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Daphtenidines A–D, new *Daphniphyllum* alkaloids from *Daphniphyllum teijsmannii*

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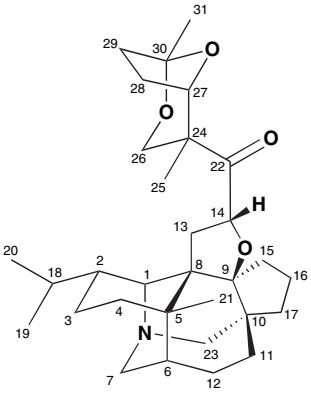
Abstract—Daphtenidines A–D (**1**–**4**), four new alkaloids were isolated from the leaves of *Daphniphyllum teijsmannii*, and the structures including relative stereochemistry were elucidated on the basis of spectroscopic data. Daphtenidines A (**1**) and B (**2**) were possessing daphnilactone A-type skeleton. This is the second isolation of daphnilactone A-type alkaloids from natural sources. Daphtenidine C (**3**) was 4-acetoxy form of daphmanidin A, while daphtenidine D (**4**) was 14-dehydro form of yuzurimine.

1. Introduction

Daphniphyllum alkaloids are a family of fused-heterocyclic natural products elaborated by trees of the genus *Daphniphyllum* (Daphniphyllaceae).[1,2] These ring systems have attracted great interest as challenging targets for total synthesis[3] as well as biosynthetic studies.[4] In our search for structurally unique and biogenetically interesting *Daphniphyllum* alkaloids,[5] four new *Daphniphyllum* alkaloids, daphtenidines A–D (**1**–**4**), were isolated from the leaves of *Daphniphyllum teijsmannii*. In this paper, we describe the isolation and structural elucidation of **1**–**4**.

2. Results and discussion

The leaves of *D. teijsmannii* were extracted with MeOH, and the MeOH extract was partitioned between EtOAc and 3% tartaric acid. Water-soluble materials, which were adjusted to pH 10 with saturated Na_2CO_3, were extracted with $CHCl_3$. $CHCl_3$-soluble materials were subjected to an LH-20 column (MeOH) followed by an amino silica gel column (hexane/EtOAc 1:0→0:1 and then $CHCl_3$/MeOH 1:0→0:1). The fractions eluted with hexane/EtOAc (4:1) were further purified by a silica gel column ($CHCl_3$/MeOH 1:0→0:1) to afford daphtenidines A (**1**, 0.00002% yield), B (**2**, 0.00002%), C (**3**, 0.0006%), and D (**4**, 0.0006%).



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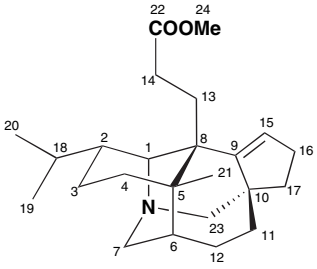

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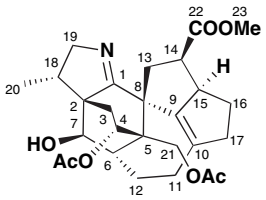

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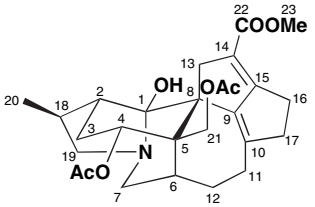

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Daphtenidine A (**1**) showed the pseudomolecular ion peak at *m/z* 498 $(M+H)^+$ in the ESIMS, and the molecular formula, $C_{31}H_{47}N_1O_4$, was established by HRESIMS [*m/z* 498.3591, $(M+H)^+$ Δ +0.8 mmu]. The IR absorption implied the presence of carbonyl group (1730 cm^{-1}). The ^{13}C NMR (Table 1) spectrum of **1** gave signals including one ketone carbonyl,

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Table 1. ^{1}H and ^{13}C NMR data of daphtenidine A (**1**) in CD_3OD

Position	δ_H		δ_C	
1	3.29	(1H, m)	62.18	d
2	1.32	(1H, m)	46.30	d
3a	1.75	(1H, m)	29.16	t
3b	1.87	(1H, m)		
4a	1.43	(1H, m)	42.32	t
4b	1.99	(1H, m)		
5			41.09	s
6	1.67	(1H, m)	47.86	d
7a	3.83	(1H, d, 14.9)	61.61	t
7b	2.48	(1H, d, 14.9)		
8			48.69	s
9			101.52	s
10			53.99	s
11a	2.17	(1H, m)	29.55	t
11b	1.60	(1H, m)		
12a	2.12	(1H, m)	32.95	t
12b	1.57	(1H, m)		
13a	2.19	(1H, m)	33.76	t
13b	2.02	(1H, m)		
14	4.96	(1H, t, 8.2)	82.37	d
15a	2.27	(1H, m)	36.73	t
15b	1.29	(1H, m)		
16a	1.71	(1H, m)	19.94	t
16b	1.69	(1H, m)		
17a	1.73	(1H, m)	39.89	t
17b	1.47	(1H, m)		
18	1.70	(1H, m)	32.39	d
19	1.00	(3H, d, 6.10)	22.69	q
20	0.95	(3H, d, 6.87)	22.23	q
21	1.20	(3H, s)	28.75	q
22			215.80	s
23a	2.82	(1H, d, 14.5)	65.11	t
23b	2.59	(1H, d, 14.5)		
24			51.57	s
25	0.91	(3H, s)	19.63	q
26a	4.69	(1H, d, 12.6)	66.98	t
26b	3.69	(1H, d, 12.6)		
27	4.71	(1H, m)	84.43	d
28	2.03	(2H, m)	26.00	t
29a	1.89	(1H, m)	35.61	t
29b	2.10	(1H, m)		
30			107.33	s
31	1.37	(3H, s)	24.86	q

six sp^3 quaternary carbons, six sp^3 methines, thirteen sp^3 methylenes, and five methyls. Among them, two methylenes (δ_C 61.61 and 65.11) and one methine (δ_C 62.18) were ascribed to those bearing a nitrogen atom.

The ^{1}H–^{1}H COSY and HOHAHA spectra of **1** revealed connectivities of five partial structures **a** (C-1 to C-4, C-2 to 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), **c** (C-13 to C-14), **d** (C-15 to C-17), and **e** (C-27 to C-29) as shown in Figure 1. HMBC correlations of H_2-7 to C-1 (δ_C 62.18) and C-23 (δ_C 65.11), and H-23a to C-1 suggested that C-1, C-7, and C-23 were connected to each other through a nitrogen atom. Connections between C-4, C-6, and C-21 via C-5 were implied by HMBC cross-peaks of H_2-4 and H_3-21 to C-5. On the other hand, connections among C-11, C-17, and C-23 via C-10 were indicated by HMBC cross-peaks of H-23a to C-11 and C-17, and H-23b to C-10 and C-11. The connection between C-9 and C-10 was implied by HMBC cross-peaks of H-11b to C-9 and H-23b to C-9. HMBC cross-peaks of H-1 to C-5 and C-8, H_2-13 to C-1, C-8, and C-9, H-14 to C-9, and H_3-21 to C-8 suggested connectivities among units **a**, **b**, **c**, and **d**, to form a nitrogen-containing hexacyclic

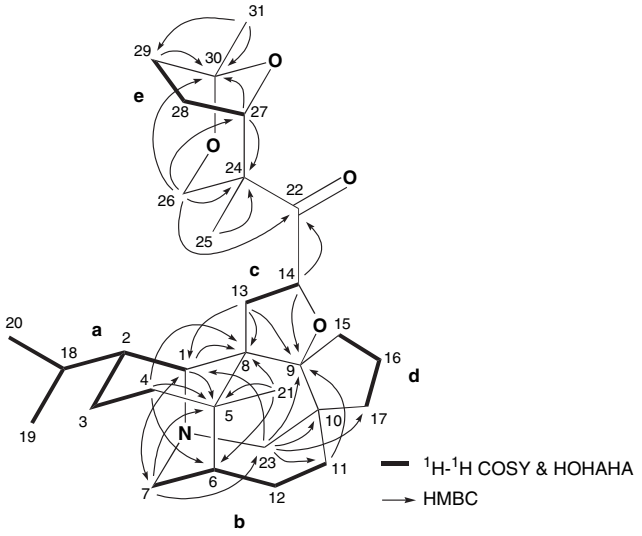


Figure 1. Selected 2D NMR correlations of daphtenidine A (**1**).

skeleton like daphnilactone A.[6] The presence of a 2,8-dioxabicyclo[3.2.1]octane moiety including unit **e** was deduced from HMBC cross-peaks of H_3-25 to C-24, H_2-26 to C-24, C-27, and C-30, H-27 to C-24 and C-30, H_2-29 to C-30, and H_3-31 to C-29 and C-30. HMBC cross-peaks of H-14 and H_2-26 to C-22 provided the connection between C-14 and C-24 via C-22. Thus, the gross structure of daphtenidine A was elucidated to be **1**.

The partial relative stereochemistry of **1** was deduced from ROESY correlations as shown in computer-generated 3D drawing (Fig. 2). These ROESY correlations indicated the relative configurations at C-2, C-9, and C-14, and chair forms of a cyclohexane (C-1 to C-5 and C-8) and a piperidine (N, C-1, C-8, and C-5 to C-7) ring in the 2-azabicyclo[3.3.1]-nonane moiety. The relative configuration at C-24 and a chair

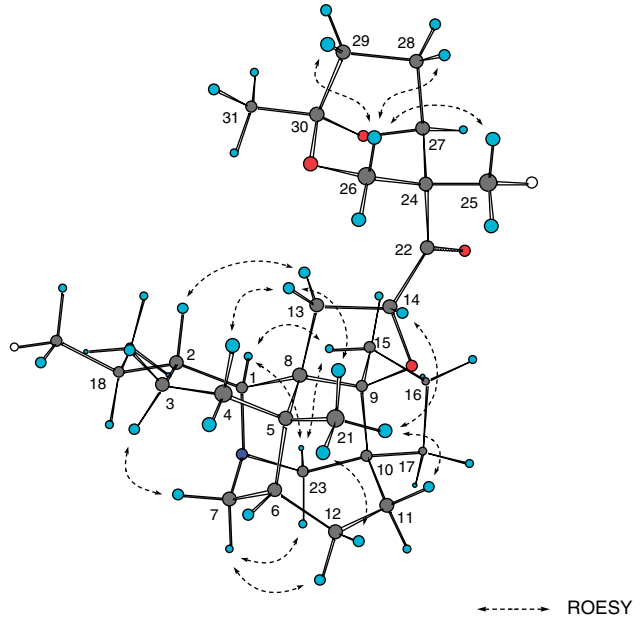


Figure 2. Selected ROESY correlations and relative stereochemistry of daphtenidine A (**1**).

form of the six-membered ring in the 2,8-dioxabicyclo [3.2.1]octane moiety was verified by ROESY correlations of H-26b to H-28 and H-29a.

Daphtenidine B (**2**) showed the pseudomolecular ion peak at *m/z* 372 $(M+H)^+$ in the ESIMS, and the molecular formula, $C_{24}H_{37}N_1O_2$, was established by HRESIMS [*m/z* 372.2899, $(M+H)^+$ Δ−0.3 mmu]. The IR absorption implied the presence of carbonyl group (1740 cm^{-1}). The ^{13}C NMR (Table 2) spectrum of **2** gave signals including one ester carbonyl, one sp^2 quaternary carbon, one sp^2 methine, three sp^3 quaternary carbons, four sp^3 methines, ten sp^3 methylenes, one methoxy, and three methyls. Among them, two methylenes (δ_C 55.34 and 73.65) and one methine (δ_C 60.23) were ascribed to those bearing a nitrogen atom.

Table 2. ^1H and ^{13}C NMR data of daphtenidine B (**2**) in CD_3OD

Position	δ_H		δ_C	
1	2.58	(1H, d, 4.4)	60.23	d
2	1.29	(1H, m)	41.45	d
3a	1.96	(1H, m)	28.82	t
3b	1.70	(1H, m)		
4a	1.96	(1H, m)	38.77	t
4b	1.51	(1H, m)		
5			38.16	s
6	1.64	(1H, m)	48.00	d
7a	3.73	(1H, dd, 15.0, 6.2)	55.34	t
7b	2.65	(1H, d, 15.0)		
8			43.72	s
9			151.16	s
10			51.40	s
11a	1.90	(1H, m)	35.58	t
11b	1.57	(1H, m)		
12a	1.79	(1H, m)	29.11	t
12b	1.57	(1H, m)		
13a	2.08	(1H, m)	26.46	t
13b	2.04	(1H, m)		
14a	2.40	(1H, m)	30.08	t
14b	2.04	(1H, m)		
15	5.44	(1H, s)	128.02	d
16a	2.48	(1H, m)	30.70	t
16b	2.24	(1H, ddd, 16.1, 8.48, 3.09)		
17a	1.69	(1H, m)	42.89	t
17b	1.57	(1H, m)		
18	1.62	(1H, m)	33.06	d
19	0.93	(3H, d, 6.50)	22.42	q
20	2.17	(3H, d, 6.22)	22.30	q
21	0.80	(3H, s)	25.32	q
22			177.42	s
23a	2.96	(1H, d, 13.3)	73.65	t
23b	2.77	(1H, d, 13.3)		
24	3.68	(3H, s)	53.09	q

The ^1H–^1H COSY and HOHAHA spectra of **2** revealed connectivities of four partial structures **a** (C-1 to C-4, C-2 to 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), **c** (C-13 to C-14), and **d** (C-15 to C-17) as shown in Figure 3. HMBC correlations were observed of H_2-7 to C-1 (δ_C 60.23) and C-23 (δ_C 73.65), and H-23a to C-1, suggesting that C-1, C-7, and C-23 were connected to each other through a nitrogen atom. The connection of a methoxycarbonyl group to C-14 was revealed from HMBC correlations of H-14 and H_3-24 to C-22. Connections among C-4, C-6, and C-21 via C-5 were indicated by HMBC cross-peaks of H_2-4, H-6, and H_3-21 to C-5. On the other hand, connections among C-11, C-17, and C-23 via C-10 were suggested by HMBC cross-peaks of H-11a, H-17a, and H-23a to C-10. Connections among C-10 and C-15 via C-9 were implied by HMBC cross-peaks of H-15 to C-10, H_2-16 to C-9, H-17a to C-9, and H-23a to C-9. HMBC cross-peaks for H-1 to C-5, H_2-13 to C-8 and C-9, H_3-21 to C-8 provided connectivities among all the units **a**–**d**, indicating the presence of a nitrogen-containing hexacyclic skeleton like daphnilactone A.[6] Thus, the gross structure of daphtenidine B was elucidated to be **2**.

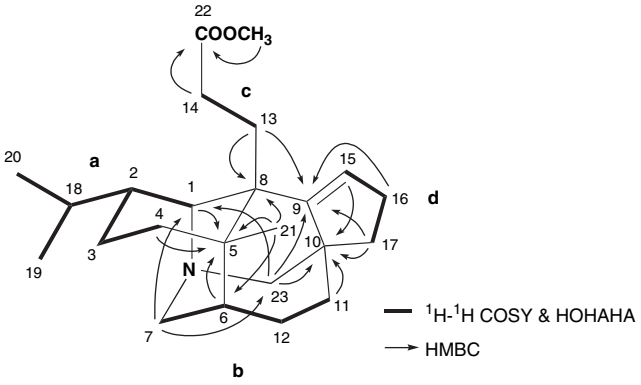


Figure 3. Selected 2D NMR correlations of daphtenidine B (**2**).

The relative stereochemistry of **2** was deduced from ROESY correlations as shown in computer-generated 3D drawing (Fig. 4). These ROESY correlations indicated the relative configuration at C-2 and chair forms of a cyclohexane (C-1 to C-5 and C-8) and a piperidine (N, C-1, C-8, and C-5 to C-7) ring in the 2-azabicyclo[3.3.1]nonane moiety.

Daphtenidine C (**3**) showed the pseudomolecular ion peak at *m/z* 486 $(M+H)^+$ in the ESIMS, and the molecular formula, $C_{27}H_{36}N_1O_7$, was established by HRESIMS [*m/z* 486.2473, $(M+H)^+$ Δ−1.9 mmu]. The IR absorption implied the presence of hydroxy group (3500 cm^{-1}) and carbonyl group (1730 cm^{-1}). The ^{13}C NMR (Table 3) spectrum of **3** gave signals including three ester carbonyls, three sp^2 quaternary

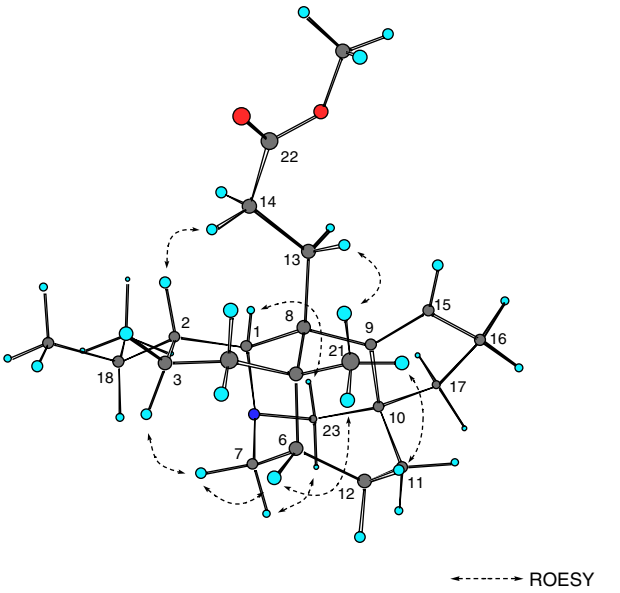


Figure 4. Selected ROESY correlations and relative stereochemistry of daphtenidine B (**2**).

Table 3. ^{1}H and ^{13}C NMR data of daphtenidine C (**3**) in CD_3OD

Position	δ_H		δ_C	
1			186.89	s
2			59.12	s
3	1.98	(2H, m)	33.50	t
4	4.89	(1H, dd, 9.6, 6.1)	73.17	d
5			53.14	s
6	2.39	(1H, m)	45.34	d
7	4.02	(1H, m)	67.95	d
8			47.42	s
9			136.17	s
10			142.43	s
11	2.27	(2H, m)	26.99	t
12a	2.05	(1H, m)	23.38	t
12b	1.90	(1H, m)		
13a	3.03	(1H, dd, 13.8, 4.3)	40.40	t
13b	2.42	(1H, m)		
14	3.15	(1H, dt, 10.0, 4.3)	44.53	d
15	3.54	(1H, m)	56.21	d
16a	1.89	(1H, m)	29.02	t
16b	1.27	(1H, m)		
17a	2.56	(1H, m)	44.77	t
17b	2.36	(1H, m)		
18	2.11	(1H, m)	38.73	d
19a	4.01	(1H, dd, 15.3, 6.9)	69.39	t
19b	3.46	(1H, d, 15.3)		
20	1.01	(3H, d, 7.1)	17.38	q
21a	4.38	(1H, d, 11.6)	66.85	t
21b	4.30	(1H, d, 11.6)		
22			177.95	s
23	3.62	(3H, s)	52.64	q
24			173.01	s
25	1.97	(3H, s)	21.83	q
26			172.64	s
27	2.00	(3H, s)	21.83	q

carbon, three sp^3 quaternary carbons, six sp^3 methines, eight sp^3 methylenes, one methoxy, and three methyls, implying that the structure of **3** was similar to that of daphmanidin A.[7] The ^{1}H–^{1}H COSY and HOHAHA spectra of **3** revealed connectivities of three partial structures **a** (C-6 to C-7 and C-12, and C-11 to C-12), **b** (C-13 to C-17), and **c** (C-18 to C-19 and C-20), which were connected to each other on the basis of HMBC correlations as shown in Figure 5. HMBC cross-peaks of H-4 and H_2-21 to acetyl carbonyl carbons (δ_C 173.01 and 172.64, respectively) revealed that the acetoxy groups were attached to C-4 and C-21.

The relative stereochemistry of **3** was deduced from NOESY correlations as shown in computer-generated 3D drawing (Fig. 6). These NOESY correlations indicated the relative configurations at C-4, C-7, C-14, and C-15 and the conformation of bicyclo[2.2.2]octane moiety (C-1 to C-8). Thus, daphtenidine C (**3**) was assigned to be 4-acetoxy form of daphmanidin A.

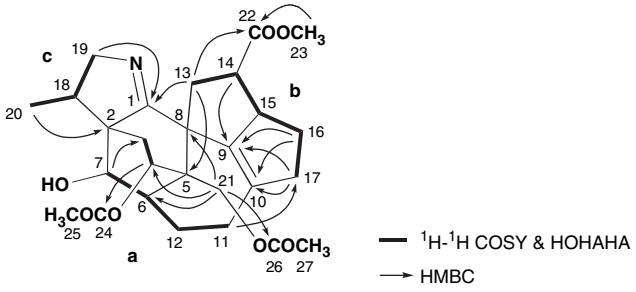


Figure 5. Selected 2D NMR correlations of daphtenidine C (**3**).

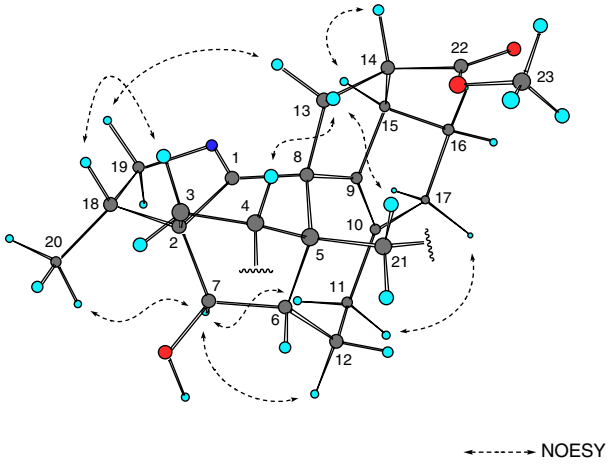


Figure 6. Selected NOESY correlations and relative stereochemistry of daphtenidine C (**3**). Two acetoxy groups were not shown.

Daphtenidine D (**4**) showed the pseudomolecular ion peak at *m/z* 486 $(M+H)^+$ in the ESIMS, and the molecular formula, $C_{27}H_{36}N_1O_7$, was established by HRESIMS [*m/z* 486.2490, $(M+H)^+$ $\Delta-0.2$ mmu]. The IR absorption implied the presence of hydroxy group (3480 cm^{-1}) and carbonyl group (1730 cm^{-1}). The ^{13}C NMR (Table 4) spectrum of **4** gave signals including three ester carbonyls, four sp^2 quaternary carbons, three sp^3 quaternary carbons, four sp^3 methines, nine sp^3 methylenes, one methoxy, and three methyls, implying that the structure of **4** was similar to that of

Table 4. ^{1}H and ^{13}C NMR data of daphtenidine D (**4**) in CD_3OD

Position	δ_H		δ_C	
1			98.35	s
2	2.39	(1H, m)	44.83	d
3a	2.00	(1H, m)	30.51	t
3b	1.74	(1H, m)		
4	5.42	(1H, dd, 11.2, 8.1)	75.14	d
5			46.56	s
6	2.60	(1H, m)	36.73	d
7a	3.40	(1H, d, 13.1)	60.34	t
7b	3.26	(1H, m,)		
8			53.71	s
9			152.45	s
10			154.28	s
11a	2.92	(1H, m)	27.56	t
11b	2.09	(1H, d, 16.8)		
12a	1.75	(1H, m)	30.34	t
12b	1.61	(1H, m)		
13a	3.37	(1H, m)	43.83	t
13b	3.08	(1H, d, 16.8)		
14			119.37	s
15			173.39	s
16	2.94.	(2H, m)	44.24	t
17a	2.72	(1H, m)	27.12	t
17b	2.63	(1H, m)		
18	2.75	(1H, m)	36.78	d
19a	3.58	(1H, dd, 11.8, 10.0)	65.58	t
19b	2.30	(1H, dd, 6.2, 11.8)		
20	1.12	(3H, d, 7.5)	16.51	q
21a	4.22	(1H, d, 11.2)	69.42	t
21b	4.17	(1H, d, 11.2)		
22			169.41	s
23	3.70	(3H, s)	52.36	q
24			173.17	s
25	1.97	(3H, s)	21.79	q
26			172.98	s
27	2.02	(3H, s)	22.09	q

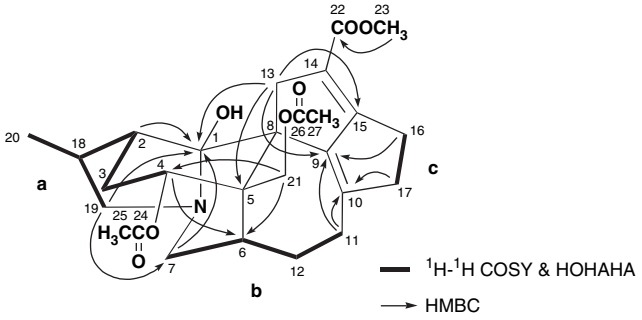


Figure 7. Selected 2D NMR correlations of daphtenidine D (**4**).

yuzurimine.[8] The ^{1}H–^{1}H COSY and HOHAHA spectra of **4** revealed connectivities of three partial structures **a** (C-2 to 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), which were connected to each other on the basis of HMBC correlations as shown in Figure 7. HMBC cross-peaks of H-4 and H_2-21 to acetyl carbonyl carbons (δ_C 173.17 and 172.98, respectively) revealed that the acetoxy groups were attached to C-4 and C-21.

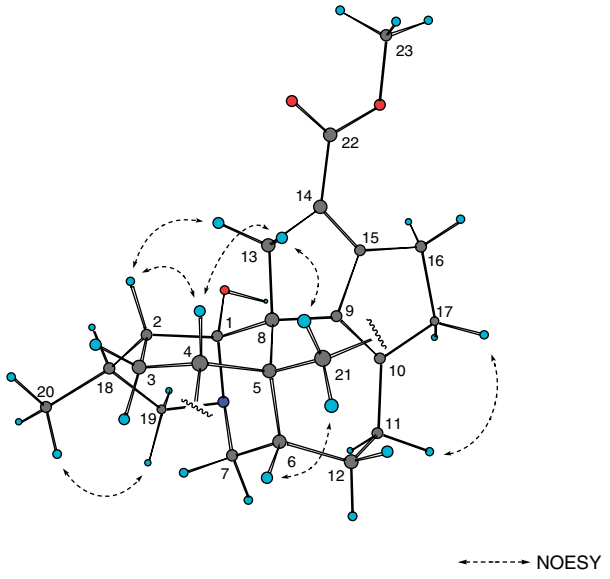
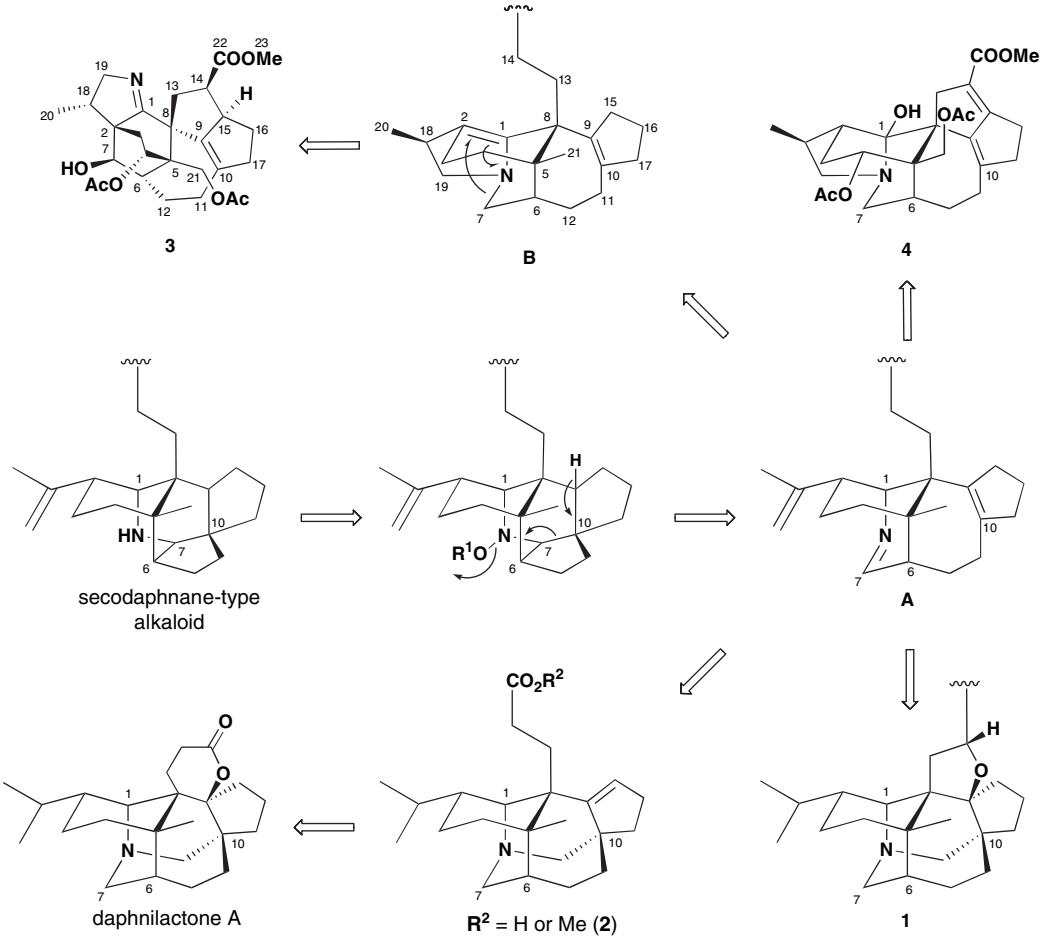


Figure 8. Selected NOESY correlations and relative stereochemistry of daphtenidine D (**4**). Two acetoxy groups were not shown.

The relative stereochemistry of **4** was deduced from NOESY correlations as shown in computer-generated 3D drawing (Fig. 8). These NOESY correlations indicated the relative configurations at C-4 and C-18, and the chair forms of a cyclohexane (C-1 to C-5 and C-8) and a piperidine (N, C-1, C-8, and C-5 to C-7) ring in the 2-azabicyclo[3.3.1]nonane moiety. Thus, daphtenidine D (**4**) was assigned to be 14-dehydro form of yuzurimine.



Scheme 1. Plausible biogenetic path of daphtenidines A–D (**1**–**4**).

Daphtenidines A (**1**) and B (**2**) were the second isolation of daphnilactone A-type alkaloids from natural sources. Daphtenidine A (**1**) was the first daphnilactone A-type alkaloid possessing a 2,8-dioxabicyclo[3.2.1]octane moiety. Daphtenidines C (**3**) and D (**4**) were the 4-acetoxy form of daphmanidin A and 14-dehydro form of yuzurimine, respectively. Biogenetically, daphtenidines A (**1**) and B (**2**) might be generated through an intermediate **A** from secodaphnane-type alkaloid,[9] followed by the formation of daphnilactone A (Scheme 1). Daphtenidine C (**3**) might be generated from intermediate **B** with cleavage of the N–C-7 bond followed by formation of the C-7–C-2 bond, while daphtenidine D (**4**) might be also generated from intermediate **A**.

Daphtenidines A–D (**1**–**4**) showed moderate cytotoxicity against murine lymphoma L1210 cells (IC_{50} 7, 3, 8, and 5 μg/mL, respectively) in vitro, while **1**–**4** did not show cytotoxicity against human epidermoid carcinoma KB cells (IC_{50}>10 μg/mL).

3. Experimental

3.1. General experimental procedures

The IR spectrum was recorded on a JASCO FTIR-230 and a Shimadzu UV-1600PC spectropolarimeter. ^1H and ^{13}C NMR spectra were recorded on a Bruker AMX-600 and a Varian Unity INOVA 600 spectrometer. The 3.31 and 49.5 ppm resonances of residual CD_3OD were used as internal references for ^1H and ^{13}C NMR spectra, respectively. ESI mass spectra were obtained on a JEOL JMS-700TZ spectrometer.

3.2. Material

The leaves of *D. teijsmannii* were collected at Okinawa in 2002. The botanical identification was made by Prof. Takakazu Shinzato, University of the Ryukyus. A voucher specimen has been deposited in the herbarium of Hokkaido University.

3.3. Isolation

The leaves of *D. teijsmannii* (2.0 kg) were crushed and extracted with MeOH. The MeOH extract was treated with 3% tartaric acid (pH 2) and then partitioned with EtOAc. The aqueous layer was treated with saturated Na_2CO_3 (aq) to pH 10 and extracted with $CHCl_3$ to give a crude alkaloidal fraction. The alkaloidal fraction was purified by an LH-20 column (MeOH) followed by an amino silica gel column (hexane/EtOAc 1:0→0:1, and then $CHCl_3$/MeOH 1:0→0:1). The fractions eluted with hexane/EtOAc (4:1) were further purified by a silica gel column ($CHCl_3$/MeOH 1:0→0:1) to afford daphtenidines A (**1**, 0.4 mg, 0.00002% yield), B (**2**, 0.3 mg, 0.00002%), C (**3**, 11.8 mg, 0.0006%), and D (**4**, 11.7 mg, 0.0006%).

3.3.1. Daphtenidine A (1). Colorless amorphous solid; $[\alpha]_D^{23}$ −3 (*c* 0.1, MeOH); IR (neat) max 2920, 2860, and 1730 cm^{-1}; ^1H and ^{13}C NMR data (Table 1); ESIMS *m/z* 498 $(M+H)^+$; HRESIMS *m/z* 498.3591 (M+H; calcd for $C_{31}H_{48}NO_4$, 498.3583).

3.3.2. Daphtenidine B (2). Colorless amorphous solid; $[\alpha]_D^{23}$ +97 (*c* 0.1, MeOH); IR (neat) max 2920, 2850, and 1740 cm^{-1}; ^1H and ^{13}C NMR data (Table 2); ESIMS *m/z* 372 $(M+H)^+$; HRESIMS *m/z* 372.2899 (M+H; calcd for $C_{24}H_{38}N_1O_2$, 372.2902).

3.3.3. Daphtenidine C (3). Colorless amorphous solid; $[\alpha]_D^{23}$ −106 (*c* 1.0, MeOH); IR (neat) max 3500, 2960, and 1730 cm^{-1}; ^1H and ^{13}C NMR data (Table 3); ESIMS *m/z* 486 $(M+H)^+$; HRESIMS *m/z* 486.2473 (M+H; calcd for $C_{27}H_{36}N_1O_7$, 486.2492).

3.3.4. Daphtenidine D (4). Colorless amorphous solid; $[\alpha]_D^{23}$ +36 (*c* 1.0, MeOH); IR (neat) max 3480, 3010, 2940, and 1730 cm^{-1}; UV (MeOH) λ_{max} 301 nm (ε 11060); ^1H and ^{13}C NMR data (Table 4); ESIMS *m/z* 486 $(M+H)^+$; HRESIMS *m/z* 486.2490 (M+H; calcd for $C_{27}H_{36}N_1O_7$, 486.2492).

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