Note

Sesquiterpene Coumarins from *Ferula foetida*

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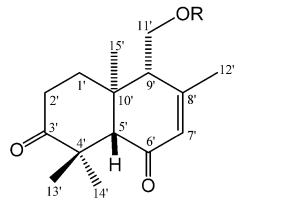
A thorough investigation of the ethyl acetate soluble fraction from a methanol extract of the resin of *Ferula foetida* has resulted in the isolation of a new sesquiterpene coumarin namely *epi*-conferdione (**1**), along with four known compounds, colladonin (**2**), karatavicinol (**3**), 8-acetoxy-5-hydroxyumbelliprenin (**4**), and asacoumarin (**5**). These structures were elucidated on the basis of extensive spectroscopic techniques, including 1D and 2D NMR spectroscopy. The absolute configuration of the new compound was established by circular dichroism (CD).

Keywords: *Ferula foetida*; Umbelliferae; Resin; Sesquiterpene coumarin; CD.

INTRODUCTION

As a part of our continuing studies on bioactive compounds from the genus *Ferula*,[1-5] we investigated the constituents of the gum resin of *Ferula foetida* (Umbelliferae), which enjoys a reputation as a folklore medicine and has been used as an anthelmintic, antirheumatic, antispasmodic, diuretic, and emmenagogue.[6-7] The coumarin constituents of the *Ferula* species have received a great deal of attention and have been studied by many groups. A recent review shows us more than 100 sesquiterpene coumarins have been isolated from the genus *Ferula*.[8] Recently, the ethyl acetate-soluble fraction from a methanol extract of *Ferula foetida* has afforded six new sulfide derivatives.[9] In the present paper, we wish to report the isolation and structure elucidation of a new and four known sesquiterpene coumarins.



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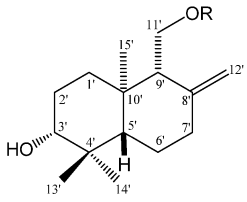

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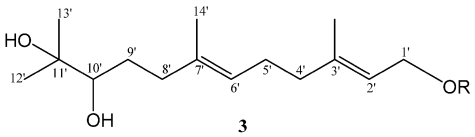

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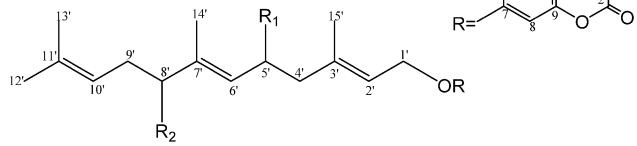

4: R_1=OH, R_2= OAc
5: R_1= R_2= OH

RESULTS AND DISCUSSION

A combination of size exclusion chromatography (Sephadex LH-20) and HPLC of the chloroform extract of the dried roots of *Ferula marmarica* L., resulted in the isolation of a new sesquiterpene coumarin namely *epi*-conferdione (**1**), along with four known compounds, colladonin (**2**),[10] karatavicinol (**3**),[11] 8-acetoxy-5-hydroxyumbelliprenin (**4**),[12] and asacoumarin (**5**).[13] The structures of known compounds were confirmed by direct comparison of their spectral data (^{1}H NMR, ^{13}C NMR and DEPT) with those reported in the corresponding literature.

Compound **1** had a molecular formula of $C_{24}H_{26}O_5$ as established by HRFABMS which showed a $[M+H]^+$ at *m/z* 395.2397 (calcd 395.2406). The structure of **1** was proved to be a bicyclic sesquiterpene coumarin from elemental analysis and spectroscopic data such as ^{1}H and ^{13}C NMR, HMQC and HMBC. In the IR spectrum, absorption bands at 1730, 1665 and 1615 cm^{-1} were in accordance with the presence of three carbonyl functions. The UV spectrum had

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maxima at 289, 298 and 321 nm characteristic of a coumarin nucleus oxygenated at the C-7 position.[14] Compound **1** displayed 24 carbon signals, nine being typical for an umbelliferone skeleton and the other 15 signals were ascribable to a sesquiterpene moiety. This suggested that **1** was derived from sesquiterpene and umbelliferone components. The downfield signal at δ_C 160.9 was assigned to the carbonyl carbon of the coumarin moiety. DEPT experiments classified the carbon signals to four methyls at δ_C 15.8, 21.7, 21.9 and 25.2, which were attributed to C-15′, C-12′, C-14′ and C-13′, respectively, two aliphatic methylenes at δ_C 33.6 and 38.1, an olefinic carbon at δ_C 129.8 and an oxygenated methylene carbon at δ_C 65.4 characteristic for C-11′, and seven methines including five for umbelliferone moiety at δ_C 113.7 (C-3), 143.2 (C-4), 129.0 (C-5), 112.9 (C-6), and 101.4 (C-8) and the other two at δ_C 62.6 (C-5′) and 54.4 (C-9′). Assignments of all protonated carbons were made by the analysis of the HMQC spectrum. It's ^{1}H-NMR spectral data revealed signals for two main moieties, coumarin and sesquiterpene. The coumarin moiety appeared as five signals (δ_H 7.66, 6.28, each 1H, d, J = 9.5 Hz, 7.40, 1H, d, J = 8.5 Hz, 6.85 1H, dd, J = 8.5, 2.5 Hz, and 6.83, 1H, d, J = 2.5 Hz). The sesquiterpene moiety displayed signals for one olefinic methine (δ_H 5.98, brs), one oxygenated methylene (δ_H 4.23, 1H, dd, J = 10.0, 4.2 Hz; 4.3, 1H, dd, J = 10.0, 3.2 Hz), two coupled methylenes (δ_H 1.94 and 2.25, 2H, each ddd, J = 12.0, 10.0, 4.0 and 12.0, 4.0, 2.4 Hz, and δ_H 2.84 and 2.35, 2H, each ddd, J = 12.0, 10.0, 2.4 and 12.0, 4.0, 2.4 Hz), two methines (δ_H 2.52, 1H, s; 2.72, 1H, brs), and four tertiary methyls (δ_H 1.99, 3H, brs; 1.45, 3H, s; 1.32, 3H, s, and 1.32, 3H, s). The location of two carbonyl groups at C-3′ and C-6′ was proven by HMBC. In the HMBC spectrum, the methine signal at δ_H 2.52 showed long-range correlations with the carbon signals at δ_C 214.0 (C-3′), 197.2 (C-6′), 129.8 (C-7′), and 54.4 (C-9′). Two methyls, H_3-13′ and H_3-14′, showed HMBC correlations to the quaternary carbons at δ_C 214.0 (C-3′) and 46.8 (C-4′). Furthermore, the methylene protons (H_2-1′) at δ_H 1.94, 2.25 and the other methylene proton (H_2-2′) at δ_H 2.84, 2.35 showed HMBC correlations to the carbonyl carbon (C-3′) at δ_C 214.0. The HMBC correlations of the secondary alcoholic protons at δ_H 4.23 and 4.30 with a carbon signal at δ_C 161.1 (C-7) indicated that the sesquiterpene unit is attached to C-7 of the coumarin moiety *via* an ether linkage. The NMR data indicated that **1** was an epimer of conferdione, which was isolated from fruit and roots of *Ferula conocula* several years ago.[15] Although the coupling constants suggested the stereochemistry of H-5′, H-9′, and H-11′, the relative stereochemistry of the chiral centers could be established by examining the various cross peaks in the NOESY spectrum, Fig. 1. The NOESY experiment supported the proposed stereochemistry. H-2′$_{axi}$ showed cross-peaks with H-14′$_{axi}$, H-15′$_{axi}$, and H-1′$_{eq}$, as well as H-5′$_{axi}$ that exhibited cross-peaks with H-13′$_{eq}$, H-1′$_{axi}$, and H-9′$_{axi}$. Besides, H-15′$_{axi}$ also revealed cross-peaks with H-11′. The absolute configuration of the new compound was determined from the CD spectra based on a previous extensive study on the absolute stereochemistry of the related compounds,[16] in which the most useful CD bands suitable for assignment of absolute configurations for bicyclic sesquiterpene coumarin ethers is the Cotton effect at approx. 207 nm (π to π^* for α,β-enone group in the ring B of the sesquiterpene moiety). The negative Cotton effects in the CD spectrum of **1** with $\Delta\varepsilon$ = -2.4 at 207 nm clearly indicated a 5′*S*, 10′*R trans*-decaline system. The value of $|\Delta\varepsilon| > 10$ at 207 nm is consistent with an axial CH_2OAr at C-9′, whereas equatorial CH_2OAr gives $|\Delta\varepsilon| < 5$. Moreover, a slight positive Cotton effect at around 300 nm due to the carbonyl n-π^* transition of cyclohexanone of **1** was observed. Thus, the absolute configuration of **1** can be proved as 5′*S*, 9′*R*, 10′*R* based on the negative sign of the short wavelength transition at 207 nm. Thus, the structure of **1** has been determined as shown, isolated for the first time in nature, and given the name, *epi*-conferdione.

EXPERIMENTAL SECTION

General Methods

Optical rotations were measured with a *JASCO P-1020* digital polarimeter. The UV spectra were obtained on

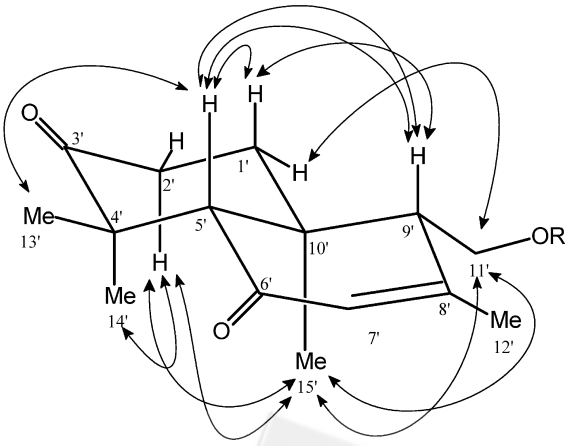

Fig. 1. Selective NOESY correlations for **1**.

a *Hitachi 200-20* spectrophotometer, and IR spectra were measured on a *Hitachi 260-30* spectrophotometer. CD spectra were measured on a *Jasco J-810* circular dichroism spectrometer. NMR (400 MHz using $CDCl_3$ as solvents for measurement) spectra were obtained on a Varian NMR spectrometer (*Unity Plus 400* and *Unity INOVA-500*) or a Bruker AMX-400 NMR spectrometer. Low-resolution EI-MS were collected on a *Quattro* GC/MS spectrometer having a direct inlet system. High-resolution FAB-MS were collected on a *Finnigan/Thermo Quest MAT 95XL* spectrometer. JASCO *PU-986* pumps and *UV-970* UV-VIS detector were used in a HPLC system. Hypersil ODS 5 μm (250 × 4.6 mm i.d.) and preparative ODS 5 μm (250 × 21.2 mm i.d.) columns were applied.

Plant Material

The commercial resin of *F. foetida* was purchased from a traditional Chinese medicine store in Kaohsiung, Taiwan, R.O.C., in December 2002.

Isolation and Purification

Dried and coarsely powdered resin (250 g) was crushed and extracted with MeOH (1 L) at rt for 24 h. The MeOH extract was concentrated in vacuo to give a residue, which was then partitioned between EtOAc and H_2O. The EtOAc layer was concentrated to give a residue (27.2 g), which was chromatographed on silica gel (600 g). The column was eluted with solvents of increasing polarity (*n*-hexane-EtOAc, EtOAc, and EtOAc-MeOH) to give 16 fractions (frs. 1-16). Fr. 12 (600 mg) was further purified on a silica gel column chromatograph (*n*-hexane-EtOAc, 1:2), then over Sephadex LH-20 (*n*-hexane: EtOAc: MeOH 3:5:2) and finally was purified by HPLC [reverse phase, (MeOH-H_2O, 80:20)] to give **1** (21 mg). Fr. 13 (900 mg) was rechromatographed on a Si-gel column, eluted with (*n*-hexane-$CHCl_3$, 1:4), then over Sephadex LH-20 (*n*-hexane: EtOAc: MeOH 3:5:3) to yield **2** (36 mg). Fr. 14 (400 mg) was separated by Sephadex LH-20 ($CHCl_3$: EtOAc: MeOH 7:5:3) and HPLC [reverse phase, (MeOH-H_2O, 70:30)] to afford **3** (27 mg). Fr. 15 (222 mg) was resubmitted to a silica gel column, eluted with (*n*-hexane:acetone, 20:80), followed by HPLC [reverse phase, (MeOH-H_2O, 60:40)] to give **4** (17 mg). Fr. 16 (460 mg) was subjected to Sephadex LH-20 eluted with MeOH, then separated by HPLC [reverse phase, (MeOH-H_2O, 50:50)], to obtain **5** (22 mg).

***Epi*-conferdione (1)**

Amorphous solid; $[\alpha]_D$ +66.6° (*c* 0.2, MeOH); UV (MeOH) λ_{max} (log ε): 289 (3.44), 298 (3.59) and 321 nm (3.12); CD (MeOH): λ_{max} ($\Delta\varepsilon$) = 207 (-2.4); IR (film) ν_{max} 1730, 1665 and 1615 cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.66 (1H, d, *J* = 9.5 Hz, H-4), 7.40 (1H, d, *J* = 8.5 Hz, H-5), 6.85 (1H, dd, *J* = 8.5, 2.5 Hz, H-6), 6.83 (1H, d, *J* = 2.5 Hz, H-8), 6.28 (1H, d, *J* = 9.5 Hz, H-3), 5.98 (1H, brs, H-7′), 4.30 (1H, dd, *J* = 10.0, 3.2, H-11′), 4.23 (1H, dd, *J* = 10.0, 4.2, H-11′), 2.84 (1H, ddd, *J* = 12.0, 10.0, 2.4 Hz, H-$2'_{axi}$), 2.72 (1H, brs, H-$9'_{axi}$), 2.52 (1H, s, H-$5'_{axi}$), 2.35 (1H, ddd, *J* = 12.0, 4.0, 2.4 Hz, H-$2'_{eq}$), 2.25 (1H, *J* = 12.0, 4.0, 2.4 Hz, H-$1'_{eq}$), 1.99 (3H, brs, 12′), 1.94 (1H, ddd , *J* = 12.0, 10.0, 4.0 Hz, H-$1'_{axi}$), 1.45 (3H, s, H-$14'_{axi}$), 1.32 (3H, s, H-$13'_{eq}$), 1.29 (3H, s, H-$15'_{axi}$); ^{13}C NMR ($CDCl_3$): δ 214.0 (C-3′), 197.2 (C-6′), 161.0 (C-7), 160.9 (C-2), 155.9 (C-9), 155.8 (C-8′), 143.2 (C-4), 129.8 (C-7′), 129.0 (C-5), 113.7 (C-3), 113.1 (C-10), 112.9 (C-6), 101.4 (C-8), 65.4 (C-11′), 62.6 (C-5′), 54.4 (C-9′), 46.8 (C-4′), 41.7 (C-10), 38.1 (C-1), 33.6 (C-2′), 25.2 (C-13′), 21.9 (C-14′), 21.7 (C-12′), 15.8 (C-15′); EIMS *m/z* (rel. int.) 394 $[M]^+$ (40), 232 [M-coumarin]$^+$ (60), 162 [M-sesquiterpene]$^+$ (100); HRFABMS *m/z* 395.2397 $[M+H]^+$ (calc. 395.2406 for $C_{24}H_{26}O_5$).

Colladonin (2)

Amorphous solid, $[\alpha]_D$ -59.1° (*c* 0.7, $CHCl_3$). IR (KBr) ν_{max} 3400, 3100, 2800, 1685, 1650, 1620 cm^{-1}. EIMS *m/z* (rel. int.) 382 $[M]^+$ (25), 364 $[M-H_2O]^+$ (40), 220 [M-coumarin]$^+$ (60), 162 [M-sesquiterpene]$^+$ (100); ^1H NMR ($CDCl_3$): δ 7.62 (1H, d, *J* = 9.6 Hz, H-4), 7.35 (1H, d, *J* = 8.8 Hz, H-5), 6.83 (1H, dd, *J* = 8.8, 2.8 Hz, H-6), 6.81 (1H, d, *J* = 2.8 Hz, H-8), 6.24 (1H, d, *J* = 9.6 Hz, H-3), 4.89 (1H, br s, H-12a), 4.81 (1H, br s, H-12b), 4.35 (1H, dd, *J* = 9.6, 4.2 Hz, H-11a), 4.27 (1H, dd, *J* = 9.6, 4.1 Hz, H-11b), 3.30 (1H, dd, *J* = 11.0, 4.2 Hz, H-3_{axi}), 2.49 (1H, m, H-7_{eq}), 2.31 (1H, t, *J* = 4.2 Hz, H-9_{axi}), 2.12 (1H, m, H-7_{axi}), 1.68 (3H, m, H-1_{eq}, H-2_{eq}, H-6_{eq}), 1.58 (1H, m, H-2_{axi}), 1.48 (1H, m, H-1_{axi}), 1.38 (1H, m, H-6_{axi}), 1.22 (1H, dd, *J* = 10.5, 6.2 Hz, H-5_{axi}), 1.04 (3H, s, H-13′), 0.88 (3H, s, H-14′), 0.83 (3H, s, H-15′); ^{13}C NMR ($CDCl_3$): δ 162.0 (C-7), 161.0 (C-2), 155.6 (C-9), 146.1 (C-8′), 143.3 (C-4), 128.6 (C-5), 118.3 (C-10), 113.2 (C-6), 112.6 (C-3), 107.5 (C-12′), 101.2 (C-8), 78.0 (C-3′), 65.3 (C-11′), 54.7 (C-5′), 54.0 (C-9′), 38.8 (C-4′), 38.5 (C-10′), 37.1 (C-7′), 36.7 (C-1′), 28.2 (C-14′), 27.4 (C-2′), 23.3 (C-6′), 15.4 (C-13′), 15.1 (C-15′).

Karatavicinol (3)

Amorphous solid, $[\alpha]_D$ +16.2° (*c* 0.6, $CHCl_3$); IR (film) ν_{max} 3500, 3050, 2900, 1620 cm^{-1}; EIMS *m/z* (rel. int.): 400 $[M]^+$ (35), 382 $[M-H_2O]^+$ (70), 364 $[M-2H_2O]^+$

(50), 239 [M-coumarin]$^+$ (60), 162 [M-sesquiterpene]$^+$ (100); ^{1}H NMR ($CDCl_3$): δ 7.62 (1H, d, *J* = 9.5 Hz, H-4), 7.30 (1H, d, *J* = 8.5 Hz, H-5), 6.80 (1H, dd, *J* = 8.5, 2.5 Hz, H-6), 6.75 (1H, d, *J* = 2.5 Hz, H-8), 6.21 (1H, d, *J* = 9.5 Hz, H-3), 5.45 (1H, t, *J* = 6.0 Hz, H-2′), 5.14 (1H, br t, *J* = 6.0 Hz, H-6′), 5.57 (1H, d, *J* = 6.0 Hz, H-1′), 3.35 (1H, dd, *J* =10.0, 2.0 Hz, H-10′), 1.73 (3H, br s, H-15′), 1.60 (3H, br s, H-14′), 1.19 (3H, s, H-13′), 1.16 (3H, s, H-12′). ^{13}C NMR ($CDCl_3$): δ 162.0 (C-7), 161.3 (C-2), 155.9 (C-10), 144.0 (C-3′), 143.6 (C-4), 135.6 (C-7′), 128.9 (C-5), 124.1 (C-6′), 118.3 (C-2′), 113.0 (C-6), 112.5 (C-9), 112.4 (C-3), 101.5 (C-8), 78.0 (C-10′), 73.0 (C-11′), 65.9 (C-1′), 39.2 (C-8′), 36.7 (C-4′), 30.0 (C-5′), 26.2 (C-9′), 26.1 (C-14′), 23.8 (C-12′), 17.0 (C-13′), 16.3 (C-15′).

8-Acetoxy-5-hydroxyumbelliprenin (4)

Colorless oil; $[\alpha]_D$ +7.9° (*c* 1.3, $CHCl_3$); UV (MeOH) λ_{max} nm: 325, 206; IR (film) ν_{max}: 3600, 1740, 1620, 1240, 820 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 7.61 (1H, d, *J* = 10.0 Hz, H-4), 7.34 (1H, d, *J* = 8.0 Hz, H-5), 6.81 (1H, dd, *J* = 8.0, 2.5 Hz, H-6), 6.78 (1H, d, *J* = 2.5 Hz, H-8), 6.22 (1H, d, *J* = 10.0 Hz, H-3), 5.53 (1H, br t, *J* = 6.5 Hz, H-2′), 5.42 (1H, br d, *J* = 8.0 Hz, H-6′), 5.04 (1H, t, *J* = 7.0 Hz, H-8′), 4.96 (1H, br t, *J* = 7.0 Hz, H-10′), 4.71 (2H, br d, *J* = 6.5 Hz, H-l′a,b), 4.66 (1H, ddd, *J* = 8.0, 8.0, 5.0 Hz, H-5′), 2.34 (1H, m, H-9′a), 2.30 (1H, br dd, *J* = 13.0, 8.0 Hz, H-4′a), 2.23 (1H, m, H-9′b), 2.18 (1H, br dd, *J* = 13.0, 5.0 Hz, H-4′b), 2.00 (s, OAc), 1.78 (3H, br s, H-14′), 1.67 (3H, br s, H-15′), 1.65 (3H, br s, H-13′), 1.58 (3H, br s, H-12′); ^{13}C NMR ($CDCl_3$): δ 170.2 ($CH_3\underline{CO}$), 161.9 (C-7), 161.2 (C-2), 155.9 (C-9), 143.4 (C-4). 138.3 (C-3′), 135.7 (C-7′), 134.3 (C-11′), 130.0 (C-6′), 128.7(C-5), 121.9 (C-2′), 118.8 (C-10′), 113.0 (C-6), 112.9 (C-3), 112.4 (C-10), 101.5 (C-8), 78.2 (C-8′), 66.0 (C-5′), 65.1 (C-1′), 47.2 (C-4′), 31.6 (C-9′), 25.7 (C-13′), 21.1 ($\underline{CH_3}CO$), 17.8 (C-12′), 17.1 (C-14′), 12.6 (C-15′).

Asacoumarin A (5)

Colourless oil, $[\alpha]_D$ +44.1° (*c* 0.7, $CHCl_3$). IR (film), ν_{max} 3616, 3448, 1728, 1614 cm^{-1}. EIMS *m/z* (rel. int.) 424 [M]$^+$ (20), 262 [M-coumarin]$^+$ (40), 162 [M-sesquiterpene]$^+$ (100); ^{1}H NMR ($CDCl_3$): δ 7.64 (1H, d, *J* = 9.5 Hz, H-4), 7.36 (1H, d, *J* = 8.4 Hz, H-5), 6.83 (1H, dd, *J* = 8.4, 2.6 Hz, H-6), 6.80 (1H, d, *J* = 2.6 Hz, H-8), 6.24 (1H, d, *J* = 9.5 Hz, H-3), 5.57 (1H, t, *J* = 6.2 Hz, H-2′), 5.44 (1H, d, *J* = 8.4 Hz, H-6′), 5.07 (1H, t, *J* = 7.0 Hz, H-10′), 4.58 (3H, m, H_2-1′, H-5′), 3.99 (1H, t, *J* = 6.7 Hz, H-8′), 1.82 (3H, br s, H-14′), 1.71 (3H, br s, H-15′), 1.70 (3H, br s, H-13′), 1.63 (3H, br s, H-12′); ^{13}C NMR ($CDCl_3$): δ 161.8 (C-7), 161.1 (C-2), 155.9 (C-9), 143.6 (C-4), 139.7 (C-3′), 138.6 (C-7′), 134.9 (C-11′), 128.7 (C-6′), 128.4 (C-5), 121.6 (C-2′), 119.9 (C-10′), 113.1 (C-6), 112.9 (C-3), 112.5 (C-10), 101.5 (C-8), 76.6 (C-8′), 66.3 (C-5′), 65.1 (C-1′), 47.2 (C-4′), 34.1 (C-9′), 25.9 (C-13′), 17.9 (C-12′), 17.1 (C-14′), 14.2 (C-15′).

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