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A Rearranged Homo-*Neo*-Clerodane Diterpenoid from *Teucrium betonicum*

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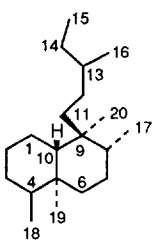
Abstract: A biogenetically unexpected diterpenoid, teubetonin, has been isolated from the aerial parts of *Teucrium betonicum* (Labiatae). Its structure [(12*S*)-6α,19;15,16-diepoxy-6β-hydroxy-7β-hydroxymethylene-18-oxo-19(5→18)*abeo*-*neo*-cleroda-4,13(16),14-trien-20,12-olide] was established by spectroscopic means, including an X-ray diffraction analysis. Teubetonin possesses a new 7β-homo-19(5→18)*abeo*-*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[1,2]. These compounds have attracted interest on account of their useful antifeedant activity[3] and fascinating and challenging structures[2d,4]. More than 160 diterpenoids have been isolated from *Teucrium* species in the last few years[2,3a,4], the greatest part of which possessing the *neo*-clerodane (**1**) or 19-nor-*neo*-clerodane hydrocarbon skeleton. Structural modifications of this framework have been found only in twelve compounds, namely, two 5,10-seco-1,6-cyclo-*neo*-clerodanes (teubrevins A and B)[2d], the 5,6-seco derivative fruticolide[5a], two 13,14,15,16-tetranor compounds (teucrolivin F[5b] and teucrolin D[5c]), two diterpenoids having the Me-17 group in a biogenetically unusual 8β-configuration (teuvincentins B and C)[5d] and five 5,10-seco-9(8→19)*abeo*-*neo*-clerodanes (teubrevins E-I) recently isolated from *T. brevifolium*[5e].

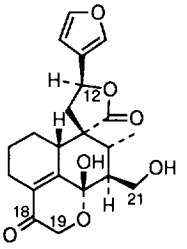
In our continued search for new antifeedants from natural sources[2d,3b,c,4,5a,b,d,e] we have studied *Teucrium betonicum* L'Hérit. (synonym *T. canescens* Forst., *T. maderense* Lam.), a species which grows in Madeira Island (Portugal). We wish to report herein the isolation and structure elucidation of a new rearranged homo-*neo*-clerodane derivative, which has been found in that plant together with other previously known diterpenoids.

RESULTS AND DISCUSSION

Repeated chromatography of the acetone extract of the aerial parts of *T. betonicum* (see Experimental) led to the isolation of the already known *neo*-clerodanes 19-acetylgnaphalin (also named teucrin H3)[6a,b], teucvin[6c,d], teucrin H2[6a] (identical to teuchamaedryn B[6e]), 6β-hydroxyteuscordin[6f], 6α-hydroxyteuscordin[6g] and teucrin E[6e,h]. In addition, a new substance, teubetonin, was also found in the same extract and its structure (**2**) established as follows.



1



2

Combustion analysis and low-resolution mass spectrometry indicated the molecular formula $C_{21}H_{24}O_7$ for teubetonin (**2**) and its IR spectrum showed hydroxyl (3580, 3360 cm^{-1}), furan (3120, 3110, 1600, 1500, 870 cm^{-1}), γ-lactone (1760 cm^{-1}) and α,β-unsaturated ketone (1680, 1630 cm^{-1}) absorptions. The ^1H and ^{13}C NMR spectra of compound **2** (Table 1) were very similar to those of several 15,16-epoxy-*neo*-cleroda-13(16),14-dien-20,12-olide derivatives previously found in other *Teucrium* species[2d,3-6], showing characteristic signals for a β-substituted furan [δ_H 7.46 m (H-16), 7.45 t (H-15) and 6.41 dd (H-14); δ_C 125.1 s (C-13), 108.1 d (C-14), 144.2 d (C-15) and 139.4 d (C-16)], a 20,12-γ-lactone [C-11 and C-12 protons as an ABX system at δ 2.50 dd (H_A-11), 2.65 dd (H_B-11) and 5.46 br t (H-12), J_{gem}=14.2 Hz, $J_{11A,12}$=8.6 Hz, $J_{11B,12}$=9.1 Hz; δ_C 53.6 s (C-9), 41.1 t (C-11), 72.3 d (C-12) and 177.0 s (C-20)] and a secondary methyl group at the 8α equatorial position [δ_H 1.08 d, 3H (Me-17) and 2.36 dq (H-8β), $J_{8,17}$=6.6 Hz, $J_{8\beta,7\alpha}$=12.1 Hz; δ_C 34.6 d (C-8) and 13.9 q (Me-17)]. In addition, teubetonin possessed a ketone function (δ_C 194.5 s) placed between a tetrasubstituted olefinic double bond [UV absorption at λ_{max} 246 nm (log ε 4.19); δ_C 131.5 s (C-4) and 151.0 s (C-5)] and an oxymethylene group [δ_H 4.14 d and 4.59 d, J_{gem}=16.5 Hz; δ_C 65.5 t (C-19)], a hemiketalic carbon [δ_C 94.9 s (C-6)] and finally, a hydroxymethylene group attached to a methine carbon [δ_H 3.93 dd and 4.61 dd, J_{gem}=10.7 Hz, J_{vic}=2.9 and 1.5 Hz, respectively; δ_C 59.4 t (C-21)].

Table 1. ^1H and ^{13}C NMR Spectroscopic Data of Compound **2**[a]

Carbon No.	δ_H	δ_C	Carbon No.	δ_H	δ_C	J_{H-H}	Hz
1	1.57 m[b]	25.35 t	14	6.41 dd	108.09 d	7α,8β	12.1
	2.12 m[b]		15	7.45 t	144.22 d	7α,21A	2.9
2	1.51 m[b]	20.30 t	16	7.46 m	139.37 d	7α,21B	1.5
	1.85 m[b]		17	1.08 d[e]	13.90 q	8β,17	6.6
3	2.03 m[b]	20.53 t	18	-	194.51 s	10β,1A	7.8
	~2.50[b,c]		19	4.14 d[b]	65.52 t	10β,1B	4.8
4	-	131.53 s		4.59 d[b]		10β,3A[d]	2.1
5	-	151.05 s	20	-	177.01 s	10β,3B[d]	~1
6	-	94.89 s	21	3.93 dd	59.37 t	11A,11B	14.2
7	2.53 ddd	45.74 d		4.61 dd		11A,12	8.6
8	2.36 dq	34.58 d	6(OH)	5.34 s[f]	-	11B,12	9.1
9	-	53.58 s				12,16	<0.3
10	2.84 br ddd[d]	42.98 d				14,15	1.8
11	2.50 dd[b]	41.07 t				14,16	0.8
	2.65 dd[b]					15,16	1.8
12	5.46 br t	72.30 d				19A,19B	16.5
13	-	125.14 s				21A,21B	10.7

[a]At 500 MHz (^1H) and 125.7 MHz (^{13}C) in $CDCl_3$ solution. Chemical shifts are relative to the solvent (residual $CHCl_3$, δ 7.25 for ^1H, and δ_{CDCl3} 77.00 for ^{13}C). ^1H NMR spectral parameters were obtained by first order approximation. All these assignments were in agreement with ^1H-^1H COSY and HMQC spectra. [b]The configuration of these protons was not determined. [c]Overlapped signal. [d]Homoallylic coupling with the H_A-3 and H_B-3 protons. [e]A 3H signal. [f]Signal interchangeable with D_2O.

The attachment of the hydroxymethylene group to the 7β equatorial position of the *neo*-clerodane framework was evidenced by double resonance experiments. Irradiating at δ 2.36 (H-8β) the Me-17 protons doublet signal (δ 1.08) appeared as a singlet and the signal at δ 2.53 (H-7α, ddd) collapsed into a double doublet, lacking the

trans-diaxial 8β,7α coupling (J=12.1 Hz). Moreover, irradiation at δ 2.53 (H-7α) modified the signals of the H-8β and C-21 methylene protons, now appearing as a quartet and an AB system, respectively.

The remaining structural part of teubetonin (**2**) was established through an examination of the heteronuclear multiple bond connectivity (HMBC) spectrum. Three bond correlations were observed between the hemiketal carbon (δ 94.9 s) and the H-8β and C-19 and C-21 methylene protons, as well as a connectivity through two bonds with the H-7α proton. The C-4 olefinic carbon (δ 131.5 s) was correlated, among others, with the H-10β and one of the C-19 methylene protons (δ 4.59), whereas the C(6)-OH hemiketal proton (δ 5.34) showed three bond connectivities with the C-5 and C-7 carbons (δ 151.0 s and 45.7 d, respectively). Other crucial observations were the correlation observed between the carbonyl carbon (C-18, δ 194.5 s) and the H_B-3 (δ 2.50, three bonds connectivity) and both C-19 methylene protons (δ 4.14 and 4.59, two bonds correlation), and the absence of cross-peaks of the C-19 methylene carbon (δ 65.5 t) with protons. This spectrum also displayed a series of connectivities which were in agreement with the *neo*-clerodane structure (**2**) of teubetonin.

From all the above data it was evident that teubetonin possessed the structure and relative configuration depicted in **2**, except for the stereochemistry at the C-6, C-10 and C-12 asymmetric centres. Although these remaining structural features could be solved from the data reported above[7] and additional NOE experiments[8], an X-ray analysis of teubetonin was undertaken in order to establish these configurations and the absolute stereochemistry of this new diterpenoid.

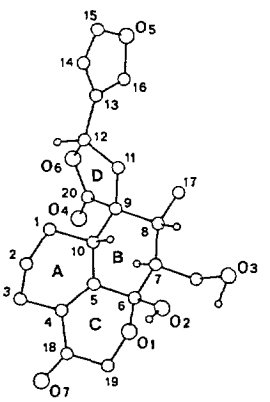


Figure 1. Atom numbering scheme and solid-state conformation of teubetonin (**2**), showing its absolute configuration. (Hydrogen atoms have been omitted for clarity, except those corresponding to C-7, C-8, C-10 and C-12 methine groups and C-6 and C-21 hydroxyl functions.)

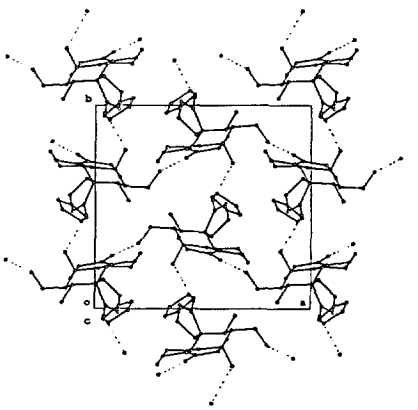


Figure 2. A *PLUTO*[16] plot of the crystal packing along the *c* axis of teubetonin (**2**), showing hydrogen-bonding between molecules in the unit cell.

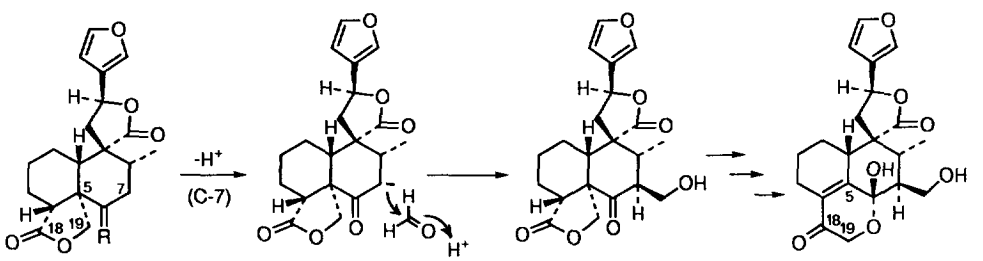
Figure 1 shows the X-ray molecular model of teubetonin confirming all the above deductions on its structure and establishing a *neo*-clerodane absolute configuration[1] with a 12*S* stereochemistry and a 6β-OH and 10β-H arrangement. In the crystalline state ring A of teubetonin (**2**, Fig. 1) shows a conformation between half-chair (C2α-C5β) and C2α-sofa, in which the C-1, C-10, C-5, C-4 and C-3 atoms define a plane from which the largest deviation is 0.098(5) Å and the small one is 0.002 Å, the C-2 atom is out of the plane by -0.633(5) Å. Ring B has a flattened chair conformation, with dihedral torsion angles between 54.2(4)° and 44.9(4)°, whereas ring C possesses a conformation similar to that of ring A, with the C-18, C-4, C-5, C-6 and C-19 atoms in a plane (major deviation 0.036(5) Å, minor deviation 0.001 Å) and the O-1 atom is out of the plane by 0.581(3) Å. Rings A, B and C are not in a plane, the largest deviation is 0.418(4) Å and the small one 0.043(4) Å,

showing the following dihedral angles: A/B=17.1(1)°, A/C=2.8(1)° and B/C=14.8(1)°. The γ-lactone (ring D) shows an envelop conformation, with the flap at C-12 [deviation 0.264(4) Å].

The crystal packing of teubetonin is shown in Figure 2. The crystal structure is stabilized by two intermolecular O-H...O interactions: O(2)...O(6)=2.749(4) Å, O(2)-OH(2)=0.928(3) Å, <[O(2)-OH(2)...O(6)]=169.8° (sym. code 1-x, y-1/2, 1/2-z), and O(3)...O(7)=3.080(5) Å, O(3)-OH(3)=1.165(4) Å, <[O(3)-OH(3)...O(7)]=104.7(2)° (sym. code 1/2+x, 1.5-y, -z). There is one intramolecular hydrogen bond between the C-6 and C-21 hydroxyl groups: O(3)...O(2)=2.807(5) Å, O(3)-OH(3)=1.165(4) Å, <[O(3)-OH(3)...O(2)]=121.3(2)° (see Figs 1 and 2).

It is not easy to rationalize a biogenetic pathway for the formation of teubetonin (**2**) starting from a *neo*-clerodane (**1**). The additional C-21 carbon of compound **2** could arise from a stereoselective aldol condensation of formaldehyde and a suitable 6-keto-*neo*-clerodane such as 6-ketoteuscordin[8b] (**3**, Scheme 1), a diterpene previously isolated from *T. scordium* and whose structure is closely related to those of teucrin E and teucrin H2 (**4** and **5**, respectively, Scheme 1) found in *T. betonicum* (see above). The formaldehyde required for the aldol condensation could be the one generated in the biosynthetic or chemical[6b,9] transformation of *neo*-clerodanes into their 19-nor derivatives, as in the case of the base-catalyzed transformation of 19-acetylgnaphalin into teucvin[6b], two *neo*-clerodanes also found in *T. betonicum*. However, we must admit that we have not been able to propose a likely mechanism for explaining the unusual 19(5→18)-*abeo* arrangement found in teubetonin (**2**).

Scheme 1



3 R=O
4 R=αOH,βH
5 R=αH,βOH

2

Finally, it is not excluded that teubetonin arises as an artefact of the isolation procedure, but this seems to be less likely because no previous 19(5→18)*abeo-neo*-clerodanes have been reported from all the *Teucrium* species investigated up to now[2-7] under identical (or almost identical) extraction and isolation procedures.

EXPERIMENTAL

Mp is uncorrected. Aerial parts of *Teucrium betonicum* L'Hérit. were collected in July 1993 at Porto Moniz, Madeira, Portugal, and voucher specimens were deposited in the Herbarium of the "Jardim Botanico da Ilha da Madeira", Portugal.

Extraction and isolation of the diterpenoids. Dried and powdered *T. betonicum* aerial parts (195 g) were extracted with Me_2CO (2 lx3) at room temperature for one week. The extract (10 g) was chromatographed on a silica gel column (Merck No. 7734, deactivated with 15% H_2O, w/v, 200 g) eluted with petrol and petrol-

EtOAc mixtures, obtaining several fractions containing different mixtures of diterpenoids (TLC). Repeated column chromatography (as above) of these fractions and crystallizations allowed the isolation of the following compounds in order of increasing chromatographic polarity: teucrin H2 (**5**, Scheme 1; 20 mg)[6a], teucvin[6c,d] (12 mg), 19-acetylgnaphalin[6a,b] (15 mg), 6β-hydroxyteuscordin[6f] (4 mg), teubetonin (**2**, 17 mg), 6α-hydroxyteuscordin[6g] (10 mg) and teucrin E (**4**, Scheme 1; 10 mg)[6e,h].

The previously known compounds were identified by their physical (mp, $[\alpha]_D$) and spectroscopic (^{1}H NMR, IR) data and by comparison (mmp, TLC) with authentic samples.

Teubetonin (**2**). Mp 199-201 °C decomp. (from MeOH); $[\alpha]_D^{26}$ +63.6° ($CHCl_3$; *c* 0.162). IR (KBr) ν_{max} cm^{-1}: 3580, 3360 (OH), 3120, 3110, 1600, 1500, 870 (furan), 1760 sh, 1735 (γ-lactone), 1680, 1630 (α,β-unsaturated ketone), 2940, 2860, 1430, 1385, 1380, 1300, 1260, 1190, 1170, 1160, 1020, 985, 965, 895, 810, 730. UV (EtOH) λ_{max} nm (log ε): 213 (4.02), 246 (4.19). ^{1}H and ^{13}C NMR: Table 1. EIMS (70 eV, direct inlet) *m/z* (rel. int.): $[M]^+$ absent, 370 $[M-H_2O]^+$ (0.7), 355 $[M-H_2O-Me]^+$ (0.4), 352 $[M-2H_2O]^+$ (2.5), 340 (11), 267 (4), 246 (11), 213 (12), 201 (99), 187 (14), 174 (21), 173 (22), 145 (34), 141 (22), 131 (30), 129 (48), 128 (47), 115 (58), 105 (40), 95 (87), 94 (52), 91 (79), 81 (59), 77 (64), 69 (37), 65 (33), 55 (46), 44 (100), 43 (68), 41 (75). Anal. Calcd. for $C_{21}H_{24}O_7$: C, 64.93; H, 6.23. Found: C, 65.08; H, 6.29%.

X-Ray structure determination of teubetonin (**2**). Compound **2** was crystallized from MeOH. A crystal of dimensions 0.22x0.18x0.15 mm was selected for data collection. Crystal data: $C_{21}H_{24}O_7$, M_r 388.42 g mol^{-1}, orthorrombic, space group $P2_12_12_1$, a=13.665(1) Å, b=12.910(2) Å, c=10.347(1) Å, V=1825.4(4) Å^3, Z=4, D_c=1.413 g cm^{-3}, λ (CuKα)=1.5418 Å, $F(000)$=824.

The cell dimensions and crystal orientation matrix were determined by a least-squares treatment of the setting angles of 37 reflections in the range $10°<\theta<33°$. Intensity data were collected with a Philips PW 1100 diffractometer and CuKα monochromated radiation; *h*, *k*, *l* ranges 0 to 17, 0 to 16 and 0 to 13, respectively; ω/2θ scan mode, scan width 1.5°, scan speed 0.05° seg^{-1}. During the data collection two standard reflections (0, 2, 0 and 0, -2, 0) were measured every 90 reflections to check the crystal stability and no intensity variation was observed. Measured reflections 3437, independent reflections 1748 [$I>2\sigma(I)$]. The data were corrected for Lorentz and polarization effects but not for absorption. The structure was solved by direct methods[10], which revealed all the non-hydrogen atoms. Positional and thermal parameters for all the non-hydrogen atoms were refined by full-matrix least-squares procedures with isotropic and anisotropic temperature factors. All the hydrogen atoms were located by difference Fourier synthesis and they were refined in the final calculations. An empirical weighting scheme was applied just not to give dependence on $<w\Delta^2F>$ vs. $<F_o>$ and $<\sin\theta/\lambda>$. The final R and R_w values are 5.2 and 5.7%, respectively. The number of variables is 253 and the final difference synthesis shows the residual electron density no greater than 0.22 eÅ^{-3}.

The absolute configuration was determined by Bijvoet methods[11] and η-refinements for the oxygen dispersors. On considering reflections with $F_o>10\sigma(F_o)$ there are 30 Friedel pairs giving the following discrepance indices[12]: $R_1=\Sigma[(F_o(+h)-F_o(-h))-(F_c(+h)-F_c(-h))]/N=0.443$ (0.475 for the reversed enantiomer); $R_2=1+\Sigma[(R_o-R_c)-1]/N=1.022$ (1.023 for the reversed enantiomer); $R_3=\Sigma[(\Delta I_o-\Delta I_c)/\Sigma(\Delta I_o)]=1.039$ (1.058 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[13] were done starting at (+x, +y, +z, Δf"=0.00), without doing average on *I*'s. The η-refinements converged to η values of 0.020(30).

Scattering factors and anomalous dispersion correction were taken from the literature[14]. All calculations were performed on a VAX 1610 computer using the *X-Ray 76 System*[15], *PLUTO*[16] and several local programs.

Lists of atomic coordinates, thermal parameters, structure factors, bond lengths, bond angles and torsion angles corresponding to teubetonin (**2**) have been deposited at the Cambridge Crystallogarphic Data Centre.

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