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Original Article

Three new sesquiterpenes from roots of *Curcuma longa*

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ABSTRACT

Objective: To study the chemical constituents from the roots of *Curcuma longa*.
Methods: The structures of the compounds were elucidated based on extensive spectral analysis, including 1D and 2D NMR, MS, UV, and CD analysis.
Results: Two new sesquiterpene compounds (1*S*,2*R*,5*R*,7*S*,8*R*)-2,8-epoxy-5-hydroxybisabola-3,10-dioen-9-one (**1**), (1*R*,2*R*,5*R*,7*S*,8*R*)-2,8-epoxy-5-hydroxybisabola-3,10-dioen-9-one (**2**), and a new natural product 6-(4-Hydroxymethylphenyl)-2-methyl-hept-2-ene-4-one (**3**) together with three known compounds *ar*-turmerone (**4**), 2-methyl-6-(4-hydroxyphenyl-3-methyl)-2-hepten-4-one (**5**) and 2-methyl-6-(4-hydroxyphenyl)-2-hepten-4-one (**6**) were isolated from *C. longa* root extract with 95% ethanol.
Conclusion: In the study, three new compounds were isolated from *C. longa*, and their absolute configurations were determined.

1. Introduction

Curcumae longae Rhizoma, the dried rhizome of *Curcuma longa* L. (Zingiberaceae, Jianghuang in Chinese), is widely cultivated in China, India, and other countries in Southeast Asia (Aditya, Shim, Yang, Lee, & Ko, 2014). *C. longa* has medicinal value, including anti-inflammatory, analgesic, anti-bacterial infection, anti-tumor, anti-oxidation, kidney and liver protection, etc. (Baghel, Baghel, Sharma, & Sikarwar, 2013). *C. longa* has anti-inflammatory (Jurenka, 2009) and antioxidant effects (Ayati et al., 2019). It is also used to treat complications of diabetes (Karlowicz-Bodalska, Han, Freier, Smolenski, & Bodalska, 2017). The main types of compounds in *C. longa* include terpenes, diarylheptanoids, phenylpropanoids, sterols, and fatty acids (Li et al, 2009). Curcumin has been widely studied as the main active constituent part of turmeric. The chemical constituents of *C. longa* were studied in this paper and two new diastereomers were obtained, (1*S*,2*R*,5*R*,7*S*,8*R*)-2,8-epoxy-5-hydroxybisabola-3,10-dioen-9-one (**1**); (1*R*,2*R*,5*R*,7*S*,8*R*)-2,8-epoxy-5-hydroxybisabola-3,10-dioen-9-one (**2**) and the absolute configuration of 6-(4-Hydroxymethylphenyl)-2-methyl-hept-2-ene-4-one (**3**) was determined for the first time together with three known compounds including sesquiterpene *ar*-turmerone (**4**), 2-methyl-6-(4-hydroxyphenyl-3-methyl)-2-hepten-4-one (**5**), 2-methyl-6-(4-hydroxyphenyl)-2-hepten-4-one (**6**). The compounds isolated from *C. longa* and the structural analysis of compounds **1**, **2** and **3** were introduced in our study.

2. Materials and methods

2.1. General experimental procedures

The NMR spectra were recorded on Bruker-ARX-400 and Bruker-AV-600 nuclear magnetic resonance instruments (TMS internal standard, Bruker, Germany). Ultraviolet spectra were recorded on SHIMADZU-2600i (Shimadzu Co., Japan). The HRESIMS data were measured on a Micromass AutoSpec UltimaE time-of-flight mass spectrophotometer (Bruker, Germany). CD spectra were obtained on a MOS-450 circular dichroism spectrometer (Nippon Beam Corporation, Japan). Optical rotations were determined on a PerkinElmer 241 polarimeter (Anton Paar, Germany). Analytical high-performance liquid chromatography in Shimadzu LC-10A analytical HPLC separation and Shimadzu LC-8A Preparative HPLC separation with Shimadzu SPD-10AT Type UV detector (Shimadzu, Japan). Column chromatography was performed on silica gel G (200–300 mesh; Qingdao Haiyang Chemical Factory, Qingdao, China) and Sephadex LH-20 (Pharmacia, Piscataway, NJ, USA) columns. Thin-layer chromatography was performed using a home-made silica gel GF254 plate, which was sprayed with a concentrated sulfuric acid-vanillin solution and then heated to develop spots. Analytical pure reagents for general chromatography and chromatographic pure reagents for high-performance liquid chromatography (Shandong Yuwang Chemical Co., Ltd.,

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Qingdao, China). The chromogenic agent 10% sulfuric acid ethanol solution was prepared according to the method of extraction and separation of the active components of Chinese herbal medicine. CDCl3 was used in all deuterated reagents (Armar, Switzerland).

2.2. Plant materials

The medicinal *C. longa* was purchased in Bozhou City, Anhui Province of China, and was identified as the dried rhizome of *C. longa* by Professor Jincai Lu of Shenyang Pharmaceutical University and preserved in the School of Traditional Chinese Materia Medica of Shenyang Pharmaceutical University (specimen No. 6202).

2.3. Extraction and isolation

The dried rhizomes of (8 kg) *C. longa* were crushed with a microtome, extract with 95% ethanol (volume percent) through the conventional heating reflux method, extracted three times, and evaporated the solvent with vacuum rotation for dryness to obtain a crude extract (about 500 g ethanol extract). The crude extract was successively extracted with petroleum ether, ethyl acetate, and *n*-butanol to obtain a three-layer extract. The ethyl acetate layer extract (350 g) was separated by silica gel column chromatography and eluted with petroleum ether ethyl acetate (100:0–100:100, volume percent) to obtain eight fractions (Frs. 1–8). Fr. 4 was further separated with a silica gel column and eluted with petroleum ether-ethyl acetate (100:1–100:100, volume percent) to obtain seven fractions (Frs. 4.1–4.7). Fr. 4.1 was purified by preparative HPLC eluted with MeOH-H_2O (50%, volume percent) to obtain compound **3** (28 mg, t_R = 72.1 min). Fr.4.3 was purified by preparative HPLC eluted with MeOH-H_2O (25%, volume percent) to obtain compounds **1** (28 mg, t_R = 27.1 min) and **2** (5 mg, t_R = 30.2 min). Fr.2 (12.5 g) was further separated by another silica gel column eluting with petroleum ether-EtOAc (100:1–100:100, volume percent) to afford seven fractions (Frs. 2.1–2.7). Fr.2.5 was separated by Sephadex LH-20 eluting with MeOH and obtained four fractions (Frs. 2.5.1–2.5.4). Fr. 2.5.4 was purified by preparative HPLC eluting with MeOH–H_2O (52%, volume percent) to yield compound **5** (45 mg, t_R = 72.0 min). Fr. 2.6 was further separated by another silica gel column eluting with petroleum ether-EtOAc (100:1–100:20) to afford seven fractions (Frs. 2.6.1–2.6.7). Fr. 2.6.2 was further separated by Sephadex LH-20 eluting with MeOH to obtain four fractions (Frs. 2.6.2.1–2.6.2.4). Fr. 2.6.2.1 was purified by preparative HPLC eluting with MeOH-H_2O (50%, volume percent) to yield compound **6** (10 mg, R_f = 0.24). Fr. 2.6.2.2 was purified by preparative HPLC eluting with MeOH-H_2O (55%, volume percent) to yield compound **4** (20 mg, t_R = 87 min).

3. Results and discussion

3.1. Structure determination

(1*S*,2*R*,5*R*,7*S*,8*R*)-2,8-Epoxy-5-hydroxybisabola-3,10-dioen-9-one (**1**) was isolated as a colorless oil (methanol). The molecular formula was established as $C_{15}H_{22}O_3$ from HR-ESI-MS [*m*/*z* 273.1461 $[M + Na]^+$ (calc.273.1463)]. The ^1H NMR (400 MHz, $CDCl_3$) spectrum (Table 1) showed two olefinic proton signals δ_H 5.66 (1H, brd, *J* = 2.4 Hz), δ_H 6.25 (1H, brs), three carbon proton signals δ_H 4.01 (1H, t, *J* = 4.4 Hz), 4.46 (1H, d, *J* = 6.9 Hz), and 4.62 (1H, brt, *J* = 4.2 Hz), four methyl proton signals δ_H 0.92 (3H, d, *J* = 7.2 Hz), 1.82 (3H, s), 1.90 (3H, s), 2.15 (3H, s). In addition, the ^{13}C NMR (100 MHz, $CDCl_3$) spectrum showed 15 carbon signals, a ketone carbonyl at δ_C 201.0, four of them are sp^2 carbons at δ_C 123.7, 139.4, 121.0 and 157.7, and 10 signals sp^3 carbons at δ_C 74.8, 67.1, 85.9, 41.6, 40.6, 32.8, 28.1, 21.2, 20.8 and 15.1 were observed. According to δ_H 4.62 (1H, brt, *J* = 4.2 Hz), 4.01 (1H, t, *J* = 4.4 Hz), 5.66 (1H, brd, *J* = 2.4 Hz) and carbon signal δ_C 41.6 (C-1), 74.8 (C-2), 123.7 (C-3), 139.4 (C-4), 67.1 (C-5), 32.8 (C-6) can be launched a cyclohexanone fragment. The structure of the heptanone side chain can be deduced from signals δ_C 201.0(C-9) and δ_H 6.25 (1H, brs), 4.62 (1H, brt, *J* = 4.2 Hz), 4.46 (1H, d, *J* = 6.9 Hz). The presence of three saturated oxycarbon signals δ_C 67.1 (C-5) and 85.9 (C-8) indicated that an epoxy structure was formed between C-2 and C-8 sites. According to the NOESY spectrum (Fig. 1) of compound **1**, H-1 was related to H-2, and H-5, H-8 was related to H-7, H-1 and H-2 were on the same side of the ring, H-5, H-7, and H-8 was on the other side of the ring. The NMR data of compound **1** suggested the planar structure was determined (Li et al, 2009). On the other hand, it was speculated that the relative configuration of compound **1** was (1*S*,2*R*,5*R*,7*S*,8*R*) or (1*R*,2*S*,5*S*,7*R*,8*S*). The absolute configuration of the compound was determined by further experiments. The absolute configuration of compound **1** was established based on CD analysis. The compound **1** displayed a negative value at 350 nm in the CD spectrum (Fig. 2), and the absolute configuration of the C-5 hydroxyl group was determined to be *R* (Frelek & Szczepek, 1999). Therefore, the absolute configuration of compound **1** was (1*S*,2*R*,5*R*,7*S*,8*R*). Based on the above information, the structure of compound **1** was determined.

(1*R*,2*R*,5*R*,7*S*,8*R*)-2,8-Epoxy-5-hydroxybisabola-3,10-dioen-9-one (**2**) was isolated as a colorless oil (methanol). The molecular formula was established as $C_{15}H_{22}O_3$ from HR-ESI-MS [*m*/*z* 273.146 1

Table 1
^1H NMR (400 MHz) and ^{13}C NMR (100 MHz) data of compounds **1–2** ($CDCl_3$, δ in 1×10^{-6}).

Positions	Compound **1**		Compound **2**	
	δ_H	δ_C	δ_H	δ_C
1	2.21 (1H, m)	41.6	1.52 (1H, m)	43.7
2	4.62 (1H, brt, *J* = 4.2 Hz)	74.8	4.56 (1H, brs)	74.4
3	5.66 (1H, brd, *J* = 2.4 Hz)	123.7	5.65 (1H, m)	122.2
4	–	139.4	–	141.6
5	4.01 (1H, t, *J* = 4.4 Hz)	67.1	4.06 (1H, m)	68.7
6	1.75–1.85 (2H, m)	32.8	2.01–2.08 (2H, m)	34.1
7	2.35 (1H, m)	40.6	2.51 (1H, m)	42.7
8	4.46 (1H, d, *J* = 6.9 Hz)	85.9	4.59 (1H, d, *J* = 6.3 Hz)	85.5
9	–	201.0	–	200.6
10	6.25 (1H, brs)	121.0	6.27 (1H, brs)	120.9
11	–	157.7	–	157.4
12	1.90 (3H, s)	28.1	1.92 (3H, s)	28.0
13	2.15 (3H, s)	21.2	2.17 (3H, s)	21.2
14	0.92 (3H, d, *J* = 7.2 Hz)	15.1	0.92 (3H, d, *J* = 7.2 Hz)	14.9
15	1.82 (3H, s)	20.8	1.83 (3H, s)	18.9

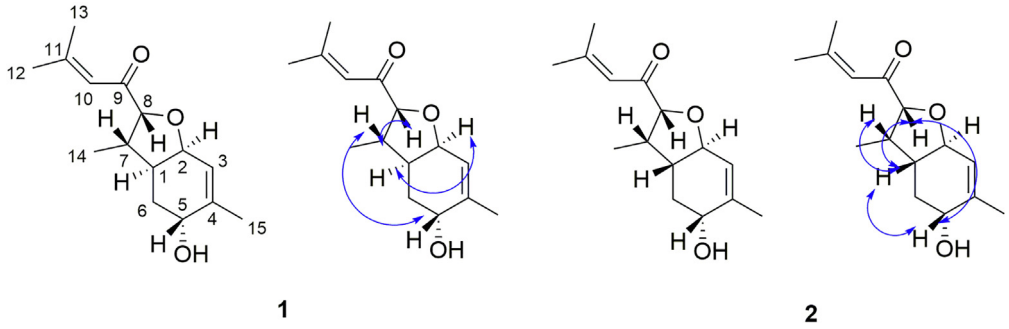

Fig. 1. Structures and key NOESY correlations of compounds 1 and 2.

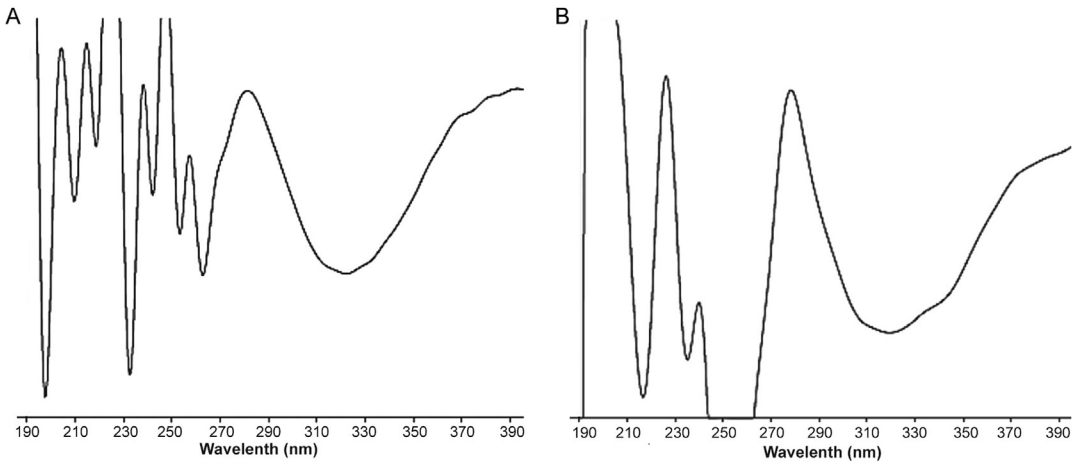

Fig. 2. $[Rh_2(OCOCF_3)_4]$ CD spectra of compound **1** (A) and **2** (B).

$[M + Na]^+$ (calc.273.1456)], ^1H NMR (400 MHz, $CDCl_3$) spectrum (Table 1) gave two olefinic hydrogen proton signals δ_H 5.65 (1H, m), 6.27 (1H, brs), three hydrogen proton signals on oxygenated carbon δ_H 4.06 (1H, m), 4.56 (1H, brs), 4.59 (1H, d, J = 6.3 Hz), four methyl proton signals δ_H 0.92 (3H, d, J = 7.2 Hz), 1.83 (3H, s), 1.92 (3H, s), 2.17 (3H, s), and methines proton signal δ_H 1.52 (1H, m). The ^{13}C NMR (100 MHz, $CDCl_3$) spectrum showed 15 carbon signals, a ketone carbonyl at δ_C 200.6, four of them were sp^2 carbons at δ_C 122.2, 141.6, 120.9, and 157.4, and 10 signals eight sp^3 carbons at δ_C 74.4, 68.7, 85.5, 42.7, 40.6, 34.1, 28.0, 21.2, 18.9 and 14.9 were observed. According to hydrogen proton signal δ_H 4.56 (1H, brs), 4.06 (1H, m), 5.65 (1H, m) and carbon signal δ_C 43.7 (C-1), 74.4 (C-2), 122.2 (C-3), 141.6 (C-4), 68.7 (C-5), 34.1 (C-6) should be launched a cyclohexanone fragment. The structure of the heptanone side chain can be deduced from signals δ_C 200.6 (C-9) and δ_H 6.27 (1H, brs), 4.56 (1H, brs), 4.59 (1H, d, J = 6.3 Hz). The presence of two saturated oxycarbon signals δ_C 68.7 (C-5) and 85.5 (C-8) indicated that an epoxy structure was formed between C-2 and C-8 sites. The comparison showed that the planar structure of compound **2** was consistent with that of compound **1**. The NOESY (Fig. 1) spectrum of compound **2** was different. H-1 was related to H-5, H-8, H-7 was related to H-8, and H-2 was not related to these hydrogens, so H-1, H-5, H-7, and H-8 were on the same side of the ring, and H-2 was on the other side of the ring. The relative configuration was estimated to be (1*R*,2*R*,5*R*,7*S*,8*R*) or (1*S*,2*S*,5*S*,7*R*,8*S*), by measuring the CD spectrum (Fig. 2) of the rhodium salt of compound **2**, it showed a negative value at 350 nm. Therefore, the absolute configuration of the hydroxyl group at the C-5 position was consistent with that of compound **1**, and the *R* was the absolute configuration of compound **2**. The absolute configuration was (1*R*,2*R*,5*R*,7*S*,8*R*).

Compound **3** was isolated as a colorless oil (methanol). $[\alpha]_D^{20}$ + 38.2 (c 0.965, MeOH). The molecular formula was established as $C_{15}H_{20}O_2$ from HR-ESI-MS [m/z 487.280 0 [2 M + Na]$^+$ (calc.487.282 4)], indicating six degrees of unsaturation. Its hydrogen spectrum, carbon spectrum, and HSQC, HMBC spectrum data showed that an isopropyl group conjugated with carbonyl δ_C 199.8 and δ_H 1.85 (3H, s), 2.09 (3H, s), 6.02 (1H, brs), and data δ_H 2.71 (1H, dd, J = 6.2, 15.8 Hz), 2.62 (1H, dd, J = 8.2, 15.8 Hz), 3.32 (1H, m), 1.24 (3H, d, J = 6.9 Hz) indicated that the compound had a side chain part characterized by the alkane sesquiterpene. The hydrogen spectrum data δ_H 7.28 (2H, d, J = 7.9 Hz), 7.21 (2H, d, J = 7.9 Hz) indicate that there was a *para*-substituted benzene ring structure, comparing the hydrogen spectrum and carbon spectrum data of compound **3** with *ar*-turmerone, it was found that some of the signals are very similar. The difference was that there was one less methyl signal than *ar*-turmerone, and δ_H 4.64 (2H, s) indicated that compound **3** oxidation occured on the aromatic ring methyl group of the *ar*-turmerone structure. Combined with the mass spectrum data, it was found that oxidation became a hydroxyl group. The carbons at δ_C 65.4 conform to the inference. In addition, in the HMBC spectrum (Fig. 3), the signal δ_H 4.64 (2H, s), δ_C 127.4 (C-3, 5), and 138.8 (C-4) were related. The above evidence proved the chemical structure of compound **3**. Compound **3** was consistent with the reaction product of *ar*-turmerone in the literature (Gaikwad & Madyastha, 2002), so it was determined that compound **3** was 6-(4-Hydroxy methyl phenyl)-2-methyl-hept-2-ene-4-one. The optical rotation value of compound **3** was positive, which was consistent with the optical rotation value of the known compound of a similar structure. It was determined that the configuration at the C-7 position was *S*. This compound is a new natural product isolated from a plant for the first time and the NMR spectrum data is given for the first time. The attribution of the hydrocarbon signal was shown.

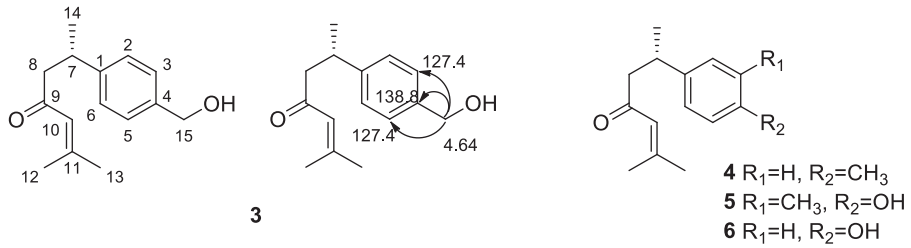

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Fig. 3. Structures of compounds **3**–**6** and HMBC correlations of compound **3**.

Table 2
NMR data of compound **3** and a known compound *ar*-turmerone reported in reference ($CDCl_3$, δ in 1×10^{-6}).

Positions	Compound **3**		*ar*-Tumerone	
	δ_C	δ_H	δ_C	δ_H
1	146.4	–	134.4	–
2, 6	127.2	7.28 (2H, d, *J* = 7.9 Hz)	128.0	7.0 (4H, s)
3, 5	127.4	7.21 (2H, d, *J* = 7.9 Hz)	125.6	–
4	138.8	–	142.6	–
7	35.5	3.32 (1H, m)	34.5	3.20 (1H, m)
8	52.6	2.71 (1H, dd, *J* = 6.2, 15.8 Hz)	51.6	2.51 (1H, dd, *J* = 6.0, 15.6 Hz)
		2.62 (1H, dd, *J* = 8.2, 15.8 Hz)		2.62 (1H, dd, *J* = 6.0, 15.6 Hz)
9	199.8	–	198.7	–
10	124.2	6.02 (1H, brs)	123.0	5.93 (1H, s)
11	155.5	–	153.9	–
12	27.8	1.85 (3H, s)	26.5	1.72 (3H, s)
13	20.8	2.09 (3H, s)	20.9	2.01 (3H, s)
14	22.1	1.24 (3H, d, *J* = 6.9 Hz)	19.9	1.15 (3H, d, *J* = 7.2 Hz)
15	65.4	4.64 (2H, s)	19.6	2.21 (3H, s)

The experiment also isolated three known compounds sesquiterpene *ar*-turmerone (**4**) 2-methyl-6-(4-hydroxyphenyl-3-methyl)-2-hepten-4-one (**5**) 2-methyl-6-(4-hydroxyphenyl)-2-hep ten-4-one (**6**) (Zeng et al., 2007), the structure of compound **4** was confirmed by co-thick layer experiment, and the physicochemical properties were consistent with those of turmeric. Compound **3** (Uehara, Yasuda, Takeya, Itokawa, & Iitaka, 1989) was determined to be an aromatic flavonoid.

3.2. Physico-chemical properties

(1*S*,2*R*,5*R*,7*S*,8*R*)-2,8-Epoxy-5-hydroxybisabola-3,10-dioen-9-on e (**1**): colorless oil, $[\alpha]_D^{20}$ −50.0 (c0.1000, MeOH). HR-ESI-MS gives the quasi-molecular ion peak *m*/*z* 273.1461 $[M + Na]^+$ (calc.273.146 3), molecular formula $C_{15}H_{22}O_3$; UV (MeOH) λmax 226 (0.50), 235 (0.50), and 237 (0.50), ^1H and ^{13}C NMR and 2D NMR data are shown in Table 1. (1*R*,2*R*,5*R*,7*S*,8*R*)-2,8-epoxy-5-hydroxybisabola-3,10-dioe n-9-one (**2**): colorless oil, $[\alpha]_D^{20}$-25.0 (c0.1000, MeOH). HR-ESI-MS gives the quasi-molecular ion peak *m*/*z* 273.1461 $[M + Na]^+$ (calc.273.145 6), molecular formula $C_{15}H_{22}O_3$; UV (MeOH) λmax 227 (0.50), 234 (0.50), and 238 (0.50), ^1H NMR and 2D NMR data are shown in Table 1. 6-(4-Hydroxymethylphenyl)-2- methyl-hept-2-ene-4-one (**3**) colorless oil, $[\alpha]_D^{20}$ + 38.2 (c0.965, MeOH). HR-ESI-MS gives the quasi-molecular ion peak *m*/*z* 487.2800 $[2M + Na]^+$ (calc.487.2824), molecular formula $C_{15}H_{20}O_2$; UV (MeOH) λmax 236 (0.52), 221 (0.52), and 219 (0.52); IR (KBr) λ_{max} 3 418, 3 093, 3 053, 3 016, 2 962, 2 929, 2 874, 1 905, 1 683, 1 616, 1 514, 1 446, 1 422, 1 383, 1 305, 1 230, 1 211, 1 126, 1 040, 1 011, 898, 884, 822, 770, 722, 695, 644, 629, 585, 537, 460 cm^{-1}; ^1H NMR and 2D NMR data are shown in Table 2.

4. Conclusion

Six compounds were isolated and identified in our study, among which two new sesquiterpenes and one new natural sesquiterpene were obtained. The results were innovative and further enriched the chemical constituents of *C. longa*. Compounds **1**–**2** were new compounds whose planar structures were reported, and their absolute configuration was determined for the first time by rhodium salt CD and NOESY spectra. Compound **3** was a new natural product whose absolute configuration was determined for the first time.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.chmed.2022.11.007.

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