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THE STRUCTURE OF LIGULARENOLIDE

A NEW SESQUITERPENE LACTONE OF EREMOPHILANE TYPE[1]

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Abstract—Ligularenolide, a constituent of "San-Shion" (root of a *Ligularia* species), was isolated and the structure was established as **1**.

IN THE course of the structural investigation of shionone,[2] a new tetracyclic triterpene from the Chinese herb drug "Shion" (root of *Aster tataricus* L.), we received delivery of a similar herb which gave no shionone by extraction. This herb was later identified as "San-Shion"[3] (mountain Shion; root of a *Ligularia* species) containing several kinds of sesquiterpenes, some of which were isolated and characterized as cyperene,[4] liguloxide[5] and furanoligularenone.[3] In this report we wish to present the isolation and structure of the fourth constituent, ligularenolide.

Ligularenolide (**1**) was isolated from the benzene extract of "San-Shion", and crystallized from light petroleum or ethyl ether as yellow needles, m.p. 134·5–135°, $[\alpha]_D$ $-332°$† (MeOH). Elemental analysis and the mass spectrum indicate the formula $C_{15}H_{18}O_2$. The IR spectrum shows characteristic bands for an α,β-unsaturated γ-lactone (1764, 1648 and 1621 cm^{-1}), and the UV spectrum indicates the presence of a conjugated system [λ_{max} (MeOH) 261† and 331 mμ (ε 3560 and 20,700)]. The PMR spectra in $CDCl_3$ and in C_6D_6 (see Figs 1a and 2a, respectively) show the presence of three Me groups: a tertiary and a secondary Me group, and one attached to a double bond. Two olefinic protons resonate at lower fields, and the A-part of an AB-type quartet [$J = (-)16·5$ Hz] arising from an allylic methylene group appears in the spectra. No resonance was observed in the region which would be expected for a proton at the lactone terminus. The PMR spectral data are listed in the Table.

PMDR and PMTR experiments on ligularenolide confirmed these assignments and led to a working structure (**1**) for ligularenolide. As shown in Fig 2 (in C_6D_6), irradiation on the olefinic proton triplet at δ 5·39 ppm (1 H) causes a collapse of the other olefinic proton doublet at δ 5·68 (1 H, $J = 0·8$ Hz) into a singlet and changes a multiplet pattern around δ 1·9 ppm (Fig 2b). In the reverse experiment, irradiation on the doublet at δ 5·68 ppm results in distinct sharpening of the triplet at δ 5·39 ppm (Fig 2c);

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† Previously these values have been reported as +33° and 241 mμ. The authors correct them to −332° and 261 mμ respectively for physical constants of the same compound with a sincere apology for our carelessness.

TABLE. PMR SPECTRAL DATA[a]

Compounds	H_1	$H_{6\alpha(B)}$	$H_{6\beta(A)}$	H_8	H_9	H_{13}	H_{14}	H_{15}
1	5·79ABX[b] (5·39AB$\underline{\mathrm{X}}$)	2·22d–m (1·73d–m)	2·85d (2·43d)	— —	5·92m (5·68d)	1·91d (1·63m)	1·00d (~0·73$\underline{\mathrm{A}}_3$B)	0·97s (0·75s)
2		1·81d–m (1·22d–m)	2·76d (2·33d)	4·62m[c] (~4·11m)		1·79t (1·63t)	0·91d (~0·66$\underline{\mathrm{A}}_3$B)	0·57s (0·24s)

[a] δ in ppm; determined in $CDCl_3$. Values in brackets 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 ($W_{1/2}$ = *ca* 22 Hz) arising from the X part of an ABC---X system.

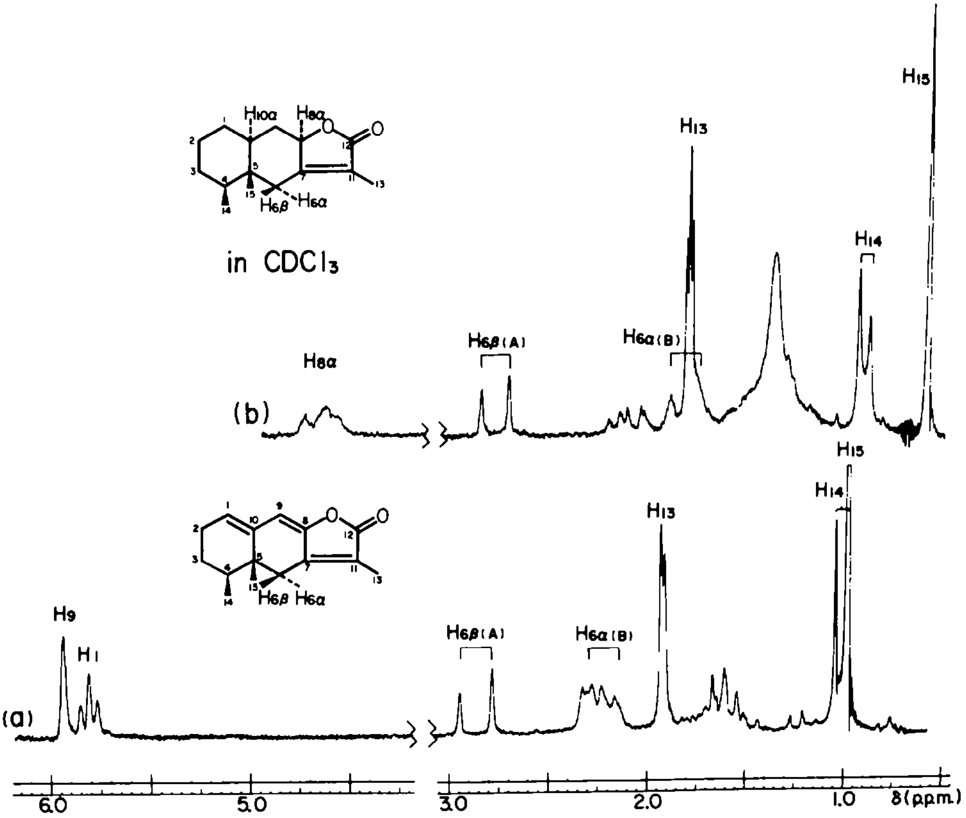


FIG 1. PMR spectra of ligularenolide (a) and tetrahydroligularenolide (b) in $CDCl_3$ at 100 MHz.

this suggests the presence of a methylene group adjacent to sp^2 carbon bearing the olefinic proton (at δ 5·39 ppm). During irradiation on the triplet signal at δ 5·39 ppm, 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 experiment results in a splitting of a broad singlet at about 181 Hz downfield from TMS into a doublet (S; Fig 2d). In turn, weak perturbation applied at the latter frequency changes the H_A-doublet into a typical perturbed pattern (S and B; Fig 2e) according to spin-tickling theory.[6] The higher-field peak of the H_B-doublet is found to be overlapped by the olefinic Me signal (Fig 2f). The lower-field broad peak of the H_B-signal collapses into a well-resolved quartet (Fig 2g) on irradiation at the tertiary Me signal (δ 0·75 ppm). The spacings of 1·7 Hz of this quartet agree well with those observed in a doublet due to the olefinic Me in $CDCl_3$. These results show the presence of long-range spin-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 Me protons (J = 1·7 Hz). This in turn suggests that the olefinic Me is attached to the double bond in the lactone ring and that the angular Me and H_B of the allylic methylene are both axial.[7]

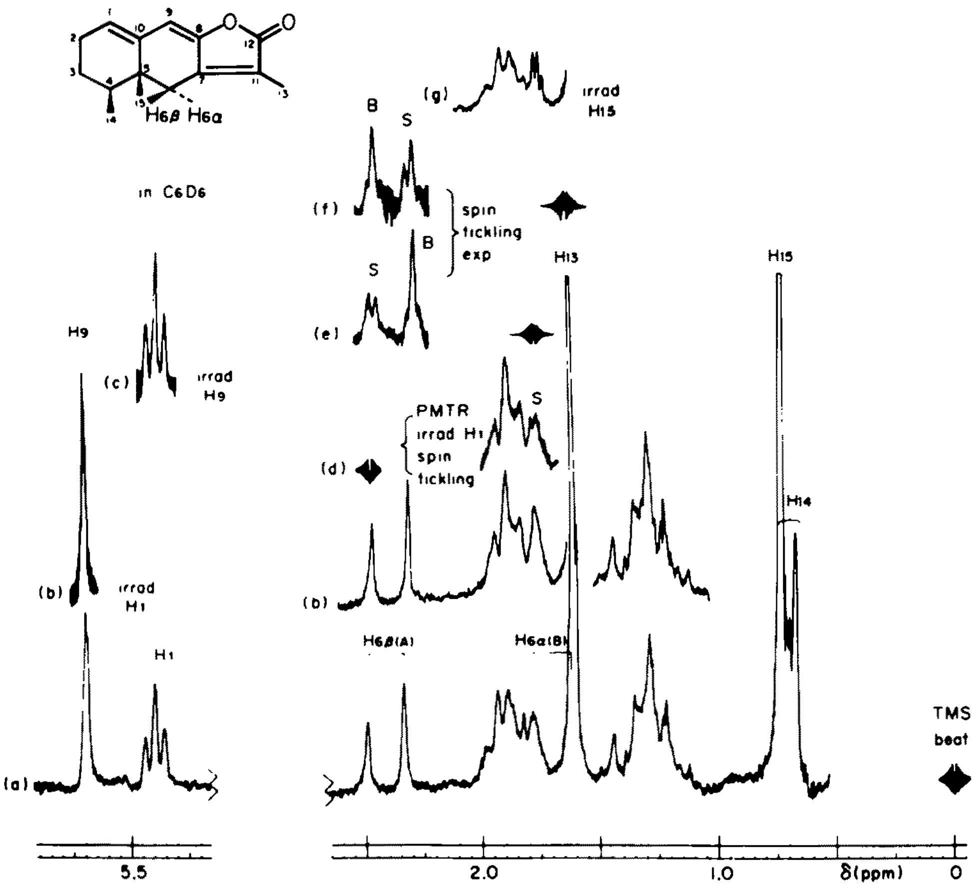
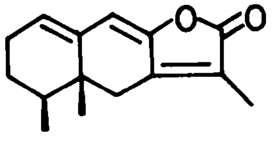


FIG 2. PMR (a), PMDR (b, c, e, f and g), and PMTR (d) spectra of ligularenolide in C_6D_6 at 100 MHz.

The above observations lead to partial structure **1a** for ligularenolide. This can be extended to a full structure **1**, including stereochemistry, by means of biogenetic considerations and on the basis of the observed features of long-range spin-couplings.[7]



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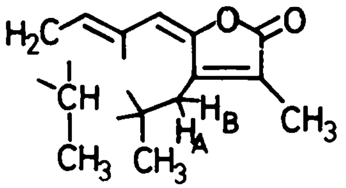


1a

Catalytic hydrogenation of ligularenolide (1) in EtOH with 5% Pd—C gave tetrahydroligularenolide (2), m.p. 114·5–115·5°, $[\alpha]_D$ −94° (MeOH). Elemental analysis and the mass spectrum indicate the formula $C_{15}H_{22}O_2$ and the uptake of two moles of hydrogen. The UV spectrum of 2 shows an absorption maximum at 222 mμ (ε 24,000) in MeOH. Taken in conjunction with the IR data (ν_{max} 1765, 1745 and 1678 cm^{-1}) this suggests that the α,β-unsaturated γ-lactone system is still present in 2. In the PMR spectra of 2 in $CDCl_3$ and in C_6D_6, besides the three Me signals shifted to higher-fields relative to those in 1 (see Figs 1b and 3a, and Table), a complex multiplet ($W_{1/2}$ = *ca* 22 Hz) due to one proton at the lactone terminus is observed instead of the disappearance of the signals arising from the olefinic protons in 1.

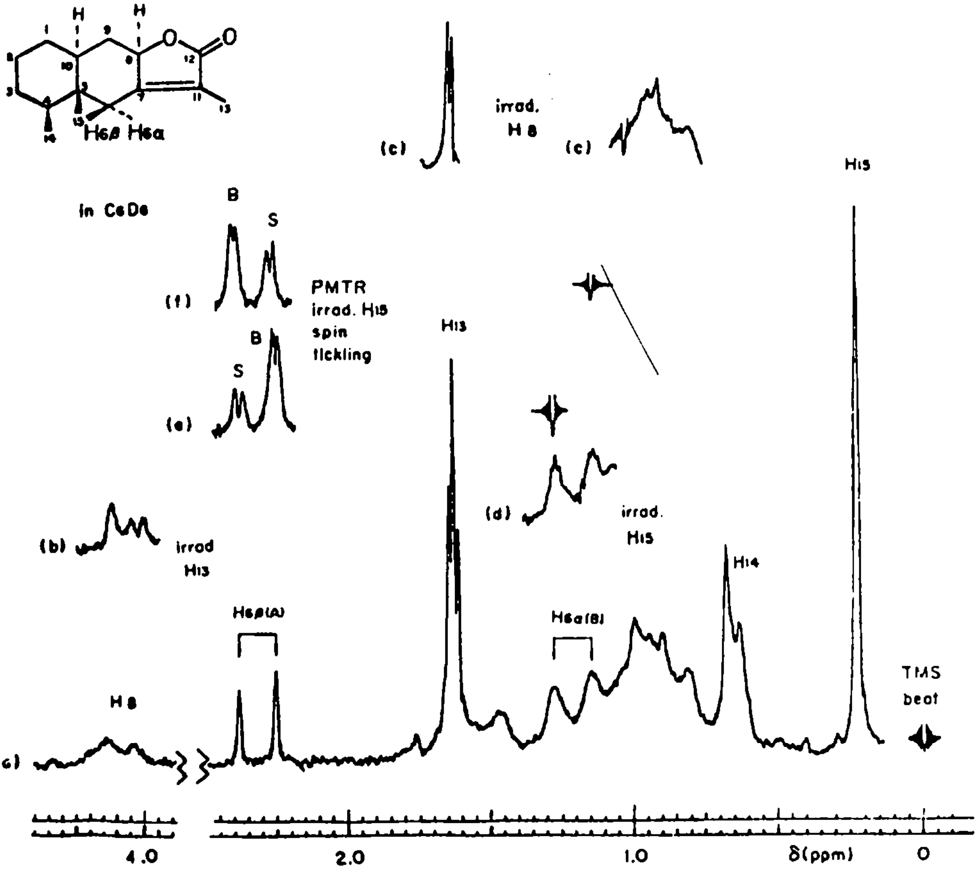
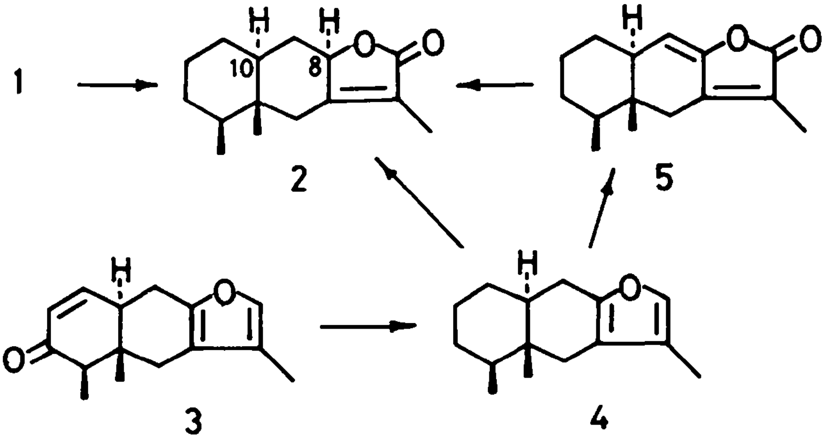


FIG 3. PMR (a), PMDR (b, c and d), and PMTR (e and f) spectra of tetrahydroligularenolide in C_6D_6 at 100 MHz.

As shown in Fig 3b (in C_6D_6), irradiation on the olefinic Me triplet at δ 1·63 ppm changes the multiplet pattern around δ 4·1 ppm attributable to the lactone terminus hydrogen. Irradiation at the frequency of 411 Hz downfield from TMS causes a collapse of the olefinic Me triplet into a doublet (Fig 3c) and changes a signal pattern around δ 1·0 ppm (Fig 3c). When irradiation is carried out on the tertiary Me signal at δ 0·24 ppm a diffuse H_B-doublet around δ 1·2 ppm collapses into a doublet of quartets (Fig 3d), whose spacings of 1·4 Hz are in accord with that observed in a doublet due to the olefinic Me (Fig 3c). The B-part of the AB-type quartet [$J = (-)13{\cdot}8$ Hz] was detected by spin-tickling experiments (Figs 3e and 3f). These PMDR and PMTR experiments revealed the presence of long-range spin-couplings of the olefinic Me to the proton on oxygen-bearing carbon ($J = 1{\cdot}4$ Hz) and to H_B of the allylic methylene ($J = 1{\cdot}4$ Hz); the latter is further coupled to the angular Me protons ($J = 0{\cdot}5$ Hz). The $W_{1/2}$ value of the signal due to the lactone terminus proton and the long-range spin-coupling between this and the olefinic Me protons imply that this hydrogen is axial. Thus, tetrahydroligularenolide can be written as **2**.

These results received support from the following chemical transformations. 10-*epi*-Furanoeremophilane (**4**)[3] prepared from furanoligularenone (**3**)[3] was oxidized by oxygen in the presence of reduced platinum catalyst to give 10-*epi*-eremophilenolide[3, 8]* in poor yield. The same 10-*epi*-eremophilenolide was also obtained by the following procedures. Oxidation of atractylon and linderene with dicyanodichlorobenzoquinone to yield their enol-lactones has already been reported by Takeda *et al.*[9] 10-*epi*-Furanoeremophilane (**4**) was treated with dicyanodichlorobenzoquinone to give a crude enol-lactone (**5**) [λ_{max} 280 mμ (MeOH)], which was found to be a mixture of **5** and 10-*epi*-eremophilenolide [λ_{max} 222 mμ (MeOH)]. The mixture in EtOH without further separation was hydrogenated with 5% Pd—C to furnish pure 10-*epi*-eremophilenolide, m.p. 114·5–115·5°, $[\alpha]_D$ −94° (MeOH), λ_{max} 222 mμ (ε 23,800) (MeOH), whose IR and PMR spectra were identical with those of tetrahydroligularenolide (**2**). The formation of tetrahydroligularenolide (**2**) (10-*epi*-eremophilenolide) on catalytic hydrogenation of ligularenolide (**1**) suggests that the hydrogen at C-8 of 10-*epi*-eremophilenolide is α-oriented.

CHART



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The correlation between ligularenolide and furanoligularenone (3) finally establishes the structure of ligularenolide (1) including the absolute configuration. The structure (2) follows for tetrahydroligularenolide.

EXPERIMENTAL

All m.ps are uncorrected. IR spectra were taken in nujol mull. Mass spectra were measured using a Hitachi Mass Spectrometer, RMU-6 Type, at the Naka Works, Hitachi, Ltd., to which company the authors' thanks are due. PMR spectra were taken with a Varian HA-100 spectrometer operating at 100 MHz using about 5% soln in $CDCl_3$ and C_6D_6 containing TMS as an internal standard. Calibration of the charts was carried out by direct readings of resonance frequencies using an HP-5212A electronic counter. The PMDR and PMTR experiments were made 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.

Isolation of ligularenolide (1). Dried roots of "San-Shion" (10 kg) were extracted with hot benzene (total 54 l). Evaporation of the solvent gave a residue which was distilled under reduced pressure (1 mmHg) at 200°. The distillate was dissolved in ether and the soln was washed with $NaHCO_3$ aq, then with water, and dried over Na_2SO_4. Evaporation of the solvent gave a dark brown residue, which was fractionally distilled under reduced pressure (2 mmHg). From the highest boiling fractions (150–160°) crude ligularenolide (*ca* 6 g) crystallized and was purified by crystallization from light petroleum or ethyl ether to afford pure 1 as yellow needles, m.p. 134·5–135°, $[\alpha]_D$ −332° (c = 0·06, MeOH); IR: 1764, 1648 and 1621 cm^{-1}, UV (MeOH): λ_{max} 331 and 261 mμ (ε 20,700 and 3,560); MS: M^+ ion *m/e* 230; PMR spectral data are recorded in the Table. (Found: C, 78·01; H, 8·03. $C_{15}H_{18}O_2$ requires: C, 78·23; H, 7·88%).

Tetrahydroligularenolide (2). A soln of 1 (93 mg) in abs EtOH (30 ml) was hydrogenated at room temp and atm pressure in the presence of Pd—C and absorbed two moles of H_2 within 15 min. The catalyst was removed by filtration and the soln was evaporated to dryness. The residue (90 mg) was crystallized from light petroleum to give 2 as white needles, m.p. 114·5–115·5°, $[\alpha]_D$ −94° (c = 0·05, MeOH); IR: 1765, 1745 and 1678 cm^{-1}; UV (MeOH): 222 mμ (ε 24,000); MS: M^+ ion *m/e* 234. PMR spectral data are reported in the Table. (Found: C, 76·87; H, 9·44. $C_{15}H_{22}O_2$ requires: C, 76·88; H, 9·46%).

Oxidation of 10-epi-*furanoeremophilane* (4) *with* O_2. 10-*epi*-Furanoeremophilane 4 (600 mg)[3] was dissolved in light petroleum (25 ml) and oxidized with O_2 at room temp for 70 hr in the presence of reduced Pt catalyst. The resulting yellow oily material (580 mg) was chromatographed over alumina (50 g). Benzene-ether (9:1) eluted a small amount of product, which was sublimed and crystallized from light petroleum to give 10-*epi*-eremophilenolide[3, 8] (12 mg) as white needles, m.p. 114·5–115·5°; IR: 1764, 1742 and 1675 cm^{-1}; UV (MeOH): λ_{max} 223 mμ (ε 24,000). The IR, UV and PMR spectra are essentially identical with those of 2.

Oxidation of 10-epi-*eremophilane* (4) *with* DDQ. A large excess of DDQ (1·4 g) was added to a soln of 4 (450 mg) in dioxan and the mixture was warmed at 45° for 15 min then filtered. Evaporation of the solvent gave a reddish brown residue (330 mg), which was sublimed to yield yellow oily material (220 mg). This material (178 mg) was dissolved in warm light petroleum, and some insoluble substances were removed by filtration. The solvent was evaporated to give a crude 5 (132 mg) (λ_{max} 280 mμ, MeOH), which contained a certain amount of 10-*epi*-eremophilenolide (λ_{max} 222 mμ, MeOH) (checked by GLC).

Conversion of enol-lactone (5) *to* 10-epi-*eremophilenolide*. The crude 5 without further purification was hydrogenated in abs EtOH in the presence of Pd—C. Filtration of catalyst and evaporation of solvent gave a residue which was dissolved in hot light petroleum. The soln was kept at −20° overnight to afford a pale yellow powder, which was sublimed and crystallized from light petroleum to give a pure 10-*epi*-eremophilenolide (30 mg) as white needles, m.p. 114·5–115·5°, $[\alpha]_D$ −94° (c = 0·04, MeOH); IR: 1769, 1742 and 1681 cm^{-1}; UV (MeOH): 222 mμ (ε 23,800); MS: M^+ ion *m/e* 234 ($C_{15}H_{22}O_2$ requires: 234). The IR, UV and PMR spectra are identical with those of 2.

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