Metabolites of Three Marine Sponges of the Genus *Plakortis*

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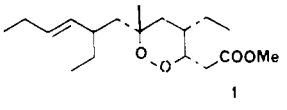
One sample of *Plakortis halichondrioides* contained the cyclic peroxides 3-epiplakortin (**9**) and 9,10-dihydro-3-epiplakortin (**10**). A second sample of *P. halichondrioides* that had been stored in ethanol gave an α,β-unsaturated ester **16** as the major secondary metabolite. A portion of the same sponge that had been frozen and then lyophilized contained the ester **16** and the lactone **19** together with the two peroxides **20** and **21** having a different, but closely related, carbon skeleton. A sample identified as *Plakortis* sp. contained two unstable peroxides (**26** and **27**) and a related aromatic hydrocarbon (**25**). All structures were elucidated by interpretation of spectral data and limited chemical-degradation reactions. The chemotaxonomic implications of these results are discussed.

Our studies of the metabolites of Caribbean sponges of the genus *Plakortis* have resulted in the isolation and identification of a number of cyclic peroxides and related metabolites. In 1978, we reported the isolation and identification of plakortin (**1**) and a related ketone **2** from *Plakortis halichondrioides*.[1] During a subsequent research cruise to Lighthouse and Glover Reefs, Belize, we collected six samples of sponges that visually resembled a preserved specimen of *P. halichondrioides*. These samples could be differentiated in the field by their texture or patterns of growth. One sample (77-098),[2] subsequently identified as *Chondrosia collectrix*, contained the cyclic peroxides **3** and **4**.[3] However, a portion of the same sample of *C. collectrix* that had been stored in ethanol prior to examination contained predominantly the hemiketal **5** and the diol **6**. The remaining five samples were all identified as *P. halichondrioides* or *Plakortis* sp.



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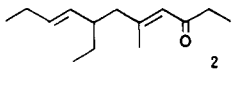

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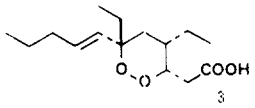

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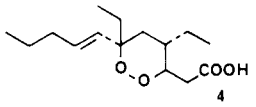

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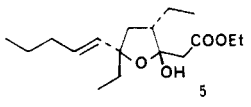

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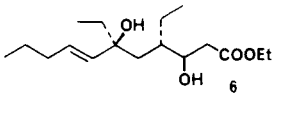

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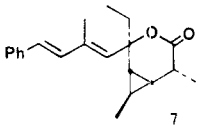

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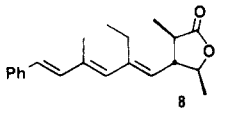

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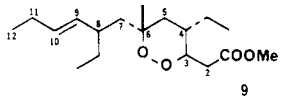
One sample (77-100) of *P. halichondrioides* contained plakortin (**1**) as the major secondary metabolite. A second sample (77-097) of *P. halichondrioides* did not contain any peroxides or related metabolites but was the source of an interesting group of aromatic compounds, exemplified by the lactones **7** and **8**.[4] We now report the structural elucidation of the metabolites of the three remaining *Plakortis* samples.

The ether-soluble material from an ethanol extract of *P. halichondrioides* (77-084) was chromatographed on Florisil to obtain a 1:1 mixture (0.22% dry weight) of 3-epiplakortin (**9**) and 9,10-dihydro-3-epiplakortin (**10**). Pure samples of the two peroxides were obtained by LC on μPorasil, using 3% ether in hexane as eluant. 3-Epiplakortin (**9**) had the molecular formula $C_{18}H_{32}O_4$ and was thus isomeric with plakortin (**1**). The spectral data suggested the epimeric relationship between 3-epiplakortin (**9**) and plakortin (**1**). In particular, the ^{1}H NMR spectra were almost identical, with the exception of the signals for the protons at C-2 and C-3. We were able to show that plakortin (**1**) and 3-epiplakortin (**9**) had the same carbon skeleton and arrangement of functional groups by chemical degradation of 3-epiplakortin (**9**) using a reaction sequence previously employed in the structural elucidation of plakortin (**1**).[1] Ozonolysis of 3-epiplakortin (**9**) followed by oxidation of the ozonide with Jones' reagent and methylation of the resulting acid with diazomethane gave the diester **11** that had lost a three-carbon fragment. Hydrogenation of the diester **11**, followed by acetylation of the product with acetic anhydride in pyridine, produced the expected γ-lactone **12** (1765, 1740 cm^{-1}).[5]



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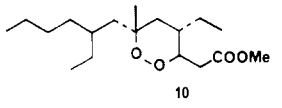

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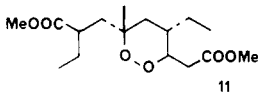

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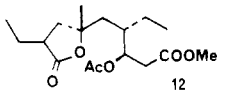

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The epimeric relationship between 3-epiplakortin (**9**) and plakortin (**1**) was assigned on the basis of a comparison of the ^{1}H NMR spectra.[6] In the spectrum of 3-epiplakortin, the C-3 proton signal at δ 4.16 (m, 1 H, J = 9, 9, 3.5 Hz) was coupled to two C-2 proton signals at δ 2.66 (dd, 1 H, J = 15.5, 3.5 Hz) and 2.38 (dd, 1 H, J = 15.5, 9 Hz). The remaining coupling constant of 9 Hz was assigned to coupling between the proton at C-3 and a single proton at C-4. When contrasted with the corresponding coupling

(1) Higgs, M. D.; Faulkner, D. J. *J. Org. Chem.* **1978**, *43*, 3454.
(2) For convenience, samples have been distinguished by their collection numbers.
(3) Stierle, D. B.; Faulkner, D. J. *J. Org. Chem.* **1979**, *44*, 964.
(4) Ravi, B. N.; Armstrong, R. W.; Faulkner, D. J. *J. Org. Chem.* **1979**, *44*, 3109.
(5) Comparison of the spectral data for diester **11** and γ-lactone **12** with the spectral data for diester **6** and γ-lactone **8** in ref 1 revealed small differences that could be rationalized on the basis of the epimeric relationships.
(6) The important regions of the ^{1}H NMR spectra of plakortin (**1**) and 3-epiplakortin (**9**) were shown as Figure 1 in ref 3.

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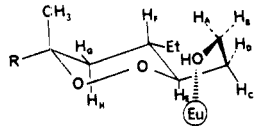
Table I. Chemical Shifts (δ), Eu(fod)$_3$-Induced Chemical Shifts (Δδ), and Calculated and Measured (Using Dreiding Models) Eu-Hydrogen Distances for Selected Hydrogen Atoms in the ^{1}H NMR Spectrum of Alcohol 13

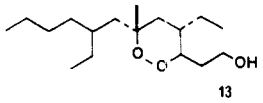


	δ	Δδ, ppm	θ	r_{calcd}, Å	r_{meas}, Å
H_A	3.76	*a*			
H_B	3.76	*a*			
H_C	~1.8	9.55	18	4.6	4.6
H_D	~2.1	7.04	15	5.2	5.3
H_E	3.84	9.22	20	4.6	4.6
H_F	~1.7	4.62	20	5.8	5.7
H_G	~1.7	2.45	28	6.7	6.6
H_H	~1.2	3.21	28	6.1	6.1
CH_3-ax	1.34	2.51	~38[b]	5.7	5.4[b]
CH_3-eq			~45[b]	4.8	6.0[b]

[a] Variation of chemical shift with added Eu(fod)$_3$ was not linear. [b] Measured for an average position of the methyl protons.

constant of 6 Hz in plakortin (**1**), the magnitude of the coupling constant requires an axial conformation for the protons at C-3 and C-4.

9,10-Dihydro-3-epiplakortin (**10**) had the molecular formula $C_{18}H_{34}O_4$. The ^{1}H NMR spectrum of 9,10-dihydro-3-epiplakortin (**10**) was almost identical with that of 3-epiplakortin (**9**), except that no olefin proton signals were observed. In order to confirm the structure, a 1:1 mixture of 3-epiplakortin (**9**) and 9,10-dihydro-3-epiplakortin (**10**) was reduced by hydrogenation over 10% palladium on charcoal catalyst to obtain a single diol (**14**) that was acetylated with acetic anhydride in pyridine to obtain a single monoacetate (**15**) in 92% yield.



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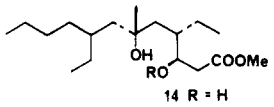
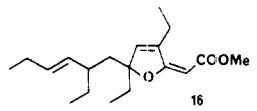


14 R = H

15 R = Ac

In order to confirm the structural assignment for 3-epiplakortin (**9**) and 9,10-dihydro-3-epiplakortin (**10**), a ^{1}H NMR lanthanide-induced-shift study was carried out on the alcohol **13** produced by reduction of 9,10-dihydro-3-epiplakortin (**10**) with lithium tri-*tert*-butoxyaluminum hydride. The LIS study, summarized in Table I, confirmed the relative stereochemistry of the groups about the peroxide ring. As in the case of plakortin (**1**), we could not assign the relative stereochemistry at C-8.

A second sample of *P. halichondrioides* (77-096) was stored both in ethanol solvent and as a frozen sample. The ether-soluble material from the sample stored, homogenized, and extracted with ethanol was chromatographed to obtain an ester **16** (1.5% dry weight). The ester **16** had the molecular formula $C_{19}H_{30}O_3$. The infrared spectrum contained a complex group of bands at 1710, 1690, and 1640 cm^{-1} that were reminiscent of the corresponding infrared bands for the unsaturated ester **17**, obtained by



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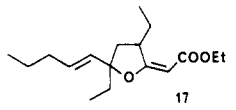

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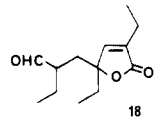
dehydration of hemiacetal **5**. The ultraviolet absorption at 282 nm (ε 8300) suggested that there was a second olefinic bond conjugated to the ester functionality. The ^{13}C NMR spectrum contained two unusual olefinic carbon signals at δ 84.4 (d) and 166.0 (s) that were similar to the C-2 (δ 87.7) and C-3 (δ 165.4) signals in ester **17**. The ^{13}C NMR spectrum also contained signals for an ester carbonyl at δ 171.5 (s), four olefinic carbons at δ 139.9 (d), 139.7 (s), 134.5 (d), and 131.9 (d), a fully-substituted oxygen-bearing carbon at δ 97.2 (s), and eleven aliphatic carbon atoms. The ^{1}H NMR spectrum contained a methyl ester signal at δ 3.69, a sharp singlet at δ 4.81, due to the proton at C-2, and a broad singlet at δ 6.18, due to the proton at C-5, that showed long-range coupling ($J \simeq 1$ Hz) to a methylene quartet at δ 2.15 (br q, 2 H, $J = 7$ Hz) in turn coupled to a methyl triplet at δ 1.14 (t, 3 H, $J = 7$ Hz). Since the ^{13}C NMR spectrum contained no singlets in the aliphatic region, the fully substituted oxygen-bearing carbon must be at C-7, thus defining the furanoid portion of the molecule.

Ozonolysis of the ester **16**, followed by treatment of the resulting ozonide with dimethyl sulfide, gave the aldehyde **18**. The molecular formula $C_{13}H_{20}O_3$ could be rationalized by assuming the ozonolysis of the 2,3-olefinic bond and the additional loss of a three-carbon unit by ozonolysis of the disubstituted olefinic bond in the side chain. The ^{1}H NMR spectrum of the aldehyde **18** contained three methyl triplets at δ 0.85, 0.94, and 1.12, indicating the presence of three "ethyl" residues, an olefinic proton signal at δ 6.73 (t, 1 H, $J = 1$ Hz) assigned to the β proton in an α,β-unsaturated γ-lactone, and an aldehyde proton signal at δ 9.53 (d, 1 H, $J = 2$ Hz) coupled to a single proton signal at δ 2.13 (m, 1 H, $J = 7, 7, 7, 3, 2$ Hz). Since the proton on the carbon adjacent to the aldehyde was coupled to four other protons, the aldehyde group must be at C-6 in aldehyde **18**. Thus, the ester **16** must have a 9,10-olefinic bond and ethyl groups at C-6 and C-8. In the ^{1}H NMR spectrum of ester **16**, a 15-Hz coupling constant between the olefinic protons at δ 5.03 (dd, 1 H, $J = 15, 7$ Hz) and 5.24 (dt, 1 H, $J = 15, 7, 7$ Hz) indicated 9*E* geometry. The chemical shift of the C-2 proton (δ 4.81) was almost the same as that of the C-2 proton (δ 4.74) in ester 18[3] and was close to the calculated value (δ 4.85) for the 2*E* geometry.

The frozen sample of *P. halichondrioides* (77-096) was lyophilized and extracted with dichloromethane. The extract was chromatographed on silica gel to obtain the ester **16** (3.0% dry weight) as the major product. A less polar fraction was separated by LC on μPorasil to obtain the γ-lactone **19** and the peroxide esters **20** and **21**. A more polar fraction contained a mixture of acids that was esterified with ethereal diazomethane solution and separated by LC on μPorasil to obtain the peroxide ester **20**.



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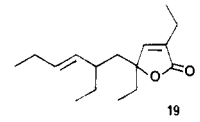

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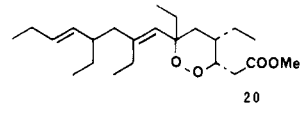

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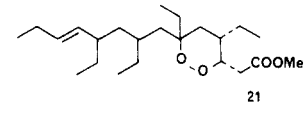

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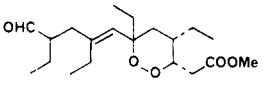
The γ-lactone **19** had the molecular formula $C_{16}H_{26}O_2$. The band at 1760 cm^{-1} in the infrared spectrum suggested the presence of an α,β-unsaturated γ-lactone ring. Comparison of the ^{1}H NMR spectrum with that of ester **16** showed the spectra to be quite similar except that the lactone **19** lacked the methyl ester signal at δ 3.69 and the C-2 proton signal at δ 4.81 and the vinyl proton in the ring had shifted from δ 6.18 in the ester to δ 6.82 in the γ-lactone. Ozonolysis of the γ-lactone **19** also gave the al-

dehyde **18**. We had expected that the peroxides **20** and **21** would have the same carbon skeleton as the ester **16**, but this was not the case. The ^{13}C NMR spectrum of peroxide **20** contained 23 signals while the highest peak in the mass spectrum was at m/e 351, resulting from the loss of ethyl from the molecular formula $C_{23}H_{40}O_4$. The ^{13}C NMR spectrum of peroxide **20** contained signals at δ 171.8 (s) and 51.2 (q) for the carbomethoxy group, at 83.9 (s) and 79.1 (d) for the carbon atoms flanking the peroxide bond, and at 142.7 (s), 133.6 (d), 132.0 (d), and 127.7 (d) assigned to a disubstituted olefin and a trisubstituted olefin. The five remaining methyl signals at δ 7.9, 11.0, 11.9, 12.4, and 14.2 in the ^{13}C NMR spectrum corresponded to five methyl triplets at δ 0.83, 0.85, 0.92, 0.97, and 0.99 in the ^1H NMR spectrum, indicating that all the remaining methyl groups were adjacent to methylene groups. The ^1H NMR spectrum contained signals that were typical of a cyclic peroxide having the plakortin (**1**) ring system and stereochemistry. In particular, the signals at δ 3.70 (s, 3 H), 3.08 (dd, 1 H, J = 16, 9.5 Hz) and 2.41 (dd, 1 H, J = 16, 3.5 Hz), both coupled to a signal at δ 4.49 (m, 1 H, J = 9.5, 6, 3.5 Hz), and 1.69 (dd, 1 H, J = 14, 4 Hz, C-5eq) defined this ring system. The presence of a ^{13}C NMR signal at δ 7.9 (q) together with the facile loss of ethyl in the mass spectrum suggested an ethyl side chain at C-6. The ^1H NMR spectrum contained a signal at δ 5.17 (s, 1 H); the trisubstituted olefinic bond must therefore be adjacent to the only tetrasubstituted carbon atom in the molecule. The ^1H NMR signals at δ 5.39 (dt, 1 H, J = 15, 6, 6 Hz) and 5.13 (dd, 1 H, J = 15, 9 Hz) indicated that the disubstituted olefinic bond was in a location similar to that in plakortin (**1**) and other molecules having a 5-ethylhex-3-ene[4] side chain. Ozonolysis of the ester **20** followed by reduction of the ozonide with dimethyl sulfide gave an aldehyde **22**, resulting from the loss of a three-



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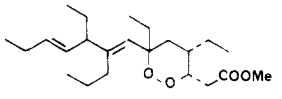
carbon fragment. The multiplicity of the aldehyde signal at δ 9.57 (d, 1 H, J = 2.5 Hz) in the ^1H NMR spectrum required the presence of a side chain at C-10. The ^1H NMR spectrum still contained a singlet at δ 5.21 due to the trisubstituted olefin that was too sterically hindered to react with ozone. Although we could not prove conclusively that the side chain shown for the ester was correct, it is strongly favored from biosynthetic arguments. Furthermore, calculations[7] of the ^{13}C NMR signals expected for structure **20** and two alternative structures **23** and **24** confirmed the structure of the side chain. We could



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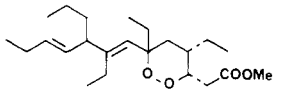

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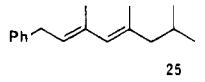
not, however, determine the stereochemistry of the side chain, which has been drawn in its most convenient form.

The minor peroxide **21** had the molecular formula $C_{23}H_{43}O_4$. The ^1H NMR spectrum of peroxide **21** was almost identical with that of peroxide **20**, except that it lacked the signal at δ 5.17 (s, 1 H) prominent in the spectrum of peroxide **20**. We therefore assumed that peroxide **21** was the 6,7-dihydro derivative of peroxide **20**.

The final sample of *Plakortis* sp. (77-044) was difficult to study because the metabolites decomposed on standing. The ethyl acetate soluble material from the ethanol extracts of *Plakortis* sp. was chromatographed on silica gel to obtain a hydrocarbon **25** (0.03% dry weight), a lactone **26** (0.09% dry weight), and an acid **27** (0.09% dry weight).



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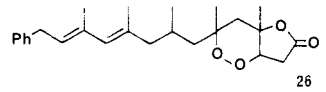

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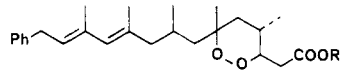
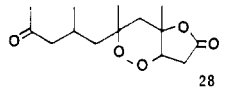


27 R = H

29 R = Me



28

The hydrocarbon **25** had the molecular formula $C_{17}H_{24}$. The structural assignment was based on interpretation of the ^1H NMR spectral data. The aromatic proton signal at δ 7.20 (m, 5 H) indicated a monosubstituted aromatic ring. The signal at δ 3.44 (d, 2 H, J = 7 Hz), assigned to a bisallylic methylene, was coupled to an olefinic signal at δ 5.43 (br t, 1 H, J = 7 Hz). The chemical shift of the remaining olefinic proton signal at δ 5.62 (br s, 1 H) suggested the presence of a conjugated diene system with methyl groups [δ 1.72 (br s, 3 H) and 1.81 (br s, 3 H)] at alternating carbon atoms. An allylic methylene proton signal at δ 1.85 (d, 2 H, J = 7 Hz) and a signal for two methyl groups at 0.83 (d, 6 H, J = 7 Hz) were both coupled to the remaining proton signal at δ ~1.76 (m, 1 H).

The lactone **26** had the molecular formula $C_{25}H_{34}O_4$. The infrared spectrum had a strong γ-lactone band at 1795 cm^{-1} but did not contain other carbonyl or hydroxyl bands. The ^{13}C NMR spectrum contained a lactone carbonyl signal at δ 173.9, ten aromatic or olefinic carbon signals, three signals at δ 82.5, 81.3, and 80.4 assigned to carbon bearing oxygen and 11 other aliphatic carbon signals. Part of the ^1H NMR spectrum closely resembled that of the hydrocarbon **25**. The signals at δ 7.20 (m, 5 H), 3.44 (d, 2 H, J = 7 Hz), 5.42 (br t, 1 H, J = 7 Hz), 5.63 (br s, 1 H), 1.81 (br s, 3 H), and 1.72 (br s, 3 H) could be assigned to a 1-phenyl-3,5-dimethyl-2,4-pentadienyl moiety. At the lactone end of the molecule, the C-2 protons gave signals at δ 2.58 (d, 1 H, J = 17 Hz) and 2.90 (dd, 1 H, J = 17, 6 Hz), the latter being coupled to an α-peroxy proton signal at δ 4.45 (d, 1 H, J = 6 Hz). The adjacent carbon atom (C-4) bears the oxygen of the γ-lactone and a methyl group [δ 1.25 (s, 3 H)]. The protons of the isolated methylene group at C-5 were observed at δ 2.21 (d, 1 H, J = 15 Hz) and 1.70 (d, 1 H, J = 15 Hz) while the methyl at C-6 gave a characteristic signal at 1.36 (s, 3 H). The remaining observable signal at δ 0.87 (d, 3 H, J = 7 Hz) was assigned to a methyl group at C-8.

Ozonolysis of the lactone **26** followed by oxidation of the ozonide with Jones' reagent gave a methyl ketone **28** having the expected molecular formula $C_{14}H_{22}O_5$. Analyses of the ^1H NMR spectrum of the ketone **28** confirmed the assignment of the methyl group at C-8. Irradiation at δ 2.21 caused the methyl signal at δ 0.95 (d, 3 H, J = 7 Hz) to become a singlet, the C-7 methylene proton signals at δ 1.42 (dd, 1 H, J = 15, 3 Hz) and 1.59 (dd, 1 H, J = 15, 9 Hz) to become an AB quartet and the C-9 methylene proton signals at δ 2.35 (d,[8] 1 H, J = 6 Hz) and 2.39 (d,[8] 1 H, J = 4 Hz) to become a doublet.[8] Thus, although the

(7) Wehrli, F. W.; Wirthlin, T. "Interpretation of Carbon-13 NMR Spectra"; Heyden: London, 1976; p 41.

(8) Only the central lines of the AB portion of the ABX coupling pattern could be observed; thus, J_{AX} = 6, J_{BX} = 4 Hz, and J_{AB} could not be measured.

signal for the proton at C-8 could not be observed, its position at δ 2.21 was implied by the decoupling data. We were unable to perform further experiments to determine the stereochemistry of the lactone **27** because the material had decomposed.

The acid **27** was even more unstable than the lactone **26** and was therefore treated with diazomethane to obtain the corresponding methyl ester **29** that had the molecular formula $C_{26}H_{38}O_4$. The ^1H NMR signals at δ 2.36 (dd, 1 H, J = 16, 8 Hz), 2.67 (dd, 1 H, J = 16, 3 Hz), 3.66 (s, 3 H), and 4.10 (dt, 1 H, J = 8, 8, 3 Hz) clearly indicated that the ester **29** contained a cyclic peroxide with the 3-epiplakortin stereochemistry. The signals at δ 7.20 (m, 5 H), 5.63 (br s, 1 H), 5.43 (br t, 1 H, J = 7 Hz), 3.44 (d, 2 H, J = 7 Hz), 1.70 (br s, 3 H), and 1.79 (br s, 3 H) were assigned to the 1-phenyl-3,5-dimethyl-2,4-pentadienyl moiety. There remained three observable signals at δ 1.35 (s, 3 H), 0.91 (d, 3 H), and 0.89 (d, 3 H) that were assigned to the methyl groups at C-6, C-4, and C-8. The ester **29** decomposed during an attempt to measure the ^{13}C NMR spectrum.

Our studies of the various samples of *Plakortis halichondrioides* and *Plakortis* sp. have resulted in the isolation of a variety of cyclic peroxides and related metabolites. All appeared to be derived biosynthetically from simple carboxylic acids via the polyketide pathway. Thus the variation in substituents at alternating carbon atoms (C-4, C-6, etc.), along the basic carboxylic acid chain, reflected the various carboxylic acids that had been incorporated. The aromatic compounds (**7**, **8**, **25**, **26**, **27**) required a biosynthesis based on the addition of various carboxylic acids to phenylacetic acid (or an equivalent aromatic precursor) and were therefore not as unusual as they first appeared. Cyclic peroxides have become increasingly familiar as sponge metabolites.[9,10] However, the isolation of metabolites having different carbon skeletons (cf., ester **16** and peroxide **20**) in the same sponge was quite unexpected. This could indicate that the sample was not homogeneous, although each of the samples investigated was collected from a single locality (often less than 1 m^2). On the basis of this study, we would predict that other samples of *Plakortis* will contain different metabolites, although each *Plakortis* metabolite should have a basic "polyketide" carbon skeleton.

Experimental Section[11]

Collection and Extraction Procedures. All sponges were collected by hand, using SCUBA (−15 to −25 m) at Lighthouse Reef, Belize. A portion of each sample was stored in ethanol (2 L), while the remainder of each sample was stored at −20 °C until required. Samples stored in ethanol were homogenized and Soxhlet extracted with ethanol. Each ethanol extract was evaporated in vacuo and the residue partitioned between water and an organic solvent. The organic extract was dried over sodium sulfate and the solvent evaporated to obtain a gum. *P. halichondrioides* [77-084] (220 g dry weight) gave 6.6 g of ether-soluble material. *P. halichondrioides* [77-096] (80 g dry weight) gave 3.0 g of ether-soluble material. *Plakortis* sp. [77-044] (125 g dry weight) gave 1.9 g of ethyl acetate soluble material.

The frozen sample of *P. halichondrioides* [77-096] was lyophilized to obtain dry sponge (200 g). The dried sponge was Soxhlet extracted with dichloromethane. The dichloromethane was evaporated to obtain a brown gum (12.6 g).

Chromatography [77-084]. The crude extract (4.5 g) was applied to a column (55 × 3 cm) of Florisil, and material was eluted with solvent mixtures of increasing polarity from hexane through ether to ethyl acetate. Elution with 5% ether in hexane gave a 1:1 mixture (325 mg, 0.22% dry weight) of 3-epiplakortin (**9**) and 9,10-dihydro-3-epiplakortin (**10**). The mixture was separated as required by LC on μPorasil, using 3% ether in hexane as eluant.

3-Epiplakortin (9): $[\alpha]_D$ +22.1° (*c* 2.5, CCl_4); IR (CCl_4) 1740, 1450, 970 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.80 (t, 3 H, J = 7 Hz), 0.88 (t, 3 H, J = 7 Hz), 0.97 (t, 3 H, J = 7 Hz), 1.32 (s, 3 H), 2.02 (m, 2 H), 2.38 (dd, 1 H, J = 15.5, 9 Hz), 2.66 (dd, 1 H, J = 15.5, 3.5 Hz), 3.68 (s, 3 H), 4.16 (m, 1 H, J = 9, 9, 3.5 Hz), 5.10 (dd, 1 H, J = 16, 7 Hz), 5.36 (dt, 1 H, J = 16, 7 Hz); ^{13}C NMR (C_6D_6) δ 170.7, 135.0, 131.6, 82.4, 81.5, 51.3, 46.6, 40.4, 40.1, 36.9, 36.6, 30.0, 25.9, 24.4, 21.1, 14.1, 11.7, 10.6; high-resolution mass spectrum, obsd m/e 312.2304, $C_{18}H_{32}O_4$ requires m/e 312.2300.

9,10-Dihydro-3-epiplakortin (10): $[\alpha]_D$ +11.9° (*c* 2.2, CCl_4); IR (CCl_4) 1740, 1450, 970 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.82 (t, 3 H, J = 7 Hz), 0.85 (t, 3 H, J = 7 Hz), 0.90 (t, 3 H, J = 7 Hz), 1.32 (s, 3 H), 1.69 (m, 2 H), 2.38 (dd, 1 H, J = 15.5, 9 Hz), 2.66 (dd, 1 H, J = 15.5, 3.5 Hz), 3.68 (s, 3 H), 4.14 (dt, 1 H, J = 9, 9, 3.5 Hz); ^{13}C NMR (C_6D_6) δ 169.7, 82.2, 82.0, 51.3, 45.3, 39.6, 39.3, 37.4, 37.3, 37.0, 36.6, 34.2, 27.5, 24.4, 21.1, 20.1, 14.6, 10.6; high-resolution mass spectrum, obsd m/e 282.2199, $C_{17}H_{30}O_3$ ($M^+ - CH_4O$) requires m/e 282.2195.

Chromatography [77-096]. The crude extract (3.0 g) was applied to a column (55 × 3 cm) of Florisil and material was eluted with solvents of increasing polarity from hexane through ether to ethyl acetate. The α,β-unsaturated ester **16** (1.9 g, 2.2% dry weight) was eluted with 20% ether in hexane.

α,β-Unsaturated ester 16: $[\alpha]_D$ +175° (*c* 1.4, CCl_4); UV (MeOH) 282 nm (ε 8300); IR (film) 1710, 1690, 1640, 1280, 1170, 980 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.77 (*t*, 3 H, J = 7 Hz), 0.78 (t, 3 H, J = 7 Hz), 0.95 (t, 3 H, J = 7 Hz), 1.14 (t, 3 H, J = 7 Hz), 2.15 (br q, 2 H, J = 7, 1 Hz), 3.69 (s, 3 H), 4.81 (s, 1 H), 5.03 (dd, 1 H, J = 15, 7 Hz), 5.24 (dt, 1 H, J = 15, 7, 7 Hz), 6.18 (br s, 1 H, $J \simeq 1$ Hz); ^{13}C NMR (C_6D_6) δ 171.5 (s), 166.0 (s), 139.9 (s), 139.7 (d), 134.5 (d), 131.9 (d), 97.2 (s), 84.4 (d), 50.1 (q), 43.6 (t), 39.9 (d), 32.4 (t), 29.6 (t), 25.9 (t), 18.7 (t), 14.1 (q), 11.9 (q), 11.5 (q), 7.9 (q); high-resolution mass spectrum, obsd m/e 306.2201, $C_{19}H_{30}O_3$ requires m/e 306.2195.

Chromatography [77-096, Lyophilized Sample]. A portion of the dichloromethane extract (2.5 g) was applied to a column (50 × 3 cm diameter) of Florisil and material was eluted with solvents of increasing polarity from hexane to ether. The α,β-unsaturated ester **16** (1.2 g, 3.0% dry weight) was eluted with 20% ether in hexane. The fraction eluted with 5% ether in hexane was rechromatographed by LC on μPorasil, using 3% ether in hexane as eluant, to obtain the lactone **19** (10 mg, 0.02% dry weight), the peroxide ester **20** (50 mg, 0.1% dry weight), and the peroxide ester **21** (30 mg, 0.06% dry weight). The fraction eluted with 50% ether in hexane contained a mixture of acids (200 mg, 0.4% dry weight) that were treated with ethereal diazomethane solution (slight excess) to obtain a mixture of methyl esters. The major product, the peroxide ester **20** (125 mg, 0.3% dry weight), was purified by LC on μPorasil.

γ-Lactone 19: IR (film) 1760 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.80 (t, 3 H, J = 7 Hz), 0.81 (t, 3 H, J = 7 Hz), 0.95 (t, 3 H, J = 7 Hz), 1.14 (t, 3 H, J = 7 Hz), 2.00 (m, 2 H), 2.31 (q, 2 H, J = 7 Hz), 5.02 (dd, 1 H, J = 16, 7 Hz), 5.35 (dt, 1 H, J = 16, 7, 7 Hz), 6.82 (t, 1 H, J = 1 Hz) or (br s, 1 H); mass spectrum, m/e 250.

Peroxide ester 20: $[\alpha]_D$ −224° (*c* 1.0, $CHCl_3$); IR (film) 1740, 1460, 950 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.83 (t, 3 H, J = 7 Hz), 0.85 (t, 3 H, J = 7 Hz), 0.92 (t, 3 H, J = 7 Hz), 0.97 (t, 3 H, J = 7 Hz), 0.99 (t, 3 H, J = 7 Hz), 2.41 (dd, 1 H, J = 16, 3 Hz), 3.08 (dd, 1 H, J = 16, 9 Hz), 3.70 (s, 3 H), 4.49 (m, 1 H, J = 9, 6, 3 Hz), 5.13 (dd, 1 H, J = 15, 9 Hz), 5.17 (s, 1 H), 5.39 (dt, 1 H, J = 15, 6, 6 Hz); ^{13}C NMR (C_6D_6) δ 171.8 (s), 142.7 (s), 133.6 (d), 132.0 (d), 127.7 (d), 83.9 (s), 79.1 (d), 51.2 (q), 43.0 (t, d), 36.3 (t), 35.7 (d), 33.4 (t), 31.6 (t), 28.2 (t), 26.0 (t), 25.2 (t), 23.0 (t), 14.2 (q), 12.4 (q), 11.9 (q), 11.0 (q), 7.9 (q); mass spectrum, m/e 351 (M − 29),

(9) Wells, R. J. *Tetrahedron Lett.* **1976**, 2637. Kashman, Y.; Rotem, M. *Ibid.* **1979**, 1707. Albericci, M.; Collart-Lempereur, M.; Braekman, J. C.; Daloze, D.; Tursch, B.; Declercq, J. P.; Germain, G.; Van Meerssche, M. *Ibid.* **1979**, 2698.

(10) Fattorusso, E.; Magno, S.; Santacroce, C.; Sica, D. *Gazz. Chim. Ital.* **1974**, *104*, 409. Sheikh, Y. M.; Djerassi, C. *Tetrahedron* **1974**, *30*, 4095. Andersen, R. J. Ph.D. Thesis, University of California, San Diego, 1975. In ref 1, last paragraph, we perpetuated the myth that photooxidation of ergosterol acetate gave a mixture of α and β peroxides. The minor peroxide has been identified as 9,11-dehydroergosterol peroxide. Fisch, M. H.; Ernst, R.; Flick, B. H.; Arditti, J.; Barton, D. H. R.; Magnus, P. D.; Menzies, I. D. *J. Chem. Soc., Chem. Commun.* **1973**, 530.

(11) For general information, see ref 4.

323 (M - 57), obsd m/e 323.2572, $C_{20}H_{35}O_3$ (M - C_2H_5 - CO) requires m/e 323.2586.

Peroxide ester 21: IR (film) 1740, 960 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.81 (t, 3 H, J = 7 Hz), 0.82 (t, 3 H, J = 7 Hz), 0.83 (t, 3 H, J = 7 Hz), 0.92 (t, 3 H, J = 7 Hz), 0.96 (t, 3 H, J = 7 Hz), 2.37 (dd, 1 H, J = 16, 3 Hz), 3.03 (dd, 1 H, J = 16, 9 Hz), 3.69 (s, 3 H), 4.49 (m, 1 H, J = 9, 6, 3 Hz), 5.07 (dd, 1 H, J = 16, 7 Hz), 5.39 (dt, 1 H, J = 16, 7, 7 Hz); mass spectrum, m/e 353 (M - 29).

Chromatography [77-044]. The crude extract (1.9 g) was applied to a column (50 × 3 cm diameter) of silica gel and fractions were eluted with solvent mixtures of increasing polarity from hexane through ether to ethyl acetate. The fractions eluted with 100% hexane contained hydrocarbon **25** (40 mg, 0.03% dry weight). Fractions eluted with 30% ether in hexane were further purified by LC on μPorasil, using 1:1 ether in hexane as eluant, to obtain the lactone **26** (100 mg, 0.09% dry weight). Elution with 100% ether gave the acid **27** (100 mg, 0.09% dry weight) that was treated with ethereal diazomethane solution to obtain the corresponding methyl ester **29**.

Hydrocarbon 25: IR (CCl_4) 2980, 1520, 980 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.83 (d, 6 H, J = 7 Hz), 1.72 (br s, 3 H), 1.81 (br s, 3 H), 1.85 (d, 2 H, J = 7 Hz), 3.44 (d, 2 H, J = 7 Hz), 5.43 (br t, 1 H, J = 7 Hz), 5.62 (br s, 1 H), 7.20 (m, 5 H); mass spectrum, m/e 228 ($C_{17}H_{24}$).

Lactone 26: IR (CCl_4) 1795, 1390, 1170 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.89 (d, 3 H, J = 7 Hz), 1.25 (s, 3 H), 1.36 (s, 3 H), 1.70 (d, 1 H, J = 15 Hz), 1.72 (br s, 3 H), 1.81 (br s, 3 H), 2.21 (d, 1 H, J = 15 Hz), 2.58 (d, 1 H, J = 17 Hz), 2.90 (dd, 1 H, J = 17, 6 Hz), 3.44 (d, 2 H, J = 7 Hz), 4.45 (d, 1 H, J = 6 Hz), 5.42 (br t, 1 H, J = 7 Hz), 5.63 (br s, 1 H), 7.20 (m, 5 H); ^{13}C NMR (acetone-d_6) 173.9, 141.6, 134.5, 133.7, 130.8, 128.5 (4 C), 127.7, 125.9, 82.5, 81.3, 80.4, 50.4, 44.2, 41.9, 34.4, 34.0, 27.1, 25.1, 24.6, 20.8, 17.4, 16.8; mass spectrum, m/e 398 ($C_{25}H_{34}O_4$).

Methyl ester 29: IR (CCl_4) 1745, 1435, 1180 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.87 (d, 3 H, J = 7 Hz), 0.89 (d, 3 H, J = 7 Hz), 1.35 (s, 3 H), 1.70 (br s, 3 H), 1.79 (br s, 3 H), 2.36 (dd, 1 H, J = 16, 8 Hz), 2.67 (dd, 1 H, J = 16, 3 Hz), 3.44 (d, 2 H, J = 7 Hz), 3.66 (s, 3 H), 4.08 (dt, 1 H, J = 8, 8, 3 Hz), 5.43 (br t, 1 H, J = 7 Hz), 5.63 (br s, 1 H), 7.20 (m, 5 H); mass spectrum, m/e 414 ($C_{26}H_{38}O_4$).

Ozonolysis of 3-Epiplakortin (9). A stream of ozone in oxygen was bubbled into a solution of 3-epiplakortin (15 mg, 0.05 mmol) in ether (5 mL) at -78 °C until a blue-colored solution resulted. Excess ozone was removed in a stream of nitrogen and the solvent was evaporated under reduced pressure. The residue was dissolved in acetone (5 mL) and Jones' reagent was added dropwise until an orange color remained. Excess reagent was destroyed with 2-propanol (1–2 drops) and the solution was filtered through silica gel (2 g) to remove the chromium salts. Evaporation of the solvent gave a residue that was treated with ethereal diazomethane solution to give the diester **11** (8 mg, 60% theoretical) as an oil: IR (CCl_4) 1740 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.86 (t, 3 H, J = 7 Hz), 0.91 (t, 3 H, J = 7 Hz), 1.32 (s, 3 H), 2.02 (m, 2 H), 2.37 (dd, 1 H, J = 15.5, 9 Hz), 2.68 (dd, 1 H, J = 15.5, 3.5 Hz), 3.68 (s, 3 H), 3.70 (s, 3 H), 4.15 (dt, 1 H, J = 9, 9, 3.5 Hz).

γ-Lactone 12. A solution of the ester **11** (8 mg, 0.03 mmol) containing 10% palladium on charcoal catalyst (2 mg) was stirred under an atmosphere of hydrogen for 10 h. The catalyst was removed by filtration and the solvent evaporated under vacuum to obtain an oil. The oil was dissolved in pyridine (1 mL) and acetic anhydride (0.5 mL) and the solution was allowed to stand at 20 °C overnight. The solvents were evaporated under vacuum and the residue was partitioned between ether and water. The ether layer was dried over sodium sulfate and the solvent evaporated to yield the γ-lactone **12** (7 mg, 84% theoretical): IR (CCl_4) 1765, 1740 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.97 (t, 3 H, J = 7 Hz), 1.01 (t, 3 H, J = 7 Hz), 1.49 (s, 3 H), 1.95 (m, 1 H), 2.02 (s, 3 H), 2.36 (dd, 1 H, J = 14, 9 Hz), 2.54 (m, 2 H), 2.70 (m, 1 H), 3.68 (s, 3 H), 5.41 (m, 1 H); high-resolution mass spectrum, obsd m/e 328.1885, $C_{17}H_{28}O_6$ requires m/e 328.1886.

Hydrogenation of a 1:1 Mixture of 3-Epiplakortin (9) and 9,10-Dihydro-3-epiplakortin (10). A solution of a 1:1 mixture of 3-epiplakortin (**9**) and 9,10-dihydro-3-epiplakortin (**10**) (20 mg, 0.03 mmol) in ether (10 mL) containing 10% palladium on charcoal catalyst (2 mg) was stirred under hydrogen for 4 h. The reaction mixture was treated as described in the previous experiment to obtain a single diol **14** that was acetylated to give a single monoacetate (**15**) (21 mg, 92% theoretical): IR (CCl_4) 3300, 1740 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.88 (t, 3 H, J = 7 Hz), 0.92 (t, 3 H, J = 7 Hz), 0.95 (t, 3 H, J = 7 Hz), 1.21 (s, 3 H), 2.04 (s, 3 H), 2.60 (m, 2 H), 3.68 (s, 3 H), 5.46 (m, 1 H).

Reduction of 9,10-Dihydro-3-epiplakortin (10) with Lithium Tri-*tert*-butoxyaluminum Hydride. Lithium tri-*tert*-butoxyaluminum hydride (50 mg, 0.2 mmol) was added to a solution of 9,10-dihydro-3-epiplakortin (**10**) (25 mg, 0.03 mmol) in dry ether (10 mL) and the solution was boiled under reflux for 1.5 h. The excess reagent was destroyed by addition of water and the reaction product was partitioned between ether and dilute hydrochloric acid. The ether extract was dried over anhydrous sodium sulfate and the solvent evaporated to give a colorless oil. The oil was purified by LC on μPorasil, using 40% ether in hexane as eluant, to obtain the alcohol **13** (20 mg, 88% theoretical): IR (CCl_4) 3300 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.84 (t, 3 H, J = 7 Hz), 0.89 (t, 6 H, J = 7 Hz), 1.35 (s, 3 H), 3.78 (t, 2 H, J = 7 Hz), 3.87 (td, 1 H, J = 9, 9, 3.5 Hz).

Lanthanide-Induced Shift Experiment. A solution of the alcohol **13** (7 mg) in deuteriochloroform (500 μL) was prepared. 220-MHz NMR spectra were recorded after each addition (5 μL) of a solution of $Eu(fod)_3$ (32 mg) in deuteriochloroform (65 μL). The induced shifts for each proton signal were calculated from a least-squares plot of chemical shift vs. quantity of reagent added. The induced shifts are summarized in Table I. Further details of the analytical method employed are given in ref 4.

Ozonolysis of Ester 16. A stream of ozone in oxygen was bubbled through a solution of the ester **16** (31 mg, 0.1 mmol) in ethyl acetate (10 mL) at -78 °C until a blue-colored solution resulted. Excess ozone was removed in a stream of nitrogen, dimethyl sulfide (2 drops) was added and the solution was stirred at room temperature for 2 h. Evaporation of the solvents, followed by removal of volatile products under high vacuum, gave the aldehyde **18** (20 mg, 90% theoretical), which was purified by chromatography on a silica gel plate using ether as eluant: UV (MeOH) 223 nm (ε 10 000); IR (CCl_4) 1760, 1730 cm^{-1}; ^1H NMR ($CDCl_3$) 0.85 (t, 3 H, J = 7 Hz), 0.94 (t, 3 H, J = 7 Hz), 1.12 (t, 3 H, J = 7 Hz), 2.13 (m, 1 H, J = 7, 7, 7, 3, 2 Hz), 2.29 (m, 4 H), 6.73 (t, 1 H, J = 1 Hz), 9.53 (d, 1 H, J = 2 Hz).

Ozonolysis of γ-Lactone 19. By use of the procedure above, the lactone **19** (2 mg) was ozonized to obtain the aldehyde **18** (1 mg), identical with the material produced from ozonolysis of ester **16**.

Ozonolysis of Peroxide Ester 20. A stream of ozone in oxygen was bubbled through a solution of the peroxide ester **20** (20 mg, 0.05 mmol) in ethyl acetate (10 mL) at -78 °C until a blue-colored solution was obtained. After the solution had been stirred for an additional 5 min, excess ozone was removed in a stream of nitrogen. Ten percent palladium on charcoal catalyst (2 mg) was added and the solution was stirred at 0 °C under an atmosphere of hydrogen for 1 h. The catalyst was removed by filtration and the solvent evaporated to obtain an oil. Chromatography of the oil on a silica gel plate (20 × 20 × 0.2 cm) using 50% ether in hexane as eluant gave the aldehyde **22** (12 mg, 70% theoretical): IR (CCl_4) 1740, 1710 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.85 (t, 3 H, J = 7 Hz), 0.93 (t, 3 H, J = 7 Hz), 0.96 (t, 3 H, J = 7 Hz), 1.00 (t, 3 H, J = 7 Hz), 3.03 (dd, 1 H, J = 16, 9 Hz), 3.71 (s, 3 H), 4.47 (m, 1 H, J = 9, 6, 3 Hz), 5.21 (s, 1 H), 9.57 (d, 1 H, J = 2.5 Hz); mass spectrum, m/e 325 (M - 29).

Ozonolysis of Lactone 26. A stream of ozone in oxygen was bubbled through a solution of the lactone **26** (20 mg, 0.05 mmol) in ethyl acetate (5 mL) at -78 °C until a blue-colored solution resulted. Excess ozone was removed in a stream of nitrogen while the solution was allowed to warm to room temperature. The solvent was evaporated under vacuum, the residue redissolved in acetone (5 mL), and a small excess of Jones' reagent added. After 10 min, excess Jones' reagent was destroyed with 2-propanol. The solution was filtered through a plug of silica and the solvent then removed under vacuum to obtain the ketone **28** (10 mg, 70% theoretical), which was purified on a silica gel plate: IR ($CHCl_3$) 1795, 1715 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.97 (d, 3 H, J = 7 Hz), 1.29 (s, 3 H), 1.36 (s, 3 H), 1.42 (dd, 1 H, J = 15, 3 Hz), 1.59 (dd, 1 H, J = 15, 9 Hz), 2.11 (s, 3 H), 2.22 (d, 1 H, J = 15 Hz), 2.35 (d,[8] 1 H, J = 6 Hz), 2.39 (d,[8] 1 H, J = 4 Hz), 2.57 (d, 1 H, J = 17 Hz), 2.93 (dd, 1 H, J = 17, 6 Hz), 4.49 (d, 1 H, J = 6 Hz); mass spectrum, m/e 270 ($C_{14}H_{22}O_5$).

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Cyclic Monoterpenoid Feeding Deterrents from the Red Marine Alga *Ochtodes crockeri*

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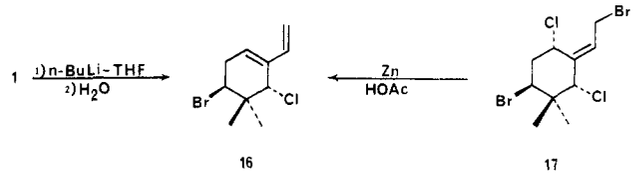
Thirteen new cyclic halogenated and oxygenated monoterpenoids along with chondrocoles A and C have been isolated from the red marine alga *Ochtodes crockeri* Setchell and Gardner from the Galapagos Islands. These new compounds have been characterized by combined spectral and chemical methods, and on the basis of laboratory feeding experiments, they appear to function as herbivore feeding deterrents in the natural environment.

Unlike other marine organisms, red seaweeds (Rhodophyta) of the families Plocamiaceae and Rhizophyllidaceae (Gigartinales) produce halogenated monoterpenoids. Within these families, the genera *Plocamium*,[2] *Chondrococcus*,[2] and *Ochtodes*[3] are known to contain large amounts of both acyclic and cyclic polyhalogenated monoterpenes. While the biological functions of these compounds are not well understood, several previously reported monoterpenes exhibit antimicrobial activity[3], and some are toxic.[4] In this paper we wish to describe the structures of 13 new cyclic monoterpenoids from the red seaweed *Ochtodes crockeri* and, further, to provide evidence that in *Ochtodes* these compounds function as herbivore feeding deterrents.

The marine alga *O. crockeri* Setchell and Gardner grows abundantly and without evidence of predation throughout the Galapagos Islands, despite the intense feeding pressure of many endemic herbivores including the voracious marine iguana *Amblrhyncus cristatus*. Collections of *O. crockeri* were made from locales near Isla Santa Cruz and Isla Isabela of the Archipelago de Colon (Galapagos Islands) in 1977 and 1978. The freshly collected algae were stored in 2-propanol and subsequently repeatedly extracted with chloroform/methanol (1:1). The combined extracts were chromatographed on silica gel, and fractions were subsequently purified by high-pressure LC (μ-Porasil) to yield compounds **1**–**15** (in order of their elution from silica gel). Compounds **1** and **4**–**15** (see Chart I) were recognized as new monoterpenoids, whereas **2** and **3**, chondrocoles A and C, had been previously isolated from the related alga *Chondrococcus hornemanni* (Mertens) Schmitz from Hawaii.[5] The structures of these new terpenoids were assigned, including relative stereochemistries,[6] by spectral analysis (^{1}H and ^{13}C NMR data, Tables I and II) including data obtained from suitable derivatives. Compounds **1**–**15** possess a monoterpenoid ring system present in three of four synergistic sex pheromones produced by the male boll weevil, *Anthonomus grandis* Bohemon.[7,8]

The diene **1** was isolated as 3% of the organic extract and analyzed for $C_{10}H_{13}Br_2Cl$ by high-resolution mass spectrometry. The three degrees of unsaturation were accounted for by two conjugated double bonds [λ_{max} 242 nm (ϵ 5300)] and one carbocyclic ring. Characteristic axial and equatorial ^{1}H NMR coupling constants for the α-bromine (C-6) methine proton (Table I) strongly suggested the presence of a six-membered ring. Futhermore, the proton chemical shifts, and a vicinal 14-Hz olefinic coupling constant, indicated a disubstituted *E* olefin to be placed at C-1–C-2. Treatment of the diene **1** with *n*-BuLi in THF at −78 °C resulted in lithium–bromine exchange which, after protonation, yielded the debromodiene **16**.



16 17

Compound **16** was also produced by treatment of the previously described monoterpene ochtodene (**17**)[2] with Zn in acetic acid. Mass spectral analysis of **16** clearly established the presence of one bromine and one chlorine atom, illustrating that the olefinic halogen at C-1 in diene **1** is bromine. Since diene **16** was identical as produced from both **1** and **17**, compound **1** must possess an equa-

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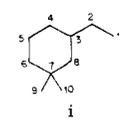
(8) We wish to suggest the name ochtodane (i) for this recently recognized monoterpene ring sytem and the numbering sequence below which is based upon geraniol.



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