Structure of the Sesquiterpene Lactone Laurenobiolide

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Summary A new germacranolide, laurenobiolide, has been isolated from *Laurus nobilis* L. and its stereostructure was elucidated on the basis of the spectroscopic data for the lactone and for some reaction products.

LAURENOBIOLIDE (I), m.p. 101—103°, $C_{17}H_{22}O_4$(M^+ 290), [α] + 17·1° (EtOH), was isolated as a major component from the roots of *Laurus nobilis* L. (Japanese name Gekkeiju). The i.r. [ν_{max}($CHCl_3$) 1760 (γ-lactone), 1738 (AcO), 1656 and 958 cm^{-1} (·C:C·)], n.m.r. [δ($CDCl_3$) 1·68 (s, two olefinic Me), 2·05 (OAc), 5·88 and 6·35 (dd, *J* 3·0 and 1·0 Hz, *exo*-CH_2), 4·0 (m, ·CH·O·CO·), 4·5—5·3 (2H, m, olefinic protons), and 5·33 p.p.m. (approx. t, ·CH·OAc), the last three signals are broadened suggesting the presence of ring inversion[1]], and c.d. spectra {$[\theta]_{208}$ + 43,800 and $[\theta]_{253}$ − 5660 (EtOH)} indicated that (I) is a germacranolide acetate.

Reduction of the lactone (I) with $NaBH_4$ (1 equiv., room temp., 30 min) yielded a mixture of dihydrolactone epimers (II) (*ca.* 1:1), one of which was isolated by fractional crystallisation: (IIa) (38%), m.p. 142—144°, $C_{17}H_{24}O_4$, (M^+ 292), $[\alpha]_D$ + 120·3° (EtOH), i.r. [ν_{max}($CHCl_3$) 1762 (γ-lactone), 1728 (OAc), and 1666 cm^{-1} (·C:C·)], n.m.r. [δ($CDCl_3$) 1·39 (d, *J* 6·8 Hz, 13-Me), 1·58 (br s, 14-Me), 1·69 (d, *J* 1·2 Hz, 15-Me), 2·00 (OAc), 4·17 (approx. t, 8-H), 4·62 (5-H), 4·84 (m, 1-H), 5·45 p.p.m. (approx. t, 6-H)]. The other epimeric isomer (IIb) was not obtained in a pure state, but the proton signals of (IIb) were clearly distinguishable from those of (IIa) in the spectrum of the mixture. The assignment of the configuration of the new methyl group in (IIa) as pseudoequatorial was suggested on the basis of the solvent shift[2] [Δδ ($CDCl_3$–C_6D_6): +0·04 in (IIa) and +0·17 in (IIb)]. Furthermore, the c.d. of (IIa) {$[\theta]_{216}$ + 111,000 (EtOH)} showed that two double bonds were transannularly "cross-oriented".[3] Hydrolysis of (IIa) followed by acidification and acetylation effected regeneration of the original dihydrolactone (IIa) indicating that the lactone linkage in (IIa) must be C(7)–C(8) and not C(7)–C(6) as in the costunolide type.[4]

Cyclisation of (IIa) with $SOCl_2$ or $POCl_3$† yielded the expected product (III) (30%) along with a minor amount of Δ^3-isomer, m.p. 120—124°, i.r. [ν_{max}($CHCl_3$) 1773 (γ-lactone),

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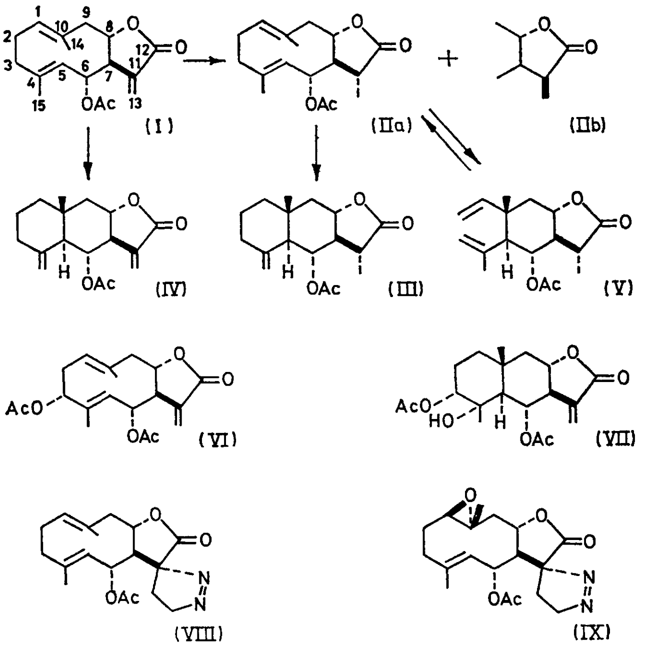
† The role of these reagents in this reaction will be described in the full paper.



1729 (OAc), and 1650 cm^{-1} (·C:C·)], n m r [δ(CDCl$_3$) 0·87 (s, 14-Me), 1·15 (d, *J* 6·8 Hz, 13-Me), 1·99 (OAc), 4·06 (ddd, *J* 12·0, 11·0, and 3·9 Hz, 8-H), 4·32 and 4·81 (br s, *exo*-CH$_2$), and 5·22 p p m (t, *J* 10·2 Hz, 6-H)] These data show that the 5-, 6-, 7-, and 8-protons are *trans*-diaxially disposed Hydrolysis of (III) followed by acidification afforded a hydroxy-acid which was relactonised to (III) by vigorous treatment with acid This implies that the lactone ring in (III) is "*trans*-fused" Since cross orientation of the double bonds in (IIa) was suggested from the c d , the ring junction of the six-membered rings in (III) may be *trans* Similarly, (I) was cyclised to (IV) (labile oil, 26%) which gave reasonable i r , n m r , and c d spectra

When (IIa) was heated at 205°, a reversible Cope rearrangement occurred to give a mixture (6:4) of (IIa) and (V), m p 138—140°, $[\alpha]_D + 12·2°$ (EtOH), i r [ν_{max} (CHCl$_3$) 1775 (γ-lactone), 1731 (OAc), 3085, 1648, and 903 cm^{-1} (·C:C·)], n m r [δ(CDCl$_3$) 1·11 (s, 14-Me), 1·15 (d, *J* 7·0 Hz, 13-Me), 1·68 (br s, 15-Me), 1·97 (OAc), 2·21 (d, *J* 10·8 Hz, 5-H), 4·08 (ddd, *J* 11·7, 11·1, and 4·0 Hz, 8-H) 4·63 and 4·95 (2H, 3-H), 5·24 (t, *J* 10·8 Hz, 6-H), 4·85—5·05 (2H, 2-H), and 5·78 p p m (dd, *J* 17·3 and 11·1 Hz, 1-H)] Again, it is highly probable that the 5-, 6-, 7-, and 8-protons are *trans*-diaxially disposed

Relative configurations of (III) and (V) were confirmed by N O E experiments Since considerable N O E s‡ were observed for [14-Me] → 6-H (8%), [14-Me] → 8-H (19%), and [6-H] → 8-H (7%), but not for [14-Me] → 5-H or [13-Me] → 6-H, then 14-Me, 6-H, and 8-H are mutually 1,3-diaxial, and the relationship between 14-Me and 5-H is virtually *trans*, and 13-Me is equatorially oriented Accordingly, the double bonds in the original germacranolides (I) and (II) must be *trans-trans* [5]

The absolute configuration of laurenobiolide (I) was suggested by comparison of the c d spectra[6] of (I) and its derivatives with those of known compounds (see Table)

As shown in the Table, the signs of the Cotton effects (CE) of laurenobiolide (I), cyclised laurenobiolide (IV), and the pyrazoline derivative (VIII) were the same as those of reference compounds (VI), (VII), and (IX), respectively. Furthermore, the sign of the CE of the saturated lactone (III), and that of (V), agree with that predicted from the lactone rule [9] Consequently, the formula (I) represents the absolute configuration of laurenobiolide

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TABLE

C d. spectra of laurenobiolide (I), *its derivatives, and some reference compounds*

Compound	λ_{max}/nm	[θ]	Solvent
Laurenobiolide (I)	253	−5650	EtOH
Chamissonin diacetate (VI)[7]	248	−3630	MeOH
Cyclised laurenobiolide (IV)	255	+1930	EtOH
Cyclised chamissonin diacetate (VII)[7]	255	+1280	MeOH
Pyrazoline derivative (VIII) of laurenobiolide	243	−8470	EtOH
	327	−55 900	
Pyrazoline derivative (IX) of pyrethrosin[8]§	237	−13,800	EtOH
	327	−51 300	
Cyclised dihydrolaurenobiolide (III)	210	−7750	EtOH
Cope product (V)	215	−8360	EtOH

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‡ Proton signals saturated are shown in square brackets

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