A new norsesquiterpenoid from the roots of *Ligularia fischeri*

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A new norsesquiterpenoid, (4*aS*,5*S*)-5,6,7,8-tetrahydro-3-hydroxy-4*a*,5-dimethylnaphthalen-2(4*a*H)-one, along with three known compounds were isolated from the roots of *Ligularia fischeri*. Their structures were identified by IR, EI-MS, HR-ESI-MS, 1D NMR and 2D NMR.

Keywords: compositae, *Ligularia fischeri*, norsesquiterpenoid

The genus *Ligularia* (Compositae) which has about 100 species that are widely distributed in China. More than 20 species are used in traditional folk medicine. This genus is an active ingredient in antipyretics, analgesics, relieving phlegm and coughs and in improving the circulation.[1–3] Previous phytochemical investigations of *Ligularia* showed that the main components were eremophilane sesquiterpenes and pyrrolizidine alkaloids with strong physiological activities.[4–8] With the aim of identifying the active constituents from the genus *Ligularia*, the roots of the perennial herb *Ligularia fischeri* were investigated. A new norsesquiterpenoid was isolated together with three known compounds. The structure of the new compound was elucidated to be (4*aS*,5*S*)-5,6,7,8-tetrahydro-3-hydroxy-4*a*,5-dimethylnaphthalen-2(4*a*H)-one **(1). T**hree known compounds were identified as (8*SR*,8*aSR*)-8-isopropenyl-6,7,8,8*a*-tetrahydro-2*H*-naphtho[1,8-*bc*]furan-2-one (platyphyllide) **(2)**,[9–12] 2-hydroxyplatyphyllide **(3)**[13–15] and 5-acetyl-7-methoxybenzofuran **(4)**.[16] The known compounds **2–4** were identified by comparing their physical properties (melting points) and their spectroscopic data (MS, IR, ^{1}H and ^{13}C NMR) with those reported in the literature. The isolation and structural elucidation of the new norsesquiterpenoid is reported here.

Compound **1**, $[\alpha]_D^{18}$–53 ° (c 1.1, $CHCl_3$), was isolated as a white amorphous powder. Its IR spectrum exhibited strong absorption bands characteristic of hydroxyl (3408 cm^{-1}), carbonyl (1670 cm^{-1}) and double bond(1635 cm^{-1}). The HR-ESI-MS experiment showed a peak of *m/z* $[M+H]^+$ 193.1223 (Calcd for $C_{12}H_{16}O_2$ + H 193.1229). Together with analysis of the ^{1}H NMR, ^{13}C NMR and DEPT spectra, the molecular formula was established as $C_{12}H_{16}O_2$, indicating five degrees of unsaturation. The ^{1}H NMR spectrum (Table 1) of **1** displayed the signals for a methyl doublet at δ 1.08 (d, J = 5.2 Hz), a methyl singlet at δ 1.15 (s), and two olefinic signals at δ 6.33 (s, CH), 6.19 (s, CH) for two pairs of trisubstituted C=C bonds. Twelve carbon signals were observed in ^{13}C NMR spectrum (Table 1), including a carbonyl carbon at δ 182.1, two methyl carbons at δ 18.3 and 16.7, an oxygenated quaternary carbon at δ 146.4 and a tetrasubstituted double bond carbon at δ 173.2. The ^{1}H and ^{13}C NMR (see Table 1) of **1** revealed signals due to two methyls, three methylenes, three methines, and four quaternary carbons, which suggested the presence of 12 carbons and a hydroxyl group for the skeleton of **1**. A comparative study revealed that the NMR data of compound **1** was similar to those of a known related compound, (4*aS*,5*S*,8*R*)-5,6,7,8-tetrahydro-3,8-dihydroxy-4*a*,5-dimethylnaphthalen-2(4*a*H)-one,[17] except for the presence of one less hydroxyl group.

Table 1 ^{1}H,^{13}C and DEPT data for compound **1** ($CDCl_3$, in ppm, TMS)[a,b]

Position	δ_H	δ_C	DEPT
1a	2.02 (m, 1H)	33.4	CH_2
1b	1.82 (m, 1H)	—	
2a	1.63 (m, 1H)	28.5	CH_2
2b	1.46 (m, 1H)	—	
3a	1.33 (m, 1H)	30.2	CH_2
3b	1.02 (m, 1H)	—	
4	1.53 (m, 1H)	44.6	CH
5	—	43.1	C
6	6.33 (s, 1H)	124.6	CH
7	—	146.4	C
8	—	182.1	C
9	6.19 (s, 1H)	121.5	CH
10	—	173.2	C
11	1.15 (s, 3H)	18.3	CH_3
12	1.08 (d, J = 5.2 Hz, 3H)	16.7	CH_3
OH	7.27 (s, 1H)	—	—

[a]Measured at 400 MHz for ^{1}H NMR and 100 MHz for ^{13}C NMR.
[b]Assigned by ^{1}H–^{1}H COSY and HMBC spectrum.

The key ^{1}H–^{1}H COSY and HMBC correlations (Fig. 2) showed that compound **1** was a tri-nor eremophilane sesquiterpene. In the HMBC spectrum, correlations of the olefinic signals (δ6.33) for HC-6 with C-5, C-7, C-8, C-10 and Me-11, and of HC-9 with C-7, C-1 and C-5, confirmed the presence of a 6(7),9(10)-dien-8-oxo moiety. This inference was supported by the presence of $\alpha,\beta,\alpha',\beta'$-unsaturated ketone absorption bands at 1716 and 1649 cm^{-1} in the IR spectrum. Correlations of the H-atom of a OH group at δ (H) 7.27 (s) with C-6, C-7 and C-8 confirmed the location of OH at C(7). The above discussed analysis of the 1D- and 2D-NMR data of compound **1** provided further evidence for the structure of **1**

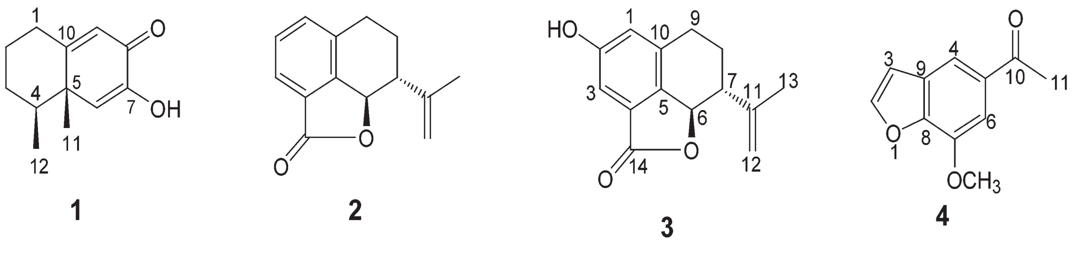

Fig. 1 The structures of compounds **1–4**.

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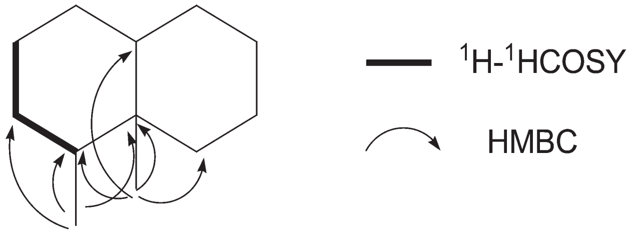

Fig. 2 The key HMBC and ^{1}H–^{1}H COSY correlations of compound **1** (only substructure shown).

(4a*S*,5*S*)-5,6,7,8-tetrahydro-3-hydroxy-4*a*,5-dimethylnaphthalen-2(4*a*H)-one.

Experimental

Melting points were determined with an X-4 Digital Display Micro-Melting point apparatus, and reported uncorrected. Optical rotations were measured in $CHCl_3$ or CH_3COCH_3 using a Perkin-Elmer 341 polarimeter. IR spectra were recorded with a Bruker Vertex 70 FT-IR spectrometer. ^{1}H, ^{13}C NMR (DEPT) and 2D NMR were recorded on a Bruker AVANCE 400 spectrometer with TMS as internal reference. HR-ESI-MS spectra were obtained on a Bruker APEX II spectrometer. EI-MS were obtained on an HP-5988 MS spectrometer. Silica gel (200–300 and 300–400 mesh) used for column chromatography (CC) and silica gel (GF_{254}) for TLC were supplied by the Qingdao Marine Chemical Factory in China. The spots of the samples were detected on TLC (silica gel, GF_{254}) under UV light at 254 nm or by heating at 110 °C after spraying with 98% H_2SO_4-C_2H_5OH (v/v = 5:95).

Plant material

Ligularia fischeri (Ledeb.) Turcz. (Compositae) was collected in Nanchuan county of Chongqing city, People's Republic of China in October 2007. The specimens were identified by Associate Prof. Hong Zhao (Marine College, Shandong University at Weihai). A voucher specimen (No. KY2007010) has been deposited in the Herbarium of the Laboratory of Botany, Marine College, Shandong University, Weihai, P. R. China.

Extraction and isolation

The air-dried roots of the plant (5.0 kg) were powdered and extracted with 95% EtOH at room temperature (15 L × 3, each extraction lasted 7 days). The combined extracts were concentrated under reduced pressure to afford a residue (192 g). The residue was suspended in H_2O (2.0 L), extracted with petroleum ether (b.p. 60–90 °C) (3.0 L), $CHCl_3$ (2.5 L), EtOAc (3.0 L) and n-BuOH (2.0 L), respectively. The EtOAc soluble fraction was concentrated to yield a residue (96 g).This residue was subjected to a silica gel column chromatography (silica gel 200–300 mesh, 1500 g) with a gradient of petroleum ether (b.p. 60–90 °C) – acetone (v/v = 60:1–1:1). Fractions were examined by TLC and combined to afford 8 pooled fractions (Fr. A–H). Fraction B was further separated by silica-gel column chromatography with a petroleum ether–acetone (40:l–10:l) gradient, and finally gave **4** (41 mg). Fraction C was separated by repeated low pressure silica gel column chromatography (silica gel 300–400 mesh) with hexane–acetone (30:1) as the eluent to afford **1** (7 mg). Fraction F was subjected to silica gel chromatography with hexane–acetone (20:1) as the eluent to give **4** pooled fractions (Fr. F1–F4). Fraction F2 was purified by prep. TLC using a petroleum ether - EtOAc (3:1) system to yield compounds **2** (13 mg) and **3** (6 mg).

(4aS,5S)-5,6,7,8-Tetrahydro-3-hydroxy-4a,5-dimethylnaphthalen-2(4aH)-one **(1):** $C_{12}H_{16}O_2$, white amorphous powder. $[\alpha]_D^{18}$–53 ° (c 1.1, $CHCl_3$). IR (KBr) cm^{-1}: 3408 (OH), 1670 (C=O), 1635 (C=C). HR-ESI-MS: *m/z*: $[M+H]^+$ 193.1223 (Calcd 193.1229). ^{1}H, ^{13}C NMR and DEPT data see Table 1.

(8SR,8aSR)-8-Isopropenyl-6,7,8,8a-tetrahydro-2H-naphtho[1,8-bc]furan-2-one (platyphyllide) (**2**): $C_{14}H_{14}O_2$, white powder. IR (KBr) cm^{-1}: 1762 (C=O), 1643 (C=C). HR-MS: *m/z*: 214.0987 (Calcd 214.0990). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.54 (m, 3H, H-1,2,3), 5.24 (d, 1H, H-6, J = 12.0 Hz), 4.98 (s, 2H, H-12), 3.16 (dd, 1H, H-7, J = 12.0, 7.8 Hz), 1.89 (s, 3H, H-13). ^{13}C NMR (100 MHz, $CDCl_3$) δ 123.1 (C-1), 149.0 (C-2), 112.6 (C-3), 134.0 (C-4), 132.4 (C-5), 80.7 (C-6), 46.5 (C-7), 26.1 (C-8), 26.9 (C-9), 130.1 (C-10), 144.3 (C-11), 124.9 (C-12), 20.8 (C-13), 170.7 (C-14).

2-Hydroxyplatyphyllide (**3**): $C_{14}H_{14}O_3$, white powder. EI-MS: *m/z*: 230 (M^+), 162 (base peak). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.26 (s, 1H, H-3), 6.91 (s, 1H, H-1), 5.47 (s, 1H, OH-2), 5.18 (d, 1H, H-6, J = 7.3 Hz), 4.96 (s, 2H, H-12), 1.87(s, 3H, H-13). ^{13}C NMR (100 MHz, $CDCl_3$): δ 120.0 (C-1), 157.6 (C-2), 108.7 (C-3), 135.3 (C-4), 126.1 (C-5), 80.5 (C-6), 46.5 (C-7), 26.1 (C-8), 26.8 (C-9), 141.7 (C-10), 144.2 (C-11), 112.4 (C-12), 20.7 (C-13), 168.3 (C-14).

5-Acetyl-7-methoxybenzofuran (**4**): $C_{11}H_{10}O_3$, colourless needles (recrystallised from $CHCl_3$), m.p. 85–87 °C. EI-MS: *m/z*: 190, 175, 147, 132, 99, 91, 89, 76, 57, 43. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.88 (s, 1H, H-4), 7.72 (d, 1H, H-2, J = 2.0 Hz), 7.52 (s, 1H, H-6), 6.88 (d, 1H, H-3, J = 2.0 Hz), 4.08 (s, 3H, CH_3O-7), 2.68 (s, 3H, H-11). ^{13}C NMR (100 MHz, $CDCl_3$): δ 146.3 (C-2), 105.4 (C-3), 116.1 (C-4), 133.8 (C-5), 107.6 (C-6), 146.3 (C-7), 147.1 (C-8), 128.7 (C-9), 197.7 (C-10), 26.6 (C-11), 56.2 (-OMe).

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