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Daphmanidin A, a Novel Hexacyclic Alkaloid from *Daphniphyllum teijsmanii*

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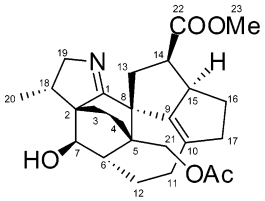
Abstract: A novel alkaloid with an unprecedented fused-hexacyclic skeleton, daphmanidin A (**1**), and a new pentacyclic alkaloid, daphmanidin B (**2**), have been isolated from the leaves of *Daphniphyllum teijsmanii*, and the structures were elucidated on the basis of spectroscopic data. The relative and absolute stereochemistry of **1** was determined by combination of NOESY correlations and a modified Mosher method.

Daphniphyllum alkaloids are a family of fused-heterocyclic natural products elaborated by trees of the genus *Daphniphyllum* (Daphniphyllaceae)[1,2] and classified into six different types of backbone skeletons.[1,3] Heathcock and co-workers have reported biomimetic synthesis of daphnane and secodaphnane type skeletons of *Daphniphyllum* alkaloids.[4] In search for structurally unique and biogenetically interesting *Daphniphyllum* alkaloids, we isolated previously some new 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] and daphnicyclidins J and K[9] with a unique hexa- or pentacyclic ring system from the leaves and stems of *D. humile* and/or *D. teijismanni* and proposed their plausible biogenesis. Further investigation on extracts of the leaves of *D. teijsmanii* resulted in the isolation of daphmanidin A (**1**), a novel alkaloid with an unprecedented fused-hexacyclic ring system, and daphmanidin B (**2**) with a pentacyclic ring system. This paper describes the isolation and structural elucidation of **1** and **2**.



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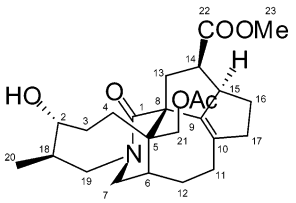

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Results and Discussion

Isolation of Daphmanidins A (1) and B (2). The leaves of *Daphniphyllum teijsmanii* were extracted with MeOH, and the extract was partitioned between AcOEt and 3% tartaric acid. Water-soluble materials, which were adjusted at pH 10 with sat. Na_2CO_3, were extracted with $CHCl_3$. $CHCl_3$-soluble materials were subjected to an amino silica gel column (hexane/AcOEt, 1:0 → 0:1), in which a fraction eluted with hexane/AcOEt (1:1) was purified by a LH-20 column ($CHCl_3$/MeOH, 1:1) followed by C_{18} HPLC (40% CH_3CN/0.1% TFA) to afford daphmanidins A (**1**, 2.2 mg, 0.0001% yield) and B (**2**, 0.6 mg, 0.00003%) as TFA salts together with a known related alkaloid, macrodaphniphyllidine (**3**).[10]

Structure of Daphmanidin A (1). Daphmanidin A (**1**) showed the pseudomolecular ion peak at *m*/*z* 428 $(M + H)^+$ in the FABMS spectrum, and the molecular formula, $C_{25}H_{33}NO_5$, was established by HRFABMS [*m*/*z* 428.2433, $(M + H)^+$, Δ −0.4 mmu]. IR absorptions implied the presence of hydroxyl (3616 cm^{-1}), ester carbonyl (1730 cm^{-1}), and imine (1675 cm^{-1}) functionalities. Analysis of ^1H and ^{13}C NMR data (Table 1) and the HMQC spectrum of **1** revealed the presence of five sp^2 and three sp^3 quaternary carbons, five sp^3 methines, nine sp^3 methylenes, and three methyl groups. Among them, one sp^3 methylene (δ_C 62.06; δ_H 3.74 and 4.36) and one sp^2 iminium carbon[8,11] (δ_C 202.93) were ascribed to those bearing a nitrogen, while two carbonyl carbons (δ_c 172.56 and 176.08), one sp^3 methine (δ_c 65.32), and one sp^3 methylene (δ_c 66.75) were ascribed to those bearing an oxygen atom.

Four partial structures (**a**−**d**) were deduced from extensive analyses of the 2D NMR data of **1** including the $^1H-^1H$ COSY, HOHAHA, HMQC, and HMBC spectra in CD_3OD (Figure 1). The ^1H and ^{13}C NMR data and HMBC correlations are presented in Table 1. HMBC

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TABLE 1. ^{1}H and ^{13}C NMR Data of Daphmanidin A (1) in CD_3OD at 300 K

	δ_H	δ_C	HMBC (^{1}H)
1		202.93	3a, 13, 18, 19
2		59.51	3, 4a, 7, 18, 19a, 20
3a	2.51 (1H, dt, 7.6, 11.9)	23.97	4, 7, 18
3b	1.68 (1H, brt, 12.3)		
4a	1.80 (1H, brt, 11.8)	29.33	3, 21
4b	1.59 (1H, ddd, 7.4, 11.2, 13.6)		
5		44.70	4, 13b, 21
6	2.09 (1H, m)	48.80	4, 21
7	4.13 (1H, dd, 1.5, 5.9)	65.32	3
8		53.79	4a, 13, 14, 21
9		135.78	11, 13, 14, 17
10		142.95	11, 17
11	2.01 (2H, m)	22.82	
12a	2.29 (1H, m)	25.84	
12b	2.33 (1H, m)		
13a	2.41 (1H, dd, 9.1, 15.7)	39.93	
13b	3.01 (1H, dd, 3.0, 15.7)		
14	3.18 (1H, dt, 3.0, 9.1)	43.41	13, 16b
15	3.59 (1H, m)	55.73	11, 13b, 14, 16b, 17
16a	2.04 (1H, m)	27.82	17b
16b	1.37 (1H, ddd, 9.7, 12.4, 19.3)		
17a	2.69 (1H, m)	44.30	
17b	2.46 (1H, m)		
18	2.48 (1H, m)	36.05	19a, 20
19a	3.74 (1H, brd, 11.8)	62.06	20
19b	4.36 (1H, dd, 7.7, 14.1)		
20	1.19 (3H, d, 7.3)	16.01	18, 19
21	4.35 (2H, brs)	66.75	
22		176.08	13, 14, 23
23	3.68 (3H, s)	52.05	
24		172.56	21, 25
25	2.06 (3H, s)	20.77	

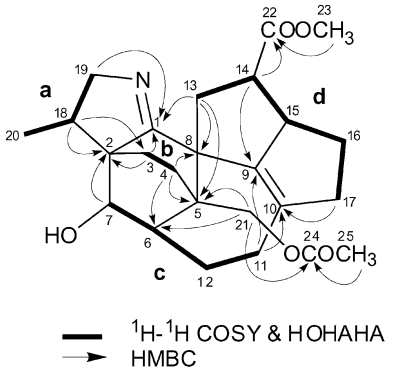

FIGURE 1. Selected 2D NMR correlations for dephmanidin A (**1**).

correlations for H-18 and H_2-3 of C-2 (δ_C 59.51) and H-18 of C-3 (δ_C 56.78) gave rise to the connectivity between C-3 and C-18 through C-2. HMBC correlations for H_2-19 and H-3a to C-1 (δ_C 202.93) showed the presence of a dihydropyrrole ring (C-1, C-2, C-18, C-19, and N-1). Connectivities between C-7 and C-2, and between C-4 and C-6 through C-5, were elucidated by HMBC cross-peaks for H-7 (δ_H 4.13) to C-2, H_2-4 to C-5 (δ_C 44.70), and C-6 (δ_C 48.80). Connectivities among C-1, C-5, and C-13 through C-8 were provided by HMBC correlations for H_2-13 to C-1, C-5, and C-8 (δ_C 53.79), and H-4a to C-8. Connectivities among C-8, C-11, C-15, and C-17 through a tetrasubstituted olefin (C-9 and C-10) were implied by long-rang correlations for H_2-11 and H-14 to C-9 (δ_C 135.78), and H_2-11 and H_2-17 to C-10 (δ_C 142.95). HMBC cross-peaks for H_2-21 and H_3-25 to C-24 (δ_C 172.56)

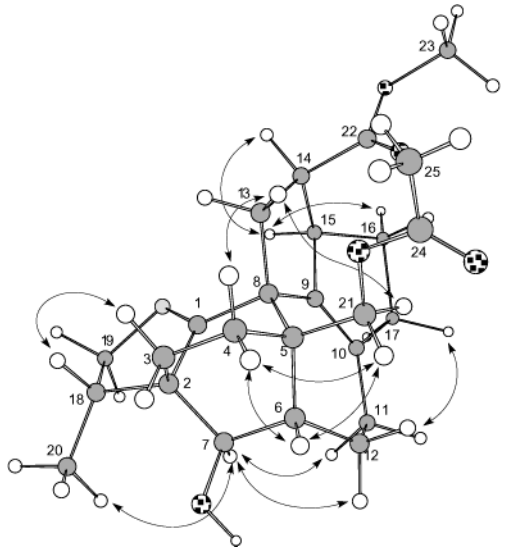

FIGURE 2. Key NOESY correlations (arrows) and relative stereochemistry for daphmanidin A (**1**).

indicated that an acetoxy group was attached to C-21, which was connected to C-5 by those for H_2-21 to C-5 and C-6. The presence of a methoxy carbonyl group at C-14 was deduced from HMBC correlations for H-14 and H_3-23 to C-22 (δ_C 176.08). Thus, the gross structure of daphmanidin A was elucidated to be **1** possessing a fused-hexacyclic ring system consisting of a dihydropyrrole ring (N-1, C-1, C-2, C-18, and C-19) with a methyl group at C-18, a bicyclo[2.2.2]octane ring (C-1 to C-8) with a hydroxyl at C-7, and a decahydrocyclopenta[*cd*]azulene ring (C-5, C-6, C-8 to C-17) with a methoxy carbonyl group at C-14 and an acetoxy methyl group at C-5.

Stereochemistry of Daphmanidin A (1). The relative stereochemistry of **1** was elucidated by NOESY correlations as depicted in the computer-generated 3D drawing (Figure 2).[12] The absolute stereochemistry of daphmanidin A (**1**) was elucidated by applying a modified Mosher method.[13] To determine the absolute configuration at C-7, **1** was converted into its (*S*)- and (*R*)-2-methoxy-2-trifluoromethylphenylacetic acid (MTPA) esters (**4a** and **4b**, respectively). $\Delta\delta$ values ($\delta_S - \delta_R$) of H-4, H-6, H_2-12, and H_3-25 showed positive values, while those of H-18, H_2-19, and H_3-20 were negative (Figure 3), suggesting that C-7 possessed *R*-configuration.

Structure and Stereochemistry of Daphmanidin B (2). Daphmanidin B (**2**) showed the pseudomolecular ion peak at *m*/*z* 446 $(M + H)^+$ in the FABMS spectrum, and the molecular formula, $C_{25}H_{36}NO_6$, was established by HRFABMS [*m*/*z* 446.2537, $(M + H)^+$, Δ −0.6 mmu]. IR absorptions implied the presence of hydroxyl (3600 cm^{-1}), ester carbonyl (1738 cm^{-1}), and amide (1670 cm^{-1}) functionalities. The ^{1}H and ^{13}C NMR (Table 2) spectra of **2** showed signals due to five sp^2 and two sp^3 quaternary carbons, five sp^3 methines, 10 sp^3 methylenes, and three methyl groups. Among them, two sp^3 methylenes (δ_C

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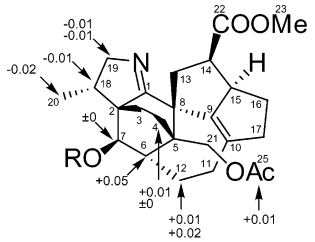

FIGURE 3. $\Delta\delta$ values [$\Delta\delta$ (in ppm) = $\delta S - \delta R$] obtained for (*S*)- and (*R*)-MTPA esters (**4a** and **4b**, respectively) of daphmanidin A (**1**).

TABLE 2. ^{1}H and ^{13}C NMR Data of Daphmanidin B (2) in CD_3OD at 300 K

	δ_H	δ_C	HMBC (^{1}H)
1		175.69	7b, 13, 19
2	3.52 (1H, m)	74.15	3, 4, 19a, 20
3a	1.73 (1H, m)	37.81	4
3b	1.90 (1H, m)		
4a	1.73 (1H, m)	37.66	3, 21
4b	1.90 (1H, m)		
5		37.66	12, 21
6	2.68 (1H, m)	38.35	4, 11b, 21
7a	3.76 (1H, dd, 7.8, 14.2)	51.46	12a, 19
7b	3.54 (1H, dd, 11.0, 14.2)		
8		45.27	6, 13b
9		139.45	11, 13, 16
10		135.95	11, 12, 16
11a	2.36 (1H, m)	25.14	6, 12a
11b	2.29 (1H, m)		
12a	2.17 (1H, m)	25.70	7a
12b	1.74 (1H, m)		
13a	2.70 (1H, dd, 8.9, 13.3)	36.17	
13b	2.34 (1H, m)		
14	3.16 (1H, m)	43.53	
15	3.35 (1H, m)	54.63	13b, 14, 16b
16a	1.88 (1H, m)	29.04	11b
16b	1.24 (1H, m)		
17a	2.30 (1H, m)	43.08	11a
17b	2.51 (1H, m)		
18	2.21 (1H, m)	37.93	3, 19a, 20
19a	4.22 (1H, dd, 6.8, 14.0)	54.77	2, 7b, 20
19b	2.44 (1H, dd, 9.8, 14.0)		
20	0.95 (3H, d, 6.8)	17.42	19b
21a	4.28 (1H, d, 11.3)	71.36	
21b	4.37 (1H, d, 11.3)		
22		177.04	13, 14, 23
23	3.65 (3H, s)	51.81	
24		172.87	25
25	2.08 (3H, s)	20.83	

51.46, δ_H 3.76 and 3.54; δ_C 54.77; δ_H 2.44 and 4.22) and one carbonyl carbon (δ_C 175.69) were ascribed to those bearing a nitrogen, while two carbonyl carbons (δ_c 172.87 and 177.04), one sp^3 methine (δ_c 74.15), and one sp^3 methylene (δ_c 71.36) were ascribed to those bearing an oxygen atom. The structure of **2** was elucidated by 2D NMR (^{1}H−^{1}H COSY, HOHAHA, HMQC, and HMBC) data. The^{1}H−^{1}H COSY and HOHAHA spectra revealed connectivities of three units **a** (C-2 to C-4, C-18 to C-2, C-19, and C-20), **b** (C-6 to C-7 and C-12, C-11 to C-12), and **c** (C-13 to C-17) (Figure 4). These three units were connected to one another on the basis of HMBC correlations as shown in Figure 4. The presence of an amide carbonyl at C-1 was revealed by HMBC correlations of H-7b, H_2-13, and H_2-19 to C-1. Thus, the structure of daphmanidin B was elucidated to be **2**, possessing a 1-azabicyclo[5.2.2]undecane moiety like daphnezomines F and G.[6]

The relative stereochemistry of **2** was deduced from NOESY correlations (Figure 4). Conformation of the unit **a** (C-2 ∼ C-5, C-18 to C-2, C-19, and N) in the 1-azabicyclo-[5.2.2]undecane moiety[6] taking a twist chair form as shown in Figure 4 was consistent with the results of conformational search using MMFF force field[14] implemented in Macromodel program.[12]

Plausible Biogenesis of Daphmanidins A (1) and B (2). A plausible biogenetic pathway for daphmanidins A (**1**) and B (**2**) is proposed as shown in Scheme 1. Daphmanidin A (**1**) might be generated from a common imine intermediate **A**, which has been proposed as a precursor of the secodaphniphylline-type skeleton (**B**) by Heathcock et al.[4] Cleavage of the C-7−C-10 bond in **B** will give an intermediate with yuzurimine-type skeleton such as macrodaphniphyllidine (**3**), while subsequent cleavage of the N-1−C-7 bond followed by formation of the C-7−C-2 bond will afford daphmanidin A (**1**). On the other hand, daphmanidin B (**2**) might be derived from the imine intermediate **A** through formation of the N-1−C-19 bond.

Cytotoxicity of Daphmanidins A (1) and B (2). Daphmanidins A (**1**) and B (**2**) exhibited cytotoxicity against murine lymphoma L1210 cells (IC_{50} 8.0 and 7.6 μg/mL, respectively) in vitro.

Experimental Section

General Procedures. ^{1}H and ^{13}C NMR spectra were recorded on a 600 MHz spectrometer equipped with an X32 computer and a 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 FID's of 2K data points and 32 scans each were employed. Chemical shifts were measured using residual CD_3OD (δ_H 3.31 and δ_C 49.00) as an internal standard. 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 leaves of *Daphniphyllum teijsmanni* (Daphniphyllaceae) were collected in Hiroshima in 2000. The botanical identification was made by Dr. S. Mukai, Miyajima Natural Botanical Garden, Hiroshima University. Voucher specimens have been deposited in the herbarium of Hokkaido University.

Isolation. The leaves of *D. teijsmanni* (2 kg) were crushed and extracted with MeOH (20 L × 2). The MeOH extract (273 g) was treated with 3% tartaric acid (pH 2) and then partitioned with AcOEt. The aqueous layer was treated with sat. Na_2CO_3 aq to pH 10 and extracted with $CHCl_3$ to give a crude alkaloidal fraction (1.9 g). This fraction was subjected to an amino silica gel column chromatography (NH-DM1020, 100μm, Fuji Silysia Chemical Ltd.; hexane/AcOEt, 1:0 → 0:1), in which a fraction eluted with hexane/AcOEt (1:1) was purified by a LH-20 column ($CHCl_3$/MeOH, 1:1) followed by C_{18} HPLC (Mightysil RP-18, 5 μm, Kanto Chemical Co., Inc., 10 × 250 mm; eluent, 40% CH_3CN/0.1% TFA; flow rate, 2 mL/min; UV detection at 205 nm) to afford daphmanidins A (**1**, 2.2 mg, 0.0001% yield) and B (**2**, 0.6 mg, 0.00003% yield), and macrodaphniphyllidine (**3**, 0.8 mg, 0.00004%).

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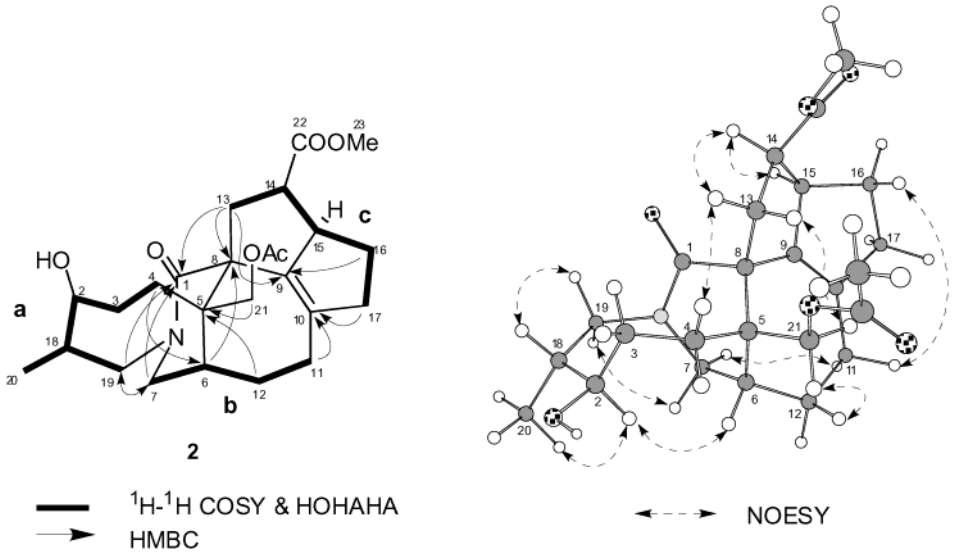
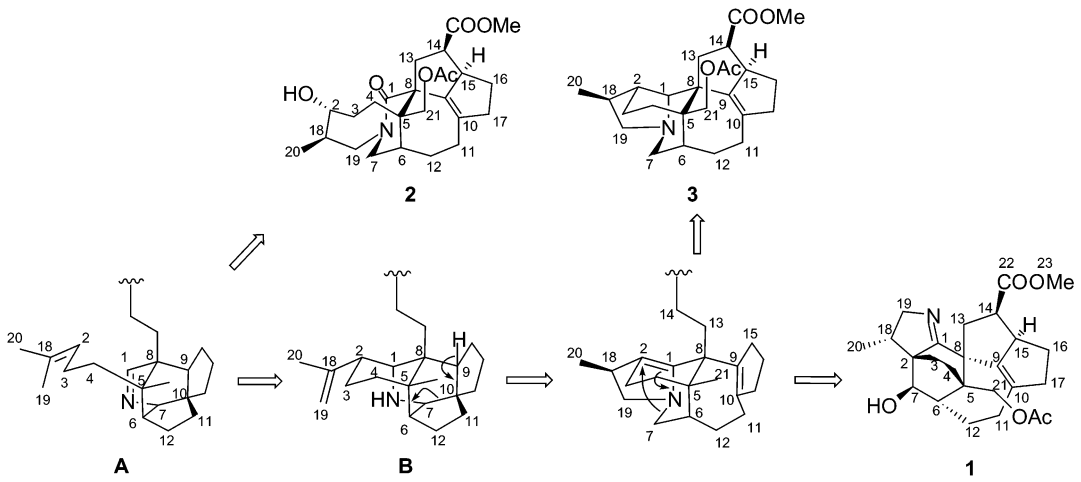


FIGURE 4. Selected 2D NMR correlations and relative stereochemistry for daphmanidin B (**2**).

SCHEME 1



Daphmanidin A (1): colorless solid; $[\alpha]_D$ −62° (*c* 0.5, MeOH); IR (neat) ν_{max} 3616, 3370, 2930, 1730, 1675, and 1190 cm^{-1}; UV (MeOH) λmax 283 nm (ϵ 2200); ^{1}H and ^{13}C NMR data (Table 1); FABMS *m*/*z* 428 (M + H)$^+$; HRFABMS *m*/*z* 428.2433 (M + H; calcd for $C_{25}H_{34}NO_5$, 428.2437).

Daphmanidin B (2): colorless solid; $[\alpha]_D$ −15° (*c* 0.2, MeOH); IR (neat) ν_{max} 3600, 3385, 2930, 1738, 1670, and 1240 cm^{-1}; ^{1}H and ^{13}C NMR data (Table 2); FABMS *m*/*z* 446 (M + H)$^+$; HRFABMS *m*/*z* 446.2537 (M + H; calcd for $C_{25}H_{36}NO_6$, 446.2543).

***(S)*-MTPA Ester (4a) of Daphmanidin A (1).** To a solution of **1** (0.2 mg) in pyridine (100 μL) were added (*R*)-(−)-MTPACl (0.8 μL) and *N*,*N*-(dimethylamino)pyridine (100 μg). The mixture was allowed to stand at 50 °C for 12 h. After addition of *N*,*N*-(dimethylamino)-1,3-propandiamine (5 μL) and evaporation of solvent, the residue was passed through a silica gel column ($CHCl_3$−MeOH, 50:1) to afford the (*S*)-MTPA ester (**4a**, 0.2 mg) of **1**. **4a**: colorless oil; ^{1}H NMR ($CDCl_3$) δ 1.57 and 1.69 (m, H-4), 2.09 (m, H-6), 5.52 (d, 4.4, H-7), 2.24 and 2.56 (m, H-12), 2.14 (m, H-18), 3.67 (m, H-19), 4.24 (dd, 7.6, 14.5, H-19), 0.82 (d, 7.1, H-20), 4.34 and 4.38 (d, 11.9, H-21), 3.65 (s, H-23), and 2.06 (s, H-25). FABMS *m*/*z* 644 (M + H)$^+$; HRFABMS *m*/*z* 644.2846 (M + H; calcd for $C_{35}H_{41}NO_7F_3$, 644.2835).

***(R)*-MTPA Ester (4b) of Daphmanidin A (1).** Daphmanidin A (**1**, 0.2 mg) was treated with The (*S*)-(+)-MTPACl (0.8 mL) by the same procedure as described above to afford the (*R*)-MTPA ester (**4b**, 0.2 mg) of **1**. **4b**: colorless oil; ^{1}H NMR ($CDCl_3$) δ 1.57 and 1.68 (m, H-4), 2.04 (m, H-6), 5.52 (br d, 4.0, H-7), 2.23 and 2.54 (m, H-12), 2.15 (m, H-18), 3.68 and 4.25 (m, H-19), 0.84 (br d, H-20), 4.38 (br s, H-21), 3.65 (s, H-23), and 2.05 (s, H-25). FABMS *m*/*z* 644 (M + H)$^+$; HRFABMS *m*/*z* 644.2847 (M + H; calcd for $C_{35}H_{41}NO_7F_3$, 644.2835).

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

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