ORGANIC LETTERS

2010
Vol. 12, No. 5
912−914

Plumisclerin A, a Diterpene with a New Skeleton from the Soft Coral *Plumigorgia terminosclera*

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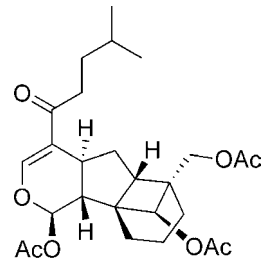
Received December 4, 2009

ABSTRACT



Plumisclerin A (1)

A novel compound, named plumisclerin A (1), was isolated from samples of the soft coral *Plumigorgia terminosclera* collected at Mayotte Island. The compound possesses the novel plumisclerane carbon skeleton, including a tricyclo[4,3,1,0^{1,5}]decane ring. Its structure and relative stereochemistry were elucidated by extensive spectroscopic analysis, including HREIMS, COSY, HSQC, HMBC, TOCSY, and NOESY experiments. In addition, the novel compound displayed *in vitro* cytotoxicity against selected cancer cell lines.

Octocorals have proven to be a rich source of diterpenoids possessing different skeletons and biological properties.[1] Among these marine organisms, members of the order Alcyonacea have yielded a large number of compounds belonging to the xenicane class, most of them having been obtained from specimens of the genus *Xenia*. An interesting group of these diterpenes incorporate in their structures a pyrane ring fused to a nine-membered carbocyclic ring to build a 2-oxabicyclo[7.4.0]tridecane system, and some of its members have displayed interesting cytotoxic[2] and antimicrobial properties.[3] Four families with different functionalities in the A ring have been identified within this structural class and are represented by the xenicins,[4] xenialactols,[5] and xeniolides A and B.[6]

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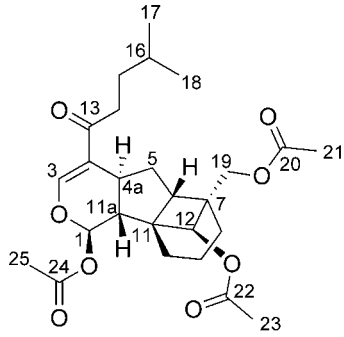
10.1021/ol902802h
Published on Web 01/28/2010

In the course of our screening program to search for new marine anticancer drugs,[7,8] we focused our attention on the cytotoxicity of crude extracts of samples of the hitherto uninvestigated soft coral *Plumigorgia terminosclera* collected at Mayotte Island.[9] Bioassay-guided fractionation of the 2-propanol extracts of frozen specimens of this organism, including RP-18 VLC chromatography followed by reversed-phase HPLC, yielded plumisclerin A (**1**), a xenicane-related diterpenoid possessing a novel carbon skeleton that incorporates a tricyclo[4,3,1,$0^{1,5}$]decane ring.



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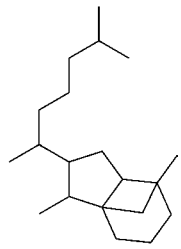

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Compound **1** was isolated as an optically active white amorphous solid. Its molecular formula was determined to be $C_{26}H_{36}O_8$ on the basis of HREIMS (*m/z* 476.2418 $[M]^+$ calcd for $C_{26}H_{36}O_8$ *m/z* 476.2410, Δ −0.8 mmu) and the presence of 26 signals in its ^{13}C NMR spectrum. Signals observed in its ^1H and ^{13}C NMR spectra (Table 1) accounted for the presence in the structure of **1** of a ketone carbonyl group (δ_C 198.5 s), one oxygenated trisusbtituted double bond (δ_C 153.3 d, 121.9 s; δ_H 7.29, d), one doubly oxygenated methine (δ_C 95.9 d; δ_H 6.50, d), oxygenated methine (δ_C 68.2 d; δ_H 4.83, s) and methylene groups (δ_C 66.1 t; δ_H 4.03 d and 3.93, d), two quaternary carbons (δ_C 53.2 and 46.6 s), three acetate functionalities (δ_C 171.0 s and 20.9 q; 170.2 s and 20.7 q; 168.7 s and 20.8 q; δ_H 2.06, 2.03, 2.09 s, respectively), and two doublet methyl groups.

HMBC correlations observed from H-3 to C-1, C-4, and C-4a and from H-1 and H-25 to C-24 (Figure 1) established the presence in the molecule of a 2-acetoxy-3,4-dihydropyrane ring similar to that found in a number of diterpenes possessing a xenicane skeleton. Analysis of the COSY, 1D TOCSY and HSQC spectra revealed the presence of three spin systems in the structure of plumisclerin A (**A**−**C**), linked through the HMBC correlations displayed in Figure 1. The spins systems **A** and **B** were connected through long-range couplings observed between H-3, H-4a, and H-14 and the carbonyl C-13. On the other hand, HMBC cross-peaks from H-6 to C-5, C-7, C-8, and C-11 and from H-10 and H-11a to C-11 established the connectivity between substructures **A** and **C** through the quaternary carbons C-7 and C-11. Additionally, correlations from H-12 to C-7, C-8, C-11, C-11a, and C-19 placed the singlet oxygenated methine H-12 between the quaternary carbons C-7 and C-11. Finally, C-19 was attached to C-7 on the basis of HMBC correlations observed between both H-19 methylene protons and carbons C-6, C-7, C-8, and C-12. The three acetate functionalities present in the molecule were placed at C-1, C-12, and C-19 on the basis of HMBC cross peaks observed between the methine or methylene protons H-1, H-12, and H-19 and the corresponding carbonyl ester carbons (C-24, C-22, and C-20, respectively).

Table 1. NMR Data of Plumisclerin A (**1**) in $CDCl_3$

	δ_H, mult, J = Hz	δ_C	NOESY
1	6.50, d, 9.8	95.9	H-4a, H-12
3	7.29, d, 2.3	153.3	H-14
4		121.9	
4a	3.07, m	38.2	H-1, H-12, H-5α
5α	2.63, ddd, 15.0, 8.4, 2.2	27.0	H-4a, H-5*β*, H-19
5*β*	1.54, m		H-5α, H-6
6	2.17, m	42.5	H-5*β*, H-10*β*, H-11a
7		46.6	
8	1.95, m; 1.70, m	28.3	
9	1.76, m; 1.73, m	15.7	
10α	1.90, m	27.4	
10*β*	1.76, m		H-6
11		53.2	
11a	1.69, dd, 12.4, 9.8	50.3	H-6
12	4.83, s	68.2	H-1, H-4a
13		198.5	
14	2.45, ddd, 7.7, 7.7, 3.8	35.4	H-3, H-17, H-18
15	1.49, m; 1.46, m	34.1	
16	1.53, m	27.8	
17	0.89, d, 6.3	22.4	H-14
18	0.88, d, 6.5	22.4	H-14
19	3.93, d, 11.6	66.1	H-5α
19	4.03, d, 11.6		H-5α
20		171.0	
21	2.06, s	20.9	
22		170.2	
23	2.03, s	20.7	
24		168.7	
25	2.09, s	20.8	

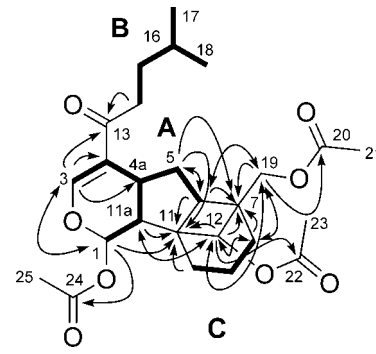

Figure 1. COSY (—) and selected HMBC (→) correlations of plumisclerin A (**1**).

(7) Reyes, F.; Fernández, R.; Urda, C.; Francesch, A.; Bueno, S.; de Eguilior, C.; Cuevas, C. *Tetrahedron* **2007**, *63*, 2432–2438.
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(9) A voucher specimen (ORMA026794) is deposited at PharmaMar.

The relative configuration of **1** was established on the basis of coupling constant analysis and NOESY data (Figure 2).

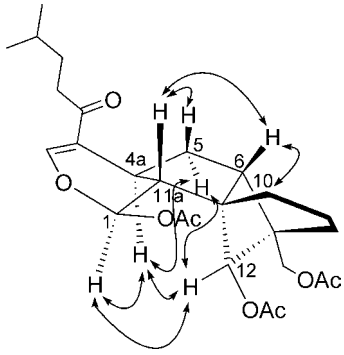

Figure 2. Key NOESY correlations and relative configuration of **1**.

The large coupling constants observed between H-1 and H-11a ($J = 9.8$ Hz) and between H-11a and H-4a ($J = 12.4$ Hz) suggested an axial orientation for all three of the protons, revealing a *trans* fusion between rings A and B. This suggestion was confirmed by a NOESY cross-peak observed between H-1 and H-4a and the absence of correlations between H-4a and H-11a. Additional NOESY correlations from proton H-4a to H-5α and H-12 and from H-1 to H-5α and H-12 (Figure 2) revealed the spatial proximity of protons H-1, H-4a, H-5α, and H-12 and determined therefore the carbon bridge C-12 to be on the α face of the molecule and an *S** configuration for this chiral center. On the other hand, correlations observed from H-6 to H-5β, H-10β, and H-11a located all these protons on the β face of the molecule as depicted in Figure 2. The relative configuration of **1** was therefore determined to be 1*R**,4a*S**,6*S**,7*R**,11*S**,11a*R**,12*S**.

Biogenetically, plumisclerin A can be originated from a xenicane precursor (**I**) by an intramolecular [2 + 2] cycloadition between double bonds placed at the Δ^6 and Δ^{11} positions (Figure 3). Further reduction and acetylation of the C-19 aldehyde function in **II** would lead to the obtention of **1**. Structure **I** and other related xenicane diterpenes possessing the acetylated enol and the Δ^6 unsaturation have also been isolated from extracts of the same organism and will be published elsewhere.

The cytotoxic actvity of **1** was tested against three human tumor cell lines, including lung (A549), colon (HT29), and breast (MDA-MB-231).[10] The compound displayed moderate cytotoxic activity against these tumor cell lines, with GI_{50} values of 4.7, 2.1, and 6.1 μM, respectively, and no selectivity among tissues.

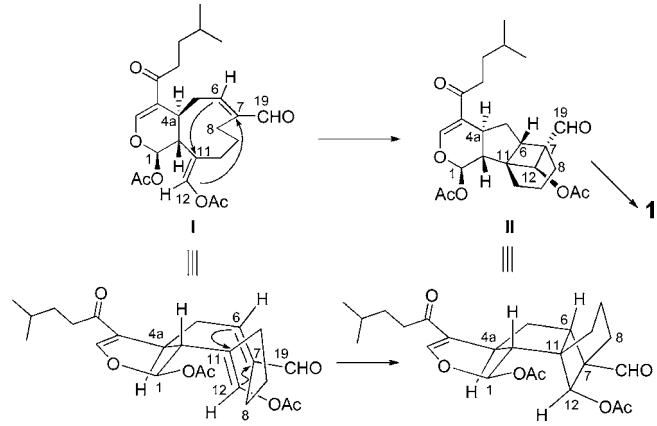

Figure 3. Suggested biogenesis of plumisclerin A (**1**).

Plumisclerin A is a novel diterpenoid containing a tricyclo[4,3,1,$0^{1,5}$]decane ring in its structure. To the best of our knowledge, this is the first description of this carbon skeleton in a natural product, and the name plumisclerane is proposed for the carbon skeleton **2**. In addition, this report constitutes the first chemical study of soft corals of the genus *Plumigorgia*. The isolation of **1**, structurally related to the xenicane diterpenoids, from samples of a genus taxonomically so distant from *Xenia* within the order Alcyonacea might perhaps indicate that plumisclerin A and the xenicanes are biosynthesized by symbiotic organisms of the flora/fauna associated with these soft corals. Additionally, the cytotoxic activity displayed by the compound indicates that it might play some role in the chemical defense of *P. terminosclera* against predators.

Acknowledgment. The authors thank their colleagues Dr. S. González (NMR Service, PharmaMar) for recording the NMR experiments and Dr. L. F. García-Fernández (Screening and MoA Department, PharmaMar) for the cytotoxicity assays. Thanks are also due to Mr. le Préfet de Mayotte and Mr. O. Busson (Directeur des Affaires Maritimes de Mayotte) for assistance in collecting the marine samples.

Supporting Information Available: Experimental procedures, NMR data (^{1}H NMR, ^{13}C NMR, COSY, and HMBC), and copies of 1D and 2D NMR spectra of plumisclerin A (**1**). This material is available free of charge via the Internet at http://pubs.acs.org.

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