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LIGULARENOLIDE. A NEW SESQUITERPENE LACTONE OF EREMOPHILANE TYPE

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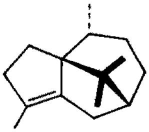
Chinese herb drug "San-Shion" (1), root of a Ligularia species, probably <u>Ligularia sibirica</u> Cass. (2), contains several kinds of sesquiterpenes, some of which were isolated and characterized as follows: cyprene (I) (3), liguloxide (II) (4), furanoligularenone (III) (1), and ligularenolide. We report here elucidation of the structure of ligularenolide.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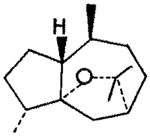
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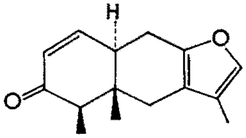
III

Ligularenolide, IV, $C_{15}H_{18}O_2$, m.p. 134.5-135°, $[\alpha]_D$ +33° (MeOH), is crystallized from petroleum ether or ethyl ether as yellow needles. Its IR spectrum shows characteristic bands of an α,β-unsaturated γ-lactone (ν_{max}^{Nujol} 1764, 1648, and 1621 cm^{-1}), and UV spectrum indicates the presence of a fully conjugated system [λ_{max}^{MeOH} 241 and 331 mμ (ε 3,560 and 20,700)]. The PMR spectra*[2] show the presence of three methyl groups; a tertiary and a secondary methyl, and one attached to sp^2 carbon. Further, there appear two olefinic proton signals at lower fields and the A-part of an AB-type quartet (J = (-)16.5 Hz)

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*[2] The PMR spectra were taken with a Varian HA-100 spectrometer operating at 100 MHz by using about 5% solutions in $CDCl_3$ and C_6D_6 containing TMS as an internal standard. Calibration of the charts were carried out by direct readings of resonance frequencies by using an HP-5212A electronic counter. The PMDR and PMTR experiments were made by using two HP-200ABR audio-oscillators in the frequency-swept and TMS- or C_6H_6-locked mode. Chemical shifts are expressed in δ (ppm downfield from TMS). Accuracies of chemical shifts and coupling constants are within ±0.02 ppm and ±0.2 Hz, respectively. We thank the NMR research group of Shionogi Research Laboratory for some PMR spectral measurements.

arising from an allylic methylene group (see the TABLE). No signal due to a proton attached to carbon bearing ether— type oxygen in the lactone ring is observed.

PMDR and PMTR experiments on IV confirmed these assignments, and further, made it possible to build up a working structure. As shown in FIG. 1 (in C_6D_6), double irradiation on the olefinic proton triplet at δ 5.39 ppm causes a collapse of the other olefinic proton doublet ($|J| = 0.8$ Hz) into a singlet and changes a multiplet pattern around δ 1.9 ppm (FIG. 1b). During this irradiation, another weak perturbation was applied at the resonance frequency of the lower-field peak of the A-part of the allylic methylene quartet to find the position of its B-part signal; this PMTR results in a splitting of a broad singlet at about 181 Hz downfield from TMS into a doublet (S; FIG. 1d). In turn, weak perturbation applied at the latter frequency changes the H_A-doublet into a typical perturbed pattern (S and B; FIG. 1e) according to the spin-tickling theory (5). The higher-field peak of the H_B-doublet is disclosed to be overlapped by the olefinic methyl signal (FIG. 1f). On double irradiation at the methyl signal (δ 0.75 ppm) the lower-field broad peak of the H_B—signal collapses into a well-resolved quartet (FIG. 1g), whose spacings of 1.7 Hz agree well with those observed in a doublet due to the olefinic methyl in $CDCl_3$. These results show the presence of long-range couplings of the two olefinic protons to each other ($|J| = 0.8$ Hz), and of H_B to the angular ($|J| = 0.5$ Hz) and the olefinic methyl protons ($|J| = 1.7$ Hz), suggesting that the olefinic methyl is attached to the double bond in the lactone ring and that the angular methyl and H_B of the isolated allylic methylene are both axial (6).

The above observations lead us to arrive at a partial structure of IVa. This can be extended to a full structure IV including stereochemistry by means of biogenetic considerations and on the basis of the observed

TABLE
PMR Spectral Data (δ in ppm)[a]

Compounds	H_1	$H_{6\alpha}$(B)	$H_{6\beta}$(A)	H_8	H_9	H_{13}	H_{14}	H_{15}
IV	5.79ABX[b] (5.39AB$\underline{X}$)	2.22d-m (1.73d-m)	2.85d (2.43d)	—	5.92m (5.68d)	1.91d (1.63m)	1.00d (~0.73$\underline{A}_3$B)	0.97s (0.75s)
V		1.81d-m (1.22d-m)	2.76d (2.33d)	4.62m[c] (~4.11m)		1.79t (1.63t)	0.91d (~0.66$\underline{A}_3$B)	0.57s (0.24s)

[a] Determined in $CDCl_3$. Values in parentheses are those observed in C_6D_6. s: singlet, d: doublet, t: triplet, m: multiplet. [b] This signal appears as a broadened triplet whose line spacings are 4.0 Hz. [c] Complex multiplet ($W_{1/2} = \sim 22$ Hz) arising from the X part of an ABC---X system.

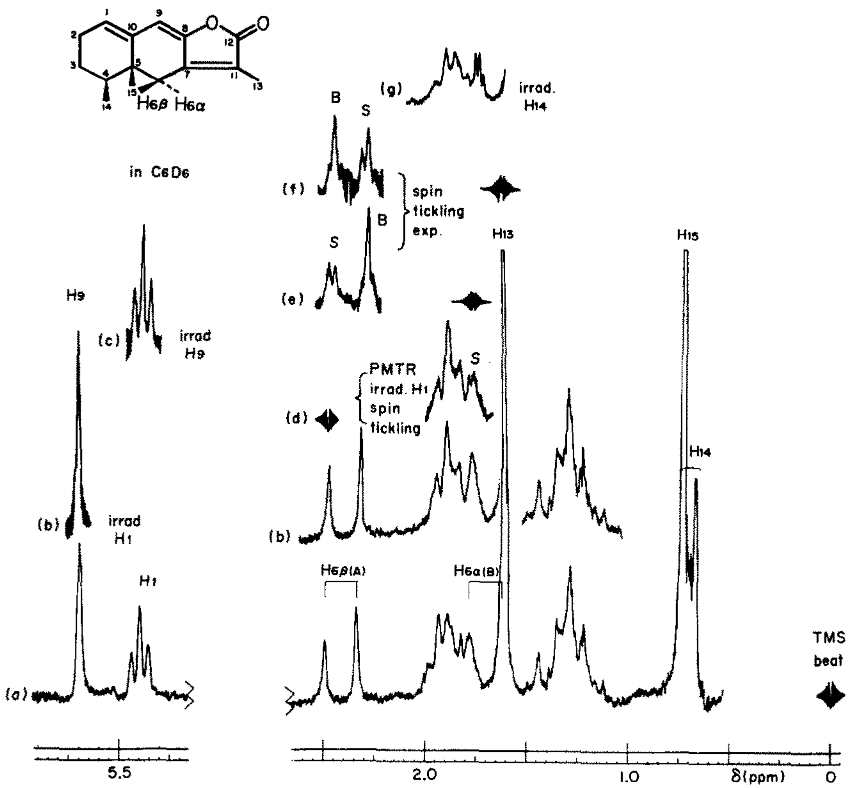
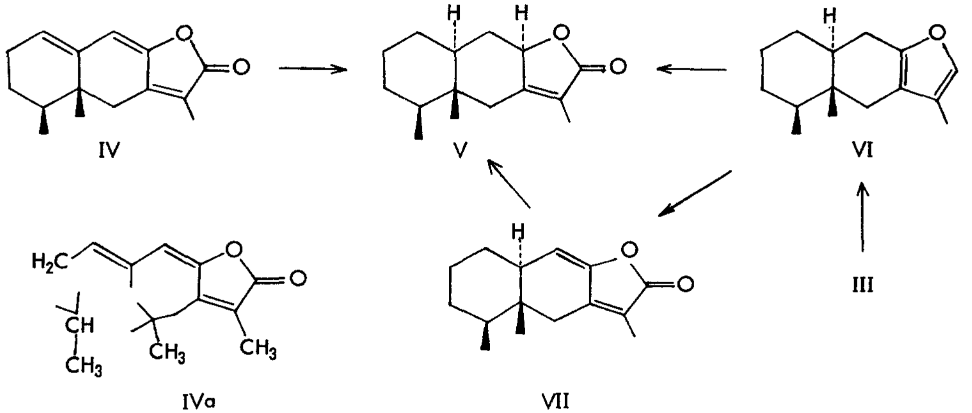


FIGURE 1. Pmr Spectra of Ligularenolide in C_6D_6 at 100 MHz.

features of long-range couplings (6).

IV was hydrogenated with 5% Pd-C in ethanol to give tetrahydroligularenolide, $C_{15}H_{22}O_2$, m.p. 114.5-115.5°, $[\alpha]_D$ -94° (MeOH), IR: ν_{max}^{Nujol} 1765, 1745, and 1678 cm^{-1} (α,β-unsaturated γ-lactone), UV: λ_{max}^{MeOH} 222 mμ (ε 24,000). In its PMR spectrum, beside the three methyl signals shifted higher-fields relative to those in IV (see the TABLE), a complex multiplet of one proton ($W_{1/2}$ =~22 Hz) due to an $\mathrm{H}-\overset{|}{\underset{|}{\mathrm{C}}}-\mathrm{O}$ group appears instead of the disappearance of the signals arising from the olefinic protons in IV. NMDR experiments in $CDCl_3$ and C_6D_6 also revealed the presence of long-range couplings of the olefinic methyl to the proton on oxygen-bearing carbon ($|J|$ = 1.4 Hz) and to H_B of the allylic methylene ($|J|$ = 1.4 Hz); the latter is further coupled to the angular methyl protons ($|J|$ = 0.5 Hz). The B-part of the AB-type quartet (J= (-)13.8 Hz) was also disclosed by spin-tickling experiments. The $W_{1/2}$ value of the $\mathrm{H-\overset{|}{\underset{|}{C}}-O}$ signal and the long-range coupling between this and the olefinic methyl protons imply that this hydrogen is axial. Thus, tetrahydroligularenolide should be expressed as V.



In fact, tetrahydroligularenolide was identified as 10-epi-eremophilenolide (V) prepared from III *via* 10-epi-furanoeremophilane (VI) (1). VI was oxydized by oxygen in the presence of reduced Pt catalyst to give V in a poor yield. On the other hand, VI was treated with dicyanodichlorobenzoquinone (7) to give an enol-lactone VII (crude, λ_{max}^{MeOH} 280 mμ), which was hydrogenated without further purification to furnish V, m.p. 114.5-115°, $[\alpha]_D$ -94° (MeOH). These lactones are identical with each other in all points of view.

The correlation between IV and III thus obtained finally establishes the structure of ligularenolide including the absolute configuration.

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