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NEO-CLERODANE DITERPENOIDS FROM *TEUCRIUM SALVIASTRUM*

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Key Word Index—*Teucrium salviastrum*; Labiatae; new neo-clerodane derivatives; teusalvins A–F; teucvidin; teucroxide.

Abstract—From the aerial parts of *Teucrium salviastrum* six new neo-clerodane diterpenoids, teusalvins A–F, have been isolated, together with the previously known diterpenes teucvidin and teucroxide. The structures of teusalvins A [15,16-epoxy-2,6-diketo-neo-cleroda-13(16),14-dien-20,12*S*-olide-18*R*,19-hemiacetal], B [15,16-epoxy-2β-hydroxy-6-keto-neo-cleroda-13(16),14-dien-20,12*S*-olide-18*R*,19-hemiacetal], C [15,16-epoxy-6β,18,19-trihydroxy-neo-cleroda-3,13(16),14-trien-20,12*R*-olide], D [15,16-epoxy-2β,6β,18,19-tetrahydroxy-neo-cleroda-3,13(16),14-trien-20,12*S*-olide], E [15,16-epoxy-2β,6β,12*S*,18-tetrahydroxy-neo-cleroda-3,13(16),14-trien-20,19-olide] and F [15,16; 19,2α-diepoxy-6β,18-dihydroxy-neo-cleroda-3,13(16),14-trien-20,12*S*-olide] were established mainly by spectroscopic means and, in the case of teusalvin F, by X-ray diffraction.

INTRODUCTION

In a continuation of our studies on diterpenoid compounds from the *Teucrium* species [1–4], we have investigated *T. salviastrum* Schreber, a species which grows in limited areas of Portugal. From the aerial parts of this plant eight diterpenoids have been isolated, two of which, teucvidin [5] and teucroxide [6], are already known. The other six are new substances (teusalvins A–F), whose structures (formulae **1**, **6**, **7**, **9**, **11** and **14**, respectively) have been established mainly by spectroscopic means.

RESULTS AND DISCUSSION

The first of the new diterpenoids, teusalvin A (**1**), had a molecular formula $C_{20}H_{22}O_7$ and its IR spectrum showed hydroxyl (3440 cm^{-1}), furanic (3150, 1510, 880 cm^{-1}), γ-lactone (1765 cm^{-1}) and ketone (1720 cm^{-1}, br) absorptions. Acetic anhydride–pyridine treatment of teusalvin A (**1**) yielded a monoacetyl derivative (**2**, $C_{22}H_{24}O_8$), the IR spectrum of which was devoid of hydroxyl absorption. The ^{1}H NMR spectrum of compound **2** (Table 1) showed a number of similarities to that of the 18-acetyl derivative (**3**) of teuscorodin (**4**), a neo-clerodane diterpenoid previously isolated from *T. scorodonia* [7]. The presence of a C-18, C-19 acetylated hemiacetal function in both compounds was revealed by the signals of the C-4β and C-18α protons (**2**: δ3.78 *ddd*, $J_{4\beta,3\alpha}$ = 8.0 Hz, $J_{4\beta,3\beta}$ = 1.6 Hz, $J_{4\beta,18\alpha}$ = 5.8 Hz; and δ6.33 *d*, respectively, Table 1. **3**: δ2.77 *ddd*, $J_{4\beta,3\alpha}$ = 9 Hz, $J_{4\beta,3\beta}$ = 6 Hz, $J_{4\beta,18\alpha}$ = 5 Hz; and δ6.13 *d*, respectively [7]). The larger chemical shift value of the C-4β proton in compound **2**, as compared with that of the same proton in compound **3** ($\Delta\delta$ + 1.01), can be explained by taking into account the presence of a C-2 ketone function in the former. A Dreiding molecular model of compound **2** revealed that the presence of the C-2 ketone function, instead of the C-2 methylene group in compound **3**, considerably flattened ring A, forcing the C-4β proton to be close to the plane of the C-6 carbonyl group.

Oxidation of teusalvin A (**1**) with Jones' reagent yielded a compound **5** identical in all respects (mp, mmp, $[\alpha]_D$, IR, ^{1}H NMR, mass spectrum) with a synthetic derivative of dihydroteugin whose structure is well known [1]. These facts clearly established structure **1** for teusalvin A, in which the 12*S* configuration was also confirmed by NOE experiments: irradiation of the Me-17 protons of **2** (δ0.88) caused an NOE enhancement of the H-14 signal (δ6.19, 6%), while no enhancement was observed in the H-12 signal (δ5.07) [8, 9].

Another of the diterpenoids, teusalvin B (**6**), had a molecular formula $C_{20}H_{24}O_7$ and also yielded compound **5** [1] on oxidation with Jones' reagent. The ^{1}H NMR spectrum of teusalvin B (**6**, Table 1) clearly indicated that it possessed an axial C-2β hydroxyl group (H-2α at δ4.28 *dddd*, $J_{2\alpha,1\alpha}$ = 2.6 Hz, $J_{2\alpha,1\beta}$ = 2.4 Hz, $J_{2\alpha,3\alpha}$ = 2.9 Hz, $J_{2\alpha,3\beta}$ = 2.1 Hz) instead of the C-2 ketone of teusalvin A (**1**). The H-4β and H-18α NMR spectroscopic pattern of teusalvin B (at δ2.82 *dd*, $J_{4\beta,3\alpha}$ = 12.3 Hz, $J_{4\beta,3\beta}$ = 6.3, $J_{4\beta,18\alpha}$ = 0 Hz; and δ4.84, *s* after addition of D_2O, respectively; see Table 1) was almost identical with that of teuscorodin (**4**, at δ2.67 *br dd*, $J_{4\beta,3\alpha}$ = 9 Hz, $J_{4\beta,3\beta}$ = 6 Hz, $J_{4\beta,18\alpha}$ < 0.3 Hz; and δ5.07 *br s*, respectively [7]), suggesting that the former possessed an 18*R*,19-hemiacetal grouping. This was confirmed by the following facts. (i) The signal of the C-12 proton of teusalvin B (**6**) appeared at δ5.40 as in all the neo-clerodan-20,12-olides isolated from the *Teucrium* species [1, 4–8], whereas in neo-clerodane-20,12-hemiacetals it appears at δ5.20–5.00 [3]. (ii) The C-18 methine and C-18 hydroxyl protons of teusalvin B were coupled together, with a *J* value of 12.1 Hz (Table 1). This large value for a coupling through a hydroxyl oxygen atom is only compatible with an

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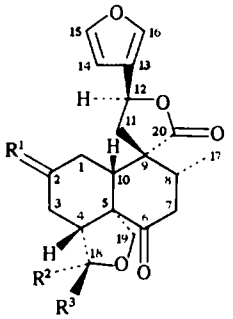
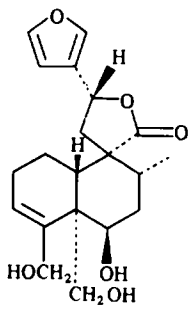


	R^1	R^2	R^3
1	O	H	OH
2	O	H	OAc
3	H_2	H	OAc
4	H_2	H	OH
5	O	O	
6	αH,βOH	H	OH



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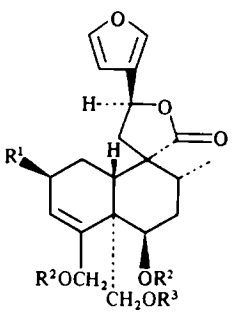
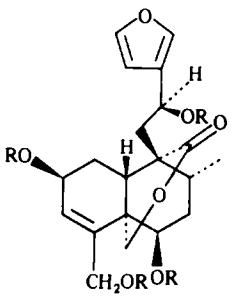
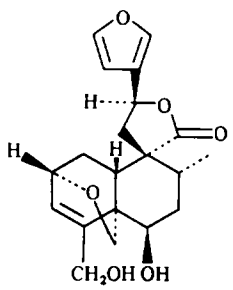


	R^1	R^2	R^3
8	H	H	Ac
9	OH	H	H
10	OAc	Ac	Ac
13	H	Ac	Ac



11 R = H
12 R = Ac



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antiperiplanar disposition of these two protons [10], which can be easily explained in the case of teusalvin B (**6**) by the existence of an intramolecular hydrogen bond between the C-18 hydroxyl group and the C-6 ketone. (iii) This was also in agreement with the observed $J_{4\beta,18\alpha}$ values in teusalvin B (**6**, $J = 0$ Hz) and teuscorodin (**4**, $J < 0.3$ Hz) [7], since the C-18 hydroxyl–C-6 ketone interactions force the C-18, C-19 hemiacetal ring to adopt a conformation in which the H-18α–H-4β dihedral angle is close to 90°.

In addition to the chemical correlation of teusalvin B (**6**) with compound **5** [1], its neo-clerodane absolute configuration was established by its CD curve, which showed a negative Cotton effect ($\Delta\varepsilon_{291.5} - 0.65$) for the C-6 ketone, as in the case of 19-acetylgnaphalin ($\Delta\varepsilon_{298.5} - 0.48$) [11], a diterpenoid whose neo-clerodane absolute stereochemistry has been established by X-ray analysis [12]. Moreover, the 12*S* configuration of teusalvin B (**6**) was also in agreement with NOE experiments, since irradiation of the Me-17 protons (δ1.13) produced no NOE enhancement of the C-12 proton signal (δ5.40) [8, 9].

Teusalvin C (**7**, $C_{20}H_{26}O_6$) showed an IR spectrum with hydroxyl (3460, 3340 cm^{-1}, broad), furanic (1510, 880 cm^{-1}) and γ-lactone (1760 cm^{-1}) absorptions. Its ^1H NMR spectrum (Table 2) was almost identical with that of teuscorodol (**8**), a diterpenoid previously isolated from *T. scorodonia* [13]. In fact, the small differences between the ^1H NMR spectra of teuscorodol (**8**) [13] and teusalvin C (Table 2) would seem to be due merely to the absence in the latter of the 19-acetyl group present in **8**. However, when the Me-17 protons of teusalvin C (**7**, δ1.11) were irradiated under NOE experimental conditions, a 9% NOE enhancement of the H-12 signal (δ5.40) was observed, whereas in the case of teuscorodol (**8**) the same experiment produced a 4% NOE enhancement of the H-14 signal and no effect on the H-12 signal [9]. These results clearly established that teusalvin C possessed structure **7** and differed from teuscorodol (**8**) [13] in its lack of the 19-acetyl group and in the configuration of its C-12 centre. The absolute configuration of teusalvin C was not ascertained; however, it is reasonable to assume that this compound belongs to the neo-clerodane series, like all the diterpenoids isolated from *Teucria* hitherto [1–8, 11–13, and references therein], including teusalvins A (**1**) and B (**6**), co-occurring in the same species. Teusalvin C, montanin C, teupolin I, 12-*epi*-teucvin [8] and teupyreinin [9] are the only neo-

Table 1. ^{1}H NMR data of compounds **2** and **6** (TMS as int. standard)*

	2†	2‡	6†
H-1α	§	2.52 *dd*	1.82 *td*
H-1β	§	2.34 *dd*	2.00§
H-2α	—	—	4.28 *dddd*
H-3α	§	2.01 *dd*	1.55 *ddd*
H-3β	§	2.21 *dd*	2.00§
H-4β	3.91 *ddd*	3.78 *ddd*	2.82 *dd*
H-7α	3.50 *t*	3.29 *t*	3.50 *t*
H-7β	§	2.26 *dd*	2.40 *dd*
H-8β	§	1.68 *ddq*	2.07§
H-10β	§	1.95 *dd*	2.73 *dd*
H_A-11	§	1.84 *dd*	2.39 *dd*
H_B-11	§	2.08 *dd*	2.50 *dd*
H-12	5.45 *t*	5.07 *t*	5.40 *t*
H-14	6.39 *dd*	6.19 *dd*	6.39 *dd*
H-15	7.47 *t*	7.24§	7.45 *t*
H-16	7.49 *m*	7.24§	7.46 *m*
Me-17	1.17 *d*	0.88 *d*	1.13 *d*
H-18α	6.36 *d*	6.33 *d*	4.84 *d*¶
H_A-19	4.17 *d*	4.10 *d*	4.08 *d*
H_B-19	4.40 *d*	4.35 *d*	4.60 *d*
OH‖	—	—	5.13 *d*
OAc	1.97 *s*	1.84 *s*	—
J (Hz)			
1α, 1β	§	18.1	13.1
1α, 2α	—	—	2.6
1β, 2α	—	—	2.4
1α, 10β	§	14.2	13.1
1β, 10β	§	3.2	3.1
2α, 3α	—	—	2.9
2α, 3β	—	—	2.1
3α, 3β	§	16.8	14.8
3α, 4β	9.4	8.0	12.3
3β, 4β	2.9	1.6	6.3
4β, 18α	5.8	5.8	0
7α, 7β	14.3	13.8	13.8
7α, 8β	14.3	13.8	13.8
7β, 8β	§	4.3	4.9
8β, 17	6.6	6.6	6.6
11A, 11B	§	14.3	14.2
11A, 12	8.6	8.0	8.7
11B, 12	8.6	9.2	8.4
14, 15	1.8	1.8	1.7
14, 16	0.9	1.1	0.9
15, 16	1.8	§	1.7
19A, 19B	11.4	11.3	11.2
OH, 18α‖	—	—	12.1

*Spectral parameters were obtained by first order approximation. All these assignments have been confirmed by double resonance experiments.

†$CDCl_3$.

‡$CDCl_3$–C_6D_6.

§Overlapped signal.

‖Disappeared after addition of D_2O.

¶Collapsed into *s* after addition of D_2O.

clerodan-20,12-olides isolated from *Teucria* until now that show the infrequent 12*R* configuration. The majority belong to the 12*S* series [8, 9 and references therein].

Teusalvins D (**9**) and E (**11**) had the same molecular formula ($C_{20}H_{26}O_7$) and were partially transformed one into the other when a methanolic solution of the diterpenoid with a trace of sodium carbonate was stirred at room temperature for 16 hr (see Experimental). Acetic anhydride–pyridine treatment of each of the two compounds gave the corresponding tetraacetates **10** and **12**. The ^{1}H NMR spectrum of compound **10** (Table 2) showed signals which were identical with those of peracetylteuscorodol (**13**) [13], i.e. characteristic of a C-18 acetylated allylic alcohol, a C-19 acetoxymethyl group, a 6β-acetoxyl group, a secondary C-17 methyl group, a C-20–C-12 γ-lactone and a β-substituted furan ring (see Table 2 and ref. [13]). In addition, the ^{1}H NMR spectrum of **10** showed the signal of the H-3 olefinic proton as a broad doublet (J = 4.2 Hz) at δ5.80 instead of the broad triplet (J = 3 Hz) at δ5.76 exhibited by the spectrum of compound **13** [13]. Double resonance experiments established that the H-3 olefinic proton of tetraacetylteusalvin D (**10**) was coupled with a one-proton (broad triplet at δ5.39) which was assigned to the H-2α proton, geminal with respect to an acetoxyl group ($J_{2\alpha,3}$ = 4.2 Hz, $J_{2\alpha,1\alpha}$ = 4.2 Hz, $J_{2\alpha,1\beta}$ < 0.3 Hz). All the above conclusions were supported by the ^{13}C NMR spectrum of tetraacetylteusalvin D (Table 3), which showed carbon atom resonances in complete agreement with structure **10** [14, 15]. Thus, teusalvin D possesses the structure depicted in formula **9**, in which the neo-clerodane absolute configuration is proposed on biogenetic grounds (see above). The 12*S* configuration was established by NOE experiments, since irradiation of the Me-17 protons of compound **10** (δ1.02) caused a 4% NOE enhancement of the H-14 signal (δ6.41) and no effect on the H-12 signal (δ5.40) [8, 9].

Teusalvin E possesses structure **11**. This was established from the ^{1}H and ^{13}C NMR data of its tetraacetyl derivative (**12**) (Tables 2 and 3). Comparison of the ^{1}H NMR spectra of compounds **10** and **12** (Table 2) showed a close similarity between them. The difference in the chemical shifts of the C-12 protons (δ6.03 in **12** and 5.40 in **10**) can be attributed to the fact that compound **12** has a C-12 acetoxyl group and a C-20–C-19 δ-lactone instead of the C-19 acetate and the C-20–C-12 γ-lactone functions of compound **10** [2, 16, 17]. These structural differences between compounds **10** and **12** were clearly reflected in their ^{13}C NMR spectra (Table 3). In particular, the chemical shifts of the C-12, C-19 and C-20 carbon atoms of compound **12** (δ64.3 *d*, 73.2 *t* and 170.8 *s*, respectively), as compared with those of **10** (δ71.9 *d*, 62.4 *t* and 176.8 *s*, respectively), rigorously established [2, 14–17] that teusalvin E (**11**) differs from teusalvin D (**9**) only in the lactone arrangement.

Since teusalvins D (**9**) and E (**11**) were partially transformed one into the other under mild basic catalysis, it was clear that the C-12 configuration of teusalvin E was *S*, as in diterpenoid **9** (see above).

Finally, the structure of teusalvin F (**14**) was established by X-ray diffraction methods. Figure 1 shows the X-ray absolute configuration of this diterpenoid. The conformation of the rings was calculated by Cremer's method [18] (Table 4). Rings A and B of the decalin moiety have a boat and a chair conformation, respectively, the system A/B being *trans* fused. The sum of the torsion angles around the C-10–C-5 bond (absolute values) is 102°, which is less than 113° [19], the usual value for a decalin moiety having the same degree of substitution at the bridgehead atoms. In the case of teusalvin F (**14**) a different value for these angles could be expected, due to the different substitution at C-5 and the presence of bulky substituents at C-4 and C-6. Rings E and F (see Fig. 1) have boat conformations

Table 2. ^{1}H NMR data of compounds **7**, **10**, **12** and **14** (TMS as int. standard)*

	7†	10‡	12‡	14†
H-1α	§	§	1.76 *td*	1.75 *ddd*
H-1β	§	§	2.47 *br dd*	1.99 *td*
H-2α	§	5.39 *br t*	5.45 *br t*	—
H-2β	§	—	—	4.46 *ddd*
H-3	5.83 *br t*	5.80 *br d*	6.00 *br d*	6.40 *d*
H-6α	4.53 *dd*	5.25 *dd*	5.18 *t*	4.22 *t*
H-7α	2.09 *td*	§	1.61 *ddd*	2.30 *td*
H-7β	1.67 *dt*	§	1.96§	1.73 *ddd*
H-8β	§	§	1.98§	2.33 *ddq*
H-10β	§	§	2.72 *dd*	2.22 *ddd*
H_A-11	2.42 *dd*	2.47 *d*	2.25 *dd*	2.31 *dd*
H_B-11	2.57 *dd*	2.47 *d*	2.67 *dd*	2.48 *dd*
H-12	5.40 *t*	5.40 *t*	6.03 *t*	5.36 *t*
H-14	6.40 *dd*	6.41 *dd*	6.46 *dd*	6.41 *dd*
H-15	7.43 *t*	7.45 *t*	7.41 *t*	7.42 *t*
H-16	7.44 *m*	7.48 *m*	7.46 *m*	7.46 *m*
Me-17	1.11 *d*	1.02 *d*	0.84 *d*	1.04 *d*
H_A-18	4.21 *br d*	4.54 *br s*	4.29 *br s*	4.18 *br d*
H_B-18	4.43 *br d*	4.54 *br s*	4.29 *br s*	4.54 *br d*
H_A-19	4.03 *d*	4.58 *d*	4.32 *d*	2.76 *dd*
H_B-19	4.38 *d*	4.79 *d*	4.53 *d*	4.76 *d*
OAc	—	2.12 *s*	2.12 *s*	—
	—	2.11 *s*	2.09 *s*	—
	—	2.07 *s*	2.08 *s*	—
	—	2.03 *s*	2.07 *s*	—
J (Hz)				
1α, 1β	§	§	14.4	11.9
1α, 2α	§	4.2	5.2	—
1α, 2β	§	—	—	3.3
1β, 2α	§	< 0.3	<0.3	—
1β, 2β	§	—	—	1.8
1α, 10β	§	§	13.9	6.4
1β, 10β	§	§	3.3	11.9
2α, 3	3.5	4.2	5.2	—
2β, 3	3.5	—	—	6.2
6α, 7α	1.9	1.9	2.7	1.8
6α, 7β	3.7	3.6	2.7	1.8
7α, 7β	14.4	§	16.4	13.0
7α, 8β	14.4	§	13.7	13.0
7β, 8β	3.7	§	§	2.8
8β, 17	7.0	6.6	6.4	6.4
11A, 11B	13.7	0	15.8	13.6
11A, 12	8.3	8.7	8.0	8.2
11B, 12	8.9	8.7	6.9	9.5
14, 15	1.7	1.8	1.7	1.8
14, 16	0.8	0.9	0.9	0.6
15, 16	1.7	1.8	1.7	1.8
18A, 18B	11.0	0	0	12.1
19A, 19B	11.7	12.0	13.7	7.9
19A, 10β	0	0	0	1.8

*Spectral parameters were obtained by first order approximation. All these assignments have been confirmed by double resonance experiments.

†$CDCl_3$–pyridine-d_5.

‡$CDCl_3$.

§Overlapped signal.

and the furan ring (D) is almost planar. The asymmetric parameters [20] (Table 4) show that all the rings of teusalvin F (**14**) have a dominant mirror symmetry.

The configurational analysis of teusalvin F (**14**, Table 4) shows that the C-6 hydroxyl group and the C-2 and C-10 hydrogen atoms are β-oriented, whereas the Me-17 group possesses an α-configuration. The configuration at the C-12 centre is *S*, the torsion angles that define this feature being given in Table 4. The crystal structure of teusalvin F (**14**) is stabilized by two hydrogen bonds between the C-6β and C-18 hydroxyl groups (O-1 . . . O-2 = 2.65 Å, HO-1 . . . O-2 = 2.03 Å, O-2 . . . O-1 = 2.726 Å, HO-2 . . . O-1 = 1.878 Å; for the numbering of the oxygen atoms see Fig. 1).

The structure established for teusalvin F (**14** and Fig. 1) was in complete agreement with its ^{1}H NMR spectrum (Table 2). In particular, the unusual chemical shift difference ($\Delta\delta$2.0) between the two C-19 methylene protons can be explained by the fact that one of them (δ2.76 *dd*, J_{gem} = 7.9 Hz, $J_{19A,10\beta}$ = 1.8 Hz) is placed in the shielding zone of the C-3–C-4 olefinic bond and adopts a *W*

Table 3. ^{13}C NMR chemical shifts of compounds **10** and **12** ($CDCl_3$, TMS as int. standard)

C	10	12	C	10	12
1	27.2 *t**	26.6 *t*	15	144.3 *d*	143.8 *d*
2	65.3 *d*	64.8 *d*†	16	139.7 *d*	140.2 *d*
3	124.2 *d*	127.8 *d*	17	16.2 *q*	16.2 *q*
4	144.1 *s*	140.1 *s*	18	66.4 *t*	64.5 *t*
5	45.0 *s*	39.9 *s*	19	62.4 *t*	73.2 *t*
6	70.1 *d*	71.6 *d*	20	176.8 *s*	170.8 *s*
7	30.6 *t*	32.3 *t*‡	OAc	170.2 *s*	170.1 *s*
8	33.4 *d*	30.4 *d*		170.1 *s*	169.9 *s*
9	51.2 *s*	48.5 *s*		169.9 *s*	169.8 *s*
10	41.9 *d*	32.8 *d*		169.7 *s*	169.7 *s*
11	44.1 *t*	33.1 *t*‡		21.3 *q*	21.3 *q*
12	71.9 *d*	64.3 *d*†		21.3 *q*	21.2 *q*
13	125.3 *s*	125.1 *s*		21.0 *q*	21.1 *q*
14	108.2 *d*	108.8 *d*		20.9 *q*	21.0 *q*

*SFORD multiplicity.

†‡Assignments bearing the same sign may be reversed.

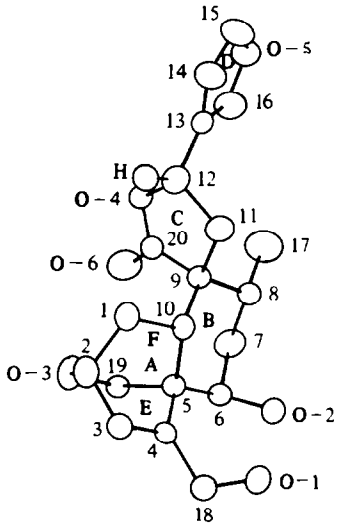

Fig. 1. X-Ray molecular model of teusalvin F (**14**).

Table 4. Conformational characteristics and configurational angles for the substituents of the rings of teusalvin F (**14**)*

(a) Torsion angles and conformational Cremer's [18] and Duax's [20] parameters

Ring	τ^1	τ^2	τ^3	τ^4	τ^5	τ^6	Q(Å)	θ(°)	ϕ(°)	(Å)
A	6	−60	59	0	−59	52	0.82	93	−63	$D_s^5 = 0.030$
B	51	−62	60	−48	42	−43	0.54	14	169	$D_s^{10} = 0.040$
C	−10	9	−6	−1	7		0.10		33	$D_s^{11} = 0.004$
D	−1	2	−2	1	0		0.02		−149	$D_s^{16} = 0.002$
E	59	−56	0	57	−52	−6	0.81	93	−2	$D_s^2 = 0.028$
F	6	51	−53	−6	66	−65	0.82	93	121	$D_s^5 = 0.010$

(b) Configurational angles (°) for the substituents of the rings

Configurational angle		Substituent angle	Ring angle
ρO(2)	[C(8)-C(7)-C(6)-O(2)] =	[C(8)-C(7)-C(6)-O(2)] − [C(8)-C(7)-C(6)-C(5)] = −62 − 60 = −123 (β)	
ρC(13)	[C(20)-O(4)-C(12)-C(13)] =	[C(20)-O(4)-C(12)-C(13)] − [C(20)-O(4)-C(12)-C(11)] = 129 − 7 = 122 (α)	
ρC(17)	[C(10)-C(9)-C(8)-C(17)] =	[C(10)-C(9)-C(8)-C(17)] − [C(10)-C(9)-C(8)-C(7)] = 176 − 51 = 125 (α)	
ρH(10)	[C(2)-C(1)-C(10)-H(10)] =	[C(2)-C(1)-C(10)-H(10)] − [C(2)-C(1)-C(10)-C(5)] = −107 − 6 = −113 (β)	
ρH(12)	[C(20)-O(4)-C(12)-H(12)] =	[C(20)-O(4)-C(12)-H(12)] − [C(20)-O(4)-C(12)-C(11)] = −111 − 7 = −118 (β)	

(c) Configuration at the asymmetric C(12) centre

ρO(4)	[C(9)-C(11)-C(12)-O(4)] =	[C(9)-C(11)-C(12)-O(4)] − [C(9)-C(11)-C(12)-H(12)] = −10 − 102 = −112	C(12) → *S*
ρC(13)	[C(9)-C(11)-C(12)-C(13)] =	[C(9)-C(11)-C(12)-C(13)] − [C(9)-C(11)-C(12)-H(12)] = −128 − 102 = −230 ≡ 130	

*The sense of the rotation is clockwise and the starting point for each ring is: ring A: τ^1 = C(1)-C(10); ring B: τ^1 = C(9)-C(8); ring C: τ^1 = C(11)-C(12); ring D: τ^1 = C(15)-O(5); ring E: τ^1 = C(19)-C(5); ring F: τ^1 = C(1)-C(10).

configuration with the 10β proton. Moreover, the 12*S* configuration of this new diterpenoid (**14**) was also in agreement [8, 9] with the observed NOE enhancement (4%) in the H-14 signal (δ6.41) when the Me-17 protons (δ1.04) were irradiated.

From a biogenetic point of view, it is reasonable to assume that teusalvin F (**14**) arises from teusalvin D (**9**) as the result of an intramolecular nucleophilic attack of the C-19 hydroxyl group at the C-2 position.

EXPERIMENTAL

Mps are uncorr. For general details on methods, see refs [1–4, 6–8, 11–13, 16]. Plant materials were collected in July 1983 at Sierra de la Estrella, Portugal, and voucher specimens were deposited in the Herbarium of the Royal Botanic Garden of Madrid, Spain.

Extraction and isolation of the diterpenoids. Dried and finely powdered *T. salviastrum* Schreber aerial parts (440 g) were extracted with Me_2CO (4 l.) at room temp. for a week. The extract (36 g) was chromatographed on a silica gel column (Merck, No. 7734, deactivated with 15% H_2O, 800 g) eluted with *n*-hexane, *n*-hexane–EtOAc mixtures, EtOAc and $CHCl_3$–MeOH mixtures. Elution with EtOAc–*n*-hexane (4:1) gave teucvidin (250 mg) [5] and elution with EtOAc and $CHCl_3$–MeOH (9:1) gave a mixture of several diterpenoids which was re-chromatographed on a silica gel column eluted with $CHCl_3$–MeOH (49:1) yielding the following compounds in order of chromatographic polarity: teusalvin A (**1**, 30 mg), teusalvin B (**6**, 5 mg), teusalvin F (**14**, 4 mg), teusalvin C (**7**, 13 mg), teucroxide (20 mg) [6], teusalvin E (**11**, 20 mg) and teusalvin D (**9**, 10 mg).

The previously known diterpenoids, teucvidin [5] and teucroxide [6], were identified by their physical (mp, $[\alpha]_D$) and spectroscopic (IR, ^{1}H NMR, MS) data and by comparison (mmp, TLC) with authentic samples.

Teusalvin A (**1**). Mp 224–227° (EtOAc); $[\alpha]_D^{19}$ + 146.0° ($CHCl_3$; *c* 0.051); IR ν_{max}^{KBr} cm^{-1}: 3440, 3150, 2980, 2940, 1765, 1720 (br), 1510, 1420, 1320, 1200, 1185, 1160, 1025, 950, 880; EIMS (direct inlet) 70 eV, *m/z* (rel. int.): 374 $[M]^+$ (27), 356 (18), 328 (47), 315 (59), 303 (22), 280 (15), 222 (24), 203 (18), 199 (18), 189 (20), 178 (50), 161 (43), 147 (31), 133 (42), 121 (31), 105 (54), 95 (100), 94 (91), 81 (54), 69 (63), 53 (41), 43 (49). $C_{20}H_{22}O_7$ M_r 374.

Acetylteusalvin A (**2**). Ac_2O–C_5H_5N treatment of **1** (10 mg) in the usual manner yielded **2** (11 mg): mp 225–228° (EtOAc–*n*-hexane); $[\alpha]_D^{21}$ + 177.7° ($CHCl_3$; *c* 0.188); IR ν_{max}^{KBr} cm^{-1}: 3170, 3150, 3130, 2980, 2940, 2880, 1760 (br), 1720 (br), 1510, 1470, 1425, 1375, 1370, 1320, 1215, 1200, 1180, 1160, 1050, 1020, 1010, 960, 915, 880, 803, 790; ^{1}H NMR (300 MHz, $CDCl_3$ and $CDCl_3$ + C_6D_6): see Table 1; EIMS (direct inlet) 70 eV, *m/z* (rel. int.): 416 $[M]^+$ (3), 374 (15), 373 (17), 357 (22), 356 (11), 328 (17), 315 (8), 303 (6), 281 (100), 189 (6), 171 (10), 167 (6), 133 (8), 121 (6), 105 (8), 95 (19), 94 (20), 91 (8), 81 (16), 69 (10), 43 (44). (Found: C, 63.28; H, 5.68. $C_{22}H_{24}O_8$ requires: C, 63.45; H, 5.81%.)

Jones' oxidation of teusalvin A (**1**) *to give compound* **5**. A soln of teusalvin A (**1**, 8 mg) in Me_2CO (3 ml) was treated with an excess of Jones' reagent at 0° for 5 min. Work-up in the usual manner yielded 6 mg of a substance [mp 280–281° (Me_2CO), $[\alpha]_D^{20}$ + 98.3° (pyridine; *c* 0.261)] identical in all respects (mmp, IR, ^{1}H NMR, MS, TLC) with the previously described compound **5** (lit. [1]: mp 276–280°, $[\alpha]_D^{22}$ + 99.4°).

Teusalvin B (**6**). Mp 199–202° (EtOAc–*n*-hexane); $[\alpha]_D^{22}$ − 10.0° ($CHCl_3$; *c* 0.052); CD nm ($\Delta\varepsilon$): 330 (0), 291.5 (−0.65), 252 (−0.17), 240 (−0.46) (MeOH; *c* 0.0216); IR ν_{max}^{KBr} cm^{-1}: 3370 (br), 3150, 3140, 2970, 2930, 2890, 1765, 1725, 1695, 1510, 1455, 1340, 1190, 1145, 1020, 875; ^{1}H NMR (300 MHz, $CDCl_3$): see Table 1; EIMS (direct inlet) 70 eV, *m/z* (rel. int.): 376 $[M]^+$ (1), 358 (7), 330 (8), 317 (21), 253 (4), 236 (8), 220 (8), 179 (15), 178 (16), 161 (22), 105 (32), 95 (82), 94 (43), 91 (44), 81 (46), 69 (50), 53 (39), 43 (46), 41 (100). (Found: C, 63.68; H, 6.53. $C_{20}H_{24}O_7$ requires: C, 63.82; H, 6.43%.)

Jones' oxidation of teusalvin B (**6**) *to give compound* **5**. This was performed in the same way as for teusalvin A (see above). Compound **6** (2 mg) yielded **5** (1.5 mg), identified by its mp, mmp, $[\alpha]_D$, MS and TLC.

Teusalvin C (7). Mp 173–175° (EtOAc–*n*-hexane); $[\alpha]_D^{20} - 50.0°$ ($CHCl_3$; *c* 0.110); IR ν_{max}^{KBr} cm^{-1}: 3460 (br), 3340 (br), 2970, 2940, 1760, 1510, 1460, 1330, 1190, 1160, 1050, 1040, 1030, 880; ^1H NMR (300 MHz, $CDCl_3$–pyridine-d_5): see Table 2; EIMS (direct inlet) 70 eV, *m/z* (rel. int.): 362 $[M]^+$ (2), 344 (2), 326 (2), 314 (12), 296 (23), 251 (10), 220 (12), 157 (26), 105 (53), 95 (79), 91 (95), 77 (74), 65 (42), 53 (58), 43 (42), 41 (100). (Found: C, 65.98; H, 7.31. $C_{20}H_{26}O_6$ requires: C, 66.28; H, 7.23%.)

Teusalvin D (9) *and tetraacetylteusalvin D* (10). The ^1H NMR spectrum of impure teusalvin D contained no acetoxyl signals. It was purified as its tetraacetyl derivative (10) in the usual manner. Compound 10, amorphous powder, mp 68–77°; $[\alpha]_D^{19} - 76.7°$ ($CHCl_3$; *c* 0.378); IR ν_{max}^{KBr} cm^{-1}: 3140, 2980, 2860, 1740 (br), 1505, 1440, 1370, 1230, 1160, 1050, 1025, 880 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): see Table 2; ^{13}C NMR (75.4 MHz, $CDCl_3$): see Table 3; EIMS (direct inlet) 70 eV, *m/z* (rel. int.): $[M]^+$ absent, 486 $[M-60]^+$ (13), 444 (13), 427 (11), 383 (43), 366 (21), 324 (45), 169 (16), 155 (22), 116 (20), 95 (29), 94 (14), 91 (15), 81 (20), 69 (11), 55 (13), 43 (100). (Found: C, 61.39; H, 6.38. $C_{28}H_{34}O_{11}$ requires: C, 61.53; H, 6.27%.)

Teusalvin E (11). An amorphous substance which melted at 104–110°; $[\alpha]_D^{19} - 41.0°$ (MeOH; *c* 0.195); IR ν_{max}^{KBr} cm^{-1}: 3400 (br), 2920, 2860, 1720, 1510, 1450, 1170, 1120, 1025, 880. The ^1H NMR spectrum of 11 was devoid of acetoxyl signals.

Tetraacetylteusalvin E (12). Ac_2O–C_5H_5N treatment of 11 (12 mg) in the usual manner yielded 12 (15 mg): an amorphous powder which melted at 70–75°; $[\alpha]_D^{22} - 84.1°$ ($CHCl_3$; *c* 0.725); IR ν_{max}^{KBr} cm^{-1}: 3150, 2990, 2960, 2890, 1740 (br), 1510, 1440, 1380, 1240, 1170, 1025, 880; ^1H NMR (300 MHz, $CDCl_3$): see Table 2; ^{13}C NMR (75.4 MHz, $CDCl_3$): see Table 3; EIMS (direct inlet) 70 eV, *m/z* (rel. int.): 546 $[M]^+$ (0.3), 504 (2), 486 (27), 444 (11), 426 (1), 384 (11), 374 (4), 366 (2), 324 (8), 306 (4), 247 (24), 213 (11), 97 (4), 95 (9), 91 (7), 81 (7), 43 (100). (Found: C, 61.32; H, 6.21. $C_{28}H_{34}O_{11}$ requires: C, 61.53; H, 6.27%.)

Interconversion of teusalvin D (9) *and teusalvin E* (11). To a soln of compound 9 (or 11) in MeOH a trace of Na_2CO_3 was added and the mixture stirred at room temp. for 16 hr. TLC (silica gel plates, $CHCl_3$–MeOH, 49:1 as eluent) showed two spots corresponding to the starting material 9 (or 11) and the isomeric compound 11 (or 9).

Teusalvin F (14). Mp 216–219° (MeOH); $[\alpha]_D^{22} + 89.9°$ ($CHCl_3$; *c* 0.149); IR ν_{max}^{KBr} cm^{-1}: 3300 (br), 3220 (br), 3150, 3120, 2980, 2925, 2885, 1756, 1510, 1465, 1340, 1330, 1190, 1160, 1030, 980, 875; ^1H NMR (300 MHz, $CDCl_3$–pyridine-d_5): see Table 2; EIMS (direct inlet) 70 eV, *m/z* (rel. int.): 360 $[M]^+$ (1), 342 (2), 330 (3), 317 (4), 314 (5), 296 (6), 267 (4), 251 (8), 202 (11), 197 (13), 179 (17), 133 (42), 129 (37), 118 (50), 105 (50), 95 (100), 91 (81), 81 (63), 55 (56), 43 (50). (Found: C, 66.42; H, 6.63. $C_{20}H_{24}O_6$ requires: C, 66.65; H, 6.71%.)

X-Ray structure determination of teusalvin F (14). Teusalvin F ($C_{20}H_{24}O_6$) crystallizes in the space group $P2_1$, $Z = 2$, with $a = 13.102$ (4), $b = 6.354$ (1), $c = 10.564$ (2) Å, $\beta = 95.951°$ and $Dc = 1.368$ g/cm^3. The intensities of the 1298 independent Friedel pairs to $\theta = 65°$ were alternately collected on an automatic four-circle diffractometer. The size of the single crystal used was 0.2 × 0.3 × 0.2 mm and during the experiment no decomposition was observed. The experimental details were: graphite-monochromated CuKα radiation ($\lambda = 1.5418$ Å), $\omega/2\theta$ scan mode, a scan rate of 0.05°/sec with the same measurement time for both backgrounds as for the peak. The intensities were corrected by Lorentz and polarization effects, while 1193 Friedel pairs were considered as observed when $I > 2\sigma(I)$ and were used for the structure determination and refinement. No absorption correction was applied ($\mu = 7.905$ cm^{-1}). The atomic scattering factors and anomalous dispersion correction were taken from the lit. [21]. The structure was solved by MULTAN [22] and refined by full-matrix least-squares methods with anisotropic thermal parameters for the non-hydrogen atoms. All the hydrogen atoms were found in difference Fourier maps and were included as fixed isotropic contributors in the refinement.

A weighting scheme was selected to prevent bias in $\langle w\Delta^2 F \rangle$ vs. $\langle |F_o| \rangle$ and vs. $\langle \sin\theta/\lambda \rangle$. Several cycles of weighted anisotropic refinement, including both *hkl* and $\overline{hkl}$ reflexions, gave the following unweighted and weighted discrepancy indices: $R = 0.060$ and $R_w = 0.075$ [23].

The absolute configuration of teusalvin F was determined by comparing the 50 more relevant Bijvoet pairs with $\Delta F_c > 0.08$ and with less experimental error, that is $F_o > 10\sigma(F_o)$. The averaged Bijvoet difference was 0.350 for the right enantiomer vs. 0.422 for the wrong one.

A list of structure factors, atomic and anisotropic thermal parameters, hydrogen atom parameters, bond distances, bond angles, torsion angles and conformational parameters are deposited at the Cambridge Crystallographic Data Centre.

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