Lipiferolide, a Cytotoxic Germacranolide, and γ-Liriodenolide, Two New Sesquiterpene Lactones from *Liriodendron tulipifera*

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Summary Chemical and spectral evidence is presented for the structure and stereochemistry of two new sesquiterpene lactone acetates, lipiferolide and γ-liriodenolide, isolated from the leaves and root bark, respectively, of *Liriodendron tulipifera* L.

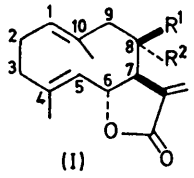
THE root bark of *L. tulipifera* L. (family Magnoliaceae) had previously yielded costunolide (Ia), tulipinolide (Ib) and epitulipinolide (Ic) as the cytotoxic† constituents.[1,2] The leaves, on the other hand, yield lipiferolide (II),‡ $C_{17}H_{22}O_5$, m.p. 118°—119°, $[\alpha]_D$ — 125° (MeOH), δ ($CDCl_3$) 1·38 (3H, s, epoxy-Me) and 2·84 p.p.m. (1H, d, *J* 8·2 Hz, epoxy-H). N.m.r. double-irradiation experiments helped establish the structure.

Epoxidation of epitulipinolide (Ic) with 1 mol. equiv. of *m*-chloroperoxybenzoic acid gave exclusively the 1,10-epoxide (III), m.p. 148—149°, $[\alpha]_D$ +28° (MeOH); δ 1·18 (3H, s, epoxy-Me), 1·90 p.p.m. (3H, d, *J* 1·3 Hz, olefinic Me), which is isomeric with lipiferolide and useful in the assignment of the position of epoxidation in both compounds. The 1,10-epoxide showed in the n.m.r. spectrum a typical split AB pattern for the C-5 and C-6 protons of the C-6 *trans* αβ-unsaturated γ-lactones with a *trans*-olefin at C-4.[2] With excess of *m*-chloroperoxybenzoic acid, epitulipinolide gave the diepoxide (IV), $C_{17}H_{22}O_6$, m.p. 207—208°, $[\alpha]_D$ — 53° (MeOH) [δ 1·38 and 1·45 p.p.m. (s, epoxy-Me)]. An identical product was obtained on epoxidation of lipiferolide, thus establishing the position of the functional

† Determined in Eagles' KB cell culture according to the protocol of the National Cancer Institute. Lipiferolide exhibited an ED_{50} of 0·16 μg/ml.

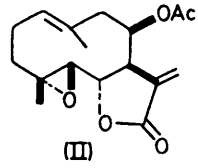
‡ Satisfactory elemental analyses and spectral data (i.r., u.v., n.m.r. and m.s.) were obtained for all new compounds.

groups, the germacrane ring, and the absolute stereochemistry at C-6, C-7, and C-8. Assignment of the other asymmetric centres necessarily follows from the discussion on γ-liriodenolide (Va).

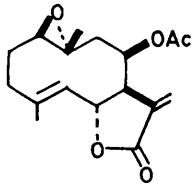


(I)

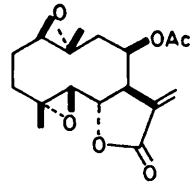
a; $R^1 = R^2 = H$
b; $R^1 = H$, $R^2 = OAc$
c; $R^1 = OAc$, $R^2 = H$



(III)

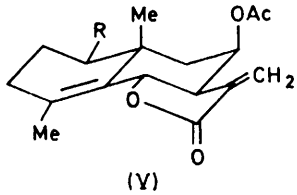


(III)



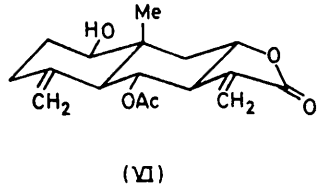
(IV)

Extended column chromatography of the ethanolic root-bark extract provided, after elution of epitulipinolide, the eudasmanolide, γ-liriodenolide (Va), $C_{17}H_{22}O_5$ (M^+ 306), m.p. 179—180°, $[\alpha]_D$ − 4° (MeOH). The n.m.r. spectrum is almost identical with that of γ-cycloepitulipinolide (Vb)[2] except for the presence of a deuterium-exchangeable proton at δ 1·7 p.p.m. (1H) and a broadened double doublet at δ 3·57 p.p.m. The J values (6·6 and 8·4 Hz) for this pattern suggest coupling to a vicinal axial and to an equatorial proton. A similar pattern is recorded for β-cyclopyrethrosin (VI)[3,4] which possesses a β-OH group at C-1, but differs from the broadened doublet pattern (J 3 Hz) of ludalbin[5] which contains α-OH at C-1. Cyclization of epitulipinolide 1,10-epoxide (III) under acid conditions gave a mixture of cyclo-products from which the γ-cyclo-isomer was isolated by partition chromatography. This was identical (mixture m.p., i.r., n.m.r. and t.l.c.) with γ-liriodenolide. Consequently, the oxygen at C-1 in epitulipinolide 1,10-epoxide must be attached as shown in (III) with C-1 in the *R*-configuration. Furthermore, the configuration at C-10 must also be *R*, since epitulipinolide (Ic) and tulipinolide (Ib) have been interrelated, and the latter compound has been transformed to laurenobiolide (VII)[6] for which the *trans–trans*-stereochemistry of the double bonds has been established.[7]

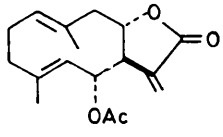


(V)

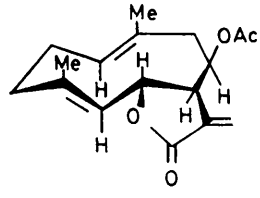
a ; R = OH
b ; R = H



(VI)



(VII)



(VIII)

Tne c.d. peak at 222 nm, $[\theta]$ + 146,000 for epitulipinolide (Ic) due to the chiral disposition of the transannular conjugation of the 1,5-diene has been related to conformation (VIII),[8] where the double bonds are 'crossed' and the vinyl methyl groups *syn*. Also, the $J_{5,6}$ value of 10 Hz is in agreement with a *trans*-arrangement of vicinal protons. Epoxidation of epitulipinolide in conformation (VIII) would give the diepoxide (IV) with stereochemistry at C-4 and -5 as *R* and *S*, respectively, requiring that in lipiferolide (II) the 4,5-epoxide be similarly placed.

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