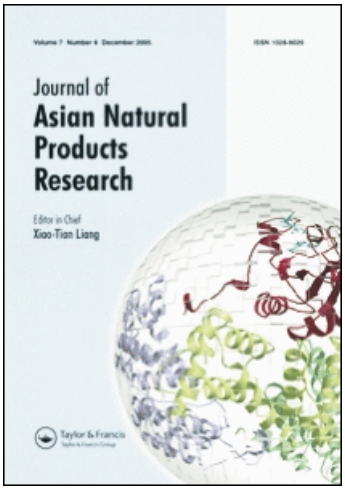

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A new decalin derivative from red yeast rice

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A new decalin derivative, monascusic acid A (**1**), together with a new natural product (**2**), was isolated from the ethanol extract of red yeast rice. Their structures were elucidated by spectroscopic methods.

Keywords: monascusic acid A; decalin; *Monascus purpureus*; red yeast rice

1. Introduction

Red yeast rice, also called as 'red mold rice' or 'Hongqu', has been used as food and traditional medicine for a long time in China [1–5]. Red yeast rice could be obtained by the fermentation of rice with fungi of the genus *Monascus* (Monascaceae). Recently, more and more attention has been paid to the secondary metabolic products of *Monascus* species especially after the discovery of monacolins, which are potent inhibitors of HMG-CoA reductase and can lower blood lipid levels in both animal models and humans [1,5,6]. In our search for biologically active and structurally unique compounds from traditional Chinese medicine, we carried out the chemical investigation on red yeast rice (fermented by *Monascus purpureus*), resulting in the isolation of a new decalin derivative (**1**) and a new natural product (**2**) (Figure 1). Their structures were determined based on spectroscopic data. Herein, we report the structure elucidation of **1**.

2. Results and discussion

Compound **1** was obtained as colorless needles, mp 119–120°C. The molecular formula of **1** was determined to be $C_{15}H_{22}O_2$ by HR-ESI-MS at *m/z* 233.1545 $[M-H]^-$. In the UV spectrum of **1**, the absorption maxima at 231, 238, and 247 nm indicated that **1** possessed a conjugated double bond [7]. The IR spectrum revealed the presence of hydroxyl (3429 cm^{-1}) and carbonyl (1698 cm^{-1}) groups. The ^1H NMR spectrum of **1** displayed two methyl signals at δ_H 0.90 (3H, d, $J = 7.0$ Hz, H-9) and 0.99 (3H, d, $J = 7.1$ Hz, H-10), and three olefinic protons at δ_H 5.44 (1H, m, H-5), 5.72 (1H, dd, $J = 9.6$, 5.9 Hz, H-3), and 5.91 (1H, d, $J = 9.6$ Hz, H-4). The ^{13}C NMR spectrum showed 15 carbon signals, including two methyl, four methylene, seven methine, and two quaternary

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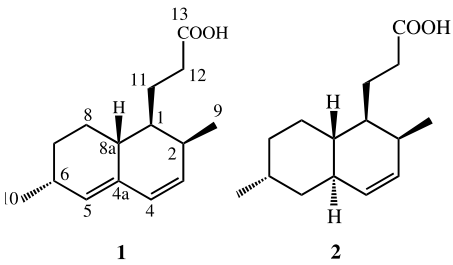

Figure 1. Chemical structures of **1** and **2**.

carbons. Comparison of the ^{13}C NMR spectral data of **1** with those of monacolin L reported in the literature [8,9] revealed that they were very similar except for the presence of a carbonyl carbon signal at δ_C 180.0 (C-13) in **1** instead of signals for the lactone ring. The combined analysis of 1D and 2D NMR spectral data of **1** suggested that compound **1** possessed a 3,4a(5)-diene decalin skeleton. The cross-peaks between H-11 (δ_H 1.45 and 2.04) and H-12 (δ_H 2.25 and 2.44) in the $^1H-^1H$ COSY spectrum of **1**, and the HMBC correlations between H-12 (δ_H 2.25 and 2.44) and C-11 (δ_C 24.4) and C-13 (δ_C 180.0) indicated the presence of a propionic acid moiety. With the aid of $^1H-^1H$ COSY, HSQC, and HMBC experiments, all the proton and carbon signals of **1** were assigned as shown in Table 1.

The HMBC correlations between H-1 (δ_H 1.45) and C-12 (δ_C 31.7) and between H-11 (δ_H 1.45 and 2.04) and C-2 (δ_C 31.4) indicated that the propionic acid moiety should be attached to the C-1 position of the decalin skeleton. Furthermore, in the HMBC spectrum, the correlations between H-9 (δ_H 0.90) and C-2 (δ_C 31.4) and C-3 (δ_C 132.8), as well as between H-10 (δ_H 0.99) and C-5 (δ_C 130.7) and C-7 (δ_C 29.3), indicated that the two methyl groups were located at the C-2 and C-6 positions of the decalin skeleton, respectively.

The relative stereochemistry of compound **1** could be determined on the basis of the ROESY correlations (Figure 2). The ROESY correlations between H-7β and H-8a, and between H-8a and H-9, indicated the β-orientation for H-8a and Me-2. Similarly, the ROESY correlations between H-8α and H-10, H-8α and H-1, as well as between H-1 and H-2 suggested that Me-6, H-1, and H-2 should be α-oriented. Thus, the structure of **1** was determined as 3-(2,6-dimethyl-1,2,6,7,8,8a-hexahydro-naphthalen-1-yl)-propanoic acid and named as monascusic acid A.

Compound **2** had been previously obtained from the cultures of *Aspergillus nidulans* mutant with controlled lovastatin biosynthesis gene [10]. In our present investigation, it was isolated and reported as a new natural product with full assignment of NMR spectral data for the first time.

3. Experimental

3.1 General experimental procedures

Melting points were determined on an XT-4 micro-melting point apparatus and were uncorrected. Optical rotation values were recorded on a JASCO P-1020 polarimeter with a 0.1 dm length cell at room temperature. UV spectra were measured on a JASCO V-550 UV/vis spectrophotometer with a 1 cm length cell. IR spectra (KBr) were recorded on a JASCO FT/IR-480 plus Fourier transform infrared spectrometer. HR-ESI-MS were obtained on an Agilent 6210 LC-MSD TOF mass spectrometer. NMR spectra were measured on a Bruker AV-400 spectrometer using tetramethylsilane as the internal standard.

Precoated silica gel GF_{254} plates for TLC and silica gel (200–300 mesh) for column chromatography (CC) were obtained from Qingdao Haiyang Chemical Group Co. Ltd (Qingdao, China). All other chemical reagents were purchased from Shanghai Chemical Reagent Co. Ltd (Shanghai, China).

3.2 Preparation of red yeast rice

Red yeast rice was obtained by fermentation of moistened rice, with a strain

Table 1. ^{1}H and ^{13}C NMR spectral data of **1** and **2** ($CDCl_3$, δ, J in Hz).[a]

	1		**2**	
Position	δ_C	δ_H, J	δ_C	δ_H, J
1	41.5 (CH)	1.45	39.9 (CH)	1.01
2	31.4 (CH)	2.30	31.9 (CH)	2.24
3	132.8 (CH)	5.72 (dd, J = 9.6, 5.9)	132.4 (CH)	5.59 (ddd, J = 9.8, 4.8, 2.7)
4	128.4 (CH)	5.91 (d, J = 9.6)	131.6 (CH)	5.30 (br d, J = 9.8)
4a	136.4 (C)	–	37.3 (CH)	1.96
5	130.7 (CH)	5.44 (m)	38.9 (CH_2)	1.47 (m, Hα), 1.27 (td, J = 13.0, 4.8, Hβ)
6	28.7 (CH)	2.33	27.5 (CH)	1.98 (m)
7	29.3 (CH_2)	1.56 (Hα) 1.74 (dq, J = 13.5, 3.0, Hβ)	32.3 (CH_2)	1.56
8	22.5 (CH_2)	1.20 (br d, J = 13.5, Hα) 1.79 (m, Hβ)	23.6 (CH_2)	1.13 (qd, J = 12.4, 4.1, Hα) 1.56 (Hβ)
8a	34.9 (CH)	2.08	41.0 (CH)	1.56
9	13.8 (CH_3)	0.90 (d, J = 7.0)	14.9 (CH_3)	0.85 (d, J = 7.0)
10	21.2 (CH_3)	0.99 (d, J = 7.1)	18.2 (CH_3)	0.98 (d, J = 7.2)
11	24.4 (CH_2)	1.45, 2.04	23.8 (CH_2)	1.38 (m), 1.96
12	31.7 (CH_2)	2.25, 2.44 (ddd, J = 15.4, 9.8, 4.9)	32.0 (CH_2)	2.24, 2.42 (ddd, J = 15.7, 10.3, 5.2)
13	180.0 (C)	–	180.3 (C)	–

Note: [a]Overlapped signals are reported without designating multiplicity.

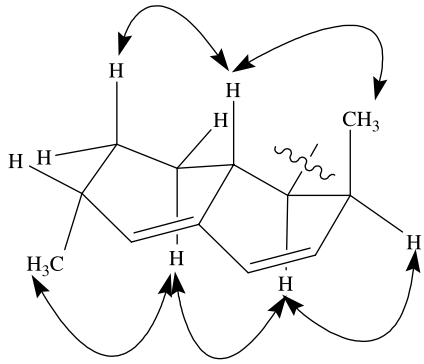

Figure 2. The key ROESY correlations of **1**.

of *M. purpureus* for 9 days at 25°C, at a pH range of 5–6.

3.3 Extraction and isolation

Dried and powdered red yeast rice (10 kg) was extracted three times with 95% ethanol at room temperature (3× 10 liters). The extracts were combined and concentrated under vacuum to yield the crude extract (800 g). The residue was suspended in 20% ethanol, and then successively partitioned with petroleum ether and ethyl acetate, respectively. After removing the solvent, the ethyl acetate extract (500 g) was separated by silica gel CC using gradient mixtures of *n*-hexane–ethyl acetate (100:0 → 0:100) as eluants to yield 15 fractions (1–15). Fraction 2 was then subjected to silica gel CC eluting with *n*-hexane–ethyl acetate (100:0 → 10:1) to afford **1** (60 mg) and a mixture. The mixture containing compound **2** was recrystallized with ethyl acetate to yield **2** (50 mg).

3.3.1 Compound *1*

Colorless needles, mp 119–120°C; $[\alpha]_D^{20}$ +220.2 ($c = 0.14$, MeOH); UV (MeOH) λ_{max} (log ε): 231 (4.30), 238 (4.41), 247 (4.20) nm; IR (KBr) ν_{max}: 3429 (OH), 2964 and 2918 (CH), 1698 (C═O), 1446 (CH_2), 1371 (CH_3), 955, 860, 763, 615 cm^{-1}; ^1H and ^{13}C NMR spectral data, see Table 1; HR-ESI-MS: *m/z* 233.1545 $[M-H]^-$ (calcd for $C_{15}H_{21}O_2$, 233.1547).

3.3.2 Compound *2*

Colorless needles, mp 131–132°C; $[\alpha]_D^{20}$ +118.7 ($c = 0.11$, MeOH); UV (MeOH) λ_{max} (log ε): end absorption; IR (KBr) ν_{max}: 3020, 2964, and 2908 (CH), 1697 (C═O), 1446 (CH_2), 1378 (CH_3), 956, 721 cm^{-1}; ^1H and ^{13}C NMR spectral data, see Table 1; HR-ESI-MS: *m/z* 235.1700 $[M-H]^-$ (calcd for $C_{15}H_{23}O_2$, 235.1704).

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