Sesquiterpenoid Derivatives from *Ferula ferulioides*. III[1)]

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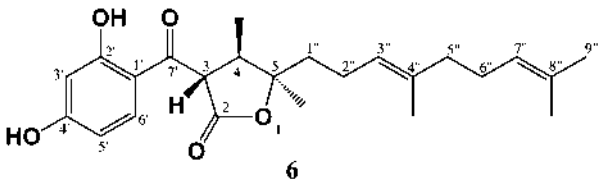
Three new prenyl-benzoylfuranone type sesquiterpenoid derivatives, 3*S-(2,4-dihydroxybenzoyl)-4*R**,5*R**-dimethyl-5-(4,8-dimethyl-3(*E*),7(*E*)-nonadien-1-yl)tetrahydro-2-furanone, 3*S**-(2,4-dihydroxybenzoyl)-4*R**,5*R**-dimethyl-5-[4-methyl-5-(4-methyl-2-furyl)-3(*E*)-penten-1-yl]tetrahydro-2-furanone and 3*S**-(2,4-dihydroxybenzoyl)-4*R**,5*S**-dimethyl-5-[4-methyl-5-(4-methyl-2-furyl)-3(*E*)-penten-1-yl]tetrahydro-2-furanone were isolated from the roots of *Ferula ferulioides*. The structures were established by comprehensive spectral analysis. The biosynthetic pathway leading to their prenyl-benzoylfuranone type sesquiterpenoids is proposed based on their structures.**

Key words *Ferula ferulioides*; Umbelliferae; sesquiterpenoid; prenyl-benzoylfuranone

Ferula ferulioides (STEUD.) KOROVIN (Umbelliferae) grows in Bulgan Somon of Hovd City, Mongolia, and has been used as a traditional medicine for the treatment of spasm. In previous papers,[1,2)] we reported the isolation of four new farnesylacetophenone type sesquiterpenoid derivatives **1**—**4** and one new farnesyl-benzofranone type sesquiterpenoid derivative **5** from this plant. The present paper deals with the isolation and the structural elucidation of three novel sesquiterpenoid derivatives from *F. ferulioides*.

The dried and powdered roots were extracted with methanol, and removal of the solvent gave waxy solid which was successively extracted with ethyl acetate and water. From the ethyl acetate extract, three novel prenyl-benzoylfuranone type sesquiterpenoids (**6**—**8**) were isolated and identified.

The molecular formula of compound **6** was determined as $C_{24}H_{32}O_5$ ($[M]^+$ at *m/z* 400.2246) by high-resolution mass spectrometry (HR-MS). The ^{1}H- and ^{13}C-NMR spectra of **6** showed the existence of a 1,2,4-trisubstituted benzene ring (δ_H 6.37, 6.41, 7.64), three olefinic-methyl groups (δ_H 1.62, 1.64, 1.69; δ_C 16.2, 17.7, 25.7), two trisubstituted double bonds (δ_H 5.10, 5.13), a ketone (δ_C 195.8), and an ester (δ_C 171.6). The ^{1}H-NMR and a correlation spectroscopy (COSY) spectra indicated that a methine at δ_H 4.26 (d, J=12 Hz), a methine at δ_H 3.11 (dq, J=7, 12 Hz) and one methyl group at δ_H 1.09 (d, J=7 Hz) were coupling as CH–CH–CH_3 at H-3,



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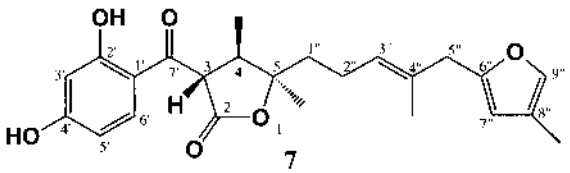

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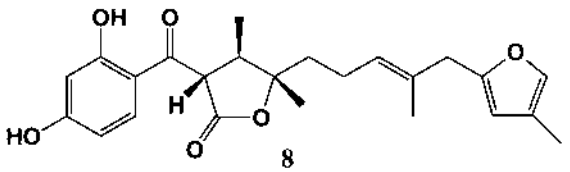

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Table 1. ^{1}H-NMR Spectral Data of Compounds **6**—**8** in $CDCl_3$

	6	7	8
3	4.26 (1H, d, J=12 Hz)	4.26 (1H, d, J=12 Hz)	4.23 (1H, d, J=12 Hz)
4	3.11 (1H, m)	3.10 (1H, m)	3.16 (1H, dq, J=7, 12 Hz)
3′	6.37 (1H, br s)	6.37 (1H, br s)	6.40 (1H, d, J=2 Hz)
5′	6.41 (1H, dd, J=2, 9 Hz)	6.41 (1H, dd, J=2, 9 Hz)	6.46 (1H, dd, J=2, 9 Hz)
6′	7.64 (1H, d, J=9 Hz)	7.62 (1H, d, J=9 Hz)	7.66 (1H, d, J=9 Hz)
1″	1.60 (2H, m)	1.62 (2H, m)	1.79 (2H, m)
2″	2.20 (2H, m)	2.23 (2H, m)	2.13 (2H, m)
3″	5.13[a)]	5.21 (1H, t, J=7 Hz)	5.21 (1H, t, J=7 Hz)
5″	2.01 (2H, m)	3.25 (2H, br s)	3.24 (2H, br s)
6″	2.09 (2H, m)		
7″	5.10[a)]	5.90 (1H, s)	5.89 (1H, s)
9″	1.69 (3H, br s)	7.08 (1H, s)	7.07 (1H, s)
4Me	1.09 (3H, d, J=7 Hz)	1.08 (3H, d, J=7 Hz)	1.07 (3H, d, J=7 Hz)
5Me	1.53 (3H, s)	1.52 (3H, s)	1.35 (3H, s)
4″Me	1.64 (3H, s)	1.64 (3H, s)	1.61 (3H, s)
8″Me	1.62 (3H, s)	2.00 (3H, br s)	1.99 (3H, br s)

a) Overlapped with other signals.

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H-4, and H-Me_{C-4}. An oxyl geminal methyl signal at δ_H 1.53 (H-Me_{C-5}) in the ^{1}H-NMR spectrum and quaternary carbon signal at δ_C 87.9 (C-5) in the ^{13}C-NMR spectrum indicated the presence of an additional tertiary oxyl group at C-5. Information concerning the location of these units was obtained from the heteronuclear multiple bond correlation (HMBC) spectrum, in which cross-peaks were observed from H-3/C-2, C-4, C-7′, H-4/C-3, C-5, C-7′, C-1″, and H-6′/C-7′, indicating that this compound has a dihydroxybenzoyl group attached to the dimethyltetrahydrofuranone. In addition, the characteristic absorption of the carbonyl group (ν 1768 cm^{-1}) in the IR spectrum of **6** supported the presence of γ-lactone structure in this compound. The structure of the side chain was deduced from a nuclear Overhauser and exchange spectroscopy (NOESY) experiment, in which cross-peaks were observed from H-3″/H-5″ and H-7″/H-9″ pairs. These results indicated an *E* configuration for the C-3″—C-5″ double bonds. Compound **6** was identified as 3-(2,4-dihydroxybenzoyl)-4,5-dimethyl-5-[4,8-dimethyl-3(*E*),7(*E*)-nonadien-1-yl]tetrahydro-2-furanone.

Table 2. ^{13}C-NMR Spectral Data of Compounds **6**—**8** in $CDCl_3$

	6	7	8
2	171.6	171.8	171.5
3	54.5	54.5	54.6
4	44.1	44.2	41.1
5	87.9	87.9	88.1
1′	114.2	114.0	114.1
2′	166.1	166.1	166.1
3′	103.6	103.5	103.7
4′	163.9	164.5	164.0
5′	108.6	108.8	108.7
6′	133.6	133.5	133.8
7′	195.8	195.7	195.6
1″	35.5	35.2	39.5
2″	22.0	22.1	22.4
3″	123.1	125.3	125.2
4″	136.5	133.3	133.1
5″	39.7	38.4	38.4
6″	26.7	154.0	154.1
7″	124.2	109.1	109.0
8″	131.5	120.6	120.6
9″	25.7	137.9	137.8
4Me	12.7	12.7	13.4
5Me	23.9	23.8	20.6
4″Me	16.2	16.1	16.0
8″Me	17.7	9.8	9.8

Compound **7** had an $[M]^+$ peak at *m/z* 412.1886 ($C_{24}H_{28}O_6$). The ^{1}H- and ^{13}C-NMR spectra of **7** were similar to those of **6** except for the presence of 4-methyl-2-furyl system (δ_H 2.00, 5.90, 7.08; δ_C 9.8, 109.1, 120.6, 137.9, 154.0) at C-5″ in place of the trisubstituted olefin present in **6**. Compound **8** had an $[M]^+$ peak at *m/z* 412.1886 ($C_{24}H_{28}O_6$). Although the ^{1}H- and ^{13}C-NMR spectra of **8** were quite similar to those of **7**, the ^{1}H-NMR chemical shift pattern of **8** was slightly different from **7** at H-Me_{C-5} (**8**: δ 1.35, **7**: δ 1.52). The HMBC experiment suggested that the plane structure of **8** was the same as that of **7**. Based on these spectral data, **7**

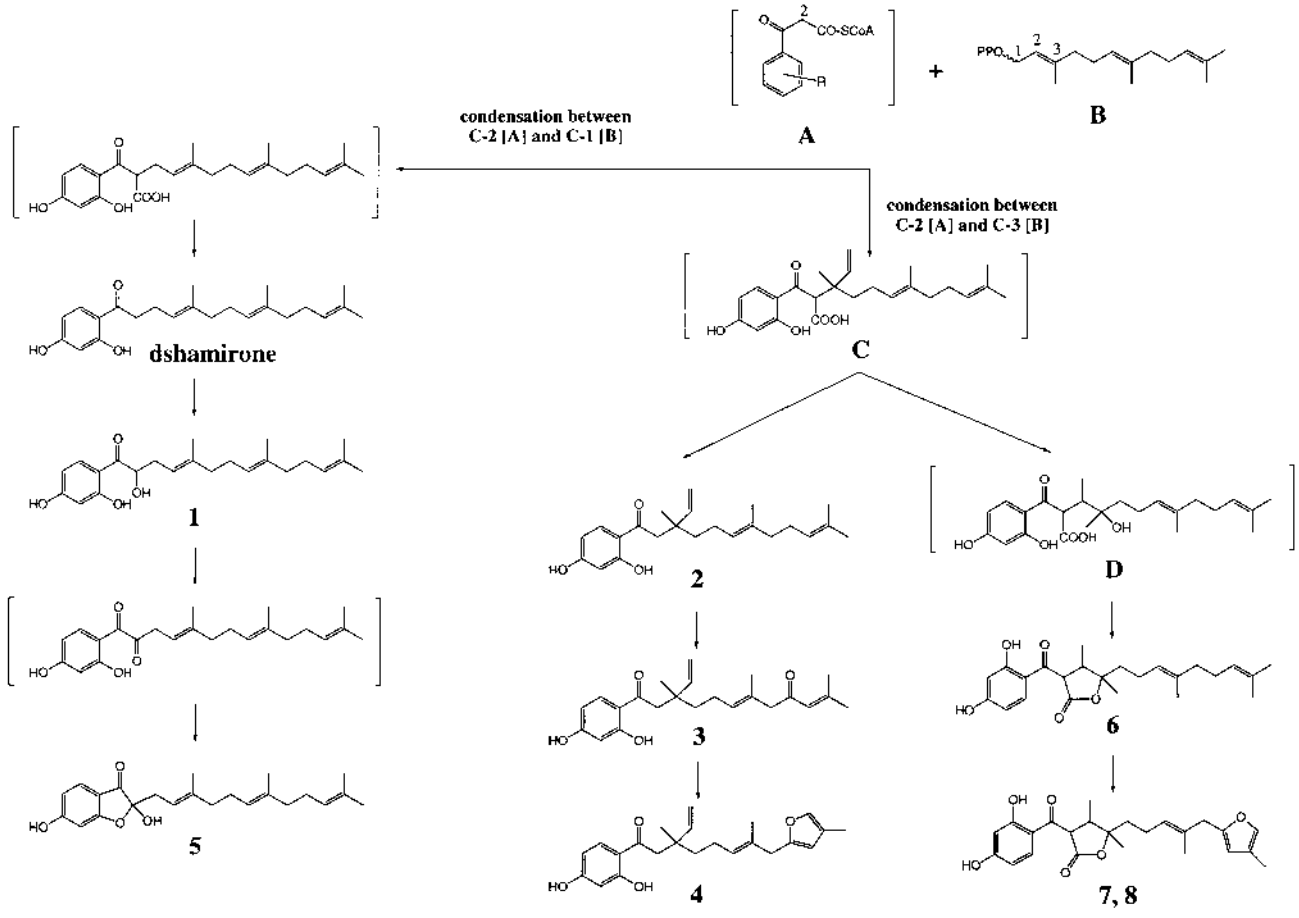

Chart 1. Proposed Biosynthesis Pathway

Compounds **1**—**8** and dshamirone were isolated in this investigation. The compounds in brackets are hypothetical precursors.

and **8** were determined to have the same plane structure as 3-(2,4-dihydroxybenzoyl)-4,5-dimethyl-5-[4-methyl-5-(4-methyl-2-furyl)-3(*E*)-penten-1-yl]tetrahydro-2-furanone.

A series of NOESY experiments was carried out with **6**—**8** to identify the relative stereochemistry of the dimethyltetrahydrofuranone moiety at C-3, C-4 and C-5. The cross-peaks were observed from the pairs: H-3/H-Me_{C-4} and H-4/H-Me_{C-5} in **6** and **7**, while from H-3/H-Me_{C-4} and H-3/H-Me_{C-5} in **8**. These NOE effects indicated the *cis*-relation between the Me_{C-4} and Me_{C-5} in **6** and **7**, the *trans*-relation between the Me_{C-4} and Me_{C-5} in **8**. Thus, compounds **6**, **7** and **8** were assigned to be 3*S**-(2,4-dihydroxybenzoyl)-4*R**,5*R**-dimethyl-5-[4,8-dimethyl-3(*E*),7(*E*)-nonadien-1-yl]tetrahydro-2-furanone, 3*S**-(2,4-dihydroxybenzoyl)-4*R**,5*R**-dimethyl-5-[4-methyl-5-(4-methyl-2-furyl)-3(*E*)-penten-1-yl]tetrahydro-2-furanone and 3*S**-(2,4-dihydroxybenzoyl)-4*R**,5*S**-dimethyl-5-[4-methyl-5-(4-methyl-2-furyl)-3(*E*)-penten-1-yl]tetrahydro-2-furanone, respectively.

In previous papers[1,2] we proposed a biosynthetic pathway leading to the sesquiterpenoid compounds **1**—**5** and dshamirone. Isolation of the compounds **6**—**8** suggests presence of an additional biosynthetic route branched from the hypothetical precursor C proposed in the previous paper[2] as shown in Chart 1. The rearrangement of the C6–C3 moiety of the intermediate C to C-2 position of the farnesyl moiety leads to formation of another hypothetical intermediate D, which is then converted to compound **6** by the intramolecular esterification. Compounds **7** and **8** may be produced by the reaction similar to the formation of compound **4** from **2** *via* **3**.

The intermediate D could convert to farnesyl-chromone or farnesyl-coumarin, if the carboxyl group at the side chain is esterified with another hydroxyl at *o*-position of the phenyl group. In fact such prenyl-chromone type and prenyl-coumarin type derivatives have been reported from *Ferula communis*.[3—9] However, from *F. ferulioides* only the prenyl-benzoylfuranone type sesquiterpenoids such as **6**—**8** have been isolated so far.

Experimental

General Procedures NMR spectra were recorded on a JEOL JNM-A500 spectrometer in $CDCl_3$ with tetramethylsilane (TMS) as internal standard. Electron impact mass spectra (EI-MS) were recorded on a JEOL JMS-DX300 spectrometer. Optical rotation was measured with a JASCO DIP-4 digital polarimeter. IR spectra were recorded on a Shimadzu FTIR-8100 spectrometer.

Plant Material The roots of *Ferula ferulioides* (Steud.) Korovin were collected in July 1996 from Bulgan Somon of Hovd City. Voucher specimens have been deposited in the Botanical Department of Mongolian State University.

Extraction and Isolation The dried and pulverized roots of *F. ferulioides* (400 g) were extracted successively with methanol under reflux. After evaporation of this extract, a part of the methanol extract (40 g) was partitioned between ethyl acetate and water. The ethyl acetate layer was dried and evaporated under reduced pressure. The residue was chromatographed on silica gel with hexane–ethyl acetate (10 : 1—1 : 1) to afford two fractions. Fraction 1 was subjected to RP-18 Lober chromatography (45—65% CH_3CN) to give **6** (10 mg); fr. 2 was subjected to RP-18 Lober chromatography (60% CH_3CN) to give **7** (4 mg) and **8** (8 mg).

3*S**-(2,4-Dihydroxybenzoyl)-4*R**,5*R**-dimethyl-5-[4,8-dimethyl-3(*E*),7(*E*)-nonadien-1-yl]tetrahydro-2-furanone (**6**): Oil, $[\alpha]_D^{23}$ +45.3° (*c*= 0.5, $CHCl_3$), EI-MS *m/z*: 400 $[M]^+$, 137 $[C_7H_5O_3]^+$, HR-MS *m/z*: 400.2246 $[M]^+$ (Calcd for $C_{24}H_{32}O_5$: 400.2250), IR ν_{max} ($CHCl_3$): 1768 cm^{-1}, ^{1}H- and ^{13}C-NMR: Tables 1, 2.

3*S**-(2,4-Dihydroxybenzoyl)-4*R**,5*R**-dimethyl-5-[4-methyl-5-(4-methyl-2-furyl)-3(*E*)-penten-1-yl]tetrahydro-2-furanone (**7**): Oil, $[\alpha]_D^{21}$ +42.8° (*c*= 0.4, $CHCl_3$), EI-MS *m/z*: 412 $[M]^+$, 137 $[C_7H_5O_3]^+$, HR-MS *m/z*: 412.1893 $[M]^+$ (Calcd for $C_{24}H_{28}O_6$: 412.1886), IR ν_{max} ($CHCl_3$): 1768 cm^{-1}, ^{1}H- and ^{13}C-NMR: Tables 1, 2.

3*S**-(2,4-Dihydroxybenzoyl)-4*R**,5*S**-dimethyl-5-[4-methyl-5-(4-methyl-2-furyl)-3(*E*)-penten-1-yl]tetrahydro-2-furanone (**8**): Oil, $[\alpha]_D^{21}$ +32.5° (*c*= 0.4, $CHCl_3$), EI-MS *m/z*: 412 $[M]^+$, 137 $[C_7H_5O_3]^+$, HR-MS *m/z*: 312.1886 $[M]^+$ (Calcd for $C_{24}H_{28}O_6$: 412.1886), IR ν_{max} ($CHCl_3$): 1768 cm^{-1}, ^{1}H- and ^{13}C-NMR: Tables 1, 2.

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