# New Brominated Labdane Diterpenes from the Red Alga *Laurencia obtusa*

Dimitra Iliopoulou,[†] Nikos Mihopoulos,[‡] Vassilios Roussis,[†] and Constantinos Vagias*[,†]

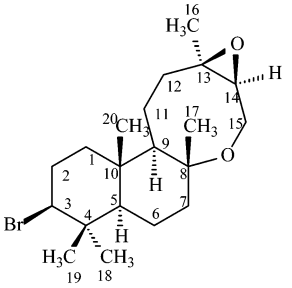
*Department of Pharmacy, Division of Pharmacognosy and Chemistry of Natural Products, University of Athens, Panepistimiopolis Zografou, Athens 15771, Greece, and Department of Natural Resources and Environment, Technological Educational Institute of Crete, Romanou 3, Chania 73133, Crete, Greece*

*Received March 19, 2003*

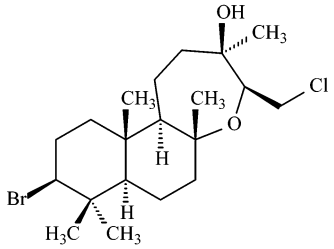
Two labdane type brominated diterpenes (**1** and **2**) containing unprecedented eight- and seven-membered ether rings have been isolated from the organic extract of the red alga *Laurencia obtusa*, collected from Mitikas Bay in the Ionean Sea, Greece. The structures of the new natural products, as well as their relative stereochemistry, were established by means of spectral data analysis, including 2D NMR experiments.

Species of the red alga genus *Laurencia* (Huds.) Lamoroux elaborate an astonishing variety of structurally unusual secondary metabolites and have been the subject of intensive research since the earliest studies on marine organisms.[1] The vast majority of *Laurencia* metabolites are $C_{15}$ acetogenins,[2−4] halogenated diterpenes,[5−11] and sesquiterpenes,[12−15] although several other structural classes have been reported.[16]

In the course of our ongoing research activities toward the isolation of biologically active compounds from marine organisms of the Greek seas,[4,14,15] we studied *Laurencia obtusa* collected from Mitikas Bay in the Ionean Sea. In this report we describe, from the nonpolar fractions, the isolation and structure elucidation of two new brominated diterpenes (**1** and **2**) containing a rare eight- and seven-membered cyclic ether, respectively, fused to a decalin moiety.




**1**




**2**

The alga was collected during the summer of 1999 from Mitikas Bay in the Ionean Sea. The $CH_2Cl_2$/MeOH extract (5.4 g) of the freeze-dried alga was subjected repeatedly to vacuum column chromatography (VCC) on silica gel and normal-phase high-performance liquid chromatography (HPLC), using mixtures of cyclohexane/EtOAc as mobile phase, to yield compounds **1** (3.5 mg) and **2** (1.1 mg) in pure form.

Compound **1** was obtained as a colorless oil. Both $^{13}C$ NMR data and HRFABMS measurements supported the molecular formula $C_{20}H_{33}BrO_2$. The monobrominated nature of the compound was immediately evident from the molecular ion peaks, which appeared of equal intensity (*m*/*z* 384, 386). The absence of hydroxyl groups was evident from the IR spectrum that had instead strong absorptions at 1117, 1060, and 872 $cm^{-1}$ characteristic of cyclic ethers and epoxides. The $^{13}C$ NMR spectrum along with the DEPT experiments showed the presence of 20 carbons corresponding to four quaternary, four methine, seven methylene, and five methyl carbon atoms. Among the carbons, five were bonded to electronegative heteroatoms, resonating at $\delta$ 79.5 (s), 68.7 (d), 60.7 (s), 63.8 (d), and 58.1 (t). Furthermore, the $^1H$ NMR spectrum revealed signals due to a halomethine group at $\delta$ 3.98 (1H, dd), a deshielded methine at $\delta$ 2.78 (1H, d), a deshielded methylene at $\delta$ 3.99 (1H, dd) and 3.88 (1H, d), three tertiary methyl groups at $\delta$ 1.08, 0.92, and 0.89, and two deshielded methyl groups at $\delta$ 1.26 and 1.14 on oxygenated carbons. The carbon signals at $\delta$ 60.7 (s) and 63.8 (d) and the proton signal at $\delta$ 2.78 (1H, d) indicated the presence of an epoxy moiety. With an unsaturation degree of 4, the structure was suggested to contain besides the epoxide three additional rings. The carbon connectivities were traced by a series of 2D NMR homonuclear and heteronuclear experiments (in both $CDCl_3$ and $C_6D_6$) (Table 1).

Comparison of spectral data of **1** with literature values[6−10] showed that the structure should be a brominated diterpene with a labdane type skeleton. Extensive analysis of the 1D and 2D NMR spectra led to a diterpene structure composed of a *trans*-decalin and an epoxide fused to an eight-membered cyclic ether.

Strong long-range correlations between carbon C-3 (68.7 ppm) and H-1, H-2, H-18, and H-19, observed in the HMBC experiments, confirmed the position of the bromine atom on C-3. The epoxy moiety was positioned on carbons C-13 and C-14 on the basis of the long-range correlation of C-16 (22.8 ppm) with H-14, C-13 (60.7 ppm) with H-11, H-12, and H-15 ($\delta$ 3.88), and C-14 (63.8 ppm) with H-15 and H-16. The ether bridge was positioned between carbons C-8 and C-15 on the basis of the long-range correlations of C-8 (79.5

* Corresponding author. Fax: +30210-7274592. E-mail: vagias@pharm.uoa.gr.
[†] University of Athens.
[‡] Technological Educational Institute of Crete.

10.1021/np0301184 CCC: $25.00 © 2003 American Chemical Society and American Society of Pharmacognosy
Published on Web 08/13/2003

**Table 1.** NMR Data of Compound **1**

| no. | $\delta_H$[a] | $\delta_C$[a] | HMBC[a] | NOESY[a] | $\delta_H$[b] | $\delta_C$[b] |
|---|---|---|---|---|---|---|
| 1$\beta$ | 1.81 (m) | 41.9 | H-9, H-20 | H-1α, H-2$\beta$, H-2α, H-20 | 1.23 (m) | 41.6 |
| 1α | 1.09 (m) | | | H-1$\beta$, H-2α, H-9 | 0.51 (m) | |
| 2$\beta$ | 2.17 (dddd, 13.3, 13.3, 13.3, 3.7)[c] | 30.9 | | H-1$\beta$, H-2α, H-19, H-20 | 1.99 (dddd, 13.3, 13.3, 13.3, 3.7) | 31.2 |
| 2α | 2.08 (m) | | | H-1$\beta$, H-1α, H-2$\beta$, H3 | 1.86 (m) | |
| 3 | 3.98 (m) | 68.7 | H-1$\beta$, H-2$\beta$, H-2α, H-18, H-19 | H-2α, H-5, H-18 | 3.70 (dd, 12.6, 4.4) | 68.6 |
| 4 | | 39.6 | H-18, H-19 | | | 39.6 |
| 5 | 0.95 (dd, 11.6, 1.7) | 56.4 | H-1$\beta$, H-6$\beta$, H-7$\beta$, H-18, H-19, H-20 | H-3, H-6α, H-7α, H-9, H-18 | 0.51 (m) | 56.3 |
| 6α | 1.72 (m) | 21.3 | | H-5, H-6$\beta$, H-18 | 1.29 (m) | 21.4 |
| 6$\beta$ | 1.40 (m) | | | H-6α, H-17, H-19, H-20 | 1.00 (m) | |
| 7α | 1.79 (m) | 36.6 | H-17 | H-5, H-7$\beta$, H-15α | 1.46 (ddd, 13.3, 13.3, 4.4) | 36.7 |
| 7$\beta$ | 1.42 (m) | | | H-7α, H-17, H-20 | 1.18 (m) | |
| 8 | | 79.5 | H-6α, H-6$\beta$, H-7α, H-9, H-15α, H-15$\beta$, H-17 | | | 79.1 |
| 9 | 1.37 (m) | 49.1 | H-7$\beta$, H-11, H-12α, H-17, H-20 | H-1α, H-5, H-11, H-14, H-15α | 1.00 (m) | 49.3 |
| 10 | | 38.2 | H-6α, H-9, H-20 | | | 38.0 |
| 11 | 1.57 (m) | 20.7 | H-12$\beta$, H-12α | H-9, H-12$\beta$, H-12α, H-16, H-17, H-20 | 1.11 (m) | 20.9 |
| 12$\beta$ | 2.40 (ddd, 13.1, 13.1, 6.8) | 31.4 | H-16 | H-11, H-12α, H-17 | 2.68 (ddd, 13.6, 13.6, 4.7) | 31.8 |
| 12α | 1.81 (m) | | | H-11, H-12$\beta$, H-16 | 1.69 (ddd, 12.9, 3.7, 3.7) | |
| 13 | | 60.7 | H-11, H-12$\beta$, H-12α, H-15$\beta$, H-16 | | | 59.9 |
| 14 | 2.78 (d, 1.8) | 63.8 | H-15α, H-15$\beta$, H-16 | H-9, H-15α, H-15$\beta$, H-16 | 2.47 (d, 2.05) | 63.4 |
| 15α | 3.99 (dd, 15.7, 1.8) | 58.1 | H-14 | H-7α, H-9, H-14, H-15$\beta$ | 3.56 (dd, 15.7, 2.0) | 58.4 |
| 15$\beta$ | 3.88 (d, 15.7) | | | H-14, H-15α | 3.87 (d, 15.7) | |
| 16 | 1.26 (s) | 22.8 | H-12$\beta$, H-12α, H-14 | H-11, H-12α, H-14 | 1.17 (s) | 22.9 |
| 17 | 1.14 (s) | 23.3 | H-7α, H-7$\beta$ | H-6$\beta$, H-7$\beta$, H-11, H-12$\beta$, H-20 | 1.03 (s) | 23.5 |
| 18 | 1.08 (s) | 30.8 | H-19 | H-3, H-5, H-6α, H-19 | 1.02 (s) | 30.9 |
| 19 | 0.92 (s) | 18.4 | H-5, H-18 | H-2$\beta$, H-6$\beta$, H-18 | 0.87 (s) | 18.5 |
| 20 | 0.89 (s) | 15.1 | H-1α, H-5, H-9 | H-1$\beta$, H-2$\beta$, H-6$\beta$, H-7$\beta$, H-11, H-17 | 0.50 (s) | 15.0 |

[a] Spectra were recorded in $CDCl_3$. [b] Spectra were recorded in $C_6D_6$. [c] *J* values in parentheses are in Hz.

ppm) with H-6, H-7, H-9, and H-15. Moreover the correlations of H-16 with C-13, H-17 with C-8, H-18/H-19 with C-4, and H-20 with C-10 confirmed the positions of the methyl groups.

The relative stereochemistry was assigned upon analysis of the coupling constants and NOESY experiments (in both $CDCl_3$ and $C_6D_6$). The coupling constants of H-3 (12.6, 4.4 Hz) that were measured in the $^1$H NMR spectrum recorded in $C_6D_6$ (in this solvent H-3 was clearly resolved) indicated the axial configuration of H-3. Moreover, the strong NOE effects between H-3/H-5, H-5/H-9, H-5/H-7α (δ 1.79), H-9/H-7α (recorded in $C_6D_6$), and H-9/H-1α (δ 1.09) indicated that these protons were axial and located on the same side of the molecule (α). Additional NOE interactions between H-19/H-2$\beta$ (δ 2.17), H-19/H-20 (recorded in $C_6D_6$), H-19/H-6$\beta$ (δ 1.40), and H-17/H-6$\beta$ implied that these protons were axially oriented and occupied the $\beta$ face of the molecule. The above observations indicated the decalin to be *trans*-fused and the eight-membered cyclic ether to be *trans*-fused to decalin, as well. Furthermore, the strong NOE effect between H-17/H-12$\beta$ (δ 2.40) and H-9/H-15α (δ 3.99) suggested boat conformation for the eight-membered ring, while the strong correlations of H-14/H-16, H-14/H-9, and H-16/H-12α (δ 1.81) indicated $\beta$ orientation for the epoxy moiety (Figure 1). According to the above observations, the relative stereochemistry for metabolite **1** was proposed as 3*S**, 5*R**, 8*R**, 9*R**, 10*S**, 13*R**, 14*S**.

Compound **2** was isolated as a colorless oil. Both $^{13}$C NMR data and HREIMS measurements supported the molecular formula $C_{20}H_{34}BrClO_2$. The HREIMS showed $[M - CH_3]^+$ peaks at *m*/*z* 405, 407, 409 with intensities of 3/4/1, confirming the presence of one bromine and one chlorine atom. The IR spectrum displayed strong absorptions for a hydroxyl group (3416 cm$^{-1}$) and a cyclic ether function (1080 cm$^{-1}$). The $^{13}$C NMR spectrum along with the DEPT experiments showed the presence of 20 carbons corresponding to four quaternary, four methine, seven methylene, and five methyl carbon atoms. Among the carbons, three were bonded to oxygens resonating at δ 78.7 (s), 74.5 (d), and 72.5 (s), and two were halogenated resonating at δ 69.0 (d) and 44.7 (t). Furthermore, the $^1$H NMR spectrum revealed signals due to a halomethine group at δ 3.95 (1H, dd), a deshielded terminal halogenated methyl (−$CHCH_2Cl$) forming a first-order ABX spin system at δ 3.67 (1H, dd), 3.43 (1H, dd), and 3.73 (1H, dd), three tertiary methyl groups at δ 1.04, 0.90, and 0.82, and two deshielded methyl groups at δ 1.11 and 1.23 on oxygenated carbons. The almost identical chemical shift of C-3 in metabolites **2** and **1** (69.0 ppm in **2**; 68.7 ppm in **1**) suggested that bromine remained on C-3 since exchange with the more electronegative chlorine would shift the carbon bearing the halogen to lower field.[15] Additionally a broad signal at δ 3.14 (1H, s) corresponding to an exchangeable proton confirmed the presence of the hydroxyl group. With an unsaturation degree of 3, the structure was

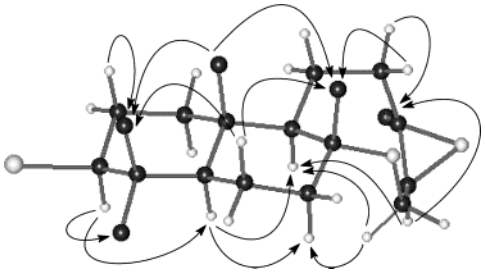


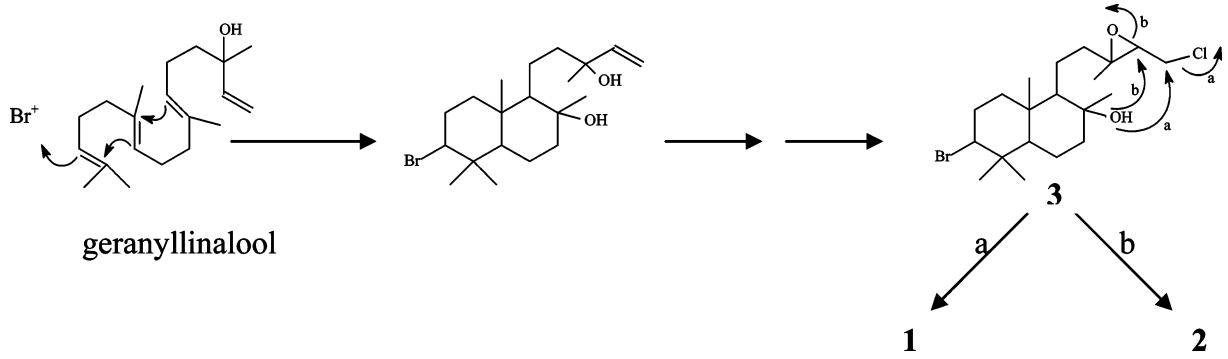
**Figure 1.** Selected NOESY correlations of compound **1**.

**Table 2.** NMR Data of Compound **2**

| no. | $\delta_H$[a] | $\delta_C$[a] | HMBC[a] | NOESY[a] |
|---|---|---|---|---|
| 1$\beta$ | 1.73 (m) | 40.9 | H-2α, H-20 | H-1α, H-2α |
| 1α | 1.04 (m) | | | H-1$\beta$, H-2α |
| 2$\beta$ | 2.20 (dddd, 13.5, 13.5, 13.5, 3.6)[b] | 30.7 | | H-2α, H-19, H-20 |
| 2α | 2.08 (m) | | | H-1$\beta$, H-1α, H-2$\beta$, H-3 |
| 3 | 3.95 (dd, 12.4, 4.3) | 69.0 | H-1$\beta$, H-2$\beta$, H-18, H-19 | H-2α, H-5, H-18 |
| 4 | | 39.7 | H-18, H-19, H-20 | |
| 5 | 0.95 (dd, 12.0, 2.1) | 56.3 | H-1$\beta$, H-7$\beta$, H-18, H-19 | H-3, H-7α, H-9 |
| 6α | 1.83 (dddd, 13.7, 2.7, 2.7, 2.7) | 22.3 | H-5 | H-6$\beta$, H-18 |
| 6$\beta$ | 1.45 (m) | | | H-6α, H-17, H-20 |
| 7$\beta$ | 1.76 (m) | 38.9 | H-6$\beta$, H-9, H-17 | H-7α |
| 7α | 1.58 (ddd, 12.8, 12.8, 3.6) | | | H-5, H-7$\beta$, H-14 |
| 8 | | 78.7 | H-7$\beta$, H-9, H-14, H-17 | |
| 9 | 1.15 (br d, 7.6) | 57.9 | H-1$\beta$, H-17, H-20 | H-5, H-14 |
| 10 | | 37.3 | H-20 | |
| 11 | 1.36 (m) | 18.1 | H-9 | H-12a, H-12b, H-20 |
| 12a | 1.70 (m) | 45.4 | H-16 | H-11, H-12b |
| 12b | 1.25 (m) | | | H-11, H-12a, −OH |
| 13 | | 72.5 | H-12a, H-16, −OH | |
| 14 | 3.73 (dd, 9.8, 2.6) | 74.5 | H-15$\beta$, H-16 | H-7α, H-9, H-15α, H-16 |
| 15α | 3.67 (dd, 11.1, 2.6) | 44.7 | H-14 | H-14, H-15$\beta$, H-16 |
| 15$\beta$ | 3.43 (dd, 11.1, 9.8) | | | H-15α, -OH |
| 16 | 1.11 (br s) | 24.9 | −OH | H-14, H-15α |
| 17 | 1.23 (s) | 24.0 | H-7α, H-9, H-11 | H-6$\beta$, H-20 |
| 18 | 1.04 (s) | 30.4 | H-19 | H-3, H-6α |
| 19 | 0.90 (s) | 17.7 | H-18 | H-2$\beta$ |
| 20 | 0.82 (s) | 16.2 | H-5, H-9 | H-2$\beta$, H-6$\beta$, H-11, H-17 |
| −OH | 3.14 (br s) | | | H-12b, H-15$\beta$ |

[a] Spectra were recorded in $CDCl_3$. [b] *J* values in parentheses are in Hz.

**Scheme 1.** Hypothetic Biogenetic Scheme for Compounds **1** and **2**




suggested to contain three rings. The carbon connectivities were traced by a series of 2D NMR homonuclear and heteronuclear experiments (Table 2). Comparison of spectral data of **2** with those of **1** showed similar spectral features for the decalin system. The NMR data of **2** exhibited resonances corresponding to the brominated *trans*-fused decalin, suggesting that this moiety also exists in compound **2**.

On the basis of the correlations of the oxygenated carbon C-13 (72.5 ppm) with H-12 ($\delta$ 1.70), −OH ($\delta$ 3.14), and H-16 as well as the correlations of the oxygenated carbon C-14 (74.5 ppm) with H-16 and H-15 ($\delta$ 3.43), and the chlorinated carbon C-15 (44.7 ppm) with H-14, observed in HMBC, the hydroxyl group was placed on C-13 and the $-CH_2Cl$ group was placed on C-14. The ether bridge was positioned between carbons C-8 and C-14 on the basis of the long-range correlations of C-8 (78.7 ppm) with H-7 ($\delta$ 1.76), H-9, and H-14. Moreover the correlations of H-16 with C-13, H-17 with C-8, H-18/H-19 with C-4, and H-20 with C-10 confirmed the positions of the methyl groups.

The relative stereochemistry of compound **2** was resolved by a combination of NOESY data and analysis of coupling constants. The coupling constants of H-3 (12.4, 4.3 Hz) that were observed in the $^1$H NMR spectrum indicated the axial configuration of H-3. The observed NOE correlations between protons H-3/H-5, H-5/H-9, and H-5/H-7α ($\delta$ 1.58), as well as between protons H-19/H-2$\beta$ ($\delta$ 2.20), H-20/H-2$\beta$, H-20/H-6$\beta$ ($\delta$ 1.45), H-17/H-20, and H-17/H-6$\beta$, indicated a *trans*-fused decalin with the same relative configuration as in metabolite **1** and *trans*-fusion for the seven-membered cyclic ether on the decalin. Furthermore, the strong NOE effect between H-9/H-14 and H-14/H-16 suggested an α orientation for H-14 and H-16. Consequently, the relative stereochemistry for metabolite **2** was deduced as 3*S**, 5*R**, 8*R**, 9*R**, 10*S**, 13*R**, 14*S**.

Metabolites **1** and **2** could result from a common decalin precursor,[6,9,10] which is formed from geranyllinalool via cyclization and bromination. Enzyme-catalyzed dehydration, followed by double-bond transposition, allylic chlorination, and epoxidation can give rise to intermediate **3**. Nucleophilic attack of the C-8 hydroxyl group of **3**, either on C-15 or on C-14, and respective elimination of chlorine or epoxide opening would lead to metabolites **1** and **2** (Scheme 1).

## Experimental Section

**General Experimental Procedures.** Optical rotations were measured using a Perkin-Elmer model 341 polarimeter and a 10 cm cell. UV spectra were aquired in spectroscopic grade $C_6H_{14}$ and $CH_2Cl_2$ on a Shimadzu UV-160A spectropho-

tometer. IR spectra were obtained using a Paragon 500 Perkin-Elmer spectrophotometer. NMR spectra were recorded using a Bruker AC 200 and a Bruker DRX 400 spectrometer. Chemical shifts are given on $\delta$ (ppm) scale using TMS as internal standard (s, singlet; d, doublet; t, triplet; m, multiplet). The 2D experiments ($^1$H−$^1$H COSY, HMQC, HMBC, NOESY) were performed using standard Bruker microprograms. High-resolution mass spectral data were provided by the Department of Chemistry and Biochemistry, University of Notre Dame, Notre Dame, IN. EIMS data were recorded on a Hewlett-Packard 5973 mass selective detector. VCC separation was performed with Kieselgel 60H (Merck), TLC analyses were performed with Kieselgel 60 $F_{254}$ (Merck aluminum support plates), and spots were visualized upon spraying with 15% $H_2SO_4$ in MeOH and heating. HPLC separations were conducted using a Pharmacia LKB 2248 model and GBC LC-1240 refractive index detector, with a Spherisorb S10W (phase sep; column size, 10 × 250 mm) column.

**Plant Material.** The alga was collected by hand at Mitikas Bay in the Ionean Sea, Greece, at a depth of 0.5−1 m during the summer of 1999. A voucher specimen is kept at the Herbarium of the Pharmacognosy Laboratory, University of Athens (ATPH/MO/99).

**Extraction and Isolation.** The alga was initially freeze-dried (151.4 g dry weight) and then exhaustively extracted at room temperature with mixtures of $CH_2Cl_2$/MeOH (2:1). The organic extract after evaporation of the solvents afforded a dark oily residue (5.4 g). The crude extract was subjected to VCC on Si gel using cyclohexane with increasing amounts (10%) of EtOAc and finally MeOH. Fraction IV (30% EtOAc in cyclohexane) (522 mg) was further purified by VCC on Si gel using cyclohexane with increasing amounts (2%) of EtOAc. Fractions IV (6% EtOAc) (39.6 mg) and V (8% EtOAc) (80.2 mg) were subjected to normal-phase HPLC chromatography, using as mobile phase cyclohexane/EtOAc (90:10), to yield pure compounds **1** (3.5 mg) and **2** (1.1 mg).

**Compound 1:** colorless oil; $[\alpha]^{20}_D$ +21.9 (*c* 0.32, $CHCl_3$); UV ($CH_2Cl_2$) $\lambda_{max}$ (log $\epsilon$) 228.9 (2.55) nm; IR ($CHCl_3$) $\nu_{max}$ 2951, 1435, 1387, 1237, 1117, 1060, 1047, 872, 811 cm$^{-1}$; NMR data ($CDCl_3$, $C_6D_6$), see Table 1; EIMS *m*/*z* 386, 384 $[M]^+$ (2:2), 371, 369 $[M - CH_3]^+$ (3:3), 269 (54), 191 (63), 135 (62), 84 (92), 69 (71), 43 (100); HRFABMS *m*/*z* 385.1767 $[M + 1]^+$ (calcd for $C_{20}H_{34}{}^{79}BrO_2$, 385.1743).

**Compound 2:** colorless oil; $[\alpha]^{20}_D$ +6.2° (*c* 0.13, $CHCl_3$); UV (*n*-hexane) $\lambda_{max}$ (log $\epsilon$) 230 (2.92) nm; IR ($CHCl_3$) $\nu_{max}$ 3416 (br), 2945, 1460, 1392, 1264, 1162, 1080, 1020, 935 cm$^{-1}$; NMR data ($CDCl_3$), see Table 2; EIMS *m*/*z* 391, 389, 387 $[M - CH_3 - H_2O]^+$ (1:4:3), 343, 341 (15:15), 325, 323 (98:100), 245, 243 (16:57), 191 (33), 135 (97), 81 (54), 69 (63), 43 (89); HREIMS *m*/*z* 407.1183 $[M - CH_3]^+$ (calcd for $C_{19}H_{31}{}^{81}Br^{35}ClO_2$, 407.1177).

**Acknowledgment.** Financial support from the Greek General Secretariat for Research and Technology is gratefully acknowledged. We wish to thank Dr. P. Panagiotides for the identification of the organism (National Center for Marine Research).

## References and Notes

(1) Faulkner, D. J. *Nat. Prod. Rep*. **2002**, *19*, 1−48.
(2) Norte, M.; Gonzalez, A. G.; Cataldo, F.; Rodriguez, M. L.; Brito, I. *Tetrahedron* **1991**, *47*, 9411−9418.
(3) König, G. M.; Wright, A. D. *J. Nat. Prod*. **1994**, *57*, 477−485.
(4) Iliopoulou, D.; Vagias, C.; Harvala, C.; Roussis, V. *Phytochemistry* **2002**, *59*, 111−116.
(5) Caccamese, S.; Toscano, R. M.; Cerrini, S.; Gavuzzo, E. *Tetrahedron Lett*. **1982**, *23*, 3415−3418.
(6) Suzuki, M.; Nakano, S.; Takahashi, Y.; Abe, T.; Masuda, M.; Takahashi, H.; Kobayashi, K. *J. Nat. Prod*. **2002**, *65*, 801−804.
(7) Kuniyoshi, M.; Marma, M. S.; Higa, T.; Bernardinelli, G.; Jefford, C. W. *J. Nat. Prod*. **2001**, *64*, 696−700.
(8) Su, J. Y.; Zhong, Y. L.; Zeng, L. M.; Wu, H. M.; Ma, K. *Phytochemistry* **1995**, *40*, 195−197.
(9) Howard, B. M.; Fenical, W. *Phytochemistry* **1980**, *19*, 2774−2276.
(10) Rodriguez, M. L.; Martin, J. D.; Estrada, D. *Acta Crystallogr. C* **1989**, *45*, 306−308.
(11) Fenical, W.; Howard, B.; Gifkins, K. B.; Clardy, J. *Tetrahedron Lett*. **1975**, *46*, 3983−3986.
(12) Brito, I.; Cueto, M.; Diaz-Marrero, A. R.; Darias, J.; San Martin, A. *J. Nat. Prod*. **2002**, *65*, 946−948.
(13) Wright, A. D.; König, G. M.; Sticher, O. *J. Nat. Prod*. **1991**, *54*, 1025−1033.
(14) Iliopoulou, D.; Roussis, V.; Pannecouque, C.; De Clercq, E.; Vagias, C. *Tetrahedron* **2002**, *58*, 6749−6755.
(15) Iliopoulou, D.; Vagias, C.; Galanakis, D.; Argyropoulos, D.; Roussis, V. *Organ. Lett*. **2002**, *4*, 3263−3266.
(16) Erickson, K. L. In *Marine Natural Products*; Scheuer, P., Eds.; Academic Press: New York, 1983; Vol. 5, pp 131−257.

NP0301184