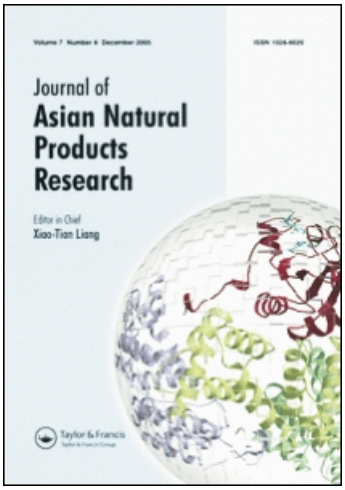

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O-methyl nakafuran-8 lactone, a new sesquiterpenoid from a hainan marine sponge *Dysidea* sp.

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A new sesquiterpenoid, *O*-methyl nakafuran-8 lactone (**1**) has been isolated from a Hainan sponge *Dysidea* sp. and the structure of the new compound proposed by spectral data, was confirmed by X-ray diffraction analysis. The complete ^{1}H- and ^{13}C-NMR assignments were made on the basis of detailed 2D NMR spectral analysis.

Compound **1** showed strong inhibitory bioactivity against PTP1B with IC_{50} value of 1.58 μM.

Keywords: *Dysidea* sp; Sesquiterpenoid; *O*-methyl nakafuran-8 lactone

1. Introduction

Dysidea (Phylum Porifera) is a large genus widely distributed in tropical and subtropical waters around the world, it is a rich source of various sesquiterpenoids and polyoxygenated steroids with interesting biological activities [1–4]. As part of our research project on the study of marine organisms from Chinese coasts aiming at searching for new bioactive secondary metabolites [5–7], we made a collection of a sponge *Dysidea* sp. (*Dysideidae*) near the Ximao Island, Sanya, Hainan Province, China. Chemical investigation of the EtOAc soluble fraction from the methanol extract of the sponge has resulted in the isolation of a new sesquiterpenoid, *O*-methyl nakafuran-8 lactone (**1**). This paper describes the isolation and structural determination by both spectroscopic methods and *X*-ray diffraction analysis of the new compound.

2. Results and discussion

Specimens of *Dysidea* sp. were collected off Sanya, Hainan Province, China, in South China Sea, and kept frozen prior to extraction. The EtOAc soluble fraction from the MeOH extract was chromatographed on a silica gel column eluting with light petroleum ether and increasing

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amounts of EtOAc. The fractions eluted with light petroleum ether/EtOAc (4:1) were further purified by Sephadex LH-20 column chromatography eluting with MeOH to afford compound **1**.

O-methyl nakafuran-8 lactone (**1**) was isolated as a colorless prism, $[\alpha]_D^{25}$-58 (*c* 0.16 $CHCl_3$). Its molecular formula, $C_{16}H_{22}O_3$, was deduced from its HREIMS {*m/z* 262.1567 $[M]^+$}. Inspection of the ^{13}C-NMR spectral data revealed the presence of one carbonyl, two olefinic linkages, a quaternary sp^3 carbon substituted by two heteroatoms (δ 113.5), one other quaternary carbon, two methines, three methylenes, three methyl groups, and a methoxy group. The total of 15 carbons except for methoxy, including three methyl groups, indicated a probable sesquiterpene. The carbonyl and two carbon–carbon double bonds left three sites of unsaturation, which was attributed to a tricyclic skeleton. From the ^{1}H-NMR data, the two olefinic protons, a singlet at δ 5.85 and a broad doublet at δ 5.80, had to be on two trisubstituted double bonds. A singlet at δ 3.13 (3H, s) was assigned to a methoxy group. An unsaturated γ-lactone [IR at 1745 cm^{-1} and UV-absorption at λ_{max} 221 nm (ϵ 8700)] accounted for one ring and the quaternary carbon at δ 113.5 (C-10) bore both the methoxy group and the lactone oxygen, as illustrated in **1a** (figure 1).

The presence of a γ-methoxy-α,β-unsaturated γ-lactone (figure 2, **1a**) with additional substituents at the β- and γ-positions [1,3] was further confirmed by comparison of ^{1}H and ^{13}C NMR data of **1** with that of model compound **2**, a metabolite isolated from a dorid nudibranch *Hypselodoris ghiselini*[1]. Spin–spin decoupling and other 2D NMR experiments suggested part of structure **1b**. In fact, the COSY spectrum showed a contiguous sequence of coupled signals from H-8 to H-12, which (δ 1.67), in turn, was further correlated with the methyl at δ 0.79 (H_3-13). On the other hand, the methylene (δ 2.41, H-4a; 2.13, H-4b; δ 24.3, C-4) exhibited clear correlations with the other adjacent methylene protons (δ 1.50, H-5a, 1.77, H-5b). Based on above evidences, we examined the possibility that the compound **1** might have the nakafuran-8 (**3**) carbon skeleton. The ^{1}H NMR spectrum of **1**, assigned as in table 1, was in excellent accord with proposed structure. In addition, HBMC spectrum also supported the assigned structure which clearly showed the correlations from H-9 to C-10, from H_2-4, H_2-5 to C-3, C-6, and from H_3-13, H_3-14, H_3-15 to C-6 establishing the overall structure of **1** (figure 1).

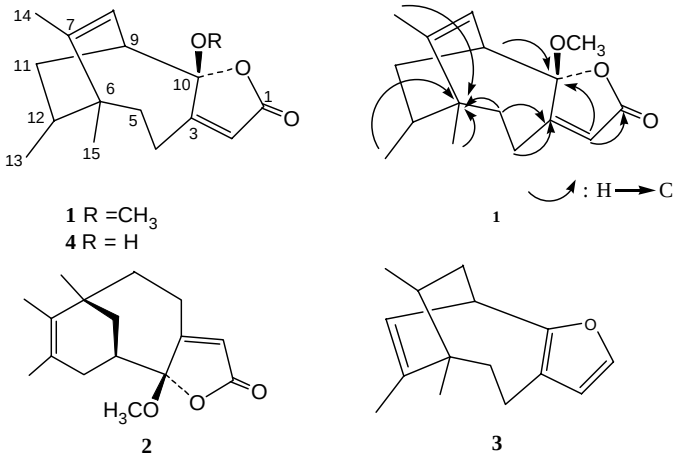
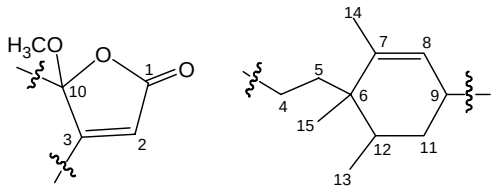


Figure 1. The structures of compounds **1**–**4** and key HMBC correlations of **1**.



1a **1b**

Figure 2. Partial structures **1a** and **1b**.

Finally the structure of *O*-methyl nakafuran-8 lactone (**1**) was ambiguously confirmed by X-ray diffraction analysis which showed relative configuration of the compound to be 9S*, 10S*, 6R*, 12S*. A view of final X-ray model is shown in figure 3.

Sesquiterpenoids with nakafuran-8 skeleton are quite rare in nature. To our knowledge only three nakafuran-8 type compounds were reported until now. This is the first report to establish nakafuran-8 type sesquiterpene by X-ray diffraction analysis. Since nakafuran-8 (**3**) is known to possess anti-feedant properties, it seems reasonable to suggest that compound **1** might also repel predators [1]. Compound **1** was also evaluated for its potential to inhibit human protein tyrosine phosphatase1B (hPTP1B), which plays a major role in the dephosphorylation of insulin receptor in many cellular and biochemical studies and is regarded as a key target for the treatment of Type-II diabetes and obesity [8]. The results showed that **1** inhibited hPTP1B activity with IC_{50} value of 1.58 μM.

3. Experimental

3.1 General experimental procedures

Optical rotation was measured in $CHCl_3$ on a Perkin–Elmer 241MC polarimeter. UV spectra were obtained on a Varian CARY 300 BIO spectrophotometer. IR spectra were recorded on

Table 1. ^{1}H- and ^{13}C-NMR data[a] assignments for compound **1** and HMBC[b] correlations observed for **1**

Position	*$^1H^d$ (mult. J in Hz)*	*$^{13}C^c$ (mult.)*	*HMBC [b] (H–C)*
1	–	170.6 (s)	–
2	5.85 (s)	120.2 (d)	C1, C3, C4, C10
3	–	170.5 (s)	–
4	2.41 (m);2.13 (m),	24.3 (t)	C2, C3
5	1.77 (m);1.50 (m)	43.8 (t)	C3
6	–	40.3 (s)	–
7	–	139.6 (s)	–
8	5.80 (d, 7.4)	123.8 (d)	C6
9	2.84 (brd, 7.4)	38.45 (d)	C8, C10
10	–	113.5 (s)	–
11	1.17 (m);1.58 (m)	31.3 (t)	C12, C13
12	1.67 (m)	38.0 (d)	C6
13	0.79 (d, 6.8 Hz)	21.5 (q)	C6, C11, C12
14	1.62 (s)	21.1 (q)	C6, C7, C8
15	1.01 (s)	25.9 (q)	C5, C6, C7, C12
2–OCH_3	3.13 (s)	50.8 (q)	C10

[a]Varian Inova 600 MHz; δ values are reported in ppm referenced to $CHCl_3$ (δ_H 7.26 and δ_C 77.0). [b]$J = 10$ Hz was used in HMBC experiment. [c] Deduced by DEPT sequence. [d]Assignments were aided by ^{1}H–^{1}H COSY, HMQC, HMBC and NOESY experiments.

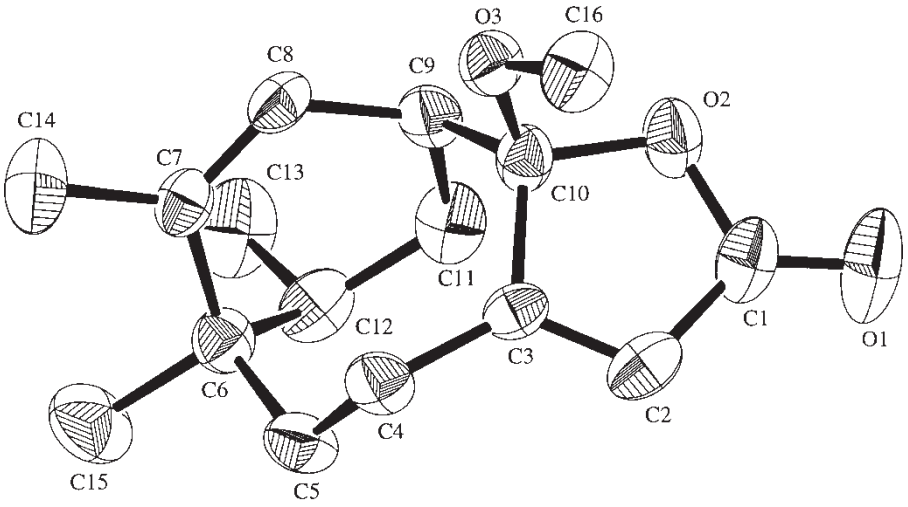


Figure 3. Perspective ORTEP drawing of compound **1**

a Nicolet Magna FT-IR 750 spectrophotometer. ^{1}H NMR (600 MHz) and ^{13}C NMR (150 MHz) spectra were recorded with a Varian Inova 600 NMR spectrometer at 600 and 150 MHz, respectively. EIMS were obtained with a Finnigan LCQ–DECA mass spectrometer. X-ray data were generated on a Rigaku AFC7R diffractometer.

3.2 Collection of biological material

Specimens of *Dysidea* sp., identified by Prof J.-S. Sim of Hannam University, Republic of Korea, were collected in June, 2003 by SCUBA techniques at a depth of − 10 m off Sanya, Hainan Province, China in the South China Sea. The sponge materials were frozen immediately and transferred to SIBS, where it was kept at − 20°C until extraction. The sponge is thickly encrusting with small lobe in form. Oscules are irregularly scattered on the surface and opened at the base of lobe. The colour is khaki in life and black in alcohol. The texture is unslick and hard. The surface is covered with small and sharply pointed conules, 0.5–1 mm height and 2–3 mm apart. The primary fibres, 150–200 μm in diameter, are heavily cored with sands. The secondary fibres, 50–70 μm in diameter, are heavily cored with sands. All fibres cored with large sands, 100–200 μm in diameter, at outside of fibres, and with small sands, 10–50 μm in diameter, in fibres. A voucher specimen of this horny sponge (registry No. Spo. 47) was deposited at the Natural History Museum, Hannam University, Korea.

3.3 Extraction and isolation

The bodies of the sponge *Dysidea* sp. (635 g, dry wt. after extraction) were chopped, then soaked in MeOH and extracted at room temperature (2000 ml × 4). The combined MeOH extracts were concentrated *in vacuo*, thus obtaining an aqueous suspension which was extracted with EtOAc (600 ml × 4). Evaporation of EtOAc extracts gave an oil (12 g) which was subjected to silica gel column chromatography using a petroleum ether–EtOAc gradient as eluent. The fraction eluted with petroleum ether/EtOAc (4:1) was further purified by a Sephadex LH-20 column eluted with MeOH to afford *O*-methyl nakafuran-8 lactone (**1**, 7.1 mg).

3.3.1 *O*-methyl nakafuran-8 lactone (1). Colorless prism; mp 172–176°C $[\alpha]_D^{25}$-58 (*c* 0.16, $CHCl_3$); IR ν_{max} (KBr) cm^{-1}: 3411, 2962, 1774, 1665 cm^{-1}; UV λ_{max} (MeOH) 221 nm (log ϵ 3.9); ^1H and ^{13}C NMR see table 1; EIMS *m/z* (%): 262 (M^+, 16), 247 (5), 123 (100); HREIMS *m/z*: 262.1567 (calcd for $C_{16}H_{22}O_3$, 262.1569).

3.3.2 X-ray analysis of 1. Single crystals of **1** suitable for X-ray diffraction analysis were obtained, by careful recrystallization from a mixed solvent system [light petroleum ether/Me_2CO (1:1)], in the form of colorless prisms. Crystal of size 0.20 × 0.20 × 0.30 mm was selected for crystallographic study. Crystal data: $C_{16}H_{22}O_3$, Orthorhombic, Space group $P2_12_12_1$ (# 19), $a = 10.649(4)$ Å, $b = 14.351(5)$ Å, $c = 9.360(5)$ Å, $\beta = 80.121\,(2)°$, $V = 1430\,(1)$ $Å^3$, $Z = 4$; $D = 1.22$ g/cm^3, $F\,(000) = 568.00$, μ(Mo-Kα) = 0.82 cm^{-1}. Intensity data were collected on a Rigaku AFC7R diffractometer with graphite monochromated Mo-Kα radiation and a 12 kW radiation anode generator; A total of 1904 reflections, of which 1126 had $I > 3\sigma(I)$, were collected in the range $13.63° < 2\theta < 21.25°$. The structure was solved by direct methods (SHELXS86) [9] and expanded using Fourier technique (DIRDIF92) [10]. The non-hydrogen atoms were refined anisotropically. Hydrogen atoms were included but not refined. It was refined by full-matrix least-squares and converged with $R = 0.052$ and $Rw = 0.063$. Drawing of the molecule was made with ORTEP.

Supporting information available: X-ray crystallographic data (excluding structure factors) for the structure **1** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 239464. Copy of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44 (0)1223-336033 or e-mail: *deposit@ccdc.cam.ac.uk*].

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