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Cytotoxic constitutents from *Cryptocarya maclurei*

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ABSTRACT

A phytochemical study of *Cryptocarya maclurei* led to isolation of five flavanones, cryptogiones G–H, and a polyketide, cryptomaclurone. The structures of the isolates were elucidated by analysis of the 1D and 2D NMR spectroscopic data, and their absolute configurations were determined by CD methods. A putative biosynthetic pathway to them is proposed. Cytotoxicity of these compounds evaluated against KB, SGC-7901 and SW 1116 cancer cell lines, with only cryptomaclurone exhibiting moderate cytotoxicity (IC_{50} 28.2, 28.4 and 16.4 μM, respectively).

1. Introduction

The genus *Cryptocarya* (Lauraceae) comprises a group of about 250 species of mostly evergreen trees, widely distributed in tropical and subtropical regions. Previous phytochemical investigations on the genus established the presence of numerous different classes of natural products, e.g., flavonoids (Chou et al., 2010; Dumontet et al., 2001; Kurniadewi et al., 2010; Feng et al., 2012; Govindachari and Parthasarathy, 1972; Govindachari et al., 1973), pyrones (Davis et al., 2010; Grkovic et al., 2011; Meragelman et al., 2009), pavines (Lee et al., 1990; Lin et al., 2002; Wu and Lin, 2001) and aporphines (Awang et al., 2008; Lee and Chen, 1993; Wu and Lin, 2001), many of which exhibited cytotoxic (Chou et al., 2010; Dumontet et al., 2001), nuclear factor-κB (NF-κB) inhibitory (Feng et al., 2012; Meragelman et al., 2009), or antitrypanosomal (Davis et al., 2010) activities. *Cryptocarya maclurei* Merr., collected in southern China, is not, however, used as a folk medicine in China. A previous study on *Cryptocarya chingii* led to isolation of several flavonoids with significant NF-κB inhibitory activity (Feng et al., 2012). As part of our effort to obtain bioactive natural products from tropical plants (Feng et al., 2012; Ge et al., 2012; Qin et al., 2011), five new flavanones, cryptogiones G–K (**1**–**5**), and a new polyketide, cryptomaclurone (**6**) (Fig. 1), were isolated from the organic extract of the stems of *C. maclurei*. The structures of the isolates were elucidated using a combination of ^1H and ^{13}C NMR and HRESIMS analysis. The absolute configurations of the new compounds were established by CD methods. Cytotoxicity was also evaluated against KB, SGC-7901, and SW 1116 cancer cell lines.

2. Results and discussion

Compound **1** was isolated as a colorless oil with a molecular formula of $C_{17}H_{16}O_6$, as determined by HRESIMS (*m*/*z* 339.0845 $[M+Na]^+$). The flavanone structure of **1** was indicated by its UV absorptions at 201 and 271 nm (Lenta et al., 2009; Zhao et al., 2007). The ^1H NMR showed signals due to a monosubstituted aromatic ring [δ_H 7.42 (m, H-3′/H-4′/H-5′), 7.57, (m, H-2′/H-6′), ring B], an ABX system in ring C [δ_H 5.61 (dd, *J* = 13.8, 3.6 Hz, H-2), 2.66 (dd, *J* = 3.6, 16.8 Hz, H-3), and 2.89 (dd, *J* = 13.8, 16.8 Hz, H-3)], four methine groups [δ_H 3.47 (q, *J* = 8.1 Hz, H-5), 4.87 (dd, *J* = 3.0, 8.1 Hz, H-6), 4.14 (dd, *J* = 7.2, 3.0 Hz, H-7), δ_H 4.37 (br d, *J* = 7.2 Hz, H-8)] and one methylene group [δ_H 2.37 (dd, *J* = 8.1, 17.1 Hz, H-11) and 2.82 (dd, *J* = 8.1, 17.1 Hz, H-11)] (Table 1). The ^{13}C NMR and HMQC spectra displayed signals ascribable to six aromatic carbons, two carbonyl group (δ_C 176.2, 191.0), a double bond (δ_C 111.4, 168.0), two methylenes (δ_C 42.3, 35.9), and five methine groups (δ_C 80.1, 31.7, 76.7, 70.6, 70.1). A substituted cyclohexene (ring A) was deduced from ^1H–^1H COSY correlations between H-8/H-7/H-6/H-5/H-11, and HMBC correlations between H-5/C-10, H-6/C-9, H-7/C-10, and H-8/C-9 (Fig. 2). The ester carbonyl group displayed HMBC correlations with H-5, H-6 and both H-11 proton signals, which indicated the presence of a γ-lactone. Furthermore, HMBC correlations were observed between H-2/C-2′(6′), C-4, C-9; H-3/C-10; and H-2′(6′)/C-2, suggesting ring A and ring B were connected via C-2 and C-1′. Finally, two hydroxyl groups at δ_H 4.91 and

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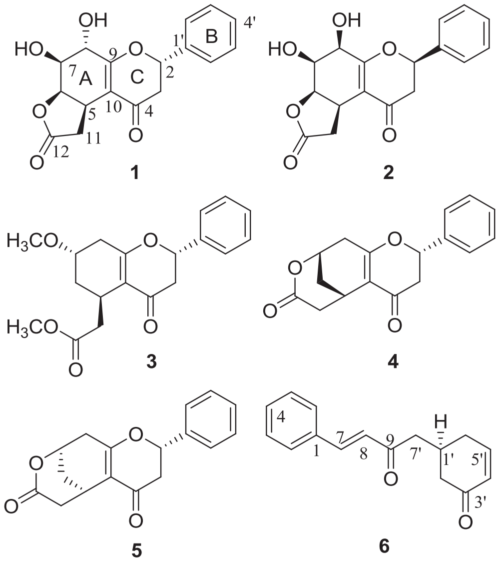

Fig. 1. Structures of **1**–**6**.

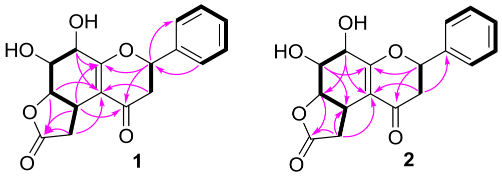

Fig. 2. Key HMBC (→), COSY (—) correlations of **1** and **2**.

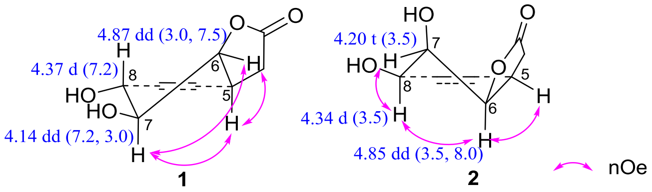

Fig. 3. Relative configurations of A ring in **1** and **2**.

5.32 were assigned to C-7 and C-8, respectively, according to their ^{1}H–^{1}H COSY correlations between 7-OH/H-7 and 8-OH/H-8.

The relative configuration of ring A was determined by ^{1}H NMR coupling constants and ROESY data (Fig. 3). The $^3J_{7,8}$ value of 7.2 Hz suggested that H-7 and H-8 were *trans*-diaxially oriented. The equatorial orientation of H-6 was inferred from the ^3J coupling constant of 3.0 Hz for H-6/H-7. In the ROESY spectrum, H-7 displayed correlation with H-5, indicating the cofacial orientation of the two protons.

The 2*S* configuration was indicated by CD spectra (Fig. 4), which showed a positive Cotton effect at 339 nm due to the $n \rightarrow \pi^*$ translation (Gaffield, 1970; Kim and Lee, 2006; Slade et al., 2005). The absolute configuration of the 7,8-diol moiety was determined by the *in situ* dimolybdenum CD method developed by Frelek, which employed $Mo_2(AcO)_4$ to generate an auxiliary chromophore (Di Bari et al., 2001; Frelek et al., 2003; Górecki et al., 2006, 2007). According to the empirical rule proposed by Snatzke (Frelek et al., 1993; Snatzke, 1979), the absolute configuration of a *vic*-diol can be deduced by the band around 310 nm (band IV) in the $Mo_2(AcO)_4$-induced CD spectrum, which originates from the chirality of the *vic*-diol expressed by the sign of the O–C–C–O torsion angle. The inherent CD contribution was subtracted to give the induced CD of the metal complex (Fig. 4). Thus, assignment of the 7*S* and 8*S* was suggested by the negative Cotton effect observed at 310 nm in the induced CD spectrum. Therefore, the structure of cryptogione G (**1**) was determined as shown in Fig. 1.

Compound **2** was obtained as a colorless oil. The ^{1}H and ^{13}C NMR spectra were almost identical to those of **1**, indicating it as a diastereomer of **1** (Table 1). Its CD spectrum showed a negative Cotton effect at 330–370 nm, indicating that **2** has a 2*R* configuration

Table 1
^{1}H and ^{13}C NMR data for **1**–**3**.

Position	**1**[a]		**2**[b]		**3**[c]	
	δ_H (*J* in Hz)	δ_C	δ_H (*J* in Hz)	δ_C	δ_H (*J* in Hz)	δ_C
2	5.61 dd (3.6, 13.8)	80.1	5.51 dd (3.5, 14.5)	82.0	5.35 dd (14.5, 3.0)	80.0
3	2.66 dd (3.6, 16.8)	42.3	2.61 dd (3.5, 17.0)	43.6	2.88 dd (14.5, 17.0)	43.3
	2.89 dd (13.8, 16.8)		2.98 dd (14.5, 17.0)		2.66 dd (17.0, 3.0)	
4		191.0		192.6		190.8
5	3.47 q (8.1)	31.7	3.56 q (10.0)	32.5	3.27 m	26.9
6	4.87 dd (3.0, 8.1)	76.7	4.85 dd (3.5, 10.0)	77.0	1.80 m	31.7
					1.94 m	
7	4.14 dd (7.2, 3.0)	70.6	4.20 t (3.5)	71.2	3.71 m	72.1
8	4.37 br d (7.2)	70.1	4.34 br d (3.5)	71.2	2.66 m	34.9
					2.45 dd (18.0, 6.0)	
9		168.0		168.5		169.7
10		111.4		112.4		114.3
11	2.37 dd (8.1, 17.1)	35.9	2.32 dd (10.0, 17.0)	35.6	2.93 dd (15.0, 4.0)	39.3
	2.82 dd (8.1, 17.1)		2.79 dd (10.0, 17.0)		2.40 dd (15.0, 9.5)	
12		176.2		177.5		172.8
1′		138.8		139.8		138.3
2′, 6′	7.56 m	126.4	7.55 d (7.5)	127.4	7.43 m	126.2
3′,5′	7.42 m	128.6	7.45 t (7.5)	129.5	7.43 m	128.8
4′	7.42 m	128.6	7.40 t (7.5)	129.5	7.43 m	128.8
7-OH	4.91 br s		5.34 br.s			
8-OH	5.32 br s		4.99 br.s			
7-OMe					3.39 s	56.1
12-OMe					3.73 s	51.5

[a] Recorded in Acetone-d_6 at 500 MHz for ^{1}H NMR, 75 MHz for ^{13}C NMR, δ in ppm, *J* in Hz.
[b] Recorded in Acetone-d_6 at 500 MHz for ^{1}H NMR, 125 MHz for ^{13}C NMR, δ in ppm, *J* in Hz.
[c] Recorded in $CDCl_3$ at 500 MHz for ^{1}H NMR, 125 MHz for ^{13}C NMR, δ in ppm, *J* in Hz.