

TERPENOIDS—XXXIV¹

TEUCVIDIN, A MINOR NORDITERPENE FROM *TEUCRIUM VISCIDUM* VAR. *MIQUELIANUM*

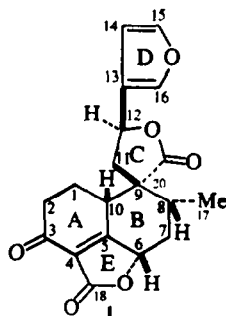
I. UCHIDA, T. FUJITA and E. FUJITA*

Institute for Chemical Research, Kyoto University, Uji, Kyoto-Fu 611, Japan

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Abstract—The structure and stereochemistry of teucvidin, a novel minor norditerpene isolated from *Teucrium viscidum* var. *Miquelianum*, has been determined and is represented by formula 5, on the basis of spectroscopic evidence and X-ray analysis. The INDOR spectroscopy proved very useful and its application is discussed in detail.

RECENTLY, we reported the isolation of a norditerpene, teucvin, from *Teucrium viscidum* Blume var. *Miquelianum* (Maxim.) Hara (Labiatae) and its structural elucidation which established structure 1 including absolute configuration.² Recently, we isolated a minor component which was named teucvidin. The physical data of teucvidin are very similar to those of teucvin except m.p. and the specific rotation, as shown in Table 1.



The presence of a teucvin-like furan ring system attached to a γ -lactone in the molecule was anticipated from the NMR, IR and Mass spectral data in addition to a positive Ehrlich test.³ Furthermore, an α,β -unsaturated γ -lactone and a secondary Me group were anticipated on the basis of UV spectrum, a positive Baljet's color reaction⁴ and NMR data. Thus, teucvidin seemed very likely to have the same planar structure as teucvin and to be a stereoisomer of the latter. Under this assumption, the 6-H and 10-H were reasonably assigned. In teucvin, the 11 H₂ were observed as the A₂ part of an A₂X type in its NMR spectrum. On the other hand, it was clarified by the INDOR experiment⁵ that the 11 H₂ of teucvidin appeared as the M and X parts of an AMX type resonance. Thus, as shown in Fig. 1, when each line of the 12-H triplet signal at δ 5.35 was monitored, two sets of INDOR signals, which may be ascribed to 11-methylene protons, appeared at ca. δ 2.60 and 1.91. This fact showed that only two protons

Table 1. Comparison of physical data of teucvidin with those of teucvin

	Teucvidin	Teucvin
Molecular formula	C ₁₉ H ₂₀ O ₅	C ₁₉ H ₂₀ O ₅
m.p.	214°	207–208°
[α] _D ²⁵ (CHCl ₃)	–70.0°	+184°
UV λ_{max} (MeOH)	217 nm (ϵ 17600)	217 nm (ϵ 17300)
IR $\nu_{max}^{CHCl_3}$ cm ⁻¹	1755, 1690, 1600, 1505, 875	1755, 1690, 1600, 1505, 875
Mass, m/e	81.034, 94.042	81.032, 94.042
NMR (δ_{CDCl_3})	(δ_{CDCl_3})	(δ_{CDCl_3})
furan α H \times 2	7.34 (m)	7.43 (m)
furan β H	6.36 (m)	6.36 (m)
12-H	5.35 (t, J8)	5.43 (t, J8.5)
6-H	5.00 br (q, J10,7)	4.74 br (t, J8.5)
10-H	3.24 (m)	2.68 (m)
11-H \times 2	2.60 (q, J14,8)	2.54 (d, J8.5)
sec. Me	1.91 (q, J14,8)	1.05 (d, J6.5)

giving quartets at δ 2.60 and 1.91 was coupled to 12-H and these three protons constituted an AMX system. The detailed data of the INDOR signal are shown in Table 2, and the coupling pattern of these protons is depicted in Fig. 2. In the AMX type resonance, in which M and X are geminal CH₂ protons and A is located in an adjacent C atom, it is assumed that J_{AM} and J_{AX} are larger than 0 and J_{AX} is smaller than 0. Under this assumption together with |J_{MX}| > J_{AM} = J_{AX} > 0 and J_{MX} < 0, the energy level diagram was prepared. This is shown in Fig. 3.

Now, comparison of this energy level diagram with Table 2 indicated an obvious consistency between them. When A₁ is monitor line, Fig. 3 shows that the transitions M₊ and X₋ connect with the transition A₁ progressively, while M₋ and X₊ with A₁ regressively. Accordingly, M₊ and X₋ should give positive INDOR signals, while M₋ and X₊ negative. In fact, the observed spectrum (Table 2) coincided completely with these considerations from the energy level diagram. Thus, the above assumptions of M

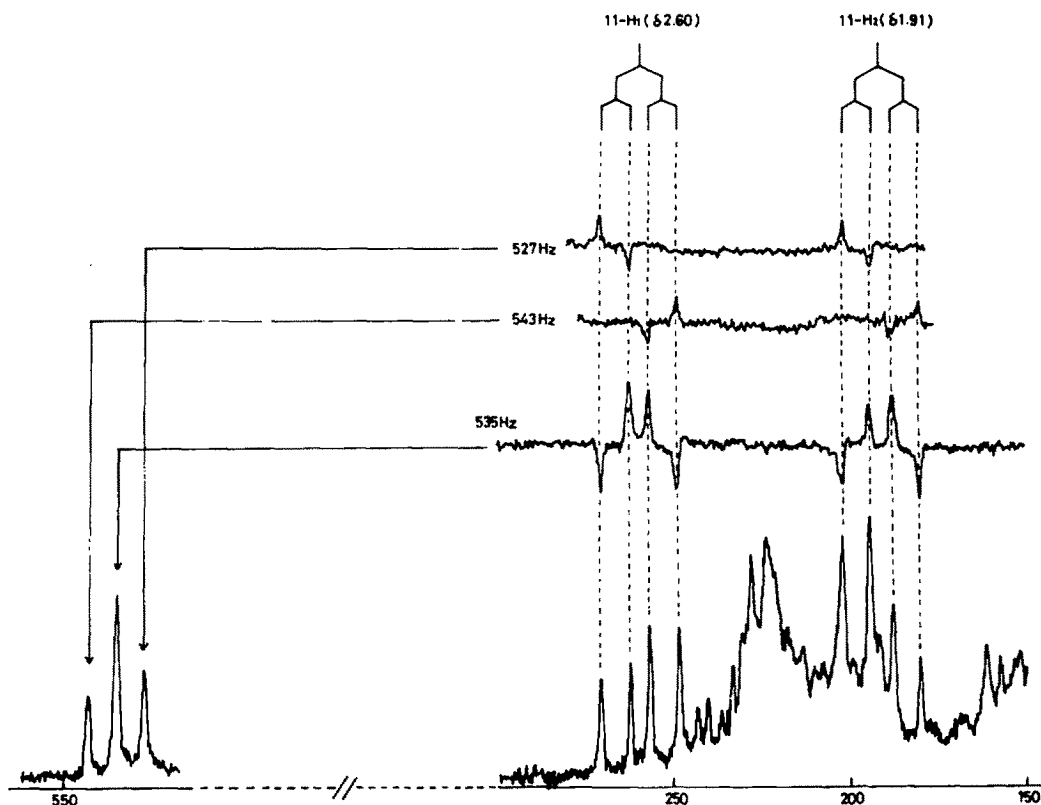


Fig. 1. INDOR spectra obtained by monitoring each transition of 12-H.

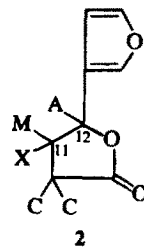
Table 2. Frequencies* (in Hz at 100 MHz) of individual lines of 11-H¹ and 11-H² obtained by INDOR on 12-H

12-H monitor lines (Hz)	observed INDOR lines of 11-H ¹				observed INDOR lines of 11-H ²			
543 (A ₁)			↓ 256.9	↓ 248.2			↓ 187.7	↑ 179.8
535 (A ₂)	↓ 271.4	↑ 263.4	↑ 257.6	↓ 250.0	↓ 202.8	↑ 194.9	↑ 188.7	↓ 181.0
527 (A ₃)	↑ 270.6	↓ 262.4			↑ 201.5	↓ 193.5		
averaged frequencies symbol	271.0 M ₁	262.9 M ₂	257.3 M ₃	249.1 M ₄	202.2 X ₁	194.2 X ₂	188.2 X ₃	180.4 X ₄

* ↑ denotes a positive INDOR signal, ↓ a negative signal.

and X to be geminal CH₂ protons and of A to be only one proton on an adjacent carbon atom were proved to be correct, and the presence of a partial structure 2 was confirmed.

As shown in Table 1, the 10-H signal of teucvidin was observed at the lower field (δ 3.24) than that of teucvin (δ 2.68), and also the secondary Me signal of teucvidin at the lower field (δ 1.35) than the corresponding 17-Me signal of teucvin (δ 1.05). These paramagnetic shifts in teucvidin can be explained by a stereochemistry assumed in Fig. 4.



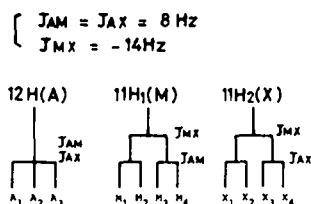
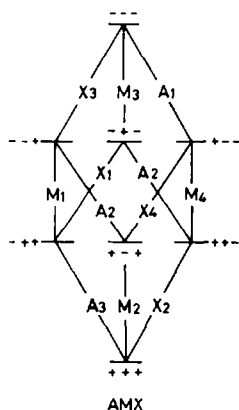
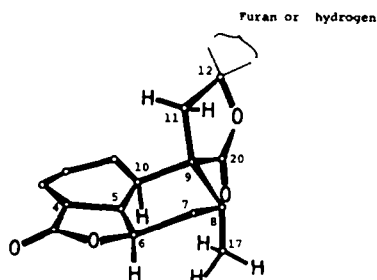
Fig. 2. The signal patterns of 12-H, 11-H¹ and 11-H².Fig. 3. Schematic energy level diagram for an AMX system: $|J_{MX}| > J_{AM} = J_{AX} > 0, J_{MX} < 0$.

Fig. 4. A presumed stereomodel of teucvidin.

In this structure, the 20-CO oxygen in the γ -lactone is in the 1,3-diaxial relationship with the 10-H and the 17-Me, and the 10-H is expected to be present nearer to the 20-CO plane than the 17-Me, because of a larger interaction of the 17-Me group with the 20-CO group. Actually, the 17-Me group may not be subject to the paramagnetic effect of the 20-CO group. Thus, the larger paramagnetic shift of 10-H is rationalized. The paramagnetic shift of the 17-Me protons, however, may rather be attributed to the paramagnetic effect of the double bond between C-4 and C-5, because they are nearly on the plane of the double bond.

Irradiation at 17-Me (δ 1.35), showed 9.8% and 10.7% of NOE at 6-H and 10-H, respectively, which supported the 1,3-diaxial relationships of the 17-Me, 6-H, and 10-H. Irradiation at 10-H (δ 3.24) showed only 4.3% of NOE at 6-H. The low increment may be ascribed to a rather long

distance between two protons because of a distortion of the ring B from a chair form by the influence of the α, β -unsaturated γ -lactone. No NOE was observed between 11-CH₂ protons and 17-Me protons, which supported the structure having *anti* relation between 8-17 and 9-11 bonds regarding the 8-9 bond, as shown in Fig. 4.

Subsequently, the INDOR experiments monitoring three lines (498, 508, and 490 Hz) of the broad quartet resonance at δ 5.00 ascribed to 6-H were carried out. The spectra are shown in Fig. 5.

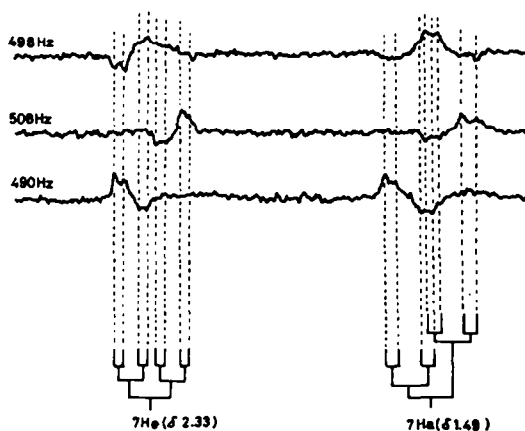


Fig. 5. INDOR spectra of 7-He and 7-Ha using three transitions, 498Hz, 508Hz and 490Hz, of 6-H as monitor lines.

Although the spectra are not very sharp because of the difficulty for setting the monitor lines of the broad 6-H signal which contains the long range couplings with protons other than 7H₂, the INDOR signal is little influenced by the protons having long range couplings with the monitor proton (6-H), since the extent with which the lines of the former protons have energy levels in common with the monitor transitions is small. Thus, the observed two sets of signals at δ 2.33 and 1.49 can be regarded as 7-He (equatorial) and 7-Ha (axial) coupled with 6-H, respectively, and 6-H, 7-He, and 7-Ha can be grasped as a three spin system of AMX type for the result of INDOR spectra of Fig. 5. Figure 6 shows the coupling pattern of these protons, and the detailed data of the INDOR spectra are shown in Table 3.

Under the assumption of $J_{MX} < 0, J_{AM} > 0$, and $J_{AX} > 0$ based on the presumption that 7-He (M) and 7-Ha (X) vicinal to 6-H (A) are geminal methylene protons, an energy level diagram was prepared, provided that the couplings of 8-H with 7-He and 7-Ha were disregarded. In Fig. 7, the detailed procedure for preparation and the

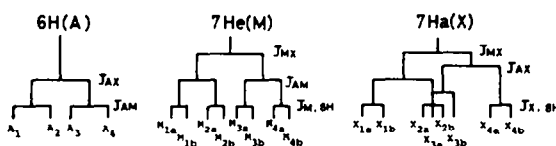


Fig. 6. The signal patterns of 6-H, 7-He and 7-Ha.

Table 3. Frequencies* (in Hz at 100 MHz) of individual lines of 7-He and 7-Ha obtained by INDOR on 6-H

6-H monitor lines (Hz)	observed INDOR lines of 7 He							
508 (A ₁)					↓ 231·5	↓ 228·5	↑ 224·4	↑ 221·5
498 (A ₂)	↓ 244·0	↓ 241·0	↑ 237·0	↑ 234·1				
490 (A ₄)	↑ 244·2	↑ 241·0	↓ 237·0	↓ 234·1				
averaged frequencies	244·1	241·0	237·0	234·1	231·5	228·5	224·4	221·5
symbol	M _{1a}	M _{1b}	M _{2a}	M _{2b}	M _{3a}	M _{3b}	M _{4a}	M _{4b}

6-H monitor lines (Hz)	observed INDOR lines of 7 H _a								
508 (A ₁)					↓ 149·2		↓ 145·2	↑ 138·4	↑ 134·3
498 (A ₂)					↑ 149·5		↑ 145·5	↓ 138·5	↓ 134·3
490 (A ₄)	↑ 161·9	↑ 158·0	↓ 151·2			↓ 147·3			
averaged frequencies	161·9	158·0	151·2		149·3	147·3	145·4	138·4	134·3
symbol	X _{1a}	X _{1b}	X _{2a}		X _{3a}	X _{2b}	X _{3b}	X _{4a}	X _{4b}

*See also footnotes of Table 2.

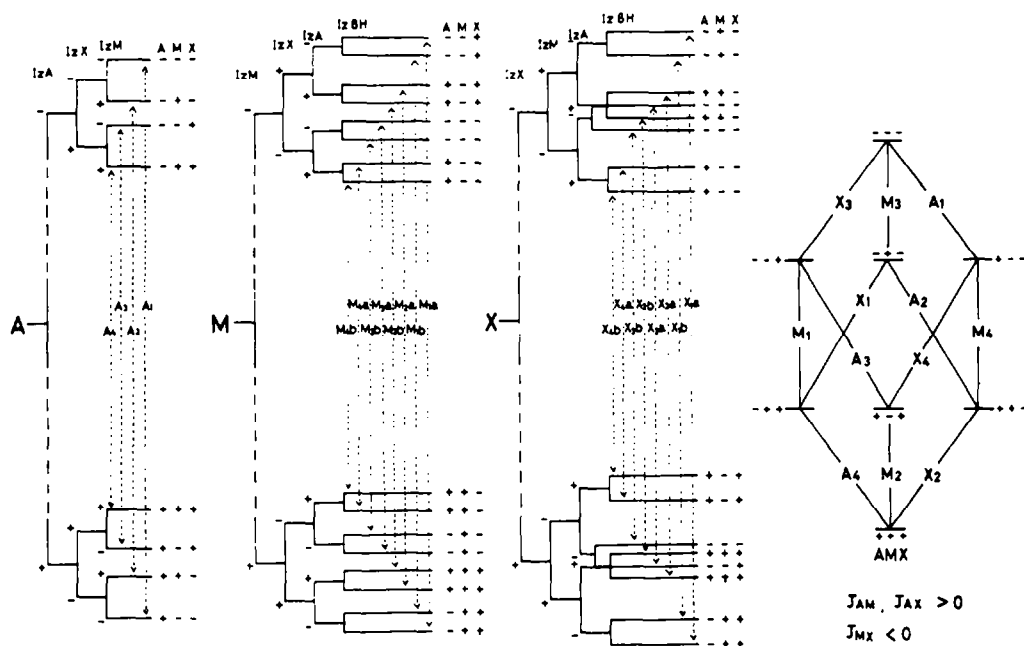


Fig. 7. Schematic energy level diagram for an AMX system; A: 6-H, M: 7-He, X: 7-Ha.

prepared diagram are shown. This diagram explains all the observed signs of INDOR spectra in Table 3. The assignment in Fig 6 was thus proved to be correct and the relative signs of the coupling constants were determined to be $J_{AM} > 0$, $J_{AX} > 0$, and $J_{MX} < 0$. The foregoing presumption of geminal methylene protons for M and X was also proved to be correct. Furthermore, another C

atom-8 adjacent to 7-methylene group was shown to be a tertiary carbon carrying an axial Me group. The coupling constants values obtained by these INDOR experiments are consistent with those estimated from the Dreiding model possessing the Newman projections shown in Fig. 8, which corresponds to a conformation of the structure shown in Fig. 4. As a result of the foregoing discussions,

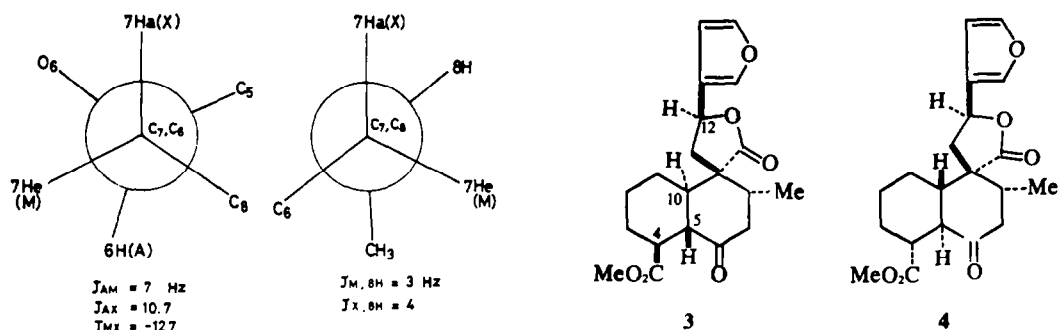


Fig. 8. Assumed conformations about 7-6 and 7-8 bonds shown by Newman projections.

teucvidin was clarified to have the structure shown in Fig. 4 or its antipodal structure, but the stereochemistry at C-12 remained unsolved.

Teucvidin on treatment with Na_2CO_3 in MeOH at reflux gave a keto-ester, $\text{C}_{20}\text{H}_{24}\text{O}_6$. The mechanism of this ester exchange reaction must be similar with that of the conversion of teucvin (1) to methyl teucvate (4).² Thus, the structure and relative configuration of methyl teucvidinate, the keto-ester derived from teucvidin, can be predicted as formula 3 except the stereochemistry of C-12.

In the NMR spectrum of compound 3 the 17-Me protons signal was observed at δ 1.10, while the corresponding signal at δ 1.35 in teucvidin. The paramagnetic shift in the latter was rationalized by the anisotropic effect of the double bond at C-4. In the compound 4, both 5-H and 7 α -H is subject to the anisotropic effect of the lactone CO group and their NMR signals were observed at δ 3.34 and 3.18, respectively.² On the other hand, in the NMR spectrum of 3 all of the protons at C-5 and C-7 were not observed at lower field

than δ 2.70. Thus, the compound 3 has a stereochemistry in which those protons are not subject to the magnetic anisotropic effect due to the γ -lactone CO group. A spectrum recorded under addition of a shift reagent, europium dipivalomethanate (EuDPM), in a ratio of 0.1 to methyl teucvate 4 showed larger shifts of 4-H and 5-H than 7 H₂. (Table 4) These observations suggested a close coordination of the metal (Eu) to both oxygen functional groups of the 4-methoxycarbonyl group and the 6-oxo group. In the spectrum recorded under addition of EuDPM in a ratio of 0.5 to methyl teucvidinate 3, a triplet of doublets at δ 4.04 and a triplet at δ 4.51 were observed, which were assigned to 4-H and 5-H, respectively, and 1,2-*trans* diaxial relationships of 5-H to 4-H and 10-H were recognized from their coupling constants (Table 4). Thus, the assignment of structure 3 including relative stereochemistry except C-12 to methyl teucvidinate was rationalized.

The remaining question, the stereochemistry of C-12, was solved by the X-ray analysis of teucvidin itself,⁶ which confirmed the structure including the relative configuration of teucvidin and methyl teucvidinate as 5 and 3, respectively.

Table 4. NMR spectral data of 4 and 3 under the addition of a reagent EuDPM

4	4 + EuDPM		
	1:0.1	$\frac{[(4)]}{[\text{EuDPM}]} \times \Delta\text{Eu}$ (ppm)	
4-H (β , ax.)	< δ 2.50 ²	δ 3.16(t.d, J11, 4)	> 6.6
5-H (d, ax.)	δ 3.34 (t, J11) ²	δ 3.88	5.4
7-H α (ax)	δ 3.18 (t.d, J13, 1) ²	δ 3.51	3.3
7-H β (eq)	δ 2.26 (q, J13, 4.5) ²	δ 2.50	2.4
-COOCH ₃	δ 3.66 (s) ²	δ 3.98	3.2
3	3 + EuDPM		
	1:1.05	$\frac{[(3)]}{[\text{EuDPM}]} \times \Delta\text{Eu}$ (ppm)	
4-H (ax.)	< δ 2.70	δ 4.40 (t.d, J11, 4)	> 2.68
5-H (ax.)	< δ 2.70	δ 4.51 (t, J11)	> 3.62
7-H ₁ (ax.)	< δ 2.70	< δ 3.25	
7-H ₂ (eq.)	< δ 2.70	< δ 3.25	
-COOCH ₃	δ 3.66 (s.)	δ 4.93	2.54

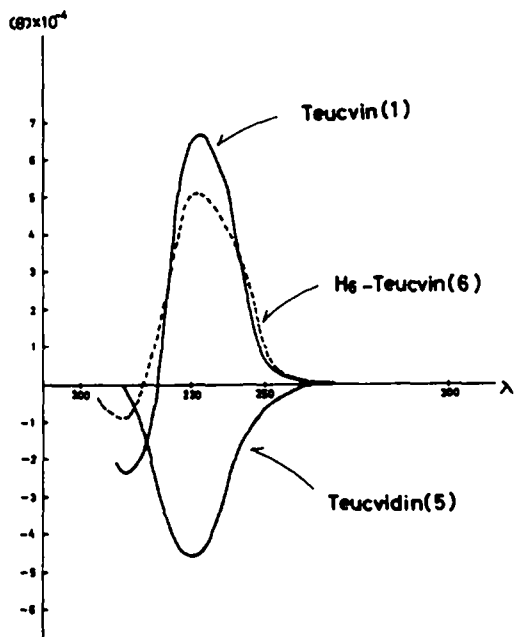
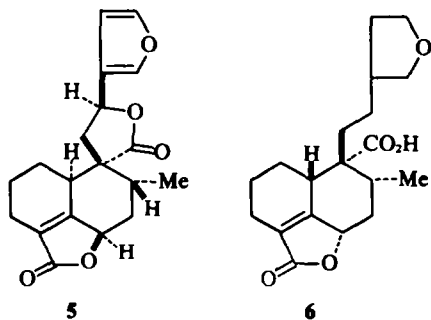


Fig. 9. CD curves of teucvin (1), teucvidin (5), and hexahydroteucvin (6).

The final problem is the absolute configuration. We concluded the absolute stereochemistry of teucvidin and methyl teucvidinate as 5 and 3, respectively, by the following investigations. The CD spectra of teucvin and teucvidin in dioxan had Cotton effects with opposite signs and nearly same intensities at about 230 nm (Fig. 9). The spectrum of hexahydroteucvin (6) derived from teucvin was also shown to have the +Cotton effect at about 230 nm like teucvin. Thus, the Cotton effects observed should be attributed to the chromophore of the α,β -unsaturated γ -lactone.



According to Snatzke *et al.*⁷ and Beecham,⁸ the sign of the Cotton effect at about 250 nm⁸ due to $n \rightarrow \pi^*$ transition of the α,β -unsaturated lactones was proposed to depend on the chirality formed by twist between two double bonds. The result of the X-ray analysis, however, indicated that the ring atoms of the butenolide in teucvidin were coplanar. Actually, the torsion angle C(4)-C(5)-C(18)-O(18) was 179.1°, that is, nearly equal to 180°. The

Cotton effects at about 230 nm in Fig. 9, therefore, may be due not to the $n \rightarrow \pi^*$ transition but to the $\pi \rightarrow \pi^*$ transition.⁹

Anyway, the observed Cotton effects were available for determination of the absolute configuration of teucvidin. As shown in Fig. 9, the CD curve of teucvidin was almost symmetrical to the curves of teucvin (1) and hexahydroteucvin (6), which suggested the antipodal relationship of the A, B and E rings system between teucvidin and teucvin (1) or hexahydroteucvin (6). This consideration is, however, based on the assumption that the conformation of the A, B and E rings system of these compounds is the same. The conformation of teucvidin molecule has been clarified by the X-ray analysis⁶ and the foregoing NMR studies, whereas that of teucvin (1) has not yet been known. Investigation on the flexibility of the molecule using the Dreiding model of teucvin (1) led to a limited problem whether the ring B is the chair form or the boat form, which must influence the CD spectrum of teucvin. The prediction that the ring B is not in a boat form (Fig. 10. T-B), but in a chair form (Fig. 10. T-A) may be

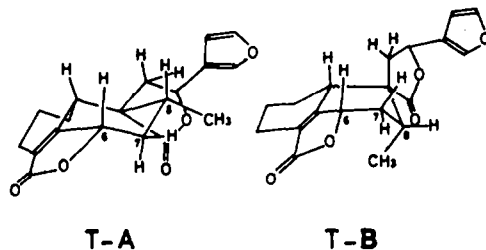
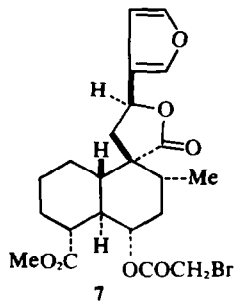


Fig. 10. Presumed stereomodels of teucvin; T-A: ring B is chair type, T-B: ring B is boat type.

provided from the following discussions. (i) In a chair form of the ring B (T-A), the 17-Me group has an equatorial conformation, and the molecule should be more stable than teucvidin. (ii) An X-ray analysis² of methyl dihydroteucvate O-bromoacetate (7) indicated that the ring B took a chair form in spite of some interaction of the furan ring and the 17-Me group. (iii) In a boat form of the ring B (T-B), the substituents at C-6 and C-7 and at C-9 and C-10 are all in eclipsed conformations.

The confirmation of the prediction was carried out by NMR investigations. The INDOR signals were observed between δ 2 and 2.45 which were ascribed to the 7-CH₂



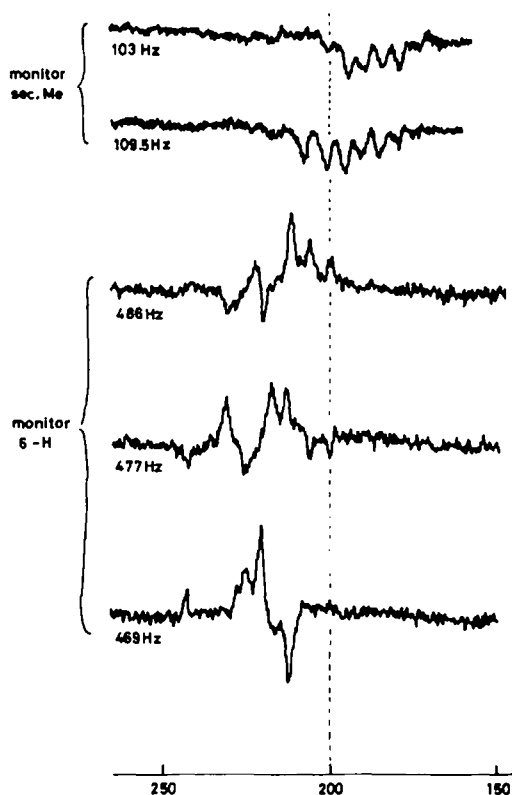


Fig. 11. INDO spectra obtained monitoring each transitions of C(17)-3H and of C(6)-H.

protons as shown in Fig. 11, when three lines (469, 477, and 486 Hz) of 6-H triplet (δ 4.74, $J = 8.5$ Hz) were used as the monitor lines. It was shown that 7-H α , 7-H β and 6-H gave an ABX type resonance. In this system, the following equation is available: $J_{6H,7H\alpha} + J_{6H,7H\beta} = 8.5 \times 2 = 17$ Hz.¹⁰ The T-B conformation is not suitable for teucvin, because $J_{6H,7H\alpha}$ is nearly 0 and $J_{6H,7H\alpha} + J_{6H,7H\beta}$ is smaller than 17 Hz. On the other hand, the T-A conformation is compatible with the observed coupling constants. The INDO signals at 210–180 Hz obtained when two lines (103 Hz and 109.5 Hz) of 17-Me doublet at δ 1.05 were used as monitors were also shown in Fig. 11. These signals were assigned to 8-H.

Analyses of the coupling constants for each INDO spectrum in Fig. 11 are difficult because of their complexity, but it is recognizable that the chemical shifts of 7-H α and 7-H β are separate from that of 8-H. Successive irradiations by 5 Hz at 180–230 Hz gave the respective NOE increments of 6-H. As shown in Fig. 12, one peak of 10% at 195–200 Hz was recognized. This corresponds to the center of 8-H which was found by the INDO spectrum. Another peak at 215 Hz which showed the maximum NOE (19.2%) should be ascribed to 7-H β .

*The 10-H and 11-CH₂ protons should give NOE to 6-H, but their chemical shifts are δ 2.68 and 2.54, respectively, and separate from the region of this experiment.

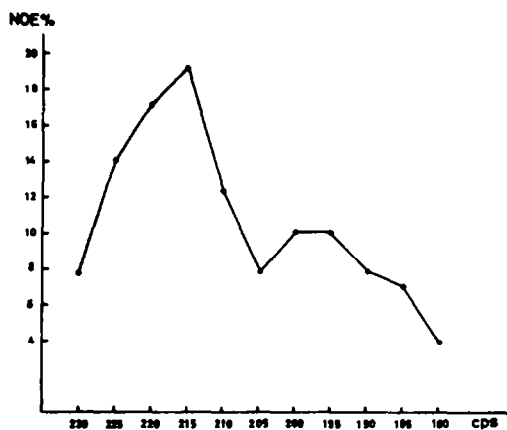


Fig. 12. NOE(%) of 6-H for the irradiated frequencies (100MHz).

These facts can be explained reasonably only by the T-A conformation.*

Thus, the ring B of teucvin was proved to be present as a chair form, and the conformation of the A, B, and E rings system to be nearly equal to that of teucvidin. The absolute structure of teucvin was, therefore, determined to be *ent*-10S-15, 16-epoxy-19-norcleroda-4,13(16),14-triene-18,6S:20,12R-diolactone (5), that is, a diastereoisomer of teucvin (1) at C-6 and C-10.

EXPERIMENTAL

M.p. was taken on a micro hot-stage and is uncorrected. The instruments used for spectral data are Hitachi model EPI-S₂ spectrometer (IR), Hitachi model EPS-3 spectrophotometer (UV), Varian Associates HA-100 spectrometer (NMR, TMS as internal standard), JEOL JMS OI SG High Resolution mass spectrometer (mass spectra), and JASCO Model ORD/CD-6 (CD). Specific rotation was measured by a JASCO DIP-180 automatic polarimeter.

Isolation of teucvin (1) and teucvidin (5). From dried plant material (3 kg) of *Teucrium viscidum* Blume var. *Miquelianum* (Maxim.) Hara, 1 (2 g) was isolated by the previously reported procedure.⁷ The mother liquors from recrystallization of teucvin from MeOH were combined and evaporation of the solvent left a residue, which was chromatographed on a silica gel column to isolate another crystalline compound (120 mg). Its recrystallization from MeOH yielded pure 5 (100 mg), m.p. 214°, $[\alpha]_D^{25} - 70.0^\circ$ (C = 0.23, CHCl₃); UV: λ_{max}^{MeOH} 217 nm (ϵ 17300); IR: $\nu_{max}^{CHCl_3}$ cm⁻¹ 1755, 1690, 1600, 1505, and 875. NMR: δ (CDCl₃) 7.43 (2H, m), 6.36 (1H, m), 5.35 (1H, t, $J = 8$ Hz, 12-H), 5.00 br (1H, q, $J = 10$ and 7 Hz, 6-H), 3.24 br (1H, m), 2.60 (1H, q, $J = 14$ and 8 Hz, 11-H'), 1.91 (1H, q, $J = 14$ and 8 Hz, 11-H²), and 1.35 (3H, d, $J = 7$ Hz, 17-Me). CD (c 0.142 in dioxan): $[\theta]_{270}^0$, $[\theta]_{230}^0 = 45800$, $[\theta]_{211}^0$, 0. (Found: C, 69.54; H, 6.23; M⁺, m/e 328-131. C₁₉H₂₀O₅ requires: C, 69.50; H, 6.14; M, 328.131). Teucvin (1) CD (c 0.128 in dioxan): $[\theta]_{280}^0$, $[\theta]_{233}^0 + 66800$, $[\theta]_{221}^0$, 0, $[\theta]_{213}^0 - 23700$, $[\theta]_{210}^0 - 21000$.

Preparation of keto ester 3 from teucvidin (5). Teucvidin (50 mg) was added in MeOH (5 ml) and the mixture was refluxed for 11 hr after the addition of Na₂CO₃ (50 mg). After filtration, the filtrate was neutralized with 1% HCl, and extracted with CHCl₃. Usual treatment of the extract gave a crude material (45 mg) which was chromatographed on a silica gel column (C₆H₆:MeOH = 9:1) to separate an amorphous product (27 mg) from teucvidin (11 mg). The product was proved to be 3 on the

basis of the following data. IR: $\nu_{\text{max}}^{\text{CHCl}_3}$ cm^{-1} 1760, 1725, 1715, 1600, 1505, and 875. NMR: δ (CDCl_3) 7.42 (2H, m), 6.36 (1H, m), 5.43 (1H, q, $J = 9$ and 7 Hz, 12-H), 3.66 (3H, s, COOMe), 3.11 (1H, q, $J = 14$ and 9 Hz, 11-H¹), 2.29 (1H, q, $J = 14$ and 7 Hz, 11-H²), and 1.10 (3H, d, $J = 7$ Hz, 17-Me). CD (c 0.833 in dioxan): $[\theta]_{320}^{\text{O}}$, $[\theta]_{290}^{\text{O}}$ -990, $[\theta]_{290}^{\text{O}}$ -1020, $[\theta]_{257.5}^{\text{O}}$ -180, $[\theta]_{222.5}^{\text{O}}$ -7200, $[\theta]_{210}^{\text{O}}$ -5600. (Found: M^+ , m/e 360.156. $\text{C}_{20}\text{H}_{24}\text{O}_6$ requires: M , 360.157).

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