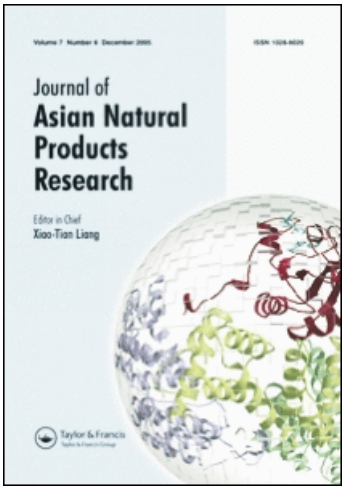

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ORIGINAL ARTICLE

Prostaglandin-like fatty acid derivatives from *Artemisia anomala*

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Four prostaglandin-like fatty acid derivatives anomalone A–D (**1**–**4**) were isolated from the aerial part of *Artemisia anomala* S. Moore. Their structures were determined on the basis of extensive spectroscopic analyses.

Keywords: *Artemisia anomala*; prostaglandin-like fatty acid derivatives; anomalone A–D

1. Introduction

Artemisia anomala S. Moore (Chinese name 'Nan-Liu-Ji-Nu'), a perennial herbaceous plant belonging to the Compositae family, has been commonly used in traditional Chinese medicines as an analgesic, antibiotic, and curing agent for wounds [1]. Previous phytochemical investigations led to the isolation of flavonoids, coumarins, and sesquiterpene lactones from *A. anomala* [2–7], and some compounds obtained by our team from this plant showed strong antitumor and anti-inflammatory activities [7]. As a continuous research of this plant, a systematic phytochemical investigation on *A. anomala* has been carried out [8–9]. Herein, we report the isolation and structural elucidation of four new prostaglandin-like fatty acid derivatives (**1**–**4**) (Figure 1) from the aerial parts of *A. anomala*.

2. Results and discussion

Compound **1** was obtained as a colorless gum. It showed a quasi-molecular ion peak at *m/z* 345.2034 $[M + Na]^+$ in its HR-ESI-MS, suggesting a molecular formula of $C_{19}H_{30}O_4$ (five degrees of unsaturation). The ^{13}C NMR spectrum (Table 2) indicated 19 C-atom signals which were classified by a DEPT experiment into two sp3 methyls, including a methoxy group, nine sp3 methylenes, an sp3 methine, an sp3 quaternary carbon, four sp2 methines, and two sp2 quaternary carbons. The presence of a conjugated cyclopentenone system was indicated by the ^1H NMR spectrum at δ_H 7.46 (1H, d, $J = 6.0$ Hz, H-10) and 6.17 (1H, d, $J = 6.0$ Hz, H-11), and the ^{13}C NMR spectrum at δ_C 132.2 (C-11), 164.1 (C-10), and 205.6 (C-12), respectively. The ^1H and ^{13}C NMR spectra demonstrated the presence of a methoxycarbonyl group at δ_H 3.66 (3H, s), δ_C 51.4 (OCH_3), 174.2 (C-1); a di-substituted olefin at δ_H 5.52 (1H, ddd, $J = 6.0$, 8.0, 11.0 Hz, H-15) and 5.47 (1H, dt, $J = 11.0$, 7.0 Hz, H-16) and at δ_C 126.4 (C-15) and 133.3 (C-16). The ^1H and ^{13}C NMR spectra of **1** were very

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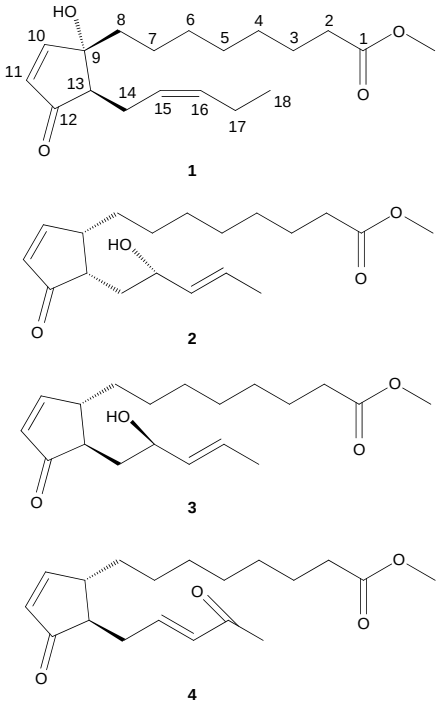

Figure 1. Structures of compounds **1**–**4**.

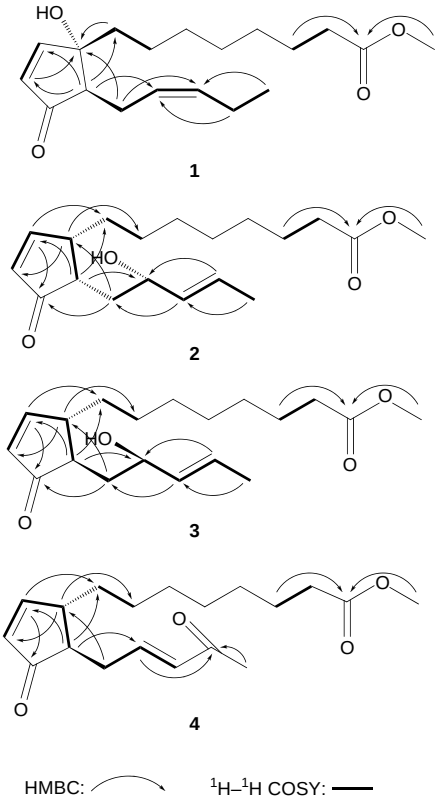

Figure 2. HMBC and ^{1}H–^{1}H COSY of compounds **1**–**4**.

similar to those of chromomoric acid methyl ester [10], indicating that both of them shared the same skeleton. The major difference between the two compounds was the position of the hydroxyl group, which was located at C-9 position in **1** by the HMBC correlations from H-14, H-11, and H-8 to C-9 (Figure 2). The relative configuration of **1** was determined by coupling constant, NOE correlations, and the Chem 3D molecular modeling studies. The coupling constant ($J_{15,16} = 11.0$ Hz) disclosed *Z* configuration for the Δ^{15} olefin, which was supported by NOE correlations between H-14 and H-17. The *cis* orientation of the two side chains on the cyclopentenone ring was elucidated from no NOE correlations between H-13 and H-8. Two possible conformations of **1** were predicted using computer (Chem-Bio3D Ultra 11.0 MM2 Minimize energy). The structures 1a and 1b are shown in Figure 3 and the latter met the requirements of NOE correlations between H-14a (δ_H 2.22) and H-8 (δ_H 1.50 and 1.80). From the above-mentioned evidence, the structure of **1** was established as methyl 8-((1*S*,5*R*)-1-hydroxy-4-oxo-5-((*Z*)-pent-2-enyl) cyclopent-2-enyl) octanoate, and named anomalone A.

Compounds **2** and **3** were obtained as a colorless gum. They shared the same molecular formula of $C_{19}H_{30}O_4$ (five degrees of unsaturation) by quasi-molecular ion peak at *m*/*z* 345.2045 and 345.2034 $[M + Na]^+$ in its HR-ESI-MS, respectively. Similarity of their ^{1}H and ^{13}C NMR suggested that **2** and **3** shared the same planar structure. Comparison of the ^{1}H and ^{13}C NMR spectral data of **2** with those of **1** revealed that the structures of **1** and **2** were similar, and the differences between them were the position of a double bond on the five-carbon side chain and the position of

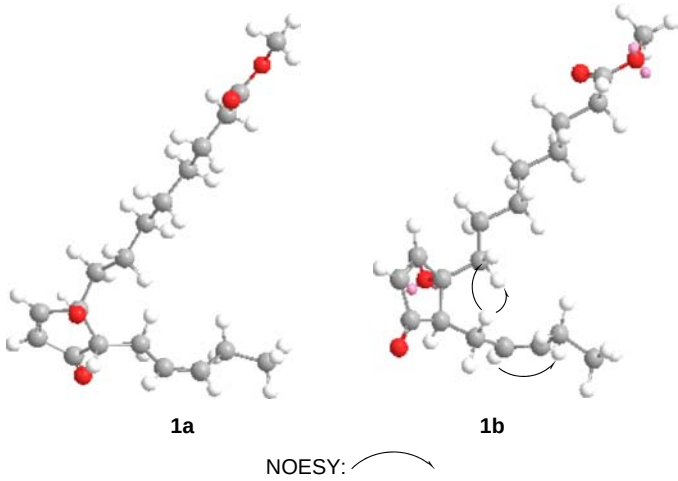

Figure 3. Two possible conformations of **1** were predicted using a computer (ChemBio3D Ultra 11.0 MM2 Minimize energy).

the hydroxyl group. The double bond occurring between C-16 and C-17 can be determined by HMBC correlations from H-18 to C-16, from H-17 to C-15, and from H-16 to C-14. The HMBC correlations of **2** from H-13, H-17 to C-15 (δ_C 70.4) suggested that C-15 was substituted by a hydroxyl group. All protons and carbons were unambiguously assigned by the extensive analysis of ^{1}H, ^{13}C, ^{1}H–^{1}H COSY, HSQC, and HMBC spectra (Figure 2). The coupling constant ($J_{16,17} = 15.0$ Hz) disclosed the *E* configuration for the Δ^{16} olefin. One of the differences between **2** and **3** was the relative configuration of C-15, which can be deduced by the comparison of their ^{1}H and ^{13}C NMR signals with those of a pair of known diastereomerism, (5*R*)-5-(4-{(1*S*,5*R*)-1-hydroxy-5-[(2*R*,3*E*)-2-hydroxypent-3-en-1-yl]-4-oxocyclopent-2-en-1-yl}butyl)dihydrofuran-2(3*H*)-one and (5*R*)-5-(4-{(1*S*,5*R*)-1-hydroxy-5-[(2*S*,3*E*)-2-hydroxypent-3-en-1-yl]-4-oxocyclopent-2-en-1-yl}butyl)dihydrofuran-2(3*H*)-one [11]. Thus, the hydroxyl groups at C-15 of **2** and **3** were determined as α- and β-configurations, respectively. The NOE correlations between H-15 and H-13 and between H-13 and H-9 in **2** suggested that H-9 and H-13 are β-oriented (Figure 4). The NOE correlation between H-15 and H-13 in **3** suggested that H-13 is α-oriented, whereas no NOEs could be discerned between H-13 and H-9 and between H-15 and H-9. These observations required a 9, 13-*trans* configuration (Figure 4). Therefore, the structure of **2** was established as methyl 8-((1*S*,5*S*)-5-((*S*,*E*)-2-hydroxypent-3-enyl)-4-oxocyclopent-2-enyl) octanoate, and named anomalone B. The structure of **3** was

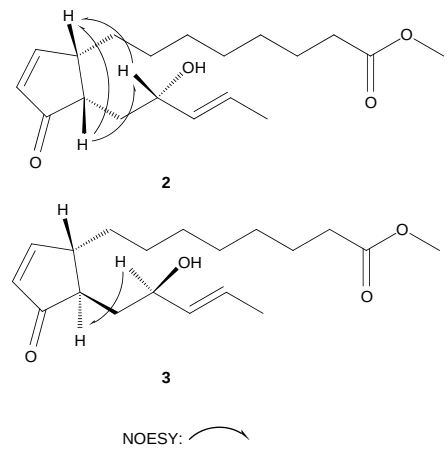

Figure 4. NOESY of compounds **2**, **3**.

established as methyl 8-((1*S*,5*R*)-5-((*R*,*E*)-2-hydroxypent-3-enyl)-4-oxocyclopent-2-enyl) octanoate, and named anomalone C.

Compound **4** was obtained as a colorless gum. It showed a quasi-molecular ion peak at *m/z* 343.1880 $[M + Na]^+$ in its HR-ESI-MS, suggesting a molecular formula of $C_{19}H_{28}O_4$ (six degrees of unsaturation). Comparison of its ^1H and ^{13}C NMR data with those of **3** revealed that they possessed a similar skeleton, and the differences between them were that the sp3 hydroxyl-bearing methine at δ_C 71.9 in **3** disappeared in **4**, while an unsaturated carbonyl group at δ_C 198.2 appeared in **4**. The carbonyl group was determined at C-17 and a di-substituted olefin occurred between C-15 and C-16 by the HMBC correlations from Me-18 (δ_H 2.23, s) and H-15 to C-17. The stereochemistry of the Δ^{15} olefin was determined as *E* configuration from its coupling constant ($J_{15,16} = 15.5$ Hz) and the *trans* orientation of the two side chains on the cyclopentenone ring with no NOE between H-13 and H-9. Two possible conformations of **4** were predicted using computer (ChemBio3D Ultra 11.0 MM2 Minimize energy). The coupling constant ($J = 2.5$ Hz) for **4** between H-9 and H-10 was the same as **2** and **3**. This required the same dihedral angle between H-9 and H-10. The structures **4**a and **4**b are shown in Figure 5 and their dihedral angles between H-9 and H-10 are obviously different. The above-mentioned evidence indicated that H-13 is α-oriented and H-9 is β-oriented. Thus, the structure of **4** was established as methyl 8-((1*S*,5*R*)-4-oxo-5-((*E*)-4-oxopent-2-enyl) oxocyclopent-2-enyl) octanoate, and named anomalone D.

3. Experimental

3.1 General experimental procedures

Optical rotation was recorded on a Perkin-Elmer 243B digital polarimeter. IR spectra were recorded on a Nexus-470 FTIR (Nicolet, Madison, WI, USA) spectrometer. NMR spectra were recorded on an Inova 500 spectrometer, operating at 500 MHz for ^1H and 125 MHz for ^{13}C. The chemical shifts were given in δ (ppm) with TMS as an internal standard and $CDCl_3$ as a solvent. HR-ESI-MS was measured on a Brucker APEX IV FT-MS spectrometer in positive ion mode. Semi-preparative HPLC was carried out on a Waters 600 instrument with ODS column (Agilent Technologies, Palo Alto, CA, USA, 250 mm × 9.4 mm, i.d., 5 μm) and C_{18} guard column with a 2996 photodiode array detector. Column chromatography was performed with silica gel (200–300 mesh; Qingdao Haiyang Chemical works, Qingdao, China) and ODS (Merck, Darmstadt, Germany).

3.2 Plant material

The aerial parts of *A. anomala* were collected from Hangzhou, Zhejiang

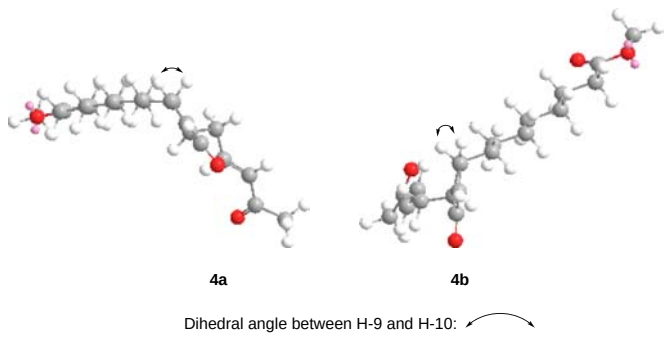

Figure 5. Two possible conformations of **4** were predicted using a computer (ChemBio3D Ultra 11.0 MM2 Minimize energy).

Province, China, in July 2008. The plant material was authenticated by Prof. Peng-Fei Tu. A voucher specimen (No. CM20071215) has been deposited at the Herbarium of the Peking University Modern Research Center for Traditional Chinese Medicine.

3.3 Extraction and isolation

Dried aerial parts (300 kg) of *A. anomala* were chopped and extracted three times with 95% EtOH. After evaporation of the solvent under reduced pressure, the residue was suspended in water and extracted with petroleum ether and chloroform, successively. The residue of the $CHCl_3$ layer (1000 g) was fractionated by silica gel column chromatography using a step-wise gradient of $CHCl_3$ and MeOH to give 72 fractions. Fractions 36–38 were subjected to ODS open column chromatography (MeOH/H_2O 40:60 to 80:20) to afford subfractions 1–5. Sub-fraction 2 was separated by semi-preparative HPLC (MeOH/H_2O 40:60) to afford **1** (30 mg), while subfraction 3 was separated by semi-preparative HPLC (MeOH/H_2O 40:60) and continuously purified by semi-preparative HPLC (MeCN/H_2O 35:65) to yield **2** (10 mg), **3** (9 mg), and **4** (11 mg).

3.3.1 Anomalone A (*1*)

A colorless gum. $[\alpha]_D^{22}$ −18.0 ($c = 0.1$, MeOH); IR (KBr) ν_{max}: 3459, 2934, 2860, 1712, 1591, 1439, 1346, 1252, 1203, 1171, 1113, 1024, 818, 699 cm^{-1}. ^1H NMR spectral data (500 MHz, $CDCl_3$), see Table 1 and ^{13}C NMR spectral data (125 MHz, $CDCl_3$), see Table 2; HR-ESI-MS *m/z*: 345.2034 $[M + Na]^+$ (calcd for $C_{19}H_{30}O_4Na$, 345.2036).

3.3.2 Anomalone B (*2*)

A colorless gum. $[\alpha]_D^{22}$ +23.5 ($c = 0.1$, MeOH); IR (KBr) ν_{max}: 3422, 2927, 2857,

Table 1. ^1H NMR spectral data (500 MHz) of **1**–**4** in $CDCl_3$.

Position	1	2	3	4
1	–	–	–	–
2	2.30 t (7.5)	2.32 t (7.5)	2.31 t (7.5)	2.32 t (7.5)
3	1.60 m	1.62 m	1.63 m	1.62 m
4	1.29 m	1.31 m	1.32 m	1.31 m
5	1.29 m	1.31 m	1.32 m	1.31 m
6	1.29 m	1.26 m	1.26 m	1.25 m
7	1.18 m	1.38 m	1.38 m	1.36 m
8	1.80 m 1.50 m	1.52 m	1.52 m	1.50 m
9	–	2.62 m	2.62 m	2.58 m
10	7.46 d (6.0)	7.62 d (2.5, 6.0)	7.62 d (2.5, 6.0)	7.61 d (2.5, 5.5)
11	6.17 d (6.0)	6.13 dd (2.0, 6.0)	6.13 dd (2.0, 6.0)	6.15 dd (2.5, 6.0)
12	–	–	–	–
13	2.59 m	2.18 ddd (2.5, 5.5, 8.0)	2.18 ddd (2.5, 6.0, 8.0)	2.13 m
14	2.22 m	1.85 ddd (5.5, 8.0, 14.0)	1.82 ddd (7.5, 9.0, 14.0)	2.62 ddd (1.5, 7.5, 14.5)
	2.53 m	1.75 dt (14.0, 5.5)	1.68 dt (14.0, 3.5)	2.43 dt (14.5, 7.5)
15	5.52 ddd (6.0, 8.0, 11.0)	4.36 m	4.25 m	6.72 dt (7.5, 15.5)
16	5.47 dt (11.0, 7.0)	5.50 dd (15.0, 7.0)	5.52 dd (15.0, 7.0)	6.11 d (15.5)
17	2.10 m	5.73 dq (15.0, 7.0)	5.72 dq (15.0, 7.0)	–
18	1.00 t (8.0)	1.70 dd (1.5, 6.0)	1.68 dd (1.5, 6.0)	2.23 s
OCH_3	3.66 s	3.67 s	3.67 s	3.67 s

Table 2. ^{13}C NMR spectral data (125 MHz) of **1**–**4** in $CDCl_3$.

Position	1	2	3	4
1	174.2	174.2	174.2	174.2
2	34.0	34.0	34.0	34.0
3	24.8	24.8	24.8	24.8
4	28.9	29.0	29.0	29.0
5	29.0	29.1	29.1	29.1
6	29.8	29.5	29.5	29.4
7	24.2	27.1	27.2	27.4
8	38.1	33.8	33.9	34.2
9	81.6	48.9	49.0	47.0
10	164.1	167.6	167.6	167.3
11	132.2	132.4	132.5	132.7
12	205.6	213.1	213.3	210.2
13	60.3	48.5	50.3	50.4
14	22.4	38.0	38.5	33.6
15	126.4	70.4	71.9	144.4
16	133.3	133.5	134.1	133.2
17	20.8	126.8	126.6	198.2
18	14.0	17.7	17.6	27.0
OCH_3	51.4	51.5	51.5	51.5

1736, 1702, 1588, 1440, 1355, 1176, 969, 806 cm^{-1}. ^1H NMR spectral data (500 MHz, $CDCl_3$), see Table 1 and ^{13}C NMR spectral data (125 MHz, $CDCl_3$), see Table 2; HR-ESI-MS *m/z*: 345.2045 $[M + Na]^+$ (calcd for $C_{19}H_{30}O_4Na$, 345.2036).

3.3.3 Anomalone C (*3*)

A colorless gum. $[\alpha]_D^{22}$ −26.5 ($c = 0.1$, MeOH); IR (KBr) ν_{max}: 3450, 2927, 2856, 1735, 1702, 1588, 1439, 1355, 1250, 1174, 969, 802 cm^{-1}. ^1H NMR spectral data (500 MHz, $CDCl_3$), see Table 1 and ^{13}C NMR spectral data (125 MHz, $CDCl_3$), see Table 2; HR-ESI-MS *m/z*: 345.2034 $[M + Na]^+$ (calcd for $C_{19}H_{30}O_4Na$, 345.2036).

3.3.4 Anomalone D (*4*)

A colorless gum. $[\alpha]_D^{22}$ −78.3 ($c = 0.1$, MeOH); IR (KBr) ν_{max}: 2927, 2856, 1736, 1706, 1676, 1631, 1589, 1437, 1360, 1253, 1173, 1099, 986 cm^{-1}. ^1H NMR spectral data (500 MHz, $CDCl_3$), see Table 1 and ^{13}C NMR spectral data (125 MHz, $CDCl_3$), see Table 2; HR-ESI-MS *m/z*: 343.1872 $[M + Na]^+$ (calcd for $C_{19}H_{28}O_4Na$, 345.1880).

Acknowledgement

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