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NEO-CLERODANE DITERPENOIDS FROM *TEUCRIUM CORYMBOSUM*

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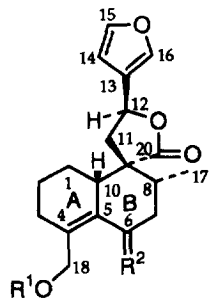
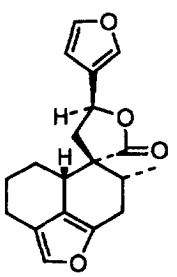
Key Word Index—*Teucrium corymbosum*; Labiatae; diterpenoids; 19-nor-neo-clerodane derivative; teucorymbin.

Abstract—A novel 19-nor-neo-clerodane derivative, teucorymbin, and three known neo-clerodanes (19-acetylgnaphalin, teucjaponin A and 6-acetylteucjaponin B) were isolated from the aerial parts of *Teucrium corymbosum*. The structure of teucorymbin [18-acetoxy-15,16-epoxy-6-oxo-19-nor-neo-cleroda-4,13(16),14-trien-20,12*S*-olide] was established by chemical and spectroscopic means.

INTRODUCTION

A large number of diterpenoids with the clerodane skeleton have been isolated from natural sources in the last few years [1–3]. Interest in these compounds has been stimulated by their biological activity as insect antifeedants and as antitumor, antimicrobial and antifungal agents [1, 3]. The genus *Teucrium* has afforded a great number of these compounds [2, 3]. In a continuation of our studies on *Teucrium* species [4–6], we have isolated from *T. corymbosum*, a plant which grows in Australia, a new 19-nor-*neo*-clerodane derivative, together with three known diterpenoids. We report herein the isolation and structure determination of the new compound.





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	R^1	R^2
1	Ac	O
2	H	αH,βOH

RESULTS AND DISCUSSION

Repeated chromatography of the acetone extract of the aerial parts of *T. corymbosum* (see Experimental) led to the isolation of the previously known *neo*-clerodane diterpenoids 19-acetylgnaphalin [7, 8], teucjaponin A [9] and 6-acetylteucjaponin B (known as a synthetic [10] and a natural [11, 12] compound), together with a new substance, teucorymbin, whose structure (**1**) was established as follows.

Compound **1** has the molecular formula $C_{21}H_{24}O_6$. Its ^1H and ^{13}C NMR spectra (Table 1) showed characteristic signals for a β-substituted furan, a spiro-20,12-γ-lactone involving the C-9, C-11, C-12 and C-20 carbons, and a C-17 secondary methyl group, identical with those found in several neo-clerodane diterpenoids isolated from *Teucrium* species [3–12]. In addition, **1** possessed a ketone function (δ_C 201.6 *s*), which had to be involved in an α,β-unsaturated enone grouping (UV absorption at λ 246.5 nm, log $\varepsilon = 3.81$; IR bands at 1665 and 1590 cm^{-1}) without olefinic protons (δ_C 144.2 *s* and 133.9 *s*), and an acetoxymethylene group [δ_H 2.05 *s*, 3H, 4.82 *br s*, 2H; δ_C 170.7 *s* and 20.8 *q* (OAc), 65.3 *t*] probably attached to one of the olefinic carbons of the α,β-unsaturated enone moiety. Moreover, the ^1H and ^{13}C NMR spectra (Table 1) also revealed that the remaining structural part of teucorymbin was constituted by four methylene and two methine groups.

All the above data were in agreement with structure **1** for teucorymbin, except for its stereochemistry. Comparison of the ^{13}C NMR spectra of **1** (Table 1) and montanin B (**2**), a 19-nor-neo-clerodane diterpenoid isolated from *T. montanum* [13, 14], further supported this conclusion. In fact, the chemical shifts of the C-1–C-3, C-9, C-11–C-17 and C-20 carbons are identical in both compounds (Table 1, ref. [14]), whereas the observed differences in the chemical shifts of the remaining carbon atoms [$\Delta\delta = \delta$ (**1**) $- \delta$ (**2**): + 9.3 (C-4), − 0.4 (C-5),

Table 1. ^1H and ^{13}C NMR spectroscopic data for compound **1***

	H	C	$J_{H,H}$	Hz
1	1.41 *qd* (α-H)	25.4 *t*†	1α,1β	11.3
	ca 2.20‡ (β-H)		1α,2α	1.9
2	1.91 *m* (α-H)§	21.0 *t*	1α,2β	11.3
	1.49 *m* (β-H)§		1α,10β	11.3
3	*ca* 2.20‡ (α-H and β-H)	27.6 *t*	7α,7β	15.8
4	—	144.2 *s*	7α,8β	13.0
5	–	133.9 *s*	7β,8β	5.0
6	–	201.6 *s*	8β,17	6.7
7	3.07 *dd* (α-H)	45.6 *t*	11(*R*),11(*S*)	14.0
	2.44 *dd* (β-H)		11(pro-*R*),12	8.7
8	2.10 *ddq*	37.1 *d*	11(pro-*S*),12	8.5
9	—	52.4 *s*	14,15	1.8
10	2.64 *m*‖	46.7 *d*	14,16	0.9
11	2.47 *dd* (pro-*R*)§	39.7 *t*	15,16	1.8
	2.54 *dd* (pro-*S*)§			
12	5.44 *br t*	72.0 *d*		
13	–	125.1 *s*		
14	6.40 *dd*	108.0 *d*		
15	7.44 *t*	144.3 *d*		
16	7.47 *m*	139.6 *d*		
17	1.07 *d* (3H)	17.7 *q*		
18	4.82 *br s* (2H)¶	65.3 *t*		
20	–	176.1 *s*		
OAc	2.05 *s* (3H)	170.7 *s*		
		20.8 *q*		

*Spectra were recorded in $CDCl_3$ at 500 MHz (^1H) and 125.7 MHz (^{13}C). Chemical shifts are relative to residual $CHCl_3$ (^1H, δ 7.25) and solvent signals (^{13}C, δ_{CDCl_3} 77.0).

†Multiplicities were determined by HMQC.

‡Overlapped signal.

§These protons were distinguished by NOE experiments (Table 2).

‖$W_{1/2}$ = 14 Hz; this proton showed homoallylic coupling with the C-3 methylene protons.

¶$W_{1/2}$ = 2 Hz.

Table 2. Some significant data for the NOESY spectrum of compound **1***

Proton (δ)	Observed NOE on protons
1α (1.41)	H-12
2β (1.49)	H-2α, H-10β
8β (2.10)	H-7β, H-10β, H-11 (pro-*R*), Me-17
10β (2.64)	H-1β, H-2β, H-8β, H-11 (pro-*S*)
12 (5.44)	H-1α, H-1β, H-11 (pro-*S*)
14 (6.40)	H-11 (pro-*R*), H-15, Me-17
Me-17 (1.07)	H-7α, H-7β, H-8β, H-11 (pro-*R*), H-14

*500 MHz, $CDCl_3$.

+ 38.1 (C-6), + 9.3 (C-7), + 4.9 (C-8), + 6.0 (C-10) and + 4.6 ppm (C-18)] are in complete agreement with the existence in **1** of a C-6 ketone and a C-18 acetoxyl group instead of the C-6β and C-18 hydroxyl groups of **2**.

The relative stereochemistry of all the asymmetric centres of teucorymbin was established from its NOESY spectrum. The data collected in Table 2 revealed that the Me-17 group and the H-14 furan proton are on the same side of the plane defined by the 20,12-lactone ring, thus establishing that the H-12 proton is on the opposite side of this plane [10, 15]. Moreover, the NOE observed between the H-12 and the C-1 methylene protons further supported this point (Table 2). The NOESY spectrum of teucorymbin also established that the C-11 methylene protons and the H-1β, H-2β, H-8β and H-10β protons are on the same side of the plane of the decalin moiety, because NOE cross-peaks were observed between these protons (Table 2, in particular the NOEs of the H-8β and H-10β protons). The data shown in Table 2 also allowed the unequivocal assignment of both methylene protons at C-11 (Table 1) and, together with the $J_{H,H}$ values compiled in Table 1, established the conformation of rings A and B of **1** as a distorted chair and a chair, respectively, in which the H-1α, H-2β, H-7α, H-8β and H-10β protons are axially oriented and the H-1β, H-2α and H-7β hydrogens and the Me-17 group are equatorial substituents.

Finally, treatment of **1** with base yielded montanin A (**3**), a 19-nor-neo-clerodane diterpenoid previously found in *T. montanum* [13] and obtained from 19-acetylgnaphalin [8, 16], the structure of which, including its neo-clerodane absolute configuration [17], is well known [8, 13, 16]. The

formation of **3** starting from **1** can be explained by an initial hydrolysis of the C-18 acetate, followed by an attack of the resulting alkoxide on the C-6 ketone and final 1,4-dehydration of the 6-hemiketal intermediate [18].

From a biogenetic point of view, it is of interest to note that the occurrence of **1** in a *Teucrium* species supports our previous conclusions [18] on the mechanism of formation of 19-nor-neo-clerodanes from 6-oxo-neo-clerodane derivatives.

EXPERIMENTAL

Mps: uncorr. Plant materials were collected in January 1994 at Anakie Gorge, Brisbane Ranges, near Melbourne (Australia), and voucher specimens were deposited in the National Herbarium of Melbourne.

Extraction and isolation of the diterpenoids. Dried and powdered aerial parts of *T. corymbosum* R. Br. (850 g) were extracted with Me_2CO (3 × 5 l) at room temp. for 1 week. The extract (71 g) was subjected to CC (silica gel, Merck No. 7734, deactivated with 15% H_2O, w/v, 500 g) eluting with petrol and petrol–EtOAc mixts. The frs eluted with EtOAc–petrol (3:2) (2 g) were rechromatographed (CC, silica gel, $CHCl_3$–MeOH, 97:3 as eluent) yielding **1** (500 mg). The frs eluted with EtOAc–petrol (7:3) (2.3 g) were rechromatographed as above, giving the following compounds in order of increasing chromatographic polarity: teucjaponin A (25 mg) [9], 6-acetylteucjaponin B (100 mg) [10–12] and 19-acetylgnaphalin (80 mg) [7, 8].

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

Teucorymbin (**1**). Mp 124–126° (EtOAc–*n*-hexane); $[\alpha]_D^{22}$ + 147.7° ($CHCl_3$; *c* 0.241). IR ν_{max}^{KBr} cm^{-1}: 3140, 1505, 870 (furan), 1750 *br* (γ-lactone and OAc), 1665, 1590 (α,β-unsaturated ketone), 2960, 1475, 1370, 1215, 1195, 1160, 1025, 820, 745, 735; UV λ_{max}^{MeOH} nm (log ε): 207.5 (3.79), 246.5 (3.81); ^{1}H and ^{13}C NMR: Table 1; EI-MS (70 eV, direct inlet) *m/z* (rel. int.): 372 $[M]^+$ (0.7), 330 $[M - ketene]^+$ (12), 312 $[M - HOAc]^+$ (5), 285 (2), 218 (4), 207 (4), 203 (4), 185 (17), 145 (11), 134 (30), 105 (15), 96 (20), 95 (35), 91 (32), 81 (21), 79 (17), 77 (17), 69 (14), 55 (20), 53 (16), 43 (100), 41 (24). (Found: C, 67.51; H, 6.32. $C_{21}H_{24}O_6$ requires: C, 67.73; H, 6.50%).

Montanin A (**3**) *from teucorymbin* (**1**). A soln of **1** (40 mg) in 5% methanolic KOH (5 ml, w/v) was stirred for 15 min at room temp. The reaction mixt. was diluted with H_2O (20 ml) and extracted with $CHCl_3$ (3 × 15 ml). The extract was dried (Na_2SO_4), filtered and evapd to dryness, giving a residue which was crystallized from EtOAc–*n*-hexane to yield **3** (26 mg): mp 125–126°; $[\alpha]_D^{21}$ + 120.2° ($CHCl_3$; *c* 0.321) (lit. [16]: mp 126–127°; $[\alpha]_D^{25}$ + 115° ($CHCl_3$; *c* 0.59)); ^{1}H NMR and MS: identical to those reported for montanin A [13, 16]. Direct comparison (mmp, TLC) with an authentic sample proved the common identity of the two compounds.

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