Daucane Sesquiterpenes from *Ferula hermonis*

Amélie Lhuillier,[†] Nicolas Fabre,*[,†] Edmond Cheble,[‡] Fathi Oueida,[‡] Séverine Maurel,[†] Alexis Valentin,[†] Isabelle Fourasté,[†] and Claude Moulis[†]

UMR-152 Laboratoire de Pharmacochimie des Substances Naturelles et Pharmacophores Redox, Faculté des Sciences Pharmaceutiques, Université Paul Sabatier, 35 Chemin des Maraîchers, F-31062 Toulouse, France, and Faculté de Pharmacie, Université Libanaise, BP 14/6573 Beyrouth, Lebanon

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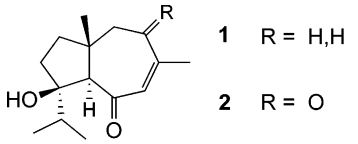
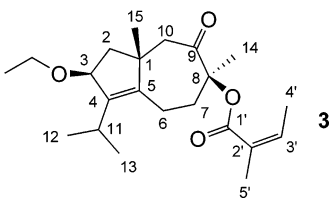
The dried roots of *Ferula hermonis* yielded three new daucanes, (1*R*,4*R*)-4-hydroxydauca-7-ene-6-one (**1**), (1*R*,4*R*)-4-hydroxydauca-7-ene-6,9-dione (**2**), and (1*R*,3*S*,8*S*)-3-ethoxy-8-angeloyloxydauca-4-en-9-one (**3**), together with the three known sesquiterpenes, ferutinin, teferidin, and (+)-α-bisabolol. The structures of compounds **1**−**3** were elucidated on the basis of spectroscopic evidence. The effect of these compounds on the proliferation of estrogen-dependent MCF-7 cells was evaluated, and it was found that compounds **1** and **3** exhibited proliferative activity, whereas **2** showed an antiproliferative effect.

Ferula (Umbelliferae) is a large genus of about 130 species distributed throughout the Mediterranean area and Central Asia.[1] Several species have been used in folk medicine. *Ferula hermonis* Boiss. is used in the Middle East as an aphrodisiac and is promoted as a natural alternative to Viagra despite concerns about its safety.[2] This genus is well documented as a good source of biologically active compounds such as sesquiterpene coumarins,[3,4] terpene alcohols, and sesquiterpene derivatives (especially daucanes, humulanes, himachalanes, and guaianes).[5−9] Previous chemical studies on *F. hermonis* showed that the main components are sesquiterpenes of the daucane type. It was reported to contain, as its main component, the *p*-hydroxybenzoate of jaeschkeanadiol (ferutinin) and other derivatives such as jaeschkeanadiol, jaeschkeanadiol benzoate, jaeschkeanadiol vanillate (teferidin), 8,9-epoxy-jaeschkeanadiol, 8,9-epoxy-jaeschkeanadiol benzoate, 14-(4′-hydroxybenzoyloxy)dauc-4,8-diene, and 14-(4′-hydroxy-3′-ethoxybenzoyloxy)dauc-4,8-diene.[10−14] We describe here the isolation and characterization of three new daucanes (**1**−**3**) and the isolation of the known compounds ferutinin, teferidin, and (+)-α-bisabolol.[10] Four of these compounds were evaluated for their effects on the proliferation of MCF-7 human breast cancer cells.



1 R = H,H

2 R = O



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Ferutinin, teferidin, and (+)-α-bisabolol have been isolated previously from *F. hermonis*, and their structures were identified by comparison of their spectral data with literature values.[13−15]

Compound **1** showed a quasi-molecular ion peak at *m/z* 237.1886 $[M + H]^+$ in its ESIMS; a molecular formula of $C_{15}H_{25}O_2$ with a precision of 2.5 ppm was deduced. The IR spectrum displayed absorptions corresponding to hydroxyl (3437 cm^{-1}) and α,*β*-unsaturated carbonyl (1642 cm^{-1}) functions. Along with the fragment at *m/z* 219 ($[M + H]^+ - H_2O$) in its mass spectrum, this confirmed that **1** has a hydroxyl group. The ^{13}C NMR spectra of **1** revealed 15 carbon resonances, suggesting a sesquiterpene skeleton for this natural product. Sesquiterpenes from the genus *Ferula* are mainly of the daucane type, which suggested that **1** might be also of this type. The occurrence of an isopropyl group [δ_H 1.80 (1H, sept., $J = 6.7$ Hz), 0.91 (3H, d, $J = 6.7$ Hz) and 0.93 (3H, d, $J = 6.7$ Hz)] and a methyl (δ_H 1.17) was indicated by the ^1H NMR spectrum. The ^{13}C NMR spectrum showed the presence of three quaternary carbon signals at δ_C 43.8, 86.2, and 158.2, a methyl signal at δ_C 22.7, and a methine signal at δ_C 62.8. These signals were very similar to those of ferutinin, which confirmed **1** to be a daucane-type sesquiterpene with characteristic signals of hydroxyl and isopropyl groups located at C-4. The four methylene carbon signals at δ_C 40.8, 35.4, 32.8, and 40.1 were similar to those of structurally related compounds;[16] the multiplets at δ_H 1.70, 1.90, 2.45, 1.93, and 1.75 were assigned to H-2*β*, H-3, H-9, H-10α, and H-10*β*, respectively, and the doublet of triplets to H-2α. The ^1H NMR spectrum also showed a vinyl methyl at δ_H 1.98 (d, $J = 1.1$ Hz) coupled to an olefinic proton at δ_H 5.92 (d, $J = 1.1$ Hz) as deduced from the COSY experiment. The remaining assignment in the structure of **1** was the location of the α,*β*-unsaturated ketone. The ^1H NMR signal assigned to H-5 was a singlet (Table 1), and the absence of coupling for H-5 in **1** suggested that the carbons adjacent to C-5 were quaternary. Indeed, H-5 showed couplings with the C-6 protons as in ferutinin (δ_{H-5} 2.01 (1H, d, $J = 10.5$ Hz)).[14] Thus, the ketone was located at C-6 and the double bond was placed between C-7 and C-8. HMBC data confirmed the assignments of the NMR signals for compound **1**. To establish the relative configuration, the methyl group C-15 was assumed to be in the *β*-position, because this methyl group is always *β* in the daucane-type compounds isolated from *Ferula* species.[3,7] The absence of a correlation between Me-15 and H-5 in the NOESY spectrum established H-5 as α. In addition, the correlation of H-5 with H-11 showed that the configuration of the isopropyl group is α, while

* To whom correspondence should be addressed. Tel: +33-5-6225-6848. Fax: +33-5-6155-4330. E-mail: nfabre@cict.fr.
[†] Université Paul Sabatier.
[‡] Université Libanaise.

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Table 1. ^{1}H NMR and ^{13}C NMR Data for Compounds **1**−**3** (in $CDCl_3$)

	1[a]			**2**[a]			**3**[b]		
position	δ_H	δ_C	HMBC	δ_H	δ_C	HMBC	δ_H	δ_C	HMBC
1		43.8	2, 3, 5, 9, 10, 15		42.9	2, 3, 5, 10, 15		46.1	2, 10, 15
2 (α)	1.46 dt (12.3, 10.2)	40.8	1, 3, 10, 15	1.58 m	40.9	3, 5, 10, 15	2.11 dd (13.4, 6.3)	40.4	1, 3, 4, 5, 15
2 (*β*)	1.70 m			1.83 m			1.72 brd (13.4)		
3	1.90 m	35.4	2, 5, 4	1.85 m	34.4	2, 11	4.18 d (6.3)	82.2	1″, 2, 4, 5
4		86.2	3, 5, 11, 12, 13		86.7	5, 11, 12, 13		142.9	2, 3, 11, 12, 13
5	2.59 s	62.8	1, 4, 6, 7, 10, 15	2.82 s	63.8	2, 3, 10, 15		145.2	2, 3, 6, 7, 10, 15
6 (α)		205.3	5		203.0	5, 7	2.44 ddd (2.8, 5.0, 13.5)	19.2	5, 7
6 (*β*)							2.21 td (2.2, 13.5)		
7 (α)	5.92 d (1.1)	130.3	5, 9, 14	6.34 d (1.4)	135.2	5, 6, 9, 14	2.24 ddd (2.2, 5.0, 14.4)	40.5	5, 6, 14
7 (*β*)							1.29 td (2.8, 13.7)		
8		158.2	9, 14		148.5	10, 14		85.9	10, 14
9	2.45 m	32.8			201.1	7, 10, 14		206.5	10, 14
10 (α)	1.93 m	40.1	1, 5, 9, 15	2.89 s	58.9	1, 2, 9, 15	2.24 d (12.0)	45.4	1, 5, 8, 9, 15
10 (*β*)	1.75 m						2.72 d (12.0)		
11	1.80 h (6.7)	38.7	4, 12, 13	1.84 h (11.5)	38.0	4, 12, 13	2.58 h (7.0)	26.7	3, 4, 12, 13
12	0.91 d (6.7)	18.4	4, 11, 13	0.89 d (11.5)	18.4	4, 11, 13	1.01 d (7.0)	22.2	4, 11, 13
13	0.93 d (6.7)	18.0	4, 11, 12	0.91 d (11.5)	18.0	4, 11, 12	1.07 d (7.0)	21.8	4, 11, 12
14	1.98 d (1.1)	28.9	7, 8, 9	2.05 d (1.4)	21.6	7, 9	1.49 s	21.7	
15	1.17 s	22.7	1, 2, 3, 5, 10	1.26 s	23.0	3, 5, 10	1.21 s	30.2	1, 2, 5
OH	5.17 s			4.45 s					
1′								167.7	5′
2′								127.5	4′, 5′
3′							6.18 qq (7.3, 1.4)	139.4	4′ 5′
4′							2.03 dq (7.3, 1.4,)	15.8	2′, 3′
5′							1.97 t (1.4)	20.6	1′, 2′, 3′
O*CH*$_2$CH$_3$							3.36 ddd (9.2, 7.0, 14.0)	64.6	3, OCH$_2$*CH*$_3$
							3.56 ddd (9.2, 7.0, 14.0)		
OCH$_2$*CH*$_3$							1.15 t (7.0)	15.8	O*CH*$_2$CH$_3$

[a] The ^{1}H and ^{13}C NMR spectra were measured at 400 and 100 MHz, respectively. [b] The ^{1}H and ^{13}C NMR spectra were measured at 500 and 125 MHz, respectively.

OH-4 is *β*. The structure of **1** was thus established as 4*β*-hydroxy-5α*H*-dauca-7-en-6-one.

Compound **2** showed a quasi-molecular ion at *m/z* 251.1655 $[M + H]^+$ in the HRESMS, in agreement with the formula $C_{15}H_{23}O_3$ (3.0 ppm). The ^{1}H and ^{13}C NMR spectra of **2** exhibited close similarities to those of compound **1** except for the presence of two ketone signals (δ_C 203.0 and 201.1) in the daucane skeleton. The IR spectrum supported the presence of carbonyl and hydroxyl groups at 1656 and 3478 cm^{-1}, respectively. The second keto group was placed at C-9 based on HMBC experiments (Table 1). The relative configuration of **2** was based on the NOESY spectrum. Thus, the structure of compound **2** was determined as 4*β*-hydroxy-5α*H*-dauca-7-ene-6,9-dione. This compound was recently described as a synthetic product from ferutinin.[17]

The ESIMS of **3** exhibited a quasi-molecular ion at *m/z* 363.2535 $[M + H]^+$ and a second diagnostic ion at *m/z* 317.2116 that appeared as base peak. These results are consistent with respective elemental compositions of $C_{22}H_{35}O_4$ (5.0 ppm) and $C_{20}H_{29}O_3$ (28.0 ppm) and suggested a neutral loss of EtOH (loss of *m/z* 46.0419 consistent with C_2H_6O at a precision of 7.1 ppm). In the ^{13}C NMR and ^{1}H NMR spectra of **3**, the previously described characteristic signals of a daucane-type sesquiterpene (an isopropyl, two methyls) were evident. The absence of a proton signal at C-5 suggested the presence of a double bond between C-4 and C-5. The ^{1}H NMR spectrum of **3** showed the presence of an unusual ethoxy group [δ_H 1.15 (3H, t, J = 7.0 Hz), 3.36 (1H, ddd, J = 7.0, 9.2, 14.0 Hz), 3.56 (1H, ddd, J = 7.0, 9.2, 14.0 Hz)]. The ^{13}C NMR spectrum revealed the presence of a ketone group (δ_C 206.5) and an ester carbonyl (δ_C 167.7). On the basis of these findings, compound **3** was assumed to be a daucane-type sesquiterpene substituted by an ethoxy and an ester group. The structure of the ester moiety was determined on the basis of ^{1}H NMR, ^{13}C NMR, and 2D NMR analysis to be an angeloyl moiety [δ_H 1.97 (3H, t, J = 1.4 Hz), 2.03 (3H, dq, J = 1.4, 7.3 Hz), 6.18 (1H, qq, J = 1.4, 7.3 Hz); δ_C 15.8 (CH_3), 20.6 (CH_3), 127.5 (C) 139.4 (CH), 167.7 (COO)] as opposed to a tigloyl moiety. Tigloyl methyl groups normally appear at higher field in the ^{13}C NMR spectrum (ca. δ_C 13.0 and 15.0, respectively).[18] The location of the ethoxy group at C-3 was determined on the basis of the HMBC coupling between C-3 and the methylene of the ethoxy moiety. The HMBC spectrum also showed correlations of C-9 and H-10 and C-9 and H-14 that confirmed the presence of the ketone at C-9. It also indicated that a methyl group at C-14 (δ_C 21.7) was attached to a quaternary carbon with an oxygen function (δ_C 85.9). The position of the angeloyl at C-8 was deduced from the comparison of its ^{13}C NMR spectrum with that of a very similar compound, the angelate derivative of webdiol.[19] This comparison also supported the presence of a double bond between C-4 and C-5. The relative configuration of **3** was assigned by the observation of correlations in the NOESY spectrum (Figure 1). Compound **3** showed a $J_{H3-H2\alpha}$ = 6.3 Hz in the ^{1}H NMR spectrum corresponding to a *syn* configuration. NOESY correlations of H-15 with H-2*β* and H-10*β*, H-3 with H-2α, and H-10α with H-14 showed that H-3, H-10α, H-2α, and H-14 are α while H-15, H-2*β*, and H-10*β* are *β*. Furthermore, the correlations of H-15 with H-5′ and H-14 with H-4′ confirmed the relative configuration of **3**. The structure of compound **3** was determined as 3α-ethoxy-8*β*-angeloyloxydauca-4-en-9-one.

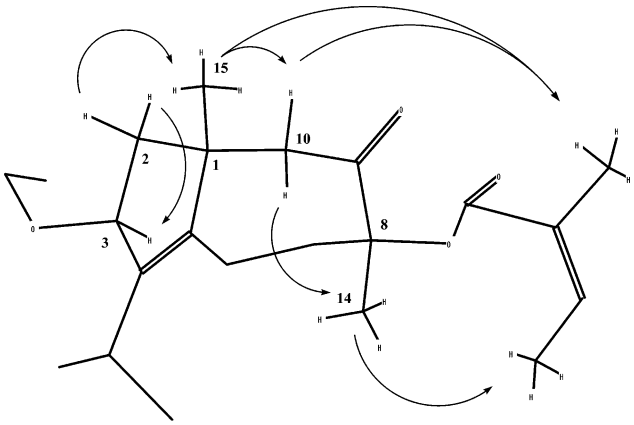

Figure 1. Spatial correlations observed in the NOESY spectrum of **3**.

The ethoxy group is a very unusual substituent among natural compounds. To verify that **3** was not an artifact, its presence was confirmed in a crude hexane extract of *F. hermonis* by HPLC and by the mass spectrometry of this directly introduced crude extract.

The absolute configurations of compounds **2** and **3** were established by their CD spectra. The chromophoric groups gave rise to an absorption band around 250 nm for these daucene compounds. The CD spectrum of **2** showed a negative Cotton effect ($\Delta\epsilon_{239}$ −7.08), as can be predicted by the back octant rule.[20] In accord with the previously reported NOESY spectrum, Me-15 lies in the upper right (−) octant due to its pseudoaxial orientation, while the remaining substituents surrounding the carbonyl chromophore lie close to the carbonyl plane and, therefore, exert low "weight" to the Cotton effect. Compound **3** showed a similar CD spectrum with a negative Cotton effect ($\Delta\epsilon_{233}$ −3.68), as can be predicted by the back octant rule. The CD spectrum of the daucone, also a daucane compound, is similar, with a negative Cotton effect ($\Delta\epsilon_{315}$ −0.72).[21] Therefore the daucone, compounds **2** and **3**, should belong to the same chiroptical series, and their configuration at C-1 should be the same. Thus, the configuration at C-1 of these compounds was *R* and compounds **2** and **3** were assigned as (1*R*,4*R*)-4-hydroxydauca-7-ene-6,9-dione and (1*R*,3*S*,8*S*)-3-ethoxy-8-angeloyloxydauca-4-en-9-one, respectively. The absolute configuration at C-1 of **1** could not be determined by the same experiment, but it was assumed to be *R*, the same as **2**, **3**, and other daucane-type sesquiterpenes, because they were isolated from the same extract. Thus, compound **1** was assigned as (1*R*,4*R*)-4-hydroxydauca-7-en-6-one.

Because of potent estrogenic activity of sesquiterpenes extracted from plants of the genus *Ferula*, the effects of a hexane extract, ferutinin, and compounds **1**−**3** on the proliferation of MCF-7 cells were evaluated (Table 2). The known phytoestrogen, genistein (4′,5,7-trihydroxyisoflavone), stimulated the growth of MCF-7 at the concentration of 3700 nM (114.8%), which confirmed some previous results obtained in the same conditions.[22] The cell growth observed for the hexane extract (in which ferutinin is the major compound) and ferutinin was biphasic with a proliferative effect at lower concentrations and an antiproliferative effect at the higher concentrations (maybe due to an antiestrogenic effect) as shown for various daucane compounds.[17] At the tested concentrations, **1** and **3** showed a strong proliferative effect with a potent cell growth for **3**. In contrast, **2** appeared antiproliferative at the same concentrations. These very interesting results will necessitate further investigations.

Table 2. Effect of Test Materials on the Proliferation of MCF-7 Human Breast Cancer Cells

test substance	concentration in μg/mL (nM)	cell proliferation (cpm)[a]	% of cell proliferation[b]
β-estradiol	(0.1)	20 304 ± 766[c]	74.6
	(1)	22 782 ± 1000[c]	130.3
	(10)	21 435 ± 1985[c]	100.0
genistein	0.1	13 769 ± 1294[c]	−72.4
	1 (3700)	22 092 ± 1614[c]	114.8
	10	13 580 ± 2073[c]	−76.7
hexane extract	0.1	19 375 ± 1025[c]	112.2
	1	28 922 ± 11 198[c]	355.8
	10	3235 ± 754[c]	−299.6
ferutinin	0.1	17 069 ± 1111[c]	53.4
	1	17 764 ± 2369[c]	71.1
	10	9224 ± 8440[c]	−146.8
compound **1**	0.1	19 564 ± 11265[c]	308.2
	1 (4200)	13 595 ± 178[c]	97.5
	10	15 970 ± 479[c]	181.4
compound **2**	0.1	10 999 ± 1583	5.9
	1 (4000)	10 081 ± 1199	−26.5
	10	2735 ± 234[c]	−285.7
compound **3**	0.1	17 176 ± 2888[c]	223.9
	1 (2800)	19 938 ± 973[c]	321.4
	10	38444 ± 7202[c]	974.4

[a] Values are average values derived from triplicate experiments (± SEM). [b] Results are expressed as % cell proliferation. Incubation without compounds or with β-estradiol (10 nM) alone were performed as controls; 0% and 100%, respectively. [c] Significantly different from control (tamoxifen alone), $p < 0.05$.

Experimental Section

General Experimental Procedures. Optical rotations were measured on a Perkin-Elmer 241 polarimeter with a sodium lamp (λ = 589 nm) in a 10 cm microcell. CD spectra were recorded on a Jobin-Yvon CD6 spectrometer. IR spectroscopy (in KBr) was performed on a Perkin-Elmer Paragon 1000 FT-IR spectrophotometer. NMR (500 and 400 MHz for ^{1}H NMR, 125 and 100 MHz for ^{13}C NMR, both using TMS as internal standard) spectra were obtained with $CDCl_3$ as solvent on a Bruker ARX 400 and a Bruker AVANCE 500 spectrometer. Chemical shifts (δ) are given in ppm, and coupling constants (J) are reported in Hz. ESIMS (positive- and negative-ion modes), 3.5 kV (MeOH−CH_3CN), were recorded on a Perkin-Elmer Sciex API 365 mass spectrometer. HRESIMS (positive-ion mode) were recorded on a Q-ToF Ultima (Waters) apparatus. Column chromatography: silica gel 60 SDS (70−200 μm). Medium-pressure column chromatography: silica gel 60 SDS (6−35 μm). Reversed-phase chromatography: Mega Bond Elut Varian C_{18} cartridge. HPLC support: Preparative HPLC was performed using a C_{18} 15 cm × 10 mm column and UV DAD Hitachi L 7455 detector. Fractionations were monitored by TLC (silica gel 60 F-254, Merck) with visualization under UV (254 and 365 nm) and with vanillin−sulfuric acid reagent. All solvents were spectral grade or distilled from glass prior to use.

Plant Material. The roots of *F. hermonis* Boiss. were collected on Mount Hermon in Lebanon in 2002 by the Laboratory of Pharmacognosy of the Faculty of Pharmacy, Lebanese University, Beirut, Lebanon, and identified by Prof. I. Fourasté. A voucher specimen (no. FHB 003) is deposited at the herbarium of the Pharmacognosy Laboratory, Faculty of Pharmacy, Toulouse, France.

Extraction and Isolation. The dried and ground roots of *F. hermonis* (5.4 g) were extracted with hexane in a Dionex ASE 100 extractor (100 bar, 50 °C). The hexane extract (1.88 g) was subjected to silica gel column chromatography (120 g) using CH_2Cl_2 for elution to give five fractions, which were concentrated in vacuo to afford oily residues. Fraction A (70 mg) was purified by HPLC (silica gel C_{18}, with MeCN(A)−H_2O-(B), 70:30, for 10 min, 70−100% of A in B for 10−20 min, and 100:0 for 20−30 min, finally returning to the initial conditions) to afford compounds **3** (5.6 mg), teferidin (3.2 mg), and

α-bisabolol (1.8 mg). Fraction B was further purified by chromatography on a reversed-phase silica gel C_{18} cartridge (MeOH−H_2O, 50:50). This column afforded compounds **1** (10.6 mg) and **2** (7.5 mg). Fraction C (100 mg) was separated by column chromatography (hexane−EtOAc, 8:2) to give ferutinin (41.3 mg). Fractions D and E were not further investigated.

Assay for Estrogenic Activity. The MCF-7 breast carcinoma cells were grown in Dulbecco's modified Eagle's minimum essential medium (BioWhittaker, Cambrex BioSciences, Verviers, Belgium) supplemented with 10% foetal bovine serum until confluence. At this point, cells were passed after trypsinization (Trypsin EDTA, BioWhittaker). Viable cells (viability estimated by Trypan blue exclusion test) were plated (10 000 cells per well) onto 96-well plates in phenol red-free medium (BioWhittaker). After overnight attachment and a wash, tamoxifen (Sigma-Aldrich Co., Steinheim, Germany; 2 μM) was added to inhibit the proliferation of the cells.[23] After 24 h more, the culture medium was removed and the plates were washed twice with Ca−Mg-free PBS (BioWhittaker), and the molecules to be tested were added at various concentrations for an additional 1 day. Positive controls were β-estradiol (Sigma-Aldrich) and genistein (Sigma-Aldrich Co., Steinheim, Germany).[22] The cell proliferation was estimated as tritiated hypoxanthine incorporation {[^{3}H]-hypoxanthine, 9.25 kBq/well for 12 h (ICN Chemicals, Paris, France)} in order to avoid interferences with the colorimetric assay.[24] Statistical analyses of differences were carried out by Dunnet's test. A p-value of less than 0.05 was considered to indicate significance.

(1*R*,4*R*)-4-Hydroxydauca-7-en-6-one (1): yellow oil, $[\alpha]_D$ +64.0° (*c* 0.38, $CHCl_3$); IR (KBr) ν_{max} 3437, 2930, 1642 cm^{-1}; UV (dioxane) λ_{max} (log ϵ) 243 (1.6) nm; ^{1}H and ^{13}C NMR, see Table 1; HRESMS *m/z* 237.1886 (calcd for $C_{15}H_{25}O_2$ [M + H]$^+$, 237.1855).

(1*R*,4*R*)-4-Hydroxydauca-7-ene-6,9-dione (2): yellow oil, $[\alpha]_D$ +47.1° (*c* 0.53, $CHCl_3$); IR (KBr) ν_{max} 3478, 2961, 1656 cm^{-1}; UV (dioxane) λ_{max} (log ϵ) 246 (1.5) nm; CD (dioxane) $\Delta\epsilon_{294}$ −1.42, $\Delta\epsilon_{239}$ −7.08; ^{1}H and ^{13}C NMR, see Table 1; HRESMS *m/z* 251.1655 (calcd for $C_{15}H_{23}O_3$ [M + H]$^+$, 251.1647).

(1*R*,3*S*,8*S*)-3-Ethoxy-8-angeloyloxydauca-4-en-9-one (3): yellow oil, $[\alpha]_D$ +71.4° (*c* 0.28, $CHCl_3$); IR (KBr) ν_{max} 3632, 1609 cm^{-1}; UV (dioxane) λ_{max} (log ϵ) 239 (1.2) nm; CD (dioxane) $\Delta\epsilon_{233}$ −3.68; ^{1}H and ^{13}C NMR, see Table 1; HRESMS *m/z* 363.2535 (calcd for $C_{22}H_{35}O_4$ [M + H]$^+$, 363.2535).

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