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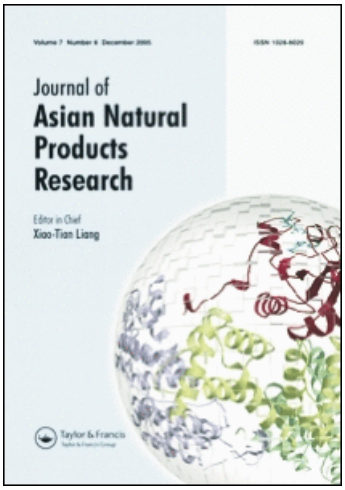

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Three novel terpenoids from the rhizomes of *Curcuma longa*

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Three novel terpenoids from the rhizomes of *Curcuma longa*

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Investigation of the EtOH extract of the rhizomes of *Curcuma longa* led to the isolation of two new sesquiterpenes, 2-methoxy-5-hydroxybisabola-3,10-diene-9-one (**1**) and 2,8-epoxy-5-hydroxybisabola-3,10-diene-9-one (**2**), one new monoterpene, 2-(2,5-dihydroxy-4-methylcyclohex-3-enyl)propanoic acid (**3**), together with five known sesquiterpenes (**4**–**8**). Among the known compounds, bisacurone A (**5**) and 4-methylene-5-hydroxybisabola-2,10-diene-9-one (**6**) were isolated from *C. longa* and genus *Curcuma* for the first time, respectively. Their structures were established on the basis of various spectroscopic analyses including HR-ESI-MS, 1D and 2D NMR, IR spectra, and by comparison of their spectral data with those of related compounds.

Keywords: *Curcuma longa*; sesquiterpene; monoterpene; 2-methoxy-5-hydroxybisabola-3,10-diene-9-one; 2,8-epoxy-5-hydroxybisabola-3,10-diene-9-one; 2-(2,5-dihydroxy-4-methylcyclohex-3-enyl)propanoic acid

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1. Introduction

Curcuma longa (Zingiberaceae family) is a perennial herb widely cultivated throughout Southeast Asia, especially in India and China. Its rhizomes have been used for centuries as a traditional herbal medicine in China, India, and Southeast Asia for the treatment of cold, diabetes, rheumatism, liver ailments, parasitic infections, skin diseases, inflammation conditions, and biliary disorders [1,2]. Chemical investigations revealed that the rhizomes of *C. longa* contained three main groups of compounds, curcuminoids, sesquiterpenes, and monoterpenes [2–8], which are responsible for the medicinal properties of this plant [9–11]. In recent years, the chemical and biochemical studies on *C. longa* available in the literature are mostly concerned with curcuminoids; however, other types of constituents have received limited attention. In spite of their rather simple structures, sesquiterpenes and monoterpenes possess a variety of commendable biological activities, such as antitumor, antioxidant, antinociceptive, antifungal, and antibacterial activities [12–16]. In our systematic research on the chemical constituents of *C. longa*, two new sesquiterpenes, 2-methoxy-5-hydroxybisabola-3,10-diene-9-one (**1**) and 2,8-epoxy-5-hydroxybisabola-3,10-diene-9-one (**2**), and one new monoterpene, 2-(2,5-dihydroxy-4-methylcyclohex-3-enyl) propanoic acid (**3**), were isolated along with five known sesquiterpenes, bisacurone (**4**), bisacurone A (**5**), 4-methylene-5-hydroxybisabola-2,10-diene-9-one (**6**), 2-methyl-6-(4-hydroxy-3-methylphenyl)-2-hepten-4-one (**7**), and turmeronol A (**8**).

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This paper describes the isolation and structural elucidation of these compounds.

2. Results and discussion

Compound **1** was obtained as a light yellow oil. Its positive-ion HR-ESI-MS showed two quasi-molecular ions $[M+Na]^+$ at *m/z* 289.1761 and $[M+H]^+$ at *m/z* 267.1962, corresponding to the molecular formula $C_{16}H_{26}O_3$. The IR absorption bands at 3398, 1682, and 1615 cm^{-1} indicated the presence of hydroxyl, α,β-unsaturated carbonyl, and double bond groups, respectively. The ^1H NMR spectrum (Table 1) showed signals of two olefinic protons at δ 6.17 (1H, s) and 5.56 (1H, s), three vinyl methyls at δ 2.10 (3H, s), 1.87 (3H, s), and 1.76 (3H, s), one methyl at δ 0.80 (3H, $J = 6.8$ Hz), two oxygen-bearing methine protons at δ 3.91 (1H, br) and 3.58 (1H, $J = 9.6$ Hz), and one methoxy group at δ 3.28 (3H, s). The ^{13}C NMR (Table 1) and DEPT spectra showed 15 carbon signals for four methyls at δ 27.4, 20.8, 20.5, and 15.2, two methylenes at δ 50.5 and 31.6, six methines at δ 126.0, 125.1, 78.2, 67.6, 38.2, and 28.5, and three quaternary carbons at δ 200.4, 154.2, and 138.7. The protonated carbons and their bonded protons were unambiguously assigned by the HSQC experiment. The ^1H and ^{13}C NMR spectra (Table 1) of **1** were similar to those of compound **4**, a known bisabolane-type sesquiterpene, bisacurone [5,17]. The main differences between the spectra of **1** and **4** were due to a double bond between C-3 and C-4 in **1** instead of a double bond between C-2 and C-3 in **4**, the presence of a methoxy group at C-2 and the absence of a hydroxyl group at C-4 in **1** (Figure 1), which was determined by the analysis of its $^1H-^1H$ COSY (Figure 2) and HMBC spectra (Figure 3). The oxygenated methine proton at δ 3.58 was assigned to be H-2 according to its $^1H-^1H$ COSY coupling correlation with H-1 [δ 1.82 (1H, m)] and HMBC correlation of its bonded carbon C-2 (δ 78.2) with H_a-6 [δ 1.71(1H, m)] and H_b-6

Table 1. ^1H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectral data for compounds **1**–**3**.

	1		**2**		**3**	
Position	δ_C	δ_H (*J*, Hz)	δ_C	δ_H (*J*, Hz)	δ_C	δ_H (*J*, Hz)
1	38.2	1.82, m	42.0	2.20, m	37.5	2.40, m
2	78.2	3.58, d (9.6)	75.9	4.57, br	74.5	4.92, br
3	126.0	5.56, s	123.9	5.48, s	119.5	5.45, s
4	138.7		140.7		143.8	
5	67.6	3.91, br	66.4	3.98, t (5.2)	63.7	3.99, br
6	31.6	1.71, m, 1.43, m	33.4	1.82–1.74, m	31.7	1.87, m, 1.76, m
7	28.5	2.46, m	41.6	2.33, m	38.7	2.40, m
8	50.5	2.41, dd (15.2, 4.4), 2.31, dd (15.2, 8.8)	86.5	4.33, d (7.2)	179.0	
9	200.4		200.7		14.0	0.89, d (7.2)
10	125.1	6.17, s	122.0	6.39, s	20.0	1.85, s
11	154.2		156.5			
12	20.5	2.10, s	20.8	2.12, s		
13	27.4	1.87, s	27.8	1.91, s		
14	15.2	0.80, d (6.8)	15.0	0.89, d (6.8)		
15	20.8	1.76, s	20.7	1.77, s		
$-OCH_3$	54.8	3.28, s				

The assignments were based on DEPT, $^1H-^1H$ COSY, HSQC, and HMBC experiments. NMR spectral data of compounds **1** and **2** were measured in acetone-d_6 and NMR spectral data of compound **3** were measured in DMSO-d_6.

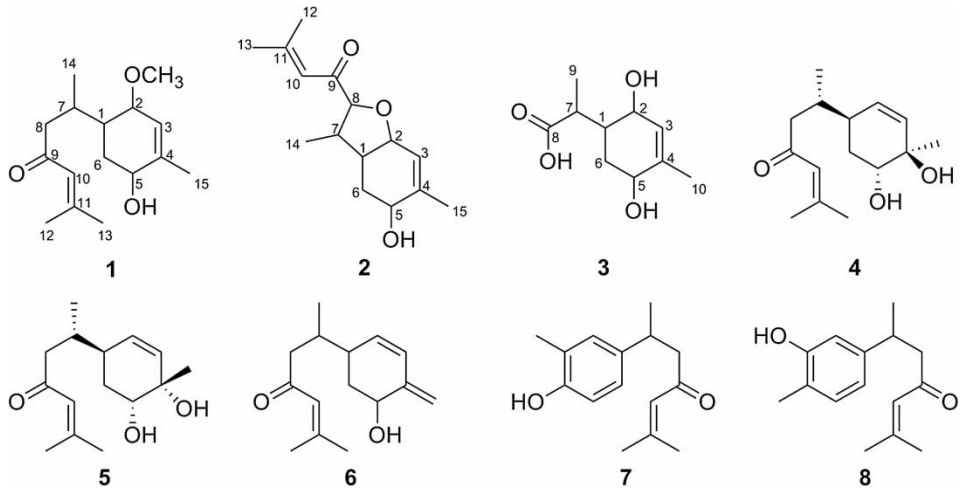

Figure 1. The structures of compounds **1**–**8**.

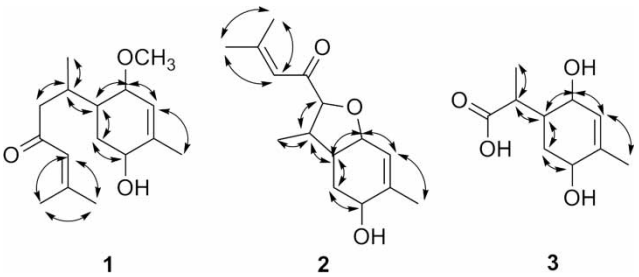

Figure 2. $^{1}H-^{1}H$ COSY correlations of compounds **1**–**3**.

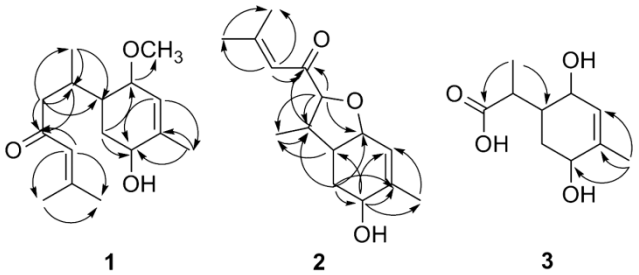

Figure 3. Key HMBC correlations of compounds **1**–**3** (from H to C).

[δ 1.43 (1H, m)]. Further, the HMBC correlation of C-2 with the methoxy group protons [δ 3.28 (3H, s)] revealed that the methoxy group was attached to C-2. Meanwhile, H-2 coupled with an olefin proton at δ 5.56 (H-3) and H-3 coupled with a vinyl methyl at δ 1.76 (H-15) in the $^{1}H-^{1}H$ COSY spectrum, suggesting the presence of a double bond between C-3 (δ 126.0) and C-4 (δ 138.7) and the absence of a hydroxyl group at C-4. The assignment was confirmed by the HMBC correlations of H-3 with C-15 (δ 20.8) and C-5 (δ 67.6), and H-15 with C-3, C-4, and C-5. In addition, the $^{1}H-^{1}H$ COSY and HMBC correlations further confirmed the bisabolane skeleton

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of **1**. Therefore, the planar structure of **1** was established as 2-methoxy-5-hydroxybisabola-3,10-diene-9-one.

Compound **2**, a colorless oil, had a molecular formula of $C_{16}H_{26}O_2$ determined from its positive-ion HR-ESI-MS on the basis of two quasi-molecular ions $[M+Na]^+$ at *m/z* 273.1451 and $[M+H]^+$ at *m/z* 251.1643. Its UV, IR, and NMR spectra (Table 1) were very similar to those of **1**, except that the signals of the methoxy group attached to C-2 and the methylene at C-8 were absent in the NMR spectrum of **2**, and an additional oxygen-bearing methine signal appeared at δ_H 4.33 (1H, d, $J = 7.2$ Hz) and δ_C 86.5 in **2**. The proton of this additional oxygen-bearing methine was assigned to H-8, which was established by its $^1H-^1H$ COSY correlation (Figure 2) with H-7 [δ 2.33 (1H, m)] and HMBC correlations (Figure 3) with C-14 (δ 15.0), C-7 (δ 41.6), and C-11(δ 156.5). In addition, the HMBC spectrum of **2** showed a correlation between H-8 and C-2 (δ 75.9), suggesting the presence of an epoxide located at C-8 (δ 86.5) and C-2. This was supported by the downfield shift of H-2 (from δ 3.58 to 4.57) as compared with that of **1** due to the epoxide group instead of a methoxy group. On the basis of the above spectral analyses, the structure of **2** was deduced as 2,8-epoxy-5-hydroxybisabola-3,10-diene-9-one. This was the first report of the presence of an epoxide between C-2 and C-8 in the structure of bisabolane-type sesquiterpene from natural sources.

Compound **3** was isolated as a light brown amorphous solid. Its molecular formula was deduced as $C_{10}H_{16}O_4$ from its positive-mode HR-ESI-MS, which exhibited a characteristic ion peak $[M+H-H_2O]^+$ at *m/z* 183.1023. The IR spectrum exhibited absorption bands for hydroxyl (3427 cm^{-1}), carbonyl (1754 cm^{-1}), and double bond (1600 cm^{-1}) groups. The ^1H NMR (Table 1) spectrum indicated the presence of one olefinic proton [δ 5.45 (1H, s)], one vinyl methyl [δ 1.85 (3H, s)], one methyl [δ 0.89 (3H, $J = 7.2$ Hz)], and two oxygen-bearing methine protons [δ 4.92 (1H, br), 3.99 (1H, br)]. The ^{13}C NMR (Table 1) and DEPT spectra displayed 10 carbon signals, including two methyls (δ 20.0, 14.0), one methylene (δ 31.7), four methines (δ 74.5, 63.7, 38.7, 37.5), and two quaternary carbons (δ 179.0, 143.8). The ^1H and ^{13}C NMR spectral data indicated the presence of a similar hexatomic ring as **2**, and the only difference was that a hydroxy group was attached to C-2 rather than an epoxide group, as judged from the absence of the HMBC correlation (Figure 3) for the epoxide group. However, the side chain was composed of one methyl [δ_H 0.89 (3H, d, $J = 7.2$ Hz, H-9); δ_C 14.0 (C-9)], one methine [δ_H 2.40 (1H, m, H-7); δ_C 38.7 (C-7)], and one carboxyl [δ_C 179.0 (C-8)], which was confirmed by the $^1H-^1H$ COSY and HMBC spectra. The $^1H-^1H$ COSY spectrum (Figure 2) showed a correlation between H-7 and H-9, and long-range correlations of H-9 with C-8 as well as H-9 with C-1 (δ 37.5) were observed in the HMBC spectrum. Accordingly, compound **3** was elucidated as 2-(2,5-dihydroxy-4-methylcyclohex-3-enyl)propanoic acid.

The five known compounds were identified as bisacurone (**4**) [5,17], bisacurone A (**5**) [12], 4-methylene-5-hydroxybisabola-2,10-diene-9-one (**6**) [18], 2-methyl-6-(4-hydroxy-3-methylphenyl)-2-hepten-4-one (**7**) [6], and turmeronol A (**8**) [19,20] by comparison of their spectral data (^1H and ^{13}C NMR and MS) with those reported in the literature. Among these known compounds, compounds **5** and **6** were isolated from *C. longa* and genus *Curcuma* for the first time, respectively.

3. Experimental

3.1 General experimental procedures

Optical rotations were measured on a JASCO P-1020 polarimeter. UV and IR spectra were recorded on an Agilent 1100

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photodiode-array detector and a Perkin-Elmer GX infrared spectrophotometer in KBr disks, respectively. ^{1}H NMR (400 MHz), ^{13}C NMR (100 MHz) and all 2D NMR spectra were run on a Bruker Avance II 400 spectrophotometer using acetone-d_6 or DMSO-d_6 as solvents. HR-ESI-MS and MS/MS data were acquired on a Macromass Q-TOF Premier™ mass spectrometer. XAD-4 macroporous resin (Rohm and Haas Corp., Philadelphia, PA, USA) was used for column chromatography. Preliminary HPLC separations were performed on an Elite preparative HPLC apparatus equipped with a UV200 II variable wavelength UV detector, using a self-made C18 (300 × 70 mm, 10–20 μm particle size) preparative column. Final purifications were carried out with a Waters parallel four-channel preparative HPLC/UV/MS system consisting of four Waters 2525 binary gradient modules, a Waters 2488 multi-channel UV detector, a Waters four-channel MUX-ZQ MS detector, and four Waters 2757 fraction collectors, using four XTerra® MS C18 (100 × 19 mm i.d., 5 μm; Waters Corp., Milford, MA, USA) preparative columns. Fractions were monitored by analytical HPLC experiments on an Agilent 1100 series using a Tigerkin ODS-2 column (5 μm, 250 × 4.6 mm i.d.; Dalian Sipore Co., Ltd, Dalian, China).

3.2 Plant material

The rhizomes of *C. longa* were collected in Chongzhou, Sichuan Province of China, in December 2004 and were identified by Xirong He, Institute of Medication, Xiyuan Hospital of China Academy of Traditional Chinese Medicine. A voucher specimen (JH0412) has been deposited at the Dalian Institute of Chemical Physics, Chinese Academy of Science, China.

3.3 Extraction and isolation

The powdered rhizomes (3 kg) of *C. longa* were extracted with 95% EtOH (three times, each 20 l) at room temperature. The combined EtOH extract was filtered and evaporated under reduced pressure to afford a residue of 306 g. A portion of the residue (248 g) was subjected to XAD-4 macroporous resin column chromatography eluting with 40, 60, 80, and 95% EtOH, and four fractions were obtained. The fraction eluted by 80% EtOH (39.7 g) was then separated by preparative HPLC eluting with a gradient of MeOH–H_2O (30–50% MeOH in 10 min, then 50–80% MeOH in 50 min, followed by a column rinsing and equilibrating procedure, flow rate 200 ml/min, detection 300 nm) to give 12 subfractions. Fraction 2 (2.1 g, t_R = 4–10.8 min), fraction 5 (2.2 g, t_R = 22.7–26.0 min), fraction 7 (3.7 g, t_R = 30.0–34.0 min), fraction 9 (2.3 g, t_R = 40.0–43.7 min), and fraction 10 (2.0 g, t_R = 43.7–47.0 min) were further fractionated on a parallel four-channel preparative HPLC/UV/MS system with acetonitrile (A) − 0.1% (v/v) aqueous formic acid (B) as the mobile phase at a flow rate of 16.37 ml/min. Fraction 2 was eluted with a gradient solvent (11% A hold for 5 min, then 11–14% A in 20 min, detection 254 nm) to afford compound **3** (12.5 mg, t_R = 6.2 min). Fraction 5 was eluted with a gradient solvent (14% A hold for 5 min, 14–18% A in 40 min, then 18–30% A in 20 min, detection 230 nm) to afford compounds **2** (14.7 mg, t_R = 26.9 min) and **4** (77.2 mg, t_R = 29.5 min). Fraction 7 was eluted with a gradient solvent (18% A hold for 10 min, 18–21% A in 10 min, 21% A hold for 30 min, then 21–25% A in 20 min, detection 260 nm) to afford compound **5** (27.2 mg, t_R = 30.0 min). Fraction 9 was eluted with a gradient solvent (22% A hold for 20 min, 22–34% A in 20 min, then 34% A hold for 20 min, detection 240 nm) to afford compounds **1** (5.8 mg, t_R = 28.4 min), **6** (85 mg, t_R = 35.8 min), and **7** (9.7 mg, t_R = 48.0 min). Fraction 10 was eluted with a gradient solvent (30% A hold for 5 min, then 30–45% A in 60 min,

detection 240 nm) to afford compound **8** (11.0 mg, $t_R = 26.6$ min).

3.3.1 2-Methoxy-5-hydroxybisabola-3,10-diene-9-one (*1*)

A light yellow oil; $[\alpha]_D^{22}$ +13.1 ($c = 0.17$, MeOH); UV λ_{max} (ACN/H_2O) 240 nm; IR (KBr) ν_{max} 3398, 2964, 2879, 1683, 1615, 1516, 1447, 1379, 1281, 1186, 1169, 1093, 1038, 1011, 968, 939, 834 cm^{-1}; ^1H and ^{13}C NMR spectral data, see Table 1; HR-ESI-MS: *m/z* 289.1761 $[M+Na]^+$ (calcd for $C_{16}H_{26}O_3Na$, 289.1780) and 267.1962 $[M+H]^+$ (calcd for $C_{16}H_{27}O_3$, 267.1960); HR-ESI–MS/MS: *m/z* 235.1722 $[M+H-CH_3OH]^+$, 217.1599 $[M+H-CH_3OH-H_2O]^+$, 119.0865 $[C_9H_{11}]^+$.

3.3.2 2,8-Epoxy-5-hydroxybisabola-3,10-diene-9-one (*2*)

A colorless oil; $[\alpha]_D^{22}$ −35.1 ($c = 0.26$, MeOH); UV λ_{max} (ACN/H_2O) 246 nm; IR (KBr) ν_{max} 3419, 2964, 2932, 2874, 1683, 1614, 1515, 1447, 1380, 1263, 1231, 1206, 1158, 1091, 1074, 1043, 1034, 1004, 965, 940, 899, 838 cm^{-1}; ^1H and ^{13}C NMR spectral data, see Table 1; HR-ESI–MS: *m/z* 273.1451 $[M+Na]^+$ (calcd for $C_{15}H_{22}O_3Na$, 273.1467) and 251.1643 $[M+H]^+$ (calcd for $C_{15}H_{23}O_3$, 251.1647); HR-ESI–MS/MS for $[M+H]^+$: *m/z* 233.1528 $[M+H-H_2O]^+$, 215.1438 $[M+H-2H_2O]^+$, 175.1124 $[C_{12}H_{15}O]^+$, 135.0809 $[C_9H_{11}O]^+$, 119.0853 $[C_9H_{11}]^+$, 83.0496 $[C_5H_7O]^+$.

3.3.3 2-(2,5-Dihydroxy-4-methylcyclohex-3-enyl)propanoic acid (*3*)

A light brown amorphous solid; $[\alpha]_D^{22}$ +1.2 ($c = 0.16$, MeOH); UV λ_{max} (ACN/H_2O) 220, 262, 292 nm; IR (KBr) ν_{max} 3427, 2964, 2930, 1754, 1600, 1569, 1449, 1423, 1281, 1098, 957, 780 cm^{-1}; ^1H and ^{13}C NMR spectral data, see Table 1; HR-ESI-MS: *m/z* 183.1023 $[M+H-H_2O]^+$ (calcd for $C_{10}H_{15}O_3$, 183.1021); HR-ESI–MS/MS: *m/z* 165.0923 $[M+H-2H_2O]^+$, 137.0956 $[M+H-H_2O-HCOOH]^+$, 119.0863 $[C_9H_{11}]^+$, 109.0648 $[C_7H_9O]^+$, 95.0498 $[C_6H_7O]^+$.

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