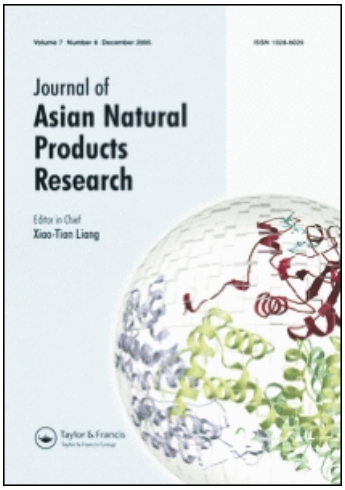

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COUMARINS FROM *PEUCEDANUM WULONGENSE*

LING-YI KONG* and FEI ZHI

Department of Natural Medicinal Chemistry, China Pharmaceutical University, Nanjing 210009, China

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A new angular dihydropyrancoumarin named wulongensin A, along with five known coumarins, (−)-anomalin, umbelliferone, (−)-smyrinol, 3′(*S*),4′(*S*)-disenecioyloxy-3′,4′-dihydroseselin, (+)-*trans*-khellactone, was isolated from the root of *Peucedanum wulongense*. The structure of wulongensin A was established as 3′(*R*)-angeloyloxy-4′(*R*)-isovaleryloxy-3′,4′-dihydroseselin by spectroscopic methods and the absolute configurations were deduced by chemical correlations with known compounds.

Keywords: *Peucedanum wulongense*; Wulongensin A; 3′(*R*)-Angeloyloxy-4′(*R*)-isovaleryloxy-3′,4′-dihydroseselin

INTRODUCTION

Peucedanum wulongense is a plant of Umbelliferae. In some areas of China, the roots of some plants of *Peucedanum* genus, including *Peucedanum wulongense*, are used as Qianhu, a traditional Chinese medicine to cure some diseases such as coughing due to pathogenic wind–heat, accumulation of phlegm and heat in the lung. So far there have been no reports about the chemistry of the title plant. We studied the chemical constituents to discover new active compounds from this plant. A new angular dihydropyrancoumarin named wulongensin A, along with five known coumarins, was isolated and the structure of wulongensin A was elucidated as 3′(*R*)-angeloyloxy-4′(*R*)-isovaleoyloxy-3′,4′-dihydroseselin by spectral analysis. The absolute configurations were deduced by chemical correlation with known compounds. This paper describes the isolation and structural elucidation of these compounds.

RESULTS AND DISCUSSION

Compound **1** was isolated as a white solid. The molecular ion peak at *m*/*z* 428.1841 in the high-resolution mass spectrum showed the molecular formula to be $C_{24}H_{28}O_7$. The signals at 1716, 1621 and 1607 cm^{-1} in the IR spectrum were assigned to the carbonyl and aromatic

*Corresponding author. Tel.: +86-25-5391289. Fax: +86-25-5301528. E-mail: lykong@jlonline.com

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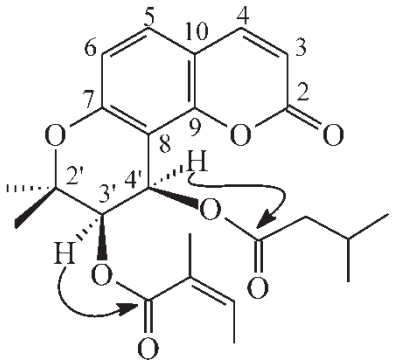

FIGURE 1 Structure and major HMBC correlations for **1**.

system of a coumarin skeleton. The ^{1}H NMR spectrum in the aromatic proton region of **1** revealed two pairs of doublets at δ 6.20 (1H, d, $J = 9.6$ Hz), 7.59 (1H, d, $J = 9.6$ Hz), 7.34 (1H, d, $J = 8.8$ Hz), 6.78 (1H, d, $J = 8.8$ Hz), which are attributed to the C-3-H, C-4-H signals of the α-pyrone ring system and C-5-H, C-6-H of the benzene ring, indicating **1** is a coumarin substituted at the C-7 and C-8 positions. A pair of doublets at δ 5.36 (1H, d, $J = 4.8$ Hz) and 6.59 (1H, d, $J = 4.8$ Hz) were assigned to the methine protons at C-3′–H and C-4′–H, showing that C-7 and C-8 of **1** formed a dihydropyran ring. The signals at δ 6.10 (1H, m), 2.02 (3H, br d), 1.85 (3H, br s) indicated the existence of $-COC(CH_3)=CHCH_3$; since no NOE enhancement between δ 2.02 and 1.85 was observed, so it should be an angeloyl. The signals at δ 2.16 (2H, d, $J = 5.6$ Hz), 1.14 (1H, m), 0.97 (3H, d, $J = 6.0$ Hz), 0.93 (3H, d, $J = 6.0$ Hz) were due to an isovaleryl group. In the HMBC spectrum, the carbonyl signal of angeloyl at δ 166.25 was correlated with the proton signal at δ 5.36 (C-3′–H), the carbonyl signal of isovaleryl at δ 171.39 was correlated with the proton signal at δ 6.59 (C-4′–H), which indicated that the angeloyloxy group was attached to C-3′ and the isovaleryloxy group was attached to C-4′ (Fig. 1).

There are two chiral carbon atoms in the molecular structure of **1**. It has been reported that the relative configuration of this type of compound can be determined from the ^{1}H NMR spectrum. The relative configuration at C-3′ and C-4′ was considered to be *cis* on the basis of the coupling constant of C-3′–H and C-4′–H being 4.8 Hz and the difference between the methyl proton signals at δ 1.46 and 1.42 of the 2′-*gem*-dimethyl group being 0.04 [1–3]. Compound **1** has a levo-rotation ($[\alpha]_D$ −36.8) and its absolute configuration was further studied by chemical correlation with known compounds. On total alkaline hydrolysis, **1** gave a mixture of two products, isolated by HPLC (Fig. 2). The compounds were identified by spectral analysis and optical activity as (+)-*cis*-khellactone (**7**) and (−)-*trans*-khellactone (**8**) as a minor artefact arising from epimerization at C-4′ because of the benzyl effect and S_N2 reaction mechanism [4]. The absolute configurations of **7** and **8** were described previously as 3′*R*, 4′*R* and 3′*R*, 4′*S* by chemical methods and X-ray diffraction analysis [5,6] and, accordingly, the absolute configuration of **1** was established as 3′*R*, 4′*R*. The chemical structure of **1** was finally elucidated as 3′(*R*)-angeloyloxy-4′(*R*)-isovarloyloxy-3′,4′-dihydroseselin. Its enantiomer, named Pd-III ($[\alpha]_D$ +25.9), was isolated from the root of same genus, *Peucedanum praeruptorum* [7].

Compounds **2**–**6** were identified as (−)-anomalin (**2**) [7], 3′(*S*),4′(*S*)-disenecioyloxy-3′,4′-dihydroseselin(**3**) [8], umbelliferone (**4**), (−)-smyrinol (**5**) [9] and *trans*-khellactone (**6**) [10] by physical constants and spectral analysis.

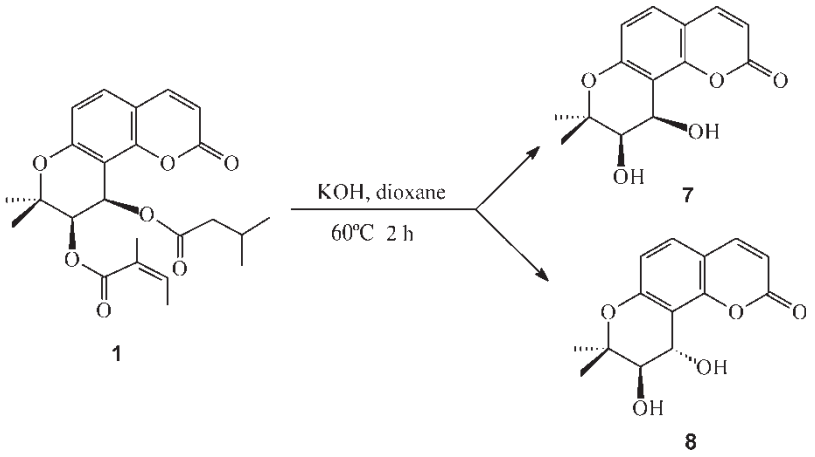

FIGURE 2 Total alkaline hydrolysis of **1**.

EXPERIMENTAL

General Experimental Procedures

Mps were determined on a X-4 micro melting-point apparatus, and are uncorrected. UV spectra were recorded on a Shimadzu UV-2501 PC spectrophotometer in MeOH solution. IR spectra were obtained on a Nicolet Impact-410 spectrometer. 1D NMR and 2D NMR spectra were recorded on a Bruker-DRX-400 spectrometer using TMS as internal standard. EI-MS spectra were measured on a JEOL-DX-300 mass spectrometer. Optical rotations were determined on a Perkin–Elmer 241 automatic polarimeter at 20°C. Preparative HPLC was carried out on a Shimadzu LC-8A equipped with a UV detector, using a Shim-Packed PREP-SIL column (10 × 250 mm, Shimadzu), detector wavelength: 320 nm, flow rate: 5.0 ml min^{-1}, mobile phase: $CHCl_3$–MeOH (49:1). Silica gel H (10–40 μm) was used for column chromatography. Petrol refers light petroleum (bp range 60–90°C).

Plant Material

Roots of *Peucedanum wulongense* were collected in Chongqing city, China, in September, 1999 and identified by Professor Chaoli Li, at the Chongqing Institute of Materia Medica, China. A voucher specimen (No 990902) was deposited in the Department of Natural Medicinal Chemistry, China Pharmaceutical University.

Extraction and Isolation

The root material (1.02 kg) was extracted with $CHCl_3$ and the resultant solution concentrated *in vacuo* to yield a residue (61 g) that was subjected to column chromatography on silica gel H (300 g), eluted with a mixture of Petrol–EtOAc with gradually increasing polarity. The first fraction (2.3 g) of Petrol–EtOAc (85:15) was subjected to column chromatography, again eluted with Petrol–EtOAc (88:12), and was finally purified with preparative TLC to give compound **1** (42 mg). The next fraction (4.2 g) of Petrol–EtOAc (80:20) was subjected to column chromatography, again eluted with Petrol–EtOAc (85:15), and was finally purified by preparative HPLC to give compounds **2** (14 mg) and **3** (28 mg). A further fraction (5.1 g)

of Petrol–EtOAc (70:30) was subjected to column chromatography, again eluted with Petrol–EtOAc (75:25), to give compounds **4** (21 mg) and **5** (38 mg). The final fraction (1.3 g) of Petrol–EtOAc (60:40) was subjected to column chromatography, and again eluted with Petrol–EtOAc (65:35), to give compound **6** (29 mg).

3′(R)-Angeloyloxy-4′(R)-isovaleryloxy-3′,4′-dihydroseselin (1)

Colourless needles, mp. 132.0–133.5°C, $[\alpha]_D$ −36.8 (*c* 0.2, $CHCl_3$). UV λ_{max}^{MeOH} (nm): 323, 255; IR ν_{max} (cm^{-1}): 3062, 2964, 2935, 2847, 1735, 1716, 1621, 1607, 1570, 1486, 1463, 1390, 1381, 1254, 1128, 1008, 844; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.20 (1H, d, $J = 9.6$ Hz, H-3), 7.59 (1H, d, $J = 9.6$ Hz, H-4), 7.34 (1H, d, $J = 8.8$ Hz, H-5), 6.78 (1H, d, $J = 8.8$ Hz, H-6), 5.36 (1H, d, $J = 4.8$ Hz, H-3′), 6.59 (1H, d, $J = 4.8$ Hz, H-4′), 1.46 (3H, s, C-2′—CH_3), 1.42 (3H, s, C-2′–CH_3), 6.10 (1H, m, H-3″), 2.02 (3H, br d, H-4″), 1.85 (3H, br s, H-5″), 2.20 (2H, m, H-2‴), 1.14 (1H, m, H-3″), 0.97 (3H, d, $J = 6.0$ Hz, H-4″), 0.93 (3H, d, $J = 6.0$ Hz, H-5‴); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 159.61 (C-2), 113.32 (C-3), 142.98 (C-4), 129.22 (C-5), 114.15 (C-6), 156.62 (C-7), 107.02 (C-8), 154.02 (C-9), 112.34 (C-10), 77.48 (C-2′), 70.15 (C-3′), 60.61 (C-4′), 25.34 (C-2′—CH_3), 22.78 (C-2′—CH_3), 166.25 (C-1″), 127.01 (C-2″), 139.45 (C-3″), 15.77(C-4″), 20.42 (C-5″), 171.39 (C-1‴), 43.11(C-2‴), 25.40 (C-3‴), 22.39 (C-4‴), 22.71 (C-5‴); HREIMS *m/z*: 428.1841 (calcd for $C_{24}H_{28}O_7$ 428.1835). EIMS *m/z* (%): 428 (M^+, 2.6), 328 (10.2), 313 (4.6), 244 (28.5) 229 (91.2), 213 (9.3), 83 (100), 55 (32.6).

Total Alkaline Hydrolysis of 3′(R)-Angeloyloxy-4′(R)-isovaleryloxy-3′,4′-dihydroseselin (1)

Compound **1** (25 mg) dissolved in dioxane (2.0 ml) was added to 0.5 M KOH (2.0 ml) and the reaction mixture was stirred at 60°C for 2 h. The solution was then neutralized with 10% H_2SO_4, extracted with $CHCl_3$, washed with 10% $NaHCO_3$, dried with Na_2SO_4, and evaporated; the residue was purified with HPLC to yield two products. The first eluant (8 mg) gave (+)-*cis*-khellactone (**7**): white needles, mp. 171.0–173.5°C, $[\alpha]_D$ +78.5 (*c* 0.05, $CHCl_3$). IR ν_{max} (cm^{-1}): 3402, 2985, 2935, 1728, 1715, 1607, 1490, 1395, 1352, 1288, 1241, 1225, 1112, 1017, 992, 843; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.24 (1H, d, $J = 9.5$ Hz, H-3), 7.89 (1H, d, $J = 9.5$ Hz, H-4), 7.44 (1H, d, $J = 8.6$ Hz, H-5), 6.78 (1H, d, $J = 8.6$ Hz, H-6), 3.77 (1H, d, $J = 4.9$ Hz, H-3′), 5.12 (1H, d, $J = 4.9$ Hz, H-4′), 1.44 (3H, s, C-2′–CH_3), 1.42 (3H, s, C-2′–CH_3), 3.45 (1H, s, OH), 2.86 (1H, s, OH); EIMS *m/z* (%): 262 (M^+, 38.8), 213 (8.5), 191 (100), 162 (23.5), 134 (18.9), 107 (4.5), 89 (3.7), 72 (11.2), 57 (7.4). The second eluant (6 mg), which contained the epimerization artefact at C-4′, gave (−)-*trans*-khellactone (**8**): white needles, mp 184.5–186.0°C, $[\alpha]_D$ −20.4 (*c* 0.05. $CHCl_3$). IR ν_{max} (cm^{-1}): 3400, 2976, 2920, 1724, 1608, 1490, 1402, 1362, 1289, 1245, 1180, 1123, 1057, 911, 832; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.25 (1H, d, $J = 9.5$ Hz, H-3), 7.65 (1H, d, $J = 9.5$ Hz, H-4), 7.30 (1H, d, $J = 8.6$ Hz, H-5), 6.79 (1H, d, $J = 8.6$ Hz, H-6), 3.86 (1H, d, $J = 6.7$ Hz, H-3′), 4.98 (1H, d, $J = 6.7$ Hz, H-4′), 1.53 (3H, s, C-2′—CH_3), 1.31 (3H, s, C-2′—CH_3), 2.56 (2H, s, 2OH). EIMS *m/z* (%): 262 (M^+, 24.6), 191 (100), 162 (32.5), 134 (18.7), 107 (10.1), 77 (15.2), 72 (19.8), 57 (8.5).

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