TÜRKİYE BİLİMSEL ve TEKNİK ARAŞTIRMA KURUMU
MATEMATİK, FİZİKİ ve BİYOLOJİK BİLİMLER ARAŞTIRMA GRUBU
PROJE NO : TBAG — 580

Ferula tingitana L. ve *Ferula communis* L. subsp. *communis* (Umbelliferae) Türlerinin Seskiterpen Esterlerinin Araştırılması

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İSTANBUL – 2018

ÖNSÖZ

Doç. Dr. Hasan Peşmen'in Türkiye Florası'nın 1972 yılında yayınlanan dördüncü cildinde yer alan "*Ferula* L." monografında ülkemizde 17 *Ferula* türü olduğu kayıtlıdır [1, 2]. Daha sonra 2005 yılında tamamlanan bir reviyon çalışmasında ülkemizde 23 *Ferula* türü ile dört alt türü olduğu saptanmıştır [3]. Ülkemizdeki *Ferula* türlerinin taksonomisi konusunda çeşitli çalışmalar yapılmasına rağmen içerdiği kimyasal bileşikler konusunda ne yazık ki yeterli çalışma bulunmamaktadır. Bu konuda ilk çalışmayı 1981 yılında ülkemizde, özellikle Hatay ilimizde "çakşır otu" olarak tanınan *Ferula elaeochytris* Korovin türü ile yaptım, gerek kimyasal gerekse biyolojik etki açısından elde ettiğimiz ilginç sonuçlar [4, 5] nedeni ile ülkemizin diğer *Ferula* türlerinin de içerdikleri biyolojik aktiviteye sahip terpenleri yönünden araştırılmasını sürdürmeye karar verdim. Bu amaçla ülkemizde ve diğer Akdeniz ülkelerinin sahil bölgelerinde yayılış gösteren iki *Ferula* türü; *Ferula tingitana* L. ve *Ferula communis* L. subsp. *communis* türlerinin seskiterpen bileşikleri yönünden incelenmesi amacıyla bu proje önerisini 1982 yılında TÜRKİYE BİLİMSEL ve TEKNİK ARAŞTIRMA KURUMU'na sundum.

Bu araştırmayı maddi ve manevi yönden destekleyen TÜRKİYE BİLİMSEL ve TEKNİK ARAŞTIRMA KURUMU yetkililerine teşekkürü bir borç bilirim.

Mahmut Miski

ÖZET

Ferula tingitana L. ve *Ferula communis* L. subsp. *communis* (Umbelliferae = Apiaceae) türleri ülkemizin Marmara, Ege ve Akdeniz bölgelerinin sahil kesimlerinde yayılış gösteren iki türdür. *Ferula tingitana* L. bitkisinin kök ekstreleri üzerinde yaptığımız fitokimyasal çalışmalarda sekiz seskiterpen ester; tingitanol (**1**), 14-*p*-anisoiloksidauk-4,8-dien (**2**), 14-*p*-anisoiloksi-4,5β-epoksidauk-8-en (**3**), dezoksodehidrolaserpitin (**4**), asetiltingitanol (**5**), asetildezoksodehidrolaserpitin (**6**), 10α-angeloiloksiyaşkeanadiol-6-*p*-hidroksi-benzoat (**7**), ferkomin (**8**), iki fenilpropanoit bileşik; laserin (**9**) ve latifolon (**10**) ile üç seskiterpen kumarin türevi; kolladonin (**11**), feselol (**12**) ve izosamarkandin angelat (**13**) (Figür 1, 2) izole edilmiş, bu bileşiklerin yapıları çeşitli spektroskopik yöntemler ve kimyasal çevrinmelerle ispatlanmıştır [6, 7, 8]. *Ferula communis* L. subsp. *communis* bitkisinin kök ekstrelerinde yaptığımız fitokimyasal araştırmalarda ise 16 seskiterpen ester; yaşkeanadiol-6-*p*-anisat (**14**), 2-keto-6-*p*-anisoil-oksidauk-3,8-dien (**15**), 14-*p*-anisoiloksidauk-4,8-dien (**2**), 14-*p*-anisoiloksi-4,5β-epoksidauk-8-en (**3**), 2α-asetoksiyaşkeanadiol-6-benzoat (**16**), 2α-asetoksiyaşkeanadiol-6-*p*-anisat (**17**), 10α-hidroksi-yaşkeanadiol-6-*p*-anisat (**18**), 10α-asetoksiyaşkeanadiol-6-*p*-anisat (**19**), 10α-angeloiloksiyaşkeanadiol-6-benzoat (**20**), 10α-angeloiloksiyaşkeanadiol-6-*p*-anisat (**21**), 10α-angeloiloksi-yaşkeanadiol-6-veratrat (**22**), 10β-hidroksi-2α-asetoksiyaşkeanadiol-6-*p*-anisat (**23**), 2α,10β-diasetoksiyaşkeanadiol-6-*p*-anisat (**24**), 2α,10α-diasetoksi-yaşkeanadiol-6-*p*-anisat (**25**), 2α,10α-diasetoksi-yaşkeanadiol-6-veratrat (**26**), ferkomin (**27**), bir seskiterpen lakton; ferkolid (**28**), bir endoperoksi içeren seskiterpen türevi; ferkoperol (**29**) ve bir fenilpropanoit türevi; 3-hidroksi-4,5-metilendioksi-propiofenon (**30**) (Figür 4, 5) izole edilmiş, bileşiklerin yapıları çeşitli spektroskopik yöntemler ve kimyasal çevrinmelerle kanıtlanmıştır [9, 10, 11].

ABSTRACT

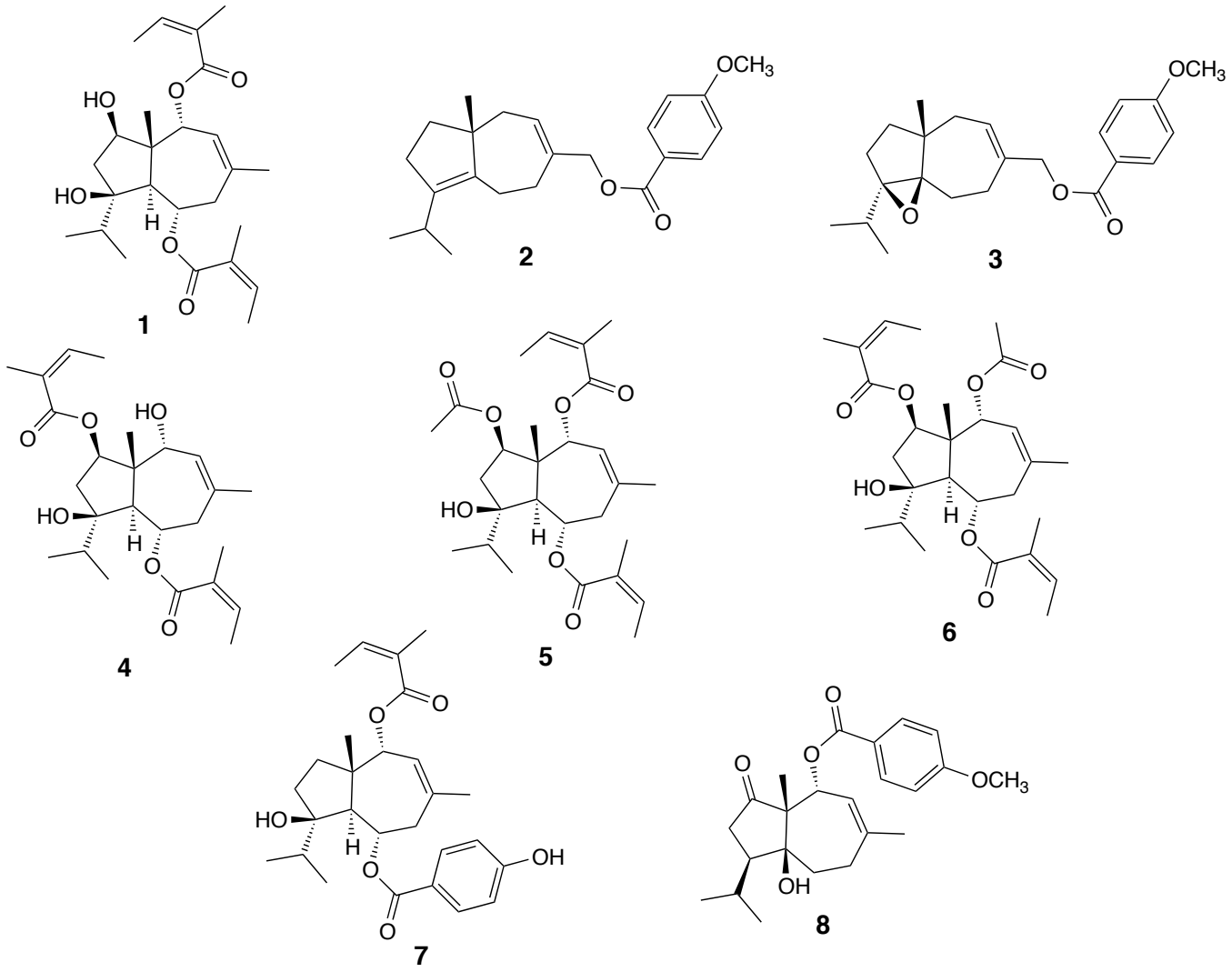
Ferula tingitana L. and Ferula communis L. subsp. communis are two species (Umbelliferae = Apiaceae) distributed through out the coastal areas of Marmara, Aegean and Mediterranean regions of Turkey. Phytochemical studies carried out on the root extracts of Ferula tingitana L. yielded eight sesquiterpene esters; tingitanol (**1**), 14-*p*-anisoyloxydauc-4,8-diene (**2**), 14-*p*-anisoyloxy-4,5β-epoxydauc-8-ene (**3**), desoxodehydrolaserpitine (**4**), acetyltingitanol (**5**), acetyldesoxodehydrolaserpitine (**6**), 10α-angeloyloxyjaeschkeanadiol-6-*p*-hydroxybenzoate (**7**), fercomin (**8**), two phenylpropanoid compounds; laserine (**9**) and latifolone (**10**), and three sesquiterpene coumarin derivatives; colladonin (**11**), feselol (**12**) and isosamarcandin angelate (**13**) (Figure 1, 2), structures of these compounds were elucidated by spectroscopic methods and chemical transformations [6, 7, 8]. In addition, phytochemical studies on the root extracts of *F. communis* L. subsp. *communis* yielded 16 sesquiterpene esters; Jaeschkeanadiol- 6-*p*-anisate (**14**), 2-keto-6-*p*-anisoyloxydauc-3,8-diene (**15**), 14-*p*-anisoyloxydauc-4,8-diene (**2**), 14-*p*-anisoyloxy-4,5β-epoxydauc-8-ene (**3**), 2α-acetoxyjaeschkeana-diol-6-benzoate (**16**), 2α-acetoxyjaeschkeanadiol-6-*p*-anisate (**17**), 10α-hydroxy-jaeschkeanadiol-6-*p*-anisate (**18**), 10α-acetoxy-jaeschkeanadiol-6-*p*-anisate (**19**), 10α-angeloyloxyjaeschkeanadiol-6-benzoate (**20**), 10α-angeloyloxyjaeschkeanadiol-6-*p*-anisate (**21**), 10α-angeloyloxy-jaeschkeanadiol-6-veratrate (**22**), 10β-hydroxy-2α-acetoxyjaeschkeanadiol-6-*p*-anisate (**23**), 2α,10β-diacetoxyjaeschkeanadiol-6-*p*-anisate (**24**), 2α,10α-diacetoxyjaeschkeanadiol-6-*p*-anisate (**25**), 2α,10α-diacetoxyjaeschkeanadiol-6-veratrate (**26**), fercomin (**27**), a sesquiterpene lactone; fercolide (**28**), an endoperoxy-sesquiterpene derivative; fercoperol (**29**) and a phenylpropanoid derivative; 3-hydroxy-4,5-methyenedioxy-propiophenone (**30**) (Figure 4, 5), structures of these compounds were elucidated by spectroscopic methods and various chemical transformations [9, 10, 11].

GİRİŞ

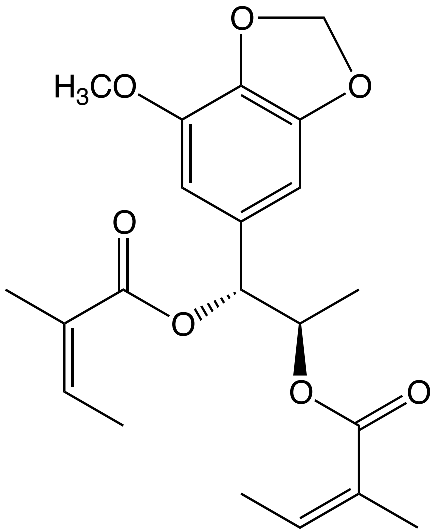
Ferula cinsinin "*Euferula* (Boiss.) Korovin" alt cinsine ait Türkiye'de iki tür bulunmaktadır; *Ferula tingitana* L. ve *Ferula communis* L. subsp. *communis*. Bu türler ülkemizde Marmara, Ege ve Akdeniz bölgelerinin sahil kesimlerinde yayılış göstermektedir [1, 2]. *Ferula communis* L. "*Ferula* (Tourn.) L." cinsinin tip örneğidir [12] ve bütün Akdeniz ülkelerinin sahil kesimlerinde yayılış gösterir, hatta Suudi Arabistan'da olan populasyon kayıtları da bulunmaktadır [13]. *Ferula tingitana* L. türünden Pedanius Dioscorides'in "De Materia Medica" adlı eserinde "Afrika Ammoniakum"u adlı drogun kaynağı olduğu ve kanser dahil çeşitli hastalıkların tedavisinde kullanıldığı kayıtlıdır [14], *Ferula communis* L. subsp. *communis* türünün yine aynı eserde "Narthex" olarak sözü edilen drogun kaynağı olduğu düşünülmekte ve bu drogun da çeşitli hastalıklarda kullanıldığından bahsedilmektedir. Ibn-i Sina "El Kanun fi't Tıb" adlı eserinde Orta Asya'da yetişen üç *Ferula* türünden elde edilen zamksı reçinelerin kanser tümörünün tedavisinde kullanıldığından bahseder [15]. *Ferula* türlerinin zamksı reçineleri seskiterpen, özellikle seskiterpen esterler ve seskiterpen kumarinler içeriği yönünden son derece zengin droglardır. Türkiye'deki *Ferula* türleri üzerinde araştırmalarımıza Hatay yöresinde (ve bütün Türkiye'de) Çakşır otu olarak bilinen *Ferula elaeochytris* Korovin türü üzerinde çalışmalarla başladık [4], bu bitkinin köklerinden elde edilen çeşitli seskiterpen esterlerinin hormonal etkileri olduğunu 1982-3 yıllarında İstanbul Üniversitesi Tıp Fakültesi'nde yapılan hayvan deneyleri ile kanıtladık [5]. *Ferula* reçinelerinde bulunan bu bileşiklerin böyle ilginç biyolojik aktivitelere sahip olması Türkiye'deki diğer *Ferula* türleri üzerinde de bu tür çalışmalar yapmaya devam etmemize neden oldu.

MATERYAL VE METOD

Ferula tingitana L. ve *Ferula communis* L. subsp. *communis* kök ekstrelerinden seskiterpen türevlerinin izolasyonu ve yapılarının tayini literatürde tanımladığımız yöntemlerle yapıldı. *Ferula tingitana* L. bitkisinin kök ekstrelerinden sekiz seskiterpen ester; tingitanol (**1**), 14-*p*-anisoiloksidauk-4,8-dien (**2**), 14-*p*-anisoil-oksi-4,5β-epoksidauk-8-en (**3**), dezoksodehidrolaserpitin (**4**), asetiltingitanol (**5**), asetildezoksodehidrolaserpitin (**6**), 10α-angeloiloksi-yaşkeanadiol-6-*p*-hidroksibenzoat (**7**), ferkomin (**8**), iki fenilpropanoit bileşiği; laserin (**9**) ve latifolon (**10**) ILE üç seskiterpen kumarin türevi; kolladonin (**11**), feselol (**12**) ve izosamarkandin angelat (**13**) (Figür 1, 2) izole edilmiş, bu bileşiklerin yapıları çeşitli spektroskopik yöntemler ve kimyasal çevrinmelerle ispatlanmıştır [6, 7, 8]. Tingitanol (**1**) bileşiğinin yapısını tayin etmek için Figür 3 te özetlendiği gibi bir dizi kimyasal transformasyonlar ve bu transformasyonlardan elde edilen bileşiklerin spektroskopik ölçümleri de molekülün yapısını kesin olarak saptamamızda yardımcı olmuştur. *Ferula communis* L. subsp. *communis* bitkisinin kök ekstrelerinden ise 16 seskiterpen ester; yaşkeanadiol-6-*p*-anisat (**14**), 2-keto-6-*p*-anisoil-oksidauk-3,8-dien (**15**), 14-*p*-anisoiloksidauk-4,8-dien (**2**), 14-*p*-anisoiloksi-4,5β-epoksidauk-8-en (**3**), 2α-asetoksiyaşkeanadiol-6-benzoat (**16**), 2α-asetoksiyaşkeanadiol-6-*p*-anisat (**17**), 10α-hidroksi-yaşkeanadiol-6-*p*-anisat (**18**), 10α-asetoksiyaşkeanadiol-6-*p*-anisat (**19**), 10α-angeloiloksiyaşkeanadiol-6-benzoat (**20**), 10α-angeloiloksi-yaşkeanadiol-6-*p*-anisat (**21**), 10α-angeloiloksiyaşkeanadiol-6-veratrat (**22**), 10β-hidroksi-2α-asetoksiyaşkeanadiol-6-*p*-anisat (**23**), 2α,10β-diasetoksi-yaşkeanadiol-6-*p*-anisat (**24**), 2α,10α-diasetoksi-yaşkeanadiol-6-*p*-anisat (**25**), 2α,10α-diasetoksi-yaşkeanadiol-6-veratrat (**26**), ferkomin (**27**), bir seskiterpen lakton; ferkolid (**28**), bir endoperoksi içeren seskiterpen türevi; ferkoperol (**29**) ve bir fenilpropanoit türevi; 3-hidroksi-4,5-metilendioksi-propiofenon (**30**) (Figür 4, 5) izole edilmiş, bileşiklerin yapıları çeşitli spektroskopik yöntemler ve kimyasal çevrinmelerle kanıtlanmıştır [9, 10, 11].



Figür 1. F*erula tingitana* L. Bitkisinin Daukan Seskiterpen Esterleri



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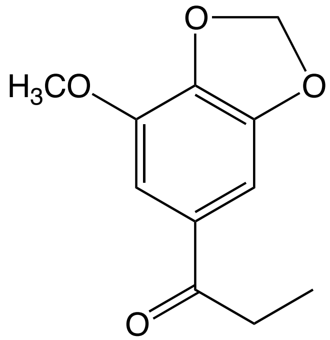

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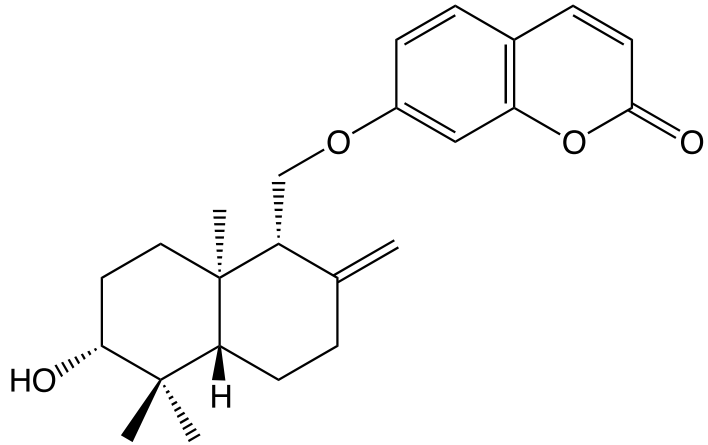

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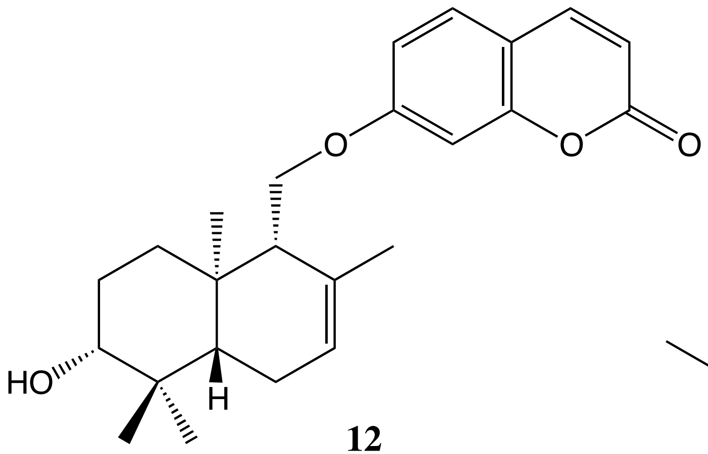

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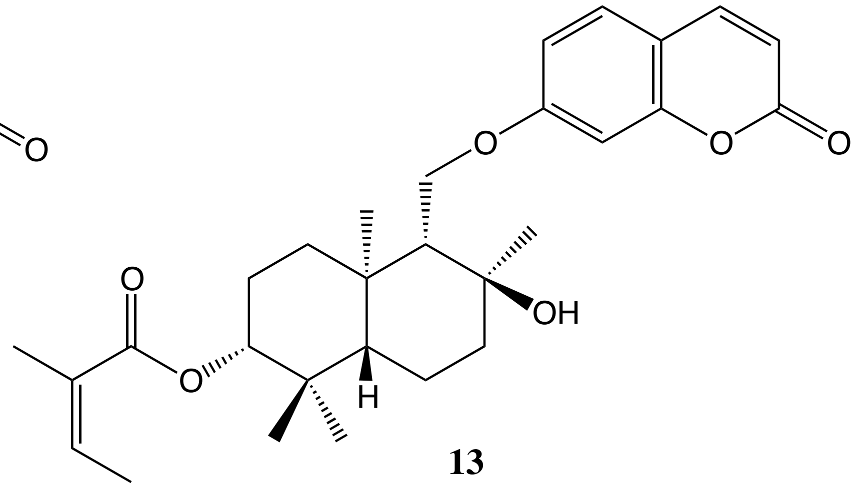

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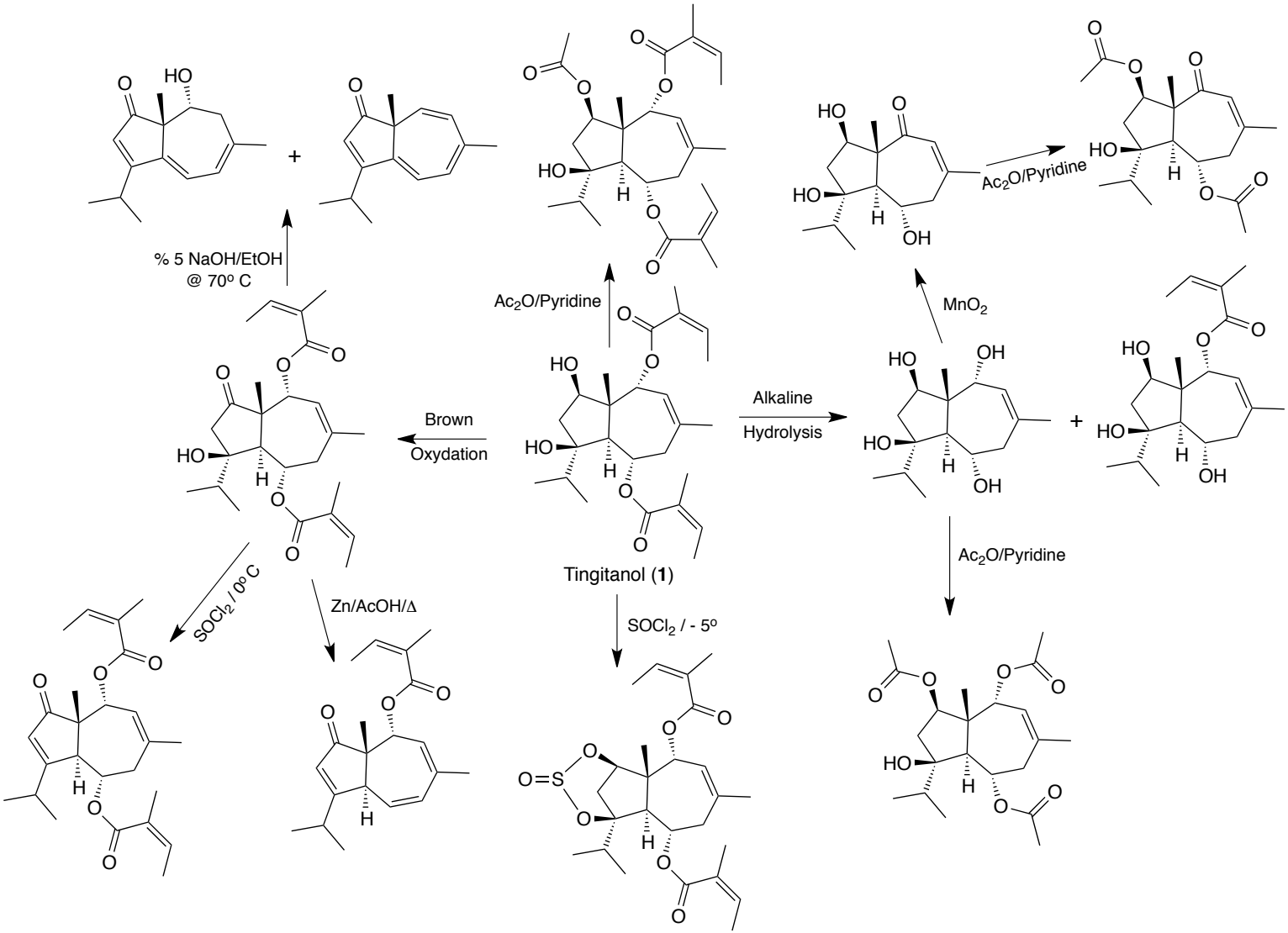
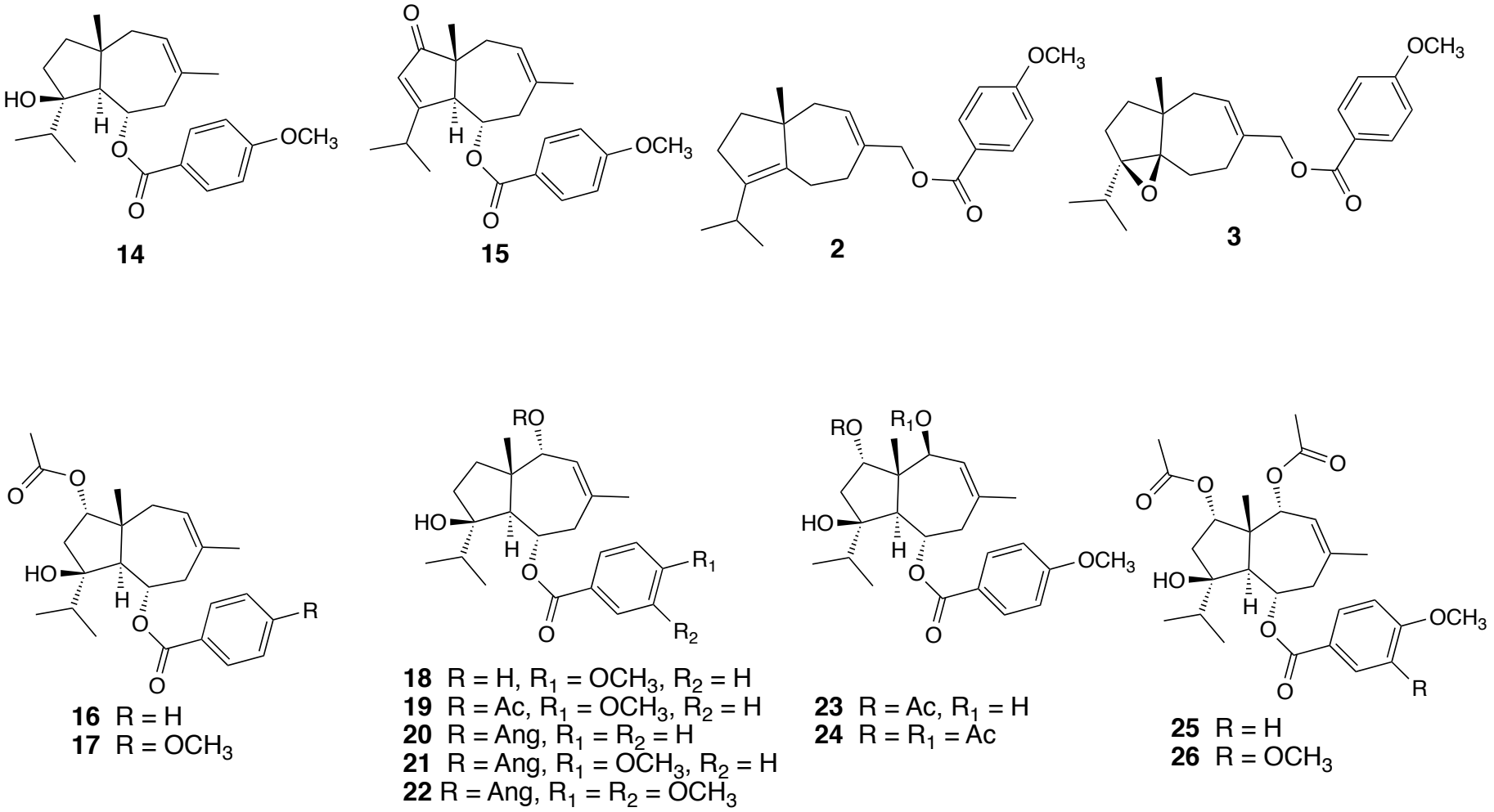
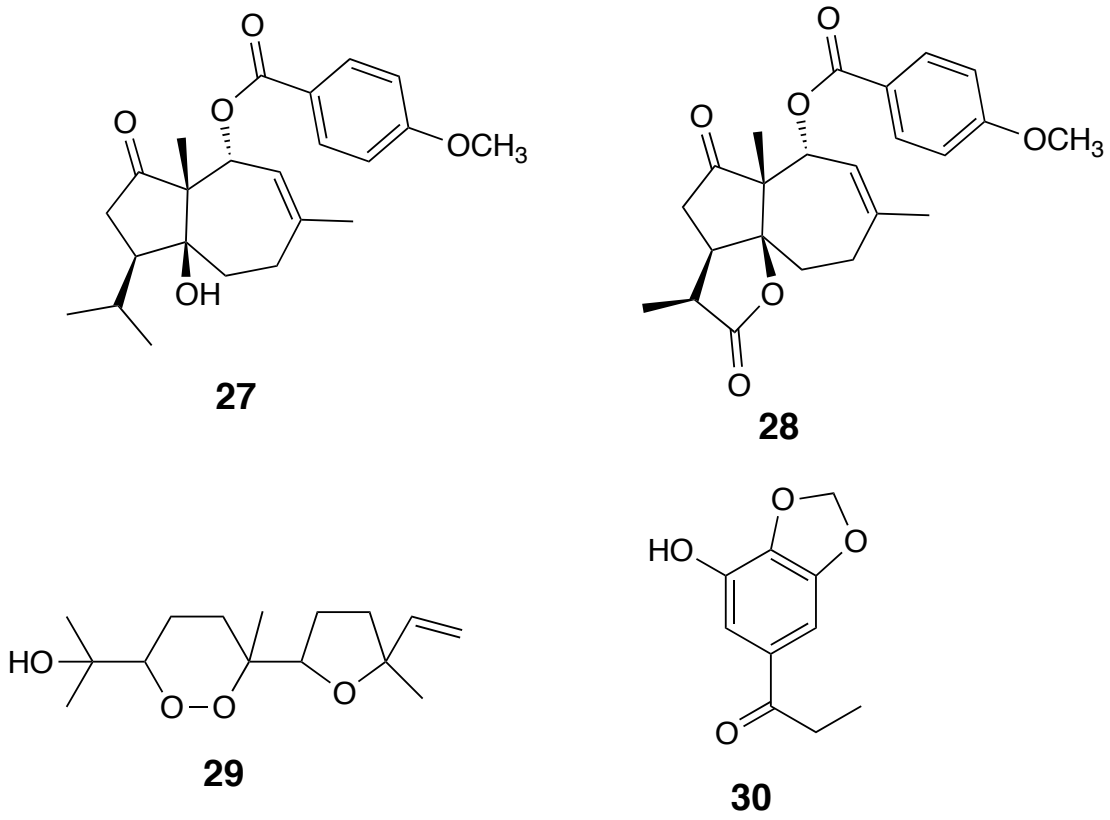
Figür 2. ***Ferula tingitana*** **L. bitkisinin fenilpropanoit ve seskiterpen kumarin bilesikleri**



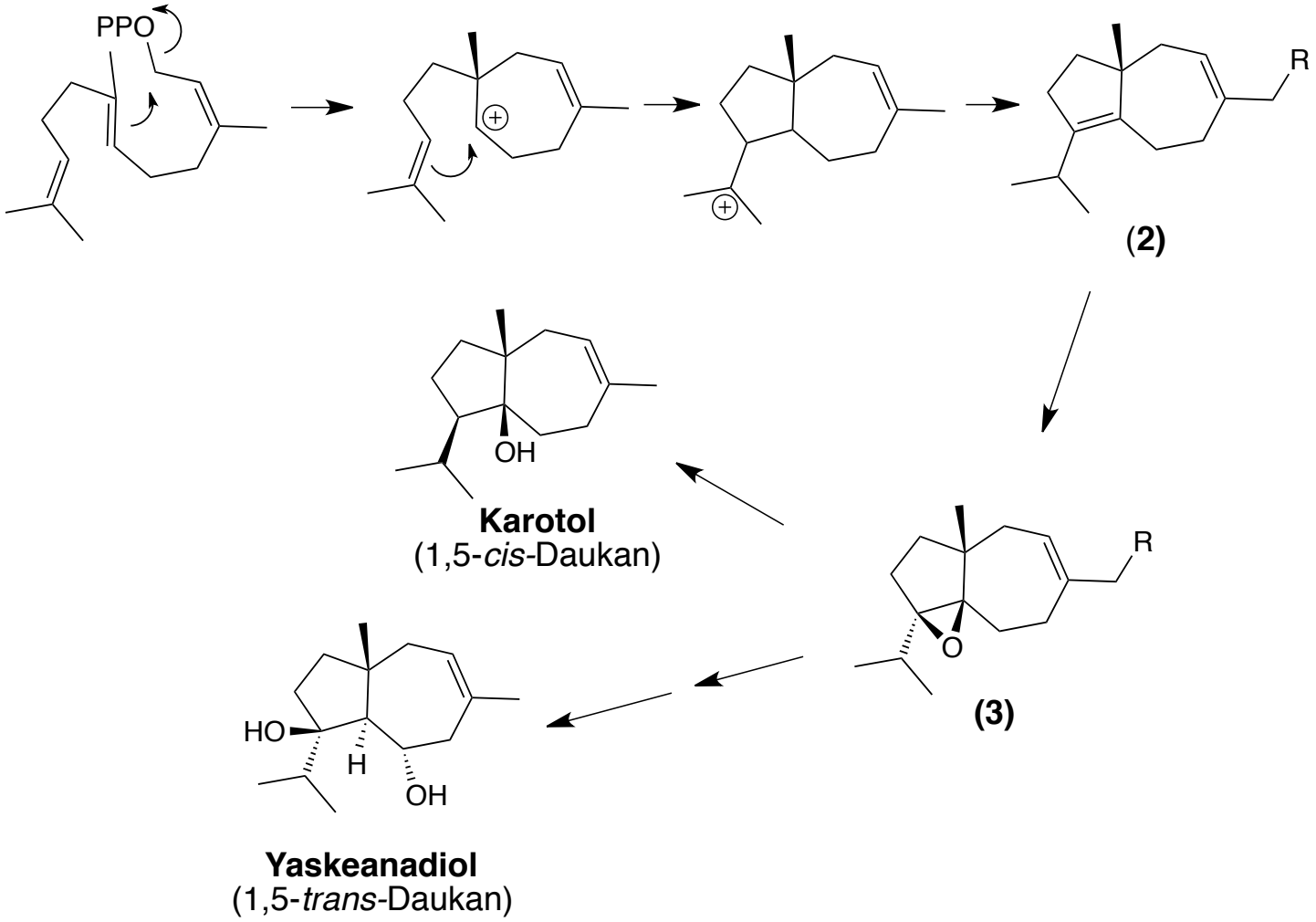
Figür 3. Tingitanol (1) bilesiginin kimyasal transformasyonlarla yapısının tayini



Figür 4. Ferula communis L. subsp. communis bitkisinin daukan esterleri



Figür 5. Ferula communis L. subsp. communis bitkisinin seskiterpen ve fenilpropanoit bilesikleri



Figür 6. 1,5-cis- ve 1,5-trans-daukan bilesiklerinin biyosentetik yolakları

SONUÇ VE TARTIŞMA

Bu araştırmada *Ferula tingitana* L. ve *Ferula communis* L. subsp. *communis* türlerinden çoğu yeni olan 27 seskiterpen türevi izole edilip yapıları spektroskopik ve kimyasal yöntemlerle aydınlatıldığı gibi, *Ferula tingitana* L. türünden izole edilen seskiterpen esterler arasında daukan türü seskiterpenlerin biyogenetik yolağının kilit noktalarında bulunan 14-*p*-anisoiloksidauk-4,8-dien (**2**), 14-*p*-anisoiloksi-4,5β-epoksidauk-8-en (**3**) gibi bazı önemli daukan esterlerinin bulunması o zamana kadar izah edilmemiş olan 1,5-*cis*- ve 1,5-*trans*-daukanların nasıl meydana geldikleri sorusuna da yanıt sağlamış oldu (Figür 6). Bu araştırmayı yaptığım yıllarda elde edilen bileşiklerin biyolojik aktivitelerinin saptanması çalışmalarını yapma imkanlarına sahip olmadığımızdan izole edilen bileşikler ve çalıştığımız ekstrelerin Pedanius Dioscorides'in "De Materia Medica" ve Ibn-i Sina'nın "El Kanun fi't Tıb" eserlerinde sözünü ettiği kanser iyileştirebilecek bir etkiye sahip olup olmadıklarını araştırmamız mümkün olmamıştır. Ancak bu çalışmayı yaptığımız 1982-84 döneminden yıllar sonra başka araştırıcılar yaptıkları sitotoksisite değerlendirme çalışmalarında *Ferula tingitana* L. bitkisinden yeni bir madde olarak izole ettiğimiz asetildezoksodehidrolaserpitin (**6**) ile laserin (**9**) adlı bileşiklerin MCF-7 göğüs kanseri hücrelerine karşı oldukça yüksek ve seçici aktivite gösterdiğini tesbit etmişlerdir (Tablo 1) [16].

Tablo 1. Asetildezoksodehidrolaserpitin (**6**) ve laserin (**9**) bileşiklerinin MCF 7/6 ile MCF 7/AZ göğüs kanseri hücrelerine karşı in vitro sitotoksik test sonuçları (aktiviteler IC50 değerleri üzerinden belirtilmiştir).

Maddeler	MTT Testi		SRB Testi	
	MCF 7/6	MCF 7/AZ	MCF 7/6	MCF 7/AZ
6	0.60 uM	2.29 uM	0.51 uM	31.87 uM
9	4.57 uM	2.46 uM	62.04 uM	7.36 uM

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Tetrahedron Vol. 40, No. 24, pp. 5197 to 5201, 1984
Printed in the U.S.A.

0040-4020/84 $3.00 + .00

A NEW SESQUITERPENE ESTER FROM *FERULA TINGITANA*

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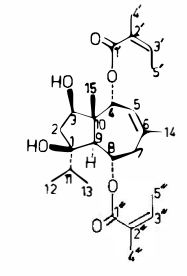
(*Received in UK* 27 *October* 1983)

Abstract—A new sesquiterpene ester, tingitanol, isolated from *Ferula tingitana* L., is assigned as 1β,3β-dihydroxy-4α,8α-diangeloyloxydauc-5-ene on the basis of spectral, analytical, and X-ray data.

An investigation of the benzene extract of *Ferula tingitana* L. yielded a new sesquiterpene ester, tingitanol (**1**). The new ester was first thought to be a known compound, namely desoxodehydrolaserpitine, which was obtained from *Laserpitium latifolium* L. by Holub *et al.*[1] However, comparison with an authentic sample (TLC, ^{1}H NMR and ^{13}C NMR) showed that they were different. We report here that tingitanol (**1**) has the structure (1β,3β-dihydroxy-4α,8α-diangeloyloxydauc-5-ene) previously suggested for desoxodehydrolaserpitine, and that in the latter compound (**2**) one of the angeloyloxy moieties is at C_3 instead of C_4.

Tingitanol (**1**) has the composition $C_{25}H_{38}O_6$ on the basis of elemental analysis and MS (M^+ 434, 1%). Its IR clearly indicated the presence of hydroxyl (3470, 1075, 1030 cm^{-1}) and ester (1700, 1260, 1230 cm^{-1}) groups. The ^{1}H NMR spectrum showed the presence of two angeloyloxy moieties with typical signals at δ 6.12 (2H, br q, J = 7 and 10 Hz), 1.88 (3H, t, J = 1 Hz), 1.92 (3H, t, J = 1 Hz) and 2.03 (6H, tt, J = 1 and 7 Hz). The resonance at δ 5.35 (1H, dt, $J_{7\beta,8\beta}$ = 3 Hz, $J_{7\alpha,8\beta}$ = 10 Hz and $J_{8\beta,9\alpha}$ = 12 Hz) and examination of Dreiding models indicated that this hydrogen, geminal to one angeloyloxy moiety, should be β and situated at C_8 in order to give such a splitting pattern. Another peak at δ 5.07 (1H, d, $J_{4\beta,5}$ = 8 Hz) showed the other hydrogen geminal to the second angeloyloxy moiety was also β and could only be at the C_4 position. The vinylic ring proton peak was at δ 5.74 (1H, br d, J = 8 Hz, H-5) and other peaks for the sesquiterpene ring were as follows: δ 3.58 (1H, dd, J = 8 and 10 Hz, H_α-3), 2.72 (1H, br t, J = 13 Hz, H_β-7), 2.52 (1H, d, $J_{8\beta,9\alpha}$ = 10 Hz, H-9), 2.2 (2H, m, H_α-2, H_α-7), 1.55 (1H, dd, J = 10 and 12 Hz, H_β-2), 1.78 (3H, br s, C_6-Me), 1.14 (3H, s, C_{10}-Me), 0.92 (3H, d, J = 7 Hz) and 0.88 (3H, d, J = 7 Hz) (–$CH(CH_3)_2$). The ^{13}C NMR spectrum of tingitanol was consistent with the suggested structure (see Experimental).

In the ^{1}H NMR spectrum of desoxodehydrolaserpitine (**2**) the signals at δ 6.13 (2H, br q, J = 7 and 10 Hz), 1.88 (6H, t, J = 1 Hz) and 2.00 (6H, dt, J = 1 and 7 Hz) showed the presence of two angeloyloxy moieties. The signal at δ 5.88 (1H, dt, J = 3 and 10 Hz, H-8) showed that one of the angeloyloxy moieties was at C_8. This signal was similar to that of tingitanol, while the double doublet at 5.04 (1H, dd, J = 8 and 10 Hz, H-3) indicated that the second angeloyloxy moiety should be at C_3 instead of C_4 as in compound **1**. The signal at δ 3.7 (1H, d, J = 7 Hz, H-4) showed the hydrogen geminal to the hydroxyl group at C_4. The ^{13}C NMR spectrum was also in agreement with the revised structure of desoxodehydrolaserpitine (**2**) (see Experimental).



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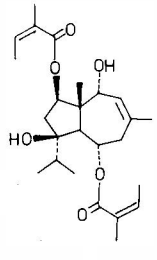

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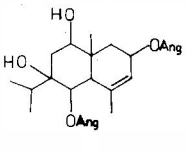

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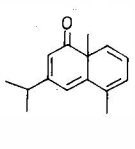

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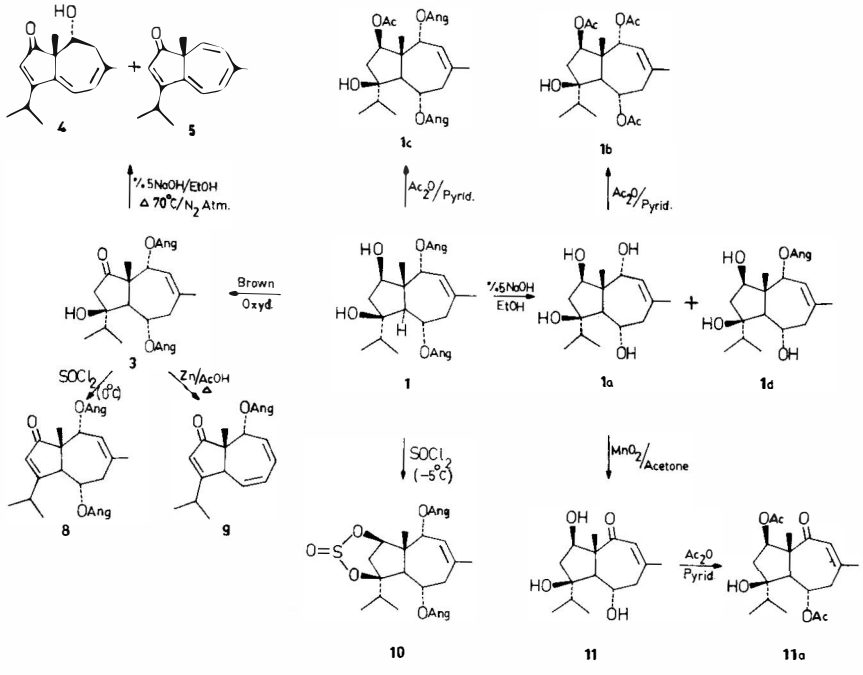
Hydrolysis of tingitanol with 5% NaOH in EtOH at room temperature yielded a tetrol (**1a**) with spectral data same as those of the hydrolysed product of **2**. Acetylation of **1a** yielded a triacetate (**1b**), the spectral data of which were as expected similar to those of the acetyl derivative of the tetrol obtained from compound **2**.

In order to prove the skeleton and the relative positions of hydroxyl groups, a series of chemical reactions were carried out (Scheme 1). Acetylation of **1** yielded a monoacetate (**1c**), in the IR spectrum of which the presence of a sharp peak at 3500 cm^{-1} indicated a tertiary hydroxyl group. Brown oxidation[2] of **1** yielded a ketone (**3**). Its IR spectrum showed a sharp hydroxyl peak at 3500 cm^{-1} and 5-membered ring ketone at 1730 cm^{-1} as well as α,β-unsaturated ester carbonyl bands at 1715 cm^{-1}. In the ^1H NMR spectrum of this product the one-proton double doublet at δ 3.58 which corresponded to H-3 disappeared, the H-4, H-5, H-8 and H-9 signals shifted downfield, while the angeloyloxy vinylic protons were resolved, giving two separate signals at δ 6.22 and 6.05. In order to remove the tertiary hydroxyl group and hydrolyse the angeloyloxy moieties, the ketone **3** was heated with 5% NaOH in EtOH under nitrogen at 70° for 2 hr,[3] yielding a mixture of two compounds. These were separated by TLC to yield compounds **4** and **5**. The UV spectrum of **4** showed extended conjugation by the peaks at 324 nm and 226 nm, indicating that the double bond at $\Delta^{5,6}$ had shifted to $\Delta^{6,7}$; its IR showing a broad hydroxyl band at 3430 cm^{-1} and a broad keto group at 1700 cm^{-1} which indicated conjugation in the five-membered ring as well as possible hydrogen bonding between the hydroxyl at C_4 and the keto group at C_3. A broad, not well resolved, triplet at δ 4.22 in the ^1H NMR spectrum showed the proton geminal to hydroxyl at C_4, while the lack of an H-9 doublet together with the UV data indicated the elimination of the C_8 hydroxyl group. Vinylic protons were found at δ 6.2 (1H, d, J = 8 Hz, H-8), 5.92 (1H, dt, J = 1 and 10 Hz, H-7) and 6.00 (1H, s, H-2). The UV spectrum of compound **5** showed additional conjugation, with peaks at 350 nm and 237 nm. Its IR spectrum showed no hydroxyl band, but the carbonyl band at 1695 cm^{-1} was much sharper. The ^1H NMR spectrum showed vinylic protons at δ 6.33 (1H, d, J = 8 Hz, H-8), 6.25 (1H, dt, J = 1 and 8 Hz, H-7), 5.98 (1H, d, J = 10 Hz, H-5†), 5.86 (1H, d, J = 9 Hz, H-4†) and 5.85 (1H, s, H-2). The UV and ^1H NMR data of compounds **4** and **5** indicated a daucane structure rather than a naphthalene structure; the only possible naphthalene structure would be **6** which should yield **7** in the above reaction; the latter should exhibit two narrow doublets (J ~ 2 Hz), two doublets (J ~ 8 Hz) and a triplet (J ~ 8 Hz) in the vinyl region of its ^1H NMR spectrum.

In order to prove the 1,3 positions of the two hydroxyl groups in the five-membered ring, a milder dehydration reaction was performed. Thionyl chloride was added to compound **3** at 0° to form compound **8**. Its UV spectrum had a maximum at 229 nm and its IR spectrum contained no hydroxyl groups. The sharp carbonyl band at 1705 cm^{-1} indicated the presence of an α,β-unsaturated five-membered ring ketone. The ^1H NMR showed the H-2 vinylic proton at δ 5.92. When the same dehydration was carried out with Zn dust in acetic acid, in addition to compound **8**, we obtained compound **9**. In this latter compound the hydroxyl at C_1 and the angeloyloxy moiety at C_8 were eliminated as well. Its ^1H NMR showed H-2 at δ 5.9 as a singlet, while the H-8 and H-7 vinylic protons were at δ 6.15 as a multiplet.

The formation of a cyclic sulfite compound (**10**) demonstrated that the hydroxyl group at C_1 and C_3

†Interchangeable.



Scheme 1.

were *cis* disposed.[4] Since the C_3 hydroxyl appeared to be β from Dreiding models, the C_1 hydroxyl should be β as well. This was confirmed by X-ray analysis of acetyltingitanol (**1c**). Finally the position of the last hydroxyl group at C_4 was further confirmed by the mild oxidation of tetrol **1a** with MnO_2 in acetone[5]; compound **11** was formed. Since this oxidation is only possible with an allylic hydroxyl group, the position of the C_4 hydroxyl was proven. Its IR spectrum showed a strong hydroxyl band at 3450 cm^{-1} and the α,β-unsaturated seven-membered ring ketone was at 1685 (sh) and 1630 cm^{-1}. Its ^1H NMR showed that the doublet for H-4 at δ 4.52 was missing and the doublet for H-5 became a singlet at 5.85. Acetylation of **11** yielded a diacetate **11a**.

X-ray analysis of the acetyltingitanol **1c** confirmed the suggested structure and the relative stereochemistry of compound **1** as shown in Fig. 1 which is an ORTEP[6] drawing of **1c**. The two rings are *trans*-fused with the five-membered ring in an envelope and the seven in a chair conformation.[7] The conformation of the five-membered ring results in steric interactions between the substituents, O(3)..C(15) = 2.768(7), O(3)..H(15a) = 2.43(4) and O(1)..C(15) = 3.171(7)Å. Each angeloyloxy moiety and the ring carbon to which it is attached is nearly planar. The two groups differ only in the orientation about the C—O bond with C(4) and O(41) being in a *cis* arrangement and O(8) and C(8) in a *trans* arrangement. The molecules are loosely packed in the crystal and the angeloyl groups exhibit high thermal motion. This is reflected in the shortened bond distances associated with these groups. No attempt was made to correct the side chain distances for thermal motion.

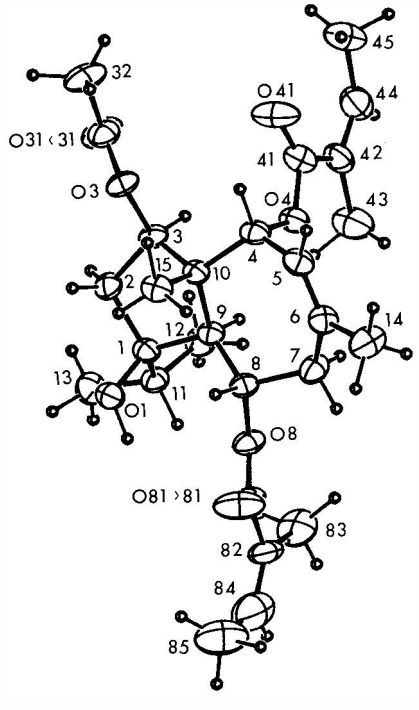


Fig. 1. Ortep drawing of compound **1**. The thermal ellipsoids of the side chains have been reduced in magnitude relative to the ring atoms.

EXPERIMENTAL

The plant material was collected from Aegean coast of Turkey (Kuşadası) in June 1982. A voucher specimen identified by Dr. E. Tuzlacı (Istanbul) was deposited in the Herbarium of the Faculty of Pharmacy, University of Istanbul (ISTE 48938).

The spectra were recorded on the following instruments: UV, Varian Techtron model 635; IR, Perkin–Elmer 577; ^1H NMR, FT-NT 200 MHz; ^{13}C NMR 22.6 MHz; MS, DuPont 21-491.

Isolation and identification of tingitanol (**1**).

Coarsely powdered roots of *Ferula tingitana* L. (Umbelliferae) (2.5 kg) were extracted with benzene in a Soxhlet. The benzene extract was concentrated *in vacuo* and chromatographed over a Sephadex LH-20 column (3 × 50 cm), eluting with ethanol. Tingitanol (**1**) was obtained from the first fractions and cleaned by passing through smaller Sephadex LH-20 columns a few times, yielding 30 g of pure tingitanol (yield 1.2%).

Tingitanol (**1**). Amorphous. IR (KBr) 3470, 2960, 2920, 2860, 1700, 1680, 1450, 1380, 1345, 1260, 1230, 1150, 1115, 1075, 1030, 950, 840, 750 cm^{-1}. ^1H NMR ($CDCl_3$): see text. ^{13}C NMR ($CDCl_3$): 168.1 (s) C_1', 167.9 (s) C_1'', 139.4 (d) C_5, 139.1 (d) C_3', 138.7 (d) C_3'', 127.7 (s) C_6, 127.6 (s) C_2', C_2'', 81.2 (s) C_1, 73.2 (d) C_3, 71.0 (d) C_8, 69.8 (d) C_4, 49.3 (d) C_9, 48.6 (s) C_{10}, 40.5 (t) C_2, 38.3 (t) C_7, 36.7 (d) C_{11}, 27.4 (q) C_{14}, 20.9 (q) C_5', 20.5 (q) C_5'', 18.3 (q) C_4', 17.2 (q) C_4'', 15.8 (q) C_{12}, C_{13}, 13.3 (q) C_{15}. MS: 70 eV (probe) (%), M^+ 434 (1), (M-18) 416 (2), (M-43) 391 (2), (M-Angeloyloxy) 334 (25), (M-Angeloyloxy-OH) 317 (12), (M-Angeloyloxy-43) 291 (60), (M-2 × Angeloyloxy-H_2O) 216 (75), 120 (100), (Angeloyl) 83 (85). (Found: C, 69.5; H, 8.8, $C_{25}H_{38}O_6$ requires C, 69.1; H, 8.8%.)

Acetyltingitanol (**1c**)

Ac_2O (1 ml) was added to tingitanol (100 mg) in pyridine (1 ml) and left at room temp for 16 hr. After work-up, the product (**1c**) crystallized from a mixture of ether:petrol (1:1), m.p. 141–143°, yield 105 mg. IR (KBr): 3510, 2960, 1730, 1710, 1650, 1460, 1440, 1375, 1360, 1260, 1230, 1150, 1095, 1085, 1040, 990 cm^{-1}. ^1H NMR ($CDCl_3$) δ 0.9 (3H, d, J = 7 Hz, Me-12), 0.94 (3H, d, J = 7 Hz, Me-13), 1.20 (3H, s, Me-15), 1.84 (3H, br s, Me-14), 1.9 (3H, t, J = 1 Hz, Me-4′), 1.95 (3H, t, J = 1 Hz, Me-4″), 2.02 (6H, dd, J = 1 and 7 Hz, Me-5′ and Me-5″), 2.05 (3H, s, OAc), 6.12 (2H, tt, J = 1 and 8 Hz, H-3′ and H-3″), 5.8 (1H, br d, J = 8 Hz, H-5), 5.38 (1H, dt, J = 2, 10 and 10 Hz, H-8), 4.82 (1H, br d, J = 8 Hz, H-4), 4.72 (1H, t, J = 9 Hz, H-3), 2.72 (1H, br t, J = 10 Hz, H_β-7), 2.70 (1H, d, J = 10 Hz, H-9), 2.42 (1H, dd, J = 8 and 14 Hz, H_α-2), 2.15 (1H, dd, J = 2 and 14 Hz, H_α-7), 1.55 (1H, dd, J = 10 and 14 Hz, H_β-2). (Found: C, 68.1; H, 8.4. $C_{27}H_{40}O_7$ requires C, 68.0; H, 8.4%.)

Hydrolysis of tingitanol

Tingitanol (100 mg) in 5% NaOH/EtOH (5 ml) was left overnight at room temp, then distilled under reduced pressure. Water was added to the residue, the aqueous solution was extracted with EtOAc, dried over anhyd. Na_2SO_4, then filtered and evaporated to dryness *in vacuo*. A mixture of two compounds was obtained; the tetrol **1a** precipitated from ether and crystallized from EtOH (yield 55 mg), while the triol **1d** was obtained by preparative TLC (using $CHCl_3$:EtOH 93:7) (yield 5 mg).

Tetrol (**1a**). M.p. 243–245° (lit.[1] 245°) (by sublimation). IR (KBr): 3440, 3380, 2950, 2840, 1670, 1500, 1470, 1430, 1380, 1330, 1300, 1250, 1145, 1130, 1120, 1060, 1015, 985, 930, 700, 600 cm^{-1}. ^1H NMR (C_5D_5N) δ 1.2 (3H, d, J = 7 Hz, Me-12), 1.22 (3H, d, J = 7 Hz, Me-13), 1.58 (3H, s, Me-15), 1.8 (3H, br s, Me-14), 6.00 (1H, br d, J = 8 Hz, H-5), 4.9 (1H, br t, J = 9 Hz, H-8), 4.7 (1H, br t, J = 8 Hz, H-3), 4.52 (1H, br d, J = 8 Hz, H-4), 3.2 (1H, d, J = 10 Hz, H-9), other peaks were between 2.8–2.2 ppm. (Found: C, 66.8; H, 9.8. $C_{15}H_{26}O_4$ requires: C, 66.6; H, 9.6%.)

Triacetate of tetrol **1b**—Tetrol (50 mg) was acetylated at room temp in the usual way (yield 60 mg), m.p. 122–124° (lit.[1] 124°). IR (KBr) 3540, 2960, 1730, 1665, 1460, 1430, 1365, 1250, 1135, 1080, 1015, 985, 790, 600 cm^{-1}. ^1H NMR ($CDCl_3$) δ 0.93 (3H, d, J = 6.5 Hz, Me-12), 0.98 (3H, d, J = 7 Hz, Me-13), 1.14 (3H, s, Me-15), 1.81 (3H, br s, Me-14), 2.04 (3H, s, OAc), 2.06 (6H, s, 2 × OAc), 5.72 (1H, br d, J = 8 Hz, H-5), 5.23 (1H, dt, J = 3, 10 and 10.5 Hz, H-8), 4.74 (1H, d, J = 8 Hz, H-4), 4.68 (1H, dd, J = 8 and 10 Hz, H-3), 2.65 (1H, d, J = 10 Hz, H-9), other peaks were between 2.5–1.5 ppm. MS 70 eV (probe) *m/z* (%) M^+ 396 (1), (M-43) 353 (3), (M-60) 336 (1), (M-43-60) 293 (35), (M-2 × 60) 276 (10), (M-2 × 60-43) 233 (70), (M-3 × 60) 216 (65), (M-3 × 60-43) 173 (95). (Found: C, 63.8; H, 8.1. $C_{21}H_{32}O_7$ requires C, 63.6; H, 8.1%.)

Triol **1d**. Amorphous. IR (KBr): 3450, 2960, 2870, 1695, 1640, 1450, 1380, 1230, 1160, 1140, 1120, 1075, 1040, 1000, 975, 930, 840 cm^{-1}. ^1H NMR ($CDCl_3$) δ 0.9 (3H, d, J = 7 Hz, Me-12), 0.96 (3H, d, J = 7 Hz, Me-13), 1.10 (3H, s, Me-15), 1.84 (3H, br s, Me-14), 1.92 (3H, t, J = 1 Hz, Me-4′), 2.02 (3H, dd, J = 1 and 7 Hz, Me-5′), 6.12 (1H, dq, J = 8 and 2 Hz, H-3′), 5.67 (1H, br d, J = 8 Hz, H-5), 5.05 (1H, d, J = 8 Hz, H-4), 4.18 (1H, dt, J = 3 and 10 Hz, H-8), other peaks were between 3.5–1.6 ppm (Found: C, 68.2; H, 9.1. $C_{20}H_{32}O_5$ requires C, 68.2; H, 91%.)

Oxidation of tingitanol

Tingitanol (200 mg) was dissolved in Et_2O, chromic acid solution (1 ml) was added and the solution was stirred at room temp for 2 hr. The ether layer was separated and washed with sat aqueous $NaHCO_3$, dried over anhyd. Na_2SO_4, filtered and evaporated, and the residue was crystallized from ether (yield 185 mg). The ketone (**3**) thus obtained had m.p. 116–118°. IR (KBr): 3500, 2970, 1730, 1715, 1640, 1460, 1380, 1230, 1150, 1040, 990, 970, 850, 750 cm^{-1}. ^1H NMR ($CDCl_3$): δ 0.94 (3H, d, J = 7 Hz, Me-12), 0.98 (3H, d, J = 7 Hz, Me-13), 1.34 (3H, s, Me-15), 1.60 (3H, br s, Me-14), 1.84 (3H, t, J = 1 Hz, Me-4′), 1.92 (3H, t, J = 1 Hz, Me-4″), 1.98 (3H, dd, J = 1 and 7 Hz, Me-5′), 2.07 (3H, dd, J = 1 and 7 Hz, Me-5″), 6.24 (1H, q, J = 7 Hz, H-3′), 6.05 (1H, q, J = 7 Hz, H-3″), 5.85 (1H, br d, J = 8 Hz, H-5), 5.5 (1H, dt, J = 5 and 10 Hz, H-8), 5.12 (1H, d, J = 7 Hz, H-4), 3.22 (1H, d, J = 10 Hz, H-9), other peaks were between 2.7–1.3 ppm. MS 70 eV (probe) *m/z* (%); no M^+ peak, (M-Angeloyl) 349 (8), (M-Angeloyloxy-H) 331 (10), (M-Angeloyloxy-Angeloyl) 249 (90), (M-2 × Angeloyloxy-H) 231 (100). (Found: C, 69.5; H, 6.4. $C_{25}H_{36}O_6$ requires C, 69.4; H, 6.3%.)

Basic dehydration of ketone

The ketone **3** (80 mg) was heated with 10 ml of 5% NaOH/EtOH to 70° for 2 hr under N_2. The reaction mixture was diluted with water and extracted with ether. The ether phase washed with dil HCl, then with water and dried over anhyd. Na_2SO_4, filtered and evaporated to dryness. A mixture of two compounds (**4** and **5**) was obtained and separated on preparative TLC plates (petrol:EtOAc 9:1) (R_f 0.3 for **4** and 0.7 for **5**).

Compound **4**. Amorphous, yield 8 mg, UV (ether): λ_{max} 324 nm (log ϵ 3.97), 226 (4.20). IR (KBr) 3430, 2980, 1700, 1600, 1550, 1450, 1380, 1260, 1150, 1075, 1040, 870, 840 cm^{-1}. ^1H NMR ($CDCl_3$) δ 0.98 (3H, s, Me-15), 1.25 (6H, t, J = 7 Hz, Me-12 and Me-13), 1.93 (3H, br s, Me-14), 6.2 (1H, d, J = 8 Hz, H-8), 5.92 (1H, dt, J = 1 and 10 Hz, H-7), 6.00 (1H, s, H-2), 4.22 (1H, br t, H-4), 2.9 (1H, septet, H-11), other peaks were between 3.5–2.0 ppm. MS 70 eV (probe) *m/z* (%) M^+ 232 (96), (M-18) 214 (20), (M-43) 189 (100), (M-43-18) 171 (60).

Compound **5**. Amorphous, yield 20 mg. UV (ether): λ_{max} 350 nm (log ϵ 3.60), 237 (4.30). IR (KBr): 2960, 2920, 1695, 1630, 1615, 1555, 1445, 1380, 1360, 1270, 1250, 1100, 850 cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.02 (3H, s, Me-15), 1.22 (3H, d, J = 7 Hz, Me-12), 1.26 (3H, d, J = 7 Hz, Me-13), 2.06 (3H, br s, Me-14), 6.33 (1H, d, J = 8 Hz, H-8), 6.25 (1H, dt, J = 1 and 8 Hz, H-7), 5.98 (1H, d, J = 10 Hz, H-5), 5.86 (1H, d, J = 9 Hz, H-4), 5.85 (1H, s, H-2), 2.9 (1H, septet, J = 5 Hz, H-11). MS 70 eV (probe) *m/z* (%) M^+ 214 (80), (M-15) 199 (85), (M-43) 171 (100).

Dehydration of ketone with thionyl chloride

To the ketone **3** (20 mg) in pyridine (1 ml), $SOCl_2$ (0.3 ml) was added dropwise at 0°C. The reaction mixture was kept at 0°–(−5°) for 1 hr, then diluted with ice water and extracted with ether. The ether layer was washed with dil HCl, 5% $NaHCO_3$ and water, then dried over anhyd. Na_2SO_4 and evaporated to dryness. The residue was crystallized from ether, giving **8** (15 mg).

Compound **8**. M.p. 120–121°. UV (ether): λ_{max}: 229 nm (log ϵ 4.15). IR (KBr): 2960, 2920, 1705, 1600, 1450, 1380, 1350, 1250, 1230, 1155, 1080, 1030, 960, 880, 845, 750, 630, 600 cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.15 (6H, d, J = 7 Hz, Me-12 and Me-13), 1.25 (3H, s, Me-15), 1.76 (3H, t, J = 1 Hz, Me-4′), 1.83 (3H, br s, Me-14), 1.90 (3H, dd, J = 1 and 7 Hz, Me-5′), 1.94 (3H, t, J = 1 Hz, Me-4″), 2.05 (3H, dd, J = 1 and 7 Hz, Me-5″), 6.15 (1H, q, J = 7 Hz, H-3′), 6.02 (1H, q, J = 7 Hz, H-3″), 5.92 (1H, s, H-2), 5.78 (1H, br d, J = 8 Hz, H-5), 5.5 (2H, m, H-4 and H-8). MS 70 eV: *m/z* (%) M^+ 414 (1), (M-Angeloyl) 331 (45), (M-Angeloyloxy) 231 (100), (Angeloyl) 83 (90).

Dehydration of ketone with Zn/AcOH

The ketone **3** (80 mg) was refluxed 5 hr with gl. AcOH and activated Zn dust (300 mg). The cooled mixture was filtered, and diluted with water, and extracted with ether. The ether phase was washed with water and dried over anhyd. Na_2SO_4, filtered and evaporated to dryness. The residue was separated on preparative TLC (petrol:EtOAc 7:3). The band R_f 0.60 was the main compound (**9**) (yield 20 mg); a small amount of compound **8** was also obtained.

Compound **9**. Amorphous. IR (KBr): 2960, 2930, 1710, 1640, 1600, 1510, 1460, 1380, 1260, 1225, 1150, 1070, 1040 cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.12 (3H, d, J = 7 Hz, Me-12), 1.14 (3H, d, J = 7 Hz, Me-13), 1.28 (3H, s, Me-15), d, 1.92 (3H, s, Me-14), 1.94 (3H, t, J = 1 Hz, Me-4′), 2.04 (3H, dd, J = 1 and 7 Hz, Me-5′), 6.27 (1H, d, J = 11 Hz, H-8), 6.15 (1H, m, H-3′), 6.10 (1H, J = 10 Hz, H-7), 5.90 (1H, s, H-2), 5.05 (1H, d, J = 15 Hz, H-4). (Found: C, 76.5; H, 8.3. $C_{20}H_{26}O_3$ requires C, 76.4; H, 8.3%.)

Cyclic sulfite of tingitanol (**10**)

Tingitanol (50 ml) in pyridine (2 ml) was cooled to − 5°, $SOCl_2$ (0.3 ml) was added and the solution left in a refrigerator for 1 hr. Compound **10** was obtained for preparative TLC ($CHCl_3$: EtOH; 98:2) (yield 25 mg). IR (KBr): 2960, 1710, 1640, 1450, 1380, 1350, 1250, 1220, 1150, 1070, 1030, 980, 960, 920, 880, 850, 800, 740, 670 cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.00 (3H, d, J = 7 Hz, Me-12), 1.07 (3H, d, J = 7 Hz, Me-13), 1.42 (3H, s, Me-15), 1.8 (3H, br s, Me-14), 1.89 (6H, t, J = 1 Hz, Me-5′ and Me-5″), 2.01 (6H, tt, J = 1 and 7 Hz, Me-4′ and Me-4″), 2.15 (1H, dd, J = 3 and 19 Hz, H_α-2), 2.26 (1H, septet, H-11), 2.67 (1H, d, J = 10.5 Hz, H-9), 3.1 (1H, dd, J = 7.5 and 18.5 Hz, H_β-2), 4.48 (1H, d, J = 4.5 Hz, H-4), 5.42 (1H, t, H_α-3), 5.44 (1H, d, J = 4.5 Hz, H-5), 5.54 (1H, ddd, J = 3, 7 and 10.5 Hz, H-8), 6.06 (1H, dq, J = 2 and 7 Hz, H-3′) and 6.13 (1H, dq, J = 2 and 7 Hz, H-3″). (Found: C, 62.6; H, 7.5. $C_{25}H_{36}O_7S$ requires C, 62.5; H, 7.5%.)

Allylic oxidation of tetrol

To tetrol **1a** (50 mg) dried acetone (10 mg) activated MnO_2 (500 ml) was added and stirred for 5 hr at room temp. After filtration the acetone was evaporated and the residue separated by p.l.c. ($CHCl_3$:EtOH 9:1); compound **11** (25 mg) was obtained.

Compound **11**. Amorphous. IR (KBr): 3450, 2960, 2880, 1685 (sh), 1630, 1470, 1440, 1375, 1060, 910 cm^{-1}. ^1H NMR ($CDCl_3$): δ 0.9 (3H, d, J = 7 Hz, Me-12), 0.98 (3H, d, J = 7 Hz, Me-13), 1.32 (3H, s, Me-15), 2.00 (2H, br s,

Me-14), 5.85 (1H, br s, H-5), 4.58 (1H, dt, J = 5 and 10 Hz, H-8), 3.97 (1H, dd, J = 7 and 12 Hz, H-3), 2.12 (1H, d, J = 10 Hz, H-9), other signals were between 2.8–1.5 ppm. (Found: C, 67.3; H, 9.0. $C_{15}H_{24}O_4$ requires: C, 67.2; H, 0.9%.)

Diacetyl derivative of compound **11**

Compound **11** (10 mg) acetylated in the usual manner, yielded 12 mg **11a**, amorphous. IR (KBr): 3450, 2920, 1720, 1650, 1430, 1360, 1240, 1135, 1070, 1020, 950 cm^{-1}. ^1H NMR ($CDCl_3$): δ 0.88 (3H, d, J = 7 Hz, Me-12), 0.92 (3H, d, J = 7Hz, Me-13), 1.42 (3H, s, Me-15), 1.96 (3H, br s, Me-14), 2.04 (3H, s, OAc), 2.08 (3H, s, OAc), 5.93 (1H, br s, H-5), 5.65 (1H, m, H-8), 4.92 (1H, t, J = 9 Hz, H-3), 2.4 (1H, d, J = 10 Hz, H-9). (Found: C, 64.8; H, 8.0. $C_{19}H_{28}O_6$ requires: C, 64.8; H, 8.0%.)

Compound **2**[1]. IR (KBr): 3470, 2960, 1690, 1640, 1450, 1380, 1350, 1250, 1230, 1170, 1080, 1040, 980, 950, 850, 750 cm^{-1}. ^1H NMR ($CDCl_3$): δ 0.92 (3H, d, J = 7 Hz, Me-12), 0.98 (3H, d, J = 7 Hz, Me-13), 1.20 (3H, s, Me-15), 1.82 (3H, br s, Me-14), 1.88 (6H, t, J = 1 Hz, Me-5′ and Me-5″), 2.00 (6H, dt, J = 1 and 7 Hz, Me-4′ and Me-4″), 6.13 (2H, br q, J = 7 and 10 Hz, H-3′ and H-3″), 5.7 (1H, br d, J = 8 Hz, H-5), 5.38 (1H, dt, J = 3 and 10 Hz, H-8), 5.04 (1H, dd, J = 8 and 10 Hz, H-3), 3.7 (1H, d, J = 7 Hz, H-4), other peaks were between 1.3–2.9 ppm. ^{13}C NMR ($CDCl_3$): 167.3 (s) C_1', 167.1 (s) C_1'', 137.7 (d) C_3', C_3'', 135.5 (d) C_5, 126.9 (s) C_2', C_2'', 125.6 (s) C_6, 80.9 (s) C_1, 73.7 (d) C_3, 69.3 (d) C_8, 67.8 (d) C_4, 48.5 (d) C_9, 46.3 (s) C_{10}, 39.1 (t) C_2, 35.9 (d) C_{11}, 35.5 (t) C_7, 26.4 (q) C_{14}, 19.6 C_5', 19.5 (q) C_5'', 17.4 (q) C_4', 16.2 (q) C_4'', 14.7 (q) C_{12}, C_{13}, 11.3 (q) C_{15}.

X-ray analysis of acetyltingitanol **1c**

A Syntex $P2_1$ diffractometer was used to collect data on an orthorhombic crystal of dimensions 0.41 × 0.37 × 0.26 mm belonging to space group $P2_12_12_1$ with a = 10.922(3), b = 23.074(4), c = 10.809(3)Å, V = 27.24(1)Å^3, Z = 4, dc = 1.162 Mg m^{-3}, and μ = 6.82 cm^{-1} (CuK_α). A total of 2183 independent reflections were collected by the $\theta:2\theta$ scan technique using CuK_α radiation (λ = 1.54178 Å) of which 2115 had intensities greater than 3σ(I). The structure was solved by direct methods.[8] Hydrogen atom positions were obtained from a difference Fourier map and least-squares refinement yielded a final R of 0.048. Atomic positional parameters (Table 1) and bond distances and valence angles (Table 2) are available from the Cambridge Crystallographic Data Centre.

Acknowledgements—This work was supported by the Scientific and Technical Research Council of Turkey (TUBITAK) (TBAG-580) granted to M. Miski and by the Robert A. Welch Foundation (Grant F-130) to T. J. Mabry.

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Journal of Natural Products
Vol. 48, No. 2, pp. 326-327, Mar-Apr 1985

SESQUITERPENE-COUMARIN ETHERS OF *FERULA TINGITANA*

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Ferula tingitana L. (Umbelliferae) is a robust perennial herb native to the Mediterranean coastal region. According to Dioscorides (1), a gum-resin from this plant is called "silphion" and has been used for treatment of several diseases; this plant has also been suggested to be one of the sources of the important medicinal gum-resin "ammoniacum." The roots were shown by tlc to contain the same major compounds as the gum resin, and because roots are more accessible, they were extracted. We previously described a new daucane ester from the petroleum ether extract of the roots (2), and here we report three known sesquiterpene-coumarin ethers, namely colladonin (3,4), isosamarcandin angelate (**1**) (5), and feselol (**2**) (6), as well as the known aromatic ketone, latifolon (7); all were obtained from the C_6H_6 extract of the roots.

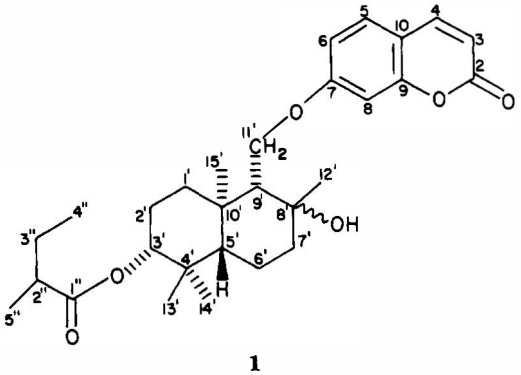
The identities of the compounds were established by comparing their spectral data (^{1}H nmr, ms, ir, and uv) as well as mp and optical rotations, to those values reported in the literature, and in the case of colladonin, comparison with an authentic sample. Because little mass spectral data were presented previously, we discuss here the ms and provide ^{13}C-nmr data for isosamarcandin angelate (**1**) and feselol (**2**) (see Experimental section).

In our work, three populations were found to exhibit the same type of umbelliferone 7-*O*-terpene ethers, compounds which are typical for the genus *Ferula* (8). Earlier reports that the roots of *F. tingitana* contain linear-furanocoumarins (9), compounds which are only rarely found in *Ferula* species, suggest that the plant material in this earlier study may have been misidentified.

EXPERIMENTAL

PLANT MATERIAL.—*F. tingitana* was collected from the Aegean Coast of Turkey (Kusadasi) in June 1982. A voucher specimen, identified by Dr. E. Tuzlaci (Istanbul), is deposited in the Herbarium of the Faculty of Pharmacy, University of Istanbul (ISTE 48938). Small samples of two other populations, from Side (Antalya) and Sütcüler (Isparta), were also analyzed; each of these populations was separated from the site of the bulk collection by over 400 km.

INSTRUMENTS.—Spectra were recorded on the following instruments: uv, Varian Techtron 635: ir, Perkin-Elmer 577; ^{1}H nmr, NT-200



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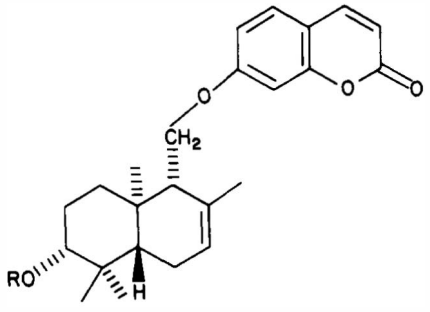

2 R=H
2a R=Ac

MHz; ^{13}C nmr, Brucker WH-90; ms, DuPont 21-490.

ISOLATION AND IDENTIFICATION OF THE COMPOUNDS.—Dried and coarsely powdered roots of *F. tingitana* (2.5 kg) were extracted in a Soxhlet apparatus with petroleum ether (2) and then C_6H_6. The C_6H_6 extract was concentrated in vacuo and chromatographed on a Sephadex LH-20 column (3×50 cm), eluted with EtOH. The compounds were obtained in the following order: feselol (150 mg), colladonin (30 mg), isosamarcandin angelate (62 mg), and latifolon (44 mg).

ISOSAMARCANDIN ANGELATE (**1**).—^{13}C nmr ($CDCl_3$) 161.3 (s, C-2), 113.3 (d, C-3), 143.5 (d, C-4), 128.8 (d, C-5), 113.4 (d, C-6), 161.8 (s, C-7), 101.6 (d, C-8), 156.0 (s, C-9), 112.8 (s, C-10), 37.9 (t, C-1′), 23.6 (t, C-2′), 80.2 (d, C-3′), 37.9 (s, C-4′), 55.1 (d, C-5′), 20.0 (t, C-6′), 44.1 (t, C-7′), 72.5 (s, C-8′), 59.4 (d, C-9′), 37.9 (s, C-10′), 66.5 (t, C-11′), 28.4 (q, C-12′), 24.7 (q, C-13′), 17.0 (q, C-14′), 15.8 (q, C-15′), 167.9 (s, C-1″), 128.5 (s, C-2″), 137.6 (d, C-3″), 16.2 (q, C-4″), 20.7 (q, C-5″); ms (probe) 70 eV *m/z* (rel. int.) 482 $[M]^+$ (9.9), 464 $[M-H_2O]^+$ (37.7), 364 $[M-C_5H_8O_2-H_2O]^+$ (40.3), 349 $[M-C_5H_8O_2-H_2O-Me]^+$ (19.9), 321 $[M-C_9H_5O_3]^+$ (8.8), 302 $[M-C_9H_6O_3-H_2O]^+$ (75.9), 219 $[M-C_9H_6O_3-C_5H_8O_2O-H_2O]^+$ (88.3), 162 $[C_9H_6O_3]^+$ (90), 83 $[C_5H_7O]^+$ (86.3). (Found: C, 72.21; H, 7.91. $C_{29}H_{38}O_6$ requires: C, 72.19; H, 7.88).

FESELOL (**2**).—^{13}C nmr ($CDCl_3$) 161.3 (s, C-2), 113.1 (d, C-3), 143.5 (d, C-4), 128.8 (d, C-5), 113.1 (d, C-6), 162.2 (s, C-7), 101.5 (d, C-8), 156.0 (s, C-9), 112.6 (s, C-10), 37.9 (t, C-1′), 27.4 (t, C-2′), 78.9 (d, C-3′), 38.8 (s, C-4′), 49.5 (d, C-5′), 23.4 (t, C-6′), 123.9 (d, C-7′), 132.4 (s, C-8′), 53.9 (d, C-9′), 35.9 (s, C-10′), 67.1 (t, C-11′), 28.1 (q, C-12′), 21.6 (q, C-13′), 15.3 (q, C-14′), 14.2 (q, C-15′); ms (probe) 70 eV *m/z* (rel. int.) 382 $[M]^+$ (50), 220 $[M-C_9H_5O_3]^+$ (65), 203 $[C_{15}H_{23}]^+$ (100), 162 $[C_9H_6O_3]^+$ (85), 133 $[C_9H_6O_3-COH]^+$ (70). (Found: C, 75.36; H, 7.88. $C_{24}H_{30}O_4$ requires: C, 75.39; H, 7.85%).

ACETYL FESELOL (**2a**).—Acetylation was carried out in the usual manner with Ac_2O in pyridine using 20 mg of **2**. The uv was similar to that of **2**, while the ir showed the hydroxyl band at 3450 of **2** had disappeared and the acetyl peak was observed at 1725 cm^{-1}. ^1H nmr ($CDCl_3$) 0.9 (3H, s, H-13′), 0.95 (3H, s, H-14′), 0.98 (3H, s, H-15′), 1.7 (3H, br s, H-12′), 2.07 (3H, s, OCO*Me*), 4.02 (1H, dd, J=10 and 6 Hz, H-11a′), 4.15 (1H, dd, J=7.5 Hz and 4 Hz, H-11b′), 4.55 (1H, br t, J=10 Hz and 5 Hz, H-3′), 5.55 (1H, br s, H-7′), 6.25 (1H, d, J=9 Hz, H-3), 6.82 (2H, m, H-6 and H-8), 7.36 (1H, d, J=9 Hz, H-5), 7.64 (1H, d, J=9 Hz, H-4); ms (probe) *m/z* (rel. int.) 424 $[M]^+$ (25), 364 $[M-AcOH]^+$ (28), 349 $[M-AcOH-Me]^+$ (12), 203 $(C_{15}H_{23}]^+$ (100), 162 $[C_9H_6O_3]^+$ (85), 133 $[C_9H_6O_3-COH]^+$ (95).

ACKNOWLEDGMENTS

The work done at the University of Istanbul was supported by the Faculty of Pharmacy, University of Istanbul, and by TUBITAK (Turkish Scientific and Technical Research Council) (TBAG-580, granted to Dr. M. Miski). The work at the University of Texas was supported by the National Institutes of Health (Grant HDO 4488) and by the Robert A. Welch Foundation (Grant F-130). Colladonin was kindly supplied by Prof. Dr. B. Rodriguez (Madrid).

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Received 22 October 1984

Journal of Natural Products
Vol. 49, No. 4, pp. 657-660, Jul-Aug 1986

NEW DAUCANE ESTERS FROM *FERULA TINGITANA*

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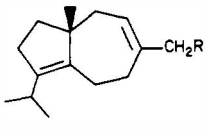
ABSTRACT.—In addition to the three known daucane esters (**2,3,8**) and one phenylpropanoid (**9**), the petroleum ether extract of the roots of *Ferula tingitana* yielded four new daucane esters: 14-*p*-anisoyloxy-dauc-4,8-diene (**1**), acetyltingitanol (**4**), acetyldesoxodehydrolaserpitine (**5**), and 4-β-hydroxy-6-α-*p*-hydroxybenzoyloxy-10-α-angeloyloxydauc-8-ene (**6**). A possible biogenetic pathway for 1,5-*cis*- and 1,5-*trans*-daucanes is presented.

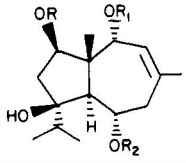
From the C_6H_6 extract of the roots of *Ferula tingitana* L., a medicinal plant from the Mediterranean region (1), we previously isolated the new sesquiterpene ester tingitanol (**2**) (2), as well as the three known sesquiterpene coumarin ethers coladonin, feselol, and isosamarcandin angelate (3). The petroleum ether extract of the same material has now yielded, in addition to tingitanol, three known and four new compounds.

RESULTS AND DISCUSSION

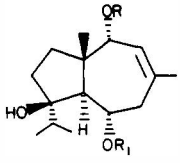
The known compounds from the petroleum ether extract were identified as desoxodehydrolaserpitine (**3**) (2,4), fercomin (**8**) (5), and laserine (**9**) (6,7) by spectral data and direct comparison with authentic samples. The structural analysis of the four new compounds (**1, 4, 5,** and **6**) follows.



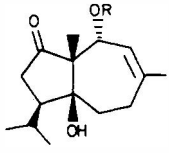
1 R=*p*-anisoyloxy
1a R=H



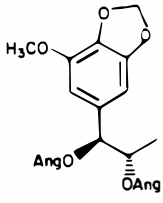
2 R=H, R_1=R_2=Ang
3 R=R_2=Ang, R_1=H
4 R=Ac, R_1=R_2=Ang
5 R=R_2=Ang, R_1=Ac



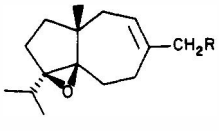
6 R=Ang, R_1=*p*-hydroxybenzoate
7 R=Ang, R_2=*p*-anisate



8 R=*p*-anisate



9



10 R=*p*-anisoyloxy

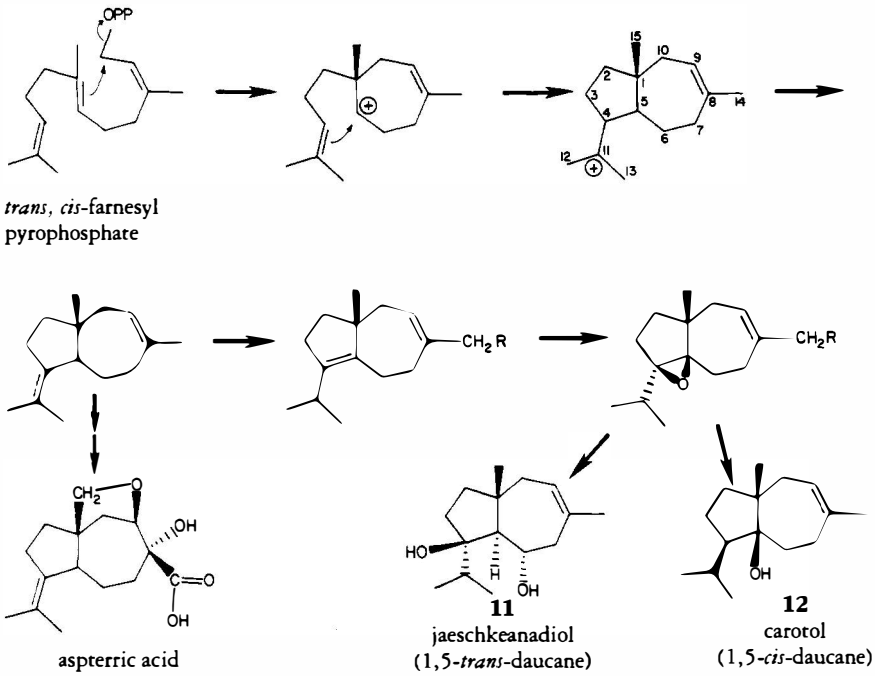
The eims of **1** exhibited a molecular ion at *m/z* 354 in accord with a $C_{23}H_{30}O_3$ molecular formula. The presence of an aromatic acyl group was established by the ir (1710, 1610, 1515, and 1260 cm^{-1}) and uv (260 nm) spectra of **1**. The acyl group in **1** was confirmed as *p*-anisate by the ^{1}H-nmr spectrum which exhibited signals similar to those for 14-*p*-anisoyloxy-4,5-β-epoxydauc-8-ene (**10**), except for the H-11 signal for **1** which appears at δ 2.69. This later feature of the ^{1}H nmr of **1** was in accord with the presence of a double bond at C-4. Furthermore, the absence of vinylic signals other than for H-9 indicated that the double bond must be between C-4 and C-5, similar to that of **1a**. Thus, **1** must be the 14-*p*-anisoyloxy derivative of daucene (**1a**).

Compound **4** was identified as acetyltingitanol by spectral data and direct comparison with the acetylation product of tingitanol (2).

Compound **5**, exhibited a similar ^{1}H-nmr spectrum to the one recorded for **4**, and acetylation of **3** to **5** established that **5** is acetyldesoxodehydrolaserpitine.

Except for side-chain signals the ^{1}H-nmr spectrum of **6** was similar to the one recorded for **7** (8) (the spectrum of **6** exhibited signals for a *p*-hydroxybenzoyl side chain). A molecular ion at *m/z* 456 ($C_{27}H_{36}O_6$) in the eims of **6**, together with a fragmentation pattern similar to that of **7**, also supported this relationship. Conversion of **6** to **7** by methylation with CH_2N_2 confirmed **6** to be 4-β-hydroxy-6-α-*p*-hydroxybenzoyloxy-10-α-angeloyloxydauc-8-ene.

It is of interest that *F. tingitana* as well as *Ferula communis, Ferula linkii,* and *Ferula lancerottensis*, members of the subgenus *Euferula* (Boiss.) Korovin, yielded both 1,5-*cis*- and 1,5-*trans*-daucane derivatives (5,8-11), which may be biogenetically related as shown in Scheme 1. These biogenetic considerations require a β-orientation for the oxirane ring of **10**, an orientation that is proposed here on the basis of the correlation of ^{13}C nmr of **10** with those of jaeschkeanadiol (**11**) and carotol (**12**). Nearly identical chemical shifts of the isopropyl methyl groups of **10** (δ 17.5 and 18.5) and **11** (δ17.8 and 18.2, in contrast to those of carotol (**12**) (δ 20.9 and 23.5), indicate the similar shielding effect of the sesquiterpene nucleus and the γ-substituent effect of the C-4



SCHEME 1.

asymmetric center on this part of the molecule; this, in turn, suggests a β stereochemistry for the epoxy group in **10**. In addition, direct comparison of the ^{1}H-nmr spectrum of **10** with that of the synthetic 4,5-β-epoxydauc-8-ene (12) clearly supported this assignment.

EXPERIMENTAL

GENERAL EXPERIMENTAL PROCEDURES.—Uv spectra were taken in MeOH; ^{1}H nmr and ^{13}C nmr in $CDCl_3$ using TMS as an internal standard at 200 MHz and 22.6 MHz, respectively. Ms were obtained with a direct inlet system at 70 eV.

PLANT MATERIAL.—The roots of *F. tingitana* were collected from the Aegean Coast of Turkey (between Kuşadası and Ephesus) in June 1982. A voucher specimen, identified by Dr. E. Tuzlacı (Istanbul), is deposited in the Herbarium of the Faculty of Pharmacy, University of Istanbul (ISTE 48938).

ISOLATION AND IDENTIFICATION OF THE COMPOUNDS.—Dried and coarsely powdered roots of *F. tingitana* (2.5 kg) were extracted with petroleum ether in a Soxhlet apparatus. Concentration of the petroleum ether extract provided 146 g of viscous oil. This oil (6 g) was chromatographed on Sephadex LH-20 columns packed in EtOH and cyclohexane-CH_2Cl_2-EtOH (7:4:1). Finally, preparative tlc [1.5-2 mm thickness, silica gel developed with cyclohexane-EtOAc mixtures (4:1 and 7:3)] was used for further purification of the compounds.

14-p-*Anisoyloxydauc-4,8-diene* (**1**).—5 mg; uv λ max nm 260; ir ν max ($CHCl_3$) 2970, 1710, 1610, 1515, 1260, and 770 cm^{-1}; ^{1}H nmr δ 8.01 (2H, d, J=9.1 Hz, H-4′ and 6′), 6.93 (2H, d, J=9.1 Hz, H-3′ and 7′), 5.86 (1H, br t, J=6.5 Hz, H-9), 4.70 (2H, br s, H-14 and 14′), 3.86 (3H, s, H-8′), 2.69 (1H, septet, H-11), 0.98 (3H, d, J=7.2 Hz, H-12), 0.95 (3H, s, H-15), 0.93 (3H, d, J=7.2 Hz, H-13); ms *m/z* (% rel. int.) 354 $[M]^+$ (7.2), 311 $[M-C_3H_7]^+$ (14.3), 218 $[M-C_8H_8O_2]^+$ (21.7), 202 $[M-C_8H_8O_3]^+$ (42), 187 $[M-C_9H_{13}O_3]^+$ (23.8), 175 $[M-C_{11}H_{15}O_2]^+$ (60.3), 159 $(M-C_{11}H_{16}O_3]^+$ (69.8), 135 [p-anisate]$^+$ (100).

Acetyltingitanol (**4**).—18 mg; for ir and ^{1}H-nmr data see Miski *et al.* (2); ms *m/z* (% rel. int.) 476 $[M]^+$ (0.2), 393 $[M-C_5H_7O]^+$ (8), 333 $[M-C_8H_{15}O_2]^+$ (25.3), 317 $[M-C_7H_{11}O_4]^+$ (6.4), 293 $[M-C_{10}H_{15}O_3]^+$ (59.2), 234 $(M-C_{12}H_{18}O_5]^+$ (81.3), 216 (82.4), 191 (63.7), 173 (94.4), 83 [angelate]$^+$ (93.3), 43 [acetate]$^+$ (100).

Acetyldesoxodehydrolaserpitine (**5**).—12 mg; ir ν max (KBr), 3500, 2980, 2960, 1732, 1710, 1695 (sh), 1645, 1260, 1228 cm^{-1}; ^{1}H nmr δ 6.15 (1H, qq, J=1.4 and 7.3 Hz, H-3′), 6.08 (1H, qq, J=1.4 and 7.3 Hz, H-3″), 5.74 (1H, br d, J=7.4 Hz, H-9), 5.36 (1H, dt, J=3.4and 10.7 Hz, H-6), 4.78 (1H, d, J=7.4 Hz, H-10), 4.76 (1H, dd, J=8.8 and 10.3 Hz, H-2α), 2.72 (1H, bt, J=14.1 Hz, H-7β), 2.70 (1H, d, J=10.7 Hz, H-5), 2.50 (1H, dd, J=8.8 and 14.1 Hz, H-3α), 2.16 (1H, dd, J=3.4 and 14.2 Hz, H-7α), 2.08 (3H, s, O*Ac*), 2.06 (3H, td, J=1.5 and 6.4 Hz, H-4′), 1.99 (3H, td, J=1.5 and 6.4 Hz, H-4″), 1.89 (6H, m, H-5′ and 5″), 1.82 (3H, br d, J=1.2 Hz, H-14), 1.58 (1H, dd, J=10.3 and 14.2 Hz, H-3β), 1.22 (3H, s, H-15), 0.98 (3H, d, J=6.8 Hz, H-12), 0.91 (3H, d, J=6.8 Hz, H-13); ms *m/z* (% rel. int.) 373 $[M-C_5H_{11}O_2]^+$ (21.5), 333 $[M-C_8H_{15}O_2]^+$ (15.7), 290 $[M-C_{10}H_{18}O_3]^+$ (10.6), 273 $[M-C_{10}H_{19}O_4]^+$ (57.4), 233 $[M-C_{13}H_{23}O_4]^+$ (13.9), 216 $[M-C_{12}H_{20}O_6]^+$ (80.6), 198 (36.4), 173 (93.9), 145 (87.5), 83 [angelate]$^+$ (100), 43 [acetate]$^+$ (67.4).

Acetylation of **4**.—Desoxodehydrolaserpitine (**4**) (10 mg) was acetylated with pyridine and Ac_2O for 15 h. The usual work-up gave 12 mg of acetyldesoxodehydrolaserpitine, identical with **5**.

4-β-Hydroxy-6-α-p-*hydroxybenzoyloxy-10-α-angeloyloxydauc-8-ene* (**6**).—16 mg; uv λ max nm 308 (sh), 258; ir ν max (KBr) 3380, 2260, 2245, 1710, 1650, 1608, 1590, 1510, 1440, 1270, 850, 770 cm^{-1}; ^{1}H nmr δ 7.95 (2H, d, J=8.4 Hz, H-4′ and 6′), 6.89 (2H, d, J=8.4 Hz, H-3′ and 7′), 6.12 (1H, qq, J=1.2 and 7.3 Hz, H-3″), 5.79 (1H, br d, J=7.1 Hz, H-9), 5.44 (1H, dt, J=2.7 and 10.7 Hz, H-6), 4.94 (1H, d, J= 7.1 Hz, H-10), 2.79 (1H, d, J=10.7 Hz, H-5), 2.78 (1H, br t, J=14.3 Hz, H-7β), 2.23 (1H, dd, J=2.7 and 14.3 Hz, H-7α), 2.06 (3H, td, J=1.2 and 7.2 Hz, H-4″), 1.98 (3H, t, J=1.2 Hz, H-5″), 1.82 (3H, br d, J=1.2 Hz, H-14), 1.23 (3H, s, H-15), 0.98 (3H, d, J=6.5 Hz, H-12), 0.86 (3H, d, J=6.5 Hz, H-13); ms *m/z* (% rel. int.) 456 $[M]^+$ (0.7), 413 $[M-C_3H_7]^+$ (1.2), 356 $[M-C_5H_8O_2]^+$ (1.1), 313 $[M-C_8H_{15}O_2]^+$ (32.4), 275 $[M-C_{10}H_{13}O_3]^+$ (6.4), 235 $[M-C_{12}H_{13}O_4]^+$ (13), 218 $[M-C_{12}H_{14}O_5]^+$ (30.9), 200 (40.2), 175 (95.7), 138 [p-hydroxybenzoic acid]$^+$ (57.6), 121 (p-hydroxybenzoate]$^+$ (100), 83 [angelate]$^+$ (67.3).

Methylation of **6**.—Compound **6** (10 mg) was reacted with CH_2N_2 (in Et_2O) for 16 h. The usual work-up gave 9 mg of **7**, identical with the natural compound (8).

ACKNOWLEDGMENTS

We thank Dr. M. Holub, Prague, Czechoslovakia, for a sample of desoxodehydrolaserpitine, Dr. L.H. Zalkow, Atlanta, Georgia, for carotol, Drs. H. Rudler and J. Levisalles, Paris, France, for ^{1}H-nmr spectra of daucene and 4,5-β-epoxydauc-8-ene. This work was supported by grants from the Scientific and Technical Research Council of Turkey (TUBITAK) (TBAG-580) granted to M. Miski and by the Robert A. Welch Foundation (Grant F-130) and National Institutes of Health (Grant GM 35-710) to T.J. Mabry.

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Received 7 March 1986

Phytochemistry, Vol 24, No 8, pp 1735–1741, 1985
Printed in Great Britain.

0031–9422/85 $3.00 + 0.00

DAUCANE ESTERS FROM *FERULA COMMUNIS* SUBSP. *COMMUNIS*

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(*Revised received* 6 *November* 1984)

Key Word Index—*Ferula communis* subsp. *communis*; Umbelliferae; sesquiterpenoids; daucane esters.

Abstract—Fourteen daucane esters together with a known propiophenone 3,4-methylenedioxy-5-hydroxy-propiophenone, were isolated from *Ferula communis* subsp. *communis*. Except for the 6-(*p*-anisic acid) ester of jaeschkeanadiol all these esters are new. Structures were elucidated using spectral properties of the esters and their partial hydrolysis products. X-ray diffraction analysis of one of the compounds confirmed its structure including the stereochemical assignments made on the basis of spectral data.

INTRODUCTION

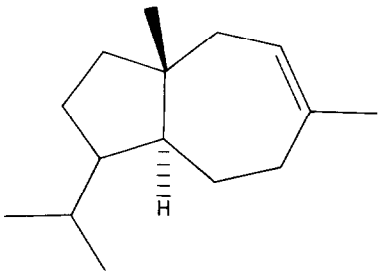
In continuation of our studies of members of the genus *Ferula* which are indigenous to Anatolia [1, 2], we investigated *Ferula communis* L. subsp. *communis*. This species, which belongs to subgenus *Euferula* Boiss, is the type species for the genus *Ferula*. *F. communis*, already well known as a medicinal plant in ancient times [3], has, for example, been used as an antihysteric and for the treatment of dysentery [4]. Previously, several sesquiterpene esters some of different skeletal types but most containing a 1,5-*trans*-fused daucane ring system were reported from other *Ferula* species [5–10].

RESULTS AND DISCUSSION

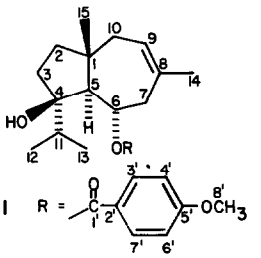
From the benzene extract of the dried roots of *Ferula communis*, we obtained one known and 13 new sesquiterpene esters and the known propiophenone **20** [1]. Each of these esters is discussed separately below.

Compound **1** ($[M]^+$ at m/z 372, $C_{23}H_{32}O_4$) was identified as the *p*-anisic acid ester of jaeschkeanadiol (ferutidin) by spectral data and direct comparison with an authentic sample [1].

Compound **2** ($[M]^+$ at m/z 368, $C_{23}H_{28}O_4$) exhibited IR absorptions characteristic for a cyclopentenone ring [1720 (sh) and 1710 cm^{-1}], as well as bands for an aromatic acyl group. In addition to the signals of the *p*-anisate portion the ^1H NMR spectrum of **2** corresponded to a daucane-type sesquiterpene nucleus, being similar to

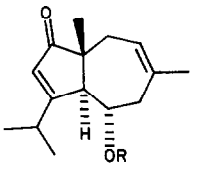


Trans-fused dauc-8-ene

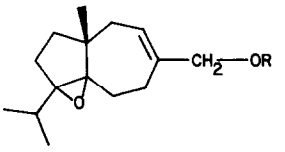


1 R = (*p*-Anisate)

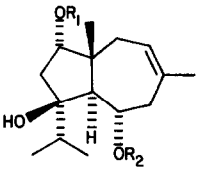
1a R = Ac



2 R = *p*-Anisate



3 R = *p*-Anisate



4 R_1 = Ac, R_2 = Benzoate
5 R_1 = Ac, R_2 = *p*-Anisate
6 R_1 = Ac, R_2 = H
7 R_1 = R_2 = H

that of dehydrated-oxytingitanol (**22**) [2]. However, since the signal for H-10 appeared in the upfield region and H-9 (a broad triplet at δ5.59) was clearly coupled to two protons it was evident that **2** was not oxygenated at C-10; thus, the *p*-anisate moiety must be the C-6α acyl group.

The ^1H NMR spectrum of compound **3** ($[M]^+$ at m/z 370, $C_{23}H_{30}O_4$) indicated that **3** also had an anisate, but showed that the C-14 methyl group present in **1** and **2** had been oxidized to a primary alcohol which is esterified with *p*-anisic acid. This finding was corroborated by a signal for C-14 at δ69.3 (*t*) in the ^{13}C NMR spectrum of **3** (see Table 1). The $[M]^+$ in the mass spectrum of **3** ($[M]^+$ at m/z 370) indicated the presence of an additional oxygen atom, which on the basis of the absence of a hydroxyl band in the IR spectrum and the presence of two signals at

Table 1. ^{13}C NMR data of **1**, **3**, **5**, **10**, **11**, **14** and **17**

	1	**3**	**5**	**10**	**11**	**14**	**17**
C-1	44.0*s*	41.9*s*	47.3*s*	46.8*s*	46.7*s*	51.1*s*	49.1*s*
C-2	31.6*t*	23.4*t*	82.8*d*	31.2*t*	30.9*t*	79.3*d*	80.6*d*
C-3	41.1*t*	28.0*t*	40.8*t*	40.5*t*	40.5*t*	41.1*t*	39.9*t*
C-4	86.2*s*	76.8*s*	85.1*s*	86.2*s*	86.1*s*	85.7*s*	84.0*s*
C-5	60.0*d*	76.0*s*	55.9*d*	51.5*d*	51.5*d*	55.5*d*	49.1*d*
C-6	71.0*d*	24.7*t*	70.4*d*	71.5*d*	71.0*d*	69.5*d*	70.0*d*
C-7	41.4*t*	22.2*t*	39.7*t*	37.4*t*	37.3*t*	39.4*t*	39.0*t*
C-8	133.6*s*	138.1*s*	133.9*s*	137.4*s*	137.4*s*	131.6*s*	135.4*s*
C-9	125.3*d*	127.2*d*	124.6*d*	124.6*d*	124.5*d*	128.6*d*	125.5*d*
C-10	41.4*t*	33.3*t*	34.9*t*	74.5*d*	74.4*d*	75.1*d*	75.1*d*
C-11	37.2*d*	33.9*d*	37.0*d*	37.4*d*	37.3*d*	37.1*d*	36.8*d*
C-12	18.5*q*	18.2*q*	18.2*q*	18.5*q*	18.5*q*	18.1*q*	18.2*q*
C-13	17.5*q*	17.8*q*	17.6*q*	17.4*q*	17.4*q*	17.5*q*	17.6*q*
C-14	26.4*q*	69.3*t*	25.9*q*	27.3*q*	27.3*q*	26.0*q*	26.0*q*
C-15	20.3*q*	20.3*q*	20.5*q*	21.0*q*	21.0*q*	21.0*q*	21.2*q*
Arom. Subst.							
C-1′	166.4*s*	165.6*s*	166.7*s*	167.2*s*	167.2*s*	166.6*s*	166.7*s*
C-2′	123.0*s*	122.3*s*	122.8*s*	130.7*s*	122.8*s*	122.5*s*	122.5*s*
C-3′	131.7*d*	131.0*d*	131.8*d*	129.8*d*	131.8*d*	131.8*d*	131.8*d*
C-4′	113.8*d*	113.1*d*	113.9*d*	128.6*d*	113.9*d*	114.0*d*	114.0*d*
C-5′	163.6*s*	162.9*s*	163.8*s*	133.2*s*	163.8*s*	163.9*s*	163.9*s*
C-6′	113.8*d*	113.1*d*	113.9*d*	129.8*d*	113.9*d*	114.0*d*	114.0*d*
C-7′	131.7*d*	131.0*d*	131.8*d*	128.6*d*	131.8*d*	131.8*d*	131.8*d*
C-8′	55.3*q*	54.7*q*	55.5*q*	—	55.4*q*	54.5*q*	55.4*q*
Angelate							
C-1″	—	—	—	166.6*s*	166.4*s*	—	—
C-2″	—	—	—	128.1*s*	127.9*s*	—	—
C-3″	—	—	—	138.5*d*	138.7*d*	—	—
C-4″	—	—	—	20.7*q*	20.6*q*	—	—
C-5″	—	—	—	15.8*q*	15.8*q*	—	—
Acetate(s)							
C-1″	—	—	170.5*s*	—	—	170.5*s**	170.2*s*
C-2″	—	—	19.8*q*	—	—	21.0*q*	21.1*q*
C-1‴	—	—	—	—	—	170.2*s**	170.2*s*
C-2‴	—	—	—	—	—	21.0*q*	21.1*q*

*Interchangeable.

δ76.8 (*s*) and 76 (*s*) in the ^{13}C NMR spectrum could be assigned to an epoxy group connected to two tertiary carbon atoms: i.e. either at C-4,C-5 or C-4,C-11. The latter possibility for the epoxide was eliminated since the ^1H NMR spectrum of **3** exhibited doublets for the 12 and 13-methyl groups, establishing the presence of a proton on C-11.

Spectral properties demonstrated that compounds **4** and **5** had both a nonaromatic and an aromatic acyl function. The ^1H NMR spectra of **4** and **5** exhibited nearly identical signals for the sesquiterpene nucleus, including a doublet at δ4.89 (1H, J = 5 Hz, H-2) coupled with a multiplet at δ2.12 for cyclopentane ring protons; the corresponding ^{13}C NMR signals for this ring indicated that one of the acyl groups must be located at the C-2α position. A *dt* signal for one proton (J = 2.5, 9.5 and 10.5 Hz) in the ^1H NMR spectrum at *ca* δ5.4 is characteristic for the C-6β acyl geminal proton of *trans*-fused daucane skeletons [1, 2] and thus located the second acyl group at C-6α in **4** and **5**.

Inspection of Dreiding models for **4** and **5** showed that relative to the C-2α acyl group, the C-6α acyl moiety is closer to the isopropyl side chain. This supported the ^1H NMR-observable effect of C-6α acyl groups on the isopropyl moiety. That is, when the isopropyl methyl doublets for **4** and **5** were compared with those for jaeschkeanadiol acetate (**1a**), tingitanol (**21**) and tingitanol acetate (**21a**) [1, 2], it was evident that **4** and **5** have these doublets separated more (*ca* Δ0.13 ppm) than do those compounds which do not have an aromatic acyl group at the C-6α position (i.e. for **1a**, **21** and **21a**, $\Delta \leqslant 0.07$ ppm). These comparisons indicate that nonaromatic substitution at C-6α would not give a separation of the doublet signals as large as 0.13 ppm for the two isopropyl methyl groups. In accord with these data the aromatic acyl substitution of **4** and **5** should be C-6α. This assignment of C-6 aromatic acyl groups for **4** and **5** was verified by the partial hydrolysis of **5**, which afforded mainly **6** and a small amount of **7**. In the ^1H NMR spectrum of **6**, the H-6 proton signal shifted to δ3.96 (1H, *dt*, J = 2.5, 10 and

10.5 Hz, Δ1.37 ppm upfield), the aromatic group signals disappeared and, significantly, two doublets for the isopropyl methyls appeared near each other (δ0.93 and 0.91, each 3H, *d*, *J* = 6.5 Hz, Δ0.02 ppm).

The ^{1}H NMR spectrum of **5** contained the *p*-anisoyl signals similar to those observed for **1–3**; **4**, however, exhibited benzoyl signals in its spectrum. In addition, the ^{1}H NMR spectra of both **4** and **5** showed the acetyl methyl signal at δ2.07 (3H, *s*). Similar chemical shifts for the C-4 assymetric centre were observed for **1**, **4** and **5** when their ^{13}C NMR spectra were compared (see Table 1), suggesting the same stereochemistry at this centre (β-OH and α-isopropyl).

For compounds **8** ($[M]^+$ at *m/z* 388, $C_{23}H_{32}O_5$), **9** ($[M]^+$ at *m/z* 430, $C_{25}H_{34}O_6$), **10** ($[M]^+$ at *m/z* 440, $C_{27}H_{36}O_5$), **11** ($[M]^+$ at *m/z* 470, $C_{28}H_{38}O_6$) and **12** ($[M]^+$ at *m/z* 500, $C_{29}H_{40}O_7$), ^{1}H NMR spectra and spin decoupling experiments (as well as other spectral data) indicated that all had the same sesquiterpene nucleus. All ^{1}H NMR spectra (except for **8**) exhibited a doublet at *ca* δ4.95 for H-10 (*J* = 7 Hz) coupled with a broad doublet at *ca* δ5.8 (1H, *J* = 7 Hz, H-9); the first signal corresponds to an acyl geminal proton and indicated that C-10 was acylated in the α position for **9–12** and that **8** (δ3.86 for H-10) therefore represents the parent C-10 hydroxyl compound. As observed in the ^{1}H NMR spectra of **4** and **5**, the spectra of **8–12** contained a *dt* (1H, *J* = *ca* 2.5, 9.5 and 10.5 Hz) at *ca* δ5.45 assignable to a C-6β acyl geminal proton in a *trans*-fused daucene skeleton. In addition, well separated isopropyl methyl doublets (Δ0.15 ppm) indicated the presence of C-6α aromatic acyl groups in **8–12**. This assignment was confirmed since the ^{1}H NMR and mass spectral differences between **11** and its partial hydrolysis product **13** are similar to those observed between the spectra of compounds **5** and **6**.

Spectra indicated that at C-6 **8**, **9** and **11** were anisates and **10** and **12** were benzoate and veratrate, respectively. In addition, **10**, **11** and **12** were clearly substituted at C-10α with an angeloyl moiety; in contrast, **9** was substituted with an acetyl group at this position.

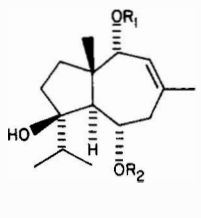
Compounds **14** ($[M]^+$ at *m/z* 446, $C_{25}H_{34}O_7$) and **15** ($[M]^+$ at *m/z* 488, $C_{27}H_{36}O_8$) exhibited similar ^{1}H NMR spectra except for the signals of the C-10 moiety. Decoupling experiments for **14** and **15** showed that a broad singlet at δ5.4 (1H), which could be attributed to the H-9 vinylic proton, interacted with a broad singlet at δ5.23 (1H, H-10) in **14** and δ4.34 (1H, H-10) in **15**. The downfield position of these latter signals indicated that both **14** and **15** were oxygenated at C-10; furthermore, the 0.89 ppm greater downfield shift observed for H-10 in **14** established the presence of an acylated hydroxyl group at C-10. Inspection of Dreiding models of **14** and **15** confirmed that a small coupling between H-9 and H-10 was only possible when the proton at C-10 was α; therefore, the C-10 acyl groups in **14** and **15** must be β.

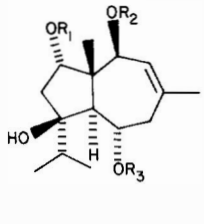
The ^{1}H NMR of **14** and **15** exhibited the same doublet at *ca* δ5.1 (1H, *J* = 5 Hz), similar to the doublets observed for H-2 in the spectra of **4** and **5**. This assignment indicated that both **14** and **15** had C-2α acyl groups. Also, the observation that the H-6 acyl geminal proton signal patterns for **14** and **15** were similar to those of **4** and **5** and **8–12**, combined with the spectral differences between **14** and its partial hydrolysis product **16**, and other characteristic ^{1}H NMR and mass spectral data indicated that **14** and **15** are C-6α anisates.

The mass and ^{1}H NMR spectra of **15** indicated that it had an acetyl moiety at C-2. Whilst the ^{1}H NMR spectrum of **14** clearly indicated two acetyl moieties at C-2 and C-10, the mass spectrum of **14** also supported two acetyl groups in addition to the C-6-α-*p*-anisoyl moiety. These assignments were confirmed when acetylation of **15** gave **14**.

Compounds **17** ($[M]^+$ at *m/z* 488, $C_{27}H_{36}O_8$) and **18** ($[M]^+$ at *m/z* 518, $C_{28}H_{38}O_9$) exhibited similar ^{1}H NMR spectra different in only a few aspects to the one recorded for **14**; these differences included a doublet at δ5.58 (1H, *J* = 6 Hz, H-9) instead of a broad singlet at δ5.4 (1H, H-9 in the spectrum of **14**) and a doublet at δ5.21 (1H, *J* = 6 Hz, H-10) instead of broad singlet at δ5.23 (1H, H-10 in the spectrum of **14**). The ^{1}H NMR data further indicated that the C-10 acyl group should be α as in compounds **9–12**. Other differences between the ^{1}H NMR spectra of **17** and **14** included the chemical shifts and coupling constants of the signals for the H-6 acyl geminal proton as well as the chemical shift of the signal for the H-5 proton. In the ^{1}H NMR spectrum of **17**, the H-6β proton signal appeared as a *ddd* at δ5.55 (1H, *J* = 4.4, 7.6 and 10.8 Hz) and H-5 at δ3.06 as a doublet (*J* = 10.8 Hz), while the signal for H-6 of **14** appeared at δ5.32 as a *dt* (1H, *J* = 2.5, 9.5 and 10.5 Hz). Indeed, the spectra of **17** and **18** exhibited elements of the spectra of both series **4–7** as well as **9–12** suggesting that **17** and **18** combined substitution patterns of both series. The ^{1}H NMR of **19**, the partial hydrolysis product of **17**, supported these assignments: the H-6 proton signal had shifted to δ4.16 and the coupling changed to a *dt* (1H, *J* = 2.3, 10.4 and 10.5 Hz); also the H-5 signal shifted to δ2.95 (1H, *d*, *J* = 10.5 Hz). In addition to these changes, the aromatic ring signals disappeared and the isopropyl methyl doublets collapsed to two close doublets (Δ0.02 ppm). Characteristic spectral properties established that **17** and **18** were *p*-anisate and veratrate, respectively, in addition to having acetyl groups at C-2 and C-10. Stereochemistry at the C-4 assymetric centre in **8–18** was confirmed by ^{13}C NMR data (Table 1), which when correlated with the ^{13}C NMR data for **1** showed a β-OH and an α-isopropyl group at C-4 in **8–18**.

The structure and stereochemistry of **17**, which were determined by spectral studies, has just been confirmed by X-ray crystallography [W. H. Watson *et al.*, personal communication]. This confirmation of structure, including stereochemistry for **17**, adds substantial support for the structures deduced for all the related daucane esters reported here.





8 R_1 = H, R_2 = *p*-Anisate

9 R_1 = Ac, R_2 = *p*-Anisate

10 R_1 = Ang, R_2 = Benzoate

11 R_1 = Ang, R_2 = *p*-Anisate

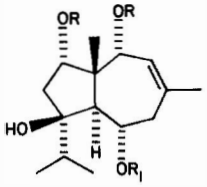
12 R_1 = Ang, R_2 = Veratrate

13 R_1 = Ang, R_2 = H

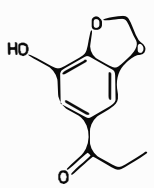
14 R_1 = R_2 = Ac, R_3 = *p*-Anisate

15 R_1 = Ac, R_2 = H, R_3 = *p*-Anisate

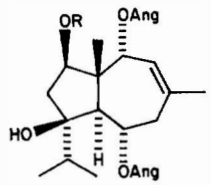
16 R_1 = R_2 = Ac, R_3 = H



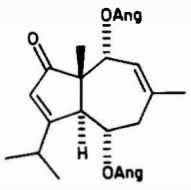
17 R = Ac, R_1 = *p*-Anisate
18 R = Ac, R_1 = Veratrate
19 R = Ac, R_1 = H



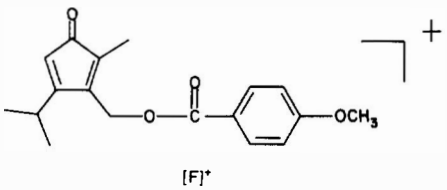
20



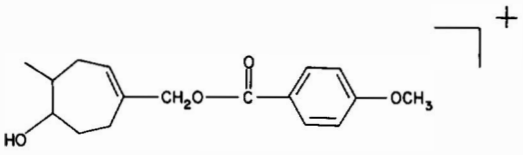
21 R = H
21a R = Ac



22



[F]$^+$



EXPERIMENTAL

General. Mps are uncorr. UV spectra were taken in $CHCl_3$ and ^{1}H NMR spectra in $CDCl_3$ (unless otherwise stated) at 200 MHz. ^{13}C NMR spectra were taken in $CDCl_3$ at 22.6 MHz. MS were obtained with a direct inlet system at 70 eV.

Plant material. Roots of *F. communis* were collected from the Atakoy area, near Istanbul in June 1983. A voucher specimen, identified by Dr. E. Tuzlaci (Istanbul), is deposited in the Herbarium of Faculty of Pharmacy, University of Istanbul (ISTE 50856).

Isolation of compounds. Dried and coarsely powdered roots (1.5 kg) were extracted with C_6H_6 in a Soxhlet. Concentrating the C_6H_6 extract *in vacuo* provided 70 g crude viscous oil. This oil (15 g) was chromatographed on a silica gel column (5 × 50 cm) packed in CH_2Cl_2 and eluted with a CH_2Cl_2–EtOAc gradient. Sephadex LH-20 columns packed in cyclohexane–CH_2Cl_2–EtOH (7:4:1 or 7:2:1) and/or prep. TLC (1.5 mm thickness, silica gel developed with cyclohexane–EtOAc mixtures, 4:1, 7:3 or 3:2) were used for further purification of the compounds.

Compound **2**. Gum (4 mg); UV λ_{max} nm (ε): 314 (sh) (310), 261 (12 840); IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 2990, 2940, 2895, 1720 (sh), 1710, 1660, 1610, 1585, 1518, 1260, 1175, 1120, 1100, 1040, 938 and 853. ^{1}H NMR: δ8.05 (2H, *d*, *J* = 8 Hz, H-3′ and H-7′), 6.96 (2H, *d*, *J* = 8 Hz, H-4′ and 6′), 5.89 (1H, *q*, *J* = 1 and 2.1 Hz, H-3), 5.59 (1H *br t*, H-9), 5.52 (1H, *ddd*, *J* = 3.2, 4.6 and 10.5 Hz, H-6), 3.89 (3H, *s*, H-8′), 3.35 (1H, *dd*, *J* = 2 and 10.5 Hz, H-5), 2.92 (1H, *br dd*, *J* = 4.6 and 15 Hz, H-7α), 2.57 (1H, *septet*, H-11), 2.29 (1H, *dd*, *J* = 3.2 and 15 Hz, H-7β), 1.78 (3H, *d*, *J* = 2 Hz, H-14), 1.26 (3H, *s*, H-15), 1.1 (3H, *d*, *J* = 6.5 Hz, H-12)* and 1.06 (3H, *d*, *J* = 6.5 Hz, H-13)*. MS *m/z* (rel. int.): 368 [M]$^+$ (1.7), 340 [M − CO]$^+$ (1.75), 300 [F]$^+$ (5.9), 290 (8.3), 234 [M − *p*-anisate + H]$^+$ (2.9), 216 [M − *p*-anisic acid]$^+$ (25.3, 201 (9.3), 191 [M − *p*-anisate − *iso*-Pr + H]$^+$ (8.3), 173 [M − *p*-anisic acid − *iso*-Pr]$^+$ (20.9), 159 (9.2), 152 [*p*-anisic acid]$^+$ (11.5), 135 [*p*-anisate]$^+$ (100), 83 (60.5).

Compound **3**. Gum (10 mg); UV λ_{max} nm (ε): 259 (15 550); IR ν_{max}^{KBr} cm^{-1}: 2960, 2940, 2880, 1710, 1648, 1608, 1580, 1512, 1455, 1372, 1319, 1260, 1170, 1104, 1036, 850 and 772. ^{1}H NMR: δ8.1 (2H, *d*, *J* = 8 Hz, H-3′ and H-7′), 6.93 (2H, *d*, *J* = 8 Hz, H-4′ and H-6′), 5.87 (1H, *br t*, H-9), 4.73 (2H, *br s*, H-14), 3.87 (3H, *s*, H-8′), 1.07 (3H, *d*, *J* = 6.5 Hz, H-12)*, 0.94 (3H, *d*, *J* = 6.5 Hz, H-13)* and 0.91 (3H, *s*, H-15). MS *m/z* (rel. int.): 370 [M]$^+$ (49.8), 355 [M − Me]$^+$ (10.1), 327 [M − *iso*-Pr]$^+$ (6.4), 289 [FA]$^+$ (11.4), 271 [FA − H_2O]$^+$ (14.3), 218 [M − *p*-anisic acid]$^+$ (78.3), 203 [M − *p*-anisic acid − Me − H_2O]$^+$ (53.5), 175 [M − *p*-anisic acid − *iso*-Pr]$^+$ (67.4), 152 [*p*-anisic acid]$^+$ (86.4), 135 [*p*-anisate]$^+$ (100), 121 (59), 107 (64.4), 92 (60.7).

Compound **4**. Gum (5 mg); UV λ_{max} nm (ε): 285 (sh) (1230), 273 (1730) and 246 (6250); IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3480, 2980, 2940, 2882, 1720, 1710, 1608, 1582, 1510, 1450, 1380, 1320, 1300, 1260, 1120, 1075, 1032 and 732. ^{1}H NMR: δ8.04 (2H, *dd*, *J* = 1 and 8.5 Hz, H-3′ and 7′), 7.59, (1H, *t d*, *J* = 1 and 8.5 Hz, H-5′), 7.48 (2H, *dt*, *J* = 1 and 8.5 Hz, H-4′ and H-6′), 5.55 (1H, *br t*, H-9), 5.47 (1H, *dt*, *J* = 2.1, 9.5 and 10.5 Hz, H-6), 4.89 (1H, *d*, *J* = 5.1 Hz, H-2), 2.53 (1H, *d*, *J* = 10.5 Hz, H-5), 2.28 (1H, *dd*, *J* = 2.1 and 15 Hz, H-7β), 2.07 (3H, *s*, H-2″), 1.84 (3H, *br s*, H-14), 1.13 (3H, *s*, H-15), 0.96 (3H, *d*, *J* = 6.5 Hz, H-12)* and 0.81 (3H, *d*, *J* = 6.5 Hz, H-13)*. MS *m/z* (rel. int.): 357 [M − *iso*-Pr]$^+$ (20.4), 297 [M − *iso*-Pr − HOAc]$^+$ (29.1), 218 [M − $C_6H_5CO_2H$ − HOAc]$^+$ (46.2), 175 [M − $C_6H_5CO_2H$ − HOAc − *iso*-Pr]$^+$ (46.2), 157 [M − $C_6H_5CO_2H$ − HOAc − H_2O]$^+$ (29.5), 147 (67.8), 122 [$C_6H_5CO_2H$]$^+$ (20.9), 105 [benzoate]$^+$ (95), 43 (64.6).

Compound **5**. Gum (105 mg); UV λ_{max} nm (ε): 261 (16 200); IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3480, 2980, 2960, 2890, 1725, 1710, 1610, 1585, 1515, 1382, 1308, 1260, 1175, 1108, 1038, 952, 938 and 855. ^{1}H NMR: δ7.99 (2H, *d*, *J* = 8.5 Hz, H-3′ and H-7′), 6.95 (2H, *d*, *J* = 8.5 Hz, H-4′ and H-6′), 5.53 (1H, *br t*, H-9), 5.33 (1H, *dt*, *J* = 2.5, 9.5 and 10 5 Hz, H-6), 4.89 (1H, *d*, *J* = 4.8 Hz, H-2), 3.88 (3H, *s*, H-8′), 2.51 (1H, *d*, *J* = 10.5 Hz, H-5), 2.27 (1H, *dd*, *J* = 2.5 and 14.5 Hz, H-7), 2.07 (3H, *s*, H-2″), 1.82 (3H, *br s*, H-14), 1.13 (3H, *s*, H-15), 0.94 (3H, *d*, *J* = 6.5 Hz, H-12)* and 0.81 (3H, *d*, *J* = 6.5 Hz, H-13)*. MS *m/z* (rel. int.): 387 [M − *iso*-Pr]$^+$ (13.9), 327 [M − HOAc-*iso*-Pr]$^+$ (74), 218 [M − *p*-anisic acid − HOAc]$^+$ (32.2), 203 [M − *p*-anisic acid − HOAc − Me]$^+$ (8), 175 [M − *p*-anisic acid − HOAc − *iso*-Pr]$^+$ (91.5), 157 [M − *p*-anisic acid − HOAc − *iso*-Pr − H_2O]$^+$ (16.3), 152 [*p*-anisic acid]$^+$ (45.2), 147 (53.1), 135 [*p*-anisate]$^+$ (100), 132, (75.2), 121 (38.1), 105 (61.3), 92 (43.4).

Partial hydrolysis of **5**. Compound **5** (30 mg) was treated with 1% NaOH in EtOH at room temp. After 2 hr, the reaction mixture was worked up in the usual manner. In addition to *p*-anisic acid, two hydrolysis products, **6** and **7**, were obtained after purification by Sephadex LH-20 column.

Compound **6**. Gum (11 mg). ^{1}H NMR: δ5.42 (1H, *br t*, H-9), 4 85 (1H, *dd*, *J* = 2 and 4.2 Hz, H-2), 3.96 (1H, *dt*, *J* = 2.5, 10

*Interchangeable.

and 10.5 Hz, H-6), 2.15 (1H, *d*, *J* = 10.5 Hz, H-5), 2.03 (3H, *s*, H-2″), 1.81 (3H, *br s*, H-14), 1.07 (3H, *s*, H-15), 0.93 (3H, *d*, *J* = 6.5 Hz, H-12)* and 0.91 (3H, *d*, *J* = 6.5 Hz, H-13)*. MS *m/z* (rel. int.): 253 $[M - iso\text{-}Pr]^+$ (1.42), 236 $[M - HOAc]^+$ (2.7), 218 $[M - HOAc - H_2O]^+$ (35), 203 $[M - HOAc - H_2O - Me]^+$ (11.9), 193 $[M - HOAc - iso\text{-}Pr]^+$ (74.6), 175 $[M - HOAc - iso\text{-}Pr - H_2O]^+$ (88.8), 157 $[M - HOAc - iso\text{-}Pr - 2 \times H_2O]^+$ (30.8), 147 (57.9), 133 (70.5), 121 (64.4), 105 (57), 71 (57.1).

Compound **7**. Amorphous solid (3 mg). ^{1}H NMR: δ5.72 (1H, *br t*, H-9), 4.05 (1H, *dt*, *J* = 2.5, 10 and 10.5 Hz, H-6), 3.79 (1H, *d*, *J* = 7.3 Hz, H-2), 2.52 (1H, *d*, *J* = 10.5 Hz, H-5), 1.82 (3H, *br s*, H-14), 1.03 (3H, *s*, H-15), 0.98 (6H, *d*, *J* = 6.5 Hz, H-12 and H-13). MS *m/z* (rel. int.): 254 $[M]^+$ (0.12), 236 $[M - H_2O]^+$ (3.7), 218 $[M - 2 \times H_2O]^+$ (17.9), 211 $[M - iso\text{-}Pr]^+$ (4.2), 200 $[M - 3 \times H_2O]^+$ (48.3), 185 $[M - 3 \times H_2O - Me]^+$ (52.1), 175 $(M - 2 \times H_2O - iso\text{-}Pr]^+$ (37.4), 157 $[M - 3 \times H_2O - iso\text{-}Pr]^+$ (100), 143 (55.3), 129 (73.9), 119 (52.8), 105 (59.8), 91 (60.4), 71 (48.8).

Compound **8**. Gum (7 mg); UV λ_{max} nm (ε); 260 (12340); IR ν_{max}^{KBr} cm^{-1}: 3480, 2978, 2935, 2875, 1700, 1605, 1580, 1505, 1450, 1378, 1260, 1150, 1100, 1030, 950, 840, 765, 690. ^{1}H NMR; δ7.98 (2H, *d*, *J* = 8.5 Hz, H-3′ and H-7′), 6.94 (2H, *d*, *J* = 8.5 Hz, H-4′ and H-6′), 5.76 (1H, *d*, *J* = 7 Hz, H-9), 5.44 (1H, *dt*, *J* = 3.8; 10.7 and 10.8 Hz, H-6), 3.88 (3H, *s*, H-8′), 3.86 (1H, *d*, *J* = 7 Hz, H-10), 2.83 (1H, *d*, *J* = 10.7 Hz, H-5), 2.27 (1H, *dd*, *J* = 3.8 and 14.5 Hz, H-7β), 1.84 (3H, *br s*, H-14), 1.14 (3H, *s*, H-15), 0.99 (3H, *d*, *J* = 6.5 Hz, H-12)* and 0.86 (3H, *d*, *J* = 6.5 Hz, H-13)*. MS *m/z* (rel. int.): 388 $[M]^+$ (0.2), 371 $[M - H_2O + H]^+$ (0.9), 345 $[M - iso\text{-}Pr]^+$ (14.1), 327 $[M - iso\text{-}Pr - H_2O]^+$ (23.1), 236 $[M - p$-anisic acid$]^+$ (16.5), 218 $[M - p$-anisic acid $- H_2O]^+$ (47), 203 $[M - p$-anisic acid $- H_2O - Me]^+$ (15.2), 201 $[M - p$-anisic acid $- 2 \times H_2O + H]^+$ (15.6), 193 $[M - p$-anisic acid $- iso\text{-}Pr]^+$ (51.3), 175 $[M - p$-anisic acid $- iso\text{-}Pr - H_2O]^+$ (83.4), 157 $[M - p$-anisic acid $- iso\text{-}Pr - 2 \times H_2O)$ (47.7), 152 $[p$-anisic acid$]^+$ (71.5), 135 $[p$-anisate$]^+$ (100), 119 (61.1), 107 (64.9), 92 (55.1).

Compound **9** Gum (7 mg); UV λ_{max} nm (ε): 262 (10840); IR ν_{max}^{KBr} cm^{-1}: 3480, 2960, 2930, 2880, 1720 (sh), 1710, 1608, 1585, 1510, 1458, 1375, 1258, 1170, 1120, 1103, 1030, 960, 850, 772 and 718. ^{1}H NMR; δ8.0 (2H, *d*, *J* = 8.5 Hz, H-3′ and H-7′), 6.94 (2H, *d*, *J* = 8.5 Hz, H-4′ and H-6′), 5.72 (1H, *br d*, *J* = 6.5 Hz, H-9), 5.42 (1H, *dt*, *J* = 2.5, 9.5 and 10.5 Hz, H-6), 4.9 (1H, *d*, *J* = 6.5 Hz, H-10), 3.88 (3H, *s*, H-8′), 2.76 (1H, *d*, *J* = 10.5 Hz, H-5), 2.26 (1H, *dd*, *J* = 2.5 and 14.5 Hz, H-7β), 2.09 (3H, *s*, H-2″), 1.82 (3H, *br s*, H-14), 1.19 (3H, *s*, H-15), 0.99 (3H, *d*, *J* = 6.5 Hz, H-12)* and 0.86 (3H, *d*, *J* = 6.5 Hz, H-13)*. MS: *m/z* (rel. int.) 430 $[M]^+$ (0.17), 387 $[M - iso\text{-}Pr]^+$ (3.4), 327 $[M - HOAc - iso\text{-}Pr]^+$ (15.9), 218 $[M - HOAc - p$-anisic acid$]^+$ (32.6), 175 $[M - HOAc - p$-anisic acid $- iso\text{-}Pr]^+$ (90.3), 157 $[M - HOAc - p$-anisic $- iso\text{-}Pr - H_2O]^+$ (38.1), 152 [p-anisic acid]$^+$ (64.4), 147 (58 4), 135 $[p$-anisate$]^+$ (100), 43 (94).

Compound **10**. Gum (82 mg); UV λ_{max} nm (ε): 282 (sh) (950), 274 (1190) and 246 (5990); IR ν_{max}^{KBr} cm^{-1}: 3510, 2962, 2940 (sh), 2880, 1710, 1650, 1605, 1588, 1455, 1388, 1320, 1278, 1238, 1162, 1120, 1045, 989, 960, 850 and 714. ^{1}H NMR: δ8.03 (2H, *dd*, *J* = 1 and 8.5 Hz, H-3′ and H-7′), 7.58 (1H, *td*, *J* = 1 and 8 5 Hz, H-5′), 7.46 (2H, *dt*, *J* = 1 and 8.5 Hz, H-4′ and H-6′), 6.12 (1H, *dq*, H-3″), 5.8 (1H, *br d*, *J* = 6.5 Hz, H-9), 5.48 (1H, *dt*, *J* = 2.5, 9.5 and 10.5 Hz, H-6), 4.95 (1H, *d*, *J* = 6.5 Hz, H-10), 2.81 (1H, *d*, *J* = 10.5 Hz, H-5), 2.25 (1H, *dd*, *J* = 2.5 and 15 Hz, H-7β), 2.05 (3H, *dd*, *J* = 1 and 6.5 Hz, H-4″), 1.98 (3H, *t*, H-5″), 1.83 (3H, *br s*, H-14), 1.23 (3H, *s*, H-15) 0.99 (3H, *d*, *J* = 6.5 Hz, H-12)* and 0.84 (3H, *d*, *J* = 6.5 Hz, H-13)*. MS *m/z* (rel. int.): 440 $[M]^+$ (0.3), 423 $[M - H_2O + H]^+$ (9.4), 341 $[M -$ angelic acid $+ H]^+$ (5.8), 323 $[M -$ angelic acid $- H_2O + H]^+$ (17.5), 319 $[M - C_6H_5CO_2H + H]^+$ (12.7), 301 $[M - C_6H_5CO_2H - H_2O + H]^+$ (7.63), 297 $[M -$ angelic acid $- iso\text{-}Pr]^+$ (14.4), 279 $[M -$ angelic acid $- iso\text{-}Pr - H_2O]^+$ (4.6), 275 $[M - C_6H_5CO_2H - iso\text{-}Pr]^+$ (28.1), 257 $[M - C_6H_5CO_2H - iso\text{-}Pr - H_2O]^+$ (15.4), 235 $[M - C_6H_5CO_2H -$ angelate$]^+$ (29.2), 219 $[M - C_6H_5CO_2H -$ angelic acid $+ H]^+$ (53.1), 201 $[M - C_6H_5CO_2H -$ angelic acid $- H_2O + H]^+$ (90.1), 175 $[M - C_6H_5CO_2H -$ angelic acid $- iso\text{-}Pr]^+$ (100), 132 (32.8), 122 $[C_6H_5CO_2H]^+$ (32.3), 105 [benzoate]$^+$ (29.2), 83 [angelate]$^+$ (70.5).

Compound **11**. Gum (134 mg); UV λ_{max} nm (ε): 261 (17750); IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3510, 2980, 2940, 2882, 1710, 1660, 1610, 1583, 1516, 1464, 1445, 1428, 1380, 1320, 1305, 1263, 1172, 1120, 1108, 1040, 960, 936 and 853. ^{1}H NMR: δ7.98 (2H, *d*, *J* = 8.5 Hz, H-3′ and H-7′), 6.95 (2H, *d*, *J* = 8.5 Hz, H-4′ and H-6′), 6.11 (1H, *dq*, H-3″), 5.79 (1H, *br d*, *J* = 7.5 Hz, H-9), 5.44 (1H, *dt*, *J* = 2.5, 9.5 and 10.5 Hz, H-6), 4.94 (1H, *d*, *J* = 7.5 Hz, H-10), 3.88 (3H, *s*, H-8′), 2.79 (1H, *d*, *J* = 10.5 Hz, H-5), 2.24 (1H, *dd*, *J* = 2 5 and 14.5 Hz, H-7β), 2 05 (3H, *dd*, *J* = 1 and 6.5 Hz, H-4″), 1.98 (3H, *t*, *J* = 1 Hz, H-5″), 1.81 (3H, *br s*, H-14), 1.22 (3H, *s*, H-15), 0.97 (3H, *d*, *J* = 6.5 Hz, H-12)* and 0.85 (3H, *d*, *J* = 6.5 Hz, H-13)*. MS *m/z* (rel. int.): 470 $[M]^+$ (0 1), 427 $[M - iso\text{-}Pr]^+$ (0.51), 327 $[M -$ angelic acid $- iso\text{-}Pr]^+$ (18.9), 275 $[M - p$-anisic acid $- iso\text{-}Pr]^+$ (12.5), 257 $[M - p$-anisic acid $- iso\text{-}Pr - H_2O]^+$ (3.93), 235 $[M - p$-anisic acid $-$ angelate$]^+$ (28.9), 218 $[M - p$-anisic acid $-$ angelic acid$]^+$ (57.6), 203 $[M - p$-anisic acid $-$ angelic acid $- Me]^+$ (22.2), 201 $[M - p$-anisic acid $-$ angelic acid $- H_2O]^+$ (26.5), 175 $[M - p$-anisic acid $-$ angelic acid $- iso\text{-}Pr]^+$ (91.5), 157 $[M - p$-anisic acid $-$ angelic acid $- iso\text{-}Pr - H_2O]^+$ (51.3), 152 $[p$-anisic acid$]^+$ (66.8), 147 (53.2), 135 $[p$-anisate$]^+$ (100), 83 [angelate]$^+$ (72.3).

Partial hydrolysis of **11**. Compound **11** (35 mg) was hydrolysed as described for **5**. After hydrolysis, **11** afforded compound **13** (12 mg).

Compound **13**. ^{1}H NMR: δ6.05 (1H, *dq*, H-3″), 5.74 (1H, *br d*, *J* = 7.9Hz, H-9), 4.93 (1H, *d*, *J* = 7.9 Hz, H-10), 4.08 (1H, *dt*, *J* = 2.5, 10.5 and 10.5 Hz, H-6), 2.47 (1H, *d*, *J* = 10.5 Hz, H-5), 2.18 (1H, *dd*, *J* = 2.5 and 14.5 Hz, H-7β), 2.01 (3H, *td*, *J* = 1 and 7 Hz, H-4″), 1.92 (3H, *t*, *J* = 1 Hz, H-5″), 1.81 (3H, *br s*, H-14), 1.13 (3H, *s*, H-15), 0.97 (3H, *d*, *J* = 6.5 Hz, H-12)* and 0.94 (3H, *d*, *J* = 6.5 Hz, H-13)*. MS *m/z* (rel. int.): 336 $[M]^+$ (0.12), 293 $[M - iso\text{-}Pr]^+$ (1.1), 275 $[M - iso\text{-}Pr - H_2O]^+$ (8.8), 257 $[M - iso\text{-}Pr - 2 \times H_2O]^+$ (6.8), 235 $[M -$ angelate $- H_2O]^+$ (16.3), 218 $[M -$ angelic acid $- H_2O]^+$ (30.9), 203 $[M -$ angelic acid $- H_2O - Me]^+$ (31), 193 $[M -$ angelic acid $- iso\text{-}Pr]^+$ (39.3), 175 $[M -$ angelic acid $- iso\text{-}Pr - H_2O]^+$ (100), 157 $[M -$ angelic acid $- iso\text{-}Pr - 2 \times H_2O]^+$ (62.6), 147 (60.5), 133 (64), 123 (76.3), 119 (74), 83 [angelate]$^+$ (81.8), 55 (86.2).

Compound **12**. Gum (15 mg); UV λ_{max} nm (ε): 295 (4220), 265 (11050); IR $\nu_{max}^{CHCl_3}$ cm^{-1} 3460, 2970, 2935, 2885, 1710 (sh), 1703, 1660, 1640, 1608, 1580, 1560, 1548, 1515, 1462, 1440, 1425, 1385, 1350, 1272, 1260, 1140, 1120, 1068, 1040, 960, 935, 880 and 850. ^{1}H NMR: δ7 68 (1H, *dd*, *J* = 2 and 8 5 Hz, H-7′), 7.54 (1H, *d*, *J* = 2 Hz, H-3′), 6.91 (1H, *d*, *J* = 8.5 Hz, H-6′), 6.11 (1H, *dq*, H-3″), 5.79 (1H, *br d*, *J* = 7.5 Hz, H-9), 5.42 (1H, *dt*, *J* = 2.5, 9.5 and 10 5 Hz, H-6), 4.94 (1H, *d*, *J* = 7 5 Hz, H-10), 3.96 (3H, *s*, H-8′)*, 3.93 (3H, *s*, H-9′)*, 2.8 (1H, *d*, *J* = 10 5 Hz, H-5), 2.27 (1H, *dd*, *J* = 2.5 and 14 5 Hz, H-7β), 2 05 (3H, *td*, *J* = 1 and 7 Hz, H-4″), 1.97 (3H, *t*, *J* = 1 Hz, H-5″), 1 83 (3H, *br s*, H-14), 1 23 (3H, *s*, H-15), 0.99 (3H, *d*, *J* = 6.7 Hz, H-12)* and 0.87 (3H, *d*, *J* = 6.7 Hz, H-13)*. MS *m/z* (rel. int.): 500 $[M]^+$ (0.24), 483 $[M - H_2O + H]^+$ (4.1), 401 $[M -$ angelic acid $+ H]^+$ (2.7), 383 $[M -$ angelic acid $- H_2O + H]^+$ (8.6), 357 $[M -$ angelic acid $- iso\text{-}Pr]^+$ (32 9), 319 $[M -$ veratric acid $+ H]^+$ (3.6), 275 $[M -$ veratic acid $- iso\text{-}Pr]^+$ (16.3), 257 $[M -$ veratric acid $- iso\text{-}Pr - H_2O]^+$ (7.2), 235 $[M -$ veratric acid $-$ angelate$]^+$ (45.6), 218 $[M -$ veratric acid $-$ angelic acid$]^+$ (55 2), 201 $[M -$ veratric acid $-$ angelic acid $- H_2O + H]^+$ (59.8), 182 [veratric acid]$^+$ (90.3), 175 $[M -$ veratric acid $-$ angelic acid $- iso\text{-}Pr]^+$, (86.4), 165 [veratrate]$^+$ (100), 157 $[M -$ veratric acid $-$ angelic acid $- iso\text{-}Pr - H_2O]^+$

(58.6), 132 (77.3), 121 (50.9), 119 (74.9), 107 (64.9), 83 [angelate]$^+$ (70.6).

Compound **14**. Gum (91 mg); UV λ_{max} nm (ε): 263 (13150); IR ν_{max}^{KBr} cm^{-1}: 3450, 2970, 2940, 2880, 2850, 1738, 1712, 1650, 1610, 1580 (sh), 1514, 1460, 1380, 1320, 1260, 1174, 1110, 1080, 1038, 970, 950, 852 and 778. ^{1}H NMR: δ7.98 (2H, *d*, J = 8.5 Hz, H-3′ and H-7′), 6.96 (2H, *d*, J = 8.5 Hz, H-4′ and H-6′), 5 51 (1H, *br s*, H-9), 5.32 (1H, *dt*, J = 2.1, 9.5 and 10.5 Hz, H-6), 5.23 (1H, *br s*, H-10), 5.09 (1H, *d*, J = 5.5 Hz, H-2), 3.88 (3H, *s*, H-8′), 2.64 (1H, *d*, J = 10.5 Hz, H-5), 2.27 (1H, *dd*, J = 2.1 and 14.5 Hz, H-7β), 2.02 (3H, *s*, H-2″), 2 (3H, *s*, H-2‴), 1.83 (3H, *br s*, H-14), 1.25 (3H, *s*, H-15), 0.96 (3H, *d*, J = 6.5 Hz, H-12)* and 0.81 (3H, *d*, J = 6.5 Hz, H-13)*. MS *m/z* (rel. int.): 488 [M]$^+$ (0.5), 471 [M − H_2O + H]$^+$ (23.7), 445 [M − *iso*-Pr]$^+$ (14.7), 429 [M − HOAc + H]$^+$ (7.8), 411 [M − HOAc − H_2O + H]$^+$ (6.6), 385 [M − HOAc − *iso*-Pr]$^+$ (19.6), 368 [M − 2 × HOAc]$^+$ (0.4), 337 [M − *p*-anisic acid + H]$^+$ (0.7), 325 [M − 2 × HOAc − *iso*-Pr]$^+$ (6.1), 319 [M − *p*-anisic acid − H_2O + H]$^+$ (4.9), 293 [M − *p*-anisic acid − *iso*-Pr]$^+$ (24.5), 277 [M − *p*-anisic acid − HOAc + H]$^+$ (30.8), 259 [M − *p*-anisic acid − HOAc − H_2O + H]$^+$ (35.2), 251 [M − *p*-anisic acid − acetate − *iso*-Pr + H]$^+$ (17.3), 233 [M − *p*-anisic acid − HOAc − *iso*-Pr]$^+$ (52.7), 217 [M − *p*-anisic acid − 2 × HOAc + H]$^+$ (56.4), 201 [M − *p*-anisic acid − 2 × HOAc − Me]$^+$ (33.7), 199 [M − *p*-anisic acid − 2 × HOAc − H_2O + H]$^+$ (38.1), 191 [M − *p*-anisic acid − HOAc − acetate − *iso*-Pr + H]$^+$ (45.7), 173 [M − *p*-anisic acid − 2 × HOAc − *iso*-Pr]$^+$ (51.9), 152 [*p*-anisic acid]$^+$ (45 2), 135 [*p*-anisate]$^+$ (100), 119 (50.3), 43 (52.4).

Partial hydrolysis of **14**. Compound **14** (30 mg) was hydrolysed as described for **5**. After hydrolysis, **14** yielded **16** (9 mg).

Compound **16**. ^{1}H NMR: δ5.42 (1H, *br s*, H-9), 5.12 (1H, *br s*, H-10), 5.04 (1H, *dd*, J = 2 and 4.2 Hz, H-2), 4.01 (1H, *dt*, J = 2.5, 10 and 10.5 Hz, H-6), 2.23 (1H, *d*, J = 10 Hz, H-5), 2 (3H, *s*, H-2″), 1.97 (3H, *s*, H-2‴), 1.81 (3H, *br s*, H-14) 1.18 (3H, *s*, H-15), 0.93 (3H, *d*, J = 6.5 Hz, H-12)* and 0.9 (3H, *d*, J = 6.5 Hz, H-13)*. MS *m/z* (rel. int.). 311 [M − *iso*-Pr]$^+$ (1.2), 294 [M − HOAc]$^+$ (3.4), 276 [M − HOAc − H_2O]$^+$ (11.2), 251 [M − HOAc − *iso*-Pr]$^+$ (87.2), 234 [M − 2 × HOAc]$^+$ (57.8), 216 [M − 2 × HOAc − H_2O]$^+$ (54.6), 201 [M − 2 × HOAc − H_2O]$^+$ (54 6), 201 [M − 2 × HOAc − H_2O − Me]$^+$ (15.8), 191 [M − 2 × HOAc − *iso*-Pr]$^+$ (77 3), 173 [M − 2 × HOAc − *iso*-Pr − H_2O]$^+$ (85.4), 149 (48.5), 145 (81.3), 135 (77.7), 121 (53.4), 71 (45.4), 43 (100)

Compound **15**. White prisms (23 mg) from hexane–EtOAc (3:1). Mp 152–4° UV λ_{max} nm (ε): 263 (11 720), IR ν_{max}^{KBr} cm^{-1}. 3460, 2965, 2930, 2875, 1703, 1672, 1603, 1580, 1510, 1468, 1440, 1420, 1380, 1315, 1275, 1258, 1170, 1128, 1100, 1085, 1033, 970, 932, 900, 850, 830, 770 and 700. ^{1}H NMR: δ7.97 (2H, *d*, J = 8.5 Hz, H-3′ and H-7′), 6.94 (2H, *d*, J = 8.5 Hz, H-4′ and H-6′), 5.39 (1H, *br s*, H-9), 5.28 (1H, *dt*, J = 2.5, 10.7 and 11.2 Hz, H-6), 5.08 (1H, *d*, J = 5 Hz, H-2), 4.34 (1H, *br s*, H-10), 3.88 (3H, *s*, H-8′), 2.52 (1H, *d*, J = 10 7 Hz, H-5), 2.22 (1H, *dd*, J = 2 5 and 14.5 Hz, H-7β), 2.12 (3H, *s*, H-2″), 1 84 (3H, *br s*, H-14), 1 17 (3H, *s*, H-15), 0.98 (3H, *d*, J = 6 5 Hz, H-12)* and 0.83 (3H, *d*, J = 6.5 Hz, H-13)*. MS *m/z* (rel. int.): 446 [M]$^+$ (0.25), 403 [M − *iso*-Pr]$^+$ (14 5), 386 [M − HOAc]$^+$ (0.6), 343 [M − HOAc − *iso*-Pr]$^+$ (16.9), 251 [M − *p*-anisic acid − *iso*-Pr]$^+$ (14.3), 234 [M − *p*-anisic acid − HOAc]$^+$ (34.8), 216 [M − *p*-anisic acid − HOAc − H_2O]$^+$ (37.5), 201 [M − *p*-anisic acid − HOAc − H_2O − Me]$^+$ (9.2), 191 [M − *p*-anisic acid − HOAc − *iso*-Pr]$^+$ (68.7), 173 [M − *p*-anisic acid − HOAc − H_2O]$^+$ (48.3), 163 (44.5), 152 [*p*-anisic acid]$^+$ (64.5), 148 (63 2), 135 [*p*-anisate]$^+$ (100), 120 (68.5), 105 (59.7), 92 (51), 77 (50.9), 71 (53), 43 (85 7).

† Partially obscured by one another

Acetylation of **15** (5 mg) with Ac_2O–C_5H_5N in the usual way, afforded **14**. Spectral properties of the product were found to be identical with our authentic sample

Compound **17**. Colorless tetragonal plates (90 mg) from hexane–EtOAc (3:1). Mp 155–156°. UV λ_{max} nm (ε): 263 (8200); IR ν_{max}^{KBr} cm^{-1}: 3520, 2975, 2940 (sh), 2885, 2860 (sh), 1739, 1720 (sh), 1693, 1650, 1608, 1580, 1465, 1442, 1380, 1320, 1302, 1258, 1172, 1130, 1103, 1080, 1031, 995, 850, 775 and 700. ^{1}H NMR: δ8.0 (2H, *d*, J = 8.5 Hz, H-3′ and H-7′), 6.96 (2H, *d*, J = 8.5 Hz, H-4′ and H-6′), 5.58 (1H, *br d*, J = 6 Hz, H-9)†, 5.55 (1H, *ddd*, J = 4.4, 7.6 and 10.8 Hz, H-6)†, 5.21 (1H, *br d*, J = 6 Hz, H-10), 5.03 (1H, *dd*, J = 2 and 6.5 Hz, H-2), 3.88 (3H, *s*, H-8′), 3.06 (1H, *d*, J = 10.8 Hz, H-5), 2.67 (1H, *dd*, J = 7.6 and 14.7 Hz, H-7α), 2.36 (1H, *dd*, J = 4.4 and 14.7 Hz, H-7β), 2.07 (3H, *s*, H-2″), 2.01 (3H, *s*, H-2‴), 1.86 (3H, *br s*, H-14), 1.22 (3H, *s*, H-15), 0.94 (3H, *d*, J = 6.7 Hz, H-12)* and 0.82 (3H, *d*, J = 6.7 Hz, H-13)*. MS *m/z* (rel. int.): 488 [M]$^+$ (0.4), 471 [M − H_2O + H]$^+$ (1.4), 445 [M − *iso*-Pr]$^+$ (3.3), 385 [M − HOAc − *iso*-Pr]$^+$ (12.5), 325 [M − 2 × HOAc − *iso*-Pr]$^+$ (5.5), 293 [M − *p*-anisic acid − *iso*-Pr]$^+$ (17.1), 276 [M − *p*-anisic acid − HOAc]$^+$ (9.3), 261 [M − *p*-anisic acid − HOAc − Me]$^+$ (4 7), 251 [M − *p*-anisic acid − acetate − *iso*-Pr + H]$^+$ (6.2), 233 [M − *p*-anisic acid − HOAc − *iso*-Pr]$^+$ (79.8), 216 [M − *p*-anisic acid − 2 × HOAc]$^+$ (60.9), 201 [M − *p*-anisic acid − 2 × HOAc − Me]$^+$ (14.2), 191 [M − *p*-anisic acid − HOAc − acetate − *iso*-Pr + H]$^+$ (66.5), 173 [M − *p*-anisic acid − 2 × HOAc − *iso*-Pr]$^+$ (85.8), 152 [*p*-anisic acid]$^+$ (70.3), 148 (63.8), 145 (76.9), 135 [*p*-anisate]$^+$ (100), 131 (48.6), 124 (54.3), 121 (69 1), 119 (73), 107 (66.7), 92 (61.7), 77 (52.9), 71 (59.2), 43 (93.6).

Partial hydrolysis of **17**. Compound **17** (34 mg) was hydrolysed as described for **5**. The product was **19** (11 mg).

Compound **19**. ^{1}H NMR: δ5.65 (1H, *br d*, J = 7 Hz, H-9), 5.11 (1H, *d*, J = 7 Hz, H-10), 4.92 (1H, *dd*, J = 1.1 and 5.8 Hz, H-2), 4.16 (1H, *dt*, J = 2.9, 10.3 and 10.5 Hz, H-6), 2.95 (1H, *d*, J = 10.3 Hz, H-5), 2.74 (1H, *dd*, J = 10.5 and 14 Hz, H-7α), 2.28 (1H, *septet*, H-11), 2.12 (1H, *dd*, J = 2.9 and 14 Hz, H-7β), 2.04 (3H, *s*, H-2″), 1 95 (3H, *s*, H-2‴), 1.81 (3H, *br s*, H-14), 1.1 (3H, *s*, H-15), 0.95 (3H, *d*, J = 6.8 Hz, H-12)* and 0.93 (3H, *d*, J = 6.8 Hz, H-13)*. MS *m/z* (rel. int): 354 [M]$^+$ (0.15), 294 [M − HOAc]$^+$ (4.8), 276 [M − HOAc − H_2O]$^+$ (11.6), 251 [M − HOAc − *iso*-Pr]$^+$ (30), 233 [M − HOAc − *iso*-Pr − H_2O]$^+$ (64), 216 [M − 2 × HOAc − H_2O]$^+$ (48.2), 201 [M − 2 × HOAc − H_2O − Me]$^+$ (30.6), 191 [M − 2 × HOAc − *iso*-Pr]$^+$ (79), 173 [M − 2 × HOAc − *iso*-Pr − H_2O]$^+$ (100), 163 (43.8), 145 (86.6), 135 (65.5), 131 (49.7), 121 (73.1), 107 (59.6), 95 (61.2), 71 (65.2), 43 (82.6).

Compound **18**. Gum (6 mg), UV λ_{max} nm (ε): 297 (3210) and 268 (6150); IR ν_{max}^{KBr} cm^{-1}: 3445, 2960, 2935, 2865, 1738, 1715, 1700 (sh), 1650, 1640, 1608, 1580, 1560, 1540, 1520, 1460, 1420, 1380, 1300 (sh), 1275, 1260, 1230, 1185, 1142, 1115, 1080, 1035, 965, 880, 770 and 700 ^{1}H NMR: δ7.68 (1H, *dd*, J = 2 and 8.5 Hz, H-7′), 7.56 (1H, *d*, J = 2 Hz, H-3′), 6.93 (1H, *d*, J = 8.5 Hz, H-6′), 5.59 (1H, *br d*, J = 6 Hz, H-9)†, 5.56 (1H, *ddd*, J = 3.2, 6.5 and 10.7 Hz, H-6)†, 5 21 (1H, *br d*, J = 6 Hz, H-10), 5.04 (1H, *dd*, J = 2 and 6.5 Hz, H-2), 3.97 (3H, *s*, H-8′)*, 3.95 (3H, *s*, H-9′)*, 3.07 (1H, *d*, J = 10.7 Hz, H-5), 2.77 (1H, *dd*, J = 6.5 and 14 3 Hz, H-7α), 2.37 (1H, *dd*, J = 3.2 and 14.3 Hz, H-7β), 2.08 (3H, *s*, H-2″), 2.02 (3H, *s*, H-2‴), 1.88 (3H, *br s*, H-14), 1 23 (3H, *s*, H-15), 0.96 (3H, *d*, J = 6.5 Hz, H-12)* and 0.83 (3H, *d*, J = 6 5 Hz, H-13)*. MS *m/z* (rel. int.). 518 [M]$^+$ (0.7), 475 [M − H_2O]$^+$ (2.1), 428 [M − HOAc − 2 × Me]$^+$ (8), 415 [M − HOAc − *iso*-Pr]$^+$ (7 7), 355 [M − 2 × HOAc − *iso*-Pr]$^+$ (2.9), 293 [M − veratric acid − *iso*-Pr]$^+$ (9.8), 276 [M − veratric acid − HOAc]$^+$ (5.7), 261 [M − veratric acid − HOAc − Me]$^+$ (2.9), 251 [M − veratric acid − acetate − *iso*-Pr + H]$^+$ (3 9), 233 [M − veratric acid − HOAc − *iso*-Pr]$^+$ (63.3), 216 [M − veratric acid − 2 × HOAc]$^+$ (34.9), 201 [M − veratric acid − 2 × HOAc − Me]$^+$ (9.6), 191 [M − veratric acid − HOAc − acetate − *iso*-Pr + H]$^+$ (49.9), 182

[veratric acid]$^+$ (89.3), 173 [M − veratric acid − 2 × HOAc − *iso*-Pr]$^+$ (80.1), 165 [veratrate]$^+$ (100), 148 (54.7), 145 (68.2), 135 (61.5), 121 (67.6), 119 (62.6), 105 (48), 95 (49.4), 79 (49.3), 71 (55.3) and 43 (76.2).

Acknowledgements—This work was supported by grants from the Scientific and Technical Research Council of Turkey (TUBITAK) (Grant TBAG-580 to M.M.) and the Robert A. Welch Foundation (Grant F-130) and the National Institutes of Health (Grant HDO-4488) to T.J M

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Phytochemistry, Vol. 25, No. 7, pp. 1673–1675, 1986.
Printed in Great Britain.

0031–9422/86 $3.00 + 0.00
Pergamon Journals Ltd.

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

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(*Received* 8 *November* 1985)

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

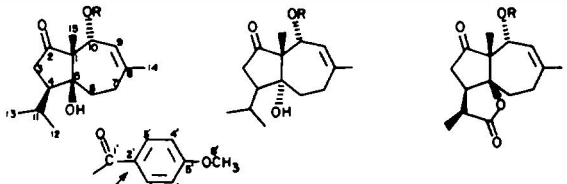
Abstract—Together with the known daucene ester 14-*p*-anisoyloxy-dauc-4,8-diene, a new ester, fercomin and the first known daucane-γ-lactone, fercolide, were isolated from *Ferula communis* subsp. *communis*. Structures for these compounds were elucidated on the basis of their spectral properties and 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

(10605); IR ν_{max}^{KBr} cm^{-1}: 3062, 2930, 1775, 1746, 1710, 1608, 1510, 1260, 1170, 1100, 1080, 980, 940, 850, 772; ^{1}H 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).

Acknowledgements—We thank Dr. M. Holub (Prague, Czechoslovakia) for a sample of daucol, Dr. L. H. Zalkow (Atlanta, GA, U.S.A.) for carotol and Dr. D. F. Wiemer (Iowa City, IA, U.S.A.) for ^{13}C NMR spectra of lasidiol angelate and lasidiol ketone. This work was supported by grants from the scientific and Technical Research Council of Turkey (TUBITAK) (Grant TBAG-580 to M.M.) and the Robert A. Welch Foundation (Grant F-130) and the National Institutes of Health (Grant 9 ROI GM-35710-21) to T.J.M.

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Journal of Natural Products
Vol. 49, No. 5, pp. 916-918, Sep-Oct 1986

FERCOPEROL, AN UNUSUAL CYCLIC-ENDOPEROXYNEROLIDOL DERIVATIVE FROM *FERULA COMMUNIS* SUBSP. *COMMUNIS*

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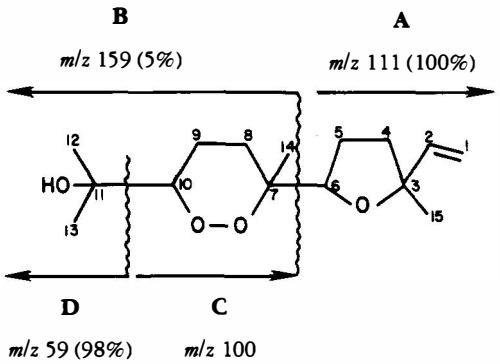
We have previously reported several daucane aromatic esters and a daucane-γ-lactone from the roots of *Ferula communis* L. subsp. *communis* (Apiaceae) (1,2), and we now describe from the same extract an unusual minor component fercoperol (**1**).

F. communis is a well-known ancient medicinal plant that has been used, for example, as an antidysenteric agent (3). Fercoperol (**1**) with its polyoxygenated endoperoxy moiety might have amoebicidal activity inasmuchas other endoperoxy-type sesquiterpenes, such as qinghaosu and yingzhaosu A, have antiparasitic activity (4,5). Notably, qinghaosu and its derivatives are used for the succesful treatment of different types of malaria. Strong antimicrobial effects have also been observed for cyclic-nerolidol derivatives (6).

To date cyclic-nerolidol derivatives are known only from species of the Compositae family, especially *Artemisia* (7-10), *Tanacetum* (6,11), and *Osmanthus* (12).

Fercoperol (**1**) did not exhibit a molecular ion in the eims; however, in its cims a molecular ion was observed at *m/z* 271 $[M+H]^+$ ($C_{15}H_{26}O_4$), which is in accord with a sesquiterpene skeleton. The ir spectrum of **1** showed absorption bands for a tertiary hydroxyl (3440 cm^{-1}, sharp) and a terminal vinyl (1645, 923 cm^{-1}).

The ^{1}H-nmr spectrum of **1** exhibited doublets of doublets for three vinylic proton at δ 5.87 (1H, J=10.6 and 17.2 Hz, H-2), 5.18 (1H, J=1.5 and 17.2 Hz, H-1), and 5.02 (1H, J=1.5 and 10.6 Hz, H-1′); double resonance experiments indicated that these three protons belonged to an isolated terminal vinylic group. The ^{1}H nmr also showed signals for two protons geminal to oxygen at δ 4.5 (1H, brt, J=6.3 Hz, H-6) and 3.88 (1H, dd, J=3.2 and 10.2 Hz, H-10), as well as a ddd signal at δ 2.28



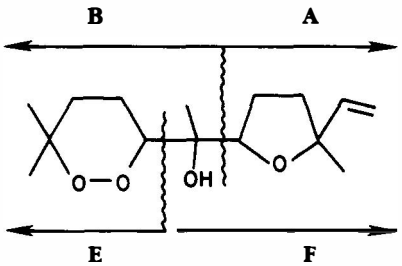
1

(1H, J=4.6, 5.8 and 14.3 Hz, H-8), four tertiary methyl signals at δ 1.31, 1.22, 1.17, 1.07 (each 3H, s, H-15, H-13, H-12, and H-14), and the remaining signals for two complex multiplets at δ 1.93 (3H) and 1.62 (4H). Double resonance experiments starting from protons geminal to oxygen indicated the presence of two isolated -O-CH-CH_2-CH_2-moieties.

Under mild conditions, **1** was not acetylated; consequently, no primary or secondary hydroxyl function is present. Also, the absence of carbonyl absorptions in the ir spectrum of **1** eliminated the presence of lactone and/or ester moieties. The ^{1}H-nmr spectrum showing two protons geminal to oxygen and a downfield tertiary methyl group confirmed the presence of two endocyclic ether groups in **1**.

Fercoperol (**1**) developed a rust-red color with acidic ammonium thiocyanate-ferrous ammonium sulfate (13) on tlc as expected for the presence of peroxy functional group(s). The lack of a hydroperoxy proton signal in its ^{1}H-nmr spectrum (14,15) and specific fragmentations in its eims indicated that one of the endocyclic ethers should be an endoperoxy group (16). The eims of **1**, together with ^{1}H-nmr data, indicated that the other endocyclic ether group should be part of a terminal 5-methyl-5-vinyltetrahydrofuran moiety; this moiety is the source of the fragment at *m/z* 111.

On the basis of the above spectral data, two structures, **1** and **2**, could be assigned to fercoperol. The presence of an abundant *m/z* 59 (98%), as well as the absence of **E**, **E**-H_2O, and **F** fragments in its ei- or cims (17,18) strongly suggest that the structure of fercoperol is **1** (no stereochemical assignments).



2

EXPERIMENTAL

The roots of *F. communis* were collected in June 1983, near Istanbul, Turkey (ISTE 50856). A voucher specimen is deposited in the Herbarium of the Faculty of Pharmacy, University of Istanbul, Turkey. The air-dried root material (1.5 kg) was coarsely powdered, extracted, and worked up as previously described (1). For the isolation of fercoperol (**1**), a portion of the fraction eluted from the silica gel column with CH_2Cl_2-EtOAc (7:3) was rechromatographed on silica gel plates (1.5-mm thickness) using cyclohexane-EtOAc (8:2, double development) to yield 7 mg of **1**.

FERCOPEROL (**1**).—Compound **1** $C_{15}H_{26}O_4$, is a gum; ir ν max $CHCl_3$ cm^{-1} 3440 (OH), 1645, 1125, 923 (-CH=CH_2); ^{1}H nmr (200 MHz, $CDCl_3$, TMS), see text; eims (probe, 70 eV) *m/z* (rel. int.) 253 [M-OH]$^+$ (0.8), 211 [M-**D**]$^+$ (1.4), 159 [**B**]$^+$ (5), 141 [**B**-H_2O]$^+$ (14), 123 [**B**-2XH_2O]$^+$ (13), 111 [**A**]$^+$ (100), 101 [**C**+H]$^+$ (38), 93 [**A**-H_2O]$^+$ (90), 83 [**C**-H_2O+H]$^+$ (70), 59 [**D**]$^+$ (98), 55 (95); cims (iso-C_4H_{10}) *m/z* (rel. int.) 271 [M+H]$^+$ (38), 253 [271-H_2O]$^+$ (12), 111 [**A**]$^+$ (100), 143 [253-**A**+H]$^+$ (20).

ACKNOWLEDGMENTS

This work was supported by grants from the Scientific and Technical Research Council of Turkey (TUBITAK) (Grant TBAG-580) to M. Miski, the National Institutes of Health (Grant GM-35710), and the Robert A. Welch foundation (Grant F-130) to T.J. Mabry.

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Received 20 January 1986