Chemistry of Coelenterates. XXI.[1a] Lactones from the Gorgonian *Pterogorgia guadalupensis*[1b,c]

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Two lactones isolated from the marine coelenterate *Pterogorgia guadalupensis*, a gorgonian, are described. One of these is a bisbutenolide, ancepsenolide (**3**); the other lactone is shown on the basis of spectroscopic data and conversion to ancepsenolide to be 2-(13-carboxy-14,15-diacetoxyhexadecanyl)-2-penten-4-olide (**1**).

The octocoral *Pterogorgia guadalupensis* Duchassaing & Michelin belongs to a group of sessile tropical reef invertebrates classified as gorgonians but more commonly known as sea fans and sea whips.[2] The fact that these stationary organisms can flourish in an environment inhabited by numerous potential predators has been attributed at least in part to the presence of endogenous organic compounds which endow these animals with a chemical means of defense.[3] Biological screening of the total extracts of various gorgonians has demonstrated[4] the presence of antimicrobial materials in these animals, and chemical investigations have resulted in the isolation and identification of various terpene hydrocarbons,[5a,b] diterpene lactones[5a-d] prostaglandins,[5e] and unusual dodecane-1,2-dilactones[5f,g] from this group of organisms. We wish herewith to report the isolation of two crystalline lactones from the gorgonian *Pterogorgia guadalupensis*. One of these exhibited mild antibiotic activity[6] against *Staphylococcus aureus* and *Mycobacterium smegmatis*, and evidence cited in this paper permits this lactone to be formulated as **1**; the other lactone, **3**, has been isolated previously[5f] from a related species of gorgonian, *Pt. anceps*.

Brief hexane extraction of a large, single, air-dried colony of *Pt. guadalupensis* afforded in 3.1% yield a white solid, mp 90.5–92.0°, which was identified as ancepsenolide (**3**) by comparison of its physical and spectral properties to those of material isolated previously (see Experimental Section)[5f]. Prolonged hexane extraction afforded in 1% yield a second compound, **1**, mp 81.1–82.9°, for which elemental and mass spectral analysis confirmed the formula $C_{26}H_{42}O_8$ (*m/e* 482).

The infrared spectrum of **1** exhibited strong, broad absorption centered at 1740 cm^{-1} (1700–1770 cm^{-1} at half peak intensity), consistent with the presence of butenolide, acetate, and carboxyl functionalities. The presence of a butenolide ring in **1** was confirmed by the uv absorption (λ_{max} 204 nm, ϵ 17,436) and one-proton multiplets in the nmr spectrum at δ 5.0 (well resolved at 220 MHz) and 7.02 ppm identical with those present in ancepsenolide (**3**).[5f] Strong, sharp absorption at δ 1.27 ppm confirmed the presence of a long methylene chain, and two partially resolved singlets at 2.08 ppm suggested the presence of two acetate residues in **1**. A neutralization equivalent verified that **1** contained a free carboxyl group, and acetyl analysis confirmed the presence of two acetate moieties.

The position of the acetate moieties in **1** was suggested by the structure of the compounds **3** and **4a** which had been isolated previously from *Pt. anceps*.[5f,g] This tentative assignment was corroborated by the presence of two distinct doublets at δ 1.17 (J = 6 Hz) and 1.35 ppm (J = 7 Hz) in the 220-MHz nmr spectrum[7] of **1** (chloroform–acetone-d_6) ascribable to the pentenolide methyl group and another methyl group in a very similar structural environment, *i.e.*, $CH_3CH(OAc)$. Confirmation of the structure **1** (without stereochemistry) was achieved by conversion of **1** *via* acid-catalyzed methanolysis to the lactone **2a** which underwent dehydration upon treatment with phosphorus oxychloride in pyridine to give ancepsenolide (**3**) in good yield (see Scheme 1). These conversions establish the overall carbon skeleton of **1** and confirm the assignment of one of the acetate moieties to the penultimate (C-15′) in the hexadecanyl residue in **1** (lactone formation).

Although the nmr signals of the protons attached to carbons bearing oxygen atoms in both **1** and **2a** overlap to give complex multiplets which do not lend themselves to facile interpretation, the corresponding absorptions in the acetate **2b**, derived from the lactone **2a** by routine acetylation, are well resolved (see Table I) and provide confirmation of the presence of three single protons on carbons bearing oxygen in **2b** and

TABLE I

LACTONE PMR ABSORPTIONS AND COUPLING CONSTANTS[a]

	Compd 2b			Compd 4b[b]		
Proton	δ	$J_{H_{14'},15'}$	J	δ	$J_{H_{14'},15'}$	J
$H_{14'}$	5.62	3	5 ($H_{14',13'}$)	5.15	0.5–1	6 ($H_{14',13'}$)
$H_{15'}$	4.59	3	6.5 ($H_{15'-Me}$)	4.50	0.5–1	6 ($H_{15'-Me}$)
H_4	5.0			5.0		

[a] Measured in $CDCl_3$ at 60 MHz. [b] See ref 5 g.

(1) (a) Papers XIX–XX in this series are, respectively, M. B. Houssain and D. van der Helm, *Recl. Trav. Chim. Pays-Bas*, **88**, 1413 (1969); R. L. Hale, J. Leclerq, B. Tursch, C. Djerassi, R. A. Gross, Jr., A. J. Weinheimer, K. Gupta, and P. J. Scheuer, *J. Amer. Chem. Soc.*, **92**, 2179 (1970). (b) Presented in part at the Food-Drugs from the Sea Symposium, Marine Technology Society, Kingston, R. I., 1969, and at the 15th Oklahoma Tetrasectional Meeting of the American Chemical Society, March 15–16, 1969. (c) This investigation was supported by NIH Training Grant 5675 from the National Heart Institute. (d) Sabbatical leave, Woods Hole Oceanographic Institution, 1969–1970; NIH Special Fellowship GM 13941.

(2) F. M. Bayer, "The Shallow-Water Octocorallia of the West Indian Region," Martinus Mijhoff, The Hague, Netherlands, 1961, pp 272–277.

(3) See, for example, R. F. Nigrelli, *Trans. N. Y. Acad. Sci.*, **24**, 496 (1962), and ref 4.

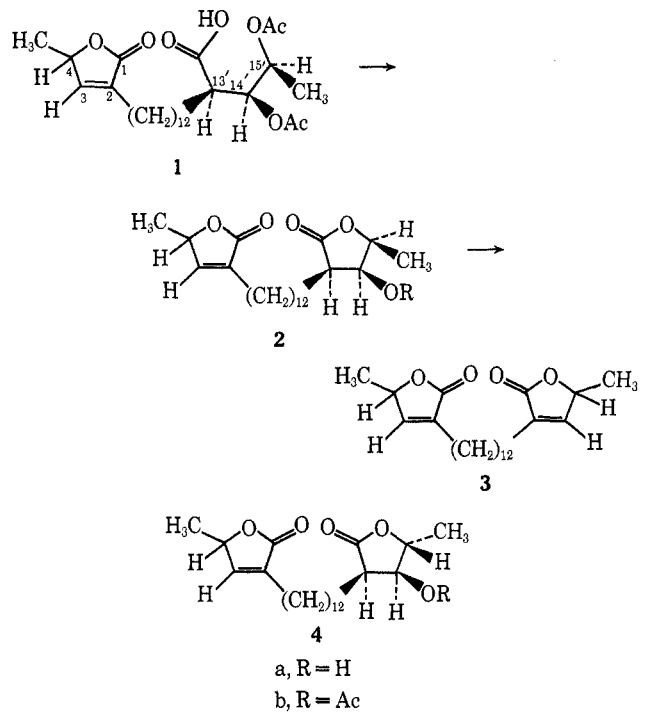
(4) L. S. Ciereszko, *ibid.*, **24**, 502 (1962).

(5) (a) A. J. Weinheimer, F. J. Schmitz, and L. S. Ciereszko, Transactions of the Drugs from the Sea Symposium, Aug 1967, Marine Technology Society, pp 135–141; (b) L. S. Ciereszko, D. H. Sifford, and A. J. Weinheimer, *Ann. N. Y. Acad. Sci.*, **90**, 917 (1960); (c) A. J. Weinheimer, R. E. Middlebrook, J. O. Bledsoe, W. E. Marsico, and T. K. B. Karns, *Chem. Commun.*, 384 (1968); (d) M. B. Hossain and D. van der Helm, *Recl. Trav. Chim. Pays-Bas*, **88**, 1413 (1969); (e) A. J. Weinheimer and R. L. Spraggins, *Tetrahedron. Lett.*, 5185 (1969); (f) F. J. Schmitz, K. W. Kraus, L. S. Ciereszko, D. H. Sifford, and A. J. Weinheimer, *ibid.*, 97 (1966); (g) F. J. Schmitz, E. D. Lorance, and L. S. Ciereszko, *J. Org. Chem.*, **34**, 1989 (1969).

(6) We thank Dr. P. Burkholder for the antimicrobial testing.

(7) Kindly provided by Dr. N. Bhacca, Louisiana State University.

SCHEME I



hence in **2a** and **1**. Thus both acetate groups in **1** must be secondary. Since an endocyclic double bond is formed upon dehydration of **2a**, the hydroxyl group in the latter and its acetate progenitor in **1** must be located at C-14′ in the hexadecanyl moiety.

The transesterification of **1** leading to the formation of **2a** is not expected to effect the carbon–oxygen bonds at C-14′ or C-15′, and hence we propose the relative stereochemistry shown for **1** and **2a** from a comparison of the coupling constant data of the acetate **2b** with that observed for the acetate **4b** (see Table I). The resonance signals for protons at C-4, -14′, and -15′ are sufficiently separated in the acetates **2b** and **4b** to permit a first-order analysis of the coupling constants. Since $J_{H_{15'}\text{-Me}}$ in **2b** can be determined from the spacing of the methyl doublet (J = 6.5 Hz), the second coupling of H-15′ (J = 3 Hz) must be due to $J_{H_{15',14'}}$. Hence it follows that the 5-Hz splitting in H-14′ must be due to $J_{H_{14',13'}}$. The large value of $J_{H_{14',13'}}$ is consistent with a small dihedral angle[8] and hence the cis stereochemistry for H-14′,13′ in **2b** just as in **4b**. The much larger value of $J_{H_{15',14'}}$ in **2b** in comparison to **4b** argues for a cis H-15′,14′ arrangement in **2b** as opposed to the trans H-15′,14′ assignment in **4b**.[5g]

Experimental Section

Melting points were determined in capillary tubes with a Thomas-Hoover melting apparatus and are corrected. Ultraviolet spectra were measured in 95% ethanol on Beckman DK-1 and Hitachi Perkin-Elmer Model 124 spectrophotometers under nitrogen sweep. Nmr spectra were determined using tetramethylsilane as an internal standard with Varian A-60 and HR-220 spectrometers. Elemental analyses were performed by Alfred Bernhardt, Mülheim, Germany. Infrared spectra were obtained on a Beckman IR-8 spectrophotometer. Mass spectra were obtained on Hitachi RMU-6A (Purdue University) and RMU-6E (University of Arkansas) spectrometers at 75 and 80 eV.

Isolation of Ancepsenolide (3) and 2-(13-Carboxy-14,15-diacetoxyhexadecanyl)-2-penten-4-olide (1).—A single colony of dried, coarsely ground *Pt. guadalupensis*, 115 g, collected near Port Royal, Jamaica, June 1967, was extracted in a continuous percolator–extractor[9] sequentially as follows (solvent, duration of extraction periods): (1) hexane, 18 hr, 48 additional hr, 96 additional hr; (2) benzene, 28 hr, 72 hr; (3) methanol, 48 hr, 72 hr. Ancepsenolide precipitated from the first hexane extract in nearly pure form (3.2 g, 3.5% crude). After chromatography over alumina (activity III) and recrystallization from a mixture of chloroform and hexane, ancepsenolide was obtained as a white solid: mp 90.5–92°; $[\alpha]_D$ +47.8°;[10] uv max (95% EtOH) 207 nm (ϵ 29,850) [lit.[5f] mp 91.5–92.0°; uv max (95% EtOH) 208 nm (ϵ 28,000)]. The nmr and ir spectra of this material were identical with those of authentic ancepsenolide.[5f]

The lactone **1** precipitated from the third hexane extract, 1.14 g, and after chromatography on silicic acid (eluent, benzene followed by benzene–ethyl acetate mixtures in which the ethyl acetate concentration was gradually increased to 10%) and recrystallization from aqueous isopropyl alcohol, it was obtained as a white solid: mp 81.1–82.9°; $[\alpha]_D$ −8.3° (0.47, $CHCl_3$); uv max (95% EtOH) 204 nm (ϵ 17,436); ir ($CHCl_3$) 3500 (w, broad), 1740 (s, broad, width at half intensity, 1700–1770), 1215 cm^{-1} (s, broad); nmr ($CHCl_3$) δ 7.02 (q, 1, J = 1.5 Hz, H-3), 4.78–5.42 (complex multiplet, 4, CO_2H, H-4, 15′,14′), 2.08 (two partially resolved singlets, acetates), 1.40 (d, J = 7 Hz, C-4 methyl), 1.28 ppm (methylene protons and C-15′ methyl partially visible as a shoulder at 1.2). Essentially the same spectrum was obtained in deuteriodimethyl sulfoxide and addition of D_2O to the sample in this solvent resulted in the loss of absorption amounting to one proton in the region of 5.4–6.1 ppm.[11]

At 220 MHz ($CDCl_3$/deuterioacetone) the following peaks were observed: 7.02 (q, J = 1.5 Hz, H-3), 5.15 (m, 2, H-14′,15′), 5.0 (dq, 1, J = 6.5, 1.5 Hz, H-4), 2.21 (t, J = 7.5 Hz, allylic methylene), 2.00, 2.02 (singlets, acetates), 1.35 (d, J = 6.5 Hz, C-4 methyl), 1.28 (s, methylene protons), 1.17 (d, J = 6 Hz, C-15′ methyl).

Anal. Calcd for $C_{26}H_{42}O_3$: C, 64.73; H, 8.71; neut equiv, 482. Found: C, 64.85; H, 8.82; neut equiv, 478. Acetyl analysis. Calcd for two acetates: 17.84. Found: 16.91.

Conversion of 1 to 2a.—A solution of 0.198 g of **1** (0.411 mmol) in 30 ml of methanol containing a few drops of concentrated hydrochloric acid was heated under reflux for 8 hr and then allowed to stand at room temperature for 5 days. Most of the methanol was removed at reduced pressure (aspirator) and the residue was dissolved in ether. The ether solution was washed with bicarbonate solution, then water, and finally dried over anhydrous sodium sulfate. Evaporation of the ether afforded **2a** in quantitative yield: mp (after recrystallization from aqueous isopropyl alcohol) 115.4–115.9°; *m/e* 380; ir ($CHCl_3$) 3320–3540 (broad peak, OH), 1752 cm^{-1} (strong, broad, lactone C=O); uv (95% EtOH) λ_{max} 209 nm (ϵ 16,694); nmr ($CDCl_3$) δ 7.03 (q, H-3), 5.0 (m, H-4); 4.25–4.85 (superimposed m's, H-14′,15′), 1.42 (pr of d, C-4,15′ methyls), 1.27 (s, polymethylene).

Acetylation of 2a.—Treatment of 78 mg (0.206 mmol) of **2a**, mp 113.6–115.1°, with pyridine–acetic anhydride (10 ml/1 ml) at room temperature for 24 hr followed by the usual work-up produced **2b** in quantitative yield: mp 55.4–56.5° after recrystallization from aqueous isopropyl alcohol; ir ($CHCl_3$) 1745 (acetate and pentenolide carbonyls), 1772 cm^{-1} (satd lactone); uv (95% EtOH) λ_{max} 209 nm (ϵ 18,840); nmr ($CDCl_3$) 7.02 (q, 1, H-3), 5.62 (dd, 1, J = 3, 5 Hz, H-14′), 5.0 (poorly resolved dq, 1, H-4), 4.59 (dq, 1, J = 3, 6.5 Hz, H-15′), 2.13 (s, acetate), 1.40 [pr of d, partially obscured by methylene peak; in benzene a pr of d at 1.03, J = 6.5 Hz (each), lactone methyls], 1.28 ppm

(8) See, for example, R. H. Bible, "Interpretation of NMR Spectra," Plenum Publishing Co., New York, N. Y., 1965, p 35 ff.

(9) L. S. Ciereszko, *J. Chem. Educ.*, **43**, 252 (1966).

(10) See, however, footnote 7, ref 5 g.

(11) This rather high field position for carboxyl proton absorption may be accounted for in part by the dilute solutions used for determining the spectrum of **1** owing to its limited solubility in $CDCl_3$: see F. A. Bovey, "Nuclear Magnetic Resonance Spectroscopy," Academic Press, New York and London, 1969, pp 82–85. Factors similar to those responsible for the upfield shift of the carboxyl protons in oospolide and related structures may also be operative in the case of **1**; see K. Nitta and Y. Yamamoto, *Tetrahedron Lett.*, 4231 (1968).

(s, polymethylene). This material is isomeric with the hydroxyancepsenolide acetate reported earlier.[5g]

Anal. Calcd for $C_{24}H_{38}O_6$: C, 68.25; H, 9.24. Found: C, 68.39; H, 9.16.

Dehydration of 2a.—Phosphorous oxychloride–pyridine dehydration of 129 mg of **2a** in the manner described for hydroxyancepsenolide[5g] afforded 96 mg (78%) of ancepsenolide: mp 91.5–94.0° after recrystallization from chloroform–hexane, $[\alpha]^{27}_{589}$ +43.3° (2.98, $CHCl_3$); infrared and nmr spectra for this product were identical with those reported for ancepsenolide;[5f,g] mmp [with an authentic sample of ancepsenolide (mp 89.5–91.5°)] 89.5–92.0°.

Registry No.—**1**, 27261-77-4; **2a**, 27261-78-5; **2b**, 27261-79-6; **3**, 27261-80-9.

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Notes

The Synthesis of (−)-$\Delta^{9(11)}$-*trans*-Tetrahydrocannabinol

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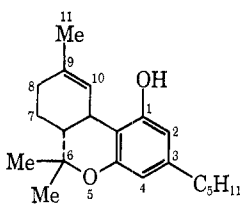
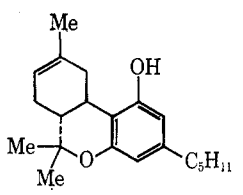
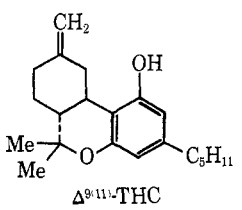
The growing interest in the chemistry and pharmacology of cannabinoids,[1] which include the active constituents of marijuana and hashish, has created a need for new methods of synthetically altering the basic dibenzopyran skeleton. We wish to describe the preparation and properties of $\Delta^{9(11)}$-*trans*-tetrahydrocannabinol ($\Delta^{9(11)}$-THC), which provides a key intermediate for the introduction of new functionalities at either C-9 or C-11.



Δ^9-THC



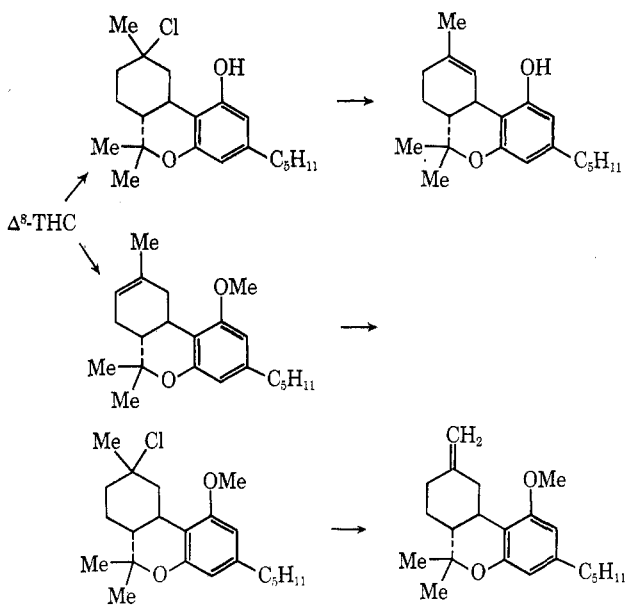
Δ^8-THC



$\Delta^{9(11)}$-THC

Although a total synthesis of racemic $\Delta^{9(11)}$-THC has been reported,[2] for biochemical studies it is desirable to have a ready source of the optically active isomer of the natural configuration. We therefore sought a method for the conversion of the readily available Δ^8 or Δ^9 isomers to $\Delta^{9(11)}$-THC. This contrathermodynamic conversion was accomplished by E2 elimination of the hydrogen chloride adduct of Δ^8- (or Δ^9-) THC (Scheme I), using the sterically hindered base potas-

SCHEME I



sium tricyclopentylcarbinolate, following the procedure recently described by Acharya and Brown.[3] It was first necessary, however, to protect the phenolic hydroxyl group, thus blocking any intramolecularly assisted elimination involving the phenolate anion (Scheme I. This intramolecular process has previously been ingeniously exploited in the conversion of Δ^8- to Δ^9-THC[2,4]).

The methyl ether was selected as a protecting group because of its stability to both the acidic and basic conditions employed in the reaction sequence and was readily obtained[5] in greater than 90% yield. Conversion of the methyl ether to the hydrogen chloride

(1) For a review, see R. Mechoulam and Y. Gaoni, *Fortschr. Chem. Org. Naturst.*, **25**, 175 (1967).

(2) K. E. Fahrenholtz, M. Lurie, and R. W. Kierstead, *J. Amer. Chem. Soc.*, **89**, 5934 (1967).

(3) S. P. Acharya and H. C. Brown, *Chem. Commun.*, 305 (1968).

(4) T. Petrzilka and C. Sikemeier, *Helv. Chim. Acta*, **50**, 1416 (1967).

(5) G. Brieger, D. Hachey, and T. Nestrick, *J. Chem. Eng. Data*, **13**, 581 (1968).