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Structurally Diverse Terpenoids from the Sea Whip *Pseudopterogorgia elisabethae* (Bayer)

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Dedicated to Professor Paul J. Scheuer in recognition of his 50th year as a faculty member of the University of Hawaii and his extensive and important contributions to the field of marine natural products chemistry

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Abstract—The extraction of a specimen of *Pseudopterogorgia elisabethae* from Colombia afforded three new diterpenes **1**–**3**, a norditerpene **4**, and a tetrisnorditerpene **5**. Metabolites **4** and **5** contain unusual carbon skeletons that are previously undescribed and therefore constitute new classes of C_{19} and C_{16} rearranged terpenes, respectively. Full details of the isolation and structure elucidation of **1**–**5**, which were established by spectroscopic methods including comprehensive 2D NMR measurements, are provided herein.

Introduction

Over the past 15 years an impressive number of structurally unique and biologically active diterpenoids have been reported from gorgonian species (sea whips, sea feathers, and sea fans; phylum Cnidaria, order Gorgonacea) belonging to the genus *Pseudopterogorgia*.[1,2] Primarily, the diterpenes from *Pseudopterogorgia* fall into four structural classes: highly oxygenated cembranes and pseudopteranes, as monomers and dimers, and the serrulatane and amphilectane-based diterpenes.[3] Recent investigations in this laboratory aimed at the discovery of gorgonian-derived metabolites with potent pharmacological activities have uncovered the presence in various *Pseudopterogorgia* species of diterpenes with unusual carbon skeletons, namely, gersolanes, verrillanes, elisabethanes, elisapteranes, and colombianes.[4–9] Concurrently, we have also uncovered several types of C_{19} rearranged metabolites having the norpseudopterane, norcembrane, elisabane, and norsandresane skeletons as well as a smaller number of C_{17} rearranged congeners (trisnorditerpenes).[10] The presence of many stereocenters and multiple rings in most of these novel carbon systems presents a considerable challenge to the elucidation of their structures. The ability of *Pseudopterogorgia* species to generate such a diverse range of terpenoid structures is unparalleled by other gorgonian genera found in the Caribbean region of the West Indies.[1] As part of our search for biologically active secondary metabolites from *Pseudopterogorgia elisabethae* (Bayer) we now report the isolation and structure elucidation of five cyclic terpenes, **1**–**5**, each one belonging to a distinct skeletal class. Elisabatin C (**1**) and *p*-benzoquinone **3** are the most recent representatives of the amphilectane and serrulatane family of diterpenes, respectively, and elisapterosin C (**2**) is the third example reported thus far of the rare elisapterane class of C_{20} rearranged diterpenes. Tricyclic compounds 4-(acetyl) amphilectolide (**4**) and amphiphenalone (**5**), on the other hand, are structurally related to the amphilectanes, but each possesses a novel carbon skeleton.

Results and Discussion

Freshly collected animals from San Andrés Island, Colombia were sun-dried, stored frozen, and subsequently extracted with 50% MeOH/$CHCl_3$. After filtration, the crude extract of *P. elisabethae* (1.0 kg) was partitioned between hexane and H_2O. The hexane extract was concentrated under vacuum to give a dark green residue, a large portion of which was fractionated by gradient silica gel flash chromatography (0–100% acetone in hexane) followed by size exclusion (Bio Beads SX-3 in toluene) and repeated normal-phase and reversed-phase SiO_2 chromatography. These experimental procedures led to pure elisabatin C (**1**) (10.2 mg, 5.0×10^{-3}% yield), elisapterosin C (**2**) (24.5 mg, 1.2×10^{-2}% yield), *p*-benzoquinone **3** (20.7 mg; 1.0×10^{-2}% yield), 4-(acetyl) amphilectolide (**4**) (9.8 mg, 4.8×10^{-2}% yield), and amphiphenalone (**5**) (2.5 mg, 1.2×10^{-3}% yield). The molecular structures of these metabolites were proposed on the basis of comprehensive analysis of the 1D and 2D NMR (^{13}C, ^{1}H, ^{1}H–^{1}H COSY, HMQC, HMBC, and NOESY) and IR, UV, and HREI-MS spectra.

Keywords: coelenterates; terpenes and terpenoids; benzoquinones; polycyclic aromatic compounds.

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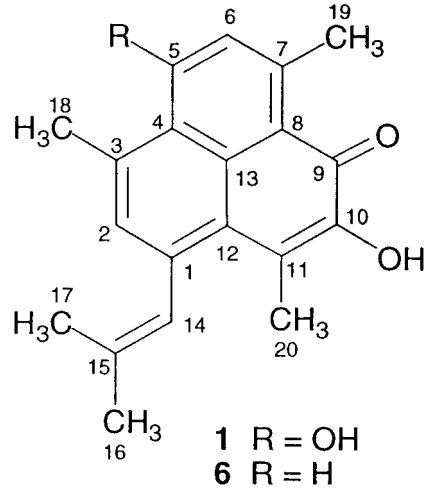
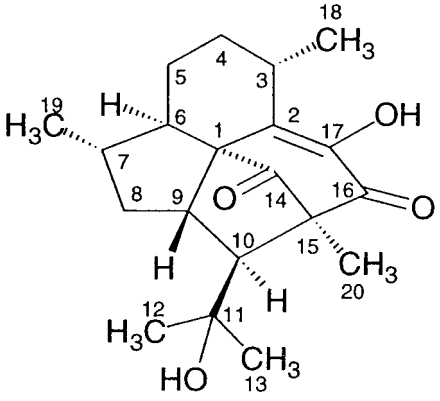
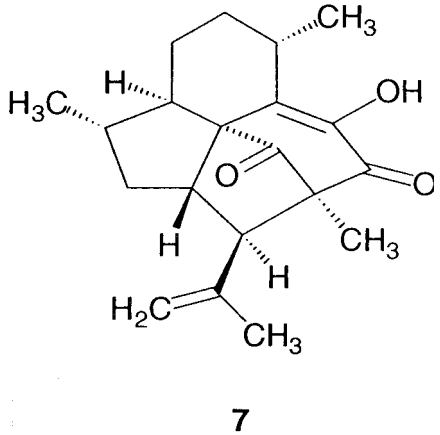
Table 1. ^{1}H NMR (300 MHz), ^{13}C NMR (75 MHz), and ^{1}H–^{1}H COSY spectral data for compounds **1–3** (assignments were aided by ^{1}H–^{1}H COSY, spin splitting patterns, DEPT, HMBC, HMQC and NOESY experiments, and chemical shift values; the δ values are in ppm and are referenced to either the residual $CHCl_3$ (7.26 ppm) or $CDCl_3$ (77.0 ppm) signals)

Atom	Elisabatin C (**1**)[a]			Elisapterosin C (**2**)[b]			*p*-Benzoquinone **3**[b]		
	δ_H, mult, intgr (*J* in Hz)	δ_C (mult)	COSY	δ_H, mult, intgr (*J* in Hz)	δ_C (mult)	COSY	δ_H, mult, intgr (*J* in Hz)	δ_C (mult)	COSY
1		129.1 (s)			60.9 (s)		2.95, br q, 1H (7.0)	26.1 (d)	H2αβ, H20
2α	6.99, br s, 1H	132.4 (d)	H18		138.6 (s)		1.86, m, 1H	25.9 (t)	H1, H2β, H3αβ
2β							1.50, m, 1H		H1, H2α, H3αβ
3α		137.5 (s)		3.18, m, 1H	28.3 (d)	H4β, H18	1.74, m, 1H	18.0 (t)	H2αβ, H3β, H4
3β							1.59, m, 1H		H2αβ, H3α, H4
4α		119.8 (s)		1.43, m, 1H	24.2 (t)	H4β, H5αβ	2.87, br t, 1H (4.5)	35.2 (d)	H3αβ, H11
4β				1.74, m, 1H		H3, H4α, H5αβ			
5α		162.5 (s)		1.51, dd, 1H (4.8, 10.7)	19.1 (t)	H4αβ, H5β, H6		187.9 (s)	
5β				1.77, m, 1H		H4αβ, H5α, H6			
6	6.90, br s, 1H	116.1 (d)	H19	2.28, br dd, 1H (5.1, 10.2)	40.3 (d)	H5αβ, H7		116.8 (s)	
7		150.6 (s)		2.00, m, 1H	41.6 (d)	H6, H19		150.6 (s)	
8α		117.5 (s)		0.85, br dd, 1H (11.9, 12.1)	44.4 (t)	H8β, H9		182.8 (s)	
8β				2.12, ddd, 1H (5.9, 6.1, 12.1)		H8α, H9			
9		177.0 (s)		2.46, ddd, 1H (5.9, 6.1, 11.9)	52.5 (d)	H8αβ, H10		143.2 (s)	
10		147.8 (s)		1.64, d, 1H (5.5)	59.7 (d)	H9		148.0 (s)	
11		121.0 (s)			71.8 (s)		1.90, m, 1H	37.3 (d)	H4, H12αβ, H18
12		125.0 (s)		1.16, s, 3H	30.3 (q)		1.97, m, 2H	38.5 (t)	H11, H13
13		141.1 (s)		1.35, s, 3H	29.3 (q)		5.61, m, 1H	139.5 (d)	H12αβ, H14
14	6.61, br s, 1H	128.6 (d)	H16, H17		203.6 (s)		5.62, m, 1H	126.2 (d)	H13
15		134.0 (s)			68.4 (s)			70.6 (s)	
16	1.87, br d, 3H (1.2)	25.5 (q)	H14, H17		194.3 (s)		1.30, br s, 3H	29.8 (q)	
17	1.52, br d, 3H (1.2)	19.1 (q)	H14, H16		146.6 (s)		1.30, br s, 3H	29.7 (q)	
18	2.84, br s, 3H	25.2 (q)	H2	1.13, d, 3H (7.1 Hz)	17.7 (q)	H3	0.81, d, 3H (6.7 Hz)	17.6 (q)	
19	2.88, br s, 3H	25.1 (q)	H6	1.03, d, 3H (6.3)	18.1 (q)	H7	1.92, s, 3H	8.2 (q)	
20	2.42, s 3H	16.7 (q)		1.54, s, 3H	15.2 (q)		1.10, d, 3H (7.0 Hz)	20.8 (q)	H1
–OH	7.73, br s, 1H			3.94, br s, 1H			6.97, s, 1H		
–OH	9.61, br s, 1H			6.13, br s, 1H					

[a] Data recorded in a mixture of $CDCl_3$ and acetone-d_6.
[b] Data recorded in $CDCl_3$.





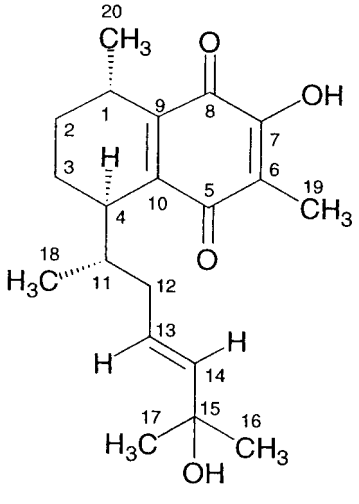


The HREI-MS and ^{13}C NMR spectral analyses of elisabatin C (**1**), isolated as red needles, suggested a molecular formula of $C_{20}H_{20}O_3$ indicating 11 degrees of unsaturation. Since the ^{13}C NMR spectrum (Table 1) contained 14 aromatic and olefinic carbon resonances, in addition to a carbonyl resonance, the molecule was judged to be tricyclic. The ^1H NMR spectrum of compound **1** contained five methyl resonances [δ 2.88 (br s, 3H), 2.84 (br s, 3H), 2.42 (s, 3H), 1.87 (br d, 3H, J=1.2 Hz), 1.52 (br d, 3H, J=1.2 Hz)] which was consistent with a diterpenoid skeleton. The presence of a hexasubstituted perinaphthenone and a conjugated trisubstituted double bond was indicated from resonances in the aromatic [δ 6.99 (br s, 1H) and 6.90 (br s, 1H)] and olefinic [δ 6.61 (br s, 1H)] region in the ^1H NMR spectrum. This was confirmed when the multiplicities of the corresponding carbons were obtained (see Table 1). The detection of four absorption maxima in the UV (MeOH) spectrum of **1** at λ_{max}=210 (ϵ 17000), 256 (ϵ 11000), 430 (ϵ 5500), and 458 (ϵ 4700) nm suggested that the perinaphthenone ring indeed had extended conjugation. An absorption at 3335 cm^{-1} in the IR spectrum, as well as a pronounced bathochromic shift (from 256 to 268 nm) in the UV spectrum upon addition of base (one drop 5% KOH/MeOH) confirmed the presence of a phenol in the molecule. Two D_2O-exchangeable protons observed at δ 9.61 (br s, 1H) and 7.73 (br s, 1H) in the ^1H NMR spectrum were assigned to aromatic hydroxyl groups. Two substituents on the perinaphthenone ring system were proposed to be aromatic methyls on the basis of two deshielded three-protons singlet resonances at δ 2.88 and 2.84. Furthermore, a ^1H–^1H COSY experiment (Table 1) showed benzylic coupling between the latter methyl protons and the aromatic resonances at δ 6.90 and 6.99, respectively, thus establishing their vicinal relationship. These data, together with the UV spectrum and the absence of further spin systems, indicated that the structure of **1** must be a highly conjugated tricyclic system. The HREI-MS of **1** gave an $[M+1]^+$ ion at m/z 309.1519 (27%), which analyzed for $C_{20}H_{21}O_3$, ascribable to the reduced form of **1**. Further HMBC,[11] NOE,[12] and long-range ^1H–^1H COSY experiments (Table 1) positioned the phenols at C-5 and C-10 and defined two aromatic methines [δ 6.99 (br s, H-2) and 6.90 (br s, H-6)], three methyl groups [δ 2.88 (br s, H-19), 2.84 (br s, H-18), 2.42 (s, H-20)], and a conjugated isobutenyl side chain [δ 6.61 (br s, 1H, H-14), 1.87 (br d, 3H, J=1.2 Hz, H-16), 1.52 (br d, 3H, J=1.2 Hz, H-17)] along the 12-carbon backbone between C-1 and C-12. Interestingly, this red pigment possessed ^1H and ^{13}C NMR features similar to known elisabatin B (**6**), a penta-substituted perinaphthenone previously isolated from the same specimen.[6] Comparison of these data with those of elisabatin B (**6**) showed that **1** possessed the same amphilectane skeleton. Notwithstanding, alternative structures to **1** were carefully considered in which the aromatic –OH's and the carbonyl were placed at different locations throughout the highly conjugated system. Although some of these isomers could not be dismissed readily by 1D NMR, IR, or UV methods, structure **1** was strongly favored by the mass spectral and 2D NMR (HMBC and NOESY) data. An interesting structural feature of compounds **1** and **6** is that they possess an unusually high unsaturation number that leads to extended aromatic conjugation. Nevertheless, as in the case of elisabatin B (**6**), a solution of elisabatin C (**1**) in $CDCl_3$ decomposes slowly upon prolonged exposure to air and light at 25°C.

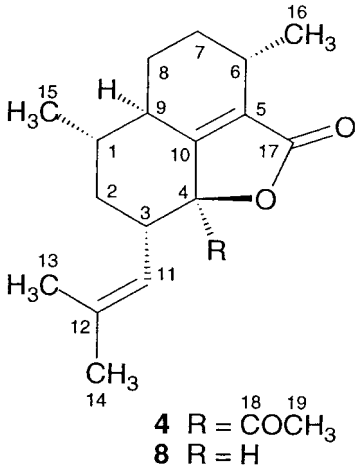
Elisapterosin C (**2**) is a colorless oil, $[\alpha]_D^{25}=-71.4°$ (c 0.7, $CHCl_3$), with a molecular formula of $C_{20}H_{28}O_4$, established by HREI-MS data and overall NMR information. In addition to a strong IR absorption at 3431 cm^{-1} indicative of hydroxyl groups, intense bands at 1755 and 1651 cm^{-1} indicated two ketone functions: one (1755 cm^{-1}) was tentatively assigned to a cyclopentanone while the other (1651 cm^{-1}) was ascribed to an α,β-unsaturated moiety

on the basis of the UV bands centered at 240 and 286 nm. The ^{1}H NMR spectrum in $CDCl_3$ (Table 1) showed two exchangeable protons, five methyl groups (two secondary and three quaternary), and eleven complex proton resonances between δ 0.8 and 3.2, suggestive of a polycyclic terpenoid structure. Observation of a sharp, exchangeable one-proton singlet at δ 6.13 in the ^{1}H NMR spectrum and a ^{13}C resonance at 146.6 (s) confirms the presence of a vinyl hydroxyl group. Except for the conspicuous absence of olefinic signals and the presence of two high field methyl singlets at δ 1.35 and 1.16 the remainder of the ^{1}H NMR spectrum of **2** could be matched with that of known elisapterosin B (**7**).[8] The ^{13}C NMR spectrum of **2** contained signals for all 20 carbons, including the following: two ketone carbonyls (δ 203.6, 194.3); two quaternary vinyl carbons (δ 146.6, 138.6), one oxygenated quaternary carbon (δ 71.8); three methylenes (δ 44.4, 24.2, 19.1); five methine carbons (δ 59.7, 52.5, 41.6, 40.3, 28.3); and five methyl groups (δ 30.3, 29.3, 18.1, 17.7, 15.2). The two signals remaining were ascribable to quaternary sp^3 carbons (δ 68.4, 60.9). To account for the four degrees of unsaturation remaining it was required that the molecule possessed four carbocyclic rings.

The assignment of tell-tale elisapterane system resonances including those of the carbinolic side chain in compound **2** was entirely supported by 2D-NMR experiments and confirmed by comparison with data for elisapterosin B (**7**).[8] HMBC long-range correlations of H_3-12 (δ 1.16) and H_3-13 (δ 1.35) with C-10 (δ 59.7) and those of H-10 (δ 1.64) with both C-12 (δ 30.3) and C-13 (δ 29.3) allowed the isopropanol side chain to be linked to C-10 and completed the unambiguous structural characterization of elisapterosin C.[13] In the same way, the relative stereochemistry about the rings substituents in elisapterosin C (**2**) (i.e., C-1, C-3, C-6, C-7, C-9, C-10, and C-15) was determined to be the same as that found in **7** by a combination of NMR methods (NOESY[14] and ^{1}H–^{1}H NMR coupling constants) coupled with NMR spectral comparisons and molecular modeling studies. Most informative was a pronounced NOESY correlation between H-9 with both H-3 and Me-12, consistent with their *cis* orientation on the top face of the molecule. The small (5.5 Hz) coupling constant between H-9 and H-10 supports the *trans* orientation shown in structure **2**, consistent with both C-9 and C-10 having the S^* configuration. Thus, the overall relative stereochemistry for **2** was assigned as 1S^*, 3S^*, 6R^*, 7S^*, 9S^*, 10S^*, and 15S^*. Elisapterosin C (**2**) is structurally very close to **7** and shows unusual NOE correlations very similar to those of elisapterosin B.



3



As in the previous case, *p*-benzoquinone **3**, an optically active orange oil, $[\alpha]_D^{25}=+220.0°$ (*c* 0.25, $CHCl_3$), also analyzed for $C_{20}H_{28}O_4$ by HREI-MS [(M)$^+$, *m/z* 332.1982, calcd for $C_{20}H_{28}O_4$, 332.1988] and by ^{13}C NMR (Table 1). The mass spectrum of this compound showed a base peak ion at *m/z* 206.0946 representing loss of $C_8H_{14}O$ due to the terpenoid 8-carbon side chain. This behavior, coupled with appropriate proton and carbon NMR bands, indicated the presence in **3** of a bicyclic diterpenoid component containing a tetra-substituted *p*-benzoquinone ring. Interpretation of the NMR spectral features indicated that such skeleton was similar to that of the aglycon portion of a related series of antiinflammatory glycosides, the *seco*-pseudopterosins A–D.[15] Excluding the sp^2 resonances due to the C_8 side chain, six sp^2 resonances were observed in the ^{13}C NMR [δ 187.9 (s), 182.8 (s), 150.6 (s), 148.0 (s), 143.2 (s), and 116.8 (s)], diagnostic of the *p*-benzoquinone constellation with an *ortho* hydroxyl functionality. The presence of such vinyl hydroxyl group was confirmed further by the observation in the ^{1}H NMR spectrum of a sharp one-proton singlet at δ 6.97 and the UV spectrum of **3**, which upon addition of one drop 5% KOH/MeOH, showed a pronounced base-induced shift from 282 to 334 nm. The ^{1}H NMR spectrum of **3** in $CDCl_3$ solution also showed a pair of signals with almost co-incident chemical shifts (δ 5.61 (m, 1H) and 5.62 (m, 1H)] for a 1,2-disubstituted double bond that could be partially resolved in benzene-d_6. The large coupling constant (15.5 Hz) observed for these olefinic protons suggested a *trans* configuration. The complete structure determination of **3** was facilitated by further interpretation of NMR data and by consideration of the results of the earlier work by Fenical et. al. with a structurally similar bicyclic *p*-benzoquinone.[3c] Comparison of these data with several derivatives of the *seco*-pseudopterosin showed that **3** possessed the same aglycon skeleton.[15] Further, ^{1}H–^{1}H COSY (Table 1) and HMBC[16] experiments positioned an allylic alcohol at C-15 and defined protons and carbons unambiguously along the 8-carbon side chain. A combination of molecular modeling studies, a NOESY NMR

Table 2. ^{1}H NMR (300 MHz), ^{13}C NMR (75 MHz), ^{1}H–^{1}H COSY, and HMBC spectral data for compounds **4** and **5** (assignments were aided by ^{1}H–^{1}H COSY, spin splitting patterns, DEPT, HMBC, HMQC and NOESY experiments, and chemical shift values. The δ values are in ppm and are referenced to either the residual $CHCl_3$ (7.26 ppm) or $CDCl_3$ (77.0 ppm) signals)

Atom	4-(Acetyl) amphilectolide (**4**)[a]				Amphiphenalone (**5**)[b]			
	δ_H, mult, intgr (*J* in Hz)	δ_C (mult)	COSY	HMBC[c]	δ_H, mult, intgr (*J* in Hz)	δ_C (mult)	COSY	HMBC[c]
1	1.24, m, 1H	39.4 (d)	H2αβ, H9, H15	H2αβ, H15		200.7 (s)		
2α	1.86, ddd, 1H (12.1, 12.1, 14.2)	36.8 (t)	H1, H2β, H3	H15	3.87, dd, 1H (2.1, 12.2)	78.3 (d)	2-OH, H3	H14
2β	1.50, ddd, 1H (4.1, 4.1, 14.2)		H1, H2α, H3					
3	2.42, ddd, 1H (4.1, 9.9, 12.1)	47.9 (d)	H2αβ, H11	H2αβ	1.53, ddq, 1H (6.8, 11.0, 12.2)	44.7 (d)	H2, H4, H14	H14
4		93.3 (s)		H2β, H3	2.45, ddd, 1H (3.3, 11.0, 11.0)	42.6 (d)	H3, H5αβ	H14
5α		128.7 (s)		H16	2.16, m, 1H	28.4 (t)	H4, H5β, H6αβ	H4, H6α
5β					1.11, m, 1H		H4, H5α, H6αβ	
6α					1.49, m, 1H	32.0 (t)	H5αβ, H6β, H7	H15
6β	2.46, m, 1H	27.0 (d)	H7αβ, H16	H7α, H8β, H16	2.21, m, 1H		H5αβ, H6α, H7	
7α	1.84, m, 1H	29.5 (t)	H6, H7β, H8αβ	H16	3.28, br dq, 1H (6.9, 12.6)	28.3 (d)	H6αβ, H15	H6α, H15
7β	1.23, m, 1H		H6, H7α, H8αβ					
8α	1.31, m, 1H	25.5 (t)	H7αβ, H8β, H9			126.3 (s)		H7, H15
8β	2.09, m, 1H		H7αβ, H8α, H9					
9	2.32, m, 1H	39.3 (d)	H1, H8αβ	H7α, H8α		150.2 (s)		
10		164.7 (s)				142.3 (s)		H16
11	4.87, br d, 1H (9.9)	121.7 (d)	H3, H13, H14	H13, H14		121.0 (s)		H16
12		136.5 (s)		H13, H14		126.4 (s)		H16
13	1.67, br d, 3H (1.2)	18.5 (q)	H11	H11, H14		140.6 (s)		
14	1.71, br d, 3H (1.2)	26.0 (q)	H11	H11, H13	1.25, d, 3H (6.3)	15.9 (q)	H3	
15	1.07, d, 3H (6.5)	18.9 (q)	H1	H1	1.24, d, 3H (6.8)	23.0 (q)	H7	
16	1.19, d, 3H (7.0)	18.1 (q)	H6		2.52, br s, 3H	14.2 (q)		
17		171.8 (s)						
18		205.7 (s)		H19				
19	2.16, s, 3H	29.1 (q)						
ArOH					7.96, br s, 2H			
2-OH					4.23, br d, 1H (2.5)		H2	

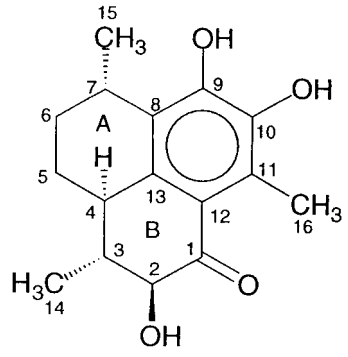
[a] Data recorded in $CDCl_3$.
[b] Data recorded in acetone-d_6.
[c] Protons correlated to carbon resonances in atom column. Parameters were optimized for $^{2,3}J_{CH}$=6 and 8 Hz.

experiment,[17] and NMR analysis of coupling constants for **3** showed that the protons at C-1, C-4, and C-11 had identical relative stereochemistries as in the *seco*-pseudopterosins A–D.[15]

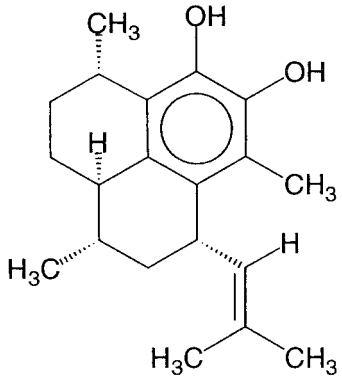
4-(Acetyl) amphilectolide (**4**), a rearranged norditerpene with a novel carbon skeleton, showed IR absorption bands for olefin (1671 cm^{-1}), ketone (1717 cm^{-1}), and α,β-unsaturated lactone carbonyl (1762 cm^{-1}) functions. The UV (MeOH) spectrum showed absorption at λ_{max} 232 nm (ϵ 10500) indicative of conjugation. The molecular formula $C_{19}H_{26}O_3$, determined by the HREI-MS and ^{13}C NMR (Table 2), indicated seven degrees of unsaturation. Resonances due to four olefinic carbons [δ_C 121.7 (d), 128.7 (s), 136.5 (s), 164.7 (s)] and two carbonyl carbons [δ_C 205.7 (s) and 171.8 (s)] in the ^{13}C NMR spectrum accounted for four double-bond equivalents, indicating that **4** was tricyclic. The lactone carbonyl group was clearly in conjugation with a tetrasubstituted olefin on the basis of its UV absorption and the chemical shift of C-10 [δ_C 164.7 (s)]. The ^1H NMR spectrum (Table 2) indicated resonances corresponding to a trisubstituted olefin [δ_H 4.87 (br d, 1H, J=9.9 Hz)] and five methyls: two secondary [δ_H 1.07 (d, 3H, J=6.5 Hz); 1.19 (d, 3H, J=7.0 Hz)], two vinyl methyl groups [δ_H 1.67 (br d, 3H, J=1.2 Hz); 1.71 (br d, 3H, J=1.2 Hz)] and an acetyl methyl [δ_H 2.16 (s, 3H)]. Segments of the ^1H and ^{13}C NMR spectra of 4-(acetyl) amphilectolide (**4**) were quite similar to those of the previously described trisnorditerpene amphilectolide (**8**)[10] except for the presence of two additional carbon signals in **4** [δ_C 205.7 (s) and 29.1 (q)] and a C-4 carbon signal [δ_C 93.3 (s)] in low field compared with a C-4 carbon signal [δ_C 83.6 (d)] of **8**. Furthermore, unlike in the ^1H NMR spectrum of **8**, there was no signal for an oxymethine in **4**; instead, a sharp methyl singlet at δ 2.16 was observed. These combined data suggested that the acetyl group in **4** must be at C-4. Analysis of the ^1H–^1H COSY spectrum suggested the presence in **4** of essentially the same 10-carbon backbone between C-1 and C-10 present in **8**. The gross skeleton was completed by the HMQC and HMBC spectra (Table 2). The connectivity from C-3 to C-4 resulted from cross-peaks from H-3 to C-4. The linkage from C-9 to C-10 and from C-5 to C-6 were inferred from long-range couplings from C-10 [δ_C 164.7 (s)] to H-9 [δ_H 2.32 (m)] and from C-5 [δ_C 128.7 (s)] to H_3-16 [δ_H 1.19 (d)], respectively. On the basis of these results, compound **4** possessed two carbocyclic rings and one butenolide ring, as in the case of **8**. The relative stereochemistry of **4** was deduced from observed NOE cross-peaks and J values for the ^1H NMR spectrum, that is, a relatively large coupling constant (9.9 Hz) between the protons at C-3 and C-11 of **4** indicates that the two protons are nearly *trans* in a preferred conformation. A molecular modeling study of **4** revealed that in such conformation, when the C-3 isobutenyl group is α-oriented, it is possible to bring Me-13 and H-3 within observable NOE distance. Indeed, weak dipolar couplings between these protons were observed. A pair of double doublets (δ 1.86) with large coupling constants (J=12.1, 12.1, 14.2 Hz) ascribable to H-2α suggests that this proton is *trans* diaxial to H-1 and H-3. NOEs from H-11 [δ 4.87 (br d)] to H_3-19 [δ 2.16 (s)] and H-2α [δ 1.86 (ddd)] and dipolar couplings from H_3-15 [δ 1.07 (d)] to both H-2α and H-9 [δ 2.32 (m)] showed that these protons occur on the same face of the tricyclic system. Therefore, the methyl group at C-1, the isobutenyl side chain at C-3, the acetyl moiety at C-4, and H-9 are all α-oriented. As in the case of **8**, the stereocenter at C-6, isolated from the rest of the molecule by two methylenes and the lactone moiety, was difficult to define by NOESY methods. The methyl group at C-6, however, was confidently assigned to the α-face of the molecule (i.e., *cis* to H-9) based on the NMR chemical shifts ascribed to Me-16 [δ_H 1.19 (d); δ_C 18.1 (q)], which were highly comparable to the known **8** [δ_H 1.23 (d); δ_C 17.8 (q)] and to the methyl group of similar constellations in the pseudopterosin A–D series.[3a] Thus, the overall relative stereochemistry for **4** was assigned as 1S^*, 3S^*, 4S^*, 6S^*, and 9R^*. Furthermore, this compound has a logical structure from a biosynthetic viewpoint. Thus, 4-(acetyl) amphilectolide (**4**) could be envisioned as a precursor for amphilectolide (**8**) via deacylation with concomitant loss of two carbons, in this case C-18 and C-19.

Amphiphenalone (**5**), a novel tetrisnorditerpene of composition $C_{16}H_{20}O_4$ based on HREI-MS and overall NMR spectral evidence (Table 2), was isolated as colorless plates, $[\alpha]_D^{25}$=+86.7° (c 0.3, acetone). Strong IR bands at 3409 and 1627 cm^{-1} suggested the presence of hydroxyl and conjugated carbonyl groups. The UV (MeOH) spectrum showed intense absorptions with maxima at λ_{max} 216 (ϵ 12000) and 288 (ϵ 6000) nm. The absorption at 3409 cm^{-1} in the IR spectrum, as well as a pronounced bathochromic shift (from 288 to 346 nm) in the UV spectrum upon addition of one drop 5% KOH/MeOH confirmed that there were aromatic hydroxyls in **5**. D_2O-exchangeable protons observed at δ 7.96 (br s, 2H) and 4.23 (br d, 1H, J=2.5 Hz) in the ^1H NMR spectrum were assigned to three hydroxyl groups. Other features of the spectrum included: a one-proton double doublet at δ 3.87 (J=2.1, 12.2 Hz) indicative of an oxymethine, a multiplet at δ 3.28 and a doublet of triplets at δ 2.45 (1H each) assigned to two benzylic hydrogens, two three-proton doublets at δ 1.24 (J=6.8 Hz) and 1.25 (J=6.3 Hz) indicating a pair of secondary methyl groups, and a three-proton singlet at δ 2.52, ascribed to an aromatic methyl. The ^{13}C NMR spectrum exhibited 16 signals ($3CH_3$, $2CH_2$, 4CH, and 7C) whose chemical shift values and multiplicity confirmed the presence of a fully substituted benzene ring [δ 150.2 (s), 142.3 (s), 140.6 (s), 126.4 (s), 126.3 (s), 121.0 (s)], a conjugated carbonyl [δ 200.7 (s)], and a secondary alcohol [δ 78.3 (d)]. Two substituents on the aromatic ring were proposed to be hydroxyl groups on the basis of two deshielded quaternary carbon resonances at δ_C 150.2 and 142.3. Spectral evidence thus required that compound **5** was tricyclic with one benzene ring and one C=O double bond. 2D NMR studies (COSY, HMQC, HMBC) revealed the connectivity and thus the gross structure of **5**. Assignments of the NMR signals are given in Table 2. Interestingly, although it appears that compound **5** contains an unprecedented carbon skeleton, the overall NMR evidence indicated that **5** possesses some structural features reminiscent of the amphilectane skeleton found in the aglycon portion of the pseudopterosins.[3a,b] Notwithstanding, comparison of their molecular formulae showed that amphiphenalone (**5**) lacked the four carbons typically ascribed to the isobutenyl side chain at C-1. In its place, a ketone carbonyl function now appears in **5** suggesting loss of the C_4 alkenyl side chain by

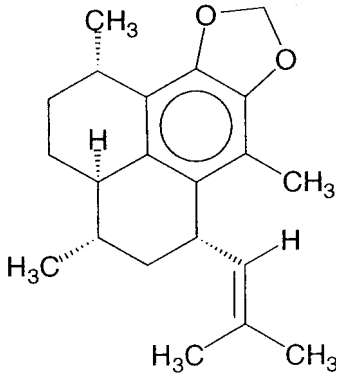
oxidative cleavage of the C-1,14 bond of an amphilectane-based precursor.[18] The $^1H-^1H$ COSY and HMBC experiments (Table 2) positioned the remaining hydroxyl function in **5** at C-2. The relative stereochemistry of **5** was elucidated from analysis of the NOESY spectrum,[19] coupling constants, and by comparisons of the NMR chemical shifts with those of known amphilectanes.[3a,b] Relatively large coupling constants (11.0 and 12.2 Hz) between H-3 and the protons at C-2 and C-4 of **5** indicated that the former proton is *trans* diaxial to H-2 and H-4. NOESY correlations of Me-14 with H-2 and H-4 suggested that these protons occur on the same face of the molecule. Additional NOESY correlations of H-4/H-5α, H-4/Me-15, H-5α/Me-14, H-5α/Me-15, H-5β/H-6β, and H-6β/H-7 revealed that ring A adopts a 'twist boat' conformation with H-4 and Me-15 in a near *cis* conformation. Therefore, H-2, H-4, and the methyl groups at C-3 and C-7 are all α-oriented. The relatively lowfield ^{13}C NMR chemical shift of the C-15 methyl group [δ 23.0 (q)] of **5** (in acetone-d_6) compared favorably to the carbon NMR shift from the same methyl group in helioporin E (**9**)[20] [δ 22.0 (q)] (in $CDCl_3$ solution) and to the methyl group of similar constellations in the pseudopterosin G–J series.[3b] Based upon comparison of their respective ^{13}C NMR data and the strong NOESY correlation between H-4 and Me-15, the stereochemistry of the methyl substituent at C-7 is suggested to be the same as those found in the aglycon portion of the pseudopterosins G–J and helioporin E (**9**).[21]



5



pseudopterosin G—J aglycone



helioporin E **(9)**

Concluding Remarks

The diverse terpenoid structures obtained from *Pseudopterogorgia elisabethae* constitute ample evidence that this animal is an important source of new classes of bioactive metabolites.[1] Biosynthetically, it is indeed remarkable that quite a number of different types of terpenoids (such as **1**–**8**) are isolated from the same species. As far as we are able to ascertain, this gorgonian species alone is responsible for the production of over twenty different skeletal classes of terpenes with unique substitution patterns and functionalities. Of considerable interest are the findings that a large number of these metabolites exhibit pharmacologically important effects, namely, cytotoxic, antibacterial, antiinflammatory and analgesic properties. The related series of metabolites, for instance, the pseudopterosins and *seco*-pseudopterosins, are potent antiinflammatory agents isolated from Bahamian specimens of *P. elisabethae*.[22] These metabolites contain both a glycoside moiety and a serrulatane (bicyclic *ortho*-hydroquinone) or amphilectane-based aglycon. Compounds **1**–**5**, while belonging to the same general structural class, do not contain a sugar moiety. We are currently investigating the potential of compounds **1**–**4** as possible antiinflammatory agents.

Experimental

General experimental procedures

Melting points were determined in a capillary tube with a Büchi 535 melting point apparatus and are uncorrected. Infrared spectra were recorded with a Nicolet Magna FT-IR 750 spectrophotometer and were referenced to polystyrene. ^1H and ^{13}C NMR spectral data and $^1H-^1H$ COSY, NOESY, DEPT, HMQC, and HMBC experiments were measured with a Bruker DPX-300 spectrometer. Chemical shifts are given as δ values against the internal residual proton signal from the solvent. Optical rotations were determined with a Perkin–Elmer polarimeter model 243B. HREI mass spectral analyses were recorded with a VG-Fisons Autospec MS system at the Material Characterization Center (MCC) of the University of Puerto Rico. Molecular mechanic calculations were performed on Insight-II 3.0/Discover Packages (Biosym Technologies, 9685 Scranton Rd., San Diego, CA 92121-2777) and implemented on a Silicon Graphics IRIS-INDIGO XS24 4000 workstation. Column chromatography was performed on silica gel (35–75 mesh) or bonded C-18 silica gel (35–75

mesh). TLC analyses were carried out using glass precoated silica gel plates. 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.

Extraction and isolation

A voucher specimen of *P. elisabethae,* collected in May 1996 off San Andrés Island, Colombia (no. PESAI-01) is stored at the Chemistry Department of the University of Puerto Rico. Our standard extraction protocol has been described elsewhere.[4] A large portion of the hexane extract (128 g) was fractionated by gradient silica gel (780 g) flash chromatography (0–100% acetone in hexane, then 100% MeOH). Fractions were pooled based on their TLC and NMR profile to yield seven primary fractions, designated as I–VII. The fraction obtained from 60% acetone in hexane [fraction IV (83.3 g)] was further purified by column chromatography over silica gel using a step gradient of EtOAc–hexane as eluant. Sixteen tertiary fractions were obtained [IV(a)–IV(p)]. Fractions IV(i) (7.1 g), IV(j) (2.4 g), and IV(k) (1.64 g) were dissolved in a small volume of toluene and purified further by size exclusion chromatography (Bio-Beads SX-3, toluene). The last fraction isolated from each column was further purified in the manner described below. Fraction IV (i-5) (2.6 g) was fractionated successively over: (a) silica gel (36 g) using 17% EtOAc in hexane; (b) ODS silica gel (10.0 g) using 10% H_2O in MeOH; (c) ODS silica gel (10.0 g) using 25% H_2O in MeOH; (d) Sephadex LH-20 (3.0 g) with $CHCl_3$ as eluant; and (e) silica gel (1.5 g) with 3% acetone in $CHCl_3$ to yield *p*-benzoquinone **3** (20.7 mg; 1.0×10^{-2}% yield). Fraction IV (j-4) (0.5 g) was chromatographed successively over: (a) silica gel (40.7 g) with 2.5% acetone in $CHCl_3$, (b) ODS silica gel (2.5 g) using 10% H_2O in MeOH, (c) ODS silica gel (2.5 g) using 25% H_2O in MeOH, and (d) silica gel (2.5 g) with 5% 2-propanol in hexane to afford elisabatin C (**1**) (10.2 mg, 5.0×10^{-3}% yield) and elisapterosin C (**2**) (24.5 mg, 1.2×10^{-2}% yield). Fraction IV (k-6) (0.1 g) was further purified by repetitive chromatography on (a) silica gel (8.0 g) using 20% EtOAc in hexane; (b) silica gel (2.2 g) with 3% acetone in $CHCl_3$; and (c) silica gel with 5% 2-propanol in hexane leading to the isolation of amphiphenalone (**5**) (2.5 mg, 1.2×10^{-3}% yield). The fraction obtained from 80% acetone in hexane [fraction V (2.48 g)] was dissolved in a small volume of toluene and purified further by size exclusion chromatography (Bio-Beads SX-3, toluene). Four tertiary fractions were obtained, designated [V(a)–V(d)]. The last fraction (4.0 g) was purified by successive column chromatography on ODS silica gel (7.0 g) using 15% H_2O in MeOH and then silica gel (1.5 g) with 2% EtOAc in hexane as eluant to give 4-acetyl amphilectolide (**4**) (9.8 mg, 4.8×10^{-3}% yield).

Elisabatin C (1). Red needles; mp 227–228°C; $[\alpha]_D^{25}=0°$ (*c* 0.5, $CHCl_3$); UV (MeOH) λ_{max} 210 nm (ϵ 17000), 256 nm (ϵ 11000), 430 nm (ϵ 5500), 458 nm (ϵ 4700), KOH 216, 268, 434, 458 nm; IR (film) 3335, 2960, 2928, 2856, 1733, 1634, 1592, 1544, 1507, 1437, 1412, 1374, 1341, 1253, 1168, 1119, 1089, 1067, 893, 854, 758, 617 cm^{-1}; ^1H NMR ($CDCl_3$ and acetone-d_6, 300 MHz) and ^{13}C NMR ($CDCl_3$ and acetone-d_6, 75 MHz) (see Table 1); EIMS *m/z* 309 $[M+1]^+$ (27), 308 $[M]^+$ (77), 294 (21), 293 (65), 279 (14), 276 (11), 265 (19), 247 (12), 209 (14), 207 (26), 205 (20), 195 (16), 193 (15), 189 (11), 165 (16), 139 (11), 118 (22), 105 (100), 92 (21), 91 (63), 79 (16), 77 (17); HREI-MS *m/z* 309.1519 $[M+1]^+$ (calcd for $C_{20}H_{21}O_3$ 309.1491), 308.1415 $[M]^+$ (calcd for $C_{20}H_{20}O_3$ 308.1412).

Elisapterosin C (2). Colorless oil; $[\alpha]_D^{25}=-71.4°$ (*c* 0.7, $CHCl_3$); UV (MeOH) λ_{max} 210 nm (ϵ 5000), 240 nm (ϵ 3800), 286 nm (ϵ 6300); IR (film) 3431, 2933, 2870, 2730, 1755, 1651, 1616, 1456, 1386, 1316, 1236, 1118, 1050, 1031, 949, 910, 889, 757, 667 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) and ^{13}C NMR ($CDCl_3$, 75 MHz) (see Table 1); EI-MS *m/z* 332 $[M]^+$ (21), 314 (7), 304 (7), 286 (31), 246 (46), 231 (42), 206 (41), 205 (32), 204 (43), 189 (39), 125 (18), 117 (21), 109 (46), 105 (30), 97 (29), 95 (26), 71 (41), 67 (37), 57 (87), 55 (100); HREI-MS *m/z* $[M]^+$ 332.1988 (calcd for $C_{20}H_{28}O_4$ 332.1988).

***p*-Benzoquinone 3.** Orange oil; $[\alpha]_D^{25}=+220.0°$ (*c* 0.25, $CHCl_3$); UV (MeOH) λ_{max} 206 nm (ϵ 16000), 282 nm (ϵ 12000), 326 nm (ϵ 1800), KOH 206, 286, 334 nm; IR (film) 3508, 3395, 2963, 2928, 2869, 1756, 1726, 1651, 1639, 1614, 1452, 1377, 1335, 1232, 1152, 1045, 973, 904, 886, 754 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) and ^{13}C NMR ($CDCl_3$, 75 MHz) (see Table 1); EI-MS *m/z* 332 $[M]^+$ (10), 314 (8), 286 (8), 246 (9), 231 (12), 206 (100), 205 (16), 204 (9), 189 (11), 138 (14), 109 (60), 105 (10), 91 (24), 77 (17); HREI-MS *m/z* $[M]^+$ 332.1982 (calcd for $C_{20}H_{28}O_4$ 332.1988).

4-(Acetyl) amphilectolide (4). Colorless oil; $[\alpha]_D^{25}=-276.7°$ (*c* 0.3, $CHCl_3$); UV (MeOH) λ_{max} 206 nm (ϵ 9100), 232 nm (ϵ 10500); IR (film) 2961, 2928, 2874, 2855, 2728, 1762, 1717, 1671, 1451, 1380, 1354, 1274, 1225, 1192, 1165, 1147, 1054, 997, 971, 928, 847, 781, 720 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) and ^{13}C NMR ($CDCl_3$, 75 MHz) (see Table 2); EI-MS *m/z* 302 $[M]^+$ (14), 274 (5), 260 (100), 259 (39), 245 (20), 241 (17), 218 (8), 215 (11), 109 (50), 91 (14), 83 (26), 77 (11), 67 (11); HREI-MS *m/z* $[M]^+$ 302.1879 (calcd for $C_{19}H_{26}O_3$ 302.1881).

Amphiphenalone (5). Colorless plates; mp 218–220°C; $[\alpha]_D^{25}=+86.7°$ (*c* 0.3, acetone); UV (MeOH) λ_{max} 216 nm (ϵ 12000), 288 nm (ϵ 6000), KOH 206, 250, 346 nm; IR (film) 3409, 2951, 2923, 2860, 1627, 1567, 1455, 1379, 1322, 1296, 1261, 1190, 1107, 1060, 1003, 962, 936, 908, 813, 778, 766 cm^{-1}; ^1H NMR (acetone-d_6, 300 MHz) and ^{13}C NMR (acetone-d_6, 75 MHz) (see Table 2); EI-MS *m/z* 276 $[M]^+$ (97), 258 (36), 243 (33), 230 (38), 218 (92), 190 (100), 175 (24), 157 (7), 128 (15), 115 (15), 91 (10), 77 (9); HREI-MS *m/z* $[M]^+$ 276.1365 (calcd for $C_{16}H_{20}O_4$ 276.1362).

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11. HMBC cross peaks for elisabatin C (**1**): H-2/C-1; H-14/C-2; Me-18/C-2; Me-18/C-3; H-2/C-4; H-6/C-4; Me-18/C-4; H-6/C-5; Me-19/C-6; Me-19/C-7; H-6/C-8; Me-19/C-8; Me-20/C-10; Me-20/C-11; H-2/C-12; Me-20/C-12; H-2/C-14; Me-16/C-14, Me-17/C-14; Me-16/C-15; Me-17/C-15; H-14/C-16; Me-17/C-16; H-14/C-17; Me-16/C-17; H-2/C-18; H-6/C-19.
12. Selected NOEs for elisabatin C (**1**): H-2/Me-17; H-2/Me-18; H-6/5-OH; H-6/Me-19; H-14/Me-16; H-14/Me-20; Me-16/Me-17.
13. HMBC cross peaks for elisapterosin C (**2**): H-6/C-1; H-8β/C-1; H-9/C-1; H-3/C-2; H-9/C-2; Me-18/C-2; H-4αβ/C-3; H-5αβ/C-3; Me-18/C-3; H-3/C-4; H-5αβ/C-4, H-6/C-4; Me-18/C-4; H-3/C-5; H-4αβ/C-5; H-6/C-5; H-7/C-5; H-4α/C-6; H-8β/C-6; Me-19/C-6; H-5αβ/C-7; H-8αβ/C-7; Me-19/C-7; H-7/C-8; H-9/C-8; H-10/C-8; Me-19/C-8; H-8α/C-9; H-10/C-9; H-8α/C-10; H-9/C-10; Me-12/C-10; Me-13/C-10; Me-20/C-10; H-9/C-11; H-10/C-11; Me-12/C-11; Me-13/C-11; H-10/C-12; Me-13/C-12; H-10/C-13; Me-12/C-13; H-6/C-14; H-9/C-14; Me-20/C-14; H-10/C-15; Me-20/C-15; H-10/C-16; Me-20/C-16; H-3/C-17; H-4αβ/C-18; H-6/C-19; H-7/C-19; H-8α/C-19; H-10/C-20.
14. Selected NOEs for elisapterosin C (**2**): H-3/H-9; H-3/H-7; H-8α/Me-19; H-8β/H-9; H-9/Me-12; H-10/Me-20.
15. Look, S. A.; Fenical, W. *Tetrahedron* **1987**, *43*, 3363–3370.
16. HMBC cross peaks for *p*-benzoquinone **3**: Me-20/C-1; Me-20/C-2; Me-18/C-4; Me-19/C-5; 7-OH/C-6; Me-19/C-6; 7-OH/C-7; Me-19/C-7; 7-OH/C-8; Me-20/C-9; H-13/C-11; Me-18/C-11; H-13/C-12; H-14/C-12; Me-18/C-12; Me-16/C-14, Me-17/C-14; H-13/C-15; H-14/C-15, Me-16/C-15; Me-17/C-15; Me-17/C-16; Me-16/C-17.
17. Selected NOEs for *p*-benzoquinone **3**: H-1/H-11; H-1/Me-20; H-4/Me-18; H-11/Me-18.
18. Although **5** is described here as a tetrisnorditerpene it is also possible that this compound is a homosesquiterpene that incorporates a carbon either from carbonate/bicarbonate (that ends up as the carbonyl at C-1) or from the one-carbon folic acid pool.
19. Selected NOEs for amphiphenalone (**5**): H-2/Me-14; H-4/H-5α; H-4/Me-14; H-4/Me-15; H-5α/Me-14; H-5α/Me-15; H-5β/H-6β; H-6β/H-7.
20. For isolation and original structural determination of helioporin E, see: Tanaka, J.; Ogawa, N.; Liang, J.; Higa, T.; Gravalos, D.G. *Tetrahedron* **1993**, *49*, 811–822.
21. The syntheses and stereochemical revision of pseudopterosin G–J aglycon and helioporin E have been reported recently, see: Lazerwith, S. E.; Johnson, T. W.; Corey, E. J. *Org. Lett.* **2000**, *2* 2389–2392. For structural revision of helioporin C and D, see: (a) Geller, T.; Schmalz, H.-G.; Bats, J. W. *Tetrahedron Lett.* **1998**, *39*, 1537–1540. (b) Geller, T.; Jakupovic, J.; Schmalz, H.-G. *Tetrahedron Lett.* **1998**, *39*, 1541–1544. (c) Hörstermann, D.; Schmalz, H.-G.; Kociok-Köhn, G. *Tetrahedron* **1999**, *55*, 6905–6916.
22. We have detected traces of pseudopterosins and *seco*-pseudopterosins in our gorgonian specimen. The presence of these diterpene glycosides is usually indicative of *P. elisabethae*. Therefore, these compounds constitute an useful chemotaxonomic marker.