Furanoeremophilane-6β,10β-diol and Its Derivatives. New Furanosesquiterpenes from *Ligularia japonica* LESS[1)]

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Three new furanosesquiterpenes have been isolated from *Ligularia japonica* LESS., and their structures including absolute configurations have been determined as furanoeremophilane-6β,10β-diol (**1**), 10β-hydroxyfuranoeremophilan-6β-yl 2′ξ-methylbutanoate (**2**), and 10β-hydroxy-6β-methoxyfuranoeremophilane (**3**).

In connection with structural studies on constituents of the genus *Ligularia* (Compositae),[2)] three new furanoereomophilane derivatives have been isolated from *Ligularia japonica* LESS. We wish to describe the structure determination leading to furanoeremophilane-6β,10β-diol (**1**), 10β-hydroxyfuranoeremophilan-6β-yl 2′ξ-methylbutanoate (**2**), and 10β-hydroxy-6β-methoxyfuranoeremophilane (**3**) for these sesquiterpenes.

A benzene extract of the roots of the plant was subjected to separation by column chromatography on silica gel to give **1** and **2**. Compound **1**, mp 120—122 °C, $[\alpha]_D$+33° (EtOH),* was positive to the Ehrlich test. The molecular formula of **1**, $C_{15}H_{22}O_3$, was determined by elemental analysis and the appearance of the molecular ion peak at *m/e* 250. The IR, UV, and PMR spectra showed the presence of a secondary methyl, a tertiary methyl, a β-methyl-substituted furan moiety with an α-proton,[2)] an allylic methylene linked to carbon with no proton, and of hydroxyl group(s) (cf. Experimental). A monoacetate (**4**), obtained by acetylation of **1** with acetic anhydride in pyridine exhibited an absorption due to an additional hydroxyl group in its IR spectrum. In the PMR spectrum of **1** in benzene, on addition of deuterium oxide, a doublet at δ 4.41 (J=7.5 Hz) due to a proton on a hydroxyl-bearing carbon changed into a singlet, while both of a doublet at δ 2.72 (J=7.5 Hz) due to a secondary hydroxyl proton and a singlet at δ 2.93 due to a tertiary hydroxyl proton disappeared. The presence in **1** of a secondary and a tertiary hydroxyl group could thus be shown.

The presence of intramolecular nuclear Overhauser effects (NOE)[3)] between a β-methyl (at C-11) on the furan ring and a proton (at C-6) on an acetoxyl-bearing carbon, as well as between the same methyl (at C-11) and an α-proton (at C-12) on the furan ring (Table 1), observed for **4**, showed that a secondary hydroxyl-bearing carbon (C-6) of **1** must be located on a β′-position (that is C-7) on the furan ring. This received support from an upfield shift[4,5)] by 0.12 ppm of a doublet at δ 2.03 (in deuteriochloroform; J=1.5 Hz) due to a β-methyl on the furan ring, when **1** was acetylated. As a nature of three (at α, β, and β′) of the four substituents on the furan ring was already clarified, the allylic methylene must be placed on an α′-position of the furan moiety for **1**. These observations led to a partial structure **A** (R=H), which could be extended, by means of biogenetic considerations, to two alternative structures, **B**(R=H) and **B′**(R=H), for **1**.

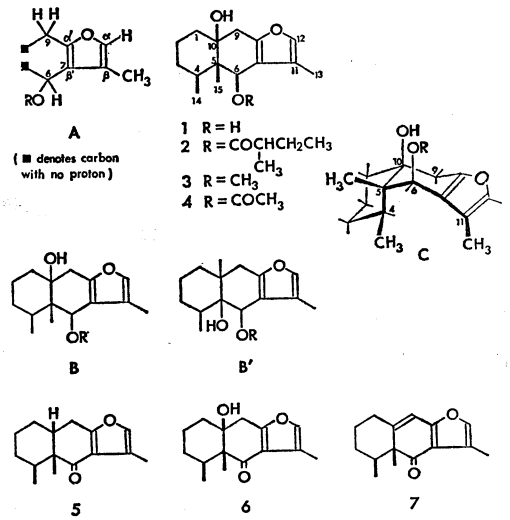

TABLE 1. NUCLEAR OVERHAUSER EFFECTS

Compounds	Solvents	Observed protons	Saturated protons	NOE[a)]
1	C_6D_6	9α-H	5-CH_3	nil
		9β-H	5-CH_3	nil
		12-H	11-CH_3	32
3	CCl_4	6-H	5-CH_3	13
4	C_6D_6	6-H	4-CH_3	21
		9α-H	5-CH_3	nil
		9β-H	5-CH_3	nil
		6-H	11-CH_3	4
		12-H	11-CH_3	20

a) The NOE's are expressed as increases in integrated signal intensities in %. The other indications are given in Experimental.

The IR spectrum of **2**, mp *ca.* 40 °C, showed a carbonyl absorption (ν_{max} 1725 cm^{-1}) due to an ester group. A molecular ion peak at *m/e* 334 ($C_{20}H_{30}O_4$) was observed in the mass spectrum of **2**, which was reduced with lithium aluminium hydride to give **1**. An acyl residue was therefore shown to be C_4H_9CO–. In the PMR spectrum of **2** in deuteriochloroform, a triplet at δ 0.88 (J=5.5 Hz) due to a primary methyl, a doublet at δ 1.14 (J=7 Hz) due to a secondary methyl, and a multiplet at δ 2.34 due to a methine proton of a –OCOCH(CH$_3$)– grouping appeared, besides signals due to protons of the structure moiety of

* Previously this value has been reported as +58° (EtOH).[1)] The authors correct it to +33° for the same compound based on recent measurement data.

1. Thus, **2** must be an ester comprising from **1** and 2ξ-methylbutanoic acid.

Successive extraction of the roots with methanol and subsequent separation by column chromatography on silica gel gave a compound **3**, mp 82—84 °C, $[\alpha]_D$+ 5° (EtOH), whose molecular formula $C_{16}H_{24}O_3$ was given by elemental analysis and mass spectrometry (M^+ at *m/e* 264). The treatment of **1** with methanol in the presence of acetic acid, or with a mixture of methyl iodide, silver oxide, and dimethylformamide, afforded **3**. A secondary hydroxyl of **1** was thus methylated to give **3**. As the absence of **3** in the benzene extract was shown by thin layer chromatography, it was suggested that **3** might be an artifact produced by extraction with methanol.

A preference of the structure **B** (R=H) over **B'** (R=H) for **1** was shown as follows. The treatment of **1** with potassium periodate resulted in no consumption of the reagent. This showed the absence in **1** of an α-glycol (especially, of an α-*cis*-glycol) system. An NOE observed between a tertiary methyl (at C-5) and a proton (at C-6) on a methoxyl-bearing carbon for **3**, and the absence of NOE between a tertiary methyl (at C-5) and each of two allylic protons (at C-9) observed for **1** and **4**, suggested that the tertiary methyl was located on C-5 (Table 1). Finally, **1** was transformed to known ligularone (**5**).[4] Oxidation of **1** with chromium trioxide gave 10β-hydroxy-6-oxofuranoeremophilane (**6**), which was dehydrated with phosphorus oxychloride in pyridine to afford 6-oxofuranoeremophil-9-ene (**7**). Hydrogenation of **7** in the presence of palladium-charcoal in ethyl acetate proceeded stereoselectively to afford a ketone (yield: *ca.* 80%) as a main product, which was found to be identical with **5** in all respects. The structure **B** was thus derived for **1**.

The IR spectrum of **1** in carbon tetrachloride (0.005 M solution) showed the presence of an intramolecular hydrogen bond between the two hydroxyls. A tertiary hydroxyl at C-10 and a secondary hydroxyl at C-6 must therefore be in a 1,3-diaxial (that is, in *cis*) relationship to each other; this led to an equatorial conformation for a proton on C-6. These data along with the absence of NOE between the tertiary methyl at C-5 and each of methylene protons at C-9 (especially, an axial proton at C-9α) as described above, suggested an equatorial nature of this methyl (at C-5). This received support from a downfield shift by 0.23 ppm observed for a signal due to the tertiary methyl at C-5 of **1**, when the solvent was replaced from deuteriochloroform to pyridine-d_5.[6] In the PMR spectra of **3**, the corresponding downfield shift was relatively small (0.08 ppm) due to a strong intramolecular hydrogen bond (ν_{OH} 3488 cm^{-1}; in 0.005 M solution of carbon tetrachloride) which could inhibit competitively the solute-solvent association. The two hydroxyls and the tertiary methyl at C-5 are therefore in *cis* relationships to one another. The two methyls at C-4 and C-5 of **1** have been shown to be *cis* according to the conversion of **1** to **5** as mentioned above. The presence of NOE between a secondary methyl at C-4 and a proton at C-6 on an acetoxyl-bearing carbon was observed

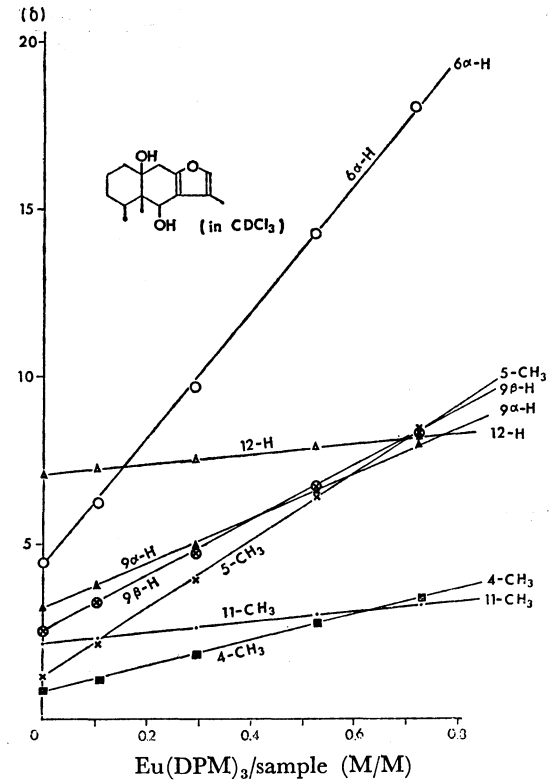

Fig. 1. Induced paramagnetic shifts for the diol(**1**)
[$Eu(DPM)_3$ was added to a 5% (w/v) soln of **1** in $CDCl_3$.]

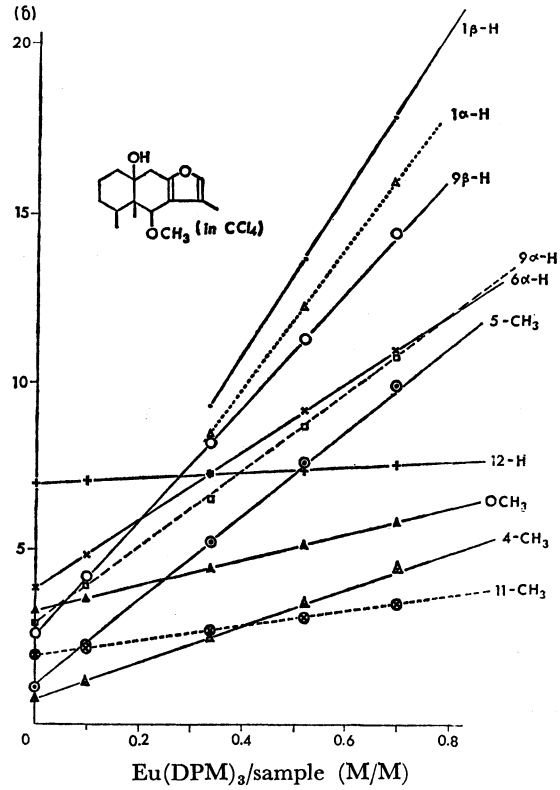

Fig. 2. Induced paramagnetic shifts for the monomethyl ether(**3**)
[$Eu(DPM)_3$ was added to a 5% (w/v) soln of **3** in CCl_4.]

for **4** (Table 1). These observations could only be explained based on a steroidal conformation of *cis*-decalin type depicted as in **C**.

The results of induced paramagnetic shift experiments[7] on the diol and the monomethyl ether were compatible with the structures **1** and **3**, respectively (Figs. 1 and 2). In the measurements for both of **1** and **3**, a large shift was observed for a signal due to a methyl at C-5. The signals due to a proton at C-9β and two protons at C-1 of **3**, as well as that due to a proton at C-6 of **1**, shifted very largely, while a smaller shift was observed for the corresponding signal due to a proton at C-6 of **3**. This could be interpreted by a preferencial association of the shift reagent, Eu(DPM)$_3$, with a hydroxyl rather than an ether group.[8]

As an absolute stereochemistry of **5** had been determined as in **5**,[4] the structure of the diol including absolute configuration should be represented by **1** with a conformation as shown in **C** (R=H). The structures **2**, **3**, and **4** followed for the ester, the monomethyl ether, and the monoacetate, respectively.

Experimental

IR spectra were measured using a Hitachi EPI-G2 spectrometer in Nujol mull, unless otherwise stated. UV spectra were determined on a Hitachi EPS-3 spectrophotometer. Measurements of optical rotation were carried out using a JASCO DIP-SL polarimeter. Mass spectra were taken on a Hitachi RMU-6-Tokugata mass spectrometer with a direct inlet system operating at 70 eV. PMR spectra were measured using a JEOL PS-100 (100 MHz) or a Hitachi R-20 (60 MHz) spectrometer. Chemical shifts were expressed in δ downfield from TMS as an internal standard, and coupling constants in Hz. For a measurement of NOE, PMR spectra were taken on a Varian HA-100 spectrometer operating at 100 MHz in the frequency-swept and internal TMS-locked mode, for *ca.* 5% (w/v) degassed solutions. NOE experiments were performed with sweep rates of 1 Hz per second for integrations and 0.2 Hz per second for signals on the spectrometer with a Hewlett-Packard HP-200ABR audio-oscillator and HP-5212A electronic counter. Accuracies are ±0.01 ppm for chemical shifts, ±0.2 Hz for coupling constants, and about ±2% for NOE values, for NOE experiments. Thin layer chromatography (tlc) was carried out on Kieselgel PF_{254} (E. Merck, Darmstadt). For column chromatography Wakogel C 200 (Wako Pure Chemical Co.) was used. All mps were determined on a hot block and reported uncorrected.

Isolation. Dried roots (1.6 kg) of *Ligularia japonica* LESS. were extracted with hot benzene (total 12 l). Evaporation of the solvent gave a residue (15 g) which was chromatographed on a column of silica gel (500 g). The eluted fractions were examined by tlc (silica gel). Fractions eluted with light petroleum–ether (10 : 1) gave, on evaporation of the solvents, a residue, which was crystallized from light petroleum to afford 10β-hydroxyfuranoeremophilan-6β-yl 2′ξ-methylbutanoate (**2**; 200 mg), mp *ca.* 40 °C; UV (EtOH) λ_{max} 218 nm (ε 9100); IR (CCl_4) 3570, 3500, 1725, 1640, 1565, 1245 cm^{-1}; PMR ($CDCl_3$) δ 0.83 (3H, d, J=7.5 Hz; methyl at C-4), 0.88 (3H, t, J=5.5 Hz; primary methyl in an acyl moiety), 1.14 (3H, d, J=7 Hz; secondary methyl in the acyl group), 1.25 (3H, s; methyl at C-5), 1.90 (3H, d, J=1.5 Hz; methyl at C-11), 2.34 (1H, m; -OCOCH(CH$_3$)- in the acyl residue), 2.65 and 3.20 (each, 1H, d, J=17.5 Hz; protons at C-9), 6.19 (1H, s; proton at C-6), 7.07 (1H, m; proton at C-12), ca. 3.3 (1H, broad signal; OH); mass spectrum *m/e* 334 (M^+; $C_{20}H_{30}O_4$), *m/e* 159 (base peak). Fractions eluted with light petroleum–ether (3 : 1) gave, on removal of the solvents, a solid, which was chromatographed on a column of silica gel (50 g). Elution with light petroleum–ether (3 : 1) and evaporation of the solvents gave a crude crystal, which was crystallized from a mixture of light petroleum and ether to afford furanoeremophilane-6β,10β-diol (**1**; 380 mg), mp 120—122 °C, $[\alpha]_D$ +33° (*c* 1.7, EtOH); UV(EtOH) λ_{max} 217 nm (ε 8000); IR (0.005 M solution of CCl_4) 3608, 3544, 3504, 1645, 1565, 1080 cm^{-1}; PMR (C_6D_6) δ 0.55 (3H, $\underline{A}_3B$, J=5.5 Hz; methyl at C-4), 1.11 (3H, s; methyl at C-5), 1.95 (3H, d, J=1.5 Hz; methyl at C-11), 2.42 (1H, d, J=17.8 Hz; proton at C-9β), 2.94 (1H, d, J=17.8 Hz; proton at C-9α), 7.00 (1H, m; proton at C-12); PMR (C_6H_6) (signals other than those described for C_6D_6) δ 2.72 (1H, d, J=7.5 Hz; OH at C-6), 2.93 (1H, s; OH at C-10), 4.41 (1H, d, J=7.5 Hz; proton at C-6); PMR ($CDCl_3$) δ 0.78 (3H, d, J=5.5 Hz; methyl at C-4), 1.22 (3H, s; methyl at C-5), 2.03 (3H, d, J=1.5 Hz; methyl at C-11), 2.53 (1H, d, J=17.8 Hz; proton at C-9β), 3.21 (1H, d, J=17.8 Hz; proton at C-9α), 4.52 (1H, s; proton at C-6), 7.08 (1H, m; proton at C-12); PMR (C_5D_5N) δ 0.75 (3H, d, J=5.5 Hz; methyl at C-4), 1.45 (3H, s; methyl at C-5), 2.11 (3H, d, J=1.5 Hz; methyl at C-11), 2.83 and 3.25 (each 1H, d, J=17.8 Hz; protons at C-9); mass spectrum *m/e* 250 (M^+), *m/e* 124 (base peak). Found: C, 72.23; H, 8.65%. Calcd for $C_{15}H_{22}O_3$: C, 71.97; H, 8.86%; mol wt 250.3.

Subsequent extraction of the roots with methanol and evaporation of the solvents gave a residue, which was passed through a column of silica gel (200 g). Fractions eluted with light petroleum–ether (5 : 1) gave, on removal of the solvents, a solid, which was sublimed at 60 °C (oil bath temperature) under 0.1 mmHg to afford 10β-hydroxy-6β-methoxyfuranoeremophilane (**3**: 60 mg), mp 82—84 °C; $[\alpha]_D$ +5° (*c* 2.0, EtOH); UV (EtOH) λ_{max} 220 nm (ε 9300); IR (0.005 M solution of CCl_4) 3488, 1634, 1560, 1084 cm^{-1}; PMR (CCl_4) δ 0.70 (3H, d, J=5.5 Hz; methyl at C-4), 1.12 (3H, s; methyl at C-5), 1.99 (3H, d, J=1.5 Hz; methyl at C-11), 2.59 (1H, d, J=17.8 Hz; proton at C-9β), 3.01 (1H, d, J=17.8 Hz; proton at C-9α), 3.28 (3H, s; methoxyl at C-6), 4.05 (1H, s; proton at C-6), 4.30 (1H, s; OH at C-10), 7.02 (1H, m; proton at C-12); PMR ($CDCl_3$) δ 0.73 (3H, d, J=5.5 Hz; methyl at C-4), 1.22 (3H, s; methyl at C-5), 2.07 (3H, d, J=1.5 Hz; methyl at C-11), 2.73 and 3.18, (each, 1H, d, J=17.8 Hz; protons at C-9), 3.39 (3H, s; methoxyl at C-6), 4.19 (1H, s; proton at C-6), 4.99 (1H, s; disappeared on addition of deuterium oxide; OH at C-10), 7.22 (1H, m; proton at C-12); PMR (C_5D_5N) δ 0.66 (3H, d, J=5.5 Hz; methyl at C-4), 1.30 (3H, s; methyl at C-5), 2.06 (3H, d, J=1.5 Hz; methyl at C-11), 2.87 and 3.20 (each, 1H, d, J=17.8 Hz; protons at C-9), 3.27 (3H, s; methoxyl at C-6), 4.25 (1H, s; proton at C-6); mass spectrum *m/e* 264 (M^+), *m/e* 138 (base peak). Found: C, 72.57; H, 9.27%. Calcd for $C_{16}H_{24}O_3$: C, 72.69; H, 9.15%; mol wt 264.4.

*Acetylation of the Diol (**1**).* A mixture of **1** (33 mg), acetic anhydride (1 ml), and pyridine (1 ml) was allowed to stand overnight at room temperature. After addition of methanol, the solvents were removed to give a residue, which was extracted with ether. The extract was treated as usual and the resulting residue was chromatographed on a column of silica gel (10 g). Elution with light petroleum–ether (10 : 1) gave, on removal of the solvents, 6β-acetoxy-10β-hydroxyfuranoeremophilane (**4**; 35 mg), an oil; IR (CCl_4) 3550, 1736, 1648, 1565, 1370, 1220, 1084, 1030 cm^{-1}; PMR (C_6D_6) δ 0.72 (3H, $\underline{A}_3B$, J=5.5 Hz; methyl at C-4), 1.04 (3H, s; methyl at C-5), 1.50 (3H, s; acetoxyl at C-6), 1.89 (3H, d, J=1.5 Hz;

methyl at C-11), 2.69 (1H, d, J=17.8 Hz; proton at C-9β), 2.99 (1H, d, J=17.8 Hz; proton at C-9α), 3.22 (1H, broad signal; OH at C-10), 6.34 (1H, s; proton at C-6), 6.94 (1H, m; proton at C-12); PMR ($CDCl_3$) δ 0.88 (3H, d, J=5.5 Hz; methyl at C-4), 1.05 (3H, s; methyl at C-5), 1.91 (3H, d, J=1.5 Hz; methyl at C-11), 2.05 (3H, s; acetoxyl at C-6), 2.65 and 3.20 (each, 1H, d, J=17.8 Hz; protons at C-9), 3.21 (1H, s; disappeared on addition of deuterium oxide; OH at C-10), 6.17 (1H, s; proton at C-6), 7.08 (1H, m; proton at C-12); PMR (C_5D_5N) δ 0.95 (3H, broad signal; methyl at C-4), 1.20 (3H, s; methyl at C-5), 1.96 (3H, d, J=1.5 Hz; methyl at C-11), 1.99 (3H, s; acetoxyl at C-6), 2.83 and 3.13 (each, 1H, d, J=17.8 Hz; protons at C-9), 6.46 (1H, proton at C-6); mass spectrum *m/e* 292 (M^+; $C_{17}H_{24}O_4$), *m/e* 124 (base peak).

*Methylation of the Diol (**1**).* (a) To a solution of **1** (30 mg) in methanol (4 ml) a drop of acetic acid was added and the resulting solution was allowed to stand at room temperature for 40 hr. After addition of water, the reaction mixture was extracted with ether. Usual work-up gave a residue which was chromatographed on a column of silica gel (10 g). Fractions eluted with light petroleum–ether (8 : 1) were collected and sublimed at 60 °C under 0.1 mmHg to afford the monomethyl ether (**3**; 20 mg), which was found to be identical (mp, mixed mp, IR, PMR, and $[\alpha]_D$) with an authentic sample of **3**. (b) A mixture of **1** (5 mg), methyl iodide (1 ml), silver oxide (20 mg), and dimethylformamide (2 drops) was heated under reflux for 6 hr. Extraction with ether and removal of the solvents gave a residue, which was purified as described above. A methylated product (2 mg) was found to be identical with the authentic specimen of **3**.

*Oxidation of the Diol (**1**).* To a solution of **1** (100 mg) in pyridine (1 ml), a solution of chromium trioxide (100 mg) in pyridine (5 ml) and water (2 drops) was added and stirred at room temperature for 40 hr. Extraction with ether and subsequent work-up as usual gave a crystal, which was crystallized from a mixture of light petroleum–ether to afford 10β-hydroxy-6-oxofuranoeremophilane (**6**; 50 mg), mp 147.5—148 °C, $[\alpha]_D$ +31° (c 1.3, EtOH); UV (EtOH) λ_{max} 268 nm (ε 3700); IR 3500, 1650, 1575, 1065 cm^{-1}; PMR ($CDCl_3$) δ 0.79 (3H, d, J=6 Hz; methyl at C-4), 1.18 (3H, s; methyl at C-5), 2.19 (3H, d, J=1.5 Hz; methyl at C-11), 2.72 and 3.50 (each, 1H, d, J=18 Hz; protons at C-9), 7.10 (1H, m; proton at C-12); mass spectrum *m/e* 248 (M^+; $C_{15}H_{20}O_3$), *m/e* 122 (base peak).

*Dehydration of the Hydroxyketone (**6**).* To a solution of **6** (50 mg) in pyridine (1 ml), phosphorus oxychloride (0.1 ml) was added dropwise with stirring. The reaction mixture was heated at 140 °C (oil bath temperature) for 35 min under an atmosphere of nitrogen. Extraction with ether and subsequent work-up as usual gave a residue, which was subjected to purification by preparative tlc to afford 6-oxofuranoeremophil-9-ene (**7**; 35 mg), mp 109—109.5 °C, $[\alpha]_D$ −410° (c 0.3, EtOH); UV (EtOH) λ_{max} 215 nm (ε 18000), 248 (7000), 334 (6700) (with shoulders at 242, 255, and 265 nm); IR 1640, 1610, 1595, 1550, 1080, 780 cm^{-1}; PMR ($CDCl_3$) δ 1.04 (3H, d, J=6 Hz; methyl at C-4), 1.22 (3H, s; methyl at C-5), 2.20 (3H, d, J=1.5 Hz; methyl at C-11), 6.37 (1H, broad s; proton at C-9), 7.01 (1H, m; proton at C-12); mass spectrum *m/e* 230 (M^+; $C_{15}H_{18}O_2$), *m/e* 175 (base peak).

*Hydrogenation of the Ketone (**7**).* The ketone (**7**; 13 mg) in ethyl acetate (5 ml) was hydrogenated in the presence of 10% palladium-charcoal (12 mg) with stirring for 1 hr. After filtration of the catalyst, the solvent was removed to give a residue (two spots on tlc). Separation by preparative tlc afforded ligularone (**5**) as a main product yield *ca.* 80%), mp 63 °C, $[\alpha]_D$ −58° (c 0.6, $CHCl_3$); UV (EtOH) λ_{max} 268 nm (ε 3300); IR 1670, 1610, 1565, 1070 cm^{-1}; PMR ($CDCl_3$) δ 0.86 (3H, d, J=7.5 Hz; methyl at C-4), 1.10 (3H, s; methyl at C-5), 2.17 (3H, d, J=1.5 Hz; methyl at C-11), 2.71 (1H, dd, J=17 and 6 Hz; proton at C-9), 2.89 (1H, dd, J=17 and 5.5 Hz; proton at C-9), 7.03 (1H, m; proton at C-12); mass spectrum *m/e* 232 (M^+; $C_{15}H_{20}O_2$), *m/e* 122 (base peak), which was found to be identical with an authentic sample of **5** in all respects. Compound corresponding to a minor spot on tlc was not further examined.

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