphnezomines C (**1**), D (**2**), and E (**3**) among which the structures of **1** and **2** were close to a nitrone intermediate synthesized by Heathcock *et al.*,[3] as one of biomimetic transformation from secodaphniphylline-type to daphniphylline-type skeletons. In this paper we describe the isolation and structure elucidation of **1** - **3**.

The stems of *D. humile* collected in Sapporo were extracted with MeOH, and the MeOH extract was partitioned between EtOAc and 3% tartaric acid. Water-soluble materials were adjusted at pH 9 with sat. Na_2CO_3 and partitioned with $CHCl_3$. $CHCl_3$-soluble materials were subjected to a C_{18} column (CH_3CN/0.1%TFA, 3:7→7:3) followed by gel filtration on Sephadex LH-20 (MeOH/$CHCl_3$, 1:1) to afford



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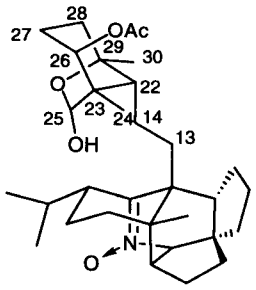

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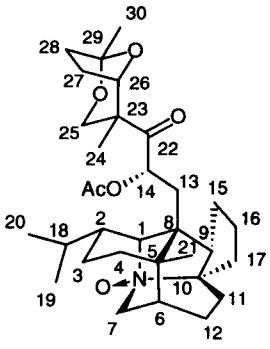

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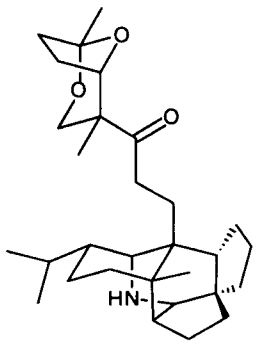

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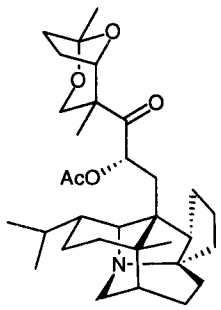

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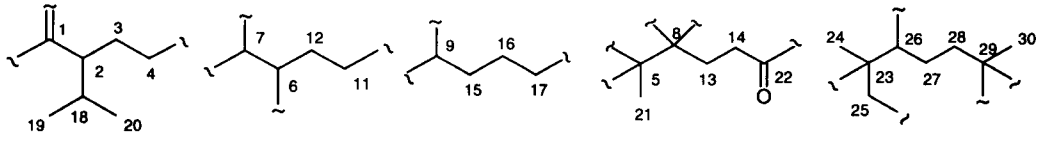
daphnezomines C (**1**, 0.0001%), D (**2**, 0.00007%), and E (**3**, 0.001%) as colorless solid together with known related alkaloids, secodaphniphylline (**4**, 0.0005%) and daphniphylline (**5**, 0.01%).

FABMS data of daphnezomine C {**1**, $[\alpha]_D^{24}$ -94° (*c* 0.3, $CHCl_3$)} showed the pseudomolecular ion at *m/z* 484 $(M+H)^+$, and the molecular formula, $C_{30}H_{45}NO_4$, was established by HRFABMS [*m/z* 484.3421, $(M+H)^+$, Δ -0.6 mmu]. In the ^{13}C NMR spectrum, totally 30 carbon signals including 7 quaternary carbons ($sp^2 \times 2$ and $sp^3 \times 5$), 6 methines (sp^3), 12 methylenes, and 5 methyls were observed. IR absorptions implied the presence of ketone carbonyl (1705 cm^{-1}) and imine (1650 cm^{-1}) groups. Since 2 out of 9 elements of unsaturation implied by the molecular formula were accounted for, **1** was inferred to possess 7 rings. Five partial structures **a** (C-1 ~ C-4 and C-18 ~ C-20), **b** (C-7, C-6, C-12, and C-11), **c** (C-9 and C-15 ~ C-17), **d** (C-21, C-5, C-8, C-13, C-14, and C-22), and **e** (C-23 ~ C-30) were assigned by detailed analyses of 2D NMR data (^1H-^1H COSY, HOHAHA, and HMQC) of **1**.

The C-7 (δ 84.19) suggested that this carbon was adjacent to a nitrogen atom, while those of C-25 (δ 65.35), C-26 (δ 80.96), and C-29 (δ 105.41) indicated that these carbons were attached to an oxygen atom. Connections among C-1, C-9, and C-13 via C-8, and among C-4, C-6, and C-21 via C-5 were implied by HMBC cross-peaks for H-9/C-8, H-9/C-1, H-13/C-8, H-21/C-4, H-21/C-5, H-21/C-6, and H-7/C-5. Long-range C-H couplings for H-7/C-10, H-9/C-10, H-9/C-11, H-16/C-11 revealed the connection between units **b** and **c** via C-10. The HMBC correlations (Table 1) provided the connectivity among four units **a**, **b**, **c**, and **d**, showing the presence of nitrogen-containing pentacyclic skeleton consisting of three 6-membered and two 5-membered rings with an isopropyl at C-2 and a methyl group at C-5, like secodaphniphylline-type skeleton. The presence of an imino group at C-1 was verified by the IR absorption (1650 cm^{-1}) and a quaternary carbon resonance (δ 157.72, C-1). The UV absorption (λ_{max} 260 nm) corroborated the presence of a nitrone group.[3,5] The position of the nitrone (C-1 ~ N) was further confirmed by HMBC correlations of H-2/C-1 and H-9/C-1.



a **b** **c** **d** **e**

The presence of a 2,8-dioxabicyclo[3.2.1]octane unit (**e**) was supported by HMBC correlations of H-25/C-23, H-25/C-26, H-25/C-29, H-26/C-27, H-26/C-29, and H-30/C-28, whose ^{1}H chemical shifts [δ_H 3.55 (H-25a), 4.29 (H-25b), 4.69 (H-26), 0.82 (H-24), and 1.43 (H-30)] were similar to those of secodaphniphylline (**4**).[1,4] The connection between units **d** and **e** via C-22 was confirmed by HMBC correlations of H-24/C-22 and H-25/C-22. Thus the gross structure of daphnezomine C was elucidated to be **1**.

The relative stereochemistry of **1** was deduced from NOESY correlations as shown in computer-generated 3D drawing (Fig. 1). NOESY correlations of H_b-4/H-2 and H-2/H_b-14 suggested that H-2, H_b-4 and the side chain at C-8 were β-oriented and the cyclohexane ring in unit **a** took a chair form. The relative configurations at C-5, C-6, C-7, C-9, and C-10 including the cis-ring junction at C-9 and C-10 were elucidated by NOESY correlations of H-6/H-7, H_a-4/H-6, H-7/H_a-12, H-7/H_a-11, H-9/H-21, and H-9/H_b-11. A chair form of the 6-membered ring in the 2,8-dioxabicyclo[3.2.1]octane unit was verified by NOESY correlations of H_b-25/H_a-27 and H_b-25/H_a-28. Thus, the relative stereostructure of daphnezomine C (**1**) was concluded as shown in Fig. 1.

The molecular formula of daphnezomine D (**2**) was determined as $C_{32}H_{49}NO_5$ by HRFABMS [*m/z* 528.3677, $(M+H)^+$, Δ -1.2 mmu]. The IR spectrum suggested the presence of hydroxyl (3390 cm^{-1}), ester (1740 cm^{-1}), and imine (1670 cm^{-1}) groups, and its UV spectrum showed an absorption (260 nm) characteristic of nitrone like that of **1**. ^{1}H and ^{13}C NMR data suggested that **2** had the same fused-pentacyclic backbone skeleton as that of **1** (N, C-1 ~ C-21), while the other resonances due to one ester carbonyl (δ 170.01), one sp^3 methine (δ 51.60), two quaternary carbons (δ 51.11 and 84.48), two oxymethines (δ 73.56 and 99.28), two sp^3 methylenes (δ 27.86 and 32.69), and three methyl groups (δ 16.93, 21.23, and 26.68), corresponded to those of the side chain (C-13, C-14, and C-22 ~ C-32), differing from that of **1**. Interpreting the COSY and HMBC spectra revealed a cyclohexane ring with an acetoxy group at C-26 and two methyl groups at C-23 and C-29, and a hemiacetal ring (C-22, C-23, C-25, and C-29), as shown in Fig. 2. Thus the structure of daphnezomine D was elucidated to be **2**. The relative stereostructure of this side chain was elucidated by NOESY correlations of H-25/H-27a, H-25/H-26, and H-22/H-28b.[6]

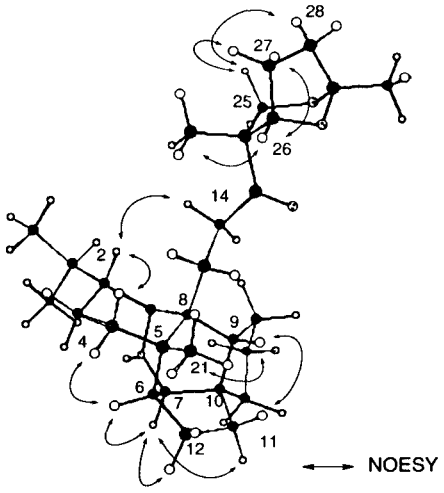


Fig. 1. Relative Stereochemistry of Daphnezomine C (**1**)

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

assignment	δH	δC	HMBC (^{1}H)
1		157.72	2, 9
2	2.26 (1H, dt, 3.4, 11.5)	53.03	
3a	1.65 (1H, m)	27.21	
3b	2.01 (1H, m)		
4a	1.09 (1H, dd, 4.7, 14.9)	38.90	21
4b	1.87 (1H, m)		
5		51.56	7, 21
6	2.19 (1H, brq, 3.0)	48.85	21
7	4.02 (1H, d, 4.8)	84.19	
8		52.73	9, 13
9	1.75 (1H, t, 8.0)	53.13	
10		50.91	7, 9
11a	1.60 (1H, m)	39.05	9, 16
11b	1.85 (1H, m)		
12	1.67 (2H, m)	22.76	
13a	1.88 (1H, m)	24.34	
13b	2.34 (1H, ddd, 4.1, 11.4, 15.1)		
14a	2.86 (1H, m)	35.82	
14b	3.14 (1H, ddd, 5.1, 11.2, 18.5)		
15a	1.33 (1H, m)	33.83	
15b	1.91 (1H, m)		
16a	1.38 (1H, m)	25.78	
16b	1.64 (1H, m)		
17	1.78 (1H, m)	36.92	
	1.83 (1H, m)		
18	2.84 (1H, m)	31.69	2
19	0.83 (3H, d, 6.8)	21.02	
20	1.05 (3H, d, 6.6)	23.24	
21	0.95 (3H, s)	20.40	
22		212.18	14, 24, 25
23		49.89	25
24	0.82 (3H, s)	17.68	
25a	3.55 (1H, d, 12.2)	65.35	
25b	4.29 (1H, dd, 1.7, 12.2)		
26	4.69 (1H, d, 6.1)	80.96	25
27a	1.95 (1H, m)	24.66	26
27b	2.10 (1H, m)		
28a	1.93 (1H, m)	33.83	30
28b	2.08 (1H, m)		
29		105.41	25, 26
30	1.43 (3H, s)	23.65	

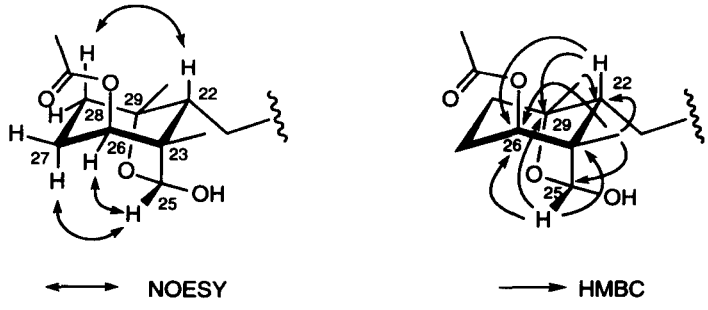
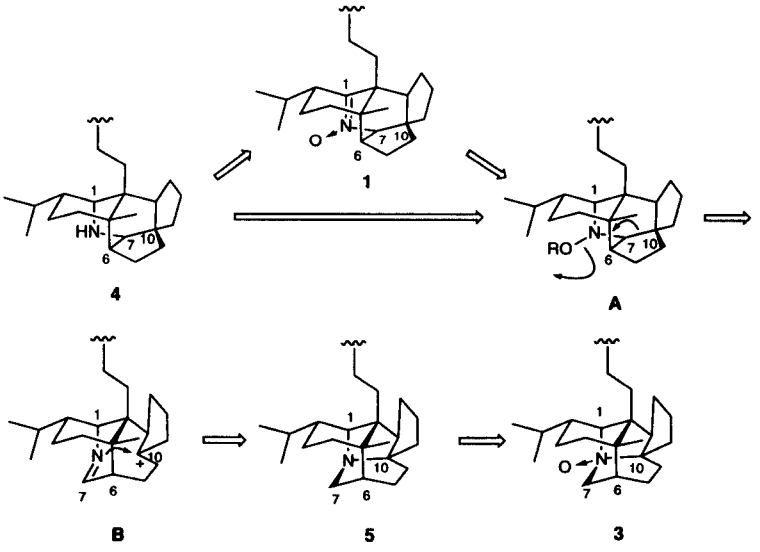


Fig. 2. NOESY and HMBC Correlations of the Side Chain of Daphnezomine D (**2**)

Daphnezomine E {**3**, $[\alpha]_D^{24}$ +31° (*c* 1.4, $CHCl_3$)} showed the pseudomolecular ion at *m/z* 544 $(M+H)^+$ and the molecular formula, $C_{32}H_{49}NO_6$, was established by HRFABMS [*m/z* 544.3653, $(M+H)^+$, Δ +1.5 mmu]. IR absorptions implied the presence of ester (1740 cm^{-1}) and ketone (1690 cm^{-1}) carbonyl functionalities. ^1H NMR data (Table 2) indicated the presence of the same 2,8-dioxabicyclo[3.2.1]octane unit in the side chain, as that of **1**, except for an acetoxy group at C-14. The ^{13}C NMR spectrum containing 7 quaternary carbons (sp^2 × 2 and sp^3 × 5), 7 sp^3 methines, 12 methylenes, and 6 methyls implied that **3** was structurally related to daphniphylline (**5**).[8] In addition, the molecular formula was larger than that of daphniphylline (**5**) by one oxygen unit. Detailed analyses of the ^{13}C NMR data (Table 2) and the comparison of the ^{13}C chemical shifts (δ 72.75, 59.18, and 90.88, respectively) of C-1, C-7, and C-10 in **3** with those (δ 62.76, 45.66, and 77.47, respectively) of daphniphylline (**5**)[8] indicated the presence of an N-oxide functionality. Oxidation of daphniphylline (**5**) with *m*-chloroperoxybenzoic acid (*m*-CPBA) afforded the N-oxide derivative, whose spectral data and the $[\alpha]_D$ value were identical with those of natural daphnezomine E (**3**). Thus daphnezomine E (**3**) was concluded to be the N-oxide form of daphniphylline (**5**).

Daphnezomines C (**1**) and D (**2**) are the first alkaloids possessing secodaphniphylline-type skeleton with a nitrone functionality, while daphnezomine E (**3**) is the first N-oxide of daphniphylline-type alkaloid, although the N-oxides of yuzurimine-type alkaloids have been reported.[10] Heathcock and co-worker[3] have proposed a biogenesis of secodaphniphylline-type to daphniphylline-type skeleton, in which initial oxidation of secodaphniphylline-type skeleton occurs on a nitrogen, followed by chemical transformation into daphniphylline-type skeleton through a ring-opened intermediate like **B** (Scheme 1). The structures of daphnezomines C (**1**) and D (**2**) are very close to a nitrone intermediate synthesized by Heathcock *et al.* Biogenetically daphniphylline-type skeleton (*e.g.*, **5**) may be generated from secodaphniphylline-type skeleton (*e.g.*, **4**) through the N-oxidation to generate an intermediate (**A**) or a nitrone like **1** and then cleavage of the C-7 - C-10 bond, followed by generation of a ring-opened imine intermediate (**B**) and then formation of another C-N bond between N-1 and C-10, along with Heathcocks' proposal (Scheme 1).



Scheme 1

Table 2. ^1H and ^{13}C NMR Data of Daphnezomine E (3) in $CDCl_3$ at 300K

assignment	δ_H	δ_C	HMBC (^1H)
1	3.69 (1H, br s)	72.75	9, 13
2	1.76 (1H, m)	39.30	19, 20
3a	1.88 (1H, m)	21.20	
3b	2.02 (1H, m)		
4a	1.64 (1H, m)	35.86	21
4b	1.99 (1H, m)		
5		36.74	
6	1.92 (1H, m)	41.52	21
7	4.15 (2H, br m)	59.18	
8		46.84	13, 21
9	2.49 (1H,m)	52.03	13, 15
10		90.88	
11a	1.79 (1H, m)	25.75	
11b	1.96 (1H, m)		
12	1.61 (2H, m)	27.85	9, 17
13a	1.55 (1H, m)	30.39	14
13b	2.64 (1H, dd, 3.2, 15.7)		
14	5.61 (1H, dd, 3.2, 12.5)	72.80	13
15a	1.53 (1H, m)	31.91	17
15b	2.36 (1H, m)		
16a	1.38 (1H, m)	24.80	17
16b	1.89 (1H, m)		
17a	1.82 (1H, m)	35.40	
17b	2.48 (1H, m)		
18	2.27 (1H, m)	29.07	19, 20
19	0.90 (3H, d, 6.4)	21.31	20
20	1.09 (3H, d, 6.2)	22.06	19
21	1.04 (3H, s)	23.73	
22		212.58	
23		50.71	24, 25
24	0.89 (3H, s)	18.69	
25a	3.71 (1H, d, 13.3)	65.19	24, 26
25b	4.46 (1H, dd, 1.7, 13.3)		
26	4.53 (1H, d, 6.8)	82.51	24
27a	1.94 (1H, m)	24.52	
27b	2.02 (1H, m)		
28a	1.89 (1H, m)	33.69	26, 30
28b	2.08 (1H, m)		
29		105.45	
30	1.45 (3H, s)	24.05	
31	2.09 (3H, s)	20.83	
32		170.14	

Daphnezomines C (1), D (2), and E (3) exhibited cytotoxicity against murine lymphoma L1210 with IC_{50} values of 6.7, 9.7 and 8.3 μg/mL, respectively, and human epidermoid carcinoma KB cells with IC_{50} values of 5.8, >10, and >10 μg/mL, respectively, in vitro.

Experimental Section

General Methods. ^1H and 2D NMR spectra were recorded in $CDCl_3$ on a 600 MHz spectrometer at 300K, while ^{13}C NMR spectra were measured on a 125 MHz. Chemical shifts were reported using residual $CDCl_3$ (δ_H 7.26 and δ_C 77.03) as internal standards. Standard pulse sequences were employed for the 2D

NMR experiments. HMBC spectra were recorded using a 50 ms delay time for long-range C-H coupling with Z-axis PFG. NOESY spectra were measured with a mixing time of 800 ms. FABMS was measured by using glycerol matrix.

Material. The stems 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.

Extraction and Isolation. The stems of *Daphniphyllum humile* (7.5 kg) were crashed and extracted with MeOH (10 L) three times to give a MeOH extract (477 g), a part (200 g) of which was treated with 3% tartaric acid to adjust to pH 2 and then partitioned with EtOAc. The aqueous layer was treated with sat. Na_2CO_3 aq. to adjust to pH 9 and extracted with $CHCl_3$ to give a crude alkaloidal fraction (14.5 g), which was subjected to C_{18} column chromatography (CH_3CN/0.1%TFA, 3:7→7:3) followed by gel filtration on Sephadex LH-20 (MeOH/$CHCl_3$, 1:1) to afford daphnezomines C (**1**, 0.0001%), D (**2**, 0.00007%), and E (**3**, 0.001%) as colorless solid together with two known related alkaloids, secodaphniphylline (**4**, 0.0005%) and daphniphylline (**5**, 0.01%).

Daphnezomine C (1). colorless solid; $[\alpha]_D^{24}$ -94° (*c* 0.3, $CHCl_3$); ^1H and ^{13}C NMR data (Table 1); FABMS *m/z* 484 $(M+H)^+$; HRFABMS *m/z* 484.3421 (M+H; calcd for $C_{30}H_{46}NO_4$, 484.3427); IR (neat) ν_{max} 2960, 1705, and 1650 cm^{-1}; UV (MeOH) λ_{max} 260 nm (ε 4500).

Daphnezomine D (2). colorless solid; $[\alpha]_D^{24}$ -151° (*c* 0.4, $CHCl_3$); FABMS *m/z* 528 $(M+H)^+$; HRFABMS *m/z* 528.3677 (M+H; calcd for $C_{32}H_{50}NO_5$, 528.3689); IR (neat) ν_{max} 3390, 2960, 1740, and 1670 cm^{-1}; UV (MeOH) λ_{max} 260 nm (ε 7000). ^1H NMR ($CDCl_3$) δ 1.76 (m, H-2), 1.69 (m, H-3a), 2.05 (m, H-3b), 1.12 (dd, 4.4, 14.5, H-4a), 1.90 (m, H-4b), 2.19 (brs, H-6), 4.03 (d, 4.7, H-7), 2.26 (td, 11.7, 3.3, H-9), 1.59 (m, H-11a), 1.76 (m, H-11b), 1.68 (m, H-12a), 1.74 (m, H-12b), 1.39 (m, H-15a), 2.09 (m, H-15b), 1.85 and 1.90 (m, H-17), 2.87 (m, H-18), 0.86 (d, 6.6, H-19), 1.05 (d, 6.3, H-20), 0.94 (s, H-21), 1.73 (m, H-22), 1.06 (s, H-24), 4.88 (s, H-25), 4.80 (d, 5.1, H-26), 1.74 and 1.95 (m, H-27), 1.70 and 2.05 (m, H-28), 1.40 (s, H-30), 2.04 (s, H-32); ^{13}C NMR ($CDCl_3$) δ 157.78 (C-1), 53.11 (C-2), 27.28 (C-3), 39.09 (C-4), 52.23 (C-5), 48.70 (C-6), 84.23 (C-7), 52.62 (C-8), 53.20 (C-9), 50.41 (C-10), 39.09 (C-11), 22.80 (C-12), 22.93 (C-13), 25.74 (C-14), 34.23 (C-15), 25.74 (C-16), 37.03 (C-17), 31.78 (C-18), 21.17 (C-19), 23.28 (C-20), 20.65 (C-21), 51.60 (C-22), 51.11 (C-23), 16.93 (C-24), 99.28 (C-25), 73.56 (C-26), 32.69 (C-27), 27.86 (C-28), 84.48 (C-29), 26.68 (C-30), 170.01 (C-31), 21.23 (C-32).

Daphnezomine E (3). colorless solid; $[\alpha]_D^{24}$ +31° (*c* 1.4, $CHCl_3$); ^1H and ^{13}C NMR data (Table 1); FABMS *m/z* 544 $(M+H)^+$; HRFABMS *m/z* 544.3653 (M+H; calcd for $C_{32}H_{50}NO_6$, 544.3638); IR (neat) ν_{max} 2950, 1740, and 1690 cm^{-1}.

Secodaphniphylline (4). colorless solid; $[\alpha]_D^{24}$ -47° (*c* 0.8, $CHCl_3$); FABMS *m/z* 470 $(M+H)^+$; IR (neat) ν_{max} 1960, 1680, and 1615 cm^{-1}. ^{13}C NMR ($CDCl_3$) δ 50.59 (C-1), 41.06 (C-2), 19.64 (C-3), 37.37 (C-4), 35.75 (C-5), 44.23 (C-6), 57.44 (C-7), 36.73 (C-8), 52.86 (C-9), 48.71 (C-10), 39.73 (C-11), 22.84 (C-12), 24.69 (C-13), 33.79 (C-14), 29.40 (C-15), 26.01 (C-16), 34.87 (C-17), 28.30 (C-18), 20.28 (C-19), 20.45 (C-20), 20.70 (C-21), 212.04 (C-22), 50.00 (C-23), 23.58 (C-24), 65.36 (C-25), 80.88 (C-26), 25.25 (C-27), 33.17 (C-28), 105.50 (C-29), 17.57 (C-30).

Daphniphylline (5). colorless solid; $[\alpha]_D^{24}$ +30° (*c* 1.1, $CHCl_3$); FABMS *m/z* 528 $(M+H)^+$; IR (CCl_4) ν_{max} 2970, 1740, and 1670 cm^{-1}. ^{13}C NMR ($CDCl_3$) δ 62.76 (C-1), 37.64 (C-2), 21.16 (C-3), 39.33 (C-4), 37.25 (C-5), 39.29 (C-6), 45.66 (C-7), 47.39 (C-8), 52.48 (C-9), 77.47 (C-10), 25.65 (C-11), 27.89 (C-12), 29.99 (C-13), 72.93 (C-14), 31.23 (C-15), 25.23 (C-16), 35.64 (C-17), 29.62 (C-18), 20.79 (C-19), 21.66 (C-20), 23.96 (C-21), 212.52 (C-22), 50.68 (C-23), 18.70 (C-24), 65.21 (C-25), 82.47 (C-26), 24.58 (C-27), 33.72 (C-28), 105.44 (C-29), 24.52 (C-30), 20.79 (C-31), 170.15 (C-32).

Oxidation of Daphniphylline (5). *m*-Chloroperoxybenzoic acid (5 mg) was added to a stirred solution of daphniphylline (**5**, 10.0 mg) in CH_2Cl_2 (0.5 ml) at room temperature. The mixture was stirred at room temperature for 1 day, and washed with 20% Na_2SO_3 (10 mL) and H_2O (10 mL), and concentrated to give a pale yellow oil (12.5 mg). The residue was subjected to silica gel column chromatography ($CHCl_3$/MeOH, 15:1) to give the N-oxide derivative (5.4 mg), whose spectral data and $[\alpha]_D$ value were identical with those of **3**.

Acknowledgment. This work was partly supported by a Grant-in-Aid for Scientific Research from the Ministry of Education, Science, Sports and Culture of Japan.

References and Notes

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