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New Terpenoid Constituents of the Southwestern Caribbean Sea Whip *Pseudopterogorgia elisabethae* (Bayer), Including a Unique Pentanorditerpene

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Seven structurally diverse terpenoids, including four diterpenes, a norditerpene, a bisnorditerpene, and a biogenetically related pentanorditerpene, have been isolated from the hexane extract of the Caribbean gorgonian octocoral *Pseudopterogorgia elisabethae*, collected near the island of San Andrés, Colombia. The structures of all the new compounds were determined by detailed spectroscopic analysis and chemical derivatization. Many of the purified isolates were evaluated in vitro as potential agents to treat neuroinflammation and also as growth inhibitors against the pathogenic microbe *Mycobacterium tuberculosis* H_{37}Rv.

Introduction

During the last twenty years considerable efforts have been dedicated to exploration of the natural products chemistry of the West Indian gorgonian octocoral *Pseudopterogorgia elisabethae* (Bayer, 1961).[1] These efforts have led to the discovery of many structurally novel natural products.[2] Throughout these investigations, strong interest in the potential applications of these secondary metabolites as prototype molecules in the development of new therapeutic agents has been maintained.[3] The pseudopterosins, for instance, are potent anti-inflammatory and analgesic agents that have been licensed to a small pharmaceutical firm for medical use as potential anti-inflammatory drugs. Unprocessed pseudopterosin extract, however, has already found its way to the marketplace and is currently being used as an additive to prevent irritation caused by exposure to the sun or chemicals in the Estée Lauder cosmetic skin care product Resilience®.[4]

Our research group in particular has focused considerable attention on assessing biomedical applications of these marine metabolites against cancer, inflammation, and infectious diseases such as malaria and tuberculosis.[5] Here we report the isolation and characterization of seven new terpene metabolites, **1**–**7**, from the gorgonian octocoral *Pseudopterogorgia elisabethae* in approximately 0.0001–0.003% yields (dry weight basis). Compounds **1**–**3** are diterpenes with the serrulatane skeleton, whereas **4**, **5**, and **6** represent a diterpene, norditerpene, and bisnorditerpene based on the elisabethane, sandresane, and *bisnorseco*-elisabethane carbon skeletons, respectively. Compound **7** contains an unusual carbon skeleton with a new class of C_{15}-rearranged pentanorditerpene. The structural characterization of these metabolites was based exclusively on the results of chemical and spectroscopic analysis.

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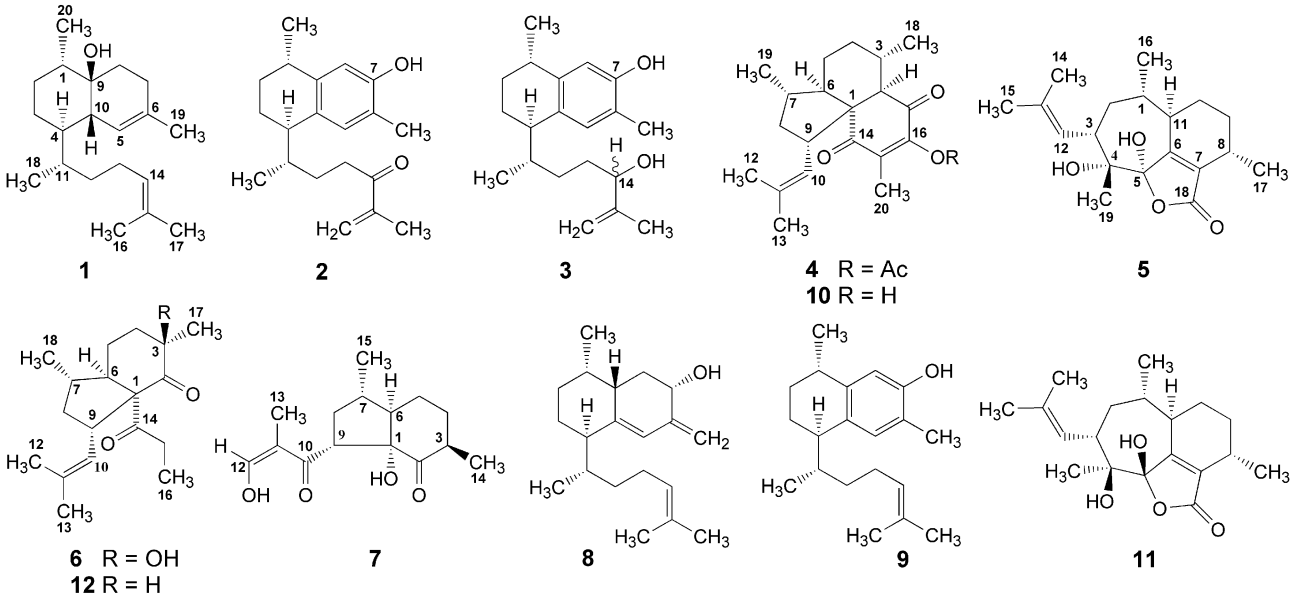
Results and Discussion

After extraction of dried *P. elisabethae* (1.0 kg, collected off San Andrés island, Colombia), with MeOH/$CHCl_3$ (1:1), the hexane extract was fractionated by successive size-exclusion chromatography (Bio-Beads SX-3 in toluene), SiO_2 chromatography, and HPLC, leading to the isolation of pure compounds **1**–**7**. Specifically, their molecular structures, including their relative stereochemistry, were elucidated by interpretation of the data obtained from 1D and 2D NMR experiments, IR, UV, and high-resolution mass spectral determinations.

Elisabethadienol (**1**), a colorless oil, was determined to have a molecular formula of $C_{20}H_{34}O$ by HREIMS {$[M]^+$, *m*/*z* 290.2606; calcd. for $C_{20}H_{34}O$, 290.2609} and by ^{13}C NMR (Table 1). The mass spectrum of this compound showed a base peak ion at *m*/*z* 161.1331 (100%) representing loss of C_8H_{15} in the form of the terpenoid eight-carbon side chain (C-11 through C-18 in structure **1**) from the $[M - H_2O]^+$ fragment ion at *m*/*z* 272.2492 (44%; Figure 1, A). This behavior, coupled with appropriate proton and carbon



NMR bands, indicated the presence in elisabethadienol (**1**) of a bicyclic diterpenoid component of composition $C_{12}H_{19}O$. Interpretation of the NMR spectral features indicated that this skeleton was similar to that of (–)-elisabethatrienol (**8**), a suspected biosynthetic intermediate in the important series of anti-inflammatory diterpene glycosides known as the pseudopterosins.[6,7] It is therefore proposed that compound **1** is a mono-hydrogenated derivative of **8**.

The ^{1}H NMR spectrum ($CDCl_3$, 500 MHz) of **1** showed two three-proton doublets at δ = 0.96 (J = 6.6 Hz) and 0.80 ppm (J = 6.9 Hz) attributable to the protons of the C-20 and C-18 secondary methyl groups, respectively. Two broad three-proton singlets at δ = 1.67 and 1.59 ppm were assigned to the olefinic C-16 and C-17 methyl groups, whereas another three-proton singlet at δ = 1.70 ppm was attributed to the C-19 methyl protons. The olefinic C-5 and C-14 methine protons resonated at δ = 5.43 (br. d, J = 5.3 Hz) and 5.07 ppm (br. t, J = 7.1 Hz), respectively. An exchangeable broad signal at δ = 1.55 ppm for –OH was also observed in the ^{1}H NMR spectrum, but disappeared when the spectrum was recorded in $D_2O/CDCl_3$.

The ^{1}H-^{1}H COSY spectrum allowed us to complete the ^{1}H NMR chemical shift assignment of **1**. The allylic C-13 protons (δ = 2.04 and 1.89 ppm) showed interactions with the C-12 methylene (δ = 1.22 ppm) and olefinic C-14 methine (δ = 5.07 ppm) protons. The C-12 methylene exhibited vicinal couplings with the C-11 methine proton (δ = 1.73 ppm), which in turn showed a ^{1}H-^{1}H spin correlation with the C-18 methyl (δ = 0.80 ppm) and C-4 methine (δ = 1.25 ppm) protons. The latter proton exhibited cross-peaks with the C-3 methylene (δ = 1.48 and 1.08 ppm) and C-10 methine (δ = 1.74 ppm) protons. Likewise, the proton at C-10 exhibited cross-peaks with the olefinic C-5 methine (δ = 5.43 ppm), which further displayed long-range allylic couplings with the C-19 methyl protons (δ = 1.70 ppm). The C-3 methylene protons exhibited additional vicinal couplings with the C-2 methylene protons (δ = 1.60 and 1.08 ppm). Cross-peaks between the C-1 methine proton (δ = 1.60 ppm) and the C-20 methyl (δ = 0.96 ppm) and C-2 methylene protons were also observed in the ^{1}H-^{1}H COSY spectrum. Interestingly, a pair of mutually coupled vicinal methylenes centered at δ = 2.11/1.98 ppm and δ = 1.62 ppm, which showed no further couplings, were ascribed to the protons attached to C-7 and C-8, respectively.

The ^{13}C NMR spectrum ($CDCl_3$, 125 MHz) showed distinct resonances for all 20 carbon atoms, which were further divided by a DEPT-135 NMR experiment into six CH, six CH_2, five CH_3, and three quaternary carbon atoms. Further interpretation of the ^{1}H, ^{13}C NMR, COSY, and HMQC spectroscopic data for **1** revealed that this compound is a serrulatane-based diterpene, as most of the signals have chemical shift values similar to those of well known model compounds, including **8**.[8] Moreover, all of the correlations observed in the HMBC spectrum supported the assigned connectivities based on the COSY data. The C-10 methine proton (δ = 1.74 ppm) showed cross-peaks with C-1 (δ = 41.9 ppm), C-3 (δ = 24.3 ppm), C-4 (δ = 47.4 ppm), C-5 (δ = 122.0 ppm), C-6 (δ = 133.8 ppm), C-8 (δ = 22.1 ppm), and C-9 (δ = 72.7 ppm), whereas the C-20 methyl protons (δ = 0.96 ppm) showed cross-peaks with C-1 (δ = 41.9 ppm), C-2 (δ = 31.2 ppm), and C-9 (δ = 72.7 ppm), thus establishing the locus of the tertiary hydroxy group at C-9. Cross-peaks between the C-19 methyl protons (δ = 1.70 ppm) and C-5 (δ = 122.0 ppm), C-6 (δ = 133.8 ppm), and C-7 (δ = 26.7 ppm) were also observed in the HMBC spectrum. The gross structure of elisabethadienol (**1**) was thus proposed to be as shown. NMR spectroscopic data for **1** and their assignments are given in Table 1.

The relative stereochemistry of **1** was deduced from observed NOE cross-peaks and J values for the ^{1}H NMR spectrum. The coupling patterns of 10-H at δ = 1.74 ppm (dd, J = 5.3 and 11.1 Hz) and 5-H at δ = 5.43 ppm (br. d, J = 5.3 Hz) helped us to assign the axial α-orientation of 4-

Table 1. ^{1}H NMR (500 MHz) and ^{13}C NMR (125 MHz) spectroscopic data (δ values, ppm) for elisabethadienol (**1**), 7-hydroxyerogorgiaenone (**2**), and 7,14-erogorgiaenediol (**3**).[a]

Position	Compound **1** ^{1}H NMR	^{13}C NMR[b]	Compound **2** ^{1}H NMR	^{13}C NMR[b]	Compound **3** ^{1}H NMR	^{13}C NMR[b]
1	1.60, m, 1 H	41.9 (CH)	2.69, m, 1 H	32.8 (CH)	2.68, m, 1 H	32.9 (CH)[c]
2α	1.60, m, 1 H	31.2 (CH_2)	1.32, m, 1 H	31.6 (CH_2)	1.93, m, 1 H	31.7 (CH_2)[c]
2β	1.08, m, 1 H		1.88, m, 1 H		1.31, m, 1 H	
3α	1.48, m, 1 H	24.3 (CH_2)	1.80, m, 1 H	21.6 (CH_2)	1.79, m, 1 H	21.6 (CH_2)[c]
3β	1.08, m, 1 H		1.49, m, 1 H		1.49, m, 1 H	
4	1.25, m, 1 H	47.4 (CH)	2.84, m, 1 H	41.1 (CH)	2.82, m, 1 H	41.0 (CH)[c]
5	5.43, br. d, 1 H (5.3 Hz)	122.0 (CH)	6.93, s, 1 H	129.8 (CH)	6.94, br. s, 1 H	129.8 (CH)[c]
6		133.8 (C)		120.8 (C)		120.8 (C)
7α	2.11, m, 1 H	26.7 (CH_2)		151.3 (C)		151.3 (C)
7β	1.98, m, 1 H					
8αβ	1.62, m, 2 H	22.1 (CH_2)	6.66, s, 1 H	112.8 (CH)	6.66, s, 1 H	112.7 (CH)
9		72.7 (C)		142.4 (C)		142.4 (C)
10	1.74, dd, 1 H (5.3, 11.1 Hz)	47.8 (CH)		131.6 (C)		131.9 (C)
11	1.73, m, 1 H	31.7 (CH)	2.11, m, 1 H	37.0 (CH)	2.10, m, 1 H	37.3 (CH)[c]
12αβ	1.22, q, 2 H (7.5 Hz)	35.8 (CH_2)	1.75, m, 1 H	29.8 (CH_2)	1.38, m, 2 H	30.9 (CH_2)[c]
			1.64, m, 1 H			
13α	2.04, br. m, 1 H	26.2 (CH_2)	2.77, t, 1 H (6.0 Hz)	36.0 (CH_2)	1.64, m, 2 H	33.3 (CH_2)[c]
13β	1.89, br. m, 1 H		2.74, t, 1 H (6.0 Hz)			
14	5.07, br. t, 1 H (7.1 Hz)	124.9 (CH)		202.5 (C)	4.09, t, 1 H (6.0 Hz)	76.3 (CH)[c]
15		131.0 (C)		144.6 (C)		147.6 (C)
16α	1.67, br. s, 1 H	25.7 (CH_3)	5.98, br. s, 1 H	124.3 (CH_2)	4.96, br. s, 1 H	111.1 (CH_2)[c]
16β			5.77, br. s, 1 H		4.86, br. s, 1 H	
17	1.59, br. s, 3 H	17.6 (CH_3)	1.89, s, 3 H	17.7 (CH_3)	1.75, s, 3 H	17.5 (CH_3)[c]
18	0.80, d, 3 H (6.9 Hz)	13.4 (CH_3)	0.65, d, 3 H (6.9 Hz)	14.3 (CH_3)	0.64, d, 3 H (6.9 Hz)	14.4 (CH_3)
19	1.70, br. s, 3 H	23.5 (CH_3)	2.20, s, 3 H	15.5 (CH_3)	2.20, s, 3 H	15.5 (CH_3)
20	0.96, d, 3 H (6.6 Hz)	15.2 (CH_3)	1.24, d, 3 H (6.9 Hz)	21.8 (CH_3)	1.24, d, 3 H (6.9 Hz)	21.8 (CH_3)
7-OH			4.55, br. s, 1 H[d]		4.50, br. s, 1 H[d]	
9-OH	1.55, br. s, 1 H[d]					

[a] Spectra were recorded in $CDCl_3$ at 25 °C. Chemical shift values are in parts per million relative to TMS. Assignments were aided by 2D NMR experiments, spin-splitting patterns, number of attached protons, and chemical shift values. [b] ^{13}C NMR multiplicities were obtained from a DEPT-135 experiment. [c] Carbon signal appears as two closely-spaced resonance lines. [d] Exchangeable proton.

H and axial β-orientation of 10-H ($J_{H\text{-}4,H\text{-}10}$ = 11.1 Hz). The observed coupling constant of 5-H and 10-H (5.3 Hz) further indicated that the C-9 hydroxy group is β-equatorially oriented. A molecular modeling study revealed that when the C-9 hydroxy group is α-oriented (i.e., *trans* to 10-H) essentially no coupling between 5-H and 10-H is predicted (i.e., $J_{H\text{-}5,H\text{-}10} < 1$ Hz) because the dihedral angle between these protons in the most stable conformation approaches 90°. Furthermore, the high relative abundance (44%) of the $[M - H_2O]^+$ ion at *m*/*z* 272 in the *cis*-annulated isomer **1** presumably reflects a greater propensity for the elimination of water from the molecular ion (Figure 1, A).[9] Extensive NOE studies afforded useful information on the stereochemistry at C-1, C-4, and C-11. In particular, 4-H and 11-H showed NOE correlations with 18-H_3 and 5-H, respectively, which established the α-orientations of 4-H and 18-H_3. The C-1 relative stereochemistry was deduced from key NOE correlations between 1-H, 3β-H, and 10-H (Figure 1, B). In spite of the difficulties involved in the assignment of the relative configuration of elisabethadienol (there are two possible major conformations in the *cis*-decaline derivative **1**), the proposed relative stereochemistry was supported by the overall similarity of the ^{13}C NMR spectroscopic data for C-1, C-4, and C-11 of **1** with those for well known model serrulatane diterpenes and *seco*-pseudopterosins.[8] From these data, the structure of elisabethadienol was determined as illustrated in **1**.

The compound 7-hydroxyerogorgiaenone (**2**) was obtained as an optically active colorless oil ($[\alpha]_D$ = +65.0). HRESIMS established a molecular formula of $C_{20}H_{28}O_2$. The UV maximum at 282 nm and IR bands at 1502 and 1455 cm^{-1} indicated the presence of an aromatic ring. The ^{1}H NMR spectrum of **2** showed two one-proton singlets at δ = 6.93 and 6.66 ppm, indicating the presence of a 1,2,4,5-tetrasubstituted benzene ring. Other features of the spectrum included two broad singlets at δ = 5.98 and 5.77 ppm (1 H each) and a methyl singlet at δ = 1.89 ppm indicative of a $H_2C{=}C(CH_3)$ group, a sharp three-proton singlet at δ = 2.20 ppm indicating an aromatic methyl, two methyl doublets at δ = 1.24 and 0.65 ppm (each J = 6.9 Hz, 3 H), and two complex multiplets at δ = 2.84 and 2.69 ppm (1 H each) suggesting two benzylic hydrogens.

The ^{13}C NMR spectrum exhibited 20 signals (four CH_3, five CH_2, five CH, and six C), the chemical shift values and

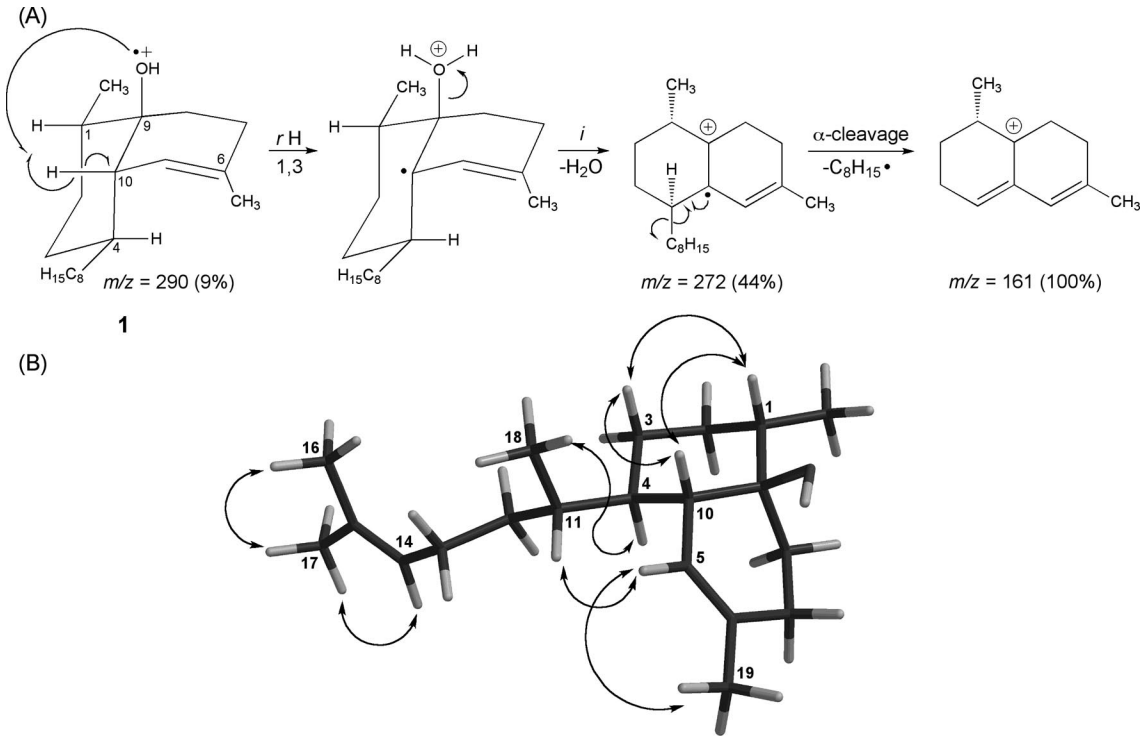


Figure 1. A) Proposed ion-decomposition mechanisms, and B) selected NOEs and conformation for elisabethadienol (**1**).

multiplicities of which confirmed the presence of a 1,2,4,5-tetrasubstituted aromatic ring [δ = 151.3 (C), 142.4 (C), 131.6 (C), 129.8 (CH), 120.8 (C), 112.8 ppm (CH)] and an isopropenyl ketone [δ = 202.5 (C), 144.6 (C), 124.3 (CH_2), 17.7 ppm (CH_3)]. The spectral evidence thus indicated that compound **2** is bicyclic with a conjugated enone and a benzene ring. It therefore appeared that compound **2**, in common with elisabethadienol (**1**) and other *P. elisabethae* metabolites, possesses a serrulatane skeleton.[8] The structure of **2**, including its relative stereochemistry, was easily determined from its 2D NMR spectra, including ^{1}H-^{1}H COSY, NOESY, HMQC, and HMBC. The ^{1}H and ^{13}C NMR (Table 1) chemical shifts of **2** were remarkably similar to those of the known 7-hydroxyerogorgiaene (**9**), except for some signals (C-12 through C-17) that displayed noticeable variations due to the presence in **2** of an isopropylene ketone residue in place of a $(CH_3)_2C{=}CH{-}CH_2$ group as in **9**.[8c] The relative positions of such atoms were clearly supported by ^{1}H-^{1}H COSY, NOESY, and HMBC results.

Compound **3**, trivially named 7,14-erogorgiaenediol, was isolated as a UV active (λ_{max} = 282 nm) colorless oil with HRESIMS and ^{13}C NMR spectroscopic data that indicated a molecular formula of $C_{20}H_{30}O_2$, two hydrogen atoms more than in the molecular formula of 7-hydroxyerogorgiaenone (**2**). Its IR spectrum contained a strong hydroxy stretching band at 3391 cm^{-1} and its ^{13}C NMR spectrum was almost identical with that of compound **2**, with the exception that the carbonyl carbon resonance at δ = 202.5 ppm in the latter compound was replaced by a hydroxy-bearing methine group at δ = 76.3 ppm. The replacement of the C-14 ketone by a secondary carbinol was supported by the presence in the ^{1}H NMR spectrum of a triplet at δ = 4.09 ppm (1 H, J = 6.0 Hz, assigned to 14-H) that showed strong HMBC couplings with the carbon signals ascribable to C-15 (δ_C = 147.6 ppm), C-16 (δ_C = 111.1 ppm), and C-17 (δ_C = 17.5 ppm). This was further confirmed by complementary HMBC correlations between 14-H and C-12 (δ_C = 30.9 ppm) and C-13 (δ_C = 33.3 ppm). Interestingly, over half of the ^{13}C NMR signals listed in Table 1 appeared as closely spaced doublets in a nearly 1:1 ratio, even though this compound showed a single peak when analyzed on normal-phase HPLC. This phenomenon suggested that compound **3** is actually an inseparable mixture of two structurally related constituents, most likely a pair of diastereomeric alcohols at the C-14 position. For the purpose of rigorous identification, **2** was reduced to furnish a 1:1 mixture of C-14 epimers, which was fully characterized by spectral methods as 7,14-erogorgiaenediol (**3**).

Data from HREIMS and ^{13}C NMR spectroscopy (Table 2) established a molecular formula of $C_{22}H_{30}O_4$ for elisabethin A acetate (**4**), thus indicating eight degrees of unsaturation. Because the ^{13}C NMR spectrum contained three carbonyl and four olefinic carbon resonances, the molecule was judged to be tricyclic. The UV spectrum showed absorption at λ_{max} = 250 nm (ε = 7400), indicative of conjugation. ^{13}C NMR signals due to quaternary carbons at δ = 202.8 (C-14), 192.0 (C-17), 154.5 (C-16), 134.2 (C-11), 133.9 (C-15), and 66.5 ppm (C-1), two broad three-proton ^{1}H NMR singlets at δ = 1.53 (13-H_3) and 1.45 ppm (12-H_3), a sharp methyl singlet at δ = 1.84 ppm (20-H_3), a one-proton doublet at δ = 2.60 ppm (J = 10.3 Hz, 2-H), and a one-proton doublet of triplets at δ = 2.83 ppm (J = 5.7,

Table 2. ^{1}H NMR (500 MHz) and ^{13}C NMR (125 MHz) spectroscopic data (δ values, ppm) for elisabethin A acetate (**4**), elisabethin G (**6**), and elisabethin H (**7**) in $CDCl_3$.[a]

Position	Compound **4** ^{1}H NMR	^{13}C NMR[b]	Compound **6** ^{1}H NMR	^{13}C NMR[b]	Compound **7** ^{1}H NMR	^{13}C NMR[b]
1		66.5 (C)		77.5 (C)		73.5 (C)
2	2.60, d, 1 H (10.3 Hz)	54.5 (CH)		213.0 (C)		207.9 (C)
3	2.39, m, 1 H	23.8 (CH)		77.8 (C)	2.98, ddq, 1 H (5.1, 6.4, 6.5 Hz)	44.5 (CH)
4α	1.24, m, 1 H	24.9 (CH_2)	1.90, m, 1 H	36.7 (CH_2)	1.54, m, 1 H	30.5 (CH_2)
4β	1.87, m, 1 H		1.90, m, 1 H		1.92, m, 1 H	
5α	1.31, m, 1 H	23.9 (CH_2)	1.96, m, 1 H	19.7 (CH_2)	1.73, m, 1 H	22.2 (CH_2)
5β	1.50, m, 1 H		1.75, m, 1 H		1.63, m, 1 H	
6	2.45, m, 1 H	46.6 (CH)	2.53, br. d, 1 H (11.5 Hz)	48.9 (CH)	1.76, m, 1 H	52.3 (CH)
7	1.78, m, 1 H	37.6 (CH)	1.57, m, 1 H	33.9 (CH)	1.87, m, 1 H	40.4 (CH)
8α	1.13, m, 1 H	39.0 (CH_2)	0.86, m, 1 H	40.1 (CH_2)	0.88, m, 1 H	37.2 (CH_2)
8β	1.60, m, 1 H		2.08, dt, 1 H (8.1, 8.4 Hz)		2.13, m, 1 H	
9	2.83, dt, 1 H (5.7, 11.2 Hz)	46.8 (CH)	4.00, ddd, 1 H (2.7, 5.1, 11.1 Hz)	41.8 (CH)	3.89, ddq, 1 H (2.0, 6.5, 9.0 Hz)	45.1 (CH)
10	4.32, br. dd, 1 H (1.2, 11.0 Hz)	125.6 (CH)	4.70, br. dd, 1 H (1.2, 11.1 Hz)	125.8 (CH)		204.9 (C)
11		134.2 (C)		132.7 (C)		134.9 (C)
12	1.45, br. s, 3 H (1.2 Hz)	17.8 (CH_3)	1.72, br. s, 3 H	17.8 (CH_3)	7.24, q, 1 H (1.4 Hz)	161.6 (CH)
13	1.53, br. s, 3 H (1.2 Hz)	25.9 (CH_3)	1.63, br. s, 3 H	25.9 (CH_3)	1.68, dd, 3 H (1.4, 2.0 Hz)	10.2 (CH_3)
14		202.8 (C)		204.6 (C)	1.03, d, 3 H (6.5 Hz)	14.7 (CH_3)
15α		133.9 (C)	2.34, dq, 1 H (7.2, 14.4 Hz)	34.1 (CH_2)	0.90, d, 3 H (6.2 Hz)	17.2 (CH_3)
15β			1.85, m, 1 H			
16		154.5 (C)	0.89, t, 3 H (7.2 Hz)	7.1 (CH_3)		
17		192.0 (C)	1.21, s, 3 H	26.1 (CH_3)		
18	1.02, d, 3 H (6.5 Hz)	22.2 (CH_3)	0.95, d, 3 H (6.3 Hz)	18.4 (CH_3)		
19	1.14, d, 3 H (6.6 Hz)	18.9 (CH_3)				
20	1.84, s, 3 H	9.4 (CH_3)				
OAc	2.28, s, 3 H	20.3 (CH_3)				
		167.8 (C)				
1-OH					4.83, br. s, 1 H[c]	
3-OH			4.02, br. s, 1 H[c]			
12-OH					7.24, br. s, 1 H[c]	

[a] Spectra were recorded at 25 °C. Chemical shift values are in parts per million relative to TMS. Assignments were aided by 2D NMR experiments, spin-splitting patterns, number of attached protons, and chemical shift values. [b] ^{13}C NMR multiplicities were obtained from a DEPT-135 experiment. [c] Exchangeable proton.

11.2 Hz, 9-H) indicated that **4** possessed the same elisabethane skeleton as found in the prototype metabolite elisabethin A (**10**).[10] Information gleaned from ^{1}H-^{1}H COSY, NOESY, HMQC, and HMBC spectra led to the formulation of structure **4** for elisabethin A acetate, and this was confirmed by direct conversion of **10** (previously isolated in this laboratory) to **4** upon acetylation.

Pure sandresolide C (**5**) was isolated as transparent thin needles that were sparingly soluble in $CDCl_3$. Interestingly, the ^{1}H and ^{13}C NMR spectroscopic data for **5** (in $CDCl_3$ solution) were very similar to those of the known sandresolide B (**11**).[11] In addition to its HREIMS data, which indicated the molecular formula $C_{19}H_{28}O_4$ for **5**, a side-by-side comparison of the NMR spectroscopic data for compounds **5** and **11** suggested that the only difference between these norditerpenes was the relative orientations of the substituents at C-4 and C-5. Among the significant variations observed in the NMR spectroscopic data were the ^{1}H NMR chemical shifts of 1-H (δ = 1.43 vs. 2.08), 3-H (δ = 2.34 vs. 3.02), 11-H (δ = 2.27 vs. 1.92), and 19-H_3 (δ = 1.21 vs. 1.12), and the ^{13}C NMR chemical shifts of C-1 (δ = 37.7 vs. 31.7), C-2 (δ = 38.1 vs. 43.8), C-3 (δ = 47.3 vs. 43.9), C-11 (δ = 41.0 vs. 46.0), and C-19 (δ = 25.9 vs. 16.9), all of which were consistent with **5** having the *R** configuration at both C-4 and C-5 (vide infra). As in the case of **1**–**4**, comprehensive 1D and 2D NMR spectroscopic data (in CD_3OD) allowed all protons and carbons to be assigned, leading to the assignment of the planar structure **5** for sandresolide C (Table 3).

The relative configurations for most of the stereocenters in the tricyclic nucleus of sandresolide C (**5**; i.e., C-1, C-3, C-4, C-8, and C-11) were assigned primarily on the basis of NOESY NMR spectroscopic data (Table 3). Thus, 1-H and 19-H_3, located on the β face of the molecule, were assigned as *cis* on the basis of their strong NOESY correlations with 3-H. Similarly, the strong NOESY correlations of 2α-H and

Table 3. ^{1}H NMR (500 MHz), ^{13}C NMR (125 MHz), ^{1}H-^{1}H COSY, NOESY, and HMBC spectroscopic data (δ values, ppm) for sandresolide C (**5**).[a]

Position	^{1}H NMR	^{13}C NMR[b]	^{1}H-^{1}H COSY	NOESY	HMBC[c]
1	2.11, m, 1 H	32.8 (CH)	2αβ-H, 11-H, 16-H_3	2β-H, 3-H, 16-H_3	16-H_3
2α	1.41, m, 1 H	44.9 (CH_2)	1-H, 2β-H, 3-H	2β-H, 12-H, 16-H_3	3-H, 16-H_3
2β	1.39, m, 1 H		1-H, 2α-H, 3-H	1-H, 2α-H, 3-H, 16-H_3	
3	2.93, dt, 1 H (5.1, 10.4 Hz)	44.8 (CH)	2αβ-H, 12-H	1-H, 2β-H, 14-H_3, 19-H_3	19-H_3
4		77.5 (C)			19-H_3
5		111.5 (C)			19-H_3
6		168.0 (C)			10α-H
7		130.1 (C)			17-H_3
8	2.46, m, 1 H	28.7 (CH)	9αβ-H, 17-H_3	9β-H, 17-H_3	17-H_3
9α	1.32, m, 1 H	34.5 (CH_2)	8-H, 9β-H, 10α-H	9β-H, 10α-H	17-H_3
9β	2.14, m, 1 H		8-H, 9α-H, 10β-H	8-H, 9α-H	
10α	2.00, br. m, 1 H	29.4 (CH_2)	9α-H, 10β-H, 11-H	9α-H, 10β-H, 11-H, 16-H_3	
10β	1.27, m, 1 H		9β-H, 10α-H, 11-H	9β-H, 10α-H	
11	2.10, m, 1 H	47.2 (CH)	1-H, 10αβ-H	10α-H, 16-H_3	16-H_3
12	5.17, dd, 1 H (1.2, 10.2 Hz)	128.2 (CH)	3-H, 14-H_3, 15-H_3	2α-H, 15-H_3, 19-H_3	3-H, 14-H_3, 15-H_3
13		131.7 (C)			3-H, 14-H_3, 15-H_3
14	1.63, br. s, 3 H	18.1 (CH_3)	12-H	3-H, 15-H_3	12-H, 15-H_3
15	1.72, br. s, 3 H	26.0 (CH_3)	12-H	12-H, 14-H_3	12-H, 14-H_3
16	0.91, d, 3 H (6.1 Hz)	21.7 (CH_3)	1-H	1-H, 2αβ-H, 10α-H, 11-H	
17	1.21, d, 3 H (6.9 Hz)	19.5 (CH_3)	8-H	8-H	9α-H
18		174.6 (C)			
19	1.29, s, 3 H	23.1 (CH_3)		3-H, 12-H	
5-OH	4.61, br. s				

[a] Spectra were recorded in CD_3OD at 25 °C. Chemical shift values are in parts per million relative to the residual CH_3OH (δ = 3.30 ppm) or CD_3OD (δ = 49.0 ppm) signals. Assignments were aided by 2D NMR experiments, spin-splitting patterns, number of attached protons, and chemical shift values. [b] ^{13}C NMR multiplicities were obtained from a DEPT-135 experiment. [c] Protons correlated to carbon resonances in the ^{13}C column. Parameters were optimized for $^{2,3}J_{CH}$ = 6 and 8 Hz.

11-H with 16-H_3 allowed the placement of these protons on the α face of the molecule. NOESY correlations between 8-H and 9β-H, located on the top face of the molecule, established their spatial proximity and thus placed the methyl group at C-8 on the α face. The calculated distances between the NOE-correlated protons are shown in Figure 2 and are highly consistent with the experimentally determined NOESY data. On the other hand, the C-5 stereocenter was difficult to define by NOESY NMR methods alone. To determine its relative configuration, molecular mechanics/dynamics calculations were performed to establish the dominant conformations of **5**.[12] The results of the conformational analysis implied that when the two hydroxy groups lie on the same α face of the molecule, **5** can adopt its most stable conformation, allowing favorable hydrogen-bonding interactions between them, which could reduce its solubility in $CDCl_3$. Indeed, the presence of a H-bond between the C-4 and C-5 hydroxy groups in sandresolide C is further supported experimentally by the fact that one of the hydroxy protons in **5** is unusually deshielded (δ = 5.25 ppm in $CDCl_3$), the presence of two clearly discernible hydroxy stretching bands (one much sharper than the other), and the presence in the ^{1}H NMR spectrum of **5** in CD_3OD of a hydroxy proton at δ = 4.61 ppm that does not readily undergo deuterium-exchange at 25 °C (see Table 3).[13] By this approach and with the aid of a molecular modeling study, the hydroxy group at C-5 was found to be on the α face of the molecule (i.e., *trans* to 19-H_3). No attempts were made to derivatize **5**, due to the paucity of the natural product.

The molecular formula of elisabethin G (**6**) was determined by HRESIMS to be $C_{18}H_{28}O_3$, requiring five degrees of unsaturation. Because two signals due to olefinic carbons and two signals arising from carbonyl carbons were observed in the ^{13}C NMR spectrum (Table 2), **6** was shown to contain two rings. The double bonds were not conjugated, because the UV showed only end absorption. The IR spectrum of **6** confirmed the presence of a hydroxy group (3430 cm^{-1}) and two carbonyl groups (1733 and 1700 cm^{-1}), which accounted for all the oxygens in the proposed molecular formula. All 18 carbons appeared in the ^{13}C NMR spectrum, and a DEPT-135 experiment indicated five CH_3, four sp^3 CH_2, three sp^3 CH, one sp^2 CH, and five quaternary carbons (two sp^3 and three sp^2).

The gross structure of elisabethin G (**6**) was deduced from analysis of 1D- and 2D-NMR spectra. The ^{1}H and ^{13}C NMR spectra of **6** recorded in $CDCl_3$ had many features in common with those of the known elisabethin C (**12**), and indeed ^{1}H-^{1}H COSY, HMQC, and HMBC experiments confirmed many of the same partial structures as determined for **12**, although the ^{13}C chemical shifts assigned to C-2 through C-4 and C-17 differed somewhat.[10] The linkages from C-4 through C-10, including connectivities to 12-H_3, 13-H_3, and 18-H_3, were unambiguously demonstrated analogously to **12**. Nevertheless, distinctively different spectral features were observed in the ^{1}H NMR spectrum, which ultimately indicated that 3-H in **12** had been replaced by a hydroxy group in elisabethin G (**6**). Interestingly, in common with **12**, the NMR signal for 9-H (δ = 4.00 ppm) seemed quite far downfield for an allylic methine,

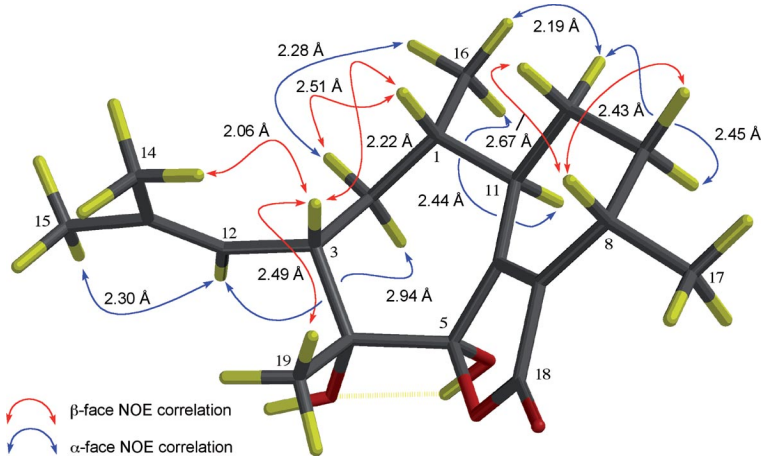


Figure 2. Conformation of sandresolide C (**5**) with minimized energy. The arrows show the NOE correlations, distances in between correlated protons are given in Ångstrøms.

whereas that for 10-H (δ = 4.70 ppm) appeared somewhat upfield for a vinylic methine.[10] This behavior suggests an unusual conformation in which 9-H and 10-H come into the deshielding and shielding cones, respectively, from nearby π-systems.

Except for C-3, the substitution pattern and relative stereochemistry about the *cis*-hydrindane ring system in compound **6** was determined to be the same as that in elisabethin C (**12**). NOEs were detected in $CDCl_3$ solution between 6-H, 18-H_3, and 15-H_2, which indicated that these protons were all on the same (α) face of the molecule. Furthermore, strong NOEs between 8α-H/18-H_3, 8α-H/10-H, and 6-H/10-H indicated that the isobutenyl side chain at C-9 must be *cis* to the methyl group at C-7. The assignment of the same relative stereochemistry for 17-H_3 in **12** as observed in **6** was based primarily on a conspicuous NOE between 5α-H and 17-H_3, which placed both of these protons on the α face. Complementary NOEs between 5α-H/6-H and 5β-H/18-H_3 helped us validate our stereochemical assignment for the pivotal 5-H methylene protons of bisnorditerpene **6**.

Elisabethin H (**7**) was obtained as a colorless oil, the molecular formula of which was established by HRFABMS as $C_{15}H_{22}O_4$. The ^{13}C and DEPT-135 NMR spectra (Table 2) showed 15 unique resonances: four quaternary, five CH, three CH_2, and three CH_3 carbons. Chemical shift values further characterized two ketone carbonyls, two olefinic carbons, and a tertiary carbinol. The IR suggested the presence of a saturated ketone (1702 cm^{-1}) and a conjugated ketone (1688 cm^{-1}). The UV spectrum showed absorption at λ_{max} = 234 nm (ε = 6600) indicative of conjugation. The overall structural elucidation of elisabethin H (**7**) required 500 MHz 2D NMR analysis experiments (^1H-^1H COSY, HMQC, HMBC, NOESY) in $CDCl_3$ as solvent. The complete atom assignments for elisabethin H are recorded in Table 2.

Connectivities from C-3 to C-9 were inferred from the COSY cross-peaks, including correlations from 3-H to 14-H_3 and from 7-H to 15-H_3 (Figure 3). Simultaneous long-range couplings (four- and five-bond, respectively) of 13-H_3 at δ = 1.68 ppm (dd, J = 1.4 and 2.0 Hz) with 12-H at δ = 7.24 ppm (q, J = 1.4 Hz) and with 9-H at δ = 3.89 ppm (ddq, J = 2.0, 6.5, and 9.0 Hz) extended connectivity from C-9 through C-13. These data allowed us to recognize the C-10 through C-13 side chain in **7** as a unique 3-hydroxy-2-methylprop-2-enoyl moiety and established it as a terminal grouping. HMBC data provided the evidence to connect the conjugated carbonyl at δ = 204.9 ppm (C-10) to the C-13 methyl group and C-9 and C-12 methines. Furthermore, the quaternary olefinic carbon at δ = 134.9 ppm (C-11) was correlated by HMBC with protons at the C-9, C-12, and C-13 positions. Thus, the connectivity from C-9 to C-13 across adjacent sp^2 quaternary carbons C-10 and C-11 was elucidated. Additional correlations in the HMBC spectra {C-1 [5α-H, 6-H, 8α-H] and C-2 [3-H, 6-H, 14-H_3]} revealed the remaining connectivities needed to recognize the polysubstituted hydrindane ring system of **7**, thus establishing its gross structure (Figure 3).

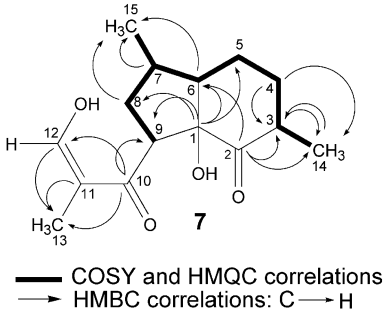


Figure 3. Partial structures for elisabethin H (**7**) generated from ^1H-^1H COSY, HMQC, and HMBC spectroscopic data.

The relative stereochemistry of elisabethin H (**7**) was assigned by a combination of NMR methods (NOESY and scalar couplings) with NMR spectral comparisons and molecular modeling studies. The geometry of the carbon–carbon double bond in enol tautomer **7** is based on the contention that in systems with intramolecular H-bonds involving

the enolic form of β-dicarbonyl compounds, the ^{13}C NMR chemical shift of the α-olefinic carbon atom (i.e., C-11) of the *Z* configuration always resonates at a lower field than that of the *E* isomer (absence of hydrogen bonding).[14] As was the case with *cis*-hydrindanes **6** and **12**, the ^{1}H NMR chemical shift value of 9-H (δ = 3.89 ppm) in elisabethin H (**7**) seemed quite far downfield for an α-carbon-bound methine. Space-filling models revealed that when the C-1 hydroxy group is α-oriented (i.e., 1*S**) the geometry of **7** is such that 9-H, which lies close to the C=O bond at C-2, cuts into the deshielding cone of the induced magnetic field. Moreover, only in this stereoisomer, which also possessed the lowest calculated energy (234 kJ mol^{-1}), are the internuclear distances such that both hydroxy groups in **7** are within hydrogen-bonding distance of the α,β-unsaturated C=O function, resulting in a further lowering of its absorption frequency (1688 cm^{-1}).[15] An NOE between 4β-H and 7-H, together with one observed between 4β-H and 14-H_3, demonstrated that these protons are close to each other, placing the methyl groups at C-3 and C-7 on the β- and α-face of the molecule, respectively. The proposed 1*S** stereochemistry and the *cis*-fused bicyclic system in **7** are thus apparent from the NOE correlations of 4β-H and H-7. Moreover, since the ^{13}C NMR chemical shift values of C-2 (δ = 207.9 ppm) and C-14 (δ = 14.7 ppm) in elisabethin H (**7**) were not in close agreement with the shift values of the corresponding carbons in elisabethin C (**12**, δ = 213.6 and 17.8 ppm, respectively),[10] it seemed likely that these compounds would have opposite relative stereochemistry at C-3. On the basis of the above spectral evidence, the structure of elisabethin H, including its relative stereochemistry, was confidently assigned as **7**. Circumstantial evidence suggests that compound **7** is actually a chemically degraded congener of elisabethin A (**10**) and not a regular sesquiterpene.[10,16] The name *pentanorseco*-elisabethane is proposed for the structurally unique carbon framework found in elisabethin H (**7**).

Biological Evaluation

As part of an ongoing search for novel anti-tuberculosis agents from Caribbean gorgonian octocorals, we screened compounds **1**, **4**, **5**, and **7** as growth inhibitors of *Mycobacterium tuberculosis* $H_{37}Rv$ at a concentration of 6.25 μg mL^{-1}.[17] Elisabethin H (**7**) exhibited the strongest inhibitory activity (51%), whereas isolates **1**, **4**, and **5** inhibited 28%, 16%, and 15% of mycobacterial growth, respectively. On the other hand, at 128 μg mL^{-1}, serrulatanes **2** and **3** strongly inhibited bacterial growth by 88% and 92%. With the purpose of contributing to the search of novel agents to treat neuroinflammation, some of these metabolites were evaluated in an in vitro anti-neuroinflammatory assay.[18] Of the compounds evaluated (**1**, **4**, **5**, and **7**), elisabethin H (**7**) was determined to be the only promising compound, because it significantly inhibited superoxide anion (O_2^-) generation from *E. coli* lipopolysaccharide (LPS) activated rat neonatal microglia in vitro (IC_{50} = 7.0 μg mL^{-1}).[19] Biological screening of sandresolide C (**5**) in the NCI 60 cell-line tumor panel indicated no significant in vitro cancer cell cytotoxicity.[20] On the other hand, **5** displayed moderate antimalarial activity (IC_{50} = 18 μg mL^{-1}) against the *Plasmodium falciparum* W2 (chloroquine-resistant) strain.[21]

Conclusions

In summary, we have carefully explored the natural products chemistry of *P. elisabethae* at the concentration range of 0.0001–0.003%, thus discovering seven structurally diverse new metabolites. Unlike many natural products previously isolated by us from this source, compounds **1**–**7** were unsuitable for X-ray analysis, so the structure determination of these compounds relied heavily upon NMR investigations and upon degradative chemical methods. Among the new compounds isolated in this study, serrulatanes **1**–**3** are of special interest as they could be regarded as biosynthetic intermediates leading to the anti-inflammatory pseudopterosins.[22] Perhaps the most interesting discovery made throughout this investigation was the isolation of a new class of C_{15}-rearranged diterpenes – namely, elisabethin H (**7**) – on the basis of that compound's structural novelty and interesting biological properties. As far as we have been able to ascertain, elisabethin H is the only example of a naturally occurring substance containing the 3-hydroxy-2-methylprop-2-enoyl moiety. Admittedly speculatively, that functionality might in fact be responsible for the purported anti-inflammatory properties of elisabethin H. Because only very small quantities of elisabethin H were obtained from this coral, it was not possible to screen further for anti-inflammatory activity. In view of this, we sought to obtain additional quantities of **7** from the remaining gorgonian extracts, but no discernible amounts could be isolated from this source. It seems likely that total synthesis will be required to access sufficient quantities of this novel metabolite for pharmaceutical evaluation.

Experimental Section

General Remarks: Optical rotations were obtained with an Autopol IV automatic polarimeter. Infrared and UV spectra were obtained with a Nicolet Magna FT-IR 750 spectrometer and a Shimadzu UV-2401 PC UV/Vis spectrophotometer, respectively. 1D- and 2D-NMR spectra were recorded with a Bruker DRX 500 FT-NMR spectrometer. Mass spectrometric determinations were generated at the Mass Spectrometry Laboratory of the University of Illinois at Urbana–Champaign. Column chromatography was performed with silica gel (35–75 mesh), whereas TLC analysis was carried out with glass pre-coated silica gel plates and the spots were visualized with the aid of a UV lamp at λ = 254 nm or by exposure to I_2 vapor. Semi-preparative HPLC was performed with a Magnum Partisil-10 semipreparative column (10μ, 10 mm × 50 cm) with a flow rate of 2 mL min^{-1} with propan-2-ol in hexane (5%). Analytical HPLC was performed with an Ultrasphere Cyano column (5μ, 4.6 mm × 25 cm) with a flow rate of 1 mL min^{-1} with propan-2-ol in hexane (4%). All HPLC separations were carried out with isocratic

elution of the mobile phase and the UV detector set at λ = 220 nm. All solvents used were either spectral grade or were distilled from glass prior to use. The percentage yield of each compound is based on the weight of the crude MeOH/$CHCl_3$ gorgonian extract.

Animal Material: Fresh specimens of the West Indian sea whip *Pseudopterogorgia elisabethae* (phylum Cnidaria, class Anthozoa, order Alcyonacea, suborder Holaxonia, family Gorgoniidae) were collected by hand at depths of 80–100 ft (SCUBA) from the coral reefs off San Andrés island, Colombia (located at N12° 33′, W81° 43′) in May 1996. A voucher specimen (No. PESAI-01) has been deposited at the Chemistry Department of the University of Puerto Rico, Río Piedras Campus. The organism was partially air-dried, frozen, and lyophilized prior to its extraction.

Extraction and Isolation Procedures: A detailed scheme for the extraction of the dry gorgonian specimen (1.0 kg) has been described previously in two separate accounts.[10,16c] Fractions IV (a) (6.47 g) and IV (b) (2.13 g) were mixed on the basis of their similar TLC and NMR (^{1}H and ^{13}C) profiles. The combined fractions were chromatographed over silica gel (200 g) with acetone in hexane (2%), leading to 17 secondary fractions (1–17).

Further purification of subfraction 9 (52.0 mg) by normal-phase HPLC (Partisil-10) afforded pure elisabethin G (**6**, 2.6 mg, 1.3X10^{-3}% yield). Fraction IV (d) (1.2 g) was purified by size exclusion chromatography (Bio-Beads SX-3 in toluene) and then was chromatographed successively over silica gel (20 g) with EtOAc in hexane (2%) and then over ODS silica gel (1.5 g) with H_2O in MeOH (10%) to yield elisabethin A acetate (**4**, 4.6 mg, 2.3×10^{-3}% yield) along with elisabethin H (**7**, 3.2 mg, 1.6×10^{-3}% yield). Following purification by size exclusion chromatography as described above, fraction IV (e) (1.2 g) was fractionated consecutively over silica gel (17.2 g) with EtOAc in hexane (2%) and then over ODS silica gel (1.2 g) with H_2O in MeOH (10%), followed by normal-phase HPLC (Cyano) to yield elisabethadienol (**1**, 3.0 mg, 1.5×10^{-3}% yield), 7-hydroxyerogorgiaenone (**2**, 1.3 mg, 6.5×10^{-4}% yield) and 7,14-erogorgiaenediol (**3**, 1.9 mg, 9.5×10^{-4}% yield). Purification of fraction IV (i) (7.1 g) by size exclusion chromatography (Bio-Beads SX-3 in toluene) followed by column chromatography over: a) silica gel (36.0 g) with EtOAc in hexane (17%), b) ODS silica gel (8.4 g) with H_2O in MeOH (10%), and c) silica gel (2.5 g) with propan-2-ol in hexane (5%) led to homogeneous sandresolide C (**5**, 5.5 mg, 2.7×10^{-3}% yield).

Elisabethadienol (1): Colorless oil. $[\alpha]_D^{25}$ = +12.0 (c = 1.0, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 500 MHz) and ^{13}C NMR ($CDCl_3$, 125 MHz): see Table 1. IR (neat): $\tilde{\nu}_{max}$ = 3404, 2957, 2923, 2869, 1662, 1455, 1381, 1352, 1238, 1123, 1002 cm^{-1}. EIMS: *m*/*z* (%) = 290 (9) $[M]^+$, 272 (44), 257 (14), 216 (10), 190 (27), 187 (26), 161 (100), 159 (38), 119 (50), 109 (29), 105 (37), 95 (25), 93 (25), 81 (35), 69 (75). HRESIMS: calcd. for $C_{20}H_{34}O$ $[M]^+$ 290.2609; found 290.2606.

7-Hydroxyerogorgiaenone (2): Colorless oil. $[\alpha]_D^{25}$ = +65.0 (c = 0.53, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 500 MHz) and ^{13}C NMR ($CDCl_3$, 125 MHz): see Table 1. IR (neat): $\tilde{\nu}_{max}$ = 3418, 2929, 2872, 1703, 1633, 1502, 1455, 1261, 1377, 1176 cm^{-1}. UV (MeOH): λ_{max} = 210 (ε = 26000), 282 (ε = 4700) nm. HRESIMS: calcd. for $C_{20}H_{28}O_2Na$ $[M + Na]^+$ 323.1987; found 323.1987.

7,14-Erogorgiaenediol (3): Colorless oil. $[\alpha]_D^{25}$ = +20.0 (c = 1.0, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 500 MHz) and ^{13}C NMR ($CDCl_3$, 125 MHz): see Table 1. IR (neat): $\tilde{\nu}_{max}$ = 3391, 3077, 2928, 2869, 1620, 1502, 1452, 1376, 1262, 1188, 1071, 1021, 899 cm^{-1}. UV (MeOH) λ_{max} = 208 (ε = 14000), 282 (ε = 2800) nm. HRESIMS: calcd. for $C_{20}H_{30}O_2Na$ $[M + Na]^+$ 325.2144; found 325.2146.

Elisabethin A Acetate (4): Colorless solid. $[\alpha]_D^{25}$ = +140.0 (c = 2.1, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 500 MHz) and ^{13}C NMR ($CDCl_3$, 125 MHz): see Table 2. IR (neat): $\tilde{\nu}_{max}$ = 2955, 2925, 2868, 1776, 1705, 1673, 1645, 1453, 1370, 1301, 1261, 1237, 1188, 1083, 1030, 923, 879, 802 cm^{-1}. UV (MeOH) λ_{max} = 204 (ε = 8500), 250 (ε = 7400) nm. EIMS: *m*/*z* (%) = 358 (2) $[M]^+$, 316 (4), 234 (5), 208 (13), 207 (100), 109 (17), 95 (5), 83 (4). HREIMS: calcd. for $C_{22}H_{30}O_4$ $[M]^+$ 358.2144; found 358.2133.

Sandresolide C (5): Transparent thin needles. $[\alpha]_D^{25}$ = +12.3 (c = 0.65, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 500 MHz) and ^{13}C NMR ($CDCl_3$, 125 MHz): see Table 3. IR (neat): $\tilde{\nu}_{max}$ = 3391 (sharp), 3263 (broad), 2950, 2936, 2867, 1767, 1665, 1446, 1403, 1368, 1260, 1080, 1066, 908 cm^{-1}. UV (MeOH) λ_{max} = 230 (ε = 13500) nm. EIMS: *m*/*z* (%) = 320 (2) $[M]^+$, 302 (4), 287 (3), 260 (57), 259 (62), 245 (17), 241 (13), 125 (35), 109 (100), 83 (50). HREIMS: calcd. for $C_{19}H_{28}O_4$ $[M]^+$ 320.1988; found 320.1986.

Elisabethin G (6): Colorless oil. $[\alpha]_D^{25}$ = +13.8 (c = 0.9, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 500 MHz) and ^{13}C NMR ($CDCl_3$, 125 MHz): see Table 2. IR (neat): $\tilde{\nu}_{max}$ = 3430, 2924, 2855, 1733, 1700, 1650, 1458, 1376, 1258, 1227, 1165, 1097, 1022, 802 cm^{-1}. HRESIMS: calcd. for $C_{18}H_{29}O_3$ $[M + H]^+$ 293.2117; found 293.2119.

Elisabethin H (7): Colorless oil. $[\alpha]_D^{25}$ = +45.3 (c = 0.75, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 500 MHz) and ^{13}C NMR ($CDCl_3$, 125 MHz): see Table 2. IR (neat): $\tilde{\nu}_{max}$ = 3451, 3371, 3082, 2955, 2929, 2871, 1702, 1688, 1633, 1449, 1376, 1323, 1141, 1105, 979, 907, 839 cm^{-1}. UV (MeOH) λ_{max} = 208 (ε = 8600), 234 (ε = 6600) nm. HRFABMS (glycerol): calcd. for $C_{15}H_{22}O_4Na$ $[M + Na]^+$ 289.1418; found 289.1416.

Reduction of 7-Hydroxyerogorgiaenone (2) with $NaBH_4$: A mixture of **2** (1.3 mg, 0.004 mmol) and $NaBH_4$ (3 mg, 0.08 mmol) in MeOH (1.0 mL) was stirred at 25 °C for 10 h. The residue obtained after concentration was eluted ($CHCl_3$) through a short plug of silica gel, concentrated, and stored in vacuo to yield an oily residue (1.5 mg), the retention time of which by TLC and NMR spectra (^{1}H and ^{13}C) conclusively identified it as 7,14-erogorgiaenediol (**3**, ≈1:1 mixture of epimers).

Acetylation of Elisabethin A (10): A solution of **10** (3.5 mg, 0.011 mmol) in a mixture of acetic anhydride (1.0 mL) and pyridine (0.5 mL) was stirred at 25 °C for 2 h. Excess reagents were removed by rotoevaporation, and after concentration and storage in vacuo we obtained a homogeneous compound (4.0 mg), the retention time of which by TLC and NMR spectra (^{1}H and ^{13}C) conclusively identified it as elisabethin A acetate (**4**).

Biological Assays: Additional experimental details for our primary in vitro anti-microbial assays against *Mycobacterium tuberculosis* and *Plasmodium falciparum* have been described previously.[17,21] The in vitro neuroinflammation and cancer cell cytotoxicity assays for compounds **1**, **4**, **5**, and **7** were carried out as indicated before.[18–20]

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sity of Illinois at Chicago). Antimalarial bioassays were performed at the Instituto de Investigaciones Científicas Avanzadas y Servicios de Alta Tecnología (Republic of Panama). I. I. R. thanks the US Department of Education, GAANN Fellowship Program (Grant P200A030197-05) for financial support. This work was partially supported by the University of Puerto Rico (NIH-SCORE Program, Grant S06GM08102).

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[13] Complete proton/deuterium exchange in CD_3OD (without a trace of acid or base catalyst) was achieved slowly after heating of sandresolide C (**5**) at 55 °C for 4–5 days. LREIMS analysis of the product obtained revealed a molecular ion species at *m*/*z* = 321.

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