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Cordatols A–D, four new anti-inflammatory bis-monoterpenoids from *Illigera cordata*

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ABSTRACT

Cordatols A–D (1–4), four new limonene-derived bis–monoterpenoids plausibly biosynthesized via hetero-Diels-Alder cyclization and sequential hydrolyses of their monoterpene precursors, were isolated from the aerial parts of *Illigera cordata*. The structures, including absolute configuration, were established by spectroscopic analysis and further confirmed by a two-steps bioinspired chemical transformation. Moreover, compounds **1–4** exhibited moderate *in vitro* anti-inflammatory activity with IC_{50} values ranging from 17.5 to 24.6 μM. This study may provide a novel structural template for potential anti-inflammatory agent discovery.

1. Introduction

The genus *Illigera* (belong to the Family Hernandiaceae) contains approximately 30 species distributed in the tropical regions of Africa and Asia, some of which (e.g., *I. grandiflora*, *I. cordata*, *I. aromatica*, *I. luzonensis*, and *I. rhodantha*) have been used for the treatment of some diseases associated with inflammation, such as rheumatic arthralgia and conjunctivitis in Chinese ethnomedicine systems, especially Zhuang and Yi tribal folk medicine [1]. The pharmacological properties of these medicinal plants are attributed to the occurrence of bioactive chemical constituents such as aporphine alkaloids [2,3], sesquiterpene [4], monoterpenoid [5] and monoterpenoid dimmers [6,7].

During our search for bioactive compounds from traditional ethnomedicine [7], cordatols A–D (**1–4**), four new limonene-derived bis-monoterpenoids, have been isolated from the aerial parts of *I. cordata* collected from the Yunnan Province of China. Cordatols A–D (**1–4**) may have derived from monoterpene precursors through *hetero*-Diels-Alder cyclization, followed by hydrolytic reaction. The structures of these novel metabolites were elucidated by a combination of NMR analysis and biomimetic chemical transformation. Furthermore, biological evaluation results suggested cordatols possess *in vitro* anti-inflammatory property. In this paper, we mainly report the structural elucidation of these new bis-monoterpenoids and anti-inflammatory activity of the isolated compounds.

2. Experiment

2.1. General

UV spectra were obtained using a Shimadzu UV-2401A spectrophotometer. IR spectra were obtained in KBr disc on a Bio-Rad Wininfmred spectrophotometer. 1D and 2D NMR spectra were determined on a Bruker AV-400 spectrometer with TMS as internal standard. Unless otherwise specified, chemical shifts (δ) are expressed in ppm with reference to the solvent signals. HRESIMS was performed on a VG Autospec-3000 spectrometer. Semi-preparative HPLC was performed on an Agilent 1100 or 1200 semi-preparative HPLC with a Zorbax SB-C18 (5 μm, 9.4 mm × 25 cm) columns or a Welch Ultimate Cellu-D chiral column (5 μm, 4.6 mm × 25 cm). Column chromatography was performed using silica gel (100–200 mesh, Qing-dao Marine Chemical, Inc., Qingdao, People's Republic of China), Lichroprep RP-18 gel (40–63 μm, Merck, Darmstadt, Germany), and MCI gel (75–150 μm, Mitsubishi Chemical Corporation, Tokyo, Japan). The fractions were monitored by TLC, and spots were visualized by heating silica gel plates sprayed with 5% H_2SO_4 in EtOH.

2.2. Plant material

The aerial parts of *Illigera cordata* was collected from Xishuangbanna

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prefecture of Yunnan Province, People's Republic of China, in September 2011. The identification of plant material was verified by Prof. Ning Yuan. A voucher specimen (YNNI-11-09-10) has been deposited in the Key Laboratory of Chemistry in Ethnic Medicinal Resources, State Ethnic Affairs Commission and Ministry of Education, Yunnan Minzu University.

2.3. Extraction, and purification

The air-dried and powdered aerial parts of *I. cordata* (10.5 kg) were extracted with 80% aqueous acetone (35 L × 3 times) at room temperature and concentrated in vacuo to yield a residue, which was partitioned between water and EtOAc. The EtOAc extract (1200 g) was decolorized on MCI gel with 90% to 95% MeOH-H_2O to obtain a yellow gum (822 g). The gum was purified by CC (column chromatography on silica gel with CH_2Cl_2-acetone gradient system 10:1, 9:1, 8:2, 7:3, 6:4, 1:1 and 0:1) to yield seven fractions A-G. Further separation of fraction B (122.5 g) on silica gel, eluted with petroleum ether-acetone (8:1–1:1), yielded fractions B1-B8. Partial fraction B6 (0.22 g) was subjected to silica gel column chromatography using petroleum ether-acetone followed by semi-preparative HPLC (75% MeOH-H_2O, flow rate 3 mL/min) to give **1** (36.8 mg, 19.0 min), **2** (2.5 mg, 17.2 min), **3** (1.8 mg, 16.5 min), and **4** (55.7 mg, 14.5 min).

2.4. Spectroscopic data

Cordatol A (**1**): $C_{38}H_{42}O_9$; yellow gum; [α]22.1 D + 83.9 (*c* 0.87, MeOH); UV (MeOH) λ_{max} (log ε) 203 (0.42), 217 (0.37), 280 (0.43) nm; IR (KBr) ν_{max} 3435, 2972, 2931, 1715, 1681, 1636, 1450, 1385, 1368, 1331, 1167, 1068, 1014, 979, 769 cm^{-1}; ^1H and ^{13}C NMR (400 and 100 MHz, in $CDCl_3$) see Tables 1 and 2; postive ESIMS *m/z* 665 [M + Na]$^+$; HRESIMS (positive ion mode) *m/z* 665.2725 [M + Na]$^+$ (calcd 665.2721 for $C_{38}H_{42}O_9Na$).

Cordatol B (**2**): $C_{38}H_{44}O_9$; yellow gum; [α]22.1 D + 74.5 (*c* 0.40, MeOH); UV (MeOH) λ_{max} (log ε) 207 (0.63), 280 (0.46) nm; IR (KBr) ν_{max} 3437, 2970, 2929, 1718, 1678, 1636, 1415, 1375, 1252, 1166, 1068, 1016, 925, 769, 700 cm^{-1}; ^1H and ^{13}C NMR (400 and 100 MHz, in $CDCl_3$) see Tables 1 and 2; postive ESIMS *m/z* 667 [M + Na]$^+$; HRESIMS (positive ion mode) *m/z* 667.2883 [M + Na]$^+$ (calcd 667.2878 for $C_{38}H_{44}O_9Na$).

Cordatol C (**3**): $C_{38}H_{44}O_9$; yellow gum; [α]22.5 D + 91.8 (*c* 0.81, MeOH); UV (MeOH) λ_{max} (log ε) 207 (0.56), 280 (0.40) nm; IR (KBr) ν_{max} 3440, 2971, 2930, 1716, 1679, 1635, 1452, 1369, 1159, 1067, 1014, 918, 700 cm^{-1}; ^1H and ^{13}C NMR (400 and 100 MHz, in $CDCl_3$) see Tables 1 and 2; postive ESIMS *m/z* 667 [M + Na]$^+$; HRESIMS (positive ion mode) *m/z* 667.2882 [M + Na]$^+$ (calcd 667.2878 for $C_{38}H_{44}O_9Na$).

Cordatol D (**4**): $C_{38}H_{46}O_9$; yellow gum; [α]22.2 D + 123.2 (*c* 0.28, MeOH); UV (MeOH) λ_{max} (log ε) 207 (0.46), 227 (0.20) nm; IR (KBr) ν_{max} 3440, 3028, 2971, 2931, 2878, 1735, 1677, 1370, 1248, 1154, 1069, 1015, 921, 751, 700 cm^{-1}; ^1H and ^{13}C NMR (400 and 100 MHz, in $CDCl_3$) see Tables 1 and 2; postive ESIMS *m/z* 669 [M + Na]$^+$; HRESIMS (positive ion mode) *m/z* 669.3042 [M + Na]$^+$ (calcd 669.3034 for $C_{38}H_{46}O_9Na$).

Table 1
^{13}C NMR data for compounds **1**–**6** (δ in ppm, **1**–**4** in $CDCl_3$, **5** and **6** in CD_3OD, 100 MHz).

No.	1	2	3	4	5	6
1	200.5 s	200.4 s	200.5 s	200.4 s	203.5 s	155.7 s
2	35.3 t	35.0 t	35.2 t	35.0 t	35.2 t	112.5 d
3	46.9 d	46.5 d	46.8 d	46.6 d	47.8 d	149.8 s
4	67.3 d	67.5 d	67.3 d	67.4 d	65.2 d	116.9 d
5	139.0 d	138.6 d	138.9 d	138.8 d	144.4 d	130.4 d
6	142.6 s	142.4 s	142.3 s	142.3 s	141.9 s	127.9 s
7	22.1 t	22.1 t	22.1 t	21.9 t	22.5 t	23.0 t
8	71.6 s	71.3 s	71.5 s	71.3 s	72.9 s	72.7 s
9	27.7 q	27.6 q	28.4 q	27.6 q	27.8 q	31.9 q
10	28.4 q	28.2 q	29.2 q	28.1 q	27.9 q	31.9 q
1′	209.9 s	209.8 s	209.7 s	209.7 s	212.5 s	212.7 s
2′	41.7 t	41.7 t	41.7 t	41.6 t	42.8 t	42.8 t
3′	45.6 d	45.6 d	45.5 d	45.5 d	48.7 d	48.7 d
4′	79.5 d	79.4 d	79.3 d	79.3 d	85.4 d	85.3 d
5′	81.6 d	81.6 d	81.5 d	81.4 d	77.8 d	77.8 d
6′	78.1 s	78.1 s	78.1 s	78.0 s	78.8 s	78.8 s
7′	30.8 t	30.7 t	30.7 t	30.6 t	31.6 t	33.3 t
8′	83.9 s	83.9 s	83.8 s	83.8 s	85.5 s	85.5 s
9′	29.6 q	27.7 q	27.7 q	29.4 q	30.0 q	30.0 q
10′	26.8 q	26.9 q	26.8 q	26.7 q	27.3 q	27.2 q
1″	166.2 s	172.1 s	166.2 s	172.2 s		
2″	117.0 d	31.0 t	116.9 d	30.9 t		
3″	146.7 d	36.1 t	146.7 d	36.2 t		
4	134.0 s	140.0 s	134.0 s	140.3 s		
5″/8″	128.4 d	128.3 d	128.5 d	128.3 d		
6″/9″	129.1d	128.7 d	129.2d	128.7 d		
7″	131.0 d	126.7 d	131.0 d	126.7 d		
1‴	166.2 s	166.2 s	172.2 s	172.2 s		
2‴	117.7 d	117.7 d	30.9 t	30.9 t		
3‴	145.9 d	146.0 d	36.3 t	36.1 t		
4‴	134.3 s	134.2 s	138.9 s	139.9 s		
5‴/8‴	128.4 d	128.8 d	128.4 d	128.4 d		
6‴/9‴	129.1d	129.1d	128.7 d	128.7 d		
7‴	130.7 d	131.7 d	126.5 d	126.5 d		

Table 2
^1H NMR data for compounds **1**–**4** (δ in ppm, in $CDCl_3$, 400 MHz).

No.	1	2	3	4
2	2.73, m 2.53, m	2.68, overlapped 2.66, overlapped	2.84, overlapped 2.66, overlapped	2.58, overlapped 2.48, overlapped
3	2.12, br s	2.13, overlapped	2.25, br s	2.09, br s
4	5.60, dd (5.9, 2.8)	5.52, dd (5.9, 2.5)	5.74, dd (5.8, 2.7)	5.44, dd (5.8, 2.8)
5	6.79, d (6.0)	6.82, d (6.0)	6.92, d (5.9)	6.75, d (5.8)
7	2.05, m 2.40, m	2.13, m 2.49, m	2.14, m 2.48, m	2.02, m 2.40, m
9	1.18, s	1.16, s	1.30, s	1.09, s
10	1.12, s	1.17, s	1.31, s	1.10, s
2′	2.72, overlapped 2.50, overlapped	2.85, overlapped 2.65, overlapped	2.79, dd (18.2, 3.8) 2.60, dd (18.2, 3.8)	2.73, dd (18.2, 3.8) 2.54, dd (18.2, 3.8)
3′	2.38, m	2.54, m	2.37, m	2.31, m
4′	5.63, br s	5.68, br s	5.65, br s	5.60, br s
5′	4.16, br s	4.30, br s	4.14 d (1.2)	4.09 d (1.0)
7′	1.73, m	1.84, m	1.84, m	1.72, m
9′	1.31, s	1.45, s	1.26, s	1.25, s
10′	1.05, s	1.19, s	1.14, s	1.07, s
2″	6.27, d (16.0)	2.94, m	6.92, d (16.0)	2.89, overlapped
3″	7.59, d (16.0)	2.65, m	7.71, d (16.0)	2.61, overlapped
5″/7″	7.38, m	7.16, m	7.52, m	7.14, m
6″/9″	7.24, m	7.26, m	7.39, m	7.21, m
7″	7.24, m	7.20, m	7.40, m	7.11, m
2‴	6.34, d (16.0)	6.49, d (16.0)	2.96, overlapped	2.89, overlapped
3‴	7.56, d (16.0)	7.75, d (16.0)	2.68, overlapped	2.61, overlapped
5‴/7‴	7.38, m	7.54, m	7.20, m	7.14, m
6‴/9‴	7.24, m	7.40, m	7.28, m	7.21, m
7‴	7.24, m	7.40, m	7.19, m	7.11, m

2.5. Anti-inflammatory assay

RAW264.7 cells (Kunming Institute of Zoology, Kunming, China) were maintained in DMEM (high Glucose) medium supplemented with 10% (v/v) fetal bovine serum, 100 μg/mL penicillin and streptomycin and HEPES at 37°C in a 5% CO_2 atmosphere. After a 24 h pre-incubation, the seeded cells were treated with gradient dilutions of test

compounds with a maximum concentration of 100 μM, followed by stimulation with LPS (1 μg/mL) for 18 h. NO production in the supernatant was assessed using the Griess reaction [8]. After 5 min incubation, the absorbance at 540 nm was measured with a 2104 Envision multilabel plate reader (PerkinElmer Life Sciences, Inc., Boston, MA, USA). IC_{50} values were calculated by Reed's method [9]. Wells with DMSO were used as a negative control, and L-NMMA (a nitric oxide synthase inhibitor, Biomedical Inc.) was used as a positive control.

2.6. Synthesis procedures

Synthesis of monoterpene (**5**): the mixture of compounds **1**–**4** (25.8 mg, approximately 0.04 mmol) was dissolved in MeCN (2 mL), and then 1 M NaOH (1.5 mL) was added and stirred for 12 h at room temperature. The resulting aqueous solution was acidified with 1 M HCl, exhaustively extracted with EtOAc (3 × 5 mL) and dried over anhydrous sodium sulfate. Concentration in vacuo gave **5** (12.5 mg, 0.03 mmol, 82%) as a white solid which was further purified by preparative HPLC.

Compound **5**: white power; ^{1}H NMR (400 MHz, CD_3OD) δ_H: 6.81 (1H, d, J = 5.6 Hz, H-5), 4.78 (1H, br s, H-5′), 4.62 (1H, br s, H-4), 4.09 (1H, br s, H-4′), 2.80–1.58 (10*H*, overlapped, H_2-2, H-3, H_2-7, H_2-2′, H-3′, and H_2-7′), 1.51 (3H, s, H_3-9′), 1.37 (3H, s, H_3-9), 1.21 (3H, s, H_3-10), and 1.12 (3H, s, H_3-10′); ^{13}C NMR (100 MHz, CD_3OD) see Table 1.

Synthesis of compounds **5** and **6** from dimericilligerate E (**7**): dimericilligerate E (**7**) [6] (72.8 mg, 0.20 mmol) was prepared by acid hydrolysis of the mixture of cordatins A–C and dimericilligerate A (155.0 mg, approximately 0.25 mmol) using previously reported method [7]. Compound **7** was further dissolved in acetone (3 mL), and then 1 M HCl (3 mL) was added and stirred for 2 h at room temperature. The resulting aqueous solution was neutralized with 1 M NaOH (PH = 7) and concentrated in vacuo to yield a residue, which was further purified by preparative HPLC to yield compounds **5** (30.5 mg, 0.09 mmol, 45%) and **6** (21.8 mg, 0.06 mmol, 30%).

Compounds **6**: white power; ^{1}H NMR (400 MHz, CD_3OD) δ_H: 7.27–6.86 (3H, overlapped, H-2, H-4, and H-5), 4.82 (1H, br s, H-5′), 4.20 (1H, br s, H-4′), 2.68–2.02 (7H, overlapped, H_2-7, H_2-2′, H-3′, and H_2-7′), 1.49 (3H, s, H_3-9′), 1.34 (6H, s, H_3-9 and H_3-10), and 1.30 (3H, s, H_3-10′); ^{13}C NMR (100 MHz, CD_3OD) see Table 1.

3. Results and discussion

3.1. Structure elucidation

Compound **1**, obtained as yellow gum, was determined to have a molecular formula of $C_{38}H_{42}O_9$, as deduced from the HRESIMS data at m/z 665.2725 $[M + Na]^+$ (calcd for $C_{38}H_{42}O_9Na$, 665.2721), indicative of 18 indices of hydrogen deficiency. Its ^{1}H NMR spectrum (see Table 2) showed diagnostic signals for two cinnamoyl moieties with *trans*-orientated vinyl groups at δ_H 6.27 (1H, d, J = 16.0 Hz), 6.34 (1H, d, J = 16.0 Hz), 7.59 (1H, d, J = 16.0 Hz), 7.56 (1H, d, J = 16.0 Hz), 7.24–7.59 (10H, m), and it was confirmed by the corresponding carbon signals at δ_C 166.2 (2C, s), 146.7 (d), 145.9 (d), 134.3 (s), 134.0 (s), 131.0 (d), 130.7 (d), 129.1 (4C, d), 128.4 (4C, d), 117.7 (d) and 117.0 (d) in the ^{13}C NMR spectrum (see Table 1). In addition to the 18 carbon signals belonging to two cinnamoyl groups (comprising 12 degrees of unsaturation), the ^{13}C NMR and DEPT spectra (see Table 1) displayed 20 close carbon resonances assignable to the basic skeleton, including four methyls, four aliphatic methylenes, six methines (three oxygen-bearing and an olefinic carbons), and six quaternary carbons (including two carbonyl groups, one olefinic and three oxygen-bearing carbons). Among the carbons, two ketone carbons and two olefinic carbons occupied three degrees of unsaturation, which suggested a tricyclic bis-monoterpenoid structure composed of subunits **a** and **b** (see Fig. 1). In fragment **a**, the presence of a six-membered ring (ring A) was established by ^{1}H–^{1}H COSY correlations among H_2-2/H-3/H-4/H-5, along

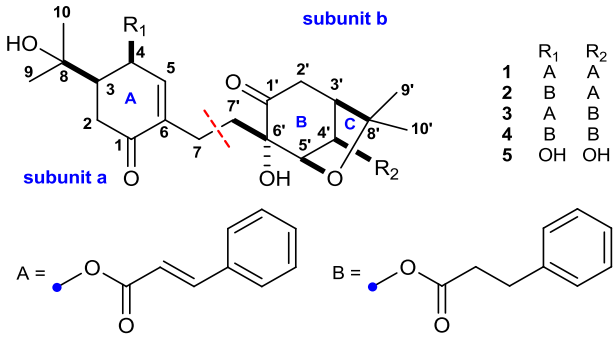

Fig. 1. The structures of cordatols A–D (**1**–**4**) and compound **5**.

with the key HMBC correlations between H_2-2 and C-1/C-6 and between H-5 and C-1/C-6 (see Fig. 3). In addition, a 1-hydroxyisopropyl group connected to C-3 was apparent from the HMBC correlations between H_3-9/H_3-10 and C-3. These data indicated that subunit **a** was a limonene-derived monoterpene motif. Similarly, it was obvious that the subunit **b** (rings B and C) was also determined to be a monoterpene moiety, which was similar to that of dimericilligerates [6,7], since the ^{1}H and ^{13}C NMR chemical shifts were nearly identical. This deduction was further supported by HMBC correlations from H_2-2′ to C-1′, C-4′ and C-6′, from H-4′ to C-2′ and C-6′, and from H-5′ to C-1′, C-6′ and C-7′ (see Fig. 3). Furthermore, the direct linkage between the two monomeric units **a** and **b** through two aliphatic methylene (C-7 and C-7′) was established by the HMBC correlations between H_2-7/C-6′, and H_2-7′/C-6, along with the ^{1}H–^{1}H COSY correlations between H_2-7 and H_2-7′. The two cinnamoyl substituents were located at C-4 and C-4′ based on the key HMBC correlation from H-4 to C-1″ and from H-4′ to C-1‴, respectively. The planar structure of **1** (see Fig. 1) were thus established to possess a tricyclic bis-monoterpenoid nucleus with two cinnamoyl groups at C-4 and C-4′.

Compounds **2** and **3** shared a molecular formula $C_{38}H_{44}O_9$ by analysis of their HRESIMS. Their 1D NMR data were quite similar to those of **1**, with the exception that one of the cinnamoyl groups in **1** was replaced by a dihydrocinnamoyl group in **2** and **3**. Such assignments were further supported by the HMBC correlations observed between H-4′/C-1‴ in **2** and between H-4/C-1″ in **3**, respectively. Similarly, a comparison of the NMR data of **1** and **4** suggested that the two cinnamoyl groups at C-4 and C-4′ in **1** were replaced by two dihydrocinnamoyl groups in **4**. Furthermore, the bis-monoterpenoid nucleus of **2**–**4**, including the relative stereochemistry, was determined to be identical to that of **1**, based on the ^{13}C chemical shifts and ROESY correlation data (see Fig. 3). The partial relative stereochemistry of **1**–**4** was then determined by a ROESY experiment. The ROESY correlations of H-4/H-3 indicated that H-3 and H-4 possessed the same orientation. Then, the cross peaks of H-4′/H-3′, H-4′/H-5′, H-3′/H_3-5′ and H-3′/H_3-10′, suggested that H-3′, H-4′, H-5′ and H_3-10′ were on the same side of the rings (see Fig. 4). However, no reliable NOESY correlation could be observed to determine the relative configuration between the subunit **a** (ring A) and the subunit **b** (rings B and C), especially the stereochemistry of the spiral carbon at C-6′.

Biosynthetically, compounds **1**–**4** may have derived from two limonene-derived *homo*-monoterpene precursors through *hetero*-Diels-Alder cyclization with remarkable region- and diastereoselectivity, followed by sequential acid hydrolyses of a dihydropyrane between C-1 and C-6′ and a terahydrofuran ring between C-5 and C-8 (see Fig. 2). According to this biogenetic ground, we supposed that **1**–**4** might have the absolute configuration of 3*R*, 4*S*, 3′*R*, 4′*R*, 5′*R* and 6′*S*. This deduction was further confirmed by the bioinspired chemical transformation. Firstly, alkaline hydrolysis of a mixture of **1**–**4** afforded a common optically pure bis-monoterpene (**5**) (see Figs. 5, S1 and S2). And then, under the acidic condition, dimericilligerate E (**7**) [6,7,10], a previously reported bis-monoterpene with the known absolute

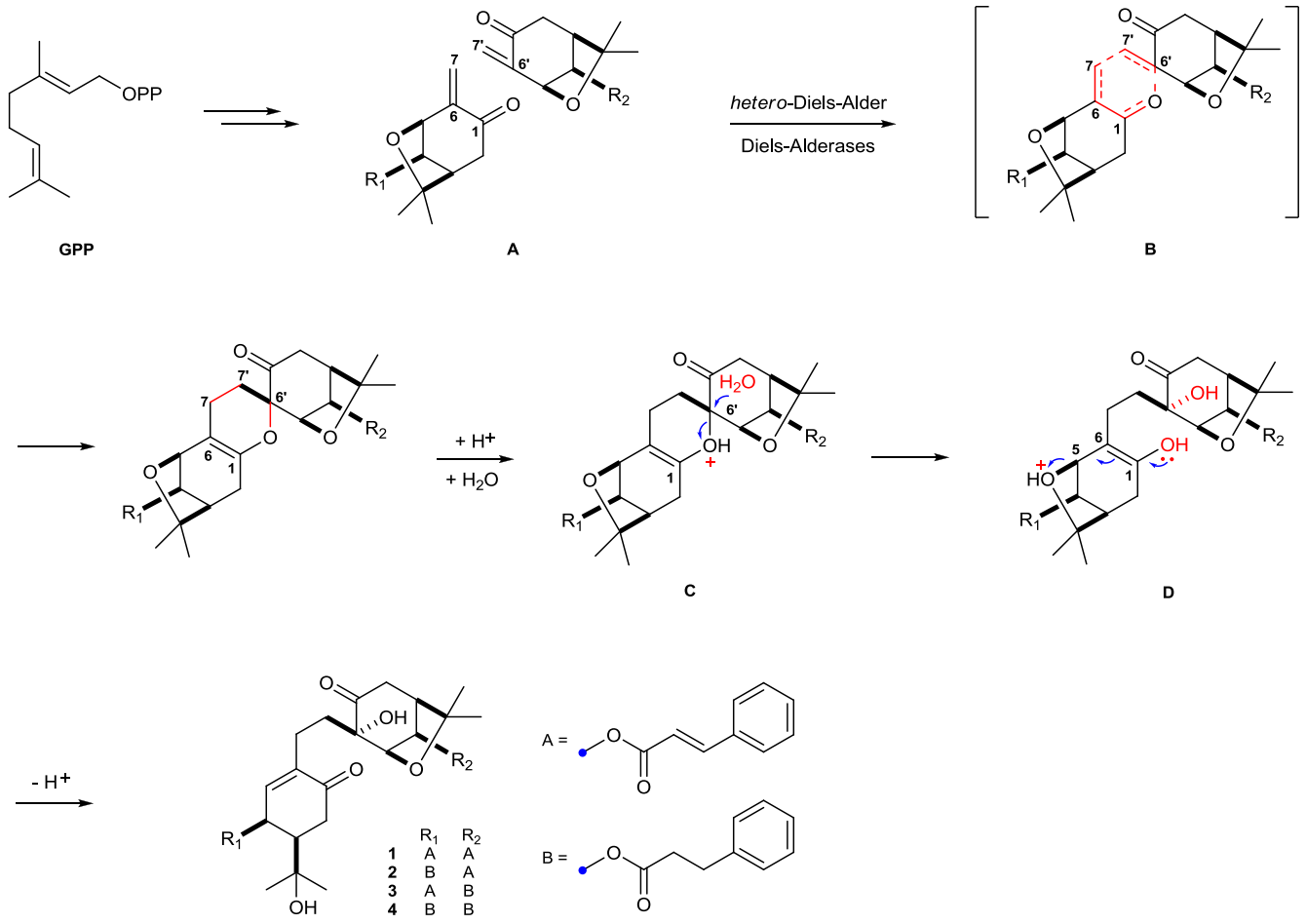

Fig. 2. Hypothetical biogenetic pathway of cordatols A–D (**1**–**4**).

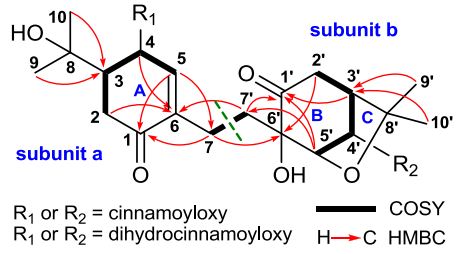

Fig. 3. Selected ^{1}H–^{1}H COSY and HMBC correlations of **1**–**4**.

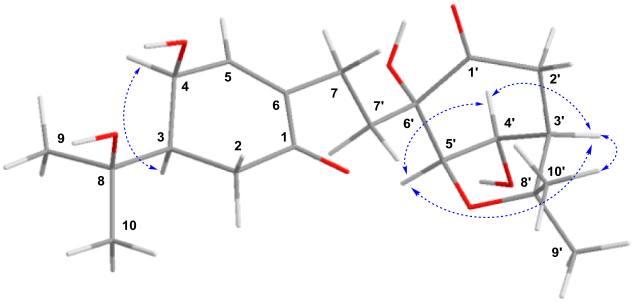

Fig. 4. Selected ROESY correlations of **1**–**5** (the nucleus part).

configuration as 3*R*, 4*R*, 5*S*, 3′*R*, 4′*R*, 5′*R*, and 6′*S*, was successfully transformed into compound **5** and a by-product **6** (see Fig. 6), which allowed determination of the absolute configurations of **1**–**4**.

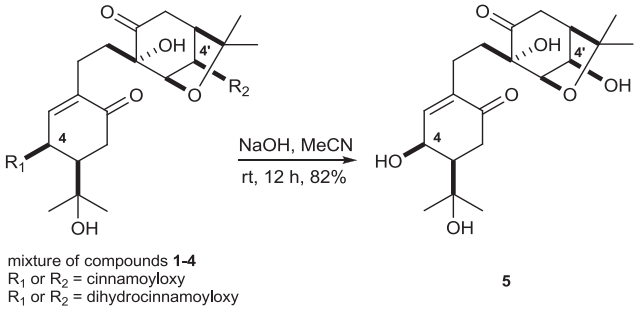

Fig. 5. Alkaline hydrolysis of a mixture of **1**–**4**.

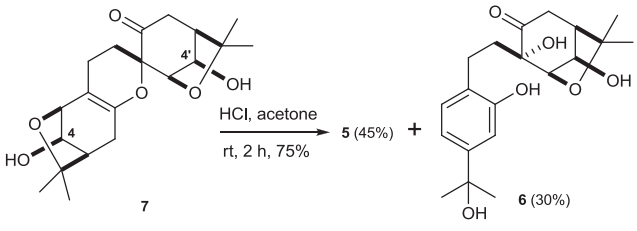

Fig. 6. Chemical transformation from dimericilligerate E (**7**) to **5**.

3.2. Biological activity assessment

Considering that the traditional applications of *I. cordata* by the Zhuang and Yi tribes in Yunnan Province are mostly related to inflammatory conditions [5,6], compounds **1**–**4** were evaluated for

inhibitory activity on lipopolysaccharide-induced nitric oxide synthase-dependent nitric oxide production in the murine macrophage cell line RAW264.7, using L-NMMA as a positive control (IC_{50} = 15.9 μM) [9]. Under non-cytotoxic concentrations (< 40 μM), compounds **1–4** exhibited potential *in vitro* anti-inflammatory activity with IC_{50} values of 17.5, 19.0, 21.6, and 24.6 μM, respectively.

4. Concluding remarks

In conclusion, cordatols A–D (1–4), four new limonene-derived bis-monoterpenoids were isolated from the aerial parts of *Illigera cordata*. They might be biosynthesized *via* an intermolecular *hetero*-Diels-Alder reactions between two *homo*-monoterpene precursors with remarkable regio- and diastereoselectivity, and *via* sequential hydrolyses of a dihydrofuran ring and a terahydrofuran ring. The stereochemical products of the [4 + 2] cycloaddition indicate that the product formation could be an enzyme-guided course [11]. Especially, their structures, including absolute configuration, were confirmed by a two-steps bioinspired chemical transformation. Additionally, compounds **1–4** exhibited moderate *in vitro* anti-inflammatory activity against NO production with IC_{50} values ranging from 17.5 to 24.6 μM. This study may provide a novel structural template for potential anti-inflammatory agent discovery.

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Conflict of interest

The authors of the present manuscript have declared that no competing interests exist.

Appendix A. Supplementary material

Supplementary data associated with this article including HPLC analyses of compounds **1–5**, 1D and/or 2D NMR spectra of **1–6** can be found online at https://doi.org/10.1016/j.bioorg.2019.02.039.

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