

Teuflidin, A Norclerodane Diterpenoid from *Teucrium flavum*

By Giuseppe Savona, Maria P. Paternostro, and Franco Piozzi,* Istituto di Chimica Organica, Università di Palermo, Via Archirafi, Palermo, Italy

James R. Hanson,* Peter B. Hitchcock,* and Sunday A. Thomas, School of Molecular Sciences, University of Sussex, Brighton, Sussex BN1 9QJ

Teuflidin, isolated from *Teucrium flavum*, has been shown to be 3 β -hydroxyteucvidin.

TEUCRIUM species (Labiatae) have afforded a number of clerodane and norclerodane diterpenoids.¹⁻³ We have previously described⁴ some clerodanes from *T. fruticans*. In continuation of this work, we now report a norclerodane, teuflidin, C₁₉H₂₀O₆ (1) which we have obtained from *T. flavum* (Yellow Germander). The i.r.

also showed a geminal coupling (J 13 Hz). They were vicinally coupled (2 and 4 Hz respectively) to a signal at δ 2.25. A methyl group doublet (δ 1.36, J 7 Hz) was also coupled to this signal. These decoupling experiments suggested the presence of the fragments:

$\text{C}-\text{CH}_2-\overset{\text{O}}{\text{C}}-\text{CH}-\text{C}$ and $\text{C}-\overset{\text{O}}{\text{C}}-\text{CH}-\text{CH}_2-\text{CH}-\text{CH}_3$. The $\text{CH}(\text{OH})$ signal (δ 4.67) had a half-width (7 Hz) corresponding to an axial alcohol.

This evidence suggested that teuflidin was a hydroxylated relative of teucvidin (2) or teucvin (3) which occur in *Teucrium viscidum*.³ Comparison of their ¹³C n.m.r. spectra (see Table I) not only supported this relationship but also suggested that the hydroxy-group was located at C-3. In teuflidin a high-field ¹³C SFORD triplet was missing and was replaced by a relatively high field $\text{CH}(\text{OH})$ doublet. One triplet had moved downfield as

Compound Carbon no.	¹³ C Signals			¹ H Signals	
	(1)	(2)	(3)	δ	J /Hz
1	17.7	21.4 ^a	21.7 ^a	<i>c</i>	
2	29.8	23.3	24.7	<i>c</i>	
3	58.7	20.1 ^a	19.7 ^a	4.67	m 7 ^d
4	128.7	127.7	126.4		
5	165.7	162.2	161.6		
6	76.2	76.1	78.3	5.03	q 7, 13
7	35.6	35.8	35.3	2.38	2, 7
				1.60	and 13
8	36.2	35.8	35.9	2.25	4, 13
9	52.1	52.1	53.5		and 13
10	38.6	38.8	42.0	3.27	2, 4
11	38.8	39.0	40.8	2.75	and 7
				1.90	q 8.5
					and 14.5
12	72.2	71.8	71.8	5.42	q 8.5
13	125.3	125.2	124.9		and 14.5
14	107.9	108.0	107.9	6.37	t 8
15	144.2	144.2	144.2	7.45	q 8.5
16	139.5	139.5	139.5	7.45	and 14.5
17	14.3	14.3	17.0	1.36	d 7
18	177.5 ^b	177.6 ^b	175.6 ^b		
20	172.0 ^b	172.5 ^b	173.0 ^b		

^{a, b} These signals may be interchanged. ^c These signals were not identified. ^d Width at half height.

absorption and ¹H n.m.r. spectra of teuflidin showed that the oxygen functions were a secondary alcohol, a γ -lactone, and $\alpha\beta$ -unsaturated- γ -lactone, and a β -substituted furan ring. ¹H (220 MHz) N.m.r. spin decoupling studies were particularly informative. A low-field triplet (δ 5.43) which we have assigned to H-12, was coupled (J 8.5 Hz) to two single-proton resonances at δ 2.75 and 1.90 which were also geminally coupled (J 14.5 Hz). These signals showed no further coupling. A quartet (δ 5.03, J 7 and 13 Hz) which was assigned to H-6, was coupled (J 7.0 Hz) to an octet (δ 2.38) and (13 Hz) to a triplet of doublets (δ 1.6). These protons

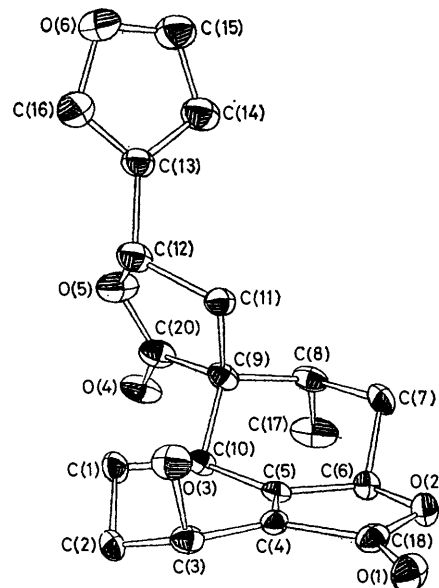


FIGURE 1

would be expected with an adjacent C-O and another showed a smaller upfield shift (3.7 p.p.m.; γ -effect of an oxygen substituent).

Although the n.m.r. data was closer to that of

³ E. Fujita, I. Uchida, and T. Fujita, *J.C.S. Perkin I*, 1974, 1547; *Tetrahedron*, 1975, **31**, 841.

⁴ G. Savona, S. Passannanti, M. P. Paternostro, F. Piozzi, J. R. Hanson, P. B. Hitchcock, and M. Siverns, *J.C.S. Perkin I*, 1978, 356.

¹ C. H. Brieskorn and T. Pfeuffer, *Chem. Ber.*, 1967, **100**, 1989.

² D. P. Popa and A. M. Reinbold, *Khim. prirod. Soedinenii*, 1972, 67; 1973, 31, 169; 1976, 752.

teucvidin, the evidence for the stereochemistry of the carbon skeleton was not conclusive, particularly as epimers at C-6 and C-10 are known in this series.³ Hence the molecule was subjected to *X*-ray analysis.

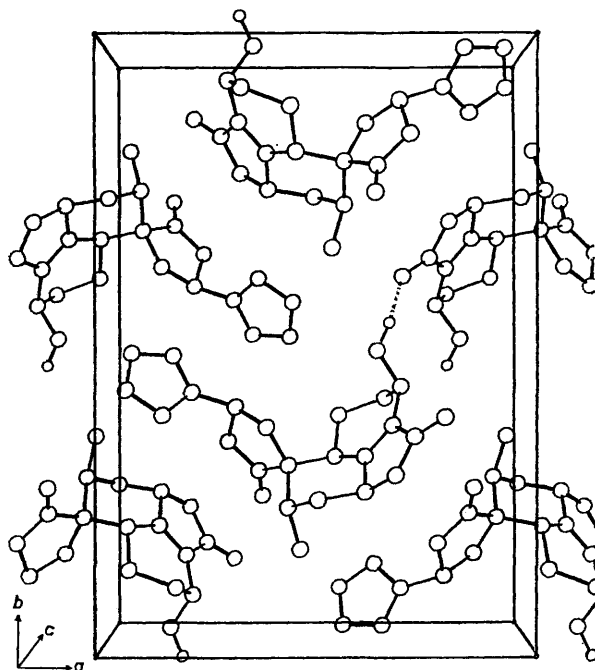
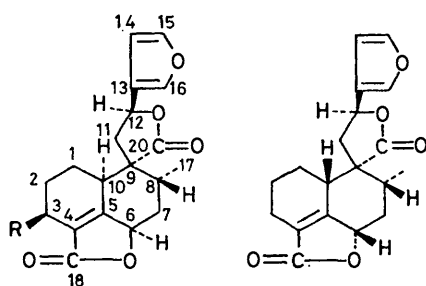


FIGURE 2

This led to the structure and relative stereochemistry shown in Figure 1. The contents of the unit cell are given in Figure 2. Ring A deviates from the preferred half-chair conformation of a cyclohexene whilst ring B is slightly distorted from the perfect chair. This is possibly due to the constraints imposed by the γ -lactone ring. The majority of the bond lengths are as would



(1) R = OH

(2) R = H

(3)

be expected. The apparently anomalous C-6-C-7 bond length is probably due to the distortion of ring B. The only relatively short intermolecular contact is that involving O-1 and O-3 with a separation of 2.78 Å. Figure 2 shows that the molecules are linked by hydrogen bonds O-3-H-16...O-1.

The sign of the circular dichroism curve associated

with the $\alpha\beta$ -unsaturated lactone has been taken³ as evidence for the absolute stereochemistry of this series. Teuffidin showed the same sign and magnitude of c.d. curve as teucvidin and hence it was assigned the same absolute stereochemistry. An interesting biosynthetic

TABLE 2

Final position parameters ($\times 10^4$) with estimated standard deviations in parentheses in the units of the last significant figure

(a) Non-hydrogen atoms

	<i>x</i>	<i>y</i>	<i>z</i>
C(1)	0 553(4)	1 211(3)	5 959(9)
C(2)	1 671(4)	0 918(3)	5 943(10)
C(3)	2 007(4)	0 704(3)	3 966(9)
C(4)	1 796(4)	1 332(3)	2 729(8)
C(5)	1 145(4)	1 862(3)	3 106(8)
C(6)	1 129(4)	2 410(3)	1 598(9)
C(7)	0 042(5)	2 515(4)	0 933(9)
C(8)	-0 663(4)	2 693(3)	2 613(11)
C(9)	-0 657(4)	2 028(3)	3 986(9)
C(10)	0 447(4)	1 895(3)	4 731(9)
C(11)	-1 164(4)	1 369(3)	3 006(9)
C(12)	-1 926(5)	1 046(4)	4 434(10)
C(13)	-2 938(5)	0 799(4)	3 655(10)
C(14)	-3 576(6)	1 163(4)	2 384(12)
C(15)	-4 424(6)	0 744(5)	2 149(15)
C(16)	-3 402(7)	0 185(4)	4 133(13)
C(17)	-0 379(5)	3 419(3)	3 484(11)
C(18)	2 254(5)	1 487(4)	0 896(10)
C(20)	-1 388(5)	2 152(4)	5 643(11)
O(1)	2 917(4)	1 163(2)	0 035(6)
O(2)	1 807(3)	2 095(2)	0 205(6)
O(3)	1 432(3)	0 101(2)	3 260(7)
O(4)	-1 316(3)	2 616(3)	6 791(7)
O(5)	-2 129(4)	1 650(3)	5 738(8)
O(6)	-4 343(5)	0 141(3)	3 189(10)

(b) Proposed co-ordinates ($\times 10^4$) of the hydrogen atoms

	<i>x</i>	<i>y</i>	<i>z</i>	Bonded to
H(1)	0 374	3 410	4 072	C(17)
H(2)	0 471	2 384	5 528	C(10)
H(3)	2 825	0 571	4 144	C(3)
H(4)	-1 417	2 749	2 275	C(8)
H(5)	-0 796	3 819	3 851	C(17)
H(6)	1 578	2 857	2 019	C(6)
H(7)	-0 265	2 031	0 126	C(7)
H(8)	-0 608	0 943	2 790	C(11)
H(9)	-0 163	2 842	0 048	C(7)
H(10)	0 033	0 792	5 529	C(1)
H(11)	-1 031	3 607	4 769	C(17)
H(12)	-1 434	0 609	5 182	C(12)
H(13)	-1 414	1 541	1 811	C(11)
H(14)	2 317	1 385	6 514	C(2)
H(15)	-3 553	1 780	1 778	C(14)
H(16)	1 737	-0 372	3 680	O(3)
H(17)	1 608	0 500	6 871	C(2)
H(18)	0 405	1 144	7 550	C(1)
H(19)	-3 467	-0 408	4 427	C(16)
H(20)	-5 227	0 799	1 510	C(15)

feature of the stereochemistry is that the 10α -hydrogen atom lies *cis* to C-20 implying that teuffidin cannot be derived directly by rearrangement of a *trans*-labdane.

EXPERIMENTAL

General experimental details have been described previously.⁵

Isolation of Teuffidin (1).—Dry leaves and twigs of

⁵ G. Savona, F. Piozzi, J. R. Hanson, and M. Siverns, *J.C.S. Perkin I*, 1976, 1607.

Teucrium flavum (collected and identified in the Botanic Gardens, Palermo) (700 g) were extracted with acetone for 1 week. The crude extract was concentrated, taken up in ethyl acetate, washed with water, dried, and the solvent evaporated. The residual gum was chromatographed on silica (Merck) deactivated with 15% water. Elution with petroleum gave plant waxes. Further elution with increasing concentrations of ethyl acetate in light petroleum

TABLE 3

Bond lengths (Å) and angles (°) in the molecule with estimated standard deviations in parentheses

(a) Bond lengths			
C(1)–C(2)	1.541(8)	C(20)–O(4)	1.192(9)
C(1)–C(10)	1.545(8)	C(20)–O(5)	1.333(8)
C(2)–C(3)	1.536(9)	C(18)–O(1)	1.213(8)
C(3)–C(4)	1.485(8)	C(18)–O(2)	1.357(8)
C(3)–O(3)	1.430(7)	C(1)–H(10)	1.069
C(4)–C(5)	1.318(7)	C(1)–H(18)	1.165
C(4)–C(18)	1.471(9)	C(2)–H(14)	1.267
C(5)–C(6)	1.483(8)	C(2)–H(17)	1.023
C(5)–C(10)	1.474(8)	C(3)–H(3)	1.092
C(6)–C(7)	1.494(8)	C(6)–H(6)	1.052
C(6)–O(2)	1.450(7)	C(7)–H(7)	1.136
C(7)–C(8)	1.547(10)	C(7)–H(9)	0.915
C(8)–C(9)	1.575(9)	C(8)–H(4)	1.008
C(8)–C(17)	1.523(10)	C(10)–H(2)	1.070
C(9)–C(10)	1.542(8)	C(11)–H(8)	1.075
C(9)–C(11)	1.550(9)	C(11)–H(13)	0.970
C(9)–C(20)	1.535(9)	C(12)–H(12)	1.158
C(11)–C(12)	1.540(9)	C(14)–H(15)	1.220
C(12)–C(13)	1.492(9)	C(15)–H(20)	1.138
C(12)–O(5)	1.480(9)	C(16)–H(19)	1.118
C(13)–C(14)	1.400(10)	C(17)–H(1)	1.059
C(13)–C(16)	1.326(11)	C(17)–H(5)	0.951
C(14)–C(15)	1.350(11)	C(17)–H(11)	1.296
C(15)–O(6)	1.344(12)	O(3)–H(16)	1.004
C(16)–O(6)	1.394(11)		
(b) Bond angles			
C(2)–C(1)–C(10)	111.4(5)	C(11)–C(9)–C(20)	102.1(5)
C(1)–C(2)–C(3)	111.2(5)	C(1)–C(10)–C(5)	111.4(4)
C(2)–C(3)–C(4)	107.5(5)	C(1)–C(10)–C(9)	114.2(4)
C(2)–C(3)–O(3)	112.4(5)	C(5)–C(10)–C(9)	107.2(5)
O(3)–C(3)–C(4)	107.5(5)	C(9)–C(11)–C(12)	105.7(5)
C(3)–C(4)–C(5)	125.0(5)	C(11)–C(12)–C(13)	115.3(6)
C(3)–C(4)–C(18)	127.8(5)	C(11)–C(12)–O(5)	104.0(5)
C(5)–C(4)–C(18)	107.2(5)	C(13)–C(12)–O(5)	108.2(5)
C(4)–C(5)–C(6)	111.4(5)	C(12)–C(13)–C(14)	127.8(6)
C(4)–C(5)–C(10)	125.6(5)	C(12)–C(13)–C(16)	123.9(7)
C(6)–C(5)–C(10)	122.8(5)	C(14)–C(13)–C(16)	108.2(6)
C(5)–C(6)–C(7)	109.6(5)	C(13)–C(14)–C(15)	106.5(7)
C(5)–C(6)–O(2)	102.8(4)	C(14)–C(15)–O(6)	109.9(8)
C(7)–C(6)–O(2)	113.4(5)	C(13)–C(16)–O(6)	108.5(7)
C(6)–C(7)–C(8)	109.3(5)	C(9)–C(20)–O(4)	126.5(6)
C(7)–C(8)–C(9)	108.7(5)	C(9)–C(20)–O(5)	112.1(6)
C(7)–C(8)–C(17)	111.4(6)	O(4)–C(20)–O(5)	121.3(7)
C(9)–C(8)–C(17)	115.3(6)	C(4)–C(18)–O(1)	130.1(6)
C(8)–C(9)–C(10)	110.2(5)	C(4)–C(18)–O(2)	108.5(5)
C(8)–C(9)–C(11)	109.0(5)	O(1)–C(18)–O(2)	121.4(6)
C(10)–C(9)–C(11)	115.0(5)	C(6)–O(2)–C(18)	109.7(5)
C(8)–C(9)–C(20)	111.4(5)	C(12)–O(5)–C(17)	111.4(5)
C(10)–C(9)–C(20)	108.9(5)	C(15)–O(6)–C(16)	106.9(6)

gave *teuflidin* (400 mg) which crystallized from ethyl acetate–light petroleum as prisms, m.p. 178 °C, $[\alpha]_D^{20}$ –100° (*c* 0.24) (Found: C, 66.3; H, 5.7. $C_{19}H_{20}O_6$ requires C, 66.3; H, 5.8%), ν_{max} 3 450, 1 770, 1 755, 1 700sh, 1 600, 875, and 800 cm^{-1} ; m/e 344 (M^+), 326, 308, 298, 232, 222, 178, 135, 105, 95, 94, 81, and 77; c.d. (0) (in dioxan) 260 (0), 225 (–58 150), 210 (0), and 205 nm (+23 100).

* 'International Tables for X-ray Crystallography,' Kynoch Press, Birmingham, 1962, vol. 1.

⁷ G. Germain and M. M. Woolfson, *Acta Cryst.*, 1968, **B24**, 91.

⁸ J. Karle, *Acta Cryst.*, 1968, **B24**, 182.

Crystal Data.— $C_{19}H_{20}O_6$, $M = 344.3$, Orthorhombic, $a = 12.905(3)$, $b = 18.455(6)$, $c = 7.180(2)$ Å, $U = 1 710.0$ Å³, $Z = 4$, $D_c = 1.337$ g cm^{-3} , $F(000) = 728$. Mo- K_α radiation $\lambda = 0.709 26$ Å, $\mu(Mo-K_\alpha) = 0.8$ cm^{-1} . Space group $P2_12_12_1$ (No. 19)⁶ from the systematic absences $0k0$ for k odd, $h00$ for h odd, $00l$ for l odd.

Crystallographic Measurements.—A colourless crystal of dimensions $0.45 \times 0.15 \times 0.1$ mm was used for data collection. Preliminary cell dimensions were derived from oscillation and Weissenberg films. Intensity data were measured on a Hilger and Watts four-circle diffractometer. Accurate cell dimensions were calculated by least-squares treatment of setting angles for 12 reflections. Diffraction data were collected by an $\omega/2\theta$ step scan for the positive octant hkl in two consecutive shells, $\theta = 2$ – 22° and 22 – 25° with Mo- K_α radiation (graphite monochromator). Each reflection was measured in 56 steps of 0.5 s each and background counts of 14 s were made at the end of each scan. After every 100 reflections, three standard reflections were remeasured and these remained constant over the data collection. The usual corrections for Lorentz and polarization factors were applied but no correction was made for absorption. Those intensities with $I > 2\sigma(I)$ based on counting statistics, were classified as significant. After averaging of equivalent reflections, there were 1 086 significant reflections out of a total of 1 781 measured.

Structure Determination.—All data were converted to normalized structure factors ($|E|$) and phases were derived by multiple-start tangent formula procedures⁷ using the 306 reflections with $|E| > 1.20$. A subsequent E -map revealed a five-membered ring and three other atoms judged to be chemically reasonable. Rough atom positions for 8 non-hydrogen atoms taken as carbon atoms were thus obtained. The remaining non-hydrogen atoms were found by tangent refinement of partial structures⁸ using the 8 atom positions to obtain the best 30 phases. The atom positions with anisotropic temperature factors were refined by full matrix least-squares using the 1 086 significant reflections with unit weight. Ambiguities between oxygen and carbon atoms were resolved on the basis of temperature factors and bond lengths. Two successive difference-Fourier maps gave the positions of the 20 hydrogen atoms. Each hydrogen atom was given the isotropic temperature factor of the carbon atom to which it is bonded. A few cycles of least-squares refinement of all non-hydrogen atoms with anisotropic temperature factors and a weighting scheme defined as $\omega = K/[\sigma^2(F) + 0.001(F)^2]$ where K is a scale constant, gave convergence at a residual $R_F = 0.059$ and $R_{\omega F} = 0.06$ when the ratio of shift to e.s.d. for any non-hydrogen parameter was everywhere less than 0.10. A further refinement including hydrogen atom parameters did not show a significant reduction in $R_{\omega F}$ based on Hamilton's⁹ R -factor test and was rejected. A final difference-Fourier map was everywhere less than 0.23 eÅ⁻³.

Initial data processing was done with local programs. Data were then converted into a format suitable for the SHELX program system of G. M. Sheldrick. Scattering factors for C, O, and H atoms were taken from ref. 10 and no allowance was made for anomalous scattering. Final atom co-ordinates are listed in Table 2. The final structure factors together with the torsion angles and thermal para-

⁹ W. C. Hamilton, *Acta Cryst.*, 1965, **18**, 502.

¹⁰ D. T. Cromer and J. B. Mann, *Acta Cryst.*, 1968, **A24**, 321; R. F. Stewart, E. R. Davidson, and W. T. Simpson, *J. Chem. Phys.*, 1965, **42**, 3175.

meters are listed in the supplementary publication (SUP No. 22304, 11 pp.).*

We thank Mr. M. Sivers for the determination of the n.m.r. spectra and Professor D. N. Kirk for the c.d. measurement. We thank Dr. B. M. Fraga for a gift of teucvidin and Professor E. Fujita for teucvin. We thank N.A.T.O.

and the National Research Council (C.N.R.), Roma, for financial support.

* For details of the supplementary publications scheme see Notice to Authors No. 7, *J.C.S. Perkin I*, 1977, Index issue.

[7/2093 Received, 29th November, 1977]
