Tetrahedron Letters No. 45, pp 3957 - 3960, 1975. Pergamon Press. Printed in Great Britain.

NEW SESQUITERPENE LACTONE AND ALDEHYDE OF *FRULLANIA TAMARISCI SUBSP. OBSCURA* (HEPATICAE).

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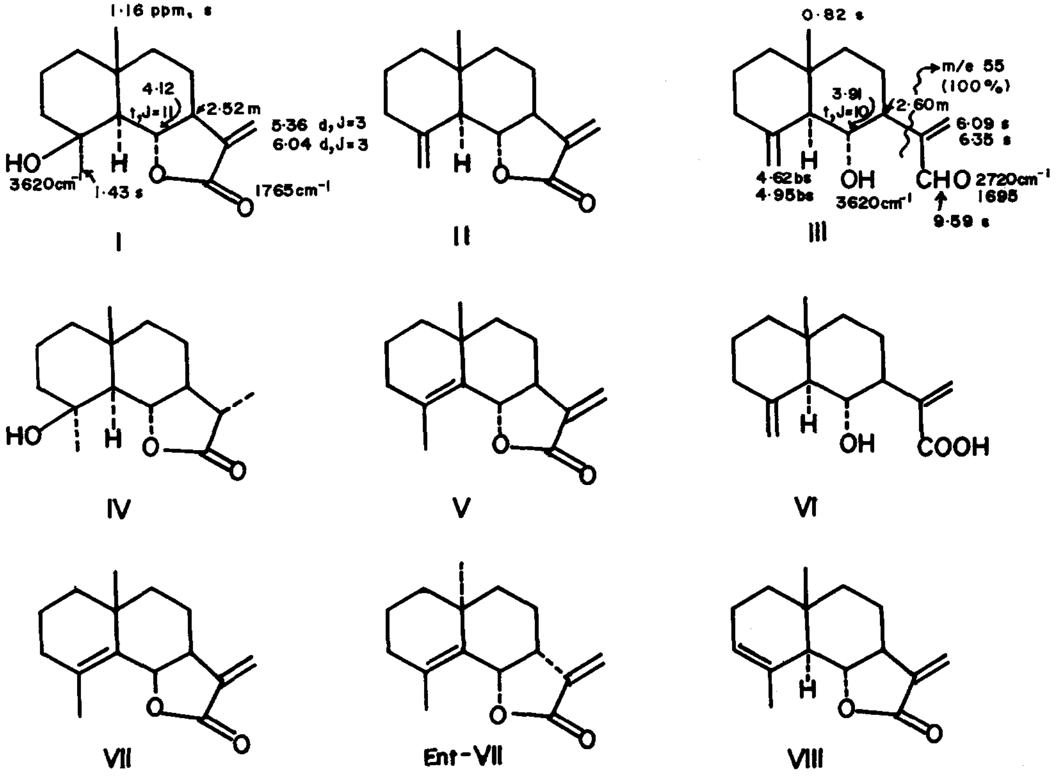
(Received in UK 1 September 1975; accepted for publication 29 September 1975)

Frullania species (Hepaticae, Jungermanniales)are widespread epiphytes[1,2] containing allergy-inducing sesquiterpene lactones. We have previously reported the isolation and synthesis of (-)-frullanolide (VII) from *F.tamarisci* (L.) Dum. and of (+)-frullanolide (ent-VII), several new ent-eudesmanolides and eremophilanolides from *F. dilatata* (L.) Dum.. These lactones are the allergenic agents (Contact dermatitis)[1,3a,b].

As part of a screening programme of the allergy-inducing components in the Frullaniaceae and of a study on the interrelation between structures of sesquiterpene lactones and biological activity, we investigated the chemical constitution of *Frullania tamarisci subsp. obscura (Verd.)* Hattori. This japanese sub-species elaborates a new sesquiterpene lactone (I) and the previously-known β-cyclocostunolide (II) having potentially allergenic properties, and a new sesquiterpene aldehyde (III), which may be one of the precursors of the eudesmanolides found in the Frullaniaceae.

F. tamarisci subsp. obscura growing on *Aesculum turbinata* was collected in October 1974. It was dried at room temperature and extracted with ether. The crude extract was carefully chromatographed on silica gel using *n*-hexane-ethyl acetate ; sesquiterpene lactones and aldehyde were separated and purified by preparative thin-layer chromatography to furnish the two eudesmanolides I and II, and III, in the respective yields of 11.3%, 1.3%, and 2.6% of the total extract.

Lactone (I). mp 148-149°C, $(\alpha)_D$ + 47° (c, 0.16), $C_{15}H_{22}O_3$ (M^+, 250). The presence of the α-methylene γ-lactone and hydroxy groups was deduced from the spectral properties (Fig.1) of the substance and from the formation of dihydroderivative (IV), mp 108-109°C, $C_{15}H_{24}O_3$ (M^+, 252) by $NaBH_4$ reduction. The 6(7) position and trans-configuration of the lactone ring was manifest in the NMR spectrum, in which H-6 showed as a triplet (J = 11Hz), and α-methylene protons both as doublets (J = 3Hz)[5]. The negative Cotton effect[6], $(\Phi)_{252\ nm}$ -2500, indicated the 6α configuration. The location of hydroxyl group at C-4 and its configuration were confirmed by the transformation of I to V. Treatment of I with thionyl chloride-pyridine yielded γ-cyclocostunolide (=arbusculin B) (V) (98% yield), mp 87-88°C, $(\alpha)_D$ +35° (c, 0.20), identical with an authentic sample derived from costunolide[7]. The large paramagnetic shifts of Me-10, Me-4 and H-6, and the preferential dehydration of I to V, established the β-disposition (axial)of the hydroxyl group. In fact, the physical, spectral and chemical properties of I were very different from those of arbusculin A (4-epimer of I), which have been isolated from *Artemisia arbuscula subsp. arbuscula*[8]. The lactone (I) is the first natural 4β-OH eudesmanolide described.



I II III

IV V VI

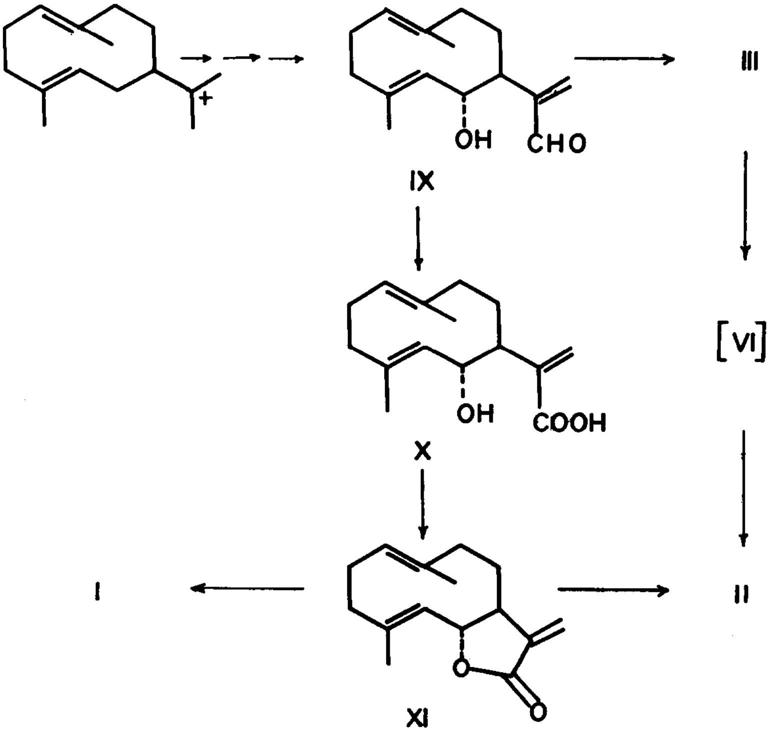
VII Ent-VII VIII

Fig. 1.

Lactone II, mp 68-69°C. (α)$_D$ +165° (c, 0.70), $C_{15}H_{22}O_3$ (M^+, 232) isolated along with lactone I was identical in all respects (NMR, IR, mp) with the authentic sample of (+)-II.

Sesquiterpene aldehyde (III): (α)$_D$ +28° (c, 0.63), $C_{15}H_{22}O_2$ (M^+, 234) The structure was deduced from the spectral properties (Fig.1) of the substance itself and from a chemical correlation. The stereochemistry of the hydroxyl and α,β-unsaturated aldehyde functions was manifest in the NMR spectrum in which H-6 showed as a triplet (J = 10Hz). The oxidation of III with Ag_2O gave an acid, mp 142-143°C, (α)$_D$ +39° (c, 0.80), $C_{15}H_{22}O_3$ (M^+ 250), whose physical, spectral and chemical properties were in accord with those of sesquiterpene acid (VI), derived from II by hydrolysis. $LiAlH_4$ reduction of II, followed by the oxidation with MnO_2 gave an aldehyde, which was identical in all respects (NMR, IR) with the natural aldehyde (III).

The cooccurrence of costunolide (XI) and eudesmanolides in *F. tamarisci* (L.) Dum.[9] may strongly support that costunolide is the precursor of cyclized lactones[8,10], eudesmanolides and eremophilanolides (from a eudesmane-type precursor *via* a 1,2 shift of an angular methyl function), although it is not possible to determine whether the ring oxidation occurs before or after construction of C_{12}-oxygenated group. Sesquiterpene aldehydes such as possible precursors of these lactones: the 6,12-oxygenated trans-cyclodecadiene (IX) are derived formally from *trans*, *trans*-farnesyl pyrophosphate by the cation-olefin cyclization, may be cyclized at a early stage prior to lactonization to give the aldehyde (III). This can be oxidized to give an acid (VI), an lactonization would afford the final product (II). The intermediate of the 4β-OH lactone (I) may be a carbonium ion derived from



ıe straightforward acid catalyzed cyclization of costunolide[10,11] to give stereospecifically the 4β-OH compound (I) *in vivo*.

It is noteworthy that VI in *F. tamarisci* (L.) Dum. and VII in *F. dilatata* (L.) Dum. are the major components[3b], however, the 4β-OH eudesmanolide (I) is the major lactone in *F. tamarisci subsp. obscura*.

The *cis*-lactones described above, V, α-cyclocostunolide (VIII) and XI found in *F. tamarisci* (L.) Dum. from Scotland[9] have not been detected in the present work. On the other hand, the present subspecies elaborates II which has not been found in *F. tamarisci* (F.) Dum.[9]. Recently, a number of liverworts have shown to elaborate the enantiomers of sesquiterpenes and diterpenes common in the higher plants[12,13]. It is very interesting to note that, of the closely related taxa, *F. tamarisci subsp. obscura* and *F. dilatata*, the first two produce universal 7β sesquiterpenes like I, III, V, and VIII, on the other hand, *F. dilatata* elaborates eudesmanolides and eremophilanolides possessing the 7α configuration (ent-compounds)[3b].

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