bromohydrin, 400 mg of silver oxide, 9.5 mL of benzene, and 9.5 mL of hexane was boiled under reflux under nitrogen for 1.25 h. After the usual workup, the residue was recrystallized from hexane (7 mL)–benzene (1.5 mL) to give 36 mg of crystals. Concentration and several days cooling of the mother liquor gave an additional 20 mg (total yield, 50%). Two recrystallizations gave an analytical sample: mp 220.0–220.7 °C dec (placed in bath at 215 °C); NMR δ 0.86 (s), 1.00 (s), 1.13 (s), 1.25 (s), 1.93 (s, $OCOCH_3$), 3.37 (br), 4.50 (br, 3α-**H**), and 9.75 (d, -C**H**O).

Anal. Calcd for $C_{29}H_{43}O_5Br$: C, 63.15; H, 7.86; Br, 14.48. Found: C, 62.73; H, 8.03; Br, 14.16.

Acknowledgment. Thanks are given to the Allied Chemical Corp. and the American Cyanamid Company for Graduate Fellowships to G.A.C.

Registry No. 1, 3903-52-4; **2a**, 70896-71-8; **2b**, 2312-00-7; **2c**, 2312-02-9; **3**, 70864-92-5; **4**, 70864-93-6; **5**, 70864-94-7; **5**-2,4-DNP, 70864-95-8; **6**, 70864-96-9; **7**, 70864-97-0; **8**, 7591-17-5; **9**, 1258-35-1; **10**, 1256-31-1; **11**, 2572-56-7; **12**, 70864-98-1; **14**, 70864-99-2; 3β-acetoxy-5α-cholestan-7-one, 6038-71-7; 3β-acetoxy-6β-bromo-5α-cholestan-7-one, 70865-00-8; methyl *B*-nor-3β-hydroxy-5α-cholestane-6-carboxylate, 70865-01-9; *B*-nor-3β-hydroxy-5α-cholestane-6-carboxylic acid, 70865-02-0; 11α,23ζ-dibromohecogenin acetate, 70896-72-9.

Some Aromatic Compounds from the Marine Sponge *Plakortis halichondrioides*

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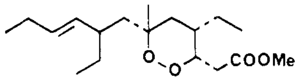
Received November 16, 1978

A sample of the marine sponge *Plakortis halichondrioides* was shown to contain *trans*-4-phenyl-3-buten-2-one (**3**), a δ-lactone **4**, two γ-lactones **5** and **6**, a hydroxy ester **7**, and two isomeric hydrocarbons **8** and **9**. The structures of the metabolites were elucidated by detailed analysis of spectral data. The probable biosynthetic correlation between the major metabolites and the relationship between these metabolites and the cyclic peroxides previously isolated from *P. halichondrioides* are discussed.

We have recently described the isolation and identification of a cyclic peroxide, plakortin (**1**), and a related ketone **2** from a sample of *Plakortis halichondrioides* from Panama.[1] During a subsequent research cruise on R/V Alpha Helix to Belize, we collected several sponges which were similar in appearance to the preserved sample of *P. halichondrioides* but which could be distinguished in the field by their patterns of growth or their texture when freshly collected. Some of these samples were indeed *Plakortis halichondrioides* and contained cyclic peroxides which were not always plakortin (**1**), however.[2] One of the samples which has been tentatively identified as *Plakortis halichondrioides* did not contain peroxides. In this paper we wish to describe the isolation and identification of a series of aromatic compounds from this chemically "abnormal" sample of *P. halichondrioides*.



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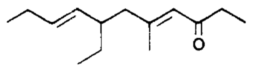

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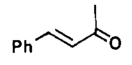

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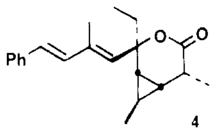

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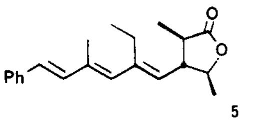

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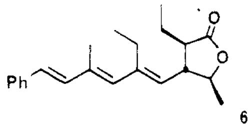

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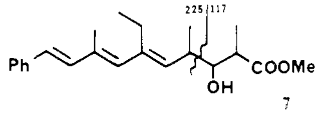

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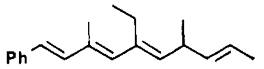

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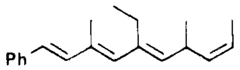

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The hexane-soluble material from an ethanol extract of *P. halichondrioides* was chromatographed on Florisil to obtain several fractions which contained aromatic compounds. Rechromatography of these fractions on silica gel gave two major compounds and five minor metabolites, some of which were purified by LC on μ-Porasil. Among the minor metabolites, *trans*-4-phenyl-3-buten-2-one (**3**) (0.006% dry weight) was identified from its spectral data.[3] The major metabolites were a δ-lactone **4** and a γ-lactone **5**. The minor metabolites included a γ-lactone **6**, a hydroxy ester **7**, and two isomeric hydrocarbons **8** and **9**.

The δ-lactone **4** (0.24% dry weight) had the molecular formula $C_{21}H_{26}O_2$. The infrared spectrum contained a band at 1740 cm^{-1} indicating the presence of an ester or δ-lactone functionality. The ^{13}C NMR spectrum confirmed the presence of 21 carbon atoms with a carbonyl carbon signal at δ 171.0, ten olefinic or aromatic carbons between δ 126 and 137, including two signals for two carbons each at δ 128.3 (d, 2C) and 126.2 (d, 2C), suggesting a monosubstituted phenyl ring, and a signal for a carbon atom bearing oxygen at δ 81.8 (s). The UV spectrum showed a strong absorption at 289 nm (ε 33 000) which suggested that the phenyl ring and both olefinic bonds were conjugated. The ^1H NMR spectrum contained signals at δ 7.31 (br d, 2 H, J = 7 Hz), 7.24 (br t, 2 H, J = 7 Hz), and 7.15

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[1] Higgs, M. D.; Faulkner, D. J. *J. Org. Chem.* **1978**, *43*, 3454.

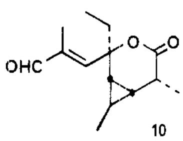
[2] Stierle, D. B.; Faulkner, D. J. Research in progress.

[3] Pouchert, C. J. "The Aldrich Library of Infrared Spectra", 2nd ed.; Aldrich Chemical Co.: Milwaukee, Wisconsin, 1975; p 745 G.

(br t, 1 H, J = 7 Hz) due to a monosubstituted phenyl ring, at δ 6.67 (d, 1 H, J = 16 Hz) and 6.50 (d, 1 H, J = 16 Hz) due to protons on a trans disubstituted olefin in the center of a conjugated system, and at δ 5.64 (br s, 1 H) due to an olefinic proton at the terminus of the conjugated system. The signal at δ 5.64 was coupled (J < 1 Hz) to a methyl signal at δ 2.01 (br s, 3 H) and no other signal. Since there is only one nonolefinic carbon signal which appears as a singlet in the off-resonance decoupled ^{13}C NMR spectrum at δ 81.8, both the conjugated olefinic chain and the δ-lactone oxygen must be attached to that carbon. The molecular formula of **4** demanded that the remaining portion of the molecule be bicyclic. Since one of the rings can be a δ-lactone ring, the presence of a complex signal at δ 0.82 (br m, 1 H) suggested that the second ring must be a cyclopropane ring. The ^{1}H NMR spectrum also contained signals due to an ethyl group attached to a fully substituted carbon at δ 1.01 (t, 3 H, J = 7 Hz) and 1.88 (q, 2 H, J = 7 Hz), a methyl signal at δ 1.20 (d, 3 H, J = 7 Hz) coupled to a signal at δ 2.57 (dq, 1 H, J = 7, 7, 7, 3 Hz), and a methyl signal at δ 1.10 (d, 3 H, J = 6 Hz) coupled to the cyclopropane proton at δ 0.82. The remaining two cyclopropane proton signals were at δ ~1.00, obscured by the methyl signal at δ 1.01. The off-resonance decoupled ^{13}C NMR spectrum contained four doublets at δ 11.6, 16.3, 33.8, and 34.5, a triplet at δ 17.0, and four quartets at δ 8.3, 13.1, 21.3 annd 27.7, as expected for the δ-lactone **4**, in which the Δ^7-olefinic bond had trans stereochemistry. Further support for this structure was obtained from a ^{1}H NMR spin-decoupling study of the δ-lactone **4** in deuteriobenzene solution, when two cyclopropane protons were clearly observed.

Ozonolysis of the δ-lactone in methanol solution at −78 °C for 5 min, followed by reduction of the ozonide with dimethyl sulfide, gave benzaldehyde and the α,β-unsaturated aldehyde **10**. The ^{1}H NMR spectrum of the aldehyde **10** contained an aldehyde proton signal at δ 9.33 (s, 1 H) and an olefinic proton signal at δ 6.29 (q, 1 H, J = 1.5 Hz) coupled to a methyl signal at δ 1.85 (d, 3 H, J = 1.5 Hz) with the remaining signals almost superimposable on the corresponding signals in the δ-lactone **4**. These data support the assignment of the location of the trisubstituted olefinic bond and the geometry of the groups about it.

Ozonolysis of the δ-lactone in methanol solution at −78 °C for 20 min gave an aldehyde **11** [^{1}H NMR (CCl$_4$) δ 9.61 (s, 1 H)] which was immediately reduced to the alcohol **12** using sodium borohydride in methanol at 0 °C. In the ^{1}H NMR spectrum of alcohol **12** (Table I) signals could be observed for every proton. The signals were assigned and coupling constants were measured using spin-decoupling techniques. The stereochemistry about the lactone ring was determined from a lanthanide induced shift (LIS) experiment using Pr(fod)$_3$ as shift reagent. A semiquantitative analysis[1] of the LIS data allowed an assignment of a praseodymium ion position for only one of the eight possible isomers of the alcohol **12**.



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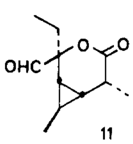

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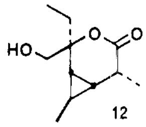

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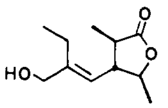

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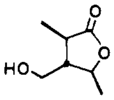

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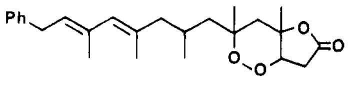

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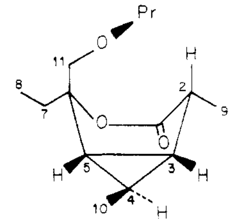
Table I. Chemical Shifts (δ), Multiplicities, Coupling Constants (J), Pr(fod)$_3$ Induced Chemical Shifts ($\Delta\delta$), and Calculated and Measured Pr-H Distances for Selected Hydrogen Atoms in the ^{1}H NMR Spectrum of Alcohol 12



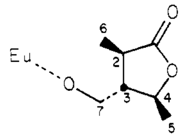
H at C no.	δ, ppm	mult	J, Hz	$\Delta\delta$	r_{calcd}, Å	r_{meas}, Å
2	2.93	dq	7,7,7,3	10.63	5.6	5.7
3	1.10	m	9,4,3	4.01	7.8	7.8
4	0.65	m	7,7,7,4,4	5.40	7.0	7.0
5	0.87	dd	9,4	6.26	6.7	6.7
7	1.78	q	7	3.98	[a]	
8	1.00	t	7	1.58	[a]	
9	1.32	d	7	4.55	7.4	7.6
10	1.13	d	6	2.04	9.7	9.2
11	3.74	s		13.6	5.2 (4.0[b])	3.8
				11.6	5.4	5.0

[a] $\theta > 30°$. [b] $\theta_{meas} = 37°$.

The second major metabolite (0.33% dry weight) was an isomeric γ-lactone **5** (IR 1770 cm^{-1}) having the molecular formula C$_{21}$H$_{26}$O$_2$. The ultraviolet absorption at 301 nm (ϵ 38 000) indicated that a third olefinic bond was conjugated to the phenyl ring. The presence of an additional two olefinic carbon signals in the ^{13}C NMR spectrum was a little ambiguous due to the overlap of several signals, but their presence could be deduced because only nine other carbon signals could be observed. The olefinic region of the ^{1}H NMR spectrum contained signals at δ 7.43 (d, 2 H, J = 7 Hz), 7.32 (t, 2 H, J = 7 Hz), and 7.20 (t, 1 H, J = 7 Hz) due to the monosubstituted phenyl group, at δ 6.85 (d, 1 H, J = 16 Hz) and 6.57 (d, 1 H, J = 16 Hz) due to the trans disubstituted olefinic protons, at δ 6.02 (br s, 1 H) due to an olefinic proton, which sharpened on irradiation of a methyl signal at δ 1.99 (br s, 3 H), and at δ 5.07 (br d, 1 H, J = 9 Hz) due to the terminal olefinic proton, which sharpened on irradiation of the methylene proton signal at δ 2.20 (q, 2 H, J = 8 Hz) coupled also to a methyl signal at δ 1.01 (t, 3 H, J = 8 Hz). The olefinic signal at δ 5.07 was coupled to a signal at δ 2.67 (dt, 1 H, J = 11, 9, 9 Hz) which was in turn coupled to two signals at δ 4.16 (dq, 1 H, J = 9, 6, 6, 6 Hz) and 2.44 (dq, 1 H, J = 11, 7, 7, 7 Hz) which were coupled to methyl signals at δ 1.40 (d, 3 H, J = 6 Hz) and 1.24 (d, 3 H, J = 7 Hz), respectively. The ^{13}C NMR spectrum is in good agreement with that expected for the γ-lactone **5**.

Ozonolysis of the γ-lactone **5** in methanol solution at −78 °C for 2 min followed by reduction of the ozonide with sodium borohydride gave benzyl alcohol and two other primary alcohols, **13** and **14**. The ^{1}H NMR spectrum of the minor alcohol **13** contained all the signals expected from the protons on the γ-lactone ring together with signals at δ 4.13 (s, 2 H) due to the hydroxymethylene protons, and δ 1.03 (t, 3 H, J = 7 Hz), 2.14 (q, 2 H, J = 7 Hz), and 5.23 (d, 1 H, J = 10 Hz) which were assigned

Table II. Chemical Shifts (δ), Multiplicities, Coupling Constants (*J*), Eu(fod)$_3$ Induced Chemical Shifts (Δδ), and Calculated and Measured Eu-H Distances for Selected Hydrogen Atoms in the ^{1}H NMR Spectrum of Alcohol 14



H at C no.	δ, ppm	mult	*J*, Hz	Δδ	r_{calcd}, Å	r_{meas}, Å
2	2.61	dq	11,7,7,7	5.70	5.6	5.7
3	1.88	m	11,9,5,4	4.98	5.9	5.9
4	4.41	dq	9,6,6,6	4.74	6.0	6.0
5	1.45	d	6	2.48	7.4	7.5
6	1.27	d	7	3.18	6.8	6.9
7	3.82	dd	11,4	7.18	5.2 (4.4[a])	4.3
7	3.75	dd	11,5			

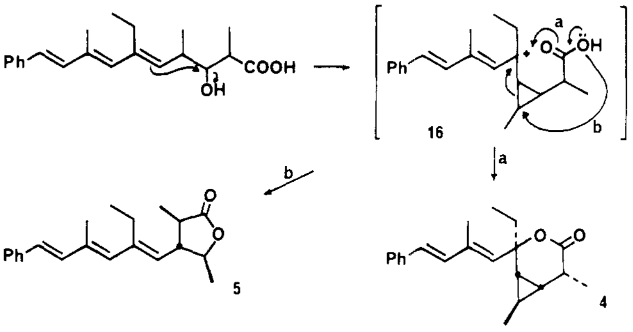
[a] $\theta_{\text{meas}} = 30°$.

to a trisubstituted olefinic proton and an ethyl group. This confirmed the positions of the methyl and ethyl groups on the polyene chain. The ^{1}H NMR spectrum of the major alcohol 14 contained signals at δ 4.41 (dq, 1 H, J = 9, 6, 6, 6 Hz), 3.82 (dd, 1 H, J = 11, 4 Hz), 3.75 (dd, 1 H, J = 11, 5 Hz), 2.61 (dq, 1 H, J = 11, 7, 7, 7 Hz), 1.99 (-OH), 1.88 (m, 1 H, J = 11, 9, 5, 4 Hz), 1.45 (d, 3 H, J = 6 Hz), and 1.27 (d, 3 H, J = 7 Hz). A lanthanide shift study on the major alcohol 14 (Table II) revealed that H_2 and H_4 were on the same face as the hydroxymethylene group.

The minor γ-lactone 6 had the molecular formula $C_{22}H_{28}O_2$. The ^{1}H NMR spectrum of γ-lactone 6 was almost identical with that of γ-lactone 5, with the exception that the signals at δ 4.16 (dq, 1 H, J = 9, 6, 6, 6 Hz) and 1.40 (d, 3 H, J = 6 Hz) in 5 were replaced by signals at δ 3.88 (m, 1 H, J = 9, 7, 3.5 Hz), 1.75 (m, 1 H, J = 14, 7, 7, 7, 3.5 Hz), 1.61 (m, 1 H, J = 14, 7, 7, 7, 7 Hz), and 1.00 (t, 3 H, J = 7 Hz) indicating the presence of an ethyl group at the carbon atom bearing oxygen. The coupling constants associated with the proton at δ 2.64 (m, J = 11, 9, 9 Hz) indicated that the relative stereochemistry of the γ-lactone 6 was identical with that of γ-lactone 5.

The hydroxy ester 7 (IR 3550, 1730 cm^{-1}) had the molecular formula $C_{22}H_{30}O_3$, suggesting the possibility that 7 might be a methyl ester derived by adding methanol to lactone 5. However, detailed examination of the ^{1}H NMR spectrum together with a complete decoupling study revealed that the hydroxy ester 7 was a β-hydroxy ester with a rearranged carbon skeleton. The signals for the aromatic protons, the olefinic protons, the vinyl methyl group, and the vinyl ethyl group were almost superimposable on the corresponding signals in γ-lactones 5 and 6. The terminal vinyl proton signal at δ 5.11 (d, 1 H, J = 10 Hz) was coupled to a signal at δ 2.57 (m, 1 H) which was coupled to both a methyl signal at δ 1.09 (d, 3 H, J = 7 Hz) and an α-hydroxy proton signal at δ 3.24 (m, 1 H). The α-hydroxy proton signal was very broad in the carbon tetrachloride spectrum due to coupling with the hydroxyl proton at δ 2.87, but on changing solvent to deuteriochloroform the α-hydroxy proton gave rise to a sharp signal at δ 3.35 (dd, 1 H, J = 8, 4 Hz). The α-hydroxy proton signal was coupled to a signal at δ 2.67 (dq, 1 H, J = 7, 7, 7, 4 Hz) which was in turn coupled to the methyl signal at δ 1.25 (d, 3 H, J = 8 Hz). The remaining methyl ester signal was at δ 3.64 (s, 3 H). The ^{13}C NMR spectrum supported this structure assignment as did the mass spectrum, which contained major fragmentation ions at *m/e* 225 and 117 due to the fragmentation shown. We could not deduce the relative stereochemistry from the coupling constants.

Scheme I. A Relationship between the Acid Corresponding to Methyl Ester 7, the δ-Lactone 4, and the γ-Lactone 5



The hydrocarbon mixture could be separated into two geometrical isomers. The major isomer 8 had the molecular formula $C_{20}H_{26}$. The ^{13}C NMR spectrum contained 14 olefinic or aromatic signals, four methyl signals, one methylene signal, and one methine carbon signal. The absorption in the ultraviolet spectrum at 305 nm (ε 32 000) indicated the presence of the same system of a phenyl group conjugated to two olefinic bonds. The third double bond must be isolated from the polyene chain by the single methine carbon. The ^{1}H NMR spectrum contained the usual signals for the aromatic protons and the protons associated with the polyene chain and its methyl and ethyl substituents. The terminal olefinic proton signal at δ 5.09 (br d, 1 H, J = 10 Hz) was coupled to a broad multiplet at δ 3.11 (br m, 1 H) which was in turn coupled to a methyl signal at δ 1.08 (d, 3 H, J = 7 Hz) and to a two-proton olefinic signal at δ 5.36, which was assigned to the two remaining olefinic protons. Since the olefinic protons acted as a net spin pair, the methyl signal at δ 1.66, also coupled to the olefinic protons, appeared as a complex multiplet. In the minor hydrocarbon 9, the vinyl methyl signal was δ 1.62 while the two olefinic protons gave a complex signal at δ 5.27. These data suggested that the major hydrocarbon was (1*E*,3*E*,5*E*,8*E*)-3,7-dimethyl-5-ethyl-1-phenyldeca-1,3,5,8-tetraene (8), while the minor isomer was (1*E*,3*E*,5*E*,8*Z*)-3,7-dimethyl-5-ethyl-1-phenyldeca-1,3,-5,8-tetraene (9).[4] Our assignment of the ^{13}C NMR spectrum of the major hydrocarbon 8 supported this assignment: in particular, a signal at ~10 ppm would be expected for the terminal methyl group in the 8*Z* isomer.

At first sight, the aromatic compounds 3–9 appeared to be so completely unrelated to the cyclic peroxide 1 or ketone 2 that we submitted new samples for identification. Again, both samples were identified as *P. halichondrioides*.[5] However, we have recently examined several different collections of *P. halichondrioides* and found some new cyclic peroxides, including the aromatic peroxide 15, which will be described elsewhere.[2] All the compounds described can be related to the β-hydroxy ester 7 which might be derived from a polyketide biosynthetic pathway involving the combination of propionate, butyrate, and phenylacetate units. The δ-lactone 4 can be related to both

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[4] See, for example, the ^{1}H NMR spectra of *cis*- and *trans*-4-methyl-2-pentene. Pouchert, C. J.; Campbell, J. R. "Aldrich Library of NMR Spectra", Vol. 1; Aldrich Chemical Co.: Milwaukee, Wisconsin, 1974; p 24.

[5] The isolation of completely different metabolites from different samples of *Disidea pallasens* has also been reported. Cf. Cimino, G.; De Stefano, S.; Guerriero, A.; Minale, L. *Tetrahedron Lett.* **1975**, 1417, 1421, 1425. Cimino, G.; De Luca, P.; De Stefano, S.; Minale, L. *Tetrahedron* **1975**, *31*, 271. Cimino, G.; De Stefano, S.; Minale, L. *Experentia* **1975**, *31*, 1117.

the hydroxy ester **7** and the γ-lactone **5** through the cyclopropyl carbinyl cation **16**, shown in Scheme I.

Experimental Section

Infrared spectra were recorded on a Perkin-Elmer Model 137 spectrophotometer. Ultraviolet spectra were recorded on a Perkin-Elmer Model 124 double beam spectrophotometer. Optical rotations were measured on a Perkin-Elmer Model 141 polarimeter, using a 10-cm microcell. ^{1}H NMR spectra were recorded on a Varian HR-220 NMR spectrometer, and ^{13}C spectra were recorded on a Varian CFT-20 NMR spectrometer; all chemical shifts are reported with respect to Me_4Si (δ 0). Low-resolution mass spectra were recorded on a Hewlett-Packard 5930A mass spectrometer. High-resolution mass spectra were supplied by the Chemistry Department of UCLA. All solvents used were either spectral grade or distilled from glass prior to use.

Collection and Extraction of *Plakortis halichondrioides*. The sample of *P. halichondrioides* was collected at Lighthouse Reef, Belize (17° 10′ N, 87° 36.6′ W) by hand using SCUBA (−15 to −20 m). The sample was immediately frozen and maintained at −20 °C until extracted. The sponge (333 g dry weight) was homogenized in ethanol (1 L) and filtered and the residue was Soxhlet extracted with ethanol (1.5 L). The combined extracts were evaporated in vacuo to obtain an aqueous concentrate which was extracted with hexane. The hexane extract was dried over sodium sulfate and the solvent was evaporated to yield a gum (19.3 g, 5.8% dry weight).

Chromatography of Crude Extract. The crude extract (6 g) in hexane was applied to a column (100 × 5 cm diameter) of Florisil and the compounds were eluted with solvents of increasing polarity from hexane through ether to ethyl acetate. A fraction eluted with 3:1 hexane–ether contained a mixture of two compounds which were separated by LC on μ-Porasil using 10% ether in hexane as eluant to obtain the ketone **3** (6 mg, 0.006% dry weight) and the hydrocarbon **8** (40 mg, 0.04% dry weight). A second fraction eluted with 3:1 hexane–ether contained the hydrocarbon **9** (6 mg, 0.006% dry weight). A fraction eluted with 1:1 hexane–ether was purified by LC on μ-Porasil using 3:1 hexane–ether to obtain the δ-lactone **4** (250 mg, 0.24% dry weight). A second fraction eluted with 1:1 hexane–ether was rechromatographed on silica gel to obtain the γ-lactone **6** (30 mg, 0.03% dry weight). A third fraction eluted with 1:1 ether–hexane was purified on a silica gel column to obtain the γ-lactone **5** (343 mg, 0.33% dry weight). A fraction eluted with 3:1 ether–hexane was purified by LC on μ-Porasil using 40% ether in hexane as eluant to yield the hydroxy ester **7** (25 mg, 0.025% dry weight).

***trans*-4-Phenyl-3-buten-2-one (3)**: IR (CCl_4) 1690, 1675, 1600 cm^{-1}; ^{1}H NMR (CCl_4) δ 2.30 (s, 3 H), 6.61 (d, 1 H, *J* = 16 Hz), 7.31 (m, 3 H), 7.38 (d, 1 H, *J* = 16 Hz), 7.49 (m, 2 H); mass spectrum *m/e* 146, 131, 105.

δ-Lactone 4: IR (CCl_4) 1740, 1610 cm^{-1}; UV (hexane) 306 (ε 19 400), 289 (ε 33 000), 219 nm (ε 17 000); ^{1}H NMR (CCl_4) δ 0.82 (m, 1 H), ~1.00 (m, 2 H), 1.01 (t, 3 H, *J* = 7 Hz), 1.10 (d, 3 H, *J* = 6 Hz), 1.20 (d, 3 H, *J* = 7 Hz), 1.88 (q, 2 H, *J* = 7 Hz), 2.01 (brs, 3 H), 2.57 (dq, 1 H, *J* = 3, 7, 7, 7 Hz), 5.64 (brs, 1 H), 6.50 (d, 1 H, *J* = 16 Hz), 6.67 (d, 1 H, *J* = 16 Hz), 7.15 (t, 1 H, *J* = 7 Hz), 7.24 (t, 2 H, *J* = 7 Hz), 7.31 (d, 2 H, *J* = 7 Hz); ^{13}C NMR (CCl_4) 171.0 (s), 137.1 (s), 136.2 (s), 134.7 (d), 133.4 (d), 128.3 (2C, d), 127.2 (d), 126.2 (2C, d), 81.8 (s), 34.5 (d), 33.8 (d), 27.7 (q), 21.3 (q), 17.0 (t), 16.3 (d), 13.1 (q), 11.6 (d), 8.3 (q); high-resolution mass measurement, obsd 310.1930, $C_{21}H_{26}O_2$ requires 310.1933.

γ-Lactone 5: IR (CCl_4) 1770, 1590 cm^{-1}; UV (hexane) 301 nm (ε 38 000), 227 nm (ε 13 100); ^{1}H NMR (CCl_4) δ 1.01 (t, 3 H, *J* = 8 Hz), 1.24 (d, 3 H, *J* = 7 Hz), 1.40 (d, 3 H, *J* = 6 Hz), 1.99 (br s, 3 H), 2.20 (q, 2 H, *J* = 8 Hz), 2.44 (dq, 1 H, *J* = 11, 7, 7, 7 Hz), 2.67 (dt, 1 H, *J* = 11, 9, 9 Hz), 4.16 (dq, 1 H, *J* = 9, 6, 6, 6 Hz), 5.07 (d, 1 H, *J* = 9 Hz), 6.02 (br s, 1 H), 6.57 (d, 1 H, *J* = 16 Hz), 6.85 (d, 1 H, *J* = 16 Hz), 7.20 (t, 1 H, *J* = 7 Hz), 7.32 (t, 2 H, *J* = 7 Hz), 7.43 (d, 2 H, *J* = 7 Hz); ^{13}C NMR (CCl_4) δ 176.6 (s), 143.0 (s), 137.3 (s), 135.2 (s), 133.7 (2C, d), 128.4 (2C, d), 127.8 (d), 127.0 (d), 126.1 (3C, d), 78.1 (d), 51.4 (d), 42.4 (d), 24.5 (t), 18.4 (q), 13.9 (q), 13.6 (q), 12.9 (q); high-resolution mass measurement, obsd 310.1930, $C_{21}H_{26}O_2$ requires 310.1933.

γ-Lactone 6: IR (CCl_4) 1770, 1590 cm^{-1}; ^{1}H NMR (CCl_4) δ 1.00 (t, 3 H, *J* = 7 Hz), 1.08 (t, 3 H, *J* = 7 Hz), 1.19 (d, 3 H, *J* = 7 Hz), 1.61 (m, 1 H, *J* = 14, 7, 7, 7, 7 Hz), 1.75 (m, 1 H, *J* = 14, 7, 7, 7, 3.5 Hz), 1.95 (3 H, s), 2.18 (q, 2 H, *J* = 7 Hz), 2.31 (dq, 1 H, *J* = 10, 7, 7, 7 Hz), 2.64 (dt, 1 H, *J* = 10, 9, 9 Hz), 3.88 (m, 1 H, *J* = 9, 7, 3.5 Hz), 5.05 (d, 1 H, *J* = 9 Hz), 5.95 (s, 1 H), 6.47 (d, 1 H, *J* = 16 Hz), 6.75 (d, 1 H, *J* = 16 Hz), 7.15 (t, 1 H, *J* = 7 Hz), 7.20 (t, 2 H, *J* = 7 Hz), 7.33 (d, 2 H, *J* = 7 Hz): mass spectrum *m/e* 324, 198, 187, 169 (100%).

Hydroxy ester 7: IR (CCl_4) 3550, 1730 cm^{-1}; UV (hexane) 305 nm (ε 33 000); ^{1}H NMR (CCl_4) δ 0.95 (t, 3 H, *J* = 7 Hz), 1.09 (d, 3 H, *J* = 6 Hz), 1.25 (d, 3 H, *J* = 8 Hz), 1.95 (d, 3 H, *J* = 2 Hz), 2.11 (m, 2 H), 2.57 (m, 1 H), 2.67 (m, 1 H, *J* = 8, 8, 8, 4 Hz), 2.87 (m, 1 H), 3.24 (m, 1 H), 3.64 (s, 3 H), 5.11 (d, 1 H, *J* = 10 Hz), 5.94 (br s, 1 H), 6.43 (d, 1 H, *J* = 16 Hz), 6.75 (d, 1 H, *J* = 16 Hz), 7.12 (t, 1 H, *J* = 7 Hz), 7.22 (t, 2 H, *J* = 7 Hz), 7.30 (d, 2 H, *J* = 7 Hz); ^{13}C NMR (C_6D_6) δ 176.6 (s), 138.8 (s), 138.3 (s), 135.3 (d), 134.9 (s), 133.7 (d), 133.2 (d), 128.9 (2C, d), 128.0 (d), 127.8 (d), 126.7 (2C, d), 78.1 (d), 51.2 (q), 42.7 (d), 37.7 (d), 24.7 (t), 17.2 (q), 15.5 (q), 14.1 (q), 13.6 (q); mass spectrum *m/e* 342, 225, 117, 91.

Hydrocarbon 8: UV (hexane) 302 nm (ε 32 000); ^{1}H NMR (CCl_4) δ 0.97 (t, 3 H, *J* = 7 Hz), 1.08 (d, 3 H, *J* = 7 Hz), 1.66 (br s, 3 H), 1.97 (s, 3 H), 2.14 (q, 2 H, *J* = 7 Hz), 3.11 (m, 1 H), 5.09 (br d, 1 H, *J* = 10 Hz), 5.36 (br m, 2 H), 5.94 (br s, 1 H), 6.41 (d, 1 H, *J* = 16 Hz), 6.74 (d, 1 H, *J* = 16 Hz), 7.11 (t, 1 H, *J* = 7 Hz), 7.20 (t, 2 H, *J* = 7 Hz), 7.32 (d, 2 H, *J* = 7 Hz); ^{13}C NMR (acetone-d_6) δ 136.4 (s), 136.1 (s), 135.8 (s), 135.6 (d), 135.1 (d), 135.0 (d), 134.2 (d), 129.2 (d), 128.7 (d), 127.7 (d), 127.6 (d), 126.9 (d), 123.4 (d), 123.3 (d), 36.1 (d), 24.7 (t), 21.6 (q), 20.6 (q), 17.9 (q), 13.4 (q); mass spectrum *m/e* 266, 197 (100%).

Hydrocarbon 9: UV (hexane) 311 (ε 34 500), 295 nm (ε 32 000); ^{1}H NMR (CCl_4) δ 0.97 (d, 3 H, *J* = 7 Hz), 0.98 (t, 3 H, *J* = 7 Hz), 1.62 (brs, 3 H), 1.82 (s, 3 H), 2.08 (q, 2 H, *J* = 7 Hz), 2.84 (br m, 1 H), 5.07 (br d, 1 H, *J* = 10 Hz), 5.27 (br m, 2 H), 5.94 (br s, 1 H), 6.42 (d, 1 H, *J* = 16 Hz), 6.77 (d, 1 H, *J* = 16 Hz), 7.12 (t, 1 H, *J* = 7 Hz), 7.21 (t, 2 H, *J* = 7 Hz), 7.31 (d, 2 H, *J* = 7 Hz); mass spectrum *m/e* 266, 197 (100%).

Ozonolysis of δ-Lactone 4. A stream of ozone was bubbled through a solution of the δ-lactone **4** (25 mg, 0.08 mmol) in methanol (10 mL) at −78 °C for 5 min. The excess ozone was removed in a stream of nitrogen. Dimethyl sulfide (0.2 mL) was added and the solution was allowed to warm to room temperature and stand for 2 h. Evaporation of the solvent gave a residue which was chromatographed by LC on μ-Porasil to obtain benzaldehyde (2 mg, 23% theoretical) and the aldehyde **10** (14 mg, 74% theoretical): IR (CCl_4) 1745, 1695 cm^{-1}; ^{1}H NMR (CCl_4) δ 0.83 (m, 1 H), 1.04 (t, 3 H, *J* = 7 Hz), 1.13 (d, 3 H, *J* = 6 Hz), 1.22 (d, 3 H, *J* = 7 Hz), 1.85 (d, 3 H, *J* = 2 Hz), 1.90 (q, 2 H, *J* = 7 Hz), 2.50 (dq, 1 H, *J* = 7, 7, 7, 3 Hz), 6.29 (q, 1 H, *J* = 2 Hz), 9.33 (s, 1 H); mass spectrum *m/e* 235 $(M - 1)^+$.

In a second experiment the δ-lactone **4** (30 mg, 0.096 mmol) in methanol (10 mL) was ozonized at −78 °C for 20 min and the resultant ozonide was reduced as in the previous experiment to obtain the aldehyde **11**. Sodium borohydride (20 mg) was added in small portions to a solution of the aldehyde **11** in methanol (10 mL) at 0 °C. The solution was stirred at 0 °C for 20 min and excess reagent was then destroyed with acetic acid (1 drop). The solvent was evaporated and the residue was partitioned between ether (3 × 20 mL) and water (10 mL). The combined ether extracts were dried over sodium sulfate and the solvent was evaporated to obtain the alcohol **12** (15 mg, 85% theoretical), which could be purified by LC on μ-Porasil: IR ($CHCl_3$) 3400, 1740 cm^{-1}; ^{1}H NMR ($CDCl_3$) see Table I; mass spectrum *m/e* 198.

Ozonolysis of γ-Lactone 5. A stream of ozone in oxygen was bubbled into a solution of the γ-lactone **5** (50 mg, 0.16 mmol) in methanol (10 mL) at −78 °C for 2 min. The excess ozone was removed in a stream of nitrogen and sodium borohydride (20 mg) was added. The reaction mixture was stirred at 25 °C for 2 h and excess reagent was destroyed by addition of aqueous acetic acid (1 drop). Evaporation of the solvent gave a residue which was triturated with ether to obtain a mixture of alcohols. The alcohols were separated by LC on μ-Porasil to obtain benzyl alcohol (5 mg, 29% theoretical), the alcohol **11** (5 mg, 16% theoretical), and the alcohol **12** (9 mg, 39% theoretical).

Lanthanide Induced Shift Studies of Alcohols 12 and 14. (A) Aliquots (10 μL) of $Pr(fod)_3$ shift reagent (19 mg) in deuteriochloroform (100 μL) were added to a solution of the alcohol

12 (9 mg) and the ^{1}H NMR spectra were recorded after each addition. The chemical shift of each signal was measured for each addition of shift reagent and the induced shift ($\Delta\delta$) corresponding to the addition of 1 equiv of shift reagent was determined by least-squares analysis (Table I). The distance (r_{calcd}) between a proton and praseodymium atom was calculated using the relationship $\Delta\delta = k/r^3$ (this approximation for $\Delta\delta = k(3\cos^2\theta - 1)/r^3$ is valid when the O-Pr-H angle (θ) is less than 20°) and compared with distances measured (r_{meas}) using a Dreiding model. In practice, this was accomplished by assuming approximate distances between the praseodymium atom and the three rigidly positioned protons on the cyclopropane ring to obtain a starting position for the praseodymium atom, that was modified as more protons were considered. The calculated distances between the praseodymium atom and protons at C-2 and C-9 corresponded to the distances measured when the lactone ring is in a pseudo-boat conformation. The stereochemistry at C-6 was determined by measuring the oxygen-praseodymium distances. The smallest Pr-O distance for this isomer was 2.5 Å, a normal value, while for the alternate isomer it was ~4.0 Å, an abnormally large distance.[6] In this conformation, the induced shifts for the protons on the ethyl group could not be explained by the simple formula since $\theta > 30°$. The hydroxymethylene protons also required a correction for θ. The calculated distances (r_{calcd}) and measured distances (r_{meas}) must differ by less than 10% for a valid correlation.

(B) Aliquots (5 μL) of Eu(fod)$_3$ shift reagent (33.5 mg) in deuteriochloroform (100 μL) were added to a solution of the alcohol **14** (5 mg) in deuteriochloroform and ^{1}H NMR spectra were recorded after each addition. The induced shifts ($\Delta\delta$) corresponding to the addition of 1 equiv of shift reagent were calculated by least-squares analysis (Table II). Using the techniques described above, a good correlation between r_{calcd} and r_{meas} was obtained for the isomer shown. For the protons at C-7, the H-Eu-O angle (θ) was measured at ~30°. Recalculation of r_{calcd} for $\theta = 30°$ gave a very good fit with the measured distance.

Alcohol 13: IR (CHCl$_3$) 3450, 1770 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 1.03 (t, 3 H, J = 7 Hz), 1.19 (d, 3 H, J = 7 Hz), 1.37 (d, 3 H, J = 6 Hz), 1.75 (br s, -OH), 2.14 (q, 2 H, J = 7 Hz), 2.44 (dq, 1 H, J = 9, 7, 7, 7 Hz), 2.61 (dt, 1 H, J = 19, 9, 9 Hz), 4.13 (br s, 2 H), 4.15 (dq, 1 H, J = 9, 6, 6, 6 Hz), 5.23 (d, 1 H, J = 10 Hz); mass spectrum m/e 198 (M$^+$).

Alcohol 14: IR (CHCl$_3$) 3400, 1770 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 1.27 (d, 3 H, J = 7 Hz), 1.45 (d, 3 H, J = 6 Hz), 1.88 (m, 1 H, J = 10, 9, 5, 4 Hz), 1.99 (s, -OH), 2.61 (dq, 1 H, J = 10, 7, 7, 7 Hz), 3.75 (dd, 1 H, J = 11, 5 Hz), 3.82 (dd, 1 H, J = 11, 4 Hz), 4.41 (dq, 1 H, J = 9, 6, 6, 6 Hz); mass spectrum m/e 144 (M$^+$).

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Registry No. **3**, 1896-62-4; **4**, 70941-32-1; **5**, 70941-33-2; **6**, 70941-34-3; **7**, 70941-35-4; **8**, 70941-36-5; **9**, 70981-88-3; **10**, 70941-37-6; **11**, 70941-38-7; **12**, 70941-39-8; **13**, 70941-40-1; **14**, 70941-41-2.

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[6] For examples see Sievers, R., Ed. "Nuclear Magnetic Resonance Shift Reagents"; Academic Press: New York, 1973.

Santolinolide B [(2*R*,3*S*,4*S*)-4-Hydroxy-2,5-dimethyl-3-vinyl-5-hexenoic Acid Lactone]. A New Irregular Monoterpene from *Artemisia tridentata tridentata*

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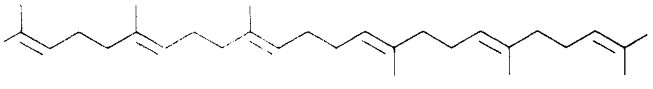
The neutral pentane extract of the leaves and flower heads of big sage (*Artemisia tridentata tridentata*) contains a new non-head-to-tail monoterpene lactone, santolinolide B (**12**). The steam distillate from the plant material contains a mixture of santolinolides A (**11**), B (**12**), B′ (**14**), and C (**13**). The absolute stereochemical structures of these diastereomers have been established.

In recent years there has been interest generated in the biosynthesis of irregular monoterpenes serving as a model for the biogenesis of the important triterpene squalene (**1**) and its immediate precursor, presqualene pyrophosphate (**2a**). It has been hypothesized that (1*R*,3*R*)-chrysanthemyl pyrophosphate (**2b**), a C-10 analogue of presqualene pyrophosphate, is the biosynthetic precursor of the non-head-to-tail monoterpenes.[1] The isolation and absolute stereochemistry of several monoterpenes lent support to this hypothesis;[2-5] however, the occurrence of (2*S*,3*R*)-santolina epoxide (**3**) is stereochemically inconsistent with the proposed biogenetic route.[6] If chrysanthemyl pyrophosphate is indeed the precursor of the irregular monoterpenes, then it must also occur as the 1*R*,3*S* cis diastereomer since optically pure (1*R*,3*R*)-*trans*-chrysanthemol (**4**) has been isolated from *Artemisia ludoviciana*.[4]



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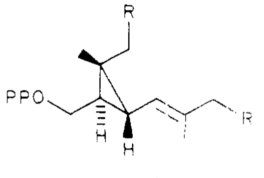

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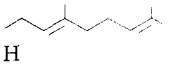
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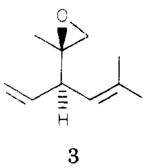

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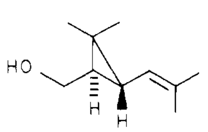

4

We have been screening plants of the Anthemidae tribe of the Compositae family for *cis*-chrysanthemol,[7,8] and as

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