Isolation of Diterpenoids of the Cladiellane Class from Gorgonians of the Genus *Muricella*

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Six diterpenoids of the cladiellane class have been isolated from two morphologically distinct populations of gorgonians of the genus *Muricella*. The structures of two novel compounds have been determined by combined spectroscopic methods. These compounds exhibited significant brine shrimp lethality and cytotoxicity.

Recently we reported the isolation and structure determination of four 9,10-secosteroids and a carotenoid pigment from two morphologically distinct populations of gorgonians of the genus *Muricella* (Paramuriceidae, order Gorgonacea) collected from Jaeju Island, Korea.[1,2] These compounds exhibited significant cytotoxicity and brine-shrimp lethality. However, careful examination of ^{1}H-NMR spectra and results of brine-shrimp lethality tests of silica vacuum flash chromatographic fractions revealed the presence of a structurally very distinct group of bioactive metabolites. In this paper, we wish to report the isolation, structure determination, and bioactivity of six diterpenoids of the cladiellane class, including two novel compounds.

Fractions eluted with moderately polar solvents (25−40% EtOAc in hexane) from silica vacuum flash chromatography of the crude extract were combined and subjected to Sephadex LH-20 column chromatography. Fractions exhibiting significant toxicity (LD_{50} < 50 ppm) against brine shrimp larvae were combined and separated by silica and reversed-phase HPLC. In this manner, five cladiellane diterpenoids (**1**−**5**) were isolated from a population of *Muricella* sp. (sample no. 92J-18), while only one compound (**6**) of the same structural class was isolated from another population (sample no. 92J-16) of gorgonians possessing distinct morphological features.[3,4]

The structures of three known metabolites, astrogorgin (**1**), ophirin (**2**), and calicophirin B (**3**), were readily determined by combinations of spectroscopic analysis and comparison with reported data for these compounds. Ophirin, previously isolated from the gorgonians *Muricella* sp. and *Astrogorgia* sp., was the major metabolite (2.60% of the crude extract), while astrogorgin and calicophirin B, known metabolites of the gorgonians *Astrogorgia* sp. and *Calicogorgia* sp., respectively, were isolated in smaller amounts (0.22 and 0.38% of the crude extract, respectively).[5−7]

A closely related metabolite (**4**) was isolated as a white solid that was analyzed for $C_{22}H_{34}O_3$ by a combination of HRMS and ^{13}C-NMR spectrometry. The ^{1}H- and ^{13}C-NMR spectra of **4** were very similar to those obtained for **3**. The only significant differences in the NMR data were the upfield displacement of signals of the acetoxyl-bearing methine at C-13 of **3**, suggesting that **4** was the 13-deacetoxyl derivative of **3**. Confirmation of the structure of **4** and NMR assignments of its protons and carbons were established by a combination of the ^{1}H COSY, HMQC, and HMBC experiments (Table 1). Compound **4** possessed asymmetric carbon centers at the same positions (C-1, -2, -3, -9, -10, and -14) as other compounds. The relative stereochemistries of these centers were determined by a NOESY experiment in which several correlations were found between the methine and methyl protons. The key correlations were those between H-2 and H-14, H-2 and Me-15, H-6 and Me-15, H-9 and Me-17, and H-10 and Me-16 (Experimental Section), which were identical with those obtained for calicophirins.[7] Thus, the relative configurations of **4** were defined as 1*R**,2*R**,3*R**,9*R**,10*R**,14*R**.

A minor metabolite (**5**) was isolated as a colorless oil. The molecular formula of this compound was deduced as $C_{26}H_{38}O_7$ by combined HRMS and ^{13}C-NMR spectrometry. NMR data of **5** were highly compatible with those derived from related compounds. Combinations of the ^{1}H COSY, HMQC, and HMBC experiments revealed that the gross structure of **5** was identical with ophirin (**1**). However, careful examination of the ^{13}C-NMR data revealed that chemical shifts of the carbons at C-7, C-8, and C-16 were significantly different from those of other compounds. The signal of the C-16 methyl carbon in particular was observed at δ 28.87, about 10 ppm lower than those of related compounds possessing the 6*E* double bonds.[8] Therefore, the geometry of the C-6 double bond of **5** must be *Z*. The *Z* geometry of the C-6 double bond was confirmed by NOEDS experiments in which the signal of Me-16 was significantly enhanced by irradiation of H-6 and H-10, while NOE enhancement was not found between H-6 and H-8. To the best of our knowledge, this is the first example of a diterpenoid of the cladiellane class possessing the 6*Z* double bond.

The crude extract of another *Muricella* sp. (92J-16) was separated by using the same chromatographic methods. A diterpenoid of the cladiellane class was isolated, and its structure was determined as cladiellin (**6**) previously isolated from the soft coral *Cladiella* sp., by combined spectroscopic methods.[9] However, compounds **1**−**5** isolated from the other population of *Muricella* sp. (92J-18) were not present. Thus, two sympatric but morphologically distinct populations of *Muricella* sp. were defined to be chemically different also.

Diterpenoids of the cladiellane class have been isolated from a variety of coelenterates of the orders

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Table 1. ^{13}C NMR Assignments for Compounds **4**, **5**, and **7**[a]

	compound					
no.	**4**		**5**		**7**	
1	40.53	d	38.34	d	37.57	d
2	87.69	d	84.31	d	91.76	d
3	89.31	s	85.95	s	78.80	s
4	32.43	t	33.60	t	36.42	t
5	22.90	t	22.48	t	23.23	t
6	129.51	d	130.37	d	130.34	d
7	126.41	s	130.43	s	127.68	s
8	43.78	t	39.05	t	45.99	t
9	80.94	d	79.85	d	82.63	d
10	46.50	d	45.30	d	49.20	d
11	132.54	s	139.38	s	137.79	s
12	121.40	d	120.81	d	125.73	d
13	22.90	t	66.32	d	65.36	d
14	38.26	d	43.22	d	51.28	d
15	21.97	q	23.81	q	26.98	q
16	19.21	q	28.87	q	18.74	q
17	22.25	q	21.66	q	21.97	q
18	28.56	d	83.60	s	73.42	s
19	21.70	q[b]	25.51	q[b]	28.22	q[b]
20	20.18	q[b]	25.41	q[b]	28.17	q[b]
Ac	169.81	s	170.45	s		
			170.00	s		
			169.92	s		
	22.86	q	22.60	q		
			22.42	q		
			21.33	q		

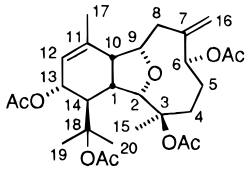
[a] Spectral data were obtained at 125 MHz in $CDCl_3$ (**4** and **5**) and CD_3OD (**7**) solutions, respectively. Assignments were aided by DEPT, HMQC, and HMBC experiments. [b] Signals are interchangeable.

Table 2. Results of Brine-Shrimp Lethality Test for the Cladiellane Diterpenoids

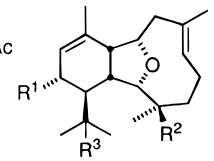
compound	brine-shrimp lethality[a]	compound	brine-shrimp lethality[a]
1	1.8	**6**	1.3
2	8.7	**7**	48.0
3	1.0	**8**	39.2
4	0.3		

[a] Results are given as LD_{50} in ppm.

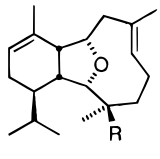
Alcyonacea and Gorgonacea.[5−7,9−11] Several compounds of this class have been reported to possess various bioactivities including antifungal, cytotoxic, and hemolytic activities as well as inhibitory activities against insect growth and cell division of fertilized sea urchin eggs. A literature survey revealed that marine cladiellins frequently possess one acetoxyl group or more at various positions of the carbon skeleton, which attracted our attention to the role of these functionalities on the bioactivity.[10] In our measurement of bioactivity, all of the natural products (**1**−**4** and **6**) exhibited significant toxicity against brine-shrimp larvae (Table 2). Interestingly among compounds **2**, **3**, and **4**, structurally varying only by the number of their acetoxyl groups, the monoacetate **4** was the most active one, while the triacetate **2** was the least active. The role of acetoxyl groups on bioactivity was further investigated by using semisynthetic hydroxyl derivatives. Treatment with $LiAlH_4$ converted the major metabolites **2** and **4** to the corresponding alcohols **7** and **8**, respectively; their structures were confirmed by combined spectroscopic methods. Compound **8** was previously isolated as a metabolite of an unidentified Pacific soft coral.[11] Compared to the natural products, **7** and **8** were much less toxic to brine-shrimp larvae (Table 2). The LD_{50} value of **8** in particular was more than 100 times higher than that of the corresponding acetate **4**. Although more systematic investigation is needed to generalize this observation, our results demonstrated the role of acetoxyl groups on the bioactivity of diterpenoids of the cladiellane class. In addition to brine-shrimp lethality, the novel diterpenoid **4** exhibited moderate in vitro cytotoxicity against human tumor cell-lines. The ED_{50} values of **4** were 12.7, 21.3, 11.6, and 13.9 μg/mL against A-549 non-small cell lung cancer, SKOV-3 ovarian cancer, SK-MEL-2 melanoma, and HCT-15 colon cancer cell-lines, respectively.



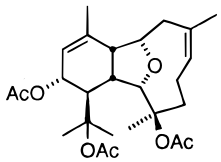
1



2 $R^1 = R^2 = R^3 = OAc$
3 $R^1 = R^2 = OAc$, $R^3 = H$
7 $R^1 = R^2 = R^3 = OH$



4 R = OAc
8 R = OH



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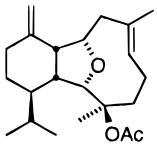

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Experimental Section

General Experimental Procedures. NMR spectra were recorded in $CDCl_3$ and CD_3OD solutions on a Varian Unity-500 spectrometer. ^1H- and ^{13}C-NMR spectra were measured at 500 and 125 MHz, respectively. All of the chemical shifts were recorded with respect to internal Me_4Si. IR spectra were recorded on a Mattson GALAXY spectrophotometer. MS were obtained by the Mass Spectrometry Facility, Department of Chemistry, University of California, Riverside. The optical rotations were measured on a JASCO digital polarimeter using a 5-cm cell. Melting points were measured on a Fisher-Johns apparatus and are reported uncorrected. All solvents used were spectral grade or were distilled from glass prior to use.

Animal Material. The animals (sample number 92J-16 and 92J-18) were collected by hand using scuba at 20−25 m depth in July 1992, along the offshore of Jaeju Island, South Sea, Korea.[3] The collected samples were briefly dried under shade and kept at −25 °C until chemically investigated. These gorgonians, *Muricella* sp. (family Paramuriceidae) are closely related to *M. perramosa* and *M. nitida* in general morphological features. However, specimens of 92J-18 differ in branching pattern, distribution of calyces, and especially the size and shape of spicules.[4] Specimens of 92J-16 are morphologically very similar to those of 92J-18. However, differences were found in the arrangements of polyps, the shape of axis, and the size and distribution of spicules.[4] In addition to the morphological differences, silica TLC analysis of the CH_2Cl_2 extracts showed a marked discrepancy between specimens of 92J-16 and 92J-18.[12]

Extraction and Isolation. Samples of 92J-18 (2.1 kg) were defrosted, macerated, and repeatedly extracted with CH_2Cl_2. The crude extracts (7.7 g) were separated by silica vacuum flash chromatography by using se-

quential mixtures of *n*-hexane and EtOAc. Fractions eluted with moderately polar solvents (25−40% EtOAc in hexane) were combined and subjected to Sephadex LH-20 column chromatography (hexane−CH_2Cl_2−EtOH 2:3:0.05). Fractions exhibiting significant toxicity against brine shrimp larvae (LC_{50} < 50 ppm) were combined and separated by semipreparative silica HPLC (YMC silica column, 15% EtOAc in hexane) to yield compounds **1**−**5** in the order of **3**, **4**, **1**, **2**, and **5**. Final purification was made by C_{18} reversed-phase HPLC (YMC ODS column, 100% CH_3CN) to give 17.3, 200.4, 21.7, 63.0, and 3.0 mg of **1**−**5**, respectively (0.22, 2.60, 0.38, 0.82, and 0.04% of crude extract, respectively).

Samples of 92J-16 (2.5 kg) were extracted and separated by using methods identical to those for 92J-18. The moderately polar fractions from silica vacuum flash chromatography of crude extract (9.23 g) were combined and then separated by LH-20 column chromatography. Bioactive fractions were combined and subjected to silica HPLC to yield partially pure **6**. Final purification by C_{18} reversed-phase HPLC (YMC ODS column, 10% H_2O in MeOH) gave 47 mg of pure compound: 0.50% of crude extract.

Astrogorgin (1): colorless gum; $[\alpha]^{25}_D$ −100.3° (*c* 1.0, $CHCl_3$) (lit.[6] $[\alpha]^{25}_D$ −118.7°); LREIMS $(M)^+$ *m*/*z* 520 (0.7, rel int), 460 (5), 400 (9), 358 (23), 298 (32), 269 (27), 175 (53), 133 (81), 105 (50), 43 (100).

Ophirin (2): white solid; mp 94−95 °C; $[\alpha]^{25}_D$ −119.7° (*c* 1.0, $CHCl_3$) (lit.[6] $[\alpha]^{25}_D$ −120.2°); HREIMS $(M)^+$ *m*/*z* obsd 462.2596; calcd for $C_{26}H_{38}O_7$, 462.2618; LRMS 462 (0.4, rel int), 402 (10), 300 (4), 174 (29), 159 (11), 145 (18), 133 (27), 43 (100).

Calicophirin B (3): colorless oil; $[\alpha]^{25}_D$ −90.0° (*c* 0.8, $CHCl_3$) (lit.[6] $[\alpha]^{25}_D$ −106°); HREIMS $(M)^+$ *m*/*z* obsd 404.2566; calcd for $C_{24}H_{36}O_5$, 404.2563; LRMS 404 (1, rel int), 344 (7), 241 (13), 201 (11), 173 (15), 147 (30), 119 (14), 93 (44), 43 (100).

Compound 4: white solid; mp 78−79 °C; $[\alpha]^{25}_D$ −34.7° (*c* 0.5, $CHCl_3$); IR (KBr) ν max 3020, 2930, 2870, 1735, 1450, 1370, 1245, 1070, 1204 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.48 (1H, ddt, *J* = 10.5, 7.1, and 1.5 Hz, H-6), 5.42 (1H, br s, H-12), 4.08 (1H, dd, *J* = 5.4, 3.4 Hz, H-9), 4.06 (1H, d, *J* = 6.8 Hz, H-2), 2.50 (1H, dd, *J* = 13.7, 5.4 Hz, H-8), 2.42 (1H, br s, H-10), 2.40 (1H, m, H-1), 2.37 (1H, m, H-5), 2.28 (1H, ddd, *J* = 13.2, 5.4, 3.4 Hz, H-4), 2.14 (1H, m, H-5), 2.08 (1H, m, H-13), 2.05 (1H, br d, *J* = 13.7 Hz, H-8), 2.00 (1H, ddd, *J* = 13.2, 11.2, 4.9 Hz, H-4), 1.93 (3H, s, Ac), 1.92 (1H, br d, *J* = 17.8 Hz, H-13), 1.81 (3H, d, *J* = 1.0 Hz, Me-16), 1.74 (3H, s, Me-15), 1.70 (3H, d, *J* = 1.5 Hz, Me-17), 1.65 (1H, d heptet, *J* = 6.8, 6.8 Hz, H-18), 1.43 (1H, ddd, *J* = 6.8, 5.4, 4.9 Hz, H-14), 0.97 (3H, d, *J* = 6.8 Hz, Me-19), 0.84 (3H, d, *J* = 6.8 Hz, Me-20); NOESY correlations H-2/H-14, H-15, and H-18; H-6/H-15; H-8/H-16; H-10/H-17; HMBC correlations (optimized for 7 Hz of coupling constant) H-8/C-6, C-7, C-9, C-10, and C-16; H-15/C-2, C-3, and C-4; H-16/C-6, C-7, and C-8; H-17/C-10, C-11, and C-12; H-19/C-14, C-18, and C-20; H-20/ C-14, C-18, and C-19; HREIMS $(M)^+$ *m*/*z* obsd 346.2528; calcd for $C_{22}H_{34}O_3$, 346.2528; LRMS 346 (10, rel int), 286 (15), 243 (15), 217 (20), 177 (16), 147 (23), 121 (21), 93 (44), 81 (22), 43 (100).

Compound 5: colorless gum; $[\alpha]^{25}_D$ −35.3° (*c* 0.1, $CHCl_3$); IR (film) ν max 2930, 2860, 1735, 1370, 1255, 1130, 1100, 1020 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.63 (1H, br d, *J* = 5.4 Hz, H-12), 5.53 (1H, dd, *J* = 10.7, 5.9 Hz, H-6), 5.37 (1H, br d, *J* = 5.4 Hz, H-13), 4.42 (1H, d, *J* = 10.3 Hz, H-2), 4.39 (1H, dd, *J* = 2.5, 1.5 Hz, H-9), 3.04 (1H, br s, H-14), 2.97 (1H, br dd, *J* = 10.3, 7.8 Hz, H-1), 2.82 (1H, d, *J* = 14.2 Hz, H-8), 2.68 (1H, dd, *J* = 12.9, 12.7 Hz, H-4), 2.59 (1H, ddd, *J* = 12.2, 10.7, 9.8 Hz, H-5), 2.45 (1H, br d, *J* = 7.8 Hz, H-10), 2.01 (3H, s, Ac), 2.00 (3H, s, Ac), 1.99 (1H, m, H-5), 1.97 (3H, s, Ac), 1.85 (1H, dd, *J* = 14.2, 4.4 Hz, H-8), 1.84 (3H, br s, Me-16), 1.78 (3H, br s, Me-17), 1.77 (3H, s, Me-15), 1.69 (1H, m, H-4), 1.57 (3H, s, Me-19), 1.36 (3H, s, Me-20); HMBC correlations (optimized for 7 Hz of coupling constant) H-15/C-3 and C-4; H-16/C-6, C-7, and C-8; H-17/C-10, C-11, and C-12; H-20/C-14, C-18, and C-19; HRCIMS $(M + NH_4)^+$ *m*/*z* obsd 480.2943; calcd for $C_{26}H_{42}NO_7$, 480.2961; LRMS (5, rel int), 403 (53), 343 (13), 300 (16), 283 (19), 213 (12), 175 (27), 151 (26), 133 (34), 43 (100).

Cladiellin (6): white solid; mp 69−71 °C; $[\alpha]^{25}_D$ −3.1° (*c* 0.5, $CHCl_3$); LREIMS $(M)^+$ *m*/*z* 346 (0.2, rel int), 288 (9), 243 (11), 177 (19), 147 (45), 123 (17), 121 (21), 93 (76), 43 (100).

Reduction of Ophirin (2). To a stirred solution of **2** (23.4 mg, 0.05 mmol) in dry Et_2O (5 mL) was added $LiAlH_4$ (24.8 mg, 0.65 mmol) and stirred under N_2 at room temperature for 3 h. After quenching the reaction by adding saturated Na_2SO_4 solution (5 mL), saturated brine solution (15 mL) was added and the organic materials were extracted with Et_2O (30 mL × 3). After drying the solution with $MgSO_4$ and removing the solvent under vacuum, the residue was subjected to C_{18} reversed-phase HPLC (100% CH_3CN) to yield **7** (16.1 mg, yield 79%) as a white solid: mp 88−89 °C; $[\alpha]^{25}_D$ −49.7° (*c* 0.1, $CHCl_3$); IR (KBr) ν max 3350, 2930, 1670, 1370, 1150, 1070, 1025 cm^{-1}; ^1H NMR (CD_3OD) δ 5.66 (1H, d, *J* = 4.9 Hz, H-12), 5.44 (1H, br dd, *J* = 8.8, 8.8 Hz, H-6), 4.39 (1H, d, *J* = 9.8 Hz, H-2), 4.34 (1H, d, *J* = 6.4 Hz, H-9), 4.24 (1H, br d, *J* = 5.4 Hz, H-13), 2.79 (1H, dd, *J* = 9.8, 8.8 Hz, H-1), 2.47 (1H, br d, *J* = 9.3 Hz, H-10), 2.41 (1H, br s, H-14), 2.41 (1H, m, H-5), 2.40 (1H, dd, *J* = 13.2, 6.3 Hz, H-8), 2.27 (1H, ddd, *J* = 13.2, 13.2, 6.8 Hz, H-4), 2.04 (1H, ddd, *J* = 13.2, 8.8, 6.8 Hz, H-5), 2.03 (1H, d, *J* = 13.2 Hz, H-8), 1.81 (3H, s, Me-16), 1.77 (3H, s, Me-17), 1.49 (1H, dd, *J* = 13.7, 6.4 Hz, H-4), 1.37 (3H, s, Me-15), 1.18 (3H, s, Me-19), 1.16 (3H, s, Me-20); HRFABMS $(M + Na)^+$ *m*/*z* obsd 359.2181; calcd for $C_{20}H_{32}NaO_4$, 359.2198.

Reduction of 4. The same reaction as described for the formation of **7** gave **8** as a white solid (yield 53%): mp 56−57 °C; $[\alpha]^{25}_D$ −18.1° (*c* 0.07, $CHCl_3$) (lit.[11] $[\alpha]^{25}_D$ −22.7°); ^1H NMR ($CDCl_3$) δ 5.52 (1H, br dd, *J* = 10.8, 6.3 Hz, H-6), 5.40 (1H, dd, *J* = 2.4, 1.5 Hz, H-12), 4.11 (1H, dd, *J* = 5.4, 2.9 Hz, H-9), 3.83 (1H, d, *J* = 7.3 Hz, H-2), 2.51 (1H, dd, *J* = 13.7, 5.4 Hz, H-8), 2.42 (2H, m, H-5, H-10), 2.39 (1H, m, H-1), 2.10 (1H, ddd, *J* = 17.5, 2.9, 2.4 Hz, H-13), 2.05 (2H, m, H-4, H-5), 2.01 (1H, br d, *J* = 13.7 Hz, H-8), 1.95 (1H, br d, *J* = 17.5 Hz, H-13), 1.83 (3H, d, *J* = 1.5 Hz, Me-16), 1.69 (3H, d, *J* = 1.5 Hz, Me-17), 1.56 (1H, m, H-18), 1.53 (1H, m, H-4), 1.50 (1H, m, H-14), 1.41 (3H, s, Me-15), 0.97 (3H, d, *J* = 6.8 Hz, Me-19), 0.84 (3H, d, *J* = 6.8 Hz, Me-20); ^{13}C NMR ($CDCl_3$) δ 132.72 (C, C-11), 129.23 (CH, C-6), 126.63 (C, C-7), 121.36 (CH, C-12), 89.70 (CH, C-2), 80.84 (CH, C-9), 77.18 (C, C-3), 46.88 (CH, C-10), 44.28 (CH_2, C-8),

40.12 (CH, C-1), 38.26 (CH, C-14), 36.67 (CH_2, C-4), 28.92 (CH, C-18), 27.38 (CH_3, C-15), 22.75 (CH_2, C-13), 21.91 (CH_2, C-5), 21.56 (CH_3, C-19), 20.62 (CH_3, C-20), 18.84 (CH_3, C-16); LREIMS *m/z* 304 (2, rel int), 286 (71), 243 (59), 218 (100), 203 (60), 177 (42), 147 (96), 135 (39), 121 (46), 105 (72), 93 (91).

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References and Notes

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(3) The voucher specimens, under the code names 92J-16 and 92J-18, are on deposit in the octocorallian collection, Natural History Museum, Ewha Womans University, Seoul, Korea under the curatorship of Jun-Im Song.
(4) Details of morphological characters for each voucher specimen are described by Seo *et al.*[1] and Rho *et al.*[2]
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