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2-KETO-19-HYDROXYTEUSCORDIN, A NEO-CLERODANE DITERPENE FROM *TEUCRIUM SCORDIUM*

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Key Word Index—*Teucrium scordium*; Labiatae; diterpenoids; teucrin E; teucrin H4; new neo-clerodane derivative; 2-keto-19-hydroxyteuscordin.

Abstract—From the aerial parts of *Teucrium scordium*, a new neo-clerodane diterpenoid, 2-keto-19-hydroxyteuscordin, has been isolated, besides the previously known diterpenoids teucrin E and teucrin H4. The structure of 2-keto-19-hydroxyteuscordin, (12*S*)-15,16-epoxy-2-keto-19-hydroxy neo-clerodane-13(16),14-dien-18β,6β:20,12-diolide, was established by chemical and spectroscopic means.

INTRODUCTION

In previous communications [1–3], we reported the isolation, from an acetone extract of *Teucrium scordium* L., of five new diterpenoids: teuscordinon [(12*S*)-15,16-epoxy-6-keto-neo-clerodane-3,13(16),14-triene-18,19:20,12-diolide], 6-keto-teuscordin [(12*S*)-15,16-epoxy-6-keto-neo-clerodane-13(16),14-diene-18,19:20,12-diolide], 6β-hydroxyteuscordin [(12*S*)-15,16-epoxy-6β-hydroxy-neo-clerodane-3,13(16),14-triene-18,19:20,12-diolide], 6α-hydroxyteuscordin [(12*S*)-15,16-epoxy-6α-hydroxy-neo-clerodane-3,13(16),14-triene-18,19:20,12-diolide] and 2β,6β-dihydroxyteuscordin [(12*S*)-15,16-epoxy-2β,6β-dihydroxy-neo-clerodane-3,13(16),14-triene-18,18:20,12-diolide], besides the known substances teucrin E [(12*S*)-15,16-epoxy-6α-hydroxy-neo-clerodane-13(16),14-diene-18,19:20,12-diolide] and teucrin H4 [(12*S*)-15,16-epoxy-2α-hydroxy-19-nor-neo-clerodane-4,13(16),14-triene-18,6β:20,12-diolide] [4–7]. In this communication, we report the structure determination of a new diterpenoid, 2-keto-19-hydroxyteuscordin (**1**), which has been isolated from the same plant.

RESULTS AND DISCUSSION

2-Keto-19-hydroxyteuscordin (**1**) had a molecular formula of $C_{20}H_{22}O_7$, from elemental analysis and mass spectroscopy. Its IR spectrum was consistent with the presence of a furan ring (3120, 1502, 1600, 872 cm^{-1}), two γ-lactone rings (1770, 1750 cm^{-1}), a ketone group (1710 cm^{-1}) and a hydroxyl group (3330 cm^{-1}). The ^1H NMR spectrum (Table 1) of **1** showed signals for a β-substituted furan ring (two α-furan protons at δ7.68 and 7.59 and one β-furan proton at δ6.49) and a secondary methyl group (δ0.92), and also showed typical absorptions for a C-20,C-12-γ-lactone (Table 1), identical to those found in the previously described diterpenoids [8–13]. In addition, **1** possessed a primary hydroxyl group attached to a fully substituted sp^3 carbon atom. This presence of the hydroxyl group in **1** was revealed by treatment with trichloroacetylisocyanate, when the resonance of the corresponding >NH proton in the ^1H NMR spectrum appeared at δ10.02 as a singlet, while the double-doublets (δ4.09 and 3.70 for 2H-19, Table 1) were reduced to an AB-type quartet (δ4.90 and 4.33, J = 12 Hz). A double-doublet at δ4.18 (Table 1), which was assigned to H_B-19, was coupled to a single proton

Table 1. ^1H NMR spectral data of compounds **1** and **2** (TMS as internal standard)

	1		**2**
H	(400 MHz, pyridine-d_5)	(100 MHz, Me_2CO-d_6)	(100 MHz, $CDCl_3$)
1β	3.08 *dd*	—	—
3β	2.62 *dd*	—	—
6	4.86 *t*	4.61 *t*	4.49 overlapped signal
7	2.82 *dd*	—	—
7β	1.85 *dddd*	—	—
8β	2.02 *ddq*	—	—
10β	3.79 *dd*	3.38 *dd*	3.04 *dd*
H_A-11	2.48 *dd*	2.64 *d*	2.65 *d*
H_B-11	2.89 *dd*		
12	5.51 *dd*	5.48 *t*	5.28 *t*
14	6.49 *dd*	6.46 *m*	6.28 *m*
15	7.59 *dd*	7.50 *m*	7.34 *m*
16	7.68 *dd*	7.63 *m*	
Me-17	0.92 *d*	1.02 *d*	1.09 *d*
H_A-19	4.42 *d*	4.09 *dd*	4.58 *d*
H_B-19	4.18 *dd*	3.70 *dd*	4.40 *d*
OAc	—	—	1.98 *s*

J (Hz): 1α, 10β = 11_A, 11_B = 11; 1β, 10β = 3.5; 3β, 4α = 3.6; 7α, 7β = 7α, 8β = 15; 8β, 7β = 4.2; 6α, 7β = 6α, 7α = 2.6; 11_A, 12 = 11_B, 12 = 8; 19_A, 19_B = 11.5; 19_B, 6α = 1.5; 8β, 17 = 6.5; 14, 15 = 15, 16 = 1.7; 14, 16 = 1.

J (Hz) of **1** in Me_2CO-d_6: 6α, 7β = 6α, 7α = 3; 1α, 10β = 11_A, 11_B = 11; 1β,10β = 4; 11_A, 12 = 11_B, 12 = 8; 19_A, 19_B = 14; 19_A, OH = 19_B, OH = 4; 8β, 17 = 6.5.

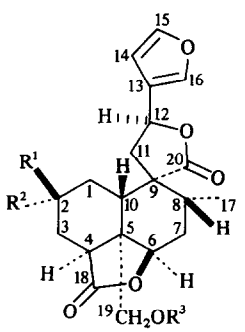
resonance at δ4.86 ($J_{19}H_{B},_{6}H\alpha$ = 1.5 Hz). On the other hand, on irradiation at δ4.86 (6-Hα), the double-doublet at δ4.18 was transformed into a doublet. Acetic anhydride–pyridine treatment of 2-keto-19-hydroxyteuscordin (**1**) yielded the derivative **2**, the ^{1}H NMR spectrum of which (Table 1) showed that the AB system (δ4.58 and 4.40), was paramagnetically shifted, thus confirming that the free alcohol group of **1** was a primary one. The presence of a keto group was indicated by IR and ^{13}C NMR (Table 2) (δ206.3) data and was confirmed by sodium borohydride reduction of **2** to give a $C_{22}H_{26}O_8$ derivative (**3**), the IR spectrum of which showed a hydroxyl absorption (3500 cm^{-1}) instead of the absorption of the keto group.

All the above data must be accommodated in a structure such as **3**. The secondary hydroxyl group was placed at C-2 in an equatorial position on the basis of the following considerations. (1) The ^{1}H NMR signal of the geminal proton of the secondary hydroxyl group appeared as a *dddd* at δ3.18 with $J_{2\beta,1\beta} = J_{2\beta,3\beta}$ = 3 Hz and $J_{2\beta,1\alpha} = J_{2\beta,3\alpha}$ = 10 Hz thus it was axial. (2) The proton at C-10 in **3** was shifted upfield ($\Delta\delta$ − 0.54) when the C-2 keto group of **2** was reduced. According to the ^{1}H–^{1}H coupling (J = 3 Hz), H-6 in compounds **1–3** was equatorial, hence the C-18/C-6 lactonic bridge must be diaxial [14], and the fact that the C-10 proton in compounds **1–3** appeared as a double-doublet (J_1 = 11 Hz, J_2 = 3–4 Hz) confirmed that it was *trans* to the C-20 lactone function [3, 7, 15–17]. All these data suggested structure **1** for 2-keto-19-hydroxyteuscordin, and this was also supported by its ^{13}C NMR spectral data. The stereochemistry of the other chiral centres and the *trans* junction of rings A and B were deduced from spin-decoupling experiments and by comparing the ^{13}C NMR chemical shift data of **1** with those reported for related compounds [9, 11, 13, 14].

Table 2. ^{13}C NMR data of compound **1** (100.6 MHz, pyridine-d_5, TMS as internal standard)

C		C	
1	29.8 *t*	11	40.9 *t*
2	206.3 *s*	12	71.9 *d*
3	38.0 *t*	13	125.6 *s*
4	42.7 *d*	14	108.7 *d*
5	47.6 *s**	15	144.7 *d*
6	78.2 *d*	16	140.7 *d*
7	37.0 *t*	17	16.1 *q*
8	32.9 *d*	18	177.1 *s*
9	47.8 *s**	19	58.3 *t*
10	43.9 *d*	20	178.7 *s*

*Assignments may be interchanged.



	R^1	R^2	R^3
1	=O	=O	H
2	=O	=O	Ac
3	H	OH	Ac

EXPERIMENTAL

Mps (Kofler apparatus) are uncorr; ^{1}H NMR and ^{13}C NMR: 100 and 400 MHz and 100.6 MHz, respectively, in pyridine-d_5, Me_2CO-d_6 or $CDCl_3$ soln with TMS as internal standard. Assignments of ^{13}C NMR chemical shifts were made with the aid of off-resonance and noise-decoupled ^{13}C NMR spectra. Plant materials were collected in July 1982 near Sadovo, Bulgaria.

Extraction and isolation of the diterpenoids. Dried and finely powdered *T. scordium* aerial parts (5.7 kg) were extracted with Me_2CO (60 l.) at room temp. for 1 week. After evapn of the solvent, the residue was treated as in refs. [18, 19]. The $CHCl_3$ extract (63 g) was chromatographed over a silica gel (1000 g, Merck, 0.063–0.200 mm, deactivated with 10% H_2O), column with $CHCl_3$, $CHCl_3$–MeOH (47:3) mixtures as eluants, yielding the following compounds in order of elution: 6-keto-teuscordin, teuscordinon, a mixture of 6β-hydroxyteuscordin and 2-keto-19-hydroxyteuscordin, teucrin E, 6α-hydroxyteuscordin, teucrin H4, 2β,6β-dihydroxyteuscordin and montanin E [20]. The mixture of 6β-hydroxyteuscordin and 2-keto-19-hydroxyteuscordin (270 mg) was rechromatographed over a silica gel (Merck, N 7754 deactivated with 10% H_2O) column eluted with $CHCl_3$–MeOH (99:1), yielding 6β-hydroxyteuscordin (140 mg), a less polar compound and 2-keto-19-hydroxyteuscordin (**1**, 120 mg), which was recrystallized from MeOH–Et_2O to yield pure compound **1** (105 mg). The previously known products (teucrins E and H4) were identified by their physical (mp, $[\alpha]_D$) and spectroscopic (IR, ^{1}H NMR) data and by comparison with authentic samples.

2-Keto-19-hydroxyteuscordin (**1**). Mp 196–199° (from Me_2CO–Et_2O); $[\alpha]_D^{28}$ +138.8° (Me_2CO; *c* 0.17); IR ν_{max}^{KBr} cm^{-1}: 3330 (OH), 3120, 1600, 1502, 872 (furan ring), 1770, 1750 (γ-lactones), 1710 (ketone), 2940, 2850, 1480, 1440, 1390, 1330, 1180, 1160, 1100, 1020, 980, 960, 920, 790, 745; ^{1}H NMR: see Table 1; MS (direct inlet) 75 eV, *m/z* (rel. int.): 374 $[M]^+$ (10), 356 $[374-H_2O]^+$ (6), 344 (11), 328 (7), 280 (4), 279 (8), 262 (5), 235 (3), 234 (7), 233 (3), 161 (8), 159 (4), 133 (5), 131 (3), 119 (10), 105 (14), 96 (11), 95 (100), 94 (38), 91 (17), 82 (15), 81 (20), 77 (11), 67 (16), 65 (10), 55 (18), 53 (9). (Found: C, 64.28; H, 6.01. $C_{20}H_{22}O_7$ requires: C, 64.16; H, 5.92%.)

Acetylation of **1**. A soln of 70 mg **1** in 0.8 ml pyridine and 0.2 ml Ac_2O was left to stand overnight at room temp. Usual work-up and recrystallization from Me_2CO–Et_2O yielded **2**, mp 128–131°; IR ν_{max}^{KBr} cm^{-1}: 3130, 1500, 870 (furan ring), 1770, 1758 (γ-lactones), 1730, 1230 (acetate), 1710 (ketone), 2950, 2840, 1390, 1360, 1310, 1180, 1150, 1020, 960, 920; ^{1}H NMR (100 MHz, $CDCl_3$): see Table 1. (Found: C, 63.09; H, 5.38. $C_{22}H_{24}O_8$ requires: C, 63.45; H, 5.78%.)

Reduction of **2**. A soln of **2** (40 mg) in MeOH was treated with excess $NaBH_4$ at room temp. for 10 min. The excess of reagent was then destroyed by addition of Me_2CO. Work-up in the usual manner yielded **3** (30 mg), mp 199–201°. IR ν_{max}^{KBr} cm^{-1}: 3500 (hydroxyl), 3160, 3130, 1510, 870 (furan ring), 1770, 1750 (γ-lactones), 1730, 1230 (acetate), 2930, 2830, 2850, 1390, 1320, 1180, 1150, 1120, 1020, 980, 960, 820, 760, 740, 720. ^{1}H NMR (100 MHz, pyridine-d_5): δ7.39 2H, *m*, H-15 and H-16), 6.37 (1H, *m*, H-14), 5.36 (1H, *t*, J = 8.5 Hz, H-12), 4.45 (1H, *t*, J = 3 Hz, H-6), 5.16 and 4.48 (AB system J = 12 Hz, 2H-19), 3.18 (1H, *dddd*, J_1 = 10, J_2 = 3 Hz, H-2), 2.50 (1H, *dd*, J_1 = 12, J_2 = 4 Hz, H-10), 2.38 (2H, *d*, J = 8.5 Hz, 2H-11), 1.96 (3H, *s*, –OAc) and 0.95

(3H, *d*, J = 6.5 Hz, H-17). (Found: C, 62.79; H, 5.87. $C_{22}H_{26}O_8$ requires: C, 63.15; H, 6.26%.) ^{1}H NMR (100 MHz, $(CD_3)_2CO$) spectral data of **1** plus trichloroacetylisocyanate: δ10.02 (1H, *s* >NH), 7.65 (1H, *m*, H-16), 7.46 (1H, *m*, H-15), 6.40 (1H, *m*, H-14), 5.49 (1H, *t*, J = 8 Hz), 4.90 and 4.33 (AB system, J = 12 Hz, 2H-19), 4.69 (1H, *t*, J = 3 Hz, H-6), 3.40 (1H, *dd*, J_1 = 11, J_2 = 3.5 Hz, H-10), 2.92 (1H, *d*, J = 11 Hz, H-11) and 1.06 (3H, *d*, J = 6.5 Hz, H-17).

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