New Acetylenic Compounds from the Stony Coral *Montipora* sp.

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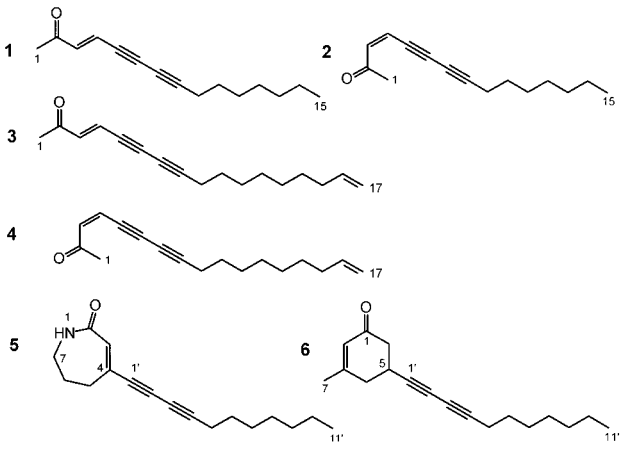
Six new acetylenic compounds (**1**−**6**) with cytotoxic activities against human solid tumor cell lines (SK-OV-3, SK-MEL-2, XF498, and HCT15) have been isolated from the stony coral *Montipora* sp. Structures of the compounds **1**−**6** were elucidated based on analysis of the NMR and MS data.

Stony corals (hard coral, scleractinian) have been overlooked as a source of bioactive compounds since many secondary metabolites are assumed to function in a defensive manner, and the calcareous body of these animals is assumed to fulfill the defensive role. Nonetheless, there are limited literature data to show that hard corals do produce interesting natural products and more recently evidence of the ecological roles of these metabolites. Of the few secondary metabolites isolated from stony corals, anthraquinoid derivatives,[1] tubastrine,[2] tubastraine,[3] and aplysinopsin[4] are known, and a few acetylenic compounds have been reported especially from the *Montipora* spp.[5−7] In the course of our search for cytotoxic constituents from marine invertebrates, significant cytotoxicity was detected in the crude extract of the stony coral *Montipora* sp. (Acroporidae). Further bioactivity-guided fractionation of this coral extract afforded a series of novel acetylenic compounds (**1**−**6**). Here we report the isolation, structure elucidation, and biological evaluation of the acetylenic compounds from the stony coral *Montipora* sp. collected from Korean waters.



Results and Discussion

Guided by the brine shrimp lethality assay,[8] the MeOH extract of the frozen corals was partitioned between H_2O and EtOAc, followed by partitioning of the EtOAc layer between H_2O and $CHCl_3$. The $CHCl_3$ layer was then subjected to successive reversed-phase flash column chromatography, MPLC, and HPLC to yield montiporynes A−F (**1**−**6**) as the causative constituents. Montiporynes A−F were generally labile at room temperature but were stable at −20 °C. The montiporynes showed moderate to marginal cytotoxicity against a small panel of human solid tumor cell lines (Table 1) with a rather selective cytotoxicity against a skin cancer cell line (SK-MEL-2). The trans isomers (**1**, **3**) of the linear chain congeners were most active, while the cis isomers (**2**, **4**) were nearly inactive. The cytotoxicities of **1** and **3** against SK-MEL-2 (human skin cancer) were comparable to that of cisplatin. All of these congeners were inactive to A549 (human lung cancer).

Table 1. In Vitro Cytotoxicities (ED_{50}, μg/mL) of Montiporynes against Human Solid Tumor Cells[a]

compound	A549	SK−OV-3	SK-MEL-2	XF498	HCT15
1	>50	3.2	1.4	1.9	3.7
3	>50	2.5	1.5	3.2	5.2
5	>50	>50	>50	>50	>50
cisplatin	0.8	1.2	1.5	0.7	1.5
2	>50	25.9	42.6	>50	>50
4	>50	45.1	43.1	>50	>50
6	>50	29.2	36.7	31.3	45.1
cisplatin	0.6	0.9	0.7	0.6	0.6

[a] A549: human lung cancer; SK-OV-3: human ovarian cancer; SK-MEL-2: human skin cancer; XF498: human CNS cancer; HCT15: human colon cancer. Compounds were assayed in two separate batches.

Montiporyne A (**1**) was isolated as a yellow gum. The molecular formula of **1** was established as $C_{15}H_{20}O$ on the basis of the HREIMS and NMR data (Table 2, 3). The molecular ion was observed at *m*/*z* 216.1522 (Δ +3.5 ppm). The NMR data were characterized by a trans disubstituted olefin (δ_H 6.57, 6.73, J = 16.1 Hz, δ_C 141.2, 124.3), a singlet methyl signal (δ_H 2.25, δ_C 27.5), a triplet methyl signal (δ_H 0.91, δ_C 14.4), a carbonyl carbon (δ_C 199.3), and four quaternary acetylenic carbons (δ_C 65.5, 72.6, 84.9, 90.5). The two triple bonds were presumed to be conjugated because only one methylene group was deshielded (δ_H 2.39) by a neighboring acetylenic function. The typical chemical shifts of the olefin (δ_C 141.2, 124.3) indicated that it is conjugated with a carbonyl function. Considering its degree of unsaturation, the structure of **1** was postulated as a linear polyunsaturated ketone. The HMBC data of **1** clearly showed the long-range correlations between the quaternary carbons and the relevant protons, as depicted in Figure 1. All four quaternary acetylenic carbons showed correlations

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Table 2. ^{1}H NMR Data of **1**−**4**[a] (300 MHz, CD_3OD)

position	1	2	3	4
1	2.25 (s)	2.38 (s)	2.25 (s)	2.38 (s)
3	6.57 (d, 16.1)	6.28 (d, 11.5)	6.55 (d, 16.1)	6.28 (d, 11.5)
4	6.73 (d, 16.1)	6.46 (d, 11.5)	6.72 (d, 16.1)	6.46 (d, 11.5)
9	2.39 (t, 6.9)	2.39 (t, 6.9)	2.38 (t, 6.9)	2.38 (t, 6.9)
10	1.56 (quint, 7.4)	1.56 (quint, 7.3)	1.56 (quint, 7.2)	1.56 (quint, 7.2)
11	1.42 (quint, 5.2)	1.29−1.42 (m)	1.28−1.42 (m)	1.28−1.42 (m)
12−14	1.29−1.35 (m)	1.29−1.42 (m)	1.28−1.42 (m)	1.28−1.42 (m)
15	0.91 (t, 7.0)	0.90 (t, 7.0)	2.10 (quart, 6.8)	2.10 (quart, 6.8)
16			5.80 (ddt, 17.0, 10.2, 6.8)	5.80 (ddt, 17.0, 10.2, 6.8)
17			4.91 (dd, 10.2, 2.1)	4.91 (dd, 10.2, 2.1)
			4.98 (dd, 17.0, 2.1)	4.98 (dd, 17.0, 2.1)

[a] Multiplicities and coupling constants are in parentheses. Compound **1** and **2** were measured at 600 and 200 MHz, respectively.

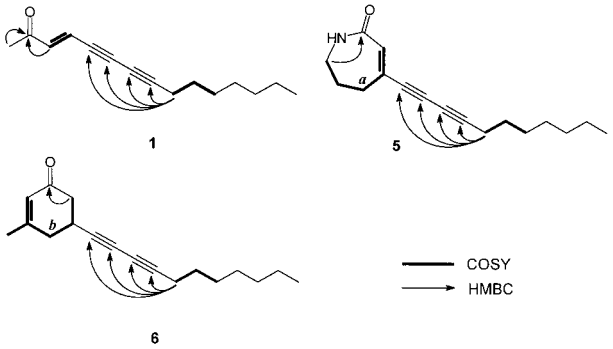

Figure 1. Diagnostic COSY and HMBC correlations of **1**, **5**, and **6**.

with the allylic protons at δ 2.39 (H-9). These allylic protons (H-9) showed weak but clear long-range (six-bond coupling) correlation with the olefinic carbon at δ 124.3 (C-4). Though shorter than this, such long-range (five-bond) coupling has been easily detected in a conjugated diyne system.[9] This quite long-range ^{1}H−^{13}C coupling might be possible through a conjugated system of two triple bonds and a double bond. Also the quaternary acetylenic carbons at δ 65.5, 84.9, and 90.5 showed correlations with the olefinic proton at δ 6.73 (H-4). The carbonyl carbon showed correlations with the olefinic proton at δ 6.57 (H-3) and the singlet methyl protons at δ 2.25 (H-1). Thus, the structure of montiporyne A was determined to be (*E*)-3-pentadecene-5,7-diyn-2-one.

Montiporyne B (**2**) was isolated as a yellow gum. Montiporyne B showed the same molecular weight and almost identical fragmentation pattern as that of **1** in the LREIMS. However, the NMR data of **2** were characterized by the presence of a cis disubstituted olefin (δ_H 6.28, 6.46, J = 11.5 Hz, δ_C 140.6, 120.5) in place of the trans disubstituted olefin, and a downfield shift of the singlet methyl signal (δ_H 2.38) compared to that of **1** (δ_H 2.25). Accordingly, **2** was postulated as a geometric isomer of **1**; thus the structure was determined to be (*Z*)-3-pentadecene-5,7-diyn-2-one.

Montiporyne C (**3**) was isolated as a yellow oil. Compared to those of **1**, the NMR data of **3** were characterized by the presence of an additional monosubstituted olefin (δ_H 4.91, 4.98, 5.80, δ_C 114.7, 140.1). Thus, the structure of **3** was presumed to be a linear polyunsaturated ketone with a terminal double bond. In the LRFABMS and LREIMS of **3**, the $[M + H]^+$ and $[M]^+$ ions were detected at *m*/*z* 243 and 242, respectively. Thus, the structure of montiporyne C was determined to be (3*E*)-3,16-heptadecadiene-5,7-diyn-2-one.

Montiporyne D (**4**) was isolated as a pale yellow oil. Montiporyne D showed almost the identical fragmentation pattern and the same molecular ion as that of **3** in the LREIMS. However, the NMR data were characterized by the presence of a cis disubstituted olefin (δ_H 6.28, 6.46, J = 11.5 Hz, δ_C 140.5, 120.5) in place of the trans disubstituted olefin and a downfield shift of the singlet methyl signal (δ_H 2.38). Accordingly, **4** was postulated as a geometric isomer of **3**, and the structure was determined to be (3*Z*)-3,16-heptadecadiene-5,7-diyn-2-one.

Table 3. ^{13}C NMR Data of **1**−**4**[a] (CD_3OD)

position	1	2	3	4
1	27.5	27.5	27.5	27.5
2	199.3	199.3	199.3	199.3
3	141.2	140.6	141.2	140.5
4	124.3	120.5	124.2	120.5
5	65.5[b]	65.6[b]	65.5[b]	65.5[b]
6	72.6[b]	72.7[b]	72.7[b]	72.7[b]
7	84.9[b]	84.9[b]	84.7[b]	84.7[b]
8	90.5[b]	90.5[b]	90.5[b]	90.5[b]
9	20.2	20.2	20.2	20.2
10	29.2	29.2	29.1	29.1
11−12	29.9, 29.8	29.9, 29.8	29.8−30.7	29.8−30.7
13	32.8	32.8	29.8−30.7	29.8−30.7
14	23.6	23.6	29.8−30.7	29.8−30.7
15	14.4	14.4	34.8	34.8
16			140.1	140.1
17			114.7	114.7

[a] Compound **1** and **2** were measured at 50 MHz; **3** and **4** were measured at 75 MHz. [b]Assignments with the same superscript in the same column may be interchanged.

As recognized in the NMR spectra, montiporynes A (**1**) and C (**3**) were always accompanied by montiporynes B (**2**) and D (**4**), respectively, as minor components. These congeners could be separated into each single component by HPLC, but slowly returned to equilibrium between two geometric isomers. The trans isomer prevailed over the cis isomer in the ratio of 12:1. Thus, it is supposed that these geometric isomers with an enone function can be transformed into each other at room temperature.

Montiporyne E (**5**) was isolated as a pale yellow gum. The molecular formula of **5** was established as $C_{17}H_{23}NO$ on the basis of the HREIMS and NMR data (Table 4). The molecular ion was observed at *m*/*z* 257.1783 (Δ +1.2 ppm). The NMR data of **5** were characterized by a trisubstituted olefin (δ_H 6.60, δ_C 115.7, 144.8), a triplet methyl group (δ_H 0.91, δ_C 14.4), a methylene group attached to a nitrogen (δ_H 3.35, δ_C 42.9), a carbonyl carbon (δ_C 170.5), and four quaternary acetylenic carbons (δ_C 65.7, 72.5, 85.5, 90.3). The chemical shift of the carbonyl carbon (δ_C 170.5) indicated that the carbonyl group is part of an amide function. The typical chemical shift of the olefin (δ_C 115.7, 144.8) indicated that it is conjugated with the carbonyl group. The COSY data of **5** revealed the partial structure ***a***, and one of the methylene groups of ***a*** was presumed to be connected to a nitrogen on the basis of its chemical shifts (δ_H 3.35, δ_C 42.9). Considering its degree of unsaturation, the presence of a cyclic structure was presumed. The HMBC data of **5** showed long-range correlations between

Table 4. ^{1}H and ^{13}C NMR Data of **5** and **6**[a] (CD_3OD)

	5		**6**	
position	^{1}H	^{13}C	^{1}H	^{13}C
1				189.5
2		170.5	5.89 (s)	126.5
3	6.60 (s)	115.7		164.2
4		144.8	2.62 (dd, 16.7, 4.6)	37.6
			2.49 (dd, 16.7, 9.0)	
5	2.75 (td, 6.5, 2.0)	28.2	3.19 (tt, 9.0, 4.6)	28.7
6	1.86 (quint, 5.4)	23.4	2.57 (dd, 16.4, 4.6)	43.4
			2.42 (dd, 16.4, 9.0)	
7	3.35 (t, 5.7)	42.9	2.00 (s)	24.5
1′		65.7[b]		65.9[b]
2′		72.5[b]		68.3[b]
3′		85.5[b]		78.8[b]
4′		90.3[b]		80.0[b]
5′	2.39 (t, 6.6)	20.2	2.25 (t, 6.6)	19.7
6′	1.56 (quint, 7.4)	29.3	1.50 (quint, 7.3)	29.4
7′	1.42 (quint, 7.5)	29.9[c]	1.39 (quint, 6.9)	29.9[c]
8′	1.29−1.34 (m)	29.8[c]	1.29−1.35 (m)	29.8[c]
9′	1.29−1.34 (m)	32.7	1.29−1.35 (m)	32.9
10′	1.29−1.34 (m)	23.6	1.29−1.35 (m)	23.7
11′	0.91 (t, 7.1)	14.4	0.90 (t, 7.0)	14.6

[a] ^{1}H and ^{13}C NMR were measured at 600 and 150 MHz, respectively. [b,c] Assignments with the same superscript in the same column may be interchanged.

the quaternary carbons and the relevant protons as depicted in Figure 1. The allylic protons at δ 2.39 (H-5′) showed correlations with all four quaternary acetylenic carbons. These allylic protons also showed a weak but clear long-range coupling with the olefinic proton at δ 6.60 (H-3) in the COSY spectrum. Thus, the structure of montiporyne E was determined to be 4-(1′,3′-undecadiynyl)-1,5,6,7-tetrahydro-2*H*-azepin-2-one.

Montiporyne F (**6**) was isolated as a pale yellow gum. The molecular formula of **6** was established as $C_{18}H_{24}O$ on the basis of the HREIMS and NMR data. The molecular ion was observed at *m*/*z* 256.1822 (Δ −2.1 ppm). The NMR data of **6** were characterized by a trisubstituted olefin (δ_H 5.89, δ_C 126.5, 164.2), a singlet methyl group (δ_H 2.00, δ_C 24.5), a triplet methyl group (δ_H 0.90, δ_C 14.6), a carbonyl carbon (δ_C 189.5), and four quaternary acetylenic carbons (δ_C 65.9, 68.3, 78.8, 80.0). The COSY data of **6** revealed the partial structure ***b***, and the chemical shift of the trisubstituted olefin (δ_C 126.5, 164.2) indicated that it is conjugated with the carbonyl group. The HMBC data of **6** showed long-range correlations between the quaternary carbons and the relevant protons as depicted in Figure 1. As in the case of montiporynes A (**1**) and E (**5**), all of the four quaternary acetylenic carbons showed correlations with the allylic protons (H-5′, δ_H 2.25). One of the methylene protons of ***b*** (H-6, δ_H 2.42, 2.57) showed correlations with the carbonyl carbon and one of the acetylenic carbons (δ_C 65.9). Thus, the structure of montiporyne F was determined to be 5-(1′,3′-undecadiynyl)-3-methyl-2-cyclohexene-1-one. The absolute configuration at C-5 was not determined.

Although various acetylenic compounds have frequently been encountered as bioactive constituents of the marine sponge *Petrosia* spp.[10] and other marine organisms,[11] montiporynes E (**5**) and F (**6**) are chemically unique, possessing a seven-membered lactam and a cyclohexenone moiety, respectively. Compounds **1**−**4** were chemically rather close to the previously reported polyacetylenes from stony corals.[5−7] While chemotactic (sperm attractant) activity was reported for the polyacetylenic alcohol from the eggs of *Montipora digitata*,[6] other biological activities such as ichthyotoxicity,[5] antimicrobial activity,[5,6] and cytotoxicity[6] were also ascribed to the polyacetylenes from stony corals.

Experimental Section

General Experimental Procedures. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AC200, a DMX600, and a Varian Unity Plus 300. Chemical shifts were reported in reference to the respective residual solvent peaks (δ_H 3.3 and δ_C 49.0 for CD_3OD). COSY, HMQC, and HMBC spectra were recorded on a Bruker DMX600. LR and HREIMS analyses were performed on a JEOL JMS-SX-102A, while FABMS data were obtained using a JEOL JMS-HX110/110A. HPLC was performed on a Gilson 370 pump with a YMC ODS-H80 (250 × 10 mm i.d., S-4 μm, 80 Å) column using a Shodex RI-71 detector at a flow rate of 1.8 mL/min and 1.5 mL/min.

Animal Material. The animals were collected by hand using scuba at a depth of 8 m on November 4, 1996, along the shore of Mundo, Cheju Island, Korea. The stony coral is closely related to *Montipora tuberculata* in general. However, these specimens differed in their characteristics as follows: corallum showed unifacial thick plates of 4−7 mm thickness (from 4 mm at margin to 7 mm on inner portion), corallites up to 1 mm in diameter immersed at 1.5−3 mm intervals, and reticulate intercalicular area covered with small papillae. Columella were absent. Septa were in two cycles with inwardly projecting spines, of which secondaries are rudimentary. Colonies were uniformly greenish brown. The collection was frozen immediately and kept in a freezer until chemically investigated. A voucher specimen was deposited in the Natural History Museum, Ewha Womans University (voucher no. EWUA. Ant. 961104).

Isolation of Compounds. The frozen coral (2.5 kg, wet weight) was extracted with MeOH at room temperature. Guided by the brine shrimp lethality assay, the MeOH extract was partitioned between water and EtOAc. The EtOAc layer was further partitioned between H_2O and $CHCl_3$ to afford 8.8 g of the $CHCl_3$ layer (LD_{50} 30−86 μg/mL), which was subjected to reversed-phase flash column chromatography (YMC Gel ODS-A, 60 Å, 500/400 mesh) eluting with a step gradient solvent system of 25→0% H_2O/MeOH to obtain 14 fractions (Fb-1−Fb-14). Fraction 4 (Fb-4, 3.11 g), which showed significant brine shrimp lethality (LD_{50} 0.1 μg/mL), was further subjected to a reversed-phase MPLC (YMC Gel ODS-A, 60 Å, 500/400 mesh) eluting with a solvent system of 33→0% H_2O/MeOH to yield 8 fractions (Fb-4-1−Fb-4-8). Fractions Fb-4-3−Fb-4-6 were combined (Fb-4′) and subjected again to a reversed-phase MPLC (YMC Gel ODS-A, 60 Å, 500/400 mesh) eluting with a solvent system of 20→5% H_2O/MeOH to yield 6 fractions. Fraction 6 (Fb-4′-6, 135 mg), which eluted at 5% H_2O/MeOH, was separated by consecutive C_{18} HPLC (YMC ODS-H80, 250 × 10 mm i.d., S-4 μm, 80 Å) eluting with 14% H_2O/MeOH and 17% H_2O/MeCN to yield compounds **1** (6.5 mg), **2** (1.2 mg), **5** (3.0 mg), and **6** (0.8 mg). Another active fraction (Fb-5, LD_{50} 0.1 μg/mL, 1.4 g) from the flash column chromatography was further subjected to a reversed-phase MPLC (YMC Gel ODS-A, 60 Å, 500/400 mesh) eluting with a solvent system of 25→14% H_2O/MeOH to yield 8 fractions (Fb-5-1−Fb-5-8). Fraction 7 (Fb-5-7, 30 mg) was separated consecutively by C_{18} HPLC (YMC ODS-H80, 250 × 10 mm i.d., S-4 μm, 80 Å) eluting with 20% H_2O/MeCN to yield compounds **3** (3.0 mg) and **4** (0.5 mg).

Montiporyne A (1): yellow gum; UV (EtOH) λ_{max} (log ϵ) 209 (4.4), 218 (4.4), 227 (4.4), 294 (4.2), 309 (4.2) nm; IR (film) ν_{max} 2926, 2228, 1729, 1463, 1273, 1073 cm^{-1}; ^{1}H NMR data, see Table 2; ^{13}C NMR data, see Table 3; LRFABMS *m*/*z* 239 $[M + Na]^+$, 217 $[M + H]^+$; LREIMS *m*/*z* 216 $[M]^+$ (28), 201 (20), 187 (27), 173 (65), 159 (50), 145 (75), 132 (70), 131 (100), 117 (63), 91 (72), 77 (40); HREIMS *m*/*z* 216.1522 (calcd for $C_{15}H_{20}O$, 216.1514).

Montiporyne B (2): yellow gum; ^{1}H NMR data, see Table 2; ^{13}C NMR data, see Table 3; LRFABMS *m*/*z* 217 $[M + H]^+$; LREIMS *m*/*z* 216 $[M]^+$ (10), 201 (10), 187 (32), 173 (31), 159 (34), 145 (67), 132 (100), 131 (64), 117 (30), 91 (36), 77 (24); HRFABMS *m*/*z* 217.1593 (calcd for $C_{15}H_{21}O$, 217.1592); HREIMS *m*/*z* 216.1497 (calcd for $C_{15}H_{20}O$, 216.1514).

Montiporyne C (3): yellow oil; ^{1}H NMR data, see Table 2; ^{13}C NMR data, see Table 3; LRFABMS *m*/*z* 243 $[M + H]^+$;

LREIMS *m*/*z* 242 $[M]^+$ (15), 241 (16), 227 (32), 213 (22), 199 (100), 185 (41), 173 (56), 171 (60), 159 (71), 145 (91), 131 (93), 129 (88), 117 (83), 91 (69), 77 (33).

Montiporyne D (4): pale yellow oil; ^{1}H NMR data, see Table 2; ^{13}C NMR data, see Table 3; LRFABMS *m*/*z* 243 $[M + H]^+$; LREIMS *m*/*z* 242 $[M]^+$ (13), 241 (12), 227 (22), 213 (21), 199 (52), 185 (25), 173 (42), 171 (47), 159 (65), 145 (83), 132 (100), 131 (74), 117 (46), 91 (42), 77 (23).

Montiporyne E (5): pale yellow gum; ^{1}H NMR data, see Table 4; ^{13}C NMR data, see Table 4; LRFABMS *m*/*z* 280 $[M + Na]^+$, 258 $[M + H]^+$; HREIMS *m*/*z* 257.1783 (calcd for $C_{17}H_{23}NO$, 257.1780).

Montiporyne F (6): pale yellow gum; ^{1}H NMR data, see Table 4; ^{13}C NMR data, see Table 4; LREIMS *m*/*z* 256 $[M]^+$ (3) 242 (5), 241 (5), 228 (33), 227 (20), 214 (65), 213 (38), 200 (26), 199 (20), 174 (71), 173 (62), 143 (45), 131 (100), 129 (78), 115 (25), 82 (27), 79 (10); HREIMS *m*/*z* 256.1822 (calcd for $C_{18}H_{24}O$, 256.1827).

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