

# JOURNAL OF NATURAL PRODUCTS

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Volume 65, Number 6

June 2002

## Full Papers

### Brominated Labdane-Type Diterpenoids from an Okinawan *Laurencia* sp.

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Received November 30, 2001

From an unidentified species of *Laurencia* collected from Okinawan waters two novel brominated metabolites, **1** and **2**, along with known halogenated compounds, 2,10-dibromo-3-chloro- $\alpha$ -chamigrene (**3**) and microcladallene A (**4**), were isolated and identified. The structures of these new compounds were established as *ent*-labdane-type bromoditerpenes, (1*S*,3*R*,5*S*,6*S*,8*S*,9*S*,10*R*,13*R*)-1-acetoxy-3-bromo-6-hydroxy-8,13-epoxy-labd-14-ene (**1**) and (3*R*,5*S*,6*S*,8*S*,9*S*,10*R*,13*R*)-3-bromo-6-hydroxy-8,13-epoxylabd-14-en-1-one (**2**), by interpretation of their spectroscopic data as well as by X-ray crystallographic analysis.

Species of the red algal genus *Laurencia* (Rhodomelaceae, Ceramiales) are well known to be prolific sources of diverse halogenated secondary metabolites, particularly terpenoids and C<sub>15</sub>-acetogenins.<sup>1,2</sup> Although *Laurencia* spp. produce several halogenated metabolites in common, most synthesize at least one specific metabolite not found in other species.<sup>3</sup> Chemical studies based on field-collected and cultured samples of several *Laurencia* species have shown that synthesis of halogenated secondary metabolite is not affected by environmental factors, e.g., temperature, photoperiod, and aeration.<sup>4,5</sup> Therefore, halogenated secondary metabolites are a useful taxonomic feature at the species level of *Laurencia*,<sup>6</sup> whose species discrimination is complicated by a high degree of morphological variation within individual species.

In our continuing studies pertaining to chemical composition of *Laurencia* species collected from the Okinawan

waters,<sup>7-9</sup> we examined an unidentified species of *Laurencia*, a strain of which was collected at Bisezaki, Motobu, Okinawa Prefecture, and cultured in our laboratory. Cultured plants were found to produce two novel brominated diterpenoids, **1** and **2**, along with a previously known sesquiterpenoid, 2,10-dibromo-3-chloro- $\alpha$ -chamigrene (**3**), isolated from several *Laurencia* species,<sup>10-13</sup> and the C<sub>15</sub>-acetogenin, microcladallene A (**4**), isolated from *L. microcladia*.<sup>14</sup> In this paper we describe the isolation and structure elucidation of these compounds using both spectroscopic and X-ray crystallographic data.

#### Results and Discussion

Partially dried specimens of cultured *Laurencia* sp. were extracted with methanol. The methanol extract was subjected to a combination of column and thin-layer chromatography to yield halogenated compounds **1-4**.

Compound **1** has the molecular formula C<sub>22</sub>H<sub>35</sub>BrO<sub>4</sub> as established by HRFDMS. Its IR spectrum showed the presence of hydroxyl ( $\nu_{\max}$  3620 cm<sup>-1</sup>) and acetoxy ( $\nu_{\max}$  1735 and 1220 cm<sup>-1</sup>) functionalities. The presence of a vinyl group was shown by characteristic signals in the <sup>1</sup>H and <sup>13</sup>C NMR spectra (Table 1) at  $\delta_{\text{H}}$  4.77 (1H, d,  $J$  = 11.0 Hz), 4.88 (1H, d,  $J$  = 17.5 Hz), and 6.10 (1H, dd,  $J$  = 17.5, 11.0 Hz);  $\delta_{\text{C}}$  148.8 (C) and 110.1 (CH<sub>2</sub>), respectively. Further-

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**Table 1.**  $^{13}\text{C}$  NMR (100 MHz, DEPT),  $^1\text{H}$  NMR (400 MHz), and HMBC Data for **1** and **2**<sup>a</sup>

position <sup>b</sup>	<b>1</b>			<b>2</b>	
	$^{13}\text{C}$ $\delta$	$^1\text{H}$ $\delta$ mult. ( <i>J</i> in Hz)	HMBC (H $\rightarrow$ C)	$^{13}\text{C}$ $\delta$	$^1\text{H}$ $\delta$ mult. ( <i>J</i> in Hz)
1	81.0	4.51 dd (11.1, 4.8)	C-9, C-10, C-18, Ac	208.5	
2 $\alpha$	37.4	2.23 ddd (13.2, 12.2, 11.1)	C-1, C-3, C-4, C-10	47.6	3.29 dd (13.8, 12.5)
$\beta$		2.51 ddd (12.2, 4.8, 4.2)	C-1, C-3, C-4, C-10		2.74 dd (12.5, 4.6)
3	64.2	3.60 dd (13.2, 4.2)	C-2, C-4, C-16, C-17	64.7	3.64 dd (13.8, 4.6)
4	40.8			41.2	
5	54.6	0.33 d (2.7)	C-1, C-3, C-4, C-6, C-10, C-17, C-18	55.1	0.53 d (2.7)
6	70.3	3.85 m	C-10	70.7	3.77 m
7 $\alpha$	51.5	1.65 dd (13.8, 2.7)	C-5, C-6	50.5	1.61 br d (11.2)
$\beta$		1.43 m			1.34 m
8	75.2			75.4	
9	59.2	1.21 dd (12.7, 2.7)	C-8, C-11	52.2	1.82 dd (12.7, 2.7)
10	42.6			53.4	
11a	19.1	1.72 m	C-8, C-9, C-12	19.5	2.13 m
b		1.49 m			1.53 m
12a	35.7	2.07 m	C-9	35.8	2.17 m
b		1.46 m	C-13		1.83 m
13	73.5			74.5	
14	148.8	6.10 dd (17.5, 11.0)		149.3	6.13 dd (18.0, 11.2)
15a	110.1	4.88 d (17.5)		110.1	4.89 d (18.0)
b		4.77 d (11.0)			4.86 d (11.2)
16	19.6	1.37 s	C-3, C-4, C-5, C-17	20.2	1.41 s
17	30.3	0.94 s	C-3, C-4, C-5, C-16	29.9	0.87 s
18	14.6	1.23 s	C-1, C-5, C-9, C-10	16.6	1.18 s
19	26.1	1.56 s	C-7, C-8, C-9	26.0	1.55 s
20	33.7	1.22 s	C-12, C-13, C-14	34.1	1.27 s
Ac	21.9	1.67 s			
Ac	170.0				
OH		0.17 br s			0.23 br s

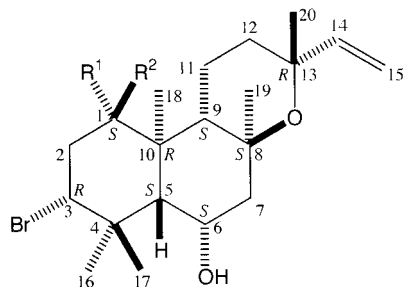
<sup>a</sup> Measured in benzene-*d*<sub>6</sub>. <sup>b</sup> Assignment was made from the HSQC spectrum.

more, the  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra revealed signals due to five tertiary methyl groups [ $\delta_{\text{H}}$  0.94, 1.22, 1.23, 1.37, and 1.56 (each 3H, s)], an acetoxymethine group [ $\delta_{\text{H}}$  4.51 (1H,

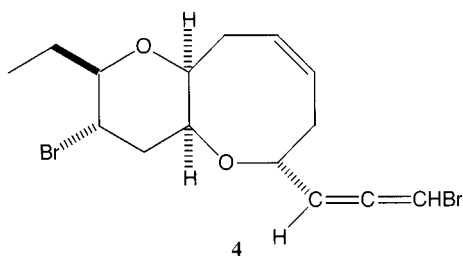
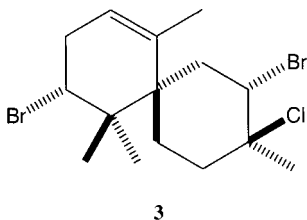
dd,  $J = 11.1, 4.8$  Hz)], a hydroxymethine group [ $\delta_{\text{H}}$  3.85 (1H, m; exchangeable by an addition of  $\text{D}_2\text{O}$ ), a bromomethine group [ $\delta_{\text{H}}$  3.60 (1H, dd,  $J = 13.2, 4.2$  Hz)], a hydroxyl proton [ $\delta_{\text{H}}$  0.17 (1H, s;  $\text{D}_2\text{O}$  exchangeable)], two quaternary carbons ( $\delta_{\text{C}}$  40.8 and 42.6), and two oxygen-bearing quaternary carbons ( $\delta_{\text{C}}$  73.5 and 75.2). Since compound **1** has five degrees of unsaturation, **1** must contain one epoxy and two carbocyclic rings.

The  $^1\text{H}$ - $^1\text{H}$  COSY and HSQC spectrum as well as the above-mentioned data showed the presence of partial structural units **a**-**g** in **1** (Figure 1). Confirmation of the partial structural units and their connectivity was made with the aid of the HMBC spectrum (Table 1). Mutual long-range correlations between two tertiary methyl groups at  $\delta_{\text{H}}$  0.94 ( $\delta_{\text{C}}$  30.3) and 1.37 ( $\delta_{\text{C}}$  19.6) indicated that these tertiary methyl groups comprise *gem*-dimethyl groups. In addition, the *gem*-dimethyl group showed long-range correlations to the methine carbon at  $\delta_{\text{C}}$  64.2 (C-3) in unit **a** and the methine carbon at  $\delta_{\text{C}}$  54.6 (C-5) in unit **b**, thus confirming that the *gem*-dimethyl group can be inserted between units **a** and **b**. The tertiary methyl groups at  $\delta_{\text{H}}$  1.23 showed long-range correlations to C-1 ( $\delta_{\text{C}}$  81.0) in unit **a**, C-5 ( $\delta_{\text{C}}$  54.6) in unit **b**, and C-9 ( $\delta_{\text{C}}$  59.2) in unit **c**, leading to a cyclohexane ring. The tertiary methyl group at  $\delta_{\text{H}}$  1.56, which is adjacent to the oxygen-bearing quaternary carbon ( $\delta_{\text{C}}$  75.2), showed long-range correlations to C-9 ( $\delta_{\text{C}}$  59.2) in unit **c** and C-7 ( $\delta_{\text{C}}$  51.5) in unit **b** to form a decalin-type skeleton. Furthermore, the remaining tertiary methyl group at  $\delta_{\text{H}}$  1.22, which is adjacent to another oxygen-bearing quaternary carbon ( $\delta_{\text{C}}$  73.5), showed long-range correlations to C-12 ( $\delta_{\text{C}}$  35.7) in unit **c** and C-14 ( $\delta_{\text{C}}$  148.8) in the vinyl group (unit **d**) to lead to a planar formula **h** for compound **1**.

The relative stereochemistry of **1** was deduced from the NOESY experiment as well as the coupling constants in the  $^1\text{H}$  NMR spectrum. The coupling constants of the methine proton ( $J = 11.1$  and  $4.8$  Hz) at C-1 and the



- 1:  $\text{R}^1 = \text{OAc}$ ,  $\text{R}^2 = \text{H}$   
 2:  $\text{R}^1 = \text{R}^2 = \text{O}$   
 5:  $\text{R}^1 = \text{R}^2 = \text{H}$



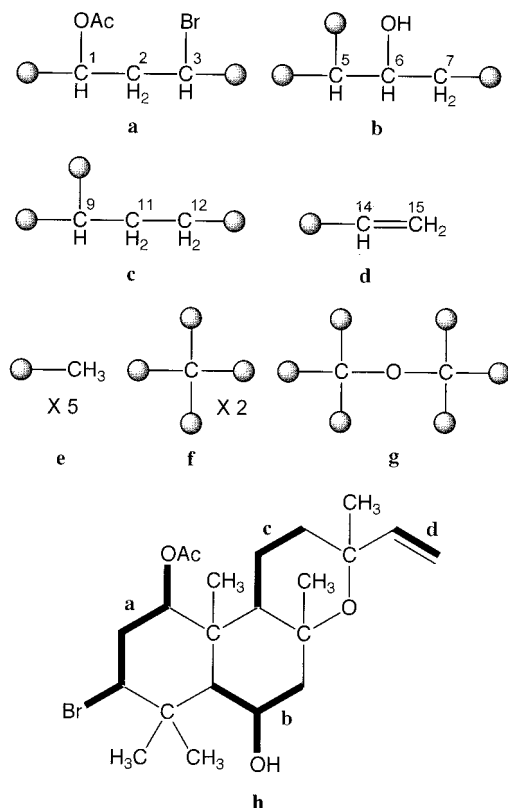


Figure 1. Partial and planar structures for **1**.

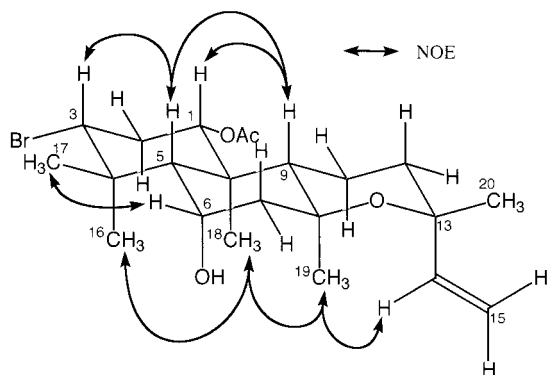


Figure 2. NOE correlations of **1**.

methine proton ( $J = 13.2$  and  $4.2$  Hz) at C-3 showed that these protons are axial in a chair cyclohexane ring. Hence both the acetoxy group at C-1 and the bromine atom at C-3 adopt an equatorial configuration. Furthermore, as shown in Figure 2, NOEs between H-3/H-5, H-5/H-9, H-1/H-9, H<sub>3</sub>-17/H-6, H<sub>3</sub>-18/H<sub>3</sub>-19, and H<sub>3</sub>-19/H-14 indicated the relative stereochemistry shown in formula **1**.

To confirm the structure assigned to **1** and establish its absolute configuration, a single-crystal X-ray crystallographic analysis was undertaken. The crystal structure (ORTEP diagram) is shown in Figure 3. The absolute configuration was assigned on the basis of the Flack parameter.<sup>15</sup> Thus the structure of compound **1** was established unambiguously as an unusual tricyclic labdane bromoditerpenoid, (1*S*,3*R*,5*S*,6*S*,8*S*,9*S*,10*R*,13*R*)-1-acetoxy-3-bromo-6-hydroxy-8,13-epoxylabd-14-ene. Compound **1** belongs to the *ent*-labdane diterpenoids and is closely related to paniculato (5), which has previously been isolated from *Laurencia paniculata* collected at Al Wakrah Bay, 30 km south of Doha, Qatar.<sup>16</sup>

Compound **2**,  $[\alpha]_D^{24} -120^\circ$  (CHCl<sub>3</sub>), was analyzed for C<sub>20</sub>H<sub>31</sub>BrO<sub>3</sub> by HRFDMS. The IR spectrum showed the

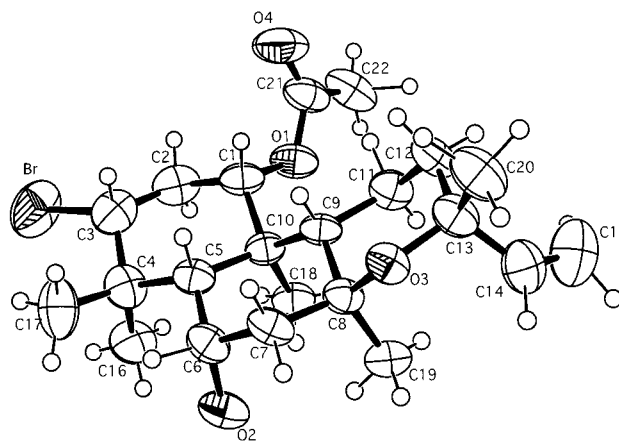


Figure 3. ORTEP view of the X-ray molecular structure of **1**.

presence of a hydroxyl group at  $\nu_{\max}$  3610 cm<sup>-1</sup> and a carbonyl group (probably six-membered ring ketone) at  $\nu_{\max}$  1710 cm<sup>-1</sup>. The <sup>1</sup>H and <sup>13</sup>C NMR spectra (Table 1) of **2** were very similar to those of **1**, showing the presence of a vinyl group, five tertiary methyl groups, a hydroxymethine group, a bromomethine group, and four quaternary carbons. The gross structure for compound **2** was determined by using 2D NMR spectra (<sup>1</sup>H-<sup>1</sup>H COSY, HSQC, and HMBC) as in the case of **1**. The relative stereochemistry was also confirmed by the NOESY spectrum to give formula **2**. Judging from co-occurrence of **1** and **2** in the same alga, **2** must have the same absolute configuration as that of **1**. In consequence, the structure of compound **2** should be assigned as (3*R*,5*S*,6*S*,8*S*,9*S*,10*R*,13*R*)-3-bromo-6-hydroxy-8,13-epoxylabd-14-en-1-one.

Compound **3** was identified as 2,10-dibromo-3-chloro- $\alpha$ -chamigrene, which was previously isolated from several *Laurencia* species,<sup>10-13</sup> by a comparison of its spectral data with those of an authentic sample. Independent structure elucidation using 1D and 2D NMR techniques (<sup>1</sup>H-<sup>1</sup>H COSY, HSQC, HMBC, and NOESY) showed compound **4** to be microcladallene A.<sup>14</sup> To date, no NMR data for microcladallene A have been reported in the literature, and therefore detailed <sup>1</sup>H and <sup>13</sup>C NMR data are described in the Experimental Section.

A labdane-type bromoditerpenoid, aplysin-20, was first isolated in 1967 by Yamamura and Hirata from the Japanese sea hare *Aplysia kurodai*.<sup>17,18</sup> Thereafter aplysin-20 has been isolated from species of the red algal genus *Laurencia*, which are known to be frequently consumed by the sea hare *Aplysia* species,<sup>1</sup> an unrecorded *Laurencia* sp. of Galapagos Island<sup>19</sup> and Japanese *Laurencia venusta*.<sup>20</sup> Moreover, several labdane bromoditerpenoids have been isolated from *Laurencia* spp.: concinndiol from *L. concinna*,<sup>21</sup> isoconcinndiol from *L. snyderae* var. *guadalupensis*,<sup>22</sup> pinnatols A, B, C, and D from *L. pinnata*,<sup>23</sup> venustanol from *L. venusta*,<sup>20</sup> and paniculato from *L. paniculata*.<sup>16</sup>

Compounds **1** and **2** are the first examples of labdane-type bromoditerpenoids possessing a functional group at C-1. Compounds **1** and **2** were inactive against several pathogenic bacteria, *Escherichia coli*, *Staphylococcus epidermidis*, *S. aureus*, *Salmonella* sp., and *Pseudomonas* sp., in a bioassay using the paper disk diffusion method.

## Experimental Section

**General Experimental Procedures.** IR spectra were recorded on a JASCO A-102 spectrophotometer. <sup>1</sup>H NMR (400 MHz) and <sup>13</sup>C NMR (100 MHz; DEPT) spectra were measured in C<sub>6</sub>D<sub>6</sub> solution, unless otherwise stated, with TMS as the internal standard by using a JEOL-JNM-EX-400 spectrometer.

LR- and HRFDMS were obtained on a JMS-01SG-2 spectrometer. Optical rotations were measured on a JASCO DIP-140 polarimeter. Si gel (Merck, Kieselgel 60, 70–230 mesh) was used for column chromatography. Si gel plates (Merck, Kieselgel 60 F<sub>254S</sub>) were used for preparative TLC (PTLC).

**Plant Material.** A sample of an unidentified *Laurencia* sp. was collected on April 24, 1993, at Bisezaki, Motobu, Okinawa Prefecture. The voucher specimen is deposited in the Herbarium of Graduate School of Science, Hokkaido University (SAP 089299).

**Culture.** Unialgal cultures were established from tetraspores. Released tetraspores were rinsed once in autoclaved seawater and then inoculated into several drops of PES medium<sup>24</sup> and mounted on half-sized microscope slide glasses placed in culture dishes (65 × 50 mm). One day later, 100 mL of medium was added to each dish, and after one month, all slides were transferred to larger dishes (65 × 85 mm) containing 200 mL of medium. Cultures were thinned out as they aged, and some plants thus removed were maintained in other dishes. Cultures were placed in a plant growth chamber illuminated with cool-white fluorescent lamps (30–40 μmol photons m<sup>-2</sup>·s<sup>-1</sup>) at 20 °C, 16:8 h L:D cycle. PES medium was changed every 4 weeks. When plants grew to 5–8 cm, they were divided into two dishes to avoid overcrowding.

**Extraction and Isolation.** Partially dried cultured specimens (22 g) were extracted with MeOH. The MeOH extract was concentrated in vacuo and then partitioned between Et<sub>2</sub>O and H<sub>2</sub>O. The Et<sub>2</sub>O layer was washed with H<sub>2</sub>O, dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, and evaporated to leave a dark green oil (290 mg), which was fractionated by Si gel column chromatography with a step gradient (hexane and EtOAc).

The fraction eluted with hexane/EtOAc (9:1) was further subjected to PTLC with hexane/EtOAc (9:1) to give 2,10-dibromo-3-chloro- $\alpha$ -chamigrene (**3**)<sup>10,11</sup> (0.2% of the extract) and microcladallene A (**4**)<sup>14</sup> (6.9%). Furthermore, the fraction eluted with hexane/EtOAc (3:1) was separated by repeated PTLC with hexane/EtOAc (4:1) to give a mixture of compounds **1** and **2**, which was treated with hot hexane to yield **1** (1.6%) from the hexane-insoluble part and **2** (1.3%) from the hexane-soluble part.

**1-Acetoxy-3-bromo-6-hydroxy-8,13-epoxylabd-14-ene (1):** colorless crystals; mp 183–184 °C; [ $\alpha$ ]<sub>D</sub><sup>24</sup> +28.0° (c 0.27, CHCl<sub>3</sub>); IR (CHCl<sub>3</sub>)  $\nu_{\max}$  3620, 3450, 1735, 1720, 1220, 1070, 1025, 925 cm<sup>-1</sup>; <sup>1</sup>H NMR and <sup>13</sup>C NMR data, Table 1; LR-FDMS *m/z* 444, 442 [M]<sup>+</sup> (27:28), 429, 427 [M - CH<sub>3</sub>]<sup>+</sup> (99:100), 385 (35), 383 (37); HRFDMS *m/z* 442.1703 (calcd for C<sub>22</sub>H<sub>35</sub>79BrO<sub>4</sub>, 442.1718).

**3-Bromo-6-hydroxy-8,13-epoxylabd-14-en-1-one (2):** colorless crystals; mp 213–214 °C; [ $\alpha$ ]<sub>D</sub><sup>24</sup> -120° (c 0.08, CHCl<sub>3</sub>); IR (CHCl<sub>3</sub>)  $\nu_{\max}$  3610, 3400, 1710, 1090, 1045, 960, 915 cm<sup>-1</sup>; <sup>1</sup>H NMR and <sup>13</sup>C NMR data, Table 1; LRFDMS *m/z* 400, 398 [M]<sup>+</sup> (30:27); HRFDMS *m/z* 398.1453 (calcd for C<sub>20</sub>H<sub>31</sub>79BrO<sub>3</sub>, 398.1458).

**X-ray Crystallographic Analysis of 1.**<sup>25</sup> A colorless prismatic crystal suitable for X-ray crystallography was obtained from a solution in MeOH. Crystal data: C<sub>22</sub>H<sub>35</sub>BrO<sub>4</sub>; orthorhombic; space group *P*2<sub>1</sub>2<sub>1</sub>2<sub>1</sub> (#19), *Z* = 4, *a* = 26.638(3) Å, *b* = 8.8035(5) Å, *c* = 9.5606(6) Å, *V* = 2242.1(3) Å<sup>3</sup>, *D*<sub>calcd</sub> = 1.314 g/cm<sup>3</sup>, crystal size 0.59 × 0.52 × 0.29 mm<sup>3</sup>, *R* = 0.034, *R*<sub>w</sub> = 0.054, Flack parameter -0.01(2). The single crystal was mounted in a sealed glass capillary. The data were collected on an Enraf-Nonius CAD4 diffractometer with graphite-monochromated Cu K $\alpha$  radiation ( $\lambda$  = 1.5418 Å) by using the  $\omega$ -2 $\theta$  scans method at 298 K. The structure was solved by direct methods (SIR92) and refined by full-matrix least-squares calculations. The non-hydrogen atoms were refined anisotropically, and hydrogen atoms were fixed at the calculated positions and refined isotropically. Empirical absorption and decay corrections were applied. In the least-squares refinements, the Flack parameter defined as  $|F| = (1 - x)|F(+)|$

+  $x|F(-)|$  was refined.<sup>15</sup> The maximum peak and minimum hole in the final difference Fourier map were 1.00 and -1.14 e Å<sup>-3</sup>, respectively. All calculations were performed with the crystallographic software package CrystalStructure.

**Microcladallene A (4):** colorless crystals; mp 91 °C; [ $\alpha$ ]<sub>D</sub><sup>24</sup> +109° (c 0.72, CHCl<sub>3</sub>); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  6.11 (1H, dd, *J* = 5.3, 2.9 Hz, H-1), 5.93 (1H, ddd, *J* = 10.3, 8.3, 7.8 Hz, H-6), 5.79 (1H, dddd, *J* = 10.3, 9.7, 7.3, 1.3 Hz, H-7), 5.44 (1H, dd, *J* = 5.3, 4.9 Hz, H-3), 4.79 (1H, ddd, *J* = 7.8, 4.9, 2.9 Hz, H-4), 4.04 (1H, ddd, *J* = 12.2, 10.3, 4.4 Hz, H-12), 3.83 (1H, br s, H-10), 3.59 (1H, ddd, *J* = 10.3, 4.9, 1.0 Hz, H-9), 3.29 (1H, ddd, *J* = 10.3, 9.3, 2.4 Hz, H-13), 2.70 (1H, m, Ha-5), 2.54 (1H, ddd, *J* = 12.7, 10.3, 9.7 Hz, Ha-8), 2.40 (1H, ddd, *J* = 13.2, 4.4, 3.9 Hz, Ha-11), 2.28 (1H, m, Hb-5), 2.27 (1H, ddd, *J* = 12.7, 7.3, 4.9 Hz, Hb-8), 2.07 (1H, ddd, *J* = 13.2, 12.2, 2.9 Hz, Hb-11), 2.05 (1H, ddq, *J* = 14.6, 2.4, 7.3 Hz, Ha-14), 1.55 (1H, ddq, *J* = 14.6, 9.3, 7.3 Hz, Hb-14), 0.99 (3H, t, *J* = 7.3 Hz, H<sub>3</sub>-15); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  203.1 (C-2), 129.1 (C-7), 129.0 (C-6), 99.9 (C-3), 83.4 (C-13), 80.6 (C-9), 74.6 (C-4), 74.5 (C-1), 70.2 (C-10), 49.3 (C-12), 43.7 (C-11), 31.4 (C-5), 31.1 (C-8), 26.4 (C-14), 11.0 (C-15).

**Acknowledgment.** This study was supported in part by a Grant-in-Aid for Scientific Research (No. 09839001) from the Ministry of Education, Science, Sports and Culture of Japan.

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- Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Center as supplementary publication nos. CCDC-170980. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB21EZ, UK (fax: (+44)1223 336-033; e-mail: deposit@ccdc.cam.ac.uk).

NP010596J