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NEO-CLERODANE DITERPENOIDS FROM *TEUCRIUM SANDRASICUM*

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Key Word Index—*Teucrium sandrasicum*; Labiatae; *neo*-clerodane diterpenoids; oxetane derivatives; teusandrins A–F.

Abstract—Six new *neo*-clerodane diterpenoids, teusandrins A-F, and two known compounds, teucjaponin B and its 6-*O*-acetyl derivative, were isolated from the aerial parts of *Teucrium sandrasicum*. The structures of the new diterpenoids [(12*S*)-6α,19-diacetoxy-4α,18; 15,16-diepoxy-8β,10β-dihydroxy-*neo*-cleroda-13(16),14-dien-20,12-olide (teusandrin A), (12*S*)-19-acetoxy-4α,18; 15,16-diepoxy-6α,8β,10β-trihydroxy-*neo*-cleroda-13(16),14-dien-20,12-olide (teusandrin B), (12*S*)-4α,19; 15,16-diepoxy-6α,8β,10β,18-tetrahydroxy-*neo*-cleroda-13(16),14-dien-20,12-olide (teusandrin C), (12*S*)-4α,19; 15,16-diepoxy-6α,10β,18-trihydroxy-*neo*-cleroda-13(16),14-dien-20,12-olide (teusandrin D), (12*S*)-4β,10β; 15,16-diepoxy-18,19-dihydroxy-6-oxo-*neo*-cleroda-13(16),14-dien-20,12-olide (teusandrin E) and (12*S*)-4β,10β; 15,16-diepoxy-6α,18,19-trihydroxy-*neo*-cleroda-13(16),14-dien-20,12-olide (teusandrin F)] were established by chemical and spectroscopic means. The probable identity between teusandrins A and B, and the previously described sandrasin A and 6-deacetylsandrasin A, respectively, is also discussed.

INTRODUCTION

A large number of diterpenoids with the *neo*-clerodane skeleton [1] have been isolated from natural sources in the last few years [2–4]. Interest in these compounds has been stimulated by their biological activity as insect antifeedants [5–10] and, recently, by their hepatotoxicity [11]. The genus *Teucrium* has afforded a great number of these compounds [2–5, 12–14]. In a continuation of our studies on *Teucrium* plants [12–14], we have investigated *T. sandrasicum*, a species from which three new *neo*-clerodanes, sandrasins A and B and 6-deacetylsandrasin A, have recently been isolated [15]. We report here the structural elucidation of six novel *neo*-clerodanes together with the identification of two already known diterpenoids, all of them found in this plant.

RESULTS AND DISCUSSION

Repeated chromatography of the acetone extract of the aerial parts of *T. sandrasicum* (see Experimental) led to the isolation of the previously known *neo*-clerodane diterpenoids teucjaponin B (**1**, found for the first time in *T. japonicum* [16]) and its 6-*O*-acetyl derivative (**2**, already known as a natural [17] and synthetic [18, 19] compound). In addition, six new *neo*-clerodanes, teusandrins A–F, were also isolated and their structures (**3**–**8**, respectively) established as follows.

Teusandrin A (**3**) had the molecular formula $C_{24}H_{30}O_{10}$ and its IR spectrum showed hydroxyl (3400 cm^{-1}), furan (3150, 1600, 1510, 875 cm^{-1}), oxirane (3060 cm^{-1}), γ-lactone (1760 cm^{-1}) and acetate (1740, 1250 cm^{-1}) absorptions. The ^1H and ^{13}C NMR spectra of **3** (Tables 1 and 2, respectively) were very similar to those of 6-*O*-acetylteucjaponin B (**2**) [17–19] showing almost identical signals for a β-substituted furan, a 4α,18-oxirane, an acetoxymethylene group at the C-19 position, an equatorial acetoxyl group attached to the C-6α position and a γ-lactone in which the C-9, C-11, C-12 and C-20 carbons are involved (see Tables 1 and 2 and refs [17–19]). In addition, teusandrin A (**3**) possessed two tertiary hydroxyl groups (ν_{max} 3400 cm^{-1}, δ_C 76.1 *s* and 82.0 *s*), which must be placed at the C-8 and C-10 positions of the *neo*-clerodane skeleton [15, 20–26]. The existence in **3** of a C-8 hydroxyl group was in agreement with the resonance

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Table 1. ^{1}H NMR spectral data of compounds **3**–**11***

H	3	4	5	6	7	8	9	10	11
1α	†	1.87†	†	2.34†	†	1.93†	2.10†	†	2.00†
1β	†	1.78†	†	2.18†	†	2.12†	2.10†	†	2.11†
2α	†	2.05†	†	2.45†	†	2.23†	2.26 *m*	†	2.11†
2β	†	1.78†	†	2.10†	†	2.23†	1.89 *m*	†	2.11†
3α	2.27†	2.23 *tdd*	†	2.18†	1.79 *ddd*	2.47†	2.16 *td*	†	1.72 *ddd*
3β	1.07 *ddd*	1.13 *ddd*	1.70 *ddd*	1.78 *dt*	†	2.23†	1.73 *ddd*	†	2.15†
6β	5.45 *br dd*	4.35 *br dd*	5.13 *dd*	4.50 *dd*	—	4.91 *br dd*	5.50 *dd*	5.35 *dd*	—
7α	2.79 *dd*	2.65 *dd*	2.97 *dd*	2.35†	2.95 *dd*	2.41 *q*	2.54 *dd*	2.47 *dd*	3.22 *dd*
7β	1.76 *dd*	1.87†	†	1.81†	2.41 *dd*	1.76 *dt*	2.02 *dd*	2.95 *dd*	2.42 *dd*
8β	—	—	—	2.18†	2.64 *ddq*	2.15†	—	—	2.48 *ddq*
11A‡	2.52 *dd*	2.48 *dd*	2.78 *dd*	2.27 *dd*	2.20 *dd*	2.15 *dd*	2.46 *dd*	2.41 *dd*	2.11 *dd*
11B§	3.11 *dd*	3.10 *dd*	3.29 *dd*	3.11 *dd*	2.88 *dd*	3.07 *dd*	3.10 *dd*	3.17 *dd*	2.92 *dd*
12	5.41 *t*	5.39 *t*	5.60 *t*	5.66 *t*	5.59 *t*	5.71 *t*	5.46 *t*	5.48 *t*	5.46 *t*
14	6.39 *dd*	6.39 *dd*	6.56 *dd*	6.65 *dd*	6.57 *dd*	6.66 *dd*	6.40 *dd*	6.39 *dd*	6.37 *dd*
15	7.43 *t*	7.43 *t*	7.59 *t*	7.72 *t*	7.66 *t*	7.71 *t*	7.44 *t*	7.46 *t*	7.44†
16	7.47 *m*	7.47 *m*	7.72 *m*	7.77 *m*	7.82 *m*	7.75 *m*	7.48 *m*	7.48 *m*	7.44†
Me-17	1.26 *s*	1.28 *s*	1.36 *s*	1.11 *d*	1.01 *d*	1.14 *d*	1.18 *s*	1.57 *s*	1.02 *d*
18A	2.44 *d*‖	2.63 *d*‖	4.01 *d*	3.87 *d*	3.91 *d*	3.88 *d*	4.26 *s*	4.19 *d*	3.99 *d*
18B	3.05 *dd*¶	3.31 *dd*¶	4.35 *d*	4.13 *d*	4.06 *d*	4.01 *d*	4.26 *s*	4.29 *d*	4.24 *d*
19A	4.46 *dd*	4.60 *br d*	4.79 *d***	4.61 *d***	4.03 *d*	3.95 *br d*	4.49 *d***	4.52 *d*	4.02 *d*
19B	5.22 *d*	5.08 *d*	5.33 *d***	4.82 *d***	4.56 *d*	4.20 *d*	4.72 *d***	4.73 *d*	4.69 *d*
OH††	3.54 *s*‡‡	3.39 *s*‡‡	6.00 *s*				2.95 *s*‡‡	—	—
	4.94 *s*§§	4.66 *s*§§	4.90 *s*				4.41 *s*§§	3.45 *d*	—
	—	2.78 *s*‖‖	3.56 *s*						
OAc	2.08 *s*	2.07 *s*	—	—	—	—	2.21 *s*	2.18 *s*	2.06 *s*
	1.98 *s*	—	—	—	—	—	2.02 *s*	2.09 *s*	2.05 *s*
	—	—	—	—	—	—	—	2.01 *s*	—

J (Hz)¶¶									
2α,3α	†	4.4	†	†	3.3	†	5.0	†	3.3
2α,3β	2.1	2.6	2.5	4.6	†	†	2.4	†	†
2β,3α	†	13.4	†	†	8.7	†	13.7	†	8.7
2β,3β	4.0	4.0	4.0	4.6	†	†	4.0	†	†
3α,3β	13.6	13.4	12.7	14.0	12.9	†	13.7	†	12.9
6β,7α	12.0	11.7	11.8	11.0	—	12.4	12.1	12.4	
6β,7β	4.5	3.4	4.5	4.6	—	3.4	4.3	3.9	—
7α,7β	14.3	14.1	13.0	†	13.5	12.4	13.4	14.3	15.7
7α,8β	—	—	—	†	12.9	12.4	—	—	13.3
7β,8β	—	—	—	†	3.5	3.4		—	3.4
8β,17		—	—	6.3	6.9	6.8	—		6.8
11A,11B	15.2	15.0	14.9	14.7	14.4	14.5	15.0	15.0	14.6
11A,12	9.2	9.2	8.9	8.8	8.8	7.8	8.8	8.8	8.0
11B,12	8.2	8.2	8.6	8.9	8.7	9.4	8.7	8.6	9.3
14,15	1.8	1.8	1.8	1.8	1.8	1.8	1.9	1.8	1.5
14,16	0.9	0.9	0.9	1.0	0.8	1.0	0.9	0.9	1.0
15,16	1.8	1.8	1.8	1.8	1.8	1.8	1.9	1.8	†
18A,18B	3.9	3.9	12.8	12.2	9.7	12.2	0	11.3	12.7
18B,3α	1.8	1.7	0	0	0	0	0	0	0
19A,19B	13.1	13.2	6.8	7.3	11.9	11.9	7.8	8.0	11.7
19A,6β	0.4	<0.4	0	0	—	<0.4	0	0	—

* Spectra were recorded in $CDCl_3$ (**3**, **4**, **9** **11**), pyridine-d_5 (**5** and **7**), or CD_3OD (**6** and **8**) solution, at 500 MHz except for **5** and **7** (300 MHz) and **10** (200 MHz). Chemical shifts are relative to residual $CHCl_3$ (δ 7.25), C_5H_5N ($\delta_{H\text{-}2}$ 8.71) or MeOH (δ 3.50). Spectral parameters were obtained by first order approximation and the assignments were in agreement with HMQC spectra.

† Overlapped signal. For some compounds, approximate chemical shift values of these protons were measured with the aid of the HMQC spectra.

‡ This proton is the pro-*R* hydrogen and its assignment was achieved by NOE experiments (Table 3).

§ This proton is the pro-*S* hydrogen and was distinguished by NOE experiments (Table 3).

‖ *Exo* hydrogen with respect to ring B.

¶ *Endo* hydrogen with respect to ring B.

** In **5**, **6**, **9** and **10**, the H_A-19 and H_B-19 protons are the pro-*S* and pro-*R* hydrogens, respectively, and they were distinguished by NOE experiments (Table 3).

†† Disappeared after addition of D_2O.

‡‡ OH at C-8β (Table 3).

§§ OH at C-10β (Table 3).

‖‖ OH at C-6α.

¶¶ Coupling values for the C-1 methylene protons and J_{gem} for the C-2 methylene protons were not determined due to overlapping.

Table 2. ^{13}C NMR spectral data of compounds **3**, **4**, **6**, **8**, **9** and **11***

C	3†	4†	6‡	8‡	9†	11†
1	29.6 *t*	29.4 *t*	31.9 *t*	26.8 *t*	29.9 *t*	24.5 *t*
2	18.9 *t*	19.1 *t*	16.3 *t*	16.2 *t*	14.6 *t*	14.7 *t*
3	31.4 *t*	30.6 *t*	31.9 *t*	24.5 *t*	29.5 *t*	24.3 *t*
4	62.9 *s*	64.9 *s*	77.2 *s*	88.7 *s*[a]	75.9 *s*	84.8 *s*
5	49.9 *s*	49.5 *s*	59.7 *s*	55.5 *s*[b]	50.8 *s*	60.7 *s*
6	67.4 *d*	66.1 *d*	67.3 *d*	72.5 *d*	68.1 *d*	209.3 *s*
7	38.4 *t*	39.7 *t*	36.0 *t*	35.5 *t*	37.2 *t*	44.9 *t*
8	76.1 *s*	76.7 *s*	34.7 *d*	38.0 *d*	77.8 *s*	33.7 *d*
9	59.4 *s*	59.6 *s*	54.0 *s*	56.0 *s*[b]	59.5 *s*	53.3 *s*
10	82.0 *s*	81.5 *s*	92.3 *s*	88.8 *s*[a]	87.7 *s*	89.4 *s*
11	35.0 *t*	35.2 *t*	37.4 *t*	36.0 *t*	33.5 *t*	35.2 *t*
12	72.2 *d*	72.1 *d*	73.8 *d*	74.8 *d*	72.5 *d*	72.8 *d*
13	125.1 *s*	125.1 *s*	126.7 *s*	126.6 *s*	124.8 *s*	125.1 *s*
14	108.0 *d*	108.0 *d*	109.3 *d*	109.4 *d*	108.1 *d*	107.9 *d*
15	144.2 *d*	144.3 *d*	145.5 *d*	145.5 *d*	144.3 *d*	144.3 *d*
16	139.6 *d*	139.6 *d*	141.3 *d*	141.1 *d*	139.6 *d*	139.2 *d*
17	26.2 *q*	26.7 *q*	17.7 *q*	17.3 *q*	26.7 *q*	16.8 *q*
18	51.7 *t*	51.6 *t*	66.7 *t*	65.4 *t*	67.7 *t*	66.3 *t*
19	63.6 *t*	63.6 *t*	71.3 *t*	60.8 *t*	70.7 *t*	62.1 *t*
20	174.5 *s*	174.3 *s*	179.1 *s*	178.8 *s*	175.6 *s*	175.0 *s*
OAc	170.7 *s*	170.7 *s*	—		171.0 *s*	170.6 *s*
	170.4 *s*	21.2 *q*	—		170.6 *s*	170.2 *s*
	21.2 *q*		—		21.8 *q*	20.9 *q*
	21.2 *q*	—	—		20.8 *q*	20.7 *q*

* Spectra were recorded at 125.7 MHz. Chemical shifts are relative to solvent signals (δ_{CDCl_3} 77.0; δ_{CD_3OD} 49.0). Multiplicities were determined by HMQC.

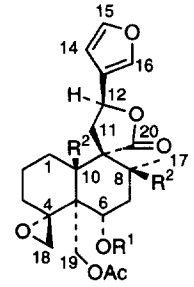
† In $CDCl_3$ solution.

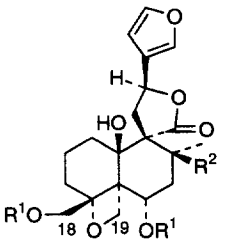
‡ In MeOH-d_4 solution.

[a,b] These assignments may be reversed.

of the C-17 methyl group at δ 1.26 as a singlet and with the pattern showed by the signals of the C-7 methylene protons ($\delta_{H\text{-}7\alpha}$ 2.79 and $\delta_{H\text{-}7\beta}$ 1.76), both appearing as double doublets ($J_{gem} = 14.3$ Hz, $J_{7\alpha,6\beta} = 12.0$ Hz and $J_{7\beta,6\beta} = 4.5$ Hz) [20,22,25,26]. The hydroxyl group of **3** at the C-10 position was supported by the downfield resonance of the C-1 and C-5 β-carbons and the upfield resonance of the C-2 and C-4 γ-carbons with respect to those of **2** [$\Delta\delta = \delta$(**3**)-δ(**2**): +6.7, +4.5, −6.0 and −1.7 ppm, respectively] [18, 19]. The presence of both C-8 and C-10 hydroxyl groups in **3** was also in agreement with the strong paramagnetic shift of its C-9 carbon (δ 59.4 *s*, β-carbon with respect to both alcohols) as compared with that of **2** (δ 50.8 *s*) [18, 19], as well as with the strong upfield shift showed by its C-11 γ-carbon (**3**: δ 35.0 *t*; **2**: δ 43.1 *t* [18, 19]). The almost identical resonances for the C-8–C-12, C-17 and C-20 carbons in **3** and teubrevin D, an 8β, 10β-dihydroxy-*neo*-clerodan-20,12-olide derivative recently isolated from *Teucrium brevifolium* [27], further confirmed this point and suggested a β-configuration for both C-8 and C-10 tertiary alcohols of **3** [$\Delta\delta = \delta$(teubrevin D)-δ(**3**): +3.9, +1.0, +1.4, 0.0, +0.4, −1.5 and −0.3 ppm for C-8–C-12, C-17 and C-20, respectively].

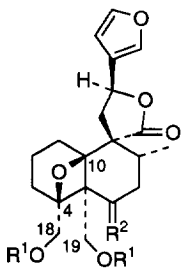
The relative configuration of all the stereogenic centres of **3** was established by NOE experiments. The data collected in Table 3 shows that H-6β, the C-18 methylene protons and both the tertiary hydroxyl groups at the C-8 and C-10 positions are on the same side of the plane defined by the substituted decalin moiety, because irradiation at δ 5.45 (H-6β) caused a NOE enhancement in the signal of the H_B-18 (*endo* proton with respect to ring **B**) and in those corresponding to the hydrogens of the hydroxyl groups (δ 3.54 *s* and 4.94 *s*) [22], thus establishing a β-configuration for both tertiary alcohols. Moreover, irradiation of the H-7α axial proton (δ 2.79) produced NOE enhancement in the signals of the Me-17 (δ 1.26) and in both C-19 methylene protons (δ 4.46 and 5.22), only compatible with a *trans*-decalin in which the H-7α and C-19 protons are in a *cis* 1,3-diaxial relationship. Finally, irradiation of the methyl singlet signal at δ 1.26 (Me-17, in an equatorial C-8α configuration) caused, among others, NOE enhancement in the signals of the H-14 and H-16 furanic protons (δ 6.39 and 7.47), whereas no effect was observed in the signal of the H-12 proton (δ 5.41), thus defining that **3** possessed a 12*S* configuration [19, 27–29], if it is a *neo*-clerodane derivative [1]. These NOE experiments also allowed the assignment of both the methylene protons at C-11, because irradiation at δ 1.26 (Me-17 protons) produced NOE enhancement in the signal of the H_A-11 (δ 2.52) proton, which must be the pro-*R* hydrogen.





	R^1	R^2
1	H	H
2	Ac	H
3	Ac	OH
4	H	OH

	R^1	R^2
5	H	OH
6	H	H
9	Ac	OH
10	Ac	OAc



	R^1	R^2
7	H	O
8	H	αOH,βH
11	Ac	O

From all the above data, it was evident that teusandrin A possessed the structure and relative stereochemistry depicted in **3**.

Teusandrin B (**4**, $C_{22}H_{28}O_9$) is the 6-deacetyl derivative of teusandrin A (**3**, $C_{24}H_{30}O_{10}$), as was revealed by the differences in their ^1H and ^{13}C NMR spectra [Tables 1 and 2: upfield resonance of the H-6β proton in **4** (δ 4.35) with respect to **3** (δ 5.45); two acetoxyl groups in **3** (δ 2.08 and 1.98) and only one in **4** (δ 2.07); δ_C 49.5 *s* (C-5), 66.1 *d* (C-6) and 39.7 *t* (C-7) in **4**, and at δ 49.9 *s*, 67.4 *d* and 38.4 *t*, respectively, in **3**]. Furthermore, NOE experiments (Table 3) confirmed that teusandrin B possessed the relative stereochemistry depicted in its formula (**4**), identical to that of **3**.

Recently, Topcu, Ulubelen and co-workers have reported [15] the isolation of two diterpenoids, sandrasin A and its 6-deacetyl derivative, from an acetone extract of *Teucrium sandrasicum* collected in the same locality that the plant material from which teusandrins A and B (**3** and **4**, respectively) have now been isolated. The structures assigned to sandrasin A and 6-deacetylsandrasin A are identical to those of **3** and **4**, respectively, except for the stereochemistry of their C-12 stereogenic centre (12*S* in **3** and **4** and 12*R* in the *neo*-clerodanes isolated by the Turkish scientists [15]). It is noteworthy that between sandrasin A and **3**, and similarly between 6-deacetylsandrasin A and **4**, there were noticeable differences in their optical rotations ($[\alpha]_D$: **3** +28.1°, sandrasin A +7°, **4** +57.5° and 6-deacetylsandrasin A +19.4°), but striking similarities in their ^1H NMR spectra and identical ^{13}C NMR spectra (Tables 1 and 2 and ref. [15]). It is known [19, 30, 31] that *neo*-clerodan-20,12-olides epimers at the C-12 asymmetric centre are clearly and reliably distinguished by their ^{13}C NMR spectra, which showed strong differences in the chemical shift of the C-8 and C-10 carbons and also noticeable variation in the resonances of their C-1, C-9, C-11, C-13 and C-17 carbons. Therefore, it is probable that sandrasin A could be identical to **3** and, consequently, that teusandrin B (**4**) and 6-deacetylsandrasin A could be the same compound. We were unable to obtain authentic samples of sandrasin A or its 6-deacetyl derivative for direct comparison with teusandrins A or B; however, it is important to note that one of the two arguments supporting a 12*R* configuration for sandrasin A is not reliable, because the observed NOE [15] between the H-11 proton of sandrasin A at δ 2.52 (H_B-11 in **3** at δ 2.52) and the H-12 proton is not a definitive reason for establishing the configuration at C-12, since both C-11 methylene protons display a NOE with the H-12 proton, although of different magnitude, as it is shown in Table 3 for compounds **4**, **6** and **11**, all of which have a 12*S* configuration.

Teusandrin C (**5**, $C_{20}H_{26}O_8$) had a β-substituted furan, a (12*S*)-20,12-γ-lactone, a 6α-hydroxyl group and two tertiary hydroxyls at the 8β and 10β positions identical to those of teusandrin B (**4**, see Tables 1 and 2). In addition, **5** possessed a C-18 hydroxymethylene group (δ_H 4.01, 1H, *d*, and 4.35, 1H, *d*, J_{gem} = 12.8 Hz) and an oxetane ring in which the C-4, C-5 and C-19 carbons are involved (δ_H 4.79, 1H, *d*, and 5.33, 1H, *d*, J_{gem} = 6.8 Hz) [32–34]. Treatment of **5** with acetic anhydride–pyridine (see Experimental) gave the 6α,18-diacetyl derivative **9** ($C_{24}H_{30}O_{10}$, 91% yield) together with minor quantities (9%) of the 6α,8β,18-triacetate (**10**, $C_{26}H_{32}O_{11}$). The ^1H and ^{13}C NMR spectra of **9** (Tables 1 and 2) confirmed the acetylation of the C-6α and C-18 hydroxyl groups of **5** [downfield shift of the H-6β proton, $\Delta\delta$ +0.37 ppm; presence in **9** of two *O*-acetyl groups at δ 2.21, 3H, *s*, and 2.02, 3H, *s*; δ_C 68.1 *d* (C-6) and 67.7 *t* (C-18)] [32–34] and revealed the existence of a 5α,19-oxetane, which was evidenced by the small geminal coupling value of the C-19 methylene protons (J_{gem} = 7.8 Hz) and by the chemical shifts of the C-4, C-5 and C-19 carbons (75.9 *s*, 50.8 *s* and 70.7 *t*, respectively), similar to those observed in other *neo*-clerodane diterpenoids possessing a 4α,19-oxetane structural moiety [32–34]. Moreover, the NOESY spectrum of **9** (Table 3) confirmed the relative stereochemistry of teusandrin C as it is shown in its formula (**5**) and allowed the unequivocal assignment of both C-19 methylene hydrogens in **9** (Tables 1 and 3).

The esterification of the C-8β tertiary hydroxyl group in **10** (see above), instead of the 10β-alcohol, was in agreement with the ^1H NMR spectrum of this

Table 3. NOE experiments on compounds **3**, **4**, **6**, **8**, **9** and **11***

		Observed NOE with protons		
	Proton(s) δ	Strong†	Medium‡	Weak§
3	H-6β (5.45)	H_B-18	H-7β	8β-OH, 10β-OH
	H-7α (2.79)	H-7β	Me-17, H_B-19	H_A-19
	Me-17 (1.26)		H_A-11 (pro-*R*), 8β-OH	H-7α, H-7β, H-14, H-16
	H_A-19 (4.46)	H_B-19		H-3α, Me-17
4	H-6β (4.35)	H_B-18	H-7β	8β-OH, 10β-OH
	H_B-11 (3.10)	H_A-11 (pro-*R*)	H-12, 10β-OH	H-1β
	H-12 (5.39)		H_B-11 (pro-*S*)	H-1α, H-1β, H_A-11 (pro-*R*)
	Me-17 (1.28)	H_A-11 (pro-*R*)	H-7α, H-7β, 8β-OH	H-14, H-16
	10β-OH (4.66)		H_B-11 (pro-*S*)	H-6β, 8β-OH)
6	H-6β (4.50)		H-7β, H-8β	H_A-18, H_B-18
	H-12 (5.66)		H_B-11 (pro-*S*)	H-1α, H-1β, H_A-11 (pro-*S*)
	Me-17 (1.11)	H-8β	H-7α, H-7β, H_A-11 (pro-*R*)	H-14
	H_A-18 (3.87)	H_B-18	H-3β	H-3α, H-6β
	H_B-18 (4.13)	H_A-18		H-3α, H-6β
	H_A-19 (4.61)	H_B-19 (pro-*R*)		H-1α, H-2α
8	H-7α (2.41)	H-7β		Me-17, H_B-19
	H-7β (1.76)	H-7α	H-6β, H-8β	Me-17
	Me-17 (1.14)		H-8β, H_A-11 (pro-*R*)	H-7α, H-7β, H-14
	H_A-18 (3.88)	H_B-18		H-3α, H-6β
	H_B-18 (4.01)	H_A-18		H-3α, H-3β
	H_A-19 (3.95)	H_B-19	H-7α	H-1α
	H_B-19 (4.20)	H_A-19		H-1α
9	H-6β (5.50)		H-7β, H_A-18, H_B-18	8β-OH, 10β-OH
	H-7α (2.54)	H-7β	H_B-19 (pro-*R*)	Me-17
	H_B-11 (3.10)	H_A-11 (pro-*R*)	H-12	H-1β, 10β-OH
	H-12 (5.46)		H_B-11 (pro-*S*)	H-1α, H-1β
	Me-17 (1.18)		H-7α, H_A-11 (pro-*R*), 8β-OH	H-7β, H-14
	H_A-19 (4.49)	H_B-19 (pro-*R*)	H-1α	
	H_B-19 (4.72)	H_A-19 (pro-*S*)	H-7α	
	8β-OH (2.95)		H-6β, 10β-OH	H_A-11 (pro-*R*)
	10β-OH (4.41)		H-6β	H_B-11 (pro-*S*), 8β-OH
11	*H*-7α (3.22)	*H*-7β		*Me*-17
	H-7β (2.42)	*H*-7α	*H*-8β	*Me*-17
	H-8β (2.48)		*H*-7β, *Me*-17	*H*$_A$-11 (pro-*R*)
	H_A-11 (2.11)	H_B-11 (pro-*S*)		H-8β, H-12, Me-17
	H_B-11 (2.92)	H_A-11 (pro-*R*)	H-12	
	H-12 (5.46)		H_B-11 (pro-*S*)	H-1α, H-1β, H_A-11 (pro-*R*)
	Me-17 (1.02)		H-7α, H-8β, H_A-11 (pro-*R*)	H-7β, H-14
	H_B-18 (4.24)	H_A-18		H-3α, H-3β
	H_A-19 (4.02)	H_B-19	H-3α	H-1α
	H_B-19 (4.69)	H_A-19		H-1α, H-3α

* Measured at 500 MHz from the NOESY spectra and, in some cases (**3**, **4** and **11**), also by the FT difference method.
† NOE enhancement > 8%.
‡ NOE enhancement 3–6%.
§ NOE enhancement 0.5–2.5%.

derivative, which showed (Table 1) a strong paramagnetic shift for the H-7β and Me-17 protons ($\Delta\delta$ +0.93 and +0.39 ppm, respectively) as compared with those of **9**. The presence in **10** of three acetoxyl groups (δ 2.18, 2.09 and 2.01) as well as the resonance of the 10β-hydroxyl proton at δ 3.45 as a doublet (J = 1.8 Hz), long-range coupled with the H-1α axial proton as a consequence of the probably existence of a hydrogen bond between this hydroxyl and the ester oxygen atom of the 8β-acetate, further supported that in **10** its C-8β alcohol is esterified.

The 8β-deoxy derivative of **5** was also present in the acetone extract of *T. sandrasicum*. This compound (**6**, teusandrin D, $C_{20}H_{26}O_7$) showed ^{1}H and ^{13}C NMR spectra almost identical with those of **5** and its derivative **9** (Tables 1 and 2). In fact, the observed differences between the ^{1}H and ^{13}C NMR spectra of these compounds were consistent with the absence in **6** of the 8β-hydroxyl group of **5**, because teusandrin D (**6**) showed a doublet signal (J = 6.3 Hz) for its C-17 methyl group (δ 1.11, 3H, *d*) and the expected variations in its ^{13}C NMR spectrum with respect to **9**

(Table 2: upfield shifts of the C-7, C-8, C-9 and C-17 carbons and downfield shifts of the C-10 and C-11 γ-carbons; $\Delta\delta$ −1.2, −43.1, −5.5, −9.0, +4.6 and +3.9 ppm, respectively). The NOESY spectrum of **6** (Table 3) further supported the structure of this diterpenoid.

Teusandrin E (**7**) had the molecular formula $C_{20}H_{24}O_7$ and its ^1H NMR spectrum (Table 1) revealed the presence in the molecule of a β-substituted furan ring, a 20, 12-γ-lactone and a secondary methyl group (δ 1.01, 3H, *d*, $J = 6.9$ Hz) attached to the C-8α position, all of them identical to those of **6**. Treatment of **7** with acetic anhydride–pyridine yielded a diacetyl derivative (**11**, $C_{24}H_{28}O_9$), the IR spectrum of which was devoid of hydroxyl absorptions. The ^1H and ^{13}C NMR spectra of **11** (Tables 1 and 2) were consistent with the presence of a ketone at the C-6 position (δ_C 209.3 *s*; C-7 methylene protons at δ 3.22 *dd* and 2.42 *dd*; H-8β at δ 2.48 *ddq*, $J_{7\alpha,7\beta} = 15.7$ Hz, $J_{7\alpha,8\beta} = 13.3$ Hz and $J_{7\beta,8\beta} = 3.4$ Hz) and two acetoxyl groups at the C-18 and C-19 [two AB systems at δ 3.99 *d* and 4.24 *d*, $J_{gem} = 12.7$ Hz (2H-18), and δ 4.02 *d* and 4.69 *d*, $J_{gem} = 11.7$ Hz (2H-19); $\delta_{C\text{-}18}$ 66.3 *t* and $\delta_{C\text{-}19}$ 62.1 *t*; two OAc groups at δ_H 2.06 *s* and 2.05 *s*, both 3H, δ_C 170.6 *s*, 170.2 *s*, 20.9 *q* and 20.7 *q*; correlation between the carboxyl carbons of the acetates and the C-18 and C-19 methylene protons in the HMBC spectrum of **11**]. In addition, the ^{13}C NMR spectrum of **11** (Table 2) showed signals for two fully substituted carbons bearing oxygen atoms (δ 84.8 *s* and 89.4 *s*), which must be assigned to the C-4 and C-10 carbons of the *neo*-clerodane skeleton. This was in agreement with the chemical shift of the C-1, C-2, C-3, C-5 and C-9 carbons of **11** as compared with those of closely related compounds, such as **6** (see Table 2). Molecular formula requirements and the absence of hydroxyl absorptions in the IR spectrum of **11** established that teusandrin E (**7**) and its derivative **11** possessed an oxetane ring between the C-4 and C-10 positions. The 4β,10β configuration of this grouping, as well as the stereochemistry of the remaining stereogenic centres in **11**, were in agreement with its NOE behaviour (Table 3). In particular, one of the C-18 methylene protons (δ 4.24) showed a NOE with both H-3α (axial) and H-3β (equatorial) protons, whereas the H-3α proton displayed a NOE with both C-19 methylene protons. These results are only compatible with a 4β,10β configuration for the oxetane of **11** and consequently, teusandrin E had the structure depicted in **7**.

The *neo*-clerodane absolute configuration [1] of teusandrin E (**7**) was established from the CD curve of its derivative **11**, which showed a negative Cotton effect ($\Delta\varepsilon_{304}$ −9.3) due to the C-6 ketone chromophore, identical with those found in other 6-oxo-*neo*-clerodane derivatives whose absolute stereochemistry is well known [18, 21, 30, 35, 36].

The last diterpenoid isolated from *T. sandrasicum*, teusandrin F ($C_{20}H_{26}O_7$), possessed structure **8**, as was evidenced by its ^1H and ^{13}C NMR spectra (Tables 1 and 2) when they were compared with those of **7** and **11**. The presence in **8** of an equatorial hydroxyl group at the C-6α position instead of the 6-keto group of **7** was in agreement with the signals of the H-6β axial proton (δ 4.91 *br dd*, $J_{6\beta,7\alpha} = 12.4$ Hz, $J_{6\beta,7\beta} = 3.4$ Hz) and the C-6 carbon (δ 72.5 *d*) of the former instead of the 6-ketone of the latter (at δ_C 209.3 *s* in its derivative **11**). Other minor differences observed between the ^1H and ^{13}C NMR spectra of **8** and **7** and **11** (e.g. in the chemical shifts, multiplicities and geminal coupling values of the C-7 methylene protons, in the chemical shift of the C-5 and C-7 carbons, etc) also supported structure **8** for teusandrin F, the relative stereochemistry of which was in agreement with NOE experiments (Table 3). These spectroscopic evidences on the structure of teusandrin F were chemically confirmed since reduction of **7** with sodium borohydride yielded a compound identical to natural teusandrin F (**8**).

The absolute stereochemistry of teusandrins A–D was not ascertained. However, on biogenetic grounds, it is reasonable to assume that they belong to the *neo*-clerodane series [1] like teusandrins E and F (**7** and **8**, see above) and other diterpenoids isolated from *Teucrium* species [2–4].

It is of interest to note that diterpenoids containing an oxetane ring involving the 4α,19 (such as in **5** and **6**), 4β,10β (as in the case of **7** and **8**) and 4β,6β positions of the *neo*-clerodane skeleton are relatively frequent among the constituents of *Teucrium* plants [2–4, 32–34, 37–39].

EXPERIMENTAL

General. Mps: uncorr. Plant materials were collected in June 1995 at Sandras Mountain, near Mugla, Köycegiz (Turkey), and voucher specimens were deposited in the Herbarium of the Faculty of Pharmacy, Anadolu University, Eskisehir, Turkey.

Extraction and isolation of the diterpenoids. Dried and powdered aerial parts of *T. sandrasicum* O. Schwarz (1 kg) were extracted with Me_2CO (3 × 4 l) at room temp. for 1 week. The extract (20 g) was subjected to CC (silica gel, Merck no. 7734, deactivated with 15% H_2O, w/v, 600 g) eluting with petrol, petrol–EtOAc mixts, EtOAc and EtOAc–MeOH mixt. The frs eluted with petrol–EtOAc (1:1) gave 6-*O*-acetylteucjaponin B (**2**, 35 mg) [17–19] and the frs eluted with EtOAc–petrol (3:1) yielded teusandrin A (**3**, 54 mg). The frs eluted with EtOAc–petrol (4:1) and pure EtOAc gave a mixt. of three substances (TLC), which were rechromatographed (radial chromatography, silica gel plates, CH_2Cl_2–MeOH 24:1 as eluent) yielding the following compounds in order of increasing chromatographic polarity: teusandrin B (**4**, 25 mg), teusandrin E (**7**, 34 mg) and teucjaponin B (**1**, 10 mg) [16]. Finally, the frs eluted with EtOAc–MeOH (19:1) were rechromatographed (CC, silica gel, CH_2Cl_2–MeOH 24:1) eluting successively teusandrin F (**8**, 15 mg), teusandrin C (**5**, 31 mg) and teusandrin D (**6**, 22 mg).

The previously known compounds, teucjaponin B (**1**) and its acetate (**2**) [16–19], were identified by their physical (mp, $[\alpha]_D$) and spectroscopic (^{1}H NMR, MS) data and by comparison (mmp, TLC) with authentic samples.

Teusandrin A (**3**). Amorphous solid, mp 80–85°, $[\alpha]_D^{22}$ +28.1° ($CHCl_3$; *c* 0.381). IR ν_{max}^{KBr} cm^{-1}: 3400 (OH), 3150, 1600, 1510, 875 (furan), 3060 (oxirane), 1760 (γ-lactone), 1740, 1250 (OAc), 2940, 2880, 1460, 1370, 1180, 1160, 1030, 990, 970, 930, 850, 800, 750; ^{1}H NMR: Table 1; ^{13}C NMR: Table 2; EIMS (70 eV, direct inlet) *m/z* (rel. int.): $[M]^+$ absent, 418 $[M-AcOH]^+$ (1.5), 400 $[M-AcOH-H_2O]^+$ (2.3), 363 (4), 358 (7), 328 (7), 297 (6), 283 (5), 265 (5), 234 (7), 203 (13), 189 (10), 177 (29), 173 (11), 164 (18), 151 (10), 147 (14), 135 (24), 121 (20), 105 (21), 95 (37), 94 (41), 91 (21), 81 (19), 55 (24), 43 (100). (Found: C, 60.31; H, 6.49. $C_{24}H_{30}O_{10}$ requires: C, 60.24; H, 6.32%).

Teusandrin B (**4**). Mp 185–187° (EtOAc–*n*-hexane), $[\alpha]_D^{21}$ +57.5° ($CHCl_3$; *c* 0.278). IR ν_{max}^{KBr} cm^{-1}: 3500, 3480, 3330 (OH), 3140, 1600, 1505, 870 (furan), 3060 (oxirane), 1750 (γ-lactone), 1730, 1250 (OAc), 2950, 2940, 2870, 1460, 1365, 1325, 1200, 1180, 1165, 1120, 1090, 1025, 985, 970, 915, 860, 815; ^{1}H NMR: Table 1; ^{13}C NMR: Table 2; EIMS (70 eV, direct inlet) *m/z* (rel. int.): 436 $[M]^+$ (0.2), 418 $[M-H_2O]^+$ (1.5), 400 $[M-2H_2O]^+$ (1.3), 376 $[M-AcOH]^+$ (2.4), 358 $[M-AcOH-H_2O]^+$ (8), 345 (20), 297 (10), 197 (10), 189 (12), 177 (17), 173 (13), 165 (12), 161 (21), 147 (16), 135 (15), 105 (13), 95 (23), 94 (41), 91 (22), 81 (42), 77 (27), 69 (18), 55 (37), 43 (100). (Found: C, 60.29; H, 6.55. $C_{22}H_{28}O_9$ requires: C, 60.54; H, 6.47%).

Teusandrin C (**5**). Mp 242–245° (EtOAc–*n*-hexane), $[\alpha]_D^{23}$ +42.6 ($CHCl_3$–MeOH 1:1; *c* 0.129). IR ν_{max}^{KBr} cm^{-1}: 3380 *br*, 3260 *br* (OH), 3140, 1610, 1505, 875 (furan), 1760 (γ-lactone), 2980, 2920, 1470, 1410, 1380, 1365, 1330, 1190, 1180, 1165, 1070, 1020, 950, 930, 870, 840, 800; ^{1}H NMR: Table 1; EIMS (70 eV, direct inlet) *m/z* (rel. int.): 394 $[M]^+$ (0.3), 376 $[M-H_2O]^+$ (1), 358 $[M-2H_2O]^+$ (2), 345 $[M-CH_2OH-H_2O]^+$ (6), 340 $[M-3H_2O]^+$ (2), 327 (3), 259 (11), 207 (7), 192 (14), 177 (12), 161 (12), 147 (14), 137 (16), 121 (13), 107 (24), 97 (22), 95 (64), 94 (100), 91 (35), 81 (45), 77 (41), 67 (23), 55 (37), 43 (97). (Found: C, 60.78; H, 6.51. $C_{20}H_{26}O_8$ requires: C, 60.90; H, 6.64%).

Teusandrin D (**6**). Mp 242–245° decomp. (EtOAc–*n*-hexane), $[\alpha]_D^{20}$ +26.7° ($CHCl_3$–MeOH 4:1; *c* 0.060). IR ν_{max}^{KBr} cm^{-1}: 3390, 3300, 3210 (OH), 3150, 1600, 1510, 880 (furan), 1750 (γ-lactone), 2930, 1470, 1340, 1190, 1155, 1115, 1065, 1010, 970, 870, 845, 800, 730; ^{1}H NMR: Table 1; ^{13}C NMR: Table 2; EIMS (70 eV, direct inlet) *m/z* (rel. int.): 378 $[M]^+$ (0.6), 360 $[M-H_2O]^+$ (2.6), 347 $[M-CH_2OH]^+$ (10), 342 $[M-2H_2O]^+$ (5), 329 $[M-CH_2OH-H_2O]^+$ (9), 314 (12), 311 (6), 283 (12), 248 (23), 207 (20), 202 (20), 189 (23), 187 (23), 178 (48), 161 (48), 145 (36), 133 (39), 129 (35), 105 (58), 95 (100), 94 (96), 91 (56), 81 (74), 79 (58), 55 (63), 43 (47), 41 (50). (Found: C, 63.71; H, 7.09. $C_{20}H_{26}O_7$ requires: C, 63.48; H, 6.93%).

Teusandrin E (**7**). Mp 221–223° (EtOAc), $[\alpha]_D^{18}$ +24.1° ($CHCl_3$–MeOH 1:1; *c* 0.166). IR ν_{max}^{KBr} cm^{-1}: 3480, 3360 (OH), 3150, 1600, 1505, 875 (furan), 1750 (γ-lactone), 1745 (ketone), 2980, 2930, 2880, 1450, 1345, 1185, 1160, 1115, 1025, 1000, 950, 920, 810, 750; ^{1}H NMR: Table 1; EIMS (70 eV, direct inlet) *m/z* (rel. int.): 376 $[M]^+$ (0.8), 358 $[M-H_2O]^+$ (3.5), 340 $[M-2H_2O]^+$ (2), 329 (11), 327 (2), 315 (12), 283 (13), 272 (12), 264 (14), 246 (21), 235 (16), 219 (17), 177 (26), 147 (25), 145 (21), 133 (28), 128 (26), 121 (26), 115 (22), 105 (24), 95 (60), 94 (100), 91 (34), 81 (36), 79 (38), 77 (35), 69 (40), 55 (37), 43 (29), 41 (35). (Found: C, 63.77; H, 6.29. $C_{20}H_{24}O_7$ requires: C, 63.82; H, 6.43%).

Teusandrin F (**8**). Mp 200–202° (EtOAc–*n*-hexane), $[\alpha]_D^{20}$ +41.9° ($CHCl_3$–MeOH 4:1; *c* 0.031). IR ν_{max}^{KBr} cm^{-1}: 3300 *br* (OH), 3150, 1510, 875 (furan), 1750 (γ-lactone), 2970, 2880, 1475, 1340, 1200, 1175, 1160, 1050, 1020, 975, 935, 930, 905, 800, 750; ^{1}H NMR: Table 1; ^{13}C NMR: Table 2; EIMS (70 eV, direct inlet) *m/z* (rel. int.): 378 $[M]^+$ (0.2), 360 $[M-H_2O]^+$ (2), 347 $[M-CH_2OH]^+$ (3), 342 $[M-2H_2O]^+$ (2), 329 (11), 324 (1), 311 (6), 301 (12), 283 (12), 236 (11), 191 (12), 189 (12), 179 (13), 161 (21), 145 (19), 133 (16), 121 (23), 105 (24), 95 (41), 94 (100), 91 (35), 81 (40), 79 (29), 77 (24), 55 (22); positive FAB-MS *m/z* (rel. int.): 379 $[MH]^+$ (100), 361 $[MH-H_2O]^+$ (10), 343 $[MH-2H_2O]^+$ (8), 325 $[MH-3H_2O]^+$ (5), 313 (15), 186 (12), 183 (10), 95 (18), 94 (23). (Found: C, 63.59; H, 6.87. $C_{20}H_{26}O_7$ requires: C, 63.48; H, 6.93%).

Compounds **9** *and* **10** *from teusandrin C* (**5**). Treatment of **5** (5 mg) with Ac_2O–pyridine (1:1, 2 ml) at room temp. for 40 hr yielded a mixt. of two derivatives (TLC), which were sepd by CC (silica gel, petrol–EtOAc, 3:2 as eluent) giving **10** (0.4 mg, less polar constituent) and **9** (4.2 mg).

Compound **9**. Mp 213–215° (EtOAc–*n*-hexane), $[\alpha]_D^{21}$ +54.9° ($CHCl_3$; *c* 0.111). IR ν_{max}^{KBr} cm^{-1}: 3370, 3290 (OH), 3150, 3140, 3120, 1600, 1505, 875 (furan), 1760 (γ-lactone), 1745, 1230 (OAc), 2970, 2940, 1480, 1420, 1380, 1360, 1325, 1180, 1160, 1120, 1100, 1025, 965, 905, 840, 805, 740; ^{1}H NMR: Table 1; ^{13}C NMR: Table 2; EIMS (70 eV, direct inlet) *m/z* (rel. int.): 478 $[M]^+$ (0.2), 460 $[M-H_2O]^+$ (0.3), 418 $[M-AcOH]^+$ (1), 405 $[M-AcOCH_2]^+$ (1), 400 $[M-AcOH-H_2O]^+$ (3), 387 (1), 358 (2), 259 (13), 213 (10), 192 (17), 176 (21), 147 (11), 129 (19), 94 (58), 91 (10), 81 (20), 55 (15), 43 (100). (Found: C, 60.57; H, 6.15. $C_{24}H_{30}O_{10}$ requires: C, 60.24; H, 6.32%).

Compound **10**. Mp 132–135° (EtOAc–*n*-hexane). ^{1}H NMR: Table 1; positive FAB-MS *m/z* (rel. int.): 521 $[MH]^+$ (25), 462 $[MH-OAc]^+$ (18), 401 $[MH-2HOAc]^+$ (15), 277 (35), 186 (40), 165 (46), 95 (47), 94 (45), 91 (48), 57 (94), 55 (89), 43 (100). ($C_{26}H_{32}O_{11}$: *M*, 520).

Compound **11** *from teusandrin E* (**7**). Treatment of **7** (13 mg) with Ac_2O–pyridine (1:1, 4 ml) at room temp. for 48 hr gave **11** (11 mg, after crystallization from EtOAc–*n*-hexane): mp 169–171°, $[\alpha]_D^{20}$ +10.2° ($CHCl_3$; *c* 0.167). CD Δε (nm): 0 (337), −9.3 (304), 0

(266), +0.47 (260), 0 (250), −10.1 (233), 0 (211) (MeOH; *c* 0.0396); IR ν_{max}^{KBr} cm^{-1}: 3150, 3140, 3120, 1600, 1510, 875 (furan), 1755 (γ-lactone), 1745, 1740, 1255, 1240 (OAc), 1705 (ketone), 2970, 2890, 1410, 1400, 1370, 1225, 1160, 1035, 1020, 965, 925, 810; ^{1}H NMR: Table 1; ^{13}C NMR: Table 2; EIMS (70 eV, direct inlet) *m/z* (rel. int.): 460 $[M]^+$ (0.2), 418 (1.3), 400 $[M-AcOH]^+$ (2.3), 372 (1), 358 (21), 354 (5), 329 (7), 312 (6), 264 (13), 246 (12), 213 (14), 203 (11), 197 (11), 173 (12), 171 (12), 161 (20), 147 (13), 133 (12), 128 (11), 121 (11), 115 (12), 105 (16), 95 (34), 94 (75), 91 (22), 81 (30), 69 (23), 43 (100). (Found: C, 62.84; H, 6.07. $C_{24}H_{28}O_9$ requires: C, 62.60; H, 6.13%).

Teusandrin F (**8**) *from teusandrin E* (**7**). A soln of **7** (3 mg) in CH_2Cl_2–MeOH (1:1, 2 ml) was treated with $NaBH_4$ at room temp. for 10 min. Work-up in the usual manner yielded a compound (2 mg) identical in all respects (mp, mmp, $[\alpha]_D$, ^{1}H NMR, MS, TLC) with **8**.

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