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Rearranged *Neo*-Clerodane Diterpenoids from *Teucrium brevifolium*

Benjamín Rodríguez*[a], María C. de la Torre[a], Maurizio Bruno[b], Caterina Fazio[b], Franco Piozzi*[b], Giuseppe Savona[b], Aurea Perales[c] and Nelly A. Arnold[d]

[a]Instituto de Química Orgánica, CSIC, Juan de la Cierva 3, 28006 Madrid, Spain; [b]Dipartimento di Chimica Organica dell'Università, Archirafi 20, 90123 Palermo, Italy; [c]Departamento de Rayos X, Instituto "Rocasolano", CSIC, Serrano 119, 28006 Madrid, Spain; [d]Istituto di Botanica Farmaceutica, Università di Camerino, 62032 Camerino, Italy

Key Words: *Teucrium brevifolium*; Labiatae; rearranged *neo*-clerodane diterpenoids; 5,10-seco-1,6-cyclo-*neo*-clerodane derivatives; structure elucidation of teubrevins A and B; biogenetic pathway.

Abstract: Two new diterpenoids, teubrevins A and B, have been isolated from the aerial parts of *Teucrium brevifolium* (Labiatae). The structures of teubrevin A [(1*R*,12*S*)-3β-acetoxy-4α,18;15,16-diepoxy-6β-hydroxy-10-oxo-5,10-seco-1,6-cyclo-*neo*-cleroda-5(19),13(16),14-trien-20,12-olide, **1**] and its 8β-hydroxy derivative (teubrevin B, **2**) were established by spectroscopic means, including an X-ray diffraction analysis of the former. Compounds **1** and **2** possess a new 5,10-seco-1,6-cyclo-*neo*-clerodane skeleton, the biogenesis of which is briefly discussed.

The genus *Teucrium* (family Labiatae) is so far the most abundant natural source of *neo*-clerodane and 19-nor-*neo*-clerodane diterpenoids[1]. These compounds have attracted a great interest on account of their useful antifeedant activity[2] and fascinating and challenging structures[3].

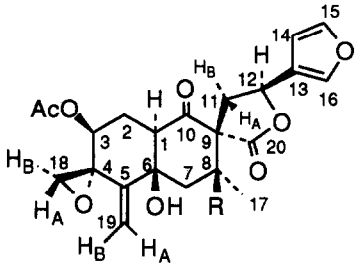
In our continued search for new insect antifeedants from natural sources[2c,3], we have studied *Teucrium brevifolium* Schreber, a species which grows in small areas of Greece. We wish to report herein the isolation and structure determination of two new rearranged *neo*-clerodane diterpenoids, teubrevins A (**1**) and B (**2**), possessing a 5,10-seco-1,6-cyclo-*neo*-clerodane skeleton which, to the best of our knowledge, has now been found for the first time in natural products.

RESULTS AND DISCUSSION

Repeated chromatography of the acetone extract of the aerial parts of *T. brevifolium* (see Experimental) led to the isolation of compounds **1** and **2** (teubrevins A and B, respectively).

Combustion analysis and low-resolution mass spectrometry indicated the molecular formula $C_{22}H_{24}O_8$ for teubrevin A (**1**) and its IR spectrum showed hydroxyl (3440 cm^{-1}), furan (3140, 1600, 1505, 875 cm^{-1}), acetate (1715, 1260 cm^{-1}), γ-lactone (1760 cm^{-1}), ketone (1705 cm^{-1}) and exocyclic methylene (3090, 1650,

910 cm^{-1}) absorptions. The ^1H and ^{13}C NMR spectra of compound **1** (Tables I and II, respectively) were very similar to those of several 3β-acetoxy-4α,18;15,16-diepoxy-*neo*-cleroda-13(16),14-dien-20,12-olide derivatives previously found in other *Teucrium* species[1,2a,3], showing characteristic signals for a 3β equatorial acetoxyl group ($\delta_{H\text{-}3\alpha}$ 5.07 dd, $J_{3\alpha,2\alpha}$=6.0 Hz, $J_{3\alpha,2\beta}$=11.4 Hz; $\delta_{C\text{-}3}$ 68.3 d), a β-substituted furan [δ_H 7.49 m (H-16), 7.44 t (H-15) and 6.41 dd (H-14); δ_C 123.9 s (C-13), 108.1 d (C-14), 144.1 d (C-15) and 140.1 d (C-16)], a 4α,18-oxirane [C-18 protons at δ 2.46 and 3.20 as an AB system, J_{gem}=6.0 Hz; δ_C 63.9 s (C-4) and 52.2 t (C-18)], a 20,12-γ-lactone [C-11 and C-12 protons as an ABX system at δ 2.15 dd (H_A-11), 3.24 dd (H_B-11) and 5.39 dd (H-12), J_{gem}=13.1 Hz, $J_{11A,12}$=9.8 Hz, $J_{11B,12}$=6.7 Hz; δ_C 59.3 s (C-9), 35.4 t (C-11), 73.3 d (C-12) and 172.4 s (C-20)] and a secondary methyl group at the 8α equatorial position [δ_H 1.21 d (Me-17), 2.37 ddq (H-8β), $J_{8,17}$=6.8 Hz; δ_C 34.8 d (C-8) and 16.5 q (C-17)]. In addition, teubrevin A possessed an exocyclic methylene group (two one-proton singlets at δ 5.27 and 5.40; δ_C 147.5 s and 110.5 t), a methine carbon attached to two fully substituted carbons and to a methylene group (δ_H 3.19 dd, $J_{a,a'}$=11.2 Hz, $J_{a,e'}$=5.1 Hz; δ_C 50.1 d), a tertiary alcohol function (δ_C 75.7 s), two methylene groups (a two-protons complex signal at δ 2.17 and two one-proton signals at δ 2.00 dd and 2.85 dd; δ_C 25.8 t and 38.8 t, respectively) and finally, a ketone function (δ_C 201.7 s).



1 R= H

2 R=OH

Double resonance experiments revealed that both the methine (δ 3.19 dd) and acetoxymethine (δ 5.07 dd) protons were coupled with the same methylene protons at δ 2.17 m, thus establishing the partial structure (C)-CHOAc-CH_2-CH-(C). Moreover, when the H-8β proton (δ 2.37 ddq) was irradiated the signal of the Me-17 group (δ 1.21 d) collapsed into a singlet and the two one-proton double-doublet signals at δ 2.00 and 2.85 (J_{gem}=13.9 Hz, $J_{8\beta,7\alpha}$=12.7 Hz, $J_{8\beta,7\beta}$=4.4 Hz) were transformed into an AB system.

All the above data, together with biogenetic reasons (see below), suggested a structure of rearranged *neo*-clerodane such as **1** for teubrevin A. This hypothesis was also supported by the heteronuclear multiple bond correlation (HMBC) spectrum of the new diterpenoid where, among others, connectivities through three bonds between the lactone (δ 172.4) and ketone (δ 201.7) carbonyl carbons and the C-11 methylene protons (δ 2.15 and 3.24) were observed, as well as between the exocyclic methylene protons (δ 5.27 and 5.40) and the carbons belonging to the oxirane (C-4, δ 63.9) and to the tertiary hydroxyl function (δ 75.7). This spectrum also displayed cross-peaks of connectivity through two bonds between the tertiary hydroxyl carbon (δ 75.7) and the C-7 methylene protons (δ 2.00 and 2.85), which in turn were connected through three bonds with the C-17 methyl carbon (δ 16.5).

Table I. ^{1}H NMR Data of Compounds **1** and **2**[a]

	1	2	*J* (Hz)	1	2
H-1α	3.19 dd	3.28 dd	1α,2α	5.1	5.9
H-2α }	2.17[b]	2.20[b]	1α,2β	11.2	10.0
H-2β }			2α,3α	6.0	6.3
H-3α	5.07 dd	5.06 dd	2β,3α	11.4	10.8
H-7α	2.85 dd	3.19 d	7α,7β	13.9	14.5
H-7β	2.00 dd	2.25 d	7α,8β	12.7	-
H-8β	2.37 ddq	-	7β,8β	4.4	-
H_A-11[c]	2.15 dd	2.40 dd	8β,17	6.8	-
H_B-11[c]	3.24 dd	3.29 dd	11A,11B	13.1	13.6
H-12	5.39 dd	5.35 dd	11A,12	9.8	10.1
H-14	6.41 dd	6.42 dd	11B,12	6.7	6.6
H-15	7.44 t	7.44 t	14,15	1.7	1.8
H-16	7.49 m	7.50 m	14,16	0.9	0.9
Me-17	1.21 d	1.40 s	15,16	1.7	1.8
H_A-18[c]	2.46 br d	2.48 br d	18A,18B	6.0	6.1
H_B-18[c]	3.20 d	3.18 d	18A,3α	<0.4	<0.4
H_A-19[d]	5.27 s	5.28 s	19A,19B	<0.4	<0.4
H_B-19[d]	5.40 s	5.43 s			
OAc	2.04 s	2.03 s			
OH	1.40 br s	3.09 br s			
	-	4.20 br s			

[a]At 300 MHz in $CDCl_3$ solution. Chemical shifts are in ppm (δ) referenced to the signal of residual $CHCl_3$ (δ 7.25). Spectral parameters were obtained by first order approximation. All these assignments were confirmed by double resonance experiments.
[b]Overlapped signal.
[c]Protons H_A-11 (pro-*R*), H_B-11 (pro-*S*), H_A-18 (pro-*S*) and H_B-18 (pro-*R*) were distinguished by NOE experiments (see Table III).
[d]Protons H_A-19 (*anti* with respect to the oxirane) and H_B-19 (*syn*) were also distinguished by NOE experiments (see Table III).

Table II. ^{13}C NMR Data of Compounds **1** and **2**[a]

C	1	2	C	1	2
1	50.1 d	50.3 d	12	73.3 d	73.2 d
2	25.8 t	25.5 t	13	123.9 s	123.9 s
3	68.3 d	68.1 d	14	108.1 d	108.2 d
4	63.9 s	61.2 s	15	144.1 d	144.2 d
5	147.5 s	148.4 s	16	140.1 d	140.2 d
6	75.7 s	77.8 s[b]	17	16.5 q	25.4 q
7	38.8 t	41.5 t	18	52.2 t	52.1 t
8	34.8 d	78.1 s[b]	19	110.5 t	111.2 t
9	59.3 s	70.3 s	20	172.4 s	172.0 s
10	201.7 s	200.0 s	OAc	169.6 s	169.9 s
11	35.4 t	32.8 t		20.9 q	20.8 q

[a]At 50.3 MHz in $CDCl_3$ solution. Chemical shifts are referenced to the signal of the solvent (δ 77.0). Multiplicities were determined by DEPT pulse sequences and, in the case of compound **1**, the assignments were confirmed by the HMQC spectrum.
[b]These assignments may be interchanged.

The relative configuration of all the asymmetric centres of this diterpenoid (**1**) was established by NOE experiments. The data collected in Table III show that the Me-17 and H-14 and H-16 furanic protons are on the same side of the plane defined by the γ-lactone ring, because positive NOE enhancement was observed in the signals of the H-14 and H-16 (δ 6.41 and 7.49, respectively) furanic protons when the Me-17 protons (δ1.21)

were irradiated, whereas no effect was produced in the signal of the H-12 proton, thus establishing a 12*S* stereochemistry in a *neo*-clerodane hydrocarbon skeleton[4]. The irradiation of the Me-17 protons also allowed the unequivocal assignment of both the C-11 methylene protons at δ 2.00 (H_A-11, pro-*R* hydrogen, positive NOE enhancement) and δ 3.34 (H_B-11, pro-*S* hydrogen, negative NOE enhancement). Irradiation of the H-3α (δ 5.07) and H-7α (δ 2.85) axial protons caused a NOE enhancement in the signal of the methine proton at δ 3.19 (H-1α), thus indicating that these hydrogens are on the same side of an A/B *trans*-decalin moiety. Moreover, irradiation at δ 2.85 (H-7α) caused a positive NOE enhancement in the H_A-19 proton (δ 5.27) and a negative one in its partner (H_B-19, δ 5.40), whereas on irradiating at δ 2.46 (H_A-18 of the oxirane) a positive NOE enhancement on H_B-19 and a negative one on H_A-19 were observed. These two last experiments confirmed the close spatial relationship between the oxirane, the exocyclic methylene and the C-7 methylene groupings of teubrevin A (**1**), and also provided the unambiguous assignment of both protons of the C-18 and C-19 methylenes.

Table III. NOE Experiments on Compounds **1** and **2**[a]

	1					**2**		
Irradiation at δ (proton)	5.07 (H-3α)	2.85 (H-7α)	1.21 (Me-17)	2.46 (H_A-18)	5.27 (H_A-19)	1.40 (Me-17)	5.28 (H_A-19)	5.43 (H_B-19)
Observed NOE enhancement[b] on								
H-1α	+++	+++	0	0	0	0	0	0
H-2α	++	0	0	0	0	0	0	0
H-3α		+	0	0	0	0	0	0
H-7α	+		++	0	+++	++	++	0
H-7β	0	++++	+	0	+++	++	+++	0
H-8β	0	0	++	0	0	*c*	*c*	*c*
H_A-11	0	0	++	0	0	++	0	0
H_B-11	0	0	-	0	0	-	0	0
H-12	0	0	0	0	0	0	0	0
H-14	0	0	+	0	0	+	0	0
H-16	0	0	+	0	0	+	0	0
Me-17	0	++		0	0		0	0
H_A-18	0	0	0		0	0	0	++
H_B-18	0	0	0	++++	0	0	0	-
H_A-19	0	++	0	-		0		++++
H_B-19	0	-	0	++	++++	0	++++	

[a]Measured at 500 MHz in $CDCl_3$ solution by the FT difference method.

[b]The signs +, ++, +++ and ++++ denote positive NOE enhancements between 0.5-1%, 1-5%, 5-10% and >20%, respectively. The sign - means a weak negative NOE enhancement (0.4-1%). Zero indicates not observed NOE enhancement.

[c]Compound **2** lacks the proton at C-8.

In order to confirm all the above deductions on the structure of teubrevin A (**1**) and establish its absolute configuration, an X-ray diffraction analysis of a single-crystal of this new diterpenoid was undertaken. Figure 1 shows the X-ray molecular model of compound **1**, supporting the preceding deductions on its structure and establishing an absolute configuration related to that of the *neo*-clerodane diterpenes[5]. In the crystalline state, the torsion angles within the six-membered rings A and B indicate that both are in a chair conformation being *trans*-fused, and the angle between them is 177.7(7)°. Furthermore, the γ-lactone (ring C) is not planar, with maximum deviation of 0.162(7) Å and endocyclic torsion angle values from -7° to 22°, whereas the furan ring is almost planar, having torsion angles from 0.010° to -1.3°. The packing of the molecule of teubrevin A (**1**) viewed down the *b* axis is displayed in Figure 2, which shows that the crystal structure is stabilized by

intermolecular hydrogen bonds between the tertiary hydroxyl group at the C-6β position (O8 hydroxyl oxygen atom in Fig. 1) and the carbonyl oxygen atom of the 3β-acetoxyl substituent (O3 in Fig. 1). The hydrogen-bonding parameters are: O8....O3=2.865(4) Å, O3....HO8=1.950(3) Å and O8---HO8....O3=169.9(1)° (x, y, z-1).

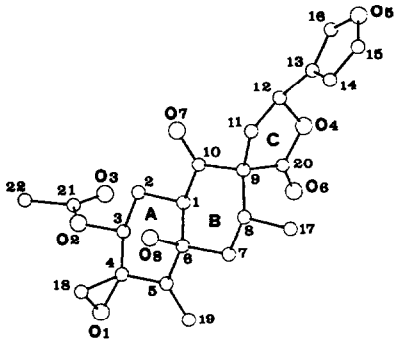


Figure 1. A perspective view of the molecular structure of teubrevin A (**1**), showing the atomic-numbering scheme.

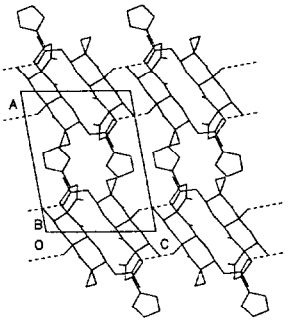
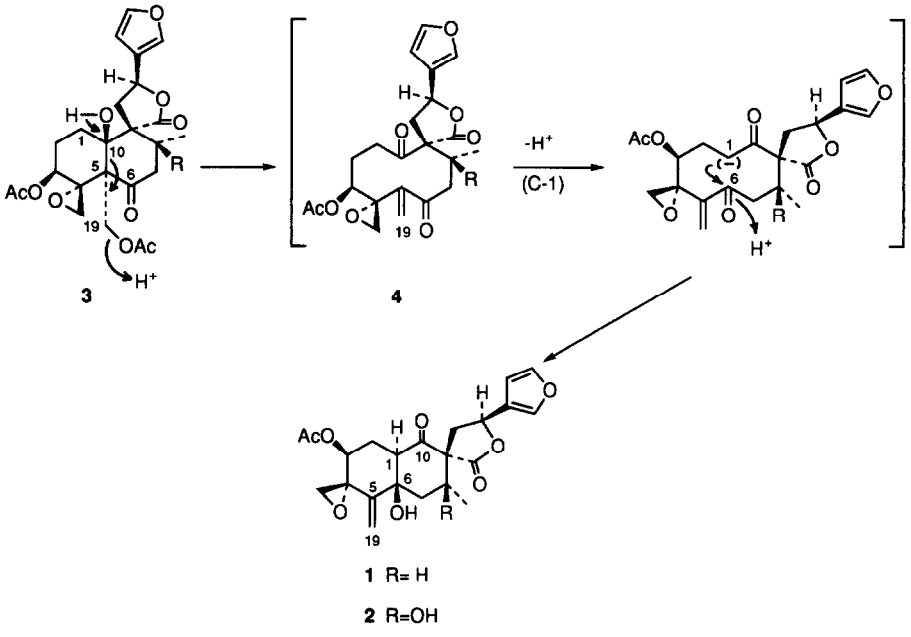


Figure 2. Crystal packing along the b axis of teubrevin A (**1**), showing hydrogen-bonding between molecules in the unit cell.

The other of the diterpenoids isolated from *T. brevifolium*, teubrevin B (**2**), possessed the molecular formula $C_{22}H_{24}O_9$ and its ^1H and ^{13}C NMR spectra (Tables I and II, respectively) were almost identical to those of teubrevin A (**1**). In fact, the observed differences between these spectra were consistent with the presence in teubrevin B (**2**) of an additional tertiary hydroxyl group at the C-8β position instead of the C-8 methine grouping of compound **1** [**2**: Me-17 as a singlet at δ 1.40; $\delta_{C\text{-}8}$ 78.1 s, down-field shift of the β-carbons (C-7, C-9 and C-17; Δδ +2.7, +11.0 and +8.9 ppm, respectively) and up-field resonance of the C-10, C-11 and C-20 γ-carbons (Δδ -1.7, -2.6 and -0.4 ppm, respectively)]. NOE experiments (Table III) established that teubrevin B (**2**) possesses the same stereochemistry at C-12 that compound **1**, and the identical behaviour of both diterpenoids on irradiating the Me-17 protons also confirmed that the C-17 methyl group of teubrevin B is in an equatorial 8α-configuration. Finally, teubrevins A and B showed a negative Cotton effect ($\Delta\varepsilon_{293}$ -0.51 and $\Delta\varepsilon_{295}$ -0.57, respectively), associated with their 10-ketone chromophore, thus establishing the same absolute configuration in both compounds (see above).

Compounds **1** and **2** are the first 5,10-seco-1,6-cyclo-*neo*-clerodane derivatives found in plants and their biogenesis may be rationalized by the mechanistic pathway depicted in Scheme 1. A suitable *neo*-clerodane precursor such as **3**, having a 10β tertiary hydroxyl group and a C-19 acetoxyl substituent[6] as leaving group[7], could produce the 5,10-seco derivative[8] intermediate **4** by a β-fragmentation reaction. A stereoselective intramolecular aldol cyclization of the intermediate **4** leads to the formation of the rearranged *neo*-clerodane hydrocarbon skeleton of teubrevins A and B (**1** and **2**, respectively).

Scheme 1



EXPERIMENTAL

Mps are uncorrected. Aerial parts of *Teucrium brevifolium* Schreber were collected in July 1991 between Menetes and Arkassa at Karpathos island, Greece, and a voucher specimen was deposited in the Herbarium of the Department of Organic Chemistry, University of Palermo, Italy.

Extraction and isolation of the diterpenoids. Dried and powdered *T. brevifolium* aerial parts (500 g) were extracted with Me_2CO (5 l x 3) at room temperature for one week. The extract (34 g) was chromatographed on a silica gel column (Merck No. 7734, deactivated with 15% H_2O, w/v, 400 g) eluted with hexane and hexane-EtOAc mixtures. The fractions eluted with EtOAc-hexane 3:1 provided a mixture of two compounds (80 mg). This mixture was subjected to radial chromatography with $CHCl_3$-MeOH 19:1 as eluent, yielding teubrevin A (**1**, 30 mg, less polar constituent) and teubrevin B (**2**, 20 mg).

Teubrevin A (**1**). Mp 194-196 °C (from EtOAc - *n*-hexane) $[\alpha]_D^{25}$ -55.9° ($CHCl_3$; *c* 0.229). CD nm ($\Delta\varepsilon$): 350 (0), 312 sh (-0.20), 301 sh (-0.45), 293 (-0.51), 286 sh (-0.45), 250 (-0.06)(MeOH; *C* 0.352). IR (KBr) ν_{max} cm^{-1}: 3440 (OH), 3140, 1600, 1505, 875 (furan), 3090, 1650, 910 (exocyclic methylene), 1760 (γ-lactone), 1715, 1260 (OAc), 1705 (ketone), 2990, 2970, 2900, 1445, 1385, 1370, 1175, 1040, 1015, 920,

800, 720, 660. ^{1}H NMR: see Table I. ^{13}C NMR: see Table II. EIMS (70 eV, direct inlet) *m/z* (relative intensity): 416 $[M]^+$ (0.9), 398 (0.8), 370 (5.7), 356 (1.6), 339 (3), 338 (2.2), 310 (10), 309 (8), 280 (14), 265 (11), 161 (12), 133 (15), 130 (24), 105 (14), 95 (41), 91 (19), 81 (18), 77 (18), 69 (13), 55 (29), 43 (100). Anal. Calcd. for $C_{22}H_{24}O_8$: C, 63.45; H, 5.81. Found: C, 63.59; H, 5.63%.

Teubrevin B (**2**). Mp 208-210 °C (EtOAc - *n*-hexane). $[\alpha]_D^{25}$ -12.5°(CHCl3; *c* 0.432). CD nm ($\Delta\varepsilon$): 330 (0), 315 sh (-0.23), 303 sh (-0.49), 295 (-0.57), 288 sh (-0.52), 252 (-0.08) (MeOH; *C* 0.310). IR (KBr) ν_{max} cm^{-1}: 3490, 3450 (OH), 3150, 3130, 3120, 1600, 1510, 875 (furan), 3080, 1650, 910 (exocyclic methylene), 3030 (oxirane), 1760 (γ-lactone), 1730, 1250 (OAc), 1710 (ketone), 2990, 2960, 2930, 1405, 1380, 1325, 1190, 1160, 1050, 1025, 985, 925, 840, 810, 740, 650. ^{1}H NMR: see Table I. ^{13}C NMR: see Table II. EIMS (70 eV, direct inlet) *m/z* (relative intensity): 432 $[M]^+$ (0.4), 414 (0.5), 396 (0.2), 372 (1.2), 355 (3), 354 (1.8), 336 (2.6), 296 (3.7), 217 (2.7), 191 (7), 163 (12), 161 (14), 135 (11), 133 (10), 95 (21), 94 (13), 91 (9), 81 (10), 79 (12), 77 (19), 55 (34), 53 (10), 43 (100). Anal. Calcd. for $C_{22}H_{24}O_9$: C, 61.10; H, 5.59. Found: C, 60.93; H, 5.68%.

X-Ray structure determination of teubrevin A (**1**). Compound **1** was crystallized from EtOAc - *n*-hexane. A crystal of dimensions 0.20x0.12x0.08 mm was selected for data collection. Crystal data: $C_{22}H_{24}O_8$; M_r 416.427 g mol^{-1}; D_c 1.3522 g cm^{-3}; *F* (000) 440; space group $P2_1$; *Z*=2; μ=8.235 cm^{-1}; cell dimensions determined by least-squares refinement on setting angles of 28 reflections (10°<2θ<25°): *a*=11.517(2) Å, *b*=10.235(1) Å, *c*=8.816(5) Å, β=100.199(5)°; *V*=1022.8(2) Å^3. The data were collected on a Philips PW 1100 four-circle diffractometer, scan type ω/2θ, scan speed 0.050 °seg^{-1}, scan width 1.50°, with graphite monochromated CuKα radiation (1.5418 Å). Two reference reflections (3, 4, -1 and -3, -4, 1) were checked every 90 reflections and they showed no intensity variation. The intensity measurement was performed in the *h*, *k*, *l* range -13≤*h*<13, 0≤*k*<11, 0≤*l*<10; θ range 2° to 65°. Number of observed reflections 1820 (Friedel pairs unmerged), unique reflections 1717 [$I>2\sigma(I)$]. The structure was solved by direct methods[9] and difference Fourier maps, and was refined by full-matrix least-squares with anisotropic thermal parameters. All the hydrogen atoms were located on Δρ maps and they were included as isotropic contributors in the refinement, but they were not refined. An empirical weighting scheme was applied so as to give no dependence in $\langle F_O \rangle$, $\langle w\Delta^2 F \rangle$ and $\langle \sin\theta/\lambda \rangle$. The final *R* and R_w values are 5.0 and 5.8%. The final difference synthesis shows the residual electron density no greater than 0.39 e Å^{-3}. The number of variables is 271, degrees of freedom 1446 and the ratio of freedom is 6.34.

The absolute configuration was determined by Bijvoet method[10] and η-refinements for the oxygen dispersors[11]. On considering reflections with $F_O>10\sigma(F_O)$ there are 15 Friedel pairs with $\Delta F>0.12$. The discrepancy indices are: $R_1=\Sigma[(F_O(+h)-F_O(-h))-(F_C(+h)-F_C(-h))]/N=0.265$ (0.355 for the reversed enantiomer), $R_2=1+\Sigma[(R_O-R_C)-1]/N=1.013$ (1.019 for the reversed enantiomer), $R_3=\Sigma[(\Delta I_O-\Delta I_C)/\Sigma(\Delta I_O)]=0.931$ (1.173 for the reversed enantiomer), where $R_O=[F_O(+h)/F_O(-h)]$, $R_C=[F_C(+h)/F_C(-h)]$, $\Delta I_O=F_O(+h)^2-F_O(-h)^2$, and $\Delta I_C=F_C(+h)^2-F_C(-h)^2$. The η-refinements were done starting at (+x, +y, +z, Δf''=0.00), without doing average on *I*'s. The refinement converged to η values of 0.034(12), thus indicating that the correct enantiomer had been chosen.

Scattering factors were taken from the literature[12]. All calculations were performed on a VAX 6410 computer using the *X-Ray 76 System*[13] and Figs. 1 and 2 were designed with *PLUTO*[14]. Lists of atomic

coordinates, thermal parameters, structure factors, bond lengths, bond angles and torsion angles corresponding to compound **1** have been deposited at the Cambridge Crystallographic Data Centre.

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5. Although the hydrocarbon skeleton of teubrevins A and B is biogenetically derived from an *ent*-labdane and they should be named *ent*-clerodanes, we prefer to use the term *neo*-clerodane proposed by Rogers, D.; Unal, G. G.; Williams, D. J.; Ley, S. V.; Sim, G. A.; Joshi, B. S.; Ravindranath, K. R. in *J. Chem. Soc. Chem. Commun.* **1979**, 97-99, which is the nomenclature used in the great part of the articles published on this subject since 1979.
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