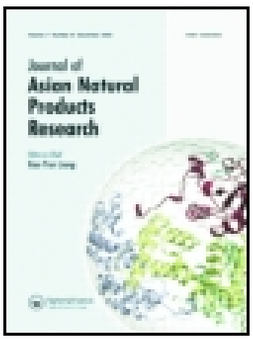

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Chemical constituents from *Piper hainanense* and their cytotoxicities

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ABSTRACT

Two new compounds, (*Z,R*)-1-phenylethylcinnamate (**1**) and (*1R,2R,3R,6S*)-pipoxide (**2**) were isolated from the aerial part of *Piper hainanense*, along with 12 known compounds, including nine benzene derivatives (**4–11**), one isobutylamide (**12**), and two polyoxygenated cyclohexene derivatives (**13–14**). Their structures were elucidated on the basis of the HRESIMS, 1D and 2D NMR spectroscopic analyses, and ECD in cases of **2** and **3**. The absolute configuration of ellipeiopsol B (**3**) was determined for the first time. All these compounds **1–14** were reported from the titled plant for the first time. Most of the isolates were tested for their cytotoxicities against five human cancer cell lines. Four of which, **2**, **3**, **9**, **14** showed moderate bioactivities. Among them, the new compound **2** showed potential cytotoxicity against SMMC-7721, MCF-7, and SW-480 with IC_{50} values of 9.7, 15.0, and 13.2 μM, respectively.

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KEYWORDS
Piperaceae; *Piper hainanense*; cytotoxicity; polyoxygenated cyclohexene derivatives; benzene derivatives; pipoxide

1. Introduction

The genus of *Piper* (Piperaceae) is widely distributed throughout the tropical and subtropical region. Due to the special flavor and taste, as well as various beneficial effects on human health, e.g. antifungal, anti-depression, anti-platelet aggregation, antiepileptic, and hepato-protective activities, piper plants have always attracted most attention [1]. The fruits from some piper plants are famous spices, while the stems or leaves of some species have been used as Chinese herbal medicines for the treatment of rheumatoid arthritis, inflammatory diseases, cerebral infarction, and angina. Previous phytochemical investigations on this genus indicated that piper alkaloids and phenolic compounds with potential bioactivities are the main characteristic metabolites [2,3].

P. hainanense, an endemic *Piper* species in China, grows widely in Hainan, Guangxi, and Guangdong provinces of China [4]. During our search for bioactive compounds from the

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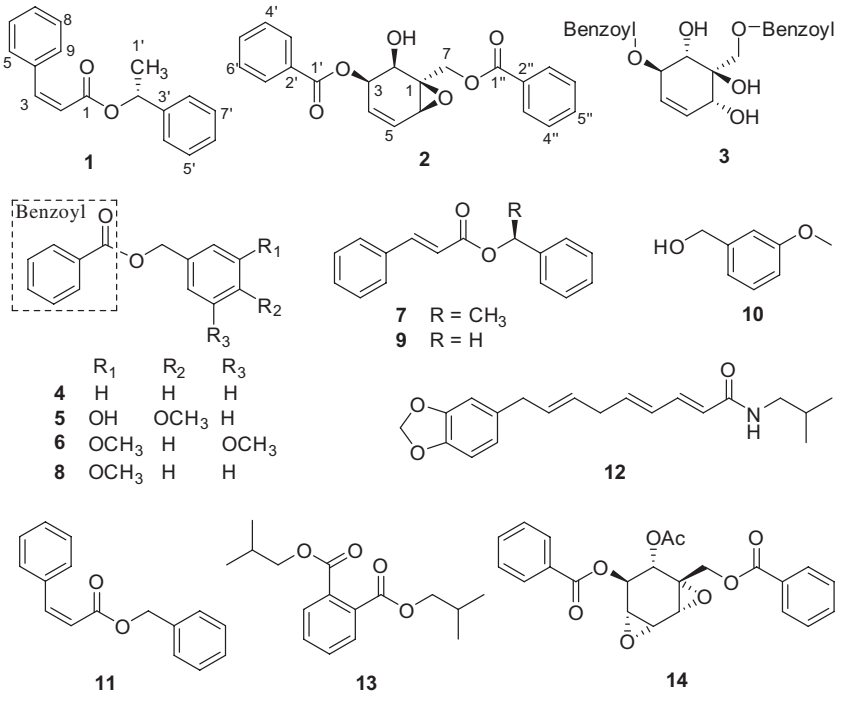

Figure 1. Chemical structures of compounds **1–14**.

Table 1. ^{1}H (600 MHz) and ^{13}C (150 MHz) NMR spectroscopic data for compound **1** ($CDCl_3$).

No.	δ_C, m	δ_H, m., *J* (Hz)	No.	δ_C, m	δ_H, m., *J* (Hz)
1	165.4, s		1′	22.1, q	1.54 (d, 6.6)
2	120.1, d	6.00 (d, 12.6)	2′	72.4, d	5.95 (q, 6.6)
3	143.2, d	6.97 (d, 12.6)	3′	141.4, s	
4	134.9, s		4′,8′	126.2, d	7.33 (overlap)
5	129.6, d	7.53 (brd, 7.2)	5′,7′	128.0, d	7.33 (overlap)
9	129.6, d	7.54 (brd, 7.2)			
6,8	128.4, d	7.31–7.34 (m)	6′	127.8, d	7.33 (overlap)
7	128.9, s	7.33 (overlap)			

piper plants [5,6], the aerial part of *P. hainanense* was chemically investigated, resulting in the isolation of 14 compounds (Figure 1). Compounds **1** and **2** are new ones, whose structures were elucidated by spectroscopic method. The absolute configuration of **3** was determined for the first time by ECD analysis. Most of the isolates were evaluated for their cytotoxicities against five human cancer cell lines (A-549 lung carcinoma, HL-60 myeloid leukemia, MCF-7 breast adenocarcinoma, SMMC-7721 hepatocellular carcinoma, and SW480 colon cancer), and the results obtained are discussed herein.

2. Results and discussion

Twelve known compounds were obtained and identified as ellipeiopsol B (**3**) [7], ascabiol (**4**) [8], 3-hydroxy-4-methoxybenzyl benzoate (**5**) [9], 3,5-dimethoxybenzyl benzoate (**6**) [10], (*E*,*S*)-1-phenyl- ethyl cinnamate (**7**) [11, 12], 3-methoxylbenzyl benzoate (**8**) [13], (*E*)-cinnamic acid benzyl ester (**9**) [14], (3-methoxy-phenyl)-methanol (**10**) [15], (*E*)-cinnamic

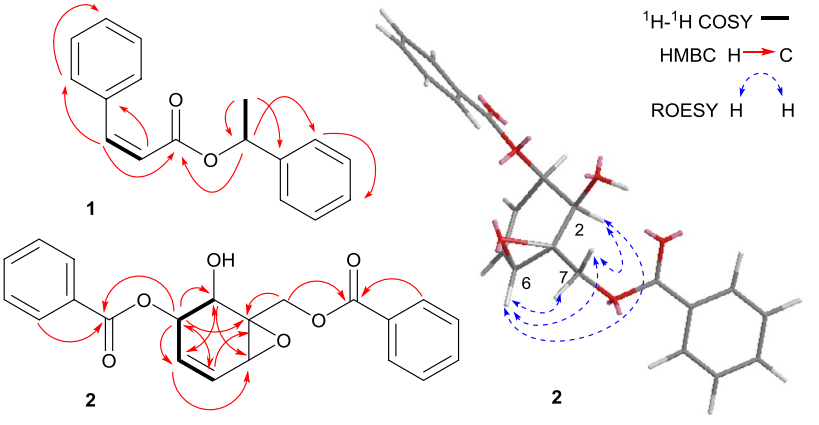

Figure 2. Key ^{1}H–^{1}H COSY, HMBC and ROESY correlations of compounds **1** and **2**.

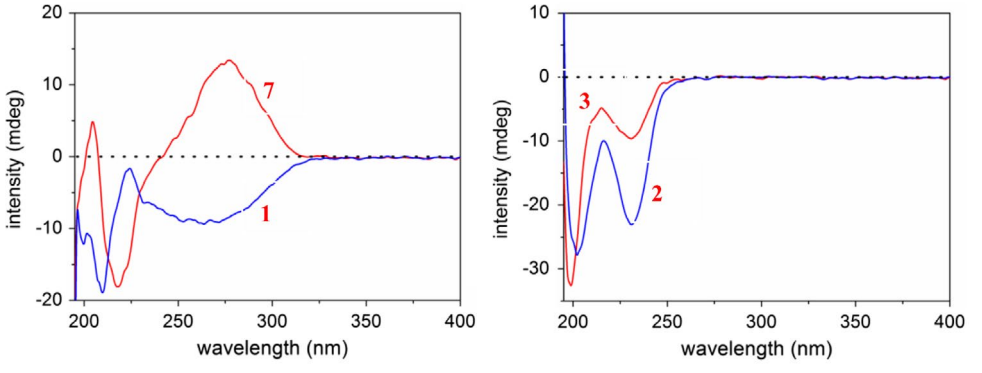

Figure 3. Experimental ECD spectra of compounds **1** (in blue) and **7** (in red), and **2** (in blue) and **3** (in red).

Table 2. ^{1}H (600 MHz) and ^{13}C (150 MHz) NMR spectroscopic data for compound **2** ($CDCl_3$).

No.	δ_C, m	δ_H, m, *J* (Hz)	No.	δ_C, m	δ_H, m, *J* (Hz)
1	64.3, s		2′	131.2[a],s	
2	67.1, d	4.44 (d, 2.3)	3′,7′	130.6[b], d	8.01[b] (br d, 7.3)
3	72.1, d	5.46 (dd, 5.8, 2.3)	4′,6′	129.6[c], d	7.41–7.45 (m)
4	129.4, d	6.11 (dd, 5.8, 9.8)	5′	134.4[d], d	7.54–7.58[d] (m)
5	131.4, d	6.44 (dd, 4.0, 9.8)	1″	167.5, s	
6	50.7, d	3.53 (d, 4.0)	2″	131.0[a], s	
7	65.2, t	5.04 (d, 12.2)	3″,7″	130.7[b], d	8.02[b] (br d, 7.3)
		4.38 (d, 12.2)	4″,6″	129.5[c], d	7.41–7.45 (m)
1′	167.3, s		5″	134.3[d], d	7.54–7.58[d] (m)

[a,b,c,d]Assignments may be interchanged.

acid benzyl ester (**11**) [16], laetispiamide A (**12**) [17], 2-methyl-propyl phthalate (**13**) [18], (+)-boesenoxide (**14**) [19], by comparison of their spectroscopic data with those reported in the literatures (Figure 1).

Compound **1** was obtained as a colorless oil. The molecular formula was established to be $C_{17}H_{16}O_2$ on the basis of HRESIMS at *m/z* 291.0782 $[M + K]^+$. Careful comparison of

the NMR data of **1** with (*E,S*)- (**7**) and (*E,R*)-1-phenylethyl cinnamate suggested that they were resembled with each other (Table 1) [11,12], except for the difference of the coupling constant and chemical shift of double bonds. In the ^{1}H NMR spectrum, the double bond signals at δ_H 6.00 and 6.97 (each 1H, d, J = 12.6 Hz, H-2, 3) were observed in **1**, while δ_H 6.65 and 7.74 (each 1H, d, J = 16.0 Hz, H-2,3) and 6.49 and 7.71 (each 1H, d, J = 16.0 Hz, H-2,3) were observed in **7** and (*E,R*)-1-phenylethyl cinnamate, respectively. The smaller coupling constant of 12.6 Hz suggested that the double bond in **1** should be *Z* rather than *E* in **7** and (*E,R*)-1-phenylethyl cinnamate. In the HMBC spectrum of **1**, correlations of H-1′ (δ_H 1.54) with C-2′ (δ_C 72.4) and C-3′ (δ_C 141.4), H-2′ (δ_H 5.95) with C-1 (δ_C 165.4) and C-4′ (δ_C 126.2), H-4′ (δ_H 7.33) with C-6′ (δ_C 127.8), H-3 (δ_H 6.97) with C-1 and C-5 (δ_C 129.6), H-2 (δ_H 6.00) with C-4 (δ_C 134.9), and H-5 (δ_H 7.53) with C-7 (δ_C 128.9) further constructed the planar structure of **1** (Figure 2). Furthermore, compound **1** was dextrorotatory ($[\alpha]_D^{20} - 174$) , whose specific rotation value compares conversely to that of **7** ($[\alpha]_D^{20} + 19$), but similar to that of (*E,R*)-1-phenylethyl cinnamate ($[\alpha]_D^{23} - 39$) [11]. The absolute configuration of **1** was proposed to be 2′*R*. The ECD spectral data (Figure 3) further supported that the absolute configuration of C-2′ was *R*. Thus, the structure of compound **1** was determined to be (*Z,R*)-1-phenylethyl cinnamate.

Compound **2** was isolated as a white amorphous powder, and possessed a molecular formula of $C_{21}H_{18}O_6$, as deduced by the positive HRESIMS (*m/z* 405.0733 $[M + K]^+$, calcd for $C_{21}H_{18}O_6$ K, 405.0735), indicating 13 degrees of unsaturation. The ^{13}C NMR spectrum displayed 21 carbon signals arising from two benzoyl groups (δ_C 167.3 -129.5), one double bond (δ_C 129.4, 131.4), one oxygenated methylene (δ_C 65.2), three oxygenated methines (δ_C 67.1, 72.1, and 50.7), and one quaternary carbon (δ_C 64.3) (Table 2). The aforementioned data were similar with those of ellipeiopsol B (**3**) [7]. However, **2** should have one more additional ring. The molecular weight of **2** was 16 Da lower than that of **3** further confirmed the existence of an oxane in **2**. The cyclohexene oxide skeleton was established by the ^{1}H-^{1}H COSY correlations of H-2/H-3/H-4/H-5, and the HMBC correlations from H-2 (δ_H 4.44) to C-1 (δ_C 64.3) and C-6 (δ_C 50.7), from H-3 (δ_H 5.46) to C-1, C-2 (δ_C 67.1), C-4 (δ_C 129.4) and C-5 (δ_C 131.4), from H-4 (δ_H 6.11) to C-2 and C-6, and from H-5 (δ_H 6.44) to C-1/C-3 (δ_C 72.1). The location of two benzoyl groups were at C-3 and C-1, respectively, as deduced by the HMBC correlations of H-3/H-3′ (δ_H 8.01) with C-1′ (δ_C 167.3), and H-7 (δ_H 5.04, 4.38) with C-1 (δ_C 64.3)/C-1" (δ_C 167.5), and H-3" (δ_H 8.02) with C-1" (Figure 2). The aforementioned data constructed the planar structure of **2**. The absolute configuration of **2** was performed by coupling constants, ROESY correlations, and ECD data. The small value of $J_{2,3}$ (2.3 Hz) suggested 2,3-*cis* configuration [20]. The oxane between C-1 and C-6 suggested that H-6 and the side chain at C-1 were at the same side. This was confirmed by the ROESY correlation between H-6 and H-7. Moreover, the ROESY correlations of H-2 with both H-7 and H-6 suggested that the oxane and hydroxyl group at C-2 were on the same side (Figure 2). The CD spectrum of **2** (Figure 3) exhibited a negative Cotton effects at 230 nm (Δε=-22.95) and 202 nm (Δε = -27.98), due to exciton coupling between the BzO group at C(3) and the nearby C = C bond (allylic benzoate), indicating 3*R* configuration [21]. On the basis of the above evidence, the absolute structure of **2** was characterized as (1*S*,2*R*,3*R*,6*S*)-pipoxide.

Compound **3**, a white amorphous powder, had a molecular formula of $C_{21}H_{18}O_6$, as determined by the positive HRESIMS (*m/z* 405.0733 $[M+K]^+$, calcd for $C_{21}H_{18}O_6$ K, 405.0735).

The ^{1}H and ^{13}C NMR data of **3** was the same as those of ellipeiopsol B [7], whose absolute configuration was not constructed. The relative configuration of **3** could be determined from the ROESY experiment and coupling constant. The ROESY correlations between H-2 and H-6, between H-3 and H-7, indicated that H-2 and H-6, and H-3 and H-7 were on the same side, respectively. The $J_{(2,3)}$ value of 8.3 Hz also indicated that H-C(2) and H-C(3) were *trans*. The experimental ECD spectrum of **3,** exhibiting the negative Cotton effects at 230 and 202 nm, were the same as those of **2**, suggesting that the absolute configuration of C-3 in **3** was *R*. Compound **3** was levorotatory ($[\alpha]_D^{20} - 322$), which compares favorably to those of **2** ($[\alpha]_D^{20} - 306$). Therefore, the absolute configuration of ellipeiopsol B (**3**) was determined for the first time to be 1*S*,2*S*,3*R*,6*R*.

Compounds **1–6**, **9**, and **11–14** were tested for their cytotoxicities against HL-60, SMMC-7721, A-549, MCF-7, and SW-480 cell lines. Among them, compounds **2**, **3**, **9**, and **14** showed cytotoxicities (Table 1 of Supporting Information). The new compound **2** (IC_{50} = 9.7, 15.0 and 13.2 μM, respectively) displayed stronger cytotoxicity against SMMC-7721, MCF-7, and SW-480 than the positive control, *cis*-platin (IC_{50} = 11.8, 18.3, and 18.1 μM, respectively).

In this study, two new compounds, (*Z,R*)-1-phenylethyl cinnamate (**1**) and (1*R*,2*R*,3*R*,6*S*)-pipoxide (**2**), were identified from the aerial parts of *P. hainanense*, along with 12 known compounds, which are reported from the titled plant for the first time. The absolute configuration of ellipeiopsol B (**3**) was determined for the first time. Most of the isolates were evaluated for their cytotoxicities against five cancer cell lines. It is noted that the polyoxygenated cyclohexene derivatives **2** and **3** displayed cytotoxicities against several human cancer cells. This kind of scaffold may present a new type of anticancer agents.

3. Experimental

3.1. General experimental procedures

Optical rotations were performed on a P-1020 polarimeter (JASCO, Tokyo, Japan). UV data were obtained on a Shimadzu UV2401PC spectrophotometer (Shimadzu, Kyoto, Japan). ECD spectra were measured on a Chirascan instrument (Applied Photophysics Ltd, UK). 1D- and 2D-NMR spectra were recorded on Bruker DRX-500 and AV-600 instruments (Bruker Biospin GmbH, Karlsruhe, Germany) operating at 500 and 600 MHz for ^{1}H NMR, and 125 and 150 MHz for ^{13}C NMR. Coupling constants are expressed in Hz, and chemical shifts are given on a ppm scale with tetramethylsilane as internal standard. ESIMS data were recorded on Waters Xevo TQ-S (Waters, Bremen, Germany). HRESIMS were recorded on an API Qstar Pulsa i spectrometer (Applied Biosystems, Framingham, MA, USA).

Column chromatography (CC) was performed with silica gel (200–300 mesh, Qingdao Marine Chemical Ltd. Qingdao, China), Sephadex LH-20 (25–100 μm, Pharmacia,Kyoto, Japan), Lichroprep RP-18 gel (40–63 μm, Merck, Darmstadt, Germany), MCI gel CHP20P (75–150 μm, Mitsubishi Chemical, Tokyo, Japan). Thin-layer chromatography (TLC) was carried out on silica gel H-precoated plates (Qingdao Marine Chemical Ltd., Qingdao, China). Spots were detected by spraying with 10% H_2SO_4 in EtOH followed by heating. Preparative HPLC (p-HPLC) was performed on a Gilson liquid chromatography (Gilson Inc, Wisconsin, USA) with a 7 μm Zorbax SB-C_{18} (21.2 × 250 mm) column (Agilent Technologies, Santa Clara, CA, USA). Semi p-HPLC separation was performed on an Agilent 1260 liquid chromatography (Agilent Technologies, Santa Clara, CA, USA) with a

5 μm Thermo BDS HYPERSIL-C_{18} column (10 × 250 mm)(Thermo Electron Corporation, New York, USA).

3.2. Plant material

The aerial parts of *Piper hainanense* were collected from Hainan Province, China, in July 2013, and were identified by Mr. Chao-Yun Hao from Chinese Academy of Tropical Agricultural Sciences. A voucher specimen (IBSC_0129146) was deposited at South China Botanical Garden, Chinese Academy of Sciences.

3.3. Extraction and isolation

The air-dried and powdered aerial parts of *P. hainanense* (1.3 kg) were extracted with methanol (60 °C). After concentrated to small volume (1 L) under reduced pressure, the methanol extract was partitioned with petroleum ether (3 × 1 L). The petroleum ether fraction (33 g) was chromatographed over silica gel (petroleum ether–EtOAc, 99:1→5:1, v/v) to give seven fractions (Fr. A–G). Fr. D (7 g) was applied to RP-18 (MeOH–H_2O) CC, preparative TLC (p-TLC) and p-HPLC to give **4** (185.6 mg) and **6** (13.0 mg). Fr. E (210 mg) was subjected to p-TLC and Semi p-HPLC to yield **1** (31.4 mg), **7** (9.2 mg), **9** (24.4 mg), and **11** (2.1 mg). Fr. F (105 mg) was separated by p-TLC to yield **8** (16.8 mg) and **10** (16.8 mg).

The concentrated methanol fraction was chromatographed over Sephadex LH-20 (MeOH–H_2O, 0:1 → 1:0, v/v) to afford 4 fractions (Fr. 1–4). Fr. 2 (70 g) was separated by MCI gel CHP20P (MeOH–H_2O, 4:6 →10:0, v/v) to give 12 fractions (Fr. 2A–2L). Further purification by silica gel ($CHCl_3$–EtOAc) CC and p-HPLC (55, 60, and 75% MeOH, and 75% ACN, v/v) to yield **5** (19.4 mg), **12** (24.4 mg) and **13** (25.0 mg), and **2** (19.8 mg), **14** (24.6 mg) and **3** (433.0 mg) from Fr. 2H and Fr.2 K, respectively.

3.3.1. (Z,R)-1-Phenylethyl cinnamate (1)

Colorless oil; $[\alpha]_D^{20}$ − 174 (*c* 0.61, MeOH); UV (MeOH) λ_{max} (logε): 268 (3.99), 204 (4.34) nm; ^1H and ^{13}C NMR spectral data, see Table 1; positive HRESIMS: *m/z* 291.0782 $[M+K]^+$ (calcd for $C_{17}H_{16}O_2$, 252.0782).

3.3.2. (1S,2R,3R,6S)-Pipoxide (2)

White amorphous powder; $[\alpha]_D^{20}$ − 306 (*c* 1.87, MeOH); UV (MeOH) λ_{max} (logε): 273 (3.26), 229 (4.43), 200 (4.34) nm; ^1H and ^{13}C NMR spectral data, see Table 2; positive HRESIMS: *m/z* 405.0733 $[M+K]^+$ (calcd for $C_{21}H_{18}O_6$, 366.0782).

3.4. Cytotoxic assay

The cytotoxic assay was performed using the MTT method, as previous method with slight modification [22]. Briefly, human tumor cells were seeded into 96-well plates and permitted to adhere for 12 h before drug addition. For suspended cells, they were seeded immediately before drug addition with an initial density of 5×10^4 cells/ml. Each cell line was incubated with different concentrations of the compounds for 48 h. DDP were used as positive controls. Cell viability was measured and IC_{50} values were calculated.

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Disclosure statement

No potential conflict of interest was reported by the authors.

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