New Sesquiterpenes from *Ferula ferulaeoides* (STEUD.) KOROVIN. VI. Isolation and Identification of Three New Dihydrofuro[2,3-*b*]chromones

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Three novel 2-prenyl-dihydrofurochromone-type sesquiterpenoid derivatives, 2,3-dihydro-7-hydroxy-2*S,3*R**-dimethyl-2-[4,8-dimethyl-3(*E*),7-nonadienyl]-furo[2,3-*b*]chromone, 2,3-dihydro-7-hydroxy-2*S**,3*R**-dimethyl-2-[4-methyl-5-(4-methyl-2-furyl)-3(*E*),7-pentenyl]-furo[2,3-*b*]chromone, and 2,3-dihydro-7-hydroxy-2*R**,3*R**-dimethyl-2-[4-methyl-5-(4-methyl-2-furyl)-3(*E*),7-pentenyl]-furo[2,3-*b*]chromone, were isolated from the roots of *Ferula ferulaeoides*. The structures were established by comprehensive spectral analysis. The biosynthetic pathway leading to these 2-prenyl-dihydrofurochromone-type sesquiterpenoids is proposed based on their structures.**

Key words *Ferula ferulaeoides*; sesquiterpenoid; 2-prenyl-dihydrofurochromone

Ferula ferulaeoides (STEUD.) KOROVIN[1)] (Umbelliferae) grows on arid land in Central Asia and has been used as a traditional medicine for stiff muscles in Mongolia. In previous papers[2)] in this series,[3—6)] we reported the isolation of prenyl-furocoumarin-type sesquiterpenoid derivatives (**1**—**5**) from *F. ferulaeoides*. Those coumarins are 2- or 3-prenyl-furocoumarin-type sesquiterpenoid derivatives, in which the prenyl side chain is attached to the C-2 or C-3 position of the furocoumarin moiety. In the course of investigation of the compounds included in *F. ferulaeoides*, we isolated three new 2-prenyl-dihydrofurochromone type sesquiterpenoids (**6**—**8**). In the present paper, we report the isolation and identification of **6**—**8** (Fig. 1).

Dried root of *F. ferulaeoides* growing in Bulgan Somon, Hovd City, Mongolia was powdered and extracted with MeOH. The extract was then partitioned between AcOEt and water. The AcOEt-soluble material (12.4 g) was separated on silica gel column chromatography and reverse-phase medium pressure liquid chromatography (MPLC) to give compounds **6** (0.05%), **7** (0.06%), and **8** (0.02%), together with other compounds previously described.

The molecular formula of compound **6** was determined to be $C_{24}H_{30}O_4$ ($[M]^+$ at *m/z* 382.2141) based on the high-resolution electron-impact (HR-EI)-MS spectrum. The ^{1}H- and ^{13}C-NMR spectra of **6** showed signals due to an ABC spin system (δ_H 6.86, 6.92, 8.07), for singlet methyl groups including three olefinic ones (δ_H 1.46, 1.59, 1.59, 1.67, δ_C 20.3, 16.0, 17.7, 25.7), two protons at tri-substituted olefins (δ_H 5.07, 5.09), one doublet methyl group (δ_H 1.36, δ_C 14.5), and a carbonyl group (δ_C 175.5). These data were similar to those of 4-oxygenated-2-farnesyl furochromones.[7)] The IR spectrum of **6** showed the absorption of a carbonyl group at 1630 cm^{-1}, which shifted from that of **1**—**5** at *ca.* 1700 cm^{-1}, indicating the existence of a conjugated ketone, not ester. The heteronuclear multiple bond connectivity (HMBC) experiment revealed that the singlet methyl group (δ_H 1.46, δ_C 20.3), the methine group (δ_H 3.40, δ_C 41.2), and the prenyl chain were connected to the oxygenated quaternary carbon (δ_C 96.2). This indicates that **6** is a 2-prenylfuro[2,3-*b*]chromone. In the nuclear Overhauser effect spectroscopy

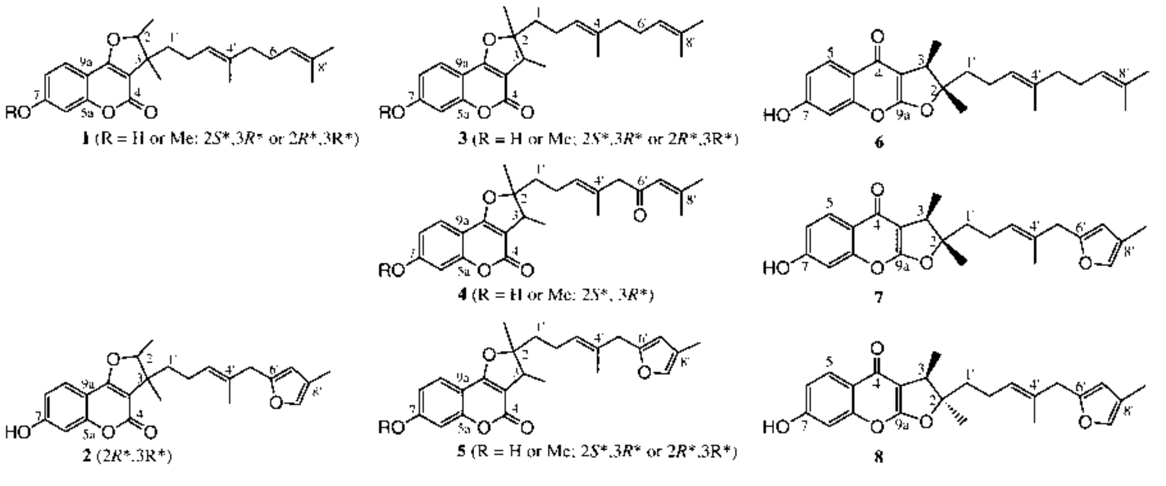

Fig. 1. Chemical Structures of **6**—**8** and Some Reported Sesquiterpenes from *F. ferulaeoides*

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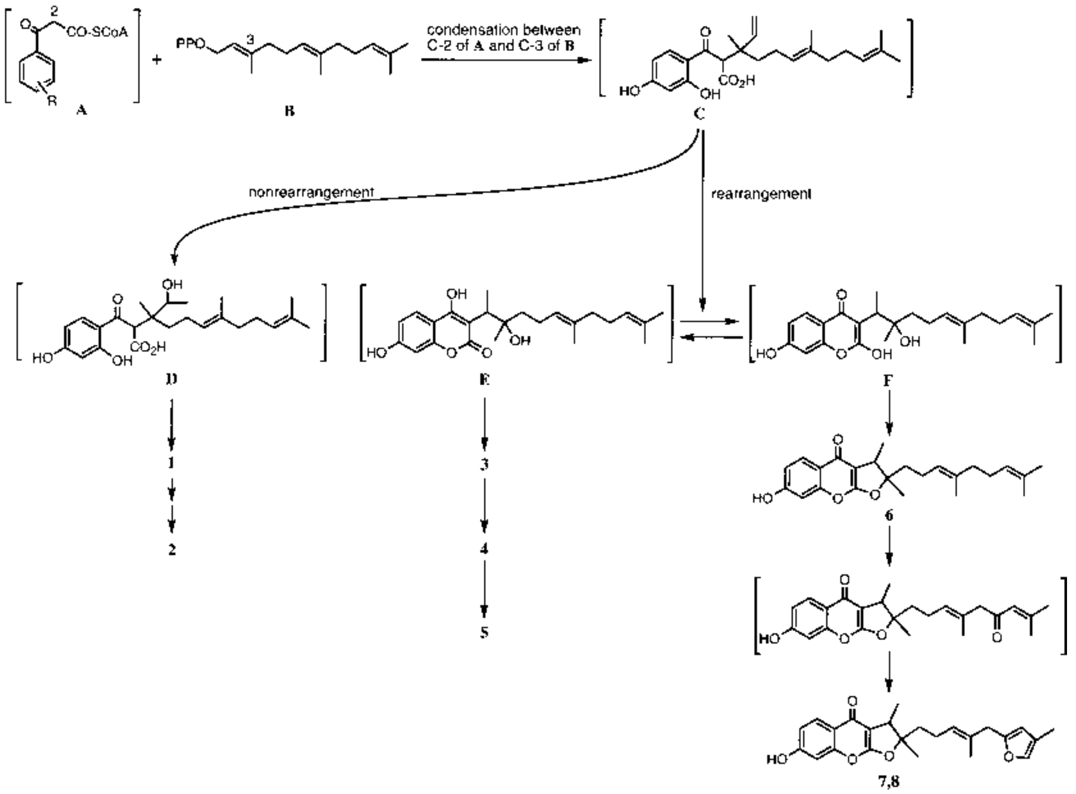

Fig. 2. Proposed Biosynthesis Pathway to **6**—**8**

The compounds in the brackets are hypothetical precursors.

Table 1. ^{1}H- and ^{13}C-NMR Spectral Data of Compounds **6**—**8**

	6		**7**		**8**	
	δ_C	δ_H	δ_C	δ_H	δ_C	δ_H
2	96.2		96.2		96.5	
3	41.2	3.40 (1H, q, J=7 Hz)	41.1	3.39 (1H, q, J=7 Hz)	43.3	3.30 (1H, q, J=7 Hz)
3a	98.7		98.7		99.2	
4	175.5		175.9		175.6	
4a	117.7		117.0		117.5	
5	127.1	8.07 (1H, d, J=9 Hz)	126.9	8.04 (1H, d, J=9 Hz)	127.2	8.07 (1H, d, J=9 Hz)
6	114.2	6.92 (1H, dd, J=2, 9 Hz)	114.6	6.93 (1H, dd, J=2, 9 Hz)	114.3	6.93 (1H, dd, J=2, 9 Hz)
7	159.5		160.9		160.2	
8	103.3	6.86 (1H, d, J=2 Hz)	103.3	6.89 (1H, d, J=2 Hz)	103.3	6.86 (1H, d, J=2 Hz)
8a	154.9		155.0		155.0	
9a	167.5		167.7		167.5	
1′	41.6	1.82 (2H, m)	41.4	1.83 (2H, m)	34.8	1.94 (2H, m)
2′	22.0	2.12 (2H, m)	22.1	2.16 (2H, m)	22.8	2.23 (2H, m)
3′	122.9	5.09[a]	125.1	5.18 (1H, t, J=7 Hz)	125.5	5.24 (1H, t, J=7 Hz)
4′	136.2		133.1		133.0	
5′	39.6	1.96 (2H, m)	38.3	3.21 (2H, s)	38.4	3.24 (2H, s)
6′	26.6	2.04 (2H, m)	154.0		154.0	
7′	124.2	5.07[a]	109.0	5.86 (1H, s)	109.0	5.89 (1H, s)
8′	131.5		120.5		120.6	
9′	25.7	1.67 (3H, s)	137.8	7.05 (1H, s)	137.8	7.07 (1H, s)
2Me	20.3	1.46 (3H, s)	20.2	1.46 (3H, s)	25.3	1.50 (3H, s)
3Me	14.5	1.36 (3H, q, J=7 Hz)	14.6	1.35 (3H, q, J=7 Hz)	14.1	1.32 (3H, q, J=7 Hz)
4′Me	16.0	1.59 (3H, s)	16.0	1.59 (3H, s)	16.0	1.64 (3H, s)
8′Me	17.7	1.59 (3H, s)	9.8	1.97 (3H, s)	9.8	1.98 (3H, s)

a) Overlapped with each other in the same column.

(NOESY) spectrum, there were cross peaks at H-3′/H-5′, which showed that the olefin at C-3′—C-4′ was *E*. A cross peak at H-2Me/H-3Me, but no cross peak between H-2Me and H-3, was observed in the NOESY spectrum. Thus two methyl groups at C-2 and C-3 are in the *cis*-orientation, and compound **6** was deduced to be 2,3-dihydro-7-hydroxy-2*S**,3*R**-dimethyl-2-[4,8-dimethyl-3(*E*),7-nonadienyl]-furo[2,3-*b*]chromone.

The molecular formula of **7** was $C_{24}H_{26}O_5$ ($[M]^+$ at *m/z* 394.1779) based on the HR-EI-MS spectrum. The ^{1}H- and ^{13}C-NMR spectra of **7** were similar to those of **6**. Instead of the terminal tri-substituted olefin of **6**, **7** have a 5-substituted-4-methyl-2-furyl system (δ_H 1.97, 5.86, 7.05, δ_C 9.8, 109.0, 120.5, 137.8, 154.0).

Compound **8** showed the same molecular formula as **7**, $C_{24}H_{26}O_5$ ($[M]^+$ at *m/z* 394.1785), in the HR-EI-MS spectrum. The ^{1}H- and ^{13}C-NMR spectra of **8** were in good agreement with those of **7**, except for C-3 (**8**: δ_C 41.1, **7**: δ_C 43.3), C-1′ (**8**: δ_C 41.4, **7**: δ_C 34.8), and C-2Me (**8**: δ_C 20.2, **7**: δ_C 25.3). As the HMBC spectra of **8** indicated that the planar structure of **8** was identical to **7**, 2,3-dihydro-7-hydroxy-2,3-dimethyl-2-[4-methyl-5-(4-methyl-2-furyl)-3(*E*),7-pentenyl]-furo[2,3-*b*]chromone, **8** was assumed to be the diastereoisomer of **7** at C-2 and C-3. To confirm the relative configuration of **7** and **8**, NOESY spectra of both compounds were measured. In the NOESY spectrum of **8**, a cross peak between H-3 and H-2Me was detected, which indicated that H-3 and the methyl group at C-2 are in the *cis*-orientation. In contrast, there was no cross peak between H-3 and H-2Me in the NOESY spectrum of **7**, but one between H-2Me and H-3Me was detected, which shows that the two methyl groups at C-2 and C-3 of **7** take the *cis*-orientation. Thus compound **7** was determined to be 2,3-dihydro-7-hydroxy-2*S**,3*R**-dimethyl-2-[4-methyl-5-(4-methyl-2-furyl)-3(*E*),7-pentenyl]-furo[2,3-*b*]chromone, and **8** to be 2,3-dihydro-7-hydroxy-2*R**,3*R**-dimethyl-2-[4-methyl-5-(4-methyl-2-furyl)-3(*E*),7-pentenyl]-furo[2,3-*b*]chromone.

We have reported various 2- or 3-prenyl-furocoumarin-type sesquiterpenoids from *F. ferulaeoides*.[2—6] The biosynthetic route of these compounds suggested that phenylpropanoid (**A**) and farnesyl-pyrophosphate (**B**) were condensed with each other to give compound **C**, followed by rearrangement to **E** and further cyclization. In the course of this route, compound **E** can be isomerized to **F**. A 2-prenyl-dihydrofurochromone-type sesquiterpenoid (**6**) should be produced by cyclization of **F**, and **7** and **8** should formed by further oxidation and cyclization of **6** and its diastereoisomer. Isolation of **6**—**8** in this report indicates the presence of an additional biosynthetic route of a series of sesquiterpenoids branched from the hypothetical tautomeric isomer **F**.

Experimental

General Procedures NMR spectra were recorded on a JEOL JNM-A500 spectrometer in $CDCl_3$ with tetramethylsilane (TMS) as an internal standard. 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 *F. ferulaeoides* (Steud.) Korovin were collected in July 1996 at Bulgan Somon, Hovd City. Voucher specimens have been deposited in the Botanical Department of the Mongolian State University.

Extraction and Isolation The dried and pulverized roots of *F. ferulaeoides* (400 g) were extracted successively with methanol under reflux. After evaporation of the solvent, part of the methanol extract (40 g) was partitioned between ethyl acetate and water. The ethyl acetate layer was evaporated under reduced pressure. The residue was chromatographed on silica gel with hexane–ethyl acetate (10 : 1—1 : 1) to afford 12 fractions. Fraction 10 was subjected to RP-18 Lober chromatography (55% CH_3CN) to give **6** (5 mg); fraction 12 was subjected to RP-18 Lober chromatography (50% CH_3CN) to give **7** (5 mg) and **8** (2 mg).

2,3-Dihydro-7-hydroxy-2*S**,3*R**-dimethyl-2-[4,8-dimethyl-3(*E*),7-nonadienyl]-furo[2,3-*b*]chromone (**6**): Colorless oil, $[\alpha]_D^{22}=\pm 0°$ ($c=0.2$, $CHCl_3$), EI-MS *m/z*: 382 $[M]^+$, 231 $[C_{13}H_{11}O_4]^+$, HR-MS *m/z*: 382.2141 $[M]^+$ (Calcd for $C_{24}H_{30}O_4$: 382.2144), IR, ν_{max} ($CHCl_3$): 1614, 1630 cm^{-1}. ^{1}H- and ^{13}C-NMR: see Table 1.

2,3-Dihydro-7-hydroxy-2*S**,3*R**-dimethyl-2-[4-methyl-5-(4-methyl-2-furyl)-3(*E*),7-pentenyl]-furo[2,3-*b*]chromone (**7**): Colorless oil, $[\alpha]_D^{22}=\pm 0°$ ($c=0.7$, $CHCl_3$), EI-MS *m/z*: 394 $[M]^+$, 231 $[C_{13}H_{11}O_4]^+$, HR-MS *m/z*: 394.1779 $[M]^+$ (Calcd for $C_{24}H_{26}O_5$: 394.1780), IR, ν_{max} ($CHCl_3$): 1616, 1630 cm^{-1}. ^{1}H- and ^{13}C-NMR: see Table 1.

2,3-Dihydro-7-hydroxy-2*R**,3*R**-dimethyl-2-[4-methyl-5-(4-methyl-2-furyl)-3(*E*),7-pentenyl]-furo[2,3-*b*]chromone (**8**): Colorless oil, $[\alpha]_D^{22}=\pm 0°$ ($c=0.7$, $CHCl_3$), EI-MS *m/z*: 394 $[M]^+$, 231 $[C_{13}H_{11}O_4]^+$, HR-MS *m/z*: 394.1785 $[M]^+$ (Calcd for $C_{24}H_{26}O_5$: 394.1780), IR, ν_{max} ($CHCl_3$): 1617, 1628 cm^{-1}. ^{1}H- and ^{13}C-NMR: see Table 1.

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References and Notes

1) In the authors' former reports,[2—6] the plant name *F. ferulioides* was incorrectly used. The correct name is *F. ferulaeoides*.
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