Chemical Investigation of Predator-Deterred Macroalgae from the Antarctic Peninsula†

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Chemical investigation of five Antarctic macroalgae whose tissues and crude extracts displayed ecologically relevant feeding deterrence in field bioassays was performed. Eleven compounds were characterized from the three red algae studied, of which four (**1**−**3** and **9**) were previously unreported, and four compounds were found from two brown algae, two (**12** and **14**) of which are new natural products. Several of these pure compounds have been individually investigated in ecological and/or pharmacological bioassays.

Marine macroalgae have been a remarkable source of chemical diversity, responsible for roughly 20% of compounds reported from marine sources,[1−3] and at least one macroalgal compound, reported from Paul Scheuer's lab, shows promise of clinical utility.[4] Compounds from macroalgae are characteristic of their biological origin: red algae (Rhodophyceae) produce largely polyhalogenated monoterpenes, sesquiterpenes, and acetogenins; brown algae (Phaeophyceae) produce primarily diterpenes, but are also rich in phlorotannins and known for their prenylated quinones or hydroquinones; and green algae (Chlorophyceae and Ulvophyceae) produce sesqui- and diterpenes and are known for their 1,4-dialdehydes.[1−3]

Ecological investigations of macroalgal compounds have in many respects been the driving force behind the development of the field of marine chemical ecology.[5,6] For example, early studies of sea hares (Anaspidian molluscs) by John Faulkner and his students demonstrated that they not only sequester dietary compounds of algal origin[7] but are capable of conversion of the compounds to new natural products.[8] Seminal studies of green algae revealed that, like their terrestrial (plant) counterparts, marine natural products could serve as feeding deterrents to potential herbivors.[9,10]

Investigations of macroalgae from polar waters surrounding Antarctica have focused largely on red algae but include several studies of brown algae.[11] Macroalgae are the dominant biomass in shallow waters along the western side of the Antarctic Peninsula, including at our study sites near Palmer Station (64°46′, 64°03′ W) and therefore play a key role in local benthic ecology.[12−15] Our interest in studying Palmer-area macroalgae was to ascertain the role of chemical ecology in structuring the near-shore Antarctic benthos. We have conducted chemical investigations of five macroalgae that displayed bioactivity in field bioassays[16] and report herein the major chemical components and aspects of their ecological and pharmacological activity.

Results and Discussion

Algae were collected from a number of sites within 3.5 km of Palmer Station at depths ranging from 3 to 39 m. Extraction of freshly collected or frozen algae with 1:1 CH_2Cl_2/CH_3OH (3×) followed by 1:1 CH_3OH/H_2O (3×) resulted in lipophilic and hydrophilic extracts. Both fresh algal material (thallus) and chemical extracts were used to bioassay their palatability toward two relevant predators, the omnivorous sea star *Odontaster validus* and the benthic omnivorous fish *Notothenia coriiceps*. Chemical extracts were also bioassayed against the herbivorous amphipod *Gondogeneia antarctica*. Bioactivity of chemical extracts in five algal species, *Delisea pulchra*, *Plocamium cartilagineum*, *Myriogramme smithii*, *Desmarestia menziesii*, and *Cystosphaera jacquinotii*, which were all unpalatable to both sea stars and fish as fresh tissue, led to chemical analyses described below. Details of the thallus and crude extract bioassays will be the subject of an upcoming report.[16]

***Delisea pulchra* (Greville) Montagne 1844 (Rhodophyceae, Bonnemaisoniales, Bonnemaisoniaceae).** Marine red alga from the family Bonnemaisoniaceae have been shown to produce a wide range of halogenated metabolites, including butenones, octenones, acetones, and from the genus *Delisea*, halogenated furanones.[17] *Delisea pulchra* has been the focus of prior ecological and bioactivity studies. Halogenated compounds from *D. pulchra* (= *D. fimbriata*) interfere with Gram-negative bacteria signaling systems, affect the growth of Gram-positive bacteria, and inhibit quorum sensing and swarming motility of marine bacteria (inhibit bacterial communication). They also inhibit surface colonization in marine bacteria and exhibit antifouling properties against barnacle larvae and macroalgal gametes.[18] Chemical investigation of *D. pulchra* collected near Palmer Station yielded three new dimeric halogenated furanones, pulchralides A−C (**1**−**3**), along with previously reported fimbrolide (**4**),[19] acetoxyfimbrolide (**5**),[20] and hydroxyfimbrolide (**6**).[20] Compounds **4**−**6** were characterized by comparison of their ^1H and ^{13}C NMR data with those previously published.

Pulchralide A (**1**) displayed the characteristic aliphatic ^1H NMR signals observed in acetoxyfimbrolide (**5**) but showed ^{13}C NMR data significantly different from **5**. In

† Dedicated to the late Dr. D. John Faulkner (Scripps) and the late Dr. Paul J. Scheuer (Hawaii) for their pioneering work on bioactive marine natural products.

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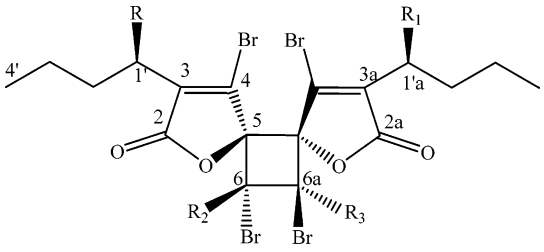


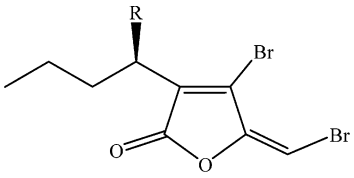
Pulchralide A (**1**): R = R_1 = OAc, R_2 = R_3 = H

Pulchralide B (**2**): R = R_1 = R_2 = R_3 = H

Pulchralide C (**3**): R = OAc, R_1 = R_2 = R_3 = H

Acetoxyfimbrolide C_2 dimer (**7**): R = R_1 = H, R_2 = R_3 = Br

Acetoxyfimbrolide meso dimer (**8**): C-5 epimer of **7**



Fimbrolide (**4**): R = H

Acetoxyfimbrolide (**5**): R = OAc

Hydroxyfimbrolide (**6**): R = OH

particular, only two ^{13}C signals were observed in the olefinic region of **1**, and the heteroatom-bearing carbon region suggested there were three heteroatom-bearing sp^3 carbons. Analysis of 2D data, including COSY, HSQC, and HMBC, confirmed the acetoxybutyl-substituted furanone ring with a vinyl halogen (Figure 1), but valences on the quaternary C-5 and its attached methine (C-6) could not be accounted for based on these data. A distinctive HMBC correlation of H-6 to the C-6/C-6a carbon was the first clue that the metabolite was a dimer, a hypothesis that could be confirmed by mass spectral data which provided the molecular formula $C_{22}H_{24}Br_4O_8$. The structure was secured and the absolute stereochemistry established by single-crystal X-ray analysis (Figure 2).

While several dimeric furanones have been described from this genus,[21] two (**7** and **8**) of which bear the central cyclobutane ring of the pulchralides, pulchralides A and C (**1** and **3**) are the first such dimers bearing the C-1′ acetoxy group. Natural products that appear as [2+2] cycloaddition products are rare. In marine algae only **7** and **8**, from *Delisea elegans*,[21] are reported. We examined the photochemistry of acetoxyfimbrolide (**5**) by exposing a solution to UV irradiation but did not observe dimer formation, supporting their biotic origin.

Pulchralides B (**2**) and C (**3**) demonstrated many of the structural features of pulchralide A (**1**). The ^1H NMR spectrum of pulchralide B lacked the acetoxymethine of **1**, and a new allylic methylene signal was found at δ 2.43, analogous to the allylic H-1′ of fimbrolide. Pulchralide B (**2**) therefore is the symmetrical fimbrolide dimer, an assignment that is fully supported by the COSY and HMBC data sets and mass spectral analysis. Pulchralide C (**3**) is the only unsymmetrical member of the group and thus displayed a much more complex ^1H NMR spectrum; analysis of the COSY spectrum illustrated two bromomethine doublets, H-6 and H-6a at δ 5.35 and 5.13, coupled with one another. Only a single acetoxy methyl group is

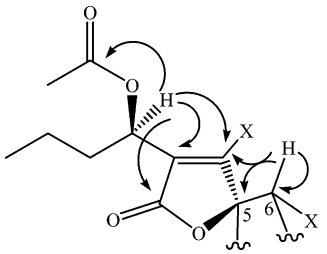


Figure 1. Key HMBC correlations determined for pulchralide A (**1**).

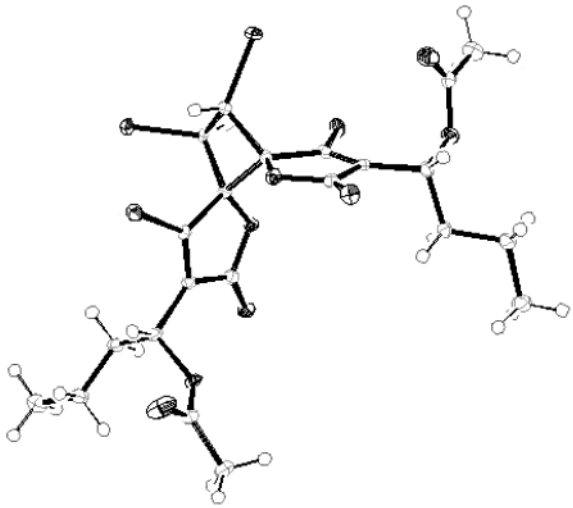


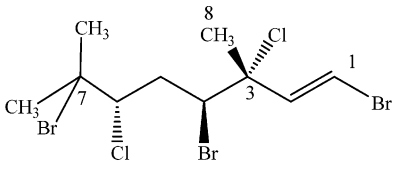
Figure 2. Perspective view of X-ray crystal structure of pulchralide A (**1**).

evident in the ^1H NMR spectrum, and HMBC correlations confirm its attachment to a butyl group and the furanone ring. Mass spectral analysis supported the unsymmetrical dimeric nature of pulchralide C.

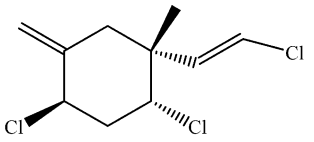
Bioactivity was greatest in acetoxyfimbrolide (**5**) and hydroxyfimbrolide (**6**). Acetoxyfimbrolide showed potent activity with 25 and 24 mm zones of inhibition (all antimicrobial assays done at 200 μg/spot) against methicillin-resistant and methicillin-sensitive *Staphylococcus aureus* (MRSA, MSSA), respectively, a 16 mm zone toward vancomycin-resistant *Enterococci faecium* (VREF), and a 17 mm zone using *Candida albicans*. Hydroxyfimbrolide displayed the same magnitude zones toward the Gram-positive bacteria (23, 23, and 14 mm for MRSA, MSSA, and VREF, respectively) and a 25 mm zone against *C. albicans*. Both compounds were modestly active against a permeabilized[22] *Escherichia coli* (9 mm hazy zone). Fimbrolide (**4**) was weakly active in antimicrobial assays (MRSA and MSSA: 7 mm hazy zone; no inhibition of other microbes tested).

***Plocamium cartilagineum* Dixon 1967 (Rhodophyceae, Plocamiales, Plocamiaceae).** Algal tissues and extracts were significantly rejected by all three predators.[16] *P. cartilagineum* is found in temperate and polar waters of the Northern and Southern Hemispheres and is common in shallow-water Antarctica environments.[23] Pioneering natural product work on Antarctic species can be traced to early analyses of this alga, which documented several linear or monocyclic monoterpenes that were highly functionalized with halogens.[24,25] These halogenated monoterpenes have become characteristic of red algae,[1−3] and some have displayed significant bioactivity. Halomon, for example, from the red alga *Porteria hornemannii*, exhibits selective antitumor activity in the National Cancer Institute's 60-cell-line panel.[26−29]

The chloroform extract of *P. cartilagineum* (1.3 kg, wet) was subjected to gradient flash chromatography to yield a fraction (90:10 hexanes/EtOAc) from which anverene (**9**), *epi*-plocamene D (**10**), and pyranoid **11** were obtained by repeated reversed-phase HPLC purification. Anverene, isolated as colorless crystals (36 mg), gave rise to a mass spectrum (CIMS) indicative of the dehydrochlorination product ($[M - HCl]^+$), displaying a five-line pattern beginning at *m*/*z* 407 and with relative intensities suggestive of three bromine atoms and one chlorine atom, thus securing a molecular formula of $C_{10}H_{15}Br_3Cl_2$ for anverene.



Anverene (**9**)



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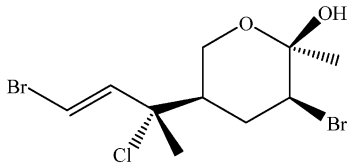

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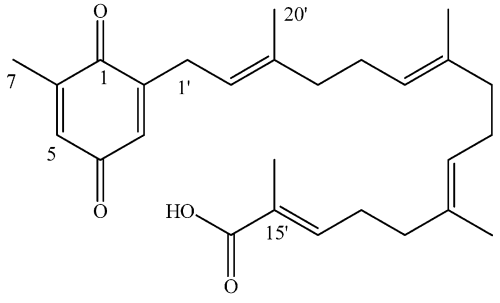


Menzoquinone (**12**)

Two mutually coupled *trans*-disubstituted olefinic protons were observed in the low-field portion of the ^{1}H NMR spectrum of anverene (**9**) at δ 6.58 and 6.40 ($J_{1,2}$ = 13.5 Hz). Two additional methines, bearing heteroatoms based on their chemical shift, were observed at δ 4.39 and 4.33. The high-field region of the ^{1}H NMR spectrum displayed a methylene group (δ 2.62, m), a singlet methyl group (δ 1.92), and a 6H singlet indicative of coincident methyl groups at δ 1.81. The low-field shift of all three methyl groups suggested they were attached to a carbon bearing a heteroatom.

Broadband and DEPT ^{13}C NMR data identified 10 carbon signals for anverene (**9**). Olefinic methine carbons were observed at δ 139.9 and 109.7, the latter of which could be identified as a vinyl halide based on its upfield shift. Resonances at δ 71.9 and 66.3 could be assigned as heteroatom-bearing quaternary carbons. Additional methine carbon atoms at δ 69.2 and 59.8 were similarly assigned as heteroatom-bearing, while the sole, aliphatic, methylene carbon resonated at δ 39.2. Three methyl groups were evident at δ 33.4, 28.8, and 25.5.

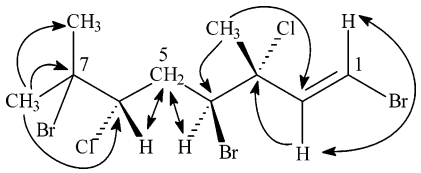


Figure 3. Key HMBC (→) and COSY (↔) correlations for anverene (**9**).

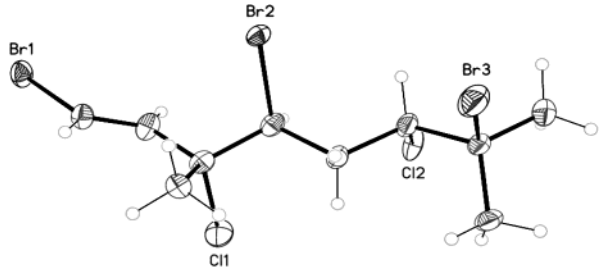


Figure 4. Perspective view of X-ray crystal structure of anverene (**9**).

Connectivity in anverene (**9**) was established by 2D NMR techniques, including COSY, HMQC, and HMBC (Figure 3). Mutually coupled olefinic methines described above established a terminus from which to elaborate the remaining connectivity. Thus, the olefinic methine at δ 6.40 (H-2) could be shown by HMBC (Figure 3) to be adjacent to the heteroatom-bearing quaternary center at δ 71.9 (C-3). Placement of the δ 25.5 (C-10) methyl group on C-3 could be rationalized by HMBC correlations of H_3-10 (δ 1.81) to C-3; H_3-10 also correlated to δ 59.8 (C-4). Further connectivity from C-4 could be achieved from COSY correlations of the two heteroatom-bearing methines at δ 4.39 (H-4) and 4.33 (H-6) to the methylene protons at δ 2.62 (H_2-5), which established the central portion of the molecule (Figure 3). The remaining quaternary carbon at δ 66.3 (C-7), besides bearing a heteroatom, displayed connectivity to H_3-8 and -9 (δ 1.81 and 1.92, respectively) in the HMBC spectrum. H_3-9 was also correlated by HMBC to C-6 and C-7, establishing a link from the *gem*-dimethyl moiety to the remainder of the molecule. To secure placement of halogen atoms and define the absolute stereochemistry of anverene, single-crystal X-ray diffraction analysis (Figure 4) was carried out. Anverene is thus (*E*,3*R*,4*S*,6*S*)-1,4,7-tribromo-3,6-dichloro-3,7-dimethyl-1-octene.

Epi-plocameme D (**10**) and pyranoid **11** were purified by reversed-phase HPLC from the same fraction containing anverene (**9**). Both compounds were fully characterized by 2D NMR techniques and concluded to be identical to the published compounds by comparison of these physical characteristics. *Epi*-plocameme D was originally reported from *Plocamium cartilagineum* collected from Anvers Island, Antarctica,[24] while **11** was isolated from *P. cartilagineum* collected off the Chilean coast.[30]

We and others have noted widespread bioactivity in *Plocamium* terpenes. Anverene (**9**) has modest but selective antibiotic activity toward VREF (8 mm zone of inhibition; no activity against MRSA, MSSA, *E. coli*, nor *C. albicans*). In field studies, anverene was significantly deterrent (57% anverene-treated pellets eaten vs 73% of controls eaten; p = 0.013) toward feeding by the amphipod *Gondogeneia antarctica* at three times the concentration it was isolated from the alga; given the imprecision of chemical isolation, this level of bioactivity is likely to be ecologically relevant. Pyranoid **11** is a similarly selective antifungal metabolite, displaying inhibition of *C. albicans* (8 mm zone; no activity against other Wyeth strains), but was largely insignificant as a feeding deterrent in field assays. *Epi*-plocamene D (**10**)

was the most active feeding deterrent toward the amphipod (19% of treated pellets eaten vs 50% of controls; $p = 0.005$) at isolated concentration (and only 1% of treated pellets eaten vs 51% of controls at 3× isolated concentration; $p = 0.005$) but, like the other terpenes studied here, had no effect on feeding by the sea star *Odontaster validus*.

***Myriogramme smithii* (J. D. Hooker and Harvey) Kylin 1924 (Rhodophyceae, Ceramiales, Delesseriaceae).** This red alga is reported only from the Antarctic Peninsula region and the Falkland Islands[23] and has not been investigated chemically. *M. smithii* extracts displayed antifeedant activity toward both sea star and amphipod predators.[16] For chemical analysis, the alga (825 g wet), which was kept frozen until use, was first extracted with 1:1 CH_2Cl_2/CH_3OH (3×) at room temperature. After separation from the aqueous layer, the organic extract was concentrated (3.85 g) and subjected to silica gel column chromatography using a stepwise gradient of hexanes/EtOAc/CH_3OH to provide six fractions. Fraction 3, eluting with 1:1 hexanes/EtOAc (167 mg), contained a complex mixture of simple aromatic compounds. The fraction was further purified by silica gel HPLC, resulting in the two major compounds *p*-hydroxybenzaldehyde (4.7 mg) and *p*-methoxyphenol (1.0 mg). In previous work we have shown *p*-hydroxybenzaldehyde to deter feeding in the sympatric sea star *Perknaster fuscus*,[31] and we therefore ascribe the aforementioned feeding deterrence to these simple aromatic compounds.

***Desmarestia menziesii* J. Agardh 1848 (Phaeophyceae, Desmarestiales, Desmarestiaceae).** This brown alga is common on the Antarctic benthos and frequently dominates communities from near the surface to depths of 10−20 m.[13−15] Brown algae are known to produce diterpenes of mixed biogenesis which are believed to be employed in chemical defenses against predators.[32] Compounds with the general structure of tetraprenyltoluquinols and chromenols are commonly biosynthesized by brown algae.[32−35]

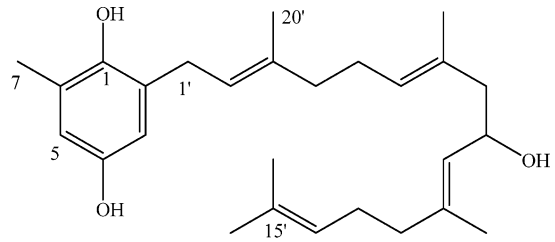
The lipophilic extract of *Desmarestia menziesii* was subjected to step gradient silica gel chromatography, and the fractions eluted with 2:8 EtOAc/hexanes yielded a new quinone derivative, menzoquinone (**12**), along with previously reported hydroquinone **13**[35] and sargadiol.[33] Known compounds were characterized by comparison of spectral data with previous reports.

Menzoquinone (**12**) was obtained as a yellow oil. The ^{1}H NMR spectrum gave rise to peaks corresponding to a trisubstituted olefinic signal at δ 6.83 (H-14′) and signals indicative of a benzoquinone moiety at δ 6.50 (H-5) and 6.42 (H-3). Other notable signals in the ^{1}H NMR spectrum included overlapping olefinic methine signals at δ 5.09 (H-2′, -6′, and -10′) and methyl singlets at δ 1.80 (H_3-17′) and 1.59 (H_3-18′, -19′, and -20′). The IR spectrum supported the presence of benzoquinone (ν_{max} 1651 cm^{-1}) and carboxylic acid (ν_{max} 2908 (br), 1680 cm^{-1}) moieties.

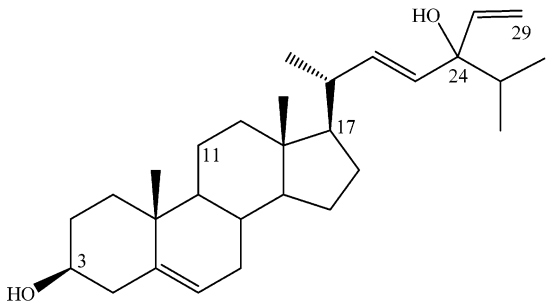
The ^{13}C NMR spectrum contained resonances for 27 carbon atoms, of which 12 olefinic carbons resonated between δ 117.9 and 148.4, two quinone carbonyls resonated at δ 187.9, and the carboxylic carbonyl resonated at δ 173.3. The high-field region contained signals corresponding to five methyl groups and seven methylene carbons based on multiplicities determined by a DEPT 135 experiment. Key HMBC correlations were observed between δ 6.83 (H-14′) and 173.3 (C-16′) and 27.5 (C-13′), between δ 1.80 (H_3-17′) and C-16′, between δ 2.07 (H-13′) and 144.8 (C-14′), between δ 3.10 (H-1′) and 187.9 (C-1), and from δ 2.08 (H_3-7) to C-1 and 133.1 (C-5). These correlations established the position of the carboxylic acid group and the position of attachment of the diterpene moiety to the quinone ring system. All additional connectivity could be established by a combination of COSY and HMBC experiments. The molecular formula was confirmed to be $C_{27}H_{36}O_4$ on the basis of the HREIMS spectrum.

The geometry about the terminal double bond was established as having an *E* configuration by consideration of the chemical shift values of the olefinic proton at δ 6.83 (H-14′). By comparison with tiglic and angelic acids, with *E* and *Z* disposed protons at δ 6.83 and 6.19, respectively,[35] H-14′ and the carboxylic acid group can be assigned as being *cis* to one another. The geometry of other double bonds in the side chain was also established as having the *E* configuration on the basis of olefinic methyl group carbon chemical shifts, thus establishing the structure of menzoquinone (**12**) as (2*E*,6*E*,10*E*,14*E*)-2,6,10,14-tetramethyl-16-(5-methyl-3,6-dioxocyclohexa-1,4-dienyl)hexadeca-2,6,10,14-tetraenoic acid. Menzoquinone differs from a synthetic derivative appearing recently in the patent literature under the name kombic acid quinone, which terminates with a *Z* olefin.[36] Menzoquinone displayed growth inhibition of MRSA, MSSA (8 and 6 mm, respectively), and VREF (7 mm zone) and significant ($p = 0.0034$) feeding deterrence of the omnivorous sea star *Odontaster validus* at 3 times the isolated concentration.

The planar structure of hydroquinone **13** was identified by comparison of its physical data to that published.[35] Our isolate bears an optical rotation opposite of the literature value, suggesting it is the enantiomer. Since the stereochemistry has not been reported, studies are continuing in our laboratory to establish the chirality of our isolate.



Hydroquinone **13**



Cystosphaerol (**14**)

***Cystosphaera jacquinotii* (Montagne) Skottsberg 1907 (Phaeophyceae, Fucales, Seirococcaceae).** Using gas-filled bladders for buoyancy, *Cystosphaera jacquinotii* rises off the benthos, giving it a tree-like appearance. To date there are no reported chemical investigations of this brown alga, which is endemic to Antarctica at the genus level.[1−3] ^{1}H NMR analysis of the crude organic extract of *C. jacquinotii* showed the presence of sterols and phaeophytin as the major constituents. The extract was fraction-

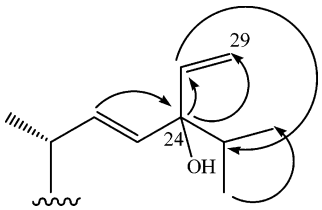


Figure 5. Key HMBC correlations for the side chain of cystosphaerol (**14**).

ated using step gradient silica gel chromatography with hexanes and EtOAc, resulting in separation of the steroid- and phaeophytin-containing fractions. Further purification of the steroid-containing fraction by HPLC yielded cystosphaerol (**14**). The ^{1}H NMR spectrum of **14** displayed the C-3 hydroxymethine peak at δ 3.56 (H-3) and five methyl groups, including angular methyl groups at δ 0.69 (H_3-18) and 1.01 (H_3-19). Taken with the olefinic methine at δ 5.37 (H-5), the nucleus of the steroid was determined to reflect that of cholesterol, and this assignment was confirmed by careful analysis of COSY and HMBC spectra.

The side chain (Figure 5) was observed to bear two olefins, one of which was disubstituted, displaying ^{1}H NMR signals at δ 5.37 (H-22) and 5.74 (H-23), and one monosubstituted, with signals at δ 5.78 (H-28), 5.27 (H_{cis}-29), and 5.17 (H_{trans}-29). The ^{13}C NMR spectrum of **14** showed signals for 29 carbons. Multiplicities of the carbon signals were determined from DEPT spectra. The ^{13}C NMR spectrum showed signals corresponding to three side-chain olefinic methine carbons at δ 137.3 (C-28), 137.4 (C-23), and 121.9 (C-22), one side-chain methylene carbon at δ 116.6 (C-29), and one side-chain quaternary carbon bearing OH at δ 89.4 (C-24).

The ^{1}H−^{1}H COSY spectrum of the cystosphaerol (**14**) side-chain protons showed connectivity between the methine proton at δ 5.78 (H-28) and H_2-29 protons (δ 5.27 and 5.17), between the methine proton at δ 2.01 (H-25) and two methyl groups at δ 0.88 (H_3-27) and 0.89 (H_3-26), and between two olefinic methine protons at δ 5.37 (H-22) and 5.74 (H-23). The HMBC spectrum showed the quaternary carbon C-24 correlated to two methyl groups, δ 0.89 (H-26) and 0.88 (H-27), the methine olefinic proton at δ 5.37 (H-22), and the olefinic methylene protons at δ 5.27 (H-29$_{cis}$) and 5.17 (H-29$_{trans}$) (Figure 5). This analysis results in the side-chain connectivity as depicted in **14**. The chemical ionization mass spectrum (CIMS) showed ions at *m*/*z* 426.4 ([M$^+$]), securing the proposed structure.

A sterol bearing the same planar structure as cystosphaerol (**14**) has been previously synthesized,[37] without stereochemical integrity at the C-24 alcohol, as a hypothesized intermediate in the biosynthesis of the phytosterol antheridiol, a compound responsible for sexual reproduction in the female part of the producing plant and which initiates formation of antheridial hyphae on the male plant. Bioactivity studies and stereochemical analysis of our isolate are continuing.

Experimental Section

General Experimental Procedures. A Rudolf Instruments Autopol IV polarimeter was used to acquire optical rotations using a sodium lamp at 25 °C. A Hewlett-Packard 8452A diode array UV/vis spectrometer was used to measure ultraviolet/visible spectra. Infrared spectra were recorded as KBr pellets using a Nicolet Avatar 320 FT-IR. ^{1}H and ^{13}C NMR, HMQC, HMBC, and ^{1}H−^{1}H COSY spectra were obtained on either a Varian Inova 500 instrument operating at 500 MHz for ^{1}H NMR and 125 MHz for ^{13}C or a Bruker Avance 250 instrument operating at 250 MHz for ^{1}H and 62.5 MHz for ^{13}C, using residual protonated solvent as ^{1}H internal standard or ^{13}C absorption lines of solvent for ^{13}C internal standard. 2D NMR techniques were optimized as followed: HMQC, J = 120 Hz; HMBC, J = 7 Hz; COSY, J = 7 Hz. Low- and high-resolution EI and CI mass measurements were taken on a Micromass 70-VSE spectrometer at the University of Illinois at Urbana−Champaign (UIUC). QTOF mass measurements were made on a Micromass Q-Tof Ultima at UIUC. Flash chromatography utilized EM Science silica gel 60, 230−400 mesh, and TLC was carried out on Whatman Partisil K6F silica gel 60 Å plates with 0.25 mm thickness or KC18F silica gel 60 Å plates with 0.20 mm thickness. HPLC analyses were conducted with either a Shimadzu LC-8A pump interfaced to a Shimadzu SPD-10A UV−vis absorbance detector and/or an Alltech ELSD 2000 evaporative light-scattering detector, or a Waters 6000 pump interfaced to a Waters 486 UV detector. Separations were achieved with either a YMC-Pack ODS-AQ (10 mm × 25 cm) or a Waters Delta-Pak C18 (25 mm × 30 cm) for reversed-phase or Phenomenex Sphereclone (10 mm × 25 cm) for normal-phase.

X-ray Crystal Structure Determination. Single crystals suitable for X-ray crystallographic analysis were selected following examination under a microscope. Single-crystal X-ray diffraction data for the compounds were collected on a Bruker-AXS SMART APEX/CCD diffractometer using Mo Kα radiation (λ = 0.7107 Å). Diffracted data were corrected for Lorentz and polarization effects and for absorption using the SAD-ABS[38] program. The structure was solved by direct methods, and the structure solution and refinement was based on $|F|^2$. All non-hydrogen atoms were refined with anisotropic displacement parameters, whereas hydrogen atoms were placed in calculated positions when possible and given isotropic U values 1.2 times that of the atom to which they are bonded. All crystallographic calculations were conducted with the SHELXTL v.6.1[39] program package.

Plant Material. Algal biomass was collected from among the islands in the vicinity of Palmer Station, Antarctica (64°46′ S, 64°03′ W) by scuba diving during the months of March−May 2000 and November−December 2001 and kept frozen until workup. Identifications were made by C.D.A. and K. B. Iken. Vouchers are maintained in the Department of Biology at the University of Alabama at Birmingham.

Extraction and Isolation. ***Delisea pulchra*.** The red alga *Delisea pulchra* (800 g wet) was extracted three times with 1:1 CH_2Cl_2/CH_3OH to yield 3.5 g of lipophilic extract, then three times with 1:1 CH_3OH/H_2O to yield 18.8 g of hydrophilic extract. The lipophilic extract was subjected to silica gel flash column chromatography to yield nine fractions. Fimbrolide (**4**, 10 mg, 0.0013%) was obtained from normal-phase HPLC of fraction 1 (1:99 EtOAc/hexanes). Acetoxyfimbrolide (**5**, 200 mg, 0.025%) and two new compounds, pulchralides B (**2**, 3 mg, 0.00038%) and C (**3**, 2.5 mg, 0.00032%), were obtained from normal-phase HPLC of fraction 3 (1:9, 12:88, 15:75 EtOAc/hexanes). Another new compound, pulchralide A (**1**, 10 mg, 0.0013%), and hydroxyfimbrolide (**6**, 10 mg, 0.0013%) were obtained from the normal-phase HPLC of fraction 5 (2:8 EtOAc/hexanes).

***Plocamium cartilagineum*.** Freshly thawed alga (1.3 kg wet weight) was extracted sequentially with $CHCl_3$ and CH_3OH (three times each). The combined $CHCl_3$ extracts were filtered and concentrated to yield 6.3 g of lipophilic extract, which was fractionated by silica gel flash chromatography to generate six fractions of increasing polarity. The second fraction, eluting with 9:1 hexanes/EtOAc (610 mg), was subjected to additional silica gel flash column chromatography using hexanes with traces of ethyl acetate. A terpene-enriched fraction (131.7 mg) was then subjected to repeated reversed-phase HPLC using 2:8 H_2O/CH_3CN to yield anverene (**9**, 36 mg, 0.0028%), *epi*-plocamene D (**10**, 60 mg, 0.0046%), and pyranoid **11** (38.7 mg, 0.0030%).

***Myriogramme smithii*.** Wet alga (825 g) was extracted with 2 L 1:1 CH_2Cl_2/CH_3OH (three times) at room temperature. This organic extract was concentrated to give 3.85 g. The

organic extract was subjected to silica gel column chromatography (5 cm × 60 cm) using a stepwise gradient of hexanes/EtOAc/CH_3OH to provide six fractions: fraction 1 (9:1:0, 687 mg), fraction 2 (3:1:0, 291 mg), fraction 3 (1:1:0, 167 mg), fraction 4 (1:3:0, 139 mg), fraction 5 (0:9:1, 238 mg), fraction 6 (0:1:1, 1.53 g). Fraction 3 was further subjected to silica gel gradient HPLC with a hexanes/EtOAc (95:5 → 80:20) to afford *p*-hydroxybenzaldehyde (4.7 mg, 0.00057%) and *p*-methoxyphenol (1.0 mg, 0.00012%).

Desmarestia menziesii. The frozen alga (3.5 kg) was extracted with 4 L 1:1 CH_2Cl_2/CH_3OH (three times) at room temperature, and the resulting extract was partitioned between chloroform and water. The organic layer was evaporated to dryness to give 14.8 g of extract. Part (7.0 g) of the extract was subjected to silica gel flash column chromatography wherein the fraction eluted with 2:8 EtOAc/hexanes was further purified by normal-phase silica gel HPLC to yield pure menzoquinone (**12**, 13.0 mg, 0.00078%). The fraction eluting with 1:4 EtOAc/hexanes was further purified by normal-phase silica gel HPLC to yield compound **13** (11.2 mg, 0.00068%) and sargadiol (14.2 mg, 0.00085%).

Cystosphaera jacquinotii. The organic extract (1:1 CH_2Cl_2/CH_3OH, 10 g) of the wet algal tissue (1 kg) showed the presence of steroids and phaeophytin as major constituents. The crude extract was fractionated using flash silica gel chromatography step gradient with 5, 10, 15, 25, 30, 50, and 75% EtOAc in hexanes, then 100% EtOAc. The phytosterol fraction, fraction 2 (400 mg), was further purified by reversed-phase HPLC using 3:75 H_2O/CH_3OH to give cystosphaerol (**14**, 30 mg, 0.0030%).

Pulchralide A (1): colorless crystals; $[\alpha]^{25}_D$ +6.0 (*c* 0.25, $CHCl_3$); IR ν_{max} 2962, 1747, 1740, 1220 cm^{-1}; UV λ_{max} 252 nm (log ϵ 4.67); ^1H NMR (500 MHz, $CDCl_3$) δ (integration, *J* (Hz), assignment) 5.58 (2H, dd, 6.5, 7.5, H-1′, -1′a), 5.17 (2H, s, H-6, -6a), 2.11 (6H, s, −COCH_3, −COCH_3a) 1.90 (4H, m, H_2-2′, -2′a), 1.36 (4H, m, H_2-3′, -3′a), 0.96 (6H, t, 7.5, H_3-4′, -4′a); ^{13}C NMR (125 MHz, $CDCl_3$) δ (multiplicity, assignment) 170.0 (C, -*C*OCH_3, -*C*OCH_3a), 164.9 (C, C-2, -2a), 139.7 (C, C-4, -4a), 134.5 (C, C-3, -3a), 90.4 (C, C-5, -5a), 68.5 (CH, C-1′, -1′a), 43.9 (CH, C-6, -6a), 33.8 (CH_2, C-2′, -2′a), 20.8 (CH_3, −CO*C*H_3, −CO*C*H_3a), 18.6 (CH_2, C-3′, -3′a), 13.8 (CH_3, C-4, -4′a); EIMS *m/z* 732/734/736/738 (1:4:6:4:1); HREIMS 734.8260 ($C_{22}H_{24}O_8{}^{79}Br_3{}^{81}Br$ requires 734.8262).

Pulchralide B (2): colorless oil; $[\alpha]^{25}_D$ +4.3 (*c* 0.06, $CHCl_3$); IR ν_{max} 2958, 1788 cm^{-1}; UV λ_{max} 245 nm (log ϵ 5.20); ^1H NMR (500 MHz, $CDCl_3$) δ (integration, *J* (Hz), assignment) 5.21 (2H, s, H-6, -6a), 2.43 (4H, t, 7.5, H_2-1′, -1′a), 1.56 (4H, m, H_2-2′, -2′a), 1.35 (4H, m, H_2-3′, -3′a), 0.94 (6H, t, 7.5, H_3-4′, -4′a); ^{13}C NMR (125 MHz, $CDCl_3$) δ (multiplicity, assignment) 167.4 (C, C-2, -2a), 138.2 (C, C-4, -4a), 137.1 (C, C-3, -3a), 90.5 (C, C-5, -5a), 44.1 (CH, C-6, -6a), 29.0 (CH_2, C-1′, -1′a), 25.5 (CH_2, C-2′, -2′a), 22.4 (CH_2, C-3′, -3′a), 13.9 (CH_3, C-4′, -4′a); EIMS *m/z* 615/617/619/621/623 (1:4:6:4:1, [M^+ − H]); HREIMS 538.8894 ([M^+ − Br], $C_{18}H_{20}O_4{}^{79}Br_2{}^{81}Br$ requires 538.8891).

Pulchralide C (3): colorless oil; $[\alpha]^{25}_D$ +11.6 (*c* 0.06, $CHCl_3$); IR ν_{max} 2961, 1786, 1741, 1234 cm^{-1}; UV λ_{max} 246 nm (log ϵ 5.16); ^1H NMR (500 MHz, $CDCl_3$) δ (integration, *J* (Hz), assignment) 5.49 (1H, t, 7.5, H-1′), 5.35 (1H, d, 10, H-6), 5.13 (1H, d, 1.9, H-6a) 2.38 (2H, t, 7.5, H_2-1′a), 2.09 (3H, s, COCH_3), 1.89 (4H, m, H_2-2′, -2′a), 1.34 (4H, m, H_2-3′, -3′a), 0.95 (6H, m, H_3-4′, -4′a); ^{13}C NMR (125 MHz, $CDCl_3$) δ (multiplicity, assignment) 170.3 (C, -*C*OCH_3), 167.0 (C, C-2), 165.3 (C, C-2a), 140.9 (C, C-4), 139.7 (C, C-4a), 135.5 (C, C-3), 134.5 (C, C-3a), 93.3 (C, C-5), 88.1 (C, C-5a), 68.8 (CH, C-1′), 47.7 (CH, C-6), 44.4 (CH, C-6a), 33.4 (CH_2, C-1′a), 28.5 (CH_2, C-2′), 25.4 (CH_2, C-2′a), 22.5 (CH_2, C-3a), 20.6 (CH_3, −CO*C*H_3), 18.7 (CH_2, C-3′a), 13.9 (CH_3, C-4′), 13.8 (CH_3, C-4′a); TOFMS *m/z* 696.8047/698.8026/700.8008/702.7991/704.7977 (1:4:6:4:1, $C_{20}H_{22}O_6{}^{79}Br_2{}^{81}Br_2Na$ requires 700.8007).

Anverene (9): colorless crystals; $[\alpha]^{25}_D$ −12 (*c* 0.25, $CHCl_3$); IR ν_{max} 2912, 2840 cm^{-1}; UV λ_{max} 198 nm (log ϵ 4.74); ^1H NMR (500 MHz, $CDCl_3$) δ (integration, *J* (Hz), assignment) 6.58 (1H, d, 13.5, H-1), 6.40 (1H, d, 13.5, H-2), 4.39 (1H, dd, 10.7, 1.7, H-4), 4.33 (1H, dd, 10.7, 1.7, H-6), 2.62 (2H, m, H_2-5), 1.92 (3H, s, H_3-9), 1.81 (3H, s, H_3-8), 1.81 (3H, s, H_3-10); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ (multiplicity, assignment) 139.9 (CH, C-2), 109.7 (CH, C-1), 71.9 (C, C-3), 69.2 (CH, C-6), 66.3 (C, C-7), 59.8 (CH, C-4), 39.2 (CH_2, C-5), 33.4 (CH_3, C-9), 28.8 (CH_3, C-8), 25.5 (CH_3, C-10); LRCIMS *m/z* 407/409/411/413/415 (13:42:50:24:4) [M − HCl]$^+$; 327/329/331 (1:2:1) [M − 2HCl − HBr]$^+$; HRCIMS 410.8 [M − HCl]$^+$.

Menzoquinone (12): optically inactive yellow oil; IR ν_{max} 2908 (br), 2845, 1680, 1651, 1288 cm^{-1}; UV (CH_3OH) λ_{max} 253 nm (log ϵ 4.69); ^1H NMR (500 MHz, $CDCl_3$) δ (integration, *J* (Hz), assignment) 6.83 (1H, t, 6.5, H-14′), 6.50 (1H, d, 1.7, H-5), 6.42 (1H, d, 1.7, H-3), 5.09 (3H, m, H-2′, -6′, -10′), 3.10 (2H, d, 7.4, H_2-1′), 2.15 (2H, m, H_2-13′), 2.07 (10H, m, H_2-4′, -5′, -8′, -9′, -12′), 2.08 (3H, d, 2.0, H_3-7), 1.80 (3H, s, H_3-17′), 1.59 (9H, s, H_3-18′, -19′, -20′); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ (multiplicity, assignment) 187.9 (2 × C, C-1, -4), 173.3 (C, C-16′), 148.4 (C, C-2), 145.8 (C, C-6), 144.8 (CH, C-14′), 139.8 (C, C-3′), 135.2 (C, C-7′), 133.6 (C, C-11′), 133.1 (CH, C-5), 132.2 (CH, C-3), 126.9 (C, C-15′), 125.2 (CH, C-6′), 123.8 (C, C-10′), 117.9 (CH, C-2′), 39.6 (CH_2, C-4′), 39.4 (CH_2, C-12′), 38.0 (CH_2, C-8′), 27.5 (2 × CH_2, C-1′, -13′), 26.5 (2 × CH_2, C-5′, -9′), 16.1 (3 × CH_3, C-18′, -19′, -20′), 11.9 (CH_3, C-17′); EIMS *m/z* (%) 424 [M^+] (10), 175 (100), 137 (21); HREIMS *m/z* 424.2617 ($C_{27}H_{36}O_4$ requires 424.2613).

(−)-Hydroquinone 13: yellow oil; $[\alpha]^{25}_D$ −17.4 (*c* 0.32, $CHCl_3$); IR ν_{max} 3465, 2965, 2920, 2850, 1655, 1645, 1610 cm^{-1}; UV (CH_3OH) λ_{max} 265 nm (log ϵ 4.35); ^1H NMR (500 MHz, $CDCl_3$) δ (integration, *J* (Hz), assignment) 6.49 (1H, d, 2.8, H-5), 6.40 (1H, d, 2.8, H-3), 5.28 (1H, br t, 7.5, H-2′), 5.22 (1H, br t, 7.0, H-6′), 5.17 (1H, d, 9.0, H-10′), 5.09 (1H, br t, 8.0, H-14′), 4.45 (1H, dt, 8.0, 6.0, H-9′), 3.28 (2H, d, 7.5, H_2-1′), 2.3−2.0 (10H, m, H_2-4′, -5′, -8′, -12′, -13′), 2.16 (3H, s, H_3-7), 1.70 (3H, s, H_3-20′)$^{\perp}$, 1.68 (3H, s, H_3-19′)$^{\perp}$, 1.68 (3H, s, H_3-18′)$^{\perp}$, 1.66 (3H, s, H_3-17′)$^{\perp}$, 1.60 (3H, s, H_3-16′); ^{13}C NMR (125 MHz, $CDCl_3$) δ (multiplicity, assignment) 149.6 (C, C-4), 146.0 (C, C-1), 138.9 (C, C-11′)†, 137.5 (C, C-3′)†, 132.3 (C, C-7′)‡, 131.9 (C, C-15′)‡, 128.6 (CH, C-6′), 127.9 (C, C-6), 126.7 (CH, C-10′), 125.8 (C, C-2), 124.2 (CH, C-14′), 123.0 (CH, C-2′), 115.6 (CH, C-5), 113.8 (CH, C-3), 65.9 (CH, C-9′), 48.2 (CH_2, C-8′), 39.7 (CH_2, C-4′)*, 39.4 (CH_2, 12′)*, 29.2 (CH_2, C-1′), 26.6 (CH_2, C-5′)^, 25.9 (CH_2, C-13′)^, 25.8 (CH_3, C-17′), 17.9 (CH_3, C-16′), 16.8 (CH_3, C-18′)$^{\pm}$, 16.5 (CH_3, C-19′)$^{\pm}$, 16.4 (CH_3, C-7), 15.9 (CH_3, C-20′)$^{\pm}$; EIMS *m/z* (%) 412 [M^+] (2), 394 (5), 257 (25), 175 (55), 137 (50), 69 (100). $^{\perp, \dagger, \ddagger, *, \wedge, \pm}$Assignments are interchangeable among group.

Cystosphaerol (14): colorless powder; $[\alpha]^{25}_D$ −32.0 (*c* 0.10, $CHCl_3$); IR ν_{max} 3300 (br), 2919 cm^{-1}; UV (hexanes) λ_{max} 199 nm (log ϵ 1.21); ^1H NMR (500 MHz, $CDCl_3$) δ (integration, *J* (Hz), assignment) 5.78 (1H, dd, 11, 18, H-28), 5.74 (1H, d, 18, H-23), 5.37 (2H, m, H-5, -22), 5.27 (1H, dd, 12, 19, H_{cis}-29), 5.17 (1H, dd, 12, 19, H_{trans}-29), 3.56 (1H, m, H-3), 2.31 (2H, d, H_2-4), 2.04 (1H, m, H_a-12), 2.01 (1H, m, H-25), 1.88 (1H, m, H_a-7), 1.86 (1H, m, H_a-15), 1.82 (2H, m, H_2-2), 1.58 (1H, m, H_a-16), 1.51 (1H, m, H-8), 1.49 (2H, m, H_2-11), 1.45 (1H, m, H-20), 1.28 (1H, m, H_b-15), 1.19 (1H, m, H_b-12), 1.16 (1H, m, H-17), 1.07 (1H, m, H_b-16), 1.06 (2H, m, H_2-1), 1.03 (1H, m, H-14), 1.02 (1H, m, H_b-7), 1.01 (3H, s, H_3-19), 0.99 (3H, d, 6, H_3-21), 0.95 (1H, m, H-9), 0.89 (3H, dd, 7, 8, H_3-26), 0.88 (3H, dd, 7, 8, H_3-27), 0.69 (3H, s, H_3-18); ^{13}C NMR ($CDCl_3$, 125 MHz) δ (multiplicity, assignment) 140.9 (C, C-5), 137.4 (CH, C-23), 137.3 (CH, C-28), 121.9 (2 × CH, C-6, -22), 116.6 (CH_2, C-29), 89.4 (C, C-24**)**, 72.1 (CH, C-3), 57.0 (CH, C-14), 56.1 (CH, C-17), 50.3 (CH, C-9), 42.6 (C, C-13), 42.5 (CH_2, C-4), 37.5 (CH_2, C-7), 36.7 (C, C-10), 36.4 (CH, C-20), 32.1 (2 × CH, C-8, −25), 31.9 (CH_2, C-2), 30.0 (CH_2, C-12), 28.8 (CH_2, C-1), 28.5 (CH_2, C-15), 24.5 (CH_2, C-16), 21.3 (CH_2, C-11), 19.6 (CH_3, C-19), 19.1 (CH_3, C-21), 17.9 (CH_3, C-27), 16.9 (CH_3, C-26), 12.1 (CH_3, C-18); EIMS *m/z* 426.4 ([$M]^+$), 271.2.

Photochemical Dimerization Study. Acetoxyfimbrolide (**5**, 1 mg) dissolved in chloroform (1 mL) was placed in sunlight for 24 h. When no change was observed by ^1H NMR spectroscopy, the sample was exposed to a 250 W mercury lamp (Hanovia type L) at intervals of 6 h for 24 h. The ^1H NMR spectrum was checked after every 6 h of exposure. No significant changes were observed in the ^1H NMR spectrum of the starting material.

Antibiotic Assays. In vitro antimicrobial activities against methicillin-sensitive (MSSA, strain 375) and -resistant (MRSA, strain 310) *Staphylococcus aureus*, vancomycin-resistant *Enterococci faecium* (VREF, strain 379), *E. coli* (strain 442), *E. coli imp* (strain 389, a mutant strain with increased permeability to large molecular weight compounds),[22] and *Candida albicans* (strain 54) were determined by agar diffusion method. Media used were Difco nutrient agar (pH 6.8) for *S. aureus*, LB (Luria-Bertani) agar for *E. faecium* and *E. coli*, and YM agar for *C. albicans*. Assay plates (9 in. × 9 in. Sumilon) were prepared by pouring 125 mL volume of agar medium (tempered at 50 °C) inoculated with an overnight broth culture of the test organisms (adjusted to approximately 10^6 cells per mL). Sample concentrations of 200 μg in 10 μL aliquots were spotted onto agar surface, and the plates were incubated at 37 °C for 18 h. The zone of growth inhibition was measured using a hand-held digital caliper.

Field Bioassay Procedures:[16] **Artificial Food Preparation.** Artificial foods consisted of 2% alginate containing 5% *Cladophora repens* (a readily consumed alga) powder.[40] Pure compounds were dissolved in a minimum volume of appropriate solvent carrier and dried onto the algal powder under reduced pressure.[41] Controls were prepared with an equal volume of solvent alone. The algal powders were treated with cold alginate solution, mixed thoroughly with the food stimulant, and then polymerized using cold 1 M $CaCl_2$. Artificial food circles, approximately 2 mm thick, were cut into smaller circular disks with cork borers for use in the amphipod assays. Remnant artificial food was then cut into cubes for use in sea star bioassays.

Sea Star Bioassays.[16,40] *Odontaster validus* were placed in a 2 m diameter circular holding tank (3200 L) equipped with running ambient seawater, where they acclimated for several days before use. Individual sea stars at the surface were offered a small piece of artificial food pellet (approximately 4 × 4 × 2 mm) containing either extract or solvent control dried onto *Cladophora repens* powder (as above). The artificial food pellet was placed within the ambulacral groove of a single, outstretched arm, equidistant between the arm tip and oral opening ($n = 10-14$). Acceptance was recorded when the sea star moved the fragment or pellet to the oral opening. Rejection was recorded when the sea star dropped the fragment or pellet or moved it away from the oral opening out of the ambulacral groove or toward the arm tip. No sea star was used more than once for data that would be statistically compared, but individuals were randomly reused for different comparisons within this study and others being conducted simultaneously. Differences between fragments or pellets and corresponding controls were determined using a Fisher's exact test of independence.[42]

Amphipod Bioassays.[16] The herbivorous amphipod *Gondogeneia antarctica* was placed in 2 or 4 L plastic bottles with holes covered by plastic mesh to allow free exchange of seawater and held in flow through seawater aquaria. Unlike the sea star and fish bioassays, this was a feeding preference assay. Twenty randomly selected amphipods were placed into each of 10 250-mL sealed bottles floating in flow-through seawater aquaria with one artificial food pellet containing extract dried onto an algal powder disk and one artificial food pellet containing only solvent-control algal powder in each bottle. Identical disks that were pairs of the disks available to the amphipods (cut from spots immediately adjacent to them in the polymerized alginate-powder mix) were placed into identical bottles but without amphipods. Thus, each amphipod assay bottle was paired with a nonamphipod control bottle. Feeding preference was determined by calculating wet mass change between the paired extract and control disks in the two bottles over the course of the experiment (usually 8−12 h). Significance of differences between the changes in the 10 paired controls and 10 paired extract treatments was compared by a Wilcoxon signed ranks test using SPSS software (SPSS Inc.).

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Supporting Information Available: ^{1}H, ^{13}C, COSY, HMQC, and HMBC NMR spectra and mass spectra for new compounds **1**, **2**, **3**, **9**, and **12**; DEPT spectra for compounds **1**, **3**, **12**, and **14**. This material is available free of charge via the Internet at http://pubs.acs.org.

References and Notes

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