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NEO-CLERODANE DITERPENOIDS FROM *TEUCRIUM MASSILIENSE*

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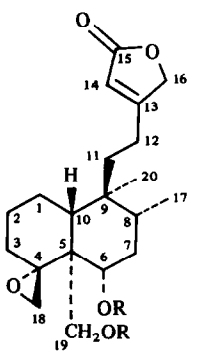
Key Word Index—*Teucrium massiliense*; Labiatae; diterpenoids; neo-clerodane derivatives; teumassilin; 6,19-diacetylteumassilin; deacetylajugarin-II; montanin C; teucjaponin A.

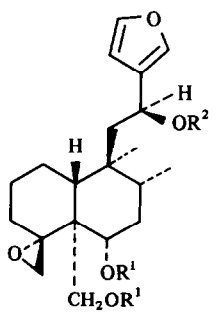
Abstract—From the aerial part of *Teucrium massiliense* three new neo-clerodane diterpenoids, deacetylajugarin-II, teumassilin and 6,19-diacetylteumassilin, have been isolated, besides the previously known diterpenes montanin C and teucjaponin A. The structures of deacetylajugarin-II (4α,18-epoxy-6α,19-dihydroxy-neo-clerodan-13-en-15,16-olide), teumassilin (4α,18:15,16-diepoxy-6α,12*S*,19-trihydroxy-neo-cleroda-13(16),14-diene) and 6,19-diacetylteumassilin (6α,19-diacetoxy-4α,18:15,16-diepoxy-12*S*-hydroxy-neo-cleroda-13(16),14-diene) were established by chemical and spectroscopic means. In addition, the previously known flavones salvigenin and cirsimaritin have also been obtained from the same source.

INTRODUCTION

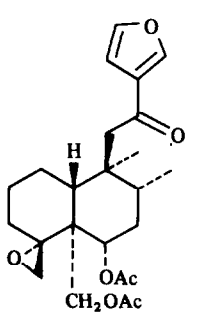
In continuation of our studies on the diterpenes from *Teucrium* species (family Labiatae) [1–4], we have now investigated *T. massiliense* L., a species which grows in some areas of the Mediterranean region. From the aerial parts of this plant we have isolated three new neo-clerodane diterpenoids in very high yields: deacetylajugarin-II (**1**, 0.73% yield from dry aerial parts), teumassilin (**3**, 0.31% yield) and 6,19-diacetylteumassilin (**4**, 0.22% yield). In addition, the previously known neo-clerodane diterpenes montanin C (0.09% yield) [5] and teucjaponin A (0.19% yield) [6] and the flavones salvigenin (5-hydroxy-6,7,4′-trimethoxyflavone, 0.10% yield) [7] and cirsimaritin (5,4′-dihydroxy-6,7-dimethoxyflavone, 0.01% yield) [8] have also been obtained from the same source. The structures and absolute configurations of the new diterpenoids (**1**, **3** and **4**) were established on the basis of spectroscopic evidence, chemical correlation, application of Horeau's method [9] and by comparison with closely related compounds.



R
1 H
2 Ac



3 $R^1=R^2=H$
4 $R^1=Ac$, $R^2=H$
5 $R^1=R^2=Ac$



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RESULTS AND DISCUSSION

The first of the new diterpenoids, deacetylajugarin-II (**1**) had a $C_{20}H_{30}O_5$ molecular formula and its IR spectrum was consistent with the presence of hydroxyl groups (3500, 3480, 3380 cm^{-1}), an oxirane ring (3075 cm^{-1}) and an α,β-unsaturated γ-lactone group bearing an α-hydrogen atom (1775, 1745, 1640 cm^{-1}). The presence of this last function in the molecule of deacetylajugarin-II (**1**) was also supported by its UV absorption at λ_{max} 218.5 nm (log ε3.95).

The ^1H NMR spectrum of deacetylajugarin-II (**1**, Table 1) showed signals of a tertiary methyl group at δ0.71 (*s*), of a secondary methyl group at 0.85 (*d*, J = 6 Hz), of an α,α-disubstituted oxirane ring at 2.42 (*d*, J_{gem} = 3.6 Hz) and 3.16 (*dd*, J_{gem} = 3.6 Hz, $J_{long\text{-}range}$ = 2.4 Hz) and of a β-substituted butenolide grouping (δ5.83, 1H, *tt*, $J_1 = J_2$ = 1.8 Hz; δ4.70, 2H, *d*, J = 1.8 Hz) [10]. In addition, the ^1H NMR spectrum of this new diterpenoid (**1**) showed signals of a hydroxymethylene group attached to a fully substituted sp^3 carbon atom (an AB system at δ4.01 and 4.30, J_{AB} = 12 Hz) and of a secondary hydroxyl group in

Table 1. ^{1}H NMR spectral data of compounds **1**–**6** (90 MHz, $CDCl_3$, TMS as internal standard)*

	1	2	3	4	5	6
H-6β	3.60 *ddd*	4.70 *ddd*	3.61 *ddd*	~ 4.75‖	4.75 *ddd*	4.75 *ddd*
2H-11	†	†	†	†	†	2.73 *s*
H-12	†	†	4.70 *dd*	~ 4.70‖	5.90 *dd*	—
H-14	5.83 *tt*	5.83 *tt*	6.35 *m*	6.38 *m*	6.35 *m*	6.73 *d*
H-15	—	—	7.34 *m*	7.37 *m*	7.33 *m*	7.43 *t*
H-16‡	4.70 *d*	4.73 *d*	7.34 *m*	7.37 *m*	7.39 *m*	8.00 *d*
Me-17	0.85 *d*	0.85 *d*	0.79 *d*	0.78 *d*	0.75 *d*	0.88 *d*
H_A-18¶	2.42 *d*	2.22 *d*	2.40 *d*	2.20 *d*	2.18 *d*	2.22 *d*
H_B-18§	3.16 *dd*	3.00 *dd*	3.15 *dd*	3.00 *dd*	2.97 *dd*	3.05 *dd*
H_A-19	4.01 *dd*	4.35 *dd*	4.03 *dd*	4.40 *dd*	4.38 *dd*	4.40 *dd*
H_B-19	4.30 *d*	4.80 *d*	4.27 *d*	4.80 *d*	4.79 *d*	4.82 *d*
Me-20	0.71 *s*	0.79 *s*	0.61 *s*	0.70 *s*	0.70 *s*	0.80 *s*
OAc	—	1.95 *s*	—	1.93 *s*	1.93 *s*	1.93 *s*
		2.10 *s*		2.08 *s*	1.99 *s*	2.10 *s*
					2.08 *s*	

J (Hz): **1** and **2**: 6β, 7α = 9–11; 6β, 7β = 6; 6β, 19A = 0.8; 14, 16 = 14, 12 = 1.8; 17, 8 = 6; 18A, 18B = 3.6–4; 18B, 3α = 2.4–2; 19A, 19B = 12; 19A, 6β = 0.8. **3**–**6**: 6β, 7α = 9; 6β, 7β = 6; 6β, 19A = 0.9–1; 14, 15 + 14, 16 = 4; 17, 8 = 6–6.8; 18A, 18B = 3.6–3.9; 18B, 3α = 2.1–2.4; 19A, 19B = 12–12.3; 19A, 6β = 0.9–1. **6**: 14, 15 = 15, 16 = 1.5.

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

†Could not be identified.

‡Two proton signal in **1** and **2**, one proton signal in **3**–**6**.

§*Endo* hydrogen with respect to ring B.

¶*Exo* hydrogen with respect to ring B.

‖Overlapped signal.

equatorial configuration (geminal proton at δ3.60, $J_{a,a'}$ = 9 Hz, $J_{a,e'}$ = 6 Hz). Double resonance experiments showed that there exists a long-range coupling (*J* = 0.8 Hz, Table 1) between the signal at δ3.60 and the signal of the A part of the AB system (δ4.01), which is typical of 6α,19-dihydroxy-neo-clerodane structures [11].

On the other hand, the ^{13}C NMR spectrum of compound **1** (Table 2) was almost identical with that reported for ajugarin-I (**2**) [10, 12], the only remarkable difference was the absence in **1** of the carbon atom resonances due to the two acetyl groups of ajugarin-I (**2**). In consequence, compound **1** must be the 19-deacetyl derivative of ajugarin-II (or the 6,19-bis-deacetyl derivative of ajugarin-I) [10]. Effectively, acetylation of **1** yielded a product (**2**) identical in all respect with ajugarin-I [10, 13], thus establishing the structure and absolute configuration depicted in **1** for this new diterpenoid. Deacetylajugarin-II (**1**) has been recently synthesized, but it was transformed without characterization into ajugarin-I (**2**) [14].

The other new diterpenoids isolated from *T. massiliense*, teumassilin (**3**) and 6,19-diacetylteumassilin (**4**), yielded the same peracetyl derivative (**5**) by acetic anhydride–pyridine treatment. The ^{1}H NMR and ^{13}C NMR spectra of these compounds (Tables 1 and 2) showed that teumassilin (**3**) and deacetylajugarin-II (**1**), and 6,19-diacetylteumassilin (**4**) and ajugarin-I (**2**) possessed an identical substituted *trans*-decaline moiety and the differences between these pairs of compounds are the presence in teumassilin (**3**) and its 6,19-diacetyl derivative (**4**) of a β-substituted furan ring and a secondary hydroxyl group placed on the C-11 or C-12 position (see Tables 1 and 2) instead of the β-substituted butenolide grouping of compounds **1** and **2**. Chromium trioxide–pyridine treatment of **4** gave a product (**6**) which showed UV absorption at λ_{max} 255 nm (log ε3.59), thus establishing that the secondary hydroxyl group was at the C-12 position. Moreover, the variation of the chemical shifts of H-14 and H-16 in the ^{1}H NMR spectra of compounds **4** and **6** (Table 1) clearly confirmed this point.

Finally, application of Horeau's method [9] to compound **4** (see Experimental and Table 3) established the absolute configuration of the C-12 hydroxyl group as *S*. The neo-clerodane [15] absolute configuration of teumassilin (**3**) and its 6,19-diacetyl derivative (**4**) was firmly supported by the fact that the partial resolution [9] caused by teumassilin (**3**, α = −0.793) was almost identical with the sum of the values obtained for compound **4** (α = −0.474) and deacetylajugarin-II (**1**, α = −0.262, see Experimental) and the neo-clerodane absolute configuration of this last compound is well-known [this work, 10, 13].

Since some of the neo-clerodane diterpenoids, such as teucjaponin A and compound **2**, exhibit interesting antifeedant and insecticidal activities [6, 10, 13, 14], it is important to note that they were found in 0.92% yield from dry aerial parts of *Teucrium massiliense*.

EXPERIMENTAL

Mps are uncorr. For general details on methods see refs [1–4]. Assignments of ^{13}C NMR chemical shifts were made with the aid of off-resonance and noise-decoupled ^{13}C NMR spectra. Plant

Table 2. ^{13}C NMR chemical shifts (in δ values from TMS) of compounds 1, 3 and 4*

	1	3	4
C-1	20.7 *t*†	21.2 *t*	21.5 *t*
C-2	25.1 *t*	24.9 *t*	24.8 *t*
C-3	31.9 *t*	32.1 *t*	32.8 *t*‡
C-4	67.4 *s*	67.7 *s*	65.2 *s*
C-5	46.4 *s*	46.6 *s*	45.5 *s*
C-6	74.2 *d*	74.5 *d*	72.6 *d*
C-7	34.1 *t*	34.1 *t*	33.1 *t*‡
C-8	34.7 *d*	35.2 *d*	35.1 *d*
C-9	38.5 *s*	39.1 *s*	39.0 *s*
C-10	47.1 *d*	47.6 *d*	48.7 *d*
C-11	34.7 *t*	45.0 *t*	45.0 *t*
C-12	22.1 *t*	62.8 *d*	62.9 *d*
C-13	173.9 *s*	131.2 *s*	131.2 *s*
C-14	115.0 *d*	108.5 *d*	108.4 *d*
C-15	170.7 *s*	143.4 *d*	143.5 *d*
C-16	73.1 *t*	138.3 *d*	138.3 *d*
C-17	15.5 *q*	15.6 *q*	15.5 *q*
C-18	48.0 *t*	48.1 *t*	48.5 *t*
C-19	61.2 *t*	61.4 *t*	61.9 *t*
C-20	17.6 *q*	17.6 *q*	17.3 *q*
OAc			171.0 *s*
			170.1 *s*
			21.1 *q*
			21.1 *q*

*In deuteriochloroform solution.
†SFORD multiplicity.
‡These assignments may reversed.

materials were collected in July 1982, at Gennargentu Mountains, Sardinia (Italy) and voucher specimens were deposited in the Herbarium of the 'Dipartimento di Biologia' of the University of Milan, Italy.

Extraction and isolation of the components. Dried and finely powdered *Teucrium massiliense* L. aerial parts (1.1 kg) were extracted with Me_2CO (15 l.) as previously described for other *Teucrium* species [1–4]. The extract (160 g) was chromatographed on a silica gel column (Merck, No. 7734, deactivated with 15% H_2O, 1.5 kg). Elution with *n*-hexane, *n*-hexane–EtOAc mixtures and pure EtOAc yielded, in order of elution, salvigenin (1.2 g), 6,19-diacetylteumassilin (**4**, 2.5 g), montanin C (1 g), cirsimaritin (200 mg), teucjaponin A (2.1 g), teumassilin (**3**, 3.5 g) and deacetylajugarin-II (**1**, 8.1 g).

The previously known compounds, salvigenin [7], montanin C [5], cirsimaritin [8] and teucjaponin A [6], were identified by their physical (mp, $[\alpha]_D$) and spectroscopic (IR, UV, ^1H NMR, ^{13}C NMR, mass spectra) data and by comparison (TLC, mmp) with authentic samples.

Deacetylajugarin-II (**1**). Mp 112–115° (from EtOAc–*n*-hexane); $[\alpha]_D^{20}$ −4.0° ($CHCl_3$; *c* 1.077); IR ν_{max}^{KBr} cm^{-1}: 3500, 3480, 3380, 3075, 3060, 2960, 2940, 2880, 1775, 1745, 1640, 1440, 1390, 1330, 1255, 1180, 1105, 1030, 1010, 905, 860, 850; UV λ_{max}^{EtOH} nm (log ε): 218.5 (3.95); ^1H NMR (90 MHz, $CDCl_3$): see Table 1; ^{13}C NMR (20.15 MHz, $CDCl_3$): see Table 2; EIMS (direct inlet) 75 eV *m/z* (rel. int.): 350 $[M]^+$ (0.8), 332 (1), 319 (29), 314 (1), 302 (23), 301 (8), 289 (8), 287 (9), 284 (4), 273 (6), 259 (5), 231 (8), 209 (7), 205 (24), 189 (40), 163 (24), 149 (21), 145 (21), 136 (55), 123 (65), 121 (46), 119 (35), 111 (50), 107 (45), 105 (47), 98 (80), 95 (65), 93 (60), 91 (58), 81 (50), 79 (65), 77 (40), 69 (48), 67 (55), 55 (75), 53 (43), 43 (60), 41 (100). (Found: C, 68.32; H, 8.39. $C_{20}H_{30}O_5$ requires: C, 68.54; H, 8.63%.)

Ajugarin-I (**2**) *from deacetylajugarin-II* (**1**). Ac_2O–pyridine treatment of **1** (80 mg) for 24 hr at room temp. yielded the derivative **2** (71 mg after crystallization from MeOH): mp 158–160°; $[\alpha]_D^{20}$ −15.0° ($CHCl_3$; *c* 1.025); IR ν_{max}^{KBr} cm^{-1}: 3080, 2950, 2890, 1780, 1750, 1735, 1640, 1455, 1380, 1260, 1230, 1175, 1140, 1095, 1045, 1035, 1010, 895, 865, 850; ^1H NMR (90 MHz, $CDCl_3$): see Table 1; EIMS (direct inlet) 75 eV *m/z* (rel. int.): $[M]^+$ absent, 404 $[M-30]^+$ (3.5), 391 (8), 375 (1), 361 (10), 331 (5), 319 (41), 314 (3), 302 (8), 301 (15), 289 (11), 271 (2), 205 (4), 203 (7), 191 (10), 189 (12), 173 (6), 147 (5), 135 (7), 121 (11), 111 (10), 105 (10), 98 (8), 95 (8), 93 (11), 91 (12), 81 (10), 79 (11), 67 (10), 55 (14), 43 (100). (Found: C, 66.15; H, 8.06. Calc. for $C_{24}H_{34}O_7$; C, 66.34; H, 7.89%.) Identical in all respects with ajugarin-I [10].

Teumassilin (**3**). A syrup, $[\alpha]_D^{20}$ −3.6° ($CHCl_3$; *c* 0.561); IR ν_{max}^{NaCl} cm^{-1}: 3400, 3140, 3060, 2940, 2890, 1505, 1455, 1390, 1250, 1165, 1090, 1060, 1030, 955, 920, 880, 845, 800; UV λ_{max}^{EtOH} nm (log ε): 212 (3.61); ^1H NMR (90 MHz, $CDCl_3$): see Table 1; ^{13}C NMR (20.15 MHz, $CDCl_3$): see Table 2; EIMS (direct inlet) 75 eV *m/z* (rel. int.): 350 $[M]^+$ (0.2), 332 (1), 319 (6), 314 (1), 301 (2), 284 (8), 208 (23), 190 (95), 175 (37), 162 (23), 161 (36), 147 (20), 135 (16), 133 (15), 123 (20), 121 (22), 119 (24), 107 (23), 105 (26), 97 (90), 95 (45), 93 (34), 91 (35), 81 (38), 79 (37), 69 (49), 67 (32), 55 (48), 53 (22), 43 (48), 41 (100). $C_{20}H_{30}O_5$ MW 350.

6,19-*Diacetylteumassilin* (**4**). Mp 155–156° (from EtOAc–*n*-hexane); $[\alpha]_D^{20}$ −19.3° ($CHCl_3$; *c* 0.192); IR ν_{max}^{KBr} cm^{-1}: 3480, 3145, 3135, 3080, 3020, 2990, 2970, 2950, 2930, 2900, 2880, 2870, 1725, 1505, 1475, 1450, 1390, 1370, 1270, 1250, 1160, 1090, 1040, 1025, 1010, 960, 920, 885, 880, 825, 708; UV λ_{max}^{EtOH} nm (log ε): 213 (3.50); ^1H NMR (90 MHz, $CDCl_3$): see Table 1; ^{13}C NMR (20.15 MHz, $CDCl_3$): see Table 2; EIMS (direct inlet) 75 eV *m/z* (rel. int.): 434 $[M]^+$ (1), 416 (2), 404 (1), 391 (4), 374 (2), 361 (3), 356 (2), 319 (22), 301 (17), 283 (4), 271 (3), 262 (5), 232 (5), 219 (9), 203 (36), 190 (28), 189 (53), 175 (16), 173 (22), 171 (32), 159 (17), 147 (17), 133 (15), 121 (18), 119 (22), 107 (17), 105 (21), 97 (71), 95 (55), 93 (2), 91 (26), 81 (28), 79 (23), 69 (38), 67 (18), 55 (28), 43 (100), 41 (65). (Found: C, 66.41; H, 8.01. $C_{24}H_{34}O_7$ requires: C, 66.34; H, 7.89%.)

Triacetylteumassilin (**5**) *from* **3** *and* **4**. Ac_2O–pyridine treatment of **3** and **4** for 24 hr at room temp. yielded the same derivatives **5**: mp 149–150° (from EtOAc–*n*-hexane); $[\alpha]_D^{20}$ −41.5° ($CHCl_3$; *c* 0.520); IR ν_{max}^{KBr} cm^{-1}: 3150, 3140, 3115, 3040, 2970, 2960, 2940, 2880, 1735, 1505, 1470, 1370, 1250, 1135, 1160, 1150, 1090, 1040, 1020, 950, 880, 810, 800, 620; ^1H NMR (90 MHz, $CDCl_3$): see Table 1; EIMS (direct inlet) 75 eV *m/z* (rel. int.): 476 $[M]^+$ (0.2), 446 (0.2), 433 (0.7), 416 (0.5), 415 (0.6), 403 (2), 361 (9), 343 (2), 323 (22), 301 (6), 263 (5), 262 (5), 221 (8), 219 (4), 203 (30), 189 (28), 185 (15), 173 (17), 159 (10), 147 (10), 133 (10), 119 (14), 105 (12), 97 (16), 95 (19), 94 (33), 91 (13), 81 (15), 79 (10), 69 (9), 67 (9), 55 (11), 43 (100). (Found: C, 65.84; H, 7.89. $C_{26}H_{36}O_8$ requires: C, 65.53; H, 7.61%.)

Compound **6** *from* 6,19-*diacetylteumassilin* (**4**). CrO_3–pyridine treatment of **4** (30 mg) in the usual manner gave **6** (22 mg after crystallization from EtOAc–*n*-hexane): mp 171–173°; $[\alpha]_D^{20}$ −1.6°, $[\alpha]_{365}^{20}$ +16.8° ($CHCl_3$; *c* 0.312); IR ν_{max}^{KBr} cm^{-1}: 3140, 3130, 3100, 3045, 2990, 2960, 2940, 2880, 1750, 1720, 1675, 1560, 1510, 1500, 1480, 1450, 1420, 1395, 1370, 1365, 1270, 1235, 1160, 1085, 1040, 920, 875, 850, 810, 795, 760, 650, 640, 630; UV λ_{max}^{EtOH} nm (log ε): 214 (3.79), 255 (3.59); ^1H NMR (90 MHz, $CDCl_3$): see Table 1; EIMS (direct inlet) 75 eV, *m/z* (rel. int.): 432 $[M]^+$ (2.5), 402 (1), 389 (4), 372 (1), 359 (4), 323 (11), 322 (4), 317 (19), 299 (3), 263 (8), 262 (10), 232 (6), 221 (4), 219 (4), 203 (50), 202 (23), 189 (49), 175 (19), 173 (25), 171 (70), 159 (22), 145 (16), 133 (11), 119 (17), 110 (23), 105 (14), 95 (85), 93 (10), 91 (15), 79 (11), 67 (10), 55 (13), 43 (100). (Found: C, 66.39; H, 7.54. $C_{24}H_{32}O_7$ requires: C, 66.65; H, 7.46%.)

Table 3. Application of Horeau's method to compounds **1**, **3** and **4**

	Compound		(±)-α-phenylbutyric anhydride		Pyridine	Partial resolution
	mg	mmol	mg	mmol	(ml)	$\alpha = \alpha_1 - 1.1\alpha_2$
1	48.0	0.1371	164.66	0.5312	2.00	−0.262
3	48.0	0.1371	164.66	0.5312	2.00	−0.793
4	59.5	0.1371	164.66	0.5312	2.00	−0.474

Application of Horeau's method to compounds **1**, **3** *and* **4**. This was performed in the usual manner [9] (see Table 3). Configuration C-12*S* in **3** and **4**: $\alpha = -0.474$ for **4** or $\alpha = -0.793 - (-0.262) = -0.531$ from the difference between the values obtained from **3** and **1**, respectively. Identical absolute configuration in **1** and **3**: $\alpha = -0.262$ for both C-6*S* equatorial hydroxyl group and C-19 primary alcohol from **1**, and $\alpha = -0.793 - (-0.474) = -0.319$ from **3** for the same centres. This experiment was performed with identical time reaction (16 hr) and temp. (18°) for the three compounds.

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