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The oxidation profile at C-18 of furanocembranolides may provide a taxonomical marker for several genera of octocorals

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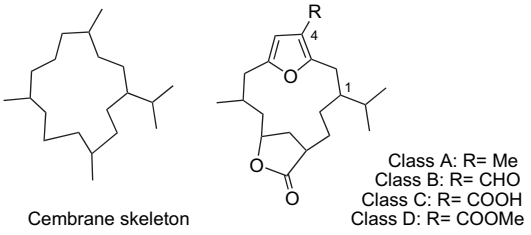
Abstract—The furanocembranolides **1–3** along with the known compounds pukalide, pukalidealdehyde, epoxypukalide, and leptolide were isolated from *Leptogorgia* spp. and their structures were determined by spectroscopic evidences. An NMR-based method using Pirkle's reagent at low temperature allowed us to determine the absolute configuration at C-10 of a γ-butenolide unit embedded in a flexible furanocembranolide network. The C-18 of furanocembranolides undergoes an oxidation cascade leading from a methyl group to a carboxylic acid/ester that appears to be genus specific. We introduce the concept *genus-specific oxidation*, a feature that provides a chemotaxonomical marker for several genera of octocorals. This concept also allowed us to propose a biogenetic pathway for these compounds.

1. Introduction

Octocorals of the genera *Pseudopterogorgia*, *Alcyonium*, *Gersemia*, *Lophogorgia*, *Leptogorgia*, and *Sinularia* have the ability to biosynthesize furanocembranolides,[1] highly oxygenated diterpenoids based on the 14-membered carbocyclic cembrane skeleton into which a substituted furan ring and a γ-lactone subunit have become embedded. Studies to date indicate that certain members of the family exhibit potent neurotoxicity,[2] in addition to antiinflammatory,[3] antifeedant activity,[4] and other biological properties.[5] Furanocembranolides have also been popular targets for total synthesis.[6]

Based on a survey on marine furanocembranolides,[7] they may be divided into four classes: those in which the substituent at the C4 position is a CH_3 (class A), and those with a more highly oxidized substituent, CHO (class B), COOH (class C), and CO_2Me (class D). The methyl group on the furan ring is prone to be oxidized in metabolites from *Pseudopterogorgia*, *Lophogorgia*, *Leptogorgia*, and *Sinularia*, the degree of oxidation varying from one genus to another. Thus, the genus *Pseudopterogorgia* is rich in furanocembranolides of classes A and C, but lacks furanocembranolides of classes B and D. The genus *Leptogorgia* produces furanic aldehyde (class B) and methyl ester derivatives (class D) whereas the genus *Lophogorgia* and *Sinularia* exclusively biosynthesize aldehyde (class B) and methyl ester derivatives (class D), respectively.



From the genera *Alcyonium* and *Gersemia* only furanocembranolides of class A have been found, no oxidized cembranoids of classes B–D have been reported.[7] It is worth to note that no naturally occurring hydroxylic intermediate has ever been reported.

2. Results and discussion

The search for marine natural products in benthic species from both sides of the Isthmus of Panama[8] prompted us to study the eastern Pacific octocoral *Leptogorgia* spp. In this paper, we report on the structures of three new furanocembranolides **1–3** along with the known compounds pukalide[9] **4**, pukalidealdehyde[10] **5**, epoxypukalide[11] **6**, and leptolide[12] **7** isolated from this species. Compounds **1–3**, **4**, and **6** fall in

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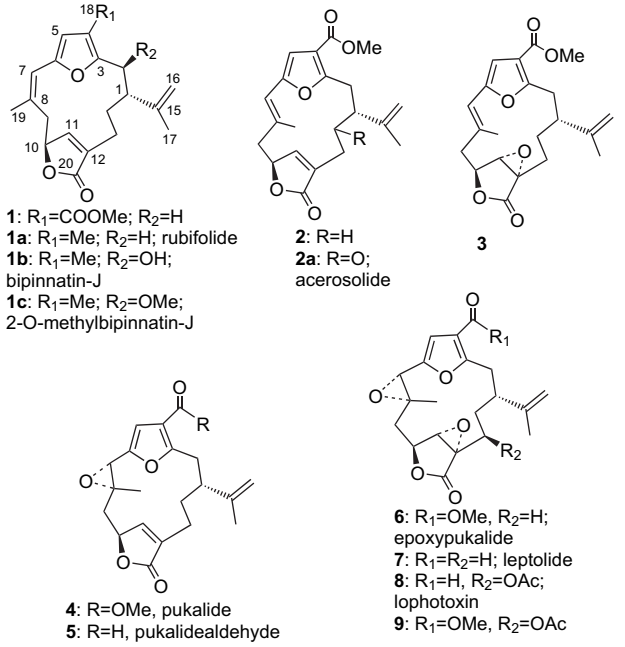
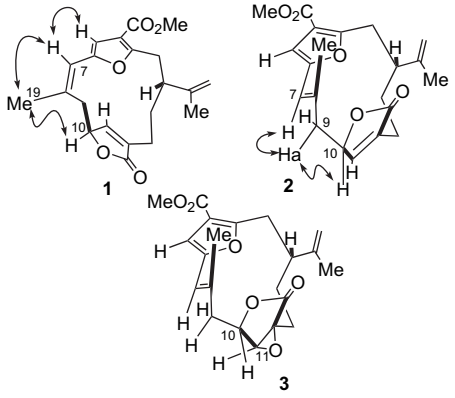
class D, **5** and **7** in class B. Compounds **1**–**7** were obtained from the crude extract of the octocoral *Leptogorgia* spp. collected at Jicarita Island, Gulf of Panama, after flash chromatography followed by gel filtration on Sephadex LH-20 and successive HPLC.



2.1. Structural elucidation

(*Z*)-Deoxypukalide **1** was a colorless oil, $[\alpha]_D^{20}$ +11 (*c* 0.4, $CHCl_3$), with a mass of 356.1636 corresponding to an elemental composition of $C_{21}H_{24}O_5$ indicating 10 degrees of unsaturation. The ^1H and ^{13}C NMR spectra of **1** (Table 1) were superimposable with those of a described synthetic (*Z*)-deoxypukalide whose relative stereochemistry was confirmed by X-ray structural analysis.[13] Thus, the relative configuration of (*Z*)-deoxypukalide is as depicted in **1**. The observed NOE (Scheme 1) between H_3-19/H-7 and H-10 is consistent with *Z* geometry of Δ^{7-8}-bond.



Scheme 1. Selected NOEs of furanocembranolides.

(*E*)-Deoxypukalide **2** was an unstable colorless oil, $[\alpha]_D^{20}$ +79.3 (*c* 0.63, $CHCl_3$), with a mass of 356.1636 corresponding to an elemental composition of $C_{21}H_{24}O_5$. The MS spectra of **2** and **1** showed the same molecular ion and a similar fragmentation pattern. The NMR spectroscopic data of **2** resembled those of compound **1**, except when the chemical shift of the respective C-19 methyl group and C-8 was compared. The observed differences suggested that both compounds are geometrical isomers at the C-7–C-8 double bond. This was assessed by comparing the C-19 and C-8 chemical shifts, Table 2, of related (*Z*)-Δ^{7-8}-furanocembranolides with the corresponding carbons of

Table 1. NMR data of compounds **1**–**3** [500 MHz, δ ppm, (*J*) Hz, $CDCl_3$]

H#/C#	Compound **1**			Compound **2**			Compound **3**		
	δ_H	δ_C	HMBC	δ_H	δ_C	HMBC	δ_H	δ_C	HMBC
1	2.41 dd (3.5, 14.4)	42.6	2, 14, 16	2.93 m	42.7	13, 15	2.30 m	46.0	3, 15
2	3.48 dd (12.9, 16.7)	32.3	1	2.95 m	32.6	16	3.35 dd (4.7, 14.4)	30.8	1, 3, 14, 15
	2.67 dd (3.6, 16.7)		1, 3, 4, 14				2.81 m		1, 3
3		160.7			160.3			160.0	
4		115.9			114.9			115.6	
5	6.42 s	110.7	6, 7, 18	6.36 s	108.3	3, 4, 6	6.45 s	108.8	3, 4, 6
6		150.6			148.6			149.6	
7	6.10 s	116.8	6, 8, 9, 19	5.96 s	118.4	6, 9, 19	6.11 s	119.4	5, 6, 9, 19
8		130.1			140.9			137.8	
9	3.13 dd (11.8, 11.8)	39.9	7, 8, 10, 11, 19	2.96 m	41.3	7, 10	2.85 dd (3.0, 14.4)	41.0	7, 8, 10, 11, 19
	2.75 dd (4.2, 11.9)		7, 8, 10, 11, 19	2.56 d (11.4)			2.58 dd (3.3, 14.1)		7, 8, 19
10	5.0 dd (4.2, 11.8)	78.5		5.16 s	79.9		4.72 dd (3.0, 3.3)	77.9	8, 11, 12, 20
11	6.94 s	151.5	10, 12, 13, 20	6.90 s	149.2	10, 20	4.03 s	61.1	10, 12, 20
12		133.3			136.1			60.9	
13	2.10 m	19.9	1, 14, 20	2.39 dd (12.7, 12.7)	21.7	1, 12, 14	2.00 m	22.6	11, 12, 14
	2.45 m		1, 12, 14, 20	2.23 d (6.3)		1, 12, 20	1.13 m		1, 14
14	1.76 m	32.0	12	1.69 m	32.5	1, 15	1.48 m		15
	1.12 ddd (3.6, 13.9, 16.9)		13, 15	1.28 m			1.33 m		
15		144.8			145.9			147.9	
16	4.92 dd (1.5, 1.5)	113.5	1, 17	5.07 s, 4.91 s	112.6	1, 17	4.74 dd (1.3, 1.3)	110.1	1, 15, 17
	4.89 s						4.67 s		
17	1.75 s	19.1	1, 15, 16	1.77 s	19.2	1, 15, 16	1.74 s	20.6	1, 15, 16
18		164.1			164.1			163.7	
19	2.01 s	25.8	7, 8, 9	1.73 s	22.5	7	1.90 s	22.6	7, 8, 9
20		174.2			174.2			171.7	
O*Me*	3.78 s	51.4	18	3.78 s	51.0	18	3.80	51.1	18

Table 2. $\delta_{C\text{-}19}$, $\delta_{C\text{-}8}$ and $\Delta\delta$ of some furanocembranolides

#	(*Z*)-C7–C8		#	(*E*)-C7–C8		$\Delta\delta_C$	
	$\delta_{C\text{-}19}$	$\delta_{C\text{-}8}$		$\delta_{C\text{-}19}$	$\delta_{C\text{-}8}$	$\Delta\delta_{C\text{-}19}$	$\Delta\delta_{C\text{-}8}$
1	25.8	130.1	**2**	22.5	140.9	3.3	10.8
1a	25.7	127.0	**3**	22.6	137.8	3.1	10.8
1b	25.7	128.9	**2a**	22.0	139.4	3.7	10.5
1c	25.9	129.4					

(*E*)-Δ^{7-8}-furanocembranolides, for example: compound **1**, rubifolide[14] **1a**, bipinnatin-J[15] **1b**, 2-*O*-methylbipinnatin-J[16] **1c** versus compound **2** and acerolide[17] **2a**.

Despite the fact that the metabolites tabulated in Table 2 belong to class A (entry **1a**–**1c**) or class D (**1**–**3**, **2a**) they showed, in their respective geometrical configurations, a regular chemical shift for C-19 (*Z*∼25 ppm, *E*∼22 ppm), whereas fluctuation of the C-8 resonance (*Z*: 127.0→130.1 ppm, *E*: 137.8→140.9 ppm) suggested this carbon is sensitive to the surrounding influences. However, the chemical shift average of C-8 is so large and differentiated that the combination of both data (δ_C and $\Delta\delta_C$) provides a useful rule to assess the geometry of the C7–C8 double bond on the flexible network of furanocembranolides of classes A–D.

The *E*-geometry of the C-7–C-8 double bond of **2** was also reinforced by NOESY experiments as shown in Scheme 1. In the energy-minimized[18] conformation **2**, the interatomic distances from H-7 and H-10 to Ha-9 given by the program are in agreement with the observed NOEs. Therefore, **2**, named (*E*)-deoxypukalide, is the *E* geometrical isomer of **1**.

Isopukalide **3** was isolated as an oil, $[\alpha]_D^{20}$ +79 (*c* 0.62, $CHCl_3$). NMR data coupled with a molecular ion at *m*/*z* 372.1589 (HREIMS) suggested a molecular formula of $C_{21}H_{24}O_6$ indicating 10 degrees of unsaturation. The fact that the molecular formula differs by 16 mass units from that of compounds **1** and **2**, but conserving the same degree of unsaturation suggested that a double bond of one of those compounds was epoxidized. By comparison of the chemical shift of C-19 and C-8 with those of the corresponding carbons of compounds **1** and **2**, Table 1, it can be inferred that the C-7–C-8 olefinic bond of **3** is not epoxidized and that its geometry was *E* (Table 2). Also, from the NMR spectroscopic data it was readily apparent that the butenolide unit of **2** changed to a corresponding epoxybutanolide in **3**. This was confirmed by the HMBC correlations H-10/C-8, C-11, C-12, C-20; H-11/C-10, C-12, C-20 and by comparison of the spectroscopic data of compound **3** with those of the positional isomer pukalide **4**.[9]

A dihedral angle of 91.3° for H-10/H-11 given by the program in the energetically favorable conformation **3** (Scheme 1) proved to be in good agreement with the absence of coupling for H-11 (δ 4.03, s, Table 1) and confirms the relative stereochemistry of C-10 and C-11 as represented in **3**. All the compounds **1**–**7** characterized in this work belong to the α series of cembranolides as depicted in Scheme 1.

2.2. Absolute configuration

An NMR-based method using Pirkle's reagent at low temperature has proven to be useful to assign the absolute configurations to a γ-butenolide-containing diterpene,[19] a fatty acid di-γ-lactone[8c] in addition to annonaceous butenolides.[20] We believe that this method may also be applicable to determine the absolute configuration at C-10 of the γ-butenolide unit embedded in a flexible furanocembranolide network. The orientation of the aromatic system of the chiral solvating agent (CSA) should be asymmetric with respect to the butenolide ring plane. Thus, the geometry of the CSA–substrate complex must produce selective shielding effects on protons of the substrate moiety. To prove the method, (*R*)- and (*S*)-2,2,2-trifluoro-1-(9-anthryl)-ethanol (TFAE) were used to form complexes with the γ-alkyl-γ-lactone fragment of the known (+)-pukalide **4**, also isolated in this work, and whose absolute stereochemistry was recently established.[12] It can be predicted that the signals for (*S*,*S*) or (*R*,*R*) solvates would appear upfield for H-10 and downfield for H_2-9 compared with their respective (*R*,*S*) or (*S*,*R*) solvates.[20] Therefore, if $\Delta(\delta_{H\text{-}10R}-\delta_{H\text{-}10S})$ is positive and/or $\Delta(\delta H_{2\text{-}9R}-\delta H_{2\text{-}9S})$ is negative then the absolute configuration at C-10 is *S*. NMR analysis of $\Delta\delta$ of H-10 and $\Delta\delta$ of H_2-9 of the two complexes, tabulated in Table 3, gave clear evidence to assign the absolute stereochemistry at C-10 as 10*S*. The *S* configuration at C-10 as well as the sign of the optical rotation agrees with those given[12] for (+)-pukalide (+43, +35 in this work).

Since the goodness of the method was established it was applied to resolve the absolute configuration of the novel compound **1**. NMR analysis of $\Delta\delta$ of H_2-9 of the two complexes is tabulated in Table 4. H-10 does not experience significative variation giving a $\Delta\delta\cong 0$. However, the negative sign and the magnitude of $\Delta\delta_{H\text{-}9a}$ and $\Delta\delta_{H\text{-}9b}$, very similar to that found for (+)-pukalide, evidence an identical 10*S* absolute stereochemistry for C-10 of compound **4**. This was also indirectly verified since the synthetic *ent*-(*Z*)-deoxypukalide, obtained from (*S*)-(−)-perillyl alcohol,[13] is the enantiomer of our (*Z*)-deoxypukalide **1** derived from the natural source. The optical rotation reported[13] for the synthetic compound *ent*-(*Z*)-deoxypukalide was −21.7 whereas +11 is given in this work for the natural metabolite. Thus, we propose the absolute configuration of **1** as depicted in the structure block. Since the naturally occurring compounds **1**–**3** and our pukalide **4** have been isolated from the same coral specimen it should be expected that all these compounds belong to the same enantiomeric series.

The present study provides a convenient NMR-based method alternative to Mosher's method to determine the

Table 3. $\delta_{H\text{-}10}$, $\delta_{H\text{-}9a}$, and $\delta_{H\text{-}9b}$ of pukalide **4** with (*R*)- and (*S*)-TFAE at 240 K

(*R*)- or (*S*)-TFAE (equiv)	$\delta_{H\text{-}10(R)}$	$\delta_{H\text{-}10(S)}$	$\Delta(\delta_{H(R)}-\delta_{H(S)})$
6	5.11516	5.11613	−0.00097
12	5.06189	5.05995	+0.00194
24	4.95050	4.90400	+0.04650
(*R*)- or (*S*)-TFAE (equiv)	$\delta_{H\text{-}9a(R)}$	$\delta_{H\text{-}9b(S)}$	$\Delta(\delta_{H(R)}-\delta_{H(S)})$
6	2.46647	2.47906	−0.01259
12	2.41513	2.43644	−0.02131
(*R*)- or (*S*)-TFAE (equiv)	$\delta_{H\text{-}9b(R)}$	$\delta_{H\text{-}9b(S)}$	$\Delta(\delta_{H(R-}\delta_{H(S)})$
6	2.05674	2.09501	−0.03827
12	1.99427	2.04658	−0.05231

Table 4. $\delta_{H\text{-}9a}$ and $\delta_{H\text{-}9b}$ of compound **1** with (*R*)- and (*S*)-TFAE at 240 K

(*R*)- or (*S*)-TFAE (equiv)	$\delta_{H\text{-}9a(R)}$	$\delta_{H\text{-}9b(S)}$	$\Delta(\delta_{H(R)}-\delta_{H(S)})$
6	3.05588	3.07428	−0.01840
12	3.01326	3.04232	−0.02906
(*R*)- or (*S*)-TFAE (equiv)	$\delta_{H\text{-}9b(R)}$	$\delta_{H\text{-}9b(S)}$	$\Delta(\delta_{H(R)}-\delta_{H(S)})$
6	2.67666	2.71250	−0.03584
12	2.62295	2.68441	−0.06146

absolute configuration of γ-butenolide-containing furanocembranolides devoid of a secondary hydroxyl group.

2.3. Taxonomical marker

Octocorals may contain algal symbionts, the zooxanthellae, that contribute to the nutrition of the host. For a long time zooxanthellae were believed to be the sole producers of terpenoids in the symbiotic association. However, the isolation of terpenoids from the azooxanthellate gorgonian *Lophogorgia alba* was interpreted as evidence that the animal itself was responsible for their production.[21] It was not until very recently[22] that biosynthetic studies of freshly metamorphosed coral polyps, both with and without zooxanthellae, have unequivocally demonstrated that control over production of terpenoid secondary metabolites lies in the coral host and that zooxanthellae are not essential for their production. Since the coral host is the true terpenoid producer, these compounds may be of chemotaxonomical importance.

We have observed that the degree of oxidation of C-18 of naturally occurring cembranolides is independent, within the genus, of the latitude where the producers are located. Indeed, since the first furanocembranolide was reported[9] in 1975 over 70 naturally occurring furanocembranolides have been discovered and they all, except one, agree with the pattern represented by classes A–D, Table 4. Lopholide **9**, which has been isolated from *Sinularia* and *Leptogorgia* spp.[12] belongs to genus/class D, however, its recent isolation from a species of genus *Lophogorgia*[23] (class B) makes this report the only exception that does not fit into this pattern.

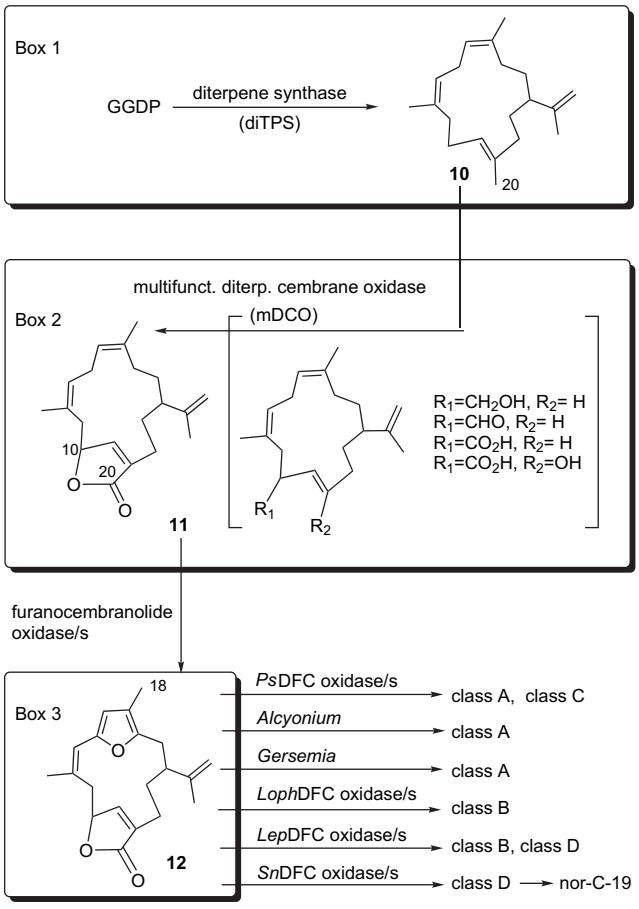
The oxidation profile of C-18 allows us to introduce the concept of *genus specific oxidation*, which provides a criterion as chemotaxonomical marker for octocorals as it is shown in Table 4. The Me-18 oxidation cascade may evolve until the methyl group is lost in a decarboxylative step, giving rise to norcembranolide-type metabolites characteristics of genus *Sinularia*, Table 5. Since the taxonomical work is difficult and time consuming the rationalization of genus/classes A–D correlation seems a relevant tool to facilitate taxonomical work dealing with several genera of octocorals.

Table 5. Correlation genus/classes A–D and nor-C-18 furanocembranolides

Genus	Class A	Class B	Class C	Class D	nor-C-18
Pseudopterogorgia (*Ps*)	X		X		
Alcyonium	X				
Gersemia	X				
Lophogorgia (*Loph*)		X			
Leptogorgia (*Lep*)		X		X	
Sinularia (*Sn*)				X	X

2.4. Biogenetic pathway

Biosynthesis of diterpene furanocembranolides (DFC) involves the formation of geranylgeranyl diphosphate (GGDP) and cyclization of GGDP by an organism-specific diterpene synthase (diTPS) to form a basic cembrane skeleton **10**, Box 1, Scheme 2.



Scheme 2. Proposed biogenetic pathway of furanocembranolides.

Whereas levels of oxidation of the C-18 is genus dependent, as said before, the corresponding Me-20 is implied in the formation of a γ-lactone subunit common to all six genera. This suggested that the biosynthesis of the γ-lactone moiety is prior to the oxidation of C-18. Thus, from cembrane **10** we speculated that an array of consecutive oxidations at C-20 to a carboxylic acid resembles a similar oxidation pathway catalyzed by a multifunctional P450 enzyme in the oxidation of a methyl substituent of *ent*-kaurene en route to *ent*-kaurenoic acid.[24] The C-20 carboxylic acid derivative is subjected to hydroxylation at C-10 leading to γ-lactone **11**, Box 2, without the apparent release of any C-20 alcohol, aldehyde, or acid intermediates (compounds in brackets).

The successive oxidation reactions at C-20 and C-10 may occur sequentially within a single catalytic cascade. Oxidations at multiple sites by a single P450 enzyme have been reported for monooxygenases involved in steroid biosynthesis.[25] This suggested that a related multifunctional diterpene cembrane P450-dependent monooxygenase (mDCO) may well operate in the biosynthesis of the γ-lactone subunit of

DFC. The network **11** may then be the matrix that evolves to a C-18 substituted furan ring derivative **12**, Box 3. Such a C-18 methyl group is prone to be enzymatically oxidized giving rise to classes A–D of DFC.

The regular correlation of genus/classes A–D suggests that the P450 enzymes involved in the sequential oxidation at a single C-18 carbon atom have narrow substrate specificity within the genus to preserve biosynthetic pathway. In this arena, species of genus *Lophogorgia* leading to C-18 aldehyde end products (Me→aldehyde) without releasing any alcohol intermediates, *Pseudopterogorgia* leading to carboxylic acid end products in three consecutive oxidation steps (Me→carboxylic acid) without releasing any alcohol or aldehyde intermediates, *Leptogorgia* with the release of aldehyde intermediates en route to a methyl ester derivatives and genera *Alcyonium* and *Gersemia* apparently devoid of C-18 oxidizing enzymes, may provide, as a whole, a valuable biological model toward a biochemical, functional genomic approach to identify the P450 gene clusters involved in the multiple oxidation profile leading to the structural diversity of DFC secondary metabolites. Understanding how genetic information is correlated with chemical structures would also prove useful in regard to secondary metabolites as taxonomical characters and evolutionary markers.

3. Experimental

3.1. General procedures

Optical rotations were measured on a Perkin–Elmer model 343 Plus polarimeter using a Na lamp at 25 °C. IR spectra were obtained with a Perkin–Elmer 1650/FTIR spectrometer. ^{1}H and ^{13}C NMR, HSQC, HMBC, and COSY spectra were measured employing a Bruker AMX 500 instrument operating at 500 MHz for ^{1}H NMR and at 125 MHz for ^{13}C NMR. Two-dimensional NMR spectra were obtained with the standard Bruker software. EIMS and HRMS data were taken on a Micromass Autospec spectrometer. HPLC separations were performed with a Hewlett–Packard 1050 (Jaigel-Sil semipreparative column, 10 μm, 20×250 mm) with hexane–EtOAc mixtures. The gel filtration column (Sephadex LH-20) used hexane–MeOH–CH_2Cl_2 (3:1:1) as solvent. The spray reagent for TLC was H_2SO_4–H_2O–AcOH (1:4:20).

3.2. Biological material

Leptogorgia spp. were collected by SCUBA diving off Jicarita (Panama) at −15 m. A voucher specimen has been deposited at Smithsonian Tropical Research Institute (Panama) with code 200511.

3.3. Extraction and isolation

Wet samples were extracted with acetone at room temperature and concentrated to give a dark residue (30.0 g). The extract was partitioned between EtOAc (3×75 ml) and water (75 ml). The EtOAc extracts were combined to obtain a brown oil (8.1 g) that was chromatographed on an LH-20 column, followed by a silica-gel column. Fractions containing cembranolides, as indicated by their ^{1}H NMR spectra, were further chromatographed by HPLC to give compounds **1** (9.9 mg), **2** (26.6 mg) (unstable), **3** (11.3 mg), and the known compounds pukalide **4** (13.3 mg), pukalidealdehyde **5** (46.5 mg), epoxypukalide **6** (19.9 mg), and leptolide **7** (61.1 mg).

3.3.1. Compound 1. Colorless oil; $[\alpha]_D^{20}$ +11 (*c* 0.37, $CHCl_3$); IR (film) ν_{max} 2937, 1750, 1716, 1435, 1229, 1071 cm^{-1}; for ^{1}H and ^{13}C NMR, see Table 1; EIMS *m/z* 356 $[M]^+$ (74), 324 (49), 228 (45), 191 (100); HREIMS 356.1621 (calcd for $C_{21}H_{24}O_5$ 356.1623).

3.3.2. Compound 2. Colorless oil; $[\alpha]_D^{20}$ +79 (*c* 0.63, $CHCl_3$); IR (film) ν_{max} 2947, 1749, 1442, 1224, 1076 cm^{-1}; for ^{1}H and ^{13}C NMR, see Table 1; EIMS *m/z* 356 $[M]^+$ (55), 324 (34), 228 (40), 191 (100); HREIMS 356.1636 (calcd for $C_{21}H_{24}O_5$ 356.1623).

3.3.3. Compound 3. Colorless oil; $[\alpha]_D^{20}$ +70 (*c* 0.62, $CHCl_3$); IR (film) ν_{max} 2946, 1777, 1709, 1444, 1229, 1085 cm^{-1}; for ^{1}H and ^{13}C NMR, see Table 1; EIMS *m/z* 372 $[M]^+$ (100), 340 (48), 192 (71), 133 (85); HREIMS 372.1589 (calcd for $C_{21}H_{24}O_6$ 372.1572).

3.3.4. Compound 4. Colorless oil; $[\alpha]_D^{20}$ +35 (*c* 0.74, $CHCl_3$).

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Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2007.06.080.

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