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THE C-12 AND C-20 CONFIGURATIONS OF SOME NEO-CLERODANE DITERPENOIDS ISOLATED FROM *TEUCRIUM* SPECIES

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Key Word Index—*Teucrium* sp.; Labiatae; diterpenoids; neo-clerodane derivatives; C-12 and C-20 configurations.

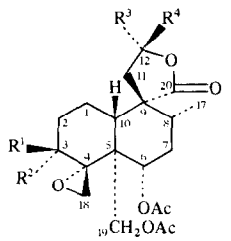
Abstract—A convenient and conclusive method for determining the C-12 stereochemistry of neo-clerodan-20,12-olide derivatives, even when only one epimer is available, is by ^{1}H NMR NOE measurements. The C-12 configuration of 26 neo-clerodane diterpenoids isolated from *Teucrium* species has been re-examined by using this type of experiment. The results indicated that all the previous assignments were correct, except for teupyreinin, where the previously assigned C-12(*S*) configuration must be amended to C-12(*R*). This was confirmed by chemical transformations and additional ^{1}H and ^{13}C NMR studies. Furthermore, the NOE experiments allowed the assignment of a C-20(*S*) configuration for teuflavin, the structure of which had previously been reported without this feature, and indicated that the previously assigned C-20(*S*) configuration for teupyreinidin must be amended to C-20(*R*). The validity of using NOE experiments to establish the C-12 and C-20 configurations in these neo-clerodane derivatives has been confirmed by applying it to compounds whose structure had already firmly established by X-ray diffraction analyses.

INTRODUCTION

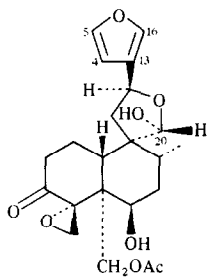
In a previous communication [1] we reported that among natural diterpenoids isolated from *Teucrium* species there were some neo-clerodan-20,12-olides which possessed a C-12(*R*) configuration instead of the more common C-12 (*S*) stereochemistry [2, 3]. Since in all these cases the pairs of C-12 epimers showed almost identical IR and mass spectra, striking similarities in their ^{1}H NMR spectra and only small differences in their ^{13}C NMR spectra, we pointed out [1] that it would be advisable to reconsider the previous assignments of the C-12 configuration of some of the neo-clerodan-20,12-olides isolated from *Teucria*. We also proposed [1] a convenient and conclusive method for establishing the C-12 configuration of this kind of compound, even when only one epimer was available; namely, an NOE experiment. In compounds in which the C-12 methine proton and the C-17 methyl protons are on the same side of the plane defined by the C-20–C-12 lactone ring [configuration C-12(*R*), e.g. compound **1a**], irradiation of the C-17 methyl protons produced an 8–12% NOE enhancement of the H-12 signal, whereas this was not observed in compounds with a C-12 (*S*) centre, such as **1b**, in which H-12 and 3H-17 protons are on opposite sides of the plane defined by the lactone ring and, consequently, widely separated.

RESULTS AND DISCUSSION

The use of this NOE criterion (Table 1) to re-examine the C-12 stereochemistry of some of the neo-clerodane diterpenoids earlier isolated by us from *Teucria* has now



	R^1	R^2	R^3	R^4
1a	OAc	H	β-furyl	H
1b	OAc	H	H	β-furyl
4	OH	H	β-furyl	H
5	O		β-furyl	H



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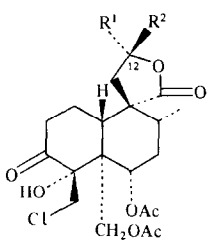
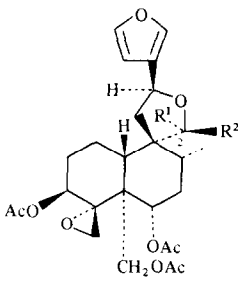


	R^1	R^2
6a	β-furyl	H
6b	H	β-furyl



	R^1	R^2
3a	OAc	H
3b	H	OAc

Table 1. The C-12 and C-20 configurations of some neo-clerodane diterpenoids isolated from *Teucria*

Compound	Previously assigned configuration C-12	C-20	NOE enhancement (%) by irradiating the Me-17 protons H-12	H-14	H-16	H-20	Configuration established by NOE experiment C-12	C-20
Neo-clerodan-20,12-olides								
19-Acetyl gnaphalin* [4–6]	*S*	—	0	6	3	—	*S*	—
19-Acetyl teuspinin* [7, 8]	*S*	—	0	5	2	—	*S*	—
Chamaedroxide* [9]	*S*	—	0	0	3	—	*S*	—
2-Hydroxy-teuscorolide [10]	*S*	—	0	0	0	—	*S*	—
Isoteuflidin [11]	*S*	—	0	3	0	—	*S*	—
Montanin C* [1, 12]	*R*	—	9	0	0	—	*R*	—
Teucjaponin A [13, 14]	*S*	—	0	5	0	—	*S*	—
Teucrin A [15, 16]	*S*	—	0	3	0	—	*S*	—
6-*epi*-Teucrin A [17]	*S*	—	0	4	0	—	*S*	—
Teucrin F [11, 18]	*S*	—	0	0	0	—	*S*	—
Teucrin G [11, 18]	*S*	—	0	3	0	—	*S*	—
Teucroxide [19]	*S*	—	0	3	2	—	*S*	—
Teuflavoside [20]	*S*	—	0	5	2	—	*S*	—
Teuflidin* [21]	*S*	—	0	3	0	—	*S*	—
Teugin [22]	*S*	—	0	5	1	—	*S*	—
Teumarin [23]	*S*	—	0	5	2	—	*S*	—
Teupyreinin (**1a**) [24]	*S*	—	10	0	0	—	*R*	—
Teuscorodin [10]	*S*	—	0	5	3	—	*S*	—
Teuscorodol [25]	*S*	—	0	4	0	—	*S*	—
Teuscorodonin [10]	*S*	—	0	3	5	—	*S*	—
Teuscorolide [25]	*S*	—	0	0	0	—	*S*	—
Neo-clerodane-20,12-hemiacetal derivatives†‡								
Eriocephalin*† [26]	*S*	*S*	0	5	0	0	*S*	*S*
Isoeriocephalin† [27]	*S*	*S*	0	5	2	0	*S*	*S*
Teuflavin (**2**)‡ [20]	*S*	§	0	4	0	10	*S*	*S*
Teupyreinidin (**3a**)† [24]	*S*	*S*	0	6	3	12	*S*	*R*
Teupyrenone [24]	*S*	*S*	0	2	0	15	*S*	*S*

*Structure established by X-ray diffraction analysis.
†Compounds with an acetylated C-20–C-12 hemiacetalic function.
‡Compounds with a C-20–C-12 hemiacetal group.
§Not previously assigned.

shown that, when the Me-17 protons are irradiated, the C-12 (*S*) configuration of neo-clerodan-20,12-olides is, moreover, associated in practically all the cases with a 2–6% NOE enhancement of the signal of the H-14 furanic proton and, in some cases, also with a 1–5% NOE enhancement of that of the H-16 furanic proton (see Table 1). The C-20 configuration* of the neo-clerodanes possessing a C-20–C-12 hemiacetalic function can also be established by this method, since by irradiating the protons of the C-17 methyl group a strong NOE enhancement (10–15%) of the H-20 signal is observed when the H-20 and 3H-17 protons are on the same side of the plane defined by the C-20–C-12 hemiacetalic ring (Table 1: teuflavin (**2**) [20], teupyrenone [24], teupyreinidin (**3a**) [24]), whereas no NOE enhancement of the H-20 signal is observed in compounds with the opposite C-20 stereochemistry (Table 1: eriocephalin [26] and isoeriocephalin [27]).

Table 1 shows the results obtained from the NOE experiments performed on selected neo-clerodane diterpenoids previously isolated by us from *Teucrium* species which possess a C-20–C-12 γ-lactone group or a C-20–C-12 hemiacetalic function. The C-12 and /or C-20 stereochemistry of most of these compounds had not been rigorously established since it was based only on biogenetic grounds and on spectroscopic similarities to closely related compounds. Furthermore, to confirm the validity of the NOE method for establishing the configuration of the C-12 and C-20 centres, Table 1 also includes the results obtained for six diterpenoids (19-acetylgnaphalin, 19-acetylteuspinin, chamaedroxide, montanin C, teuflidin and eriocephalin) whose structures have been firmly established by X-ray diffraction analyses.

The data shown in Table 1 clearly indicate that the C-12 (*S*) configuration previously assigned for all the diterpenoids therein is correct, except for teupyreinin [24], where irradiation of the Me-17 protons causes a 10% NOE enhancement of the H-12 proton signal, as also

*In accordance with the convention of Canh, Ingold and Prelog, a 20(*R*) [or 20 (*S*)] carbon atom of a neo-clerodane-20,12-hemiacetal must be defined as 20(*S*) [or 20(*R*)] when the hemiacetalic hydroxyl group is acetylated, although the C-20 absolute configuration is the same in both cases.

occurs in montanin C, a diterpenoid in which an identical NOE enhancement was observed and whose C-12(*R*) configuration has been well established by an X-ray diffraction analysis [1]. Thus, the previously assigned [24] structure of teupyreinin (**1b**) must be amended to that depicted in formula **1a**. The 10% NOE enhancement of the H-20 proton signal in teuflavin [20] (**2**, see Table 1) established a *cis* spatial relationship between this hydrogen and the C-17 methyl group and, consequently, teuflavin (**2**) possesses a C-20 (*S*) configuration, which was not previously defined [20]. Finally, on the basis of the observed strong NOE (12% enhancement) between the C-20 and Me-17 protons, the previously assigned C-20 (*S*) stereochemistry of teupyreinidin (**3b**) [24] must be amended to C-20 (*R*) (**3a**). This NOE was not found in eriocephalin (see Table 1), a diterpenoid whose C-20 (*S*) configuration is well known [26].

The C-12 (*R*) configuration of teupyreinin (**1a**) now established by means of the NOE experiment is also in agreement with other spectroscopic evidence reported by us [1] that distinguished, although less conclusively, between C-12 epimers. Teupyreinin (**1a**) was correlated with a C-12 epimer in the following way. Treatment of teupyreinin (**1a**) with sodium carbonate in a methanol solution at room temperature yielded predominantly the derivative **4**, which was transformed into compound **5** by oxidation with chromium trioxide–pyridine. Treatment of compound **5** with hydrochloric acid in chloroform solution [28] yielded the chlorohydrin **6a**. On the basis of ^{1}H NMR and ^{13}C NMR spectroscopic data, it could be deduced that the chlorohydrin **6a** was the C-12 epimer of tafricanin B (**6b**), a neo-clerodane diterpenoid isolated from *Teucrium africanum* whose structure has been firmly established [28]. The ^{1}H NMR and ^{13}C NMR differences between tafricanin B [**6b**, configuration C-12 (*S*)] and its C-12 (*R*) epimer (**6a**) shown in Table 2 are in complete agreement with our previous observations [1] for other pairs of C-12 epimers, thus confirming the C-12 (*R*) stereochemistry for teupyreinin (**1a**) deduced from the NOE experiment.

The results obtained in this work firmly establish the structures of all the neo-clerodane diterpenoids isolated by us from *Teucria*. Although Table 1 contains only some of these compounds, the rest of them were either chemically correlated with some of those reported here or had structures already firmly established by X-ray diffraction analysis.

Table 2. The more significant ^{1}H NMR and ^{13}C NMR differences between the C-12 epimeric compounds **6a** and **6b***

Proton signal	^{1}H NMR†		Carbon atom	^{13}C NMR‡	
	6a	**6b**		**6a**	**6b**
H-12	5.46	5.40	C-1	23.8	24.9
Me-17	1.17	1.06	C-8	41.1	38.4
			C-9	52.4	52.2
			C-10	47.1	48.9

*Taken from ref. [28].
†In δ values from internal TMS, $CDCl_3$ solution.
‡In ppm downfield from TMS, $CDCl_3$ solution.

EXPERIMENTAL

Mps are uncorr. For general details on methods, see refs. [1, 7–11, 17, 19–27]. The proton NOE measurements were made at 300 MHz by the FT difference method with the decoupler operating in the gated mode.

3-Deacetylteupyreinin (**4**) *from teupyreinin* (**1a**). To a MeOH (100 ml) soln of compound **1a** (1 g) was added 1 g of Na_2CO_3 and the mixture was stirred at room temp. (24°) for 7 hr. The mixture was then diluted with H_2O and extracted with $CHCl_3$. Work up in the usual manner yielded a residue which was crystallized from EtOAc to give pure **4** (630 mg), mp 250–253°; $[\alpha]_D^{22}$ +6.1° ($CHCl_3$; *c* 0.578); IR ν_{max}^{KBr} cm^{-1}: 3515 (OH), 3140, 3120, 1500, 877 (furan ring), 1765 (γ-lactone), 1740, 1725, 1265, 1240 (acetates), 2985, 2960, 2880, 1450, 1390, 1150, 1130, 1045, 1030, 820, 760, 750; ^{1}H NMR (90 MHz, $CDCl_3$): δ7.40 (2H, *m*, $W_{1/2}$ = 3 Hz, H-15 and H-16), 6.34 (1H, *dd*, $J_{14,15}$ = 1.8 Hz, $J_{14,16}$ = 1 Hz, H-14), 5.36 (1H, *t*, *J* = 8.5 Hz, H-12), 5.35 and 4.35 (an AB system, J_{AB} = 12 Hz, 2H-19), 4.85 (1H, *dd*, $J_{aa'}$ = 11 Hz, $J_{ae'}$ = 5 Hz, H-6β), 4.14 (1H, *dd*, $J_{aa'}$ = 10 Hz, $J_{ae'}$ = 6 Hz, H-3α), 2.81 and 2.72 (an AB system, J_{AB} = 4.5 Hz, 2H-18), 2.50 and 2.30 (1H each, *dd*, *dd*, J_{gem} = 13 Hz, J_{vic} = 8.5 Hz, 2H-11), 2.03 and 1.94 (3H each, *s*, *s*, two OAc) and 1.10 (3H, *d*, *J* = 6 Hz, Me-17); EIMS (direct inlet) 75 eV, *m/z* (rel. int.): 462 [M]$^+$ (0.1), 444 (0.2), 403 (0.4), 402 (0.2), 389 (0.3), 371 (2), 329 (4), 311 (4), 267 (3), 173 (8), 145 (9), 96 (19), 95 (27), 94 (13), 91 (16), 81 (21), 67 (10), 55 (10), 53 (10), 43 (100). (Found: C, 62.41; H, 6.48. $C_{24}H_{30}O_9$ requires: C, 62.32; H, 6.54%.)

Oxidation of compound **4** *to give compound* **5**. Oxidation of **4** (600 mg) with the CrO_3–pyridine complex in pyridine soln in the usual manner yielded **5** (560 mg after chromatographic purification): an amorphous solid which melted at 110–120°; $[\alpha]_D^{22}$ +51.2° ($CHCl_3$; *c* 0.613); IR ν_{max}^{KBr} cm^{-1}: 3150, 3130, 1510, 877 (furan ring), 1760 (γ-lactone), 1740 (br), 1240 (acetates), 1720 (ketone), 2970, 1480, 1370, 1160, 1140, 1090, 1040, 950, 800; ^{1}H NMR (90 MHz, $CDCl_3$): δ7.42 (2H, *m*, $W_{1/2}$ = 3 Hz, H-15 and H-16), 6.38 (1H, *dd*, $J_{14,15}$ = 1.8 Hz, $J_{14,16}$ = 1 Hz, H-14), 5.45 (1H, *t*, *J* = 8.4 Hz, H-12), 5.39 and 4.85 (an AB system, J_{AB} = 11.7 Hz, 2H-19), 4.90 (1H, *dd*, $J_{aa'}$ = 11.4 Hz, $J_{ae'}$ = 4.2 Hz, H-6β), 3.13 and 2.45 (an AB system, J_{AB} = 5.4 Hz, 2H-18), 2.50 (2H, overlapped signal, 2H-11), 2.01 and 1.90 (3H each, *s*, *s*, two OAc) and 1.15 (3H, *d*, *J* = 6 Hz, Me-17); ^{13}C NMR (75.4 MHz, $CDCl_3$): δ, SFORD multiplicity (carbon number): 22.2 *t* (1), 39.3 *t* (2), 203.3 *s* (3), 65.2 *s* (4), 45.8 *s* (5), 70.8 *d* (6), 32.9 *t* (7), 40.8 *d* (8), 52.4 *s* (9), 49.0 *d* (10), 44.2 *t* (11), 72.2 *d* (12), 125.1 *s* (13), 107.8 *d* (14), 144.4 *d* (15), 139.1 *d* (16), 16.8 *q* (17), 51.0 *t* (18), 63.1 *t* (19), 176.0 *s* (20), 170.3 *s*, 169.5 *s*, 21.2 *q*, 20.6 *q* (two OAc); EIMS (direct inlet) 75 eV, *m/z* (rel. int.): 460 [M]$^+$ (0.2), 416 (0.5), 401 (0.4), 400 (0.3), 387 (0.7), 340 (6), 328 (7), 327 (9), 311 (6), 310 (4), 267 (7), 173 (14), 145 (14), 131 (14), 117 (18), 105 (22), 96 (57), 95 (62), 94 (31), 91 (33), 81 (49), 67 (20), 55 (23), 43 (100). (Found: C, 62.40; H, 6.19. $C_{24}H_{28}O_9$ requires: C, 62.60; H, 6.13%.)

The C-12 epimer of compound **5** was previously described [28] as a synthetic derivative of tafricanin B (**6b**). It had mp 201°; $[\alpha]_D^{20}$ −5.4°, and a slightly different ^{1}H NMR spectrum: $\delta_{Me\text{-}17}$ 1.03.

Chlorohydrin **6a** *from compound* **5**. Treatment of a $CHCl_3$ (10 ml) soln of compound **5** (100 mg) with conc HCl (1 ml) overnight at room temp. and with stirring, quantitatively yielded the chlorohydrin **6a**, mp 268–270° (from EtOH); $[\alpha]_D^{22}$ +1.7°, $[\alpha]_{365}^{22}$ −19.3° ($CHCl_3$; *c* 0.415); IR ν_{max}^{KBr} cm^{-1}: 3430 (hydroxyl group), 3160, 3120, 1503, 880 (furan ring), 1760 (γ-lactone), 1740 (br), 1245 (acetates), 2980, 1435, 1370, 1190, 1165, 1150, 1050, 1030, 800, 750; ^{1}H NMR (90 MHz, $CDCl_3$): δ7.43 (2H, *m*, $W_{1/2}$ = 3 Hz, H-15 and H-16), 6.37 (1H, *dd*, $J_{14,15}$ = 1.8 Hz, $J_{14,16}$ = 0.9 Hz, H-14), 5.46 (1H, *t*, *J* = 8.4 Hz, H-12), 5.33 and 5.03 (an AB system, J_{AB} = 11.7 Hz, 2H-19), 5.20 (1H, *dd*, $J_{aa'}$ = 11.6 Hz, $J_{ae'}$ = 4.2 Hz, H-6β), 3.98 (2H, *s*, 2H-18), 2.64 and 2.47 (the AB

part of an ABX system, J_{AB} = 12 Hz, $J_{AX} = J_{BX}$ = 8.4 Hz, 2H-11), 2.05 and 1.87 (3H each, *s*, *s*, two OAc) and 1.17 (3H, *d*, *J* = 6 Hz, Me-17); ^{13}C NMR (75.4 MHz, $CDCl_3$): δ, SFORD multiplicity (carbon number) 23.8 *t* (1), 36.9 *t* (2), 206.1 *s* (3), 80.1 *s* (4), 51.7 *s* (5), 70.6 *d* (6), 33.3 *t* (7), 41.1 *d* (8), 52.4 *s* (9), 47.1 *d* (10), 44.8 *t* (11), 71.8 *d* (12), 125.2 *s* (13), 107.8 *d* (14), 144.4 *d* (15), 139.0 *d* (16), 16.7 *q* (17), 47.5 *t* (18), 62.2 *t* (19), 175.7 *s* (20), 170.7 *s*, 169.5 *s*, 21.5 *q*, 20.7 *q* (two OAc); EIMS (direct inlet) 75 eV, *m/z* (rel. int.): 498 and 496 $[M]^+$ (0.3 and 1, respectively), 478 (0.5), 461 (1.5), 436 (1.5), 418 (2), 408 (3), 396 (3), 394 (10), 378 (2.5), 376 (9), 359 (6), 350 (7), 348 (21), 299 (46), 271 (11), 256 (10), 236 (12), 211 (17), 178 (21), 159 (23), 105 (30), 96 (32), 95 (71), 94 (68), 91 (34), 81 (61), 67 (22), 55 (28), 43 (100). (Found: C, 57.98; H, 6.00; Cl, 7.19. $C_{24}H_{29}O_9Cl$ requires: C, 58.00; H, 5.88; Cl, 7.14%.)

Tafricanin B (**6b**) [28], mp 255–256°; $[\alpha]_D^{20}$ +14.6°; for ^{1}H NMR and ^{13}C NMR differences with compound **6a** see Table 2.

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