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New acyclic diterpenoids from the fruits of *Aphanamixis grandifolia* and structure revision of nemoralisin B

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ABSTRACT

Four new acyclic diterpenoids (i.e., nemoralisin B (**1**) and nemoralisins H–J (**2**–**4**)) along with three known acyclic diterpenoids (i.e., nemoralisin, nemoralisin A, and nemoralisin D) were isolated from the fruits of *Aphanamixis grandifolia*. Their structures were determined by extensive spectroscopic studies using NMR spectroscopy and mass spectrometry. In addition, the structure of nemoralisin B has been revised from the previously reported α,β-unsaturated δ-lactone structure to an α,β-unsaturated γ-lactone one. Nemoralisin J (**4**) exhibited moderate inhibitory activity against lipopolysaccharide-induced nitric oxide production in RAW 264.7 cells with an IC_{50} value of 9.96 μM.

1. Introduction

The genus *Aphanamixis* (Meliaceae), which consists of approximately 25 species, is primarily distributed in the tropical and subtropical areas of Southeast Asia, such as India, Malaysia, Indonesia, and China (Pen and David, 2008). *Aphanamixis grandifolia* Bl. is an evergreen timber tree, and the roots and leaves have been used as a traditional Chinese medicine for the treatment of colds, limb numbness, and inconvenient flexion. Previous phytochemical investigations of this species have led to the isolation of limonoids (Wang et al., 2012; Zhang et al., 2011, 2013a,c), triterpenoids (Wang et al., 2013; Zeng et al., 2012), phenylpropanoids (Tang et al., 2007), sesquiterpenoids (Soares et al., 2012; Yuan et al., 2013), and alkaloids (Harmon et al., 1979), and some of these compounds exhibit a wide range of biological activities (Cai et al., 2012; Falah et al., 2008; Guo et al., 2012). In our continuing search for bioactive metabolites from the Meliaceae family, further study of the fruits of *A. grandifolia* was performed. Therefore, four new acyclic diterpenoids (Fig. 1) (i.e., nemoralisin B (**1**) and nemoralisins H–J (**2**–**4**)) along with three known diterpenoids (i.e., nemoralisin (He et al., 2007), nemoralisins A (Zhang et al., 2013b), and nemoralisin D (Zhang et al., 2013a,c)) were isolated from the EtOAc extracts of *A. grandifolia*. Herein, we report the isolation, structural elucidation, and bioactivity of these new acyclic diterpenoids as well as the structure revision of nemoralisin B.

2. Results and discussion

Nemoralisins B (**1**) was obtained as a colorless oil, and its molecular formula (i.e., $C_{20}H_{28}O_5$) was established from the molecular ion peak $[M]^+$ at m/z 348.1934 (calcd for 348.1937) in its positive HREIMS. The ^1H NMR spectrum (Table 1) contained signals corresponding to three typical olefinic protons and five methyl groups. The ^{13}C NMR data along with DEPT experiments (Table 2) indicated 20 carbon signals including five methyls, three methylenes, six methines (three olefinic and two oxygenated methines), and six quaternary carbons (two olefinic, one carbonyl, and one ketone carbons). The aforementioned information indicated that the NMR data of **1** resembled those of nemoralisin (He et al., 2007), except for the presence of a hydroxyl group at C-8 as well as an α,β-unsaturated γ-lactone in **1** and the absence of an α,β-unsaturated δ-lactone in the latter. The HMBC correlations

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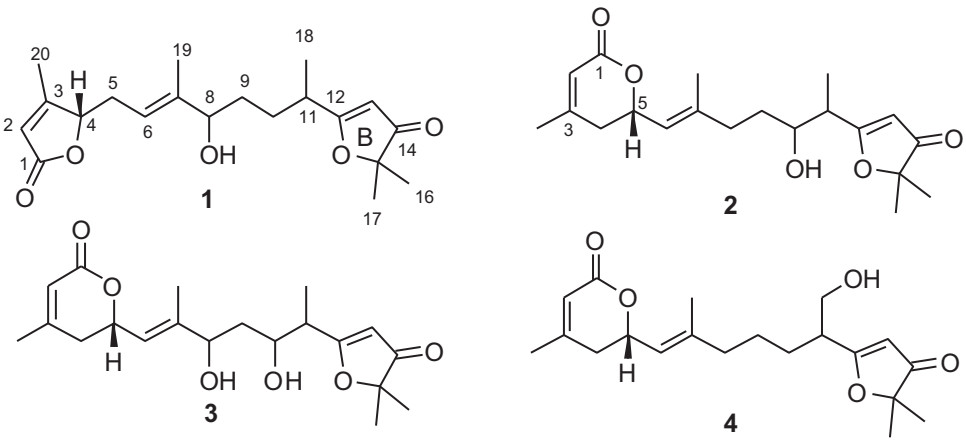

Fig. 1. Structures of compounds **1**–**4**.

from Me-20 (δ_H 2.09, s) to C-2 (δ_C 117.7), C-3 (δ_C 168.1), and C-4 (δ_C 84.0) and from H-4 (δ_H 4.94, br.t, J = 4.4 Hz) to C-1 (δ_C 173.2), C-3 (δ_C 168.1), C-5 (δ_C 30.0), and C-6 (δ_C 118.2) as well as the ^{1}H–^{1}H COSY cross-peaks of H-4 (δ_H 4.94, br.t, J = 4.4 Hz)/H_2-5 (δ_H 2.36, dt, J = 14.1, 6.8 Hz; 2.75, ddd, J = 14.1, 6.8, 4.4) and H_2-5/H-6 (δ_H 5.36, t, J = 6.8 Hz) (Fig. 2) unambiguously confirmed that the A-ring was an α,β-unsaturated five-membered lactone. In addition, the hydroxyl group was placed at C-8 by the key HMBC correlation between Me-19 (δ_H 1.65, s) and C-8 (δ_C 77.2) along with ^{1}H–^{1}H COSY cross-peaks of H-8/H_2-9. Therefore, the planar structure of **1** was established as shown in Fig. 1.

In the ROESY spectrum, the present correlations of H_2-5/Me-19 and the absent correlation of H-6/Me-19 indicated the existence of an *E*-geometry for the $\Delta^{6(7)}$ double bond. The ECD spectrum of **1** exhibited a negative Cotton effect at 210 nm ($\Delta\varepsilon$–20.74), which indicated that the absolute configuration of **1** at C-4 was *S* (Beecham, 1972). The 1D and 2D NMR data of compound **1** was identical to those of nemoralisin B (Zhang et al., 2013b). The previously reported α,β-unsaturated δ-lactone of A-ring in nemoralisin B (Zhang et al., 2013b) was deduced by ^{13}C NMR chemical shift comparison to the known nemoralisin A (Zhang et al., 2013b). We assume that the large chemical shift discrepancy (ca. $\Delta\delta$ +10.2) at C-5 between nemoralisin B and nemoralisin A was caused by the different ring tensions between an α,β-unsaturated γ-lactone and an α,β-unsaturated δ-lactone as well as the deshielding effect of the double bond in A-ring. In addition, the NMR data of an α,β-unsaturated γ-lactone of nemoralisin B were in good agreement with those of 5-(3-methyl-2-butenyl)-4-methyl-2(5*H*)-furanone (Pedro and Carmen, 1994). Therefore, the structure of nemoralisin B should be revised to **1**, as shown in Fig. 1. However, the configurations at C-8 and C-11 could not be assigned from the available data.

Nemoralisin H (**2**), which is a colorless oil, had a molecular formula of $C_{20}H_{28}O_5$ based on the HREIMS data (*m*/*z* 348.1938 $[M]^+$, calcd for 348.1937). The similarity between the ^{1}H and ^{13}C NMR data (Tables 1 and 2) of **2** and those of nemoralisin A (Zhang et al., 2013b) indicated that both compounds shared the same rings system, and the only difference was that the hydroxyl group (δ_H 3.75, m; δ_C 73.1) was located at C-10 in **2** rather than at C-8 in the latter. This assignment was supported by the HMBC correlation from H-18 (δ_H 1.27, d, J = 7.0 Hz) to C-10 (δ_C 73.1), which was confirmed by the ^{1}H–^{1}H COSY cross peak of H-11 (δ_H 2.77, m) with H-10 (δ_H 3.75, m). The ROESY correlations of Me-19/H_2-5 indicated an *E*-geometry for the $\Delta^{6(7)}$ double bond. The absolute configuration of **2** at C-5 was identical to that of nemoralisin D (Zhang et al., 2013a,c), which is based on their similar ECD curves. Therefore, the structure of **2** is shown in Fig. 1.

Nemoralisin I (**3**) has a molecular formula of $C_{20}H_{28}O_6$ based on HREIMS at *m*/*z* 364.1879 $[M]^+$ (calcd for 364.1886). The ^{1}H and ^{13}C NMR data were very similar to those of **2** with 16 mass units more

Table 1
^{1}H NMR data assignment of compounds **1**–**4**.

Position	**1**[a]	**2**[b]	**3**[a]	**4**[b]
2	5.86, s	5.83, s	5.87, s	5.82, s
4a	4.94, br.t (4.4)	2.38, dd (17.9, 11.5)	2.44, dd (18.0, 11.5)	2.37, dd (17.8, 11.6)
4b		2.21, dd (17.9, 4.0)	2.26, dd (18.0, 4.0)	2.20, dd (17.8, 3.9)
5a	2.36, dt (14.1, 6.8)	5.1, ddd (11.5, 8.5, 4.0)	5.16, ddd (11.5, 8.5, 4.0)	5.10, ddd (11.6, 8.6, 3.9)
5b	2.75, ddd (14.1, 6.8, 4.4)			
6	5.36, t (6.8)	5.36, d (8.5)	5.69, d (8.5)	5.32, d (8.6)
8a	4.02, t (6.3)	2.27, m	4.32, t (6.8)	2.04, m
8b		2.12, m		2.04, m
9a	1.54, m	1.58, m	1.67, m	1.47, m
9b	1.54, m	1.65, m	1.67, m	1.47, m
10a	1.71, m	3.75, m	4.13, dd (11.8, 5.7)	1.61, m
10b	1.47, m			1.61, m
11	2.66, m	2.77, m	2.83, m	2.77, m
13	5.38, s	5.44, s	5.49, s	5.44, s
16	1.39, s	1.38, s	1.42, s	1.38, s
17	1.39, s	1.39, s	1.40, s	1.38, s
18	1.25, d (7.0)	1.27, d (7.0)	1.29, d (7.0)	3.78, m
19	1.65, s	1.68, s	1.76, s	1.68, s
20	2.09, s	1.99, s	2.03, s	1.99, s

[a] Data measured at 600 MHz.
[b] Data measured at 500 MHz.

Table 2
^{13}C NMR data assignment of compounds **1**–**4**.

Position	**1**[a]	**2**[b]	**3**[a]	**4**[b]
1	173.2	165.2	165.2	165.3
2	117.7	116.6	116.8	116.6
3	168.1	157.0	157.3	157.1
4	84.0	35.0	34.9	35.0
5	30.0	74.0	73.7	74.1
6	118.2	122.3	122.8	122.4
7	141.9	142.1	143.9	141.8
8	77.2	35.5	77.2	39.0
9	32.1	32.4	38.2	24.7
10	30.2	73.1	74.0	28.1
11	35.6	41.9	42.3	44.2
12	195.8	192.6	192.7	192.1
13	100.2	101.8	102.0	102.1
14	208.1	207.8	207.4	207.3
15	88.7	88.6	88.8	88.6
16	23.1	22.9	23.2	22.8
17	23.1	22.9	23.1	22.9
18	17.9	14.2	13.5	63.6
19	12.2	16.9	13.1	16.5
20	14.2	23.0	23.3	23.0

[a] Data measured at 150 MHz.
[b] Data measured at 125 MHz.

than that of **2**. Inspection of the NMR data led to the conclusion that an additional hydroxyl group appeared at C-8 in **3**, which was clearly confirmed by the HMBC correlation from H-19 (δ_H 1.76, s) to C-8 (δ_C 77.2) as well as the ^{1}H–^{1}H COSY cross-peaks of H-8 (δ_H 4.32, t, J = 6.8 Hz) with H_2-9 (δ_H 1.67, m, 2H). The planar structure of compound **3** was confirmed by a combination analysis of the HSQC, HMBC, and ^{1}H–^{1}H COSY data. Therefore, the structure of nemoralisin I was established as shown in Fig. 1. The experimental ECD curves of **3** were identical to those of nemoralisin D (Zhang et al., 2013a,c), which established the absolute configuration of **3** as (5*S*)-**3**.

Nemoralisin J (**4**) possessed the same molecular formula as **2** according to the HREIMS. The ^{1}H and ^{13}C NMR data of **4** were closely related to those of **2**. The major differences included the disappearance of a hydroxyl group at C-10 in **4** and the presence of a hydroxymethyl group at C-18 (δ_C 63.6), which were confirmed by the HMBC correlations of H_2-10 (δ_H 1.61, m, 2H) and H-11 (δ_H 2.77, m) with C-18 (δ_C 63.8). In addition, the *E*-geometry of the $\Delta^{6(7)}$ double bond was confirmed by the ROESY correlations of Me-19/H_2-5 and H-6/H_2-4. Therefore, the structure of compound **4** was assigned as depicted. The experimental ECD spectrum of **4** was identical to that of nemoralisin D, which established the absolute configuration at C-5 as (5*S*)-**4**, while the chiral center at C-11 remains unassigned.

Compounds **1**–**4** were evaluated for their inhibitory activity against lipopolysaccharide-induced nitric oxide production in RAW 264.7 cells. Nemoralisin J (**4**) exhibited moderate inhibitory activity with an IC_{50} value of 9.96 μM. However, the other compounds were inactive in this assay ($IC_{50} > 25$ μM).

3. Experiment

3.1. General experimental procedure

Optical rotations were measured with a JASCO P-1020 digital polarimeter (Jasco, Tokyo, Japan). UV spectra were recorded on a Shimadzu UV-2401 PC spectrophotometer (Shimadzu, Tokyo, Japan). IR spectra were scanning with Bruker Tensor-27 infrared spectrophotometer with KBr disk (Bruker, Karlsruhe, Germany). ESI-MS and HR-EI-MS spectra were obtained on Brucker HCT/E squire (Bruker, Karlsruhe, Germany) and Waters Autospec Premier P776 spectrum (Waters, Millford, MA, USA). ECD spectra were obtained on a Photophysics Chirascan spectrometer. 1D and 2D NMR spectra were recorded on Bruker AM-400, Bruker DRX-500 spectrometer and Bruker Avance III 600 spectrometers (Bruker, Karlsruhe, Germany) with TMS as internal standard. Semi-preparative HPLC was performed on an Agilent 1100 liquid chromatograph with a Waters X-Bridge C_{18} column (4.6 mm × 250 mm, 5 μm) with a flow rate of 5.0 mL/min, detected by a binary channel UV detector. Column chromatography was performed on silica gel (200–300 and 300–400 mesh; Qingdao Marine Chemical, Inc., Qingdao, PR China) and Sephadex LH-20 (40–70 μm, Amersham Pharmacia Biotech AB, Uppsala, Sweden), and Chromatorex Rp-C_{18} gel (20–45 mm; Merck, Darmstadt, Germany). Thin layer chromatography (TLC plates; Qingdao Marine Chemical Inc., Qingdao, China) spots were visualized under UV light and by dipping into 5% H_2SO_4 in EtOH followed by heating.

3.2. Plant material

The fruits of *A. gradifolia* were collected from Jinping, Yunnan Province, People's Republic of China, in September 2010. The plant samples were authenticated by Prof. Xun Gong (Kunming Institute of Botany, Chinese Academy of Sciences). A voucher specimen (No. KUN 0596224) was deposited at the Key Laboratory of Phytochemistry and Plant Resources in West China, Kunming Institute of Botany, Chinese Academy of Sciences.

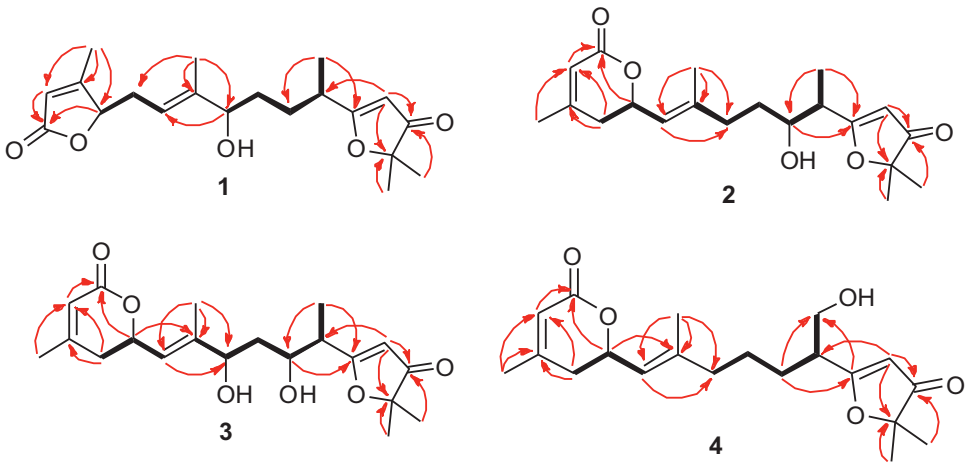

Fig. 2. HMBC (arrow) and ^{1}H–^{1}H COSY (bold) correlations of **1**–**4**.

3.3. Extraction and isolation

The air-dried and powdered fruits of *A. grandifolia* (7.0 kg) were extracted with 95% EtOH (3× 20 L) under reflux for three times (4, 3, and 3 h, respectively) at 60 °C respectively. After removal of the EtOH by evaporation, the combined EtOH extracts were concentrated under vacuum to give a crude extract (750 g), which was suspended in water and then partitioned successively with petroleum ether and EtOAc. The EtOAc extract (280 g) was subjected to a silica gel column, eluted with petroleum ether–acetone (from 1:0 to 1:1) and then eluted with chloroform–methanol (from 15:1 to 0:1) to yield seven fractions (Fr. 1–7). Fraction 5 (23 g) was chromatographed over a silica gel column, eluted with a gradient of chloroform – acetone (9:1–2:1), to give three fractions (Fr. 5A–5C). Fr. 5B (1.5 g) was then separated over a Rp-C_{18} gel column (MeOH/H_2O from 4:6 to 10:0) to obtain three fractions (Fr. 5B1–5B3). Fr. 5B3 (600 mg) was chromatographed on Sephadex LH-20 (MeOH) to obtain Fr. 3B3A (400 mg), which was further purified by a silica gel column ($CHCl_3$:MeOH, 40:1) to obtain compounds **4** (4 mg), **2** (3 mg), and **1** (2 mg).

Fr. 5 C (15.0 g) was separated over a Rp-C_{18} gel column (MeOH/H_2O from 3:7 to 10:0) to obtain four fractions (Fr. 5C1–5C4). Fr. 5C1 (1.2 g) was chromatographed over a silica gel column, eluted with a gradient of petroleum ether–ethyl acetate (9:1 to 1:1), to obtain three fractions (Fr. 5C1A–5C1D). Fr. 5C1A (30 mg) was chromatographed on Sephadex LH-20 (acetone) and further purified by HPLC using a Waters X-bridge C18 (4.6 mm × 250 mm, 5 μm) column with 30% MeOH/H_2O to obtain **3** (2 mg).

3.3.1. Compound *1*

Colorless oil. $[\alpha]^{27}_D$ = −12.5 (*c* = 0.17, MeOH); UV (MeOH) λ_{max} (log ε) 205 (1.08), 262 (0.80) nm; CD (0.00103 M, MeOH) λ_{max} ($\Delta\varepsilon$) 210 (–20.74); IR (KBr) ν_{max} 3439, 2931, 1758, 1699, 1457, 1440, 1382 cm^{-1}; ^1H NMR and ^{13}C NMR data, see (Tables 1 and 2); positive ESIMS *m/z* 371 $[M+Na]^+$; HREIMS *m/z* 348.1934 $[M]^+$ (calcd for $C_{20}H_{28}O_5$, 348.1937).

3.3.2. Nemoralisin H (*2*)

Colorless oil. $[\alpha]^{25}_D$ = −83.1 (*c* = 0.17, MeOH); UV (MeOH) λ_{max} (log ε) 202 (1.58), 262 (1.49) nm; CD (0.00087 M, MeOH) λ_{max} ($\Delta\varepsilon$) 210 (−5.48), 225 (−1.83), 253 (−5.82); IR (KBr) ν_{max} 3434, 2978, 2932, 1586, 1316, 1248, 1073 cm^{-1}; ^1H NMR and ^{13}C NMR data, see (Tables 1 and 2); positive ESIMS *m/z* 371 $[M+Na]^+$; HREIMS *m/z* 348.1938 $[M]^+$ (calcd for $C_{20}H_{28}O_5$, 348.1937).

3.3.3. Nemoralisin I (*3*)

Colorless oil. $[\alpha]^{25}_D$ = −17.6 (*c* = 0.16, MeOH); UV (MeOH) λ_{max} (log ε) 203 (1.06), 263 (0.84) nm; CD (0.00044 M, MeOH) λ_{max} ($\Delta\varepsilon$) 211 (−3.43), 225 (−1.12), 253 (−4.30); IR (KBr) ν_{max} 3432, 1696, 1641, 1460, 1383, 1278, 1176 cm^{-1}; ^1H NMR and ^{13}C NMR data, see (Tables 1 and 2); positive ESIMS *m/z* 387 $[M+Na]^+$; HREIMS *m/z* 364.1879 $[M]^+$ (calcd for $C_{20}H_{28}O_5$, 364.1886).

3.3.4. Nemoralisin J (*4*)

Colorless oil. $[\alpha]^{27}_D$ = −27.8 (*c* = 0.20, MeOH); UV (MeOH) λ_{max} (log ε) 203 (1.24), 263 (1.1) nm; CD (0.00078 M, MeOH) λ_{max} ($\Delta\varepsilon$) 213 (−9.66), 228 (−4.12), 253 (−10.48); IR (KBr) ν_{max} 3434, 2977, 1699, 1457, 1437, 1383, 1316, 1224 cm^{-1}; ^1H NMR and ^{13}C NMR data, see (Tables 1 and 2); positive ESIMS *m/z* 371 $[M+Na]^+$; HREIMS *m/z* 348.1929 $[M]^+$ (calcd for $C_{20}H_{28}O_5$, 348.1937).

3.4. Inhibition of nitric oxide production assay

Inhibition of NO production was determined in LPS-stimulated RAW 264.7 macrophage cell lines. Murine monocytic RAW 264.7 macrophages were dispensed into 96-well plates (2 × 10^5 cells/well) containing RPMI 1640 medium (Hyclone, UT, USA) with 10% FBS under a humidified atmosphere of 5% CO_2 at 37 °C. After 24 h preincubation, cells were treated with serial dilutions of all isolated compounds with the maximum concentration of 25 μM in the presence of 1 μg/mL LPS for18 h. Each compound was dissolved in DMSO and further diluted in medium to produce different concentrations. NO production in each well was assessed by adding 100 μL of Griess reagents A and B to 100 μL of each supernatant from LPS or the compound-treated cells in triplicate. After 5 min incubation, the absorbance was measured at 570 nm with a 2104 Envision multilabel plate reader (Perkin-Elmer Life Sciences, Inc., Boston, MA, USA). Cytotoxicity was determined by the MTT assay (Mosmann, 1983). MG-132 was used as a positive control. The assay was performed as described previously (Zhou et al., 2011).

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at http://dx.doi.org/10.1016/j.phytol.2014.02.005.

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