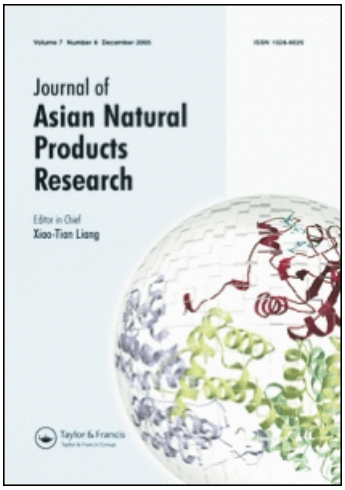

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A new spiro-sesquiterpene from the sponge *Dysidea fragilis*

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Note

A new spiro-sesquiterpene from the sponge *Dysidea fragilis*

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A new spiro-sesquiterpene, spirofragilin (**1**), along with a known related sesquiterpene, dehydroherbadysidolide (**2**), have been isolated from the marine sponge *Dysidea fragilis* collected in the South China Sea. The structure of **1** was elucidated on the basis of detailed spectroscopic analysis.

Keywords: Marine sponge; *Dysidea fragilis*; Spiro-sesquiterpene; Spirofragilin

1. Introduction

Sponges of the genus *Dysidea* are prolific sources of sesquiterpenes, polybrominated diphenyl ethers and chlorinated amino acid derivatives [1]. Further, the genus *Dysidea* produces "scalemic" mixtures of sesquiterpenoids from geographically diverse sponges [2,3]. A literature survey revealed that sponge *Dysidea fragilis* has afforded polybrominated diphenyl ethers [4], cytotoxic azacyclo propene lipid derivatives [5,6], diketopiperazines [7] and sesquiterpenes [8–13].

As part of our ongoing project on the study of marine organisms from the Chinese coasts [14,15], we made a collection of *D. fragilis* off the Ximao Island, Hainan Province, China. On the separation of the Et_2O-soluble fraction of the acetone extract of the sponge, a new unusual spiro-sesquiterpenoid, spirofragilin (**1**), and a known related compound, dehydroherbadysidolide (**2**), were isolated. This paper deals with the isolation and structural elucidation of the new spiro-sesquiterpenoid from *D. fragilis*.

2. Results and discussion

The sponge was exhaustively extracted with Me_2CO and the extract was partitioned between Et_2O and H_2O. The Et_2O-soluble portion was subjected to column chromatography on silica

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gel eluting with petroleum/Et_2O system. This procedure resulted in the isolation of a new spiro-sesquiterpenoid, named spirofragilin (**1**), and a known related compound (**2**) whose structure was identified as dehydroherbadysidolide by analysis of its spectral data and by comparison with the data reported in literature [13].

Spirofragilin (**1**), colourless solid, $[\alpha]_D^{20}$ + 141 (*c* 0.43, $CHCl_3$), showed the molecular ion $[M]^+$ at *m/z* 236 in EI-MS and the molecular formula $C_{15}H_{24}O_2$ was established by HREI-MS, indicating four degrees of unsaturation. Inspection of the ^{13}C NMR spectral data for **1** revealed the presence of three methyls, five sp^3 methylenes, four methines, two sp^3 quaternary carbons and one sp^2 quaternary carbon. The total 15 carbons indicated that **1** was a sesquiterpene. The trisubstituted double bond (δ_C 133.0, s; 125.1, d) left three sites of unsaturation attributed to a tricyclic skeleton. From the ^1H NMR data, the olefinic proton singlet at δ 5.39 had to be on the trisubstituted double bond. A singlet at δ 1.66 was assigned to a vinylic methyl. Two singlets at δ 1.21 and 1.07 were ascribable to a germinal dimethyl group. A singlet at δ 4.97 suggested the methine bore two oxygen atoms, meaning the presence of hemiketal moiety in **1**. The foregoing spectral data of **1** is very reminiscent of those of the co-occurring metabolite **2** and the model compound **3**, (+)-12,13-dihydro-14-methoxy-14-deacetoxyspirodysin, which was reported from the same species from India [11]. In fact, the ^{13}C NMR data of **1** and **3** (table 1) were almost the same except for that of C-14. The molecular weight of **1** was 14 mass units less than that of **3**; together with the lack of the ^{13}C NMR resonance at δ 53.9, this clearly indicated that **1** is a 14-*O*-demethyl derivative of **3**. However, it is noteworthy that some ^{13}C NMR assignments of **3** were quite different from what we made. Because the structure of **1** was confirmed by detailed analysis of 2D NMR spectra ($^1H-^1H$ COSY, HMQC, HMBC, TOCSY), ^{13}C NMR data for **3** should be reassigned. In addition, due to the use of MeOH during the isolation procedure of **3**, it was

Table 1. ^1H NMR and ^{13}C NMR data of compound **1**, and ^{13}C NMR data of **2**, **3**.

Position	***1*** [a,b]		***2*** [a,b]	***3*** *[11]*
	δ ^1H *(J in Hz)* δ	δ ^{13}C	δ ^{13}C	δ ^{13}C
1	–	44.2 s	48.6 s	44.8
2	–	56.6 s	60.7 s	56.8
3α	1.32 m	43.8 t	40.4 t	34.5[c]
3β	1.97 dd (13.9, 10.7)			
4β	2.73 br s	35.3 d	35.3 d	53.9[d]
5	5.39 br s	125.1 d	124.7 d	125.2
6	–	133.0 s	133.1 s	132.9
7α	1.25 m	30.0 t	28.7 t	44.7[c]
7β	1.86 d (7.8)			
8a	1.29 m	23.6 t	21.4 t	23.7
8b	1.73 m			
9β	1.58 m	51.5 d	43.4 d	35.6[d]
10	1.07 s	21.9 q	22.1 q	23.7[e]
11	1.21 s	26.9 q	24.4 q	27.3
12a	1.63 m	34.4 t	112.6 d	30.1[c]
12b	2.26 ddd (21.0, 9.0, 9.0)			
13a	3.77 ddd (9.0, 8.1, 8.1)	66.6 t	141.1 d	66.2
13b	4.05 ddd (9.0, 8.1, 1.5)			
14	4.97 s	104.3 d	181.0 s	110.9
15	1.66 br s	23.7 q	23.8 q	21.8[e]
OMe	–	–	–	51.6[d]

[a]In ppm from internal TMS in $CDCl_3$ solution.
[b]Assignments aided by 2D NMR experiments.
[c–e]Assignments should be interchanged according to corresponding assignments in **1**.

possible that **3** was an artifact instead of a natural product. Finally, since the relative stereochemistry at C-2 and C-14 of **3** was undefined, we have investigated the NOESY spectrum of **1**.

The relative stereochemistry of **1** at C-2, C-4, C-9 and C-14 determined by NOESY experiments matched that of herbadysidolid (**4**) [13,17] and spirodysin (**5**) [13,16], giving NOE correlations (figure 1) between H-4 and H-9, H-9 and H_3-11, H_3-11 and H-14, and H_3-10 and H_b-12.

The absolute stereochemistry of **1** is unknown. However, because of **1** an $[\alpha]_D^{20}$ of $+141$, **3** an $[\alpha]_D^{20}$ of $+195$ [11], and **5** an $[\alpha]_D^{20}$ of $+24$ [16], they likely share the same absolute configuration.

3. Experimental

3.1 General experimental procedures

IR spectra were recorded on a Nicolet Magna FT-IR 750 spectrometer; ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker AV500 (500 MHz for ^{1}H and 125 MHz for ^{13}C) spectrometer. Chemical shifts (δ) are reported in ppm relative to an internal TMS standard, coupling constants (J) are in Hz. ^{1}H NMR and ^{13}C NMR data were assigned by ^{1}H–^{1}H COSY, HMQC, HMBC and NOESY experiments. The HREI-MS spectrum was recorded on a MAT-711 mass spectrometer. Commercial Si gel plates (Qing Dao Hai Yang Chemical Group) were used for TLC.

3.2 Collection of biological material

The examined sample was collected from Ximao Island, Hainan Province, China in January 2003 and identified by Professor J.-H. Li of the Institute of Oceanology, CAS. Freshly collected sponge tissue was frozen on site and stored at -20°C until workup. A voucher specimen is available for inspection at the Herbarium of the Institute of Materia Medica, SIBS-CAS.

3.3 Extraction and isolation

The frozen marine sponge (dry weight 138 g) was extracted with acetone at room temperature. The acetone extract was concentrated *in vacuo* and the resulting residue was

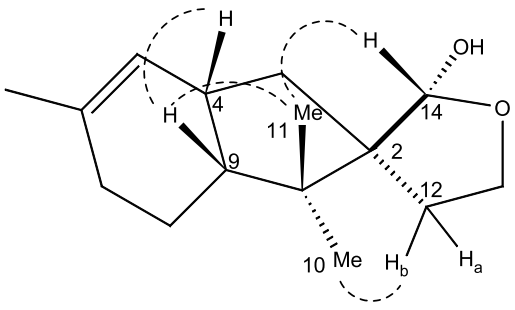

Figure 1. Key NOESY correlations of **1**.

partitioned between H_2O and Et_2O. The Et_2O extract (3.2 g) was chromatographed on a silica gel column using eluents of increasing polarity from light petroleum ether to Et_2O. The fractions eluted with 20% Et_2O/petroleum ether were further purified by Sephadex LH-20 ($CHCl_3$ as eluent) affording **1** (11.6 mg); the fractions eluted with 10% Et_2O/petroleum ether were further purified by being chromatographed on a silica gel column eluted with 8% EtOAc in hexane to give **2** (6.9 mg).

3.3.1 Spirofragilin (1). Colourless solid, $[\alpha]_D^{20} + 141$ (c 0.43, $CHCl_3$); IR ν_{max} (KBr) cm^{-1}: 3396, 2928, 1716, 1466, 1363, 1014, 974, 903; EI-MS m/z (%): 236 (M^+, 5), 221 (16), 218 (28), 203 (35), 175 (24), 162 (23), 147 (24), 119 (20), 111 (100), 94(20), 79(20); HREI-MS m/z: 236.1761 (calcd for $C_{15}H_{24}O_2$, 236.1746); ^1H NMR ($CHCl_3$, 500 MHz): see table 1; ^{13}C NMR ($CHCl_3$, 125 MHz): see table 1.

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