The Absolute Stereochemistry of some Clerodane Diterpenoids from *Teucrium* Species

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The absolute configurations of 19-acetylgnaphalin, and another diterpenoid from *T. gnaphalodes*, probably identical with teucrin P_1, have been determined by *X*-ray analysis; they belong to the neoclerodane series. Isofruticolone has also been shown to belong to this series.

A LARGE number of diterpenoids with the *trans*-clerodane skeleton have been isolated in the last few years. Interest in these compounds has been stimulated by their biological activity as insect antifeedants, antitumour, antimicrobial, and antifungal agents. They have been isolated from genera of the families Verbenaceae (*Clerodendron*, *Caryopteris*), Euphorbiaceae (*Croton*, *Mallotus*), Compositae (*Baccharis*, *Haplopappus*, *Olearia*, *Conyza*, *Hinterhubera*, *Nidorella*, *Printzia*), Sapindaceae (*Dodonaea*), Dicrastylidaceae (*Cyanostegia*), Hamamelidaceae (*Callicarpa*), Annonaceae (*Annona*), Caesalpiniaceae (*Gossweilerodendron*), Leguminosae (*Hardwickia*), and Labiatae (*Ajuta*, *Teucrium*, *Salvia*, and *Stychys*).[1] Recently the absolute stereochemistry assigned to the first member of the series, clerodin, has been revised.[2] This had implications for other members of the series. There also appears to be some ambiguity in deductions drawn from the sign of the Cotton effect on C-6 ketones. It has been suggested that those clerodanes which have been related to the new clerodin stereochemistry are known as neoclerodanes (1).† Almost all the *trans*-clerodanes whose absolute configuration has been unambiguously established belong to the neoclerodane series. We have recently described [3-8] the structures of a group of *trans*-clerodane diterpenoids from *Teucrium* species and assigned their absolute configuration by means of *X*-ray analysis, c.d. curves, or chemical correlation. In this paper we discuss these structures in the light of the new stereochemistry of clerodin and present further evidence concerning their absolute configuration.

RESULTS AND DISCUSSION

Teuflidin (from *T. flavum*) (3) [3] which is identical with teucrin H_1 (from *T. hyrcanicum*) [9] has the neoclerodane configuration which was established by *X*-ray analysis and by the negative c.d. curve of the $\alpha\beta$-unsaturated lactone which was identical with that of teucvidin (4).[10] Our assignment has been confirmed independently.[9] Teuflin (from *T. flavum*) (5) [8] also has the neoclerodane stereochemistry, on the basis of an *X*-ray analysis and the c.d. curve of the $\alpha\beta$-unsaturated lactone. Eriocephalin (from *T. eriocephalum*) (6) [4] was assigned to the neoclerodane series on the basis of a Bijvoet analysis of the *X*-ray data. It has a positive c.d. curve associated with the C-6 ketone. Gnaphalin (7), gnaphalidin (8), and 19-acetylgnaphalin (9) (from *T. gnaphalodes* L'Her.)[5] have been assigned to the neoclerodane series. These three products are inter-related and also related to montanin-A (10) [11] and teucvin (11).[12] 19-Acetylgnaphalin is identical to teucrin H_3 (from *T. hyrcanicum*), for which the same stereochemistry was proposed in an independent study.[9]

Whilst gnaphalin and its relatives show a negative c.d. curve for the C-6 ketone, the ajugarin derivatives, for which the *ent*-neoclerodane stereochemistry is now proposed, also show a negative Cotton effect. This also sheds some doubt on the absolute stereochemistry of fruticolone (12),[6] isofruticolone (13),[6] and 8β-hydroxyfruticolone (14) [7] which were assigned a neoclerodane skeleton on the basis of the c.d. curve of the C-6 ketone. Fruticolone and isofruticolone are related through a common diketone. The c.d. curve of the ring A C-1 ketone of isofruticolone is negative (295 nm, $\Delta\varepsilon$ −2.00 in MeOH) in agreement with that calculated for a 1-oxo-5α-19-nor-steroid.[13] Hence isofruticolone, and thus fruticolone, have the neoclerodane stereochemistry. Reduction of 19-acetylgnaphalin (9) with sodium borohydride afforded the 6α- (equatorial) epimer (15). Application of Horeau's method [14] to this alcohol showed that it possessed the 6*S* configuration, in complete agreement with a neoclerodane absolute stereochemistry.

Acetylation of (15) gave a product, $C_{24}H_{30}O_8$, with a structure (16) that has also been attributed [15] to montanin-C (from *T. montanum*). The acetate has also been prepared by Mollov and co-workers.[16] The alcohol (15) is identical with a new natural product, teupolin 1, isolated [16] from *T. polium*. The spectral data are in agreement although we found m.p. 256—259 °C, $[\alpha]_D^{17}$

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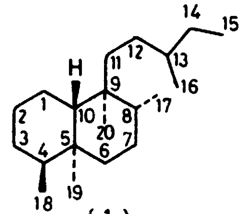
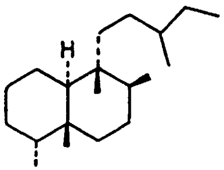
† There is a risk of confusion in this new nomenclature since the neoclerodanes (1) are related biogenetically to *ent*-labdanes in which C-20 is an α-substituent, whilst the *ent*-neoclerodanes (2) are related biogenetically to the *normal* labdanes, in which C-20 is a β-substituent.



(1)



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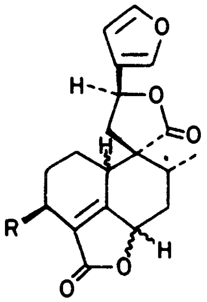
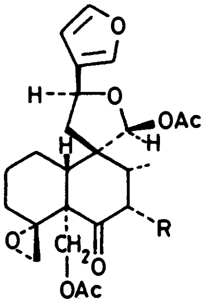
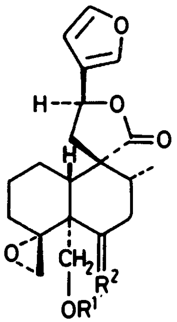


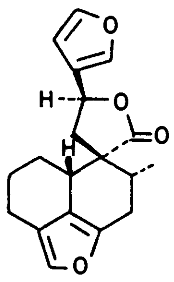
(3) R = OH, 6α—H, 10α—H; teuflidin
(4) R = H, 6α—H, 10α—H; teucvidin
(5) R = H, 6α—H, 10β—H; teuflin
(11) R = H, 6β—H, 10β—H; teucvin



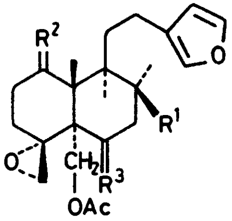
(6) R = OH; eriocephalin
(8) R = H; gnaphalidin



(7) R^1 = H, R^2 = O; gnaphalin
(9) R^1 = Ac, R^2 = O; acetylgnaphalin
(15) R^1 = Ac, R^2 = α—OH, β—H
(16) R^1 = Ac, R^2 = α—OAc, β—H



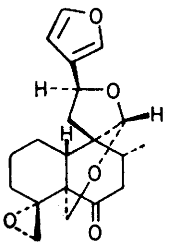
(10) montanin—A



(12) R^1 = H; R^2 = α—OH, β—H; R^3 = O
(13) R^1 = H; R^2 = O R^3 = α—H, β—OH
(14) R^1 = OH; R^2 = α—OH, β—H; R^3 = O

+68.1° whereas Mollov and co-workers reported m.p. 211—213 °C, $[\alpha]_D^{20}$ +60°. The discrepancy in m.p. may arise through polymorphism. The acetate (16) prepared by Mollov and co-workers[16] has spectral data in agreement with ours, but both differ from those of natural montanin-C, leaving the structure of the latter in doubt. Our product has m.p. 163—164 °C, $[\alpha]_D^{17}$ +33.5°; the product of Mollov and co-workers is a resin (no $[\alpha]_D$ given) whilst montanin-C has m.p. 181—183 °C, $[\alpha]_D$ +8.4°.

We have re-examined *T. gnaphalodes* and isolated a fourth diterpenoid, $C_{20}H_{24}O_5$, in addition to gnaphalin, 19-acetylgnaphalin and gnaphalidine. Spectral data suggested that the structure of the new diterpenoid was (17), which was confirmed by *X*-ray analysis (see below).



(17)

This structure has recently been assigned to teucrin P_1 (from *T. polium*). Teucrin P_1 from *T. polium*[16,17] has m.p. 164—166 °C, $[\alpha]_D$ +6.6°, whilst our product has m.p. 165—168 °C, $[\alpha]_D^{22}$ −13°.

X-Ray analyses were performed on 19-acetylgnaphalin (9) and on the diterpenoid (17) (= teucrin P_1?) to provide definitive evidence for their absolute stereochemistry. Both compounds were shown to belong to the neo-clerodane series. The structures were solved using the multisolution tangent formula approach, MULTAN.[18] All hydrogen atoms were located on difference maps calculated for those observed reflections within sin θ/λ 0.5 Å^{-1} and phases corresponding to the least-squares anisotropic refinement of non-hydrogen atoms. For each compound a convenient weighting system[19] was chosen to prevent bias in $\langle w(\Delta^2 F)\rangle$ *vs.* $\langle F_o\rangle$ or *vs.* sin θ/λ, where $\Delta^2F = ||F_o| - |F_c||^2$. These weighting schemes were used to refine,[20] by full-matrix least-squares, the right enantiomers of both compounds. Both *hkl* and $\bar{h}\bar{k}\bar{l}$ reflections were used in the refinements, where the anomalous dispersion corrections for C and O atoms were considered. The co-ordinates of the H atoms (isotropic fixed contribution) were considered as variables in the last steps of the refinements. Both refinements converged to the *R* factors listed in the Table. The observed and calculated structure factors, atomic co-ordinates, anisotropic thermal parameters, Bijvoet pairs, bond lengths, torsional angles, and hydrogen-bond data are deposited as Supplementary Publication No. SUP 22985 (53 pp.).*

Crystal data (standard deviations in parentheses)

	$C_{22}H_{26}O_7$ (9)	$C_{20}H_{24}O_5$ (17)
Molecular weight	402.45	344.39
Space group	$P2_12_12_1$	$P2_12_12_1$
a/Å	18.038 2(4)	12.537 6(4)
b/Å	16.624 2(5)	11 833 2(3)
c/Å	6.641 1(1)	11.535 4(6)
U/Å^3	1 991.5(1)	1 711.4(2)
Z	4	4
D_c/g cm^{-3}	1.34	1.34
μ/cm^{-1}	7.87	7.41
F(000)	856	736
Radiation	Cu-K_α	Cu-K_α
Monochromator	graphite	graphite
Scan mode	ω—2θ	ω—2θ
Scan speed (° min^{-1})	2.1	2.6
Intensity decay	No	No
$\theta_{max.}$/°	65	65
Independent Friedel pairs alternately collected	1 971	1 682
Observed [$I > 3\sigma(I)$] Friedel pairs used for refinement	1 842	1 300
Friedel pairs/parameter in refinement	5	5
R	0.043	0.077
R'	0.055	0.100

In the determination of the absolute configurations, the use of the anomalous dispersion effects of C and O atoms for Cu-*K* radiation gave poor indications of the right enantiomers with all observed non-centrosymmetric Friedel pairs. For this reason we selected the *N* more relevant Bijvoet pairs[21] (*hkl* and $\bar{h}\bar{k}\bar{l}$) which gave a clear indication of the correct absolute configuration of both compounds, shown in Figures 1 and 2. All equivalent reflections of some of these Bijvoet pairs were re-measured in a new experiment, at very low scan speed and avoiding absorption effects. These results are listed in Table 6 of SUP 22985. The re-measured data clearly show an improvement in the enantiomeric distinction.

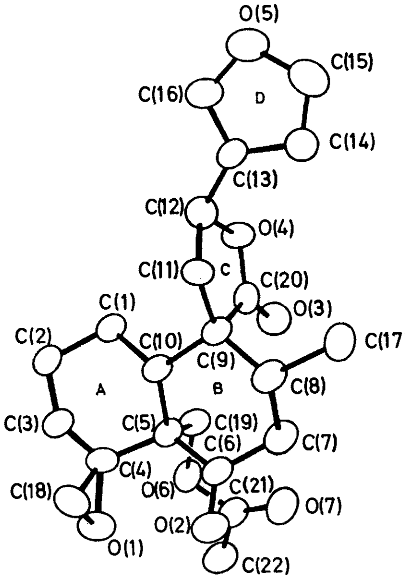


FIGURE 1 Computer drawing of the right enantiomer of $C_{22}H_{26}O_7$ [compound (9)]

The conformations of the rings of 19-acetylgnaphalin are ring A, chair; ring B, chair; ring C, envelope with C-11 at the flap; and ring D, planar. The conformations

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* For details see Notice to Authors No. 7, *J. Chem. Soc., Perkin Trans. I*, 1980, Index issue.

of the rings of compound (17) are ring A, chair; ring B, boat with C-7 and C-10 at the flaps; ring C, envelope with C-12 at the flap; ring D, planar; and ring E, boat with C-10 and the oxygen at the flaps. It is important to note that eriocephalin (6) and compound (17), which show a positive Cotton effect in the c.d. curves of the 6-ketones, have ring B in a boat conformation. In contrast-19-acetylgnaphalin (9), which has a negative c.d. curve, possesses a chair conformation for this ring.

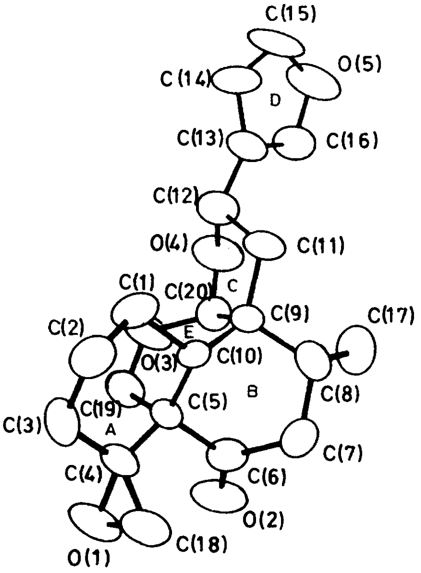

FIGURE 2 Computer drawing of the right enantiomer of $C_{20}H_{24}O_5$ [compound (17)]

EXPERIMENTAL

M.p.s were determined on a Kofler apparatus and are uncorrected. Optical rotations were determined on a Perkin-Elmer 141 polarimeter in a 1-dm cell. I.r. spectra were determined on a P.E. 257 spectrometer, whilst ^1H and ^{13}C n.m.r. spectra were determined at 90 or 100 MHz and 25.2 MHz in $CDCl_3$ solution on Varian instruments. Mass spectra were obtained on a Hitachi RMU-6MG. Chromatography was carried out on Merck silica, 70—230 mesh.

Extraction of Teucrium gnaphalodes *and Separation of the Diterpenes*.—The plant was collected in April 1978 near Chinchon, Madrid. The air-dried aerial portion (2.100 kg) was extracted with acetone (10 l) at room temperature for 6 days. The solvent was evaporated and the residue chromatographed directly on silica gel, eluant light petroleum (alkanes, fats, and waxes) then light petroleum–ethyl acetate. The light petroleum–ethyl acetate (70 : 30) successively eluted (17) (=teucrin P_1?) (100 mg) and gnaphalidin (8) (200 mg); light petroleum–ethyl acetate (50 : 50) eluted 19-acetylgnaphalin (9) (2 g) and gnaphalin (7) (1.1 g). The chromatography must be rapid to avoid transformation of gnaphalin into montanin-A.

Physical and spectral data for 19-acetylgnaphalin, gnaphalin, and gnaphalidin have been reported previously.[5] Product (17) has m.p. 165—168 °C (from EtOAc–light petroleum), $[\alpha]_D^{22}$ $-13.0°$ ($CHCl_3$, *c* 0.368) (Found: C, 69.75; H, 7.2. Calc. for $C_{20}H_{24}O_5$: C, 69.75; H, 7.02%); *m/e* 344 (M^+), 330, 329, 326, 315, 314, 285, 95, 94 (base peak), 91, and 81; $\nu_{max.}$ (Nujol) 1 705 (broad), 870, and 795 cm^{-1}; c.d. (EtOH, *c*; 0.546) $\Delta\varepsilon_{303}$ $+0.93$; δ($CDCl_3$, 100 MHz) 1.07 (3 H, d, *J* 7 Hz, Me), 2.91 (1 H, d, *J* 5.5 Hz, epoxide proton), 3.98 and 4.50 (2 H, AB quartet, *J* 12 Hz, CH_2OCH), 5.10 (1 H, t, *J* 8.3 Hz, H-12), 5.13 (1 H, s H-20), 6.40 (1 H, m, furan β-proton), and 7.44 (2 H, m, furan α-protons); δ_C ($CDCl_3$, 25.2 MHz) 23.6(t, C-1), 23.6(t, C-2), 30.9(t, C-3), 58.3(s, C-4), 51.5(s, C.5), 209.5(s, C-6), 45.4(t, C-7), 36.1(d, C-8), 47.0(s, C-9), 45.0(d, C-10), 39.9(t, C-11), 70.7(d, C-12), 126.8(s, C-13), 108.4(d, C-14), 143.5(d, C-15), 138.9(d, C-16), 16.8(q, C-17), 50.9(t, C-18), 62.8(t, C-19), and 100.4(d, C-20).

Transformation of 19-*Acetylgnaphalin* (9) *into Montanin-A* (10).—A sample of (9) (200 mg) dissolved in 5% methanolic KOH (5 ml) was allowed to stand at room temperature for 15 min; the solvent was evaporated and the residue taken up in EtOAc and washed with dilute HCl; chromatography on silica gel yielded montanin-A (150 mg), m.p. 126—127 °C (from EtOAc–light petroleum), $[\alpha]_D^{27}$ $+115°$ ($CHCl_3$, *c* 0.59) (lit.,[11] $[\alpha]_D$ 11.5°); the mass spectrum, ^1H n.m.r., and i.r. data of this product [5] are in agreement with those reported [11] for montanin-A; direct comparison with an authentic specimen * proved the identity of the two products.

Transformation of Gnaphalin (7) *into Montanin-A* (10).—Slow chromatography of (7) (50 mg) in EtOAc–light petroleum or $CHCl_3$ solution on silica gel (20 g) gave an almost quantitative yield of montanin-A, m.p. 126—127 °C.

Transformation of Montanin-A (10) *into Teucvin* (11).—A solution of (10) (100 mg) in $CHCl_3$ (10 ml) was exposed to daylight for 5 days at room temperature.[11] The mixture of products was chromatographed on silica gel: EtOAc–light petroleum (30 : 70) eluted teucvin (30 mg), m.p. 205—207 °C (from EtOAc–n-hexane), $[\alpha]_D^{28}$ $+186.1°$ ($CHCl_3$, *c* 0.59) (lit.,[12] m.p. 207—208 °C, $[\alpha]_D^{18°}$ $+184°$). Direct comparison (m.s., i.r., ^1H n.m.r.) with an authentic sample proved the identity of the products.

Reduction of 19-*Acetylgnaphalin with* $NaBH_4$ (9).—A solution of (9) (500 mg) and $NABH_4$ (300 mg) in dioxan (30 ml) and methanol (10 ml) was left at room temperature for 15 min. The usual treatment gave the 6α-hydroxy-epimer (15) (400 mg), m.p. 256—259 °C (from EtOAc–light petroleum), $[\alpha]_D^{17}$ $+68.1°$ ($CHCl_3$, *c* 0.43) (Found: C, 65.3; H, 7.15. Calc. for $C_{22}H_{28}O_7$: C, 65.33; H, 6.98%); *m/e* 404 (M^+), 386, 373, 344, 331, 326, 315, 314, 297, 268, 252, 219, 208, 171, 159, 123, 96 (base peak), 95, and 81; $\nu_{max.}$ (KBr) 3 515, 3 480, 1 760, 1 720, 1 260, and 880; δ_H ($CDCl_3$, 90 MHz) 1.03 (3 H, d, *J* 7 Hz, Me), 2.02 (3 H, s, OCOMe), 3.30 (1 H, m, epoxide proton), 4.70 and 5.07 (2 H, AB quartet, *J* 13 Hz, CH_2OAc), 3.57 (1 H, dd, *J* 11 and 4.5 Hz, H-6), 5.37 (1 H, t, *J* 8.5 Hz, H-12), 6.38 (1 H, m, furan β-proton), and 7.45 (2 H, m, furan α-protons); δ_C ($CDCl_3$, 25.2 MHz) 22.6(t, C-1), 25.0(t, C-2), 31.3(t, C-3), 66.5(s, C-4), 45.3(s, C-5), 73.4(d, C-6), 33.8(t, C-7), 38.9(d, C-8), 51.1(s, C-9), 52.5(d, C-10), 43.6(t, C-11), 71.3(d, C-12), 125.0(s, C-13), 107.8(d, C-14), 144.0(d, C-15), 139.3(d, C-16), 16.5(q, C-17), 48.4(t, C-18), 61.6(t, C-19), and 175.6(s, C-20); acetate Me resonance at δ 21.2; acetate Co resonance at δ 170.3. For physical data, see text and compare ref. 16.

Application of the Horeau Method [14] *to Compound* (15).—A mixture of (±)-α-phenylbutyric anhydride (0.258 mmol) and compound (15) (0.075 7 mmol) in pyridine solution (2

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* We thank Professor N. M. Mollov for the sample.

ml) was kept at room temperature for 20 h); $\alpha_1 = +1.045$; $\alpha_2 = +0.978$; $\alpha_1 - 1.1$ $\alpha_2 = -0.030\,8$ at 589 nm, configuration 6*S*. At 436 nm, $-0.196\,4$: configurations 6*S*.

Acetylation of Compound (15) *to give Compound* (16).—The usual acetic anhydride–pyridine treatment of (15) gave the derivative (16) in high yield, m.p. 163—164 °C (from Et_2O–light petroleum), $[\alpha]_D^{17}$ +33.5° ($CHCl_3$, *c* 0.97), (Found: C, 64.5; H, 6.85. Calc. for $C_{24}H_{30}O_8$: C, 64.56; H, 6.77%); *m/e* 415 (*M* − 31), 403 (*M* − 43), 386 (*M* − 60), 373, (*M* − 73), 356, 331, 314, 298, 254, 204, 159, 96 (base peak), 95, and 81; $\nu_{max.}$ (KBr) 1 740 (br), 1 250, and 880 cm^{-1}; δ_H ($CDCl_3$, 90 MHz) 1.00 (3 H, d, *J* 7 Hz, Me), 1.95 and 2.06 (3 H each, s, 2 × OCOMe), 2.96 (1 H, m, epoxide proton), 4,46 and 5.21 (2 H, AB quartet, *J* 13 Hz, CH_2OAc), 4.76 (1 H, dd, *J* 11 and 4.5 Hz, H-6), 5.31 (1 H, t, *J* 8.5 Hz, H-12), 6.31 (1 H, m, furan β-proton), and 7.38 (2 H, m, furan α-protons); δ_C ($CDCl_3$, 25.2 MHz) 22.9(t, C-1), 24.9(t, C-2), 32.6(t, C-3), 64.6(s, C-4), 45.4(s, C-5), 71.5(d, C-6), 32.1(t, C-7), 38.1(d, C-8), 50.8(s, C-9), 52.9(d, C-10), 43.1(t, C-11), 71.8(d, C-12), 125.0(s, C-13), 107.0(d, C-14), 144.0(d, C-15), 139.4(d, C-16), 16.4(q, C-17), 48.2(t, C-18), 61.5(t, C-19), and 175.7(s, C-20); acetate Me resonances at δ 21.1; acetate CO resonances at δ 169.8 and 170.1. For comparison of physical data, see text and refs. 15 and 16.

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