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Rare merosesquiterpenoids from basidiomycete *Craterellus odoratus* and their inhibition of 11β-hydroxysteroid dehydrogenases

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ABSTRACT

Rare merosesquiterpenoids, craterellins A–C (**1**–**3**), were isolated from cultures of basidiomycete *Craterellus odoratus* together with the previously known massarinolin C (**4**). Structures of **1**–**3** were elucidated on the basis of extensive spectroscopic analysis. Compounds **1**–**3** possess a rare, epoxymethylenecyclohexanetriol-bicyclofarnesane sesquiterpene hybrid skeleton. Compounds **1**–**4** were evaluated for their inhibitory activities against two isozymes of 11β-hydroxysteroid dehydrogenases (11β-HSD1 and 11β-HSD2).

1. Introduction

The fungus *Craterellus odoratus* (Schwein.) Fr. (Cantharellaceae) is characterized by possessing a bright orange or yellow cap. In mainland China, this mushroom is widespread, although it has not been chemically investigated. Over the last 10 years, our research has been focusing on bioactive secondary metabolites from the untapped resources of higher fungi collected in China (Liu, 2005, 2006; Liu et al., 2007; Zhou et al., 2008). The present study on cultures of *C. odoratus* led to the isolation of three new compounds craterellins (A–C) (**1**–**3**), which are rare merosesquiterpenoids characterized by a hybrid of methyl hydroquinone and bicyclofarnesane. Thus far, no more than 10 of these merosesquiterpenes have been reported (Sassa and Yoshikoshi, 1983; Sassa and Nukina, 1984; Ayer et al., 1990; Fujimoto et al., 2001). Also massarinolin C (**4**) was obtained. Compounds **1**–**4** were tested for their inhibitory activities against two isozymes of 11β-hydroxysteroid dehydrogenases (11β-HSD).

2. Results and discussion

Compound **1** was obtained as a white powder. Its molecular formula was determined to be $C_{22}H_{34}O_4$ on the basis of a positive-ion HRESIMS at *m/z* 385.2357 (calcd. for $C_{22}H_{34}O_4Na$, 385.2354) and the ^{13}C NMR (DEPT) spectrum. The IR spectrum showed absorptions at 3406 and 1640 cm^{-1}, indicating a presence of hydroxyl group and double bond. The ^{13}C NMR spectrum (Table 2) exhibited 22 carbon signals, including two trisubstituted double-bond resonances at δ 138.6 (s), 123.1 (d); 136.4 (s), and 122.8 (d). Also observed were five oxygen-bearing carbons at δ 67.9 (d), 66.3 (d), 63.0 (t), 62.0 (s), and 58.6 (d), and four methyl signals at δ 33.7 (q), 22.4 (q), 22.3 (q), and 14.3 (q). The NMR spectroscopic data of **1** (Tables 1 and 2) were similar to those of macrophorin A (Sassa and Yoshikoshi, 1983). A significant difference was that the C-1′ keto carbonyl signal of macrophorin A was absent in **1**. The resonance was replaced by oxygenated methine resonances at δ_C 67.9 (d, C-1′) and δ_H 4.19 (br. s, H-1′). Furthermore, instead of a terminal double bond signal, resonances appeared at δ_C 136.4 (s, C-8), 122.8 (d, C-7), and 22.4 (q, C-12). The keto carbonyl group of macrophorin A was reduced to a hydroxyl group in **1**. The terminal double bond was changed into a trisubstituted olefin moiety. This was further supported by the HMBC correlations, in which correlations of H-1′ to C-2′, C-3′, C-5′ and C-6′ were observed. There were also

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Table 1
^{1}H NMR spectroscopic data (500 MHz, CD_3OD) of compounds **1–3**.

No.	1	2	3
1	0.93 (1H, ddd, 13.3, 12.9, 2.7, H_α)	1.09 (1H, ddd, 12.9, 12.5, 4.7, H_α)	0.90 (1H, m, H_α)
	1.83 (1H, m, H_β)	1.86 (1H, m, H_β)	1.80 (1H, br. d, 13.5, H_β)
2	1.46 (1H, m, H_α)	1.61 (2H, m)	1.45 (1H, m, H_α)
	1.59 (1H, m, H_β)		1.57 (1H, m, H_β)
3	1.20 (1H, m, H_α)	3.18 (1H, dd, 10.7, 5.0)	1.19 (1H, m, H_α)
	1.43 (1H, br. d, 12.7, H_β)		1.42 (1H, br. d, 12.9, Hβ)
5	1.22 (1H, dd, 12.3, 4.5)	1.21 (1H, dd, 10.4, 6.3)	1.20 (1H, m)
6	1.88 (1H, m, H_β)	1.98 (2H, m)	1.86 (1H, m, H_β)
	1.99 (1H, br. d, 17.4, H_α)		1.97 (1H, m, H_α)
7	5.39 (1H, br. s)	5.40 (1H, br. s)	5.36 (1H, br. s)
9	1.59 (1H, m)	1.58 (1H, m)	1.48 (1H, m)
11	1.85 (1H, m)	1.87 (1H, m)	1.93 (1H, br. d, 16.0)
	2.14 (1H, br. d, 15.8)	2.12 (1H, br. d, 15.5)	2.00 (1H, dd, 16.0, 8.3)
12	1.67 (3H, br. s)	1.67 (3H, br. s)	1.65 (3H, br. s)
13	0.87 (3H, s)	0.96 (3H, s)	0.86 (3H, s)
14	0.90 (3H, s)	0.84 (3H, s)	0.89 (3H, s)
15	0.81 (3H, s)	0.81 (3H, s)	0.80 (3H, s)
1′	4.19 (1H, br. s)	4.19 (1H, br. s)	3.49 (1H, d, 7.6)
2′	5.68 (1H, br. s)	5.68 (1H, br. s)	3.81 (1H, br. d, 7.6)
4′	4.56 (1H, br. s)	4.56 (1H, br. s)	4.53 (1H, br. s)
5′	3.25 (1H, br. s)	3.24 (1H, br. d, 1.6)	3.12 (1H, br. s)
7′	4.12 (1H, br. d, 14.3)	4.12 (1H, br. d, 14.1)	5.24 (1H, br. s)
	4.20 (1H, br. d, 14.3)	4.20 (1H, br. d, 14.1)	5.27 (1H, br. s)

Table 2
^{13}C NMR spectroscopic data (125 MHz, CD_3OD) of compounds **1–3**.

No.	1	2	3
1	40.7 (t)	38.8 (t)	40.6 (t)
2	19.8 (t)	28.1 (t)	19.8 (t)
3	43.5 (t)	79.8 (d)	43.5 (t)
4	33.9 (s)	39.8 (s)	33.9 (s)
5	51.6 (d)	51.1 (d)	51.6 (d)
6	24.9 (t)	24.6 (t)	24.9 (t)
7	122.8 (d)	122.8 (d)	122.6 (d)
8	136.4 (s)	136.3 (s)	136.7 (s)
9	48.1 (d)	48.0 (d)	47.9 (d)
10	37.3 (s)	37.1 (s)	37.3 (s)
11	27.3 (t)	27.3 (t)	26.4 (t)
12	22.4 (q)	22.3 (q)	22.3 (q)
13	33.7 (q)	28.6 (q)	33.7 (q)
14	22.3 (q)	15.7 (q)	22.3 (q)
15	14.3 (q)	14.3 (q)	14.3 (q)
1′	67.9 (d)	67.8 (d)	76.8 (d)
2′	123.1 (d)	123.1 (d)	75.5 (d)
3′	138.6 (s)	138.6 (s)	146.7 (s)
4′	66.3 (d)	66.3 (d)	70.3 (d)
5′	58.6 (d)	58.7 (d)	61.3 (d)
6′	62.0 (s)	62.0 (s)	61.5 (s)
7′	63.0 (t)	63.0 (t)	108.4 (t)

correlations between H-12 and C-7, C-8, C-9. The relative configuration of **1** was deduced by comparison with the NMR spectroscopic data of macrophorin A. From the ROESY spectrum, correlations were detected between H-4′/H-5′, H-5′/H-9, and H-5/H-9. The hydroxyl group at C-1′ was determined to be in an α configuration, because a ROESY correlation between H-1′ and H-5′ was not detected**.** The structure of **1** was established as shown in Fig. 1, and has been named craterellin A.

Compound **2** was purified as a colorless oil with a molecular formula of $C_{22}H_{34}O_5$, based on the positive-ion HRESIMS at *m/z* 401.2311 (calcd for $C_{22}H_{34}O_5Na$, 401.2303) and the ^{13}C NMR (DEPT) spectrum. The IR spectrum showed absorption bands for hydroxyl (3420 cm^{-1}) and double bond (1653 cm^{-1}) groups. The

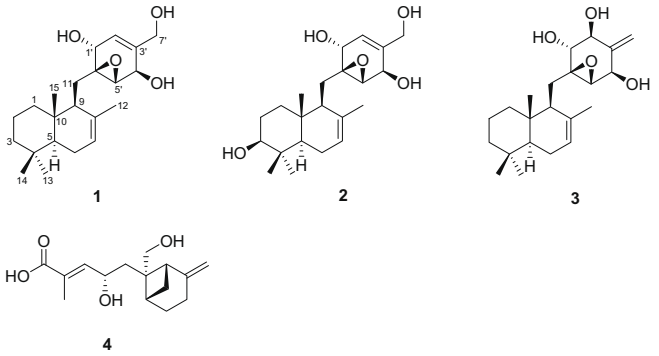

Fig. 1. Structures of compounds **1–4**.

NMR spectroscopic data (Tables 1 and 2) were similar to those of craterellin A (**1**). These findings suggested that **2** is also a merosesquiterpenoid derivative. The obvious differences were the characteristic oxymethine signals at δ_C 79.8 (d) and δ_H 3.18 (dd, J = 10.7, 5.0 Hz) that appeared in **2**, suggesting that the C-3 methylene of **1** was substituted by a β-hydroxy group. This conclusion was supported by the HMBC correlations from H-3 to C-13 and C-14. It was further supported by the ROESY correlations from H-3 to H-5 and H-13. Consequently, structure **2** (craterellin B) was determined as shown in Fig. 1.

Compound **3** was obtained as a white powder. The HRESIMS of **3** showed an $[M+Na]^+$ quasi-molecular ion peak at *m/z* 385.2345, corresponding to the molecular formula $C_{22}H_{34}O_4$, and representing six degrees of unsaturation. The IR spectrum displayed absorption bands diagnostic of hydroxy (3425 cm^{-1}) and double bond (1630, 892 cm^{-1}) functionalities. The NMR spectroscopic characteristics (Tables 1 and 2) were similar to those of craterellin A (**1**). The significant differences were that the trisubstituted double bond signals of **1** were replaced by the exocyclic double-bond resonances at δ_C 146.7 (s) and 108.4 (t), and oxygen-bearing methine signals at δ_C 75.5(d) and δ_H 3.81 (br. d, J = 7.6 Hz) that appeared in **3**, suggesting that the C-2′ was linked with a hydroxyl group. This was supported by the HMBC correlations from the proton at δ_H 3.81 (br. d, J = 7.6 Hz) to C-1′, C-3′ and C-7′. The configuration of the hydroxyl group at C-2′ was determined to be in β because the ROESY correlations between H-2′ and H-4′, and typical *trans* coupling between H-1′ and H-2′. The structure of **3** (craterellin C) was established as shown in Fig. 1.

Compounds **4** was isolated as colorless oil. The NMR spectroscopic data were in accordance with massarinolin C (Oh et al., 1999).

No evidence is available concerning the absolute stereochemistry of the craterellins. The craterellins and related compounds in the literature are clearly derived from a farnesyl toly-hydroquinone precursor (Scheepers et al., 2006; Li et al., 2003; Son et al., 2002). It is not obvious whether the bicyclic nucleus is formed first followed by oxidative modifications of the tolylhydroquinone or the reverse order occurs.

Glucocorticoid hormones play important roles in many biological and physiological processes. They are regulated in a tissue-specific manner by 11β-hydroxysteroid dehydrogenase (11β-HSD1 and 11β-HSD2) enzymes. These enzymes catalyze the interconversion of active 11-hydroxyglucocorticoids (cortisol in humans and corticosterone in rodents) and their inert 11-keto forms (cortisone in humans and 11-dehydrocorticosterone in rodents) (Draper and Stewart, 2005). 11β-HSD1 is highly expressed in the liver, gonads, adipose tissue and brain. It serves to regenerate active glucocorticoids from inactive forms. Therefore, it amplifies local glucocorticoid actions (Seckl and Walker, 2001). In turn,

Table 3
Inhibitory activities of compounds **1**–**4** against isozymes of 11β-hydroxysteroid dehydrogenases.

Compounds	Mouse HSD1 IC_{50} (μg/mL)	Human HSD1 IC_{50} (μg/mL)	Mouse HSD2 (150 μg/mL) inhibition effect	Human HSD2 IC_{50} (μg/mL)
Glycyrrhizinic acid[a]	29.5	18.6		0.71
1	36.3	9.1	Inactive	1.5
2	54.8	3.5	Inactive	>100
3	93.3	14.8	Inactive	25.4
4	19.7	3.1	Inactive	10.6

[a] IC_{50} values in nM.

11β-HSD2 is predominantly expressed in aldosterone target cells, such as the kidney and colon, and catalyzes the inactivation of glucocorticoids, thereby preventing excessive activation of the mineralocorticoid receptor. Excessive activation would result in sodium retention, hypoglycemia, and hypertension.

Compounds **1**–**4** were tested for inhibitory activities against two isozymes of 11β-hydroxysteroid dehydrogenases (11β-HSD1 and 11β-HSD2). Among them, **1** demonstrated significant inhibitory activities against human 11β-HSD2 with IC_{50} value of 1.5 μg/mL (Table 3).

3. Concluding remarks

In conclusion, three new merosesquiterpenoids, craterellins A–C (**1**–**3**), were isolated from cultures of basidiomycete *Craterellus odoratus* together with the previously known massarinolin C (**4**). Compounds **1**–**3** possess a rare, epoxymethylenecyclohexanetriol-bicyclo-farnesane sesquiterpene hybrid skeleton. The discovery of compounds **1**–**3** is a further addition to the diverse merosesquiterpenoids. Their presence as markers may be helpful in chemotaxonomical classifications. The inhibitory activities against two isozymes of 11β-hydroxysteroid dehydrogenases (11β-HSD1 and 11β-HSD2) of compounds **1**–**4** were investigated.

4. Experimental

4.1. General experimental procedures

Optical rotations were obtained on a Horiba SEPA-300 polarimeter. IR spectra were taken on a Bruker Tensor 27 FT-IR spectrometer with KBr pellets. NMR spectra were recorded with a Bruker DRX-500 instrument in CD_3OD (δ_H 3.30 ppm, δ_C 49.00 ppm) at room temperature. FABMS and ESIMS (including HRESIMS) were measured on VG Auto Spec-3000 and API QSTAR Pulsar I mass spectrometers, respectively. Silica gel (200–300 mesh, Qingdao Marine Chemical Inc., People's Republic of China), RP-18 gel (40–75 μm, Fuji Silysia Chemical Ltd., Japan) and Sephadex LH-20 (Amersham Biosciences, Sweden) were used for column chromatography. Fractions were monitored by TLC. Spots were visualized by heating silica gel plates immersed in vanillin–H_2SO_4 in ethanol.

4.2. Fungal material and cultivation conditions

The fungus *C. odoratus* was collected from the southern part of the Gaoligong Mountains in Yunnan Province, People's Republic of China, in July 2007. The fungus was identified by Prof. Mu Zang at the Kunming Institute of Botany. A voucher specimen (HFG07004) was deposited at the Herbarium of Kunming Institute of Botany. The culture medium consisted of potato (peeled, 200 g), glucose (20 g), KH_2PO_4 (3 g), $MgSO_4$ (1.5 g), citric acid (0.1 g), and thiamine hydrochloride (10 mg), in 1 L sterilized H_2O. Reagent bottles were used as a flask (size: 500 mL; volume of media: 350 mL). The pH value was adjusted to 6.5 before autoclaving. Fermentation was carried out on a shaker at 22 °C and 140 rpm for 20 days.

4.3. Extraction and isolation

The culture broth (21 L) was extracted three times with EtOAc (3 × 7 L). The conbined EtOAc extracts were evaporated in vacuo to give a residue (3.0 g). The residue was subjected to silica gel column chromatography (CC) with a gradient elution system of petroleum ether–acetone (100:0–0:100) to obtain eight fractions. Fraction 5 was eluted with petroleum ether–acetone (5:1). It was then subjected to Sephadex LH-20 CC ($CHCl_3$–MeOH, 1:1) and silica gel CC ($CHCl_3$–MeOH, 50:1) to afford **1** (10.2 mg). Fraction 6 was eluted with petroleum ether–acetone (5:1). It was subjected to Sephadex LH-20 ($CHCl_3$–MeOH, 1:1) and silica gel CC ($CHCl_3$–MeOH, 20:1) to yield **2** (7.0 mg). Fraction 7 was eluted with petroleum ether-acetone (2:1). It was then subjected to Sephadex LH-20 ($CHCl_3$–MeOH, 1:1) and silica gel CC to afford fractions 7a ($CHCl_3$–MeOH, 60:1) and 7b (MeOH). Fraction 7a was evaporated to dryness. The residue was recrystallized from $CHCl_3$–MeOH to give **3** (4.1 mg). Fraction 7b was separated by C_{18} CC (MeOH–H_2O, 40:60) to afford **4** (6.0 mg).

4.4. Craterellin A (*1*)

White amorphous powder; $[\alpha]_D^{26}$ −37.5 (*c* 0.24, MeOH); IR (KBr) ν_{max} cm^{-1}: 3405, 2949, 2920, 2865, 2845, 1640, 1457, 1387, 1364, 1268, 1209, 1156, 1079, 1020; for ^1H and ^{13}C NMR spectroscopic data, see Tables 1 and 2; ESIMS (pos.) *m/z*: 385 ($[M+Na]^+$); HRESIMS (pos.) *m/z*: 385.2357 (calcd. for $C_{22}H_{34}O_4Na$ 385.2354).

4.5. Craterellin B (*2*)

Colorless oil; $[\alpha]_D^{26}$ −27.5 (*c* 0.09, MeOH); IR (KBr) ν_{max} cm^{-1}: 3420, 2927, 1653, 1444, 1384, 1060, 1022; for ^1H and ^{13}C NMR spectroscopic data, see Tables 1 and 2; ESIMS (pos.) *m/z*: 401 ($[M+Na]^+$); HRESIMS (pos.) *m/z*: 401.2311 (calcd. for $C_{22}H_{34}O_5Na$ 401.2303).

4.6. Craterellin C (*3*)

White amorphous powder; $[\alpha]_D^{26}$ +23.1 (*c* 0.07, MeOH); IR (KBr) ν_{max} cm^{-1}: 3425, 2924, 1630, 1459, 1386, 1021, 892; for ^1H and ^{13}C NMR spectroscopic data, see Tables 1 and 2; ESIMS (pos.) *m/z*: 385 ($[M+Na]^+$); HRESIMS (pos.) *m/z*: 385.2345 (calcd. for $C_{22}H_{34}O_4$ 385.2354).

4.7. Massarinolin C (*4*)

Colorless oil; lit (Oh et al., 1999) $[\alpha]_D^{27}$ +6.3 (*c* 0.8, MeOH); for ^1H and ^{13}C NMR data are in accordance with the reported data (Oh et al., 1999). FABMS (neg.) *m/z*: 265 ($[M-H]^-$).

4.8. Bioassay

The inhibitory activities of the compounds on human or mouse 11β-HSD1 and 11β-HSD2 were determined using scintillation proximity assay (SPA). Microsomes containing 11β-HSD1 or 11β-HSD2 were used according to our previous studies (Yang et al., 2008). The full-length cDNAs of human or murine 11β-HSD1 and 11β-HSD2 were isolated from the cDNA libraries provided by NIH Mammalian Gene Collection. The cDNAs were cloned into pcDNA3 expression vectors. HEK-293 cells were transfected with the pcDNA3-derived expression plasmid and selected by cultivation in the presence of 700 μg/mL of G418. The microsomal fraction

overexpressing 11β-HSD1 or 11β-HSD2 was prepared from the HEK-293 cells, which were stable transfected with 11β-HSD1 or 11β-HSD2. The fraction was then used as the enzyme source for SPA. Microsomes containing human or mouse 11β-HSD1 were incubated with NADPH and [^{3}H]cortisone. The product, [^{3}H]cortisol, was specifically captured by a monoclonal antibody coupled to protein A-coated SPA beads. The 11β-HSD2 screening was performed by incubating 11β-HSD2 microsomes with [^{3}H]cortisol and NAD^+ and monitoring substrate disappearance. IC_{50} values were calculated by using Prism Version 4 (GraphPad Software, San Diego, CA).

All tests were done in triplicate with glycyrrhizinic acid as a positive control. IC_{50} ($X \pm SD$, $n = 3$) values were calculated by using Prism Version 4 (GraphPad Software, San Diego, CA). The IC_{50} values of glycyrrhizinic acid (positive control) were 29.5, 18.6 and 0.71 *n*M for mouse 11β-HSD1, human 11β-HSD1, and human 11β-HSD2, respectively.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.phytochem.2009.09.020.

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