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A NEW GERMACRANOLIDE FROM *TANACETUM DENSUM* SSP *SIVASICUM* (COMPOSITAE)

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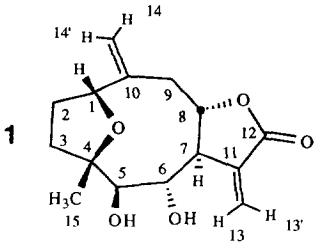
Abstract: A new germacranolide [**1**] was isolated from the aerial parts of *Tanacetum densum* ssp. *sivasicum* (Compositae), a species endemic to Turkey.

INTRODUCTION

Members of the *Tanacetum* genus are important medicinal plants found throughout the world which have been used in traditional medicines throughout the world.[1] In Turkey, 44 different species of *Tanacetum* are known, at least 15 of which are endemic.[2] One such endemic species, *T. densum*, is further classified into four subspecies: subsp. *sivasicum*, subsp. *laxum*, subsp. *amani*, and subsp. *eginense*. As with other members of the Compositae family, *T. densum* has been shown to produce a variety of sesquiterpenes, and investigations into subsp. *sivasicum* have previously yielded eudesmanolides, germacranolides, guaianolides, and farnesol derivatives.[3,4] In this paper we report a new germacranolide **1** from *T. densum* subsp. *sivasicum* .

RESULTS AND DISCUSSION

Isolation and Characterization. Germacranolide **1** was isolated from the aerial parts of *T. densum* subsp. *sivasicum* by standard methods (see Experimental). The ^{1}H NMR spectrum of **1** in $CDCl_3$ (Table 1) was reminiscent of that of the isomeric *cis* germacranolide diol **2**, previously reported from *T. argyrophyllum* also collected in Turkey.[5] Better spectral dispersion for **1** was obtained using CD_2Cl_2 as the solvent wherein all 17 magnetically distinct protons were observed (in $CDCl_3$ H8 and H14' overlapped; H7 and H9β were partially overlapped in both solvents). This spectrum together with the ^{13}C NMR spectra (including DEPT for multiplicity assignment and the heteronuclear ^{1}H,^{13}C COSY spectrum) which showed 15 carbon resonances, IR (KBr), and the HRMS (CI *m/z* 281.1351, $[M+1]^+$, calc'd for $C_{15}H_{21}O_5$ 281.1389, six units of unsaturation)



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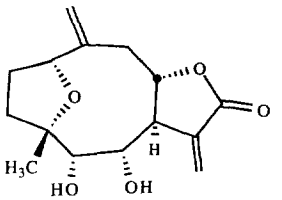

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Table 1. NMR Chemical Shift Assignments for **1**.

Position	^{13}C (CD_2Cl_2)[a]	^1H (CD_2Cl_2)[b]	^1H ($CDCl_3$)
1	82.6 (d)	4.64 (dd, *J* = 7.3, 7.3 Hz)	4.63 (dd, *J* = 7.4, 7.3 Hz)
2α	29.7 (t)	2.03 (dddd, *J* = 13.7, 10.7, 7.8, 7.3 Hz)	2.04 (dddd,*J* = 13.7, 10.0, 8.1, 7.3 Hz)
2β	-	2.14 (dddd, *J* = 13.7, 8.9, 7.3, 2.3 Hz)	2.18 (dddd, *J* = 13.7, 9.4, 7.4, 2.4 Hz)
3α	37.5 (t)	2.27 (ddd, *J* = 12.5, 7.8, 2.3 Hz)	2.27 (ddd, *J* = 12.7, 8.1, 2.4 Hz)
3β	-	1.77 (ddd, *J* = 12.5, 10.7, 8.9 Hz)	1.78 (ddd, *J* = 12.7, 10.0, 9.4 Hz)
4	85.0 (s)	-	-
5	76.2 (d)	3.55 (d, *J* = 7.6 Hz)	3.53 (d,*J* = 7.8 Hz)[e]
6	70.5 (d)	3.84 (dd, *J* = 9.0, 7.6 Hz)	3.83 (dd, *J* = 8.7, 7.8 Hz)[e]
7	51.4 (d)	2.86 (overlapped)[c]	2.84 (overlapped)[d]
8	80.9 (d)	4.93 (ddd, *J* = 7.5, 7.5, 4.4 Hz)	4.93 (overlapped)[f]
9α	41.4 (t)	2.44 (dd, *J* = 14.6, 7.5 Hz)	2.39 (dd, *J* = 14.5, 8.0)
9β	-	2.89 (dd, *J* = 14.6, 4.4 Hz)	2.93 (dd, *J* = 14.5, 4.9)
10	147.9 (s)	-	-
11	137.7 (s)	-	-
12	170.5 (s)	-	-
13	126.8 (t)	6.23 (dd, *J* = 3.1, 1.5 Hz)	6.20 (dd, *J* = 2.7, 1.1 Hz)
13'	-	6.30 (dd, *J* = 2.8, 1.5 Hz)	6.39 (dd, *J* = 3.1, 1.1 Hz)
14	114.3 (t)	4.96 (br s)	4.95 (br s)
14'	-	5.00 (br s)	4.97 (br s)
15	20.2 (q)	1.23 (s)	1.23 (s)
OH	-	3.35 (br s); 3.45 (br s)[d]	3.60 (br s, 2H)[d,e]

(a) Carbon multiplicities determined from a DEPT experiment. (b) For exocyclic methylene protons, the downfield signal is arbitrarily designated by prime. Actual stereochemical assignment of the exocyclic methylene proton pairs H13/H13' and H14/H14' was only completed in CD_2Cl_2. (c) H7 was overlapped with H9β; coupling constants for H7 could be established from coupled partners: CD_2Cl_2 (dddd, *J* = 9.0, 7.5, 3.1, 2.8 Hz). (d) Exchangeable with D_2O. (e) The chemical shift of the hydroxyl protons was concentration dependent, and coupling of H5 and H6 with their respective hydroxyl protons was observed in very dilute samples, and was dependent upon the amount of water present; with high dilution: δ 2.89 (d, *J* = 3.4 Hz, 6-OH), 2.79 (d, *J* = 4.2 Hz, 5-OH).

suggested that **1** was a germacranolide with an α-methyleno-γ-lactone (IR: 1760 cm^{-1}; ^1H NMR δ 6.23 [dd, *J* = 3.1, 1.5 Hz, H13], 6.30 [dd, *J* = 2.8, 1.5 Hz, H13']; ^{13}C NMR δ 170.5 [s, C12], 137.7 [s, C11], 126.8 [t, C13]), a second exocyclic methylene group (^1H NMR δ 4.96 [br s, H14], 5.00 [br s, H14'];

^{13}C NMR δ 147.9 [s, C10], 114.3 [t, C14]), and two secondary alcohols (IR: 3220 cm^{-1}; ^{1}H NMR δ 3.35 [br s, OH, exchangeable with D_2O], 3.45 [br s, OH, exchangeable with D_2O], 3.55 [d, J = 7.6 Hz, H5], 3.84 [dd, J = 9.0, 7.6 Hz, H6]; ^{13}C NMR δ 76.2 [d, C5], 70.5 [d, C6]). A single, weak band at 1660 cm^{-1}, typical for an exocyclic methylene unit was also observed in the IR spectrum. The remaining unit of unsaturation required by the mass spectrum was easily accomodated by the tetrahydrofuran unit, which also accounted for the presence of the remaining oxygen and the remaining two oxygenated carbons (^{13}C NMR δ 82.6 [d, C1], 85.0 [s, C4); ^{1}H NMR δ 4.64 [dd, J = 7.3, 7.3 Hz, H1).

Two distinct scalar coupled proton spin systems were easily delineated in the $^{1}H,^{1}H$-COSY spectrum: H14' to H1 through H3α/H3β, and H5 through H9α/H9β (the stereochemical assignment of methylene pairs follows from coupling constants and NOE studies as discussed below). Thus, the methine proton on an oxygenated carbon of the tetrahydrofuran (H1) coupled to a methylene gem pair of protons (δ 2.03, dddd, J = 13.7, 10.7, 7.8, 7.3 Hz, H2α, and 2.14, dddd, J = 13.7, 8.9, 7.3, 2.3 Hz, H2β), both of which in turn coupled to a second gem pair of methylene protons (δ 1.77, ddd, J = 12.5, 10.4, 8.9 Hz, H3β, and 2.27, ddd, J = 12.5, 7.8, 2.3 Hz, H3α). The gem-nature of the sets of methylene protons was confirmed by the heteronuclear $^{1}H,^{13}C$-COSY spectrum: δ 29.7 [C2], 41.4 [C3]. The H1 methine proton also showed weak coupling in the $^{1}H,^{1}H$-COSY spectrum to a the H14' broad singlet, thereby extending this proton coupled spin system through C10 to the C14 exocyclic methylene.

The second scalar coupled spin system extended through sequential methine protons and terminated with the remaining methylene gem pair (H5 through H9). Of the four methine protons, three were on oxygenated carbons: H5 and H6 as carbinol protons of secondary alcohols (*vide supra*) and the acylated carbinol proton of the lactone ring (δ 4.93, ddd, J = 7.5, 7.5, 4.4 Hz, H8; ^{13}C: δ 80.9, C8). The upfield methine proton (δ 2.87, H7) was partially overlapped with one of the methylene protons terminating this second proton coupled spin system (δ 2.89, dd, J = 14.6, 4.4 Hz, H9β). Coupling from this methine (H7), however, could be discerned in the $^{1}H,^{1}H$-COSY spectrum to both low field exocyclic methylene protons of the α-methyleno-γ-lactone (H13/H13').[6] The γ-lactone functionality was thus located between the vicinal diol and C9 methylene groups of this spin system. Of note in this spin system was the couplings between the four methines ($^{3}J_{5,6}$ = 7.6 Hz, $^{3}J_{6,7}$ = 9.0 Hz, $^{3}J_{7,8}$ = 7.5 Hz, $^{3}J_{8,9\alpha}$ = 7.5 Hz) suggesting a sequential *trans* relationship between these protons, later confirmed by NOE studies. The remaining quaternary oxygenated carbon (δ 85.0, C4), to which must be attached the remaining methyl singlet (δ 1.23, s, H15; ^{13}C δ 20.2, C15), must be one of the linkage points between the two proton coupled spin systems and accounts for all the remaining protons and carbons.

Linking the two proton spin systems and completing the skeleton of **1** was accomplished by the observation of long range homonuclear couplings in the long range $^{1}H,^{1}H$-COSY spectrum (LRCOSY, Δ = 300 ms) and long range heteronuclear couplings in selective INEPT (SINEPT) and FLOCK[7,8] experiments (Table 2). In the LRCOSY spectrum, couplings were observed from both H9α (δ 2.44, dd, J = 14.6, 7.5 Hz) and H9β to the same exocyclic methylene protons (H14/H14') which had observable couplings with H1, linking C1 with C9 through C10. In similar fashion, long range couplings were also observed between the methyl singlet (H15) and H3α, as well as between the H15 methyl protons and H5, thereby completing the linkage of the proton spin systems through C4. These observations along with the COSY require a 7,8-lactonic ring.

The germacranolide skeleton of **1** deduced from the homonuclear couplings was confirmed by heteronuclear couplings observed in SINEPT and FLOCK experiments (Table 2). In particular, heteronuclear

Table 2. Diagnostic NOE's and Heteronuclear Couplings of **1**.

NOE Pairs[a]	$^2J_{C,H}$ and $^3J_{C,H}$[b]
H1: H9β, H14'	H1 → C4
H3α: H5	H3β → C5
H3β: H15	-
H5: H2α, H3α, H7, H9α	-
H6: H8, H15	H6 → C4, C5, C8
H8: H6, H9β	-
H9α: H5, H14	H9α → C1, C8, C10, C14
H13: H7, H13	-
H13': H13	H13' → C7, C11
-	H14 → C1, C9
H15: H3β, H6	H15 → C3, C4, C5

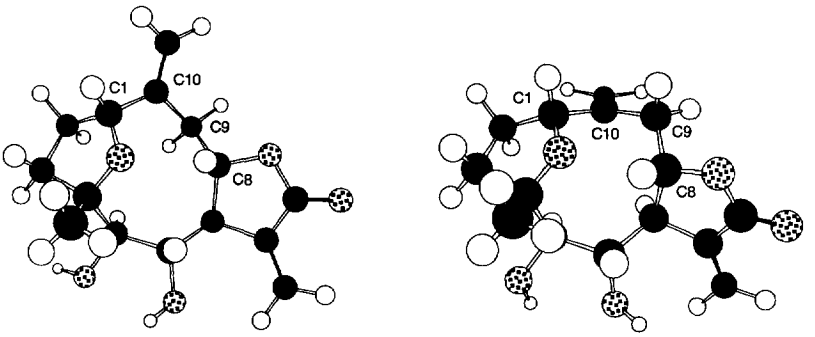
(a) From DNOE experiments; saturation resonance is listed before the colon.
(b) From selective INEPT (H6, H9α, H15) and FLOCK experiments.

couplings were detected between H9α and both olefinic carbons C10 (^{2}J) and C14 (^{3}J) as well as with C1. Heteronuclear coupling between H6 and C4 confirmed the location of this oxygenated quaternary carbon and the other linkage site between the two proton coupled spin systems. In addition, the tetrahydrofuran unit was confirmed by the observation of a polarization transfer from H1 to C4 in a SINEPT experiment.

With the skeleton of **1** established, the assignment of the relative and absolute stereochemistry remained. The "anti" relationship of the C5/C6 vicinal diol was initially suggested by $^3J_{5,6}$ = 7.6 Hz. This value contrasts sharply with that found in the isomeric *cis* diol **2** coupling of $^3J_{5,6}$ = 2.5 Hz, though caution has to be exerted in this comparison since the tetrahydrofuran stereochemistry is also different. The *trans* lactone stereochemistry at C7/C8, often difficult to establish by coupling constants,[6b,9] was confirmed by NOE's observed in the NOESY and DNOE spectra between H6 and H8, and between H5 and H7 as well as with H9α. These two diaxial-type NOE's are incompatible with a *cis*-fused γ-lactone.[10] The "sequential anti" stereochemistry of H5 through H8 was thus defined by these NOE's confirming the stereochemistry indicated by the coupling constants. The relative stereochemistry at C4 was also confirmed by NOE's: H6 with H15, H5 with H3α and with H2α, and H15 with H3β. These NOE's require that the tetrahydrofuran dimethylene bridge, H5, and H7 lie on the same face of the molecule, and that H6, H8, and the H15 methyl group lie on the opposite face. These NOE's, as well as those observed between H1 with H2β and H3β, along with the coupling constants, also distinguished the diastereotopic C2, C3, and C9 methylene protons. The exocyclic C14 methylene protons were also distinguished from the NOE's: H1/H14', with a negative NOE between H1/H14 in a DNOE experiment, and H9α/H14; the C13 methylene protons were assigned on the basis of their chemical shifts with the downfield resonance (H13') assigned to the proton syn to the carbonyl oxygen.[6b] This was supported by an NOE observed between H7 and H13.

Molecular modelling studies indicated two close lying minima (within 1 kcal/mol) differing primarily in the C1-C10-C9-C8 torsion angle (Figure 1). In the lower energy conformation **1A** H9α is oriented in axial fashion on the α-face while in conformation **1B** H9β is axially oriented on the β-face. In conformation **1A** the interproton distances for which NOE's were observed are 3.0 Å or less with the exception of the H1 - H9β distance (4.3 Å). In conformation **1B** the interproton distances for observed NOE's are 2.9 Å or less (H1 - H9β is 2.8 Å in **1B**) except H5 - H9α (4.5 Å). This latter interproton distance, however, is only 2.4 Å in **1A**. These modelling experiments, in accord with the NOE and coupling constant observations, indicate that **1** populates both **1A** and **1B** with rapid interconversion on the NMR time scale.

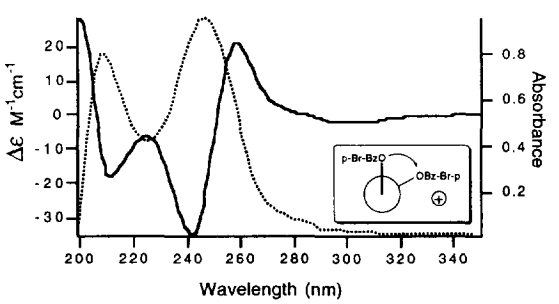
The *trans* diol functionality provided a textbook opportunity to apply the CD exciton chirality method



Conformation **1A** Conformation **1B**

Figure 1. Two minimum energy conformations of **1** found by molecular modelling. Carbon atoms are shaded, oxygens are speckled, and hydrogens are open.

using the bis-*p*-bromobenzoates.[11] Bis-*p*-bromobenzoate derivative **3** was prepared in quantitative yield from **1** by standard DCC coupling procedures.[12] The UV spectrum of **3** showed a λ_{max} at 248 nm (ε 44,200) due to the *p*-bromobenzoate chromophores, while the CD spectrum showed the classic exciton coupling with positive chirality: A_{obsd} = +58.8 (Figure 2).[13] The UV spectrum of **1** showed end absorbance only, typical for α-methyleno-γ-lactones.[14] The absolute stereochemistry was therefore concluded to be (5*R*, 6*S*), with the full structure of **1** assigned as shown.[15]



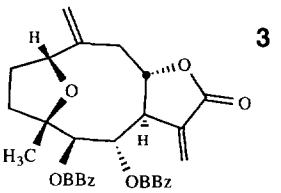


Figure 2. CD spectrum of bis-*p*-bromobenzoate **3** (solid line) superimposed on UV curve (dashed line). BBz = *p*-bromobenzoate.

EXPERIMENTAL

General. ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ and CD_2Cl_2 on a Varian XL-400 (93.94 kG, ^1H 400 MHz, ^{13}C 100 MHz). In the proton spectra, the residual protio solvent resonances were used as internal references: $CHCl_3$ δ 7.24 and $CDHCl_2$ δ 5.32. In the carbon spectra, the ^{13}C resonance of deuterio solvents were used as internal references: $^{13}CDCl_3$ δ 77.0 and $^{13}CD_2Cl_2$ δ 53.8. All NMR pulse sequences were run using standard Varian software, version 6.1c, except the FLOCK sequence which was added to the sequence library according to Reynolds' program.[7] Selective INEPT experiments were performed with excitation and refocusing delays optimized according to the formulae Δ1 = 1/2J (0.077 s) and Δ2 = 1/3J (0.051 s), with J set to either 4 or 7 Hz;[16] the long range COSY spectra ($^1H/^1H$, LRCOSY) utilized a delay time of 300 ms before and after the mixing pulse.[17] Proton assignments for **3** were made with the assistance of a $^1H,^1H$-COSY and 2D-

NOE spectra. Molecular modelling was performed on a Silicon Graphics workstation utilizing the QUANTA/CHARMm program. *Tanacetum densum* subsp. *sivascum* was collected from Central Turkey (Sivas), voucher speciman (Nr. 200) on deposit in the Herbarium of the Faculty of Science and Art, University of Cumhuriyet, Sivas, Turkey. Pet ether refers to petroleum ether bp 40 - 60 °C; preparative TLC was run on silica gel plates (silica gel 60-PF_{254}, 1 mm thickness). Infrared spectra were recorded on a Perkin-Elmer 1800 FTIR spectrophotometer.

Isolation of ***1***. Dried, powdered aerial parts (4.16 kg) were extracted successively with pet ether, $CHCl_3$, and EtOH. The $CHCl_3$, and EtOH extracts were combined and evaporated to dryness in vacuo, and the residue dissolved in MeOH and placed in a refrigerator (4 °C) for several hours. The precipitate was removed by filtration and the filtrate (MeOH solution) was concentrated in vacuo. The viscous residue was applied to a silica gel column and eluted with a gradient of pet ether with increasing amounts of Et_2O (step gradient eluting with pet ether, then pet ether with 5%, 15%, 25% and 50% Et_2O, followed by Et_2O, 10% MeOH in Et_2O, then MeOH) to provide eight fractions. The last two fractions were combined and further separated by preparative TLC, eluting with Et_2O. The most polar band was purified by flash chromatography on silica gel ($CHCl_3$:MeOH, 15:1) to provide **1** (23 mg). CD (MeOH) 250 (-0.6); ; IR (KBr, ν_{max} cm^{-1}) 3220 (OH), 1760 (C=O), 1660 (C=C); UV (MeOH, λ_{max}) 209 (ε 2050), 263 (240); ^1H NMR and ^{13}C NMR, see Table 1; HRMS (CI, ammonia) *m/z* 281.1351, $[M+1]^+$, calc'd for $C_{15}H_{21}O_5$ 281.1389.

Preparation of Bis-p-bromobenzoate ***3***. To a solution of **1** (2.8 mg, 0.01 mmole), DCC (5.7 mg, 0.028 mmole), DMAP (3.1 mg, 0.025 mmole) in anhydrous CH_2Cl_2 (1.0 mL) at 0 °C was added a solution of *p*-bromobenzoic acid (4.4 mg, 0.022 mmole) in anhydrous CH_2Cl_2 (1.0 mL) with stirring. The reaction mixture was stirred at 0 °C for 15 min, then the temperature allowed to rise to room temperature, and the mixture stirred for an additional 45 min, at which time **1** was determined to be completely consumed by TLC (hexanes:CH_2Cl_2, 1:1). The solvent was removed in vacuo and the residue purified by preparative TLC (hexanes:CH_2Cl_2, 1:1) to give **3** (6.5 mg, 0.01 mmole) in quantitative yield as colorless crystals: mp 210 °C; $[\alpha]^{20}_D$ -23.3 (*c* 0.06 g/100 mL, MeOH); UV (MeOH) λ_{max} 208 nm (end absorbance), 248 (ε 44,200); CD (MeOH) 210 nm ($\Delta\varepsilon$ -20.0), 242 (-39.4), 258 (+19.4); IR (KBr) 1765 (C=O), 1726 (C=O) cm^{-1}; ^1H NMR (CD_2Cl_2, 400 MHz) δ 7.61 (d, *J* = 8.7 Hz, 1H), 7.60 (d, *J* = 8.7 Hz, 1H), 7.38 (d, *J* = 8.7 Hz, 1H), 7.35 (d, *J* = 8.7 Hz), 6.14 (dd, *J* = 3.1, 0.6 Hz, H13'), 5.64 (dd, *J* = 2.7, 0.6 Hz, H13), 5.57 (dd, *J* = 9.2, 7.7 Hz, H6), 5.32 (overlapped with $CDHCl_2$, H5), 5.22 (ddd, *J* = 8.3, 6.6, 4.9 Hz, H8), 5.15 (bs, H14'), 5.12 (bs, H14), 4.77 (dd, *J* = 7.1, 7.1 Hz, H1), 3.50 (dddd, *J* = 9.2, 6.6, 3.1, 2.7 Hz, H7), 3.06 (dd, *J* = 14.4, 4.9, H9β), 2.60 (dd, *J* = 14.4, 8.3, H9α), 2.23 (dddd, *J* = 13.1, 9.3, 7.1, 4.1, H2β), 2.19 (dddd, *J* = 13.1, 9.3, 7.3, 7.1 Hz, H2α), 2.03 (ddd, *J* = 12.9, 7.3, 4.1, H3α), 1.84 (ddd, *J* = 12.9, 9.3, 9.3, H3β), 1.54 (s, H15); ^{13}C NMR (CD_2Cl_2, 100 MHz) δ 178.5, 165.4, 164.5, 147.1, 136.0, 132.1 (2 X C), 131.9 (2 X C), 131.3, 131.3, 128.8, 128.3, 128.1 (2 X C), 126.8, 115.5, 83.8, 82.9, 80.7, 76.6, 72.1, 48.6, 42.1, 37.5, 29.5, 21.9; LRMS (CI, NH_3, 150 eV) *m/z* (relative intensity) 649 (58, $[M+1]^+$), 647 (100, $[M+1]^+$), 645 (645 $[M+1]^+$), 569 (46, $[M+1-^{79}Br]^+$), 567 (42, $[M+1-^{81}Br]^+$), 489 (71), 185 (63), 183 (64) 105 (72); HRMS (EI, 70 eV) *m/z* 645.0113 ($[M+1]^+$), calc'd for $C_{29}H_{27}{}^{79}Br_2O_7$ 645.0123.

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REFERENCES

1. For example: Duke, J. A., In *Handbook of Medicinal Plants*, CRC Press: Boca Raton, Florida, 1987, pp 474 - 475.
2. Grierson, A. J. C. In *Flora of Turkey and the East Aegean Islands*, Vol. 5; Davis, P. H., Ed.; Edinburgh University Press: Edinburgh, 1975, pp 256 - 292.
3. Goren, N.; Bozok-Johansson, C.; Jakupovic, J.; Lin, L.-J.; Shieh, H.-L.; Cordell, G. A.; Celik, N. *Phytochemistry* **1992**, *31*, 101.
4. Goren, N. *Phytochemistry* **1993**, *34*, 743.
5. Goren, N.; Jakupovic, J.; Topal, S. *Phytochemistry* **1990**, *29*, 1467.
6. The appearance of both methylene protons of the α-methyleno-γ-lactone subunit below 6 ppm (Table 1) with readily apparent gem coupling (1.5 Hz in CD_2Cl_2) suggested the presence of an adjacent α-OH at C6, analogous these signature chemical shifts and gem couplings in 7,6-lactones: (a) Yoshioka, H.; Mabry, T. J.; Irwin, M. A.; Geissman, T. A.; Samek, Z. *Tetrahedron* **1971**, *27*, 3317. (b) Fischer, N. H.; Olivier, E. J.; Fischer, H. D. In *Prog. Chem. Org. Nat. Prod.*, Herz, W.; Grisebach, H.; Kirby, G. W., Eds; Springer-Verlag: New York, 1979; Vol. 38, pp 58 - 133.
7. Reynolds, W. F.; McLean, S.; Perpick-Dumont, M.; Enriquez, R. G. *Magn. Reson. Chem.* **1989**, *27*, 162.
8. In newer instruments with inverse detection available, HMBC would be employed.
9. Samek, Z. *Coll. Czech. Chem. Commun.* **1978**, *43*, 3210.
10. Assignment of the lactone stereochemistry based on the allylic couplings between H7 and H13/H13' $^4J \approx 3.0$ Hz in combination with $^3J_{6,7} \approx 8.0$ Hz as observed with **1** is ambiguous (see Ref 9).
11. (a) N. Harada; K. Nakanishi "Circular Dichroic Spectroscopy - Exciton Coupling In Organic Chemistry"; University Science Books: Mill Valley, CA; 1983. (b) Nakanishi, K.; Berova, N. In *Circular Dichroism: Principles and Applications*, Nakanishi, K.; Berova, N.; Woody, R. W., Eds.; VCH Publishers: New York, 1994, pp 361 - 398.
12. The procedure used was adapted from: Panek, J. S.; Sparks, M. A. *Tetrahedron Asymm.* **1990**, *1*, 801.
13. The amplitude (A_{obsd}) of an exciton-split CD curve is defined as the difference in Δε (longer wavelength Δε minus shorter wavelength Δε) of the split extrema (see Ref. 10).
14. Irwin, M. A., PhD Thesis, University of California at Los Angeles, 1971.
15. This confirms the absolute stereochemistry predicted by the oxygenation pattern in accord with the usual absolute stereochemistry of Compositae germacranolides (see Ref. 6b). Assignment of the absolute stereochemistry from the $n \rightarrow \pi^*$ transition is ambiguous for 7,8-lactonic germacranolides such as **1** where

more than one conformation may be populated (see Ref. 6b, page 93).The modelling studies of **1** predict the two populated conformations will have opposite lactone chiralities.

16. Bax, A. *J. Magn. Reson.* **1984**, *57*, 314.
17. Bax, A.; Freeman, R. *J. Magn. Reson.* **1981**, *44*, 542.

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