New Xenicane Diterpenoids from the Gorgonian *Acalycigorgia inermis*

Jung-Rae Rho, Hyi-Seung Lee, Youngwan Seo, Ki Woong Cho, and Jongheon Shin*

Marine Natural Products Laboratory, Korea Ocean Research & Development Institute, Ansan P.O. Box 29, Seoul 425-600, Korea

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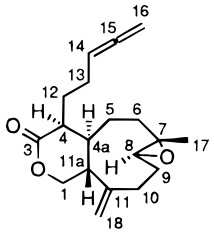
Acalycixeniolides C−F (**1**−**4**), four new diterpenoids of the xenicane class, have been isolated from the gorgonian *Acalycigorgia inermis*. The structures of these compounds have been determined by combined spectroscopic methods. These compounds exhibited cytotoxicity against a human leukemia cell-line.

Diterpenoids of the xenicane and related carbon skeletal classes are widely recognized as bioactive constituents of marine organisms such as brown algae and coelenterates.[1] Among coelenterates, these metabolites have been frequently isolated from gorgonians (Gorgonacea) and soft corals (Alcyonacea).[1−4] As a part of our search for bioactive substances from marine invertebrates, we encountered the orange-colored gorgonian *Acalycigorgia inermis* Hedlund (family Acanthogorgiidae) from the sandy bottom offshore from Keomun Island, Korea. The crude organic extract of this animal exhibited considerable brine shrimp lethality (LC_{50} 127 ppm) and cytotoxicity against the P-388 cell line (LC_{50} 37 μg/mL). Guided by the bioactivity tests and ^{1}H NMR analysis, vacuum flash chromatography on silica of the crude extract followed by silica and reversed-phase HPLC yielded several diterpenoids of the xenicane class. Herein we describe the structure elucidations of acalycixeniolides C−F (**1**−**4**) as the cytotoxic constituents of *A. inermis*.[5] Literature survey revealed that previous work on *A. inermis* and an unidentified *Acalycigorgia* also yielded xenicane diterpenoids.[6−9]



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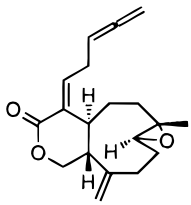

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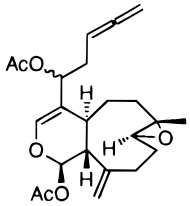

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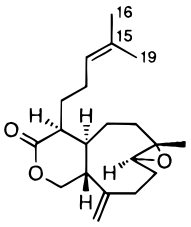

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Acalycixeniolide C (**1**) was isolated as an amorphous solid that analyzed for $C_{19}H_{26}O_3$ by combined HREIMS and ^{13}C NMR spectrometry. The ^{13}C NMR spectrum of this compound showed two downfield carbon signals at δ 208.5 and 174.9 (Table 1). Combined with the absorption bands at 1955 and 1745 cm^{-1} in the IR spectrum, these carbon signals were interpreted as an allene and an ester carbonyl, respectively. Of the three oxygen atoms of this molecule, the remaining one was thought to form an epoxide from an observation of carbon signals at δ 61.8 (CH) and 59.1 (C) in the ^{13}C NMR spectrum. In addition, the presence of an exo-olefin group was revealed by carbon signals at δ 150.6 (C) and 113.8 (CH_2).

Table 1. ^{13}C NMR Assignments for Compounds **1**−**4**[a]

position	**1**	**2**	**3**	**4**
1	70.7 (t)	71.1 (t)	91.2 (d)	70.7 (t)
3	174.9 (s)	170.1 (s)	141.3 (d)	175.0 (s)
4	41.2 (d)	134.9 (s)	115.2 (s)	41.3 (d)
4a	44.6 (d)	42.3 (d)	36.6 (d)	44.4 (d)
5	28.6 (t)	35.9 (t)	29.7 (t)	28.5 (t)
6	39.7 (t)	39.6 (t)	39.6 (t)	39.8 (t)
7	59.1 (s)	59.0 (s)	59.8 (s)	59.1 (s)
8	61.8 (d)	62.5 (d)	62.5 (d)	61.9 (d)
9	25.2 (t)	25.3 (t)	24.5 (t)	25.3 (t)
10	33.6 (t)	32.1 (t)	32.6 (t)	33.6 (t)
11	150.6 (s)	149.2 (s)	148.4 (s)	150.7 (s)
11a	48.6 (d)	49.0 (d)	47.5 (d)	48.5 (d)
12	26.0 (t)	137.3 (d)	73.8 (d)	26.8 (t)
13	25.7 (t)	26.7 (t)	31.8 (t)	25.3 (t)
14	89.0 (d)	86.7 (d)	85.2 (d)	123.2 (d)
15	208.5 (s)	208.9 (s)	209.4 (s)	133.0 (s)
16	75.5 (t)	76.6 (t)	75.5 (t)	25.8 (q)
17	16.2 (q)	16.6 (q)	16.6 (q)	16.2 (q)
18	113.8 (t)	115.3 (t)	114.7 (t)	113.6 (t)
19				17.9 (q)
1-OAc			169.4 (s)	
			21.0 (q)	
12-OAc			170.1 (s)	
			21.4 (q)	

[a] Measured in $CDCl_3$ solutions. Assignments were aided by DEPT, gradient HSQC, and gradient HMBC experiments.

With the aid of this information, the gross structure of **1** was determined by a combination of ^{1}H COSY, TOCSY, gradient HSQC, and gradient HMBC experiments. Chemical shifts of the proton signals at δ 5.11 (1H, quint, J = 6.8 Hz), 4.70 (2H, m), and 2.09 (2H, m), together with the mutual couplings among them, revealed the presence of a terminal allene moiety. This interpretation was confirmed by direct and long-range correlations between the signals of these protons and carbons at δ 208.5, 89.0, and 75.5. The proton spin system containing the allene group was extended further by a TOCSY correlation, which included all of the proton signals of the allene and methines at δ 2.94 (1H, q, J = 6.4 Hz) and 2.15 (1H, m). A long-range coupling of the carbonyl carbon at δ 174.9 with the β- and γ-allenic protons at δ 2.07 and 2.94, respectively, placed an ester group in the vicinity of the allene group. In

* To whom correspondence should be addressed. Tel.: 82 (345) 400-6170. Fax: 82 (345) 408-4493. E-mail: jhshin@sari.kordi.re.kr.

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addition, the gradient HMBC correlations of the ester and a methine carbon at δ 44.6, bearing the proton at δ 2.15 in the ^{1}H NMR spectrum, with oxymethylene protons at δ 4.28 and 3.97, revealed the presence of a six-membered lactone.

The remaining part of the molecule was also determined by combined 2D NMR experiments. Chemical shifts of a methine carbon at δ 61.8 and its attached proton at δ 2.91 (1H, dd, J = 10.3, 4.9 Hz), assigned on the basis of the gradient HSQC data, were indicative of an epoxide group. The attachment of a methyl group at this group was revealed by the long-range correlations between the methyl protons at δ 1.37 and epoxide carbons. Another long-range correlation was also observed between the same protons and a methylene carbon at δ 39.7. A combination of the TOCSY and gradient HSQC experiments containing the signals of protons and carbon of this methylene revealed a connection of the epoxide with the lactone moiety through an ethylene group (C-5 and C-6). Similarly, the epoxide and exo-olefin were found to be linked with each other by an ethylene group (C-9 and C-10) on the basis of the ^{1}H COSY, TOCSY, and HMBC data. Finally, the connection of the exo-olefin with the six-membered lactone moiety was determined by the gradient HMBC correlations of the oxymethylene (H-1) and exomethylene (H-18) protons with neighboring carbons. Thus, the planar structure of acalycixeniolide C was defined as a bicyclic norditerpene lactone of the 19-norxenicane class possessing an allene functionality. Literature survey revealed that the 19-norxenicane lactone−allene framework of this compound is precedented by ginamallene and acalycixeniolide B from several Japanese species of *Acalycigorgia*.[7,8]

The relative stereochemisty of **1** was determined by a ROESY experiment. The H-17 methyl proton signal at δ 1.37 showed strong correlations with the H-5β, H-9β, H-10β, and H-11a protons at δ 1.12, 1.49, 2.13, and 2.37, respectively. On the other hand, the same experiment showed spatial proximity of the H-8 epoxide proton at δ 2.91 with the H-4a and H-10α protons at δ 2.15 and 2.55, respectively. Therefore, the orientation of the ring junction and geometry of the epoxide were assigned as trans for both. The H-4a proton was correlated further with the H-18 exo-olefinic proton at δ 5.09, which in turn correlated with the H-1α and H-4 protons at δ 3.97 and 2.94, respectively. These results were identical to the previous ones based on X-ray cystallographic analysis and NMR studies.[6,10] The relative configurations of the whole molecule were assigned as 4*S**,4a*S**,7*S**,8*S**,11a*R**.

The molecular formula of acalycixeniolide D (**2**) was deduced as $C_{19}H_{24}O_3$ by HREIMS and ^{13}C NMR methods. The NMR data for this compound were highly compatible with those obtained for **1**. The most noticeable difference in the ^{13}C NMR data was the replacement of signals for a methine and a methylene by those of a double bond (Table 1). Corresponding change was also observed in the ^{1}H NMR spectra in that a signal of a new olefinic proton appeared at δ 6.55 (dd, J = 8.1, 7.1 Hz). In addition, the IR and UV data showed new absorption bands at 1730 cm^{-1} and 220 nm, respectively. These spectral changes could be readily accommodated by placement of an additional double bond at C-4(12), thus converting the ester group to an α,β-unsaturated one that was confirmed by combined 2D NMR experiments. The crucial evidence was the gradient HMBC correlations between the signals of the H-12 olefinic proton and the C-3, C-4a, and C-14 carbons. The geometry of the new double bond was assigned as *E*, because ROESY correlations with H-4a and H-5 protons were observed not for H-12 but for H-13. Thus, the structure of **2** was defined as the 4(12)-didehydro analogue of **1**. Interestingly, comparison of the NMR data between these compounds revealed that the presence of an additional double bond at C-4(12) significantly influenced (0.1 ~ 0.2 ppm) the chemical shifts of the protons in such remote parts as H-6, H-8, H-10, and H-11.

Acalycixeniolide E (**3**) was isolated as a colorless gum that analyzed for $C_{23}H_{30}O_6$ by HREIMS and ^{13}C NMR analysis. Including the appearance of four additional carbon signals in the ^{13}C NMR spectra, the NMR data for this compound differ significantly from those of **1** and **2**. Signals of a highly differentiated double bond appeared at δ 141.3 (CH) and 115.2 (C) in the ^{13}C NMR spectrum (Table 1). In the ^{1}H NMR data, signals of the H-1 methylene disappeared and new downfield signals were observed at δ 6.54 (1H, d, J = 1.5 Hz), 5.96 (1H, d, J = 2.4 Hz), and 5.33 (1H, t, J = 7.3 Hz). In addition, signals of two acetoxyl groups were present in the ^{1}H and ^{13}C NMR spectra. Careful examination of the spectral data revealed that **3** possessed the same nine-membered ring and allene moiety as **1**, and all of the structural changes occurred only at the lactone and side chain. These structural changes were determined by combined 2D NMR data. Starting from the allene, an extension of the proton spin system by the ^{1}H COSY, TOCSY, and gradient HSQC data revealed the presence of an oxygenated functionality at C-12. The HMBC correlations of the H-12 proton at δ 5.33 and the methyl proton at δ 2.03 with the carbonyl carbon at δ 170.1 placed an acetoxyl group at C-12. Further long-range correlations of the former with neighboring carbons showed the presence of a double bond at C-3. Similarly, the gradient HSQC and HMBC experiments placed another acetoxyl group at C-1 of the molecule. The oxygen bridge between C-1 and C-3 was evident from mutual HMBC correlations between the carbons and protons at these positions. Thus, the structure of acalycixeniolide E was defined as a diacetoxylated norditerpene of the xenicane class. Compound **3** possessed new asymmetric centers at C-1 and C-12. The relative configuration at C-1 was assigned as *R** on the basis of a ROESY correlation of H-1 with H-18. Due to the free-rotation of the side chain, however, the stereochemistry at C-12 was not determined. The H-12 oxymethine proton showed correlations with both of the H-3 and one (δ 2.07) of the H-5 methylene protons.

The molecular formula of acalycixeniolide F (**4**) was deduced as $C_{20}H_{30}O_3$ by HREIMS and ^{13}C NMR spectrometry. Although the spectral data for this compound were comparable to those of other xenicanes, the ^{13}C NMR data of this compound revealed the replacement of the carbon signals of the terminal allene group of **1**−**3** by those of a dimethyl olefin functionality frequently found in xenicane diterpenoids. Corresponding changes were also observed in the ^{1}H NMR data in that proton signals for the additional olefin and vinyl methyls were found at δ 5.09 (1H, t, J = 7.8 Hz, H-14), 1.73 (3H, s, H-16), and 1.60 (3H, s, H-19), respectively. Thus, the structure of **4** was defined as a diterpenoid of the xenicane class, which might be the biogenetic precursor of **1** and other norditerpenoids containing the terminal allene functionality.

Xenicane diterpenoids and related metabolites exhibit diverse and potent bioactivities.[1] For example, acalycixeniolides A and B, previously isolated from the Japanese specimen of *A. inermis*, inhibited cell division of the fertilized starfish eggs.[6] In our measurement of bioactivity, compounds **1**−**4** exhibited cytotoxicity against the human leukemia cell line K562 with LC_{50} values of 1.6, 52.0, 4.7,

and 0.2 μg/mL, respectively. It is very interesting to note that compound **4**, having a terminal dimethylvinyl moiety, exhibits cytotoxicity of an order of magnitude more potent than other xenicanes having an allene group at this position. On the other hand, **2**, bearing an α,β-unsaturated lactone group, is considerably less active than the others.

Experimental Section

General Experimental Procedures. Melting points were measured on a Fisher−Johns apparatus and are uncorrected. Optical rotations were measured on a JASCO digital polarimeter using a 5-cm cell. IR spectra were recorded on a Mattson GALAXY spectrophotometer. UV spectra were obtained in methanol using a Milton−Roy spectrophotometer. NMR spectra were recorded in $CDCl_3$ solutions on a Varian Unity 500 spectrometer. Proton and carbon NMR spectra were measured at 500 and 125 MHz, respectively. Chemical shifts are reported with respect to internal Me_4Si. Mass spectra were provided by Korea Basic Science Institute, Taejeon, Korea. All solvents used were spectral grade or were distilled prior to use.

Animal Material. *Acalycigorgia inermis* (sample number 91K-4) was collected by hand using scuba at 20−25 m depth in November 1991, off the shore of Keomun Island, Korea. The collected samples were briefly dried under shade and kept at −25 °C until chemically investigated. The same animals (sample number 94K-11) were obtained again at the same area in August 1994. Vouchers from both collections had identical morphological characteristics, including color, branching pattern, and size and shape of spicules.[11] Furthermore, silica TLC analysis of the CH_2Cl_2 extracts from the selected colonies (10 from each collection) showed chemical homogeneity among specimens collected at different times.

Extraction and Isolation. The combined animals (10 kg) were defrosted, macerated, and repeatedly extracted with CH_2Cl_2 (10 L × 3) and MeOH (10 L × 2). The combined crude extracts (41.2 g) were separated by silica vacuum flash chromatography by using stepped gradient mixtures of *n*-hexane and EtOAc as eluents. Fractions eluted with moderately polar solvents (40−45% EtOAc in hexane) were combined and subjected to semipreparative silica HPLC (YMC silica column, 30% EtOAc in hexane) to afford, in order of elution, compounds **1**, **3**, and **2**. Purification was made by C_{18} reversed-phase HPLC (YMC ODS-A column, 15% aqueous MeOH) to give 71.4, 28.1, and 30.9 mg of **1**−**3**, respectively. The fraction eluted with 50% EtOAc in hexane from flash chromatography was dried and separated by reversed-phase HPLC (10% aqueous MeOH) to yield compound **4**. Final purification was accomplished by reversed-phase HPLC (25% aqueous MeOH) to yield 11.1 mg of **4**.

Acalycixeniolide C (**1**): amorphous solid; mp 91−93 °C; $[\alpha]^{25}_D$ 43.2° (*c* 0.4, MeOH); IR (KBr) ν_{max} 2940, 2860, 1955, 1745, 1640, 1450, 1390, 1145, 1030 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.19 (1H, s, H-18), 5.11 (1H, quint, J = 6.8 Hz, H-14), 5.09 (1H, s, H-18), 4.70 (2H, m, H-16), 4.28 (1H, dd, J = 11.7, 6.3 Hz, H-1), 3.97 (1H, dd, J = 11.7, 11.7 Hz, H-1), 2.94 (1H, q, J = 6.4 Hz, H-4), 2.91 (1H, dd, J = 10.3, 4.9 Hz, H-8), 2.55 (1H, br dd, J = 12.6, 9.8 Hz, H-10), 2.37 (1H, ddd, J = 11.7, 6.3, 2.5 Hz, H-11a), 2.30 (1H, ddd, 13.2, 9.3, 4.9 Hz, H-9), 2.25 (1H, ddd, J = 13.2, 3.4, 3.4 Hz, H-6), 2.15 (1H, m, H-4a), 2.13 (1H, m, H-10), 2.09 (2H, m, H-13), 2.07 (1H, m, H-12), 1.78 (1H, ddd, J = 14.1, 3.9, 3.4 Hz, H-5), 1.56 (1H, m, H-12), 1.49 (1H, dddd, J = 13.2, 10.3, 9.8, 1.5 Hz, H-9), 1.37 (3H, s, H-17), 1.12 (1H, dddd, J = 14.1, 13.2, 11.2, 3.4 Hz, H-5), 1.00 (1H, ddd, J = 13.2, 13.2, 3.9 Hz, H-6); ^{13}C NMR data, see Table 1; HMBC correlations (7 Hz) H-1/C-3, C-4a, C-11, C-11a; H-4/C-3, C-4a, C-5; H-5/C-4, C-4a, C-6, C-7, C-11a; H-6/C-4a, C-5, C-7, C-8, C-17; H-8/C-6, C-9; H-9/C-7, C-8, C-10, C-11; H-10/C-8, C-9, C-11, C-11a, C-18; H-11a/C-10, C-11, C-18; H-12/C-3, C-4, C-4a, C-13, C-14; H-14/C-12, C-16; H-16/C-15; H-17/C-6, C-7, C-8; H-18/C-1, C-10, C-11, C-11a; HREIMS $(M)^+$ *m/z* obsd 302.1875; calcd for $C_{19}H_{26}O_3$, 302.1882.

Acalycixeniolide D (**2**): amorphous solid; mp 87−90 °C; $[\alpha]^{25}_D$ 162.7° (*c* 0.1, MeOH); IR (KBr) ν_{max} 2935, 2870, 1955, 1730, 1645, 1455, 1390, 1320, 1255, 1180 cm^{-1}; UV (MeOH) λ_{max} (log ϵ) 220 (3.75) nm; ^1H NMR ($CDCl_3$) δ 6.55 (1H, dd, J = 8.1, 7.1 Hz, H-12), 5.17 (1H, quint, J = 6.4 Hz, H-14), 5.16 (1H, s, H-18), 5.00 (1H, s, H-18), 4.77 (2H, m, H-16), 4.16 (1H, dd, J = 11.2, 5.4 Hz, H-1), 3.65 (1H, dd, J = 11.2, 11.2 Hz, H-1), 2.98 (2H, dd, J = 10.2, 4.4 Hz, H-4a, H-8), 2.87 (2H, m, H-13), 2.47 (2H, m, H-10, H-11a), 2.30 (1H, br ddd, J = 13.9, 8.3, 4.4 Hz, H-9), 2.23 (2H, m, H-6, H-10), 1.64 (2H, m, H-5), 1.50 (1H, m, H-9), 1.38 (3H, s, H-17), 1.19 (1H, ddd, J = 13.2, 13.2, 5.4 Hz, H-6); ^{13}C NMR data, see Table 1; HMBC correlations (7 Hz) H-1/C-3, C-4a; H-10/C-8, C-9, C-11, C-11a, C-18; H-11a/C-1; H-12/C-3, C-4a, C-14; H-14/C-12, C-15, C-16; H-17/C-6, C-7, C-8; H-18/C-10, C-11a; HREIMS $(M)^+$ *m/z* obsd 300.1714; calcd for $C_{19}H_{24}O_3$, 300.1726.

Acalycixeniolide E (**3**): colorless gum; $[\alpha]^{25}_D$ 41.5° (*c* 0.3, MeOH); IR (KBr) ν_{max} 2930, 2860, 1955, 1735, 1665, 1440, 1370, 1235, 1150, 1015 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.54 (1H, d, J = 1.5 Hz, H-3), 5.96 (1H, d, J = 2.4 Hz, H-1), 5.33 (1H, t, J = 7.3 Hz, H-12), 5.04 (1H, s, H-18), 4.98 (1H, quint, J = 6.8 Hz, H-14), 4.92 (1H, s, H-18), 4.69 (2H, m, H-16), 3.00 (1H, dd, J = 10.7, 3.9 Hz, H-8), 2.44 (1H, m, H-13), 2.42 (1H, m, H-10), 2.39 (2H, m, H-10, H-11a), 2.31 (1H, m, H-13), 2.28 (1H, m, H-9), 2.26 (1H, br dd, J = 10.8, 2.4 Hz, H-4a), 2.22 (1H, ddd, J = 13.2, 3.4, 3.4 Hz, H-6), 2.08 (3H, s, 1-OAC), 2.07 (1H, m, H-5), 2.03 (3H, s, 12-OAc), 1.66 (1H, m, H-5), 1.49 (1H, dddd, J = 13.7, 10.3, 9.3, 4.4 Hz, H-9), 1.32 (3H, s, H-17), 1.14 (1H, ddd, J = 13.2, 13.2, 4.4 Hz, H-6); ^{13}C NMR data, see Table 1; HMBC correlations (7 Hz) H-1/C-3, C-4a, 1-OAc; H-3/C-1, C-4, C-4a, C-12; H-4a/C-5, C-6, C-11, C-11a; H-6/C-5, C-7, C-17; H-8/C-9; H-10/C-8, C-11, C-11a; H-12/C-3, C-4, C-4a, C-13, C-14, 12-OAc; H-13/C-15; H-14/C-12, C-15, C-16; H-17/C-6, C-7, C-8; H-18/C-10, C-11, C-11a; HREIMS $(M)^+$ *m/z* obsd 402.2037; calcd for $C_{23}H_{30}O_6$, 402.2043.

Acalycixeniolide F (**4**): colorless gum; $[\alpha]^{25}_D$ 46.8° (*c* 0.1, MeOH); IR (KBr) ν_{max} 2930, 2860, 1745, 1540, 1455, 1390, 1140 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.17 (1H, s, H-18), 5.09 (1H, t, J = 7.8 Hz, H-14), 5.02 (1H, s, H-18), 4.27 (1H, dd, J = 12.2, 6.8 Hz, H-1), 3.94 (1H, dd, J = 12.2, 12.2 Hz, H-1), 2.90 (1H, dd, J = 10.3, 4.9 Hz, H-8), 2.83 (1H, q, J = 6.4 Hz, H-4), 2.54 (1H, br dd, J = 12.7, 9.8 Hz, H-10), 2.35 (1H, ddd, J = 12.2, 6.8, 3.4 Hz, H-11a), 2.30 (1H, br ddd, J = 13.2, 9.7, 4.9 Hz, H-9), 2.25 (1H, ddd, J = 13.2, 3.9, 2.9 Hz, H-6), 2.13 (1H, ddd, J = 12.7, 9.7, 9.7 Hz, H-10), 2.10 (1H, m, H-4a), 2.06 (2H, m, H-13), 1.97 (1H, m, H-12), 1.79 (1H, br ddd, J = 13.7, 3.9, 3.9 Hz, H-5), 1.73 (3H, s, H-16), 1.60 (3H, s, H-19), 1.51 (1H, m, H-12), 1.48 (1H, m, H-9), 1.37 (3H, s, H-17), 1.09 (1H, dddd, J = 13.7, 13.7, 10.7, 2.9 Hz, H-5), 0.99 (1H, ddd, J = 13.7, 13.2, 3.9 Hz, H-6); ^{13}C NMR data, see Table 1; HMBC correlations (7 Hz) H-1/C-3, C-4a, C-11a; H-4/C-3, C-4a, C-5, C-12; H-5/C-6; H-8/C-9; H-12/C-3, C-4, C-13, C-14; H-16/C-14, C-15, C-19; H-17/C-6, C-7, C-8; H-18/C-1, C-4a, C-10, C-11; H-19/C-14, C-15, C-16; HREIMS $(M)^+$ *m/z* obsd 318.2191; calcd for $C_{20}H_{30}O_3$, 318.2195.

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(11) Specimens of *A. inermis* (voucher numbers 91K-4 and 94K-11) are on deposit in the octocorallian collection, National History Museum, Ewha Womans University, Seoul, Korea, under the curatorship of Dr. J.-I. Song.

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