Molecules **2006**, *11*, 808-816

molecules
ISSN 1420-3049
http://www.mdpi.org

Full Paper

New Caulerpenyne-derived Metabolites of an *Elysia* Sacoglossan from the South Indian Coast

M. Letizia Ciavatta [1,*], M. Pilar Lopez Gresa [2], Margherita Gavagnin [1], Emiliano Manzo [1], Ernesto Mollo [1], Lisette D'Souza [3] and Guido Cimino [1]

1 Istituto di Chimica Biomolecolare, CNR, Via Campi Flegrei 34, I 80078-Pozzuoli (Na), Italy
2 Centro Ecologia Quimica Agricola, Universidad Politecnica Valencia, Campus de Vera, Correos 22012- 46071 Valencia, Spain
3 National Institute of Oceanography, CSIR, Dona Paula, 403 004 Goa, India

* Author to whom correspondence should be addressed; E-mail: lciavatta@icmib.na.cnr.it

Received: 13 September 2006; in revised form: 12 October 2006 / Accepted: 23 October 2006 / Published: 25 October 2006

Abstract: Chemical analysis of the secondary metabolite pattern of the sacoglossan mollusc *Elysia* cf. *expansa*, collected along South Indian coasts, showed the presence of the typical *Caulerpa*-derived sesquiterpene caulerpenyne (**1**) and two new minor co-occurring metabolites, the compounds dihydrocaulerpenyne (**4**) and expansinol (**5**). The chemical characterization of these molecules, structurally related to **1**, is reported.

Keywords: Caulerpenyne, Sesquiterpenes, Sacoglossans, Elysia, NMR.

Introduction

Sacoglossan molluscs are herbivorous and primarily associated, with a few exceptions, with siphonalean green algae [1]. They are often well camouflaged, as much of their color being derived from the chloroplasts of algae on which they feed [2,3]. The order Sacoglossa includes both shelled and shell-less species, it has been reported that shelled sacoglossans, all belonging to the superfamily Oxynoidea, feed exclusively on the morphologically variable algal genus *Caulerpa*, while changes in the diet occur in the major groups of shell-less species [4]. The dietary relationship between *Caulerpa* and its shelled sacoglossan predators has been confirmed by the presence of typical *Caulerpa*

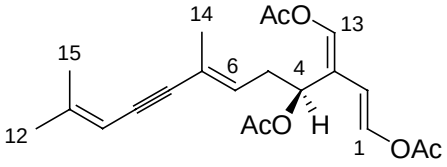
metabolites and/or their derivatives, in the molluscs [5]. On the other hand, shell-less sacoglossans, belonging to the genus *Elysia*, are able to either accumulate sesquiterpenoids [6], diterpenoids [6] and depsipeptides [7,8] from their algal prey, modify such molecules [6,9] or biosynthesize *de novo* polypropionates [10,11]. However, in analogy with shelled sacoglossans [12-14], a trophic relationship between some Caribbean *Elysia* species and *Caulerpa* has also been demonstrated by chemical studies [6], while there is a lack of chemical information about the Indo-Pacific species that seems to have similar alimentary habits.

The ability of *Caulerpa*-feeder molluscs to transform dietary caulerpenyne (**1**), the main *Caulerpa* sesquiterpene [15], into the toxic aldehyde derivatives, oxytoxin-1 (**2**) and oxytoxin-2 (**3**), has been also suggested for different oxynoidean [12,13] and elysioidean species [6]. The lipase-mediated conversion of caulerpenyne (**1**) into oxytoxin-2 (**3**) has been recently demonstrated in cell-free preparations of Mediterranean sacoglossan *Oxynoe olivacea* [16].

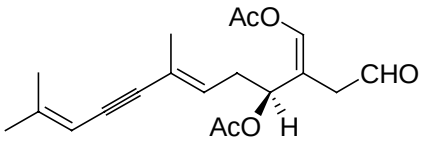
We report here the first chemical study of a shell-less Indo-Pacific *Caulerpa*-feeder sacoglossan mollusc, collected along the South Indian coasts and tentatively identified as *Elysia* cf. *expansa*, it showed a secondary metabolite pattern dominated by caulerpenyne (**1**) [15] co-occurring with two novel minor metabolites, dihydrocaulerpenyne (**4**) and expansinol (**5**). A small amount of the pigment caulerpin (**6**), already isolated from several *Caulerpa* algae [17,18], was also detected in the extract. We report here the chemical characterization of compounds **4** and **5** using a variety of spectroscopic methods as well as by comparison with appropriate synthesized model compounds.

Results and Discussion

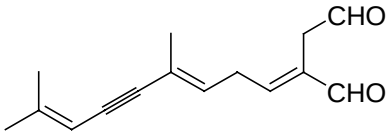
TLC analyses in different eluent systems of the ether extracts of the external (obtained by ultrasound treatment) and internal parts of *Elysia* cf. *expansa* showed different metabolite compositions. In particular, the ether extract of the external parts was characterized by a main UV positive spot at R_f 0.6 (light petroleum/diethyl ether, 1:1), along with a series of minor more polar (R_f 0.55-0.2) UV-visible compounds, whereas the extract of internal parts was constituted mainly by the typical lipids (fatty acid glycerides), as confirmed by ^{1}H-NMR analysis. The external part extract was submitted to LH-20 Sephadex column chromatography to obtain two fractions containing the metabolites at R_f 0.6-0.2 These two fractions were separately purified by silica-gel column chromatography to give the main component, caulerpenyne (**1**), and enriched fractions containing minor related metabolites, which were further purified by reverse-phase HPLC, to afford two unprecedented molecules, named dihydrocaulerpenyne (**4**) and expansinol (**5**). The known pigment caulerpin (**6**) was also isolated from the extract. Caulerpenyne (**1**) [15] and caulerpin (**6**) [17,18] were identified by comparison of their ^{1}H-NMR, mass spectra and [α] values with literature data. The new compounds **4** and **5**, both structurally related to the main metabolite caulerpenyne (**1**), were characterized as described below.



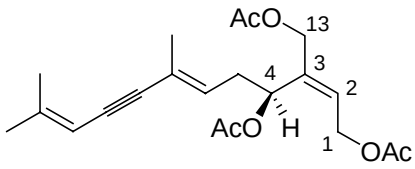
1



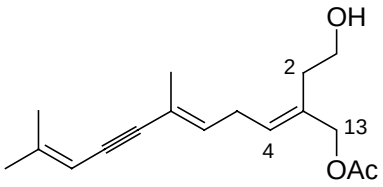
2



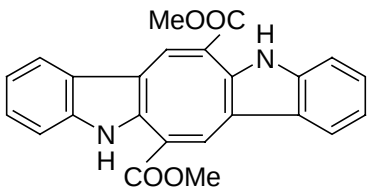
3



4



5



6

The molecular formula $C_{21}H_{28}O_6$ of dihydrocaulerpenyne (**4**) was derived from the sodiated molecular peak at *m/z* 399.1781 in the HR-ESIMS spectrum. Preliminary NMR analysis of compound **4** displayed strong spectral similarities with caulerpenyne (**1**), suggesting a linear sesquiterpene skeleton with the same functionalization. In fact, the ^{1}H-NMR spectrum of sesquiterpene **4** at 400MHz showed high fields signal attributable to three vinyl methyls at δ 1.82 (3H, bs, H_3-15), δ 1.81 (3H, bs, H_3-14) and δ 1.46 (3H, bs, H_3-12), three acetoxy groups at δ 1.64 (3H, s, OAc-1), δ 1.57 (3H, s, OAc-4) and δ 1.63 (3H, s, OAc-13), and an allylic methylene at δ 2.49 (1H, m, H-5a) and 2.30 (1H, m, H-5b), analogous with caulerpenyne (**1**). On the other hand, the low field proton pattern of **4** was different from that of **1**, as it displayed the same olefinic multiplets at δ 5.88 (1H, t, *J*=7.0 Hz, H-6) and δ 5.42 (1H, bs, H-10), along with a double doublet at δ 5.63 (1H, dd, *J*=6.6, 7.7 Hz, H-4), which was up-field shifted with respect to the corresponding proton in caulerpenyne (**1**), but it lacked the signals due to the 1,4-diacetoxy-1,4-butadiene moiety. In their place, two methylene multiplets at δ 4.77 (2H, m, H_2-1) and at δ 4.55 (2H, ABq, *J*= 13.4 Hz, H_2-13), and an additional vinyl signal at δ 5.72 (1H, t, *J*= 6.4 Hz, H-2) were observed in the spectrum of compound **4**, suggesting the presence of a 1,4-diacetoxy-2-butene moiety. Analysis of the ^{13}C-NMR spectrum confirmed this hypothesis, and **4** was thus identified as the 1,4-dihydroderivative of caulerpenyne (**1**). The stereochemistry at C-4 was assumed to be the same as caulerpenyne (**1**), whereas the *Z*-stereochemistry of the C-2/C-3 double bond was established by a series of n.O.e. difference experiments, whereby diagnostic n.O.e. effects were observed between H_2-13 (δ 4.55) and H-2 (δ 5.72) as well as between H_2-1 (δ 4.77) and H-4 (δ 5.63). All ^{1}H- and ^{13}C-NMR resonances (Table 1) were fully assigned by mono- and bi-dimensional NMR experiments (COSY, HSQC, HMBC) and were in complete agreement with the proposed structure.

Table 1 NMR Spectroscopic Data[a] (400 MHz, C_6D_6) for dihydrocaulerpenyne **(4)** and expansinol (**5**)

	4		**5**	
Position	δ_C, mult.	δ_H (*J* in Hz)	δ_C, mult.	δ_H (*J* in Hz)
1	60.1, CH_2	4.77, m	60.8, CH_2	3.36, m
2	127.4, CH	5.72, t (6.4)	32.1, CH_2	2.09, bt (6.6)
3	136.7, qC	-	132.3, qC	-
4	70.8, CH	5.63, dd (6.6, 7.7)	129.0, CH	5.35, bt (7.6)
5	32.6, CH_2	2.30/2.49 m	27.2, CH_2	2.65, bt (7.1)
6	130.3, CH	5.88, t (7.0)	133.8, CH	5.86, bt (6.9)
7	123.0, qC	-	119.4, qC	-
8	94.8, qC	-	94.8, qC	-
9	86.1, qC	-	n. d.	-
10	106.2, CH	5.42, bs	106.2, CH	5.47, bs
11	147.6, qC	-	146.9, qC	-
12	24.5, CH_3	1.46, bs	24.3, CH_3	1.49, bs
13	63.9, CH_2	4.55, ABq (13.4)	68.1, CH_2	4.41, s
14	17.8, CH_3	1.81, bs	17.5, CH_3	1.77, bs
15	20.9, CH_3	1.82, bs	20.7, CH_3	1.84, bs
OAc-1	169.7, qC			
	20.3, CH_3	1.64[b], s		
OAc-4	169.3, qC			
	20.2, CH_3	1.57, s		
OAc-13	169.7, qC		169.7, qC	
	20.3, CH_3	1.63[b], s	20.5, CH_3	1.64, s

[a]Assignments aided by COSY, HSQC, HMBC
[b]Values maybe interchanged

The more polar compound, expansinol (**5**), was quite unstable and displayed a sodiated molecular ion at *m/z* 299.1620 ($C_{17}H_{24}O_3$). Spectral data analysis indicated a close relationship between **5** with compounds of caulerpenyne family, showing the structural differences with known caulerpenyne derivatives in the oxidized terminal part of the molecule. The ^{1}H-NMR spectrum contained signals due to one acetoxy group (δ 1.64, 3H, s, OAc-13) and three vinyl methyls at δ 1.84 (3H, bs, H_3-15), δ 1.77 (3H, bs, H_3-14) and δ 1.49 (3H, bs, H_3-12). Three olefinic multiplets at δ 5.86 (1H, bt, 6.9 Hz, H-6); δ 5.47 (1H, bs, H-10) and δ 5.35 (1H, bt, 7.6 Hz, H-4) supported the presence of three trisubstituted double bonds in accordance with caulerpenyne skeleton. In addition, the ^{1}H-NMR spectrum showed signals attributed to two oxygen-bearing methylenes, one of which (δ 4.41, 2H, s, H_2-13) was isolated and another one, resonating at δ 3.36 (2H, m, H_2-1), which was further coupled to an allylic methylene at δ 2.09 (2H, bt, 6.6 Hz, H_2-2). A multiplet at δ 2.65 (2H, bt, 7.1 Hz, H_2-5) assigned to a bis-allylic methylene group completed the ^{1}H-NMR spectrum. These data suggested that **5** was the monoacetyl ester of a diol derivative of caulerpenyne, i.e. **7** (the 3*E*-isomer) or **8** (the 3*Z*-isomer), previously obtained from caulerpenyne (**1**) by sodium borohydride reduction [15]. Unfortunately, the degradation of expansinol (**5**) prevented the recording of n.O.e. difference experiments, which had been planned to determine the stereochemistry of C-3/C-4 double bond.

We therefore decided to synthesize the model diol derivatives **7** and **8**, starting from natural caulerpenyne, and compare their NMR data with that of expansinol (**5**). An aliquot of sample of **1** was

submitted to $NaBH_4$ reduction as reported in the literature [15] giving the expected mixture of **7** and **8** (ratio 5:1).

Figure 1. Selected ^{1}H- and ^{13}C-NMR values for compounds **7** (3*E*-isomer) and **8** (3*Z*-isomer).

7 **8**

The ^{1}H-NMR spectrum of this mixture showed distinct H_2-2, H-4 and H_2-13 signals for both diols, so NMR analysis (^{13}C NMR, HSQC, and n.O.e. difference experiments) was directly conducted on the mixture, in order to identify the two isomers. The proton and carbon assignments of the terminal diol moieties of compounds **7** and **8** are reported in Figure 1. Comparison of these data with those of **5** clearly indicated the 3*E*-stereochemistry for the natural mono-acetyl derivative. Particularly diagnostic was the ^{13}C-NMR shift assigned to C-2 (32.1 ppm).

Conclusions

Analogously with *Elysia* species from the Caribbean area, but in contrast with Oxynoidean sacoglossans, *Elysia* cf. *expansa* has revealed a *Caulerpa*-derived metabolism, dominated by the presence of caulerpenyne (**1**) (14% of ether extract of the external part). In addition, two caulerpenyne-related molecules, compounds **4** and **5**, and the pigment caulerpin (**6**) have been detected in trace amounts in the extract (ca. 0.2%, 0.1% and 0.3% of ether extract of the external part, respectively). The ethereal extracts of several *Caulerpa* spp. samples, collected in small amounts from the same habitat as the sacoglossan were also analyzed by HPLC chromatography, showing the presence of caulerpenyne (**1**) and caulerpin (**6**) in all samples, whereas compounds **4** and **5** were not detectable. This finding raises the question of whether compounds **4** and **5** may be the result of transformation of **1** by the sacoglossan or whether the molluscs may simply accumulate very minor algal compounds. A series of caulerpenyne-derived products related to compounds **4** and **5**, have in fact been reported from several tropical *Caulerpa* algae [19-22]. However, in contrast to the majority of *Caulerpa*-feeder sacoglossans, the defensive toxins, oxytoxin-1 (**2**) and oxytoxin-2 (**3**), were not found in *Elysia* cf. *expansa*. It has been suggested that these compounds are obtained by oxynoidean and elysioidean sacoglossans by transforming dietary caulerpenyne (**1**) [6,12,13,16], but they have also been reported to be produced in *Caulerpa* algae by a wound-activated defensive mechanism [23,24]. An alternative hypothesis suggests that the two toxins are either minor metabolites selectively accumulated from algae or they are formed during the suctorial feeding of the alga by a wound-activated mechanism. Recently, it has been rigorously proven that the sacoglossan *Oxynoe olivacea* contains two different kinds of lipases that selectively can hydrolyze one of the two enol-acetates displayed by caulerpenyne [16]. These results are further supported by the data reported in this work. In fact, the presence in *Elysia* cf. *expansa* of large amounts of caulerpenyne proves that this sesquiterpenoid can be accumulated by the mollusc without a relevant wound-activated degradation. On the other side, it is

noteworthy to observe the close chemical analogy between Indo-Pacific *Elysia* cf. *expansa* and the co-generic Caribbean *E. nisbeti* [6]. Both sacoglossans seem to be unable to biotransform dietary caulerpenyne, with an important accumulation of this metabolite. In summary, the structural analogy of compounds **4** and **5** with those described in other Caulerpa algae seems to support a dietary accumulation in the mollusc of minor algal metabolites whereas the absence of toxins **2** and **3** suggests that Oxynoidea and Elysioidea sacoglossans possess different hydrolytic enzymatic systems.

Experimental

General

Silica-gel chromatography was performed using pre-coated Merck F_{254} plates and Merck Kieselgel 60 powder. Sephadex LH-20 for molecular exclusion chromatography was purchased from Pharmacia (Uppsala, Sweden). HPLC purification was carried out on a Shimadzu LC-10AD liquid chromatograph equipped with an UV SPD-10A wavelength detector. Optical rotations were measured on a Jasco DIP 370 digital polarimeter. IR spectra were recorded on a BioRad FTS 155 FT-IR spectrophotometer. NMR experiments were recorded at ICB-NMR Service Centre. 1D- and 2D-NMR spectra were acquired in C_6D_6 (δ values are reported referred to the $C_6\underline{H}_6$ signal at 7.15 ppm) on a Bruker Avance-400 operating at 400 MHz, using an inverse probe fitted with a gradient along the Z-axis. ^{13}C-NMR were recorded on a Bruker DPX-300 operating at 300 MHz (δ values are reported referenced to $\underline{C}_6D_6$, 128.0 ppm) using a dual probe. High resolution ESIMS were performed on a Micromass Q-TOF Micro^{TM} coupled with a Waters Alliance 2695 HPLC. The instrument was calibrated by using a PEG mixture from 200 to 1000 amu (resolution specification 5000 FWHM, deviation <5 ppm RMS in the presence of a known lock mass).

Biological material

70 specimens of *Elysia* cf. *expansa* (average size 2.5 cm) were collected off Mandapam, Tamil Nadu (India), in January 2001, at a depth of 3-7 meters. The molluscs were immediately frozen and stored at –20°C till the extraction. The animals, showing a distinctive black line along parapodial edges, were tentatively identified as *Elysia* cf. *expansa*. A voucher specimen is deposited at ICB (code I 12). Samples of different co-occurring *Caulerpa* spp. were also deposited at ICB (codes I 33, I 35, I 45, I 66, I 67, I 69).

Extraction and isolation procedure

E. expansa (70 individuals) was first extracted with portions of acetone under ultrasound irradiation (each 100 mL x 3) to obtain metabolites present in the external part of the mollusc. The organic fraction was evaporated under vacuum and the resulting aqueous suspension was partitioned between diethyl ether and water. The organic phase was concentrated affording 770 mg of crude external part extract. The whole animal residue was homogenized with a pestle and extracted with acetone (3 x 50 mL). After removing the organic solvent the aqueous suspension was extracted with diethyl ether. The

organic portion was evaporated affording 70 mg of crude internal part extract. Both extracts were analysed by TLC chromatography and ^{1}H-NMR spectroscopy. The external ether soluble fraction (770 mg), was chromatographed on a Sephadex LH-20 column (eluent: 1:1 $CHCl_3/CH_3OH$) to give five fractions: I (150 mg), II (220 mg), III (120 mg), IV (250 mg) and V (40 mg). Fractions III and IV were submitted to further purification on a silica-gel column (light petroleum ether with increasing amounts of diethyl ether). Fraction III yielded several fractions, some of which were subjected to HPLC purification (Chromasil C18, CH_3OH/H_2O gradient, flow 1 mL/min) to give caulerpenyne (**1**, 50 mg) and compound **4** (1.2 mg). Fraction IV was submitted first to silica-gel column chromatography and then to HPLC (Chromasil C18, CH_3OH/H_2O gradient, flow 1 mL/min), again affording caulerpenyne (**1**, 60.0 mg), along with expansinol (**5**, 0.4 mg). Fraction V was subjected to silica-gel column chromatography (petroleum ether/diethyl ether) to give caulerpin **6** (2.0 mg). Samples of *Caulerpa* spp. were extracted with acetone (3x50 mL) and, after removing the organic solvent, the residual aqueous fractions were extracted with diethyl ether. Thin layer chromatography of *Caulerpa* ethereal extracts revealed only the presence of caulerpenyne (**1**) and caulerpin (**6**) in comparison with those of the animals.

Characterization data

Dihydrocaulerpenyne (**4**): R_f = 0.6 (1:1 light petroleum ether-diethyl ether); $[\alpha]_D^{25}$= - 49.5° (c= 1 mg, $CHCl_3$); IR ν_{max} (liquid film): 2983, 2922, 2848, 1743, 1431, 1371, 1226, 1025 cm^{-1}; UV (CH_3OH) λ_{max} (log ε) 283 (4.33), 270 (4.46), 203 (4.40) nm; HRESIMS: *m/z* 399.1781 (calculated for $C_{21}H_{28}O_6Na$: 399.1784); ^{1}H- and ^{13}C-NMR data are given in Table 1.

Expansinol (**5**): R_f = 0.35 (1:1light petroleum ether-diethyl ether); $[\alpha]_D^{25}$= - 14.0° (c= 0.4 mg, $CHCl_3$); IR ν_{max} (liquid film): 2929, 2856, 1740, 1443, 1381, 1234, 1034 cm^{-1}; UV (CH_3OH) λ_{max} (log ε) 283 (4.27) 269 (4.33) 203 (4.31) nm; HRESIMS: *m/z* 299.1620 (calculated for $C_{17}H_{24}O_3Na$: 299.1623); ^{1}H- and ^{13}C-NMR data are given in Table 1.

Acknowledgements

We thank ICB Mass Service and ICB NMR Service Centre (Mrs. D. Melck is kindly acknowledged), Mr. C. Iodice for spectrophotometric measurements and Mr. R. Turco for graphical work. This work was partially supported by a bilateral CNR-CSIR project.

References

1. Jensen, K. R. A review of sacoglossan diets, with comparative notes on radular and buccal anatomy. *Malacol. Rev*. **1980**, *13*, 55-77.
2. Clark, K.B.; Busacca, M. Feeding specificity and chloroplast retention in four tropical ascoglossa, with a discussion of the extent of chloroplast symbiosis and the evolution of the order. *J. Moll. Stud*. **1978**, *44*, 272-282.

3. Marin, A.; Ros, J. Ultrastructural and ecological aspects of the development of chloroplast retention in the sacoglossan gastropod *Elysia timida*. *J. Moll. Stud.* **1993**, *59*, 95-104.
4. Jensen, K. R. Evolution of sacoglossans (Mollusca, Opisthobranchia) and the ecological association with their food plants. *Evol. Ecol.* **1997**, *11*, 305-335.
5. Cimino, G.; Fontana, A.; Gavagnin, M. Marine opisthobranch molluscs: chemistry and ecology in sacoglossans and dorids. *Curr. Org. Chem.* **1999**, *3*, 327-372.
6. Gavagnin, M.; Mollo, E.; Monatanaro, D.; Ortea, J., Cimino, G. Chemical studies of Caribbean sacoglossans: dietary relationships with green algae and ecological implications. *J. Chem. Ecol.* **2000**, *26*, 1563-1578.
7. Horgen, F. D.; delos Santos, D. B.; Goetz, G.; Sakamoto, B.; Kan, Y.; Nagai, H.; Scheuer, P. J. A new depsipeptide from the sacoglossan mollusk *Elysia ornata* and the green alga *Bryopsis* species. *J. Nat. Prod.* **2000**, *63*, 152-154.
8. Becerro, M. A.; Goetz, G.; Paul, V. J., Scheuer, P. J. Chemical defenses of the sacoglossan mollusk *Elysia rufescens* and its host alga *Bryopsis* sp. *J. Chem. Ecol.* **2001**, *27*, 2287-2299.
9. Paul, V. J., Van Alstyne, K. L. Use of ingested algal diterpenoids by *Elysia imedae* Macnae (Opisthobranchia: Ascoglossa) as antipredator defenses. *J. Exp. Mar. Biol. Ecol.* **1988**, *119*, 15-29.
10. Gavagnin, M.; Marin, A.; Mollo, E.; Crispino, A.; Villani, G.; Cimino, G. Secondary metabolites from Mediterranean Elysioidea: origin and biological role. *Comp. Biochem. Physiol.* **1994**, *108B*, 107-115.
11. Gavagnin, M.; Spinella, A.; Marin, A.; Castelluccio, F.; Cimino, G. Polypropionates from the Mediterranean mollusk *Elysia timida*. *J. Nat. Prod.* **1994**, *57*, 298-304.
12. Cimino, G.; Crispino, A.; Di Marzo, V.; Gavagnin, M.; Ros, J. D. Oxytoxins, bioactive molecules produced by the marine opisthobranch mollusc *Oxynoe olivacea* from a diet-derived precursor. *Experientia* **1990**, *46*, 767-770.
13. Gavagnin, M.; Marin, A.; Castelluccio, F.; Villani, G.; Cimino, G. Defensive relationship between *Caulerpa prolifera* and its shelled sacoglossan predators. *J. Exp. Mar. Biol. Ecol.* **1994**, *175*, 197-210.
14. Fontana, A.; Ciavatta, M. L.; Mollo, E.; Naik, C. G.; Wahidulla, S.; D'Souza, L.; Cimino, G. Volvatellin, caulerpenyne-related product from the sacoglossan *Volvatella* sp. *J. Nat. Prod.* **1999**, *62*, 931-933.
15. Amico, V.; Oriente, G.; Piattelli, M.; Tringali, C. Caulerpenyne, an unusual sesquiterpenoid from the green alga *Caulerpa prolifera*. *Tetrahedron Lett.* **1978**, *38*, 3593-3596.
16. Cutignano, A.; Notti, V.; D'Ippolito, G.; Domenech Coll, A.; Cimino, G.; Fontana, A. Lipase-mediated production of defensive toxins in the marine mollusc *Oxynoe olivacea*. *Org. Biomol. Chem.* **2004**, *2*, 3167-3171.
17. Maiti, B. C.; Thomas, R. H.; Mahendran, M. The structure of caulerpin, a pigment from *Caulerpa* algae. *J. Chem. Res. Synop.*, **1978**, 126-127.
18. Schwede, J. G.; Cardellina II, J. H.; Grodi,, S. H.; James, T. R.; Blackman, A. Distribution of the pigment caulerpin in species of the green alga *Caulerpa*. *Phytochemistry* **1987**, *26*, 155-158.

19. Guerriero, A.; Meinesz, A.; D'Ambrosio, M.; Pietra, F. Isolation of toxic and potentially toxic sesqui- and monoterpenes from the tropical green seaweed *Caulerpa taxifolia* which has invaded the region of Cap Martin and Monaco. *Helv. Chim. Acta* **1992**, *75*, 689-695.
20. Guerriero, A.; Marchetti, F.; D'Ambrosio, M.; Senesi, S.; Dini, F.; Pietra, F. New ecotoxicologically and biogenetically relevant terpenes of the tropical green seaweed *Caulerpa taxifolia* which is invading the Mediterranean. *Helv. Chim. Acta* **1993**, *76* 855-864.
21. Guerriero, A.; Depentori, D.; D'Ambrosio, M.; Durante, M.; Dini, F.; Pietra, F. Chlorophyll-photosensitised photodegradation of caulerpenyne; a potential harmful sesquiterpenoid from tropical green seaweeds in the genus *Caulerpa*. *J. Chem. Soc. Chem. Commun*. **1994**, 2083-2084.
22. Guerriero, A.; D'Ambrosio, M. Epoxycaulerpenynes: reactivity and diastereoselective and highly regioselective synthesis by dimethyldioxirane oxidation of caulerpenyne. *Eur. J. Org. Chem*. **1999**, 1985-1990.
23. Jung, V.; Pohnert, G. Rapid wound-activated transformation of the green algal defensive metabolite caulerpenyne. *Tetrahedron* **2001**, *57*, 7169-7172.
24. Jung, V.; Thibaut, T.; Meinesz, A.; Pohnert, G. Comparison of the wound-activated transformation of caulerpenyne by invasive and non-invasive *Caulerpa* species of the Mediterranean. *J. Chem. Ecol.*, **2002**, *28*, 2091-2104.

Sample Availability: Samples of the compounds **1**, **4** and **6** are available from authors.