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A NEW COUMARIN FROM *FERULA LOSCOSII* AND THE CORRECT STRUCTURE OF COLADONIN*

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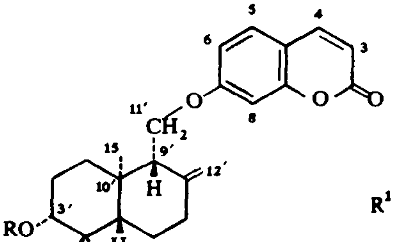
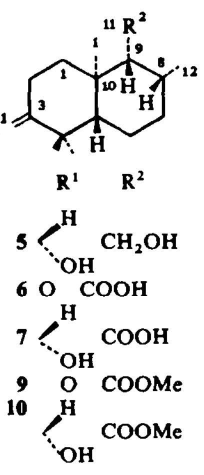
Key Word Index—*Ferula loscosii*; Umbelliferae; coumarins; isovaleryl coladonin; structural determination.

Abstract—From the roots of *Ferula loscosii* the coumarins umbelliprenin, coladin and coladonin and the new natural isovaleryl derivative of the latter have been isolated. A study which confirms the structure of coladonin and its difference from farnesiferol A is also given.

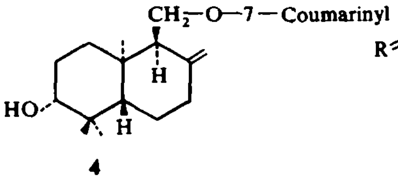
Continuing our investigations on constituents of *Ferula loscosii* (Lge) Wk [1] we have now isolated from the roots of this plant the previously known coumarins umbelliprenin [2], coladonin (1) and coladin (2) [3]. In addition, the new natural isovaleryl derivative of coladonin (3) has also been obtained from the same source. The structure of this new natural ester has been confirmed by partial synthesis from coladonin (see Experimental).



1 R = H
2 R = Ac
3 R = $COCH_2CHMe_2$
8 R = COPh



	R^1	R^2
5	H, OH	CH_2OH
6	O	COOH
7	H, OH	COOH
9	O	COOMe
10	H, OH	COOMe



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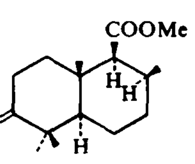

11 R = O
12 R = H, OH

There exists a controversy about the structure of coladonin (1) [4, 5]. The configuration of the —CH_2-*O*-7-coumarinyl group on C-9′ has been established both as *ent-β* [4] and as *ent-α* [5]. The latter assignment [5] identifies coladonin with farnesiferol A, 4 [6]. By comparison of an authentic sample of farnesiferol A (4) provided by Professor Arigoni with 1 isolated from *F. losocosii* we have reached the following conclusions: (a) The PMR spectrum of farnesiferol A reported by Saidkhodzhaev *et al.* [5] does not correspond to the spectrum of the compound previously isolated by Arigoni *et al.*, the structure of which has also been confirmed by synthesis [7]. (b) The correct structure of coladonin is that proposed by Perelson *et al.* [4], and differs from farnesiferol A only in the stereochemistry on C-9′. Thus the only differences between the PMR spectra of 1 and 4 appear in the signals due to protons on C-11′, the exocyclic methylene (C-12′) and the C-Me groups. In 1 the signal for the C-11′ protons appears at δ 4.17 as a doublet (J = 5.5 Hz) and those for the exocyclic methylene as two broad singlets ($W_{\frac{1}{2}}$ = 4 Hz) at δ 4.52 and 4.88. In farnesiferol A (4) C-11′ protons appear as an AB part of an ABX system (δ_A 4.27, δ_B 4, J_{AB} = 10 Hz, $J_{AX} = J_{BX}$ = 5.5 Hz) and C-12′ protons show two distinct triplets (J = 1.5 Hz) at δ 4.7 and 4.79. All these data indicate that these compounds may be epimeric at C-9′, which was also confirmed by the fact that the singlets for C-Me protons appear at δ 1.01, 0.83 and 0.8 in 1 and at δ 1.04, 0.98 and 0.8 in 4.

Hydrogenation of 1 yielded stereospecifically 5. Jones oxidation of 5 gave the keto acid 6 which was quantitatively transformed into compound 7 by $NaBH_4$ treatment. Compound 7 was recovered unchanged after prolonged reaction with NaOMe, this being indicative of an equatorial configuration of the carboxyl group [8]. The PMR spectrum of 7 shows a doublet at δ 2.22 due to the axial proton attached to C-9. The value $J_{8,9}$ = 4.5 Hz indicates the equatorial orientation of the proton on C-8. This result confirms the stereospecificity of the hydrogenation of 1.

The location of the secondary OH group at C-3 and its equatorial configuration are based on the following arguments. The geminal proton of this OH appears

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* Dedicated to the memory of the late Prof. Hans Schmid (Zürich).

as a quartet at δ 3.2 ($J_{a,a}$ = 9–10 Hz, $J_{a,e}$ = 6 Hz) in the PMR spectra of compounds **1**, **4**, **5** and **7**; thus the —OH is equatorialy oriented and placed on C-1 or C-3 of the proposed skeleton. The $NaBH_4$ reduction of **6** to yield only **7** confirms the equatorial configuration of the OH function. The fact that the OH geminal proton appears at the same field in the PMR spectra of **5** (δ 3.20) and **7** (δ 3.19) indicates the absence of C-1–C-11 interactions [9] and excludes C-1 as the site of attachment of the secondary OH. On the other hand, application (see Experimental) of Horeau's method [10] to coladonin (**1**) and the Brewster's 'benzoate rule' [11] to **1** and **8** also confirm the location of the equatorial OH group at C-3′ on a molecule with the absolute stereochemistry depicted in the formula. The negative Cotton effect ($\Delta\varepsilon_{287}$ − 0.21) showed by the keto acid **6** further confirms this point [12].

Finally, the confirmation of all the above deductions and then corroboration of structure **1** for coladonin [4] is substantiated by the fact that **9** and **10** (prepared by methylation of acids **6** and **7**, respectively) are enantiomeric with products **11** and **12** previously obtained by Ruzicka *et al.* [13, 14] in the degradation of oleanolic acid.

EXPERIMENTAL

Mps were determined in a Kofler apparatus and are uncorr. The optical rotations were measured in $CHCl_3$ soln with 1 dm cells. PMR spectra were measured at 100 MHz in $CDCl_3$ soln with TMS as internal standard. Plant materials were collected in May 1976 near Aranjuez (Madrid), identified by Dr. J. Borja, Department of Botany, Faculty of Pharmacy (Madrid) and voucher specimens (No 90066) were deposited in the Herbarium of this Faculty.

Extraction and isolation of coumarins. Dried and finely powdered *F. loscosii* roots (290 g) were extracted repeatedly with Et_2O. The extracts were concd *in vacuo* to leave a residue (20 g), which after chromatography on a Si gel column (250 g) (eluent $CHCl_3$ and $CHCl_3$–MeOH 50:1), subsequent column rechromatography using the same conditions and final purification by PLC yielded the following compounds. *Umbelliprenin* (25 mg) mp 61–63° (MeOH), identical in all respects (mp, IR and PMR) with an authentic sample. *Coladonin* (**1**, 785 mg) mp 159–160° (MeOH), $[\alpha]_D^{22°}$ − 58° (*c* 0.97), identical with an authentic sample provided by Perelson [3]. *Coladin* (**2**, 375 mg) mp 149–151° (MeOH), $[\alpha]_D^{22°}$ − 75° (*c* 1.08), identical to the compound obtained by acetylation of coladonin (see below). *Isovaleryl coladonin* (**3**, 710 mg) mp 86–88° (Et_2O–pentane), $[\alpha]_D^{24°}$ − 65° (*c* 0.92). λ_{max}^{EtOH} nm (log ε) 206 (4.46), 251 *sh* (3.55), 324 (4.25), λ_{min} 260 (3.23). ν_{max}^{Nujol} 1710, 1620 cm^{-1}. PMR (δ): 7.57 (*d*, *J* = 9.5 Hz, H-4), 7.31 (*m*, H-5), 6.77 (2H, *m*, H-6 and H-8), 6.18 (*d*, *J* = 9.5 Hz, H-3), 4.86 (1H, broad *s*, $W_{\frac{1}{2}}$ = 4 Hz, one C-12′ proton), 4.5 (two overlapped signals, C-3′ and one C-12′ protons), 4·15 (*d*, *J* = 6 Hz, C-11′ protons) and between 0.98 and 0.86 Me signals integrating for 15 H. MS (70 eV, direct inlet) M^+ at *m/e* 466, $C_{29}H_{38}O_5$ MW 466. Identical in all respects with synthetic product (see below).

Synthesis of compounds **2** *and* **3** *from coladonin* (**1**). Coladonin (40 mg) in Ac_2O (0.2 ml) and anhydrous Py (0.2 ml) 48 hr at room temp. gave **2**. Treatment of **1** (40 mg) with isovaleryl chloride (0.2 ml) in C_6H_6 soln (2 ml) 6 hr under reflux gave a compound identical with natural **3**.

Coladonin benzoate (**8**). To a Py soln (1 ml) of **1** (50 mg) was added ArCOCl (0.5 ml) and the mixture heated at 100° for 48 hr. The solvent was evapd and the residue purified by PLC ($CHCl_3$–MeOH 100:1) giving **8**. Mp 163–165° (Et_2O), $[\alpha]_D^{22°}$ − 81° (*c* 0.96); ν_{max}^{Nujol} 1716, 1617 cm^{-1}. PMR (δ): 8.01 (2H, *m*, *o*-benzoyl protons), 7.58 (*d*, *J* = 9.5 Hz, H-4), 7.43 (3H, *m*, *m*- and *p*-benzoyl protons), 7.32 (*m*, H-5), 6.79 (2H, *m*, H-6 and H-8), 6.2 (*d*, *J* = 9.5 Hz, H-3), 4.92 and 4.55 (1H each, *br. s*, $W_{\frac{1}{2}}$ = 5 Hz, C-12′ protons), 4.77 (*q*, J_{aa} = 9 Hz, J_{ae} = 5 Hz, C-3′ proton), 4.2 (2H, *d*, *J* = 6 Hz, C-11′ protons) and C-Me *s* at 1.06, 0.99 and 0.92. MS (70 eV, direct inlet) M^+ at *m/e* 486, $C_{31}H_{34}O_5$ MW 486. Application of the benzoate rule [11]: **8** $[M]_D$ − 394°, **1** $[M]_D$ − 221°; $\Delta[M]_D$ − 173°. Absolute stereochemistry 3′*R*.

Application of Horeau's method [10] *to* **1**. A mixture of coladonin (**1**, 117 mg) and (±)-α-phenylbutyric anhydride (189 mg) in Py soln (2 ml) was kept at room temp. for 48 hr. $\alpha_1 = -4.189$, $\alpha_2 = -4.57$; $\alpha_1 - 1.1\ \alpha_2 = +0.838$. Optical yield 35%. Configuration 3′*R*. The soln of coladonin α-phenylbutyrate was diluted with C_6H_6 and washed with aq. $NaHCO_3$ and H_2O. The solvent was evapd *in vacuo* and the residue purified by PLC ($CHCl_3$–MeOH 20:1). Mp 100–101° (Et_2O), $\nu_{max}^{CHCl_3}$ 1720, 1610 cm^{-1}. PMR (δ): 7.57 (*d*, *J* = 9.5 Hz, H-4), 7.32 (*m*, H-5), 7.25 (5H, *m*, phenyl protons), 6.76 (2H, *m*, H-6 and H-8), 6.19 (*d*, *J* = 9.5 Hz, H-3), 4.87 and 4.5 (1H each, *br. s*, $W_{\frac{1}{2}}$ = 4 Hz, C-12′ protons), 4.5 (*m*, overlapped, C-3′ proton), 4.15 (2H, *d*, *J* = 6 Hz, C-11′ protons), 3.42 (1H, *t*, *J* = 7.5 Hz, Ph—C$\underline{H}$—CO—), 0.9 (3H, *t*, *J* = 7.5 Hz, —CH_2—C$\underline{H}_3$), C-Me *s* at 0.84, 0.77 and 0.63. MS (70 eV, direct inlet) M^+ at *m/e* 528, $C_{34}H_{40}O_5$ MW 528.

Catalytic hydrogenation of coladonin (**5**). An EtOH–HOAc (3:1) soln (25 ml) of **1** (150 mg) was hydrogenated with PtO_2 (80 mg) at room temp. and atm. pres. for 6 hr. After the treatment described in ref. [6], 42 mg of **5** were isolated. Mp 178–180° (Et_2O), $[\alpha]_D^{22°}$ − 13° (*c* 0.48), ν_{max}^{Nujol} 3300 cm^{-1}. PMR (δ): C-11 protons as an AB part of an ABX system (δ_A 3.82, δ_B 3.58, J_{AB} = 11 Hz, J_{AX} = 5 Hz, J_{BX} = 10 Hz), 3.2 (1H, *q*, J_{ae} = 10 Hz, J_{ae} = 6 Hz, C-3 proton), 0.95 (3H, *d*, *J* = 7 Hz, C-12 protons) and C-Me *s* at 0.98, 0.86 and 0.78. MS (70 eV, direct inlet) M^+ at *m/e* 240. $C_{15}H_{28}O_2$ MW 240.

Keto acid **6** *and its Me ester* **9**. Excess Jones reagent was added to an Me_2CO soln (5 ml) of the diol **5** (50 mg) and the mixture left for 2 hr at room temp. Workup yielded **6** (40 mg) which was crystallized from Et_2O–pentane: mp 164–166°, $[\alpha]_D^{22°}$ − 16° (*c* 0.41); ν_{max}^{Nujol} 3200, 1728, 1700, 1610, 1385 cm^{-1}. CD curve (C 0.289, EtOH) $[\theta]_{287}$ − 690°. PMR (δ): 1.12 (3H, *d*, *J* = 7 Hz, C-12 protons), C-Me *s* at 1.34, 1.08 and 1.06. MS (70 eV, direct inlet) M^+ at *m/e* 252, $C_{15}H_{24}O_3$ MW 252. Treatment of compound **6** with CH_2N_2–Et_2O soln gave **9**, as a syrup, $[\alpha]_D^{21°}$ − 15° (*c* 1.08); ν_{max}^{NaCl} 1730, 1703 cm^{-1}. PMR (δ): 3.61 (3H, *s*, —COOMe), 1.07 (3H, *d*, *J* = 7 Hz, C-12 protons), C-Me *s* at 1.36, 1.07 and 1.05. MS (70 eV, direct inlet) M^+ at *m/e* 266, $C_{16}H_{26}O_3$ MW 266. Me ester **9** is enantiomeric with **11** (lit. [13]: mp 47–49°, $[\alpha]_D$ + 17°).

Hydroxyacid **7** *and its Me ester* **10**. To an EtOH soln (8 ml) of **6** (30 mg), $NaBH_4$ (60 mg) was slowly added at room temp. and the soln kept for 5 hr. After usual treatment, only **7** (25 mg) was obtained. Mp 168–170° (Et_2O–pentane), $[\alpha]_D^{22°}$ − 9° (*c* 0.66); ν_{max}^{Nujol} 3430, 3220, 1725, 1670 cm^{-1}, $\nu_{max}^{CHCl_3}$ 3400, 3150, 1700 cm^{-1}. PMR (δ): 3.19 (1H, *q*, J_{aa} = 9 Hz, J_{ae} = 6 Hz, C-3 proton), 2.22 (1H, *d*, *J* = 4.5 Hz, C-9 proton), 1.08 (3H, *d*, *J* = 7 Hz, C-12 protons), C-Me *s* at 1.2, 0.98 and 0.81. MS (70 eV, direct inlet) M^+ at *m/e* 254, $C_{15}H_{26}O_3$ MW 254.

Me ester **10**. Prepared in the usual manner. Mp 145–146° (Et_2O–pentane), $[\alpha]_D^{22°}$ − 13° (*c* 1.20); ν_{max}^{Nujol} 3240, 1727 cm^{-1}. PMR (δ): 3.58 (3H, *s*, —COOMe), 3.18 (1H, *q*, J_{aa} = 9 Hz, J_{ae} = 6 Hz, C-3 proton), 1.04 (3H, *d*, *J* = 7 Hz, C-12 protons), C-Me *s* at 1.2, 0.96 and 0.79. MS (70 eV, direct inlet) M^+ at *m/e* 268, $C_{16}H_{28}O_3$ MW 268. Compound **10** is enantiomeric with **12** (lit. [13]: mp 146–147°, $[\alpha]_D$ + 15°).

Alkaline treatment of **7**. The hydroxyacid **7** (30 mg) was refluxed for 60 hr in NaOMe–MeOH soln as previously described [8]. Compound **7** was recovered
this reaction (identical mp, $[\alpha]_D$, IR and PMR).

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