Full Papers

Briarane-Type Diterpenoids from the Okinawan Soft Coral *Pachyclavularia violacea*

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Received May 25, 2005

Four new briarane-type diterpenoids, pachyclavulides A (**1**), B (**2**), C (**3**), and D (**4**), were isolated from the Okinawan soft coral *Pachyclavularia violacea*. The structures of these compounds were elucidated on the basis of the results of spectroscopic analysis. The absolute configuration of pachyclavulide A (**1**) was determined by the X-ray crystallographic analysis of its *p*-bromobenzoyl ester.

Briarane-type diterpenoids have been noted owing to their structural features and biological activity.[1−3] The structures of these diterpenoids are characterized by a highly oxygenated bicyclo[8.4.0]-tetradecane skeleton frequently with a γ-lactone moiety. These diterpenoids exhibited a variety of biological activities such as antiinflammatory,[4] cyctotoxicity,[5] and reversal of multidrug resistance.[6,7] More than 300 briarane-type diterpenoids have been reported so far mainly from gorgonian octocorals of the genera *Briareum*, *Ellisera*, and *Junicella* and from sea pens of the genera *Stylatura*, *Pteroides*, and *Ptilosarcus*. On the contrary, examples of this type of diterpenoids from alcyonarian and stoloniferan soft corals are limited. Only two reports[8,9] were published on the briarane-type diterpenoids from the stoloniferan soft coral of the genus *Pachyclavularia*. Our continuing investigations[10−12] on Okinawan invertebrates have resulted in the isolation of four new briarane-type diterpenoids, pachyclavulides A (**1**), B (**2**), C (**3**), and D (**4**), from *Pachyclavularia violacea*. This paper describes the structural elucidation of these compounds.

The isolation and purifucation were carried out as described in the Experimental Section.

Results and Discussion

The molecular formula of pachyclavulide A (**1**) was found to be $C_{26}H_{38}O_{10}$ by HRESIMS and ^{13}C NMR data. The IR spectrum showed absorptions at 3442 cm^{-1} due to hydroxyl groups and at 1775, 1745, 1734, 1260, and 1217 cm^{-1} due to ester groups. The ^{13}C NMR spectrum (Table 1) disclosed the signals due to seven methyls, three sp^3 methylenes, three sp^3 methines, five sp^3 oxymethines, one sp^3 quaternary carbon, one sp^3 quaternary carbon bearing an oxygen function, two sp^2 carbons, and four carbonyl carbons. The low-field carbonyl carbon [δ_C 177.0 (C-19)], coupled with the IR absorption at 1775 cm^{-1}, suggested the presence of a γ-lacone moiety in **1**. The ^1H NMR spectrum (Table 1) showed the signals due to two secondary methyls, one tertiary methyl, one olefinic methyl, three acetoxyl methyls, five oxymethines, and one olefinic proton. These spectral data, coupled with the degrees of unsaturation (8), suggested that compound **1** is a tricyclic diterpenoid with a γ-lactone, three acetoxyl groups, and a trisubstituted olefin.

The HMQC analysis revealed the assignment of each direct C−H bonding in **1** as summarized in Table 1. The $^1H-^1H$ correlations obtained from the $^1H-^1H$ COSY exhibited partial structures **a**−**d**, as depicted in Figure 2. These partial structures were connected by the HMBC analysis, leading to the gross structure of **1**; the key correlations observed in the HMBC spectrum are shown by broken arrows in Figure 3.

The *Z* configuration of the trisubstituted double bond at C-5 was determined by the NOE correlation between the olefinic methyl (H-16) and the olefinic proton (H-6), as shown by the broken arrow in Figure 4. The relative stereochemistry of the 10 chiral centers in **1** was deduced from the analysis of NOE correlations with suppoting information from vicinal coupling constants (Table 1). The absolute stereochemistry of **1** was determined by X-ray crystallographic analysis of *p*-bromobenzoate **5**, which was prepared by treatment of **1** with *p*-bromobenzoic acid in the presence of EDC and DMAP, as shown in Figure 5.

The molecular formula of pachyclavulide B (**2**) was found to be $C_{26}H_{34}O_{10}$ by HRESIMS and ^{13}C NMR data. The IR spectrum showed absorptions at 3416 cm^{-1} due to hydroxyl groups and at 1770, 1732, 1251, and 1225 cm^{-1} due to ester groups. The ^{13}C NMR spectrum (Table 1) disclosed the signals due to six methyls, one sp^3 methylene, one sp^3 oxymethylene, two sp^3 methines, four sp^3 oxymethines, one sp^3 quaternary carbon, one sp^3 quaternary carbon bearing an oxygen function, four sp^2 methines, two sp^2 quaternary carbons, and four carbonyl carbons. The low-field carbonyl carbon at δ_C 176.1 (C), coupled with the IR absorption at 1770 cm^{-1}, suggested the presence of a γ-lactone moiety in **2**. The ^1H NMR (Table 1) showed the signals due to one secondary methyl, one tertiary methyl, one olefinic methyl, three acetoxyl methyls, one oxymethylene, four oxymethines, and four olefinic protons. These spectral data, coupled with the degrees of unsaturation (10), suggested that compound **2** was a tricyclic diterpenoid with a γ-lactone, three acetoxyl groups, a hydroxylmethyl group, and three olefins.

The HMQC analysis revealed the assignment of each direct C−H bonding in **2** as summarized in Table 1. The skeletal structure of **2** was deduced from $^1H-^1H$ COSY and HMBC correlations as shown in Figure 6.

The *Z* configuration of the disubstituted double bond at C-3 was determined by the proton coupling constant (J = 10.9 Hz) between the olefinic protons H-3 and H-4. The *E* configuration of the trisubstituted double bond at C-5 was demonstrated by the NOE correlation between the olefinic proton (H-6) and the olefinic hydroxymethyl (H-16), as shown by the broken arrow in Figure 7. The relative stereochemistry of the eight chiral centers of **2** was also deduced by the analysis of NOE correlations. The absolute

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10.1021/np0580661 CCC: $33.50
Published on Web 12/16/2005

Table 1. ^{13}C and ^{1}H NMR Data of Compounds **1** and **2**[a]

	1			**2**	
no.	δ_C	δ_H	no.	δ_C	δ_H
1	45.3 (C)		1	43.5 (C)	
2	76.0 (CH)	4.92 (1H, d, 6.4)	2	76.0 (CH)	5.43 (1H, d, 9.8)
3	31.1 (CH_2)	1.51 (1H, m)	3	131.8 (CH)	5.73 (1H, dd, 9.8, 10.9)
		2.76 (1H, dt, 4.8, 15.1)	4	128.6 (CH)	6.28 (1H, d, 10.9)
4	28.8 (CH_2)	2.45 (1H, m)	5	146.2 (C)	
		2.00 (1H, m)	6	122.4 (CH)	5.79 (1H, dd, 1.4, 8.9)
5	146.8 (C)		7	80.0 (CH)	5.21 (1H, d, 8.9)
6	117.7 (CH)	5.38 (1H, d, 9.7)	8	81.1 (C)	
7	79.0 (CH)	5.16 (1H, d, 9.7)	9	69.8 (CH)	5.87 (1H, d, 4.9)
8	82.0 (C)		10	39.7 (CH)	3.05 (1H, br s)
9	75.3 (CH)	5.26 (1H, br s)	11	134.0 (C)	
10	37.9 (CH)	2.56 (1H, br s)	12	120.6 (CH)	5.44 (1H, br s)
11	44.2 (CH)	2.04 (1H, m)	13	26.6 (CH_2)	1.97 (1H, t, 18.0)
12	66.9 (CH)	3.98 (1H, td, 4.4, 11.3)			2.29 (1H, br d, 19.1)
13	28.9 (CH_2)	1.75 (2H, m)	14	72.8 (CH)	4.98 (1H, br s)
14	77.2 (CH)	4.74 (1H, br s)	15	14.8 (CH_3)	1.01 (3H, s)
15	15.1 (CH_3)	1.067 (3H, s)	16	63.9 (CH_2)	4.26 (1H, d, 14.8)
16	27.6 (CH_3)	2.02 (3H, br s)			4.42 (1H, d, 14.8)
17	43.5 (CH)	2.43 (1H, q, 7.1)	17	44.4 (CH)	2.43 (1H, q, 7.2)
18	6.5 (CH_3)	1.17 (3H, d, 7.1)	18	7.5 (CH_3)	1.29 (3H, d, 7.2)
19	177.0 (C)		19	177.0 (C)	
20	9.0 (CH_3)	1.074 (3H, d, 7.5)	20	24.6 (CH_3)	1.95 (3H, br s)
Ac[b]	170.6 (C)		Ac[b]	170.6 (C)	
	21.4 (CH_3)	1.98 (3H, s)		21.36 (CH_3)	2.01 (3H, s)
Ac[c]	169.0 (C)		Ac[c]	169.8 (C)	
	21.7 (CH_3)	2.18 (3H, s)		21.7 (CH_3)	2.16 (3H, s)
Ac[d]	170.6 (C)		Ac[d]	169.8 (C)	
	21.2 (CH_3)	1.94 (3H, s)		21.3 (CH_3)	1.98 (3H, s)
OH		3.50 (1H, br s)	OH		3.11 (1H, s)
			OH		3.25 (1H, br s)

[a] ^{13}C NMR: 125 MHz in $CDCl_3$. ^{1}H NMR: 500 MHz in $CDCl_3$. *J* in Hz. Assignments of the ^{13}C and ^{1}H signals were made on the basis of HMQC. [b,c,d] The positions of these acetoxyl groups are at C-2 for b, C-9 for c, and C-14 for d.

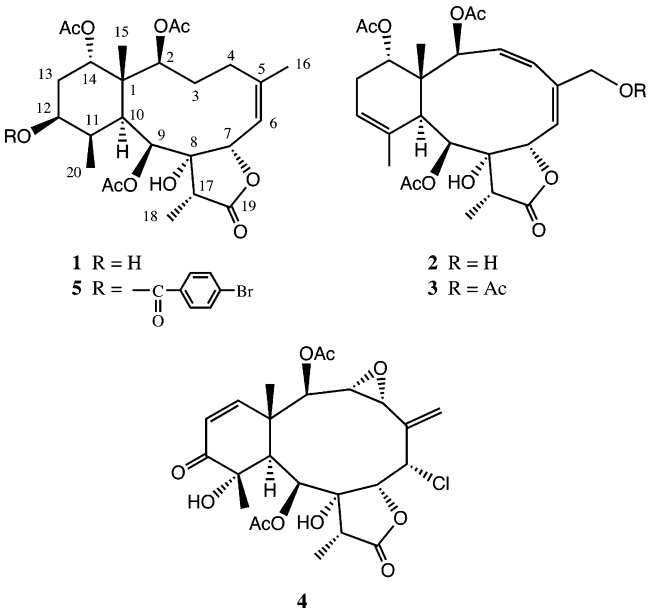

Figure 1. Structures of new diterpenoids.

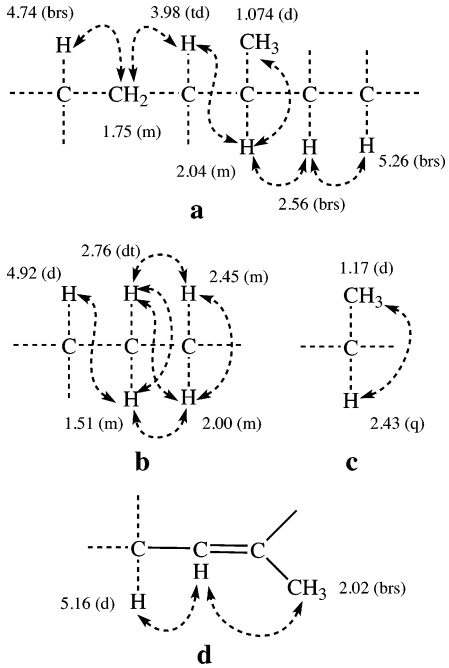

Figure 2. Partial structures, ^{1}H NMR data, and $^{1}H-^{1}H$ correlations (broken arrows) of pachyclavulide A (**1**).

stereochemistry of **2** must be the same as that of **1** present in the same soft coral.

The molecular formula of pachyclavulide C (**3**) was found to be $C_{28}H_{36}O_{11}$ by HRESIMS and ^{13}C NMR data. The ^{13}C and ^{1}H NMR data of **3** (Table 2) were very similar to those of **2**, except for the signals due to a primary acetoxyl group instead of the primary hydroxyl group in **2**, indicating that compound **3** was the corresponding tetraacetate of triacetate **2**. This was confirmed by the chemical conversion. Acetylation of **2** with acetic anhydride in pyridine afforded an acetate, the ^{1}H NMR spectrum and $[\alpha]_D$ value of which were identical with those of **3**.

The molecular formula of pachyclavulide D (**4**), containing a chlorine atom, was found to be $C_{24}H_{29}ClO_{10}$ by HRESIMS and ^{13}C NMR data. The IR spectrum showed absorptions at 3300 cm^{-1} due to hydroxyl groups, at 1779, 1747, and 1210 cm^{-1} due to ester groups, and at 1698 cm^{-1} due to a conjugated carbonyl group. The ^{13}C NMR spectrum (Table 2) disclosed the signals due to five methyls, eight sp^3 methines, two sp^3 quaternary carbons, one sp^2 methylene, two sp^2 methines, one sp^2 quaternary carbon, and four carbonyl carbons. The low-field ester carbonyl carbon [δ_C 174.3

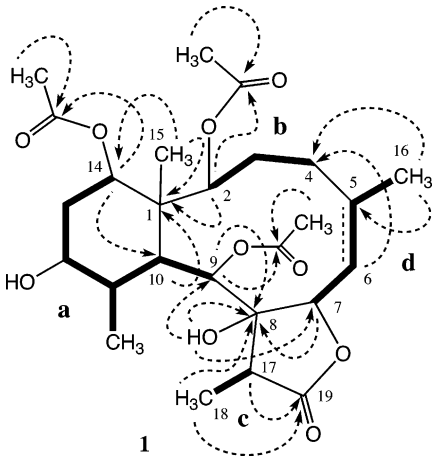

Figure 3. Gross structure, $^1H-^1H$ correlations (bold lines), and key HMBC correlations (broken arrows) of pachyclavulide A (**1**).

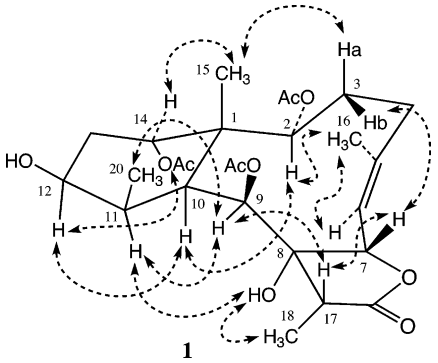

Figure 4. Key NOE correlations (broken arrows) and possible conformation for pachyclavulide A (**1**).

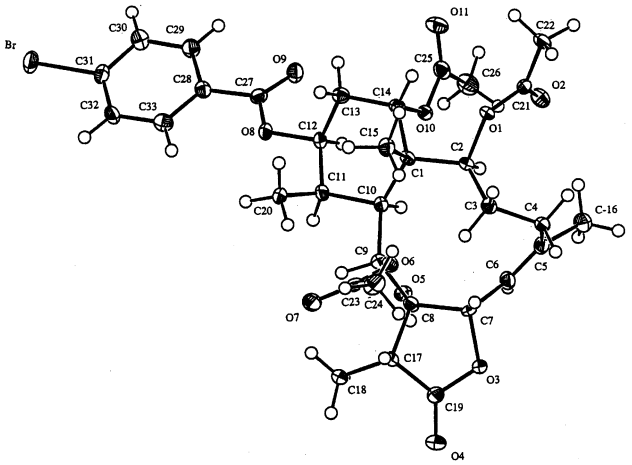

Figure 5. Perspective view (ORTEP) of the molecule of compound **5**.

(C)], coupled with the IR absorption at 1779 cm^{-1}, suggested the presence of a γ-lactone moiety in **4**. On the other hand, the high-field ketonic carbonyl carbon [δ_C 198.7 (C)] suggested that the carbonyl group was conjugated with a carbon−carbon double bond. The ^1H NMR spectrum (Table 2) showed the signals due to one secondary methyl, two tertiary methyls, two acetoxyl methyls, one methine bearing a chlorine atom, five oxymethines, one exomethylene, and two olefinic methines. These spectral data, coupled with the degrees of unsaturation (10), suggested that compound **4** is a tetracyclic diterpenoid with a γ-lactone, an α,β-unsaturated ketone, an epoxide, an exocyclic olefin, and two acetoxyl groups.

The HMQC analysis revealed the assignment of each direct C−H bonding in **4** as summarized in Table 2. The $^1H-^1H$ correlations

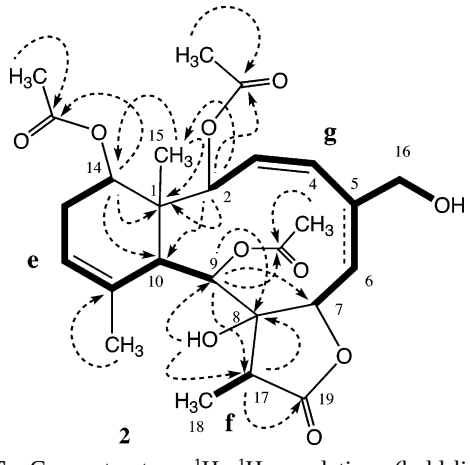

Figure 6. Gross structure, $^1H-^1H$ correlations (bold lines), and key HMBC correlations (broken arrows) of pachyclavulide B (**2**).

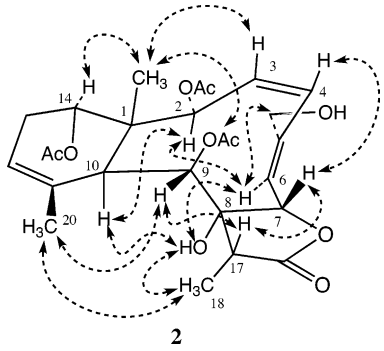

Figure 7. Key NOE correlations (broken arrows) and possible conformation for pachyclavulide B (**2**).

obtained from the $^1H-^1H$ COSY exhibited partial structures **h**−**k**. These partial structures were connected by HMBC correlations, as shown by broken arrows in Figure 8, to afford the gross structure for **4**. The relative stereochemistry of the 11 chiral centers in **4** was deduced by the NOE analysis (Figure 9). The absolute stereochemistry of **4** must be the same as that of **1** present in the same soft coral.

Experimental Section

General Experimental Procedures. Optical rotations were measured with a JASCO DIP-370 automatic polarimeter. IR spectra were recorded with a Perkin-Elmer FT-IR 1600 spectrophotometer. All NMR spectra were recorded with a Bruker DRX-500 (^1H, 500 MHz; ^{13}C, 125 MHz) spectrometer. $^1H-^1H$ COSY, NOESY, HMQC, and HMBC spectra were measured using standard Bruker pulse sequences. Chemical shifts are given on a δ (ppm) scale with $CHCl_3$ (^1H, 7.26 ppm) and $CDCl_3$ (^{13}C, 77.0 ppm) as the internal standard. Mass spectra were taken with a Micromass LCT spectrometer.

Animal Material. The soft coral *Pachyclavularia violacea* (order Stolonifera, class Clavularidae) was collected from a coral reef off Ishigaki Island, Okinawa Prefecture, Japan, in September 1995. A voucher specimen has been deposited at Tokyo University of Pharmacy and Life Science, Tokyo, Japan.

Extraction and Isolation. Wet specimens (2.3 kg) of the soft coral collected in 1995 were extracted with MeOH. The MeOH extract (103 g) was partitioned between EtOAc and H_2O to obtain an EtOAc-soluble portion (41.0 g). A part (1.98 g) of the EtOAc-soluble portion was chromatographed on a silica gel column. Elution with hexane−EtOAc (1:1) afforded five fractions. The fourth fraction (278 mg) was subjected to normal-phase HPLC [hexane−2-propanol (3:1)] to afford four fractions. Further repeated purification of each fraction using normal- and reversed-phase HPLCs afforded pachyclavulide C (**3**) (4.0 mg) from the first fraction (16.1 mg) and pachyclavulides A (**1**) (7.1 mg), B (**2**) (3.8 mg), and D (**4**) (1.9 mg) from the fourth fraction (278 mg).

Pachyclavulide A (1): colorless amorphous solid; $[\alpha]^{25}_D$ −4.7 (*c* 0.58, $CHCl_3$); IR ν_{max} (film) 3442, 1775, 1745, 1734, 1260, 1217 cm^{-1};

Table 2. ^{13}C and ^{1}H NMR Data of Compounds **3** and **4**[a]

	3			**4**	
no.	δ_C	δ_H	no.	δ_C	δ_H
1	43.4 (C)		1	43.4 (C)	
2	74.6 (CH)	5.45 (1H, d, 9.4)	2	75.5 (CH)	4.85 (1H, d, 9.0)
3	132.9 (CH)	5.76 (1H, dd, 9.4, 10.9)	3	59.5 (CH)	3.49 (1H, dd, 3.7, 8.9)
4	126.7 (CH)	6.22 (1H, d, 10.9)	4	58.3 (CH)	3.66 (1H, d, 3.7)
5	141.6 (C)		5	133.8 (C)	
6	120.8 (CH)	5.58 (1H, d, 8.7)	6	59.8 (CH)	5.19 (1H, d, 3.5)
7	79.7 (CH)	5.20 (1H, d, 8.7)	7	77.8 (CH)	5.06 (1H, d, 3.5)
8	81.1 (C)		8	82.1 (C)	
9	69.7 (CH)	5.87 (1H, d, 4.8)	9	69.2 (CH)	5.85 (1H, d, 6.4)
10	39.8 (CH)	3.00 (1H, br s)	10	43.3 (CH)	2.77 (1H, d, 6.4)
11	133.8 (C)		11	75.8 (C)	
12	120.8 (CH)	5.45 (1H, d, 9.4)	12	198.7 (C)	
13	26.7 (CH_2)	2.00 (1H, m)	13	121.7 (CH)	6.09 (1H, d, 10.6)
		2.28 (1H, br d, 19.1)	14	155.4(CH)	6.53 (1H, d, 10.6)
14	72.6 (CH_2)	4.97 (1H, br s)	15	14.6 (CH_3)	1.01 (3H, s)
15	14.8 (CH_3)	1.00 (3H, s)	16	118.9 (CH_2)	5.65 (1H, d, 2.1)
16	63.7 (CH_2)	4.60 (1H, d, 15.8)			6.02 (1H, d, 2.1)
	5.20 (1H, d, 15.8)	17	46.3 (CH)	2.47 (1H, q, 7.1)	
17	44.4 (CH)	2.44 (1H, q, 7.2)	18	6.8 (CH_3)	1.26 (3H, d, 7.1)
18	7.5 (CH_3)	1.28 (3H, d, 7.2)	19	174.3 (C)	
19	175.9 (C)		20	25.3 (CH_3)	1.49 (3H, br s)
20	24.5 (CH_3)	1.95 (3H, br s)	Ac[b]	169.4 (C)	
Ac[b]	169.4 (C)			20.9 (CH_3)	2.22 (3H, s)
	21.2 (CH_3)	1.98 (3H, s)	Ac[c]	169.3 (C)	
Ac[c]	169.8 (C)			21.8 (CH_3)	2.28 (3H, s)
	21.6 (CH_3)	2.16 (3H, s)		21.7 (CH_3)	2.16 (3H, s)
Ac[d]	171.1 (C)		OH		4.90 (1H, s)
	21.3 (CH_3)	2.00 (3H, s)	OH		5.47 (1H, br s)
Ac[e]	171.1 (C)				
	21.3 (CH_3)	2.13 (3H, s)			

[a] ^{13}C NMR: 125 MHz in $CDCl_3$. ^{1}H NMR: 500 MHz in $CDCl_3$. *J* in Hz. Assignments of the ^{13}C and ^{1}H signals were made on the basis of HMQC. [b,c,d] The positions of these acetoxyl groups are at C-2 for b, C-9 for c, and C-14 for d.

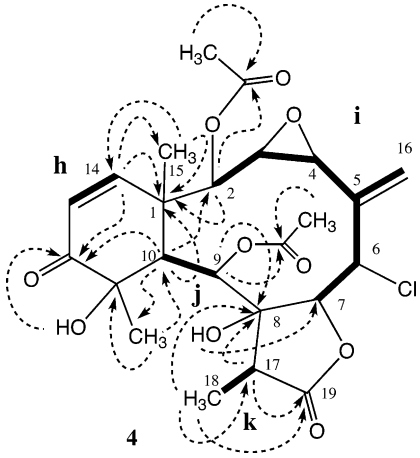

Figure 8. Gross structure, $^{1}H-^{1}H$ correlations (bold lines), and key HMBC correlations (broken arrows) of pachyclavulide D (**4**).

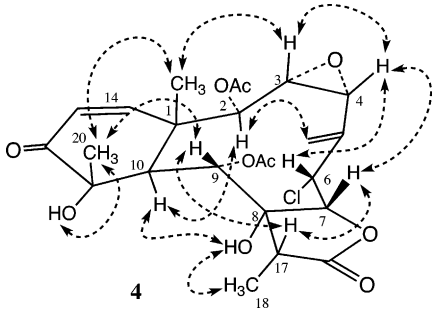

Figure 9. Key NOE correlations (broken arrows) and possible conformation for pachyclavulide D (**4**).

^{13}C and ^{1}H NMR, see Table 1; HRESIMS *m/z* 511.2539 $[M + H]^+$ (calcd for $C_{26}H_{39}O_{10}$, 511.2534).

Pachyclavulide B (2): colorless amorphous solid; $[\alpha]^{25}_D$ −2.9 (*c* 0.27, $CHCl_3$); IR ν_{max} (film) 3416, 1770, 1732, 1251, 1225 cm^{-1}; ^{13}C and ^{1}H NMR, see Table 1; HRESIMS *m/z* 529.2031 $[M + Na]^+$ (calcd for $C_{26}H_{34}O_{10}Na$, 529.2050).

Pachyclavulide C (3): colorless amorphous solid; $[\alpha]^{25}_D$ −19.8 (*c* 0.81, $CHCl_3$); IR ν_{max} (film) 3446, 1770, 1731, 1714, 876 cm^{-1}; ^{13}C and ^{1}H NMR, see Table 2; HRESIMS *m/z* 571.2155 $[M + Na]^+$ (calcd for $C_{28}H_{36}O_{11}Na$, 571.2173).

Pachyclavulide D (4): colorless amorphous solid; $[\alpha]^{25}_D$ −30 (*c* 0.04, $CHCl_3$); IR ν_{max} (film) 3300, 1779, 1747, 1698, 1210 cm^{-1}; ^{13}C and ^{1}H NMR, see Table 2; HRESIMS *m/z* 513.1531 $[M + H]^+$ (calcd for $C_{24}H_{30}{}^{35}ClO_{10}$, 513.1528).

Esterification of Pachyclavulide A (1). To a solution of **1** (10 mg) in CH_2Cl_2 (1.0 mL) were added *p*-bromobenzoic acid (40 mg), EDC (48 mg), and DMAP (2 mg), and the mixture was stirred at room temperature for 36 h. The reaction mixture was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography to give *p*-bromobenzoate **5** (14.5 mg) in quantitative yield.

***p*-Bromobenzoate 5:** colorless prisms; ^{1}H NMR (500 MHz, $CDCl_3$, δ ppm) 1.16 (3H, s), 1.22 (3H, d, *J* = 7.1 Hz), 1.23 (3H, d, *J* = 7.7 Hz), 2.00 (3H, s), 2.08 (3H, s), 2.09 (3H, br s), 2.23 (3H, s), 2.34 (1H, m), 2.45 (1H, q, *J* = 7.1 Hz), 2.66 (1H, dd, *J* = 2.5, 4.9 Hz), 2.80 (1H, dt, *J* = 5.6, 15.2 Hz), 4.88 (1H, m), 4.99 (1H, d, *J* = 6.9 Hz), 5.21 (1H, d, *J* = 9.7 Hz), 5.32 (1H, d, *J* = 2.5 Hz), 5.33−5.41 (2H, m), 7.58 (2H, d, *J* = 8.6 Hz), 7.85 (2H, d, *J* = 8.6 Hz).

Acetylation of Pachyclavulide B (2). To a solution of **2** (0.5 mg) in CH_2Cl_2 (0.3 mL) were added pyridine (5 drops) and acetic anhydride (5 drops). The mixture was stirred for 1 h at room temperature. After addition of excess H_2O the mixture was extracted with ether, and the ethereal layer was successively washed with aqueous $NaHCO_3$, H_2O, aqueous $CuSO_4$, H_2O, and saturated aqueous NaCl, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography to give an acetate, the ^{1}H NMR spectrum of which was identical with that of pachyclavulide C (**3**). The optical rotation data [$[\alpha]^{25}_D$ −20.0 (*c* 0.04, $CHCl_3$)] of the acetate also coincided with that of **3**.

X-ray Crystal Structure Determination of 5. A colorless prism of **5** was obtained by recrystallization from hexane−EtOAc (5:1). A single crystal with dimensions of 0.43 × 0.33 × 0.25 mm was used for X-ray diffraction studies on a Mac Science DIP2020 diffractometer employing graphite-monochromated Mo Kα radiation ($\lambda = 0.71073$ Å). The structure was solved by a direct method using SIR97[13] in the maXus program system and refined by SHELXL97[14] using 11 077 reflections [$I > 2.00\sigma(I)$] for 884 parameters. The final R value is 0.035.

Crystal Data: $2(C_{33}H_{41}BrO_{11})\cdot C_4H_8O_2\cdot 2(H_2O)$, monoclinic with space group $P2_1$, with $a = 11.1960(5)$ Å, $b = 25.7150(5)$ Å, $c = 13.8270(6)$ Å, $V = 3643.1$ (2) Å, and $Z = 2$. Crystallographic data for the structure reported in this paper have been deposited with Cambridge Crystallographic Data Centre (deposition number CCDC 284180). Copies of the data can be obtained, free of charge, on application to the Director, CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44-(0)1223-336033 or e-mail: deposite@ccdc.cam.ac.uk).

Acknowledgment. The authors express appreciation to H. Fukaya, Tokyo University of Pharmacy and Life Science, for conducting the X-ray crystallographic analysis.

Supporting Information Available: Copies of ^{1}H and ^{13}C NMR spectra of pachyclavulides A−D (**1**−**4**). These materials are available free of charge via the Internet at http://pubs.acs.org.

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NP0580661