Pergamon

SCIENCE DIRECT®

Tetrahedron 59 (2003) 3575–3579

TETRAHEDRON

Daphnezomines P, Q, R and S, new alkaloids from *Daphniphyllum humile*

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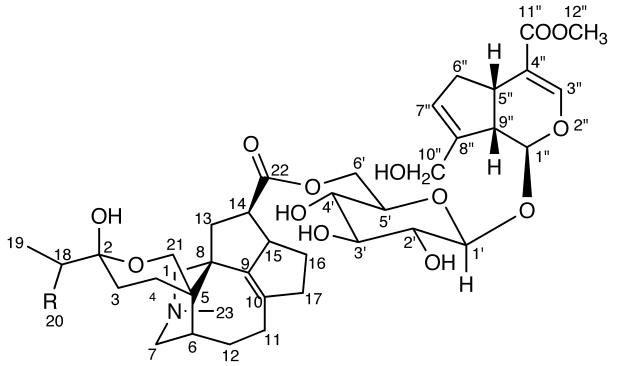
Received 13 March 2003; revised 1 April 2003; accepted 3 April 2003

Abstract—Four new alkaloids, daphnezomines P–S (**1**–**4**), have been isolated from the fruits of *Daphniphyllum humile*, and the structures and the stereochemistry were elucidated on the basis of spectroscopic data including 2D NMR and MS/MS spectra, and chemical correlations. Daphnezomines P (**1**) and Q (**2**) were the first *Daphniphyllum* alkaloids with an iridoid glycoside moiety.

Structural diversity of *Daphniphyllum* alkaloids with unique ring systems may be explained by unique biogenetic process involving repeated fission of C–C and/or C–N bonds followed by rearrangements, recyclization, and so on.[1] In our search for *Daphniphyllum* alkaloids with unique ring systems, a series of novel alkaloids such as daphnezomines A–O,[2] daphnicyclidins A–H,[3] J, and K,[4] and daphmanidine A,[5] have been isolated from *D. humile* and *D. teijsmanni*. Our interest has been focused on isolation of structurally interesting alkaloids and biosynthetically important intermediates to clarify the biogenetic pathway. Further investigation of extracts of the fruits of *Daphniphyllum humile* (Daphniphyllaceae) resulted in the isolation of four new alkaloids, daphnezomines P–S (**1**–**4**). Daphnezomines P (**1**) and Q (**2**) were the first *Daphniphyllum* alkaloids with an iridoid glycoside moiety. In this paper we describe the isolation and structure elucidation of **1**–**4**.



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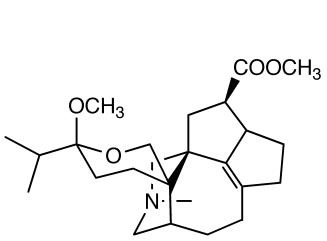

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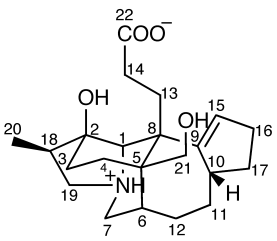

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The fruits of *D. humile* collected in Sapporo were extracted with MeOH, and the MeOH extract was partitioned between EtOAc and 3% tartaric acid. Water-soluble materials were adjusted at pH 9 with sat. Na_2CO_3 and partitioned with $CHCl_3$ and then *n*-BuOH. *n*-BuOH-soluble materials were subjected to an amino silica gel column ($CHCl_3$/MeOH/H_2O, 8:3:0.5→5:5:1) followed by C_{18} HPLC (CH_3CN/0.1% TFA, 1:4) to afford daphnezomines P (**1**, 0.02%), Q (**2**, 0.006%), and R (**3**, 0.004%) as colorless solids. Water-soluble fraction was subjected to an HP-20 column chromatography (H_2O→MeOH) followed by amino silica gel column chromatography ($CHCl_3$/MeOH/H_2O, 7:3:0.5) to give daphnezomine S (**4**, 0.0007%) as colorless solids together with a known related alkaloid, zwitter ionic alkaloid[6] (0.0005%).

Daphnezomine P (**1**) showed the pseudomolecular ion peak at *m/z* 760 $(M+H)^+$ in the FABMS, and the molecular formula, $C_{40}H_{57}NO_{13}$, was established by HRFABMS [*m/z* 760.3930, $(M+H)^+$, Δ +2.1 mmu]. IR absorptions implied the presence of hydroxyl and carbonyl (3421 and

Keywords: *Daphniphyllum* alkaloids; iridoid glycoside; NMR; MS/MS.

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0040–4020/03/$ - see front matter
doi:10.1016/S0040-4020(03)00542-8

1684 cm^{-1}, respectively) functionalities. ^1H and ^{13}C NMR data (Table 1) revealed 40 carbon signals due to six sp^2 and three sp^3 quaternary carbons, two sp^2 methines, 12 sp^3 methines, 13 sp^3 methylenes, and four methyl groups. Among them, two sp^3 methylene (δ_C 57.6; δ_H 3.13 and 3.19; δ_C 55.5; δ_H 3.53 and 3.48) and one methyl (δ_C 45.8; δ_H 2.90) were ascribed to those bearing a nitrogen. Since five out of 13 elements of unsaturation were accounted for, **1** was inferred to possess eight rings. Six partial structures **a** (C-18–C-20), **b** (C-3 and C-4), **c** (C-6–C-7 and C-11–C-12), **d** (C-13–C-17), **e** (C-1′–C-6′), and **f** (C-1″, C-5″–C-7″, and C-9″), and two isolated methylenes (C-1 and C-21) which were attached to a nitrogen and an oxygen, respectively, were deduced from detailed analyses of 2D NMR data (^1H–^1H COSY, HOHAHA, HMQC, and HMQC-HOHAHA) of **1**.

Connections among units **a** and **b**, and C-21 via hemiacetal quaternary carbon C-2 (δ_C 102.1) were implied by HMBC cross-peaks for H_3-19, H_3-20, H_2-3, and H_2-21 to C-2. HMBC cross-peaks for H_2-21 to C-4 (δ_C 23.2) and C-5 (δ_C 37.1) indicated that an sp^3 quaternary carbon (C-5) was located between C-4 and C-21. HMBC correlations of H_2-4 and H_2-21 to C-6 (δ_C 33.6) through C-5 revealed that unit **c**

Table 1. ^1H and ^{13}C NMR data of daphnezomines P–S (**1**–**4**) in CD_3OD at 300 K

	δ_H				δ_C			
	1	**2**	**3**	**4**	**1**	**2**	**3**	**4**
1a	3.13 d (12.5)	3.17 m	3.14 d (12.5)	3.52 s	57.6	57.6	57.6	72.9
1b	3.19 m	3.19 m	3.20 d (12.5)					
2					102.1	100.4	102.2	77.8
3a	1.96 dd (2.7, 13.7)	1.97 m	1.95 m	1.68 m	23.1	23.1	23.2	28.1
3b	1.75 m	1.70 m	1.71 m	1.85 m				
4a	1.75 m	1.73 m	1.93 m	1.47 m	23.2	23.2	23.2	31.2
4b	1.70 dd (9.4, 12.3)	1.69 m	1.68 m	2.32 m				
5					37.1	37.1	37.1	42.8
6	2.57 m	2.63 brs	2.58 brs	2.41 m	33.6	33.6	33.6	39.3
7a	3.53 d (13.7)	3.51 m	3.48 dd (5.2, 13.8)	2.58 m	55.5	55.7	55.5	57.7
7b	3.48 m	3.47 m	3.53 brd (13.0)	3.27 m				
8					46.9	46.9	46.9	42.8
9					143.1	143.2	143.1	152.4
10				2.94 brt (9.0)	138.5	138.5	138.5	48.9
11a	1.77 m	1.77 m	1.75 m	1.70 m	26.2	26.4	26.3	33.2
11b	2.35 m	2.34 m	2.42 m	1.93 m				
12a	2.36 m	2.29 m	2.34 m	1.37 m	26.5	26.5	26.4	31.7
12b	2.40 m	2.43 m	2.45 m	2.24 m				
13a	1.79 m	1.77 m	1.79 m	2.05 m	39.7	39.8	39.8	35.3
13b	2.77 m	2.76 m	2.76 m	2.28 m				
14	2.99 dt (2.7, 10.1)	3.00 m	2.99 m	2.06, 2.18 m	43.2	43.2	43.3	32.6
15	3.61 m	3.65 m	3.62 m	5.73 s	55.7	55.7	55.7	130.0
16a	1.41 m	1.60 m	1.33 t (10.2)	1.29 m	29.3	29.4	29.0	30.4
16b	1.90 m	2.06 m	1.90 m	2.48 m				
17a	2.42 m	2.40 m	2.39 m	1.59 m	43.9	43.9	43.8	33.6
17b	2.67 m	2.67 m	2.69 brs	2.12 m				
18a	2.07 m	1.45 m	2.08 m	2.24 m	32.4	30.7	32.5	45.1
18b		1.90 m						
19	0.85 d (7.0)	0.86 t (7.4)	0.86 d (7.0)	2.48, 3.77 m	16.7	8.0	16.7	63.5
20	0.93 d (6.8)		0.94 d (6.9)	1.05 d (6.9)	17.6		17.6	11.7
21a	3.76 dd (2.8, 12.5)	3.86 brd (11.1)	3.78 dd (2.7, 12.6)	3.64 d (10.7)	63.2	63.1	63.3	67.3
21b	4.08 d (12.5)	4.11 m	4.11 d (12.5)	4.28 d (10.7)				
22					175.6	175.7	176.4	182.8
23	2.90 s	2.90 s	2.90 s		45.8	45.8	45.8	
1′	4.71 d (7.9)	4.71 d (7.8)			100.1	100.2		
2′	3.23 dd (8.0, 9.1)	3.23 dd (8.5, 8.5)			74.8	74.8		
3′	3.40 dd (9.1, 9.1)	3.39 dd (9.1, 9.1)			77.6	76.6		
4′	3.30 dd (9.1, 9.1)	3.31 m			71.6	71.6		
5′	3.48 m	3.47 m			75.8	75.8		
6′a	4.14 dd (6.3, 12.0)	4.13 m			64.5	64.5		
6′b	4.48 dd (1.7, 12.0)	4.48 brd (10.8)						
1″	5.01 d (7.9)	5.01 d (7.9)			98.3	98.3		
3″	7.52 s	7.51 s			153.3	153.3		
4″					112.9	112.9		
5″	3.17 m	3.18 m			36.8	36.8		
6″a	2.07 m	2.08 m			39.9	39.9		
6″b	2.86 dd (8.7, 16.6)	2.86 m						
7″	5.82 s	5.81 s			128.8	128.9		
8″					145.0	145.0		
9″	2.75 m	2.74 m			46.7	46.7		
10″a	4.21 d (14.0)	4.21 d (13.2)			61.5	61.6		
10″b	4.26 d (14.0)	4.23 d (13.2)						
11″					170.7	170.7		
12″	3.35 s	3.35 s	3.65 s		49.4	49.5	51.7	

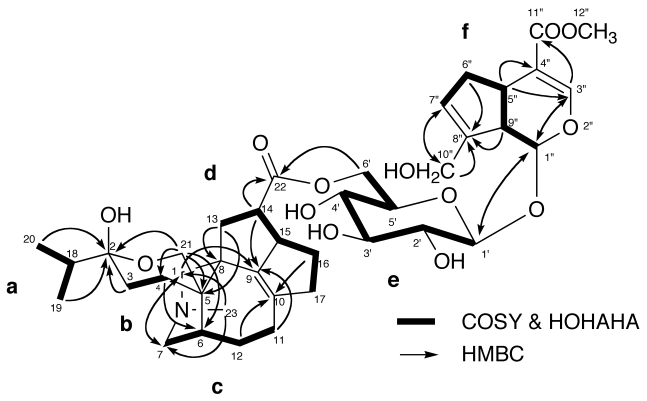

Figure 1. Selected 2D NMR correlations for daphnezomine P (**1**).

was attached to C-5. The presence of a consecutive quaternary carbon (C-8) was verified by long-range C–H couplings for H_2-13 to C-5 and C-8. Connections among units **c** and **d**, C-1, and tetrasubstituted olefin (C-9 and C-10) were provided by HMBC correlations of H_2-1, H-14, and H_2-11 to C-9 (δ_C 143.1) and H_2-12 and H_2-16 to C-10 (δ_C 138.5). In addition to the above HMBC correlations, correlations among three carbons (C-1, C-7, and C-23) attached to a nitrogen led to the backbone skeleton of daphnigracine as an alkaloidal part (units **a**–**d**). Furthermore, HMBC correlations of H-14 and H_2-6′ in unit **e** to C-22 (δ_C 175.6) revealed that C-6′ was attached to C-22. The carbon signals at δ_C 100.1, 74.8, 77.6, 71.6, 75.8, and 64.5 indicated the presence of a glucopyranose with an ester group at C-6′. The HMBC correlation from a proton signal at δ 4.71 (H-1′) to a carbon signal at δ 98.3 (C-1″) indicated that the glucopyranose in unit **e** was attached to C-1″ in unit **f**. The glucoside linkage was assigned as β from observation of an anomeric proton signal at δ_H 4.71 (1H, d, J=7.9 Hz). HMBC correlations in unit **f** as shown in Figure 1 were consistent with those of genipin, which is the genin part of geniposide.

Further evidence supporting the proposed structure of **1** was provided by tandem mass spectrometry through examination of the collision-induced dissociation (CID) mass spectrum of the $(M+H)^+$ ions. The positive ion FABMS/MS spectra of **1** showed product ion peaks generated by fissions at the ester bond between units **d** and **e** and the ether bond between units **e** and **f** (Fig. 2).

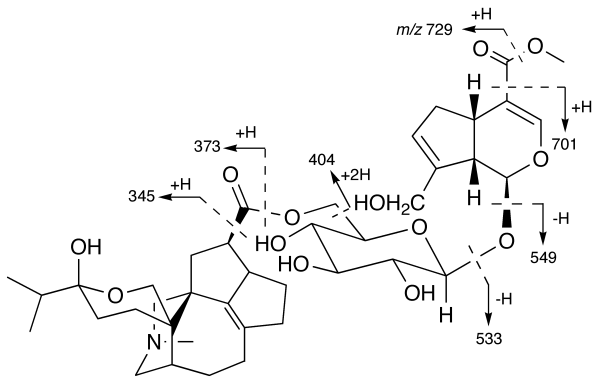

Figure 2. Fragmentation patterns observed in positive FABMS/MS spectrum of daphnezomine P (**1**) [precursor ion, *m/z* 760].

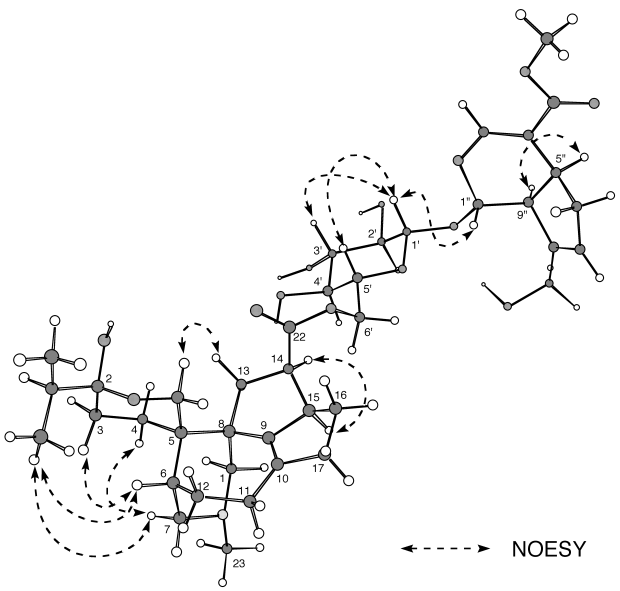

Figure 3. Selected NOESY correlations and relative stereochemistry for daphnezomine P (**1**).

The relative stereochemistry of **1** was elucidated from NOESY correlations as shown in computer-generated 3D drawing (Fig. 3). The absolute configurations of alkaloid, sugar, and iridoid parts in **1** were elucidated by alkaline hydrolysis of **1**, which gave daphnigracine[7] and geniposidic acid.[8] Therefore, the structure and the absolute stereochemistry of daphnezomine P (**1**) were assigned as shown.

Daphnezomine Q [**2**, $[\alpha]_D$=+10° (*c* 0.6, MeOH)] showed the pseudomolecular ion peak at *m/z* 746 $(M+H)^+$ and the molecular formula, $C_{39}H_{55}NO_{13}$, was established by HRFABMS [*m/z* 746.3735, $(M+H)^+$, Δ −1.8 mmu]. IR absorptions implied the presence of hydroxyl (3409 cm^{-1}) and carbonyl (1680 cm^{-1}) functionalities. The ^{13}C NMR (Table 1) spectrum showed signals due to nine quaternary carbons (sp^2×6 and sp^3×3), two sp^2 methines, 11 sp^3 methines, 14 methylenes, and three methyls, indicating that **2** was an alkaloid related to **1**. Hydrolysis of **2** afforded daphnigraciline and geniposidic acid, whose spectral data and $[\alpha]_D$ value were identical with those of natural daphnigraciline[7] and geniposidic acid.[8] Thus, the structure and the absolute stereochemistry of daphnezomine Q (**2**) were elucidated as shown.

HRFABMS data [*m/z* 418.2957, $(M+H)^+$, Δ 0.0 mmu] of daphnezomine R (**3**) established the molecular formula, $C_{25}H_{40}NO_4$, which was larger than that of daphnigracine[7] by a CH_2 unit. The NMR data of **3** were analogous to those of daphnigracine except for the following observation: a methoxy signal (δ_H 3.65) lacking in daphnigracine appeared for **3**. The HMBC correlation of a methoxy signal (δ_H 3.65) to C-2 (δ_C 100.4) suggested that the methoxy group was attached to C-2. Methylation of daphnigracine with MeOH containing AcOH afforded **3**.[7] Thus, the structure and absolute stereochemistry of daphnezomine R (**3**) were elucidated as shown.

HRFABMS data [*m/z* 376.2463 $(M+H)^+$, Δ −2.5 mmu] of daphnezomine S (**4**) revealed the molecular formula,

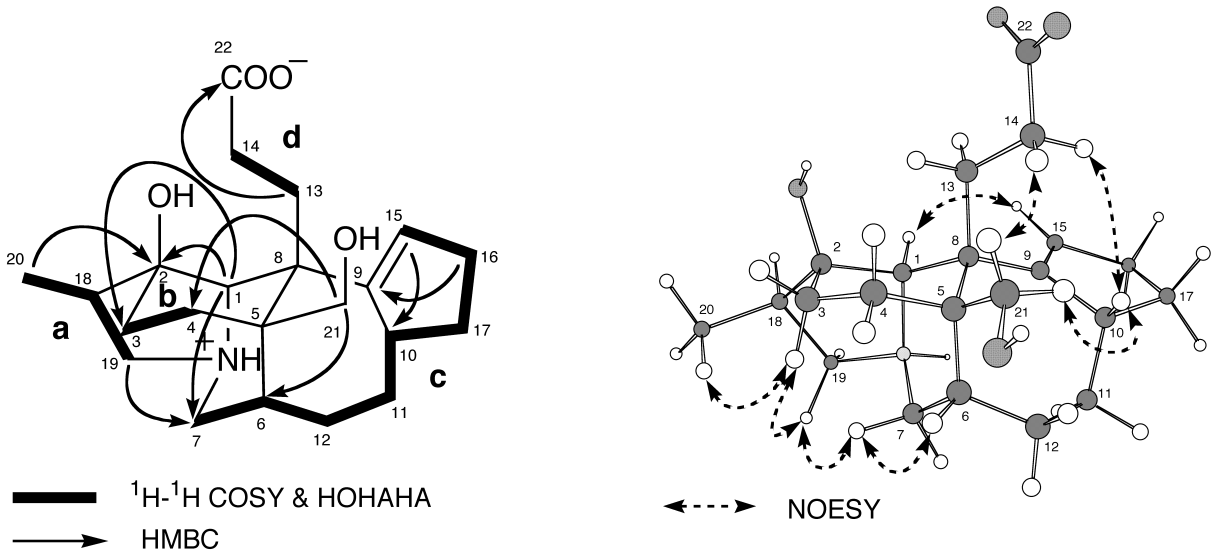

Figure 4. Selected 2D NMR correlations and relative stereochemistry for daphnezomine S (**4**).

$C_{22}H_{33}NO_4$. The ^1H and ^{13}C NMR (Table 1) spectra of **4** showed signals due to two sp^2 and three sp^3 quaternary carbons, one sp^2 methine, four sp^3 methines, 11 methylenes, and one methyl, suggesting that **4** had a backbone skeleton similar to that of daphnezomine H.[2] The ^{13}C NMR spectrum revealed signals due to three carbons bearing a nitrogen (δ_C 72.9, d; 57.7, t; 63.5, t) and two carbons bearing an oxygen (δ_C 77.8, s; 67.3, t). The gross structure of **4** was elucidated by 2D NMR ($^1H-^1H$ COSY, HOHAHA, HMQC, and HMBC) data (Fig. 4). The $^1H-^1H$ COSY and HOHAHA spectra revealed connectivities of partial structures **a** (C-18 to C-19 and C-20), **b** (C-3 to C-4), **c** (C-6 to C-7, C-10 to C-12, and C-15 to C-17), and **d** (C-13 to C-14) along with two isolated methine (C-1) and methylene (C-21). These four units **a**–**d** were connected to one another on the basis of HMBC correlations of H_3-20 and H-1 to C-2, H-1 to C-3 and C-7, H_2-19 to C-7, H_2-21 to C-4 and C-6, H-15 to C-10, and H_2-16 to C-9. The presence of a carboxylate at C-22 was indicated by HMBC correlations of H_2-13 to C-22. The relative stereochemistry of **4** was deduced from NOESY correlations (Fig. 4). Treatment of **4** with 90% formic acid gave a lactone, whose spectral data and $[\alpha]_D$ value were identical with those of daphnezomine H.[2] Thus, daphnezomine S (**4**) was concluded to be a zwitter ionic alkaloid[6] with a hydroxyl at C-2.

Daphnezomines P (**1**), Q (**2**), R (**3**), and S (**4**) exhibited cytotoxicity against murine lymphoma L1210 cells with IC_{50} values of 8.5, 9.2, 4.8, and 2.7 μg/mL, respectively.

1. Experimental

1.1. General methods

^1H and 2D NMR spectra were recorded on a 600 MHz spectrometer at 300 K, while ^{13}C NMR spectra were measured on a 150 MHz spectrometer. The NMR samples of daphnezomines P–S (**1**–**4**) were prepared by dissolving 1.5 mg each in 30 μL of CD_3OD in 2.5 mm micro cells (Shigemi Co. Ltd) and chemical shifts were recorded using residual CD_3OD (δ_H 3.31 and δ_C 49.0) as internal standards. Standard pulse sequences were employed for the 2D NMR experiments. COSY, HOHAHA, and NOESY spectra were measured with spectral widths of both dimensions of 4800 Hz, and 32 scans with two dummy scans were accumulated into 1 K data points for each of 256 t_1 increments. NOESY and HOHAHA spectra in the phase sensitive mode were measured with a mixing time of 800 and 30 ms, respectively. For HMQC spectra in the phase sensitive mode and HMBC spectra, a total of 256 increments of 1 K data points were collected. For HMBC spectra with *Z*-axis PFG, a 50 ms delay time was used for long-range C–H coupling. Zero-filling to 1 K for F_1 and multiplication with squared cosine-bell windows shifted in both dimensions were performed prior to 2D Fourier transformation. FABMS was measured by using glycerol as a matrix.

1.2. Material

The fruits of *Daphniphyllum humile* were collected in Sapporo in 2001. The botanical identification was made by Mr N. Yoshida, Health Sciences University of Hokkaido. A voucher specimen has been deposited in the herbarium of Hokkaido University.

1.3. Extraction and isolation

The fruits (288 g) of *Daphniphyllum humile* were crushed and extracted with MeOH (1 L×3) to give MeOH extract (38 g). The MeOH extract was treated with 3% tartaric acid to adjust at pH 2 and then partitioned with EtOAc. The aqueous layer was treated with sat. Na_2CO_3 aq. to adjust at pH 9 and extracted with $CHCl_3$, and then *n*-BuOH to give two crude alkaloidal fractions (0.8 and 2.6 g, respectively). The *n*-BuOH extract was subjected to an amino silica gel column chromatography ($CHCl_3$/MeOH/H_2O, 8:3:0.5→5:5:1) followed by C_{18} HPLC (CH_3CN/0.1% TFA, 1:4) to give daphnezomines P (**1**, 0.02%), Q (**2**, 0.006%), and R (**3**, 0.004%) together with known related alkaloids, daphnigraciline (0.002%), daphnigracine (0.02%), and yuzurine (0.001%). Water-soluble fraction was subjected to an HP-20 column chromatography

(H_2O→MeOH) followed by amino silica gel column chromatography ($CHCl_3$/MeOH/H_2O, 7:3:0.5) to give daphnezomine S (**4**, 0.0007%) together with a known related alkaloid, zwitter ionic alkaloid[6] (0.0005%). Daphnezomine P (**1**) could be detected by C_{18} HPLC analysis of the squeezed juice made of the fresh fruits.

1.3.1. Daphnezomine P (1). A colorless solid; $[\alpha]_D$=+10° (*c* 1.0, MeOH); IR (KBr) ν_{max} 3421, 2924, 1684, 1404, and 1191 cm^{-1}; UV (MeOH) λ_{max} 232 nm (ε 10,000); ^1H and ^{13}C NMR data (Table 1); FABMS *m/z* 760 $(M+H)^+$; HRFABMS *m/z* 760.3930 (M+H; calcd for $C_{40}H_{58}NO_{13}$, 760.3909).

1.3.2. Daphnezomine Q (2). A colorless solid; $[\alpha]_D$=+10° (*c* 0.6, MeOH); IR (KBr) ν_{max} 3409, 2932, 1680, 1460, 1200, 1146, and 1083 cm^{-1}; UV (MeOH) λ_{max} 233 nm (ε 10,000); ^1H and ^{13}C NMR data (Table 1); FABMS *m/z* 746 $(M+H)^+$; HRFABMS *m/z* 746.3735 (M+H; calcd for $C_{39}H_{56}NO_{13}$, 746.3753).

1.3.3. Daphnezomine R (3). A colorless solid; $[\alpha]_D$=−14° (*c* 1.0, MeOH); IR (KBr) ν_{max} 2934, 1734, 1554, 1458, 1174, and 1041 cm^{-1}; ^1H and ^{13}C NMR data (Table 1); FABMS *m/z* 418 $(M+H)^+$; HRFABMS *m/z* 418.2957 (M+H; calcd for $C_{25}H_{40}NO_4$, 418.2957).

1.3.4. Daphnezomine S (4). A colorless solid; $[\alpha]_D$=−7° (*c* 1.0, MeOH); IR (KBr) ν_{max} 3403, 2934, 1564, 1392, and 1036 cm^{-1}; ^1H and ^{13}C NMR data (Table 1); FABMS *m/z* 376 $(M+H)^+$; HRFABMS *m/z* 376.2463 (M+H; calcd for $C_{22}H_{34}NO_4$, 376.2488).

1.4. Alkaline hydrolysis of daphnezomines P (1) and Q (2)

To a solution of daphnezomine P (**1**, 1 mg) in 2% KOH (1 mL) was allowed to stand at room temperature for 1.5 h. The residue was dissolved in CH_3OH (0.1 mL) and filtered. After evaporation, the residue was subjected to an HP-20 column to give daphnigracine[7] (0.5 mg) and geniposidic acid[8] (0.3 mg), whose spectral data and $[\alpha]_D$ value were identical with those of the authentic specimen of daphnigracine and geniposidic acid. Hydrolysis of daphnezomine Q (**2**) by the same procedure as described above afforded daphnigraciline[7] and geniposidic acid.[8]

1.5. Conversion of daphnigracine into daphnezomine R (3)

A solution of daphnigracine (1 mg) in MeOH containing AcOH was stirred at room temperature for 12 h, and then concentrated under reduced pressure to give a compound, whose spectral data and $[\alpha]_D$ value were identical with those of daphnezomine R (**3**).

1.6. Lactonization of daphnezomine S (4)

A solution of daphnezomine S (**4**) (1 mg) in 88% formic acid (0.1 mL) was allowed to stand at 85°C overnight. The aqueous solution was made basic with Na_2CO_3 and extracted with $CHCl_3$. The extract was washed with sat. NaCl aq. and water. Removal of the solvent gave a colorless oil, whose spectral data and $[\alpha]_D$ value were identical with those of daphnezomine H.[2]

Acknowledgements

The authors thank Mrs S. Oka and Miss M. Kiuchi, Center for Instrumental Analysis, Hokkaido University, for measurements of FABMS and FABMS/MS, and Mr N. Yoshida, Health Sciences University of Hokkaido, for botanical identification. This work was partly supported by a Grant-in-Aid for Scientific Research from the Ministry of Education, Culture, Sports, Science, and Technology of Japan.

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