Halogenated Monoterpene Aldehydes from the South African Marine Alga *Plocamium corallorhiza*

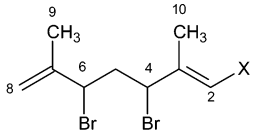
Maryssa G. A. Mann,[†] Henry B. Mkwananzi,[†] Edith M. Antunes,[†] Catherine E. Whibley,[‡] Denver T. Hendricks,[‡] John J. Bolton,[§] and Denzil R. Beukes*[,†]

Division of Pharmaceutical Chemistry, Faculty of Pharmacy, Rhodes University, Artillery Road, Grahamstown 6140, South Africa, Department of Botany, University of Cape Town, Private Bag, Rondebosch 7701, South Africa, and Division of Medical Biochemistry, Faculty of Health Sciences, University of Cape Town, Private Bag X3, Observatory 7935, South Africa

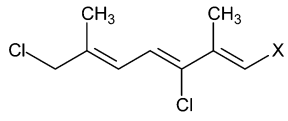
Received October 31, 2006

Four new halogenated monoterpene aldehydes (**1**−**4**) have been isolated from the South African marine red alga *Plocamium corallorhiza*, along with the known compounds 4,6-dibromo-1,1-dichloro-3,7-dimethyl-2*E*,7-octadiene (**5**) and 1,4,8-tribromo-3,7-dichloro-3,7-dimethyl-1*E*,5*E*-octadiene (**10**). The structures of the new compounds were determined by interpretation of their spectroscopic data and synthesis and mass spectrometric analysis of their pentafluorobenzyloxime (PFBO) derivatives.

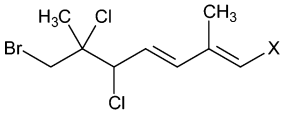
The genus *Plocamium* (Rhodophyta) comprises over 40 marine algal species, which are widely distributed throughout the world's oceans.[1] Chemical investigations of a number of these algae have been productive, resulting in the isolation of a considerable number of acylic and cyclic halogenated monoterpene natural products containing multiple halogen atoms.[2] It is thought that the incorporation of halogens into the monoterpene skeleton is facilitated by a vanadium haloperoxidase enzyme.[3] *Plocamium corallorhiza* (Turner) Hooker & Harvey (Plocamiaceae, Plocamiales) is commonly encountered in the subtidal fringe along the coast of South Africa.[4] We have recently reported the isolation and characterization of polyhalogenated monoterpenes featuring an unusual *gem*-dichloride moiety from *P. corallorhiza* obtained from the west coast of South Africa.[5] In a continuation of our studies of the secondary metabolites produced by South African marine algae, we have investigated a collection of *P. corallorhiza* obtained from the southeast coast of South Africa. Intriguingly, this collection of *P. corallorhiza* produced a series of unstable halogenated monoterpene aldehydes (**1**−**4**) that were not detected in the west coast collection.



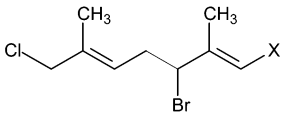
1 X = CHO
5 X = $CHCl_2$
6 X = $CH{=}NOCH_2C_6F_5$



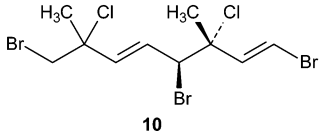
2 X = CHO
7 X = $CH{=}NOCH_2C_6F_5$



3 X = CHO
8 X = $CH{=}NCH_2C_6F_5$



4 X = CHO
9 X = $CH{=}NCH_2C_6F_5$



10

Results and Discussion

P. corallorhiza was collected at low tide near Kenton-On-Sea, South Africa, during January 2006 and extracted sequentially with MeOH and CH_2Cl_2/MeOH (2:1). These extracts were combined, concentrated, and fractionated by solvent partitioning to give *n*-hexane, CH_2Cl_2, EtOAc, and aqueous fractions. Clearly discernible aldehyde signals were present in the ^{1}H NMR spectra of the *n*-hexane and CH_2Cl_2 fractions, and these were further fractionated by silica gel column chromatography (EtOAc/*n*-hexane). Final purification was achieved by semipreparative normal-phase HPLC (EtOAc/*n*-hexane) to obtain the two known compounds 4,6-dibromo-1,1-dichloro-3,7-dimethyl-2*E*,7-octadiene (**5**)[5] and 1,4,8-tribromo-3,7-dichloro-3,7-dimethyl-1*E*,5*E*-octadiene (**10**)[6] as well as four new, unstable, halogenated monoterpene aldehydes (**1**−**4**).

Compound **1**, the major aldehyde metabolite, was isolated as an unstable, optically active oil, which rapidly degraded when exposed to air at room temperature. The ^{1}H NMR spectrum of **1** (Table 1), in combination with the ^{1}H−^{1}H COSY spectrum, was highly informative, indicating the presence of two mutually coupled methine resonances at δ 10.01 (1H, d, J = 7.3 Hz) and δ 6.05 (1H, d, J = 7.3 Hz) and two one-proton singlets at δ 5.11 and 4.96. These features were consistent with an α,β-unsaturated aldehyde and terminal alkene moieties, respectively. An infrared absorption band at 1676 cm^{-1} and ^{13}C NMR signal at δ 191.2 confirmed the presence of the aldehyde functional group. Analysis of the ^{13}C NMR and DEPT data (Table 1) indicated the presence of an aldehyde (δ 191.2), two double bonds (δ 115.0, 127.8, 143.7, and 157.3), a methylene (δ 42.7), two halomethines (δ 56.1 and 56.0), and two olefinic methyl groups (δ 14.5 and 18.5). ^{1}H−^{1}H COSY, HSQC, and HMBC data were used to delineate the planar structure of **1**. The methyl resonance at δ 2.31 showed strong HMBC correlations to a quaternary carbon at δ 157.3, a halomethine at δ 56.1, and an olefinic methine at δ 127.8, while the proton (δ 6.05) attached to the latter carbon showed a strong ^{1}H−^{1}H COSY correlation to the aldehyde signal at δ 10.01. This information is consistent with the presence of a $-CHX-C(CH_3){=}CH-CHO$ partial structure for **1** (Figure 1). HMBC correlations from the second olefinic methyl signal at δ 1.88 to a quaternary carbon at δ 143.7, an olefinic methylene at δ 115.0, and a halomethine at δ 56.0 established the second partial structure as $CH_2{=}C(CH_3)-CH(X)-$ (Figure 1). Finally, the methylene at δ 2.42 showed HMBC and ^{1}H−^{1}H COSY correlations to the two carbons at δ 56.0 and 56.1 to support the structure for **1** (Figure 1). The C-4 and C-6 ^{13}C NMR chemical shifts (δ 56.0 and 56.1) were in agreement with those of related brominated compounds.[7] The instability of aldehydes **1**−**4** frustrated our efforts to obtain reliable mass spectrometry

* Corresponding author. Tel: +27-46-6038395. Fax: +27-46-6361205. E-mail: d.beukes@ru.ac.za.
[†] Rhodes University.
[‡] Division of Medical Biochemistry, University of Cape Town.
[§] Department of Botany, University of Cape Town.

10.1021/np060547c CCC: $37.00 © 2007 American Chemical Society and American Society of Pharmacognosy
Published on Web 03/08/2007

Table 1. ^{1}H (400 MHz) and ^{13}C NMR (100 MHz) Data of **1**−**4** in $CDCl_3$

	1		**2**		**3**		**4**	
C #	δ_C	δ_H, multi., *J* (Hz)	δ_C	δ_H, multi., *J* (Hz)	δ_C	δ_H, multi., *J* (Hz)	δ_C	δ_H, multi., *J* (Hz)
1	191.2	10.01, d, 7.3	191.2	10.15, d, 7.7	191.1	10.15, d, 8.0	191.2	10.03, d, 7.3
2	127.8	6.05, d, 7.3	128.5	6.62, d, 7.7	131.0	6.00, d, 8.0	127.5	6.02,d, 7.3
3	157.3		150.6		150.0		157.9	
4	56.1	4.72, d, 7.6	135.0		138.1	6.53, d, 16.0	56.5	4.47, t, 7.6
5	42.7	2.42, t, 7.0	126.2	7.02, d, 10.6	131.0	6.33, dd, 9.0, 16.0	34.8	2.78, m,
6	56.0	4.72, d, 7.6	125.1	6.71, d, 10.6	65.8	4.91, d, 9.0	124.9	5.43, t, 6.6
7	143.7		142.0		71.1		135.6	
8a	115.0	5.11, s	51.2	4.15, s	40.6	3.82, d, 11.0	51.2	3.98, s
8b		4.96, s				3.65, d, 11.0		
9	18.5	1.88, s	15.9	2.00, s	25.6	1.83, s	14.7	1.81, s
10	14.5	2.31, s	14.7	2.41, s	13.2	2.30, s	13.8	2.25, s

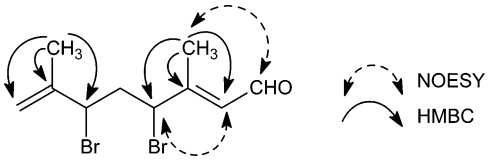


Figure 1. Key HMBC and NOESY correlations for aldehyde **1**.

data for these compounds. For this reason we prepared dinitrophenylhydrazone (DNPH),[8a] carboxyethylethylidene (CET),[8b] and pentafluorobenzyloxime (PFBO)[8c] derivatives of **1** on a milligram scale and analyzed each by atmospheric pressure chemical ionization mass spectrometry (APCIMS). Although both the CET and PFBO derivatives of **1** gave the expected molecular ion peaks, the latter method (Scheme 1) was preferred due to the rapid reaction times and mild reaction conditions. The LRAPCIMS mass spectrum of PFB-oxime derivative **6** showed a prominent isotope cluster at *m*/*z* 504/506/508 in a ratio (1:2:1) indicative of two bromine atoms. High-resolution electrospray ionization mass spectrometry (HRESIMS) provided a molecular formula of $C_{17}H_{17}NOF_5Br_2$ (*m*/*z* 503.9567, $[M + H]^+$) for **6**, consistent with a molecular formula of $C_{10}H_{14}Br_2O$ for **1**.

No information on the configurations of the chiral carbons at C-4 and C-6 was obtained. The geometry of the C-2/C-3 double bond was assigned as *E* on the basis of a strong NOESY correlation between H-1 and CH_3-10.

Compound **1** is related to plocoralide B (**5**)[5] and 1-chloro-4,6-dibromo-3,7-dimethyl-2,7-octadiene,[7] previously isolated from *P. corallorhiza* and *P. violaceum*.

The second aldehyde (**2**) was isolated as an optically inactive yellow-green oil. An α,β-unsaturated aldehyde (δ 10.15, d, J = 7.7 Hz and δ 6.62, d, J = 7.7 Hz) was immediately apparent from the ^{1}H NMR spectrum of **2**. In addition, two mutually coupled olefinic methines [δ 7.02 (d, J = 10.6 Hz) and δ 6.71 (d, J = 10.6 Hz)] and a halomethylene singlet at δ 4.15 were prominent. Ten signals were observed in the ^{13}C NMR spectrum, indicating the presence of an aldehyde (δ 191.2), three double bonds (δ 150.6, 142.0, 135.0, 128.5, 126.2, and 125.1), two olefinic methyls (δ 15.9 and 14.7), and one methylene (δ 51.2) (Table 1).

As for compound **1**, the interpretation of 1D and 2D NMR data established partial structures of the molecule and ultimately led to the elucidation of the planar structure of **2**. The halomethylene was placed at C-8 on the basis of HMBC correlations from the methyl at δ 2.00 to olefinic carbons at δ 125.1 and 142.0 and the methylene at δ 51.2. In addition, the carbon signal at δ 125.1 showed an HSQC correlation to a proton signal at δ 6.71 (1H, d, J = 10.6 Hz), which in turn showed ^{1}H−^{1}H COSY correlations to an olefinic methine at δ 7.02 (d, J = 10.6 Hz) to provide the partial structure $XCH_2C(CH_3)$═CH−CH═. A second fragment (−C═C(X)−$C(CH_3)$═CH−CHO) was constructed from the observation of HMBC correlations from the olefinic methyl protons at δ 2.41 to carbons at δ 191.2, 128.5, 135.0, and 150.6. HMBC correlations from the methine at δ 7.02 to carbons at δ 135.0, 150.6, and 142.0, as well as ^{1}H−^{1}H COSY correlations to the proton at δ 6.71, joined the fragments.

Compound **2** also failed to give decipherable mass spectra and was therefore also converted to its PFB-oxime (**7**). HRESIMS of the latter gave a molecular ion peak at *m*/*z* 414.0451 $[M + H]^+$, in agreement with a molecular formula of $C_{17}H_{14}Cl_2F_5NO$ for **7**. The ^{13}C NMR chemical shifts of the quaternary carbon at δ 135.0 and the methylene at δ 51.2 are consistent with an olefinic chlorine substituent and a chloromethylene, respectively.[9]

A NOESY correlation between H-1 and CH_3-10 confirmed the *E*-geometry for the C-2/C-3 double bond, while correlations from H-5 to CH_3-9 and CH_3-10 are consistent with *Z*- and *E*-geometries for the C-4/C-5 and C-6/C-7 double bonds, respectively.

Aldehyde **3** was isolated as an optically active oil. The ^{1}H NMR and ^{1}H−^{1}H COSY spectroscopic data of **3** revealed the presence of a −CH═CH−CH(X)− partial structure [δ 6.53 (d, J = 16.0 Hz), 6.33 (dd, J = 16.0 and 9.0 Hz) and δ 4.91 (d, J = 9.0)], while the ^{13}C NMR spectrum indicated the presence of two double bonds and three halogen-bearing carbons. A planar structure of $X-CH_2C(CH_3)X-CHX-CH$═$CH-C(CH_3)$═CH−CHO was deduced from 1D and 2D NMR data.

The ^{13}C NMR chemical shifts of C-6 and C-7 (δ 65.8 and 71.1) are consistent with chlorine atoms at these positions, while a bromine atom must be accommodated at C-8 to account for the chemical shift of δ 40.6.[9] This was confirmed by the molecular formula of $C_{17}H_{16}NOF_5Cl_2Br$ (*m*/*z* 493.9713) obtained from the HRESIMS spectrum of the PFBO-oxime of **3** (**8**).

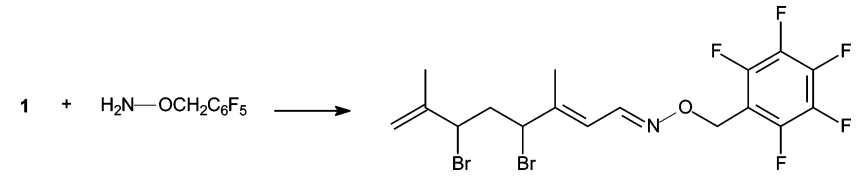
The *E*-geometry of the C-4/C-5 double bond was deduced from the $J_{4,5}$ coupling constant (16.0 Hz) and confirmed by a NOESY correlation between H-4 and H-6. NOESY correlations between H-1 and CH_3-10 and H-2 and H-4 allowed the assignment of the C-2/C-3 double bond as *E*.

Compound **4** was also isolated as an optically active yellow oil that also exhibited the typical signals of an α,β-unsaturated aldehyde in its ^{1}H NMR spectrum. The ^{13}C and DEPT NMR spectra showed signals indicative of two double bonds, an aldehyde, and a halomethine. The 2D NMR data were consistent with the structure shown for compound **4**. HRESIMS of the PFB-oxime of **4** (**9**) ($C_{17}H_{17}NOF_5{}^{79}Br^{35}Cl$, *m*/*z* 460.0148) indicated the presence of one bromine and one chlorine atom in compound **4**. The ^{13}C NMR chemical shifts of the signals for C-8 and C-4 were consistent with chlorine and bromine atoms,[9] respectively, at these positions. NOESY correlations between H-1 and H-10 and between H-6 and H-8 suggested *E*-geometries for both the C-2/C-3 and C-6/C-7 double bonds.

Compounds **1** and **3** were evaluated for cytotoxicity toward an esophageal cancer cell line. In spite of its apparent instability, compound **1** showed moderate to good activity (IC_{50} 7.5 μM) in this assay, while **3** was only weakly active (IC_{50} 64.8 μM). Compounds **2** and **4** degraded before their biological activity could be established.

Aldehydes **1**−**4** are new members of a small number of marine halogenated monoterpene aldehydes of which cartilagineal[10] was the first to be reported. The similarity of aldehyde **1** to plocoralide B (**5**) may suggest that compounds **1**−**4** are degradation products

Scheme 1. Derivatization of **1** with Pentafluorobenzylhydroxylamine Hydrochloride (PFBHA·HCl)



6

formed during the isolation process. However, lyophilization of freshly collected *P. corallorhiza* followed by extraction with CH_2Cl_2 clearly showed the presence of the aldehyde signals in the ^1H NMR spectrum. In addition, although this is the first report of an aldehyde group at C-1 in a marine halogenated monoterpene, this functional group is also present in a number of terrestrial monoterpenes (e.g., geranial).

Experimental Section

General Experimental Procedures. Optical rotations were measured on a Perkin-Elmer 141 polarimeter. IR spectra were obtained as films on KBr disks using a Perkin-Elmer Spectrum 2000 FT-IR spectrometer. All NMR spectra were recorded on a Bruker Avance 400 NMR spectrometer using standard pulse sequences. Spectra were referenced to residual protonated solvent resonances ($CHCl_3$ δ_H 7.25, δ_C 77.0). Compounds were purified using a Spectra-Physics IsoChrom LC HPLC system, equipped with a rheodyne injector, a Waters R401 differential refractometer, and a Rikadenki chart recorder. Normal-phase HPLC was performed using a Whatman Magnum 10 Partisil 9 column. LRAPCIMS spectra were recorded on a ThermoFinnigan MAT LCQ ion trap mass spectrometer with Xcalibur software. HRESIMS spectra were acquired on a Waters API-TOF Ultima mass spectrometer using positive electrospray ionization at the Mass Spectrometry Unit at Stellenbosch University, Stellenbosch, South Africa.

Collection, Extraction, and Isolation. *Plocamium corallorhiza* was collected at low tide near Kenton-On-Sea on the southeast coast of South Africa, in January 2006, and kept frozen until extraction. Taxonomic identification was based on comparison of biological features to other voucher samples in our repository. A voucher specimen (#KOS06-14) is retained at the Faculty of Pharmacy, Rhodes University, South Africa.

Frozen *P. corallorhiza* (31.5 g dry wt after extraction) was initially steeped in MeOH at 4 °C for 1 h and filtered, and the solids were extracted exhaustively with CH_2Cl_2/MeOH (2:1) at ambient temperature. The crude MeOH and CH_2Cl_2/MeOH extracts were reduced *in vacuo* and extracted with CH_2Cl_2. The combined CH_2Cl_2 extracts were dried and partitioned between *n*-hexane and MeOH/H_2O (9:1), and the latter was further partitioned between MeOH/H_2O (7:3) and CH_2Cl_2 to give *n*-hexane (1.44 g) and CH_2Cl_2 (0.38 g) crude fractions after drying. Aldehyde signals were clearly discernible from the ^1H NMR spectra of the *n*-hexane and CH_2Cl_2 fractions, and these were fractionated by silica gel column chromatography using a stepwise gradient of *n*-hexane/EtOAc and EtOAc/MeOH. Fractions eluting with *n*-hexane, *n*-hexane/EtOAc (9:1), and *n*-hexane/EtOAc (8:2) were further purified by repeated semipreparative normal-phase HPLC (*n*-hexane/EtOAc) to give the new compounds **1** (61 mg), **2** (2 mg), **3** (2 mg), and **4** (<1 mg) in addition to the known metabolites 4,6-dibromo-1,1-dichloro-3,7-dimethyl-2*E*,7-octadiene (**5**, 10 mg) and 1,4,8-tribromo-3,7-dichloro-3,7-dimethyl-1*E*,5*E*-octadiene (**10**, 9 mg).

4,6-Dibromo-3,7-dimethylocta-2,7-dienal (1): yellow-green oil; $[\alpha]^{28}_D$ −27 (*c* 0.0028, $CHCl_3$); UV (*n*-hexane) λ_{max} 231 nm (log ϵ 3.8); IR (dry film, KBr) ν_{max} 2923, 2851, 2253, 1676, 1378, 1112, 907, 731, 650 cm $^{-1}$; ^1H NMR ($CDCl_3$, 400 MHz) and ^{13}C NMR ($CDCl_3$, 100 MHz), see Table 1; HMBC correlations, H-1/C-2; H-2/C-4/C-10; H-4/C-2, C-3, C-5; CH_2-5/C-3, C-6, C-7; H-6/C-5, C-7; CH_2-8/C-6, C-7, C-9; CH_3-9/C-6, C-7, C-8; CH_3-10/C-2, C-3, C-4; NOESY correlations, H-1/H-2, CH_3-10; H-2/H-1; H-4/CH_2-5, CH_3-10; CH_2-5/H-4, H-6; H-6/CH_2-5, CH_3-9; H-8a/CH_3-9; CH_3-9/H-8a, H-6; CH_3-10/H-1, H-4; LRAPCIMS of aldehyde **1** *m*/*z* 309/311/313 $[M]^+$; LRAPCIMS of PFB-oxime of **1** (=compound **6**) *m*/*z* 504/506/508 $[M + H]^+$; HRESIMS of PFB-oxime of **1** (=compound **6**) *m*/*z* 503.9608 (calcd for $C_{17}H_{17}NOF_5{}^{79}Br_2$, 503.9597).

4,8-Dichloro-3,7-dimethylocta-2,4,6-trienal (2): green oil; UV (*n*-hexane) λ_{max} 330, 316, 321 nm (log ϵ 3.9); IR (dry film, KBr) ν_{max} 2254, 1662, 1168, 980, 939, 907, 852, 792, 736, 655 cm $^{-1}$; ^1H NMR ($CDCl_3$, 400 MHz) and ^{13}C NMR ($CDCl_3$, 100 MHz), see Table 1; HMBC correlations, H-1/C-2; H-2/C-3, C-4, C-10; H-5/C-3, C-4, C-7; H-6/C-3, C-8, CH_3-9; CH_2-8/C-6, C-7, C-9; CH_3-9/C-6, C-7, C-8; CH_3-10/C-2, C-3, C-4; NOESY correlations, H-1/H-2, CH_3-10; H-2/H-1; H-5/CH_3-9, CH_3-10; H-6/CH_2-8; CH_2-8/H-6; CH_3-9/H-5; CH_3-10/H-1, H-5; HRESIMS of PFB-oxime of **2** (=compound **7**) *m*/*z* 414.0437 (calcd for $C_{17}H_{15}NOF_5{}^{35}Cl_2$, 414.0451).

8-Bromo-6,7-dichloro-3,7-dimethylocta-2,4-dienal (3): yellow oil; $[\alpha]^{28}_D$ −68 (*c* 0.0006, $CHCl_3$); UV (*n*-hexane) λ_{max} 266 nm (log ϵ 3.6); IR (dry film, KBr) ν_{max} 2251, 1667, 1378, 908, 733, 650 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) and ^{13}C NMR ($CDCl_3$, 100 MHz), see Table 1; HMBC correlations, H-1/C-2; H-2/C-4, C-10; H-4/C-3, C-5, C-6, C-10; H-5/C-3, C-4; H-6/C-4, C-5, C-8, C-9; CH_2-8/C-6, C-7, C-9; CH_3-9/C-6, C-7, C-8; CH_3-10/C-2, C-3, C-4; NOESY correlations, H-1/CH_3-10; H-4/H-2, H-6; H-5/H-6; H-6/H-5, CH_2-8; CH_2-8/H-6; CH_3-9/H-8; CH_3-10/H-1, H-5; HRESIMS of PFB-oxime of **3** (=compound **8**) *m*/*z* 493.9706 (calcd for $C_{17}H_{16}NOF_5{}^{35}Cl_2{}^{79}Br$, 493.9712).

4-Bromo-8-chloro-3,7-dimethylocta-2,6-dienal (4): yellow oil; $[\alpha]^{28}_D$ −24 (*c* 0.001, $CHCl_3$); UV (*n*-hexane) λ_{max} 235 nm (log ϵ 3.6); IR (dry film, KBr) ν_{max} 2254, 1674, 960, 870 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) and ^{13}C NMR ($CDCl_3$, 100 MHz), see Table 1; HMBC correlations, H-1/C-2; H-2/C-3, C-5, C-10; H-4/C-10, C-5; CH_2-5/C-3, C-4, C-6, C-7; H-6/C-8, C-9; CH_2-8/C-6, C-7, C-9; CH_3-9/C-6, C-7, C-8; CH_3-10/C-2, C-3, C-4; NOESY correlations, H-1/H-2, CH_3-10; H-2/H-4, CH_2-5; H-4/H-2, CH_2-5, H-6, CH_3-10; H-5/H-4, CH_3-9, CH_3-10; H-6/H-4, H-5, CH_2-8; CH_2-8/H-6, CH_3-9; CH_3-9/CH_2-8; CH_3-10/H-1, H-4; HRESIMS of PFB-oxime of **4** (=compound **9**) *m*/*z* 460.0148 (calcd for $C_{17}H_{17}NOF_5{}^{79}Br^{35}Cl$, 460.0102).

General Procedure for the Derivatization of Aldehydes with PFBHA·HCl. To a solution of the aldehyde (~1 mg) in CH_3CN (0.5 mL) was added *O*-2,3,4,5,6-pentafluorobenzylhydroxylamine hydrochloride (~1 mg) dissolved in CH_3CN (0.5 mL). $MgSO_4$ (5 mg, anhydrous) was added to the reaction mixture, which was then stirred at room temperature. The course of the reaction was followed by normal-phase TLC analysis (*n*-hexane/EtOAc, 9:1). When the reaction was complete (4 h), the crude oxime product was extracted with *n*-hexane and purified by HPLC (*n*-hexane/EtOAc, 95:5).

Cytotoxicity Assays. IC_{50} values for compounds were determined as described previously.[11] Briefly, WHCO1 esophageal cancer cells were cultured in DMEM with 10% FCS, in a humidified, 37 °C, 5% CO_2 atmosphere. Cells were plated in 96-well plates and treated (in quadruplicate) with varying concentrations of each compound. After 48 h, plates were processed using the MTT kit (Roche #1465007), absorbance was read on an Anthos microplate reader 2001, and IC_{50} curves were calculated using GraphPad Prism version 4.00 for Windows (GraphPad Software, San Diego, CA, www.graphpad.com).

Acknowledgment. The authors thank the South African Department of Environmental Affairs and Tourism for a marine research permit and M. T. Davies-Coleman (Dept. of Chemistry, Rhodes University, Grahamstown, South Africa) and P. L. Colin (Coral Reef Research Foundation, Koror, Palau) for providing an underwater photograph of *Plocamium corallorhiza*. This research was supported by grants from Rhodes University and the South African National Research Foundation.

Supporting Information Available: Tables of spectroscopic data and ^1H and ^{13}C spectra of **1**−**4**. This material is available free of charge via the Internet at http://pubs.acs.org.

References and Notes

(1) Saunders, G. W.; Lehmkuhl, K. V. *Eur. J. Phycol.* **2005**, *40*, 293−312.
(2) (a) Blunt, J. W.; Copp, B. R.; Munro, M. H. G.; Northcote, P. T.; Prinsep, M. R. *Nat. Prod. Rep.* **2006**, *23*, 26−78. (b) Kladi, M.; Vagias, C.; Roussis, V. *Phytochem. Rev.* **2004**, *3*, 337−366.
(3) Vaillancourt, F. H.; Yeh, E.; Vosburg, D. A.; Garneau-Tsodikova, S.; Walsh, C. T. *Chem. Rev.* **2006**, *106*, 3364−3378.
(4) Stegenga, H.; Bolton, J. J.; Anderson, R. J. *Seaweeds of the South African West Coast: Contributions from the Bolus Herbarium*; Creda Press: Cape Town, 1997; Vol. 18, 655 pp.
(5) Knott, M. G.; Mwkananzi, H.; Arendse, C. E.; Hendricks, D. T.; Bolton, J. J.; Beukes, D. R. *Phytochemistry* **2005**, *66*, 1108−1112.
(6) (a) Stierle, D. B.; Wing, R. M.; Sims, J. J. *Tetrahedron* **1979**, *35*, 2855−2859. (b) Ireland, C.; Stallard, M. O.; Faulkner, D. J. *J. Org. Chem.* **1976**, *41*, 2461−2465.
(7) Crews, P.; Kho-Wiseman, E. *J. Org. Chem.* **1977**, *42*, 2812−2815.
(8) (a) Andreoli, A.; Manini, P.; Corradi, M.; Mutti, A.; Niessen, W. M. A. *Rapid Commun. Mass Spectrom.* **2003**, *17*, 637−645. (b) d'Ippolito, G.; Iadicicco, O.; Romano, G.; Fontana, A. *Tetrahedron Lett.* **2002**, *43*, 6137−6140. (c) Spiteller, G.; Kern, W.; Spiteller, P. *J. Chromatogr. A* **1999**, *843*, 29−98.
(9) Crews, P.; Naylor, S.; Hanke, F. J.; Hogue, E. R.; Kho, E.; Braslau, R. *J. Org. Chem.* **1984**, *49*, 1371−1377.
(10) Crews, P.; Kho, E. *J. Org. Chem.* **1974**, *39*, 3303−3304.
(11) Rajput, P.; Moss, J. R.; Hutton, A. T.; Hendricks, D. T.; Arendse, C. E.; Imrie, C. *J. Organomet. Chem.* **2004**, *689*, 1553−1568.

NP060547C