Further Kabiramides and Halichondramides, Cytotoxic Macrolides Embracing Trisoxazole, from the *Hexabranchus* Egg Masses[1]

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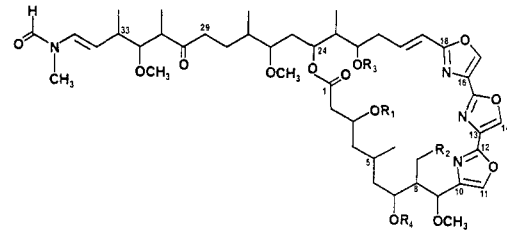
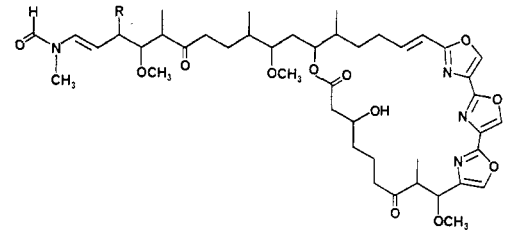
Six cytotoxic macrolides, kabiramides A (**2**), B (**3**), D (**4**), E (**5**), dihydrohalichondramide (**6**), and 33-methyldihydrohalichondramide (**7**) have been isolated from the *Hexabranchus* egg masses. Their structures have been elucidated by spectroscopic methods. They were cytotoxic against murine leukemia cells and fertilized sea urchin eggs.

Nudibranch mollusks possess well-developed chemical defenses, which have attracted the attention of natural products chemists.[2,3] Although they are quite distinct in shape and color and are avoided by predators, the chemistry of their egg masses had been overlooked until recent discoveries of the extraordinary bioactive macrolides, ulapualides A and B[4] and kabiramide C (**1**).[5] We have looked further into related metabolites of the egg masses deposited by *Hexabranchus* sp. collected at Kabira Bay, Ishigaki Island of the Ryukyus, and Hachijo Island of the Izu Archipelago. From these we have isolated six bioactive macrolides, viz. kabiramides A (**2**), B (**3**), D (**4**), and E (**5**), dihydrohalichondramide (**6**), and 33-methyldihydrohalichondramide (**7**). We report here the isolation and structure elucidation of **2**–**7**. Egg masses of *Hexabranchus* sp. were extracted with MeOH, and the extract was subjected to silica gel column chromatography ($CHCl_3$–MeOH, 98:2). The antifungal fractions were purified by reverse-phase HPLC (ODS, 76% MeOH in water). Kabiramides A–E were obtained from the Kabira collection, while dihydrohalichondramide, 33-methyldihydrohalichondramide, and ulapualide B were isolated from the Hachijo collection. The structure of kabiramide C has been elucidated by extensive NMR measurements, which led us to assign all ^1H and ^{13}C NMR signals.[4-6]



1: R_1 = $CONH_2$; R_2 = H; R_3 = CH_3; R_4 = H
2: R_1 = $CONH_2$; R_2 = OH; R_3 = CH_3; R_4 = H
3: R_1 = $CONH_2$; R_2 = H; R_3 = H; R_4 = H
4: R_1 = H; R_2 = H; R_3 = CH_3; R_4 = H
5: R_1 = $COCH_3$; R_2 = H; R_3 = CH_3; R_4 = H
8: R_1 = $CONH_2$; R_2 = $OCOCH_3$; R_3 = CH_3; R_4 = $COCH_3$
9: R_1 = $CONH_2$; R_2 = H; R_3 = $COCH_3$; R_4 = $COCH_3$
10: R_1 = $COCH_3$; R_2 = H; R_3 = CH_3; R_4 = $COCH_3$



6: R = H
7: R = CH_3

Kabiramide A (**2**) was the most polar of the seven metabolites isolated from the egg masses. The UV and ^1H and ^{13}C NMR spectra (Tables I and II) indicated that this compound is related to kabiramide C (**1**).[7] The fast atom bombardment (FAB) mass spectrum revealed a molecular weight of 957, indicating that one additional oxygen was present in the molecule. The COSY spectrum revealed that the partial structures from C-2 to C-5 and C-19 to C-35 were identical with those of kabiramide C. Several discrepancies were observed for protons around C-8: one of the C-6 methylene protons appeared at lower field (δ 1.80 vs 1.66 in **1**) and downfield shifts for H-7 (δ 4.28 vs 3.81) and for H-9 (δ 4.91 vs 4.78). Most significant was the presence of a hydroxymethyl group [δ 3.66 (br dd, J = 3.5, 11.5 Hz), 3.98 (br dd, J = 4.0, 11.5 Hz)] at C-8 instead of a methyl group in **1**. Similarly, the ^{13}C NMR spectrum (Table II) of **2** was identical with that of **1** except for signals of C-7 (δ 70.6 vs 74.4 in **1**), C-8 (δ 44.8 vs 37.3 in **1**), and the absence of a C-8 methyl. A hydroxymethyl carbon appeared at δ 61.6 (t). The position of the two free hydroxyl groups was inferred from the ^1H NMR data of the diacetate **8**, which displayed two methyl singlets at δ 1.93 and 2.07, H-7 methine at δ 5.32 (1 H, br t), and a pair of methylene protons at δ 4.05 (2 H, d, J = 6.5 Hz). These data confirmed that kabiramide A possesses a hydroxymethyl group attached to C-8 instead of a methyl group as in kabiramide C.

Kabiramide B (**3**) is slightly more polar than kabiramide C as judged from silica gel TLC and ODS HPLC. The presence of the trisoxazole moiety was apparent from the UV and ^1H and ^{13}C NMR spectra (Table I and II). The FAB mass spectrum gave an MH^+ ion at m/z 928. The

(1) Part 25 of the bioactive marine metabolites series. Part 24: Kato, Y.; Fusetani, N.; Matsunaga, S.; Hashimoto, K.; Koseki, K. *J. Org. Chem.* **1988**, *53*, 3930.
(2) Faulkner, D. J. *Nat. Prod. Rep.* **1984**, *1*, 241 and 551; **1986**, *3*, 1; **1987**, *4*, 539.
(3) Karuso, P. *Bioorganic Marine Chemistry 1*; Scheuer, P. J., Ed.; Springer-Verlag: New York, 1987; pp 31–60.
(4) Roesener, J. A.; Scheuer, P. J. *J. Am. Chem. Soc.* **1986**, *108*, 846.
(5) Matsunaga, S.; Fusetani, N.; Hashimoto, K.; Koseki, K.; Noma, M. *J. Am. Chem. Soc.* **1986**, *108*, 847.
(6) The numbering of the carbon atoms in **1** has been revised due to biogenetic considerations discussed in ref 9.
(7) As in the case of **1**, ^1H and ^{13}C NMR signals for **2**–**7** in the vicinity of the *N*-methylformamide terminus were doubled.

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Table I. ^{1}H NMR Data for 1–7

	1[b]	2[a]	3[a]	4[a]	5[a]	6[c]	7[c]
2	2.39, 2.56	2.40, 2.56	2.40, 2.60	2.32, 2.45	2.55, 2.76	2.50, 2.50	2.50, 2.50
3	5.13	5.19	5.16	4.27	5.58	4.31	4.28
3-$CONH_2$	6.48	6.34	*d*		2.24[e]		
4	1.31, 1.82	1.32, 1.86	1.34, 1.88	0.99, 1.91	1.25, 1.93	1.63, 1.70	1.61, 1.72
5	1.89	1.86	1.88	2.25	1.75	1.89, 1.93	1.90, 1.90
5-Me	0.89	0.96	0.91	0.99	0.91		
6	1.66, 1.66	1.65, 1.80	1.70, 1.70	1.47, 1.52	1.52, 1.52	2.60, 2.69	2.58, 2.68
7	3.81	4.28	3.82	3.84	3.89		
7-OH	3.13						
8	2.13	2.07	2.08	2.20	2.06	3.28	3.31
8-Me	0.97	3.66, 3.98[f]	0.99	0.80	0.88	0.95	0.93
9	4.78	4.91	4.83	4.41	4.58	4.65	4.63
9-OMe	3.42	3.49[g]	3.43	3.38	3.33	3.35	3.32
11	7.55	7.63	7.57	7.63	7.57	7.58	7.56
14	8.07	8.09	8.07	8.10	8.09	8.08	8.06
17	8.01	8.02	8.02	8.06	8.04	8.04	8.02
19	6.26	6.28	6.30	6.27	6.30	6.34	6.32
20	7.44	7.39	7.28	7.08	7.02	7.05	7.03
21	2.38, 2.78	2.40, 2.76	2.23, 2.54	2.32, 2.71	2.37, 2.66	2.21, 2.45	2.20, 2.42
22	3.65	3.61	4.13	3.50	3.29	1.34, 1.70	1.32, 1.69
22-OMe	3.40	3.40	3.75[h]	3.29	3.32		
23	1.82	1.85	1.63	1.62	1.70	1.75	1.76
23-Me	0.85	0.87	0.95	0.87	0.98	0.89	0.87
24	5.29	5.30	5.00	5.27	5.25	5.11	5.07
25	1.44, 1.63	1.45, 1.65	1.46, 1.78	1.40, 1.60	1.45, 1.73	1.47, 1.57	1.48, 1.55
26	2.99	2.99	3.05	2.89	2.90	2.96	2.96
26-OMe	3.30	3.32	3.34	3.30	3.30	3.32	3.31
27	1.69	1.72	1.70	1.70	1.70	1.70	1.68
27-Me	0.80	0.81	0.80	0.78	0.81	0.82	0.80
28	1.25, 1.75	1.25, 1.75	1.26, 1.78	1.23, 1.75	1.26, 1.75	1.27, 1.77	1.26, 1.75
29	2.49, 2.49	2.50, 2.50	2.50, 2.50	2.49, 2.49	2.49, 2.49	2.50, 2.50	2.49, 2.49
31	2.66 (2.63)	2.67 (2.64)[i]	2.67 (2.65)	2.65 (2.62)	2.66 (2.64)	2.72	2.65
31-Me	0.87	0.89	0.90	0.90	0.91	0.98	0.89
32	3.28	3.29	3.28	3.27	3.29	3.45	3.30
32-OMe	3.31	3.31	3.33	3.31	3.32	3.28	3.30
33	2.40	2.40	2.40	2.37	2.37	2.14, 2.45	2.37
33-Me	1.13	1.14	1.13	1.13	1.14		1.12
34	5.08 (5.10)	5.09 (5.11)	5.09 (5.10)	5.08 (5.09)	5.09 (5.10)	5.08	5.07
35	6.43 (7.10)	6.44 (7.11)	6.44 (7.11)	6.42 (7.10)	6.44 (7.10)	6.51 (7.17)	6.43 (7.09)
35-NMe	3.00 (3.05)	3.02 (3.05)	3.02 (3.06)	3.01 (3.05)	3.02 (3.06)	3.02 (3.06)	3.01 (3.05)
35-NHCHO	8.26 (8.04)	8.26 (8.05)	8.27 (8.05)	8.26 (8.05)	8.27 (8.06)	8.27 (8.05)	8.26 (8.04)

[a] 500 MHz. Assignments were made by COSY spectrum. [b] From ref 4. Coupling constants for resolved protons are given in ref 4. [c] 400 MHz. Assignments are made by COSY spectrum. [d] Not observed. [e] Methyl protons of the acetyl group. [f] Methylene protons. [g] Assignments for the OCH_3 protons were tentative except in the case of 1. [h] Hydroxyl proton. [i] Chemical shifts for the minor rotamer are shown in parentheses.

NMR data revealed only three methoxy signals; one of the four methoxy groups of 1 appeared to be replaced by a hydroxyl group in **3**. The COSY spectrum revealed that kabiramide B had the same carbon framework as kabiramide C. The position of the additional free hydroxyl group was deduced to be at C-22 by comparing the ^{1}H and ^{13}C chemical shifts with those of **1**. The H-22 signal was shifted significantly downfield in Kabiramide B (Table I). Differences in ^{13}C signals were also observed, including a large upfield shift observed for C-22 (11.0 ppm) and some changes for C-20, C-21, C-23, C-23-methyl, and C-25 (Table II). The presence of free hydroxyl groups at C-7 and C-22 was also verified by the ^{1}H NMR spectrum of the diacetate **9** [δ 2.03 (3 H, s), 2.09 (3 H, s)], in which H-7 and H-22 methine protons were shifted downfield to δ 5.10.

The UV spectrum of kabiramide D (**4**) was virtually identical with those of other kabiramides, and the ^{13}C NMR signals for C-10–C-35 were almost superimposable on those of **1**. These features implied the presence of the common trisoxazole moiety conjugated with a disubstituted double bond. ^{1}H NMR data including a COSY spectrum revealed that **4** has the same carbon skeleton as kabiramide C (Table I). However, the chemical shifts for the H-3, H_2-4, and H-5 signals differed considerably from those of **1**, with the H-3 signal in **4** appearing at 0.86 ppm higher field than that of **1**. The carbon signal for the carbamate ester group observed at δ 157 in **1–3** was absent in **4** (Table II), and the FAB mass spectrum gave an MH^+ ion at m/z 899 (43 Da lower than **1**). These data indicated that the C-3 carbamoyl group in **1** was missing in **4**, and this was supported by the ^{1}H NMR spectrum of the diacetate **10**: H-3 and H-7 signals appeared at δ 5.57 and 5.10, respectively, in **10**.

Kabiramide E (**5**) had intense IR absorptions at 1730 and 1240 cm^{-1}, which were not observed for **1–4**. The UV spectrum and ^{1}H and ^{13}C NMR data indicated the presence of the common conjugated trisoxazole moiety. The COSY spectrum and ^{13}C NMR data (Tables I and II) indicated that **5** possessed the same carbon framework as **1**. The most significant difference was the presence of an acetyl group [δ 22.0 (q), 170.4 (s)] at C-3 instead of a carbamate ester group in **1–3**. This was also supported by the FAB mass spectrum (MH^+, m/z 941). Kabiramide E gave a monoacetate **10** identical with the diacetate derived from **4**. Thus, **5** is 3-*O*-decarbamoyl-3-*O*-acetylkabiramide C.

Dihydrohalichondramide (**6**) was the major component of the Hachijo collection of the *Hexabranchus* egg masses, which were much lighter in color than those from the Kabira collection. The FAB mass spectrum (MH^+, m/z 839) and the ^{13}C NMR spectrum led us to assign a molecular formula of $C_{44}H_{62}N_4O_{12}$. The ^{1}H and ^{13}C NMR

Table II. ^{13}C NMR Data for 1–7

	1[c]	2[a]	3[b]	4[a]	5[a]	6[d]	7[e]
1	171.6	171.4	171.9	172.7	171.6	172.8	172.8
2	43.0	42.8[f]	42.8	43.9[f]	40.5[f]	42.8	42.8
3	69.3	69.5	70.3	67.1[g]	67.6[g]	68.7	68.6
3-$CONH_2$	157.3	157.3	157.6		22.0, 170.4[l]		
4	45.1	45.0[f]	45.3	44.7[f]	42.6	37.2	37.1
5	25.1	25.7	25.3	24.9	25.2	20.2	20.2
5-Me	18.2	18.7	18.3	21.1	19.5		
6	43.6	42.8	43.3	44.4[f]	43.7[f]	42.4	42.4
7	74.4	70.6	73.5	71.3[g]	72.1[g]	211.6	211.7
8	37.3	44.8	37.2	40.2[h]	40.7[h]	48.3	48.3
8-Me	10.6	61.6[i]	10.6	13.5	12.1	10.3	10.4
9	78.3	78.7	78.3	78.8	79.1	78.3	78.1
9-OMe	57.6	58.6[j]	57.6	58.1	58.1	57.1	57.1
10	141.6	141.9	141.5	139.6	139.6	140.0	139.9
11	135.5	135.6	135.7	137.2	136.2	136.2	136.3
12	155.4	155.7	155.3	155.5	155.4	155.0	155.0
13	131.1	131.2	131.0	131.1	131.5	131.4	131.4
14	136.8	137.1	136.9	137.3	137.4	137.4	137.4[g]
15	156.4	156.5	156.4	156.8	156.5	156.3	156.3
16	129.9	130.0	129.7	130.0	130.5	130.2	130.1
17	137.1	137.5	137.2	137.5	137.5	137.4	137.5[g]
18	163.2	163.2	163.3	163.0	162.5	163.1	163.1
19	115.4	115.7	115.1	116.4	116.9	115.5	115.4
20	142.0	142.0	145.4	141.3	140.7	143.8	143.9
21	34.0	34.3	37.8	34.0	34.1	29.0	29.0
22	79.2	79.5	68.2	79.9	80.5	31.4	31.4
22-OMe	57.4	57.6		57.7	57.4		
23	40.5	40.7	42.6	42.5[h]	40.0[h]	35.9	35.6
23-Me	8.4	8.5	9.2	9.1	8.3	15.2	15.1
24	74.1	74.1	74.3	72.5[g]	73.8[g]	74.2	74.2
25	33.1	33.0	34.5	33.2	32.6	32.1	32.0
26	82.0	82.1	82.1	81.9	81.8	81.9	81.8
26-OMe	57.9	57.9	57.8	58.1	57.8	57.7	58.1
27	34.6 (34.7)[k]	34.7	34.5	34.7	34.7	34.7	34.7
27-Me	15.5	15.6	15.5	15.6	15.6	15.5	15.4
28	25.1 (25.0)	25.0	25.0	25.0	25.0	25.0	24.9
29	42.3 (42.4)	42.4	42.3	42.5	42.5	41.5 (41.3)	42.3 (42.4)
30	214.0 (214.1)	214.1 (214.2)	214.1 (214.2)	214.1 (214.2)	214.1	213.5	214.2 (214.1)
31	49.0 (49.1)	49.1	49.0 (49.1)	49.1	49.2	48.9	49.1 (49.2)
31-Me	13.5 (13.6)	13.7	13.6	13.7	13.7	12.9 (12.8)	13.5
32	87.3 (87.4)	87.4	87.3 (87.4)	87.4 (87.5)	87.4 (87.5)	82.4	87.3 (87.4)
32-OMe	61.3	61.4	61.3	61.4	61.4	57.7 (57.5)	61.4
33	37.4 (37.6)	37.5 (37.7)	37.4 (37.6)	37.5 (37.7)	37.6 (37.8)	30.5 (30.3)	37.4 (37.6)
33-Me	19.3 (19.4)	19.4	19.3	19.4	19.5		19.3
34	111.4 (113.2)	111.5 (113.2)	111.3 (113.1)	111.5 (113.2)	111.5 (113.2)	105.5 (107.1)	111.4 (113.2)
35	128.7 (124.8)	128.8 (124.8)	128.7 (124.8)	128.8 (124.8)	128.8 (124.8)	130.2 (126.4)	128.8 (124.8)
35-NMe	27.6 (33.1)	27.7 (33.1)	27.6 (33.1)	27.7 (33.2)	27.7 (33.2)	27.5 (33.0)	27.6 (33.1)
35-NCHO	162.1 (160.8)	162.2 (161.1)	162.1 (160.8)	162.2 (160.9)	162.2 (161.0)	162.1 (160.8)	162.2 (160.9)

[a] 25 MHz. Assignments were made by comparison with those for 1. [b] 125 MHz. Assignments were made by (C, H) COSY spectrum. [c] From ref 4. [d] 100 MHz. Assignments were made by (C, H) COSY spectrum. [e] 100 MHz. Assignments were made by comparison with those for 1–6. [f–h] Assignments may be interchanged within a column. [i] Methylene carbon. [j] Assignments for the OCH_3 carbons in all the compounds except 1 are tentative. [k] Chemical shifts for the minor rotamer are shown in parentheses. [l] Acetate group.

spectra showed the presence of a conjugated trisoxazole moiety and the ene-*N*-methylformyl terminal side chain characteristic of this class of compounds. Partial structures consisting of C-2–C-6, C-8, and C-9, C-19–C-29, and C-31–C-35 were deduced from careful interpretation of homonuclear and heteronuclear COSY spectra. The chemical shift values for the protons on C-2, C-6, C-8, C-29, and C-31 (δ 2.49–3.31) suggested that these carbons are adjacent to carbonyl carbons. The presence of an *O*-acyl group on C-24 was inferred from the chemical shift of 5.11 ppm for the H-24 signal. Three methyl ethers could be placed on C-9, C-26, and C-32 on the basis of the ^{13}C shifts of 78.1, 81.8, and 87.3 (87.4) ppm, respectively. Therefore, the remaining oxygenated methine (C-3) must be substituted by a free hydroxyl group. Connectivity of the partial structures mentioned above was accomplished as follows. The doubled C-29 methylene carbon, which must be in the side chain, was joined to C-31 via a ketone carbon. The polarized Δ^{19}-olefin was connected to C-18 on the basis of coupling between C-18 and H-20, which was demonstrated by an LSPD experiment.[8] The connectivity between C-9 and C-10 was apparent from the presence of a long-range coupling between H-9 and H-11. Enhancement of H_2-6 signals upon irradiation of C-8 methyl protons in a qualitative NOE difference experiment indicated that C-8 and C-6 were joined through the remaining ketone carbon. Finally esterification of the C-24 oxygen with the C-1 carboxyl carbon led us to assign the gross structure as **6**. Interestingly, **6** possesses a 5,6-dihydrohalichondramide structure. Halichondramide was isolated from a Pacific sponge *Halichondria* sp.[9]

The second compound from the Hachijo collection was identified as ulapualide B based on the FAB mass and NMR spectral data.[4] The third compound, 33-methyl-

(8) Seto, H.; Sasaki, T.; Yonehara, H.; Uzawa, J. *Tetrahedron Lett.* **1978**, *923*.

(9) Kernan, M. R.; Faulkner, D. J. *Tetrahedron Lett.* **1987**, *28*, 2809. Professor Faulkner has also isolated dihydrohalichondramide from the Pacific nudibranch *Hexabranchus sanguineus* and its egg masses (private communication).

dihydrohalichondramide (7) possessed a molecular formula larger by one methylene than that of 6. The ^{13}C NMR spectrum of 7 was almost superimposable on that of 6 except for the signals assignable to a unit from C-31 to C-35. The signals for the terminal portion of the side chain of 7 were, however, superimposable on those of 1–5, thereby indicating that 7 possessed a 33-methylated dihydrohalichondramide structure. This was supported by COSY spectroscopy which enabled us to make a full ^1H signal assignment.

Kabiramides and 6 and 7 were strongly active in the sea urchin egg assay (IC_{99}: 2, 1 μg/mL; 6 and 7, 0.5 μg/mL; 1 and 3–5, 0.2 μg/mL) and also cytotoxic against L1210 cells (IC_{50}: 1, 0.01 μg/mL; 2, 3, and 6, 0.03 μg/mL; 4 and 5, 0.02 μg/mL; 7, 0.05 μg/mL). A recent report of the isolation of kabiramides B and C and halichondramide from the sponges of the genus *Halichondria*[9] strongly suggests that compounds of this class are accumulated from sponge(s) on which nudibranchs feed, though we have not been able to specify the origin. A biogenesis of the trisoxazole moiety has been proposed by Moore and coworkers.[10]

Experimental Section

Infrared spectra were recorded on a JASCO IR-G spectrometer. Ultraviolet spectra were measured on a Hitachi 330 spectrophotometer. Optical rotations were determined by a JASCO DIP-140 polarimeter. ^1H and ^{13}C NMR spectra were recorded on either a Bruker AM500 NMR spectrometer, a JEOL GX400 NMR spectrometer, or a JEOL FX100 NMR spectrometer. Mass spectra were measured on a JEOL DX303 mass spectrometer.

Collection of the Egg Masses. Specimens of the egg masses of *Hexabranchus* sp. were collected by hand at Kabira Bay (−1 to −2 m) in Ishigaki Island of the Ryukyus, or in Hachijo Island (−15 m) of the Izu Archipelago. The egg masses were frozen immediately after collection and kept frozen at −20 °C until extraction.

Extraction and Isolation. The egg masses (220 g of the Kabira collection and 50 g of the Hachijo collection) were separately homogenized in MeOH, and the MeOH extract was evaporated under reduced pressure. The $CHCl_3$-soluble portion of each extract was applied to a silica gel column (2 × 30 cm) and developed with $CHCl_3$–MeOH (98:2). Fractions were monitored by bioautography on silica gel TLC ($CHCl_3$–MeOH, 98:2) with *Penicillium chrysogenum*. Antifungal fractions were collected and filtered through a short ODS column (Fuji-Devison, 2 × 5 cm) with 90% MeOH in water. The effluent was further subjected to HPLC on an ODS column (YMC, 2 × 30 cm) with 76% MeOH in water to yield kabiramide A (2, 10 mg), kabiramide B (3, 14 mg), kabiramide C (1, 70 mg), kabiramide D (4, 6 mg), and kabiramide E (5, 6 mg), in order of elution, from the Kabira collection and dihydrohalichondramide (6, 23 mg), ulapualide B (13 mg) and 33-methyldihydrohalichondramide (7, 11 mg), in order of elution, from the Hachijo collection.

Kabiramide A (2): $[\alpha]^{23}_D$ +6° (*c* 0.1, $CHCl_3$); UV λ_{max} (MeOH) 245 nm (ε 25 000); IR (neat) 3450, 2850, 1720, 1650, 1460, 1375, 1270, 1090, 910, 760 cm^{-1}; ^1H NMR ($CDCl_3$) see Table I; ^{13}C NMR ($CDCl_3$) see Table II; FABMS (diethanolamine) *m/z* 958 (MH^+).

Kabiramide B (3): $[\alpha]^{23}_D$ +8° (*c* 0.1, $CHCl_3$); UV λ_{max} (MeOH) 245 nm (ε 24 000); IR (neat) 3450, 3330, 3150, 2850, 1710, 1650, 1590, 1550, 1460, 1370, 1275, 1090, 910, 760 cm^{-1}; ^1H NMR ($CDCl_3$) see Table I; ^{13}C NMR ($CDCl_3$) see Table II; FABMS (diethanolamine) *m/z* 928 (MH^+).

Kabiramide D (4): $[\alpha]^{23}_D$ −5° (*c* 0.1, $CHCl_3$); UV λ_{max} (MeOH) 245 nm (ε 23 000); IR (neat) 3450, 3150, 2850, 1720, 1685, 1650, 1555, 1460, 1370, 1275, 1090, 910, 760 cm^{-1}; ^1H NMR ($CDCl_3$) see Table I; ^{13}C NMR ($CDCl_3$) see Table II; FABMS (diethanolamine) *m/z* 899 (MH^+).

Kabiramide E (5): $[\alpha]^{23}_D$ −20° (*c* 0.1, $CHCl_3$); UV λ_{max} (MeOH) 245 nm (ε 25 000); IR (neat) 3450, 3150, 2880, 1730, 1685, 1650, 1460, 1370, 1270, 1240, 1085, 910, 760 cm^{-1}; FABMS (diethanolamine) *m/z* 941 (MH^+); ^1H NMR ($CDCl_3$) see Table I; ^{13}C NMR ($CDCl_3$) see Table II.

Dihydrohalichondramide (6): $[\alpha]^{23}_D$ −55° (*c* 0.5, $CHCl_3$); UV λ_{max} (MeOH) 245 nm (ε 26 800); IR (neat) 3400, 3150, 2850, 1720, 1700, 1655, 1460, 1375, 1265, 1090, 910, 760 cm^{-1}; FAB mass spectrum (diethanolamine) *m/z* 944 (MH + diethanolamine)$^+$, 861 (M + Na)$^+$, 839 $(MH)^+$, 821 (MH − H_2O)$^+$; ^1H NMR ($CDCl_3$) see Table I; ^{13}C NMR ($CDCl_3$) see Table II.

33-Methyldihydrohalichondramide (7): $[\alpha]^{23}_D$ − 53° (*c* 0.5, $CHCl_3$); UV λ_{max} (MeOH) 242 nm (ε 24 600); IR (neat) 3400, 3150, 2850, 1720, 1700, 1655, 1460, 1370, 1270, 1090, 910, 750 cm^{-1}; FAB mass spectrum (diethanolamine) *m/z* 958 (MH + diethanolamine)$^+$, 875 (M + Na)$^+$, 853 $(MH)^+$, 835 (MH − H_2O)$^+$; ^1H NMR ($CDCl_3$) see Table I; ^{13}C NMR ($CDCl_3$) see Table II.

Acetylation of Kabiramides. To 1 mg of each kabiramide in pyridine (1 mL) was added acetic anhydride (1 mL). After being stirred overnight at room temperature, the reaction mixture was sonicated for 10 min and evaporated azeotropically with toluene. Each product was purified by ODS HPLC (YMC, 1 × 30 cm) with 78% MeOH in water.

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(10) Ishibashi, M.; Moore, R. E.; Patterson, G. M. L.; Xu, C.; Clardy, J. *J. Org. Chem.* **1986**, *51*, 5300.