New Cytotoxic Metabolites from a Marine Sponge *Homaxinella* sp.

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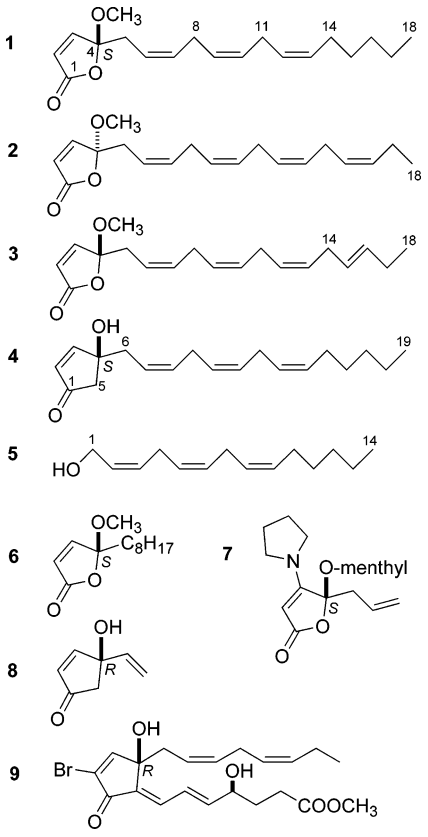
Three new butenolides (**1**−**3**), a new cyclopentenone derivative (**4**), and a known alcohol (**5**) were isolated from a marine sponge *Homaxinella* sp. by bioactivity-guided fractionation. The planar structures were established on the basis of NMR and MS analyses. The stereochemistry of the butenolides and cyclopentenone derivative was defined on the basis of optical rotation and CD spectroscopy. The compounds were tested for cytotoxicity against a panel of five human solid tumor cell lines and displayed marginal to significant activity.

Marine sponges of the genus *Homaxinella* are reported to contain various sterols,[1,2] cytotoxic bromopyrroles,[3] and antimicrobial metabolites.[4] In the course of investigating bioactive metabolites from marine invertebrates, we have noticed significant toxicity in the crude extract of the sponge *Homaxinella* sp. (family Axinellidae, order Halichondrida) to brine shrimp larvae (LD_{50}, 57 μg/mL). Guided by brine shrimp lethality,[5] three new butenolides (**1**−**3**), a new cyclopentenone derivative (**4**), and a known polyunsaturated alcohol (**5**) were isolated from the MeOH extract of the sponge. Butenolides and related cyclopentenone derivatives are a class of compounds that are occasionally encountered among various marine organisms such as sponges,[6,7] fungi,[8] bacteria,[9] gorgonians,[10−14] sea pens,[15] and soft corals.[16] As a family, butenolides share a common α,β-unsaturated γ-lactone moiety, with various substitution patterns. Biological activities of butenolides include antibiotic,[16,17] antitumor,[13] enzyme inhibitory,[17] and phytotoxic activity[8] and brine shrimp toxicity.[16] Chemical structures of **1**−**4** were similar to the butenolides and cyclopentenone derivative of the marine sponge *Plakortis* sp.[6,7] (family Plakinidae, order Homosclerophorida), which is taxonomically distant from *Homaxinella*. We report here the structure elucidation and cytotoxicity evaluation of these metabolites.

The MeOH extract of the sponge was partitioned between H_2O and CH_2Cl_2. The CH_2Cl_2 layer was further partitioned between aqueous MeOH and *n*-hexane. The aqueous MeOH layer, which was most toxic to brine shrimp larvae, was successively fractionated employing ODS reversed-phase flash column chromatography and HPLC to afford compounds **1**−**5**.

Homaxinolide A (**1**) was isolated as a light yellow oil, and its molecular formula was established as $C_{19}H_{28}O_3$ on the basis of NMR and MS analyses. The FABMS spectrum of **1** showed the $[M + Na]^+$ ion at *m/z* 327. The ^1H NMR spectrum of **1** showed two mutually coupled olefinic proton signals at δ 7.36 (d, J = 6.0 Hz, H-3) and 6.29 (d, J = 6.0 Hz, H-2). This observation combined with the ^{13}C NMR signals at δ 171.9 (C-1), 155.5 (C-3), and 126.0 (C-2), along with the UV absorption[6] at 203 nm and the IR absorption at 1765 cm^{-1}, suggested the presence of an α,β-unsaturated γ-lactone moiety. The HMBC data of **1** indicated that the lactone moiety is γ-methoxy-γ-alkyl-disubstituted butenolide. HMBC correlations of H-2 and H-3 with the quaternary carbon signals at δ 171.9 (C-1) and 112.5 (C-4) were observed. The HMBC experiment further confirmed the correlation of the methoxy proton signal at δ 3.22 to the quaternary carbon signal at δ 112.5 (C-4), to which an alkyl chain was attached (Figure 1). The ^1H NMR spectrum showed two multiplets in the region from δ 5.3 to 5.5 for olefinic protons of the alkyl chain. The ^{13}C NMR spectrum showed the presence of eight olefinic carbons. The geometry of the double bonds of the alkyl chain was determined to be *cis* on the basis of chemical shifts of the diallylic and



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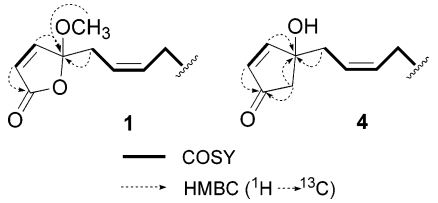

Figure 1. Key COSY and HMBC correlations of compounds **1** and **4**.

allylic carbons (vide infra),[18,19] which were observed at δ 26.6 (C-8), 26.5 (C-11), and 28.2 (C-14), respectively.

The stereochemistry at C-4 was defined as *S* by comparison of optical rotation with the synthetic γ-methoxy-γ-alkyl-disubstituted butenolide (**6**).[20] The synthesized model compound **6** with *S* configuration was reported to show a positive optical rotation ($[\alpha]_D$ +43°). Compound **1** also showed a positive optical rotation ($[\alpha]_D$ +20°); hence the same configuration was presumed. Stereochemical assignment was further corroborated by CD spectroscopy. The CD spectrum of **1** showed a strong positive Cotton effect at 205 nm ($\pi - \pi^*$). This pattern of Cotton effect was similar to that of the 5,5-disubstituted 2(5*H*)-furanone derivative (**7**).[21] The *S* configuration at C-4 was only tentatively proposed because the structural similarity between **1** and **7** was not quite high. Therefore, compound **1** was characterized as (6*Z*,9*Z*,12*Z*)-(*S*)-4-methoxyoctadeca-2,6,9,12-tetraen-4-olide.

Homaxinolide B (**2**) was also isolated as a light yellow oil, and its molecular formula was established as $C_{19}H_{26}O_3$ on the basis of NMR and HRFABMS measurements. The exact mass of the $[M + Na]^+$ ion (*m*/*z* 325.1786) of **2** matched well with the expected molecular formula of $C_{19}H_{26}O_3Na$ (Δ +0.6 mmu). The ^1H and ^{13}C NMR data of **2** were almost identical to those of **1** (Tables 1 and 2) except for the degree of unsaturation. The COSY spectrum of **2** showed correlation of the terminal methyl protons at δ 0.97 (H-18, J = 7.0 Hz) with the allylic protons at δ 2.08 (H-17, J = 7.0 Hz). The HMBC spectrum also revealed the correlation of the terminal methyl protons with the allylic carbon at δ 20.5 (C-17) and the olefinic carbon at δ 131.3 (C-16). Absolute configuration of this butenolide at C-4 was proposed on the basis of optical rotation and CD spectroscopy. Compound **2** showed a negative optical rotation ($[\alpha]^{21}_D$ −10°), which is opposite of that of **1**. A negative Cotton effect at 206 nm ($\pi - \pi^*$) and a positive Cotton effect at 257 nm (n $-$ π^*) indicated that it is epimeric to **1**. Therefore, compound **2** was characterized as (6*Z*,9*Z*,12*Z*,15*Z*)-(*R*)-4-methoxyoctadeca-2,6,9,12,15-pentaen-4-olide. Compounds **1** and **2** might be produced from the biogenetic precursors (**A** or **B**), which can be easily epimerized (Figure 2).

Homaxinolide C (**3**) was isolated as a pale yellow oil with a molecular formula $C_{19}H_{26}O_3$, which was determined on the basis of ^{13}C NMR and MS analyses. The FABMS spectrum of **3** showed the $[M + Na]^+$ ion at *m*/*z* 325, indicating that it is isomeric to compound **2**. The ^1H NMR data of **3** were almost identical to those of **2** except for subtle differences in the signals of the allylic (H-17) and diallylic (H-14) protons. The difference was also obvious in the ^{13}C NMR data (Table 2). The ^{13}C NMR chemical shift of a penultimate allylic carbon adjacent to a *cis* double bond is reported to be about δ 21, while that of a *trans* double

Table 2. ^{13}C NMR Data of Compounds **1**−**5** (CD_3OD)

position	**1**[a]	**2**[b]	**3**[a]	**4**[a]	**5**[b]
1	171.9	171.9	171.9	208.5	55.5
2	126.0	126.0	126.0	133.8	129.6
3	155.5	155.5	155.5	168.3	129.4
4	112.5	112.5	112.1	79.5	26.0
5	35.9	35.9	35.9	48.7	130.0
6	133.7	133.7	133.7	38.6	127.4
7	129.8	129.8	129.6	132.5	25.5
8	26.6[c]	26.5[c]	26.6[c]	124.7	127.6
9	128.7	128.7	122.3	26.5[c]	129.8
10	128.3	128.3	128.5	129.7	26.8
11	26.5[c]	26.5[c]	26.5[c]	128.6	29.2
12	122.5	122.5	122.5	26.6[c]	29.4
13	131.3	131.1	131.2	128.5	31.2
14	28.2	26.6	31.3	131.3	22.4
15	30.5	122.5	129.2	28.2	12.8
16	32.6	131.3	133.5	30.4	
17	23.6	20.5	26.4[c]	32.6	
18	14.4	14.3	14.3	23.6	
19				14.4	
OCH_3	51.7	51.7	51.7		

[a] Spectra were measured at 50 MHz. [b] Signals were assigned by HMBC and HSQC experiments (500 MHz). [c] Assignments with the same superscript in the same column may be interchanged.

Table 1. ^1H NMR Data of Compounds **1**−**5** (CD_3OD, 500 MHz)[a]

position	**1**	**2**	**3**	**4**	**5**
1					4.30 (d, 5.5)
2	6.29 (d, 6.0)	6.29 (d, 5.5)	6.29 (d, 6.0)	6.10 (d, 6.0)	5.55 (m)
3	7.36 (d, 6.0)	7.36 (d, 5.5)	7.36 (d, 6.0)	7.48 (d, 6.0)	5.53 (m)
4					2.85 (t, 6.5)[b]
5	2.72 (m)	2.72 (m)	2.73 (m)	2.33 (d, 18.0)	5.35 (m)
				2.49 (d, 18.0)	
6	5.53 (m)	5.53 (m)	5.55 (m)	2.48 (dd, 15.0, 7.0)	5.29 (m)
				2.58 (dd, 15.0, 7.5)	
7	5.38−5.31 (m)	5.36−5.32 (m)	5.47−5.32 (m)	5.52 (m)	2.81 (t, 6.5)[b]
8	2.82 (t, 7.0)[b]	2.85 (m)[b]	2.81 (t, 6.0)[b]	5.38 (m)	5.40 (m)
9	5.38−5.31 (m)	5.36−5.32 (m)	5.47−5.32 (m)	2.83 (t, 6.5)[b]	5.34 (m)
10	5.38−5.31 (m)	5.36−5.32 (m)	5.47−5.32 (m)	5.35 (m)	2.06 (q, 7.0)
11	2.80 (t, 7.0)[b]	2.80 (m)[b]	2.81 (t, 6.0)[b]	5.34 (m)	1.35 (m)
12	5.38−5.31 (m)	5.36−5.32 (m)	5.47−5.32 (m)	2.80 (t, 6.5)[b]	1.28 (m)
13	5.38−5.31 (m)	5.36−5.32 (m)	5.47−5.32 (m)	5.32 (m)	1.29 (m)
14	2.07 (q, 7.0)	2.81 (m)[b]	2.75 (t, 5.5)	5.33 (m)	0.90 (t, 7.0)
15	1.25 (m)	5.36−5.32 (m)	5.47−5.32 (m)	2.06 (q, 7.0)	
16	1.35 (m)	5.36−5.32 (m)	5.47−5.32 (m)	1.35 (m)	
17	1.31 (m)	2.08 (quint, 7.0)	2.00 (quint, 8.0)	1.28 (m)	
18	0.90 (t, 7.0)	0.97 (t, 7.0)	0.96 (t, 8.0)	1.33 (m)	
19				0.90 (t, 7.0)	
OCH_3	3.22 (s)	3.22 (s)	3.22 (s)		

[a] Multiplicities and coupling constants are in parentheses. [b] Assignments with the same superscript in the same column may be interchanged.

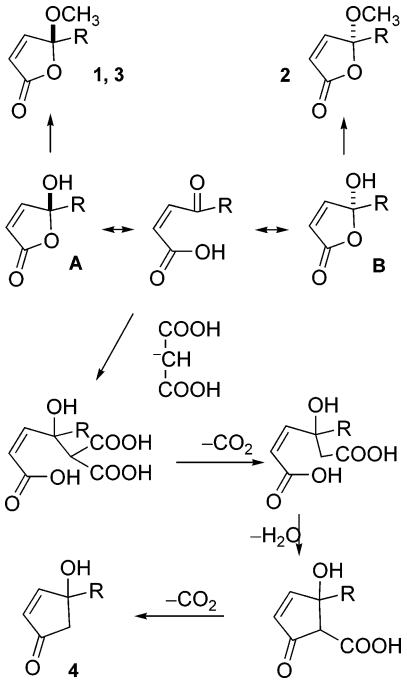

Figure 2. Possible epimerization of butenolides **A** and **B** and their transformation into cyclopentenone (**4**).[7]

bond is reported to be about δ 26.[22] The allylic carbon (C-17) of **3** was observed at δ 26.4; hence Δ^{15} was assigned an *E* configuration. Similarly, the ^{13}C NMR chemical shift of a diallylic carbon between a *cis*−*trans* double-bond pair is reported to be about δ 30, while those between *cis*−*cis* and *trans*−*trans* double bonds are reported to be about δ 25 and 35, respectively.[19] The diallylic carbon signal (C-14) of **3** was observed at δ 31.3, and accordingly the relationship of $\Delta^{12,15}$ was assigned as *cis*−*trans*. Compound **3** showed a positive optical rotation ($[\alpha]^{21}_D$ +14°) and the same pattern of Cotton effects as those of **1**. Thus, the absolute configuration at C-4 was proposed as *S*. Accordingly, the structure of **3** was defined as (6*Z*,9*Z*,12*Z*,15*E*)-(*S*)-4-methoxyoctadeca-2,6,9,12,15-pentaen-4-olide.

Homaxinone A (**4**) was isolated as a light yellow oil. The molecular formula of **4** was established as $C_{19}H_{28}O_2$ on the basis of ^{13}C NMR and MS analyses. The FABMS spectrum of **4** showed the $[M + Na]^+$ ion at *m*/*z* 311. The ^{1}H and ^{13}C NMR spectral data suggested the presence of an enone moiety, a quaternary carbinol carbon, and an unsaturated alkyl chain. The ^{1}H NMR spectrum showed two doublets centered at δ 2.33 (J = 18.0 Hz) and 2.49 (J = 18.0 Hz), which were assigned to the protons attached to C-5. Two doublets of doublets centered at δ 2.48 (J = 15.0, 7.0 Hz) and 2.58 (J = 15.0, 7.5 Hz) were assigned to nonequivalent allylic protons (H-6). The ^{13}C NMR spectrum of **4** displayed carbon signals for an enone moiety at δ 208.5 (C-1), 133.8 (C-2), and 168.3 (C-3). These values were consistent with those reported for a cyclopentenone moiety, i.e., δ 209.8 (C-1), 134.2 (C-2), and 165.3 (C-3).[23] HMBC results confirmed the presence of a γ-hydroxy-γ-alkyl cyclopentenone moiety (Figure 1).

The absolute configuration at C-4 was proposed by comparison of optical rotation and CD data with those of model γ-hydroxy-γ-alkyl cyclopentenones. The optical rotations of the model compounds, (4*R*)-trichodenone A (**8**) and (4*S*)-trichodenone A, were reported to be +141.6° and −145.4°,[24] respectively, while that of **4** was +22°. Stereochemical assignment was further corroborated by CD spectroscopy. Homaxinone A (**4**) showed a positive Cotton effect at 235 nm and a negative Cotton effect at 258 nm, which was in accordance with that of bromo-substituted cyclopentenone, bromovulone I (**9**).[22] Thus, the absolute configuration was tentatively assigned as 4*S*. Accordingly, the structure of **4** was defined as (*S*)-4-hydroxy-4-(2*Z*,5*Z*,8*Z*-tetradeca-2,5,8-trienyl)cyclopent-2-en-1-one. As proposed for the biosynthesis of untenone A,[7] the butenolides **1**−**3** derived from fatty acids may serve as biogenetic precursor of cyclopentenones such as homaxinone A (**4**) (Figure 2).

Table 3. Cytotoxicity Data of Compounds **1**−**5**[a]

compound	A549	SK-OV-3	SK-MEL-2	XF498	HCT15
1	10.1	16.1	2.7	9.9	8.9
2	32.1	>30.0	4.5	>30.0	17.5
3	>30.0	>30.0	14.9	>30.0	34.8
4	5.4	4.4	2.6	4.9	2.9
5	>30.0	19.8	74.1	>30.0	25.5
doxorubicin	0.07	0.24	0.12	0.12	0.17

[a] Data expressed in ED_{50} values (μg/mL). A549, human lung cancer; SK-OV-3, human ovarian cancer; SK-MEL-2, human skin cancer; XF498, human CNS cancer; HCT 15, human colon cancer.

A polyunsaturated alcohol **5** was isolated as a minor constituent from the MeOH extract. Compound **5** was a colorless oil with a strong fishy smell. The ESIMS of **5** showed the $[M - H_2O]^+$ ion at *m*/*z* 190. The structure of **5** was confirmed by COSY, HMBC, and HSQC experiments. This alcohol has previously been reported only from industrial sources as an intermediate in the synthesis of 9-hydroxy eicosatetraenoic acid (9-HETE).[25]

The isolated compounds **1**−**5** were evaluated for cytotoxicity against a panel of five human tumor cell lines and showed marginal to significant activity (Table 3). The cyclopentenone derivative **4** exhibited higher potency than butenolides **1**−**3**. The butenolides **1**−**3** showed rather a selective toxicity to the human skin cancer cell line (SK-MEL-2). Considering the level of cytotoxicity, further modification studies of compound **4** to improve the level of potency may be of interest.

Experimental Section

General Experimental Procedures. Optical rotations were obtained using a JASCO DIP-370 digital polarimeter. CD spectra were measured using a JASCO J-715 spectropolarimeter (sensitivity 50 mdeg, resolution 0.2 nm). UV spectra were obtained in MeOH, using a Shimadzu mini 1240 UV−vis spectrophotometer. The IR spectrum was measured using a JASCO FT/IR-410 spectrometer. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AC200 and a Varian INOVA 500. Chemical shifts were reported with reference to the respective solvent peaks (δ_H 3.30 and δ_C 49.0 for CD_3OD). FABMS data were obtained on a JEOL JMS SX-102A. ESIMS data were obtained using a Finnigan DecaXP. HPLC was performed with a YMC-Pack ODS column (250 × 10 mm, 5 μm, 120 Å) and a C18-5E Shodex packed column (250 × 10 mm, 5 μm, 100 Å) using a Gilson 133-RI detector.

Animal Material. The sponge was collected by using scuba at a depth of 20 m in August 1998, off the coast of Jeju Island, Korea. The collected sample was frozen immediately. The specimen (sample no. J98J-1) was taxonomically identified as a species of the genus *Homaxinella* (family Axinellidae, order Halichondrida).[26] It was a massive sponge, with a size up to 7.5 × 4 × 1.5 cm. The surface of the body was rough owing to the projecting spicules. Texture was hard, and it was a shade of dark orange in life. The skeleton has megascleres, thick styles (800−950 × 20 μm), and thin styles (800−940 × 9−10 μm). A voucher specimen (registry no. Spo. 39) was deposited at the Natural History Museum, Hannam University, Daejon, Korea, under the curatorship of C.J.S.

Extraction and Isolation. The frozen sponge (7 kg) was extracted with MeOH at room temperature. The MeOH extract showed toxicity against brine shrimp larvae (LD_{50} 57 μg/mL).

The MeOH extract was partitioned between CH_2Cl_2 and water. The CH_2Cl_2 layer was further partitioned between aqueous MeOH and *n*-hexane. The aqueous MeOH fraction was subjected to step gradient reversed-phase flash column chromatography (YMC gel ODS-A, 60 Å, 400/500 mesh) with a solvent system of 60−100% MeOH to afford 22 fractions. Fraction 11 (506.8 mg), one of the bioactive fractions (LD_{50} 10 μg/mL), was again subjected to reversed-phase flash column chromatography (YMC ODS-A, 120 Å, 30/50 μm) eluting with a step gradient solvent system of 60−100% MeOH. Compound **1** (3.9 mg) was obtained by separation of subfraction 5 (52.2 mg) on a reversed-phase HPLC column (C18-5E Shodex packed, 250 × 10 mm, 5 μm, 100 Å) eluting with 84% MeOH. Successive reversed-phase HPLC (C18-5E Shodex packed, 250 × 10 mm, 5 μm, 100 Å) eluting with 84% MeOH followed by another reversed-phase HPLC (YMC-Pack ODS, 250 × 10 mm, 5 μm, 120 Å) eluting with 78% afforded compounds **2** (0.7 mg), **5** (0.9 mg), **3** (0.9 mg), and **4** (1.2 mg).

Homaxinolide A (1): light yellow oil; $[\alpha]^{21}_D$ +20° (*c* 0.33, MeOH); UV (MeOH) λ_{max} nm (log ϵ) 203 (1.3), 230 (0.8), 270 (0.2); CD (*c* 1 × 10^{-4} M, MeOH) $\Delta\epsilon$ (nm) +0.50 (200), +0.63 (205), 0 (213), −0.17 (257), 0 (313), +0.03 (336), 0 (371); IR (film) ν_{max} 1765 cm^{-1}; ^{1}H NMR data, see Table 1; ^{13}C NMR data, see Table 2; FABMS *m*/*z* 327 $[M + Na]^+$.

Homaxinolide B (2): light yellow oil; $[\alpha]^{21}_D$ −10° (*c* 0.27, MeOH); UV (MeOH) λ_{max} nm (log ϵ) 203 (1.1), 226 (0.3), 270 (0.2); CD (*c* 1 × 10^{-4} M, MeOH) $\Delta\epsilon$ (nm) −0.04 (200), −0.58 (206), 0 (217), +0.37 (242), +0.21 (257), 0 (268); ^{1}H NMR data, see Table 1; ^{13}C NMR data, see Table 2; FABMS *m*/*z* 325 $[M + Na]^+$; HRFABMS *m*/*z* 325.1786 (calcd for $C_{19}H_{26}O_3Na$, 325.1780).

Homaxinolide C (3): pale yellow oil; $[\alpha]^{21}_D$ +14° (*c* 0.43, MeOH); UV (MeOH) λ_{max} nm (log ϵ) 203 (1.4), 228 (0.3), 278 (0.2); CD (*c* 1 × 10^{-4} M, MeOH) $\Delta\epsilon$ (nm) +0.28 (200), +0.37 (205), 0 (254), −0.03 (259), 0 (268); ^{1}H NMR data, see Table 1; ^{13}C NMR data, see Table 2; FABMS *m*/*z* 325 $[M + Na]^+$.

Homaxinone A (4): light yellow oil; $[\alpha]^{21}_D$ +22° (*c* 0.48, MeOH); UV (MeOH) λ_{max} nm (log ϵ) 204 (1.3), 226 (1.0), 266 (0.37), 313 (0.03); CD (*c* 1 × 10^{-4} M, MeOH) $\Delta\epsilon$ (nm) −0.24 (200), 0 (224), +0.05 (235), 0 (246), −0.04 (258), 0 (274), +0.01 (282), +0.01 (316); ^{1}H NMR data, see Table 1; ^{13}C NMR data, see Table 2; FABMS *m*/*z* 311 $[M + Na]^+$; ESIMS *m*/*z* 289 $[M + H]^+$.

(2*Z*,5*Z*,8*Z*)-Tetradeca-2,5,8-trien-1-ol (5): colorless oil; ^{1}H NMR data, see Table 1; ^{13}C NMR data, see Table 2; ESIMS *m*/*z* 190 $[M - H_2O]^+$.

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Supporting Information Available: CD spectra of compounds **1**, **2**, and **4**. This material is available free of charge via the Internet at http://pubs.acs.org.

References and Notes

(1) Eggersdorfer, M. L.; Kokke, W. C. M. C.; Crandell, C. W.; Hochlowski, J. E.; Djerassi, C. *J. Org. Chem*. **1982**, *47*, 5304−5309.
(2) Seldes, A. M.; Rovirosa, J.; Martin, A. S.; Gros, E. G. *Comp. Biochem. Physiol*. **1986**, *83*, 841−842.
(3) Umeyama, A.; Ito, S.; Yuasa, E.; Arihara, S.; Yamada, T. *J. Nat. Prod*. **1998**, *61*, 1433−1434.
(4) Sharma, G. M.; Vig, B.; Burkholder, P. R. *Drugs Sea, Trans. Symp*. **1968**, 119−126.
(5) Meyer, B. N.; Ferrigni, N. R.; Putnam, J. E.; Jacobsen, L. B.; Nicholas, D. E.; McLaughlin, J. L. *Planta Med*. **1982**, *45*, 31−34.
(6) Guzman, F. S. D.; Schmitz, F. J. *J. Nat. Prod*. **1990**, *53*, 926−931.
(7) Ishibashi, M.; Takeuchi, S.; Kobayashi, J. *Tetrahedron Lett*. **1993**, *34*, 3749−3750.
(8) Evidente, A.; Sparapano, L. *J. Nat. Prod*. **1994**, *57*, 1720−1725.
(9) Mukku, V. J. R. V.; Speitling, M.; Laatsch, H.; Helmke, E. *J. Nat. Prod*. **2000**, *63*, 1570−1572.
(10) Schmitz, F. J.; Kraus, K. W.; Ciereszko, L. S.; Sifford, D. H.; Weinheimer, A. J. *Tetrahedron Lett*. **1966**, *1*, 97−104.
(11) Schmitz, F. J.; Lorance, E. D.; Ciereszko, L. S. *J. Org. Chem*. **1969**, *34*, 1989−1990.
(12) Schmitz, F. J.; Lorance, E. D. *J. Org. Chem*. **1971**, *36*, 719−721.
(13) Rodriguez, A. D.; Ramirez, C. *J. Nat. Prod*. **1994**, *57*, 339−347.
(14) Guo, Y.; Gavanin, M.; Mollo, E.; Trivellone, E.; Cimino, G. *J. Nat. Prod*. **1999**, *62*, 1194−1196.
(15) Anjaneyulu, A. S. R.; Prakash, C. V. S. *Ind. J. Chem*. **1994**, *33*, 55−58.
(16) Rezanka, T., Dembitsky, V. M. *Tetrahedron* **2001**, *57*, 8743−8749.
(17) Braun, D.; Pauli, N.; Sequin, U.; Zähner, H. *FEMS Microbiol. Lett*. **1995**, *126*, 37−42.
(18) Rossi, R.; Carpita, A.; Quirici, M. G.; Veracini, C. A. *Tetrahedron* **1982**, *38*, 639−644.
(19) Doi, Y.; Ishibashi, M.; Kobayashi, J. *Tetrahedron* **1994**, *50*, 8651−8656.
(20) Miller, M.; Hegedus, L. S. *J. Org. Chem*. **1993**, *58*, 6779−6785.
(21) Gawronski, J. K.; Chen, Q. H.; Geng, Z.; Huang, B.; Martin, M. R.; Mateo, A. I.; Brzostowska, M.; Rychlewska, U.; Feringa, B. L. *Chirality* **1997**, *9*, 537−544.
(22) Rezanka, T.; Dembitsky, V. M. *Eur. J. Org. Chem*. **2003**, 309−316.
(23) Kalinowski, H. O.; Berger, S.; Braun, S. *Carbon-13 NMR Spectroscopy;* John Wiley & Sons: Chichester, 1984; p 269.
(24) Usami, Y.; Ikura, T.; Amagata, T.; Numata, A. *Tetrahedron: Asymm*. **2000**, *11*, 3711−3725.
(25) Yadav, J. S.; Bhanu, L. R. M.; Dutta, D. *Tetrahedron* **1998**, *54*, 3929−3934.
(26) The family Axinellidae was grouped into the order Axinellida in previous references.[2] Hooper's revised systematics was employed in this paper. Hooper, J. N. A. *Guide to Sponge Collection and Identification*; Queensland Museum: Brisbane, 1994; pp 1−109.

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