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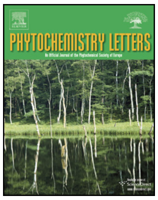

Isopimaranes and eremophilanes from the wood-decay fungus *Xylaria allantoidea* BCC 23163

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ABSTRACT

Three new isopimarane diterpenes, xylallantins A–C (**1**–**3**), a new eremophilane sesquiterpene, eremoxylarin C (**7**), and an *O*-methyl derivative of diplosporin (**10**), together with seven known compounds, xylarenolide (**4**), hymatoxins E (**5**) and K (**6**), eremoxylarin A (**8**), 07H239-A (**9**), acuminatopyrone (**11**), and coriloxin (**12**), were isolated from the fermentation broth of the wood-decay fungus *Xylaria allantoidea* BCC 23163. The structures were elucidated by analyses of NMR spectroscopic and mass spectrometry data. Xylallantin A (**1**) showed cytotoxicity to NCI-H187 cells (IC_{50} 17 μg/ml), while eremoxylarin C (**7**) exhibited activity against *Plasmodium falciparum* K1 (IC_{50} 3.1 μg/ml) and cytotoxicity to NCI-H187 cells (IC_{50} 6.7 μg/ml).

1. Introduction

Xylaria is a diverse genus of plant-associated fungi, which is composed of more than 600 described species. This genus has been the source of a wide range of bioactive compounds such as cytochalasins (Abate et al., 1997), eremophilane sesquiterpenoids (Singh et al., 1999; Smith et al., 2002; McDonald et al., 2004), pimarane diterpenoids (Borgschulte et al., 1991; Isaka et al., 2011), triterpenoid glycosides (Deyrup et al., 2007), xyloketals (Lin et al., 2001), lactones (Boonphong et al., 2001), and cyclopeptides (Wu et al., 2011). However, many rare species in this genus remain underexplored. As part of our research program on bioactive fungal metabolites, a saprobic fungus *Xylaria allantoidea* BCC 23163 was investigated. There has been no previous chemical evaluation of this species to date. A culture broth extract showed cytotoxicity to NCI-H187 cancer cells (IC_{50} 39 μg/ml) and displayed a unique ^1H NMR spectroscopic profile suggesting the presence of several terpenoid metabolites. Scale-up fermentations and chemical studies led to the isolation and characterization of three new isopimarane diterpenes, xylallantins A–C (**1**–**3**), a new eremophilane sesquiterpene, eremoxylarin C (**7**), and an *O*-methyl derivative of diplosporin (**10**). Seven known compounds, xylarenolide (**4**) (Li et al., 2010), hymatoxin E (**5**) (Borgschulte et al., 1991), hymatoxin K (**6**) (Jossang et al., 1995), eremoxylarin A (**8**) (Shiono and Murayama, 2005), 07H239-A (**9**) (McDonald et al., 2004), acuminatopyrone (**11**) (Visconti et al., 1994), and coriloxin (**12**) (Shiono et al., 2005), were also isolated from the same culture broth extract (Fig. 1).

2. Results and discussion

Xylallantin A (**1**) was isolated as a minor diterpene constituent of the broth extract. The molecular formula of **1** was determined to be $C_{20}H_{30}O_6$ by HRESIMS. The IR spectrum exhibited intense and broad absorption band at ν_{max} 3328 cm^{-1}, which suggested the presence of OH groups. The ^1H and ^{13}C NMR, DEPT135, and HMQC spectroscopic data revealed that **1** contained a trisubstituted olefin (δ_C 137.0; δ_C 130.3, δ_H 5.79), a vinyl group (δ_C 148.5, δ_H 5.86; δ_C 109.9, δ_H 5.01 and 4.92), an acetal carbon (δ_C 107.7), an oxygenated quaternary carbon (δ_C 75.4), three oxygenated methines, an oxymethylene, three quaternary carbons, a methine, three methylenes, and three methyl groups. The planar structure was deduced on the basis of COSY and HMBC correlations (Table 1). Thus, two methyl groups at δ_H 1.34 (δ_C 28.0, CH_3-18) and 1.27 (δ_C 23.3, CH_3-19) showed HMBC correlations to each other. These protons (H_3-18 and H_3-19) also exhibited correlations to a quaternary carbon at δ_C 36.3 (C-4), a secondary alcohol carbon at δ_C 77.8 (δ_H 3.52, CH-3), and a methine carbon at δ_C 42.6 (δ_H 2.75, s, CH-5). H-5 exhibited HMBC correlations to C-1, C-4, C-6, C-9, C-10, C-18, C-19, and C-20, while diastereotopic oxymethylene

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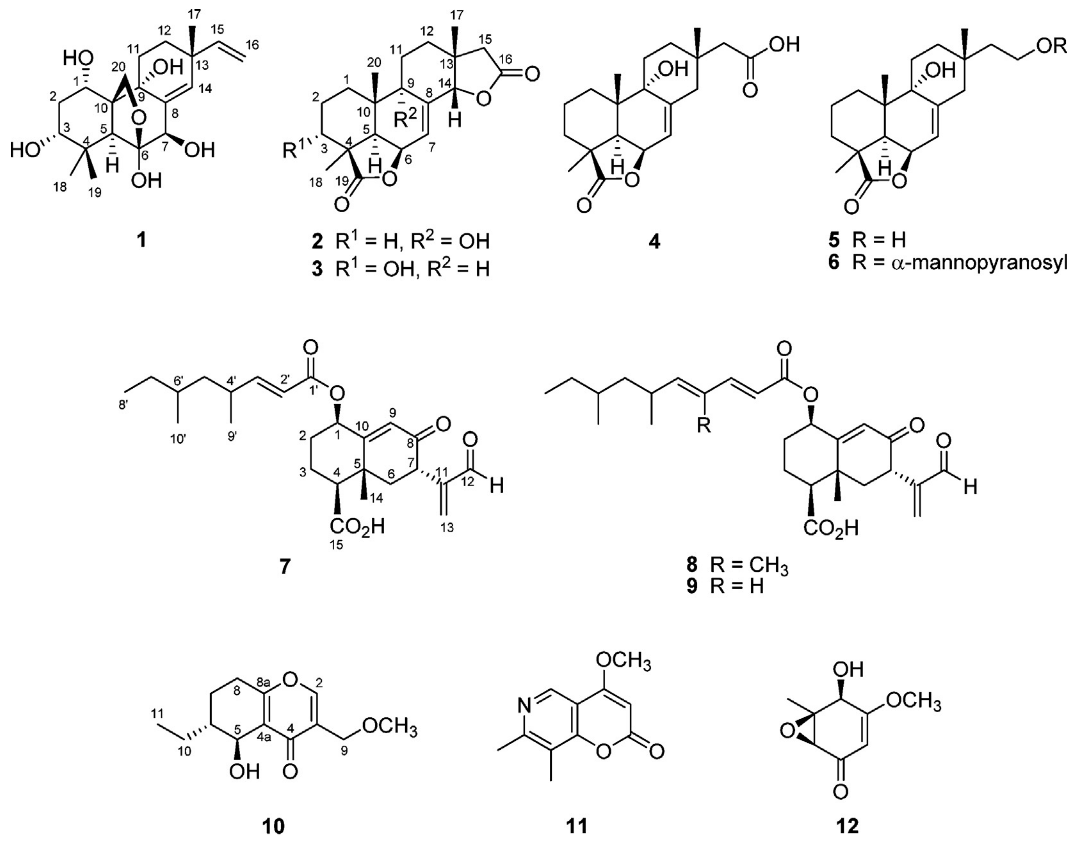

Fig. 1. Structures of compounds **1**–**12**.

protons at δ_H 3.57 (d, J = 9.0 Hz; H_a-20) and 3.34 (d, J = 9.0 Hz; H_b-20) showed correlations to C-1, C-5, C-6, C-9, and C-10. The presence of a hemiacetal (C-6) was revealed by the HMBC correlations from 6-OH (δ_H 4.81, s) to C-5, C-6, and C-7. Another tertiary alcohol at δ_H 4.51 (9-OH) showed HMBC correlations to C-8, C-9, and C-10. The trisubstituted olefin was assigned to C-8/C-14 based on the HMBC correlations from the olefinic methine H-14 to C-9, C-12, and C-15. HMBC correlations from H_3-17 to C-12, C-13, C-14, and C-15, and the correlations from H-15 to C-13, C-14, and C-17 revealed the connections of the methyl group (CH_3-17) and the vinyl group to the quaternary carbon C-13. The relative configuration was elucidated on the basis of the NOESY correlations (Fig. 2). One of the oxymethylene protons, H_a-20 (δ_H 3.57) showed NOESY correlations to H_β-3 and H_3-19. Other key NOESY correlations on the β-face are those from H_β-11 to H_b-20 (δ_H 3.34) and H_3-17. NOESY correlations H-5/H-7 and H-5/9-OH indicated the 7β-hydroxy and 9α-hydroxy groups, respectively. H-1 resonated as a multiplet signal in the ^1H NMR spectrum. Although the coupling constants were not measurable, the spectrum indicated small J-values for H-1/H_α-2 and H-1/H_β-2, suggesting an equatorial (β) orientation of H-1. Similarly, the small J-values for H-3/H_α-2 and H-3/H_β-2 suggested the equatorial (β)

Table 1
NMR spectroscopic data for xylallantin A (**1**) in acetone-d_6.

No.	δ_C, mult.	δ_H, mult. (J in Hz)	HMBC
1	69.0, CH	4.07, m	
2	30.4, CH_2	α 1.93, m; β 2.24, m	
3	77.8, CH	3.52, m	
4	36.3, qC		
5	42.6, CH	2.75, s	1, 4, 6, 9, 10, 18, 19, 20
6	107.7, qC		
7	76.0, CH	4.09, d (10.0)	
8	137.0, qC		
9	75.4, qC		
10	54.6, qC		
11	27.6, CH_2	α 1.94, m; β 1.96, m	
12	30.1, CH_2	α 1.97, m; β 1.44, m	
13	37.5, qC		
14	130.3, CH	5.79, m	9, 12, 15
15	148.5, CH	5.86, dd (17.5, 10.6)	13, 14, 17
16	109.9, CH_2	5.01, dd (17.5, 1.2)	13, 15
		4.92, dd (10.6, 1.2)	13, 15
17	23.5, CH_3	1.06, s	12, 13, 14, 15
18	28.0, CH_3	1.34, s	3, 4, 5, 19
19	23.3, CH_3	1.27, s	3, 4, 5, 18
20	69.3, CH_2	3.57, d (9.0); 3.34, d (9.0)	1, 5, 6, 9, 10
1-OH		5.70, d (6.8)	1, 2
3-OH		5.12, d (5.5)	2
6-OH		4.81, s	5, 6, 7
7-OH		4.02, d (10.0)	
9-OH		4.51, s	8, 9, 10

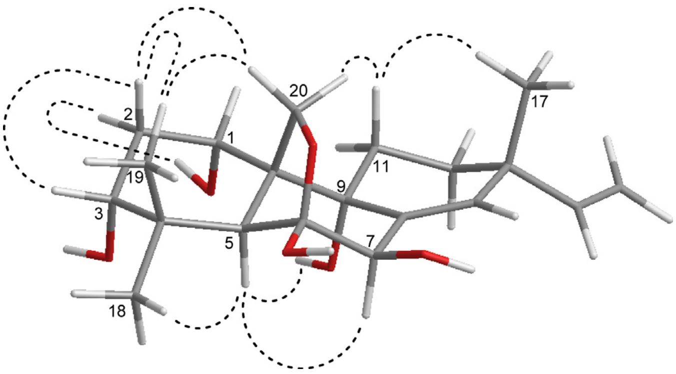

Fig. 2. Key NOESY correlations for **1**.