

## 5'-Hydroxyzearalenol, a new $\beta$ -resorcylic macrolide from *Fusarium* sp. 05ABR26

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### Abstract

A new  $\beta$ -resorcylic macrolide, 5'-hydroxyzearalenol (**1**), was isolated from the culture broth of a marine-derived fungus *Fusarium* sp. 05ABR26. Three known compounds, zearalenone (**2**), 8'-hydroxyzearalenone (**3**) and zearalenol (**4**) were also isolated. The structure and relative stereochemistry of **1** were elucidated on the basis of spectroscopic data and single-crystal X-ray diffraction data. Compound **2** displayed potent inhibitory activity against *Pyricularia oryzae* with a MIC value of 6.25  $\mu$ g/mL, while compound **3** was much less active; however, **1** and **4** showed no obvious activity.

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Zearalenone (**2**), a  $\beta$ -resorcylic macrolide, was first isolated in 1962 from the fungus *Gibberella zeae* (*Fusarium graminearum*) [1]. The major mycotoxicity of zearalenone and its metabolites is attributed to their anabolic and estrogenic activities [2]. Cytotoxic and genotoxic effects of zearalenone were also reported [3]. In our search for structurally unique and bioactive substances from marine-derived fungi [4], 5'-hydroxyzearalenol (**1**), a new derivative of zearalenone was isolated from the culture broth of a marine-derived fungus *Fusarium* sp. 05ABR26 together with three known compounds, which were assigned as zearalenone (**2**), 8'-hydroxyzearalenone (**3**) and zearalenol (**4**) [5–7]. In this paper, the structure elucidation of compounds **1–4** is described; furthermore, the bioactivity against *Pyricularia oryzae* (*P. oryzae*) is discussed [8].

*Fusarium* sp. 05ABR26, which was isolated from a sponge collected in Miura Peninsula of Japan, was fermented in a 1-l Erlenmeyer flask containing 200 mL of potato dextrose medium (a half nutrient, 50% sea water) at 20 °C for 21 days. The culture broth (1 L) was added to 1 L of 80% (v/v) aqueous acetone, and then stirred for 30 min at room temperature. After the acetone extracts were filtered and concentrated *in vacuo*, the resulting aqueous solution was extracted three times with 1 L of ethyl acetate (EtOAc). The EtOAc extract (319.1 mg) was subjected to a sephadex LH-20 column and eluted with *n*-hexane/CH<sub>2</sub>Cl<sub>2</sub>/MeOH (4:5:1) to give fractions E-1–E-4, and bioactivity against *P. oryzae* was detected in fractions E-2 and E-3. Fraction E-2 was separated with an ODS column (75% MeOH/H<sub>2</sub>O) to

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Table 1  
NMR data of 5'-hydroxyzearalenol (**1**)<sup>a</sup>

Position	$\delta_C$ (mult <sup>b</sup> )	$\delta_H$ (mult, $J$ in Hz)	<sup>1</sup> H- <sup>1</sup> H COSY	HMBC <sup>c</sup>
1	109.6 s			3, 5
2	161.9 s			3
3	102.4 d	6.19 d (2.3)	5	5
4	162.1 s			5
5	106.7 d	6.40 d (2.3)	3	3, 1'
6	141.5 s			1', 2'
1'	130.2 d	6.60 d (16.0)	2'	5, 3'
2'	132.8 d	6.15 dt (16.0, 5.5)	1', 3'	3', 4'
3'	28.2 t	2.36 m	2', 4'	1', 2'
4'	28.7 t	1.84 m, 1.67 m	3', 5'	3'
5'	71.3 d	3.74 m <sup>d</sup>	4'	3', 7'
6'	75.6 d	3.75 m <sup>d</sup>	7'	4'
7'	33.1 t	1.69 m, 1.56 m	6'	
8'	21.5 t	1.52 m	9''	9'
9'	36.1 t	1.81 m, 1.66 m	8', 10'	10'-Me
10'	73.1 d	5.12 m	9', 10'-Me	9', 10'-Me
12'	172.2 s	10'-Me	20.3 q	1.34 d (6.3)

<sup>a</sup> Data recorded in CD<sub>3</sub>OD on a Varian Mercury plus 400 instrument.

<sup>b</sup> <sup>13</sup>C NMR multiplicities were obtained from a DEPT-135 experiment.

<sup>c</sup> Protons correlated to carbon resonances in the <sup>13</sup>C column.

<sup>d</sup> Signal partially overlapped.

afford **2** (25.1 mg). Fraction E-3 was further purified by repeated silica gel column chromatography (CHCl<sub>3</sub>/EtOAc and *n*-hexane/acetone) followed by ODS column (60% MeOH/H<sub>2</sub>O) to give **1** (9.1 mg), **3** (59.5 mg) and **4** (4.9 mg).

5'-Hydroxyzearalenol (**1**) was isolated as colorless crystals, with a mp 168–170 °C,  $[\alpha]_D^{20.4} + 60.7$  (*c* 0.01, MeOH), and molecular formula of C<sub>18</sub>H<sub>24</sub>O<sub>6</sub> established by HRESIMS at *m/z* 335.1494 [M-H]<sup>-</sup> (calcd for C<sub>18</sub>H<sub>23</sub>O<sub>6</sub> 335.1495), suggesting seven degrees of unsaturation. The IR spectral absorptions at 3565, 3347 and 1645 cm<sup>-1</sup> implied the presence of hydroxyl and conjugated ester group(s). <sup>1</sup>H and <sup>13</sup>C NMR data for **1** were similar to those of zearalenol [6], except for additional signals due to the hydroxyl group of **1**.

The <sup>13</sup>C and DEPT-135 NMR spectral data showed 18 carbons including one methyl, five sp<sup>3</sup> methylenes, four sp<sup>2</sup> methines, three sp<sup>3</sup> methines, and five quaternary carbons. Among them, three methine carbons at  $\delta_C$  75.6 (C-6'), 73.1 (C-10') and 71.3 (C-5') were thought to have connections to oxygens. The <sup>1</sup>H NMR spectrum (Table 1) exhibited signals for two coupled olefinic protons at  $\delta_H$  6.15 (dt,  $J = 16.0$  and 5.5 Hz) and 6.60 (d,  $J = 16.0$  Hz) assigned to the H-2' and H-1' vicinal protons, respectively. The presence of a  $\beta$ -resorcyolate group (partial structure **a**, Fig. 1) was indicated by some typical <sup>1</sup>H and <sup>13</sup>C NMR resonances (Table 1) according to the presence of an ester group (C-12',  $\delta$  172.2), four quaternary carbons (C-1,  $\delta$  109.6; C-2,  $\delta$  161.9; C-4,  $\delta$  162.1; C-6,  $\delta$  141.5) and two coupled aromatic protons at  $\delta_H$  6.19 (d,  $J = 2.3$  Hz, H-3) and 6.40 (d,  $J = 2.3$  Hz, H-5). The above functionalities accounted for six out of the seven degrees of unsaturation; the one remaining degree of unsaturation therefore indicated that **1** is a macrolide.

After association all of the carbon signals with the corresponding signals for directly bonded protons via an HSQC experiment in CD<sub>3</sub>OD, <sup>1</sup>H-<sup>1</sup>H COSY and HMBC spectral measurements were recorded (Table 1). The <sup>1</sup>H-<sup>1</sup>H COSY spectra of **1** revealed connectivity of three structural units, **b** (C-1' to C-5'), **c** (C-6' to C-7'), and **d** (C-8' to C-10'Me) as

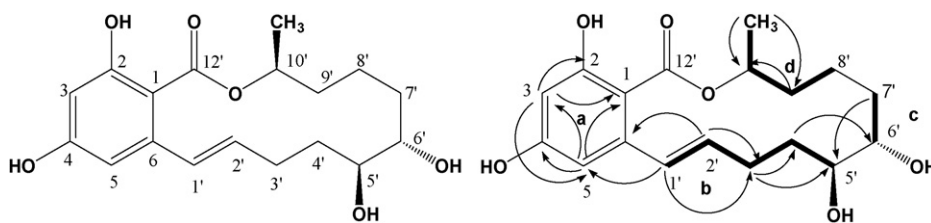


Fig. 1. The structure, key <sup>1</sup>H-<sup>1</sup>H COSY (—) and HMBC (↷) correlations of **1**.

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