Reaction of Pentafluorobenzene (3). A total of 2.3 g (68%) of white solid was obtained. The product was identified as 2,3,5,6-tetrafluorophenol (7) (^{1}H NMR, ^{19}F NMR, GC/MS, and IR). ^{19}F NMR ($CDCl_3$): δ 1.34 (m, 2 F), -21.31 (m, 2 F). ^{1}H NMR ($CDCl_3$): δ 6.62 (m, 1 H), 5.5 (broad s, 1 H). IR (CCl_4): ν_{max} (cm^{-1}) 3670, 3560, 3200 (broad) (OH), 1640, 1560, 1500 (C-F), 1085, 935 (C-F). GC/MS: *m/e* 166 (M), 137 (M - COH), 118, 99, 68.

Reaction of 1,2,3,4-Tetrafluorobenzene (2). After 3.5 h, standard workup, and distillation, 1.3 g of 2,3,4-trifluorophenol (**8a**) was obtained (44% yield). ^{19}F NMR ($CDCl_3$): δ -4.64 (dd, $J_{2,3}$ = 20.4 Hz, $J_{2,4}$ = 6.75 Hz, 1 F), -20.5 (dd, $J_{2,3}$ = 20.4 Hz, $J_{3,4}$ = 13 Hz, 1 F), -21.27 (dd, $J_{3,4}$ = 13 Hz, $J_{2,4}$ = 6.75 Hz, 1 F). Decoupling of the protons afforded only ortho-coupled fluorine atoms. ^{1}H NMR ($CDCl_3$): δ 6.82 (m, 1 H), 6.66 (m, 1 H), 5.7 (broad s). IR (CCl_4): ν_{max} (cm^{-1}) 3640, 3570, 3270 (broad) (OH), 1630, 1505 (C-F), 980, 969 (C-F). GC/MS: *m/e* 148 (M), 128 (M - HF), 119, 100, 81.

Acknowledgment. We thank Dr. S. Zitrin and Mrs. Z. Tamiri from the laboratories of the Israel Police Headquarters for mass spectroscopic determinations. Financial support of the Ernst D. Bergmann Foundation, The Research and Development Authority of the Hebrew University, is acknowledged.

Registry No. 1, 392-56-3; 2, 551-62-2; 3, 363-72-4; 4, 367-11-3; 5, 372-18-9; 6, 540-36-3; 7, 769-39-1; 8a, 2822-41-5; 8b, 99627-05-1; 9, 771-61-9; 10, 372-38-3; 11a, 367-27-1; 11b, 2713-34-0; tetrabutylammonium hydrogen sulfate, 32503-27-8; tributylmethylammonium hydrogen sulfate, 79494-37-4; tetrabutylammonium bromide, 1643-19-2; tetraoctylammonium bromide, 14866-33-2; tetraethylammonium hydrogen sulfate, 16873-13-5.

Supplementary Material Available: ^{19}F NMR, IR, and mass spectra of compounds 7, 8, and 9 (9 pages). Ordering information is given on any current masthead page.

A New Abietane Diterpene from *Salvia wiedemannii* Boiss

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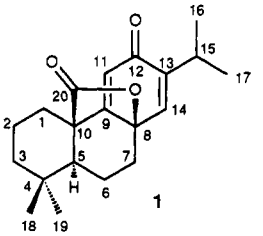
Species of *Salvia* (Labiatae) are prominent members of the pharmacopia of numerous countries throughout the world.[1] Perhaps the best known example is *S. miltiorrhiza*, Chinese sage, from the roots of which numerous abietanoid diterpenes have been isolated which are thought to be the active components of the medicine prepared from this species.[2] *Salvia* species are also commonly employed as traditional medicines in Turkey, where 87 different species are found, 44 of which are endemic to Turkey.[3] One of these latter species is *S. wiedemannii*, which has also yielded abietanoid diterpenes from the extract of the aerial parts of the plant.[4] Further examination of this extract has led to the isolation of a new abietane diterpene **1** which bears the intriguing cross-conjugated dienone functionality.



1

The appearance of 20 carbons in the ^{13}C NMR spectra[5] and the high-resolution mass spectrum, which showed a molecular ion *m/z* 314.1854 requiring a molecular formula of $C_{20}H_{26}O_3$ and therefore eight units of unsaturation, suggested a diterpene with two trisubstituted double bonds (δ 115.5, d, and 165.9, s; 148.0, s, and 135.2 d), a lactone group (^{13}C NMR δ 175.5; IR 1785 cm^{-1}), and a conjugated ketone (^{13}C NMR δ 184.4; IR 1640 cm^{-1}). The appearance of an isopropyl group as one of the double-bond substituents as suggested by the downfield shift of the methine proton (^{1}H NMR δ 1.03 and 1.07, both d, J = 6.8 Hz; δ 2.97, sept, J = 6.8; ^{13}C NMR δ 21.4 and 21.8, both q; δ 26.5, d) was highly reminescent of an abietane skeleton. The COSY (homonuclear correlation) and HETCOR (one-bond ^{1}H/^{13}C heteronuclear correlation) spectra enabled the two isolated spin systems of C-1 through C-3 (three sequential methylene groups), and C-5 through C-7 (a methine and two methylenes in sequence) to be delineated. A FLOCK spectrum[6] (for long-range ^{1}H/^{13}C heteronuclear scalar correlation) which showed three-bond coupling from H-18 to C-19, and from H-19 to C-18 confirmed the geminal nature of the methyl singlets in the ^{1}H NMR spectrum (the one-bond couplings were originally assigned from the HETCOR spectrum). Long-range heteronuclear couplings also apparent in this spectrum indicated that the *gem*-dimethyl group connected the two spin systems (C-1 through C-3 and C-5 through C-7) by couplings between both H-18 and H-19 with C-3, C-4, and C-5.

These observations indicated the typical abietane nature of the A and B rings, with the angular C-20 oxidized to a lactone carbonyl (δ 175.5), similar to that found in carnosol,[7] with the remaining units of unsaturation (two double bonds and the ketone) located in the C ring. The coupling between H-5 and the H-6 protons ($J_{5,6\beta}$ = 12.2 Hz, $J_{5,6\alpha}$ = 5.1 Hz, Table I) confirmed the axial orientation of H-5 (relative to the B ring) and hence the trans stereochemistry of the A,B ring fusion, as expected. The location of the lactone carbonyl at C-20 was supported by long-range heteronuclear couplings to this carbonyl carbon (δ 175.5) from H-1α and H-5 observed in the cross-section at the C20 resonance frequency of the FLOCK spectrum.

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(5) Only eighteen signals appeared in the ^{13}C NMR spectrum due to the overlap of two signals at δ 20.1 and at 26.4. Since the overlapped signals were of different multiplicity in each case, both the APT and the DEPT spectra revealed the resonances for the carbons which appeared at each of these chemical shifts. (See Table I for complete assignments.)

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0022-3263/91/1956-7354$02.50/0

Table I. ^{13}C and ^{1}H NMR Chemical Shifts of 1 in $CDCl_3$

position	^{13}C (m)	^{1}H (m, J)
1β	26.4 (t)	1.86 (dd, J = 12.7, 4.2 Hz)
1α		1.57 (ddd, J = 13.2, 12.7, 4.7 Hz)[a]
2β	17.6 (t)	2.16 (ddddd, J = 13.2, 13.2, 12.1, 4.2, 3.2 Hz)
2α		1.60 (ddd, J = 13.2, 4.7, 3.0 Hz)[a]
3β	41.2 (t)	1.54 (dd, J = 12.8, 3.2 Hz)[a]
3α		1.23 (ddd, J = 12.8, 12.1, 3.0 Hz)
4	34.3 (s)	-
5	52.9 (d)	1.50 (dd, J = 12.2, 5.1 Hz)[a]
6β	20.2 (t)	1.69 (dddd, J = 12.3, 12.2, 11.2, 5.8 Hz)
6α		1.93 (ddd, J = 11.2, 6.0, 5.1 Hz)
7β	37.9 (t)	2.42 (dd, J = 13.6, 5.8 Hz)
7α		1.46 (ddd, J = 13.6, 12.3, 6.0 Hz)[a]
8	78.7 (s)	-
9	165.9 (s)	-
10	50.3 (s)	-
11	115.5 (d)	5.92 (s)
12	184.4 (s)	-
13	148.0 (s)	-
14	135.2 (d)	6.70 (s)
15	26.5 (d)	2.97 (sept, J = 6.8 Hz)
16	21.4 (q)	1.03 (d, J = 6.8 Hz)
17	21.8 (q)	1.07 (d, J = 6.8 Hz)
18	20.1 (q)	0.98 (s)
19	32.3 (q)	0.92 (s)
20	175.5 (s)	-

[a] Proton peaks were overlapped, exact chemical shifts were obtained by the cross-sections of 2D-HETCOR spectrum, the coupling constants from HOMO-2DJ and 1D proton decoupling experiments.

Table II. ^{1}H NOE's for 1

position	^{1}H NOE's[a]	position	^{1}H NOE's[a]
H-19	H-6α, H-5	H-6α	H-5, H-6β
H-18	H-2β, H-6β	H-2β	H-1β, H-2α
H-14	H-7β	H-1β	H-2α, H-1α
H-11	H-1α	H-15	H-16 and 17
H-7β	H-6β, H-7α		

[a] From 2D-NOE spectrum run in $CDCl_3$.

With only two olefinic protons as yet unaccounted for, both C-8 and C-9 must be nonprotonated.

No coupling was observed between the two olefinic protons even in a long-range COSY experiment, suggesting that these protons have a 1,4-arrangement. This led to 1 as the most likely structure, an abietane skeleton. Long-range heteronuclear coupling observed in the FLOCK spectrum between the low-field proton at δ 6.70, a chemical shift suggestive of an olefinic proton at the β-position of an α,β-unsaturated ketone, with the ketone carbonyl carbon (δ 184.4) as well as the isopropyl methine carbon required that the isopropyl group be adjacent to this proton, with the ketone carbonyl also three bonds away. Further, an NOE was observed between this low-field olefinic proton and H-7β in a difference experiment (H-7β/H-14 internuclear distance estimated to be 2.68 Å by molecular mechanics calculations), supporting the location of this olefinic proton at C-14.

An NOE between the higher field olefinic proton (H-11, δ 5.92) and H-1α supported this structure (H1α/H11 internuclear distance estimated to be 2.31 Å by molecular mechanics calculations, see Table II for other NOE's). Further confirmation also came from the observation of long-range heteronuclear coupling between H-11 with the oxygenated quaternary carbon at δ 78.7 (assigned to C-8) and C-10 (δ 50.3), as well as coupling between H-14 and C-9. These heteronuclear couplings were observed in the FLOCK spectrum as well as in selective INEPT experiments (Table III).

The CD spectrum of 1 showed a split Cotton effect indicative of exciton coupling between the n→π* transition

Table III. ^{13}C–^{1}H Long-Range Couplings for 1[a]

^{1}H	^{13}C	^{1}H	^{13}C
H-1α	C-20 (FLOCK)	H-18	C-3, C-4, C-5, C-19 (FLOCK)
H-5	C-20 (FLOCK)	H-19	C-3, C-4, C-5, C-18 (FLOCK)
H-11	C-8 (FLOCK), C-10, C-13 (SINEPT)	H-16	C-13, C-15, C-17 (FLOCK)
		H-17	C-13, C-15, C-16 (FLOCK)
H-14	C-9, C-12, C-15 (FLOCK)		

[a] Spectra run in $CDCl_3$. SINEPT = selective INEPT. Couplings labeled SINEPT were not observed in FLOCK.

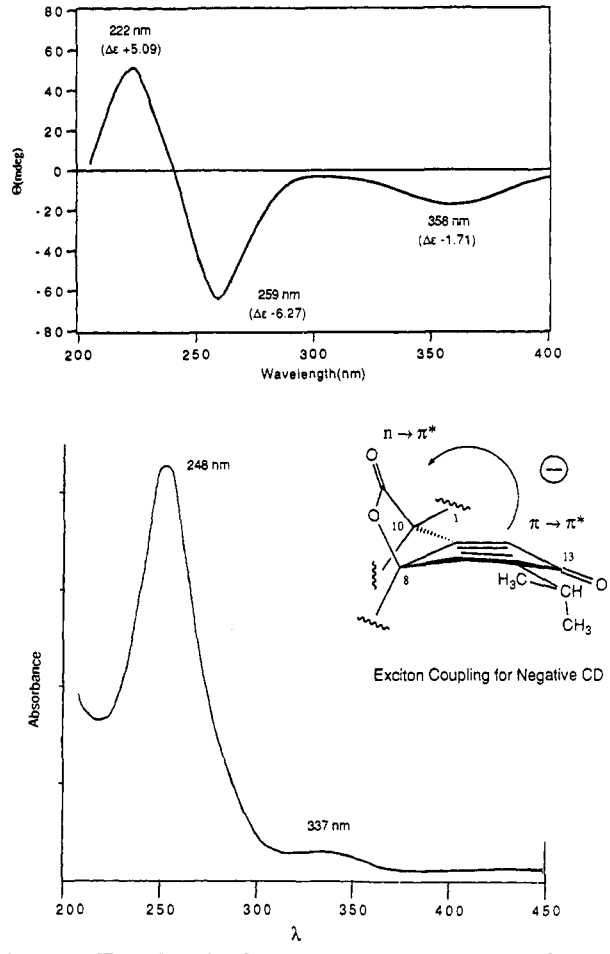
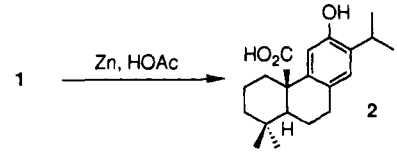


Figure 1. Top: Circular dichroism spectrum of 1 in CH_3OH with split Cotton effect due to negative chirality of lactone n→π* and dienone π→π* exciton coupling. Bottom: UV spectrum of 1 also in CH_3OH.

Scheme I



of the γ-lactone and the π→π* transition of the cross-conjugated dienone system with negative chirality (259 nm, Δε −6.27 and 222 nm, Δε +5.09). This split CD suggested 8*R*,10*R* absolute stereochemistry (Figure 1). Zinc reduction in acetic acid produced the known diterpene (+)-pisiferic acid 2,[8] confirming the absolute stereochemistry assignment (see Scheme I). The absolute stereo-

(8) Isolation and structure of pisiferic acid: (a) Fukui, H.; Koshimizu, K.; Egawa, H. *Agric. Biol. Chem.* **1978**, *42*, 1419. (b) Yatagai, M.; Shirato, T.; Hayashi, Y.; Fukuhara, N.; Takahashi, T. *Mokuzai Gakkaishi* **1978**, *24*, 267; *Chem. Abstr.* **1978**, *89*, 110032g.

chemistry of 2 had been established by conversion to *O,O'*-dimethylcarnosol[8a] and by total synthesis of both enantiomers of methyl pisiferate.[9] The *O*-methyl ether of 2[4a] and pisiferal[4b] have previously been reported in *S. wiedemannii*.

Pisiferic acid has well-established biological activity as a general cytotoxic agent,[10] and its methyl ether is an important defensive compound.[10,11] In contrast, 1 showed no activity against a variety of bacteria, fungi, and tumor cell lines. Thus 1 this may represent a stored supply of the defensive compound pisiferic acid in the leaves of *S. wiedemannii*.

Experimental Section

General. Melting points are uncorrected. ^1H and ^{13}C NMR spectra were recorded at 93.94 kG (400 MHz for ^1H, 100 MHz for ^{13}C) in $CDCl_3$ unless otherwise noted using the 7.24 ppm resonance of residual $CHCl_3$ and the 77.0 ppm resonance of $^{13}CDCl_3$ as internal references for ^1H and ^{13}C, respectively. Molecular modeling employed the QUANTA/CHARMm program on a Silicon Graphics work station.

NMR Multipulse Sequences. All 1D and 2D pulse sequences were run using standard Varian software, version 6.1c, except the FLOCK[6] experiment which was added to the sequence library according to Reynolds' program. ^{13}C multiplicities were assigned with the DEPT experiment, and ^{13}C assignments were completed using the HETCOR experiment for one-bond heteronuclear couplings (^1H,^{13}C), and the FLOCK and selective INEPT sequences for two- and three-bond heteronuclear couplings (^1H, ^{13}C). The FLOCK sequence employed two fixed delays of $\Delta1 = 0.072$ s and $\Delta2 = 0.040$ s.[6] Selective INEPT experiments were recorded with the excitation and refocusing delays optimized for different coupling constants according to the formulae $\Delta1 = {}^1/_2\,J$ and $\Delta2 = {}^1/_3\,J$, respectively.[12]

Isolation of 8-Hydroxy-12-oxoabieta-9(11),13-dien-20-oic Acid 8,20-Lactone (1). *S. wiedemannii* Boiss. was collected in the Haymana region of Central Turkey. The air-dried plant (aerial parts, 1.2 kg) was extracted with petroleum ether and then with acetone. The residue from the acetone extract (20 g) was then fractionated on a silica gel column eluting first with petroleum ether and then with a petroleum ether/ethyl acetate step gradient. The fraction eluting with 20% ethyl acetate in petroleum ether contained 1. This crude fraction (500 mg) was purified by chromatography on Sephadex LH-20, eluting with petroleum ether/$CHCl_3$/MeOH (7:4:1), and then by preparative TLC, eluting with $CHCl_3$/acetone (98:2) to give 1 as white crystals (80 mg, 0.0067% dry wt): mp 161-163 °C; $[\alpha]_D$ -167° (0.2 g/100 mL, CH_2Cl_2); CD (CH_3OH) 222 nm ($\Delta\epsilon$ 5.09), 259 (-6.27), 358 (-1.71); IR (KBr) 2920, 1785, 1690, 1640, 1390, 1370 cm^{-1}; UV (MeOH) λ_{max} 248 (ϵ 18190), 337 (ϵ 107); LRMS (EI, 70 eV) *m/z* (relative intensity) 315 ([M + 1]$^+$, 13), 314 (M$^+$, 49), 299 (25), 287 (26), 286 (100), 271 (22), 270 (53), 243 (34), 227 (17), 217 (13), 204 (11), 202 (39), 201 (13), 199 (11), 187 (21), 185 (12); HRMS (EI, 70 eV) *m/z* 314.1854 (M$^+$, calcd for $C_{20}H_{26}O_3$ 314.1882); ^1H and ^{13}C NMR, see Table I.

Reduction of 1 to (+)-Pisiferic Acid (2). To a solution of 1 (5 mg, 0.016 mmol) in glacial acetic acid (3 mL) was added freshly activated zinc powder (100 mg), and the mixture was stirred at rt for 4 h. Saturated brine solution (3 mL) was added, and the mixture was extracted with $CHCl_3$ (4 × 4 mL). The combined $CHCl_3$ extracts were washed with water and dried (Na_2SO_4), and the $CHCl_3$ was evaporated in vacuo. The residue was purified by flash chromatography on silica gel ($CHCl_3$/MeOH, 10:1) to give pure 2 (4 mg, 79% yield) as a white solid: mp 184-186 °C (lit.[8b] mp 185-186 °C); $[\alpha]_D$ +165° (*c* 0.19 g/100 mL, CH_3OH) [lit.[8a] $[\alpha]_D$ +177° (*c* 0.35, CH_3OH)]; CD (CH_3OH) 238 nm ($\Delta\epsilon$ +9.58); ^1H NMR ($CDCl_3$, 400 MHz) δ 6.89 (s, H-14), 6.67 (s, H-11), 3.10 (sept, J = 6.8 Hz, H-15), 2.88 (dd, J = 16.2, 5.9 Hz, H-7β), 2.82-2.76 (2H m, H-7α and H-1β), 2.44 (dddd, J = 13.1, 12.0, 11.0, 5.9 Hz, H-6β), 1.94 (m, H-2β), 1.87 (ddd, J = 11.0, 4.4, 2.8 Hz, H-6α), 1.60 (ddd, J = 13.7, 3.4, 3.2 Hz, H-2α), 1.49 (dd, J = 13.1, 2.8 Hz, H-5), 1.45 (dd, J = 13.1, 3.0 H-3β), 1.22 (2 H, m, H-1α and H-3α), 1.22 (3 H, d, J = 6.8 Hz, H-17), 1.21 (3 H, d, J = 6.8 Hz, H-16), 0.95 (3 H, s, H-19), 0.83 (3 H, s, H-18); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 180.1 (s, C-20), 150.7 (s, C-12), 138.2 (s, C-9), 133.5 (s, C-13), 129.1 (s, C-8), 127.4 (d, C-14), 112.3 (d, C-11), 52.2 (d, C-5), 41.7 (t, C-3), 36.7 (s, C-10), 34.0 (t, C-1), 32.1 (q, C-19), 29.7 (s, C-4), 29.3 (t, C-7), 26.8 (d, C-15), 22.6 (q, C-16 or C-17), 22.4 (q, C-17 or C-16), 20.3 (t, C-6), 20.1 (q, C-18), 18.5 (t, C-2); LRMS (CI, NH_3, 150 eV) *m/z* (relative intensity) 334 ([M + NH_4]$^+$, 100), 271 ([M - COOH]$^+$, 24); HRMS (CI, NH_3, 150 eV) *m/z* 334.2387 ([M + NH_4]$^+$), calcd for $C_{20}H_{32}NO_3$ 334.2382.[13]

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Supplementary Material Available: ^1H, ^{13}C, and DEPT one-dimensional NMR spectra, DQCOSY (double quantum filtered, phase-sensitive COSY), 2D-NOE, HETCOR, and FLOCK two-dimensional NMR spectra of 1; ^1H, ^{13}C, and APT NMR spectra of 2 (8 pages). Ordering information is given on any current masthead page.

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(13) Comparison of the ^1H NMR chemical shifts in $CDCl_3$ with those previously reported for 2 confirmed the structure (refs 8a and 8b). The IR and UV data were also identical. Since the ^{13}C NMR data had not been previously determined, however, we essentially did a complete structure assignment to confirm the structure of 2, thereby enabling assignments of all chemical shifts.

Synthesis of (±)-α-Allokainic Acid via the Zinc Acetate Catalyzed Cyclization of γ-Isocyano Silyl Enolates

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Kainoid amino acids like kainic acid,[1] domoic acid,[2] and acromelic acid[3] have attracted attention because they

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