New Furanosesquiterpenes from *Ligularia Fischeri* Turcz.[1)] 1*β*, 10*β*-Epoxyfuranoeremophilan-6*β*-ol and Its Derivative

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Two new furanosesquiterpenes, isolated from *Ligularia Fischeri* Turcz. (collected at Shiramine), were shown to be 1*β*,10*β*-epoxyfuranoeremophilan-6*β*-ol (**1**) and 1*β*,10*β*-epoxyfuranoeremophilan-6*β*-yl 2-hydroxymethylprop-2-enoate (**2**).

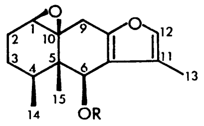
It has been reported by Ishii *et al.* that *Ligularia Fischeri* Turcz. (collected at Kurama) contained several sesquiterpenes, namely, ligularol,[2)] ligularone,[2)] furanoeremophilane,[3)] eremoligenol,[3)] 6*β*-hydroxyeremophilenolide,[3)] liguloxide,[4)] liguloxidol,[4)] and liguloxidol acetate.[4)] During chemical investigation on the genus *Ligularia* (Compositae) and related plants,[5)] two new furanosesquiterpenes were isolated from *Ligularia Fischeri* Turcz. (collected at Shiramine).[6)] We wish to describe the structure determination leading to 1*β*, 10*β*-epoxyfuranoeremophilan-6*β*-ol (**1**) and 1*β*,10*β*-epoxyfuranoeremophilan-6*β*-yl 2-hydroxymethylprop-2-enoate (**2**) for these sesquiterpenes.

An ether extract of the roots of the plant was subjected to separation by column and preparative thin layer chromatography to give **1** and **2**. Compound **1**, a colorless oil, was positive to the Ehrlich test. A molecular ion peak at *m/e* 248 ($C_{15}H_{20}O_3$) was observed in the mass spectrum. 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,[5)] a proton on an oxygen-bearing carbon, an allylic methylene linked to a carbon with no proton, an allylic proton on a hydroxyl-bearing carbon, and a hydroxyl group (*cf.* Table and Experimental).

These spectral data observed for **1** are closely related to those of furanoeremophilane-6*β*,10*β*-diol (**3**),[7,8)] recently isolated from *L. japonica* Less. Treatment of **1** in tetrahydrofuran with lithium aluminium hydride under reflux yielded a diol, which was found to be identical with **3**. This showed the presence in **1** of a furanoeremophilane skeleton (**4**); a hydroxyl group of **1** must be placed on C-6*β*. The presence of homoallylic coupling (*J*=2 Hz) between a proton at C-6*α* and one of the allylic methylene protons (proton at C-9*α*) was shown by PMDR experiments. Therefore the proton at C-6*α* was inferred to be in a quasi-axial conformation.

A nature of two of the three oxygen atoms involved in **1** was thus characterized. The IR spectrum of **1** showed no carbonyl absorption. In the PMR spectrum of **1**, the signal due to a proton on an oxygen-bearing carbon (C-1) appeared at *δ* 3.06, while the corresponding signal was absent in the spectrum of **3**. The conversion of **1** to **3**, as well as the spectral data of **1** mentioned above, suggested that the third oxygen of **1** was involved as an epoxy ring and located on C-1*β* and C-10*β* as shown in **1**.

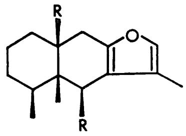
These observations received support from induced paramagnetic shift experiments[9)] on **1** (Table), coupled with PMDR technique. The shift reagent, Eu(dpm)$_3$, associated more strongly with a hydroxyl rather than an ether group.[10)] Signals due to protons at C-4 and C-15 shifted very largely. A small shift was observed for signals due to protons at C-14. Therefore, the epoxy ring was shown to be in a *β*-configuration; an 1*α*,10*α*-epoxide structure must cause a large shift for signals due to C-14 protons. As the absolute stereochemistry of the diol was determined as shown in **3**,[8)] the structure including absolute configuration of **1** should be represented by 1*β*,10*β*-epoxyfuranoeremophilan-6*β*-ol (**1**). The results summarized in Table are best interpreted on the basis of a stereostructure (**1′**), in which rings A and B adopt a half-chair and a half-boat conformation respectively.



1 R = H

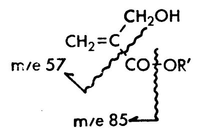
2 R = $-CO-\underset{|}{C}=CH_2$ / CH_2OH

5 R = $-CO-\underset{|}{C}H-CH_3$ / CH_2OH

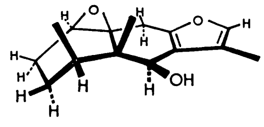


3 R = OH

4 R = H



2′



1′

The IR and UV spectra of **2** showed the presence of *α*,*β*-unsaturated ester group (*cf.* Experimental). A molecular ion peak at *m/e* 332 ($C_{19}H_{24}O_5$) was observed in the mass spectrum of **2**. The ester (**2**) was reduced with lithium aluminium hydride in ether to give **1**. Treatment of **2** with methanolic potassium hydroxide at room temperature afforded **1**. An acyl residue present in **2** was therefore inferred to be [C_3H_5O]–CO–. In the PMR spectrum of **2**, there appeared signals due to protons of a terminal methylene and a hydroxymethyl group (*cf.* Experimental), other than those due to the structure moiety of **1**. Hydrogenation of **2** in ethanol in the presence of palladium-charcoal yielded a dihydro derivative (**5**). In the PMR spectrum of **5**, a methyl signal at *δ* 1.26 and a methine proton signal at *δ* 2.77 newly appeared, while

Table. PMR spectral data of **1**

	1α-H	2α-H	2β-H	3α-H	3β-H	4α-H	6α-H	9α-H	9β-H	12-H	13-H	14-H	15-H	OH
δ_{CDCl_3}[a]	3.06 (br. s)	—[b]	—[b]	—[b]	—[b]	1.5 (m)	4.86 (br. s)	3.22[c] (d)	2.11 (d)	7.07 (q)	2.09 (d)	1.11 (d)	1.14 (s)	1.9[d] (s)
$\delta_{Eu(dpm)_3}$[e]	11.45 (AB$\underline{X}$)	5.0 (m)	6.8 (m)	5.9 (m)	2.6 (m)	16.3 (m)	—[f]	10.73 (d)	9.08 (d)	10.17 (br. s)	7.62 (d)	5.55 (d)	12.88 (s)	
δ[g]	−8.4					−14.8		−7.5	−7.0	−3.1	−5.5	−4.4	−11.7	

Coupling constants[a]:

$J_{1\alpha,2\alpha}=5$ $J_{1\alpha,2\beta}=<1$ $J_{2\alpha,2\beta}=15$ $J_{2\alpha,3\alpha}=7$ $J_{2\alpha,3\beta}=1.5$

$J_{2\beta,3\alpha}=15$ $J_{2\beta,3\beta}=5$ $J_{3\alpha,3\beta}=15$ $J_{3\alpha,4\alpha}=5$ $J_{3\beta,4\alpha}=1.5$

$J_{4\alpha,14}=7$ $J_{9\alpha,9\beta}=16$ $J_{12,13}=1.5$ $J_{6\alpha,9\alpha}=2$

a) Chemical shifts are expressed in downfield from TMS and coupling constants in Hz. b) Unresolved signals. c) With further splitting due to homoallylic coupling $J_{6\alpha,9\alpha}$. d) Disappeared on addition of D_2O. e) 0.97 M equivalent of $Eu(dpm)_3$ was added to the 2% (w/w) solution of **1**. f) Not measured. g) $\delta=\delta_{CDCl_3}-\delta_{Eu(dpm)_3}$.

signals due to a terminal methylene group were absent.

These observations led to a structure **2′** for the ester (**2**). This received support from an appearance of intense peaks at *m/e* 85 and *m/e* 57[11] due to fissions as shown in **2′**; these peaks were absent in the mass spectrum of **1**. The structure including absolute stereochemistry of the ester must be 1β,10β-epoxyfuranoeremophilan-6β-yl 2-hydroxymethylprop-2-enoate (**2**). The same acyl group as that of **2** has been described to be present as a part of the structures of vernodalin[11] and cynaropicrin.[12]

Experimental

IR spectra were measured using a Hitachi EPI-G2 spectrometer. UV spectra were determined on a Hitachi EPS-3 spectrometer. 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 4H-100 (100 MHz), a JEOL 3H-60 (60 MHz), a Hitachi R-20 (60 MHz) or a Hitachi R-24 (60 MHz) spectrometer. Chemical shifts were expressed in δ downfield from TMS as an internal standard, and coupling constants in Hz. Thin layer chromatography (tlc) was carried out on Kieselgel G nach Stahl, Kieselgel GF_{254} nach Stahl, and Kieselgel 60 PF_{254} (E. Merck, Darmstadt). For column chromatography Wakogel C-200 (Wako Pure Chem. Ind.) was used. All mps were determined on a hot block and reported uncorrected.

Isolation. Dried and sliced roots (226 g) of *Ligularia Fischeri* Turcz. (collected at Shiramine, Ishikawa Prefecture) were extracted thrice with ether (total 4.5 l) at room temperature. Evaporation of the solvent gave a residue (7 g) which was chromatographed on a column of silica gel (100 g). The eluted fractions were examined by tlc (silica gel). After elution with light petroleum–ether (100: 1; 1.9 l) and then light petroleum–ether (50: 1; 750 ml), fractions eluted with light petroleum–ether (9: 1; 600 ml) were combined. Evaporation of the solvents gave a residue, which was purified by silica gel column chromatography and preparative tlc to afford 1β,10β-epoxyfuranoeremophilan-6β-ol (**1**; 50 mg), an oil, $[\alpha]_D$ −45° (*c* 0.11, EtOH); UV (EtOH) λ_{max} 215.5 nm (ε 7000); IR (liquid) 3450, 1645, and 1570 cm^{-1}; PMR data are described in Table; mass spectrum *m/e* 248 [relative intensity 7%, M$^+$ ($C_{15}H_{20}O_3$)] and 123 (100%).

Subsequent elution with light petroleum–ether (4: 1; 1 l) gave, on removal of the solvents, a residue, which was purified by silica gel column chromatography to yield 1β,10β-epoxyfuranoeremophilan-6β-yl 2-hydroxymethylprop-2-enoate (**2**; 2.6 g), an oil, $[\alpha]_D$ −9° (*c* 0.84, EtOH); UV (EtOH) λ_{max} 215 nm (ε 15000); IR (liquid) 3460, 1718, 1645, 1570, and 1160 cm^{-1}; PMR ($CDCl_3$) δ 1.05 (3H, d, *J*=7 Hz; protons at C-14), 1.22 (3H, s; protons at C-15), 1.79 (3H, d, *J*=1.5 Hz; protons at C-13), 2.15 (1H, d, *J*=16 Hz; proton at C-9β), 3.10 (1H, br.s; proton at C-1α), 3.23 (1H, dd, *J*=16 and *J*=2 Hz; proton at C-9α), 6.46 (1H, m; proton at C-6α), 7.09 (1H, q, *J*=1.5 Hz; proton at C-12), 4.38 (2H, br.s; $CH_2{=}\overset{|}{C}{-}C\underline{H}_2OH$), 5.92 (1H, dt, *J*=1.6 and *J*=1.2 Hz; $C\underline{H}_2{=}\overset{|}{C}{-}CH_2{-}$), 6.32 (1H, dt, *J*=1.6 and *J*=1 Hz; $C\underline{H}_2{=}\overset{|}{C}{-}CH_2{-}$), and 2.92 (1H, br.s; OH; disappeared on addition of D_2O); mass spectrum *m/e* 332 (6%, M$^+$), *m/e* 109 (100%), *m/e* 85 (94%), and *m/e* 57 (50%). Found: C, 68.62; H, 7.43%. Calcd for $C_{19}H_{24}O_5$: C, 68.65; H, 7.28%. The ester (**2**) was unstable on exposure to the air, and could be stored under a nitrogen atmosphere in an icebox.

*Reduction of **2** in Ether with Lithium Aluminium Hydride.* To a solution of **2** (143 mg) in dry ether (10 ml) was added lithium aluminium hydride (50 mg) and the mixture was stirred at room temperature under a nitrogen atmosphere. After completion of the reaction, the excess reagent was decomposed with water. Extraction with ether and evaporation of the solvent gave a residue, which was chromatographed on a column of silica gel to afford an oil (15 mg). This oil was found to be identical with **1** in all respects.

*Hydrolysis of **2**.* To a solution of potassium hydroxide (0.2 g) in methanol (4 ml) was added **2** (141 mg) and the mixture was stirred for 12 hr under a nitrogen atmosphere at room temperature. After removal of the solvent, the residue was extracted with ether to give **1** (86 mg).

*Reduction of **1** in Tetrahydrofuran with Lithium Aluminium Hydride.* Compound **1** (132 mg) in dry tetrahydrofuran (6 ml) was refluxed with lithium aluminium hydride (50 mg) for 2.5 hr under a nitrogen atmosphere. The mixture was treated as usual and the resulting residue was chromatographed on a column of silica gel (12 g) using light petroleum–ether (7: 1) as eluent to give a crystalline product (45 mg), mp 123 °C; $[\alpha]_D$ +37° (*c* 0.23, EtOH); Found: C, 72.23; H, 9.07%. Calcd for $C_{15}H_{22}O_3$: C, 71.97; H, 8.86%. This compound was found to be identical with an authentic sample of furanoeremophilane-6β,10β-diol (**3**)[7,8] in respects of mp, mixed mp, $[\alpha]_D$, IR, PMR, mass spectrum, and tlc.

*Hydrogenation of **2** Over Palladium-charcoal.* A solution of **2** (42 mg) in ethanol (10 ml) was hydrogenated in the presence of 10% palladium-charcoal (8 mg) at room temperature. Filtration of the catalyst and evaporation of the solvent gave a residue, which was purified by preparative tlc to afford 1β,10β-epoxyfuranoeremophilan-6β-yl 2-hydroxymethylpropanoate (**5**; 8 mg), an oil, IR (liquid) 3440, 1730, 1640, and 1565 cm^{-1}; PMR ($CDCl_3$) δ 1.09 (3H, d, *J*=7 Hz;

protons at C-14), 1.22 (3H, s; protons at C-15), 1.87 (3H, d, $J=1.5$ Hz; protons at C-13), 2.16 (1H, d, $J=16$ Hz; proton at C-9β), 3.10 (1H, br.s; proton at C-1α), 3.27 (1H, d, $J=16$ Hz; proton at C-9α), 6.43 (1H, m; proton at C-6α), 7.08 (1H, q, $J=1.5$ Hz; proton at C-12), 1.26 (3H, d, $J=7$ Hz; $-\mathrm{CO}-\overset{|}{\mathrm{C}}\mathrm{H}-\mathrm{C}\underline{\mathrm{H}}_3$), 2.77 (1H, m; $-\mathrm{CO}-\mathrm{C}\underline{\mathrm{H}}(\mathrm{CH_2OH})-\mathrm{CH_3}$), 3.78 (2H, m; $-\mathrm{CO}-\overset{|}{\mathrm{C}}\mathrm{H}-\mathrm{C}\underline{\mathrm{H}}_2\mathrm{OH}$), and 1.6 (1H, br.s; OH; disappeared on addition of D_2O); mass spectrum *m/e* 334 [1%, M^+ ($C_{19}H_{26}O_5$)], *m/e* 87 (20%, $[\mathrm{CO-CH(CH_2OH)-CH_3}]^+$), *m/e* 59 (25%, $[\mathrm{HOCH_2-CH-CH_3}]^+$), and *m/e* 55 (100%).

References

1) A preliminary account of this paper: Y. Moriyama, T. Sato, H. Nagano, Y. Tanahashi, and T. Takahashi, *Chem. Lett.*, **1972**, 637.

2) H. Ishii, T. Tozyo, and H. Minato, *Tetrahedron*, **21**, 2605 (1965).

3) H. Ishii, T. Tozyo, and H. Minato, *J. Chem. Soc.*, *C*, **1966**, 1545.

4) H. Ishii, T. Tozyo, and H. Minato, *Chem. Commun.*, **1968**, 1534; H. Ishii, T. Tozyo, M. Nakamura, and H. Minato, *Tetrahedron*, **26**, 2911 (1970), and references therein.

5) F. Patil, G. Ourisson, Y. Tanahashi, M. Wada, and T. Takahashi, *Bull. Soc. Chim. France*, **1968**, 1047; T. Murae, Y. Tanahashi, and T. Takahashi, *Tetrahedron*, **24**, 2177 (1968); Y. Ishizaki, Y. Tanahashi, T. Takahashi, and K. Tori, *Chem. Commun.*, **1969**, 551; Y. Tanahashi, T. Takahashi, and H. Koyama, *Bull. Nat. Sci. Mus. Tokyo*, **12**, 633 (1969); Y. Ishizaki, Y. Tanahashi, T. Takahashi, and K. Tori, *Tetrahedron*, **26**, 5387 (1970); M. Tada, Y. Moriyama, Y. Tanahashi, T. Takahashi, M. Fukuyama, and K. Sato, *Tetrahedron Lett.*, **1971**, 4007; H. Nagano, Y. Moriyama, Y. Tanahashi, T. Takahashi, M. Fukuyama, and K. Sato, *Chem. Lett.*, **1972**, 13; H. Nagano and T. Takahashi, This Bulletin, **45**, 1935 (1972); H. Nagano, Y. Tanahashi, Y. Moriyama, and T. Takahashi, *ibid.*, **46**, 2840 (1973); Y. Moriyama, T. Tsuyuki, T. Takahashi, and H. Koyama, *Phytochemistry*, **13**, 288 (1974).

6) Koyama has described the presence of two types of *Ligularia Fischeri* Turcz. in Japan [H. Koyama, *Acta Phytotax. Geobot.*, **22**, 75 (1966)]. The tlc and glc data for constituents of our plant were very similar to those of *L. sibirica* Cass., collected at Prague by one of the authors, but different from those of *L. Fischeri* Turcz., collected at Karuizawa (late-flowering species), which contained ligularone *etc.* We are thankful to Dr. H. Koyama, National Science Museum, Tokyo, for recognition of our plant as *L. Fischeri* Turcz. (collected at Shiramine) from plant taxonomical point of view.

7) M. Tada, Y. Moriyama, Y. Tanahashi, T. Takahashi, M. Fukuyama, and K. Sato, *Tetrahedron Lett.*, **1971**, 4007.

8) M. Tada, Y. Tanahashi, Y. Moriyama, and T. Takahashi, *ibid.*, **1972**, 5255.

9) C. C. Hinckley, *J. Amer. Chem. Soc.*, **91**, 5160 (1969).

10) J. K. M. Sanders and D. H. Williams, *ibid.*, **93**, 641 (1971).

11) S. M. Kupchan, R. J. Hemingway, A. Karim, and D. Werner, *J. Org. Chem.*, **34**, 3908 (1969).

12) Z. Samek, M. Holub, B. Drozdz, G. Iommi, A. Corbella, and P. Gariboldi, *Tetrahedron Lett.*, **1971**, 4775.