New Sesquiterpenes and Calebin Derivatives from *Curcuma longa*

YongChi Zeng,[a] Feng Qiu,*[,a] Kyoko Takahashi,[b] JianMu Liang,[a] GeXia Qu,[a] and XinSheng Yao[a]

[a] *Department of Natural Products Chemistry 81#, Shenyang Pharmaceutical University; 103 Wenhua Avenue, Shenyang, 110016, P. R. China: and* [b] *Department of Medicinal Resources, Graduate School of Pharmaceutical Sciences, Osaka University; Osaka 565–0871, Japan.* Received February 8, 2007; accepted March 31, 2007

One novel sesquiterpene with new skeleton, (6*S*)-2-methyl-6-(4-hydroxyphenyl-3-methyl)-2-hepten-4-one (1), two new bisabolane sesquiterpenes, (6*S*)-2-methyl-6-(4-hydroxyphenyl)-2-hepten-4-one (2), (6*S*)-2-methyl-6-(4-formylphenyl)-2-hepten-4-one (3), and two calebin derivatives, 4″-(4‴-hydroxyphenyl-3‴-methoxy)-2″-oxo-3″-butenyl-3-(4′-hydroxyphenyl)-propenoate (4) and 4″-(4‴-hydroxyphenyl)-2″-oxo-3″-butenyl-3-(4′-hydroxyphenyl-3′-methoxy)-propenoate (5) were isolated along with five known bisabolane sesquiterpenes from *Curcuma longa*. 1—4 were new compounds and 5 was a new natural product. Their structures were established by spectral methods.

Key words *Curcuma longa*; sesquiterpene; bisabolane; calebin derivative

The rhizomes of *Curcuma longa* has played an important role in the pharmaceutical, food and textile industries, and has been widely used as a traditional herbal medicine in China, Japan and southeastern Asia due to its beneficial effects such as inhibiting carcinogenesis and cancer growth,[1,2] bilious regulating functions,[3] reducing cholesterol levels,[4,5] and antioxidant,[6] anti-human immunodeficiency virus,[7] anti-inflammatory[8—10] and antiarthritic[11] activities. With regard to the chemical constituents of this plant, essential oil and curcuminoids were shown to be the major active principles, and the content of bisabolane-type sesquiterpenes in volatile oil is high. Bisabolane-type sesquiterpenes have been reported to show antitumor,[12] antifungal,[13] anti-bacteria,[14] antioxidant[15] and antivenom[16] effects. Calebin A was reported to have the great ability to protect cells from beta-amyloid insult.[17] Although great attentions have been paid to the chemical and pharmacological research of curcumin, demethoxycurcumin and bisdemethoxycurcumin, there was little information on the other types of constituents. In this study, we carried out a systematic chemical research on the bisabolane-type sesquiterpenes and calebin derivatives of *C. longa*, and obtained one novel sesquiterpene with new framework, two new bisabolane-type sesquiterpenes and two calebin derivatives.

Also isolated were five known bisabolane-type sesquiterpenes, which could be identified by comparison of their physico-chemical and spectroscopic properties with published data: 5-hydroxyl-ar-turmerone (**6**),[14] turmeronol B (**7**),[18] bisabolone (**8**),[19] bisabolone-4-one (**9**),[20] turmeronol A (**10**).[18]

Results and Discussion

The high-resolution ESI-MS of compound **1** showed the quasi-molecular ion $[M+Na]^+$ at *m/z* 255.1336 (Calcd 255.1361), corresponding to the molecular formula $C_{15}H_{20}O_2$, which was further supported by the ^{1}H- and ^{13}C-NMR spectral data. The ^{1}H-NMR spectrum revealed an isopropylidene group [δ 1.86 (3H, s), 2.10 (3H, s) and 6.03 (1H, s)] conjugated with a carbonyl group, a secondary methyl group [δ 1.22 (3H, d, J=6.9 Hz)], which was almost identical with the signal pattern of the side chain of turmeronol A.[18] The ^{1}H- and ^{13}C-NMR spectra displayed a set of 1,3,4-trisubstituted benzene ring signals [δ 6.96 (1H, br s), 6.92 (1H, br d, J=8.1 Hz) and 6.68 (1H, d, J=8.1 Hz)] and a hydrogen of hydroxyl signal [δ 5.01 (1H, br s)]. In the HMBC spectrum, correlations from H-2 (δ 6.96) to C-4 (δ 152.1), C-6 (δ 125.1) and C-15 (δ 15.9); H-5 (δ 6.68) to C-1 (δ 138.7), C-3 (δ 123.5) and C-4 (δ 152.1); H-15 (δ 2.22) to C-2 (δ 129.4), C-3 (δ 123.5) and C-4 (δ 152.4); H-6 (δ 6.92) to C-2 (δ 129.4) further indicated the existence of 4-hydroxyphenyl-3-methyl moiety, and moreover, correlations from H-2 (δ 6.96) and H-6 (δ 6.92) to C-7 (δ 35.0) revealed the junction be-

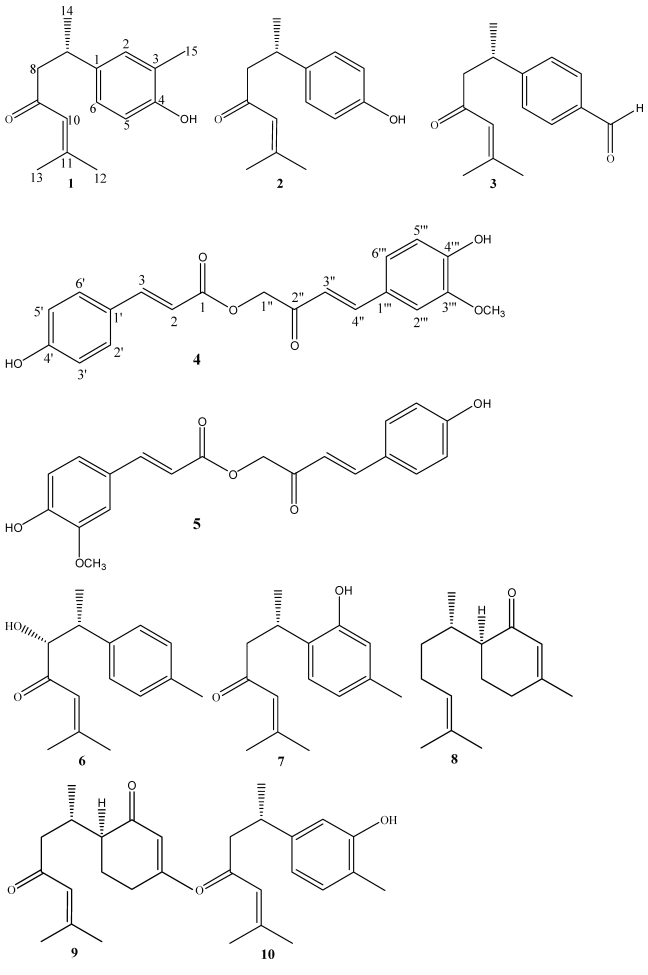

Fig. 1. Structures of Compounds from *Curcuma longa*

* To whom correspondence should be addressed. e-mail: fengqiu2000@tom.com

tween the side chain and the phenyl moiety at C-7/C-1. In addition, H-15 only correlated with H-2 in the NOSEY spectrum, which further established the structure of compound **1**. Thus, compound **1** was elucidated as 2-methyl-6-(4-hydroxyphenyl-3-methyl)-2-hepten-4-one.

The absolute stereochemistry of compound **1** was determined by comparing the optical rotation value with that of turmeronol A (**10**) and turmeronol B (**7**),[18] which was isolated from *C. longa* and previously established as 7*S*, had the similar structure skeleton. Since compound **1** showed positive value of the specific rotation just as turmeronol A and turmeronol B did, the configuration at C-7 was supposed to be *S*.

In the high-resolution ESI-MS of compound **2**, the quasi-molecular ion $[M+Na]^+$ was observed at *m/z* 241.1189 (Calcd 241.1204). Thus the molecular formula was determined to be $C_{14}H_{18}O_2$ with combination of the ^{1}H- and ^{13}C-NMR spectral data. The ^{1}H- and ^{13}C-NMR spectra displayed a set of 1,4-disubstituted benzene ring signals [δ 7.06 (2H, d, J=8.3 Hz), 6.72 (2H, d, J=8.3 Hz)], which assigned to δ 127.8 (2C) and 115.2 (2C), respectively, and a hydroxyl signal [δ 5.47 (1H, br s)]. The ^{1}H-NMR also showed an isopropylidene group [δ 1.86 (3H, s), 2.09 (3H, s) and 6.03 (1H, s)] conjugated with a carbonyl group, a secondary methyl group [δ 1.24 (3H, d, J=6.9 Hz)], which was almost identical with the signal pattern of the side chain of compound **1**. Thus, compound **2** was elucidated as 2-methyl-6-(4-hydroxypheny)-2-hepten-4-one. Since it exhibited positive value of the specific rotation, the stereostructure of **2** was supposed to be the same as that of **1**.

In the high-resolution ESI-MS of compound **3**, the quasi-molecular ion $[M+Na]^+$ at *m/z* 253.1248 (Calcd 253.1204) was observed. Thus the molecular formula was determined to be $C_{15}H_{18}O_2$ with combination of the ^{1}H- and ^{13}C-NMR spectral data. The ^{1}H- and ^{13}C-NMR spectra also displayed a set of 1,4-disubstituted benzene ring signals [δ 7.81 (2H, d, J=8.2 Hz), 7.39 (2H, d, J=8.2 Hz)] assigned to δ 130.1 (2C) and 127.6 (2C), respectively, and a same side chain as that of **3** except for the presence of the ^{1}H signal at δ 9.97 (1H, s) assigned to δ 192.1 (a formyl) instead of that at δ 5.47 (1H, br s) of **2**. Therefore, compound **3** was established as 2-methyl-6-(4-formylphenyl)-2-hepten-4-one. Since it exhibited positive value of the specific rotation, the stereostructure of **3** was supposed to be the same as that of **2**.

Compounds **4** and **5** were a pair of isomers and obtained as a mixture together. Their high-resolution ESI-MS showed the quasi-molecular ion $[M+Na]^+$ at *m/z* 377.1005 (Calcd 377.1001). The ^{13}C- and ^{1}H-NMR spectra revealed two extremely similar groups of signals, which suggested that there were a pair of isomers with the same molecular formula of $C_{20}H_{18}O_6$. The two groups of signals, one is stronger (corresponding to compound **5**) and the other is weaker (corresponding to compound **4**). The ^{13}C- and ^{1}H-NMR and HMQC spectra displayed two sets of 1,3,4-trisubstituted benzene ring signals [δ 7.16 (1H, dd, J=1.8, 8.4 Hz), 7.33 (1H, d, J=1.8 Hz), 6.80 (1H, d, J=8.4 Hz) and δ 7.15 (1H, dd, J=1.8, 8.4 Hz), 7.36 (1H, d, J=1.8 Hz), 6.80 (1H, d, J=8.4 Hz)], two sets of 1,4-disubstituted benzene ring signals [δ 7.59 (2H, d, J=8.2 Hz), 6.81 (2H, d, J=8.2 Hz) and δ 7.58 (2H, d, J=8.3 Hz), 6.81 (2H, d, J=8.3 Hz)], four pairs of trans olefinic protons [δ 7.62 (1H, d, J=15.9 Hz), 6.50 (1H, d, J=15.9 Hz); δ 7.61 (1H, d, J=16.0 Hz), 6.83 (1H, d, J=16.0 Hz); δ 7.62 (1H, d, J=16.3 Hz), 6.76 (1H, d, J=16.3 Hz) and δ 7.60 (1H, d, J=15.9 Hz), 6.58 (1H, d, J=15.9 Hz)], two overlapped methylene proton signals [δ 5.11 (4H, s)] and two overlapped methoxyl groups [δ 3.81 (6H, s)], two overlapped carbonyls (δ 192.7) and two overlapped ester carbonyls (δ 166.2). The chemical shift of the H-1″ protons at δ_H 5.11 (4H, s) and the ^{13}C-NMR chemical shift of the C-1″ at δ_C 67.2 suggest that it is two same methylene groups between a carbonyl carbon and an ester oxygen, assigned to compounds **4** and **5**, respectively. This assignment was confirmed by HMBC correlations of H-1″ (δ 5.11) with C-1 (δ 166.2) and C-2″ (δ 192.7). For compound **4**, in the HMBC, correlations from H-3″ (δ 6.83) to C-2″ (δ 192.7) and C-1‴ (δ 125.7), H-5‴ (δ 6.80) to C-1‴ (δ 125.7), H-2‴ (δ 7.33) to C-4″ (δ 143.9), H-2 (δ 6.50) to C-1′ (δ 125.1), H-3′,6′ (δ 6.81) to C-1′ (δ 125.1), H-3 (δ 7.62) to C-

Table 1. The ^{13}C- (75 MHz) and ^{1}H-NMR (300 MHz) Data of **1**—**3** ($CDCl_3$, δ in ppm)

Position	**1**		**2**		**3**	
	δ_C	δ_H	δ_C	δ_H	δ_C	δ_H
1	138.7		138.4		134.7	
2	129.4	6.96 (1H, br s)	127.8	7.06 (1H, d, J=8.3)	127.6	7.39 (1H, d, J=8.2)
3	123.5		115.2	6.72 (1H, d, J=8.3)	130.1	7.81 (1H, d, J=8.2)
4	152.1		154.0		154.0	
5	114.8	6.68 (1H, d, J=8.1)	115.2	6.72 (1H, d, J=8.3)	130.1	7.81 (1H, d, J=8.2)
6	125.1	6.92 (1H, br d, J=8.1)	127.8	7.06 (1H, d, J=8.3)	127.6	7.39 (1H, d, J=8.2)
7	35.0	3.23 (1H, m)	35.1	3.26 (1H, m)	35.7	3.45 (1H, m)
8	52.9	2.69 (1H, dd, J=6.8, 15.4); 2.61 (1H, dd, J=7.7, 15.4)	52.8	2.69 (1H, dd, J=6.2, 15.4); 2.60 (1H, dd, J=8.1, 15.4)	51.8	2.76 (1H, dd, J=6.7, 16.2); 2.68 (1H, dd, J=7.6, 16.2)
9	200.3		200.5		198.8	
10	124.1	6.03 (1H, s)	124.0	6.03 (1H, s)	123.8	6.02 (1H, s)
11	155.3		155.6		156.0	
12	27.7	1.86 (3H, s)	27.7	1.86 (3H, s)	27.7	1.87 (3H, s)
13	20.7	2.10 (3H, s)	20.8	2.09 (3H, s)	20.8	2.10 (3H, s)
14	22.2	1.22 (3H, d, J=6.9)	22.2	1.24 (3H, d, J=6.9)	21.7	1.29 (3H, d, J=6.9)
15	15.9	2.22 (3H, s)			192.1	9.97 (1H, s)
	4-OH	5.01 (1H, br s)	4-OH	5.47 (1H, br s)		

^{1}H- and ^{13}C-NMR recorded on ARX300, HMQC and HMBC on AV600, in $CDCl_3$, δ in ppm.

Table 2. The ^{13}C- (75 MHz) and ^{1}H-NMR (300 MHz) Data of **4**, **5** (DMSO, δ in ppm)

Position	**4**		**5**	
	δ_C	δ_H	δ_C	δ_H
1	166.2		166.2	
2	113.6	6.50 (1H, d, J=15.9)	113.9	6.58 (1H, d, J=15.9)
3	145.6	7.62 (1H, d, J=15.9)	145.9	7.60 (1H, d, J=15.9)
1′	125.1		125.6	
2′	130.6	7.59 (1H, d, J=8.2)	111.4	7.36 (1H, d, J=1.8)
3′	115.9	6.81 (1H, d, J=8.2)	148.1	
4′	160.1		149.6	
5′	115.9	6.81 (1H, d, J=8.2)	115.6	6.80 (1H, d, J=8.4)
6′	130.6	7.59 (1H, d, J=8.2)	123.5	7.15 (1H, dd, J=1.8, 8.4)
1″	67.2	5.11 (2H, s)	67.2	5.11 (2H, s)
2″	192.7		192.7	
3″	119.6	6.83 (1H, d, J=16.0)	119.3	6.76 (1H, d, J=16.3)
4″	143.9	7.62 (1H, d, J=16.0)	143.6	7.62 (1H, d, J=16.3)
1‴	125.7		125.2	
2‴	111.4	7.33 (1H, d, J=1.8)	130.8	7.58 (1H, d, J=8.3)
3‴	148.1		116.0	6.81 (1H, d, J=8.3)
4‴	149.9		160.4	
5‴	115.7	6.80 (1H, d, J=8.4)	116.0	6.81 (1H, d, J=8.3)
6‴	123.8	7.16 (1H, dd, J=1.8, 8.4)	130.8	7.58 (1H, d, J=8.3)
3‴-OCH_3	55.8	3.81 (3H, s)		
3′-OCH_3			55.6	3.81 (3H, s)
4′-OH		10.0 (1H, s)		9.63 (1H, s)
4″-OH		9.71 (1H, s)		10.1 (1H, s)

^{1}H- and ^{13}C-NMR recorded on ARX300, HMQC and HMBC on AV600, in DMSO-d_6, δ in ppm.

1 (δ 166.2) and C-2′,6′ (δ 130.6) further elucidated **4** as 4″-(4‴-hydroxyphenyl-3‴-methoxy)-2″-oxo-3″-butenyl-3-(4′-hydroxyphenyl)-propenoate. For compound **5**, in the HMBC, correlations from H-2 (δ 6.58) to C-1′ (δ 125.6), H-5′ (δ 6.80) to C-1′ (δ 125.6), H-2′ (δ 7.36) to C-3 (δ 145.9), H-3 (δ 7.60) to C-1 (δ 166.2), H-4″ (δ 7.62) to C-2″ (δ 192.7) and C-2‴,6‴ (δ 130.8), H-3″ (δ 6.76) to C-1‴ (δ 125.2), H-3‴,5‴ (δ 6.81) to C-1‴ (δ 125.2) further determined **5** as 4″-(4‴-hydroxyphenyl)-2″-oxo-3″-butenyl-3-(4′-hydroxyphenyl-3′-methoxy)-propenoate. To our best knowledge, compound **4** was first reported here as a new component and compound **5** was first isolated from plant, which represents a new natural product. The protons and carbons of **4** and **5** were fully assigned on the basis of 2D-NMR techniques, including HMQC and HMBC.

Experimental

General Experimental Procedure Optical rotation values were measured on a Perkin-Elmer 241 MC polarimeter. NMR spectra were measured on Bruker AV-400 or Bruker ARX-300 or AV-600 spectrometers, using TMS as an internal standard. HR-ESI-MS spectra were recorded on a IKOU0328-5 mass spectrometer.

Silica gel for column chromatography (200—300 mesh), and silica gel G_{60} for thin-layer chromatography were products of Qingdao Marine Chemical Factory. Reverse-phase preparatory TLC was performed using products from Merck Company. Sephadex LH-20 and ODS were the products of Pharmacia Company. Analysis HPLC was performed using a C-18 column (C-18, 250×4.6 mm, Inertsil Park; detector: UV). Preparative HPLC was performed using a C-8 column (C-8, 250×20 mm, Inertsil Pak; detector: UV) and a C-18 column (C-18, 250×20 mm, Inertsil Pak; detector: UV).

The purity of reagents for HPLC was 99.9%. Other chemicals were analytical grade, and all of them were bought from store room of Shenyang pharmaceutical university.

Plant Materials The dry rhizomes of *C. longa* were collected from Gui Zhou province, China. A voucher specimen was identified by Prof. Qi-Shi Sun, and deposited at the Department of Natural Products Chemistry, Shenyang Pharmaceutical University, China.

Extraction and Isolation The dry rhizomes of *C. longa* (2.5 kg) were pulverized then ultrasonically extracted with 8×80% EtOH for 3 times for 0.5 h. The EtOH solution was combined and condensed to give 362 g of extract which was chromatographed on a silica gel column using a $CHCl_3$–MeOH gradient solvent system to yeild 17 fractions (Fr. A—Q). Fr. C (16.2 g) was further subjected to column chromatography on a silica gel with a cyclohexane–EtOAc gradient system to give 11 fractions (Fr. C1—11). Fr. C4 was further chromatographed on a C-18 reverse-phase open column to yield Fr. C41 (MeOH : H_2O 60 : 40) and Fr. C42 (MeOH : H_2O 80 : 40), then Fr. C41 was purified by HPLC (C-8 column, MeOH : H_2O 65 : 35, t_R: 34.6 min) to afford **6** (79.8 mg), and Fr. C42 was also purified by HPLC (C-8 column, MeOH : H_2O 70 : 30, t_R: 55.4 min) to afford **8** (330.1 mg). Fr. C6 was purified by C-18 reverse-phase open column chromatography (MeOH : H_2O 60 : 40) followed by HPLC (C-8 column, MeOH : H_2O 55 : 45, t_R: 81.5 min) to yield **7** (36 mg). Fr. D (31.5 g) was further subjected to column chromatography on a silica gel with a cyclohexane–EtOAc gradient system to give 11 fractions (Fr. D1—11). Fr. D4 was purified by C-18 reverse-phase open column chromatography (MeOH : H_2O 60 : 40) followed by HPLC (C-8 column, MeOH : H_2O 60 : 40, t_R: 42.3 min) to yield **3** (4.5 mg). Fr. D6 was subjected to column chromatography on a silica gel with cyclohexane–EtOAc (10 : 1) to yield 2 fractions (Fr. D61 and Fr. D62). Fr. D61 was purified by HPLC (C-8 column, MeOH : H_2O 55 : 45, t_R: 75.1 min) to yeild **1** (11.8 mg). Fr. D62 was also purified by HPLC (C-18 column, MeOH : H_2O 60 : 40, t_R: 22.3, 25.3 and 39.9 min) to afford **2** (11.1 mg), **9** (153.5 mg) and **10** (186.7 mg), respectively. Fr. G (21.6 g) was further subjected to column chromatography on a silica gel with a $CHCl_3$–MeOH gradient system to give 5 fractions (Fr. G1—5). Fr. G2 was chromatographed on C-18 reversed-phase open column (MeOH : H_2O 40 : 60, 60 : 40) to yield 7 fractions (Fr. G21—27), Fr. G23 was purified by HPLC (C-8 column, MeOH : H_2O 38 : 62, t_R: 148.2 min) to yield the mixture of **4** and **5** (7.9 mg).

(6*S*)-2-Methyl-6-(4-hydroxyphenyl-3-methyl)-2-hepten-4-one (**1**): Viscous oil. $[\alpha]_D^{25}$ +51.1° (c=0.9, MeOH). ^{1}H- and ^{13}C-NMR: see Table 1. HR-ESI-MS: 255.1336 ($[M+Na]^+$, $C_{15}H_{20}NaO_2$; Calcd 255.1361).

(6*S*)-2-Methyl-6-(4-hydroxypheny)-2-hepten-4-one (**2**): Viscous oil. $[\alpha]_D^{25}$ +76.7° (c=0.6, MeOH). ^{1}H- and ^{13}C-NMR: see Table 1. HR-ESI-MS: 241.1189 ($[M+Na]^+$, $C_{14}H_{18}NaO_2$, Calcd 241.1204).

(6*S*)-2-Methyl-6-(4-formylphenyl)-2-hepten-4-one (**3**): Viscous oil. $[\alpha]_D^{25}$ +63.3° (c=0.2, MeOH). ^{1}H- and ^{13}C-NMR: see Table 1. HR-ESI-MS: 253.1248 ($[M+Na]^+$, $C_{15}H_{18}NaO_2$; Calcd 253.1204).

4″-(4‴-Hydroxyphenyl-3‴-methoxy)-2″-oxo-3″-butenyl-3-(4′-hydroxyphenyl)-propenoate (**4**) and 4″-(4‴-hydroxyphenyl)-2″-oxo-3″-butenyl-3-(4′-hydroxyphenyl-3′-methoxy)-propenoate (**5**), light yellow amorphous powder. ^{1}H- and ^{13}C-NMR: see Table 2. HR-ESI-MS: 377.1005 ($[M+Na]^+$, $C_{20}H_{18}NaO_6$, Calcd 377.1001).

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