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Daphnioldhanins A–C, Alkaloids from *Daphniphyllum oldhami*

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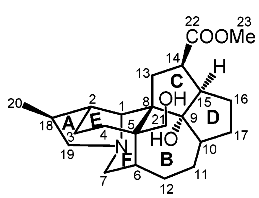
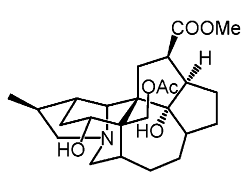
Three new *Daphniphyllum* alkaloids, daphnioldhanins A–C (**1**–**3**), along with four known ones, were isolated from the aerial parts of saplings of *Daphniphyllum oldhami*. The structures of these alkaloids were established by spectroscopic methods. The relative configuration of **1** was further confirmed by a single-crystal X-ray diffraction analysis. In addition, the ^{1}H and ^{13}C NMR data of the free base of daphmanidin A (**4**) were compared with its hydrochloric salt form.

The skeletal types of *Daphniphyllum* alkaloids from the *Daphniphyllum* genus are structurally diverse and fascinating.[1,2] In recent years, more than 60 new *Daphniphyllum* alkaloids were reported.[2–5,11] These alkaloids with unique complex polycyclic systems led to much focus on their total synthesis, biosynthetic pathway, and bioactivity.[6,7]

We previously reported some novel alkaloids such as calycinine A[8] and calycilactone A[9] from *Daphniphyllum calycinum*. In our continuing search for new alkaloids, three new *Daphniphyllum* alkaloids (**1**–**3**) with six saturated fused rings, as well as deoxycalyciphylline B,[4f] deoxyisocalyciphylline B,[4f] daphmanidin A (**4**),[4g] and zwitterionic alkaloid,[10] were isolated from the saplings of *Daphniphyllum oldhami*. Daphnioldhanins A and B (**1**, **2**) possessed the new yuzurimine-type skeleton with a hydroxyl group at C-9, and daphnioldhanin A (**1**) was also the first compound with a similar skeleton analyzed with single-crystal X-ray diffraction. This paper describes the isolation and structural elucidation of **1**–**3**.



1



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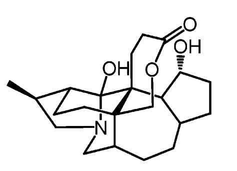

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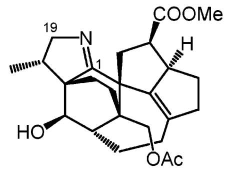

4 (**daphmanidin A**)

Results and Discussion

The molecular formula of compound **1** was established as $C_{23}H_{35}NO_4$ by positive HRESIMS (m/z 390.2637, $[M + H]^+$, calcd 390.2644), indicating the presence of seven degrees of unsaturation. IR absorption bands at 3417 and 1732 cm^{-1} implied that **1** possessed a hydroxyl and ester carbonyl. The ^{1}H and ^{13}C NMR data (Table 1) and the HSQC spectrum of **1** revealed the presence of 23 carbon signals, comprising four quaternary carbons, seven methines, 10 methylenes, and two methyl groups. An ester carbonyl (δ_C 174.9, C=O) accounted for one degree of unsaturation, which suggested that **1** possessed six rings. Two methylenes (δ_C 56.2, δ_H 3.85 and 3.12; δ_C 64.0, δ_H 4.10 and 2.63) and one methine (δ_C 69.6, δ_H 4.07) were typical of nitrogen-bearing groups, similar to those in the alkaloid yuzurimine B.[11]

Comparison of the NMR data of **1** with those of yuzurimine B showed close similarities, except for the following observation: one sp^3 methine (δ_C 46.4, δ_H 2.23) and one strongly deshielded sp^3 quaternary carbon (δ_C 93.2) bearing one hydroxyl group for **1** were displayed by the olefin carbons of yuzurimine B,[11] implying that they likely shared the same planar structural moiety at rings **A**, **E**, and **F**. The hydroxyl group was assigned to C-9 at δ_C 93.2 on the basis of the HMBC correlations of H-10, H-15, H-16, and H-17 to C-9. The gross structure of **1** was finally established from its 2D NMR spectra (HSQC, ^{1}H–^{1}H COSY, and HMBC) as shown in Figure 1. Three partial structures, **a** (C-2 to C-1 and C-18, C-1 to C-4, 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-13 to C-17), were revealed by the ^{1}H–^{1}H COSY spectrum. By analysis of the HMBC spectrum (Figure 1), the linkage of the three structural fragments **a**–**c** could be established via the nitrogen atom and three quaternary carbons (C-5, C-8, and C-9), and C-10.

The relative configuration of **1** was consistent with that of yuzurimine B,[1c,11] as deduced from ROESY spectroscopy (Figure 1), except that the hydroxyl at C-9 was not confirmed, which could be ultimately determined by a single-crystal X-ray diffraction in Figure 2. The crystal structure showed the hydroxyl at C-9 to be α-oriented, the three five-membered rings **A**, **C**, and **D** to adopt envelope conformations, the two six-membered rings **E** and **F** to be in chair conformations, and the seven-membered ring **B** to be in a twist-boat conformation. The relative configuration proposed by the ROESY spectrum was consistent with that established by the single-crystal X-ray diffraction.

Daphnioldhanin B (**2**) was established to have a molecular formula of $C_{25}H_{37}NO_5$ on the basis of positive HRESIMS (m/z 432.2740 $[M + H]^+$, calcd 432.2749). The IR spectrum suggested the presence of hydroxyl (3438 cm^{-1}) and ester carbonyl (1736 cm^{-1}) groups. ^{1}H and ^{13}C NMR data of **2** (Table 1) and the HMQC spectrum provided evidence that **2** possessed 25 carbons signals, including five quaternary carbons, nine methylenes, eight methines,

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Table 1. ^{1}H (400 Hz $CDCl_3$) and ^{13}C (100 Hz) NMR Data of Daphnioldhanins A−C (**1**−**3**)

no.	**1**[a] δ_H multi, J (Hz)	**1**[a] δ_C	**2**[b] δ_H multi, J (Hz)	**2**[b] δ_C	**3**[b] δ_H multi, J (Hz)	**3**[b] δ_C
1	4.07 (m)	69.6	3.96 (m)	55.8		101.9
2	2.26 (m)	38.6	2.35 (dd, 9.6, 14.4)	38.6	2.57 (m)	39.6
3a	1.71 (m)	18.3	1.73 (m)	18.4	1.72 (m)	20.7
3b	1.39 (m)				1.75 (m)	
4a	2.04 (m)	35.6	4.22 (brs)	68.9	1.97 (m)	33.3
4b	1.62 (m)					
5		39.5		38.7		42.0
6	2.36 (m)	38.8	2.45 (m)	39.0	2.26 (m)	38.4
7a	3.85 (m)	56.2	3.11 (m)	56.2	3.21 (m)	57.5
7b	3.12 (m)		4.08 (m)		3.01 (d, 13.6)	
8		48.9		48.7		43.8
9		93.2		93.2	3.26 (m)	64.1
10	2.23 (m)	46.4	2.21 (m)	46.8	2.59 (m)	49.9
11a	1.86 (m)	28.5	1.27 (m)	29.0	1.74 (m)	31.2
11b	1.37 (m)		1.47 (m)			
12a	1.98 (m)	21.0	1.47 (m)	21.0	1.45 (m)	33.0
12b	1.44 (m)					
13a	2.35 (m)	34.2	2.05 (m)	34.8	2.25 (m)	29.3
13b	1.92 (m)		2.32 (m)		2.11 (m)	
14	3.08 (m)	41.7	3.10 (m)	41.6	2.59 (m)	28.4
					2.43 (m)	
15	2.77 (dd, 19.5, 9.2)	55.8	2.83 (dd, 9.2, 18.8)	55.8	4.25 (br)	80.5
16a	1.44 (m)	26.8	1.31 (m)	26.8	2.33 (m)	31.9
16b	1.76 (m)		1.81 (m)			
17a	1.60 (m)	32.2	1.65 (m)	32.4	1.63 (m)	31.6
17b	1.48 (m)					
18	2.52 (m)	36.0	1.67 (m)	36.2	2.42 (m)	36.2
19a	4.10 (m)	64.0	2.68 (brs)	64.2	2.31 (m)	63.2
19b	2.63 (m)		4.22 (brs)		3.26 (m)	
20	1.01 (d, 6.71)	12.3	1.05 (d, 6.0)	12.6	1.14 (d, 7.1)	16.2
21a	4.02 (m)	66.5	4.28 (d, 11.2)	69.2	4.27 (d, 11.2)	65.7
21b	3.84 (m)		4.66 (d, 11.2)		3.81 (d, 11.2)	
22		174.9		173.8		174.4
23	3.60 (s, 3H)	51.6	3.68 (s, 3H)	51.6		
24				170.9		
25			2.09 (s, 3H)	20.9		

[a] Measured in $CDCl_3$−CD_3OD (10:1). [b] Measured in $CDCl_3$.

one methyl, and two *O*-methyls. The 1D NMR data of **2** were similar to those of **1**, suggesting that the two alkaloids share the same basic skeleton. Detailed analysis of the 2D NMR data, including the HMQC, ^{1}H−^{1}H COSY, and HMBC spectra (Figure 3), confirmed the above deduction. Compared with compound **1**, the main differences were the presence of a C-4 hydroxyl group (δ_C 68.9; δ_H 4.22) and a C-21 *O*-acetyl group (δ_C 69.2; δ_H 4.28 and 4.66) in **2**. The locations of the hydroxyl and acetoxyl groups were determined by the HMBC cross-peaks from H-2 and H-3 to C-4, H-4 and H-6 to C-21, and H_2-21 to C-24 (δ_C 170.9), respectively. The planar structure of daphnioldhanin B (**2**) was determined to be 4-hydroxy-21-*O*-acetyldaphnioldhanin A (**1**).

The relative configuration of **2** was elucidated to be the same as that of daphnioldhanin A (**1**), as judged from the ROESY spectrum in Figure 3. The ROESY cross-peak for H-4/H-13b suggested that H-4 was in an α-orientation.

Daphnioldhanin C (**3**) had a molecular formula of $C_{22}H_{34}NO_4$ by positive HRESIMS (m/z 376.2489 $[M + H]^+$, calcd 376.2487). IR absorptions were indicative of the presence of hydroxyl (3438 cm^{-1}) and ester carbonyl (1736 cm^{-1}) groups. The ^{13}C NMR spectroscopic data (Table 1) indicated the presence of one methyl, 11 methylenes, and four quaternary carbons. 1D and 2D NMR spectra (HMQC, ^{1}H−^{1}H COSY, and HMBC) (Figure 4) suggested that the structure of **3** was closely related to the known alkaloid daphnilactone B.[2l,12] By comparing with daphnilactone B, the major differences were the loss of the olefin carbons of daphnilactone B instead of one sp^3 methine and one deshielded sp^3 quaternary carbon (δ_C 93.2) bearing a hydroxyl group and the presence of one hydroxyl group for **3**. In the HMBC spectrum, the correlations of H-16 and H-17 to C-15, and H-2 and H-3 to C-1, indicated the locations of one hydroxyl at C-15 (δ_C 80.5) and one at C-1 (δ_C 101.9). The presence of a seven-membered lactone ring as in daphnilactone B was revealed by the HMBC correlations of H_2-14 to C-22 (δ_C 174.4), H_2-13 to C-8 (δ_C 43.8), and H_2-21 to C-8 and C-22. The connectivities between C-10 and C-15 via C-9, and between C-21 and C-4 via C-5, were implied by the HMBC cross-peaks for H-10 to C-9, H-15 to C-10, and H_2-21 to C-4. Connectivities between C-1, C-7, and C-19 through N-1 were indicated by the correlation of H_2-19 to C-7 and C-1. Finally, the connectivities of the **a**, **b**, **c**, and **d** units as inferred from ^{1}H−^{1}H COSY were confirmed by the HMBC cross-peaks of H_2-13 to C-1, C-5, C-8, C-9, and H_2-11, H_2-16, H_2-17 to C-9 and C-10.

As shown in Figure 4, the relative configuration of daphnioldhanin C (**3**) was identical to that of daphnilactone B[2l,12] on the basis of ROESY data of **3**. Two chair conformations for the cyclohexane ring (C-1−C-5 and C-8) and the piperidine ring (N-1, C-1, C-8, and C-5−C-7) were suggested by ROESY correlations of H-3b/H-7, H-4a/H-13a, and H-2/H-13b. The ROESY cross-peaks for H_3-20/H-19a, H-19a/H-7a, H-7a/H-6, H-6/H-12a, H-12a/H-21a, H-21a/H-9, H-9/H-10, and H-9/H-15 indicated that H_3-20, H-19a, H-21a, H-10, H-9, and H-15 were β-oriented.

Analysis of the 1D NMR data (Table 2), 2D NMR spectra (HSQC, ^{1}H−^{1}H COSY, HMBC, and ROESY), IR, and positive HRESIMS spectra of **4** revealed that compound **4** had the same structure as daphmanidin A.[4g] The ^{13}C NMR shift (δ_C 188.5, C-1) of **4** isolated by us implied that **4** was the free base of daphmanidin A.[4g] By adding 0.05 mL of 3% HCl into **4** in CD_3OD, almost the same NMR data as those of the TFA salt of daphmanidin A[4g] were obtained. The ^{1}H and ^{13}C NMR data of the free base of daphmanidin A are shown in Table 2.

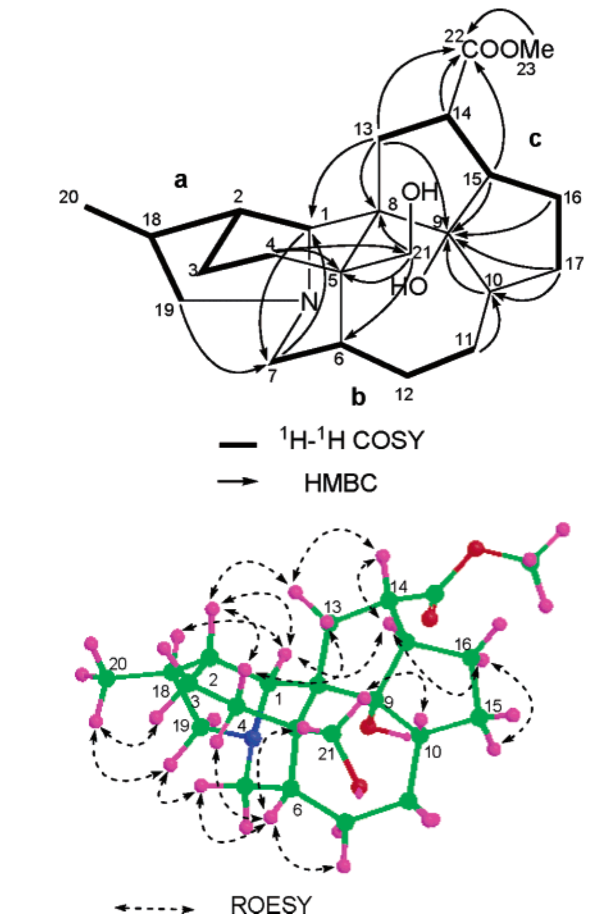

Figure 1. Selected 2D NMR correlations for daphnioldhanin A (**1**).

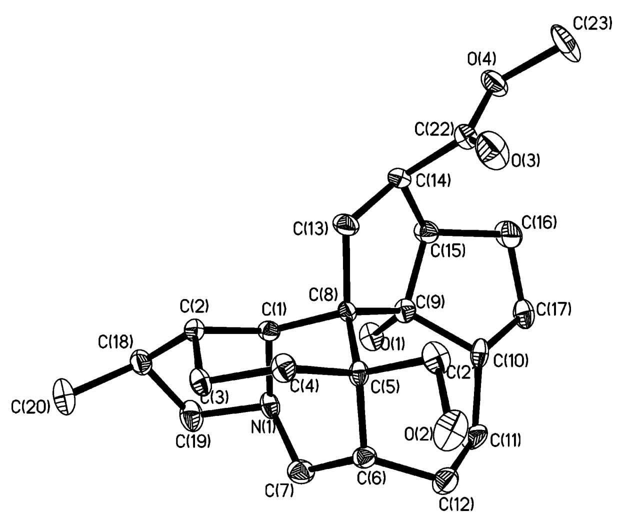

Figure 2. Single-crystal X-ray structure of daphnioldhanin A (**1**).

Experimental Section

General Experimental Procedures. Melting points were obtained on an X-4 apparatus and are uncorrected. Optical rotations were measured on a Horiba SEPA-300 high sensitive polarimeter or JASCO DIP-370 digital polarimeter. IR spectra were recorded on a Bio-Rad FTS-135 spectrometer with KBr pellets. NMR spectra were obtained on a Bruker AM-400 or DPX-500 NMR spectrometer with TMS as internal standard. ESIMS were measured on a Waters 2695 HPLC-Thermo Finnigan LCQ Advantage ion trap mass spectrometer. HRESIMS was measured by VG Auto Spec 3000 spectrometer. Column chromatography was carried out on silica gel (200−300 mesh; Qingdao Marine Chemical Factory, Qingdao, People's Republic of China), silica gel H (10−40 μm; Qingdao), and Sephadex LH-20 (40−70 μm; Amersham Pharmacia Biotech AB, Uppsala, Sweden). Preparative TLC plates (1.0−1.5 mm; Qingdao) and TLC plates (0.20−0.25 mm; Qingdao) were performed with glass precoated silica gel GF_{254}. Solvents used for extraction and isolation were distilled prior to use.

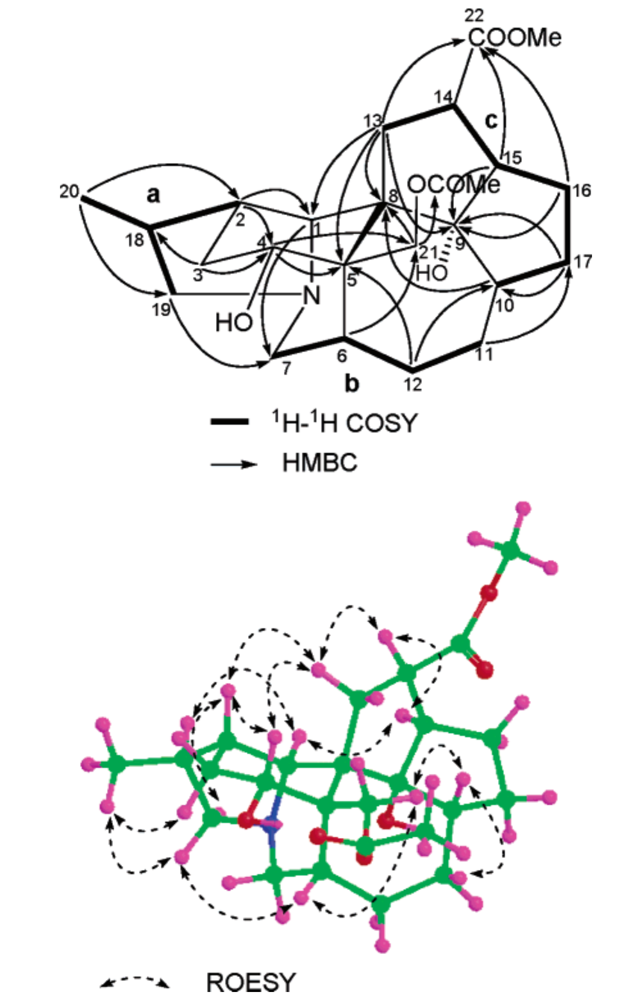

Figure 3. Selected 2D NMR correlations for daphnioldhanin B (**2**).

Plant Material. *D. oldhami* was collected from Jinping County of Guizhou Province, People's Republic of China, in March 2005, and identified by Prof. Xun Chen of Guizhou Academy of Sciences. A voucher specimen (GY 05032601) was deposited in the Herbarium of the Key Laboratory of Chemistry for Natural Product of Guizhou Province and Chinese Academy of Sciences.

Extraction and Isolation. The powdered aerial parts of fresh saplings (100.0 kg) of *D. oldhami* were percolated three times with 75% EtOH to give a crude extract. The extract was concentrated to dryness under reduced pressure, followed by partitioning between EtOAc and 3% tartaric acid. The aqueous phase was adjusted to pH 9 with saturated Na_2CO_3 and extracted with $CHCl_3$ to give crude alkaloids (100.0 g). The crude alkaloids were subjected to a silica gel column eluted with $CHCl_3$−MeOH (1:0 to 0:1) to obtain five major fractions (F_1−F_5). Fraction F_4, eluted with $CHCl_3$−MeOH (50:1), was separated and purified by repeated column chromatography on silica gel with $CHCl_3$−MeOH (60:1) and petroleum ether−Et_2NH (20:1 to 4:1), followed by Sephadex LH-20 column chromatography eluted with $CHCl_3$−MeOH (1:1) to afford daphnioldhanin A (**1**, 8 mg), daphnioldhanin B (**2**, 15 mg), deoxycalyciphylline B (30 mg), and deoxyisocalyciphylline B (25 mg). Fraction F_3 was subjected to repeated column chromatography over silica gel H with petroleum ether−acetone−Et_2NH (15:3:1 to 15:5:1), followed by preparative TLC with petroleum ether−Et_2NH (20:1) to give daphnioldhanin C (**3**, 8 mg) and daphmanidin A (**4**, 8 mg) and recrystallization from MeOH−H_2O (10:1) to obtain zwitterionic alkaloid (25 mg).

Table 2. ^{1}H (500 Hz) and ^{13}C (125 Hz) Data of Daphmanidin A (**4**)

	daphmanidin A[a]		daphmanidin A[b]		daphmanidin A[c]	
no.	δ_H mult, *J* (Hz)	δ_C	δ_H mult, *J* (Hz)	δ_C	δ_H mult, *J* (Hz)	δ_C
1		202.9		203.0		188.5
2		59.5		59.5		58.5
3a	2.51 (dt, 7.6, 11.9)	24.0	2.50 (dt, 7.5, 12.0)	23.9	2.14 (m)	23.7
3b	1.68 (brt, 12.3)		1.67 (brt, 12.4)		1.30 (m)	
4a	1.80 (brt, 11.8)	29.3	1.76 (brt, 12.2)	29.2	1.62 (brt, 11.4)	29.8
4b	1.59 (ddd, 7.4, 11.2, 13.6)		1.56 (ddd, 7.3, 11.0, 13.8)		1.44 (m)	
5		44.7		44.7		44.0
6	2.09 (m)	48.8	2.08 (m)	48.8	2.10 (m)	48.7
7	4.13 (dd, 1.5, 5.9)	65.3	4.12 (brd, 6.1)	65.3	4.02 (brd, 6.0)	67.5
8		53.7		53.7		53.0
9		135.8		135.5		135.2
10		143.0		143.2		141.5
11	2.01 (m)	22.8	2.00 (m)	22.7	1.98 (m)	23.3
12a	2.29 (m)	25.8	2.27 (m)	25.8	2.18 (m)	26.0
12b	2.33 (m)		2.32 (m)		2.24 (m)	
13a	2.41 (dd, 9.1, 15.7)	39.3	2.44 (m)	39.9	2.37 (m)	39.8
13b	3.01 (dd, 3.0, 15.7)		3.00(dd, 3.0, 15.7)		2.63(dd, 4.1, 14.1)	
14	3.18 (dt, 3.0, 9.1)	43.4	3.24 (dt, 3.0, 9.1)	43.4	3.12 (dt, 4.1, 9.2)	43.7
15	3.59 (m)	55.7	3.59 (m)	55.7	3.55 (m)	55.8
16a	2.04 (m)	27.8	2.01 (m)	27.7	1.73 (m)	28.2
16b	1.37 (m)		1.35 (m)		1.23 (m)	
17a	2.69 (m)	44.3	2.64 (m)	44.3	2.55 (m)	43.9
17b	2.46 (m)		2.44 (m)		2.38 (m)	
18	2.52 (m)	36.1	2.49 (m)	35.8	2.07 (m)	38.2
19a	3.74 (brd, 11.8)	62.1	3.73 (brd, 11.8)	61.9	3.97 (dd, 7.0, 15.2)	68.3
19b					3.42 (dd, 1.1, 15.2)	
20	1.19 (d, 7.3, 3H)	16.0	1.14 (d, 7.2, 3H)	16.0	1.00 (d, 7.2, 3H)	16.7
21a	4.35 (brs)	66.8	4.35 (brs)	66.8	4.32 (d, 14.6)	67.7
21b					4.24 (d, 14.6)	
22		176.1		176.3		177.2
23	3.68 (s, 3H)	52.1	3.66 (s, 3H)	52.1	3.63 (s, 3H)	51.8
24		172.6		172.9		172.9
25	2.06 (s, 3H)	20.8	2.08 (s, 3H)	20.8	2.04 (s, 3H)	20.9

[a] TFA salt of daphmanidin A was measured in CD_3OD.[4g] [b] **4** was measured in mixed solvent (CD_3OD and 0.05 mL of 3% HCl/3 mL). [c] **4** was measured in CD_3OD.

Daphnioldhanin A (1): colorless, lumpish crystals (petroleum ether−Et_2NH, 20:1); mp 118 °C; $[\alpha]^{18}_D$ −30.2 (*c* 1.07, $CHCl_3$); IR (KBr) ν_{max} 3417, 2954, 1732, and 1630 cm^{-1}; ^{1}H and ^{13}C NMR, see Table 1; ESIMS (positive) *m/z* 390 [M + H]$^+$; HRESIMS (positive) *m/z* 390.2637 [M + H]$^+$ (calcd for $C_{23}H_{36}NO_4$, 390.2644).

Daphnioldhanin B (2): colorless needles (petroleum ether−$CHCl_3$, 20:1); mp 204 °C; $[\alpha]^{17}_D$ −39.1 (*c* 0.57, $CHCl_3$); IR (KBr) ν_{max} 3438, 2928, 1736, and 1620 cm^{-1}; ^{1}H and ^{13}C NMR, see Table 1; ESIMS (positive) *m/z* 432 [M + H]$^+$; HRESIMS (positive) *m/z* 432.2740 [M + H]$^+$ (calcd for $C_{25}H_{38}NO_5$, 432.2749).

Daphnioldhanin C (3): colorless, amorphous solid; $[\alpha]^{14}_D$ −20.3 (*c* 0.85, $CHCl_3$); IR (KBr) ν_{max} 3425, 2926, 1744, and 1631 cm^{-1}; ^{1}H and ^{13}C NMR, see Table 1; ESIMS (positive) *m/z* 376 [M + H]$^+$; HRESIMS (positive) *m/z* 376.2489 [M + H]$^+$ (calcd for $C_{22}H_{34}NO_4$, 376.2487).

X-ray Diffraction of 1.[13] Crystal data: $C_{23}H_{35}NO_4$, MW = 389.52, orthorhombic system, space group $P2_12_12_1$, crystal cell parameters: a = 7.913(2) Å, b = 9.484(2) Å, c = 26.271(2) Å, V = 1971.6(7) Å^3, Z = 4, d = 1.312 g/cm^3. A colorless, lumpish crystal of dimensions 0.20 × 0.40 × 0.50 mm was used for X-ray measurements on a MAC DIP-2030K diffractometer with graphite-monochromated Mo Kα radiation; the $2\theta_{max}$ value was set at 50.0°. The total number of independent reflections measured was 2260, of which 2250 were considered to be observed ($|F|^2 \geq 2\sigma|F|^2$). The crystal structure of **1** was solved by the direct method SHELXS-97[14] and expanded using difference Fourier techniques, refined by the program and method NOMCSDP[15] and full-matrix least-squares calculations. H atoms were fixed at calculated positions. The final indices were R_1 = 0.0749, wR_2 = 0.1806, S = 1.390, $(\Delta/\sigma)_{max}$ = 0.017, $(\Delta/\rho)_{min}$ = −0.415 e/Å, $(\Delta/\rho)_{max}$ = 0.308 e/Å.

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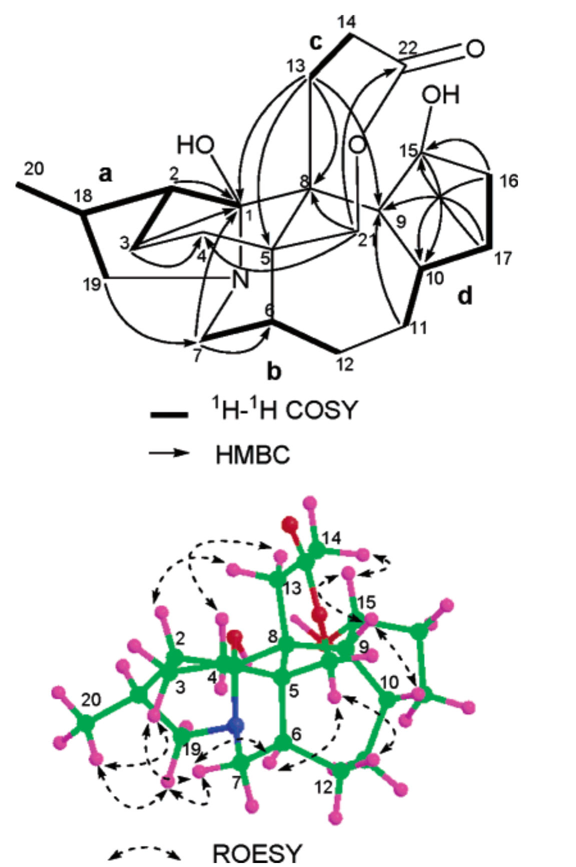

Figure 4. Selected 2D NMR correlations for daphnioldhanin C (**3**).

Supporting Information Available: 1D, 2D NMR, HRESIMS, and IR spectra for **1** and **3** and crystal data of **1**. This information is available free of charge via the Internet at http://pubs.acs.org.

References and Notes

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(13) Crystallographic data for daphnioldhanins A (**1**) reported in this paper have been deposited at the Cambridge Crystallographic Data Centre, CCDC 603146. Copies of the data can be obtained, free of charge, on application to the Director, CCDC, 12 Union Road, Cambridge CB21EZ, UK (fax: +44-(0) 1223-336033 or e-mail: deposit@ccdc.cam.ac.uk).

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