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Tetrahedron Letters
Tetrahedron Letters 46 (2005) 4499–4500

Xenibellal, a novel norditerpenoid from the Formosan soft coral *Xenia umbellata*

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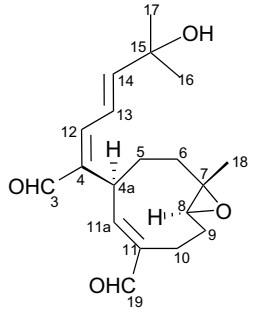
Received 14 March 2005; revised 13 April 2005; accepted 15 April 2005
Available online 17 May 2005

Abstract—Xenibellal, isolated from the soft coral *Xenia umbellata*, is an unprecedented norditerpenoid. The structure of xenibellal was established by extensive analysis of spectroscopic data.

The soft corals of genus *Xenia* are rich in diterpenoids.[1] As part of our search for novel bioactive substances from marine and terrestrial organisms,[2–4] the soft coral *Xenia umbellata* Lamarck was studied, because CH_2Cl_2 extracts showed significant cytotoxicity to A549 (human lung adenocarcinoma), HT-29 (human colon adenocarcinoma), and P-388 (mouse lymphocytic leukemia) cell cultures as determined by standard procedures.[5,6] Bioassay-guided fractionation resulted in the isolation of a novel cytotoxic norditerpenoid (novel carbon skeleton), xenibellal (**1**).



1

Compound **1** was isolated as a colorless oil, $[\alpha]_D^{25}$ +12 (*c* 0.1, $CHCl_3$). The IR spectrum of **1** exhibited absorptions due to hydroxyl (3420 cm^{-1}) and conjugated aldehyde (1712, 1650 cm^{-1}) groups. The presence of the conjugated aldehyde was also confirmed by the UV spectrum [λ_{max} 236 nm]. HRESIMS suggested a molecular formula of $C_{19}H_{26}O_4$ $[M+H]^+$ *m/z* 319.1906 (Δ + 0.0002 mmu).

The structure of **1** was completely solved by a combination of 1D and 2D NMR methods. The carbon resonances at δ_C 194.1 (s), 139.5 (s), 149.5 (d), 120.8 (d), and 153.8 (d), in the ^{13}C NMR and DEPT spectra showed the presence of an α,β,γ,δ-unsaturated aldehyde, while the quaternary carbon signals at δ_C 59.3 (s) along with the methine carbon signal at δ_C 65.8 (d) indicated the presence of a trisubstituted epoxy (Table 1). The quaternary carbon signals at δ_C 142.0 (s) and 195.3 (s) along with the methine olefinic carbon signals at δ_C 155.8 (d) indicated the presence of an α,β-unsaturated aldehyde Furthermore, the presence of an oxygenated carbon was inferred from the carbon signal at δ_C 71.2 (s). Four methylene groups were deduced from four triplet signals at δ_C 19.8–37.5, a methine signal at d 36.3 (d), and, finally, three methyl groups from two quartet signals at δ_C 29.8 (q) and 17.5 (q).

The ^1H NMR spectrum confirmed the presence of an α,β,γ,δ-unsaturated aldehyde by the fact that signals were observed at δ_H 9.38, 6.82, 6.85, and 6.42. In addition, one oxygenated methine was observed at δ_H 3.04. Two intense singlet signals are also observed at δ_H 1.42 and 1.43 (s, 3H each), and these correspond to two methyl groups. In this manner, the seven degrees of unsaturation present in **1** were established.

Keywords: Xenibellal; *Xenia umbellata*.
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doi:10.1016/j.tetlet.2005.04.118

Table 1. ^{1}H and ^{13}C NMR data of **1** (300 and 75 MHz, respectively, in $CDCl_3$) (δ, in ppm relative to TMS)

Pos.	δ_H[a]	δ_C[a]
3	9.38 s	194.1
4		139.5
4α	4.08 t (10.5)[b]	36.3
5α	1.87 m	30.3
5β	2.50 m	
6α	2.20 m	37.5
6β	1.25 m	
7		59.3
8	3.04 dd (10.5, 2.1)	65.8
9α	1.07 m	
9β	2.21 m	24.6
10α	2.21 m	
10β	2.96 m	19.8
11		142.0
11a	6.73 d (10.5)	155.8
12	6.82 m	149.5
13	6.85 m	120.8
14	6.42 dq (13.6, 3.6)	153.8
15		71.2
16	1.42 s	29.8
17	1.43 s	29.8
18	0.92 s	17.5
19	9.37 s	195.3

[a] Assigned by DEPT, COSY, NOESY, HSQC, and HMBC experiments.
[b] Coupling constant in Hertz in parentheses.

The combined use of ^{1}H–^{1}H COSY and HMQC on **1** allowed us to distinguish three spin systems (see **a**–**c** in Fig. 1) and two methyl groups linked to an oxygenated quaternary carbon. A HMBC experiment was used to assemble the skeletal fragments through quaternary carbons and heteroatoms. Thus, these substructures were connected through HMBC correlations between the protons H-3 (δ_H 9.38) and the carbons C-4 (δ_C 139.0), C-12 (δ_C 149.5), and C-4a (δ_C 36.3), between the protons H-19 (δ_H 9.37) and the carbon C-11a (δ_C 155.8), C-11 (δ_C 142.0), and C-10 (δ_C 19.8), and between the methyl protons Me-18 (δ_H 0.92) and carbons C-6 (δ_C 37.5), C-7 (δ_C 59.3), and C-8 (δ_C 65.8). These relationships are represented in Figure 1. All these data allowed us to identify compound **1** as a new norditerpenoid with novel skeleton.

With the gross structure of **1** in hand, the relative stereochemistry of compound **1** was deduced from NOESY

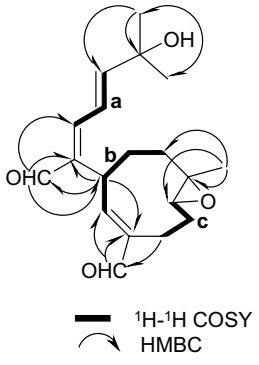

Figure 1. Key COSY and HMBC correlations of **1**.

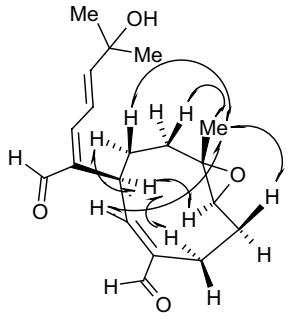

Figure 2. Key NOESY correlations of **1**.

correlations (Fig. 2), and by comparison of its spectroscopic data to those of xenia diterpenes.[7–10] The relative stereochemistry of **1** was deduced from NOESY correlations (Fig. 2), and by comparison of its spectroscopic data to those of xenia diterpenes.[7–10] The *E* geometry was assigned to the $\Delta^{4,12}$ and $\Delta^{13,14}$ double bonds by comparing the ^{1}H and ^{13}C NMR data with xenia diterpenes containing similar side chains.[7–10] The NOE correlations from Me-18 to H-11a/H-5β/H-6β and NOE correlations from H-4a to H-8/10α/H-5α were observed. This suggests that H-11a and Me-18 are on β face of the molecule while H-4a and H-8 are on the opposite, α face, of the molecule.

Xenibellal (**1**) exhibited cytotoxicity against P-388 cell line with ED_{50} of 3.2 μg/mL.

Acknowledgements

We thank Professor J. M. Pezzuto, Department of Medicinal Chemistry and Molecular Pharmacology, Purdue University, for providing P-388 cell line. This work was supported by grants from the National Science Council of Taiwan awarded to C.-Y.D.

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