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Plocoralides A–C, polyhalogenated monoterpenes from the marine alga *Plocamium corallorhiza*

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Abstract

Three new polyhalogenated monoterpenes, plocoralides A–C (**1**–**3**) along with three known compounds (**4**–**6**) have been isolated from the organic extract of the red alga *P. corallorhiza*. Structures of the new compounds were characterized as 4,8-dibromo-1,1-dichloro-3,7-dimethyl-2*E*,6*E*-octadiene (**1**), 4,6-dibromo-1,1-dichloro-3,7-dimethyl-2*E*,7-octadiene (**2**) and 4,8-dibromo-1,1,7-trichloro-3,7-dimethyl-2*E*,5*Z*-octadiene (**3**) on the basis of one- and two-dimensional NMR spectroscopic data and MS analyses. Compounds **2**–**6** show moderate cytotoxicity toward esophageal cancer cells.

Keywords: *Plocamium corallorhiza*; Halogenated monoterpenes; Plocoralides

1. Introduction

Red algae (Rhodophyta) of the genera *Plocamium*, *Chondrococcus* and *Ochtodes* produce a wealth of biologically active linear and cyclic polyhalogenated monoterpenes (Faulkner, 2002; Blunt et al., 2003). These metabolites exhibit a range of biological activities including antifeedant effects on reef herbivores (Paul et al., 1980, 1988; Sakata et al., 1991), antimicrobial (König et al., 1999), insecticidal (San-Martin et al., 1991; Argandona et al., 2002), antitubercular (König et al., 2000) and anticancer (Fuller et al., 1992, 1994) activities. As part of a programme to investigate the chemistry of South African marine algae we have studied the nonpolar constituents from *Plocamium corallorhiza* (Turner) Hooker & Harvey (Plocamiaceae, Plocamiales). *P. corallorhiza* is common and abundant in South Africa, often dominating large areas of rock in the subtidal fringe and shallow subtidal due to its masses of spreading coralloid attachment structures (hence the species name, meaning 'coralloid roots'; Stegenga et al., 1997). This seaweed has also been reported from Namibia, Mozambique, St. Paul and Amsterdam Islands in the southern Indian Ocean, and Madagascar (Guiry and Nic Dhonncha, 2003). In South Africa, *P. corallorhiza* is harvested as feed for cultivated abalone (Anderson et al., 2003).

In the present work, we report on the isolation, structure elucidation and biological activity of three new ocimene-type polyhalogenated metabolites, plocoralides A–C (**1**–**3**) as well as three known compounds (**4**–**6**) from an organic extract of *P. corallorhiza*. The structures of compounds **1**–**3** are based on a regular isoprenoid carbon skeleton and are characterized by a rare 1,1-dichloro-2-ene moiety.

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2. Results and discussion

Specimens of *P. corallorhiza* were collected from the intertidal zone at Kalk Bay near Cape Town, South Africa and immediately frozen. The partially thawed sample was extracted sequentially with MeOH and CH_2Cl_2. Fractionation of the CH_2Cl_2 extract by silica gel column chromatography (hexane–EtOAc) gave several fractions which were further purified by semi-preparative normal phase HPLC to yield compounds **1**–**6**.

A molecular formula of $C_{10}H_{14}Br_2Cl_2$ was deduced from HREIMS and ^{13}C NMR data for plocoralide A (**1**). The low resolution mass spectrum of **1** did not show a molecular ion peak but instead exhibited an isotopic cluster at *m/z* 281/283/285/287 $[M - Br]^+$ with relative intensities indicative of one bromine and two chlorine atoms. The ^1H NMR spectrum of **1** showed two mutually coupled, low field methine resonances at δ 6.35 (d, $J = 9.4$ Hz) and 5.93 (d, $J = 9.4$ Hz). These signals showed HMQC correlations to carbon signals at δ 66.6 and 128.3, respectively, which are consistent with a dichloromethyl moiety attached to a double bond (Crews et al., 1984; Naylor et al., 1983). The ^{13}C, DEPT and HMQC NMR data also indicated the presence of two trisubstituted double bonds, two halomethine carbons (δ 66.6 and 56.8), a halomethylene (δ 40.2) and two olefinic methyl signals (15.2 and 12.9). Two main fragments, **a** and **b**, could be constructed from ^1H–^1H COSY and HMBC data as follows (Fig. 1, Table 1). The olefinic methyl signal at δ 1.88 (H_3-10) showed HMBC correlations to signals at δ 128.3 (C-2), 138.3 (C-3) and 56.8 (C-4) while the olefinic methine at δ 5.93 (H-2) showed vicinal coupling ($J = 9.4$ Hz) to the proton at δ 6.35 (H-1) to give fragment **a**. Fragment **b** followed from the observation of HMBC correlations from the second olefinic methyl signal (δ 1.78, H_3-9) to a methine carbon at δ 125.8 (C-6), a quaternary carbon at δ 135.7 (C-7) and a methylene carbon at δ 40.2 (C-8). ^1H–^1H COSY and HMBC correlations from the methylene multiplet centered at δ 2.67 (H-5) to the methine resonances at δ 56.8 (C-4) and 125.8 (C-6) connected the two fragments. The positions of the two bromine atoms required by the molecular formula followed from an analysis of the ^{13}C NMR chemical shifts for the methylene at δ 40.2 (C-8) and the methine carbon at δ 56.8 (C-4) (Crews et al., 1984). The *E*-geometry of the two double bonds was deduced from the ^{13}C NMR upfield chemical shifts for C-9 (δ 15.2) and C-10 (δ 12.2) due to a γ-effect from C-5 and C-1, respectively (Crews and Kho-Wiseman, 1977). This assignment was confirmed by the observation of NOE enhancements between H-1 and H_3-10 and between H-6 and H_2-8. The configuration of the chiral center at C-4 was not determined and decomposition of this sample at room temperature precluded any further spectroscopic or biological studies. Plocoralide A (**1**) is thus 4,8-dibromo-1,1-dichloro-3,7-dimethyl-2*E*,6*E*-octadiene.

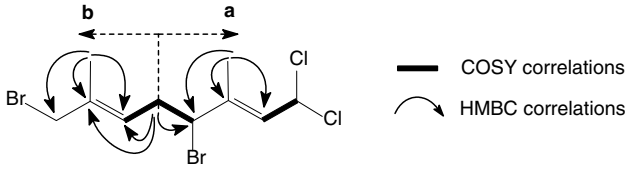

Fig. 1. Selected ^1H–^1H COSY and HMBC correlations for plocoralide A (**1**).

The ^1H NMR spectrum of plocoralide B (**2**) showed the same two mutually coupled, deshielded methine resonances at δ 6.36 ($J = 9.4$ Hz) and 5.95 ($J = 9.4$ Hz) as seen in **1**, which suggested a similar dichloromethyl moiety adjacent to a double bond. HREIMS data indicated that **2** was isomeric with **1** and therefore also had a molecular formula of $C_{10}H_{14}Br_2Cl_2$. The ^{13}C and DEPT NMR spectra revealed the presence of two double bonds, one of which was a terminal alkene, three halomethines, a methylene and two olefinic methyl groups. Further comparison of the ^1H and ^{13}C NMR data for compounds **1** and **2** suggested that the latter contained the same $-CH(Br)C(CH_3)=CHCHCl_2$ fragment (fragment **a**) as seen in **1**. This was confirmed by ^1H–^1H COSY and HMBC data (Table 1). The second fragment was constructed from the observation of HMBC correlations from the vinylic methylene protons at δ 5.12 and 4.97 (H_2-8) to carbon resonances at δ 18.3 (C-9), 143.5 (C-7) and 56.0 (C-6). The methine signal at δ 4.63, which overlapped with the H-4 methine, showed vicinal coupling to the methylene at δ 2.41 which was assigned to H-5 and thus completed the gross structural assignment of plocoralide B (**2**). Placement of the halogens and the geometry of the Δ^2 double bond followed from a comparison of the ^{13}C NMR chemical shift data of **2** with those of plocoralide A (**1**) and preplocamene (**7**) (Crews and Kho-Wiseman, 1977). Plocoralide B (**2**) is thus 4,6-dibromo-1,1-dichloro-3,7-dimethyl-2*E*, 7-octadiene.

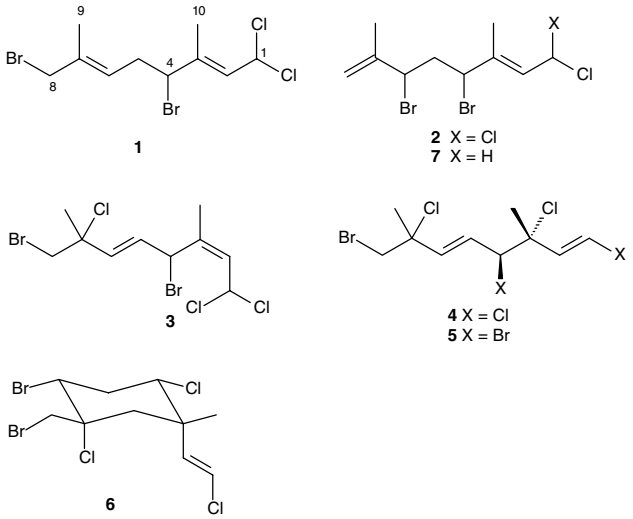

Table 1
^{1}H (400 MHz, $CDCl_3$), ^{13}C (100 MHz, $CDCl_3$) and HMBC data for compounds **1**–**3**

No.	**1**			**2**			**3**		
	δ_C	δ_H (J in Hz)	HMBC	δ_C	δ_H (J in Hz)	HMBC	δ_C	δ_H (J in Hz)	HMBC
1	66.6, d	6.35, d, 9.4	–	66.5, d	6.36, d, 9.4	C-3	65.3, d	6.52, dd, 9.7, 1.8	C-3
2	128.3, d	5.93, d, 9.4	–	128.6, d	5.95, dd, 9.4, 1	C-10, C-4	129.1, d	5.80, dd, 9.7, 1.8	C-10
3	138.3, s	–	–	137.4, s	–	–	136.7, s	–	–
4	56.8, d	4.41, t, 7.6	C-2, C-3, C-10	55.9,[a] d	4.62,[b] t, 7.1	C-3, C-5, C-6, C10	56.8, d	5.33, m	C-3, C-5, C-10
5a	35.6, t	2.75, ddd, 15.2, 7.6, 6.8	C-4, C-6, C-7	43.1, t	2.41, t, 7.1	C-3, C-4, C-6, C-7	128.65/128.53,[c] d	5.91, m	C-4, C-6, C-7
5b		2.63, ddd, 15.2, 7.6, 6.8	C-4, C-6, C-7						
6	125.8, d	5.48, t, 6.8	–	56.0,[a] d	4.63,[b] t. 7.1	C-5, C-7, C-9, C-8	135.85/135.82,[c] d	5.97, m	C-4, C-5, C-7
7	135.7, s	–	–	143.5, s	–	–	67.0, s	–	–
8a	40.2, t	3.93, s	C-6, C-7, C-9	115.2, t	5.12, s	C-9, C-6, C-7	41.71/41.63,[c] t	3.68, d, 2.4	C-6, C-7, C-9
8b					4.97, s				
9	15.2, q	1.78, s	C-6, C-7, C-8	18.3, q	1.89, s	C-6, C-8, C-7	27.67/27.66,[c] q	1.81, s	C-6, C-7, C-8
10	12.9, q	1.88, s	C-2, C-3, C-4	13.2, q	1.89, s	C-4, C-3, C-2	18.58/18.56,[c] q	1.88, s	C-2, C-3, C-4

[a,b] Assignments may be interchanged due to proximity of signals.
[c] Signals appear as doublets.

The ^{13}C NMR and HREIMS data of plocoralide C (**3**) suggested a molecular formula of $C_{10}H_{13}Br_2Cl_3$ for this compound. A dichloromethyl moiety attached to a double bond was immediately evident from the characteristic doublets at δ 6.52 (d, $J = 9.7$) and 5.80 (d, $J = 9.7$) in the ^{1}H NMR spectrum of **3**. Two double bonds, two halomethines, a quaternary carbon also attached to a halogen, one methylene and two methyl groups were evident from ^{13}C and DEPT data. An analysis of ^{1}H–^{1}H COSY and HMBC data (Table 1) indicated that **3** also contained a –CH(Br)C(CH_3)=CH$CHCl_2$ fragment (fragment **a**) as seen in compounds **1** and **2**. The remaining subunit was unambiguously assigned from the observation of HMBC correlations from the methyl signal at δ 1.81 (H-9) to carbon signals at δ 41.7 (C-8), 67.0 (C-7) and 135.8 (C-6); and COSY correlations from the proton at δ 5.97 (H-6) to signals at δ 5.91 (H-5) and 5.33 (H-4). The ^{13}C NMR chemical shifts of C-7 and C-8 suggested chlorine and bromine substituents at these positions. The *E*-geometry of the Δ^5 double bond followed from the vicinal coupling constant of 15.5 Hz for H-5 and H-6. Interestingly, while compounds **1**–**3** contain the same –CH(Br)C(CH_3)=$CHCl_2$ moiety, the C-10 carbon was 5 ppm downfield in **3** suggesting a *Z*-geometry for the Δ^2 double bond (Crews and Kho-Wiseman, 1977). This was confirmed by the observation of strong NOE enhancements between H-1 and H-4 and between H-2 and H_3-10. Although the relative configurations at C-4 and C-7 could not be determined, an intriguing doubling of some ^{13}C signals (Table 1) is suggestive of an isomeric mixture. Compound **3** is therefore 4,8-dibromo-1,1,7-trichloro-3,7-dimethyl-2*Z*,5*E*-octadiene.

Compounds **4**–**6** were identified by comparison of their spectroscopic data with those of the known metabolites 8-bromo-1,3,4,7-tetrachloro-3,7-dimethyl-1*E*,5*E*-octadiene (**4**) (Stierle et al., 1979), 1,4,8-tribromo-3,7-dichloro-3,7-dimethyl-1*E*,5*E*-octadiene (**5**) (Stierle et al., 1979; Ireland et al., 1976) and 4-bromo-5-bromomethyl-1-chlorovinyl-2,5-dichloromethylcyclohexane (**6**) (Higgs et al., 1977).

Previous studies have shown that halogenated monoterpenes were cytotoxic to human tumor cells (Fuller et al., 1992, 1994). Compounds **2**–**6** were thus evaluated for their in vitro cytotoxicity against a human esophageal cancer cell line (WHCO1). These compounds showed moderate to good activity in this assay with IC_{50} values of 9.3, 33.8, 17.2, 18.1 and 34.8 μM, respectively. This level of activity compares favorably to the commonly used chemotherapeutic compound cis-platin, which has an IC_{50} of 13 μM in this assay. Interestingly, König et al. (2000) reported a similar level of cytotoxicity (IC_{50} 33.3 μM) for compound **6** towards KB cancer cells in addition to moderate activity towards *Mycobacterium tuberculosis*.

The new metabolites (**1**–**3**) reported here further illustrate the versatility of seaweeds of the *Placamium* genus for producing a variety of polyhalogenated monoterpenes. Although the –$CHCl_2$ unit has previously been found in metabolites from *P. cartilagineum* (Mynderse and Faulkner, 1975) this is the first report of this moiety at C-1.

3. Experimental

3.1. General

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. The ^{1}H (400 MHz), ^{13}C (100 MHz), DEPT-135, HMQC, HMBC, COSY-90 NMR spectra were all 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, which was equipped with a rheodyne injector, a Waters R401 differential refractometer, and a Rikadenki chart recorder. In all cases normal phase chromatography was performed using a Whatman Magnum 10 Partisil 9 column. Low resolution mass spectra (EIMS) were recorded on a Finnigan MAT GCQ mass spectrometer at 70 eV while high resolution (HREIMS) spectra were obtained on a Micromass 70-70E spectrometer at the Mass Spectrometry Unit at Potchefstroom University, Potchefstroom, South Africa.

3.2. Plant material

P. corallorhiza was collected from the intertidal zone at Kalk Bay near Cape Town, South Africa, in March 2002 and kept frozen until extraction. A voucher specimen (No. CT02001) is retained at the Faculty of Pharmacy, Rhodes University, South Africa.

3.3. Extraction and isolation

The frozen sample (14.3 g) was steeped in cold MeOH for 6 h, the MeOH drained off and the algal material extracted with CH_2Cl_2 (3 × 500 mL). Silica gel chromatography of the CH_2Cl_2 extract (1.05 g) using hexane with increasing proportions of EtOAc as eluant gave six fractions. Fraction 1 (291 mg) was further purified by repeated normal phase HPLC (hexane–EtOAc, 95:5 to 100:0) to give **1** (2.3 mg, 0.016% dry wt), **2** (2.6 mg, 0.018% dry wt), **3** (15.8 mg, 0.11% dry wt), **4** (5.5 mg, 0.0.039% dry wt), **5** (1.1 mg, 0.007% dry wt) and **6** (2.9 mg, 0.02% dry wt).

3.4. Plocoralide A: 4,8-dibromo-1,1-dichloro-3,7-dimethyl-2E,6E-octadiene (*1*)

Colourless oil; IR (film) ν_{max} 1380, 1207, 707 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) see Table 1; ^{13}C NMR ($CDCl_3$, 100 MHz) see Table 1; LRMS (70 eV), *m/z* (int, %) 287/285/283/281 $[M - Br]^+$ (10/19/13/4), 251/249247 (9/32/25), 215/213 (17/17), 205/203 (25/34), 169/167 (40/100), 131 (42), 105 (33), 91 (42), 79/81 (17/17), 67 (23); HREIMS *m/z* 361.8840 (calc. for $C_{10}H_{14}{}^{79}Br_2{}^{35}Cl_2$, 361.8839).

3.5. Plocoralide B: 4,6-dibromo-1,1-dichloro-3,7-dimethyl-2E,7-octadiene (*2*)

Colourless oil; $[\alpha]_D$ −15° (*c* 0.02, $CHCl_3$); IR (film) ν_{max} 2919, 2343, 2361, 1654, 1437, 1389, 1206, 1107, 865, 707 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) see Table 1; ^{13}C NMR ($CDCl_3$, 100 MHz) see Table 1; LRMS (70 eV), *m/z* (int, %) 285 287/285/283/281 $[M - Br]^+$ (10/19/13/4), 251/249247 (9/32/25), 215/213 (17/17), 205/203 (25/34), 169/167 (40/100), 131 (42), 105 (33), 91 (42), 79/81 (17/17), 67 (23); HREIMS *m/z* 361.8841 (calc. for $C_{10}H_{14}{}^{79}Br_2{}^{35}Cl_2$, 361.8839).

3.6. Plocoralide C: 4,8-dibromo-1,1,7-trichloro-3,7-dimethyl-2E,5Z-octadiene (*3*)

Colourless oil; $[\alpha]_D$ −43° (*c* 0.03, $CHCl_3$); IR (film) ν_{max} 2984, 2925, 2361, 2342, 1653, 1447, 1435, 1380, 966, 866 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) see Table 1; ^{13}C NMR ($CDCl_3$, 100 MHz) see Table 1; LRMS (70 eV), *m/z* (int, %) 323/321/319 $[M - Br]^+$ (6/23/38/19), 287/285/283/281 $[M - Br - Cl]^+$ (3/17/35/20), 247 (28), 237 (30), 201 (100), 165 (51), 153 (55), 129 (40), 115 (23), 91 (42); HREIMS *m/z* 316.9262 $[M - Br]^+$ (calc. for $C_{10}H_{13}{}^{79}Br^{35}Cl_2$, 316.9266).

3.7. 8-Bromo-1,3,4,7-tetrachloro-3,7-dimethyl-1E,5E-octadiene (*4*)

As previously reported (Stierle et al., 1979).

3.8. 1,4,8-Tribromo-3,7-dichloro-3,7-dimethyl-1E,5E-octadiene (*5*)

As previously reported (Stierle et al., 1979; Ireland et al., 1976).

3.9. (1R*,2S*,4S*,5S*)-4-Bromo-5-bromomethyl-1E-chlorovinyl-2,5-dichloromethylcyclohexane (*6*)

As previously reported (Higgs et al., 1977).

3.10. Cytotoxicity assays

Cells were routinely maintained at 37 °C, 5% CO_2 and cultured in DMEM supplemented with 10% fetal calf serum, 100 U/mL penicillin and 100 μg/mL streptomycin. Cytotoxicity of compounds **2**–**6** were evaluated by crystal violet screening as previously described (Rajput et al., 2004). IC_{50} values were determined in the esophageal squamous cell carcinoma line WHCO1 (Rajput et al., 2004; Davies-Coleman et al., 2003).

Acknowledgments

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References

Anderson, R.J., Bolton, J.J., Molloy, F.J., Rotmann, K.W.G., 2003. Commercial seaweeds in southern Africa. In: Chapman, A.R.O., Anderson, R.J, Vreeland, V.J., Davison, I.R. (Eds.), Proceedings of the 17th International Seaweed Symposium. Oxford University Press, Cape Town, pp. 1–12.

Argandona, V.H., Rovirosa, J., San-Martin, A., Riquelme, A., Diaz-Marrero, A.R., Cueto, M., Darias, J., Santana, O., Guadano, A., Gonzalez-Coloma, A., 2002. Antifeedant effects of marine halogenated monoterpenes. Journal of Agricultural and Food Chemistry 50, 7029–7033.

Blunt, J.W, Copp, B.R., Munro, M.H.G., Northcote, P.T., Prinsep, M.R., 2003. Marine natural products. Natural Product Reports 20, 1–48.

Crews, P., Kho-Wiseman, E., 1977. Acyclic polyhalogenated monoterpenes from the red alga *Plocamium violaceum*. Journal of Organic Chemistry 42, 2812–2815.

Crews, P., Naylor, S., Hanke, F.J., Hogue, E.R., Kho, E., Braslau, R., 1984. Halogen regiochemistry and substituent stereochemistry determination in marine monoterpenes by ^{13}C NMR. Journal of Organic Chemistry 49, 1371–1377.

Davies-Coleman, M.T., Dzeha, T.M., Gray, C.A., Hess, S., Pannel, L.K., Hendricks, D.T., Arendse, C.E., 2003. Isolation of homodolastatin 16, a new cyclic depsipeptide from a Kenyan collection of *Lyngbya majuscula*. Journal of Natural Products 66, 712–715.

Faulkner, D.J., 2002. Marine natural products. Natural Product Reports 19, 1–48, and previous reports in this series.

Fuller, R.W., Cardellina II, J.H., Kato, Y., Brinen, L.S., Clardy, J., Snader, K.M., Boyd, M.R., 1992. A pentahalogenated monoterpene from the red alga *Portieria hornemannii* produces a novel cytotoxicity profile against a diverse panel of human tumor cell lines. Journal of Medicinal Chemistry 35, 3007–3011.

Fuller, R.W., Cardellina II, J.H., Jurek, J., Scheuer, P.J., Alvarado-Lindner, B., McGuire, M., Gray, G.N., Steiner, J.R., Clardy, J., Menez, E., Shoemaker, R.H., Newman, D.J., Snader, K.M., Boyd, M.R., 1994. Isolation and structure/activity features of halomon-related antitumor monoterpenes from the red alga *Portieria hornemannii*. Journal of Medicinal Chemistry 37, 4407–4411.

Guiry, M.D., Nic Dhonncha, E., 2003. *AlgaeBase version 2.0*. Worldwide electronic publication, National University of Ireland, Galway. http://www.algaebase.org (accessed 16.07.2003).

Higgs, M.D., Vanderah, D.J., Faulkner, D.J., 1977. Polyhalogenated monoterpenes from *Plocamium cartilagineum* from the British coast. Tetrahedron 33, 2775–2780.

Ireland, C., Stallard, M.O., Faulkner, D.J., Finer, J., Clardy, J., 1976. Some chemical constituents of the digestive gland of the sea hare *Aplysia californica*. Journal of Organic Chemistry 41, 2461–2465.

König, G.M., Wright, A.D., Franzblau, S.G., 2000. Assessment of antimycobacterial activity of a series of mainly marine derived natural products. Planta Medica 66, 337–342.

König, G.M., Wright, A.D., Linden, A.D., 1999. *Plocamium hamatum* and its monoterpenes: chemical and biological investigations of the tropical marine red alga. Phytochemistry 52, 1047–1053.

Mynderse, J.S., Faulkner, D.J., 1975. Polyhalogenated monoterpenes from the red alga *Plocamium cartilagineum*. Tetrahedron 31, 1963–1967.

Naylor, S., Hanke, F.J., Manes, L.V., Crews, P., 1983. Chemical and biological aspects of marine monoterpenes. Progress in the Chemistry of Organic Natural Products 44, 189–241.

Paul, V.J., Hay, M.E., Duffy, J.E., Fenical, W., Gustafson, K., 1988. Chemical defense in the seaweed *Ochtodes secundiramea*. Effects of its monoterpenoid components upon diverse coral-reef herbivores. Journal of Experimental Marine Biology and Ecology 114, 249–260.

Paul, V.J., McConnell, O.J., Fenical, W., 1980. Cyclic monoterpenoid feeding deterrents from the red marine alga *Ochtodes crockeri*. Journal of Organic Chemistry 45, 3401–3407.

Rajput, P., Moss, J.R., Hutton, A.T., Hendricks, D.T., Arendse, C.E., Imrie, C., 2004. Synthesis, characterization and cytotoxicity of some palladium(II), platinum(II), rhodium(I) and iridium(I) complexes of ferrocenylpyridine and related ligands. Crystal and molecular structure of *trans*-dichlorobis(3-ferrocenylpyridine)palladium(II). Journal of Organometallic Chemistry 689, 1553–1568.

Sakata, K., Iwase, Y., Ina, K., Fujita, D., 1991. Chemical studies on feeding inhibitors for marine herbivores. Part II. Halogenated terpenes isolated from the red alga *Plocamium leptophyllum* as feeding inhibitors for marine herbivores. Nippon Suisan Gakkaishi 57, 743–746.

San-Martin, A., Negrete, R., Rovirosa, J., 1991. Insecticide and acaricide activities of polyhalogenated monoterpenes from Chilean *Plocamium cartilagineum*. Phytochemistry 30, 2165–2169.

Stegenga, H., Bolton, J.J., Anderson, R.J., 1997. Seaweeds of the South African West Coast: Contributions from the Bolus Herbarium, 18. Creda Press, Cape Town, 655pp.

Stierle, D.B., Wing, R.M., Sims, J.J., 1979. Marine natural products. XVI. Polyhalogenated acyclic monoterpenes from the red alga *Plocamium* of Antarctica. Tetrahedron 35, 2855–2859.