Terpenoids. Part XXXII.[1] Structure and Stereochemistry of Teucvin, a Novel Norclerodane-type Diterpene from *Teucrium viscidum var. Miquelianum*

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On the basis of the results of an *X*-ray analysis on a bromine-containing derivative (5) and some chemical reactions on teucvin and its derivatives, the absolute structure of the natural product has been determined to be *ent*-(6*R*.12*R*)-15,16-epoxy-19-nor-9,4-friedolabda-4,13(16),14-triene-18,6:20,12-diolactone (2).

Our investigation on diterpenoids of Labiatae has been extended from the *Isodon* to the *Teucrium* genus. We have isolated a new crystalline norditerpene, teucvin,[2] from the neutral extract of *Teucrium fiscidum* Blume *var. Miquelianum* (Maxim.) Hara (Japanese name, '*Tsurunibakusa*').

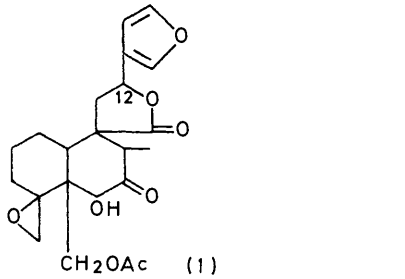
Teucvin, $C_{19}H_{20}O_5$, was shown to contain two lactone groups giving $pK_{a'}$ values of 8·4 and 6·5 by lactone titration. Its i.r. absorptions at 1600, 1505, and 875 cm^{-1} and positive Ehrlich test [3] indicated the presence of a furan ring. The n.m.r. spectrum showed multiplets at δ 7·43 (2H) and 6·37 (1H), which were assigned to the α-protons and β-proton on the furan ring, respectively. Thus, all the oxygen functions were characterized and the presence of a β-substituted furan ring was indicated. A strong i.r. absorption at 1755 cm^{-1} may be attributed to overlapping of the absorptions due to two carbonyl groups of the lactones, and at least one of them must belong to a γ-lactone.

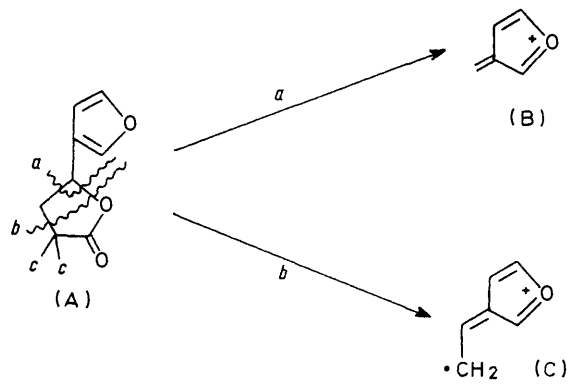
A triplet (1H, *J* 8·5 Hz) at δ 5·43 was quite similar to the resonance [δ 5·45 (t, *J* 8 Hz)] of the C-12 proton of pikropolin (1) which had been isolated from *Teucrium polium* and characterized by Brieskorn and Pfeuffer.[4] Decoupling experiments showed that it was the X part of an A_2X type signal and the A_2 part appeared as a doublet (*J* 8·5 Hz) at δ 2·54. These findings led to the assumption of a partial structure (A) which was supported by mass spectral fragmentations into (B) and (C) (Scheme 1).[4]

Teucvin was treated with sodium carbonate in refluxing methanol to give a crystalline product, $C_{20}H_{24}O_6$, in good yield. This compound was presumed to be a keto-ester on the basis of i.r. (1720 and 1740 cm^{-1}) and n.m.r. [δ 3·66 (3H, s)] data. Its reduction with sodium borohydride afforded a hydroxy-ester $C_{20}H_{26}O_6$, which on Jones oxidation regenerated the original keto-ester. I.r. absorption at 1755 cm^{-1} and A_2X type n.m.r. signals at δ 2·47 (1H, d, *J* 8·5 Hz), 2·45 (1H, d, *J* 8·5 Hz), and 5·44 (1H, t, *J* 8·5 Hz) characteristic of teucvin itself were still present in the keto-ester, indicating that the partial structure (A) remained intact during the foregoing treatment.

There was also a secondary methyl group in teucvin, which was recognized by a doublet at δ 1·05 (3H, *J* 6·5 Hz) changing to a singlet on irradiation at 179 Hz in the 100 MHz n.m.r. spectrum.

The difficulty in getting a satisfactory amount of teucvin for chemical degradation work prompted us to apply *X*-ray crystallography. The bromoacetate of the foregoing hydroxy-ester was prepared as orthorhombic single crystals, which were shown to have structure (5) (including the absolute configuration) by *X*-ray analysis.[2] Treatment of (5) with sodium carbonate in refluxing methanol regenerated the hydroxy-ester. Thus the structures (3) and (4) (Scheme 2) are assigned to the foregoing keto-ester and hydroxy-ester, respectively. Ketone (3) showed a positive Cotton effect in the $n \longrightarrow \pi^*$ region in its c.d. curve, which corroborates the absolute configuration shown.





Scheme 1

Chemical investigations confirmed the structure (3) for the keto-ester: (i) reaction with ethane-1,2-diol gave a quantitative yield of acetal (6); and (ii) reduction with lithium aluminium hydride in tetrahydrofuran at room temperature gave the diol (7), and in refluxing tetrahydrofuran, the tetraol (8).

The second lactone group in teucvin should, therefore, be formed between C-6 and C-18. Teucvin showed u.v. absorption at 217 nm which could be attributed to an

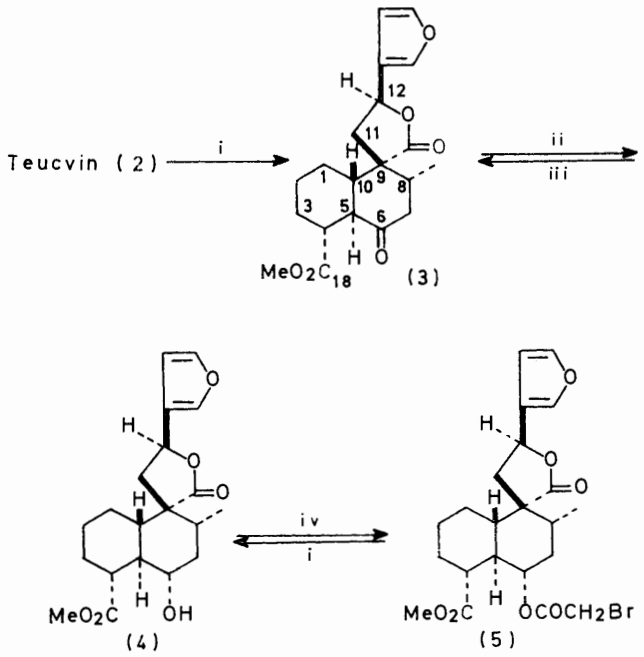
[1] Part XXXI, E. Fujita, M. Node, Y. Nagao, and T. Fujita, *Yakugaku Zasshi*, in the press.

[2] Preliminary communication of a part of this work, E. Fujita, I. Uchida, T. Fujita, N. Masaki, and K. Osaki, *J.C.S. Chem. Comm.*, 1973, 793.

[3] T. Reichstein, *Helv. Chim. Acta*, 1932, **15**, 1110.

[4] C. H. Brieskorn and T. Pfeuffer, *Chem. Ber.*, 1967, **100**, 1998.

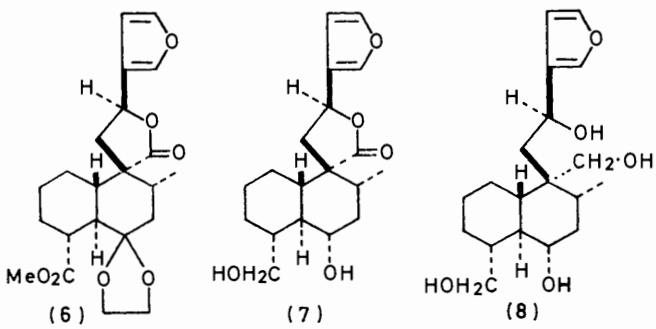
αβ-unsaturated γ-lactone. Sometimes, however, a furan ring system can have such a u.v. absorption.[5,6] The u.v. spectra of (3) and (7) did not show absorption



SCHEME 2

Reagents: i, Na_2CO_3–MeOH; ii, $NaBH_4$; iii, Jones oxidation; iv, $BrCH_2COBr$

maxima over 210 nm, while the hexahydro-derivative of teucvin, which corresponded to a product formed *via* hydrogenolysis followed by hydrogenation of the furan ring, showed an absorption maximum at 224 nm. Thus, the maximum u.v. absorption at 217 nm in teucvin was shown to be due to an αβ-unsaturated γ-lactone chromophore. Furthermore, teucvin gave positive results in the Baljet [7] and Kedde [8] reactions, which are characteristic of αβ-unsaturated lactones. The hexahydro-derivative also gave a positive reslt in the Baljet reaction. Consequently, teucvin was proved to have structure (2)



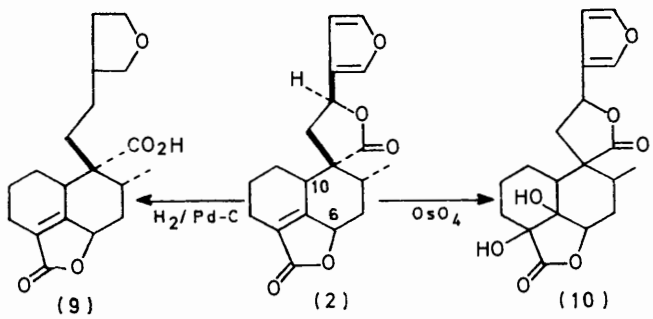
with the configurations at C-6 and C-10 unspecified. The hexahydro-derivative, therefore, must have structure (9). Teucvin was treated with osmium tetraoxide to give a diol, $C_{19}H_{22}O_7$, (10) (Scheme 3).

[5] T. Kamikawa and T. Kubota, *Tetrahedron*, 1961, **12**, 262.
[6] G. L. LuKas, J. C. N. Ma, J. A. McCloskey, and R. E. Wolff, *Tetrahedron*, 1964, **20**, 1789.
[7] H. Baljet, *Z. Analyt. Chem.*, 1938, **113**, 378.

The remaining problem was the determination of configuration at C-6 and C-10. Investigation of Dreiding models indicated that both 6β-, 10β-H, and 6α-, 10α-H systems were stable but that 6β-, 10α-H and 6α-, 10β-H systems were unstable because of a large strain. In the last (6α-, 10β-H) system particularly, C(6)-H is nearly in the plane of the γ-lactone carbonyl group and a paramagnetic shift is to be expected in the n.m.r. spectrum; in fact the signal was at δ 4·74, a rather high field [9,10] for the γ-proton of an αβ-unsaturated γ-lactone.

Teucvin was treated with sodium carbonate in refluxing MeOD for 18 h to give (11), $C_{20}H_{19}D_5O_6$, in good yield. Reduction of (11) by lithium aluminium hydride at room temperature gave the diol (12), $C_{19}H_{21}D_5O_5$, whose diacetate (13) showed a singlet for C(6)-H and an AB quartet for C(18)-H_2 in its n.m.r. spectrum. Thus, (11) was shown to have one D at each of C-4 and C-5 and D_2 at C-7.

Teucvin on the same treatment as above for 1 h gave in good yield another product (14), $C_{19}H_{18}D_2O_5$, whose n.m.r. spectrum lacked signals due to C(6)-H and C(10)-H. This compound regenerated teucvin when treated with sodium carbonate in refluxing methanol for 30 min. Thus, deuteriation at C-10 in (11) was also elucidated.



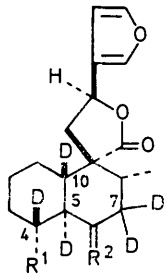
SCHEME 3

The pentadeuterio-derivative (11) on treatment with sodium carbonate in refluxing methanol for 7 h gave a trideuterio-derivative (15), whose n.m.r. spectrum showed a triplet (*J* 13 Hz) at δ 3·18 and a quartet (*J* 13 and 4·5 Hz) at 2·26. A detailed investigation of the INDOR spectrum [11] of (3) resulted in the assignments of the former to the α-H and the latter to the β-H at C-7. Treatment of (3) with sodium carbonate in refluxing MeOD for 10 h afforded the C(7)-D_2 derivative (16). Deuteriation at C-7 of (11), therefore, occurred *via* cleavage of the lactone ring to form a ketone at C-6 followed by enolization in MeOD.

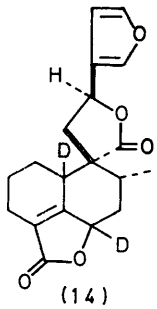
Teucvin was refluxed in 0·1N-NaOH [in a mixture of methyl cellosolve and water (4 : 1)] for 10 min to yield

[8] J. E. Bush and D. A. H. Taylor, *Biochem. J.*, 1952, **52**, 643.
[9] Varian Associates, ' High Resolution NMR Spectra Catalog,' compiled by N. S. Bhacca, L. F. Johnson, and J. N. Shoolery, National Press, U.S.A., 1962, vol. I, no. 51.
[10] H. Kaise, K. Munakata, and T. Sassa, *Tetrahedron Letters*, 1972, 3789.
[11] W. von Philipsborn, *Angew. Chem. Internat. Edn.*, 1971, **10**, 472.

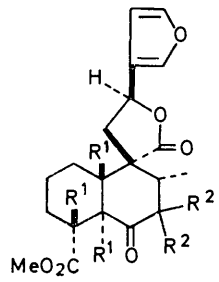
the keto-acid (17) as the major product and (18) and (19) as the minor products. The structure of (19) was



(11) R^1 = CO_2Me, R^2 = O
(12) R^1 = CH_2OH, R^2 = α-OH, β-H
(13) R^1 = CH_2OAc, R^2 = α-OAc, β-H



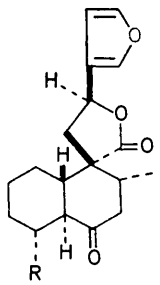
(14)



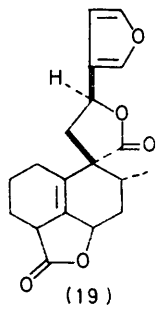
(15) R^1 = D, R^2 = H
(16) R^1 = H, R^2 = D

determined from the following data: (i) the molecular formula is the same as that of teucvin; (ii) in the i.r. spectrum, the absorptions at 1750 and 1690 cm^{-1} characteristic of the αβ-unsaturated γ-lactone disappeared and instead a strong overlapping absorption at 1770 cm^{-1} due to two γ-lactone rings was observed; (iii) the n.m.r. spectrum showed the signals of protons on C-4 and C-6 at δ 3·08 and 4·88, respectively; this was confirmed by the INDOR technique. When treated as above for 3 h, teucvin gave only (17), which was characterized as the methyl ester (3). The compound (19) is, therefore regarded as the product formed under kinetically controlled conditions.

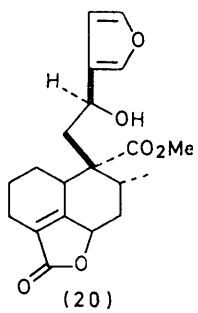
Treatment of teucvin with potassium t-butoxide in t-butyl alcohol under reflux and subsequent methylation of the product with diazomethane afforded (3) and a new product (20) besides (19) and recovered starting material. Similar treatment of teucvin with potassium t-butoxide in dimethyl sulphoxide gave (19) although in low yield, accompanied by unchanged teucvin. On the other hand, treatment of teucvin with potassium t-butoxide or sodium methoxide in refluxing benzene gave no reaction. Thus teucvin only reacts with alkali in polar solvents, and product (19) is formed under kinetic



(17) R = CO_2H
(18) R = $CO_2[CH_2]_2OMe$



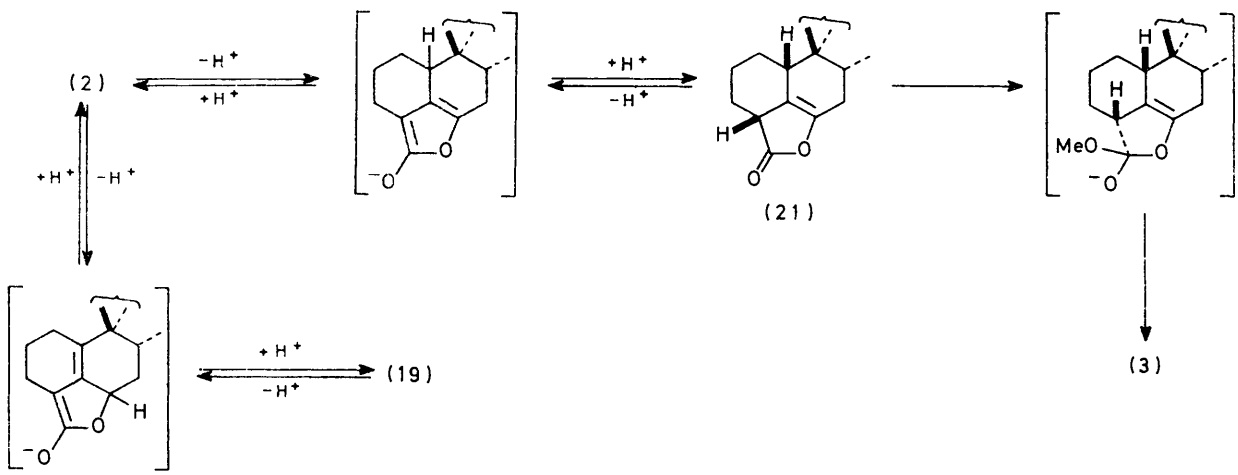
(19)



(20)

control or conditions where the enolate anion is readily formed from the αβ-unsaturated γ-lactone system.

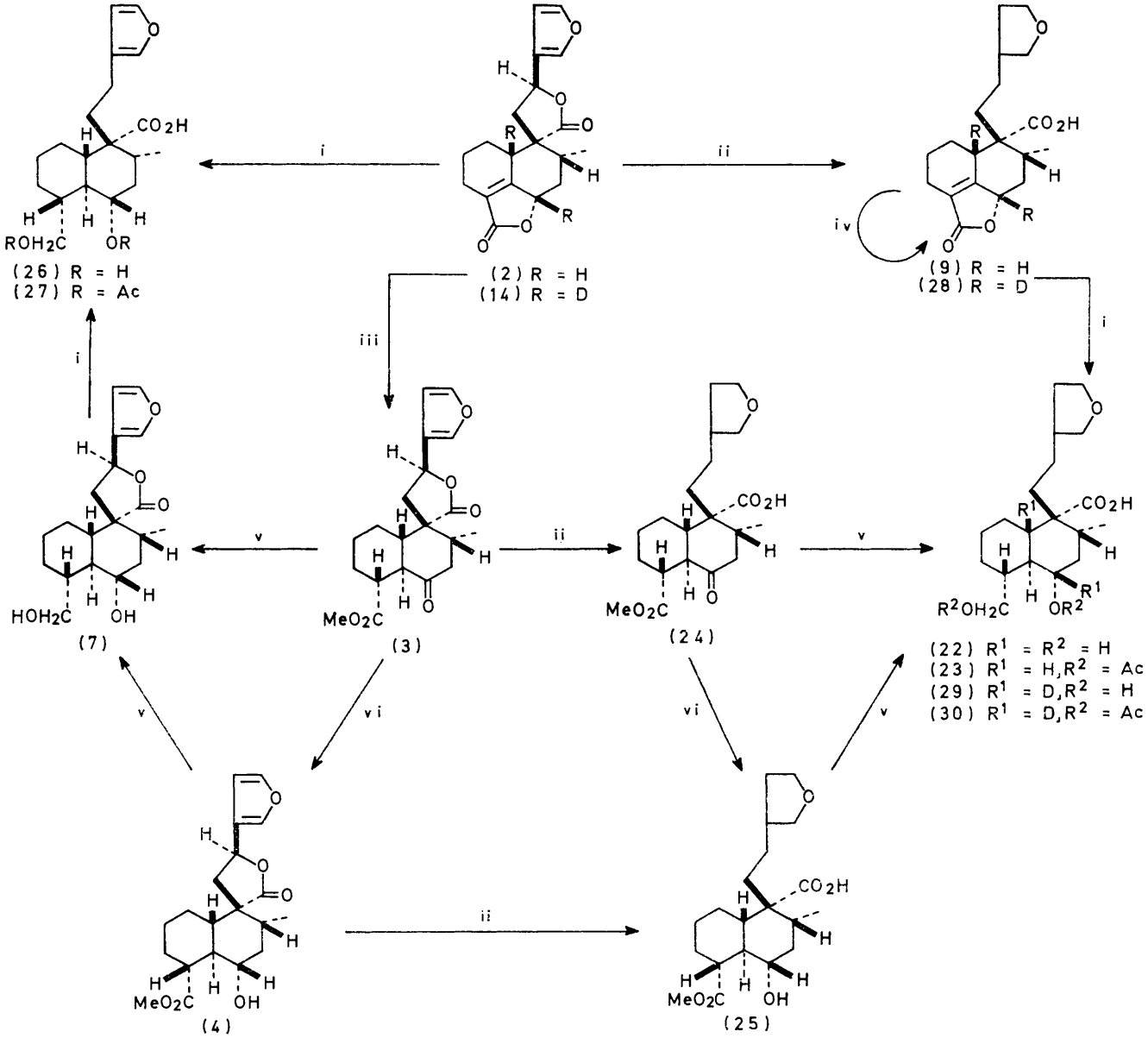
On the basis of the foregoing data, the formation of (3) in good yield from the reaction of teucvin with sodium carbonate in refluxing methanol is represented as in Scheme 4.



SCHEME 4

The formation of (14) as the sole product from teucvin (2) on reaction with sodium carbonate in refluxing MeOD for a short time can be explained by the rapid equilibria between (2) and (21) and between (2) and (19). Recovery of teucvin from (14) by treatment with sodium carbonate in refluxing methanol for a short time also supported these equilibria, both of which should favour teucvin itself because of its energetically most stable structure. Since the recovered teucvin maintains the original configuration, the configuration at C-10 of (21) must be the same as that of teucvin. The configuration at C-10 of (3) is naturally the same as that of (21), and hence teucvin (2) and the keto-ester (3) have the same configuration at C-10. The absolute configuration of (3) has been established as described above. Thus, it is concluded that teucvin has a β-hydrogen at C-10. The β-configuration of C(6)-H is also predicted from the foregoing examination of the Dreiding model.

The absolute configurations of C-6 and C-10 were finally established by the following chemical evidence. Teucvin hexahydro-derivative (9) was subjected to Birch reduction to give the diol carboxylic acid (22) in good yield. Acetylation gave the diacetate (23). The ketoester (3) on catalytic hydrogenation gave the hexahydro-derivative (24). Reduction of (24) with lithium aluminium hydride yielded a diol carboxylic acid, whose R_F value on t.l.c. and i.r. and mass spectra were identical with those of (22). Catalytic hydrogenation of (4) gave (25) which was identical with the product from reduction of (24) with sodium borohydride. Reduction of (25)

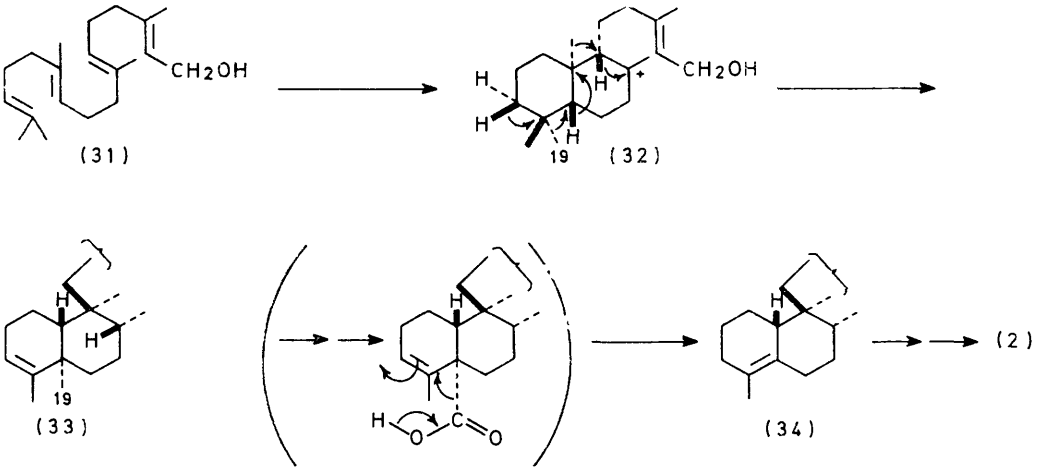


SCHEME 5

Reagents: i, Birch reduction; ii, H_2/Pd–C; iii, Na_2CO_3–MeOH; iv, Li–EtOH, room temp.; v, $LiAlH_4$; vi, $NaBH_4$

with lithium aluminium hydride afforded (22) again. All the compounds (22)—(25) were homogeneous on t.l.c., but remained oily. Although the stereochemistry of C-13 was somewhat equivocal, the products obtained *via* three different routes were judged to be the same substance of structure (22), by comparison of their t.l.c. and i.r. and mass spectra and those of diacetates.

Birch reduction of teucvin itself under similar conditions gave a diol carboxylic acid, although in low yield, besides (22). On the other hand, lithium aluminium hydride reduction of (4) gave (7), which had been obtained from reduction of (3) with lithium aluminium hydride. Birch reduction of (7) yielded a carboxy-group followed by decarboxylation into (34). Then, oxidation at C-6 and C-18 followed by formation of the αβ-unsaturated γ-lactone may take place. The formation of another γ-lactone and furan ring must occur in some step(s) between (33) and (2).



SCHEME 6

diol carboxylic acid (26). The n.m.r. spectrum of its diacetate (27) supported its structure. The compound (26) was proved to be identical with the foregoing product from Birch reduction of teucvin. The 6- and 10-protons of teucvin, therefore, were shown to have β-configurations, *i.e.* the absolute configurations at C-6 and C-10 of teucvin were *S* and *R*, respectively, unless Birch reduction of teucvin had inverted these configurations.

Even treatment of (9) with lithium in ethanol at room temperature for 45 min caused no change. Subsequently, the 6,10-dideuterio-derivative of (9) obtained by catalytic hydrogenation of [6,10-$^2H_2$]teucvin (14), *i.e.*, compound (28), $C_{19}H_{24}D_2O_5$, on Birch reduction gave (29), $C_{19}H_{30}D_2O_5$. This compound showed the same R_F value as (22) on t.l.c. The n.m.r. spectrum of its diacetate (30) did not show a signal for the C(6)-H. These facts confirmed the maintenance of the original configurations at C-6 and C-10 during the Birch reduction. Thus, the structure and absolute configuration of teucvin were established as (2) in Scheme 5.

Finally, the biogenesis of teucvin might be as outlined in Scheme 6. Geranylgeraniol (31) is converted into an *ent*-labdane type intermediate (32), whose Wagner–Meerwein rearrangement results in the formation of an *ent*-clerodane type compound (33). Oxidative elimination of C-19 may occur, for instance, *via* oxidation to a

EXPERIMENTAL

M.p.s were taken on a micro hot-stage. I.r. spectra were recorded on a Hitachi model EPI-S_2 spectrometer for chloroform solutions, unless otherwise stated. U.v. spectra were determined on a Hitachi model EPS-3 spectrophotometer for methanol solutions. N.m.r. spectra were recorded with Varian T-60, A-60, or HA-100 spectrometers in deuteriochloroform unless otherwise stated; signals are reported in p.p.m. from tetramethylsilane as internal standard. Mass spectra were determined on a JMS-OISG double-focusing mass spectrometer. Mallinckrodt silicic acid and Kieselgel 0·05—0·2 mm (Merck) were used for column chromatography. Plates coated with silica gel G nach Stahl (Merck) or DC-Fertigplatten Kieselgel (Schichtdicke 0·25 mm) (Merck) were used for t.l.c.

Isolation of Teucvin (2).—The dry plant material [*Teucrium viscidum* Bl. *var. Miquelianum* (Maxim.) Hara] (3 kg) was digested in ether for 30 days. The extract was evaporated to leave a residue (90 g), which was extracted with ethyl acetate. After washing with 10% aqueous sodium carbonate and 1% HCl, washing with water, drying, and evaporation of the solvent left the crude component (53·5 g), which was chromatographed on a silica gel column. Elution with 10% acetone–dichloromethane gave crude crystals (2 g), which were recrystallized from methanol to yield pure *teucvin*, m.p. 207—208°, $[\alpha]_D^{18}$ +184° (*c* 0·12 in $CHCl_3$), $\lambda_{max.}$ (MeOH) 217 nm (ε 17,200), $\nu_{max.}$ 1755, 1690, 1505, and 875 cm^{-1}, δ 7·43 (2H, m), 6·37 (1H, m), 5·43 (1H, t, *J* 8·5 Hz, 12-H), 4·74br (1H, t, *J* 8·5 Hz, 6-H), 2·68br (1H, m, 10-H), 2·54 (2H, d, *J* 8·5 Hz, 11-H_2), and 1·05 (3H, d, *J* 6·5 Hz, 8-Me) (Found: C, 67·7; H, 6·25. $C_{19}H_{20}O_5$,0·5H_2O requires C, 67·6; H, 6·3%).

Lactone Titration * *of Teucvin* (2).—To 0·1N-sodium hydroxide in a mixture of methyl cellosolve and water (4 : 1) (10 ml) was added teucvin (55 mg), and the mixture

* Radiometer TTT1c (pH titrator) was used.

was heated for 3 h. The solution was titrated with 0·8N-HCl to give pK_a's 8·4 and 6·5. The acid solution after determination of pK_a' was neutralized with aqueous sodium carbonate and extracted with dichloromethane. The crude product (40 mg) obtained by the usual treatment of the extract was methylated with diazomethane. The crude product (42 mg) was purified by silica gel column chromatography to give crystals (23 mg), which were recrystallized from methanol to yield ent-(12R)-15,16-*epoxy*-12-*hydroxy*-6-*oxo*-19-*nor*-9,4-*friedolabda*-13(16),14-*diene*-18,20-*dioic acid* 20,12-*lactone* 18-*methyl ester* (3), m.p. 175—177°, $\nu_{max.}$ 1755, 1740, 1720, 1600, 1505, 1160, and 875 cm^{-1}, δ 7·42 (2H, m), 6·36 (1H, m), 5·44 (1H, t, *J* 8·5 Hz, 12-H), 3·66 (3H, s), 3·34 (1H, t, *J* 11 Hz, 5α-H), 3·18 (1H, t of d, *J* 13 and 1 Hz, 7α-H), 2·47 [1H, d, *J* 8·5 Hz (11-H_a–12-H), 11-H_a], 2·45 (1H, d, *J* 8·5 Hz (11-H_b–12-H), 11-H_b], 2·26 (1H, q, *J* 13 and 4·5 Hz, 7β-H), and 1·08 (3H, d, *J* 6·5 Hz, 8-Me) (Found: C, 66·7; H, 6·8%; M^+, 360. $C_{20}H_{24}O_6$ requires C, 66·75; H, 6·7%; *M*, 360).

Preparation of the Keto-ester (3) *from Teucvin* (2) *by Ester Exchange Reaction*.—Teucvin (500 mg) and sodium carbonate (500 mg) in methanol (50 ml) were refluxed for 16 h. The residue from filtration was washed with dichloromethane, and the combined filtrate and washing were neutralized with 1% hydrochloric acid and concentrated *in vacuo*. Dichloromethane was then added and the mixture washed with water. Evaporation of the solvent after drying left a crystalline residue (505 mg), which yielded pure crystals (450 mg), m.p. 175—177° (from methanol), which were identical with (3) (mixed m.p. and i.r.), c.d. (*c* 0·155, dioxan) $[\theta]_{318}$ 0, $[\theta]_{288}$ +2180, $[\theta]_{252·5}$ 0, $[\theta]_{231·5}$ −2490, $[\theta]_{221}$ 0, and $[\theta]_{210}$ +4200.

Sodium Borohydride Reduction of the Keto-ester (3).—To a solution of (3) (240 mg) in tetrahydrofuran (25 ml) was added a solution of sodium borohydride (240 mg) in tetrahydrofuran (25 ml), and the mixture was stirred for 2 h at room temperature. Filtration left a residue, which was washed with dichloromethane. Filtrate and washing were combined and neutralized with acetic acid, and the mixture was concentrated at 30° *in vacuo*. The concentrated mixture was extracted with dichloromethane and the extract was treated as usual to give a crude mixture of products (211 mg), which was chromatographed on a silica gel column to separate a crystalline product A (165 mg) and the second crystalline product B (35 mg). On recrystallization from ether–methanol–chloroform, A gave ent-(6R,12R)-15,16-*epoxy*-6,12-*dihydroxy*-19-*nor*-9,4-*friedolabda*-13(16),14-*diene*-18,20-*dioic acid* 20,12-*lactone* 18-*methyl ester* (4), m.p. 207—210°, $\nu_{max.}$ 3600, 1760, 1725, 1600, 1505, 1160, and 875 cm^{-1}, δ 7·45 (2H, m), 6·40 (1H, m), 5·40 (1H, t, *J* 8·5 Hz, 12-H), 3·65 (3H, s), 2·39 (2H, d, *J* 8·5 Hz, 11-H_2), 3·30 (1H, m, 6-H), and 1·00 (3H, d, *J* 6·5 Hz, 8-Me) (Found: C, 66·35; H, 7·15%; M^+, 362. $C_{20}H_{26}O_6$ requires C, 66·3; H, 7·25%; *M*, 362). Recrystallization of B from ether yielded ent-(6R,12R)-15,16-*epoxy*-6,18-*dihydroxy*-19-*nor*-9,4-*friedolabda*-13(16),14-*dien*-20,12-*olactone* (7) (25 mg), m.p. 185—188°, $\nu_{max.}$ 1755, 1505, 1160, 1025, and 875 cm^{-1}, δ 7·45 (2H, m), 6·40 (1H, m), 5·39 (1H, t, *J* 8·5 Hz, 12-H), 3·68br (2H, m, 18-H_2), 2·38 (2H, d, *J* 8·5 Hz, 11-H_2), and 1·00 (3H, d, *J* 6·5 Hz) (Found: C, 68·15; H, 7·95%; M^+, 334·176. $C_{19}H_{26}O_5$ requires C, 68·15; H, 7·85%; *M*, 334·178).

Lithium Aluminium Hydride Reduction of (3) *to give* (7).—To a solution of (3) (50 mg) in tetrahydrofuran (5 ml) was added a mixture of lithium aluminium hydride (50 mg) in tetrahydrofuran (5 ml), and the mixture was stirred for 20 min at room temperature. Ethyl acetate was added dropwise under ice-cooling to decompose excess of the reagent, and then the mixture was extracted with ethyl acetate under addition of aqueous sodium chloride, and the extract was treated as usual. The crystalline product was purified by chromatography on a silica gel column and recrystallization from ether to afford pure crystals (25 mg), m.p. 185—188°, which were identical with the authentic sample of (7) (mixed m.p. and i.r.).

Acetylation of (4).—The usual acetylation of (4) (49 mg) with acetic anhydride and pyridine yielded crude acetate (50 mg), which was recrystallized from methanol to give pure *acetate* (35 mg), m.p. 230—231°, $\nu_{max.}$ (KBr) 1755, 1725, 1510, 1255, 1165, and 875 cm^{-1}, δ 7·45 (2H, m), 6·40 (1H, m), 5·38 (1H, t. *J* 8·5 Hz, 12-H), 4·54 (1H, m, $W_{\frac{1}{2}}$ 20 Hz, 6-H), 3·70 (3H, s), 2·40 (2H, d, *J* 8·5 Hz, 11-H_2), 1·96 (3H, s), and 0·99 (3H, d, *J* 6 Hz) (Found: M^+, 404·186. $C_{22}H_{28}O_7$ requires *M*, 404·184).

Bromoacetate (5).—A solution of the hydroxy-ester (4) (63 mg) in dichloromethane (10 ml) was added to freshly distilled α-pinene (1 ml). Freshly distilled bromoacetyl bromide (1 ml) was added to this, and the mixture was refluxed for 18 h under anhydrous conditions. After addition of ice–water, the mixture was extracted with dichloromethane, and the extract on usual work-up gave an oily product (66 mg), which was chromatographed on a silica gel column to yield a homogeneous oily substance (55 mg). Crystallization and recrystallization from methanol–ether yielded ent-(6R,12R)-6-*bromoacetoxy*-15,16-*epoxy*-12-*hydroxy*-19-*nor*-9,4-*friedolabda*-13(16),14-*diene*-18,20-*dioic acid* 20,12-*lactone* 18-*methyl ester* (5) (30 mg), m.p. 170°, $\nu_{max.}$ 1755, 1725, 1505, 1160, and 875 cm^{-1}, δ 7·45 (2H, m, 2 × α-H of furan), 6·40 (1H, m, β-H of furan), 5·40 (1H, t, *J* 8·5 Hz, 12-H), 4·65 (1H, t of d, *J* 10 and 5 Hz, 6-H), 3·76 (2H, s, −O·CO·CH_2Br), 3·70 (3H, s, CO_2Me), 2·41 (2H, d, *J* 8·5 Hz, 11-H_2), and 1·02 (3H, d, *J* 6 Hz, 8-Me) (Found: C, 54·4; H, 5·65. $C_{22}H_{27}BrO_7$ requires C, 54·25; H, 5·6%).

Hydrolysis of (5) *into* (4).—The bromoacetate (5) (12 mg) was treated with sodium carbonate (12 mg) in refluxing methanol (2 ml) for 1 h. Filtration left a residue, which was washed with dichloromethane. The filtrate and washing were combined, and a large quantity of dichloromethane was added. The mixture was washed with aqueous sodium chloride to remove base. After drying the organic layer, the solvent was evaporated off to leave a crystalline residue (7 mg), which was identical with the hydroxy-ester (4) by t.l.c. and i.r. comparison.

Acetylation of (7).—The diol (7) (15 mg) was treated with acetic anhydride (0·3 ml) in pyridine (0·3 ml) at room temperature overnight. The usual treatment and purification of the crude product (17 mg) by chromatography on a silica gel column yielded an amorphous *diacetate* (15 mg) which was homogeneous on t.l.c. (dichloromethane–acetone, 9 : 1) showing R_F 0·85, $\nu_{max.}$ 1755, 1725, 1505, 1255, 1025, and 875 cm^{-1}, δ 7·43 (2H, m), 6·40 (1H, m), 5·40 (1H, t, *J* 8·5 Hz, 12-H), 4·66 (1H, td, *J* 9·5 and 6 Hz, 6-H), 4·08 (2H, m, 18-H_2), 2·39 (2H, d, *J* 8·5 Hz, 11-H_2), 0·96 (3H, d, *J* 6·5 Hz), and 2·03 (6H, s, 2 × Ac) (Found: M^+, 418·199. $C_{23}H_{30}O_7$ requires *M*, 418·199).

Jones Oxidation of the Hydroxy-ester (4).—To a solution of (4) (7 mg) in acetone was added a drop of Jones reagent and the mixture was stirred for 10 min under ice-cooling. The mixture was added to cold aqueous sodium chloride

and extracted with ether. The usual treatment of the extract gave a crystalline product (6·5 mg), which was recrystallized from methanol to yield pure substance, m.p. 175—177°, identical with the keto-ester (3) (mixed m.p. and i.r.).

Ehrlich Reaction of Teucvin (2).—T.l.c. of teucvin (2) (silica gel, dichloromethane–acetone, 4 : 1) showed a red spot (R_F 0·8), when a solution of *p*-dimethylaminobenzaldehyde (1 g) in ethanol (20 ml) and conc. hydrochloric acid was sprayed on.

Acetalization of the Keto-ester (3).—To a mixture of toluene (5 ml) and ethylene glycol (0·4 ml) were added (3) (50 mg) and toluene-*p*-sulphonic acid (4 mg), and the mixture was heated at 140° under a water separator for 2 h during which *ca.* half the volume of the solvent was distilled off. The reaction mixture was made alkaline by 5% aqueous sodium carbonate and extracted with ethyl acetate. The extract was treated as usual to give crude crystals (52 mg), which on recrystallization from methanol yielded ent-(12R)-15,16-*epoxy*-6,6-*ethylenedioxy*-12-*hydroxy*-19-*nor*-9,4-*friedolabda*-13(16),14-*diene*-18,20-*dioic acid* 20,12-*lactone* 18-*methyl ester* (6) (44 mg), m.p. 243—245°, $\nu_{max.}$ 1760, 1725, 1165, 1115, and 875 cm^{-1}, δ 7·44 (2H, m), 6·40 (1H, m), 5·37 (1H, t, *J* 8·5 Hz, 12-H), 3·91 (4H, m, $-OCH_2CH_2O-$), 3·62 (3H, s), 2·40 (2H, d, *J* 8·5 Hz, 11-H_2), and 0·98 (3H, d, *J* 6 Hz) (Found: C, 65·6; H, 6·9%; M^+, 404·180. $C_{22}H_{28}O_7$ requires C, 65·35; H, 7·0%; *M*, 404·184).

The Tetraol (8) *and its Tetra-acetate*.—To a solution of the keto-ester (3) (100 mg) in tetrahydrofuran (10 ml) was added a suspension of lithium aluminium hydride (200 mg) in tetrahydrofuran (10 ml), and the mixture was refluxed for 5 h. Ethyl acetate was slowly added under ice-cooling in order to decompose excess of the reagent. After addition of aqueous sodium chloride, the mixture was extracted with ethyl acetate. The extract on usual treatment gave an oily homogeneous product (90 mg), which was crystallized from chloroform to yield ent-(6R,12R)-15,16-*epoxy*-19-*nor*-9,4-*friedolabda*-13(16),14-*diene*-6,12,18,20-*tetraol* (8), m.p. 147—149°, $\nu_{max.}$ 3600, 3400, 1505, 1020, and 875 cm^{-1} (Found: M^+, 338·207. $C_{19}H_{30}O_5$ requires *M*, 338·209). A mixture of (8) (25 mg) in acetic anhydride (1·5 ml) and pyridine (1·5 ml) was left at room temperature overnight. Usual treatment of the mixture gave crude product (30 mg), which was chromatographed to afford the oily tetra-acetate (26 mg), $\nu_{max.}$ 1730, 1505, 1375, 1240, 1027, and 875 cm^{-1}, δ 7·42 (2H, m), 6·40 (1H, m), 5·93 (1H, q, *J* 8·5 and 3·5 Hz, 12-H), 4·62 (1H, m, 6-H), 4·12 (2H, s, 20-H_2), 4·00 (2H, m, 18-H_2), 2·05, 2·03, 2·02, and 1·99 (each 3H, s, OAc), and 0·88 (3H, d, *J* 6·0 Hz, 8-Me).

Catalytic Hydrogenation of Teucvin (2) *to its Hexahydroderivative* (9).—Teucvin (2) (500 mg) was hydrogenated in 99% methanol (100 ml) over 5% Pd–C (600 mg), and 2·8 mol. equiv. of hydrogen was consumed. Evaporation of the solvent after filtration left a residue (502 mg), which was purified by chromatography on a silica gel column to yield amorphous ent-(6R)-15,16-*epoxy*-6-*hydroxy*-19-*nor*-9,4-*friedolabd*-4-*ene*-18,20-*dioic acid* 18,6-*lactone* (9) (490 mg), $\nu_{max.}$ 1745 and 1690 cm^{-1}, δ 4·74br (1H, t, *J* 8·5 Hz, 6-H), 9·13br (1H, s, CO_2H), and 1·00 (3H, d, *J* 6·5 Hz, 8-Me) (Found: M^+, 334·181. $C_{19}H_{26}O_5$ requires *M*, 334·178). *Methyl ester*: oily, $\nu_{max.}$ 1745, 1725, and 1690 cm^{-1}, δ 4·72br (1H, t, $W_{\frac{1}{2}}$ 17 Hz, 6-H), 2·65br (1H, m, 10-H), 3·62 (3H, s, $-CO_2Me$), and 0·95 (3H, d, *J* 6·5 Hz) (Found: M^+, 348·192. $C_{20}H_{28}O_5$ requires *M*, 348·194).

Oxidation of Teucvin with Osmium Tetraoxide.—To a solution of teucvin (2) (200 mg) in dry tetrahydrofuran (20 ml) was added osmium tetraoxide (280 mg) and pyridine (0·4 ml), and the mixture was left for 6 days at room temperature. The concentrated mixture was dissolved in dichloromethane, and hydrogen sulphide gas was passed through. Filtration removed the precipitate, which was washed with dichloromethane and acetone. The filtrate and washing were combined and evaporation of the solvent left a residue (150 mg), which was chromatographed on a silica gel column to separate oily diol (10) (42 mg) and starting material (2) (15 mg). ent-(6R,12R)-15,16-*Epoxy*-4,5-*dihydroxy*-19-*nor*-9,4-*friedolabda*-13(16),14-*diene*-18,6:20,12-*diolactone* (10) was crystallized from methanol, m.p. 183—184°, $\nu_{max.}$ 3500, 1765, 1600, 1505, 1160, 1020, and 875 cm^{-1}, no $\lambda_{max.}$ over 210 nm, δ 7·45 (2H, m), 6·41 (1H, m), 5·39 (1H, q, *J* 5·5 and 10 Hz, 12-H), 4·54br (1H, t, *J* 8·5 Hz, 6-H), 2·86 (1H, q, *J* 5·5 and 13 Hz, 11-H_a), 2·26 (1H, q, *J* 10 and 13 Hz, 11-H_b), and 1·16 (3H, d, *J* 6·2 Hz, 8-Me) (Found: M^+, 362·139. $C_{19}H_{22}O_7$ requires *M*, 362·137.

Baljet Reaction.—To teucvin (2) (1 mg) or its hexahydroderivative (9) (1 mg) was added a mixture (1 ml) of equal volumes of 1% picric acid solution in ethanol and 10% aqueous NaOH. The mixture slowly became orange-red.

Kedde Reaction.—When a solution of 3,5-dinitrobenzoic acid (100 mg) in 0·5N-potassium hydroxide in 50% methanol (10 ml) was added dropwise to teucvin (2), it slowly became red-violet.

Treatment of Teucvin (2) *with Sodium Carbonate in Refluxing Deuteriomethanol for* 18 *h*.—A mixture of teucvin (2) (200 mg) and anhydrous sodium carbonate (200 mg) in deuteriomethanol (20 ml) was refluxed for 18 h. The mixture was filtered and the residue was washed with dichloromethane. To the combined and cooled filtrate and washing was added a large quantity of dichloromethane and the mixture was washed with aqueous sodium chloride to remove alkali, dried, and evaporated to leave a crystalline product (182 mg), whose R_F value on t.l.c. was same with that of the keto-ester (3). Recrystallization from methanol gave ent-(12R)-[4,5,7,7,10-$^2H_5$]-15,16-*epoxy*-12-*hydroxy*-6-*oxo*-19-*nor*-9,4-*friedolabda*-13(16),14-*diene*-18,20-*dioic acid* 20,12-*lactone* 18-*methyl ester* (11), m.p. 175—177°, $\nu_{max.}$ 2120 (C–D), 1755, 1730, 1710, 1600, 1505, and 875 cm^{-1}, δ 7·50 (2H, m, 2α-H of furan ring), 6·45 (1H, m, β-H of furan ring), 5·48 (1H, t, *J* 8·5 Hz, 12-H), 3·66 (3H, s, CO_2Me), 2·47 [1H, d, *J* 8·5 Hz (11-H_a–12-H), 11-H_a], 2·45 [1H, d, *J* 8·5 Hz (11-H_b–12-H), 11-H_b], and 1·07 (3H, d, *J* 6·5 Hz) (Found: M^+, 365·188. $C_{20}H_{19}D_5O_6$ requires *M*, 365·189).

Lithium Aluminium Hydride Reduction of (11).—To a solution of (11) (50 mg) in tetrahydrofuran (5 ml) was added a mixture of lithium aluminium hydride (50 mg) in tetrahydrofuran (5 ml), and the mixture was stirred for 20 min at room temperature. Ethyl acetate was added under ice-cooling to decompose excess of the reagent, then the mixture was extracted with ethyl acetate. Usual treatment of the extract gave crude crystals (43 mg), which were recrystallized from methanol to yield ent-(6R,12R)-[4,5,7,7,10-$^2H_5$]-15,16-*epoxy*-6,18-*dihydroxy*-19-*nor*-9,4-*friedolabda*-13(16),14-*dien*-20,12-*olactone* (12) as crystals, m.p. 181—182° (Found: M^+, 339·212. $C_{19}H_{21}D_5O_5$ requires *M*, 339·209). The diol (38 mg) on the usual acetylation with acetic anhydride in pyridine gave the *diacetate* (13) (42 mg), which on recrystallization from methanol

yielded pure crystals, m.p. 101—103°, $\nu_{max.}$ (KBr) 2130 (C–D), 1755, 1730, 1510, 1255, 1240, and 875 cm^{-1}, δ 7·40 (2H, m), 6·40 (1H, m), 5·38 (1H, t, *J* 8·5 Hz, 12-H), 4·36 (1H, s, 6-H), 4·11 and 4·02 (each 1H, AB-type, *J* 11·4 Hz, 18-H_2), 2·40 (2H, d, *J* 8·5 Hz, 11-H_2), 2·07 (6H, s, 2 × OAc), and 0·97 (3H, d, *J* 6·0 Hz) (Found: M^+, 423·232. $C_{23}H_{25}D_5O_7$ requires *M*, 423·231).

Treatment of Teucvin (2) *with Sodium Carbonate in Refluxing Deuteriomethanol for* 1 *h.*—A mixture of teucvin (100 mg) and anhydrous sodium carbonate (100 mg) in deuteriomethanol (10 ml) was refluxed for 1 h. The mixture was treated as usual to give 6,10-*dideuterioteucvin* (14) (83 mg), m.p. 206—208° (from methanol), having the same R_F value as teucvin, $\nu_{max.}$ 2120 (C–D), 1755, 1690, 1600, 1505, and 875 cm^{-1}, δ 7·43 (2H, m), 6·37 (1H, m), 5·43 (1H, t, *J* 8·5 Hz, 12-H), 2·54 (2H, d, *J* 8·5 Hz, 11-H_2), and 1·05 (3H, d, *J* 6·5 Hz) (Found: M^+, 330·146. $C_{19}H_{18}D_2O_5$ requires *M*, 330·144).

Conversion of 6,10-*Dideuterioteucvin* (14) *into Teucvin* (2).—A mixture of (14) (50 mg) and anhydrous sodium carbonate (50 mg) in methanol (5 ml) was refluxed for 30 min. Usual treatment of the mixture gave crude teucvin (40 mg), which was recrystallized from methanol to yield pure compound (27 mg), m.p. 205—208°, identified by mixed m.p., i.r., n.m.r., and mass spectra.

The [4,5,10-$^2H_3$]*Keto-ester* (15).—The [$^2H_5$]keto-ester (11) (35 mg) was treated with anhydrous sodium carbonate (35 mg) in refluxing methanol (4 ml) for 7 h. Usual treatment gave a crude crystalline product (26 mg), which had the same R_F value on t.l.c. as the starting material. Recrystallization from methanol yielded ent-(12R)-[4,5,10-$^2H_3$]-15,16-*epoxy*-12-*hydroxy*-6-*oxo*-19-*nor*-9,4-*friedolabda*-13(16),14-*diene*-18,20-*dioic acid* 20,12-*lactone* 18-*methyl ester* (15), m.p. 164—165°, $\nu_{max.}$ (KBr) 1750, 1730, 1710, 1600, 1505, and 875 cm^{-1}, δ 7·43 (2H, m), 6·40 (1H, m), 5·44 (1H, t, *J* 8·5 Hz, 12-H), 3·66 (3H, s, CO_2Me), 3·18 (1H, t, *J* 13 Hz, 7α-H), 2·46 [1H, d, *J* 8·5 Hz (11-H_a–12-H), 11-H_a], 2·44 [1H, d, *J* 8·5 Hz (11-H_b–12-H), 11-H_b], 2·26 (1H, q, *J* 13 and 4·5 Hz, 7β-H), and 1·08 (3H, d, *J* 6·5 Hz) (Found: M^+, 363·177. $C_{20}H_{21}D_3O_6$ requires *M*, 363·176).

Treatment of the Keto-ester (3) *with Sodium Carbonate in Refluxing Deuteriomethanol.*—A mixture of (3) (50 mg) and anhydrous sodium carbonate (50 mg) in deuteriomethanol (10 ml) was refluxed for 10 h. Usual work-up gave ent-(12R)-[7,7-$^2H_2$]-15,16-*epoxy*-12-*hydroxy*-6-*oxo*-19-*nor*-9,4-*friedolabda*-13(16),14-*diene*-18,20-*dioic acid* 20,12-*lactone* 18-*methyl ester* (16) (52 mg), which was recrystallized from methanol to yield pure compound, m.p. 161—163°, showing the same R_F value on t.l.c. as (3), $\nu_{max.}$ (KBr) 1750, 1735, 1710, 1600, 1505, and 875 cm-^{1}, δ 7·45 (2H, m), 6·41 (1H, m), 5·44 (1H, t, *J* 8·5 Hz, 12-H), 3·66 (3H, s, CO_2Me), 3·34 (1H, t, *J* 11 Hz, 5α-H), 2·46 [1H, d, *J* 8·5 Hz (11-H_a–12-H), 11-H_a], 2·44 [1H, d, *J* 8·5 Hz (11-H_b–12-H), 11-H_b], and 1·08 (3H, d, *J* 6·5 Hz) (Found: M^+, 362·166. $C_{20}H_{32}D_2O_6$ requires *M*, 362·170).

Treatment of Teucvin (2) *with* 0·1N-*Sodium Hydroxide.*—To 0·1N-sodium hydroxide (40 ml) in a mixture of methyl cellosolve and water (4 : 1) was added teucvin (200 mg), and the mixture was heated at 135° for 10 min. After neutralization with 10% hydrochloric acid and concentration, the mixture was acidified by addition of 10% hydrochloric acid, then extracted with ethyl acetate. Usual work-up gave a crude mixture (180 mg), which was chromatographed on silica gel column to separate products (19) (15 mg), (18) (30 mg), and (17) (85 mg); ent-(12R)-15,16-*epoxy*-12-*hydroxy*-6-*oxo*-19-*nor*-9,4-*friedolabda*-13(16),14-*diene*-18,20-*dioic acid* 20,12-*lactone* (17), m.p. 228—229°, $\nu_{max.}$ 3200—2400, 1755, 1710, 1600, 1505, 1175, 1160, and 875 cm^{-1}, δ 7·46 (2H, m), 6·42 (1H, m), 5·43 (1H, t, *J* 8·5 Hz, 12-H), 2·43 (2H, d, *J* 8·5 Hz, 11-H_2), and 1·09 (3H, d, *J* 6 Hz) (Found: M^+, 346·139. $C_{19}H_{22}O_6$ requires *M*, 346·141); the 2-*methoxyethyl ester* (18), m.p. 96°, $\nu_{max.}$ 1755, 1730, 1715, 1600, 1505, 1175, 1160, and 875 cm^{-1}, δ 7·49 (2H, m), 6·42 (1H, m), 5·43 (1H, t, *J* 8·5 Hz, 12-H), 4·25 (2H, t, *J* 6 Hz, $-CO_2CH_2CH_2OMe$), 3·59 (2H, t, *J* 6 Hz, $-CO_2CH_2CH_2OMe$), 3·40 (3H, s, OMe), 2·46 (2H, d, *J* 8·5 Hz, 11-H_2), and 1·05 (3H, d, *J* 6·5 Hz) (Found: M^+, 404·158. $C_{22}H_{28}O_7$ requires *M*, 404·184); ent-(6R,12R)-15,16-*epoxy*-19-*nor*-9,4-*friedolabda*-5(10),13(16),14-*triene*-18,6:20,12-*diolactone* (19), oil, $\nu_{max.}$ 1770, 1505, and 875 cm^{-1}, δ 7·50 (2-H, m, 2 × α-H of furan ring), 6·43 (1H, m, β-H of furan ring), 5·45 (1H, t, *J* 8·5 Hz, 12-H), 4·88br (1H, t, *J* 8·5 Hz, 6-H), 3·08 (1H, m, 4-H), 2·66 (1H, q, *J* 8·5 and 14 Hz, 11-H_a), 2·26 (1H, q, *J* 8·5 and 14 Hz, 11-H_b), and 1·13 (3H, d, *J* 6 Hz) (Found: M^+, 328·129. $C_{19}H_{20}O_5$ requires *M*, 328·131).

Treatment of Teucvin with Potassium t-Butoxide in t-Butyl Alcohol.—Potassium (25 mg) was dissolved in t-butyl alcohol (10 ml) under nitrogen with warming. To this solution was added teucvin (2) (100 mg), and the mixture was heated at 115° for 40 min under nitrogen. After acidifying with 10% hydrochloric acid, it was extracted with dichloromethane. Usual work-up gave a crude mixture (76 mg), which was chromatographed on silica gel column to separate the dilactone (19) (5 mg) and teucvin (3 mg). Polar fractions [R_F <0·19 on t.l.c. in dichloromethane–acetone (19 : 1)] (47 mg) were methylated with diazomethane, and the methylated mixture (45 mg) was chromatographed on silica gel column to separate the keto-ester (3) (10 mg) and ent-(6R,12R)-15,16-*epoxy*-6,12-*dihydroxy*-19-*nor*-9,4-*friedolabda*-4,13(16),14-*triene*-18,20-*dioic acid* 18,6-*lactone* 20-*methyl ester* (20) (20 mg), oil, $\nu_{max.}$ 1745, 1720, 1690, 1505, and 875 cm^{-1}, δ 7·43 (2H, m, 2 × α-H of furan ring), 6·47 (1H, m, β-H of furan ring), 4·94 (1H, t, *J* 6 Hz, 12-H), 4·82 (1H, m, 6-H), 3·60 (3H, s, CO_2Me), and 0·92 (3H, d, *J* 6 Hz) (Found: M^+, 360·153. $C_{20}H_{24}O_6$ requires *M*, 360·157).

Treatment of Teucvin with Potassium t-Butoxide in Dimethyl Sulphoxide.—Potassium (28 mg) was dissolved in t-butyl alcohol (2 ml) by warming. Evaporation of the solvent with repeated addition of benzene to remove t-butyl alcohol left potassium t-butoxide, to which a solution of teucvin (2) (100 mg) in dimethyl sulphoxide (4 ml) was added. The mixture was stirred at 80° for 2 h. After acidification, under ice-cooling, with water and 10% hydrochloric acid, the mixture was extracted with dichloromethane. Usual work-up gave a mixture (84 mg), which was separated into the starting material (40 mg) and the dilactone (19) (5 mg) (identified by t.l.c. and i.r.) by chromatography on a silica gel column.

Birch Reduction of the Hexahydro-derivative (9) *of Teucvin.*—To a solution of lithium (100 mg) in liquid ammonia (30 ml) was added a solution of teucvin hexahydro-derivative (9) (100 mg) in absolute ethanol (3 ml), and the mixture was stirred for 45 min. After addition of ammonium chloride to decompose excess of lithium, ammonia was allowed to evaporate off at room temperature to leave a residue, which, after acidifying with 10% hydrochloric acid under ice-cooling, was extracted with ethyl acetate. Usual work-up and chromatography of the crude product

(92 mg) gave ent-15,16-*epoxy*-6β,18-*dihydroxy*-19-*nor*-9,4-*friedolabdan*-20-*oic acid* (22) (57 mg), oil, $\nu_{max.}$ 3350, 1695, and 1048 cm^{-1} (Found: M^+, 340·222. $C_{19}H_{32}O_5$ requires M, 340·225). The diol (22) (29 mg) was acetylated by acetic anhydride (1·5 ml) in pyridine (1·5 ml) and the crude product was chromatographed on a silica gel column to yield the *diacetate* (23) (26 mg), oil, $\nu_{max.}$ 1725, 1685, and 1250 cm^{-1}, δ 4·62 (1H, m, $W_{\frac{1}{2}}$ 24 Hz, 6-H), 2·03 (6H, s, 2 × OAc), and 0·95 (3H, d, J 6 Hz) (Found: M^+, 424·248. $C_{23}H_{36}O_7$ requires M, 424·246).

Hydrogenation of the Keto-ester (3).—The keto-ester (3) (50 mg) was hydrogenated in 99% methanol over 5% Pd–C (3·2 mol. equiv. of hydrogen were absorbed). Usual work-up gave a crude product (54 mg), which was purified by chromatography on a silica gel column to yield ent-15,16-*epoxy*-6-*oxo*-19-*nor*-9,4-*friedolabdane*-18,20-*dioic acid* 18-*methyl ester* (24) (47 mg), oil, $\nu_{max.}$ 1730, 1710, and 1175 cm^{-1}, δ 7·84br (1H, s, CO_2H), 3·72 (3H, s, CO_2Me), 3·03 (1H, t of d, J 13 and 1 Hz, 7α-H), and 1·02 (3H, d, J 6·5 Hz) (Found: M^+, 366·203. $C_{20}H_{30}O_6$ requires M, 366·204).

Lithium Aluminium Hydride Reduction of the Keto-ester (24).—To a solution of (24) (50 mg) in tetrahydrofuran (6 ml) was added a mixture of lithium aluminium hydride (120 mg) in tetrahydrofuran (6 ml), and the mixture was refluxed for 2 h. Usual work-up gave an oily product (42 mg) which was purified by chromatography on a silica gel column to yield a pure oil (26 mg), which was identical with (22) (t.l.c., i.r., and mass spectra). The diacetate of this compound was identical with (23) (t.l.c., i.r., and n.m.r. spectra).

Hydrogenation of the Hydroxy-ester (4).—Hydrogenation of (4) (100 mg) in 99% methanol (20 ml) over 5% Pd–C (120 mg) consumed 3 mol. equiv. of hydrogen. Usual work-up gave a crude product (103 mg), which was purified by chromatography on a silica gel column to give oily ent-15,16-*epoxy*-6β-*hydroxy*-19-*nor*-9,4-*friedolabdane*-18,20-*dioic acid* 18-*methyl ester* (25) (72 mg), $\nu_{max.}$ 3600, 3500—2400, 1720, 1690, and 1170 cm^{-1}, δ [$(CD_3)_2CO$] 8·04 (1H, s, CO_2H), 3·56 (3H, s, CO_2Me), and 0·98 (3H, d, J 6 Hz) (Found: M^+, 368·220. $C_{20}H_{32}O_6$ requires M, 368·220).

Sodium Borohydride Reduction of the Ketone (24).—To a solution of (24) (30 mg) in tetrahydrofuran (4 ml) was added sodium borohydride (30 mg), and the mixture was stirred for 1 h under ice-cooling. After filtration, the filtrate was neutralized with dil. acetic acid and concentrated *in vacuo*. Acidifying with 10% hydrochloric acid, extraction of the mixture with ethyl acetate, and usual work-up gave crude substance (31 mg), which was purified by chromatography on a silica gel column to isolate a pure oil (24 mg); its identity with (25) was shown by t.l.c. and i.r. spectrum.

Lithium Aluminium Hydride Reduction of Compound (25).—To a solution of compound (25) (70 mg) in tetrahydrofuran (7 ml) was added a mixture of lithium aluminium hydride (70 mg) in tetrahydrofuran (7 ml), and the mixture was stirred for 35 min at room temperature. Usual work-up gave the diol (22) (52 mg) (identified by t.l.c. and i.r.). Usual acetylation of the substance (40 mg) with acetic anhydride (2 ml) and pyridine (2 ml) gave the oily diacetate (23) (35 mg) (t.l.c. and i.r.).

Birch Reduction of Teucvin (2).—To a solution of lithium (300 mg) in liquid ammonia (30 ml) was added a solution of teucvin (2) (100 mg) in a mixture of ethanol (3 ml) and tetrahydrofuran (2 ml) under stirring, and the mixture was stirred for 45 min. Usual work-up gave a crude substance (82 mg), which was chromatographed on a silica gel column to separate ent-15,16-*epoxy*-6β,18-*dihydroxy*-19-*nor*-9,4-*friedolabda*-13(16),14-*dien*-20-*oic acid* (26) (16 mg), m.p. 210—212° (from ethyl acetate), $\nu_{max.}$ (KBr) 1712, 1505, 1185, 1045, 1020, and 875 cm^{-1} (Found: C, 67·75; H, 8·55%; M^+, 336·194. $C_{19}H_{20}O_5$ requires C, 67·85; H, 8·4%; M, 336·194), and the hexahydro-derivative (22) (30 mg).

Lithium Aluminium Hydride Reduction of the Hydroxy-ester (4).—To a solution of (4) (28 mg) in tetrahydrofuran (2 ml) was added a mixture of lithium aluminium hydride (28 mg) in tetrahydrofuran (2 ml), and the mixture was stirred for 15 min at room temperature. Usual work-up gave a crystalline product (27 mg), which was purified by chromatography on a silica gel column and recrystallization from ether to yield a pure diol, m.p. 185—188°, identical with an authentic sample of (7) (mixed m.p. and i.r. spectrum).

Birch Reduction of the Diol (7).—To a solution of lithium (227 mg) in liquid ammonia (30 ml) was added dropwise a solution of the diol (7) (73 mg) in a mixture of ethanol (3 ml) and tetrahydrofuran (2 ml), and the mixture was stirred for 45 min. Usual work-up gave a mixture of acidic products, which was separated by chromatography on a silica gel column into a crystalline and an amorphous product. The former was recrystallized to yield a pure compound (44 mg), m.p. 210—212° (from ethyl acetate) (Found: M^+, 336·193. $C_{19}H_{28}O_5$ requires M, 336·194), identical with the diol acid (26) (mixed m.p. and i.r. comparison). The amorphous product (20 mg) was identical with the hexahydro-derivative (22) (i.r. comparison).

Acetylation of the Diol Carboxylic Acid (26).—The usual acetylation procedure with (26) (30 mg) using acetic anlhydride (2 ml) and pyridine (2 ml) yielded the *diacetate* (27) (26 mg) as an oil, $\nu_{max.}$ 1725, 1685, 1500, 1250, and 870 cm^{-1}, δ 7·37 (2H, m, 2 × α-H of furan ring), 6·28 (1H, m, β-H of furan ring), 4·65 (1H, m, $W_{\frac{1}{2}}$ 28 Hz, 6-H), 4·06 (2H, m, 18-H_2), 2·05 (6H, s, 2 × Ac), and 0·96 (3H, d, J 6 Hz) (Found: M^+, 420·215. $C_{23}H_{32}O_7$ requires M, 420·215).

Hydrogenation of [6,10-$^2H_2$]*Teucvin* (14).—[6,10-$^2H_2$]-Teucvin (14) (157 mg) was hydrogenated in 99% methanol (30 ml) over 5% Pd–C (190 mg) to absorb 3 mol. equiv. of hydrogen. Usual work-up and purification of the crude product by chromatography over a silica gel column gave ent-(6R)-[6,10-$^2H_2$]-15,16-*epoxy*-6-*hydroxy*-19-*nor*-9,4-*friedolabd*-4-*ene*-18,20-*dioic acid* 18,6-*lactone* (28) as an oil, $\nu_{max.}$ 1745 and 1695 cm^{-1}, δ 9·00 (1H, s, CO_2H) and 1·00 (3H, d, J 6·5 Hz) (Found: M^+, 336·192. $C_{19}H_{24}D_2O_5$ requires M, 336·191).

Birch Reduction of the Dideuterio-derivative (28).—Birch reduction of (28) (125 mg) with lithium (450 mg), ethanol (3·5 ml), and liquid ammonia (30 ml) gave as major product ent-[6,10-$^2H_2$]-15,16-*epoxy*-6β,18-*dihydroxy*-19-*nor*-9,4-*friedolabdan*-20-*oic acid* (29) (75 mg) as an oil, $\nu_{max.}$ 3350, 2120 (C–D), 1695, and 1048 cm^{-1} (Found: M^+, 342·239. $C_{19}H_{30}D_2O_5$ requires M, 342·238).

Acetylation of the [6,10-$^2H_2$]*Diol Carboxylic Acid* (29).—Acetylation of (29) (60 mg) by acetic anhydride (4 ml) and pyridine (4 ml) and usual work-up gave the *diacetate* (30) (60 mg) as an oil, $\nu_{max.}$ 1725, 1685, and 1250 cm^{-1}, δ 2·03 (1H, s, 2 × OAc) and 0·93 (3H, d, J 6 Hz) (Found: M^+, 426·256. $C_{23}H_{34}D_2O_7$ requires M, 426·259).

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