

Halogenated metabolites from Japanese *Laurencia* spp.

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Received 26 January 2005; received in revised form 21 June 2005

Available online 23 September 2005

Abstract

Further investigation of *Laurencia* species from Japanese waters, which were collected at three locations, yielded brominated metabolites, a labdane- type diterpene and a C₁₅ acetogenin possessing a terminal bromoallene group. Their structures were deduced from analysis of spectroscopic data.

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Keywords: *Laurencia*; Rhodomelaceae; Red alga; C₁₅ acetogenin; Diterpene; Sesquiterpene; Halogenated compound; Chemotaxonomy

1. Introduction

In connection with our continuing studies (Vairappan et al., 2001; Masuda et al., 2002; Takahashi et al., 2002; Suzuki et al., 2002a,b) on chemical compositions of the red algal genus *Laurencia* from Japanese waters, we examined undescribed specimens collected from three different locations; Chinzei (Saga Prefecture), Hachijo-jima Island (Tokyo) and Miyake-jima Island (Tokyo). The Chinzei collection contained a new brominated C₁₅ acetogenin (**1**), which was designated as chinzellene, and a new brominated diterpene (**2**) along with a known bromoallenic C₁₅ acetogenin (**3**) (Suzuki et al., 1989).

Diterpene (**2**) was also isolated from the Hachijo-jima collection that contained other new C₁₅ acetogenins, whose structural elucidation is in progress. On the other hand, the Miyake-jima collection afforded known sesquiterpenes, 2,10-dibromo-3-chloro- α -chamigrene (**4**) (Howard and Fenical, 1975; Suzuki et al., 1979; Takahashi et al., 1999) and laurinterol (**5**) (Irie et al., 1970; Suzuki and Kurosawa, 1979), and another known bromoallenic C₁₅ acetogenin (**6**) (Suzuki and Kurosawa, 1985). In this paper we report the isolation and structures of these halogenated compounds.

2. Results and discussion

Chinzellene (**1**), $[\alpha]_D^{21} + 184^\circ$ (CHCl₃), which was the major metabolite of the Chinzei sample, was obtained as colorless oil and analyzed for C₁₅H₁₈Br₂O₃ by its HR-EIMS. Its IR spectrum showed a characteristic band for a terminal bromoallene moiety at ν_{\max} 1960 cm⁻¹ and no bands for hydroxyl and carbonyl groups, suggesting that three oxygen atoms of **1** were

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assumed to be involved in ether linkages. The presence of a terminal bromoallene moiety was also proven by typical signals in the ^1H and ^{13}C NMR spectra (Table 1) [δ_{H} 6.06 (1H, *dd*, $J = 5.9, 1.5$ Hz) and 5.37 (1H, *dd*, $J = 5.9, 5.9$ Hz); δ_{C} 201.9 (C), 101.1 (CH) and 73.6 (CH)]. The quaternary carbon at δ_{C} 116.5 in the ^{13}C NMR spectrum of **1** suggested the presence of an acetal moiety. Moreover, the NMR spectra indicated the presence of a 1,2-disubstituted cyclopropane ring [δ_{H} 0.76 (2H, *m*) and δ_{C} 8.3 (CH₂)].

Detailed analysis of the ^1H and ^{13}C NMR spectra, as well as HSQC and ^1H – ^1H COSY spectra, showed the presence of partial structural units **1a**–**1d** in the molecule of chinzallene (**1**) (Fig. 1). In the partial structures, the substituents of bromine or oxygen atoms at C4, C6, C7, C8 and C13 were verified based upon the chemical shifts of the pertinent carbons at δ_{C} 76.5, 82.8, 90.6, 58.1 and 83.8, respectively. Since the C₁₅ cyclic ether acetogenins found in *Laurencia* are assumed to be derived from straight-chain C₁₅ precursors, laurediols

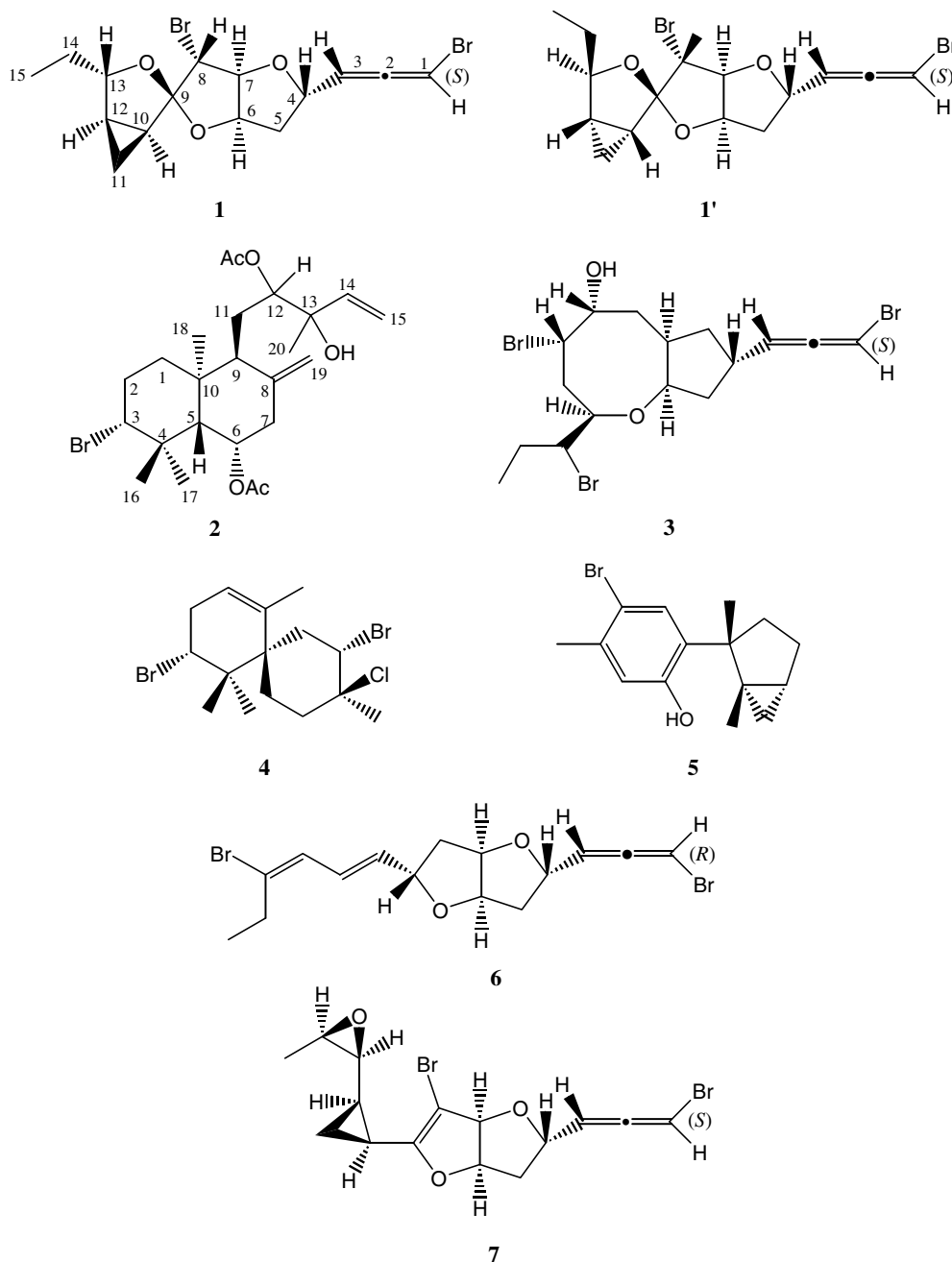


Table 1
 ^{13}C NMR (100 MHz, DEFT), ^1H NMR (400 MHz), and HMBC data^a for **1**

C	$^{13}\text{C}^b$ (δ)	^1H (δ)	Multiplicity, J (Hz)	Long-range spectroscopic correlations
1	73.6	6.06	dd , $J = 5.9, 1.5$	H-3
2	201.9			H-1, H-3, H-4
3	101.1	5.37	dd , $J = 5.9, 5.9$	H-1, H α -5
4	76.5	5.10	$dddd$, $J = 8.8, 5.9, 5.4, 1.5$	H-3, H α -5, H-6, H-7
5	39.9	2.41	dd , $J = 13.7, 5.4(\text{H}\beta)$	H-3, H-6
		1.80	ddd , $J = 13.7, 8.8, 4.9(\text{H}\alpha)$	
6	82.8	4.99	dd , $J = 4.9, 4.9$	H β -5, H-7, H-8
7	90.6	4.97	d , $J = 4.9$	H β -5, H-6, H-7, H-8
8	58.1	4.18	s	H-6
9	116.5			H-6, H-7, H-10, H $_2$ -11, H-12, H-13
10	22.4	2.29	m	H $_2$ -11, H-12, H-13
11	8.3	0.76	m	H-13
12	22.0	1.56	m	H $_2$ -11, H-13
13	83.8	3.97	dd , $J = 8.3, 6.3$	H-10, H $_2$ -11, H-12, H $_2$ -14, H $_3$ -15
14	29.5	1.59	m	H-13, H $_3$ -15
15	9.8	0.95	dd , $J = 7.3, 7.3$	H-13, H $_2$ -14

^a Measured in chloroform- d_1 .

^b Assigned by the HSQC spectrum.

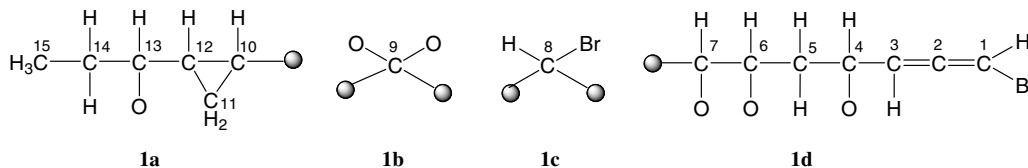


Fig. 1. Partial structural units for **1**.

(Kurosawa et al., 1972), units **1b** and **1c** must be inserted between C7 and C10. The formula for chinzellene was established by analysis of the HMBC spectrum (Table 1). A long-range correlation between an isolated methine proton (H-8, δ_{H} 4.18 (s)) and C-6 indicated the connection of C7 (**1d**) and C8 (**1c**). Correlations between C9, the acetal carbon at δ_{C} 116.5, and H-7, H-10, H $_2$ -11 and H-12 showed connections between C10 (**1a**) and C9 (**1b**) as well as C9 and C8. Furthermore, the HMBC spectrum revealed correlations between H-7/C4, H-6/C9 and H13/C9, confirming the placement of the ether links between C4/C7, C6/C9 and C9/C13 to lead to the structure of **1** for chinzellene.

The relative stereochemistry was determined through coupling constants of the ^1H NMR spectroscopic data together with analysis of the NOESY spectrum. The ^1H NMR spectrum of **1** showed coupling constants of $J_{4,5\alpha} = 8.8$ Hz, $J_{4,5\beta} = 5.4$ Hz, $J_{5\alpha,6} = 4.9$ Hz, $J_{5\beta,6} = 0$ Hz, $J_{6,7} = 4.9$ Hz and $J_{7,8} = 0$ Hz. These data were very similar to those of a bromoallene (**6**), which was isolated from the Miyake-jima sample and *Laurencia okamurai* (as *Laurencia okamurai*) (Suzuki and Kurosawa, 1985). The stereochemistry between H-6 and H-7 was shown to be *cis* by their coupling constant ($J_{6,7} = 4.9$ Hz). The *cis*-relationship between H-6 and H-7 was also verified by a NOE correlation between both protons. The J -values between H β -5/H-6 and H-7/H-8 were observed as 0 Hz,

thus indicating that the dihedral angles between H β -5 and H-6 and between H-7 and H-8 are approximately 90° . Hence, the configurations between H β -5 and H-6 and between H-7 and H-8 are both *trans*. Similarly, the J -value (0 Hz) between H-12 and H-13 showed that the configuration between H-12 and H-13 is *trans*. Furthermore, the absence of NOEs between H-8/H $_2$ -11 and H-8/H-10 indicated that the configuration between the H-8 and C9–C10 bond is *trans* and therefore the C9–C10 bond is in an *exo*-configuration. Close similarity of J -values of H-4 in compounds **1** and **6** revealed that the bromoallene side chain of **1** is the same *exo*-configuration as **6**. Judging from the strong positive rotation of **1**, the absolute configuration of the bromoallene moiety would be assigned as *S* by application of Lowe's rule (Lowe, 1965). Thus the structure of chinzellene would be represented by formula **1** or **1'**, excluding the relative configuration between C3 and C4, which remains unsettled.

Chinzellene (**1**) has a structure very similar to okamuraallene (**7**) and its congeners, which have been isolated from *Laurencia intricata* Lamouroux (Suzuki et al., 1989; Suzuki et al., 1991). Recently, okamuraallene (**7**) was found in *L. intricata* as the major metabolite, that had been collected at Chinzei (Masuda et al., 2002). In addition, a bromoallenic C $_{15}$ acetogenin (**3**) was previously isolated from *L. intricata* (Suzuki et al., 1989).

Compound **2**, colorless oil, $[\alpha]_D^{24} + 39.3^\circ$ (CHCl_3), having a molecular formula of $\text{C}_{24}\text{H}_{37}\text{BrO}_5$, was obtained from both the Chinzei and Hachijo-jima samples. Its IR spectrum showed the presence of hydroxyl and acetoxyl groups at ν_{max} 3510, 1730 and 1230 cm^{-1} . The presence of these oxygen-containing functionalities was also evident in the ^1H NMR spectrum (Table 2), which revealed signals due to a hydroxyl proton at δ_{H} 1.85 (1H, s; D_2O exchangeable) and two acetoxyl methyls at δ_{H} 2.04 and 2.10 (each 3H, s). Thus five oxygen atoms implied by the molecular formula of **2** have all been assigned. Furthermore, the ^1H and ^{13}C NMR spectra (Table 2) showed the presence of a vinyl group [δ_{H} 5.17 (1H, d, $J = 17.6\text{ Hz}$), 5.31 (1H, d, $J = 10.7\text{ Hz}$) and 5.80 (1H, dd, $J = 17.6, 10.7\text{ Hz}$); δ_{C} 115.2 (CH_2) and 141.1 (CH)] and a vinylidene group [δ_{H} 4.75 (1H, s) and 4.84 (1H, s); δ_{C} 114.5 (CH_2) and 141.9 (C)]. In addition, the ^1H and ^{13}C NMR spectra revealed signals due to four tertiary methyl groups [δ_{H} 1.12, 1.13, 1.23 and 1.25 (each 3H, s)] and three quaternary carbons [δ_{C} 38.6, 40.2 and 75.4 (each C)]. The ^1H – ^1H COSY and HSQC spectra as well as the above-mentioned data

showed the presence of partial structural units **2a**–**2c** in the molecule (Fig. 2). Confirmation of the partial structural units and their connectivity were made by analysis of the HMBC spectrum (Table 2). Mutual long-range correlations between two tertiary methyls at δ_{H} 1.12 (δ_{C} 19.2) and 1.13 (δ_{C} 30.6) indicated that these methyls comprise a *gem*-dimethyl group. Moreover, these *gem*-dimethyls (H_3 -16 and H_3 -17) showed long-range correlations to C3 at δ_{C} 69.0 in unit **2a** and C5 at δ_{C} 49.0 in unit **2b**, thus confirming that the *gem*-dimethyl group can be inserted between C3 and C5. A correlation between the vinylidene proton (H_2 -19) and C7 (δ_{C} 36.4) indicated that another end (C7) of **2b** was connected to the vinylidene group to lead to an expanded formula **2d**.

The tertiary methyl (H_3 -20) at δ_{H} 1.23, which is adjacent to the oxygen-bearing quaternary carbon (C13; δ_{C} 75.4), showed long-range correlations to C12 (δ_{C} 77.2) in unit **2c** and the vinyl methine carbon (C14; δ_{C} 141.1) to give an expanded formula **2e**. Furthermore, the remaining tertiary methyl (H_3 -18) at δ_{H} 1.25, which is attached to C10 (δ_{C} 38.6), showed long-range correlations to C1 (δ_{C} 39.0), C5 and C9 (δ_{C} 53.4). In addition, C9 (δ_{C} 53.4) had a long-range correlation to vinylidene proton (H_2 -19), leading to the formula **2** with a labdane skeleton. The relative stereochemistry of **2** was deduced from the coupling constants in the ^1H NMR spectrum as well as from the NOESY experiment.

The coupling constants of the methine proton ($J = 13.2$ and 4.2 Hz) at C3 showed that the H-3 is axial in a chair cyclohexane ring and hence the bromine atom adopts an equatorial configuration. Furthermore, a NOE correlation between H-3 and H-5 indicated that the proton at C5 is axial. The J -value (2.9 Hz) between H-5 and H-6 showed that the proton at C6 is equatorial and therefore the acetoxyl group is axial. Based on the above-mentioned data together with NOEs between H-5/H-6, H_a -2/ H_3 -18 and H_3 -18/H-9, the relative stereochemistry would be shown as Fig. 3, while the stereochemistry at C12 and C13 remains undetermined.

Thus the structure of **2** was assigned as (3*R**,5*S**,6*S**,9*S**,10*S**)-3-bromo-6,12-diacetoxy-13-hydroxylabd-8(19),14-diene. Compound **2** is closely related to (–)-paniculatol, which has previously been isolated from *Laurencia paniculata* (C. Agardh) J. Agardh collected at Al Wakrah Bay, 30 km south of Doha, Qatar (Briand et al., 1997).

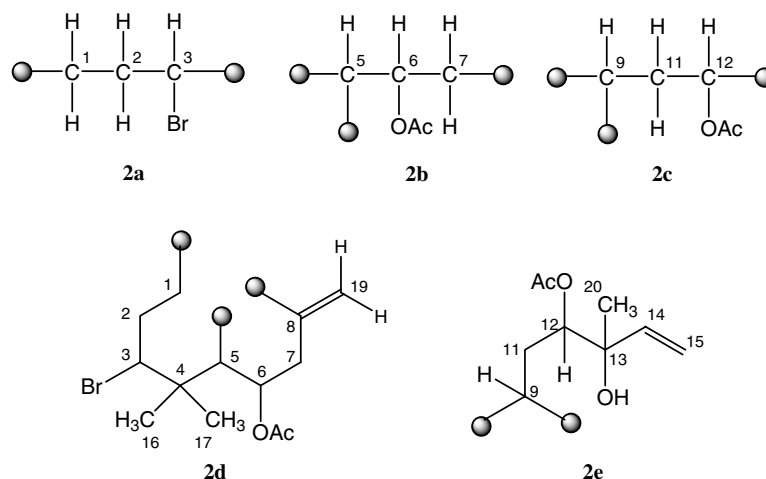
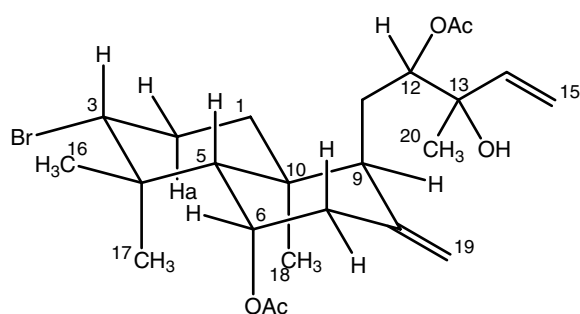
Compound **6** was a major metabolite of a specimen collected at Miyake-jima Island and found to be identical with a bromoallene that has previously been obtained from *Laurencia okamurae* (as *Laurencia okamurai*) Yamada collected at Ago Bay, Mie Prefecture (Suzuki and Kurosawa, 1985). Recently, compound **6** was also found as aplysiallene from the sea hare *Aplysia kurodai* Baba, which was collected from Echizen Coast, Fukui Prefecture (Okamoto et al., 2001). Our reported chemical shift values and assignment of carbon signals in the

Table 2
 ^{13}C NMR (100 MHz, DEPT), ^1H NMR (400 MHz), and HMBC data^a for **2**

C	$^{13}\text{C}^b$ (δ)	^1H (δ)	Multiplicity, J (Hz)	Long range spectroscopic correlations
1	39.0	1.72 1.08	<i>m</i> , (Ha) <i>m</i> , (Hb)	H-5, H ₃ -18
2	31.2	2.26 2.14	<i>m</i> , (Ha) <i>m</i> , (Hb)	H-3
3	69.0	3.94	<i>dd</i> , $J = 13.2, 4.2$	H ₃ -16, H ₃ -17
4	40.2			H ₃ -16, H ₃ -17
5	49.0	1.33	<i>d</i> , $J = 2.9$	H ₃ -16, H ₃ -17, H ₃ -18
6	71.0	5.39	<i>m</i>	
7	36.4	2.23	<i>m</i>	H ₂ -19
8	141.9			H-9, H _a -11, H ₂ -19
9	53.4	1.67	<i>m</i>	H ₃ -18, H ₂ -19
10	38.6			H _a -1
11	26.1	1.87 1.55	<i>m</i> , (Ha) <i>m</i> , (Hb)	
12	77.2	4.76	<i>d</i> , $J = 10.2$	H ₃ -20
13	75.4			H-14, H ₂ -15, H ₃ -20
14	141.1	5.80	<i>dd</i> , $J = 17.6, 10.7$	H _a -15, H ₃ -20
15	115.2	5.31 5.17	<i>d</i> , $J = 10.7$ (Ha) <i>d</i> , $J = 17.6$ (Hb)	
16	19.2	1.12	<i>s</i>	H-5, H ₃ -17
17	30.6	1.13	<i>s</i>	H-5, H ₃ -16
18	25.4	1.25	<i>s</i>	H _b -1, H-9
19	114.5	4.84 4.75	<i>s</i> , (Ha) <i>s</i> , (Hb)	
20	25.1	1.23	<i>s</i>	
OH		1.85	<i>s</i>	
Ac1	170.2			H-12
Ac2	171.0			
Me1	21.7	2.04	<i>s</i>	
Me2	21.1	2.10	<i>s</i>	

^a Measured in chloroform- d_1 .

^b Assigned by the HSQC spectrum.

Fig. 2. Partial structural units for **2**.Fig. 3. Stereochemistry of **2**.

^{13}C NMR spectrum of **6** had been mistaken and hence the corrected chemical shifts as well as their assignment are described in Section 3. Compounds **1** and **2** were inactive against some marine bacteria in a bioassay using the paper disc diffusion method (Vairappan et al., 2001).

Chemical compositions of two samples from Chinzei (Saga Prefecture) and Hachijo-jima Island (Tokyo) had a close resemblance to those of *Laurencia intricata* Lamouroux (Suzuki et al., 1989, 2002b; Masuda et al., 2002). Another sample from Miyakejima-island (Tokyo) was found to be chemically related to *Laurencia okamurai* Yamada (Suzuki et al., 1979; Suzuki and Kurosawa, 1985). Findings from this study gave additional information on chemotaxonomical relevance of halogenated metabolites in the red algal genus *Laurencia*.

3. Experimental

3.1. General

^1H NMR (400 MHz) and ^{13}C NMR (100 MHz), TMS as int. standard; Low and high resolution MS:

70 eV; CC: silica gel (Merck, Kieselgel 60, 70–230 mesh); Prep. TLC: silica gel plate (Merck, Kieselgel 60_{254s}). The known compounds were identified by comparison of spectroscopic data as well as optical rotations with those of authentic samples.

3.2. Collection

Specimens of *Laurencia* sp. were collected from three different locations; (1) sample of *Laurencia* sp. (SAP 089394) from Hatomisaki, Chinzei, Saga Prefecture, collected on July 18, 1997, (2) sample of *Laurencia* sp. (SAP 094609) from Nanbarasenjokiki, Hachijo-jima Island, Tokyo, collected on July 11, 1998, and (3) sample of *Laurencia* sp. (SAP 094612) from Tsubota, Miyake-jima Island, Tokyo, collected on July 14, 1998. The voucher specimens are deposited in the Herbarium of Graduate School of Science, Hokkaido University (SAP).

3.3. Extraction and isolation of the Chinzei specimen (SAP 089394)

The partially dried alga (20 g) was extracted with 500 mL MeOH. The MeOH solution was concentrated in vacuo and partitioned between 200 mL Et₂O and 100 mL H₂O. The Et₂O solution was washed with H₂O, dried (anhydrous Na₂SO₄) and evaporated to leave a dark green oil (311 mg). The extract (200 mg) was then fractionated by Si gel cc with a step gradient (hexane and EtOAc). The fraction (27.3 mg) eluted with hexane/EtOAc (9:1) was further separated by repeated prep. TLC with toluene or toluene/EtOAc (3:1) to give chinzallene (**1**) (10.0 mg; 0.078% based on the weight of dried alga). The fraction (33.5 mg) eluted with hexane/EtOAc (1:1) was separated by repeated prep. TLC with toluene/EtOAc (3:1) or hexane/acetone (3:1) to give compounds **2** (3.5 mg; 0.027%) and **3** (4.0 mg; 0.031%). Compound **3** was identified as a

C₁₅ acetogenin that was previously found from *Laurencia intricata* Lamouroux (Suzuki et al., 1989).

3.4. Compound 1

Oil: $[\alpha]_D^{21} + 184^\circ$ (CHCl₃; *c* 0.57); IR V_{\max} (neat) cm⁻¹: 3060, 1960, 1380, 1360, 1125, 1080, 1051, 960, 860; for ¹H and ¹³C NMR (CDCl₃) spectra, see Table 1; LR-EMS *m/z* (rel. int.): 408, 406, 404 (1:2:1) [M]⁺, 379, 377, 375 (16:29:16) [M – C₂H₅]⁺, 327, 225 (10:9) [M – Br]⁺, 309, 307 (49:49), 289, 287 (19:18) [M – C₃H₂Br]⁺, 271, 269 (40:41), 228 (35), 190 (64), 120 (49), 97 (50), 91 (34), 81 (39), 43 (100); HR-EIMS *m/z*: 405.9605. Calc. for C₁₅H₁₈⁷⁹Br⁸¹BrO₃ 405.9610 [M].

3.5. Compound 2

Oil: $[\alpha]_D^{24} + 39.3^\circ$ (CHCl₃; *c* 0.25); IR V_{\max} (neat) cm⁻¹: 3510, 1730, 1368, 1230, 1025; for ¹H and ¹³C NMR spectra, see, Table 2; LR-FDMS *m/z* (rel. int.): 487, 485 (24:23) [M + H]⁺, 427, 425 (10:10) [M + H – CH₃CO₂H]⁺; LR-EIMS *m/z* (rel. int.): 426, 424 (2:2) [M – CH₃CO₂H]⁺, 366, 364 (20:19) [M – CH₃CO₂Hx2]⁺, 285 (31) [M – CH₃CO₂Hx2 – Br]⁺, 267 (27), 201 (29), 187 (41), 145 (31), 119 (42), 114 (42), 71 (66), 69 (41), 43 (100); HR-FDMS *m/z*: 487.1860. Calc. for C₂₄H₃₈⁸¹BrO₅, 487.1882 [M + H].

3.6. Extraction and isolation of the Hachijo-jima Island specimen (SAP 094609)

The partially dried alga (80 g) from Hachijo-jima Island was treated as described above to give a dark green oil (1.23 g). The extract (400 mg) was then separated by Si gel column chromatography followed by prep. TLC with hexane/EtOAc (3:1) to yield **2** (23.6 mg; 0.091%).

3.7. Extraction and isolation of the Miyake-jima Island specimen (SAP 094612)

The partially dried alga (70 g) from Miyake-jima Island was treated as described above to give a dark green oil (1.40 g). The extract (290 mg) was separated by Si gel column chromatography. The fraction (23.3 mg) eluted with hexane/EtOAc (9:1) was further separated by prep. TLC with hexane/toluene (1:1) to give compound **4** (1.9 mg; 0.013%), which was identified as 2,10-dibromo-3-chloro- α -chamigrene that has previously been found from other *Laurencia*; *Laurencia* sp. (Howard and Fenical, 1975), *Laurencia nipponica* Yamada (as *Laurencia glandulifera* Kützinger) (Suzuki et al., 1979), and *Laurencia japonensis* Abe et Masuda (Takahashi et al., 1999). The fraction (78.2 mg) eluted with hexane/EtOAc (3:1) was then

separated by repeated prep. TLC with toluene or hexane/EtOAc (3:1) to give compounds **5** (8.1 mg; 0.056%) and **6** (18.7 mg; 0.13%). Compound **5** was identified as laurinterol that was previously isolated from *Laurencia okamurai* (as *Laurencia intermedia* or *Laurencia okamurai*) Yamada (Irie et al., 1970; Suzuki and Kurosawa, 1979) and compound **6** was identified as a C₁₅ acetogenin, which has previously been found from *Laurencia okamurai* (as *Laurencia okamurai*) (Suzuki and Kurosawa, 1985).

3.8. Compound 6

¹³C NMR (CDCl₃); CH₃: δ 13.4 (C15), CH₂: δ 29.7 (C14), 40.7 (C5), 41.4 (C8), CH: δ 73.9 (C1), 76.6 (C4), 79.7 (C9), 83.9 (C6), 84.1 (C7), 101.0 (C3), 125.9 (C11), 130.4 (C12), 133.1 (C10), C: δ 132.2 (C13), 201.8 (C2).

Acknowledgements

This research was supported in part by a 21st Century Center of Excellence (COE) Program on “Neo-Science of Natural History” (Program Leader: Professor Hisatoshi Okada) at Hokkaido University financed by the Ministry of Education, Culture, Sports, Science and Technology, Japan (to M.M.).

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