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Note

Structural Revision of Guttiferone F and 30-*epi*-Cambogin

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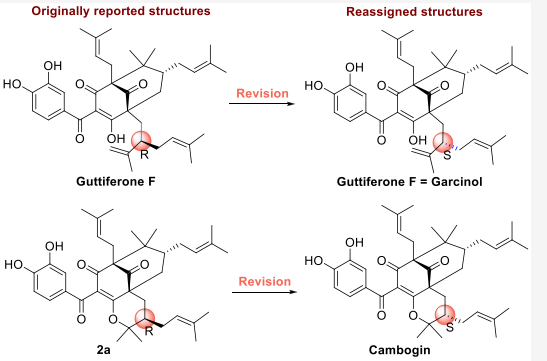
ABSTRACT: Guttiferone F, a natural polyprenylated polycyclic acylphloroglucinol, was originally assigned as the 30-epimer of garcinol by NMR data analyses. Conversion of guttiferone F in the presence of acid afforded its cyclized form (**2a**), which was previously assigned as 30-*epi*-cambogin. However, the absolute configurations of guttiferone F and **2a** have not been determined. Reinvestigation of the structures of those two compounds, using X-ray and NMR data analyses and chemical transformation, revealed that the original assignment of the C-30 absolute configuration in guttiferone F and **2a** should be inverted. Guttiferone F is indeed garcinol, and **2a**, which was previously identified as 30-*epi*-cambogin, is cambogin.



In 1999, Fuller and co-workers reported the isolation of a new natural polyprenylated polycyclic acylphloroglucinol (PPAP), guttiferone F, from the root wood of *Allanblackia stuhlmannii*. Its structure was identified as the C-30 epimer of garcinol by extensive NMR data analyses and by treatment with acid to afford its analogue (**2a**), previously assigned as 30-*epi*-cambogin.[1] These two compounds received a significant amount of attention.[2−12] In a recent investigation, guttiferone F was also isolated from the twigs of *Garcinia esculenta* Y. H. Li.[13] The bioactive investigation revealed that guttiferone F induced HeLa cell caspase 3-mediated apoptosis[4] and prostate cancer cell apoptosis under serum starvation via Ca^{2+} and c-Jun-N-terminal kinase (JNK) elevation.[14,15] An in vivo study showed that guttiferone F significantly inhibited the growth of the xenograft model using PC3 cells, combined with caloric restriction.[14] These results suggested that guttiferone F is a potential anticancer compound. However, the assignment of the absolute configuration of guttiferone F is a challenging task due to its structural complexity. Herein, we reinvestigated the absolute configurations of guttiferone F and **2a** using chemical transformation and X-ray and NMR data analyses. These data revealed that the original assignment of the C-30 absolute configuration of guttiferone F and **2a** should be inverted, and their structures should be revised as garcinol and cambogin, respectively. The HRMS, ^{1}H and ^{13}C NMR, and optical rotation data of **1**, reisolated from the twigs of *G. esculenta*, were highly similar to those of guttiferone F[1] (Table 1 and Experimental Section). Its structure was originally assigned as the C-30 epimer of garcinol based on its acid-catalyzed conversion to **2a** (Schemes 1 and 2).[1] However, little evidence, except the spectroscopic data comparison with garcinol and cambogin, was presented to support the configurational assignments of guttiferone F and **2a** due to their structural complexity and instrumentation limitations previously. In the current study, experimental and calculated ECD data were tentatively used to determine the absolute configuration of **1**. However, the calculated ECD spectrum of both (1*R*,5*R*,7*R*,30*S*)-**1** and (1*R*,5*R*,7*R*,30*R*)-**1** matched well with the experimental ECD spectrum of **1** (Figure 1), which indicated that the ECD data could not be used to determine the C-30 absolute configuration. Since attempts to confirm the absolute configuration of **1** using ECD data failed, attempts were made to obtain its crystals suitable for X-ray diffraction analysis. Indeed, crystals of **1** (CDCC 2032861) were obtained by the slow evaporation of a MeCN solution at room temperature. The X-ray diffraction experiments with Cu Kα radiation not only permitted definition of the 2D structure but also allowed the assignment of the absolute configuration of **1** as (1*R*,5*R*,7*R*,30*S*) [Figure 2, Flack parameter value 0.14(7)]. This result provided definitive evidence for assigning the (30*S*) absolute configuration of **1**, which was in accordance with garcinol instead of 30-*epi*-garcinol.

Fuller et al.[1] compared NMR spectra of guttiferone F in methanol-d_4 + 0.1% TFA with those of garcinol in $CDCl_3$.[16] Since the NMR solvent has a significant influence on the chemical shift values, even for the same compound, their NMR data cannot be simply used to determine the structure of

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Table 1. ^{1}H and ^{13}C NMR Spectroscopic Data of Guttiferone F, Garcinol, and 1

	recorded in methanol-d_4 + 0.1% TFA				recorded in $CDCl_3$	
	guttiferone F (ref)[a]		**1**[b]		garcinol (ref)[c]	**1**[d]
no.	δ_C	δ_H (J in Hz)	δ_C	δ_H (J in Hz)	δ_C	δ_C
1	69.4		69.8		69.9	69.9
2	193.7		194.3		195.2	194.5
3	117.9		118.0		116.0	116.0
4	196.1		196.3		194.0	194.1
5	59.7		60.0		58.1	58.0
6	50.2		50.4		42.7	42.7
7	47.9	1.49, m	48.1	1.48, m	47.0	47.0
8	43.8	2.24, d (13.5)	43.9	2.25, d (14.0)	49.8	49.7
		2.04, dd (13.5, 7.4)		2.05, m		
9	210.6		210.8		207.1	209.4
10	195.5		195.6		199.1	198.6
11	129.5		129.7		127.8	128.1
12	117.3	7.19, d (2.0)	117.4	7.19, d (2.1)	116.6	116.5
13	146.3		146.4		143.9	143.8
14	152.5		152.6		149.9	149.9
15	115.0	6.68, d (8.0)	115.2	6.69, d (8.3)	114.4	114.4
16	125.3	6.96, dd (8.0, 2.0)	125.4	6.97, dd (8.3, 2.1)	120.2	120.3
17	27.1	2.71, dd (13.0, 9.0)	27.2	2.72, dd (13.3, 9.3)	27.2	27.2
		2.56, dd (13.0, 3.0)		2.57, dd (13.3, 3.2)		
18	121.3	5.03, m	121.5	5.07, m	122.8	122.8
19	135.9		136.0		135.5	135.3
20	26.4	1.73, s	26.6	1.74, s	26.2	26.2
21	18.3	1.69, s	18.5	1.70, s	18.4	18.5
22	23.2	1.15, s	23.3	1.16, s	22.9	22.8
23	27.3	0.99, s	27.5	1.00, s	27.2	27.2
24	30.3	2.09, m	30.4	2.09, m	29.1	29.1
		2.02, m		2.02, m		
25	125.6	4.87, m	125.7	4.87, m	123.9	124.0
26	133.6		133.8		133.1	133.0
27	25.9	1.65, s	26.1	1.66, s	25.9	25.9
28	18.2	1.49, s	18.4	1.50, s	18.1	18.1
29	37.3	1.98, m	37.5	1.98, m	36.3	36.3
		1.92, dd (13.5, 4.5)		1.92, dd (14.0, 5.4)		
30	45.2	2.62, m	45.4	2.63, m	43.7	43.7
31	149.5		149.6		148.2	148.2
32	113.0	4.45 (2H), s	113.1	4.46, d (3.9)	112.9	112.8
33	18.2	1.58, s	18.4	1.59, s	17.8	17.8
34	33.5	2.01, m	33.6	2.02, m	32.8	32.8
35	124.1	5.03, m	124.3	5.03, m	124.2	124.3
36	132.7		132.8		132.2	132.1
37	26.0	1.65, s	26.1	1.66, s	26.0	26.0
38	18.2	1.57, s	18.4	1.58, s	18.1	18.0

[a]Recorded at 500 MHz (^{1}H) and 125 MHz (^{13}C). [b]Recorded at 400 MHz (^{1}H) and 100 MHz (^{13}C). [c]Recorded at 150 MHz (^{13}C). [d]Recorded at 150 MHz (^{13}C).

guttiferone F as the C-30 epimer of garcinol. To clarify this problem, the ^{1}H and ^{13}C NMR spectra of **1** were remeasured in $CDCl_3$, and these data were similar to those of garcinol (Table 1 and Experimental Section).[16−18] On the basis of the above analysis, we concluded that guttiferone F is actually garcinol, instead of 30-*epi*-garcinol (Table 2).

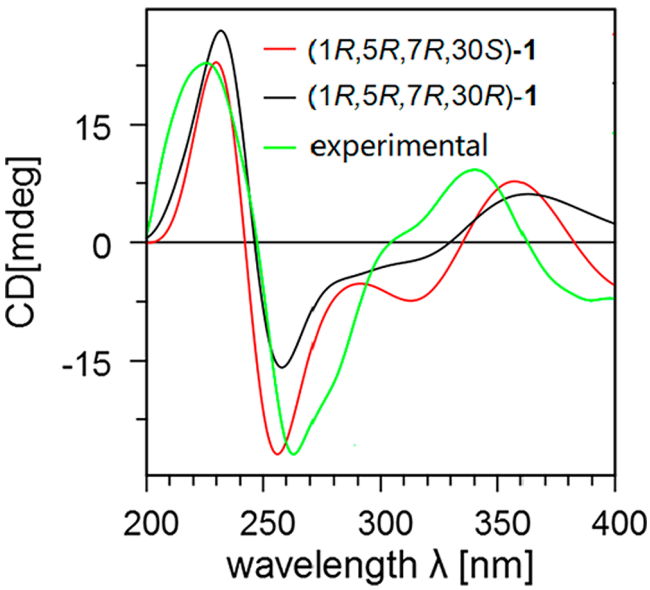

Figure 1. Experimental and calculated ECD spectra of **1**.

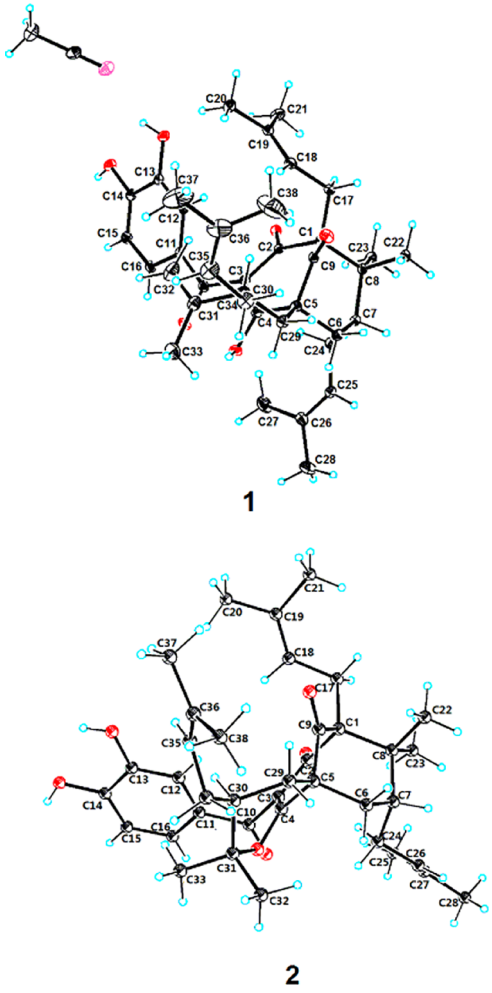

Figure 2. X-ray crystallographic structures of **1** and **2**.

In order to further verify the epimeric configuration at C-30 of guttiferone F, Fuller et al. transformed it via acid treatment into the substituted tetrahydropyran (**2a**) (Scheme 2). When the reaction was repeated using the same reaction conditions,[1] the

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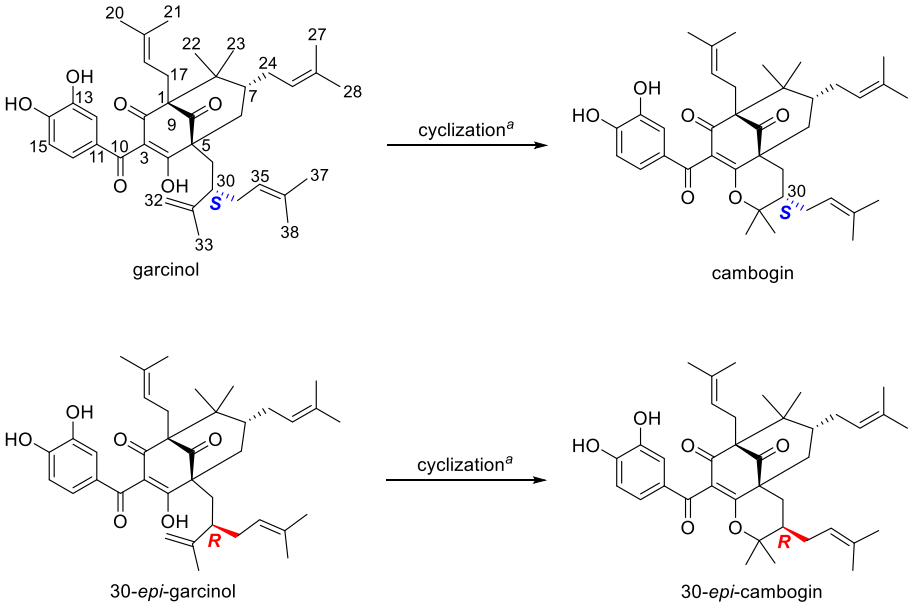
Scheme 1. Structures of Garcinol, Cambogin, and Their C-30 Epimers



[a]Reaction conditions: garcinol was refluxed with benzene solution containing traces of acid, such as HCl or CF_3COOH, or heated at about 200 °C for 5−10 min.

Scheme 2. Originally Reported and Reassigned Structures of Guttiferone F and 2a

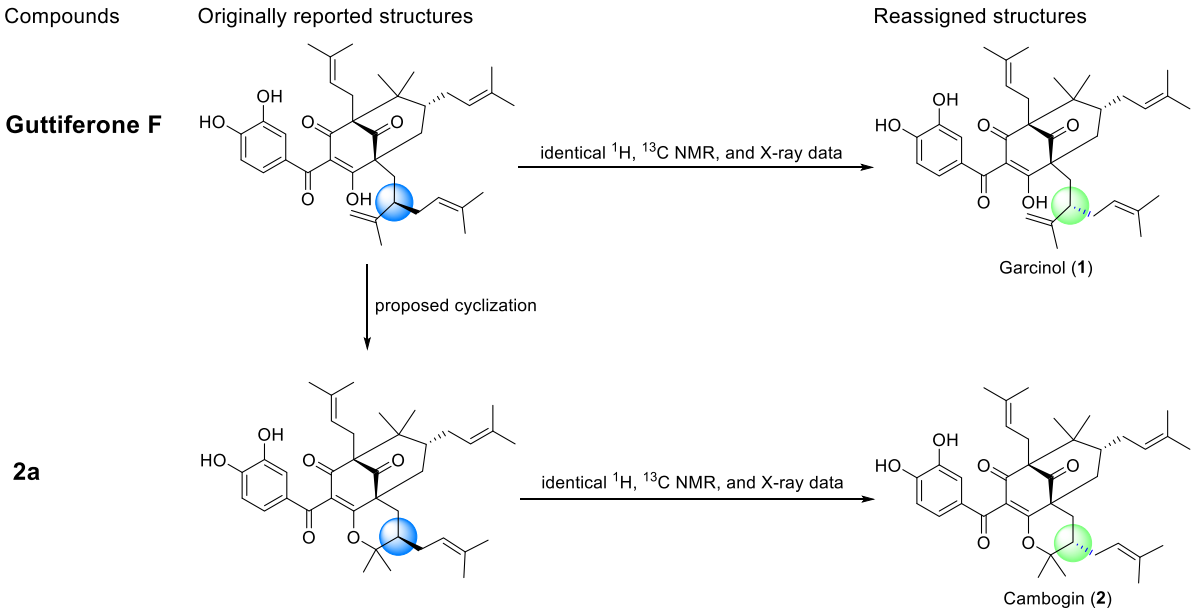


Table 2. Comparison of the Chemical Shift Values of C-29−C-32 for 1 in $CDCl_3$ and Methanol-d_4 + 0.1% TFA

	recorded in $CDCl_3$		recorded in methanol-d_4 + 0.1% TFA	
no.	garcinol (ref)	**1**	guttiferone F (ref)	**1**
29	36.3	36.3	37.3	37.5
30	43.7	43.7	45.2	45.4
31	148.2	148.2	149.5	149.6
32	112.9	112.8	113.0	113.1

major reaction product **2** was obtained as colorless prisms from an acetone/MeOH solution. Examination of the ^{1}H and ^{13}C NMR data (Table 3), as well as the value of the specific rotation, confirmed that the structure of **2** and **2a** was the same (Scheme 2). The absolute configuration of **2** was assigned as (1*R*,5*R*,7*R*,30*S*) by single-crystal X-ray (Cu Kα) diffraction data analysis, which showed that the absolute configuration of **2** was the same as that of cambogin (Figure 2). The Flack parameter was refined, giving a value of 0.06(4), which indicates the correct handedness. This is different from the orientation of the substituent at C-30 originally assigned for **2a**. In addition, the NMR data of **2** in pyridine-d_5 were also similar to the literature data of cambogin (Table 3), the absolute configuration of which was confirmed by X-ray crystallographic data analysis.[19] Therefore, **2a** is actually cambogin, not 30-*epi*-cambogin as originally proposed.

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Table 3. ^{1}H and ^{13}C NMR Spectroscopic Data of 2a, 2, and Cambogin

	recorded in methanol-d_4 + 0.1% TFA				recorded in pyridine-d_5			
	2a (ref)[a]		**2**[b]		cambogin (ref)[d]		**2**[e]	
no.	δ_C	δ_H (J in Hz)	δ_C	δ_H (J in Hz)	δ_C	δ_H (J in Hz)	δ_C	δ_H (J in Hz)
1	69.6		69.6		69.2		69.1	
2	196.3		196.5		195.0		195.0	
3	110.2		[c]		127.2		127.1	
4	173.9		173.8		171.4		171.4	
5	52.6		52.8		52.2		52.1	
6	46.7		47.2		46.8		46.7	
7	47.5	1.50, m	47.6	1.50, m	47.0	1.59, dt (6.2, 6.1)	46.9	1.59, m
8	40.0	2.28, d (14.0)	40.2	2.28, d (14.6)	39.8	2.43, brd (14.1)	39.8	2.42, brd (14.5)
		2.02, dd (14.5, 7.4)		2.02, dd (14.6, 7.3)		2.11, dd (14.1, 7.3)		2.09, dd (14.5, 7.4)
9	208.0		208.1		207.9		207.9	
10	194.3		194.4		193.0		193.0	
11	131.2		131.3		130.0		130.8	
12	116.3	7.24, d (2.0)	116.4	7.24, d (2.0)	116.6	8.05, d (2.0)	116.5	8.08, d (2.0)
13	146.8		146.7		147.8		147.7	
14	152.5		152.7		153.7		153.7	
15	115.6	6.73, d (8.0)	115.8	6.73, d (8.0)	116.5	7.28, d (8.1)	116.4	7.28, d (8.2)
16	124.4	7.02, dd (8.0, 2.0)	124.5	7.03, dd (8.0, 2.0)	124.3	7.68, dd (8.1, 2.0)	124.4	7.69, dd (8.2, 2.0)
17	26.5	2.63, dd (13.8, 8.0)	26.7	2.64, dd (12.9, 8.8)	26.7	2.95, dd (13.5, 7.6)	26.6	2.94, dd (13.5, 7.7)
		2.43, dd (13.5, 5.0)		2.44, dd (13.3, 5.3)		2.76, dd (13.7, 5.6)		2.75, dd (13.5, 5.5)
18	121.1	4.91, m	121.3	4.91, m	121.7	5.42, brt (6.5)	121.6	5.42, t (6.3)
19	135.3		135.6		134.5		134.4	
20	26.3	1.58, s	26.3	1.59, s	26.6	1.57, s	26.5	1.56, s
21	18.2	1.57, s	18.2	1.58, s	18.8	1.71, s	18.7	1.70, s
22	22.8	1.14, s	23.0	1.15, s	27.1	1.05, s	27.0	1.04, s
23	27.0	0.98, s	27.2	0.98, s	23.1	1.30, s	23.0	1.29, s
24	30.5	2.67, m	30.7	2.68, m	30.4	3.21, ddd (14.4, 10.7, 9.5)	30.3	3.20, m
		2.12, m		2.12, m		1.82, ddd (14.2, 9.5, 9.5)		1.81, m
25	126.2	4.91, m	126.7	4.91, m	126.4	5.09, brt (6.5)	126.4	5.07, m
26	133.5		134.1		132.9		133.3	
27	26.1	1.68, s	26.1	1.69, s	26.5	1.74, s	26.4	1.74, s
28	18.5	1.66, s	18.8	1.67, s	19.0	1.91, s	18.9	1.91, s
29	29.0	3.02, dd (14.0, 3.0)	29.4	3.03, dd (14.2, 3.6)	29.1	3.27, dd (13.9, 3.1)	29.0	3.27, dd (14.2, 3.5)
		1.01, dd (14.0)		1.03, m		1.14, dd (13.9, 13.7)		1.14, m
30	44.7	1.36, m	44.8	1.38, m	43.8	1.66, dt (9.9, 5.0)	43.7	1.66, m
31	88.1		88.4		87.2		87.1	
32	29.0	0.90, s	29.2	0.90, s	21.7	1.23, s	21.6	1.22, s
33	21.3	1.25, s	21.7	1.26, s	29.4	1.07, s	29.3	1.07, s
34	30.5	2.05, m	30.7	2.08, m	30.4	2.42 brd (14.1)	30.3	2.42, d (14.5)
		1.83, m		1.83, m		1.96 brd (14.1)		1.98, m
35	122.8	5.20, m	123.1	5.21, t (7.0)	122.8	5.09, brt (6.5)	122.7	5.07, m
36	134.6		134.8		133.7		133.7	
37	26.1	1.78, s	26.1	1.79, s	26.2	1.68, s	26.1	1.67, s
38	17.8	1.63, s	18.2	1.64, s	18.3	1.56, s	18.2	1.55, s

[a]Recorded at 500 MHz (^{1}H) and 125 MHz (^{13}C). [b]Recorded at 400 MHz (^{1}H) and 100 MHz (^{13}C). [c]Not detected. [d]Recorded at 500 MHz (^{1}H) and 125 MHz (^{13}C). [e]Recorded at 400 MHz (^{1}H) and 100 MHz (^{13}C).

In summary, our reinvestigation of the structure determination of guttiferone F and **2a**, using X-ray and NMR data analyses and chemical transformation, revealed that the assigned absolute configuration of C-30 in guttiferone F and **2a** should be inverted and their structures should be reassigned as garcinol and cambogin, respectively. In recent years, the absolute configurations of PPAPs have been determined by X-ray diffraction data or comparison of their experimental and calculated ECD spectra. However, the absolute configurations of many PPAPs are difficult to define by single-crystal X-ray diffraction because they are more often than not obtained as gums or oils. Although ECD methods have been widely used to determine the absolute configuration of many PPAPs, this method is not suitable to assign the absolute configuration of a stereocenter located far away from the chromophores,[20] such as C-30 in garcinol. The absolute configuration of many derivatives of garcinol remains unknown and needs to be further investigated.[13,21,22] In view of such problems, our team is now focusing on establishing a strategy to quickly synthesize a class of PPAPs with chiral side chains by asymmetric total synthesis, including 30-*epi*-garcinol.

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EXPERIMENTAL SECTION

General Experimental Procedures. Optical rotations were measured using an Autopol VI polarimeter. Ultraviolet absorption spectra were recorded on a UV-2401 PC spectrophotometer. ECD spectra were recorded on a Chirascan-plus spectrometer (Applied Photophysics Ltd., Surrey, UK). IR spectra were recorded on a PerkinElmer 577 spectrometer. NMR spectra were measured on Bruker AV-400 and Bruker AV-600 spectrometers. Mass spectrometry was performed on a SYNAPT G2-Si HDMS (Waters Corp., Manchester, UK) with an electrospray ion source (Waters, Milford, MA, USA) connected to a lock-mass apparatus, which performed real-time calibration correction. Column chromatography was performed with CHP20P MCI gel (75−150 μm, Mitsubishi Chemical Corporation, Japan), silica gel (100−200 or 200−300 mesh, Qingdao Haiyang Chemical Co., Ltd.), Sephadex LH-20 (GE Healthcare Bio-Sciences AB, Sweden), and reversed-phase C_{18} silica gel (50 μm, YMC, Kyoto, Japan). Precoated TLC sheets of silica gel 60 GF254 (Qingdao Haiyang Chemical Co., Ltd.) were used.

Plant Material. The *G. esculenta* plants, including twigs and leaves, were collected in Nujiang, Yunnan, People's Republic of China, in September 2014. The sample was identified by Dr. Hongmei Zhang, Shanghai University of Traditional Chinese Medicine. A voucher specimen (Herbarium No. 20140901) was deposited at the School of Pharmacy, Shanghai University of Traditional Chinese Medicine.

Isolation of Compound 1. The dried and powdered plants of *G. esculenta*, including twigs and leaves (23 kg), were extracted by refluxing with 95% EtOH (4 × 200 L). The combined crude extracts were evaporated, diluted with H_2O, and extracted with petroleum ether and EtOAc. The petroleum ether-soluble extract (350 g) was subjected to passage over an MCI column eluted with H_2O and 95% EtOH. The 95% EtOH-eluting fraction (249.3 g) was chromatographed by a silica gel column using a gradient of petroleum ether/acetone (100:0 to 50:50, v/v) to afford 16 fractions, A−P, as described previously.[23] Fraction D was separated by ODS and eluted in a step-gradient manner with MeOH/H_2O (5:95 to 100:0), to afford compound **1** (1.5 g).

Garcinol (1): yellow gum; $[\alpha]_D^{20}$ −160 (*c* 0.04, $CHCl_3$); UV (MeOH) λ_{max} (log ε) 280 (3.47) nm; ECD (*c* 4.85 × 10^{-4} M, MeOH) λ_{max} nm ($\Delta\varepsilon$) 198 (−27.99), 225 (+13.12), 269 (−21.29); IR (KBr) ν_{max} 3396, 2969, 2923, 1727, 1639, 1602, 1523, 1442, 1375, 1290, 1193, 1116, 892, 777 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.01−6.98 (m, 2H), 6.65 (d, *J* = 8.2 Hz, 1H), 5.10 (m, 1H), 5.04 (d, *J* = 8.2 Hz, 1H), 4.92 (t, *J* = 7.0 Hz, 1H), 4.40 (d, *J* = 24.0 Hz, 2H), 2.77−2.71 (m, 2H), 2.59−2.56 (m, 1H), 2.35 (d, *J* = 14.0, 1H), 2.15−2.08 (m, 4H), 1.95−2.01 (m, 2H), 1.93−1.85 (m, 2H), 1.80 (s, 3H), 1.73 (s, 3H), 1.69 (s, 3H), 1.67 (s, 3H), 1.60 (s, 3H), 1.54 (s, 3H), 1.44−1.42 (m, 2H), 1.25 (s, 3H), 1.15 (s, 3H), 1.05 (m, 1H), 1.01 (s, 3H); HRESIMS *m/z* 603.3687 $[M + H]^+$ (calcd for $C_{38}H_{51}O_6$, 603.3686).

Crystal Data for 1. $C_{40}H_{53}NO_6$ (M = 643.83 g/mol): monoclinic, space group $P2_1$ (no. 4), *a* = 10.8272(4) Å, *b* = 9.0795(3) Å, *c* = 19.3623(7) Å, β = 103.0290(10)°, *V* = 1854.42(11) $Å^3$, *Z* = 2, *T* = 173.0 K, μ(Cu Kα) = 0.607 mm^{-1}, D_{calc} = 1.153 g/cm^3, 13 031 reflections measured (4.684° ≤ 2θ ≤ 136.366°), 6546 unique (R_{int} = 0.0253, R_{sigma} = 0.0339), which were used in all calculations. The final R_1 was 0.0350 ($I > 2\sigma(I)$) and wR_2 was 0.0943. Flack parameter = 0.14(7). Hooft = 0.14(7). Crystallographic data for **1** have been deposited at the Cambridge Crystallographic Data Center (deposition number: CCDC 2032861).

Conversion of 1 to 2. A solution of 10 mg of **1** in 5 mL of toluene and 30 μL of concentrated HCl was refluxed for 40 min. After cooling, the reaction mixture was washed with H_2O (3 × 5 mL) and evaporated to dryness. Compound **2** (3.5 mg) was obtained as colorless prismatic crystals from acetone/MeOH. The conversion can also be achieved thermally by heating **1** (10 mg) at 200 °C for 5 min, from which 5 mg of **2** was obtained under the same recrystallization conditions.

Cambogin (2): colorless prismatic crystal; mp 238−239 °C; $[\alpha]_D^{20}$ −132 (*c* 0.02, $CHCl_3$); UV (MeOH) λ_{max} (log ε) 234 (3.66), 279 (3.73) nm; ECD (*c* 6.31 × 10^{-4} M, MeOH) λ_{max} nm ($\Delta\varepsilon$) 228 (+8.18), 263 (−10.03), 343 (+3.35); IR (KBr) ν_{max} 3461, 2971, 2925, 1720, 1670, 1598, 1517, 1440, 1371, 1292, 1182, 1105, 773, 640 cm^{-1}; HRESIMS *m/z* 603.3687 $[M + H]^+$ (calcd for $C_{38}H_{51}O_6$, 603.3686).

Crystal Data for 2. $C_{38}H_{50}O_6$ (M = 602.78 g/mol): monoclinic, space group $P2_1$ (no. 4), *a* = 14.5894(3) Å, *b* = 11.1597(3) Å, *c* = 20.4193(5) Å, β = 93.6280(10)°, *V* = 3317.87(14) $Å^3$, *Z* = 4, *T* = 173.01 K, μ(Cu Kα) = 0.636 mm^{-1}, D_{calc} = 1.207 g/cm^3, 22 097 reflections measured (6.07° ≤ 2θ ≤ 136.87°), 11 551 unique (R_{int} = 0.0209, R_{sigma} = 0.0294), which were used in all calculations. The final R_1 was 0.0295 ($I > 2\sigma(I)$) and wR_2 was 0.0826. Flack parameter = 0.06(4). Hooft = 0.06(4). Crystallographic data for **2** have been deposited at the Cambridge Crystallographic Data Center (deposition number: CCDC 2032864).

Computational Details. The calculations of **1** were performed using Gaussian 09. Conformational analysis was initially carried out using Accelrys Discovery Studio 2.5 to generate conformers by Best, then minimized by Smart Minimizer using the CHARMm molecular mechanics force field. The minimized conformers were optimized at the B3LYP/6-31G(d,g) level in the gas phase. Room-temperature equilibrium populations were calculated according to the Boltzmann distribution law. The ECD calculations were performed using TDDFT at the B3LYP/6-31G(d,p) level in the gas phase. SpecDis 1.61 was used to visualize the ECD spectra of **1** after a Boltzmann statistical weighting, to generate the Gaussian curve, and for comparison with experimental data.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.jnatprod.0c01031.

HRESIMS, IR, ECD, NMR spectra, and X-ray crystallographic data of compounds **1** and **2** (PDF)

Single-crystal X-ray diffraction data for compound **1** (CIF)

Single-crystal X-ray diffraction data for compound **2** (CIF)

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Notes

The authors declare no competing financial interest.
Crystallographic data for the structure(s) have been deposited with the Cambridge Crystallographic Data Centre. Copies of the data can be obtained, free of charge, on application to the Director, CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: + 44-(0)1223-336033 or e-mail: deposit@ccdc.cam.ac.uk).

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