Oxygenated Sesquiterpenoids from a Nonpoisonous Sardinian Chemotype of Giant Fennel (*Ferula communis*)

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The roots of the nonpoisonous chemotype of giant fennel (*Ferula communis)* from Sardinia afforded a novel cadinanetriol (**1**), whose structure was established by spectroscopic data and confirmed by synthesis from the *E*,*E*-$\Delta^{1(10),5}$ germacradiene allohedycariol. A number of known compounds were also identified. Despite the lack of morphological differences, a broad chemical diversity exists within giant fennel, underlying the contrasting data on its poisonous properties.

The recognition that a haemorrhagic disease in Canadian cattle was due to the ingestion of moldy sweet clover raised considerable interest in the scientific community, eventually leading to the discovery of the anticoagulant activity of dicoumarol and to the synthesis of clinically useful cardiovascular drugs such as Warfarin.[1] A similar syndrome, named ferulosis, had been known to plague livestock in Sardinia.[2] Despite scientific studies spanning well over a century, it was only in 1925 that ferulosis was unambiguously related to the consumption of giant fennel (*Ferula communis* L., Umbelliferae).[3] The correlation proved difficult to establish, since giant fennel occasionally failed to elicit toxic effects in livestock. As a result, ferulosis was long considered an infectious disease, an event that might well have delayed discovery of the anticoagulant activity of coumarins by several decades.

To explain the contrasting observations on the toxicity of giant fennel, the existence of different chemotypes was postulated as early as 1925.[3] These findings were largely ignored in the scientific community, to the point that doubts on the toxicity of giant fennel still lingered on,[4] and the structure of the major haemorrhagic toxin of the plant, the prenylated 4-hydroxycoumarin ferulenol, was not reported until 40 years later.[5] In the late 1980s, we showed that two distinct chemotypes of giant fennel grow in Sardinia and reported the structure elucidation[6] and total synthesis[7] of the major coumarinic toxins of the plant. The study of the nonpoisonous chemotype was hampered by its scanty distribution and by the lack of diagnostic morphologic elements to differentiate between poisonous and nonpoisonous plants. A preliminary investigation gave the phytoestrogen ferutinin and the sesquiterpene alcohol allohedycariol (= 4*S*,7*S*,*E*,*E*-germacra-1(10),5-dien-11-ol),[6a] but the shortage of plant material prevented the characterization of further, less abundant constituents.

To get a reliable source of the nonpoisonous chemotype, over 150 samples of latex obtained from plants growing all over Sardinia were analyzed.[8] This evidenced that the distribution of the nonpoisonous chemotype is limited to three enclaves and guided the collection of sufficient plant material to characterize its constituents. Thus, an acetone extract from the roots was fractionated by open column chromatography on silica gel to afford three major constituents, the daucane esters ferutinin (2.1%)[6a,9] and jaeskeanadiol benzoate (1.1%)[10] and the sesquiterpene alcohol allohedycariol (0.7%).[6a,11] All the other compounds obtained were present in much lower concentration, and their isolation required further chromatographic steps, including HPLC. Four additional jaeskeanadiol esters (anisate, angelate, ferulate, and veratrate),[12] two 1-hydroxyjaeskeanadiol esters (diangelate and 1-acetate-5-angelate),[13] two siol esters (*p*-hydroxybenzoate and anisate),[6a] three sesquiterpene coumarin ethers (isosamarcandine angelate,[13] colladonine,[14] and feselol[15]), and three phenylpropanoids (2-epielmanticine,[16] methoxylatifolol,[17] and methoxylatifolone[17]) as well as the novel cadinane triol **1** were obtained.

The HRMS of **1** showed a $[M - H_2O]^+$ peak at 238.1911, corresponding to the molecular formula $C_{15}H_{15}O_3$. Since the ^{13}C NMR spectrum lacked resonances of unsaturated carbons, **1** was bicyclic. The ^{13}C NMR spectrum showed three deshielded oxygenated carbons, an oxymethine and two quaternary centers, and the remaining signals were assigned to four methyls, four methylenes, and four methines by DEPT experiments. The ^1H NMR spectrum displayed signals indicative of an oxygenated sesquiterpene, key functionalities easily discernible being an oxymethine proton and four methyls, three of which quaternary. Severe overlapping in the high-field region of the ^1H NMR spectrum was overcome by 2D measurements, and scalar (COSY) and dipolar (NOESY) $^1H-^1H$ correlations, as well as one-bond (HMQC) and long-range (HMBC) $^1H-^{13}C$ correlations, suggested the cadinane structure **1**, with the relative configuration indicated. The triol **1** bears an obvious biogenetic relationship with allohedycariol, from which it could be derived by transannular cyclization of a 5,6-epoxide. To support this relationship and establish the absolute configuration of the isolated product, the conversion of allohedycariol into **1** was investigated.

The transannular cyclization of germacradiene monoepoxides is a key event in the biosynthesis of sesquiterpenoids and has been the subject of a considerable body of investigation.[18] Most data available regard compounds of the $\Delta^{1(10),4}$-type, that is, derivatives of germacrene A, and there are few reports on compounds such as allohedycariol, having the functionalization pattern of germacrene D ($\Delta^{1(10),5}$). Allohedycariol was fairly stable in air, but treatment with epoxidizing reagents did trigger an oxidative

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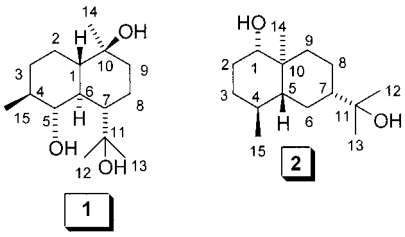
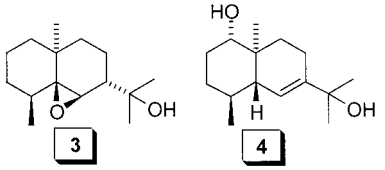
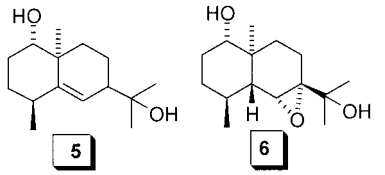
cyclization. Thus, reaction with *m*-chloroperoxybenzoic acid (MCPBA) in CH_2Cl_2 gave, after aqueous workup, a mixture containing a product with the same chromatographic behavior as **1**. ^{1}H NMR analysis of the epoxidation mixture confirmed this finding, and various reagents (MCPBA, buffered MCPBA, dimethyldioxirane, trifluoromethyldioxirane) were tried to optimize the formation of **1**. The best results were observed with MCPBA in buffered THF, which gave the cadinane triol **1** as the major reaction product (24% yield), identical (^{1}H NMR, MS, $[\alpha]_D$) to the natural product. The eudesmane diol **2** and the epoxyalcohol **3** were also obtained (14 and 8%, respectively). The reaction of allohedycariol with MCPBA in nonbuffered CH_2Cl_2 gave as major reaction product the eudesmane diol **2** (23%), accompanied by substantial amounts of the epoxyalcohol **3** (18%), the diols **4**,**5** (15%), the cadinane **1** (14%), and the epoxydiol **6** (10%). None of the eudesmane derivatives obtained in the epoxidation studies were present in the plant extract (HPLC and NMR analysis), and their structure elucidation was accomplished using the same basic NMR experiments detailed for **1**. The formation of eudesmane drivatives **2**−**6** is mechanistically detailed in the Supporting Information and affords chemical precedent for a novel biogenetic pathway linking eudesmanes and germacranes. Since the formation of **1** from allohedycariol required chemical manipulation and gave also compounds not present in the plant extract, it is reasonable to assume that **1** is a true natural product and not an artifact of isolation and/or purification procedures.







The results of this study demonstrate that, despite the lack of morphological differences, a broad chemical diversity occurs within giant fennel, even in an insular environment where infraspecific diversity tends to be low.[19] Apart from the occurrence of the same phenylpropanes and siol esters, the only other chemical trait shared by the two chemotypes of *F. communis* growing in Sardinia is the accumulation of *ent*-sesquiterpenes (aristolanes[20] and germacranes, respectively), a rare feature in higher plants. Daucane esters are widespread in plants from the genus *Ferula*,[21] but the accumulation of sizable amounts of specific esters is rare.[22] In this context, the nonpoisonous chemotype of giant fennel from Sardinia is a viable source of the powerful phytoestrogen ferutinin,[23,24] providing the opportunity to prepare a variety of analogues to elucidate the mechanism of its hormonal activity.

Experimental Section

General Experimental Procedures. Optical rotations were measured on a Perkin-Elmer 241 polarimeter. IR spectra were recorded on a Shimadzu DR 8001 spectrophotometer. HRMS (EI, 70 eV) were taken on a VG 7070 EQ spectrometer. ^{1}H and ^{13}C NMR spectra were taken on a Bruker DRX-500 spectrometer (500 and 125 MHz, respectively). Silica gel 60 (70−230 mesh, Merck) was used for open-column chromatography (CC). A Waters Microporasil column (0.8 × 30 cm) was used for HPLC, with detection by a Waters differential refractometer 340. Known compounds were identified by comparison of their spectroscopic data (^{1}H NMR, MS) with the published values (see references in the main text).

Plant Material. *Ferula communis* L. was collected in Seneghe (Oristano, Sardinia) in March 2000 and was identified by M.B. A voucher specimen (612b) is deposited at the Dipartimento di Scienze Botaniche, Università di Cagliari.

Extraction and Isolation. The dried powdered root (208 g) was extracted with acetone (3 × 1 L) to give 19.5 g (9.4%) of a yellowish oil. The latter was chromatographed on silica gel (150 g) using a hexane−EtOAc gradient system (from 95:5 to 6:4). Altogether, 515 fractions (ca. 15 mL each) were collected. These were combined into nine primary fractions (A−I). Fractions B (1.4 g, 0.7%), C (2.2 g, 1.1%), and E (3.8 g) were pure compounds, identified as allohedycariol, jasekanadiol benzoate, and ferutinin, respectively. Fraction A was made up essentially by triglycerides and was not further investigated. Fraction D (0.6 g) was purified by HPLC (hexanes−EtOAc, 8:2) to afford the phenylpropanoids methoxylatifolone (21 mg) and 2-epielmanticine (65 mg). Fraction F was further purified by CC (hexanes−EtOAc, 9:1) to afford ferutinin (0.4 g, overall yield 4.2 g, 2.1%) and a mixture further separated by HPLC (hexanes−EtOAc, 7:3) to afford siol angelate (3.8 mg), siol anisate (8 mg), methoxylatifolol (21 mg), jaeskeanadiol ferulate (8 mg), jaeskeanadiol veratrate (7 mg), and jaeskanadiol angelate (2 mg). Franction G (210 mg) was purified by HPLC (hexanes−EtOAc, 7:3) to afford 1-hydroxyjaeskanadiol diangelate (8 mg), 1-hydroxyjaeskanadiol 1-acetate-5-angelate (3 mg), and compound **1** (81 mg). No pure chemical entity could be obtained from fraction H, while fraction I afforded, after purification by HPLC (hexanes−EtOAc, 6:4), the coumarins isosamarcandine angelate (8.6 mg), feselol (30 mg), and colladonine (25 mg).

(1*S*,4*S*,5*R*,6*S*,7*S*,10*S*)-5,10,11-Cadinanetriol (1): white crystals (petroleum ether), mp 51 °C; $[\alpha]^{25}_D$ +6 (CH_2Cl_2, *c* 0.8); IR (KBr) ν_{max} 3432, 1460, 1375, 1184, 1040, 1011 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.88 (1H, dd, J = 10, 10 Hz, H-5), 1.81 (1H, ddd, J = 13.1, 3, 3 Hz, H-9α), 1.77 (1H, m, H-2β), 1.76 (1H, m, H-3α), 1.63 (1H, dddd, J = 12.6, 4, 4, 4 Hz, H-8β), 1.52 (1H, ddd, J = 13, 13, 4 Hz, H-9β), 1.44 (1H, m, H-7), 1.40 (1H, m, H-4), 1.36 (1H, m, H-1), 1.32 (3H, s, H-12), 1.20 (1H, m, H-8α), 1.17 (3H, s, H-14), 1.09 (1H, m, H-2α), 1.08 (3H, s, H-13), 0.98 (3H, d, J = 6.4 Hz, H-15), 0.98 (1H, m, H-6), 0.95 (1H, m, H-3β); ^{13}C NMR ($CDCl_3$) 85.0 (d, C-5), 81.7 (d, C-11), 73.1 (s, C-10), 52.9 (d, C-7), 51.2 (d, C-6), 48.2 (d, C-1), 43.3 (t, C-9), 38.1 (d, C-4), 33.3 (t, C-3), 29.0 (q, C-12), 25.0 (q, C-13), 25.0 (t, C-2), 23.7 (t, C-8), 21.7 (q, C-14), 18.8 (q, C-15); HREIMS *m*/*z* 238.1911 [M − H_2O]$^+$ (4) (calcd for $C_{15}H_{28}O_3$ − H_2O, 238.1933).

Epoxidation of allohedycariol: (a) In buffered THF: to a solution of allohedycariol (550 mg, 2.49 mmol) in THF (10 mL) were added solid $NaHCO_3$ (250 mg, 3 mmol) and 85% MCPBA (506 mg, corresponding to 2.49 mmol, 1 molar equiv). After 5 min the reaction was worked up by partitioning between EtOAc and 5% aqueous Na_2CO_3 (50 mL each). The organic phase was washed with brine, dried (Na_2SO_4), and evaporated. The semisolid residue was purified by CC (20 g silica gel, hexanes−EtOAc gradient (from 9:1 to 7:3)) to give, in order of elution, **3** (47 mg, 8%), **1** (153 mg, 24%), and **2** (84 mg, 14%). (b) In nonbuffered CH_2Cl_2: to a solution of allo-

hedycariol (200 mg, 0.90 mmol) in dry CH_2Cl_2 (5 mL) was added 85% MCPBA (182 mg, corresponding to 0.90 mmol). After stirring at room temperature for 5 min, the reaction was worked up as described above. The crude residue was purified by CC (silica gel, 10 g hexane−EtOAc gradient, from 8:2 to 6:4) to give, in order of elution, **3** (38 mg, 18%), **1** (32 mg, 14%), a mixture of **4** and **5** (ca. 1:1, 32 mg, 15%), **6** (23 mg, 10%), and **2** (50 mg, 23%). **4** and **5** could be further separated by HPLC (hexanes−EtOAc, 5:5).

(1*R*,4*R*,5*R*,7*R*,10*R*)-Eudesmane-1,11-diol (2): white powder (petroleum ether), mp 63 °C; $[\alpha]^{25}_D$ +21 (CH_2Cl_2, *c* 0.8); IR (KBr) ν_{max} 3431, 1456, 1389, 1163, 1034, 926 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.34 (1H, dd, J = 4.8, 11.1 Hz, H-1), 1.96 (1H, dd, J = 6.9, 12.3 Hz, H-9α), 1.73 (1H, m, H-3α), 1.67 (1H, m, H-2β), 1.52 (1H, m, H-4), 1.46 (1H, m, H-2α), 1.40 (2H, m, H-8α,β), 1.21 (3H, s, H-12), 1.20 (2H, m, H-6α,β), 1.16 (3H, s, H-13), 0.98 (1H, m, H-9β), 0.97 (3H, d, J = 6.4 Hz, H-15), 0.96 (3H, s, H-14), 0.90 (1H, dd, J = 4, 4 Hz, H-7), 0.86 (1H, m, H-3β), 0.50 (1H, dd, J = 4.9, 11.7 Hz, H-5); ^{13}C NMR ($CDCl_3$) δ 77.7 (d, C-1), 69.9 (s, C-11), 60.7 (d, C-5), 57.8 (s, C-10), 51.6 (d, C-7), 43.3 (t, C-9), 34.6 (t, C-3), 30.8 (t, C-2), 29.4 (d, C-4), 29.0 (q, C-12), 28.4 (q, C-13), 24.4 (t, C-6), 21.7 (t, C-8), 20.3 (q, C-15), 14.2 (q, C-14); HREIMS *m*/*z* 240.2101 $[M]^+$ (5) (calcd for $C_{15}H_{28}O_2$, 240.2089).

(4*S*,5*S*,6*R*,7*R*,10*R*)-Eudesma-5-en-11-ol epoxide (3): white crystals (petroleum ether), mp 103−106 °C; $[\alpha]^{25}_D$ +38 (CH_2Cl_2, *c* 0.54); IR (KBr) ν_{max} 3314, 1464, 1369, 1186, 1125, 935 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.27 (1H, s, H-6), 2.06 (1H, ddq, J = 12.6, 6.6, 3.8 Hz, H-4), 1.94 (1H, dd, J = 11.5, 7.8 Hz, H-7), 1.57 (1H, m, H-2β), 1.56 (1H, m, H-3α), 1.54 (1H, m, H-9β), 1.46 (1H, m, H-1β), 1.43 (1H, m, H-8β), 1.33 (1H, m, H-1α), 1.32 (1H, m, H-3β), 1.25 (1H, m, H-8α), 1.26 (3H, s, H-12), 1.22 (3H, s, H-13), 1.09 (3H, s, H-14), 0.97 (1H, ddd, J = 13.0, 4, 4 Hz, H-9α), 0.68 (3H, d, J = 6.7 Hz, H-15); ^{13}C NMR ($CDCl_3$) δ 72.6 (s, C-11), 67.3 (s, C-5), 56.9 (d, C-6), 45.6 (d, C-7), 37.4 (t, C-1), 34.0 (t, C-9), 33.7 (s, C-10), 33.0 (t, C-3), 29.8 (d, C-4), 28.7 (q, C-12), 25.4 (q, C-13), 21.7 (t, C-2), 20.7 (q, C-14), 19.0 (t, C-8), 14.5 (q, C-15); HREIMS *m*/*z* 238.1920 $[M]^+$ (5) (calcd for $C_{15}H_{26}O_2$, 238.1933).

(1*R*,4*S*,5*S*,10*R*)-Eudesma-6-en-1,11-diol (4): colorless gum; ^1H NMR ($CDCl_3$) δ 5.72 (1H, s, H-6), 3.29 (1H, dd, J = 10, 3 Hz, H-1), 2.12 (2H, m, H-8α,β), 1.98 (1H, ddd, J = 11, 6, 2 Hz, H-9β), 1.74 (1H, m, H-3β), 1.72 (1H, m, H-2α), 1.62 (1H, m, H-2β), 1.41 (1H, m, H-5), 1.36 (1H, m, H-4), 1.33 (3H, s, H-12), 1.32 (3H, s, H-13), 1.25 (1H, m, H-9α), 1.06 (1H, m, H-3α), 0.93 (3H, d, J = 6.5, H-15), 0.77 (3H, s, H-14); ^{13}C NMR ($CDCl_3$) δ 142.9 (s, C-7), 118.6 (s, C-6), 78.1 (d, C-1), 73.0 (s, C-11), 48.9 (d, C-5), 37.4 (s, C-10), 34.2 (t, C-3), 33.6 (t, C-9), 30.1 (t, C-2), 29.2 (q, C-12), 29.3 (d, C-4), 29.0 (q, C-13), 21.6 (t, C-8), 19.3 (q, C-15), 10.1 (q, C-14); HREIMS *m*/*z* 238.1941 $[M]^+$ (2) (calcd for $C_{15}H_{26}O_2$, 238.1933).

(1*R*,4*S*,7*S*,10*R*)-Eudesma-5-en-1,11-diol (5): colorless gum; ^1H NMR ($CDCl_3$) δ 5.45 (1H, d, J = 1.5 Hz, H-6), 3.25 (1H, dd, J = 11.6, 4.4 Hz, H-1), 2.17 (1H, m, H-4), 2.10 (1H, m, H-7), 1.94 (1H, ddd, J = 12.6, 3.7, 2.1 Hz, H-9α), 1.75 (1H, m, H-3β), 1.74 (1H, m, H-2β), 1.72 (1H, m, H-8β), 1.66 (1H, m, H-2α), 1.36 (1H, m, H-9β), 1.27 (1H, m, H-8α), 1.24 (3H, s, H-12), 1.18 (3H, s, H-13), 1.04 (3H, s, H-14), 1.02 (3H, d, J = 6.5, H-15), 1.00 (1H, m, H-3α); ^{13}C NMR ($CDCl_3$) δ 147.2 (s, C-5), 119.6 (d, C-6), 80.2 (d, C-1), 73.0 (s, C-11), 47.8 (d, C-7), 40.3 (s, C-10), 36.6 (t, C-9), 33.3 (t, C-3), 32.3 (d, C-4), 30.5 (t, C-2), 27.9 (q, C-12), 25.7 (q, C-13), 20.3 (t, C-8), 18.4 (q, C-15), 17.8 (q, C-14); HREIMS *m*/*z* 238.1946 $[M]^+$ (2) (calcd for $C_{15}H_{26}O_2$, 238.1933).

(1*R*,4*S*,5*S*,6*R*,7*S*,10*R*)-Eudesma-6-en-1,11-diol epoxide (6): white crystals (petroleum ether), mp 59 °C; $[\alpha]^{25}_D$ +28 (CH_2Cl_2, *c* 0.2); IR (KBr) ν_{max} 3420, 1450, 1360, 1192, 1106, 935 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.19 (1H, dd, J = 10, 4 Hz, H-1), 3.14 (1H, s, H-6), 1.93 (1H, m, H-8β), 1.80 (1H, m, H-8α), 1.80 (1H, m, H-9α), 1.78 (1H, m, H-3α), 1.73 (1H, m, H-2β), 1.58 (1H, m, H-2α), 1.45 (1H, m, H-4), 1.31 (3H, s, H-12), 1.28 (3H, s, H-13), 1.06 (1H, m, H-3β), 1.04 (1H, m, H-9β), 1.03 (3H, d, J = 6.7 Hz, H-15), 0.94 (1H, d, J = 12.7 Hz, H-5), 0.79 (3H, s, H-14); ^{13}C NMR ($CDCl_3$) δ 77.1 (d, C-1), 70.0 (s, C-11), 64.7 (s, C-7), 56.1 (d, C-6), 50.7 (d, C-5), 36.9 (s, C-10), 33.8 (t, C-3), 30.5 (t, C-9), 29.9 (t, C-2), 28.8 (d, C-4), 26.0 (q, C-13), 25.1 (q, C-12), 20.1 (t, C-8), 19.1 (q, C-15), 10.9 (q, C-14); HREIMS *m*/*z* 254.1876 $[M]^+$ (5) (calcd for $C_{15}H_{26}O_3$, 254.1882).

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Supporting Information Available: Discussion of the mechanistic rationale for the formation of the cadinane **1** and the eudesmanes **2**−**6** from the epoxidation of allohedycariol. This material is available free of charge via the Internet at http://pubs.acs.org.

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