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Sandresolides A and B: novel *nor*-diterpenes from the sea whip *Pseudopterogorgia elisabethae* (Bayer) [†]

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Abstract

A recent chemical study of the hexane extracts of *Pseudopterogorgia elisabethae* led to the isolation of two novel *nor*-diterpenes **1** and **2**, in addition to a known sesquiterpene **3**. The structures were established by spectroscopic and X-ray diffraction studies. © 1999 Elsevier Science Ltd. All rights reserved.

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Sesquiterpenes and diterpenes having a wide variety of both well-known and rare carbon skeletons are the most common gorgonian and soft coral metabolites.[1] Among Caribbean gorgonians, members of the genus *Pseudopterogorgia* are prolific in nature, with 15 known species, of which about six species have been chemically investigated.[2] It was from *Pseudopterogorgia elisabethae* (Bayer) that the pseudopterosins, a family of antiinflammatory amphilectane-based diterpene glycosides, were first reported in 1986, and since that time several related compounds such as the *seco*-pseudopterosins, the elisabethins, the elisabatins, pseudopteroxazole, and *seco*-pseudopteroxazole, have been described.[3] As part of our continuing interest in the bioactive secondary metabolites of *P. elisabethae*, we have further examined the hexane extracts of a specimen weighting 1.0 kg (dry wt) collected off San Andrés Island, Colombia during May 1996.[4]

The 1:1 chloroform and methanol extract of *P. elisabethae* was subjected to gel filtration chromatography (Bio-Beads SX-3, toluene) followed by successive silica gel chromatography to afford two new diterpenoid compounds possessing the novel *nor*-sandresane carbon skeleton, named sandresolide A (**1**) and sandresolide B (**2**), and the known sesquiterpene (+)-aristolone (**3**).[5] The structures of metabolites **1** and **2** were determined by 1D and 2D NMR (^{13}C, ^{1}H, ^{1}H–^{1}H COSY, HMQC, HMBC, and NOESY spectra) and IR, UV, and HRMS studies, and that of sesquiterpene **3** (61.1 mg, yield=0.077%) was determined by spectral and X-ray crystallographic analysis.

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[‡] Graduate student sponsored by the NIH–MBRS Program of the University of Puerto Rico.

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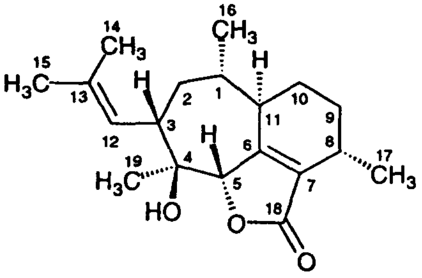


1

The IR data for sandresolide A (**1**) indicated the presence of hydroxyl (3406 cm^{-1}) and carbonyl (1752 cm^{-1}) functionalities, the peak at 1752 cm^{-1} strongly suggesting the presence of a butenolide moiety.[6] HREIMS data indicated a molecular ion consistent with a molecular formula of $C_{19}H_{28}O_3$. The 300 MHz ^1H NMR spectrum of **1** in $CDCl_3$ was poorly defined due to signal overlapping. However, it was satisfactorily resolved when measured at 500 MHz. Inspection of the ^1H NMR spectral data of **1** (Table 1) showed five methyl groups, a one-proton olefinic signal at δ 5.07, a deshielded one-proton signal at δ 4.84 indicative of a proton attached to a carbon bearing either hydroxyl or ether functionalities, and three complex resonances at δ 2.70, 2.50, and 1.95 ascribable to allylic protons, suggestive of a polycyclic terpenoid structure. The ^{13}C NMR spectrum of sandresolide A showed signals characteristic of one carbonyl, four alkene carbons (three quaternary), two oxygenated carbons (at δ 88.0 and 75.0), and 12 carbons between δ 15.9 and 47.9, while the DEPT spectrum indicated that five CH_3, three CH_2, six CH, and five quaternary carbons were present. The UV (MeOH) absorption at 226 nm (ε 12000), when considered with the presence of an ester carbonyl, indicated that one alkene and the carbonyl function were present as a conjugated system. The remaining three degrees of unsaturation required that the molecule possess two carbocyclic rings and one lactone.

Several substructures in sandresolide A (**1**) (Fig. 1) were established using a combination of homo- and heteronuclear 2D NMR techniques. The proton NMR COSY spectrum showed correlations allowing connections between C-8 and C-3 through C-11, and between C-17 and C-8, C-16 and C-1, and C-3 and C-12 to be established. These fragments could be defined using data obtained from HMBC experiments. Correlations from methyl protons, in particular, led to the confident assignment of substructure **A** (see Table 1). The location of the isobutenyl group, for example, was defined on the basis of an HMBC correlation between the C-14 and C-15 methyl protons and C-12 together with complementary HMBC correlations between H-3 and C-2, C-12, and C-13. Substructure **B** was assigned by interpretation of long-range proton COSY data which showed correlations between the C-19 methyl protons and H-5,[7] and by analysis of HMBC data which showed correlations between the C-19 methyl protons and C-4 and C-5. What remained to be assigned were three sp^2 carbons comprised by the butenolide moiety (substructure **C**). The unusually low field chemical shift of C-6 (δ 164.4) combined with the UV absorption at 226 nm, led to the definition of substructure **C**. Substructures **A**–**C** were connected using a number of key HMBC NMR correlations. Substructures **A** and **B**, for example, were linked by correlations between H-3 and C-4, H-19 and C-3, and between H-5 and C-3. Substructures **B** and **C** were connected by the observation of HMBC correlations between H-5 and C-6 and C-7. Finally, numerous HMBC correlations were used to assign the quaternary alkene carbons at C-6 (correlations with H-10αβ and H-11) and C-7 (correlations with H-9β, H-11, and H-17). In addition, the long-range proton NMR COSY spectrum showed correlations allowing connections between H-5 and H-8, and between H-5 and H-11. Applying these combined NMR methods resulted in the unambiguous assignment of all protons and carbons as listed in Table 1 and allowed the complete planar structure for sandresolide A (**1**) to be assigned.

Table 1

^{1}H NMR, ^{13}C NMR and HMBC spectral data for sandresolide A and sandresolide B[a]

Position	Sandresolide A (1)[b]			Sandresolide B (2)[c]		
	δ, mult (*J* in Hz)	^{13}C	HMBC	δ, mult (*J* in Hz)	^{13}C	HMBC
1	1.61, m	34.8, d	H2β, H11, H16	2.08, m	31.7, d	H2β, H3, H16
2α	1.20, m	43.9, t	H3, H11, H12, H16	1.18, m	43.8, t	H16
2β	1.65, m			1.57, m		
3	2.70, dt (3.5, 9.7)	47.9, d	H1, H2αβ, H5, H12, H19	3.02, ddd (3.9, 8.5, 10.0)	43.9, d	H2β, H19
4		75.0, s	H2β, H3, H5, H19		77.2, s	H2β, H19
5	4.84, br s	88.0, d	H3, H19		108.2, s	H3, H19
6		164.4, s	H5, H10αβ, H11		162.0, s	
7		130.1, s	H5, H9β, H11, H17		132.4, s	H17
8	2.50, m	27.4, d	H9β, H10αβ, H17	2.53, m	27.5, d	H17
9α	1.24, m	33.0, t	H10αβ, H17	1.24, m	33.2, t	H17
9β	2.17, m			2.18, m		
10α	2.01, m	27.9, t	H9β, H11	2.00, m	28.2, t	H9α
10β	2.01, m			2.00, m		
11	1.95, m	45.4, d	H1, H2αβ, H9β, H16	1.92, m	46.0,	H2β, H9β, H16
12	5.07, d (9.7)	123.6, d	H3, H14, H15	5.05, br d (10.0)	124.3, d	H14, H15
13		134.7, s	H3, H14, H15		134.8, s	H14, H15
14	1.72, br s	18.4, q	H12, H15	1.72, d (1.2)	18.4, q	H12, H15
15	1.77, br s	26.2, q	H12, H14	1.77, d (1.1)	26.2, q	H12, H14
16	0.98, d (6.7)	21.0, q	H2β	0.94, d (6.8)	21.0, q	H2β
17	1.25, d (6.3)	19.3, q		1.24, d (6.5)	19.1, q	
18		172.3, s			170.8, s	
19	0.95, br s	15.9, q	H3, H5	1.12, br s	16.9, q	H3

[a] Assignments were aided by ^{1}H-^{1}H COSY, spin splitting patterns, HMBC, HMQC and NOESY experiments, numbers of attached protons, 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. [b] Data recorded in $CDCl_3$ at 500 MHz. [c] Data recorded in $CDCl_3$ at 300 MHz.

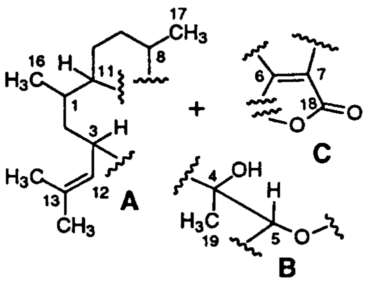
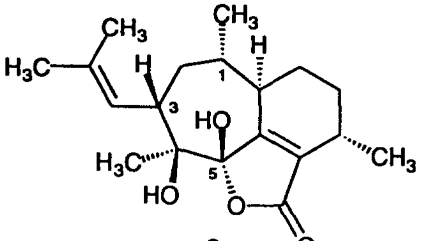


Figure 1. Substructures of sandresolide A (**1**)

The deduced structure for sandresolide A (**1**) was also strongly supported by HREIMS.[6] Compound **1** fragmented to give several structurally significant ions. Elimination of a water molecule from the molecular ion [*m/z*=304 (36%)] dominated the upper mass range to give a peak at *m/z*=286 (9%). Initial fragmentation of the ester bond followed by cleavage of the C-5/C-6 and C-2/C-3 bonds yielded dominant ions at *m/z*=125 (base peak, $C_8H_{13}O$) and *m/z*=179 (52%, $C_{11}H_{15}O_2$) characteristic of the lower and upper half of the molecule, respectively. The mass sum of these complementary even-electron ions is equivalent to the molecular weight of **1**.



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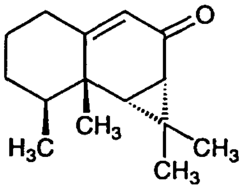

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The ^1H and ^{13}C NMR data for sandresolide B (**2**)[8] were very similar to those of sandresolide A. HRFABMS data indicated the molecular formula $C_{19}H_{28}O_4$ for sandresolide B, suggesting that the only difference between **1** and **2** was the identity of the substituent at C-5. The only significant variations in the NMR data were the ^1H NMR chemical shift of H-1 (δ 1.61 versus 2.08), H-3 (δ 2.70 versus 3.02), and Me-19 (δ 0.95 versus 1.12), and the ^{13}C NMR chemical shift of C-5 (δ 88.0 versus 108.2), all of which were consistent with the presence of a hydroxyl instead of a hydrogen substituent on the top face of the molecule (i.e., *cis* to H-1 and H-3). As in the case of **1**, comprehensive NMR data allowed all protons and carbons to be assigned, leading to the assignment of the planar structure, **2**, for sandresolide B.

The relative configurations for the stereocenters in the bicyclic nuclei of the sandresolides (i.e., C-1, C-3, C-4, C-5, and C-11) were assigned primarily on the basis of NOESY NMR data acquired with sandresolide A (**1**). Thus H-1, H-3 and H-5, located in the β face of the molecule, were assigned as *cis* based upon their strong NOESY correlations. Similarly, NOESY correlations between Me-19 and H-12 located on the bottom face of the molecule established their spatial proximity. The strong NOESY correlations of Me-16 with H-10α and H-11 allowed the placement of these protons in the α face of the molecule. The stereocenter at C-8, isolated from the remainder of the molecule by two methylenes and the butenolide system, was difficult to define by NOESY NMR methods. Fortunately, since a similar cyclohexene substructure with a methyl substituent is present in the pseudopterosin series,[3a–d] which was defined by X-ray methods, a comparison of relevant NMR data was performed. Using this approach and a molecular modeling study, the methyl group at C-8 was illustrated to be in the α face of the molecule (i.e., *cis* to H-11).

The sandresolides represent a unique new class of *nor*-diterpenes. Biogenetically, the novel *nor*-sandresane skeleton could stem from the adventitious rearrangement of an amphilectane-based diterpene involving loss of a carbon atom and concomitant 1,2-alkyl shift with ring expansion.[9]

Acknowledgements

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6. Compound **1** (7.8 mg; yield=9.78×10^{-3}%): a yellowish oil; $[\alpha]_D^{28}$ +23.8 (*c* 1.3, $CHCl_3$); IR (neat) 3406, 2928, 2854, 1752, 1655, 1457, 1378, 1129, 1026, 952 cm^{-1}; UV (MeOH) λ_{max}=226 nm (ε 12000); EIMS *m/z*: $[M]^+$ 304 (36), 286 (9), 179 (52), 152 (22), 125 (100), 109 (62); HREIMS *m/z*: $[M]^+$ 304.2045 (calcd for $C_{19}H_{28}O_3$, 304.2038).
7. This coupling across four single bonds in the W-configuration agrees with the proposed stereochemistry at C-4/C-5.
8. Compound **2** (4.0 mg; yield=5.01×10^{-3}%): a yellowish oil; $[\alpha]_D^{28}$ −18.0 (*c* 1.0, $CHCl_3$); IR (neat) 3423, 1741, 1457, 1379 cm^{-1}; UV (MeOH) λ_{max}=220 nm (ε 10000); HRFABMS *m/z*: $[M+Na]^+$ 343.1879 (calcd for $C_{19}H_{28}O_4Na$, 343.1885).
9. A pinacol rearrangement would account for the proposed 1,2-alkyl shift and the ensuing $C_6 \rightarrow C_7$ ring expansion.