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FERCOLIDE, A TYPE OF SESQUITERPENE LACTONE FROM *FERULA COMMUNIS* SUBSP. *COMMUNIS* AND THE CORRECT STRUCTURE OF VAGINATIN

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Key Word Index—*Ferula communis*; Apiaceae; sesquiterpenes; daucane esters; daucane-γ-lactone.

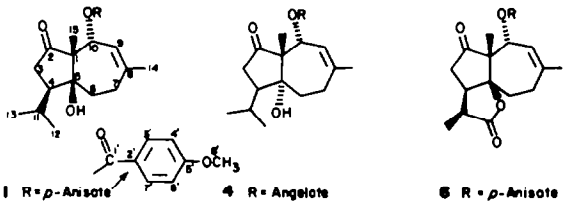
Abstract—Together with the known daucene ester 14-*p*-anisoyloxy-dauc-4,8-diene, a new ester, fercomin and the first known daucane-γ-lactone, fercolide, were isolated from *Ferula communis* subsp. *communis*. Structures for these compounds were elucidated on the basis of their spectral properties and the structure of fercomin was confirmed by X-ray analysis. A revised structure of vaginatin is discussed.

INTRODUCTION

Ferula communis L. (Apiaceae), which is referred to as 'narthex' by the Romans and has been used for treatment of several diseases [1], previously yielded one known and thirteen new daucane esters from the benzene extract of the roots [2]. Further investigation of the same extract yielded a known and two new daucane derivatives.

RESULTS AND DISCUSSION

The known daucane ester was identified as the 14-*p*-anisoyloxy-dauc-4,8-diene by spectral data and direct comparison with an authentic sample [3]. The new daucane ester fercomin (1) crystallized from a hexane–ether mixture as colourless hexagonal plates. The IR spectrum of 1 indicated the presence of hydroxyl (3520, 1030 cm^{-1}), cyclopentanone (1740 sh, 1730 cm^{-1}) and aromatic ester (1710, 1608, 1580, 1512 and 1260 cm^{-1}) groups. The electron impact (EI) mass spectrum of 1 showed a molecular ion at m/z 386. The ^{13}C NMR data (Table 1) also indicated the presence of an aromatic acyl moiety, a saturated five membered ring ketone, a tertiary hydroxyl group and a total of nine degrees of unsaturation. Based on EIMS and ^{13}C NMR data 1 must be bicyclic sesquiterpene ester with a composition of $C_{23}H_{30}O_5$; since the presence of a cyclopentanone was indicated by previous spectral data, the bicyclic structure should be a five and seven membered ring system.



1 R = *p*-Anisate
2 R = Angelate
3 R = Acetate
4 R = Angelate
5 R = Acetate
6 R = *p*-Anisate

The ^1H NMR spectrum of 1 and spin decoupling experiments showed, in addition to the *p*-anisoyl side chain signals, the presence of a tertiary methyl signal at δ1.1 (3H, *s*), two isopropyl methyl doublets at δ1.02 and 1.14 (both 3H, *d*, J = 6.5 Hz), and an acyl geminal proton doublet at δ5.72 (1H, J = 9 Hz). The latter signal was coupled to only a broad vinylic proton doublet at δ5.46 (1H, J = 9 Hz) which showed allylic coupling with a vinylic methyl signal located at δ1.76 (3H, *br s*). The other proton signals of the sesquiterpene nucleus appeared as two complex multiplets centred at δ2.45 and 2.15. Separation of these complex multiplets by lanthanide shift inducers revealed the presence of two isolated vicinal methylene carbons and provided a partial structure of R–CH_2–CH(R)–isopropyl (R = nonprotonated carbon atom).

On the basis of the above spectral data 1 should be 2-keto-5-hydroxy-9-*p*-anisoyloxy-dauc-8-ene. To assign the stereochemistry of fercomin (1) we compared the ^{13}C NMR data of 1 with those of carotol, daucol, lasidiol angelate [4] and lasidiol ketone (Table 1). This comparison clearly indicated that fercomin (1) must have the same stereochemistry at C-1, C-4 and C-5 as carotol, a compound whose stereochemistry is well established by single crystal X-ray analysis [5, 6] and total synthesis [7–9]. Recently, single crystal X-ray analysis of 1 confirmed our assignment [W. H. Watson, personal communication].

Consequently, correlation of all available ^{13}C NMR data (Table 1) with those reported for vaginatin (previous structure = 4), the 10-angelate derivative of the 10-alcohol derived from 1, which previously was reported from *Selinum vaginatum* C. B. Clarke (Apiaceae) [10] and *Inula chritmoides* L. (Compositae) [11], as well as the analogous 10-acetate derivative (previous structure = 5) which was isolated from *Sium latijugum* C. B. Clarke (Apiaceae) [12] seeds, indicated that 4 and 5 must have structures 2 and 3, respectively. The latter compound was also previously reported correctly as 3 from *Sium latifolium* L. [13], which is in agreement with our assignment.

Table 1. ^{13}C NMR data of sesquiterpenoids

C	1	2a*	2b*	6	7	8	9	10
1	60.2 *s*	60.3 *s*	60.3 *s*	59.2 *s*	48.5 *s*	45.9 *s*	53.5 *s*	65.0 *s*
2	220.1 *s*	220.0 *s*	220.0 *s*	217.0 *s*	24.0 *t*	26.5 *t*	24.8 *t*	24.5 *t*
3	38.4 *t*	38.6 *t*	38.6 *t*	37.4 *t*	33.9 *t*	29.6 *t*	35.3 *t*	32.7 *t*
4	51.5 *d*	50.9 *d*	50.9 *d*	45.8 *d*	52.0 *d*	52.8 *s*	56.2 *d*	56.9 *d*
5	82.4 *s*	82.4 *s*	82.4 *s*	93.1 *s*	83.8 *s*	91.8 *s*	83.2 *s*	81.5 *s*
6	37.3 *t*	37.2 *t*	29.2 *t*	34.9 *t*	38.2 *t*	41.5 *t*	35.8 *t*	39.4 *t*
7	29.1 *t*	29.2 *t*	37.2 *t*	29.7 *t*	29.0 *t*	41.2 *t*	30.3 *t*	31.0 *t*
8	146.4 *s*	145.1 *s*	145.1 *s*	147.2 *s*	137.9 *s*	85.5 *s*	142.2 *s*	153.1 *s*
9	119.6 *d*	119.9 *d*	119.9 *d*	119.0 *d*	121.8 *d*	71.7 *d*	122.2 *d*	126.5 *d*
10	76.1 *d*	75.8 *d*	75.8 *d*	76.1 *d*	38.9 *t*	33.2 *t*	77.3 *d*	206.6 *s*
11	26.2 *d*	26.4 *d*	26.4 *d*	38.4 *d*	27.0 *d*	61.7 *d*	26.7 *d*	27.2 *d*
12	21.3 *q*	21.1 *q*	21.1 *q*	177.4 *s*	20.9 *q*	21.8 *q*	21.3 *q*	21.1 *q*
13	24.9 *q*	24.6 *q*	18.3 *q*	11.0 *q*	23.5 *q*	23.0 *q*	24.3 *q*	23.0 *q*
14	26.4 *q*	26.4 *q*	24.6 *q*	26.1 *q*	24.7 *q*	23.5 *q*	25.6 *q*	25.7 *q*
15	18.2 *q*	18.3 *q*	26.4 *q*	18.6 *q*	20.9 *q*	22.6 *q*	22.7 *q*	24.0 *q*
1'	165.0 *s*	166.2 *s*	166.2 *s*	164.7 *s*			167.4 *s*	
2'	122.8 *s*	127.2 *s*	127.2 *s*	122.3 *s*			127.8 *s*	
3'	131.5 *d*	138.9 *d*	138.9 *d*	131.4 *d*			138.3 *s*	
4'	113.8 *d*	20.7 *q*	20.7 *q*	114.0 *d*			20.8 *q*	
5'	163.6 *s*	15.7 *q*	15.7 *q*	163.7 *s*			15.7 *q*	
6'	113.8 *d*			114.0 *d*				
7'	131.5 *d*			131.4 *d*				
8'	55.5 *q*			55.5 *q*				

*2a, Corrected assignments for vaginatin; 2b, previously proposed [5] assignments for vaginatin. 1 = fercomin, 6 = fercolide, 7 = carotol, 8 = daucol, 9 = lasidiol angelate, 10 = lasidiol ketone.

The second new compound, fercolide (6), was isolated as an amorphous solid; its IR spectrum showed the presence of a saturated γ-lactone (1775 cm^{-1}), a five membered ring ketone (1746 cm^{-1}) and an aromatic acyl (1710, 1608, 1510 and 1260 cm^{-1}) group. The EIMS of 6 exhibited a molecular ion at 398 ($C_{23}H_{26}O_6$). *p*-Anisoyl and allylic acyl group signals in the ^{1}H NMR spectrum of 6 were similar to those exhibited by these groups in fercomin (1). However, the spectrum lacked one isopropyl methyl doublet; moreover, well separated ring protons, in addition to the IR spectrum data for 6, revealed γ-lactone formation between the C-4 isopropyl side chain and the C-5 hydroxyl group. The presence of a lactone carbonyl signal (177.4 ppm) in the ^{13}C NMR of 6 (Table 1) as well as altered chemical shifts for C-4, C-5 and the isopropyl moiety of the molecule in comparison to that of fercomin (1) verified the lactone system.

The β-methyl configuration of C-11 has been established on the basis of ^{1}H NMR double resonance experiments and ^{13}C NMR data for 6; upon irradiation of the C-11 methyl doublet at δ1.28 (J = 7 Hz), a doublet quartet at δ3.21 (1H, J = 7 and 7.4 Hz, H-11) collapsed to a doublet (J = 7.4 Hz); this $J_{7,11}$ constant is characteristic for 11α,13-dihydro-sesquiterpene-γ-lactones [14]. Also in the ^{13}C NMR of 6 (Table 1) reciprocal shielding effects were observed due to the small dihedral angle [15] between C-13 and C-3, thus verifying the proposed stereochemistry at C-11.

Previously, several other common types of sesquiterpene lactone (e.g. germacranolides, eudesmanolides, guaianolides, eremophilanolides) have been isolated from the Apiaceae [16–18]. Although the best known major source of daucane-type sesquiterpenes is the Apiaceae [19, 20] until now daucane lactones were never reported from this family. The only known daucane-δ-lactone hercynolactone (= fastigiolide) has been reported from the Hepaticeae [21] and the Compositae [22].

EXPERIMENTAL

Plant material. The roots of *F. communis* were collected from Ataköy area, near Istanbul (Turkey) in June, 1983. A voucher specimen was deposited in the Herbarium, Faculty of Pharmacy, University of Istanbul (ISTE 50856).

Isolation. Dried and coarsely powdered roots (1.5 kg) were worked up according to previously reported procedures [2]. When the polar sesquiterpene fraction (630 mg) was chromatographed twice over a Sephadex LH-20 column (2.5 × 50 cm) packed in cyclohexane–CH_2Cl_2–EtOH (7:4:1) 160 mg of 1 was obtained. The remaining non-separated fractions were combined and subjected to prep. silica gel TLC separations [1.5 mm thickness, double development with cyclohexane–EtOAc (3:2) mixture]. This prep. TLC separation yielded 10 (6 mg) and 6 (32 mg) as amorphous solids.

Fercomin (1). Colourless hexagonal plates from hexane–Et_2O (3:1), mp 130–132°; UV λ_{max}^{MeOH} nm (ε): 261 (10955); IR ν_{max}^{KBr} cm^{-1}: 3520; 3070, 2860, 1740 (sh), 1730, 1710, 1608, 1580, 1512, 1320, 1275, 1260, 1170, 1100, 1030, 1003, 962, 840, 850, 772; ^{1}H NMR ($CDCl_3$, 200 MHz): δ7.88 (2H, *d*, J = 8.8 Hz, H-3' and 7'), 6.9 (2H, *d*, J = 8.8 Hz, H-4' and 6'), 5.72 (1H, *br d*, J = 9 Hz, H-9), 5.46 (1H, *d*, J = 9 Hz, H-10), 3.86 (3H, *S*, H-8'), 1.76 (3H, *br s*, H-15), 1.14 (3H, *d*, J = 6.5 Hz, H-12), 1.1 (3H, *S*, H-15), 1.02 (3H, *d*, J = 6.5 Hz, H-13); MS *m/z* (rel. int.): 386 [M]$^+$ (4), 368 (10.8), 343 (6.8), 289 (16.5), 251 (86.3), 235 (49.5), 233 (53.2), 217 (39.2), 191 (55.7), 152 (56.5), 135 (100).

Fercolide (6). Amorphous mass; UV λ_{max}^{MeOH} nm (ε): 261

(10 605); IR ν_{max}^{KBr} cm^{-1}: 3062, 2930, 1775, 1746, 1710, 1608, 1510, 1260, 1170, 1100, 1080, 980, 940, 850, 772; ^1H NMR ($CDCl_3$, 200 MHz): δ7.85 (2H, *d*, *J* = 8.8 Hz, H-3' and 7'), 6.94 (2H, *d*, *J* = 8.8 Hz, H-4' and 6') 5.76 (1H, *br d*, *J* = 8.2 Hz, H-9), 5.48 (1H, *d*, *J* = 8.2 Hz, H-10), 3.88 (3H, *s*, H-8'), 3.21 (1H, *dq*, *J* = 7 and 7.4 Hz, H-11), 3.03 (1H, *ddd*, *J* = 7.4, 8.6 and 10.5 Hz, H-4), 2.48 (1H, *dd*, *J* = 8.6 and 19 Hz, H-2α), 2.26 (1H, *dd*, *J* = 10.5 and 19 Hz, H-2β), 1.78 (3H, *br s*, H-14), 1.28 (3H, *d*, *J* = 7 Hz, H-13), 1.22 (3H, *s*, H-15); MS *m/z* (rel. int.): 398 $[M]^+$ (12.7), 316 (8), 263 (83), 246 (52.5), 219 (39.9), 173 (56.2), 152 (68.5), 135 (100).

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