

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.

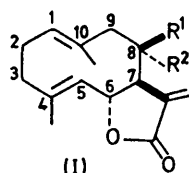
THE root bark of *L. tulipifera* L. (family Magnoliaceae) had previously yielded costunolide (Ia), tulipinolide (Ib) and epitulipinolide (Ic) as the cytotoxic† constituents.^{1,2} The leaves, on the other hand, yield lipiferolide (II), ‡ C₁₇H₂₂O₅, m.p. 118°—119°, [α]_D - 125° (MeOH), δ (CDCl₃) 1.38 (3H, 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°, [α]_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* $\alpha\beta$ -unsaturated γ -lactones with a *trans*-olefin at C-4.² With excess of *m*-chloroperoxybenzoic acid, epitulipinolide gave the diepoxide (IV), C₁₇H₂₂O₆, m.p. 207—208°, [α]_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

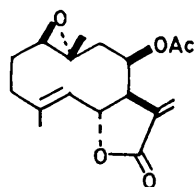
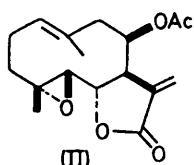
† Determined in Eagles' KB cell culture according to the protocol of the National Cancer Institute. Lipiferolide exhibited an ED₅₀ of 0.16 μ g/ml.

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

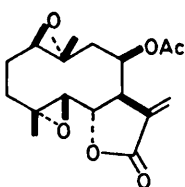
groups, the germacrane ring, and the absolute stereochemistry at C-6, C-7, and C-8. Assignment of the other asymmetric centres necessarily follows from the discussion on γ -liriodenolide (Va).



- (I)
 a; $R^1 = R^2 = H$
 b; $R^1 = H, R^2 = OAc$
 c; $R^1 = OAc, R^2 = H$

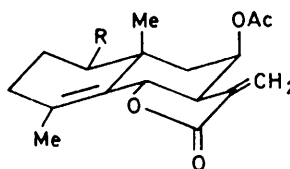


(III)



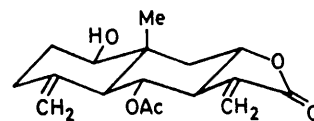
(IV)

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

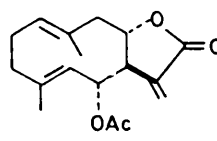


(V)

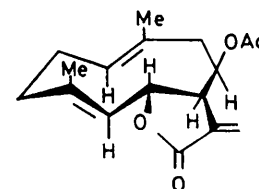
- a; $R = OH$
 b; $R = H$



(VI)



(VII)



(VIII)

Extended column chromatography of the ethanolic root-bark extract provided, after elution of epitulipinolide, the eudasmanolide, γ -liriodenolide (Va), $C_{17}H_{24}O_6$ (M^+ 306), m.p. 179–180°, $[\alpha]_D - 4^\circ$ (MeOH). The n.m.r. spectrum is almost identical with that of γ -cycloepitulipinolide (Vb)³ 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 ludalbin⁵ 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 -

The 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.

This research has been supported in part by a research grant from the U.S. Public Health Service for which we are grateful.

(Received, 4th August 1972; Com. 1374.)

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