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Rearranged *Neo*-Clerodane Diterpenoids from *Teucrium brevifolium* and their Biogenetic Pathway

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

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

Abstract: Seven new diterpenoids, teubrevins C-I (**1-7** repectively), have been isolated from the aerial parts of *Teucrium brevifolium* and their structures established by spectroscopic means, including an X-ray diffraction analysis of teubrevin I (**7**). All these diterpenoids belong to the *neo*-clerodane-type and five of them (**3-7**) possess an unusual rearranged skeleton having an eight-membered ring carbocycle. The conformation of this ring in each compound was established by exhaustive NMR spectroscopic studies (**3-6**) and from X-ray data (**7**). A biogenetic pathway which explains the formation of the 5,10-seco-9(8→19)*abeo*-*neo*-clerodane skeleton of **5-7** and their 7,8,17-trinor derivatives (**3** and **4**) starting from teubrevin D (**2**) is also discussed.

A large number of *neo*-clerodane and 19-nor-*neo*-clerodane diterpenoids[1] have been isolated from plants in the last few years[2]. These compounds have attracted interest owing to their biological activities, especially as insect antifeedants[3]. Up to date, the most abundant source of this kind of compounds are the plants belonging to the genus *Teucrium* (family Labiatae), from which about 150 *neo*-clerodanes have been isolated[2,4].

Recently[5], we reported the isolation of two 5,10-seco-1,6-cyclo-*neo*-clerodane derivatives (teubrevins A and B) from the acetone extract of the aerial parts of *Teucrium brevifolium* Schreber. A thorough study of the same extract has now allowed the isolation of seven additional diterpene constituents. We wish to report herein the isolation and structure determination of these new compounds.

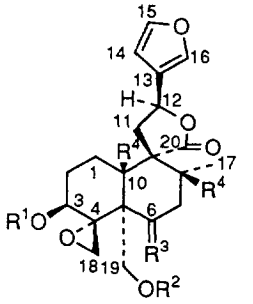
RESULTS AND DISCUSSION

Repeated and careful chromatography of the acetone extract of the aerial parts of *T. brevifolium* (see Experimental) led to the isolation of compounds **1-7** (teubrevins C-I, respectively)[6].

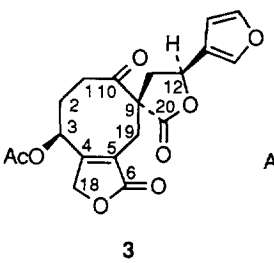
Teubrevin C was identical to the diacetyl derivative of teulepicin[7a] (**8**) and the product obtained by oxidation of teumicropodin[7b](**9**), thus possessing structure **1**. This is the first case in which compound **1** was isolated from a natural source.

Combustion analysis and low-resolution mass spectrometry indicated the molecular formula $C_{24}H_{28}O_{11}$ for teubrevin D (**2**) and its ^1H and ^{13}C NMR spectra (Tables 1 and 2, respectively) were very similar to those of teubrevin C (**1**, $C_{24}H_{28}O_9$)[7a]. The observed differences were consistent with the presence in the former of two

tertiary hydroxyl groups at the C-8 and C-10 positions [ν_{max} 3615, 3540, 3440, 3360 cm^{-1}; δ_C 80.0 s (C-8) and 83.4 s (C-10); Me-17 protons as a singlet at δ 1.33] instead of the C-8 and C-10 methine groups of the latter.



	R^1	R^2	R^3	R^4
1	Ac	Ac	O	H
2	Ac	Ac	O	OH
8	H	H	O	H
9	Ac	Ac	αOH,βH	H



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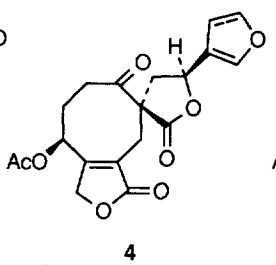

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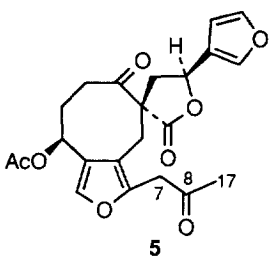

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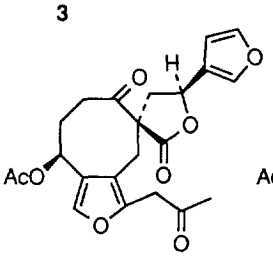

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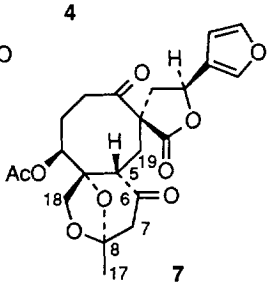

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The ^1H NMR spectroscopic behaviour of the C-7 methylene protons in compounds **1** (an ABX system, J_{gem}=13.6 Hz, $J_{7\alpha,8\beta}$=13.6 Hz, $J_{7\beta,8\beta}$=4.0 Hz)[7a] and **2** (an AB system; J_{gem}=14.4 Hz, Table 1) further supported that in teubrevin D C-8 was a fully substituted carbon atom. The C-8 and C-10 tertiary alcohols of compound **2** must be in a *cis* β-configuration, because they showed IR absorptions corresponding to associated hydroxyl groups (ν_{max} 3440, 3360 cm^{-1}) and even more relevant, the chemical shifts of the C-6, C-11 and C-20 γ-carbons were diamagnetically shifted with respect to those of **1** [$\Delta\delta$ (**2**-**1**)=-2.3 (C-6), -8.1 (C-11) and -1.6 ppm (C-20), respectively]. In particular, the strong shielding shown by the C-11 carbon must be attributed to a γ-gauche effect of the oxygen substituents at the 8β and 10β positions[8,9]. This conclusion was also in agreement with the ^1H and ^{13}C resonances of the Me-17 group of teubrevin D (**2**, δ_H 1.33, δ_C 24.7) as compared with the data reported for other *neo*-clerodane derivatives having an 8β-hydroxyl group (δ_H 1.27-1.54, δ_C 24.1-26.7)[9].

The *neo*-clerodane absolute stereochemistry[1] of teubrevin D was established from its CD curve, which showed a negative Cotton effect associated with the C-6 ketone chromophore ($\Delta\varepsilon_{298}$ -0.71) like in several 6-oxo-*neo*-clerodane derivatives previously described[7a,8b,10]. Finally, NOE experiments (Table 3) evidenced that the furan and the Me-17 group of teubrevin D are on the same side of the plane defined by the 20,12-lactone, thus establishing a 12*S* absolute configuration for this asymmetric centre[11].

From all the above data it was evident that teubrevin D possessed the structure depicted in **2**.

The ^1H and ^{13}C NMR spectra (Tables 1 and 2, respectively) of teubrevin E (**3**, $C_{19}H_{18}O_8$) showed that it possessed a spiro 20,12-γ-lactone and a β-substituted furan identical with those found in compounds **1** and **2**. In addition, teubrevin E (**3**) had an acetoxyl group (δ_H 2.12 s, 3H; δ_C 169.3 s and 20.6 q) equatorially attached to a secondary carbon (geminal proton at δ 5.94 br dd, $J_{a,a'}$=11.7 Hz, $J_{a,e'}$=2.6 Hz; δ_C 71.0 d), an α,β-unsaturated γ-lactone without olefinic protons [δ_C 162.4 s (C-4), 123.9 s (C-5), 172.2 s (C-6) and 69.3 t

Table 1. ^{1}H NMR Spectroscopic Data of Compounds **2**-**7**[a]

H	2	3	4	5	6	7
1α	~1.98[b]	3.56 td[c]	2.24 ddd[d]	3.39 ddd[c]	~2.15[b,d]	~2.38[b]
1β	~1.98[b]	2.33 ddd[d]	4.06 td[c]	2.34 ddd[d]	3.89 td[c]	3.66 ddd[c]
2α	~1.98[b]	2.22 dddd[d]	2.16 dddd[c]	2.24 dddd[d]	~2.33[b,c]	~2.22[b]
2β	~1.98[b]	2.05 dddd[c]	2.32 m[d]	2.05 dddd[c]	~2.13[b,d]	~1.82 m
3α	5.43 dd	5.94 br dd[c]	5.23 dd[d]	5.79 ddd[c]	5.93 br dd[d]	5.20 dd[c]
5β	-	-	-	-	-	3.46 m
7A	2.38 d	-	-	3.55 d	3.59 d	2.45 d
7B	4.17 d	-	-	3.58 d	3.63 d	2.66 d
11A[e]	2.61 dd	2.34 dd	2.64 dd	1.94 dd	2.20 dd	~2.22[b]
11B[e]	3.25 dd	3.19 dd	2.93 dd	3.10 dd	2.97 dd	3.12 dd
12	5.49 br t	5.24 dd	5.58 br t	5.18 dd	5.53 br t	5.42 br t
14	6.41 dd	6.44 dd	6.38 dd	6.43 dd	6.39 dd	6.38 dd
15	7.46 t	7.43 t	7.40 t	7.44 t	7.40 t	7.41 t
16	7.51 m	7.53 m	7.47 m	7.50 m	7.47 m	7.47 m
Me-17	1.33 s	-	-	2.14 s	2.19 s	1.48 s
18A[e]	2.76 d	4.65 dt	4.64 dd	7.23 d	7.30 br s	3.79 d
18B[e]	3.57 d	4.79 dt	4.92 dd	-	-	4.14 br d
19A[e]	4.56 d	2.78 br d	2.91 dd	2.78 d	2.83 dd	~2.38[b]
19B[e]	5.66 d	3.54 d	3.58 dd	3.58 d	3.77 d	~2.38[b]
OAc	2.05 s	2.12 s	2.16 s	2.10 s	2.10 s	2.08 s
	2.01 s	-	-	-	-	-
OH[f]	4.76 s	-	-	-	-	-
	3.21 s	-	-	-	-	-
J (Hz)						
1α,1β	*b*	13.1	12.7	13.4	13.6	12.7
1α,2α	*b*	2.0	2.4	1.9	*b*	*b*
1α,2β	*b*	13.1	6.6	12.2	*b*	*b*
1β,2α	*b*	7.8	12.7	7.6	13.6	12.7
1β,2β	*b*	2.3	2.0	1.9	2.3	5.9
2α,2β	*b*	13.1	14.6	12.9	*b*	*b*
2α,3α	5.8	2.6	2.3	3.2	2.3	2.9
2β,3α	11.2	11.7	5.2	10.7	5.0	10.7
3α,18A	0	0.7	0	1.0	*g*	0
3α,18B	0	1.3	0	-	-	0
5β,18B	-	-	-	-	-	<0.3
5β,19A	-	-	-	-	-	*g*
5β,19B	-	-	-	-	-	*g*
7A,7B	14.4	-	-	16.5	16.0	17.6
11A,11B	15.4	13.4	13.8	12.5	13.9	13.7
11A,12	8.8	10.0	7.2	10.2	7.1	*b*
11B,12	8.5	6.0	8.3	5.6	8.0	8.8
14,15	1.7	1.7	1.7	1.7	1.8	1.7
14,16	1.0	0.8	0.9	0.7	0.8	0.9
15,16	1.7	1.7	1.7	1.7	1.8	1.7
18A,18B	5.6	18.1	17.8	-	-	7.8
18A,19A	0	0.7	1.4	0	0	0
18A,19B	0	0	0	0	0	0
18B,19A	0	1.3	0	-	-	0
18B,19B	0	0	0.6	-	-	0
19A,19B	13.2	13.8	14.0	15.1	14.8	*b*

[a]At 500 MHz in $CDCl_3$ solution. Chemical shifts are relative to the residual $CHCl_3$ (δ 7.25). Spectral parameters were obtained by first order approximation. All these assignments were in agreement with ^{1}H-^{1}H COSY and HMQC spectra and, in the case of **5**, also with the HMBC spectrum. [b]Overlapped signal. [c]Axial proton. [d]Equatorial proton. [e]In some compounds both the methylene protons at C-11, C-18 and C-19 were distinguished by NOE experiments (see Table 3). [f]Disappeared after addition of D_2O. [g]Not measured.

(C-18)], a non-conjugated ketone (ν_{max} 1715 cm^{-1}, δ_C 202.8 s), a methylene carbon placed between fully substituted carbon atoms [two protons as an AB system at δ 2.78 and 3.54, J_{gem}=13.8 Hz; δ_C 29.5 t (C-19)] and two contiguous methylene groups (C-1 and C-2, see Tables 1 and 2). Double resonance experiments, as well as the ^1H-^1H COSY spectrum of teubrevin E (**3**), revealed that the geminal proton to the acetoxyl group was coupled with one of the two contiguous methylene groups (vicinal couplings of 11.7 and 2.6 Hz with the methylene protons at δ 2.05 dddd and 2.22 dddd, respectively) and long-range coupled with both methylene protons corresponding to the α,β-unsaturated γ-lactone part (at δ 4.65 dt and 4.79 dt, J_{gem}=18.1 Hz, $J_{long\text{-}range}$=0.7 and 1.3 Hz, respectively), which in turn showed homoallylic coupling with one of the protons of the isolated methylene group appearing at δ 2.78 (J=1.3 and 0.7 Hz). These results and molecular formula requirements suggested that teubrevin E possessed an eight-membered carbocycle structural part, and this was established from its heteronuclear multiple bond connectivity (HMBC) spectrum, which also provided conclusive proofs on the structure of this diterpenoid. Three bond correlations were observed between the geminal proton of the acetoxyl group (H-3) and the C-18 methylene carbon, as well as between both protons corresponding to the isolated methylene group (see above, H_A-19 and H_B-19) and the C-4, C-6, C-11 and C-20 carbons. Similarly, the ketone carbon (C-10) showed connectivities with both protons of the C-2, C-11 and C-19 methylene groups, whereas the C-3 carbon correlated with the C-1 and C-18 methylene protons. With these crucial relationships established, it was evident that the structure of teubrevin E is **3**, except for its stereochemistry at the C-3, C-9 and C-11 asymmetric centres.

Table 2. ^{13}C NMR Spectroscopic Data of Compounds **2**-**7**[a]

C	2	3	4	5	6	7
1	28.6 t	33.2 t	31.7 t	33.1 t	31.5 t	33.2 t
2	26.5 t	31.1 t	29.9 t	33.9 t	32.9 t	27.1 t
3	66.1 d	71.0 d	67.1 d	69.5 d	67.1 d	69.1 d[b]
4	60.9 s[c]	162.4 s	161.8 s	125.6 s	123.7 s[c]	83.4 s[b]
5	60.7 s[c]	123.9 s[c]	125.5 s	114.3 s	114.9 s	52.3 d
6	203.7 s	172.2 s[d]	173.7 s[c]	146.6 s	147.2 s	207.1 s[b]
7	50.2 t	-	-	41.9 t	42.0 t	50.0 t
8	80.0 s[d]	-	-	203.2 s	203.1 s	106.8 s
9	60.4 s[c]	66.1 s	64.0 s	65.6 s	63.6 s	59.6 s
10	83.4 s[d]	202.8 s	204.8 s	203.8 s	205.6 s	204.8 s
11	35.0 t	36.4 t	33.0 t	37.8 t	33.6 t	34.8 t
12	72.6 d	73.7 d	72.4 d	72.9 d	71.8 d	71.2 d
13	124.7 s	123.0 s[c]	123.3 s	123.2 s	123.4 s[c]	123.2 s
14	108.0 d	108.5 d	108.5 d	108.2 d	108.5 d	108.5 d
15	144.4 d	144.1 d	144.0 d	144.1 d	144.0 d	144.2 d
16	139.7 d	140.6 d	140.5 d	140.3 d	140.3 d	140.6 d
17	24.7 q	-	-	29.4 q	29.5 q	23.9 q
18	44.6 t	69.3 t	70.9 t	138.5 d	141.4 d	70.9 t[b]
19	63.9 t	29.5 t	28.3 t	29.8 t	29.6 t	36.8 t[b]
20	174.8 s	172.7 s[d]	173.4 s[c]	172.5 s	173.5 s	173.1 s
OAc	171.2 s	169.3 s	170.0 s	169.4 s	169.6 s	169.5 s
	169.9 s	20.6 q	20.6 q	21.0 q	21.3 q	20.9 q
	21.0 q	-	-	-	-	-
	21.6 q	-	-	-	-	-

[a]At 125.7 MHz in $CDCl_3$ solution. Chemical shifts are relative to the solvent (δ_{CDCl3} 77.00). Multiplicities were determined from the HMQC spectra and, in the case of **5**, the assignments of the non-protonated carbons were in agreement with the HMBC spectrum. [b]Broadened signal. [c,d]These assignments may be interchanged within the same column, but those given here are considered to be the most likely.

Table 3. Some Significant NOEs Observed in the NOESY Spectra of Compounds **2-6**[a,b]

	Observed proton (δ)	NOE enhancement with protons
2	H_A-7 (2.38)	H_B-7, Me-17
	Me-17 (1.33)	H_A-7, H_B-7, H_A-11[c], H-14
3	H-3α (5.94)	H-1α, H-2α, H_A-18(α)[c], H_B-19(α)[c]
	H_A-11 (2.34)[c]	H_B-11, H-14, H-16, H_A-19(β)[d]
	H_B-11 (3.19)[d]	H_A-11, H-12
4	H-3α (5.23)	H-2α, H-2β, H_A-18, H_B-18
	H_A-11 (2.64)[d]	H_B-11, H-12, H_A-19[c]
	H_B-11 (2.93)[c]	H_A-11, H-14, H-16
	H_B-19 (3.58)[d]	H-1β, H_A-19[c]
5	H-1α (3.39)	H-1β, H-2α, H-3α, H_B-19(α)[c]
	H-3α (5.79)	H-1α, H-2α, H-18, H_B-19(α)[c]
	H_A-7 and H_B-7 (3.55, 3.58)	H_A-11, H_A-19(β)[d]
	H_A-11 (1.94)[c]	H_A-7, H_B-7, H_B-11, H-14, H-16, H_A-19(β)[d]
	H_B-11 (3.10)[d]	H_A-11, H-12
6	H-3α (5.93)	H-2α, H-2β, H-18
	H_A-11 (2.20)[d]	H_A-7, H_B-7, H_B-11, H_A-19[c]
	H_B-11 (2.97)[c]	H_A-11, H-14, H-16
	H_A-19 (2.83)[c]	H_A-7, H_B-7, H_A-11, H-12, H_B-19[d]
	H_B-19 (3.77)[d]	H-1β, H_A-19[c]

[a]At 500 MHz in $CDCl_3$ solution. [b]In some compounds, both the C-11, C-18 and C-19 methylene protons were distinguished by these NOESY spectra: [c]pro-*R* hydrogen, [d]pro-*S* hydrogen. (In compounds **3-6**, the order of priority for the substituents at C-19 is C-9>C-5.)

The relative configuration of teubrevin E depicted in **3** was deduced from a NOESY experiment. The axial H-3α proton showed NOEs with the axial H-1α, the equatorial H-2α, H_A-18 (α configuration) and H_B-19 (α configuration) protons, whereas the H_A-11 proton showed, among others, NOEs with the H-14 and H-16 furanic and the H_A-19 (β) protons (Table 3), thus establishing that the H-1α, H-3α and H_B-19 protons are on the same side (α-face) of the plane defined by the eight-membered ring and the H_A-19 and the C-11 methylene protons are on the opposite one (β-face). These results established that the eight-membered carbocycle of teubrevin E possesses a twist-boat-chair (TBC) conformation[12] (see Fig. 1), in which C-3 and C-19 are below and C-9 and C-10 are over the plane defined by the C-1, C-2, C-4 and C-5 carbons. In this conformation the C-10 keto and C-20 lactone groups are in the more stable 1,3-antiperiplanar arrangement contributing to stabilize (together with the C-4 and C-5 sp^2 carbons) the TBC conformation of the eight-membered ring of teubrevin E (**3**). In addition, the NOESY spectrum also supported a 12*S** configuration for **3**, because the NOEs exhibited by the H_A-11 proton with the H_A-19 and furanic protons (see above and Table 3) evidenced the closeness of all these hydrogens.

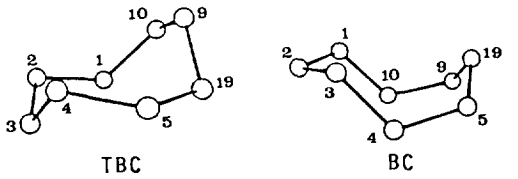


Figure 1. A perspective view of the twist-boat-chair (TBC) conformation of the eight-membered ring in teubrevins E (**3**) and G (**5**) and the boat-chair (BC) conformation of teubrevins F (**4**) and H (**6**).

Compound **3** showed two Cotton effects in its CD curve. The first one ($\Delta\varepsilon_{299}$ -3.41) must be attributed to the C-10 ketone chromophore, and the second one ($\Delta\varepsilon_{242}$ +4.26) could be associated with the lowest energy $\pi \rightarrow \pi^*$ transition of the olefinic double bond of the 6,18-lactone having the acetoxyl substituent at the allylic C-3 position[13]. In the TBC conformation established for teubrevin E (**3**), the C(5)=C(4)-C(3)-OAc chromophore has a *transoid* right-handed chirality (see the molecular model of **3**) if teubrevin E possesses the absolute configuration shown in **3**, which is in agreement[13] with the observed positive Cotton effect at 242 nm (Δε+4.26).

The ^1H and ^{13}C NMR spectra of teubrevin F (**4**, $C_{19}H_{18}O_8$) showed striking similarities with those of compound **3** (see Tables 1 and 2). The only noticeable spectroscopic differences between teubrevins E (**3**) and F were observed in the chemical shifts of the C-3 and C-11 carbons (δ 71.0 and 36.4, and δ 67.1 and 33.0, respectively; Table 2) and the H-3 and H-12 protons (δ 5.94 and 5.24, and 5.23 and 5.58, respectively; Table 1), and also in the coupling values of the H-3 proton (J=11.7 and 2.6 Hz in **3**, and 5.2 and 2.3 Hz in **4**). Moreover, teubrevin F showed a positive Cotton effect associated with its C-10 ketone chromophore ($\Delta\varepsilon_{296}$ +1.74), opposite to that of teubrevin E (**3**, $\Delta\varepsilon_{299}$ -3.41). Apart from the stereochemistry at C-12[14], these results suggested two plausible structural hypothesis for teubrevin F: first, epimer at C-3 of teubrevin E (**3**) with the same TBC conformation of the eight-membered ring or with a different one; and second, epimer at C-9 (structure **4**) with a different eight-membered ring conformation[15]. The first structural possibility seemed to be less likely, taking into account the opposite sign of the Cotton effects of teubrevins E (**3**) and F (see above). On the contrary, the second structural hypothesis (**4**) was strongly supported by the NOESY spectrum of teubrevin F (Table 3). The equatorial H-3α proton showed NOEs only with both C-2 and C-18 methylene protons, and H_B-19 gave NOEs only with its partner (H_A-19) and the axial H-1β proton, and not with the C-11 protons. Moreover, the H_A-11 proton showed NOE with H_A-19 whereas H_B-11 gave NOEs with the H-14 and H-16 furanic protons (see Tables 1 and 3). These NOE results must be accommodated to a structure such is **4** for teubrevin F (see its molecular model), in which the eight-membered ring possesses a boat-chair (BC) conformation[12a] (Fig. 1) having the C-10 keto and C-20 lactone carbonyl groups in the more stable 1,3-antiperiplanar conformation.

Therefore, teubrevins E (**3**) and F (**4**) are epimers at C-9 and this structural difference may be also supported on biogenetic grounds (see below).

Teubrevin G (**5**, $C_{22}H_{22}O_8$) showed ^1H and ^{13}C NMR spectra similar to those of teubrevin E (**3**, Tables 1 and 2). The observed differences were consintent with the presence in the former of a trisubstituted furan possessing a 2-oxo-propyl side chain at the C-6 position [δ_H 7.23 d, J_{allyl}=1.0 Hz (H-18), 3.55 d and 3.58 d, J_{gem}=16.5 Hz (H_A-7 and H_B-7), and 2.14 s, 3H (Me-17); δ_C 125.6 s (C-4), 114.3 s (C-5), 146.6 s (C-6), 41.9 t (C-7), 203.2 s (C-8), 29.4 q (C-17) and 138.5 d (C-18)] instead of the α,β-unsaturated γ-lactone of the latter. The identical pattern shown by the H-3α and C-1, C-2 and C-19 methylene protons in compounds **3** and **5** (Table 1), together with the negative Cotton effect associated with the C-10 ketone of teubrevin G (**5**, $\Delta\varepsilon_{289}$ -2.20) established that this diterpenoid also possesses the eight-membered ring in a TBC conformation[12] like teubrevin E (**3**). Moreover, the ^{13}C NMR data (Table 2) as well as the NOESY spectrum of teubrevin G (Table 3) also supported structure **5** for this compound.

The C-9 epimer of diterpene **5**, teubrevin H (**6**, $C_{22}H_{22}O_8$), was also present in the acetone extract of *T. brevifolium*. The ^1H and ^{13}C NMR spectra of this substance (**6**), as compared with those of compounds **4** and **5** (Tables 1 and 2), clearly revealed that teubrevin H had the structure depicted in **6** and that its eight-membered ring possessed a boat-chair conformation[12] such as in teubrevin F (**4**). The positive Cotton effect of teubrevin H at 288 nm ($\Delta\varepsilon$ +2.29) further supported this point.

The structure of the last diterpenoid isolated from *T. brevifolium*, teubrevin I (**7**, $C_{22}H_{24}O_9$), was solved by an X-ray diffraction analysis. Figure 2 shows the fascinating molecular structure of teubrevin I in which the eight-membered carbocyclic ring (A, Fig. 2) and the substituted tetrahydropyranone moiety (ring C, Fig. 2) have a *cis* junction with an angle of 143.3 (7)°. The endocyclic torsion angles show that the eight-membered ring has a boat-chair (BC) conformation[12a] [torsion angles C(1)-C(10)=-109.8 (1.8)°, C(5)-C(19)=103.9

(1.8)°, C(10)-C(9)=69.7 (2.0)° and C(9)-C(10)=-65.0 (1.9)°]. In this BC conformation of teubrevin I the near symmetry of the eight-membered ring reflected across the local pseudomirror passes through the C-3 and C-9 carbons (Fig. 2), whereas in teubrevins F (**4**) and H (**6**) the local pseudomirror of their boat-chair eight-membered carbocycle passes through the C-2 and C-19 carbons (Fig.1). The six-membered ring of teubrevin I (**7**, ring C, Fig.2) has a distorted half-chair conformation with dihedral angles around C-6 of 2.4 (2.4)° and 9.0 (2.3)°, while the dihedral angles around O-1 are 82.9 (1.7)° and 74.0 (1.8)°; the five-membered ring involving the C-4, O-1, C-8, O-2 and C-18 atoms (ring B, Fig. 2) and the spirolactone (ring D) show envelop conformations with the flap at O-1 and C-11 respectively, whereas the furan ring (E) is planar as could be expected. The molecular packing of teubrevin I in the unit cell viewed along the *c* axis is shown in Figure 3, where the molecules are held together by normal van der Waals forces[16].

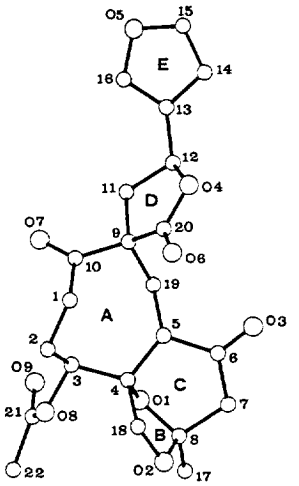


Figure 2. A perspective view of the molecular structure of teubrevin I (**7**), showing the atomic-numbering scheme (hydrogens are omitted for clarity).

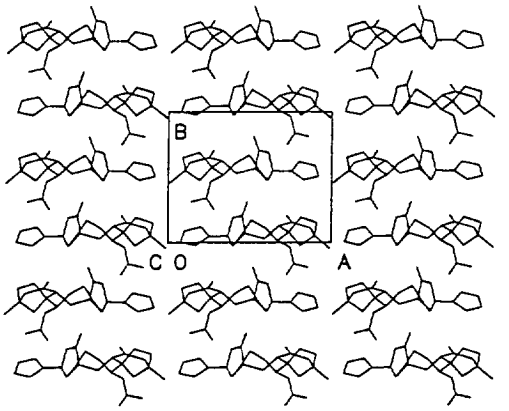
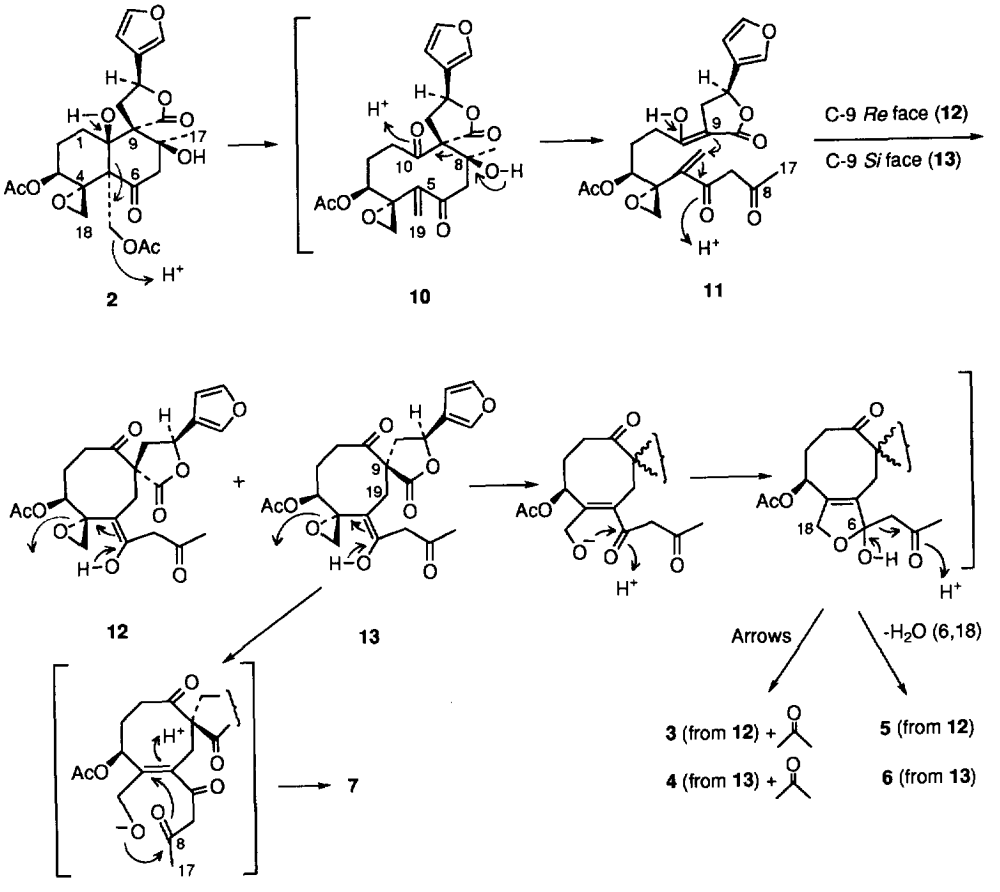


Figure 3. A *PLUTO*[23] plot of the crystal packing along the *c* axis of teubrevin I (**7**).

On the other hand, the ^{1}H and ^{13}C NMR data of teubrevin I (Tables 1 and 2), as well as its CD curve (see Experimental), were in complete agreement with the structure depicted in **7** and Fig. 2 for this diterpenoid[17].

Teubrevins E-I (**3**-**7**, respectively) are the first reported compounds having a rearranged *neo*-clerodane skeleton with an eight-membered ring and their biogenesis may be rationalized by the mechanistic pathway depicted in Scheme 1, in which the postulated precursor for all these rearranged diterpenes is teubrevin D (**2**), a *neo*-clerodane derivative also found in *T. brevifolium* (see above). Teubrevin D (**2**, Scheme 1) could produce the 5,10-seco derivative[18] intermediate **10** by a β-fragmentation reaction[5]. The intermediate **10** undergoes a retroaldol reaction on its 8-hydroxy-10-ketone moiety yielding the intermediate **11**. An intramolecular cyclization of **11** from the C-9 *Re* and *Si* faces (see Scheme 1), followed by a 4α,18-oxirane-opening reaction[19], leads to the C-9 epimeric intermediates **12** and **13** that could produce compounds **3**-**7** as it is shown in Scheme 1.

Scheme 1



Finally, it is of interest to note that, on biogenetic grounds (Scheme 1), the absolute stereochemistry of compounds **3-7** is the one depicted in their formulae, because all of them could be derived biogenetically from the *neo*-clerodane[1] diterpene teubrevin D (**2**).

EXPERIMENTAL

Mps are uncorrected. Aerial parts of *Teucrium brevifolium* Schreber were collected in July 1991 between Menetes and Ankassa, Karpathos Island, Greece, and voucher specimens were 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 x3) 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 petrol and petrol-

EtOAc mixtures. Fractions of 250 ml were collected as follows: 1-10 (petrol), 11-20 (petrol-EtOAc 9:1), 21-25 (petrol-EtOAc 4:1), 26-30 (petrol-EtOAc 7:3), 31-45 (petrol-EtOAc 1:1), 46-50 (EtOAc-petrol 3:1) and 51-60 (EtOAc). The residue of fractions 42-47 (2 g) was rechromatographed over a silica gel column eluting 4 fractions of 100 ml each with petrol-EtOAc 4:1, 3:2, 2:3 and 1:4. The first one containing **3-6** (140 mg) was subjected to rechromatography (silica gel column eluted with petrol-EtOAc 1:1) obtaining 50 mg of **5** and a mixture of **3**, **4** and **6** (55 mg). From this mixture **6** (15 mg) was separated by centrifugal preparative TLC using 2-mm silica gel P_{254} disk and eluting with $CHCl_3$-MeOH 32:1. The remaining mixture of **3** and **4** was separated by TLC on silica gel analytical plates developed 36 times with hexane-EtOAc 6:1, yielding **3** (14 mg, less polar compound) and **4** (8 mg).

The second fraction (80 mg) containing **7** and teubrevins A and B[5] was rechromatographed (silica gel column eluted with $CHCl_3$-MeOH 19:1) to give **7** (9 mg) and a mixture of teubrevins A and B (60 mg, easily separated by radial chromatography[5]).

Compound **1** was purified from the third fraction (30 mg) by radial chromatography (silica gel disk, CH_2Cl_2-MeOH 99:1 as eluent) obtaining 5 mg of clean compound.

Finally, **2** was isolated (8 mg) from the last fraction (100 mg) as the more polar compound (radial chromatography, silica gel disk, $CHCl_3$-MeOH 19:1 as eluent).

Compounds **1-7** were detected in the original extract by TLC, thus showing that the rearranged diterpenes **3-7** are not artefacts of the isolation procedure.

Teubrevin C (**1**) [(12*S*)-3β,19-diacetoxy-4α,18;15,16-diepoxy-6-oxo-*neo*-cleroda-13(16),14-dien-20,12-olide]. Mp 190-192 °C (from EtOAc - *n*-hexane); $[\alpha]_D^{22}$ +33° ($CHCl_3$; *c* 0.121). Lit.[7] mp 189-190 °C and 192-194 °C; $[\alpha]_D^{18}$ +36.6° and +34.5°. IR, ^1H NMR and mass spectra identical to those previously reported[7]. Comparison (mixed mp, TLC behaviour) with an authentic sample[7] confirmed the identity.

Teubrevin D (**2**) [(12*S*)-3β,19-diacetoxy-4α,18;15,16-diepoxy-8β,10β-dihydroxy-6-oxo-*neo*-cleroda-13(16),14-dien-20,12-olide]. Mp 182-184 °C (EtOAc - *n*-hexane); $[\alpha]_D^{22}$ +19.5° ($CHCl_3$; *c* 0.277). CD nm (Δε): 343 (0), 298 (-0.71), 249 (0), 225 (-0.62) (MeOH; *c* 0.0334). IR (KBr) ν_{max} cm^{-1}: 3615, 3540, 3440, 3360 (OH), 3140, 3100, 1500, 875 (furan), 3020 (oxirane), 1750 (γ-lactone), 1720, 1250 (OAc), 1710 (ketone), 2980, 2940, 1420, 1385, 1370, 1200, 1170, 1050, 1030, 950, 900, 800. ^1H NMR: Table 1. ^{13}C NMR: Table 2. EIMS (70 eV, direct inlet) *m/z* (rel. int.): $[M]^+$ absent, 474 $[M-H_2O]^+$ (0.1), 432 $[M-HOAc]^+$ (0.3), 414 $[M-H_2O-HOAc]^+$ (2.3), 374 (6), 354 (5), 312 (4), 179 (13), 165 (11), 161 (17), 133 (14), 95 (32), 94 (16), 91 (14), 77 (19), 60 (10), 55 (16), 43 (100). Anal. Calcd. for $C_{24}H_{28}O_{11}$: C, 58.53; H, 5.73. Found: C, 58.76; H, 5.69%.

Teubrevin E (**3**) [(9*S*,12*S*)-3β-acetoxy-15,16-epoxy-10-oxo-5,10-seco-9(8→19)*abeo*-7,8,17-trinor-*neo*-cleroda-4,13(16),14-triene-6,18;20,12-diolide]. Mp 188-190 °C (EtOAc - *n*-hexane); $[\alpha]_D^{20}$ -8.6° ($CHCl_3$; *c* 0.058). CD nm (Δε): 334 (0), 299 (-3.41), 266 (0), 242 (+4.26), 224 (0) (MeOH; *c* 0.0158). UV (MeOH) λ_{max} nm (log ε): 210 (4.12), 283 sh (2.46). IR (KBr) ν_{max} cm^{-1}: 3120, 1505, 875 (furan), 1760, 1675 (α,β-unsaturated γ-lactone), 1755 (γ-lactone), 1750, 1230 (OAc), 1715 (ketone), 2940, 1460, 1360, 1175, 1035, 1020, 980, 925, 800. ^1H NMR: Table 1. ^{13}C NMR: Table 2. EIMS (70 eV, direct inlet) *m/z* (rel. int.): 374

$[M]^+$ (25), 346 (5), 329 (4), 314 (4), 286 (48), 241 (9), 191 (20), 95 (100), 94 (21), 91 (13), 81 (21), 77 (20), 65 (12), 55 (20), 43 (80). Anal. Calcd. for $C_{19}H_{18}O_8$: C, 60.96; H, 4.85. Found: C, 61.12; H, 4.73%.

Teubrevin F (**4**) [(9*R*,12*S*)-3β-acetoxy-15,16-epoxy-10-oxo-5,10-seco-9(8→19)*abeo*-7,8,17-trinor-*neo*-cleroda-4,13(16),14-triene-6,18;20,12-diolide]. Amorphous solid, mp 50-60 °C; $[\alpha]_D^{20}$ +14.9°($CHCl_3$; *c* 0.187). CD nm (Δε): 335 (0), 296 (+1.74), 265 (0), 252 (-0.65), 244 (0), 238 (+0.86) (MeOH; *c* 0.021). IR (NaCl) ν_{max} cm^{-1}: 3140, 1510, 875 (furan), 1760 br, 1675, 1240 (γ-lactone, α,β-unsaturated γ-lactone and OAc), 1720 (ketone), 2940, 1440, 1370, 1180, 1160, 1040, 1015, 960, 900, 800. ^1H NMR: Table 1. ^{13}C NMR: Table 2. EIMS (70 eV, direct inlet) *m/z* (rel. int.): 374 $[M]^+$ (22), 346 (2), 331 (5), 329 (3), 314 (4), 286 (15), 241 (7), 191 (7), 147 (16), 134 (24), 107 (22), 95 (94), 94 (34), 91 (32), 81 (25), 77 (30), 65 (14), 55 (24), 43 (100). Anal. Calcd. for $C_{19}H_{18}O_8$: C, 60.96; H, 4.85. Found: C, 60.71; H, 4.76%.

Teubrevin G (**5**) [(9*S*,12*S*)-3β-acetoxy-6,18;15,16-diepoxy-8,10-dioxo-5,10-seco-9(8→19)*abeo-neo*-cleroda-4(18),5,13(16),14-tetraen-20,12-olide]. Amorphous solid, mp 70-80 °C; $[\alpha]_D^{21}$ -64.1° ($CHCl_3$; *c* 0.382). CD nm (Δε): 330 (0), 289 (-2.20), 251 (-0.07), 225 (-2.30) (MeOH; *c* 0.023). UV (MeOH) λ_{max} nm (log ε): 209 (3.99), 280 (2.17). IR (KBr) ν_{max} cm^{-1}: 3140, 1630, 1600, 1560, 1510, 875 (furans), 1770 (γ-lactone), 1740, 1245 (OAc), 1715 br (ketones), 2940, 1445, 1375, 1360, 1175, 1160, 1030, 980, 945, 925, 800, 755, 735. ^1H NMR: Table 1. ^{13}C NMR: Table 2. EIMS (70 eV, direct inlet) *m/z* (rel. int.): 414 $[M]^+$ (1), 370 (0.7), 354 (0.8), 310 (3), 267 (3), 189 (3), 161 (4), 133 (4), 131 (4), 95 (10), 94 (4), 91 (10), 81 (5), 77 (8), 55 (6), 43 (100). Anal. Calcd. for $C_{22}H_{22}O_8$: C, 63.76; H, 5.35. Found: C, 63.49; H, 5.21%.

Teubrevin H (**6**) [(9*R*,12*S*)-3β-acetoxy-6,18;15,16-diepoxy-8,10-dioxo-5,10-seco-9(8→19)*abeo-neo*-cleroda-4(18),5,13(16),14-tetraen-20,12-olide]. Amorphous solid, mp 70-80 °C; $[\alpha]_D^{17}$ +56.6° ($CHCl_3$; *c* 0.106). CD nm (Δε): 324 (0), 288 (+2.29), 260 (0), 232 (-3.77), 223 (0) (MeOH; *c* 0.0204). IR (KBr) ν_{max} cm^{-1}: 3140, 1630, 1560, 1510, 875 (furans), 1770 (γ-lactone), 1740, 1245 (OAc), 1715 br (ketones), 2930, 1440, 1370, 1175, 1160, 1025, 950, 930, 800, 750, 735. ^1H NMR: Table 1. ^{13}C NMR: Table 2. EIMS (70 eV, direct inlet) *m/z* (rel. int.): 414 $[M]^+$ (0.03), 370 (0.03), 354 (0.06), 310 (0.3), 282 (0.2), 267 (0.6), 223 (0.5), 211 (0.5), 203 (0.6), 189 (2), 161 (4), 133 (5), 131 (3), 107 (4), 95 (26), 91 (16), 81 (20), 79 (13), 77 (15), 65 (11), 55 (17), 43 (100). Anal. Calcd. for $C_{22}H_{22}O_8$: C, 63.76; H, 5.35. Found: C, 63.81; H, 5.11%.

Teubrevin I (**7**) [(5*S*,9*R*,12*S*)-3β-acetoxy-4α,8;8,18;15,16-triepoxy-6,10-dioxo-5,10-seco-9(8→19)*abeo-neo*-cleroda-13(16)14-dien-20,12-olide]. Mp 214-216 °C (EtOAc - *n*-hexane); $[\alpha]_D^{22}$ +44.1° ($CHCl_3$; *c* 0.118). CD nm (Δε): 340 (0), 320 (+0.18), 315 (+0.17), 308 (+0.22), 302 (+0.090), 299 (+0.095), 296 (0), 291 (-0.10), 276 (-0.26), 257 (-0.14),~255 (-1.44) (MeOH; *c* 0.012). IR (KBr) ν_{max} cm^{-1}: 3140, 3120, 1510, 875 (furan), 1750 (γ-lactone), 1740, 1250 (OAc), 1710 (ketones), 2990, 2880, 1470, 1450, 1390, 1340, 1170, 1160, 1035, 1010, 960, 910, 800, 695. ^1H NMR: Table 1. ^{13}C NMR: Table 2. EIMS (70 eV, direct inlet) *m/z* (rel. int.): 432 $[M]^+$ (2), 390 (3), 373 (2.5), 372 (1.5), 313 (7), 268 (11), 161 (8), 147 (13), 141 (12), 138 (10), 95 (17), 94 (15), 91 (15), 81 (17), 55 (24), 43 (100). Anal. Calcd. for $C_{22}H_{24}O_9$: C, 61.10; H, 5.59. Found: C, 61.29; H, 5.47%.

X-Ray structure determination of teubrevin I (**7**). Compound **7** was crystallized from EtOAc - *n*-hexane. A crystal of dimensions 0.16x0.12x0.08 mm was selected for data collection. Crystal data: $C_{22}H_{24}O_9$, M_r 432.426 g mol^{-1}; D_c 1.4216 g cm^{-3}; systematic absences $0k0$, k odd; space group $P2_1$; Z=2; μ=8.918 cm^{-1}; $F(000)$ 456; cell dimensions determined by least-squares refinement of 26 reflections for lattice parameters with $10°<\theta<27°$: a=12.7696(9) Å, b=10.0880(4) Å, c=7.8520(5) Å, β=92.909(5)°. The data were collected on a Philips PW 1100 four-circle diffractometer, with graphite monochromated CuKα radiation (1.5418 Å), scan mode $\omega/2\theta$, scan width 1.5°, scan speed 0.050 ° seg^{-1}. Two reference reflections were measured every 90 reflections and they showed no intensity variation. The intensity measurement was performed in the h, k, l range $-15\leq h<15$, $0\leq k<12$, $0\leq l<10$; number of measured reflections 1813, observed reflections 1685 [$I>2\sigma(I)$]. The data were corrected for Lorentz and polarization effects but not for absorption. The structure was solved by direct methods, *SIR88*[20]. All the non-H atoms were refined by full-matrix least-squares refinement, first with isotropic and later with anisotropic thermal parameters to values of the residual R=6.7%. At this point, the H-atoms were located in difference Fourier synthesis, but some of them were placed in calculated positions with C-H distances of 1.00 Å. In the final calculations the positions of the H-atoms were refined except for those with calculated positions (H-atoms at carbons C-7, C-17 and C-22). An empirical weighting scheme was applied so as to give no dependence in $\langle w\Delta^2F\rangle$ vs. $\langle F_o\rangle$ and $\langle \sin\theta/\lambda\rangle$. The final R and R_w values are 4.0% and 4.5%, respectively. The final difference synthesis shows the residual electron density no greater than 0.22 eÅ^{-3}. The number of variables is 344, degrees of freedom 1341 and the ratio of freedom is 4.90.

All calculations were carried out on a VAX 6410 computer using the *X-Ray 76 System*[21], *PARST*[22], *PLUTO*[23] and several local programs. Scattering factors were taken from the literature[24]. Lists of atomic coordinates, thermal parameters, structure factors, bond lengths, bond angles and torsion angles corresponding to compound **7** have been deposited at the Cambridge Crystallographic Data Centre.

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REFERENCES AND NOTES

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6. The nomenclature and numbering system for teubrevins E-I (**3-7**, respectively) are based on those in *neo*-clerodane diterpenes. This decision was taken since these substances can be biogenetically generated from a *neo*-clerodane derivative such as teubrevin D (**2**; see discussion of results).

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14. The differences shown between the ^{1}H and ^{13}C NMR and CD spectra of compound **3** and **4** preclude the possibility that these diterpenes differ only in the stereochemistry at the C-12 asymmetric centre (see ref. 11).
15. Another structural posibility for teubrevin F, namely epimer of teubrevin E (**3**) at both C-3 and C-9 carbons, must be discarded because it is the enantiomer of **3** in the carbocyclic part corresponding to the eight-membered ring and, in this case, the spectroscopic behaviour of the C-3 and C-11 carbons and the H-3 proton must be the same in both compounds. Furthermore, a structural difference between **3** and **4** only due to a conformational change in their eight-membered carbocycle is very unlikely, since the ^{1}H NMR spectra of these compounds did not change when they were recorded at -10, 30 or 50 °C.
16. In the crystalline state, teubrevin I (**7**) shows the following intermolecular contacts shorter than the van der Waals radii: O(3)...C(2)=3.23(1) Å (symmetry code x, y, z-1), O(3)...C(11)=3.26(3) Å (1-x, 1/2+y, 1-z), O(3)...C(16)=3.10(4) Å (1-x, 1/2+y, 1-z) and O(6)...H(12)=2.55(5) Å (1-x, 1/2+y, 1-z).
17. It is of interest to indicate that the signals of the C-3, C-4, C-6, C-18 and C-19 carbons appeared as broadened singlets in the ^{13}C NMR spectrum of teubrevin I (**7**, Table 2), probably due to an equilibrium between slightly different conformations.
18. Some 5,10-seco-*neo*-clerod-5(19)-ene derivatives are known as natural products; see Bohlmann, F.; Grenz, M.; Wegner, P.; Jakupovic, J. *Liebigs Ann. Chem.* **1983**, 2008-2020. Singh, P.; Jain, S.; Jakupovic, J. *Phytochemistry* **1988**, *27*, 1537-1539.
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