Pseudopterane and Norcembrane Diterpenoids from the Caribbean Sea Plume *Pseudopterogorgia acerosa*

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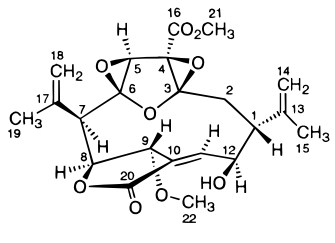
Received August 13, 1997

A chemical study of the common Caribbean sea plume *Pseudopterogorgia acerosa* from Puerto Rico has produced two previously undescribed secondary metabolites. One of them, **1**, is a new representative of the pseudopterane family of diterpenes possessing the uncommon 3,4;5,6 diepoxyfuran moiety. The other metabolite, **2**, is a rare norcembranolide diterpene. Their chemical structures, including relative stereochemistry, were established by detailed analysis of the spectral data in addition to NMR spectral comparisons with known pseudopterane and cembrane models.

Sea plumes of the genus *Pseudopterogorgia* are abundant and chemically rich marine invertebrates responsible for the production of several classes of structurally complex metabolites.[2] Several Caribbean species of *Pseudopterogorgia* are well-known for their ability to biosynthesize diterpenoids based on the 12-membered carbocyclic pseudopterane skeleton.[3] Because pseudopterane and cembrane diterpenes have been reported to co-occur in several of these species, it has been suggested that the pseudopterane skeleton might arise from a ring contraction of a cembrane.[4] Pseudopterane and cembrane diterpenoids have also been found to coexist in Pacific Ocean specimens of the cold water soft coral *Gersemia rubiformis*.[5] Since 1990, more than 20 pseudopteranoids, some of them containing nitrogen, have been reported from specimens of *P. acerosa* collected around Puerto Rico and the coast of Tobago.[6] In continuation of our investigation of the extracts of Puerto Rican specimens of this organism we report here the isolation and structure determination of two additional metabolites. One of these, *β*,*β*-diepoxypseudopterolide−MeOH adduct (**1**), is structurally related to the known metabolite pseudopterolide−MeOH adduct (**3**),[6d] and gorgiacerolide (**2**) represents the first norcembrane diterpene isolated from a species of *Pseudopterogorgia*.



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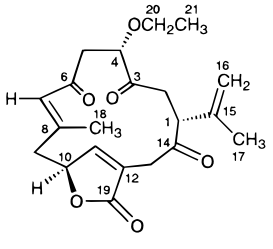

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A single collection of *P. acerosa* from La Parguera, Puerto Rico, produced 6.7 kg of the wet gorgonian coral.[6f] Partitioning of an aqueous suspension of the crude extract against hexane and H_2O gave lipophilic solubles (368.0 g), which accounted for 58.0% of the total organic content of *P. acerosa*. Re-extraction of the lipid-free aqueous suspension with $CHCl_3$ followed by concentration yielded 39.3 g (6.2%) of organic solubles. A total of 12 pseudopteranoids were obtained pure from the latter extract after routine application of adsorption and normal-phase chromatography, namely, pseudopterolide, pseudopterolide−MeOH adduct (**3**), deoxypseudopterolide, gorgiacerodiol, isogorgiacerodiol, pseudopteradiene, pseudopteradienoic acid, 11-pseudopteranol, pseudopteranoic acid, diepoxygorgiacerodiol, alanolide, and aceropterine.[6] Recent efforts have now provided all the ^{1}H NMR and ^{13}C NMR chemical shift and coupling data shown in Table 1 for the new pseudopteranoid and norcembranoid analogues **1** and **2** described here for the first time.

The HRFABMS of *β*,*β*-diepoxypseudopterolide−MeOH adduct (**1**) established its molecular formula as $C_{22}H_{26}O_9$, signifying 10 sites of unsaturation. IR spectroscopy indicated the presence of hydroxy (3421 cm^{-1}) in addition to olefin (3079 cm^{-1}), unsaturated *γ*-lactone (1740 cm^{-1}), and ester (1736 cm^{-1}) groups common to many of these metabolites. After the ^{1}H NMR and ^{13}C NMR spectra had been obtained, it became evident that the furan moiety present in most pseudopterane derivatives was absent from **1**; however, the isopropenyl side chains, the unsaturated *γ*-lactone, and the 4-carbomethoxy group present in most other pseudopteranoids were intact in compound **1** (Table 1). The presence of two singly oxygenated ^{13}C NMR signals at *δ* 62.5 (s, C-4) and 57.0 (d, C-5) were characteristic of epoxide carbons, and when these signals were combined with the presence of signals for two doubly oxygenated carbons at *δ* 101.0 (s, C-3) and 96.3 (s, C-6), we concluded that the furan ring had been modified by epoxidation.[6c−d,7] Moreover, the signals at *δ* 166.0 (s, C-16) and 53.5 (q, C-21) in the ^{13}C NMR spectrum, coupled with the strong IR absorption at 1260 cm^{-1}, and two singlets in the ^{1}H NMR spectrum at *δ* 4.14 (1H, H-5) and 3.97 (3H, Me-21), indicated that **1** possessed a similar α,α′,*β*,*β*′-

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S0163-3864(97)00385-6 CCC: $15.00
Published on Web 02/25/1998

Table 1. ^{1}H (300 MHz) and ^{13}C (75 MHz) NMR Spectral Data for Compounds **1** and **2** in $CDCl_3$

	1		**2**	
position	δ_H, mult, intrgt (J in Hz)[a]	δ_C (mult)[b]	δ_H,mult, intrgt (J in Hz)[a]	δ_C (mult)[b]
1	3.11, m, 1H	45.0 (d)	3.78, dd, 1H (3.3, 11.1)	55.8 (d)
2a	1.64, dd, 1H (5.4, 16.5)	32.1 (t)	2.49, dd, 1H (3.3, 16.2)	44.4 (t)
2b	2.46, dd, 1H (2.4, 16.5)		3.08, dd, 1H (11.1, 16.2)	
3		101.0 (s)		205.4 (s)[c]
4		62.5 (s)	4.01, br t, 1H (5.7)	80.3 (d)
5	4.14, br s, 1H	57.0 (d)	2.70, d, 2H (5.7)	45.2 (t)
6		96.3 (s)		200.6 (s)
7	2.41, br d, 1H (4.5)	51.9 (d)	6.00, d, 1H (1.2)	124.6 (d)
8	4.90, br d, 1H (4.5)	83.6 (d)		151.8 (s)
9a	4.24, br s, 1H	80.0 (d)	2.77, dd, 1H (6.0, 13.5)	42.9 (t)
9b			2.69, dd, 1H (8.1, 13.5)	
10		131.3 (s)	5.30, br m, 1H	79.6 (d)
11	6.70, d, 1H (9.0)	146.4 (d)	7.45, br s, 1H	150.7 (d)
12	3.86, m, 1H	69.5 (d)		128.2 (s)
13a		144.4 (s)	3.03, br d, 1H (15.3)	36.9 (t)
13b			3.82, br d, 1H (15.3)	
14a	4.92, br s, 1H	114.4 (t)		205.6 (s)[c]
14b	4.95, br s, 1H			
15	1.71, br s, 3H	18.4 (q)		139.9 (s)
16a		166.0 (s)	4.94, br s, 1H	116.3 (t)
16b			5.00, br s, 1H	
17		136.4 (s)	1.70, br s, 3H	20.3 (q)
18a	5.17, br s, 1H	117.3 (t)	2.13, br d, 3H (1.2)	21.5 (q)
18b	5.22, br s, 1H			
19	1.91, br s, 3H	22.3 (q)		173.5 (s)
20a		170.2 (s)	3.43, ddq, 1H (2.1,6.9,22.8)	66.1 (t)
20b			3.51, ddq, 1H (2.1,6.9,22.8)	
21	3.97, s, 3H	53.5 (q)	1.18, t, 3H (6.9)	15.2 (q)
22	3.33, s, 3H	55.2 (q)		
12-OH	4.56, d, 1H (12.0)			

[a] Chemical shift values are in parts per million relative to TMS. Spectra were recorded at 25 °C. [b] ^{13}C NMR multiplicities were obtained by Attached Proton Test (APT) sequences. [c] Values with identical superscripts within a column may be interchanged.

diepoxy-β-carbomethoxyfuran constellation as that found in diepoxygorgiacerone (**4**)[6d] or diepoxygorgiacerodiol.[6f] The carbonyl absorption at 1740 cm^{-1}, along with the 1H signal at δ 6.70 (H-11) and 3H singlet at δ 3.33 (Me-22) in the ^{1}H NMR spectrum, and carbon resonances at δ 170.2 (s, C-20), 146.4 (d, C-11), 131.3 (s, C-10), 83.6 (d, C-8), 80.0 (d, C-9), and 55.2 (q, Me-22) in the ^{13}C NMR spectrum were ascribed to a β-methoxy α,β' unsaturated γ-lactone functionality such as that found in pseudopterolide−MeOH adduct (**3**).[6d] The ^{13}C NMR line pairs observed at δ 144.4 (s, C-13)/136.4 (s, C-17) and 114.4 (t, C-14)/117.3 (t, C-18) and the ^{1}H NMR broad singlets at δ 4.92/4.95 and 5.17/5.22 were confidently assigned to two isopropylene groups. A fourth oxygen-bearing methine was indicated by the ^{1}H signal at δ 3.86 (1H, m, H-12) and the ^{13}C signal at δ 69.5 (d, C-12), which suggested the presence of an allylic secondary alcohol function. Coupling between this proton signal and the olefinic proton signal at δ 6.70 (H-11) was observed in the ^{1}H−^{1}H COSY spectrum. The signal at δ 3.86 (H-12) was likewise shown to be coupled to the methine proton at δ 3.11 (H-1) and to the doublet signal at δ 4.56 (1H, J = 12.0 Hz, 12-OH). The 12-OH signal assignment was confirmed by exchange with CD_3OD and the fact that the signal at δ 4.56 lacked a ^1J-correlation with a ^{13}C signal in a HETCOR experiment. These data effectively established the site of attachment of the hydroxyl group at C-12. Comparisons of the NMR spectral data for **1** with those of pseudopterolide−MeOH adduct (**3**), diepoxygorgiacerone (**4**), and diepoxygorgiacerodiol together with the UV spectrum (λ_{max} = 246 nm; ϵ 1890), led to the conclusion that **1** was the 3,4;5,6 diepoxyfuran derivative of **3**.

Consideration of ^{1}H NMR and ^{13}C NMR data (Table 1) as well as 2D NOE measurements, allowed the relative stereochemistry of **1** to be assigned. In the NOESY spectrum, the δ 4.14 proton (H-5) gave a cross peak with the methine proton at δ 2.41 (H-7), which in turn gave a cross peak with the lactonic methine located at δ 4.90 (H-8). These observations established a cis relative stereochemistry between these protons. The 3,4;5,6-diepoxide function is shown as being on the β-face of **1** on the basis of the strong NOE between H-5 and H-7. The β relative stereochemistry of the epoxides was also established from comparison of the ^{13}C NMR spectral data of **1** with those of diepoxygorgiacerone (**4**) whose epoxy groups were demonstrated to be α-oriented by X-ray crystallographic analysis.[6c] The ^{13}C NMR signals ascribed to C-4 and C-5 in **1** showed considerable differences in chemical shifts and had shifted from δ 59.8 and 54.2 in diepoxygorgiacerone to δ 62.5 and 57.0 in **1**, respectively. Also, H-7 experienced a considerable highfield shift in $CDCl_3$ solution and had shifted from 3.29 ppm in diepoxygorgiacerone (**4**) (3.33 ppm in diepoxygorgiacerodiol) to δ 2.41 in **1**. Epimerization at C-3, C-4, C-5, and C-6 in **1** would account for these spectral differences. The C-5,7,8 constellation was correlated with the C-1,12 array through their NOEs (or lack of them) to H-9. Thus, the proton signals at δ 2.41 (H-7) and 6.70 (H-11) each gave NOE responses to the one-proton signal at δ 4.24 (H-9). H-11, in turn, showed strong NOEs with H-12 (δ 3.86) and Me-22 (δ 3.33). This established the α-orientation of H-12. Moreover, an intense NOE between H-2a (δ 1.64) and H-12 argued for a cis (α) relative stereochemistry between these protons. On the other hand, the absence

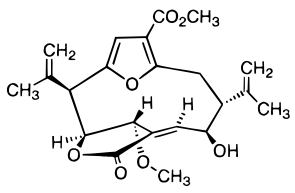
of a NOE response between H-12 and H-1 (δ 3.11) suggested a trans relationship between them [a weak NOE cross peak between H-1 and H-2b (δ 2.46) confirmed the β-configuration of the former proton].

β,β-Diepoxypseudopterolide−MeOH adduct (**1**) has a logical structure from a biosynthetic viewpoint. Compound **3** could be envisioned as a precursor for **1** via oxidation of the 2,5-dialkyl-3-(carboxymethyl)furan functionality. With the carbomethoxyfuran ring moiety in **3** hanging almost perpendicularly over the γ-butyrolactone ring, the "back" molecular face is clearly somewhat more congested indicating that the oxidation of **3** must involve the furan's "front" face.

Gorgiacerolide (**2**) shared only a few spectral features in common with compound **1**. HREIMS established a molecular formula of $C_{21}H_{26}O_6$ for this compound. Except for a weak absorption near 3083 cm^{-1} indicative of an olefin functionality, the IR spectrum of **2** indicated that this compound contained many different functional groups as **1**, that is, an α,β-unsaturated ketone, an α,β-unsaturated γ-lactone, and two aliphatic ketone moieties. Because there were significantly large differences in both ^1H and ^{13}C chemical shift values at most positions in **2** when compared to **1** (see Table 1), it was quickly thought that **2** was a cembranoid rather than a pseudopterane-type diterpene.

The ^1H NMR and ^{13}C NMR data (Table 1) observed for gorgiacerolide (**2**) showed a subtle resemblance to the data reported for epilophodione (**5**)[5a] and acerosolide (**6**),[6b] suggesting that these metabolites had similar constitution and differed only in some of their functionalities. Carbon resonances at 79.6 (d, C-10), 150.7 (d, C-11), 128.2 (s, C-12), and 173.5 (s, C-19) ppm and a proton resonance at 7.45 (br s, 1H, H-11) ppm could be assigned to an α,γ-disubstituted α,β-unsaturated γ-lactone identical with the corresponding substructures of **5** and **6**. Two aliphatic ketones [^{13}C NMR: 205.4 (s, C-3), 205.6 (s, C-14)], an ethoxy group [^{13}C NMR: 66.1 (t, C-20), 15.2 (q, C-21); ^1H NMR: 3.51 (ddq, 1H), 3.43 (ddq, 1H), 1.18 (t, 3H, J = 6.9 Hz)], an isopropylene residue [^{13}C NMR: 139.9 (s, C-15), 116.3 (t, C-16), 20.3 (q, Me-17); ^1H NMR: 4.94 (br s, 1H), 5.00 (br s, 1H), 1.70 (br s, 3H], and a α,β-unsaturated enone bearing a methyl group [^{13}C NMR: 200.6 (s, C-6), 124.6 (d, C-7), 151.8 (s, C-8), 21.5 (q, Me-18); ^1H NMR: 6.00 (br s, 1H), 2.13 (br d, 3H, J = 1.2 Hz)] were also readily apparent. Four aliphatic methylene carbons [^{13}C NMR: 36.9 (C-13), 42.9 (C-9), 44.4 (C-2), 45.2 (C-5)] accounted for the rest of the atoms in gorgiacerolide (**2**). The gross structure of **2** was determined by a detailed analysis of 1D and 2D NMR spectra. The tracking of cross peaks in the $^1H-^1H$ COSY and $^1H-^{13}C$ COSY NMR spectra led to seven isolated spin systems that were connected together in the proper sequence by HMBC data.[8] The cembranoid structure **2** effectively accommodated all the identified structural fragments of gorgiacerolide; however, the carbon framework depicted in **2** lacked the methyl group normally found at C-4 in the regular cembrane skeleton. Instead, our combined spectral data placed the ethoxy group unambiguously at C-4.[9] Because we did not use EtOH during the isolation and purification procedures, nor was our material stored in EtOH, we rule out the possibility that gorgiacerolide is an artifact of the purification process.

The relative stereochemistry of **2**, containing only three chiral centers, was partially deduced from combination of the NOESY data with the $^1H-^1H$ coupling constants as shown in Table 1. No NOE could be demonstrated between the C-18 methyl protons and the H-7 olefinic proton in gorgiacerolide (**2**), a result that is consistent with the C-7,8 olefinic bond having the *E* configuration found in epilophodione (**5**) and acerosolide (**6**). In addition, the ^{13}C NMR shifts at δ 42.9 (t, C-9) and 21.5 (q, C-18) distinctively established the *E* configuration about the C-7,8 olefin in **2**. The $^1H-^1H$ coupling constants, derived from the multiplets observed in the standard ^1H spectrum, for the protons at C-1, C-2, and C-9 provided evidence that the stereochemistry at C-1 and C-10 in gorgiacerolide (**2**) is the same as that in β,β-diepoxypseudopterolide−MeOH adduct (**1**). Molecular models show that there is a conformation in which all of the dihedral angles are compatible with the coupling constants obtained for protons H-1 and H-9a,b (see Supporting Information). Our coupling-constant analysis, however, fell short of providing the configurational assignment at the remaining chiral center (C-4) because the conformation of the macrocycle could not be assigned unequivocally. To address the question of relative stereochemistry at C-4, we used a combination of NOESY NMR data and MM+ molecular mechanics calculations. We considered both diastereoisomers, one with the isopropenyl/ethoxy groups cis [that is, C-1(*R**), C-4 (*S**), and C-10 (*S**)] and the diastereoisomer with those groups trans [C-1(*R**), C-4 (*R**), and C-10 (*S**)], and systematic conformational searching was carried out. Both isomers had similar steric energies after geometry optimization, but there were obvious predicted differences in NOE to distinguish them. For the trans isomer, the MM+ calculations predicted NOE couplings between the ethoxy methyl protons (Me-21) and protons H-7 and H-9, whereas for the cis isomer, which was 2.7 kcal lower in strain energy, no obvious NOEs were anticipated involving the ethoxy protons. Because the NOESY spectrum of **2** revealed a general absence of NOEs involving H-20 and Me-21, therefore, we tentatively assign the relative configuration of the ethoxy group as 4 (*S**). Moreover, only the cis diastereoisomer **2** is consistent with the ethoxy methylene protons (H-20) being magnetically nonequivalent (see Table 1), as one of the proton lies much closer to the C-3 carbonyl than the other.



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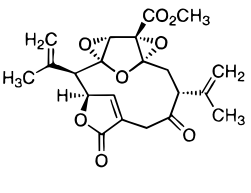

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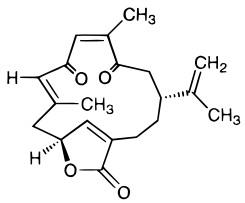

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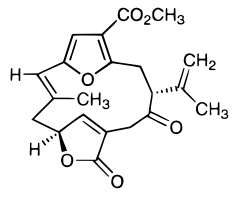

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Our examination of the chemistry of Puerto Rican specimens of *P. acerosa* showed that this gorgonian elaborates interesting diterpenes that are related structurally to those found in specimens collected in other Caribbean locations. The isolation of diterpenes **1** and **2** is of interest for a number of reasons: first, the structural complexity and biological importance of many pseudopterane and cembranoid metabolites are well established, and second, *P. acerosa* is one of only two organisms known to elaborate both pseudopterane and cembrane diterpenes, a fact that supports the theory that metabolites belonging to these skeleton classes are intimately related biogenetically.[10]

Experimental Section

General Experimental Procedures. For general experimental procedures, see Rodríguez and Soto.[6f] Calculations in MM^+ were performed on SPARTAN 4.1 (Wavefunction, Inc., Irvine, CA 92715) and implemented on a Silicon Graphics IRIS−INDIGO XS24-40000 workstation.

Collection and Extraction Procedures. The Caribbean sea plume *P. acerosa* (Pallas) was collected by hand using scuba at depths of 5−10 m in December 1994, from La Parguera, Lajas, Puerto Rico. A voucher specimen (no. PPAC-01) is stored at the Chemistry Department of the University of Puerto Rico. The wet animal (6.7 kg) was blended with MeOH−$CHCl_3$ (1:1) (6 × 1 L), and after filtration, the crude extract was evaporated under vacuum to yield a green residue (634 g). After partitioning the crude oil between hexane and H_2O, the aqueous suspension was extracted with $CHCl_3$. The $CHCl_3$ extract was purified subsequently as described before.[6f] Si gel (250 g) column chromatography of fraction VIII (5.02 g) with 20% Me_2CO in hexane gave fractions 1 through 6. Fraction 3 (285 mg) was subsequently purified by successive HPLC [(a) 20% iPrOH in hexane and (b) 5% iPrOH in hexane] to yield 18.4 mg of pure *β,β*-diepoxypseudopterolide−MeOH adduct (**1**). Fraction XI (1.20 g) was chromatographed over a Si gel column (75 g) to yield fractions 1 through 12. Successive HPLC of fraction 12 [(a) 30% iPrOH in hexane and (b) 10% iPrOH in hexane] afforded 7.0 mg of pure gorgiacerolide (**2**).

***β,β*-Diepoxypseudopterolide−MeOH adduct (1):** yellowish oil; $[\alpha]^{25}_D$ +4.0° (*c* 3.5, $CHCl_3$); IR (neat) 3421, 3079, 3013, 2955, 2927, 2854, 1740, 1736, 1652, 1586, 1456, 1437, 1375, 1260, 1184, 1095, 1036, 1020, 982, 907, 756 cm^{-1}; UV λ_{max} ($CHCl_3$) 246 nm (ϵ 1890); ^1H NMR (300 MHz, $CDCl_3$), see Table 1; ^{13}C NMR (75 MHz, $CDCl_3$), see Table 1; HRFABMS *m/z* $[M + Li]^+$ 441.1735 (calcd for $C_{22}H_{26}O_9Li$, 441.1737).

Gorgiacerolide (2): colorless oil; $[\alpha]^{25}_D$ +15.0° (*c* 1.2, $CHCl_3$); IR (neat) 3083, 2963, 2926, 1755, 1734, 1716, 1700, 1684, 1616, 1436, 1260, 1202, 1089, 1021, 901, 865, 799, 759 cm^{-1}; UV λ_{max} ($CHCl_3$) 248 nm (ϵ 2500); ^1H NMR (300 MHz, $CDCl_3$), see Table 1; ^{13}C NMR (75 MHz, $CDCl_3$), see Table 1; EIMS *m/z* 374 (15), 356 (6), 330 (11), 302 (15), 284 (5), 259 (14), 242 (11), 220 (24), 178 (42), 161 (15), 148 (20), 123 (36), 109 (56), 96 (62), 82 (100), 67 (50), 53 (35), 43 (65); HREIMS *m/z* $[M]^+$ 374.1733 (calcd for $C_{21}H_{26}O_6$, 374.1729).

Acknowledgment. The assistance of Dr. P. Yoshioka, A. Boulanger, A. Sostre, and A. E. Pomales in specimen collection is gratefully acknowledged. We gratefully appreciate the taxonomic assignment provided by Dr. Paul Yoshioka. The HRFABMS spectral determination was performed by the Midwest Center for Mass Spectrometry, a NSF Regional Facility (grant no. CHE8211164). The HREIMS and HMBC experiments were performed by Mr. Rafael Almodóvar and Catherine Ramírez, respectively. This study was supported by the NSF-EPSCoR (grant no. R118610677), NIH-MBRS (grant no. S06RR08102-17), and NSF-MRCE (grant no. R11-8802961) Programs.

Supporting Information Available: Structures of known pseudopterane diterpenes from *P. acerosa* and three-dimensional structure of the lowest energy conformer of gorgiacerolide (**2**) (2 pages). Ordering information is given on any current masthead page.

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(8) The correlations observed in the HMBC spectrum of **2** were: H-1 [C-3, C-14, C-15, C-16]; H-2a [C-3, C-14], H-2b [C-1, C-3, C-14]; H-4 [C-2, C-3, C-5, C-20]; H-5ab [C-3, C-4, C- 6, C-7]; H-7 [C-5, C-6, C-9, C-18]; H-9ab [C-8, C-10, C-11, C-18]; H-11 [C-10, C-19]; H-13a [C-1, C-12, C-14]; H-13b [C-11, C-12, C-14]; H-16ab [C-1, C-15, C-17]; H-17 [C- 1, C-15, C-16]; H-18 [C-7, C-8, C-9]; H-21 [C-20].
(9) A prominent fragment ion at *m/z* 330 in the HREIMS of **2**, corresponding to the loss of one molecule of acetaldehyde via a McLafferty rearrangement, established the locus of the ethoxy group at either position C-4 or C-5; however, a strong HMBC correlation between H-4 (δ 4.01) and C-3 (δ 205.4) and the absence of an HMBC correlation between the signal at δ 4.01 and C-6 (δ 200.6), effectively placed the ethoxy group at C-4. Moreover, because H-7 (δ 6.00) did not correlate with the carbon atom bearing the ethoxy group (δ 80.3), clearly the EtO group must be at C-4.
(10) The biogenetic relationship between two diterpenoids of the cembrane and pseudopterane classes obtained from the related gorgonian species *Pseudopterogorgia bipinnata* has been recently demonstrated (see Rodríguez, A. D.; Shi, J.-G. *J. Org. Chem*. **1998**, *63*, 420−421).

NP9703858