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Communications

Chatancin, a PAF Antagonist from a Soft Coral, *Sarcophyton* sp.

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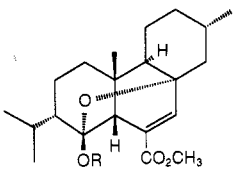
Summary: A PAF antagonist, chatancin, was isolated from a soft coral, *Sarcophyton* sp. Its structure (**1a**) was determined to be (1*R*,2*S*,4a*R*,4b*R*,7*S*,8a*S*,10a*R*)-4a,7-dimethyl-1,8a-epoxy-1-hydroxy-2-isopropyl-10-(methoxycarbonyl)-1,2,3,4,4a,4b,5,6,7,8,8a,10a-dodecahydrophenanthrene on the basis of chemical and physical evidences and X-ray crystallographic analysis.

Platelet activating factor (PAF) is a naturally occurring etherphospholipid [1-*O*-alkyl-2(*R*)-acetylglyceryl-3-phosphorylcholine], that is a mediator of anaphylaxis released by a number of stimulated cells such as basophils, neutrophils, platelets, macrophages, and so on. It causes platelet aggregation, chemotaxis and degranulation of polymorphonuclear leukocytes, smooth muscle contraction, vascular permeability, and hypotention.[1] Recent studies have further shown that PAF may be concerned with many inflammatory, respiratory, and cardiovascular diseases. A variety of PAF antagonists including PAF related and unrelated synthetic compounds[1] and natural products isolated from microorganisms[2] and higher plants[3] has been found.

In order to isolate PAF antagonists from marine organisms, we systematically screened extracts of marine organisms for inhibition of PAF-induced platelet aggregation and binding of PAF to its receptors to find several active extracts. Here we report the isolation, characterization, and PAF antagonistic activities of an active principle, chatancin (**1a**), from a soft coral, *Sarcophyton* sp.

Sarcophyton sp. (wet weight 100 kg) was collected at Chatancho Okinawa in 1987 and extracted with MeOH. The MeOH extract was partitioned between *n*-hexane and 90% aqueous MeOH. An activity-directed separation of active *n*-hexane extract (300 g) on silica gel and reverse-phase chromatography gave the active compound $C_{21}H_{32}O_4$, chatancin (**1a**).[4] The IR spectrum showed the presence of a hydroxyl [ν_{max} ($CHCl_3$): 3620 cm^{-1}] and an ester [ν_{max} ($CHCl_3$: 1715 cm^{-1}]. The UV spectrum indicated the ester was conjugated with a double bond [λ_{max} (CH_3CN): 218 nm (7500)]. ^1H–^1H COSY and ^{13}C NMR showed the presence of a tertiary methyl [δ_H 0.71 (s), δ_C 24.8 (q)], a secondary methyl [δ_H 1.00 (d), δ_C 22.8 (q)], an isopropyl [δ_H 0.920 (d), 0.924 (d), 2.34 (m), δ_C 18.7 (q), 23.5 (q), 26.3 (d)], a methoxycarbonyl [δ_H 3.76 (s), δ_C 52.3 (q), 167.2 (s)], a hemiketal (δ_C 99.9), an olefinic double bond



1a R=H
1b R=COPh

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(4) Mp: 106–8 °C. $[\alpha]_D$: +10.5° ($CHCl_3$, *c* 1.0) as colorless needles (1.15 g) recrystallized from aqueous MeOH. Chatancin (**1a**) was analyzed for $C_{21}H_{32}O_4$ (HREIMS: M^+ *m/z* 348.23125, calcd 348.23005). Anal. Calcd for $C_{21}H_{32}O_4$: C, 72.37; H, 9.26. Found: C, 72.57; H, 9.49. IR [ν_{max} ($CHCl_3$)]: 3620, 1715, 1630, 1460, 1420, 1380, 1340, 1275, 1170, 1075, 985 cm^{-1}. EIMS (*m/z*): 348, 330, 316, 219 (base peak), 187, 159, 119, 105.

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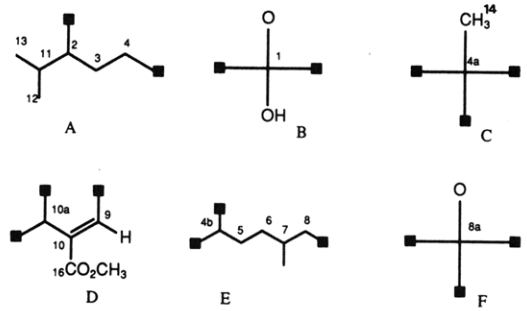
Table I. ^1H and ^{13}C NMR Assignments of Chatancin (1a) in CD_3OD

structure assignment	^{13}C (mult)	^1H (mult, J, Hz)
1	99.9 (s)	
2	50.8 (d)	1.37 (ddd, J = 13.1, 4.0, 2.4)
3	19.3 (t)	1.48 (m)
		1.61 (qd, J = 13.1, 4.3)
4	40.0 (t)	1.27 (td, J = 13.1, 4.3)
		1.57 (m)
4a	37.3 (s)	
4b	49.1 (d)	1.40 (dd, J = 13.0, 3.0)
5	28.5 (t)	0.71 (qd, J = 13.0, 3.0)
		1.54 (qd, J = 3.0, 13.0)
6	36.0 (t)	0.91 (m)
		1.69 (br d, J = 13.0)
7	30.9 (d)	1.66 (m)
8	43.5 (t)	1.19 (t, J = 12.5)
		2.04 (ddd, J = 12.5, 3.5, 2.0)
8a	77.1 (s)	
9	144.5 (d)	7.20 (d, J = 2.0)
10	137.0 (s)	
10a	54.4 (d)	2.65 (d, J = 2.0)
11	26.3 (d)	2.34 (sep × d, J = 6.7, 2.4)
12	18.7 (q)	0.920 (d, J = 6.7)
13	23.5 (q)	0.924 (d, J = 6.7)
14	24.8 (q)	0.70 (s)
15	22.8 (q)	1.00 (d, J = 6.2)
16	167.2 (s)	
17	52.3 (q)	3.76 (s)

[δ_H 7.20 (d), δ_C 137.0 (s), 144.5 (d)], and a quarternary carbon bearing an oxygen [δ_C 77.0 (s)] (Table I). More significantly the spectra showed that these functional groups were placed on six partial structures (A–F). The



reasonable connection of these partial structures was provided by ^1H–^{13}C long-range COSY experiments. The long-range coupling of H_{10a} with C_1 and C_{4a} suggested the linkage of B, C, and D. The correlation of A, C, and E was given by the long-range couplings of H_{14} with C_4 and C_{4b}. The linkage of D, E, and F was obtained from the long-range couplings of H_8 and H_9 with C_{8a}. The coupling of H_3 with C_1 gave the linkage of A and B. Thus, the planar structure **1a** is proposed for chatancin.

In order to confirm the proposed structure and to determine its stereochemistry, a single-crystal X-ray analysis of its benzoate **1b**[5] (mp 152–4 °C) was conducted. The structure was determined by the direct method (MULTAN 78) and successive block-diagonal least-squares and Fourier syntheses. Parameters were refined by using anisotropic temperature factors to R = 0.041 for 2193 reflections [$|F_o| > 3\sigma(F_o)$]. A perspective drawing of **1b** is given in Figure 1.

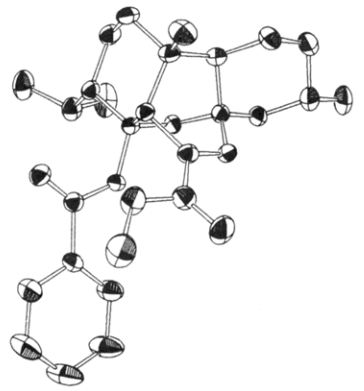
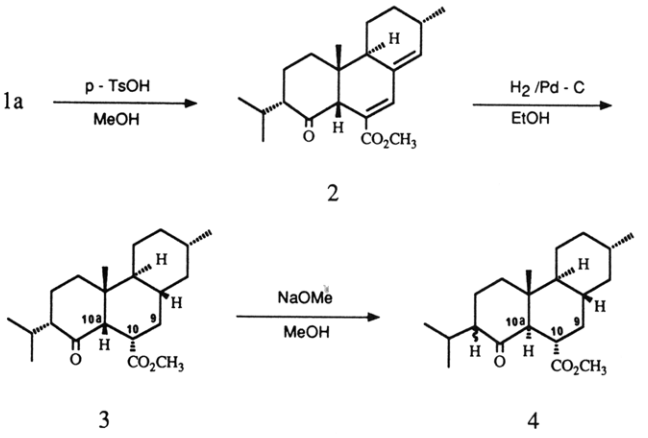


Figure 1. Perspective drawing of chatancin benzoate (**1b**).

Scheme I



The absolute configuration was determined from CD spectra of carbonyl compounds **3** and **4**. They were prepared as follows: Chatancin was easily dehydrated to a compound **2**[6] on treatment with *p*-TsOH in MeOH at room temperature. Catalytic hydrogenation of **2** over 10% Pd–C gave **3**[7] which was epimerized to a trans isomer **4**[8] on heating under reflux with NaOMe in MeOH. The stereochemistry and conformation (all chair forms) of **3** and **4** were determined by ^1H NMR decoupling experiments,[9] as shown in Scheme I.

In the CD spectra, **3** and **4** showed a positive Cotton effect ($[\theta]_{294}$ +2.02) and the negative one ($[\theta]_{292}$ −6.01), respectively, suggesting the absolute configurations as shown in **3** and **4** on the basis of the octant rule.

Chatancin can therefore be depicted as (1*R*,2*S*,4a*R*,4b*R*,7*S*,8a*S*,10a*R*)-4a,7-dimethyl-1,8a-epoxy-

(5) ^1H NMR (δ, CD_3OD): 0.77 (1 H, qd, J = 13.0, 3.0 Hz), 0.78 (3 H, s), 0.89 (3 H, d, J = 7.0 Hz), 0.97 (3 H, d, J = 7.0 Hz), 1.05 (3 H, d, J = 6.2 Hz), 1.33 (1 H, t, J = 12.8 Hz), 1.40 (1 H, td, J = 12.8, 4.4 Hz), 1.5–1.8 (8 H, m), 1.91 (1 H, sep x d, J = 7.0, 3.0 Hz), 2.19 (1 H, ddd, J = 12.8, 4.4, 2.0 Hz), 2.64 (1 H, ddd, J = 12.8, 4.4, 2.0 Hz), 3.46 (3 H, s), 3.73 (1 H, d, J = 1,8 Hz), 7.22 (1 H, d, J = 1.8 Hz), 7.40 (2 H, t, J = 8.0 Hz), 7.53 (1 H, dt, J = 8.0, 1.8 Hz), 7.81 (2 H, dd, J = 8.0, 1.8 Hz). ^{13}C NMR (δ, CD_3OD): 18.4 (q), 18.9 (t), 22.6 (q), 23.2 (q), 25.8 (q), 27.1 (d), 28.1 (t), 30.6 (d), 35.5 (t), 37.1 (s), 38.4 (t), 42.8 (t), 46.2 (d), 49.2 (d), 49.7 (d), 52.2 (s), 77.4 (s), 103.9 (s), 129.1 (2 d), 130.1 (s), 131.6 (2 d), 133.7 (d), 135.9 (s), 143.5 (d), 166.5 (s), 169.7 (s). IR [ν_{max} (KBr)]: 1716, 1640, 1600, 1580, 1450, 1281 cm^{-1}. EIMS (m/z): 330, 298, 217, 211, 159, 105, 77. UV [λ_{max} (EtOH)]: 228 nm (12 600). Anal. Calcd for $C_{28}H_{36}O_5$: C, 74.34; H, 7.97. Found: C, 74.31; H, 8.02.

(6) Oil. HREIMS: M^+ m/z 330.21994, calcd for $C_{21}H_{30}O_3$ 330.21949.
(7) Oil. HREIMS: M^+ m/z 334.25172, calcd for $C_{21}H_{34}O_3$ 334.25079).
(8) Mp: 92–3 °C HREIMS: m/z 334.25261, calcd for $C_{21}H_{34}O_3$ 334.25079.
(9) **3**. ^1H NMR (δ, $CDCl_3$): 1.51 (9α-H, q, J = 12.7 Hz), 1.91 (9β-H, br td, J = 3.9, 12.7 Hz), 2.55 (10β-H, td, J = 3.9, 12.7 Hz), 2.86 (10aβ-H, br d, J = 3.9 Hz). There was observed a w-shaped long-lange coupling between 9β-H and 10a β-H, supporting the chair conformation of the B ring. ^{13}C NMR (δ, $CDCl_3$): 18.3 (q), 21.0 (q), 21.8 (t), 22.5 (q), 23.1 (q), 25.0 (t), 25.7 (d), 31.3 (t), 32.4 (d), 35.4 (t), 35.7 (t), 35.9 (d), 38.2 (d), 42.0 (s), 42.2 (d), 43.4 (t), 51.5 (q), 55.7 (d), 59.8 (d), 175.5 (s), 210.7 (s). **4**. ^1H NMR (δ, $CDCl_3$): 1.04 (9α-H, q, J = 12.5 Hz), 1.86 (9β-H, td J = 3.9, 12.5 Hz), 2.52 (10aα-H, d, J = 12.5 Hz), 2.62 (10β-H, dt J = 3.9, 12.5 Hz). ^{13}C NMR (δ, $CDCl_3$): 14.0 (q), 18.3 (q), 21.1 (q), 22.5 (q), 24.6 (t), 25.6 (t), 25.8 (d), 32.3 (d), 35.3 (t), 35.6 (d) 37.0 (t), 37.5 (t), 38.8 (d), 42.7 (s), 43.1 (t), 51.6 (q), 52.7 (d), 55.6 (d), 60.8 (d), 176.6 (s), 212.2 (s).

1-hydroxy-2-isopropyl-10-(methoxycarbonyl)-1,2,3,4,4a,4b,5,6,7,8,8a,10a-dedecahydrophenanthrene (**1a**). Marine organisms frequently produce different phenanthrene-based diterpenes[10] from those in terrestrial microorganisms or plants.[11] Chatancin provides a new class of diterpenes and biosynthetic interests.

Chatancin (**1a**) inhibited PAF-induced platelet aggregation (IC_{50} 2.2 μM) and the binding of PAF to its receptors (IC_{50} 0.32 μM), but had no effect (>300 μM) on adenosine diphosphate induced, arachidonic acid induced, and collagen-induced platelet aggregation. Thus chatancin is a new type of specific PAF antagonist initially isolated from marine sources. The hemiketal or ether moiety accounts for its activity, because **3** and **4** had no activity. The details will be reported elsewhere in due course.

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Supplementary Material Available: Experimental procedures and the data of X-ray analysis (9 pages). Ordering information is given on any current masthead page.

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Dimethyl Sulfoxide Phase C–H Bond Dissociation Energies for Phenalene and Benzanthrene

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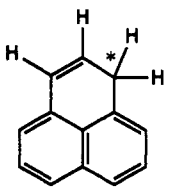
Summary: Comparisons of fluorene, phenalene, and benzanthrene sp^3C-H homolytic bond dissociation energy data, data collected with the aid of a cycle that utilizes acid-base and redox data collected in dimethyl sulfoxide solution, indicate that the sp^3C-H bonds in phenalene and benzanthrene are about 18 and 16 kcal/mol weaker (in a homolytic sense) than the sp^3C-H bond in fluorene.

Phenalene (**1**) and fluorene (**2**) are isomeric aromatic hydrocarbons that have long fascinated organic chemists.[1] The planarity, symmetry, and stability displayed by the anionic, radical, and cationic derivatives of phenalene[2,3] and fluorene[4] have prompted many investigations of their chemistry.[5] Much of the interest in phenalene results from



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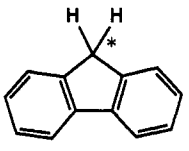

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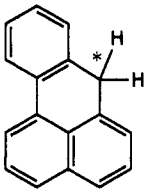

3

its presence,[6] and the presence of the phenalenyl radical,[7] in liquids derived from fossil fuels. Since most of the chemical reactions associated with the combustion and conversion of fossil fuels are thought to involve free radicals, it is surprising that there are no experimental bond dissociation energies (BDEs) for the indicated bond in phenalene.[8] In this paper, with the aid of dimethyl sulfoxide (DMSO) phase acidity[9] and redox data, we report DMSO-phase C–H BDEs for phenalene (**1**), fluorene (**2**), and benzanthrene (**3**), an analogue of phenalene.

Table I. Dimethyl Sulfoxide Phase Acidity Constants (pK_a's) for Phenalene (1), Fluorene (2), and Benzanthrene (3), Second Harmonic Alternating Current Voltammetry Crossing Potentials ($E_{1/2}$, in Volts, vs NHE) for the Oxidations of Carbanions Derived from 1–3,[14] and ΔpK_a and ΔBDE Values for 1 and 3, Relative to 2 (kcal/mol)

acid	pK_a	$E_{1/2}$	ΔpK_a, kcal/mol	ΔBDE[15]
phenalene (**1**)[16]	18.2[17]	−0.73	−6.0	−18
fluorene (**2**)[18]	22.6[9]	−0.21[19]	(0)	(0)
benzanthrene (**3**)[16]	20.2[20]	−0.74	−3.3	−16

Estimates of *relative* DMSO-phase BDEs for acids H–A have been obtained via eq 1, where pK_a(H–A) is the

$$\Delta BDE(H\text{–}A) = 1.37\ pK_a(H\text{–}A) + 23.06E_{1/2}(A^-) \quad (1)$$

DMSO-phase equilibrium acidity constant for organic acid H–A, and $E_{1/2}$ (A^-) is the DMSO-phase reversible oxidation potential for the conjugate base, A^- derived from H–A.[10] Equation 1 has been shown to yield DMSO,[11] and aqueous phase[12] BDE data that agree with gas-phase values, when a constant of about 56 kcal/mol is added to its right side.[13]

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(14) Electrochemistry conditions: DMSO solvent; 0.1 M $Et_4N^+BF_4^-$ electrolyte; Pt working and Ag/AgI reference electrodes (ferrocene/ferrocenium = +0.875 V as internal standard, values corrected to NHE by subtracting 0.125 V). SHACV: 20/110° ϕ shift, ac amplitude = 25 mV, and frequency = 50 Hz. CV: 0.1 V/s sweep rate.
(15) The uncertainties in the absolute and ΔBDE data in Table I are estimated to be ±3 and ±1 kcal/mol, respectively.[11,12]
(16) Syntheses of phenalene (**1**) and benzanthrene (**3**): Boudjouk, P.; Johnson, P. D. *J. Org. Chem.* **1978**, *43*, 3979–3980. Melting point, thin-layer chromatography, and NMR data for these species were used to ensure sample purity, and were consistent with literature values.

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