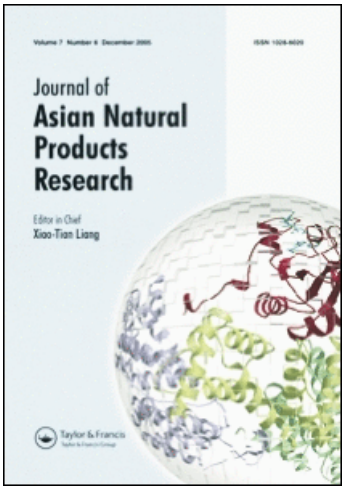

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Novel coumarin and furan from the roots of *Angelica pubescens* f. *biserrata*

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A new natural coumarin, angepubebisin (**1**), and a new furan, angepubefurin (**2**), together with the five known compounds, umbelliferone, angelol B (**3**), ulopterol (**4**), peucedanol (**5**), and scopoletin, were isolated from the roots of *Angelica pubescens* Maxim. f. *biserrata* Shan et Yuan. The structures of angepubebisin (**1**) and known compounds were determined by spectroscopic methods, including IR, UV, EI-MS, HR-FTICR-MS, 1D-, and 2D-NMR spectral analyses, and angepubefurin (**2**) was determined by HR-FTICR-MS and X-ray diffraction analyses.

Keywords: *Angelica pubescens* f. *biserrata*; Umbelliferae; coumarin; furan; angepubebisin; angepubefurin

1. Introduction

Angelica pubescens Maxim. f. *biserrata* Shan et Yuan (Umbelliferae) is a plant both wild and cultivated in Hubei, Sichuan, and Shanxi Provinces of China and Korea. The roots have been used as a traditional Chinese medicine for the treatment of rheumatic arthritis with pain in the lower back and knees, headache due to the attack of cold, and the spasmodic pain of the limbs [1]. The roots were known to contain numerous coumarins, some of which were to be active as inhibitor of thromboxane formation in platelets and phosphoinositide breakdown, and antiproliferatory and relaxant effect on the trachealis [2–5]. In this paper, we report the isolation and structural elucidation of a novel coumarin, named angepubebisin (**1**), and a novel furan, named angepubefurin (**2**) (Figure 1), together with the five known compounds as umbelliferone [6], angelol B (**3**) [7], ulopterol (**4**) [8], peucedanol (**5**) [8], and scopoletin [6]. The structures of **1** and **3** were fully characterized by detailed NMR investigations including ^{1}H NMR, ^{13}C NMR, ^{1}H–^{1}H COSY, HSQC, HMBC, and NOESY experiments. Scopoletin was isolated from the title plant for the first time.

2. Results and discussion

Compound **1** was isolated as an amorphous powder. Based on the positive HR-FTICR-MS of **1** indicating $[M+H]^+$ at m/z 417.1901, its molecular formula was deduced to be $C_{23}H_{28}O_7$. This conclusion was also supported by its data of ^{1}H NMR, ^{13}C NMR, and DEPT (Table 1). The UV spectrum had the absorption maxima at 245, 296, and 322 nm characteristic of a coumarin nucleus oxygenated at the C-7 position [9]. The IR

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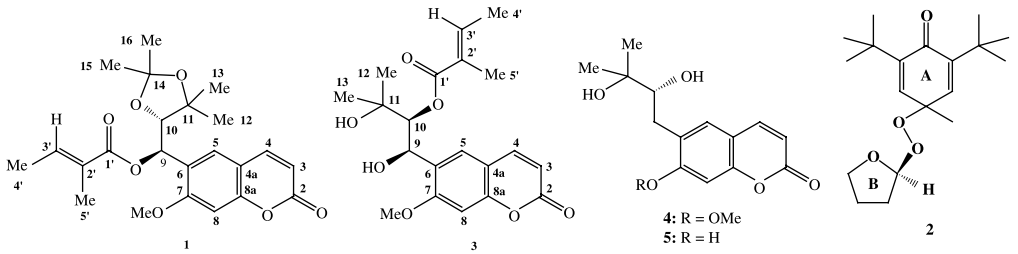

Figure 1. Structures of compounds **1**–**5**.

absorption bands at 1734 and 1704 cm^{-1} indicated the presence of a lactone and an α,β-unsaturated carbonyl group. The intense absorption band at 1621 cm^{-1} was characteristic of conjugated C–C double bonds. The ^{1}H and ^{13}C NMR spectral profile of parent skeleton of **1** resembled those of angelol B (**3**), which also exhibited signals assigned to a 6,7-disubstituted coumarin [δ_H 6.27 (1H, d, $J = 9.6$ Hz, H-3), 7.64 (1H, d, $J = 9.6$ Hz, H-4), 7.46 (1H, s, H-5), 6.83 (1H, s, H-8), and δ_C 160.9 s (C-2), 113.5 d (C-3), 143.4 d (C-4), 112.2 s (C-4a), 128.0 d (C-5), 124.0 s (C-6), 159.6 s (C-7), 99.4 d (C-8), and 155.7 s (C-8a)] and a methoxyl group [δ_H 3.95 (3H, s); δ_C 56.2 q]. In addition, a tigloyl group

Table 1. ^{1}H (500 MHz) and ^{13}C (125 MHz) NMR spectral data for compounds **1** and **3**[a].

		1			**3**	
		HMQC			HMQC	
C	H	δ_H (*J*/Hz)	$\delta_{C,DEPT}$	HMBC (C–H)	δ_H (*J*/Hz)	$\delta_{C,DEPT}$
2			160.9 s	H-3, H-4		161.3 s
3	3	6.27 d (9.6)	113.5 d		6.22 d (9.3)	113.1 d
4	4	7.64 d (9.6)	143.4 d	H-5	7.56 d (9.3)	143.5 d
4a			112.2 s	H-3, H-8		111.9 s
5	5	7.46 s	128.0 d	H-4, H-9	7.57 s	126.3 d
6			124.0 s	H-8, H-9		126.6 s
7			159.6 s	—OCH_3, H-5, H-8, -9		159.0 s
8	8	6.83 s	99.4 d		6.74 s	98.5 d
8a			155.7 s	H-4, H-5, H-8		155.2 s
9	9	6.19 d (5.7)	67.9 d	H-5	5.62 brs	67.6 d
10	10	4.17 d (5.7)	83.7 d	H-13, H-14, H-9	5.11 brs	76.0 d
11			79.9 s	H-13, H-14		74.8 s
12	12	1.04 s	26.9 q	H-10, H-14	1.24 s	28.1 q
13	13	1.18 s	23.3 q	H-10, H-13	1.57 s	26.1 q
14			107.2 s	H-15, H-16	–	–
15	15	1.35 s	27.2 q	H-16	–	–
16	16	1.50 s	28.5 q	H-15	–	–
1′			166.8 s	H-5′, H-9, H-3′		166.7 s
2′			128.6 s	H-4′, H-5′		127.8 s
3′	3′	6.97 dq-like	138.2 d	H-4′, H-5′	6.79 dq-like	137.8 d
4′	4′	1.82 d (7.8)	14.5 q		1.73 d (7.2)	14.3 q
5′	5′	1.84 s	12.1 q	H-3′	1.67 s	12.0 q
OCH_3	OCH_3	3.95 s	56.2 q		3.92 s	56.1 q

[a] Measured in $CDCl_3$. All values are in parts per million and assignments were made by ^{1}H–^{1}H COSY, HSQC, HMBC, and DEPT spectral data. Proton coupling constants (*J*) in Hertz. Carbon multiplicity was established from HSQC and DEPT data, s, C; d, CH; t, CH_2, q, CH_3.

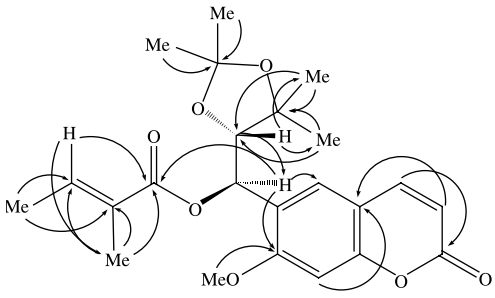

Figure 2. Key HMBC correlations of **1** (from H to C).

[δ_H 6.97 (1H, dq-like, H-3′), 1.82 (3H, d, $J = 7.8$ Hz, H_3-4′), and 1.84 (3H, s, H_3-5′); δ_C 166.8 s (C-1′), 128.6 s (C-2′), 138.2 d (C-3′), 14.5 q (C-4′), and 12.1 q (C-5′)] and a eight carbons side chain from the ^{13}C NMR, DEPT, and HMBC spectra were also observed. In the HMBC spectrum of **1** (Figure 2), the correlations between H-9 (δ_H 6.19) and C-5 (δ_C 128.0), C-6 (δ_C 124.0), and C-7 (δ_C 159.6) of coumarin skeleton, and H-9 and C═O (δ_C 166.8) of the tigloyl group suggested that the C-9 was directly linked at C-6 and the tigloyl group attached to C-9. In the ^{1}H–^{1}H COSY spectrum of **1**, correlation was found between H-9 and H-10 (δ_H 4.17). In the side chain, the ^{13}C NMR, DEPT, and HMBC spectra showed eight carbon signals, among which two pairs of *gem*-dimethyl at δ_C 23.3 q and 26.9 q, 27.2 q and 28.5 q, an oxymethine at δ_C 83.7 d, two quaternary carbons at δ_C 79.9 s and 107.2 s. Furthermore, structure of the side chain of **1** was characterized by HMBC correlations between H-9 and C-10 (δ_C 83.7); H-10 and C-12 (δ_C 26.9), C-13 (δ_C 23.3); H_3-12 (δ_H 1.04) and C-13 (δ_C 23.3), C-11 (δ_C 79.9), C-10 (δ_C 83.7); H_3-13 (δ_H 1.18) and C-12 (δ_C 26.9), C-11 (δ_C 79.9), C-10 (δ_C 83.7); H_3-15 (δ_H 1.35) and C-16 (δ_C 28.5), C-14 (δ_C 107.2); H_3-16 (δ_H 1.50) and C-15 (δ_C 27.2), C-14 (δ_C 107.2). The stereo configurations of H-9 and H-10 were found to be *trans* because of the large vicinal coupling constants ($J_{H9,H10} = 5.7$ Hz) [7,10,11], while one of the *cis* appears broad single peak, respectively. On the basis of the above evidence, the structure of **1** was determined as shown in Figure 1. Because compound **1** had been obtained previously from angelol B (**3**) via the chemical conversion method [10], it was thus determined as a new natural product and named angepubebisin.

Compound **2** was obtained as a colorless block and its molecular formula was deduced as $C_{19}H_{30}O_4$ by the ion peak at *m/z* 323.2224 $[M + H]^+$ in the positive HR-FTICR-MS. The structure of **2** was determined by the analysis of single-crystal X-ray diffraction because its yield was very little in this experiment. Crystals suitable for single-crystal X-ray diffraction were grown by slow evaporation of a CH_2Cl_2:MeOH (3:1) mixture solution at 283 K to give a colorless block. X-ray diffraction intensity data for **2** were collected on a MAC DIP-2030 K diffractometer with graphite-monochromated Mo Kα radiation ($\lambda = 0.71073$ Å) by the $\omega - 2\theta$ scans ($2\theta_{max} = 50°$) and was corrected by Lorentz and polarization. The crystal formed in the triclinic system with $P - 1$ space group was $a = 9.4836$ (3) Å, $b = 9.5741$ (3) Å, $c = 11.9855$ (3) Å, $\alpha = 88.067$ (2)°, $\beta = 85.909$ (2)°, $\gamma = 63.350$ (2)°, with two molecule ($C_{19}H_{30}O_4$) in the asymmetric unit. The total number of independent reflections measured was 4250, of which 3018 were observed ($|F|^2 \geq 2\sigma|F|^2$). The structure was solved by the direct method (SHELXL-97) [12] and expanded using difference Fourier techniques, refined by SHELXL-97 and full-matrix least-squares calculations to a final indices of 0.0543 (R_1) ($wR_2 = 0.1760$, $S = 1.023$). X-ray structure of **2** showing relative configuration is given in Figure 3. The molecular packing of **2** is given in Figure 4. The molecule of **2** consists of two ring moieties: a six-membered ring A (2,5-cyclohexadien-1-one) and a five-membered ring B (furan ring). Ring A adopts a near planar geometry because of steric hindrances created by the two *meta-tert*-butyl groups and ring B adopts an envelope conformation. The dihedral angle of A/B was 72.3°. Because the molecular arrangement of **2** in the crystal state belongs to the triclinic system with the space group $P - 1$, it cannot exhibit optical activity. None of an

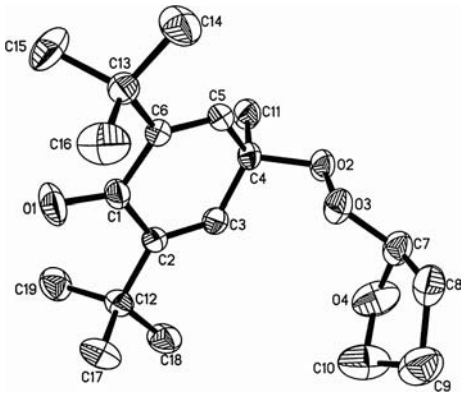

Figure 3. X-ray structure of **2** showing relative configuration.

intramolecular and the intermolecular hydrogen bond relationship was observed, and the van der Waals force is of great importance for the sterically stable arrangements of the intermolecules in the crystal state. Finally, the chemical structure of compound **2** was determined to be 2,6-di(*tert*-butyl)-4-methyl-4-[(2*S*)-tetrahydro-2-furanyl peroxy]-2,5-cyclohexadien-1-one. It was a novel compound, and named angepubefurin.

Compound **3** was isolated as a colorless prism, mp 152–154°C. The positive HR-FTICR-MS showed the $[M + H]^+$ at *m/z* 377.1598, consistent with the molecular formula of $C_{20}H_{24}O_7$. It was also supported by its data of NMR and DEPT. Finally, all of the signals of ^1H and ^{13}C NMR of **3** have been full characterized by the detailed ^1H–^1H COSY, HSQC, HMBC, DEPT, and NOESY spectra for the first time. Compound **3** was characterized as Figure 1 and identified as angelol B [7].

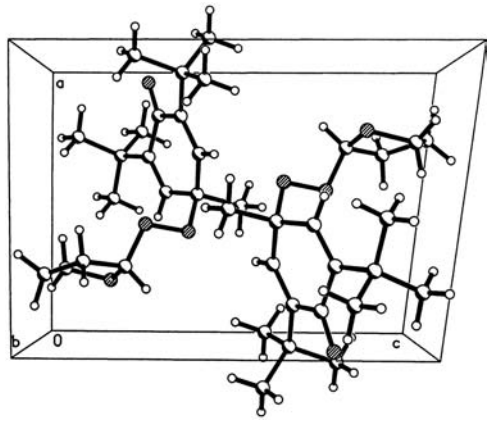

Figure 4. The molecular packing of **2**.

3. Experimental

3.1 General experimental procedures

Melting points were measured with a XT-4 micro-melting point apparatus and are uncorrected. Optical rotation was measured on an Autopol III polarimeter (Rudolph Research Analytical, Flanders, NJ, USA) with $CHCl_3$ as solvent. The UV spectra were obtained on a Varian Cary-300 UV–vis photometer (Varian Inc., Palo Alto, CA, USA) in MeOH solution. The IR spectra were recorded using KBr discs on a Thermo Nicolet FTIR Nexus 470 spectrophotometer (Thermo Nicolet Corporation, Madison, WI, USA). The ^1H and ^{13}C NMR spectra were recorded on a Varian Inova-500 spectrometer (Varian Inc.) using $CDCl_3$ or DMSO-d_6 as solvent and TMS as internal standard operating at 500 MHz for ^1H NMR and 125 MHz for ^{13}C NMR, respectively. EI-MS, ESI-MS, and HR-FTICR-MS (high-resolution Fourier transform ion cyclotron resonance mass spectrum) were measured on a Finnigan TRACE 2000 (Finnigan Company, Sunnyvale, CA, USA), MDS SCIEX API QSTAR (Applied Biosystems/MDS Sciex, Foster City, CA, USA), and Bruker Daltonics APEX™ IV FT-ICR mass spectrometer (Bruker Daltonics, Inc., Bremen, Germany). Single-crystal X-ray diffraction analysis was performed on a MAC DIP-2030 diffractometer (Mac Science, Tokyo, Japan). Column chromatography was performed on silica gel (200–300 mesh; Qingdao Marine Chemical Company, Qingdao, China). Preparative TLC was conducted using silica gel coated plates. TLC analyses were taken on silica gel $60F_{254}$ (Qingdao Marine Chemical Company) and the spots were detected by heating after being sprayed with 20%H_2SO_4 in ethanol (v/v) or by UV irradiation at 254 or 365 nm.

3.2 Plant material

The roots of *A. pubescens* f. *biserrata* were collected from 'The China National GAP Base of Chinese Materia Medica for *A. pubescens* Maxim. f. *biserrata* Shan et Yuan' at Wufeng County, Hubei Province, China, in April 2003, and were identified by Prof. Ke-Qin Wang of Hubei Academy of Traditional Chinese Medicine, China. A voucher specimen (No. 20030401) has been deposited in the State Key Laboratory of Natural and Biomimetic Drugs, School of Pharmaceutical Sciences, Peking University, China.

3.3 Extraction and isolation

The powdered dried roots (4 kg) were refluently extracted with MeOH (4 × 16 l, 2 h/time). The MeOH extract was concentrated *in vacuo* to give a dark viscous residue (1200 g, yield 30%). The extract was further suspended in MeOH (1 l) and extracted with cyclohexane (5 × 3 l) to afford cyclohexane extract (40 g, 1%). The MeOH layer was concentrated *in vacuo* to yield a dark viscous residue (1020 g, 25.5%), which was suspended in water (1 l) and partitioned successively with EtOAc (5 × 2 l) and *n*-BuOH saturated with H_2O (5 × 2 l) to afford EtOAc extract (130 g, 3.25%), *n*-BuOH extract (42 g, 1.05%), and water-soluble residue (800 g, 20%). The EtOAc extract (130 g) was chromatographed on a silica gel column and eluted by petroleum ether–EtOAc with increasing amounts of EtOAc, and gave in the following order compounds umbelliferone (5 mg), angelol B (20 mg), ulopterol (3 mg), peucedanol (3.5 mg), scopoletin (4 mg), and a mixture (12 mg). The mixture was recrystallized by CH_2Cl_2–MeOH (3:1) to furnish compounds **1** (11 mg) and **2** (0.5 mg).

3.3.1 Angepubebisin (*1*)

An amorphous powder; $C_{23}H_{28}O_7$; $[\alpha]_D^{20}$ − 59 ($c = 0.09$, $CHCl_3$); UV (MeOH) λ_{max} (nm, log ε): 221 (4.60), 245 (1.32), 296 (4.11), and 322 (4.32); IR (KBr) ν_{max} (cm^{-1}): 2980, 1734 (lactone C═O), 1704 (α,β-unsaturated C═O), 1621, 1566, 1384, 1365, 1257, 1206, 1141, 1118, 1051, 1015, 912, 822, 733, and 476; ^1H NMR (500 MHz, $CDCl_3$) and ^{13}C NMR (125 MHz, $CDCl_3$) spectral data were shown in Table 1; EI-MS *m/z*: 417 $[M + H]^+$, 401 $[M - Me]^+$, 341 $[M - 5Me]^+$, 288, 259, 230, 205, 189, 158, 129, 83, 71, 59, and 55; positive ESI–TOF-MS *m/z*: 439 $[M + Na]^+$ and 417 $[M + H]^+$; positive HR-FTICR-MS *m/z*: 417.1901 $[M + H]^+$ (calcd for $C_{23}H_{29}O_7$, 417.1907).

3.3.2 Angepubefurin (*2*)

A colorless block (CH_2Cl_2:MeOH = 3:1); $C_{19}H_{30}O_4$, *M*r = 322.43; triclinic system with $P - 1$ space group, $a = 9.4836$ (3) Å, $b = 9.5741$ (3) Å, $c = 11.9855$ (3) Å, $\alpha = 88.067$ (2)°, $\beta = 85.909$ (2)°, $\gamma = 63.350$ (2)°, $V = 970.15$ (5) $Å^3$, $Z = 2$, $D_{calc} = 1.104$ g/cm^3; $F(000) = 352$, crystal dimensions 0.20 × 0.40 × 0.50 mm, $T = 293$ K. Positive HR-FTICR-MS *m/z*: 323.2224 $[M + H]^+$ (calcd for $C_{19}H_{31}O_4$, 323.2222).

3.3.3 Angelol B (*3*)

A colorless prism, mp 152–154°C; $[\alpha]_D^{20}$ − 89 ($c = 0.15$, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) and ^{13}C NMR (125 MHz, $CDCl_3$) spectral data were shown in Table 1; positive ESI-TOF-MS *m/z*: 377 $[M + H]^+$ and 399 $[M + Na]^+$; positive HR-FTICR-MS *m/z*: 377.1598 $[M + H]^+$ (calcd for $C_{20}H_{25}O_7$, 377.1600).

Acknowledgements

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