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NOTE

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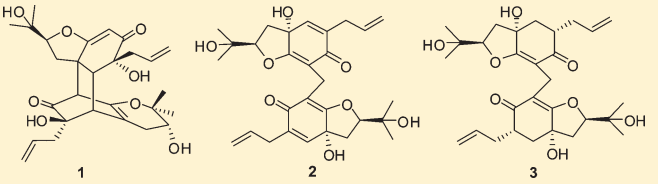
Dimeric Prenylated C_6-C_3 Compounds from the Stem Bark of *Illicium oligandrum*

Wen-Zhao Tang,[†] Shuang-Gang Ma,[†] Jing Qu, Shi-Shan Yu,* Yun-Bao Liu, Dong-Min Su, and Jing Liu

Key Laboratory of Bioactive Substance and Resources Utilization of Chinese Herbal Medicine, Ministry of Education, Institute of Materia Medica, Chinese Academy of Medical Sciences and Peking Union Medical College, No. 1 Xian nong tan Street, 100050, Beijing, People's Republic of China

Supporting Information

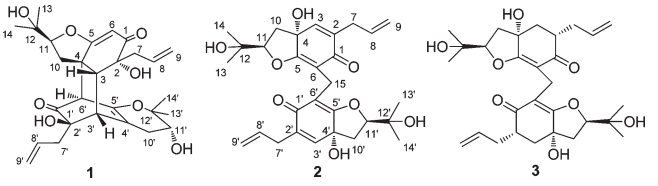
ABSTRACT: Three new dimeric prenylated C_6-C_3 compounds, namely, illicidiones A (**1**), B (**2**), and C (**3**), were isolated from the stem bark of *Illicium oligandrum*. The structure and absolute configuration of these compounds were determined by extensive spectroscopic and chemical analyses, including NMR, modified Mosher method, and single-crystal X-ray study. Compounds **1**−**3** exhibited weak anti-inflammatory activities.



Prenylated C_6-C_3 compounds, also known as phytoquinoids, are characteristic constituents of the genus *Illicium* (Magnoliaceae).[1−3] The skeletal structure of these compounds includes a saturated or an unsaturated cyclohexanone with an allyl group and an oxygenated prenyl group at C-2 and C-4, respectively. In some cases, the prenyl group forms a furanoid ring at C-5. From a chemical point of view, prenylated C_6-C_3 compounds contain the structural units of a lignan [$C_6 + C_3$] and an isoprene [C_5]. Some prenylated C_6-C_3 compounds possess activities for cancer chemoprevention.[4,5]

Illicium oligandrum, a toxic shrub of this genus, is used in folk medicine for treating rheumatoid arthritis. Several new rearranged prenylated C_6-C_3 compounds, sesquiterpenes, lignans and phenolic diglycosides were isolated from this plant.[6−8] As a result of our continued search for the bioactive constituents of this plant, three new dimers, illicidiones A (**1**), B (**2**), and C (**3**), were isolated from the $CHCl_3$ extract of the stem bark of *I. oligandrum*. This study is the first report of prenylated C_6-C_3 dimers. Herein, we report the isolation, structural elucidation, and anti-inflammatory activity for compounds **1**−**3**.

Compounds **1**−**3** displayed several common spectroscopic characteristics. The UV and IR spectra showed absorptions of conjugated carbonyl and hydroxy groups. NMR analysis showed distinctive features of prenylated C_6-C_3 compounds isolated from some plants of the genus *Illicium*.



Illicidione A (**1**) was obtained as colorless prisms (MeOH). Its molecular formula, $C_{28}H_{36}O_8$, was established by HRESIMS (*m*/*z* 523.2299 $[M + Na]^+$, calcd for $C_{28}H_{36}O_8Na$ 523.2308), ^{13}C NMR, and various DEPT data. IR absorptions revealed the presence of hydroxy (3524 and 3258 cm^{-1}), unconjugated carbonyl (1733 cm^{-1}), α,β-conjugated carbonyl (1672, 1642 cm^{-1}), and olefinic bond (1619 cm^{-1}) groups. The ^{13}C NMR spectrum showed 28 carbon resonances, which were categorized through DEPT experiments as two carbonyl, eight quaternary, eight methine, six methylene, and four methyl carbons. The ^1H NMR, $^1H-^1H$ COSY, and HMBC spectra indicated the presence of four hydroxy groups that could be exchanged by D_2O, four methyl groups, two allyl groups, and two partial structural fragments with ABX spin patterns [$C(10)H_2-C(11)H$ and $C(10')H_2-C(11')H$]. These characteristic NMR data indicated that compound **1** was a prenylated C_6-C_3 dimer[9] comprising moieties **A** and **B** (Figure 1).

NMR characteristics of moiety **A** were similar to those of 2,3-dehydroillifunone C.[9] Significant ^{13}C NMR differences between moiety **A** and 2,3-dehydroillifunone C were the upfield shifts of C-2, C-3, and C-4 ($\Delta\delta$ 58.5, 95.1, and 20.1), implying the presence of OH-2 and disappearance of an olefinic bond in moiety **A**. For moiety **B**, compared with C-12 (δ 70.5) in moiety **A**, C-12′ was downfield shifted by $\Delta\delta$ 8.6, which suggested that C-12′ was attached to C-5′ via an oxygen atom to form a dihydropyrano ring.[10] This ring with an olefinic bond at C-4′ and C-5′ was further confirmed by four-bond HMBCs of CH_3-13′/C-5′ and H_2-10′/C-4′, 5′. An exchangeable doublet at δ 4.15 (OH-11′) and $^1H-^1H$ COSY correlations of H-10′/H-11′/H (OH-11′) were observed, indicating the presence of a partial structural fragment of $C(10')H_2-C(11')H-OH$ in moiety **B**. The linkages between moieties **A** and **B** from C-3 to C-3′ and C-4 to C-6′ were verified by the HMBCs of H-3/C-2′, 3′, 4′, H-3′/C-2, 3, 4, and

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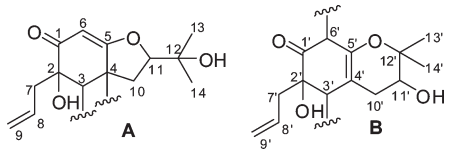

Figure 1. Structures of moieties **A** and **B** in **1**.

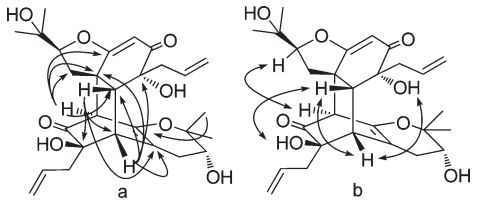

Figure 2. HMBC correlations (a) and NOEs (b) of **1**.

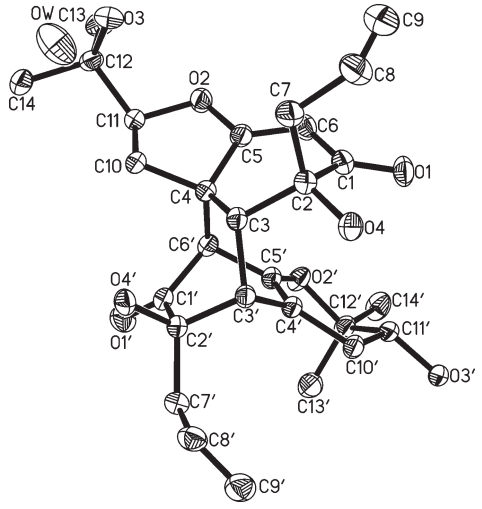

Figure 3. ORTEP drawing of **1**.

H-6′/C-3, 4, 5, 10 (Figure 2) and a strong vicinal coupling ^{1}H−^{1}H COSY correlation of H-3/H-3′.

The stereochemistry of **1** was elucidated on the basis of NOE correlations (Figure 2), CD data, single-crystal X-ray diffraction analysis, and a modified Mosher method. Irradiation of H-3 (δ 2.95) showed an NOE association of OH-2′ (δ 4.56) to indicate the β-orientation of OH-2′. The NOE association between OH-2 (δ 4.19) and H-3′ (δ 3.14) indicated the α-orientation of OH-2. Additionally, the α-orientation of H-11 was suggested by the NOE association between H-11 (δ 4.66) and H-6′ (δ 2.83). These results were comfirmed by single-crystal X-ray diffraction analysis of **1** (Figure 3). The absolute configuration could be established by CD analysis. As in bicyclo[2,2,2]oct-5-en-2-one, the orientation of the β,γ-unsaturated carbonyl moiety determines the sign of the Cotton effect.[11] The CD spectrum of **1** shows a negative Cotton effect at 304 nm for the n → π^* transition of the β,γ-unsaturated carbonyl moiety, which is identical to that of bacchopetiolone.[12] Therefore, C-2′ possesses the *R* absolute configuration. Combined with the relative configuration, the absolute configurations for C-3′, C-6′, C-2, C-3, C-4, and C-11 were assigned as *R*, *S*, *R*, *R*, *R*, and *S*, respectively. In addition, the positive Cotton effect at 253 nm for the $\pi \rightarrow \pi^*$ transition of the α,β-unsaturated carbonyl

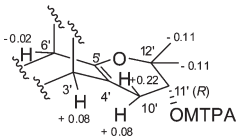

Figure 4. ^{1}H NMR chemical shift differences of the MTPA ester derivatives of **1**.

moiety confirms the 4*R* absolute configuration.[13,14] Using a modified Mosher method,[15] the absolute configuration of C-11′ was determined as *R*, on the basis of the analysis of the diagnostic proton chemical shift values between protons of the (*S*)- and (*R*)-MTPA esters of **1** (**1b** and **1a**) (Figure 4). Thus, compound **1**, named illicidione A, was determined to possess the 2*R*, 3*R*, 4*R*, 11*S*, 2′*R*, 3′*R*, 6′*S*, 11′*R* absolute configuration.

Illicidione B (**2**) was obtained as a white powder. Its molecular formula was established as $C_{29}H_{36}O_8$ from HRESIMS, ^{13}C NMR, and various DEPT data. The ^{1}H and ^{13}C NMR spectra showed an additional methylene resonance in the upfield (δ 3.23; δ 17.5) region compared to the spectra of 2,3-dehydroillifunone C and distinctive features of 2,3-dehydroillifunone C except that C-6 was transformed to a quaternary olefinic carbon.[9] Therefore, the MS and NMR data revealed that **2** was a dimeric prenylated C_6-C_3 compound connected by a methylene group. The connection C-6−CH_2−C-6′ was further confirmed by the HMBCs between H_2-15 (δ 3.23) and C-1, 1′ (δ 187.5), C-5, 5′ (δ 175.8), and C-6, 6′ (δ 108.6). The $[\alpha]^{20}_D$ value and the CD spectrum of **2** were similar to those of 2,3-dehydroillifunone C (see Supporting Information). Thus, the two monomeric moieties in **2** were identical.

Illicidione C (**3**) was obtained as a white powder. Its molecular formula was determined as $C_{29}H_{40}O_8$ from HRESIMS and ^{13}C NMR data. The ^{1}H and ^{13}C NMR spectra of **3**, like those of compound **2**, showed signals for an additional methylene group in the upfield (δ 3.15; δ 17.3) region and a C-6-substituted illifunone D.[1] Thus, compound **3** was also a prenylated C_6-C_3 dimer and supported by the same HMBCs of H_2-15/C-1, 1′, 5, 5′, 6, 6′. The $[\alpha]^{20}_D$ value and the CD spectrum of **3** were similar to those of illifunone D (see Supporting Information). Therefore, compound **3** was identified as an illifunone D dimer connected by a methylene group at C-6, 6′.

The anti-inflammatory effects of **1**, **2**, and **3** were determined. Compounds **1**−**3** were assessed by measuring the inhibitory ratios of β-glucuronidase release in rat polymorphonuclear leukocytes (PMNS) induced by the platelet-activating factor (PAF) in vitro.[16] The inhibitory ratios of **1**−**3** were 38.2%, 18.6%, and 25.3% at a concentration of 10 μM, respectively. Ginkgolide B was used as a positive control, with an inhibitory ratio of 83.5% at 10 μM.

EXPERIMENTAL SECTION

General Experimental Procedures. Melting points were determined on an XT-4 micro melting point apparatus (uncorrected). Optical rotations were measured on a Perkin-Elmer 341 digital polarimeter at 589 nm. UV spectra were recorded on a Hitachi UV-240 spectrophotometer. CD analysis was performed on a JASCO J-810 spectropolarimeter with a 0.1 cm cell at room temperature under the following conditions: speed 200 nm/min, time constant 1 s, and bandwidth 2.0 nm. IR spectra were recorded on KBr disks using a Nicolet Impact 410 FT-IR spectrophotometer. NMR spectra were obtained on an Inova 400 MHz spectrometer. The HSQC and HMBC experiments were optimized for 140.0 and 8.0 Hz, respectively. ESIMS were measured on

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Table 1. ^{1}H (400 MHz) and ^{13}C (100 MHz) NMR Data of Compound 1 (acetone-d_6)

position	δ_C	δ_H (J in Hz)	position	δ_C	δ_H (J in Hz)
1	198.9		1′	206.6	
2	77.1		2′	75.1	
3	44.1	2.95 (d, 2.8)	3′	44.7	3.14 (d, 2.8)
4	52.9		4′	108.6	
5	177.1		5′	145.5	
6	96.6	5.28 (s)	6′	60.1	2.83 (s)
7	49.9	2.22 (d, 7.2)	7′	41.4	2.57 (dd, 14.4, 5.6)
		2.22 (d, 7.2)			2.23 (dd, 14.4, 8.8)
8	133.6	5.61 (m)	8′	134.2	5.98 (m)
9	118.4	4.97 (d, 12.0)	9′	118.9	5.14 (d, 9.6)
		4.96 (d, 14.8)			5.10 (d, 16.4)
10	35.3	2.33 (dd, 12.8, 10.4)	10′	30.6	2.14 (dd, 16.4, 2.0)
		2.13 (dd, 10.4, 5.6)			1.88 (dd, 16.4, 7.6)
11	90.2	4.66 (dd, 10.4, 5.6)	11′	69.4	3.43
					(ddd, 7.6, 5.2, 2.0)
12	70.5		12′	79.1	
13	26.6	1.33 (s)	13′	25.7	1.14 (s)
14	26.3	1.15 (s)	14′	20.5	1.05 (s)
2-OH		4.19 (s)	2′-OH		4.56 (s)
12-OH		3.89 (s)	11′-OH		4.15 (d, 5.2)

an Agilent 1100 Series LC/MSD trap mass spectrometer. HRESIMS values were measured on a Bruker FTMS APEXIII 7.0T mass spectrometer. Column chromatography was performed on silica gel (200−300 mesh, Qingdao Marine Chemical Factory, China), ODS (40−70 μm, Merck), and Sephadex LH-20 (Amersham Pharmacia Biotech AB, Sweden). HPLC was carried out on a Shimadzu LC-6AD with an SPD-10A detector. A reversed-phase C_{18} column (YMC Pack ODS-A 20 × 250 mm, 10 μm) and TLC with glass precoated silica gel GF254 plates (Qingdao Marine Chemical Factory, China) were employed. Spots were visualized under UV light or by spraying with 10% H_2SO_4 in 95% EtOH, followed by heating.

Plant Material. The stem bark of *Illicium oligandrum* was collected from Guangxi Province, China, in September 2004 and identified by Prof. Song-ji Wei of Guangxi Traditional Medical College. A voucher specimen (No. 04086) was deposited in the herbarium of the Institute of Materia Medica, Chinese Academy of Medical Sciences and Peking Union Medical College.

Extraction and Isolation. The air-dried stem bark of *I. oligandrum* (3.0 kg) was extracted under reflux with 95% aqueous EtOH. The residue (540 g) obtained by concentrating the EtOH extract in vacuo was suspended in H_2O, then partitioned successively with petroleum ether, $CHCl_3$, EtOAc, and *n*-BuOH. The $CHCl_3$ extract (70 g) was chromatographed on a silica gel column eluted with petroleum ether−Me_2CO (40:1 to 1:1 gradient) to yield fractions A_1−A_6. Fraction A_5 (7.2 g) was again chromatographed over a silica gel column with petroleum ether−Me_2CO (10:1, 5:1, 3:1, and 1:1, v/v) to give fractions D_1−D_5. Fraction D_3 (1.8 g) was separated by an RP C_{18} column (aqueous MeOH, 40%) to yield **1** (70 mg). Fraction D_2 (2.5 g) was separated on a silica gel column repeatedly with petroleum ether−EtOAc (20:1, 10:1, 5:1, 3:1, and 1:1, v/v) to give fractions E_1−E_6. Fraction E_2 (125 mg) was purified by RP-HPLC with MeOH−H_2O (60:40) as mobile phase to yield **2** (47 mg). Compound **3** (41 mg) was obtained from fraction E_3 (118 mg) by RP-HPLC with MeOH−H_2O (58:42) as mobile phase.

Illicidione A (**1**): colorless prism; mp 213−215 °C; $[\alpha]^{20}_D$ +36.5 (*c* 0.5, MeOH); UV (MeOH) (log ε) λ_{max} 265 (4.26) nm; CD (MeOH) λ_{max} (mdeg) 253 (+20), 304 (−16.2) nm; IR (KBr) ν_{max} 3524, 3258, 2978, 1733, 1672, 1642, 1619, 1414 cm^{-1}; ^{1}H and ^{13}C NMR data, see Table 1; ESIMS (positive) *m*/*z* 501.2 $[M + H]^+$; HRESIMS (positive) *m*/*z* 501.2472 $[M + H]^+$ (calcd for $C_{28}H_{37}O_8$ 501.2488), 523.2299 $[M + Na]^+$ (calcd for $C_{28}H_{36}O_8Na$ 523.2308).

Table 2. ^{1}H (400 MHz) and ^{13}C (100 MHz) NMR Data of 2 and 3 (acetone-d_6)

	2		3	
position	δ_C	δ_H (J in Hz)	δ_C	δ_H (J in Hz)
1	187.5		200.4	
2	138.8		44.7	2.23 (m)
3	137.0	6.57 (s)	34.6	1.83 (dd, 16.4, 9.2)
				2.31 (d, 16.4)
4	73.0		76.7	
5	175.8		175.8	
6	108.6		110.0	
7	34.1	2.87 (2 H, d, 6.8)	38.7	2.46 (m); 2.66 (m)
8	136.4	5.75 (m)	138.6	5.83 (m)
9	116.8	5.00 (d, 16.0)	116.6	5.04 (d, 16.4)
		4.94 (d, 9.2)		5.00 (d, 9.2)
10	36.3	2.20 (dd, 12.4, 4.8)	40.7	2.29 (m)
		2.08 (dd, 12.4, 9.6)		2.17 (dd, 12.4, 9.6)
11	92.5	4.86 (dd, 9.6, 4.8)	91.2	4.74 (dd, 9.6, 5.2)
12	70.3		70.1	
13	28.0	1.51 (s)	28.2	1.48 (s)
14	24.6	1.07 (s)	24.6	1.04 (s)
15	17.4	3.23 (2H, s)	17.3	3.15 (2H, s)
4-OH		4.70 (s)		4.52 (s)
12-OH		4.43 (s)		4.44 (s)

Esterification of 1. A 16 μL portion of (*S*)-MTPACl was added to a solution of **1** (8.6 mg) in pyridine (0.5 mL), and the mixture was kept at room temperature for 2 h. The reaction mixture was diluted with EtOH, evaporated, and purified by preparative silica gel TLC developed with *n*-hexane−Et_2O (9:1) to afford the (*R*)-MTPA ester **1a** (3.2 mg). In the same manner, compound **1** (9.8 mg) was treated with (*R*)-MTPACl to give the (*S*)-MTPA ester **1b** (3.6 mg).

*(R)-MTPA ester (**1a**):* ^{1}H NMR (500 MHz, acetone-d_6) δ 7.49−7.44 (5H, m, aromatic), 5.84 (1H, m, H-8′), 5.62 (1H, m, H-8), 5.31 (1H, s, H-6), 5.02 (1H, t, *J* = 5.0 Hz, H-11′), 5.00 (1H, d, *J* = 8.0 Hz, H-9′a), 4.97 (1H, d, *J* = 13.0 Hz, H-9′b), 4.73−4.67 (2H, m, H_2-9), 4.55, 4.27, 3.90 (each 1H, s, OH × 3), 3.46 (3H, s, OCH_3 of MTPA), 3.14 (1H, d, *J* = 2.5 Hz, H-3′), 2.99 (1H, d, *J* = 2.5 Hz, H-3), 2.91 (1H, s, H-6′), 2.47 (1H, dd, *J* = 18.0, 5.0 Hz, H-10′α), 1.91 (1H, dd, *J* = 18.0, 5.0 Hz, H-10′*β*), 2.35 (1H, dd, *J* = 13.0, 10.5 Hz, H-10α), 2.15 (1H, dd, *J* = 13.0, 5.5 Hz, H-10*β*), 2.45 (1H, dd, *J* = 16.5, 5.5 Hz, H-7′a), 2.00 (1H, dd, *J* = 16.5, 9.5 Hz, H-7′b), 2.23 (2H, d, *J* = 7.0 Hz, H_2-7), 1.35 (3H, s, CH_3-13), 1.14 (3H, s, CH_3-14), 1.20 (3H, s, CH_3-13′), 1.13 (3H, s, CH_3-14′); ESIMS (positive) *m*/*z* 717.2 $[M + H]^+$, 739.2 $[M + Na]^+$.

*(S)-MTPA ester (**1b**):* ^{1}H NMR (500 MHz, acetone-d_6) δ 7.52−7.47 (5H, m, aromatic), 5.99 (1H, m, H-8′), 5.63 (1H, m, H-8), 5.32 (1H, s, H-6), 5.14 (1H, d, *J* = 10.5 Hz, H-9′a), 5.09 (1H, d, *J* = 17.0 Hz, H-9′b), 5.01 (1H, m, H-11′), 5.00−4.97 (2H, m, H_2-9), 4.67 (1H, dd, *J* = 10.5, 5.5 Hz, H-11), 4.64, 4.30, 3.90 (each 1H, s, OH × 3), 3.43 (3H, s, OCH_3 of MTPA), 3.22 (1H, d, *J* = 2.5 Hz, H-3′), 3.02 (1H, d, *J* = 2.5 Hz, H-3), 2.89 (1H, s, H-6′), 2.55 (1H, dd, *J* = 17.0, 5.5 Hz, H-10′α), 2.13 (1H, dd, *J* = 17.0, 5.5 Hz, H-10′*β*), 2.36 (1H, dd, *J* = 12.5, 10.0 Hz, H-10α), 2.17 (1H, m, H-10*β*), 2.59 (1H, dd, *J* = 14.5, 5.5 Hz, H-7′a), 2.16 (1H, m, H-7′b), 2.24 (2H, d, *J* = 7.0 Hz, H_2-7), 1.35 (3H, s, CH_3-13), 1.15 (3H, s, CH_3-14), 1.09 (3H, s, CH_3-13′), 1.02 (3H, s, CH_3-14′); ESIMS (positive) *m*/*z* 717.2 $[M + H]^+$.

X-ray Structural Determination of Illicidione A (1). X-ray diffraction intensity data of **1** were collected on an MAC DIP-2030K

diffractometer with graphite-monochromated Mo Kα radiation (λ = 0.71073 Å) by the ω scan technique [scan width 0−180°, $2\theta \leq 50°$]. Crystal data: $C_{28}H_{36}O_8 \cdot H_2O$, MW 518.57, colorless prism crystals with size 0.10 × 0.30 × 0.60 mm^3, monoclinic, space group $P2_1$, T = 253(2) K, a = 9.393(1) Å, b = 14.905(1) Å, c = 19.192(1) Å, V = 2686.9(4) Å^3, D_c = 1.282 g/cm^3, Z = 4. 2755 reflections were collected, of which 2619 with $|F|^2 \geq 2\sigma|F|^2$ were observed. The structure was solved by direct methods and refined by block-matrix least-squares procedure to R_1 = 0.0463, wR_2 = 0.1264 ($w = 1/\sigma|F|^2$). Hydrogen positions were found from difference Fourier maps and geometric calculations. All calculations were carried out on a personal computer using the SHELX-97 program system.

CCDC-759134 (for **1**) contains supplementary crystallographic data. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Illicidione B (***2***)*:* white powder; $[\alpha]^{20}_D$ −24.4 (*c* 0.4, MeOH); UV (MeOH) (log ε) λ_{max} 242 (4.26), 315 (3.28) nm; CD (MeOH) λ_{max} (mdeg) 253 (−88.2), 306 (−62.0), 341 (+58.0) nm; IR (KBr) ν_{max} 3418, 2977, 1676, 1642, 1619, 1345, 1209 cm^{-1}; ^{1}H and ^{13}C NMR data, see Table 2; ESIMS (positive) m/z 513.2 $[M + H]^+$, 535.2 $[M + Na]^+$; HRESIMS (positive) m/z 535.2305 $[M + Na]^+$ (calcd for $C_{29}H_{36}O_8Na$ 535.2302).

Illicidione C (***3***)*:* white powder; $[\alpha]^{20}_D$ +9.4 (*c* 0.15, MeOH); UV (MeOH) (log ε) λ_{max} 265 (4.43) nm; CD (MeOH) λ_{max} (mdeg) 261 (−61.4), 305 (+41.2) nm; IR (KBr) ν_{max} 3361, 2975, 1656, 1624, 1594, 1346, 1217, 1036, 805 cm^{-1}; ^{1}H and ^{13}C NMR data, see Table 2; ESIMS (positive) m/z 539.2 $[M + Na]^+$; HRESIMS (positive) m/z 517.2800 $[M + H]^+$ (calcd. for $C_{29}H_{41}O_8$ 517.2795).

Anti-inflammatory Activity Assay. On the basis of reported procedures,[16] the anti-inflammatory activities of compounds **1**−**3** were assayed by measuring the inhibition of the platelet-activating factor induced release of β-glucuronidase from rat polymorphonuclear leukocytes in vitro.

■ ASSOCIATED CONTENT

Supporting Information. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: yushishan@imm.ac.cn. Tel: +86-10-63165326. Fax: +86-10-63017757.

Author Contributions

†These authors contributed equally to this work.

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