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Difengpienols A and B, two new sesqui-neolignans with anti-inflammatory activity from the bark of *Illicium difengpi*

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ABSTRACT

As part of our ongoing search for novel and bioactive natural products in Karst plants, two new sesqui-neolignans, difengpienol A (**1**) and difengpienol B (**2**), together with two known analogues (**3** and **4**), were isolated from the stem bark of *Illicium difengpi*. Their structures were elucidated by analysis of spectroscopic data. Difengpienol A (**1**) possessed a unique 1, 4-dibenzodioxocine moiety. All isolates were evaluated for inhibitory effects against lipopolysaccharide (LPS)-induced nitric oxide (NO) production in RAW264.7 macrophages cells. Compounds **1** and **2** showed moderate inhibitory effects on NO production with IC_{50} values of 16.9 and 23.8 μM. A biosynthetic pathway was also proposed for **1** and **2**.

1. Introduction

Sesqui-neolignans are a rather rare class of phenylpropanoids presumably derived from three C6–C3 units linked by *ortho, ortho*-coupling or *ortho, para*-coupling (Sy and Brown, 1996). Since macranthol, the first example of this type of natural product, was discovered from *Illicium macranthum* in 1989 (Kouno et al., 1989), a series of diverse sesqui-neolignans with different oxygenation and aromatization patterns have been isolated from plants of the *Illicium* genus (Dong et al., 2012, 2013; Kouno et al., 1991; Liu et al., 2010; Moriyama et al., 2007; Yin et al., 2013). Some of these compounds exhibited anti-AChE, neurotrophic, cytotoxic, and anti-oral microbial activities.

Illicium difengpi K. I. B et K. I. M. (Illiciaceae), native to China, is a toxic shrub that grows in the mountainous Karst areas of Guangxi Province. Its stem bark is listed in the Chinese Pharmacopeia as a traditional Chinese medicine to treat rheumatoid arthritis, lumbar muscle strain and traumatic injury. In our previous paper, four new and seven known lignan glycosides were isolated from the *n*-BuOH-soluble fraction of an ethanol extract of this plant (Pan et al., 2016). As part of our continuing search for novel and bioactive natural products from Karst plants, the CH_2Cl_2-soluble fraction of the ethanol extract from the stem barks of *I. difengpi* was investigated, which led to the isolation of two new sesqui-neolignans named difengpienol A (**1**) and difengpienol B (**2**), together with dunnianol (**3**) and isodunnianol (**4**) (Fig. 1). In this paper, we describe the structural elucidation and plausible biosynthetic pathway of the new compounds, as well as the anti-inflammatory activity of all isolates.

2. Results and discussion

Compound **1** was obtained as an amorphous oil, and had the molecular formula $C_{29}H_{30}O_6$ with fifteen degrees of unsaturation as deduced from HR-EI-MS *m/z* 474.2040 $[M]^+$. The IR absorption bands at 3426, 1639, and 1494 cm^{-1} revealed the presence of hydroxyl and phenyl groups. The ^{1}H-NMR spectrum (Table 1) exhibited signals for two 1,2,4-trisubstituted benzene rings [δ_H 7.25 (1H, d, J = 2.0 Hz, H-3), 7.18 (1H, dd, J = 8.0, 2.0 Hz, H-5), 7.04 (1H, d, J = 8.0 Hz, H-6); δ_H 7.25 (1H, d, J = 2.0 Hz, H-3′), 7.24 (1H, dd, J = 8.0, 2.0 Hz, H-5′), 7.23 (1H, d, J = 8.0 Hz, H-6′)], two allyl groups [δ_H 3.43 (2H, d, J = 7.0 Hz, H-7), 5.98 (1H, ddt, J = 17.0, 10.0, 7.0 Hz, H-8), 5.10 (1H, J = 17.0, 1.5 Hz, H-9a), 5.03 (1H, J = 10.0, 1.5 Hz, H-9b); δ_H .45 (2H, d, J = 7.0 Hz, H-7′), 6.04 (1H, ddt, J = 17.0, 10.0, 7.0 Hz, H-8′), 5.14 (1H, J = 17.0, 1.5 Hz, H-9′a), 5.05 (1H, J = 10.0, 1.5 Hz, H-9′b)], a symmetrical 1,2,4,6-tetrasubstituted aromatic ring at δ_H 6.73 (2H, s), two methoxyl groups [δ_H 3.82 (6H, s)], as well as three aliphatic proton signals at δ_H 4.78 (1H, d, J = 10.0 Hz, H-7″), 4.09 (1H, ddt, J = 10.0, 7.0, 2.5 Hz, H-8″), 3.57 (1H, dd, J = 12.0, 2.0 Hz, H-9″a), and 3.50 (1H, dd, J = 12.0, 7.0 Hz, H-9″b). The ^{13}C-NMR spectrum (Table 1), assigned by the aid of routine analyses of DEPT, ^{1}H-^{1}H COSY, HSQC and HMBC spectra, revealed 29 carbon signals due to eighteen aromatic carbons ranging from

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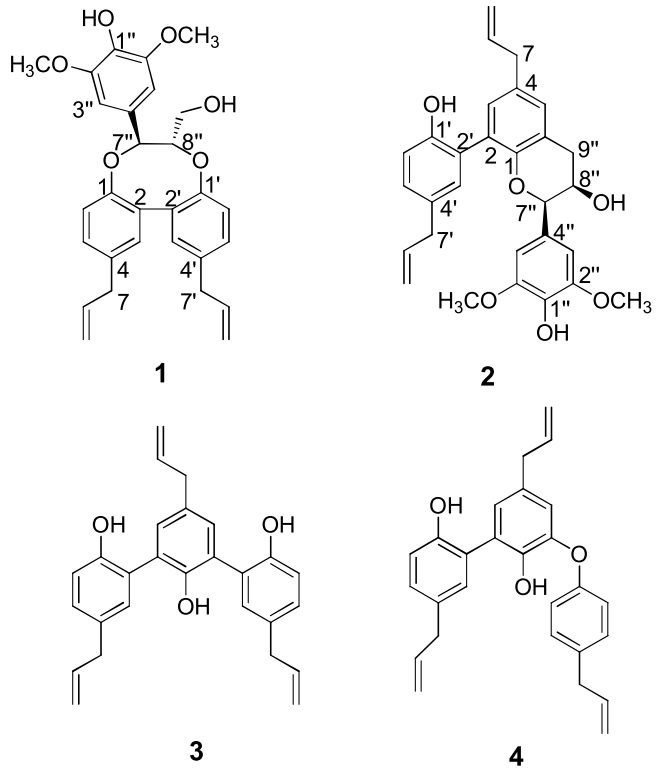


Fig. 1. Structures of compounds **1**–**4**.

δ_C 105.6 to δ_C 158.1, four olefinic carbons at δ_C 115.9, 116.0, 138.7, and 138.7, three oxygenated aliphatic carbons at δ_C 62.7, 88.5 and 90.7, two methoxyl carbons at δ_C 56.7 and 56.7, and two methylene aliphatic carbons at δ_C 40.2 and 40.3. These characteristic NMR data unambiguously indicated **1** was a sesqui-neolignan with a highly symmetrical skeleton. Among these, two 1,2,4-trisubstituted benzene rings and two allyl groups were evident to form a symmetrical magnolol moiety. The HMBC correlations (Fig. 2) of H-3″/H-5″ with C-1″, C-2″, and C-6″ as well as OCH_3 with C-2″ and C-6″ revealed the presence of a symmetrical 1,2,4,6-tetrasubstituted aromatic ring with OCH_3 groups attached to C-2″ and C-6″. The presence of the CH(O) − CH(O) − CH_2(O) moiety connected to C-4″ was deduced based on HMBC correlations of H-7″ with C-3″, C-4″, C-5″ and C-8″ as well as $^1H-^1H$ COSY experiment. Since the magnolol moiety and the 1,3,4,5-tetrasubstituted aromatic ring accounted for 14 degrees of unsaturation, the remaining degree of unsaturation indicated a eight-membered ring as a 1,4-dibenzodioxocine unit between the above two units. The conclusion was confirmed by the HMBC correlations from H-7″ to C-1 together with the downfield shifts of C-7″ (δ_C 88.5) and C-8″ (δ_C 90.7).

The *threo* orientation for H-7″ and H-8″ on the 1,4-dioxocane ring was deduced from the large coupling constant (J = 10.0 Hz) between H-7″ and H-8″. Since a single crystal of **1** could not be obtained for X-ray experiments, considering the similarity between 1,4-dioxocane ring and 1,4-dioxane ring, the absolute configurations at C-7″ and C-8″ were determined by comparison of the circular dichroism (CD) spectrum with those of analogous neolignans containing a dioxane ring (Kim et al., 2005; Arnoldi and Merlini, 1985). The positive Cotton effects at 231 nm and the negative Cotton effects at 284 nm allowed the assignment of 7″S, 8″S configurations. Therefore, the structure of compound **1** was established as Fig. 1 and named difengpienol A.

Difengpienol A (**1**) is a sesqui-neolignan with a unique dibenzodioxocin ring formed through a o,o-dihydroxybiphenyl unit etherifing with a phenylpropanoid unit. Since Brunow's group first discovered dibenzodioxocin as a new structural unit from wood lignin in 1995 (Karhunen et al., 1995a), model compounds for this structure were then synthesized (Karhunen et al., 1995b; Karhunen, et al., 1996). As far as we know, dibenzodioxocin merely represented a structural unit rather than a true natural product. Difengpienol A (**1**) should thus be regarded as the first natural product with a dibenzodioxocin structure.

Compound **2** was isolated as an amorphous solid. The negative-mode HR-ESI-MS of **2** showed quasi-molecular ion peak at m/z 473.1782 $[M-H]^-$, corresponding to a molecular formula of $C_{29}H_{30}O_6$ with 15 degrees of unsaturation. The ^1H- and ^{13}C-NMR data (Table 1) had signals for structure fragments very similar to those in **1**, such as a 1,2,4-trisubstituted aromatic ring, two 1,2,4,6-tetrasubstituted aromatic rings, two allyl groups, two methoxy groups, two oxygenated aliphatic carbons, and a methylene aliphatic carbon. These facts indicated that **2** was a sesqui-neolignan with a non-aromatic C6 ring (Shih et al., 2013). The presence of a symmetrical 1,2,4,6-tetrasubstituted aromatic ring with OCH_3 groups attached to C-2″ and C-6″ was deduced from the HMBC correlations of H-3″/H-5″ (δ_H 6.59) with C-1″, C-2″, C-4″ and C-6″as well as OCH_3 (δ_H 3.82) with C-2″ and C-6″ (Fig. 2). The HMBC correlations of H-7″ (δ_H 4.73) with C-3″, C-4″, C-5″, C-8″ and C-9″ as well as of H-9″a (δ_H 3.15)/H-9″b (δ_H 2.93) with C-1, C-5, C-6, C-7″ and C-8″ supported that the presence of a fragment CH(O) − CH(O) − CH_2 connected to C-4″ and C-6. The chemical shifts and one remaining degree of unsaturation implied the formation of a dihydrobenzopyran ring between C-1 and C-7″, which was further confirmed by the weak but distinct HMBC correlation of H-7″ with C-1 (Fig. 2). On the basis of the fact that the CD spectrum of compound **2** displayed negative Cotton effect at 242 nm and 280 nm, the absolute configurations were deduced as 7″R and 8″R (Antus et al., 2001; Rensburg et al., 1999). Thus, compound **2** was elucidated as Fig. 1 and named difengpienol B.

Sesqui-neolignans are the characteristic secondary metabolites of *Illicium* plants, which were mainly the cross-coupled products at the para and ortho positions between different benzene rings. However, difengpienols A (**1**) and B (**2**) are proposed to be assembled by oxidative cross-coupling of C6–C3 units between an allyl group and a benzene ring. As depicted in Scheme 1, difengpienols A (**1**) and B (**2**) were proposed to be derived from the trimers A and B respectively, the cross-coupled products between different radical intermediates of 4-allylphenol and magnolol. An intramolecular oxy-Michael addition of one phenol to the center enone of trimer A would lead to intermediate **3**, followed by oxidation to afford difengpienol A (**1**). Difengpienol B (**2**) would be produced from the trimer B via intermediate **4** by aromatization, followed by oxidation and dehydration.

Considering that the stem bark of *Illicium difengpi* has been applied for the treatment of rheumatic arthritis in China, we investigated the inhibitory effects of all isolates on NO production in LPS-induced RAW264.7 macrophages cells. As shown in Table 2, compounds **1**–**4** inhibited NO production with IC_{50} values of 16.9, 23.8, 45.3, and 32.6 μM, respectively, with parthenolide as the positive control (IC_{50} value: 12.9 μM). Of these, compounds **1** and **2** showed moderate anti-inflammatory activity.

3. Experimental

3.1. General experimental procedures

Optical rotations were measured using a Jasco P-1020 polarimeter. UV data was recorded using a Shimadzu UV-2401 A spectrophotometer. IR spectrum was obtained on a Bruker Tensor-27 spectrometer with KBr pellets. 1D and 2D NMR spectra were performed on Bruker DRX-500 spectrometer with TMS as internal standard. Chemical shifts (δ) were expressed in ppm with reference to the solvent signals. Mass spectra were recorded on a Bruker HCT spectrometer (ESI mode) and Waters Auto Spec Premier P776 instrument (HREI mode). Column chromatography (CC) was performed using silica gel (200 − 300 mesh, Qingdao Marine Chemical Co. Ltd., Qingdao, People's Republic of China), MCI gel (75 − 150 μm; Mitsubishi Chemical Corporation, Japan), and

Table 1
^{1}H- (500 MHz) and ^{13}C- (125 MHz) NMR data for compounds **1** and **2.**

position	**1**[b]		**2**[c]		position	**1**[b]		**2**[c]	
	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	158.1		148.7		1″	136.9[a]		135.1	
2	133.2		126.1		2″	148.8		147.3	
3	130.3[a]	7.25 d (2.0)	129.4	6.99 s	3″	105.6	6.73 s	103.6	6.59 s
4	136.9[a]		133.8		4″	130.2[a]		128.2	
5	130.1[a]	7.18 dd (8.0, 2.0)	130.9	7.01 s	5″	105.6	6.73 s	103.6	6.59 s
6	123.5	7.04 d (8.0)	120.9		6″	148.8		147.3	
7	40.2	3.43 d (7.0)	39.5	3.36 d (7.0)	7″	88.5	4.78 d (10.0)	82.8	4.73 d (8.0)
8	138.8[a]	5.98 ddt (17.0, 10.0, 7.0)	137.5	5.96 ddd (17.0, 10.0, 7.0)	8″	90.7	4.09 ddt (10.0, 7.0, 2.5)	68.2	4.08 ddd (9.0, 8.0, 5.0)
9	115.9	5.10 dd (17.0, 1.5) 5.03 dd (10.0, 1.5)	115.6	5.01 ddd (17.0, 10.0, 1.5)	9″	62.7	3.57 dd (12.0, 2.0) 3.50 dd (12.0, 7.0)	33.3	3.15 dd (16.0, 5.0) 2.93 dd (16.0, 9.0)
1′	158.0		152.1		$OCH_3\times2$	56.7	3.82 s	56.4	3.82 s
2′	133.2		126.1						
3′	130.2[a]	7.25 d (2.0)	131.2	7.04 d (2.0)					
4′	136.9[a]		132.4						
5′	130.1[a]	7.24 dd (8.0, 2.0)	129.9	7.03 d (9.0, 2.0)					
6′	123.6	7.23 d (8.0)	117.3	6.84 d (9.0)					
7′	40.3	3.45 d (7.0)	39.5	3.32 d (7.0)					
8′	138.7[a]	6.04 ddt (17.0, 10.0, 7.0)	137.9	5.90 ddd (17.0, 10.0, 7.0)					
9′	116.0	5.14 dd (17.0, 1.5) 5.05 dd (10.0, 1.5)	116.1	5.07 ddd (17.0, 10.0, 1.5)					

[a] All assignments were aided by extensive analyses of 1D and 2D NMR (COSY, HMQC, HMBC, and NOSEY).
[b] Measured in acetone-d_6.
[c] Measured in $CDCl_3$.

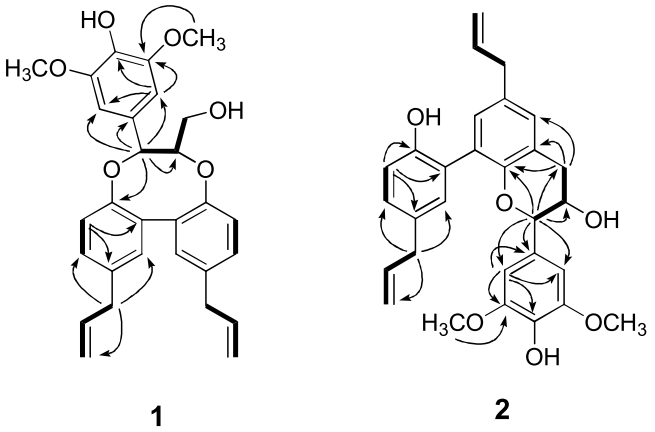


Fig. 2. Key HMBC (→) and ^{1}H-^{1}H COSY (—) correlations of **1** and **2**.

Sephadex LH-20 (Amersham Pharmacia Biotech, Sweden). Fractions were monitored by TLC (GF254, Qingdao Marine Chemical Co. Ltd., Qingdao), and spots were visualized by heating silica gel plates sprayed with 10% H_2SO_4 in EtOH. All solvents were distilled prior to use.

3.2. Plant material

Illicium difengpi were collected from Duan County, Guangxi Province, China, in 2014 and identified by Prof. Hui Tang (Guangxi Institute of Botany). A voucher specimen (CTM201402) was deposited at the Guangxi Key Laboratory of Functional Phytochemicals Research and Utilization, Guangxi Institute of Botany, China.

3.3. Extraction and isolation

The air-dried stem barks of *I. difengpi* (15 kg) were extracted with 95% EtOH (20 L × 24 h × 3) at room temperature and evaporated in vacuo to give a crude extract, which was then partitioned successively with petroleum ether (1.5 L × 3), CH_2Cl_2 (1.5 L × 3), EtOAc (1.5 L × 3) and *n*-BuOH (1.5 L × 3). The CH_2Cl_2 portion (500 g) was chromatographed over a silica gel column eluting a gradient petroleum ether/EtOAc (1:0→0:1) to obtain five fractions (Fr. 1–5). Fr.3 was subjected to a Sephadex LH-20 column ($CHCl_3$/MeOH, 1:1) and further purified by semipreparative HPLC (Agilent 1100 HPLC system, Zorbax SB-C18, 250 × 9.4 mm; UV detector; CH_3CN–H_2O, 35:65–65:35) to afford compounds **1** (5 mg), **2** (10 mg), **3** (22 mg), and **4** (45 mg).

3.3.1. Difengpienol A (1)

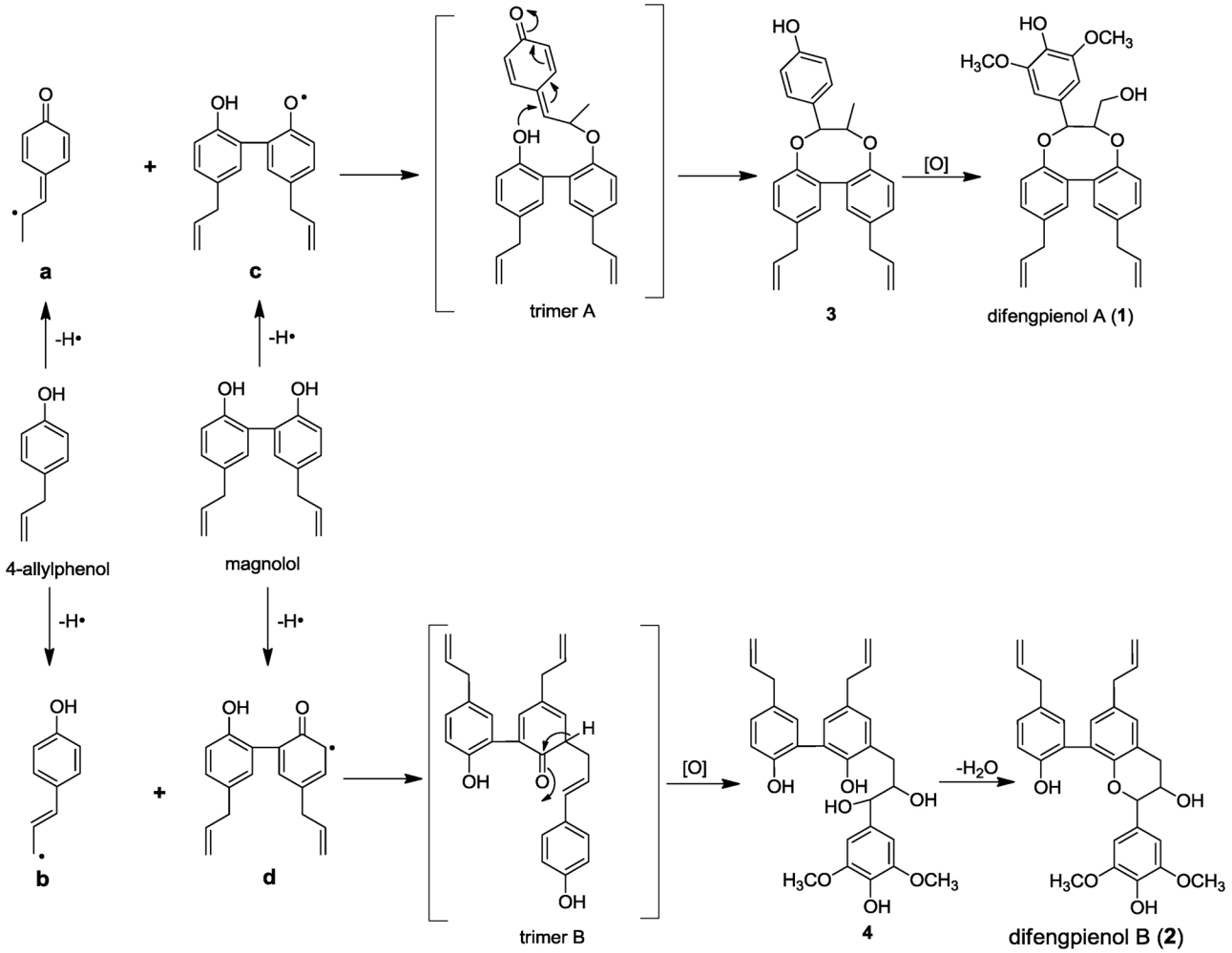
Amorphous oil; $[\alpha]^{23.9}_{D}$ –60.9 (*c* = 0.23, MeOH); UV (MeOH) λ_{max} nm (log ε): 208 (4.59), 240 (4.08), 277 (3.52); CD (MeOH) λ_{max} ($\Delta\varepsilon$): 226(–2.40), 231 (1.31), 284 (–1.21) nm; IR (KBr) ν_{max} cm^{-1}: 3426, 2926, 1713, 1639, 1617, 1494, 1462, 1250, 1218, 1117; EI-MS *m/z*: 474 $[M]^+$; HR-EI-MS *m/z* 474.2040 $[M]^+$ (calcd. for $C_{29}H_{30}O_6$, 474.2042). ^{1}H- and ^{13}C-NMR data, see Table 1.

3.3.2. Difengpienol B (2)

Amorphous solid; $[\alpha]^{23.8}_{D}$ –20.8 (*c* = 0.26, MeOH); UV (MeOH) λ_{max} nm (log ε): 206 (4.74), 288 (3.72); CD (MeOH) λ_{max} ($\Delta\varepsilon$): 213 (4.41), 242 (–2.29), 280 (–1.43) nm; IR (KBr) ν_{max} cm^{-1}: 3426, 2925, 1617, 1464, 1217, 1114; ESI-MS *m/z*: 473 $[M-H]^-$; HR-ESI-MS *m/z* 473.1982 $[M-H]^-$ (calcd. for $C_{29}H_{30}O_6$, 473.1970). ^{1}H- and ^{13}C-NMR data, see Table 1.

3.4. Inhibitory assay of NO production

Raw264.7 macrophage cells were cultured in high glucose DMEM supplemented with 10% fetal bovine serum, 100 units/mL penicillin and 100 μg/mL streptomycin. Cells were grown at 37 °C in a humidified atmosphere containing 5% CO_2. Inhibitory assays of NO production were carried out as previously described (Yan et al., 2016). Briefly, RAW264.7 cells were harvested and seeded into 96-well plates (3×10^4 cells/well) and preincubated at 37 °C for 24 h. After serum starvation for 12 h, cells were pretreated with various concentrations of compounds (0–50 μM) for 30 min, and then stimulated with 1 μg/mL of LPS for 24 h. The nitrite concentration in the culture supernatant was evaluated by using the Griess reagent. MTT assay was used to evaluate the effect of compounds on cell viability.



Scheme 1. Plausible biosynthetic pathways for **1** and **2**.

Table 2
Inhibitory effects of compounds **1–4** against LPS-Induced NO production in RAW 264.7 macrophage cells.

Samples	Cell Viability[a] (%)	NO Inhibition IC_{50} (μM)
1	92.5 ± 1.3	16.9 ± 2.0
2	85.2 ± 1.8	23.8 ± 1.3
3	95.2 ± 2.2	45.3 ± 1.5
4	93.3 ± 1.6	32.6 ± 2.1
Parthenolide[b]	97.6 ± 1.2	12.9 ± 1.3

[a] Cell viability was evaluated by the MTT assay to ascertain the cytotoxicity to RAW264.7 cells at a concentration of 25 μM.
[b] Positive control.

4. Appendix A Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi

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