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REARRANGED ABIETANE DITERPENOIDS FROM THE ROOT OF *TEUCRIUM POLIUM* SUBSP. *VINCENTINUM*

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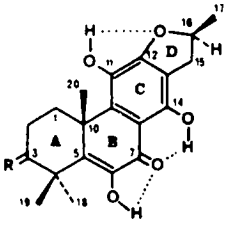
Abstract.— From the root of *Teucrium polium* subsp. *vincentinum* (Labiatae) four new rearranged abietane derivatives, teuvincenones A, B, C, and D (**1** - **4**, respectively), have been isolated. Two of these compounds, teuvincenones C (**3**) and D (**4**), possess a novel hydrocarbon skeleton which contains a cyclopropane ring constituted by the C-3, C-4, and C-18 carbons of the 17(15 → 16)- *abeo* -abietane framework. The structures of these diterpenoids were established mainly by spectroscopic means and, in the case of teuvincenones A (**1**) and C (**3**), also confirmed by X-ray diffraction analyses.

Although more than a hundred neoclerodane diterpenoids have been isolated from the aerial parts of the *Teucrium* species (family Labiatae) in the last few years[1], studies on diterpene constituents of the root of these plants have not been reported.

Now we have investigated the root of *Teucrium polium* L. subsp. *vincentinum* (Rouy) D. Wood, a small shrub which grows on the coastline of Cape São Vicente (Portugal). From the acetone extract of this material four new diterpenoids, teuvincenones A, B, C, and D, have been isolated. Two of these substances, teuvincenones A (**1**) and B (**2**), belong to the 17(15 → 16)-*abeo* -abietane class, whereas the other two, teuvincenones C (**3**) and D (**4**), possess a novel hydrocarbon skeleton of 17(15→16)- *abeo* -3 α,18-cycloabietane. We report here the isolation and structure elucidation of these diterpenoids.

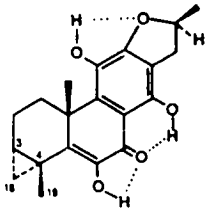
RESULTS AND DISCUSSION

Repeated column chromatography of the acetone extract of the root of *Teucrium polium* subsp. *vincentinum* (see Experimental Section) led to the isolation of compounds **1** - **4** (teuvincenones A, B, C, and D, respectively).



1 R = O

2 R = H, H



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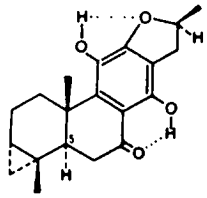

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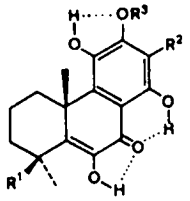
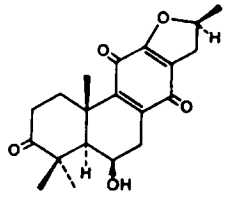


5 R^1 = Me, R^2 = $CHMe_2$, R^3 = H

6 R^1 = CH_2OOCH, R^2 = $CH_2CH{=}CH_2$, R^3 = H

7 R^1 = CH_2OOCH, R^2 = $CH_2CHOHMe$, R^3 = H

8 R^1 = R^3 = Me, R^2 = $CHMe_2$



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Combustion analysis and mass spectrometry indicated the molecular formula $C_{20}H_{22}O_6$ for teuvincenone A (**1**). Its IR spectrum showed phenolic (3470, 3425, 3320 broad, cm^{-1}) aryl ketone[2] (1648, 1620, 1580 cm^{-1}), and saturated ketone (1708 cm^{-1}) absorptions. The presence in compound **1** of a phenolic system conjugated with a diosphenol moiety was revealed by its UV spectra obtained after addition of base, aluminium chloride and aluminium chloride plus hydrochloric acid (Table I), which showed characteristic band shifts of this cross-conjugated chromophore.[2,3] In fact, the UV spectrum of teuvincenone A (**1**) obtained in neutral medium (Table I) was identical with those reported[4] for coleon U (**5**), lanugons R (**6**) and S (**7**), and other related diterpenoids having the 6,11,12,14-tetrahydroxy-5,8,11,13-tetraen-7-one functionality in abietane and 17(15 → 16)- *abeo*-abietane frameworks. Thus, it was evident that teuvincenone A and compounds **5**, **6**, and **7** possess the same chromophore, in which five of the six oxygen atoms of the new diterpenoid (**1**) are involved, whereas the other one must be forming the non conjugated keto group detected in the IR spectrum (ν_{CO} at 1708 cm^{-1}).

However, it was the ^1H NMR spectrum of teuvincenone A that provided the most information and established a structure such as **1** for this new diterpenoid, except for the configuration at its C-16 asymmetric centre. In fact, this spectrum (Table II) showed signals corresponding to three methyl groups attached to fully substituted carbon atoms (singlets at δ 1.58, 1.54, and 1.45) and three hydroxyl protons (singlets at δ 12.44, 6.94, and 4.91), which were almost identical with

Table I. UV spectra of compounds **1 - 4** and **9** [ν_{max} nm (log ε)]

	MeOH	+NaOMe	+$AlCl_3$	+$AlCl_3$-HCl	+NaOAc-H_3BO_3
1	266 (4.06)	266 (4.05)	267 (4.07)	267 sh (4.02)	266 (4.06)
	287 (3.89)	282 sh (3.94)	274 sh (4.04)	274 (4.05)	287 (3.90)
	330 (3.79)	332 (3.77)	290 (3.88)	307 (3.93)	330 (3.79)
	382 (3.91)	384 (3.81)	310 (3.91)	317 sh (3.87)	382 (3.90)
			320 sh (3.87)	368 (3.88)	
			374 (3.91)	442 (3.93)	
			446 (3.88)		
2	266 (4.08)	266 (4.08)	266 (4.12)	267 sh (4.08)	266 (4.03)
	290 (3.94)	290 (3.95)	274 (4.12)	274 (4.12)	290 (3.97)
	334 (3.81)	336 (3.79)	313 (4.03)	311 (4.03)	335 (3.82)
	382 (3.90)	383 (3.94)	378 (3.89)	320 sh (3.96)	3.82 (4.01)
			448 (4.08)	372 (3.84)	
				446 (4.01)	
3	266 (4.05)	266.5 (4.04)	268 sh (4.03)	268 sh (4.03)	266 (4.05)
	289 (3.91)	290 (3.94)	275 (4.07)	274.5 (4.07)	289 (3.91)
	332 (3.74)	333 (3.72)	3.15 (3.97)	310.5 (3.94)	332 (3.74)
	380 (3.89)	380 (3.83)	378 (3.75)	319 sh (3.89)	380 (3.89)
			447 (4.05)	371 (3.74)	
				444 (3.99)	
4	238 (3.81)	238 sh (3.80)	238 sh (3.82)	235 sh (3.94)	*a*
	246 sh (3.75)	298 (3.85)	277 (3.51)	275 (3.58)	
	297 (3.86)	354 (3.56)	328 (4.05)	323 (4.07)	
	353 (3.61)		404 (3.57)	399 (3.60)	
9	282 (3.90)	*b*	*b*	*b*	*a*

a Not measured.

b No variation was observed.

those assigned by Eugster and co-workers[4a] to the C-18, C-19, and C-20 tertiary methyl groups (δ 1.44, 1.44, and 1.65, respectively), the C-6 diosphenol proton (δ 6.95 s), and the C-11 (δ 5.77) and C-14 (δ 12.64 s) phenolic protons of the 12-*O*-methyl derivative (**8**) of coleon U (**5**). The very deshielded resonance of one of the hydroxyl protons of teuvincenone A (δ 12.44 s), together with its slow exchange with D_2O, confirmed the existence of a phenolic group at the C-14 position, which is forming a strong intramolecular hydrogen bond with the C-7 ketone function.[4]

In addition, the ^1H NMR spectrum of teuvincenone A (**1**, Table II) showed two independent spin subsystems with no interrelating cross peaks in the COSY spectrum. Double resonance

experiments, together with the proton connectivities revealed by the COSY spectrum, clearly established that teuvincenone A possesses a structural fragment similar to the C-13-attached side chain of lanugon S[4b] (**7**), since one of these independent spin subsystems showed the signals of a benzylic methylene group (two protons at δ 3.43 dd, J_{gem} = 15.5 Hz, J_{vic} = 9.0 Hz, and δ 2.91 dd, J_{gem} = 15.5 Hz, J_{vic} = 7.3 Hz) coupled with a methine proton (a double doublet of quartets signal at δ 5.18, J_1 = 9.0 Hz, J_2 = 7.3 Hz, J_3 = 6.3 Hz) which, in turn, was connected to a secondary methyl group (δ 1.55 d, J = 6.3 Hz). This structural part of teuvincenone A must be forming an α-methyl dihydrofuran condensed with the completely substituted aromatic ring, because the resonances of its C-16 methine and C-17 methyl protons (see above) appeared at lower field than in lanugon S (**7**, δ 4.33 and 1.32, respectively[4b]). The heteroatom of this dihydrofuran fragment must be attached to the C-12 position, since no shifts were observed in the UV spectrum of teuvincenone A when it was obtained in presence of boric acid plus sodium acetate (see Table I, compound **1**), thus excluding the existence of an *ortho*-diphenol group[2,3] in the molecule of this new diterpenoid. The existence in compound **1** of a phenolic proton strongly chelated (singlet at δ 12.44, see above), which was undoubtedly assigned to the C-14 phenol function[4], also supported this conclusion and ruled out an alternative structure with the dihydrofuranic oxygen atom attached to the C-14 position. (For additional positive proofs on this point, see below).

The other of the two independent spin subsystems shown in the ^{1}H NMR spectrum of teuvincenone A (**1**, Table II) was constituted by four protons belonging to two adjacent methylene groups, which were placed between a fully substituted sp^3 carbon atom and a keto group, since a high geminal coupling value of 16.2 Hz was observed for two of these protons (see Table II: data for H-1α, H-1β, H-2α, and H-2β of compound **1**). Due to the downfield resonance of one of these four protons (δ 3.34 ddd, J_{gem} = 13.7 Hz, two vicinal couplings of 6.3 and 4.0 Hz) it was immediately recognised as the H-1β equatorial proton of abietane derivatives possessing a C-11 hydroxyl group and an aromatic ring C[2,4]. The rather deshielded position of this proton is caused[4] by its coplanarity with the aromatic ring C and its close proximity to the oxygen lone pairs of the C-11 hydroxyl group. In agreement with these data teuvincenone A has its saturated ketone function at the C-3 position.

All the above conclusions on the structure of teuvincenone A (**1**) were also supported by its ^{13}C NMR spectrum (Table III), which exhibited the expected twenty signals, including two carbonyl carbons at δ 214.50 s (C-3) and δ 182.92 s (C-7), eight non protonated sp^2 carbons (C-5, C-6, C-8, C-9, and C-11 to C-14), three methylene sp^3 carbons (C-1, C-2, and C-15), and a methine sp^3 carbon bearing an oxygen atom (δ 83.54 d, C-16), these and the remaining signals being in complete agreement with a structure such as **1** (see Table III). In particular, the location of the saturated keto group of teuvincenone A at the C-3 position instead of the C-1 position was clearly revealed by comparing the ^{13}C NMR spectra of this diterpenoid (compound **1**, Table III) and coleon U (**5**)[4a]. Effectively, the C-3 ketone function causes strong deshielding effects in the C-2 (Δδ +14.78) and C-4 (Δδ +12.18) β-carbons and upfield shifts of the γ-carbons (C-1, C-18, and C-19; Δδ -1.85, -7.24, and -5.52, respectively).

Apart from the above reasons, the closure of the dihydrofuran fragment of teuvincenone A (**1**) at the C-12 and not at the C-14 position was rigorously established by additional spectroscopic

Table II. ^{1}H NMR data of compounds **1** - **4**, and **9**[a,b]

	1	**2**	**3**	**4**	**9**
H-1α	1.86 dt	*h*	0.92[h]	0.89 br td	*h*
H-1β	3.34 ddd	3.06 m	2.80 br ddd	3.05 dd	2.74 dt
H-2α	2.75 ddd[d]	*h*	1.88 ddt	1.80 dddd	*h*
H-2β	2.73 ddd[d]	*h*	2.32 br tt	2.18 tt	*h*
H-3α	-	*h*	-[h]	-	-
H-3β	-	*h*	0.99[h]	0.72 m	-
H-5α	-	-	-	1.90 dd	1.07 t
H-6α	-	-	-	2.69 dd	4.67 dt
H-6β	-	-	-	2.72 dd	-
H-7α	-	-	-	-	2.59 dd
H-7β	-	-	-	-	2.82 dt
H-15α	3.43 dd	3.40 dd	3.40 dd	3.35 dd	3.16 dd
H-15β	2.91 dd	2.88 dd	2.88 dd	2.83 dd	2.63 dd
H-16α	5.18 ddq	5.14 ddq	5.14 ddq	5.11 ddq	5.07 ddq
Me-17	1.55 d	1.53 d	1.53 d	1.50 d	1.49 d
H-18 endo	-	-	0.46 br dd	0.13 br dd	-
H-18 exo	-	-	0.84 br dd	0.53 dd	-
Me-18	1.54 s[e]	1.45 s[b]	-	-	1.22 s[g]
Me-19	1.45 s[e]	1.43 s[b]	1.44 br s	1.06 br s	1.12 s[g]
Me-20	1.58 s	1.66 s	1.65 br s	1.38 s	1.64 s
OH-6[c]	6.94 s	6.94 s	6.57 s	-	*h*
OH-11[c]	4.91 s	4.73 s	4.72 s	4.64 s	-
OH-14[c]	12.44 s	12.60 s	12.60 s	13.26 s	-
J (Hz)					
1α,1β	13.7	*h*	13.4	13.3	13.2
1α,2α	9.9	*h*	5.5	6.6	*h*
1α,2β	9.9	*h*	11.9	13.0	*h*
1β,2α	4.0	*h*	1.6	1.7	3.7
1β,2β	6.3	*h*	5.9	6.6	3.7
2α,2β	16.2	*h*	13.9	14.3	*h*
2α,3α	-	*h*	-	-	-
2α,3β	-	*h*	1.6	0.6	-
2β,3α	-	*h*	-	-	-
2β,3β	-	*h*	5.9	6.6	-
3α,3β	-	*h*	-	-	-
3β,18 endo	-	-	5.2	5.7	-
3β,18 exo	-	-	8.7	9.3	-
5α,6α	-	-	-	7.9	1.4
5α,6β	-	-	-	11.0	-
5α,7β	-	-	-	-	1.4
6α,6β	-	-	-	15.9	-
6α,7α	-	-	-	-	5.3
6α,7β	-	-	-	-	1.4
7α,7β	-	-	-	-	21.0
15α,15β	15.5	15.2	15.2	15.3	16.6
15α,16α	9.0	9.1	8.7	9.1	9.7
15β,16α	7.3	7.3	7.3	7.4	8.0
16α,17	6.3	6.6	6.5	6.5	6.1
18 endo, 18 exo	-	-	4.6	4.3	-

[a] At 300 MHz in $CDCl_3$ solution, with Me_4Si as internal standard; chemical shifts are in ppm (δ). [b] Spectral parameters were obtained by first order approximation. All these assignments were confirmed by double resonance experiments and ^{1}H-^{1}H COSY spectra. [c] Disappeared after addition of D_2O. [d,e,b,g] Assignments bearing the same letter may be interchanged, but those given here are considered to be the most likely. [h] Overlapped signal.

Table III. ^{13}C NMR chemical shifts of compounds **1** and **3**[a]

C	1[b]	1[c]	1[d]	3[e]
1	27.05 t[f]	27.49 t	27.48 t	25.85 t
2	33.08 t	33.55 t	33.55 t	20.29 t
3	214.50 s	214.14 s	214.31 s	18.18 d
4	48.68 s	49.20 s	49.20 s	17.89 s
5	139.99 s[g]	141.11 s	141.10 s	141.23 s[g]
6	140.03 s[g]	142.14 s	142.08 s	142.35 s[g]
7	182.92 s	184.60 s	184.55 s	183.09 s
8	107.14 s	108.43 s	108.39 s	107.99 s
9	135.20 s	137.03 s	137.02 s	137.90 s
10	40.60 s	41.55 s	41.54 s	39.80 s
11	131.20 s	133.30 s	133.28 s	132.78 s
12	153.80 s	153.82 s	153.78 s	153.24 s
13	111.50 s	112.27 s	112.24 s	111.24 s
14	154.83 s	156.81 s	156.85 s	155.93 s
15	34.35 t	34.38 t	34.38 t	34.23 t
16	83.54 d	82.43 d	82.47 d	82.15 d
17	21.98 q	21.72 q[g]	21.74 q[g]	21.88 q
18	24.36 q	24.53 q	24.52 q	17.66 t
19	21.08 q	21.66 q[g]	21.64 q[g]	19.01 q
20	20.11 q	20.43 q	20.43 q	23.20 q

[a] In parts per million downfield from internal Me_4Si; at 75.4 MHz. Chemical shifts are accurate to ± 0.005 ppm.
[b] In $CDCl_3$ solution.
[c] In pyridine-d_5 solution.
[d] In pyridine-d_5 solution after addition of H_3BO_3, see ref. 5.
[e] In $CDCl_3$-pyridine-d_5 (9 : 1) solution.
[f] SFORD multiplicity.
[g] These assignments may be reversed.

and chemical evidences. It is known[5] that boric acid induces shifts and causes a marked broadening of the signals of the carbon atoms bearing 1,2-glycol and *ortho*-diphenol systems and, also, those of some of the other carbons near these functions. The ^{13}C NMR spectra of compound **1** obtained in pyridine-d_5 solution and after addition of boric acid (Table III) were identical, thus confirming that teuvincenone A does not possess any *ortho*-diphenol grouping. On the other hand, catalytic hydrogenation of compound **1** gave a substance (**9**, $C_{20}H_{24}O_5$), the UV and IR spectra of which

showed characteristic absorptions of a substituted *p*-benzoquinone group[4] (λ_{max} 282 nm, log ε 3.90; ν_{max} 1675, 1653, 1640, 1580 cm^{-1}). This result was also in agreement with the existence of two phenolic groups at the C-11 and C-14 positions of teuvincenone A (**1**). The formation of a compound such as **9** can be explained by a stereoselective *cis*-addition of hydrogen from the more accessible α-side of the C-5, C-6 double bond of teuvincenone A, a loss of the C-7 keto group by hydrogenolysis and finally, an easy air-oxidation of the *p*-dihydroxy aromatic ring due to the disappearance of the strong hydrogen bond between the C-14 phenol group and the C-7 ketone of compound **1**. An identical behaviour has been pointed out[4d] in the catalytic hydrogenation of coleon U (**5**).

From all the above data, it was evident that teuvincenone A possesses the structure and relative stereochemistry depicted in **1**, except for the configuration of its C-16 asymmetric centre. In order to elucidate this point conclusively and establish the absolute configuration of the diterpenoid, a single crystal X-ray determination of teuvincenone A was undertaken. Figure 1 shows the X-ray molecular model of compound **1**, confirming all the above deductions and establishing a C-16(*S*) stereochemistry and a *normal* abietane absolute configuration for this new diterpenoid. Furthermore, the crystal structure of teuvincenone A has two crystallographycally independent molecules in the asymmetric unit (**1a** and **1b**, see Fig. 1) and they present only small differences. In both cases (**1a** and **1b**), ring A has a distorted boat conformation, that could be described as between a twist-boat and a boat conformation, and rings B, C and D are almost coplanar, only the C-15 and C-16 carbon atoms are out of this plane for -0.16 and 0.23 Å, respectively. The angles between rings B and C, and C and D are 3° and 6° in molecule **1a** and 2° and 7° for molecule **1b**, respectively. The packing of the molecules is due to a network of inter and intramolecular hydrogen bonds, the details of which are given in Table IV (for some comments on the data in Table IV, see below).

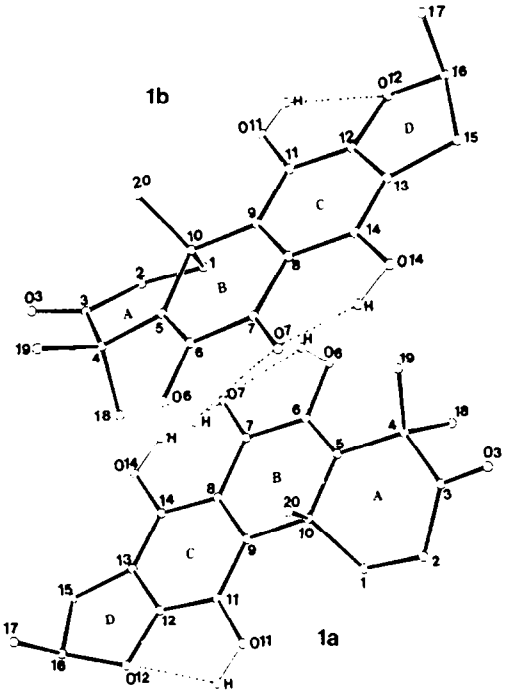

Figure 1. X-ray molecular structure of the asymmetric unit of teuvincenone A (**1**), showing its absolute configuration and the two crystallographycally independent molecules (**1a** and **1b**)

Another of the new diterpenoids, teuvincenone B (**2**), had a molecular formula $C_{20}H_{24}O_5$ and its UV spectra obtained in methanol and by addition of shift reagents

Table IV. Hydrogen-bonding data of teuvincenones A (**1**) and C (**3**) in the crystal structures[a]

Molecule	Symmetric relations[b]	Bond Donor...Acceptor	Donor-H	Bond length (Å) Donor...Acceptor	H...Acceptor	D-H...O angle (°)
1a	(b)	O(6)-H(6)...O(3)[c]	0.96	2.82	2.02	139
	(a)	O(6)-H(6)...O(7)	0.96	2.64	2.14	111
	(a)	O(11)-H(11)...O(12)	0.90	2.81	2.48	102
	(e)	O(11)-H(11)...O(14)[c]	0.90	3.18	2.31	160
	(f)	O(14)-H(14)...O(12)[c]	0.98	2.91	2.46	108
	(a)	O(14)-H(14)...O(7)	0.98	2.61	1.71	150
1b	(g)	O(6)-H(6)...O(3)[c]	0.92	2.73	2.00	136
	(a)	O(6)-H(6)...O(7)	0.92	2.64	2.11	115
	(a)	O(11)-H(11)...O(12)	0.96	2.84	2.47	103
	(c)	O(11)-H(11)...O(14)[c]	0.96	2.85	1.90	170
	(a)	O(14)-H(14)...O(7)	0.99	2.57	1.69	146
	(d)	O(14)-H(14)...O(12)[c]	0.99	2.92	2.35	115
3a	(a)	O(6)-H(6)...O(7)	1.15	2.61	2.00	109
	(a)	O(11)-H(11)...O(12)	1.01	2.81	2.00	135
	(a)	O(11)-H(11)...O(14)[c]	1.01	2.77	2.14	118
	(a)	O(14)-H(14)...O(7)	0.96	2.55	1.89	124
	(h)	O(14)-H(14)...O(12)[c]	0.96	2.81	2.39	106
3b	(a)	O(6)-H(6)...O(7)	0.97	2.57	2.09	109
	(a)	O(11)-H(11)...O(12)	1.19	2.78	2.28	102
	(h)	O(11)-H(11)...O(14)[c]	1.19	2.83	1.67	163
	(a)	O(14)-H(14)...O(7)	0.99	2.54	1.75	134
	(a)	O(14)-H(14)...O(12)[c]	0.99	2.93	2.41	112

[a] For the numbering of the oxygen atoms, see Figures 1 and 3.

[b] (a) x,y,z; (b) 1-x,1/2+y,1-z; (c) 1-x,-1/2+y,2-z; (d) 1-x-1/2+y,1-z; (e) -x,1/2+y,-z; (f) -x,-1/2+y,-z; (g) -x,-1/2+y,1-z; (h) 1-x,y,z.

[c] Intermolecular hydrogen bond.

(Table I) were identical with those of teuvincenone A (**1**), thus establishing the same chromophore in both substances. The ^{1}H NMR spectrum of compound **2** showed a series of signals (see Table II) which confirmed that this diterpenoid possesses rings B, C, and D as in compound **1**, and also revealed the occurrence of three tertiary methyl groups. Since the difference between the molecular formulae of compounds **1** and **2** is the substitution of an oxygen of the former by two hydrogens in the latter, it was clear that teuvincenone B (**2**) was the 3-deoxo derivative of

teuvincenone A (**1**). This conclusion was in agreement with the absence of saturated carbonyl absorptions in the IR spectrum of compound **2** (see Experimental Section).

The stereochemistry at the C-16 centre of teuvincenones A (**1**, αH,βMe, see above) and B (**2**) must be the same, as it was revealed by the almost identical chemical shifts and, less conclusive proof in this case, coupling values of their H-15α, H-15β, H-16α, and Me-17 protons (see Table II). The absolute configuration of teuvincenone B was not solved by direct methods, but the variation of its specific rotation compared with that of teuvincenone A (see Table V) supports an identical absolute stereochemistry in both compounds.

Table V. Specific rotations of compounds **1** - **4**, and **9** [a]

Compound	Temperature (°C)	c	$[\alpha]_{D(589)}$	$\|\alpha\|_{578}$	$\|\alpha\|_{546}$	$[\alpha]_{436}$
1	19	0.051	-13.7	-21.6	-35.3	-2215.7
2	26	0.058	-10.3	-13.8	-29.3	-1586.6
3	29	0.069	-10.1	-14.5	-18.8	[b]
4	29	0.108	+129.6	+134.3	+160.2	+398.1
9	29	0.071	+51.4	+34.3	+65.7	[b]

[a] Values in degrees, $CHCl_3$ solution.
[b] Not measured.

The third of the new diterpenoids, teuvincenone C (**3**, $C_{20}H_{22}O_5$) had UV, ^1H and ^{13}C NMR spectra (Tables I, II, and III) in complete agreement with the existence in its molecule of a structural part, constituted by rings B, C and D, identical with that of teuvincenones A (**1**) and B (**2**). The complete ^1H NMR assignment of teuvincenone C (**3**) was obtained by ^1H-^1H COSY and extensive double resonance experiments, which showed that the rest of its structure was constituted by a continuous thirteen-protons subsystem. This fragment is formed by two tertiary methyl groups long range coupled (broad singlets at δ 1.65 and 1.44), two adjacent methylene groups (four one-proton signals at δ 0.92, 1.88, 2.32, and 2.80, see Table II), and a 1,1,2-trisubstituted cyclopropane (one-proton signals at δ 0.46 br dd, 0.84 br dd, and 0.90 m, partially overlapped signal). The occurrence of this last fragment was rigorously confirmed from ^{13}C NMR data of compound **3** (Table III), which showed three carbon atom resonances at δ 17.66, 17.89, and 18.18 (SFORD multiplicities triplet, singlet, and doublet, respectively) typical of this carbocycle.[6]

A careful inspection of the homonuclear 2D map of teuvincenone C (**3**) revealed the occurrence of cross peaks due to W-type long range couplings, only compatible with a spatial arrangement of the protons as it is shown in Figure 2. Moreover, NOE measurements clearly established that the C-20 methyl and the C-18 methylene groups are *trans*-oriented, since irradiation at δ 1.65 (Me-20) caused NOE enhancement in the signals of the H-1β (δ 2.80, 12% NOE

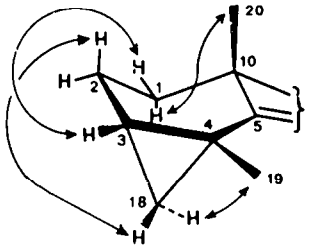

Figure 2. Conformation of ring A of teuvincenone C (**3**), showing carbon atom numbering and the observed ^{1}H-^{1}H long range couplings (W-type).

enhancement) and H-2β (δ 2.32, 17%) protons, whereas the signal of the C-18 endo proton (δ 0.46) was not affected. On the contrary, in compounds such as metasequoic acid A, possessing a *cis*-relationship between the C-20 methyl and C-18 methylene protons, irradiation of the C-20 protons causes a noticeable NOE enhancement in the signal of the C-18 endo proton.[6]

In accordance with the preceding data teuvincenone C possesses structure **3**, in which ring A has a distorted $^{4}C_{1}$ conformation (Figure 2). This structure was confirmed and its *normal* abietane absolute configuration established by X-ray diffraction analysis of a single crystal. The molecular structure of teuvincenone C determined from the X-ray data is illustrated in Figure 3. The crystal of compound **3** has two crystallographycally independent molecules (**3a** and **3b**, see Figure 3) in the asymmetric unit and presents many similarities with teuvincenone A (**1**, see above). In molecules **3a** and **3b** ring A has a conformation which is between an envelope (^{2}E) and a half-chair ($^{2}H_{1}$ conformation, and rings B and C are nearly planar, the larger deviations out of the plane being 0.05 and 0.02 Å, respectively. In molecule **3a** ring D presents an envelope conformation with the flap at C-16, but it is quite flat since the values of the torsion angles are not larger than 6°, whereas in molecule **3b**, although this ring has also an envelope conformation with the flap at C-16, the torsion angles have greater values than in molecule **3a** and are of 15°. The cyclopropane moiety shows the normal geometry for this kind of rings and the angles between it and ring A are 130° and 113° for molecules **3a** and **3b**, respectively. In both molecules (**3a** and **3b**) the angles between rings B and C, and C and D are small and the greater value is 6°.

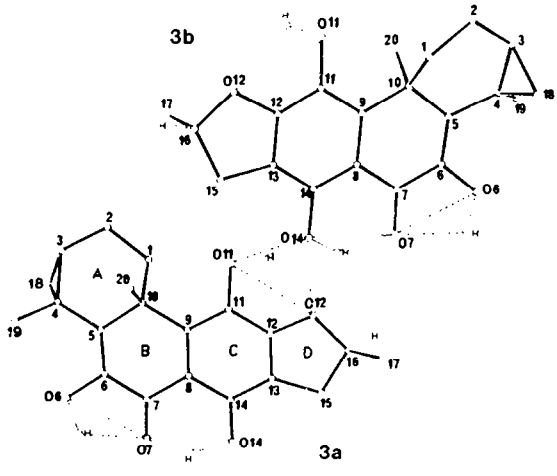

Figure 3. X-ray molecular structures of the two crystallographycally independent molecules of teuvincenone C (**3a** and **3b**) in the asymmetric unit, showing the absolute configuration and the network of inter and intramolecular hydrogen bonds.

As in the case of compound **1**, the packing of the molecules of teuvincenone C (**3**) is due to a net-

work of inter and intramolecular hydrogen bonds, which are shown in Figure 3 and whose details with their symmetry codes are listed in Table IV. It is observed that in the intramolecular hydrogen bonds of compounds **1** and **3** the H...O distances are longer, the O...O distances are shorter and, consequently, the O-H...O angles are smaller than in the intermolecular ones. This is typical of hydrogen bonds involved in bifurcated hydrogen bonds.

The last of the new diterpenoids isolated from the acetone extract of the root of *Teucrium polium* subsp. *vincentinum*, teuvincenone D (**4**), had a molecular formula $C_{20}H_{24}O_4$ and the presence in its structure of a substituted *p*-dihydroxyphenyl moiety conjugated with a ketone function was revealed by its UV spectra obtained after addition of shift reagents[2,3] (see Table I).

Inspection of the ^{1}H NMR spectrum of teuvincenone D (**4**, Table II) clearly revealed that this new diterpenoid possessed two structural fragments identical with those found in teuvincenone C (**3**), namely the α-methyl dihydrofuran condensed with the aromatic ring and the bicyclo[4,1,0] heptane moiety bearing two tertiary methyl groups (C-19 and C-20) in which ring A is involved. In particular, the attachment at C-12 position of the oxygen atom belonging to the dihydrofuran fragment was evidenced by the deshielded signal of the C-14 phenolic proton (δ 13.26), which is forming a hydrogen bond with the C-7 keto group.[4] The almost identical chemical shifts of the C-15 methylene, C-16 methine and C-17 methyl protons in compounds **3** and **4** (see Table II) established the same C-16 stereochemistry in both substances.

In addition, the ^{1}H NMR spectrum of teuvincenone D (**4**) showed the presence of an independent spin subsystem corresponding to three protons, which were undoubtedly assigned to the H-5α, H-6α, and H-6β protons of abieta-8,11,13-trien-7-one derivatives.[2,4] A double doublet signal at δ 2.72 (H-6β) showed two large couplings (J_{gem} = 15.9 Hz, J_{vic} = 11.0 Hz), thus establishing a *trans*-diaxial relationship between this methylene proton and its vicinal partner (H-5α, at δ 1.90 dd, $J_{aa'}$ = 11.0 Hz, $J_{ae'}$ = 7.9 Hz), and therefore the A/B ring junction was recognised as *trans*. In agreement with this conclusion, an NOE experiment showed that irradiation at δ 0.13 (H-18 endo proton) produced a strong NOE enhancement (14 %) of the signal corresponding to the H-5α proton together with small effects in the H-1α (axial) and H-2α (pseudoequatorial) proton signals (3.3 % and 2.3 % NOE enhancements, respectively).

The absolute configuration of teuvincenone D was not ascertained. However, it is reasonable to assume that it possesses a *normal* abietane absolute stereochemistry, since compound **4** showed specific rotations of positive sign and increasing value between 589 nm and 436 nm (Table V), as other abietane diterpenoids[2] having a chromophore of aryl ketone at C-7. This assumption was also supported on biogenetic grounds, because all the other diterpenoids co-occurring in the same plant (**1**, **2**, and **3**) belong to the *normal* series.[7]

Teuvincenones C (**3**) and D (**4**) are the first examples of diterpenoids having a 17(15→16)-*abeo*-3α,18-cycloabietane hydrocarbon skeleton and they should be considered as biogenetic intermediates between the 17(15→16)-*abeo*-abietanes, such as teuvincenones A (**1**) and B (**2**) and lanugons R (**6**) and S (**7**),[4b] and the 17(15→16),18(4→3)-di*abeo*-abietane derivatives, such as plectrinon B and plectranthon J.[4e]

EXPERIMENTAL

Melting points were determined in a Kofler apparatus and are uncorrected. Optical rotations were measured with a Perkin-Elmer 141 polarimeter, with a 1-dm cell. Elemental analyses were carried out in Madrid with the help of a Heraeus CHN-O-Rapid analyzer. IR spectra were determined on a Perkin-Elmer 681 spectrophotometer and UV spectra were measured with a Perkin-Elmer 402 spectrophotometer. ^1H and ^{13}C NMR spectra were obtained at 300 and 75.4 MHz, respectively, on a Varian XL-300 spectrometer, in $CDCl_3$ or pyridine-d_5 solution with Me_4Si as an internal standard. The proton NOE measurements were made at 300 MHz by the FT difference method, with the decoupler operating in the gated mode. Mass spectra were obtained on a VG 12-250 spectrometer (mode EI, 70 eV, solid probe).

Extraction and isolation of the diterpenoids. Dried and finely powdered roots of *Teucrium polium* L. subsp. *vincentinum* (Rouy) D. Wood[8] (6.64 kg) were extracted with Me_2CO for 1 week at room temperature. The solvent was removed in vacuum to yield 132 g of a gummy extract, which was subjected to column chromatography over Si-gel (Merck, No. 7734, deactivated with 15% water, 1.5 kg). Mixtures of petroleum ether-EtOAc of increasing polarity were used as eluents.

From the fractions eluted with petroleum ether-EtOAc (19:1) 53 mg of teuvincenone B (**2**) were isolated. Extensive purification by column chromatography of the fraction eluted with petroleum ether-EtOAc (9:1) led to the isolation of teuvincenone C (**3**, 26 mg) and teuvincenone D (**4**, 17 mg, less polar compound of these two diterpenoids). Finally, elution with petroleum ether -EtOAc (2:1) yielded teuvincenone A (**1**, 380 mg).

Teuvincenone A [**1**; (16*S*)-12,16-epoxy-6,11,14-trihydroxy-17(15 → 16)-*abeo* -abieta-5,8,11, 13-tetraene-3,7-dione]. Mp 259-262°C dec. (EtOAc-*n*-hexane, orange-coloured prisms); [α] values: see Table V; IR (KBr) ν_{max} (cm^{-1}) 3470, 3425, 3320, 3005, 2985, 2940, 2860, 1708, 1648, 1620, 1580, 1465, 1390, 1320, 1250, 1205, 1160, 1030, 1005, 985, 910, 895, 830, 810; UV: see Table I; ^1H NMR: see Table II; ^{13}C NMR: see Table III; MS, *m/z* (relative intensity) 358 (M^+, 100, base peak), 343 (50), 341 (6), 340 (4), 325 (26), 315 (18), 302 (42), 300 (19), 274 (70), 270 (33), 245 (14), 128 (10), 115 (13), 91 (11), 83 (17), 77 (11), 55 (13). Anal. Calcd. for $C_{20}H_{22}O_6$: C, 67.02; H, 6.19. Found: C, 66.83; H, 5.98.

Teuvincenone B [**2**; (16*S*)-12,16-epoxy-6,11,14-trihydroxy-17(15 → 16)-*abeo*-abieta-5,8,11,13 -tetraen-7-one]. Mp 210-212°C (EtOAc-*n*-hexane, orange-coloured prisms); [α] values: see Table V; IR (KBr) ν_{max} (cm^{-1}) 3390, 3300, 2960, 2920, 2870, 1645, 1615, 1570, 1465, 1395, 1320, 1250, 1170, 1145, 1065, 1045, 1010, 985, 925, 830; UV: see Table I; ^1H NMR: see Table II; MS, *m/z* (relative intensity) 344 (M^+, 69), 329 (100, base peak), 314 (9), 301 (12), 274 (96), 262 (34), 261 (22), 247 (10), 115 (12), 83 (28), 69 (20), 55 (20). Anal. Calcd. for $C_{20}H_{24}O_5$: C, 69.75; H, 7.02. Found: C, 69.93; H, 6.89.

Teuvincenone C [**3**; (16*S*)-12,16-epoxy-6,11,14-trihydroxy-17 (15 → 16)-*abeo* -3α,18-cyclo-abieta-5,8,11,13-tetraen-7-one]. Mp 198-200°C (Me_2CO-*n*-hexane, yellow prisms); [α] values: see

Table V; IR (KBr) ν_{max} (cm^{-1}) 3415, 3310, 3060, 2980, 2920, 2860, 1645, 1615, 1575, 1470, 1445, 1395, 1345, 1320, 1250, 1220, 1160, 1140, 1065, 1040, 1015, 995, 910, 830; UV: see Table I; ^1H NMR: see Table II; ^{13}C NMR: see Table III; MS, *m/z* (relative intensity) 342 (M^+, 100, base peak), 327 (23), 325 (4), 324 (3), 314 (10), 312 (5), 309 (6), 299 (19), 274 (11). Anal. Calcd. for $C_{20}H_{22}O_5$: C, 70.16; H, 6.48. Found: C, 70.31; H, 6.30.

Teuvincenone D [**4**; (16*S*)-12,16-epoxy-11,14-dihydroxy-17(15→16)-*abeo*-3α,18-cycloabieta-8,11,13-trien-7-one]. Mp 196-198°C (EtOAc-*n*-hexane, pale yellow needles); [α] values: see Table V; IR (KBr) ν_{max} (cm^{-1}) 3340, 3065, 2980, 2940, 2870, 1635, 1460, 1410, 1360, 1325, 1250, 1185, 1095, 1085, 1015, 885, 810; UV: see Table I; ^1H NMR: see Table II; MS, *m/z* (relative intensity) 328 (M^+, 100, base peak), 313 (29), 311 (4), 299 (4), 295 (3), 285 (5), 273 (23), 271 (8), 259 (6), 245 (17), 219 (10), 55 (10). Anal. Calcd. for $C_{20}H_{24}O_4$: C, 73.14; H, 7.37. Found: C, 72.93; H, 7.51.

Catalytic hydrogenation of teuvincenone A (1) to give compound 9 [(16*S*)-12,16-epoxy-6β-hydroxy-17(15→16)-*abeo*-abieta-8,12-diene-3,11,14-trione]. Compound **1** (100 mg) in AcOH (30 mL) was hydrogenated with PtO_2 (Adams type, 15 mg) as catalyst for 5 h. After the usual work up and chromatographic purification (Si-gel column eluted with $CHCl_3$), compound **9** (43 mg) was obtained: mp 220-222°C (EtOAc-*n*-hexane, orange-coloured needles); [α] values: see Table V; IR (KBr) ν_{max} (cm^{-1}) 3360, 2970, 2940, 2870, 1695, 1675, 1653, 1640, 1580, 1463, 1375, 1220, 1130, 1090, 1045, 945; UV: see Table I; ^1H NMR: see Table II; MS, *m/z* (relative intensity) 344 (M^+, 1), 329 (2), 326 (2), 311 (2), 299 (10), 235 (11), 207 (17), 91 (12), 77 (11), 55 (14), 43 (28), 40 (100, base peak). Anal. Calcd. for $C_{20}H_{24}O_5$: C, 69.75; H, 7.02. Found: C, 69.60; H, 7.19.

X-Ray structure determination of teuvincenones A (1) and C (3).

Crystals of compounds **1** and **3** with approximate dimensions of 0.20 x 0.25 x 0.18 and 0.30 x 0.10 x 0.20 mm respectively, were used for the crystal diffraction analysis. Formula: $C_{20}H_{22}O_6$ (**1**), $C_{20}H_{22}O_5$ (**3**); formula weight: 358.38 (**1**), 342.38 (**3**); D_c (g cm^{-3}): 0.6807 (**1**), 0.6543 (**3**). Cell parameters were determined from least-squares analysis of 60 high-angle reflections, range of 2θ from 21° to 79°, and 40 high-angle reflections, range of 2θ from 20° to 80°, for **1** and **3**, respectively. Compound **1**: $P2_1$; a = 12.141(1), b = 14.546(1), c = 10.497(1) Å; β = 109.394 (3)°; Z = 4. Compound **3**: $P4_32_12$; $a = b$ = 13.691(3), c = 37.090(3) Å; Z = 16. The lattice parameters and the intensities were measured on a Philips PW 1100 diffractometer, with graphite-monochromated CuKα radiation (1.5418 Å) in the ω/2θ scan mode. No. of unic reflections: 3249 for **1** and 3246 for **3**; No. of observed reflections with $I > 2\sigma$ (I): 2763 and 3195 for **1** and **3**, respectively. The intensities of two standard reflections were monitored every 90 reflections, showing no significant variation in the intensity. The structures were solved by direct methods and difference Fourier maps; method of locating H-atoms: ΔF map; weighting scheme: empirical, to prevent trends in $<\omega\Delta^2F>$ vs. $<F_o>$ and $<\sin\theta/\lambda>$. Maximum height in final F map: 0.32 $e\text{Å}^{-3}$ and 0.44 $e\text{Å}^{-3}$ for **1** and **3**, respectively; values of R and R_w 3.4 and 4.1 for **1**, and 6.7 and 7.9 for **3**. The absolute configuration was determined by Bijvoet method. No. of Bijvoet pairs with greater F_c: 75 and 88 for **1** and **3**, respectively; averaged Bijvoet difference: 0.83 vs. 1.543 for **1**, and 0.944 vs. 1.180 for **3**. Scattering factors and f' and f" values were taken from the literature.[9] All the calculations

were performed on a WAX 11/750 computer using the MULTAN 80[10a], DIRDIF[10b] and X-RAY 76[10c] programs. List of atom parameters, anisotropic thermal parameters, structure factors, and H-atom parameters corresponding to compounds **1** and **3** have been deposited at the Cambridge Crystallographic Data Centre.

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