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Studies on Terpenoids and Related Alicyclic Compounds. X.[1] Total Synthesis of Sesquiterpenoid, (±)-Ligularone

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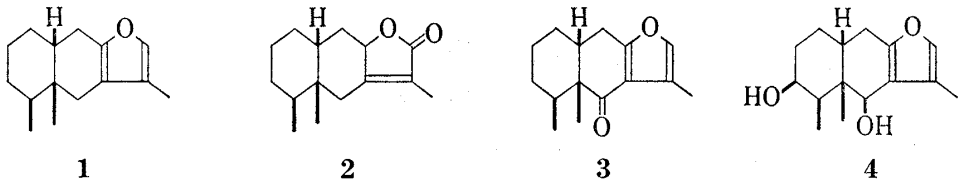
The total synthesis of (±)-ligularone (**3**) *via* diene adduct (**17**) is described. 3,5-Dimethylbenzofuran-4,7-quinone (**14**) was prepared starting from resorcinol. A mixture of **14** and diene (**16**) was refluxed in benzene for 48 hr to afford the desired adduct (**17**) in 70% yield. Treatment of **17** with silica gel gave 10-epimer (**20**). **20** was reduced with $NaBH_4$ followed by treatment of aq-AcOH to give 3,6-dioxo-9β-ol (**21**) and 9α-ol (**22**). Dehydration of **21** and **22** gave **23** which was epimerized to give 4β-methyl compound (**24**), in low yield. Catalytic reduction of **24** gave furanoeremophilan-3,6-dione (**28**). **28** was also synthesized by catalytic reduction of **23** followed by acid-epimerization of the resulting diketone (**30**), in good yield. Stereochemistry of diketone (**28**) and (**30**) are discussed by nuclear magnetic resonance (NMR) spectrometry. Desulfurization of thioketal of **28** followed by catalytic reduction of the resulting product afforded (±)-ligularone (**3**). The infrared and NMR of (±)-(**3**) were identical with those of natural ligularone. Furanoeremophilan-3,6,9-trione (**36**) was synthesized from diene adduct (**17**) and (**20**) *via* (**34**) and (**35**) in good yield, respectively.

Keywords——sesquiterpene; furanoeremophilane; (±)-ligularone; total synthesis; Diels-Alder reaction; stereochemistry; *cis*-dehydration; furanoeremophilan-3,6-dione; 3,5-dimethylbenzofuran-4,7-quinone

The bicyclic and tricyclic eremophilane-furanoeremophilane family sesquiterpenoids are widely distributed in *Petasites* and *Senecioneae* species (Compositae). Furanoeremophilanes are interesting non-farnesyl sesquiterpenoids having A/B ring *cis*-decalin system and characterized by *cis*-vicinal dimethyl groups at carbon 4 and 5 and containing a furan or butenolide ring (**1**—**5**). Research in *Petasites* and related species has been achieved by several groups,[3a-g]

1) Part IX. K. Yamakawa, R. Sakaguchi, T. Nakamura, and K. Watanabe, *Chem. Lett. Jpn.*, **1976**, 991.
2) Location: *Ichigaya-funagawara-machi, Shinjuku-ku, Tokyo 162, Japan.*
3) *a*) F. Sorm, *Pure Appl. Chem.*, **21**, 263 (1970); L. Novotny, V. Herout, and F. Sorm, *Coll. Czech. Chem. Commun.*, **29**, 2182, 2189 (1964); L. Novotny, Z. Samek, and F. Sorm, *ibid.*, **31**, 371 (1966); L. Novitny, Z. Samek, J. Harmatha, and F. Sorm, *ibid.*, **34**, 336 (1969); J. Harmatha, Z. Samek, L. Novotny, V. Herout, and F. Sorm, *ibid.*, **34**, 1739 (1969); Z. Samek, J. Harmatha, L. Novotny, and F. Sorm, *ibid.*, **34**, 2792 (1969); L. Novotny, J. Toman, F. Stary, A.D. Marquez, and V. Herout, *Phytochem.*, **5**, 1281 (1966); L. Novotny, J. Toman, and V. Herout, *ibid.*, **7**, 1349 (1968); L. Novotny, K. Kotova, J. Toman, and V. Herout, *ibid.*, **11**, 2795 (1972); L. Novotny, V. Herout, and F. Sorm, *Tetrahedron Lett.*, **1961**, 697; L. Novotny, Z. Samek, V. Herout, and F. Sorm, *ibid.*, **1968**, 1401; J. Harmatha, Z. Samek, L. Novotny, V. Herout, and F. Sorm, *ibid.*, **1968**, 1409; *b*) H. Nagano, Y. Tanahashi, Y. Moriyama, and T. Takahashi, *Bull. Chem. Soc. Jpn.*, **46**, 2840 (1973); T. Sato, Y. Moriyama, H. Nagano, Y. Tanahashi, and T. Takahashi, *ibid.*, **48**, 112 (1975); F. Patil, J. -M. Lehn, G. Ourisson, Y. Tanahashi, and T. Takahashi, *Bull. Soc. Chim. Fr.*, **1965**, 3085; F. Patil, G. Ourisson, Y. Tanahashi, M. Wada, and T. Takahashi, *ibid.*, **1968**, 1047; M. Tada, Y. Moriyama, Y. Tanahashi, and T. Takahashi, *Tetrahedron Lett.*, **1971**, 4007; Y. Ishizaki, Y. Tanahashi, and T. Takahashi, *Chem. Commun.*, **1969**, 551; Y. Ishizaki, Y. Tanahashi, T. Takahashi, *Tetrahedron*, **26**, 5387 (1970); Y. Moriyama and T. Takahashi, *Chem. Pharm. Bull.* (Tokyo), **24**, 360 (1976); *c*) F. Bohlmann, C. Zdero, and M. Grenz, *Chem. Ber.*, **107**, 2730 (1974); F. Bohlmann and C. Zdero, *ibid.*, **107**, 2912 (1974); F. Bohlmann, C. Zdero, and M. Grenz, *ibid.*, **107**, 3928 (1974); F. Bohlmann and C. Zdero, *ibid.*, **109**, 819 (1976); F. Bohlmann and A. Suwita, **109**, 1230 (1976); F. Bohlmann, C. Zdero, N. Rao, *ibid.*, **105**, 3523 (1972); F. Bohlmann and C. Zdero, *ibid.*, **106**, 3614 (1973); F. Bohlmann, A. Suwita, and P. Mahanta, *ibid.*, **109**, 3570 (1976); F. Bohlmann and N. Rao, *Tetrahedron Lett.*, **1973**, 613; *d*) T. Kurihara, K. Ro, H. Takeda, and H. Ito, *Annual Report of Tohoku College of Pharmacy*, **13**, 75 (1966); *e*) D.E.A. Rivett and G.R. Woolard, *Tetrahedron*, **23**, 2431 (1967); G.A. Eagle, D.E.A. Rivett, D.H. Williams, and R.G. Wilson, *ibid.*, **25**, 5227 (1969); *f*) L.R. Hahn, A. Guzman, and J. Romo, *Tetrahedron*, **24**, 477 (1968); *g*) B.L. Flamm, J.A. Pettus, Jr., J.J. Sims, J.P. Springer, and J. Clardy, *Tetrahedron Lett.*, **1976**, 2671.

and large numbers of eremophilane and furanoeremophilane sesquiterpenoids were isolated and structures determined. Although some total syntheses of eremophilanes have been reported,[4] few papers have recently been published on the total synthesis of furanoeremophilanes.[5]



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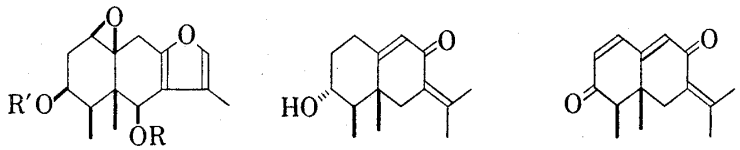

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The author (K.Y.)[6] previously reported total synthesis of (±)-isopetasol (**6**) and (±)-warburgiadion (**7**) by the Robinson annulation method. In the paper, we reported 4-methyl group of the octaline derivative was easily epimerized to desired *cis*-vicinal dimethyl groups due to enolization by 3-oxo group. We now wish to report the total synthesis of furanoeremophilane, (±)-ligularone (**3**)[7] *via* the Diels-Alder reaction. An important key intermediate diene adduct (**17**),[8] which possesses masked 3-oxo group, was synthesized by the Diels-Alder reaction of furanoquinone (**14**) and 3-ethoxy-1,3-pentadiene (**16**). The diene adduct (**17**) is significant compound toward the total synthesis of some oxygenated furanoeremophilanes.

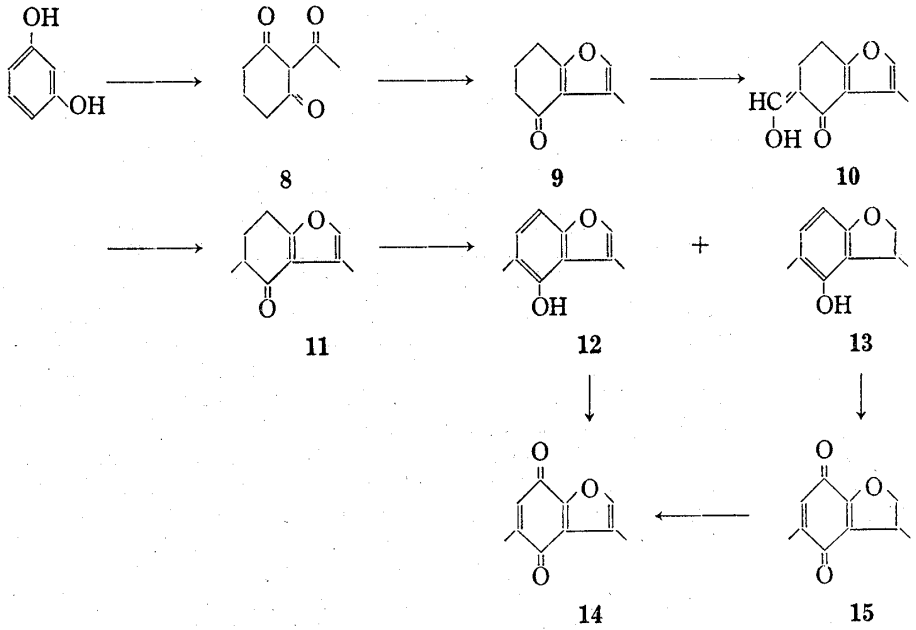


Chart 1

4) C.H. Heathcock in ApSimon ed., "The Total Synthesis of Natural Products," Vol. 2, John Wiley and Sons, New York, 1973, p. 361.
5) T. Tatee and T. Takahashi, *Bull. Chem. Soc. Jpn*, **48**, 281 (1975); I. Nagakura, S. Maeda, M. Ueno, M. Funamizu, and Y. Kitahara, *Chem. Lett.*, **1975**, 1143.
6) K. Yamakawa, I. Izuta, H. Oka, and R. Sakaguchi, *Tetrahedron Lett.*, **1974**, 2187.
7) H. Ishii, T. Tozyo, and H. Minato, *Tetrahedron*, **21**, 2605 (1965).
8) Previously reported on the 17th Symposium on the Chemistry of Terpenes, Essential Oils and Aromatics, Okayama, October, 1973; Symposium Papers p. 216.

3,5-Dimethylbenzofuran-4,7-quinone (**14**) as dienophile has been prepared starting from resorcinol. Reaction of 2-acetylcyclohexane-1,3-dione (**8**)[9] with diazomethane and followed treatment with perchloric acid gave 3-methyl-4-oxofuranocyclohexane (**9**)[10] in 30% yield. Formylation of **9** afforded **10** as pale yellow crystal in 95% yield. Methylation of **10** with methyl iodide in the presence of sodium hydride and subsequent treatment of the product with 5% sodium hydroxide gave methylated compound (**11**), mp 36—38°, together with O-methylated compound in 68% and 20% yield, respectively. Dehydrogenation of **11** with palladium charcoal catalyst in *p*-cymene in a sealed tube was carried out at 200° for 3 hr to give a mixture of phenolic compound (**12**), mp 74—75°, and a small amount of dihydro compound (**13**). Chromatographic separation of the mixture of phenolic compounds was failed due to easy oxidation on silica gel column. Then, oxidation of a mixture of **12** and **13**, without purification, by Fremy's salt gave a mixture of quinone derivatives (**14**) and (**15**). Chromatographic separation of the quinones on silica gel gave **14**, mp 100—102°, as yellow needles in 54% yield and **15**, mp 77—78°, as orange red prisms in 20% yield from **11**. The compound (**15**) was converted into furanoquinone (**14**) by dehydrogenation with dichlorodicyano-*p*-benzoquinone under heating at 180° in diphenyl ether, quantitatively.

The Diels-Alder reaction of furanoquinone (**14**) and 3-ethoxy-1,3-pentadiene (**16**)[11] was made in refluxing dry benzene for 48 hr. The adduct [*cis*-"*ortho*" **17** or *cis*-"*meta*" **18**], mp 135—137°, was obtained in 70% yield. The structure of the adduct (**17**) was determined

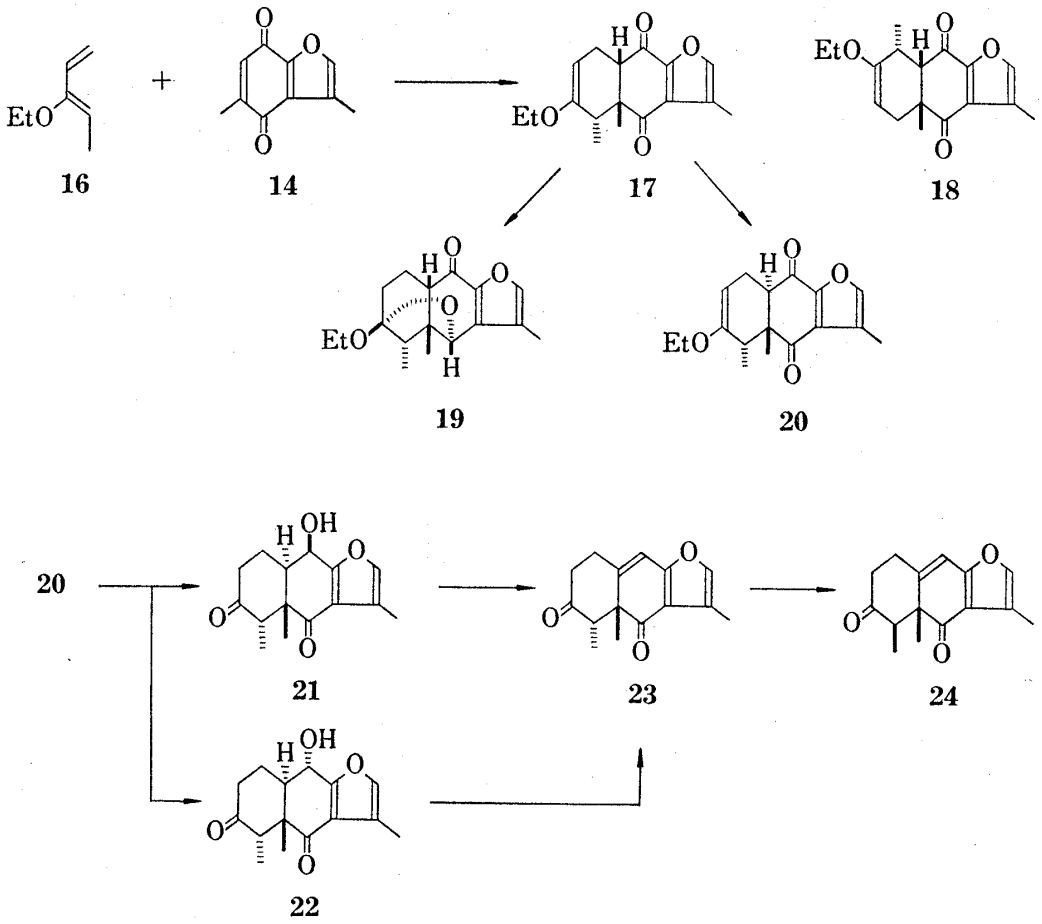


Chart 2

9) H. Smith, *J. Chem. Soc.*, **1953**, 803.
10) G. Nowy, W. Riedl, and H. Simon, *Chem. Ber.*, **99**, 2075 (1966).
11) L.H. Sarett, R.M. Ludes, G.I. Poos, J.M. Robinson, R.E. Beyler, J.M. Vandegrift, and G.E. Arth, *J. Am. Chem. Soc.*, **74**, 1393 (1952).

by nuclear magnetic resonance (NMR) spectroscopy with decoupling techniques and using the NMR shift reagent, $Eu(FOD)_3$. A 4-proton appeared as quartet signals which was confirmed by using $Eu(FOD)_{3'}$ and the signals changed to singlet signal by irradiation at the 4-methyl group (δ 0.68). From these results, the structure of the adduct should be shown *cis*-"*ortho*" (**17**). A/B ring junction and 4-methyl group of the adduct (**17**) should be shown *cis* fusion and α-orientation, respectively, on the basis of the reaction mode[12] and epimerization of 10-hydrogen and 4-methyl group under acidic condition as described below. A/B ring *cis* fusion are also supported by the fact that the adduct (**17**) easily formed rigid A/B *cis* cyclic ether (**19**) by reduction of **17** with sodium borohydride followed by treatment with silica gel.[8]

On treatment with silica gel, the adduct (**17**) was epimerized to A/B ring *trans*-adduct (**20**), mp 150—152°, as yellow crystal, quantitatively. Selective reduction of 9-keto group of the adduct (**20**) with sodium borohydride in methanol gave 3,6-dioxo-9β-ol (**21**), mp 234—235.5°, in 28% yield and 3,6-dioxo-9α-ol (**22**), mp 214—216°, in 64% yield. Configuration of the hydroxyl group of **21** and **22** was confirmed by NMR spectroscopy, triplet signals (δ 4.91) and double doublet signals (δ 4.69) for 9α-H and 9β-H, respectively.

9β-Hydroxy compound (**21**) in benzene containing catalytic amount of *p*-toluenesulfonic acid was refluxed to give an olefin (**23**), mp 149—150°, in 90% yield, which showed λ_{max}^{EtOH} 336 nm as characteristic chromophore of **23**. While, treatment of 9α-hydroxy compound (**22**) under similar condition gave unchanged starting material (**22**). Then, **22** was treated with methyl-(carboxysulfamoyl)triethylammonium hydroxide inner salt[13] in benzene at 50° to yield an olefin (**23**), in 60% yield by intramolecular *cis*-elimination. Refluxing of **23** in benzene with catalytic amount of *p*-toluenesulfonic acid for 2 hr gave 4β-methyl epimer (**24**), mp 119—120°, in low yield (8—10% yield). The infrared (IR), ultraviolet (UV), and NMR spectra of the diketone (**24**) were in good agreement with those of **24** derived from the natural nemosenin A–D reported by Novotny, *et al.*[14]

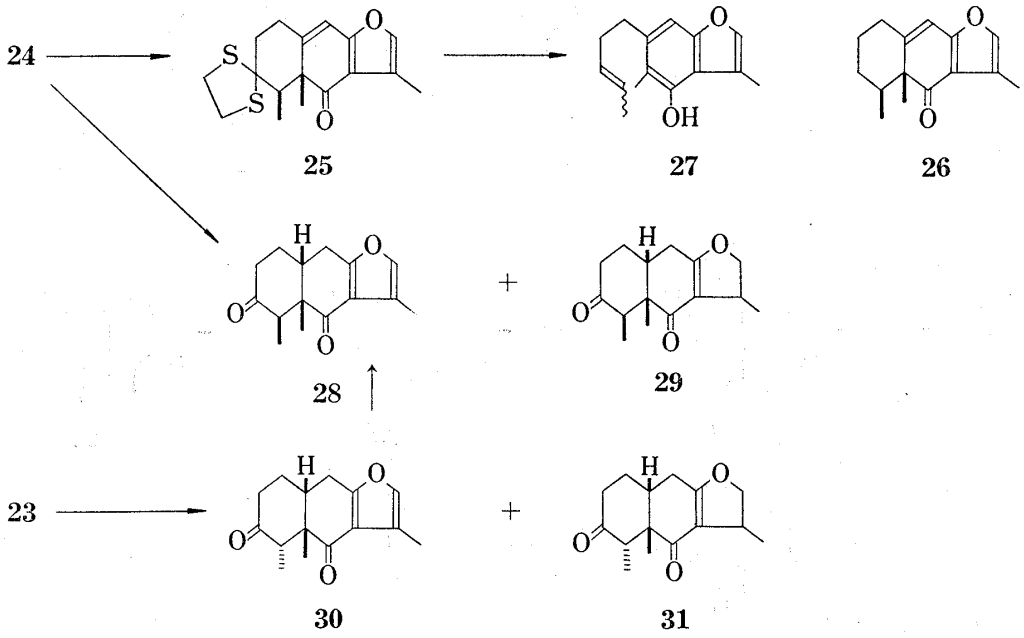


Chart 3

12) R.B. Woodward and R. Hoffmann, "The Conservation of Orbital Symmetry" Academic Press 1970, p. 145.
13) E.M. Burgess, H.R. Penton, Jr., and E.A. Taylor, *J. Org. Chem.*, **38**, 26 (1973).
14) L. Novotny, M. Krojidlo, Z. Samek, J. Kohoutova, and F. Sorm, *Coll. Czech. Chem. Commun.*, **38**, 739 (1973).

The diketone (**24**) was converted into ethanedithioketal (**25**). Attempted reductive desulfurization of **25** with W-2 Raney nickel in refluxing ethanol into desired ketone (**26**) gave unexpected furanophenol derivative (**27**) which showed very similar UV spectrum pattern to that of furanophenol compound (**12**) as described above.

Then, catalytic reduction of **24** with palladium-charcoal in ethyl acetate afforded a diketone (**28**), mp 176—178°, in 80% yield together with a trace of dihydro compound (**29**). The IR and NMR spectra of **28** were identical with those of the degradation product (**28**) from (+)-furanofukinol (**4**) reported by Naya, *et al.*[15]

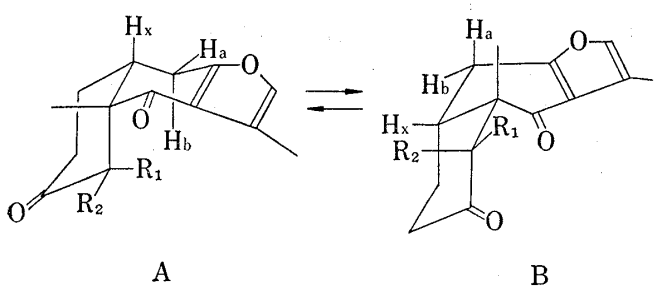
The preparation of diketone (**28**) was improved by the following synthetic route. Catalytic reduction of enone (**23**) with palladium-charcoal in ethanol gave diketone (**30**) in 79% yield together with a trace of **31**. Epimerization of 4-methyl group of **30** in refluxing benzene containing catalytic amount of *p*-toluenesulfonic acid afforded furanoeremophilan-3,6-dione (**28**) quantitatively.

Stereochemistry of diketone (**28**) and (**30**) are considered on the basis of the reaction mode, conformational analysis, and NMR spectrometry. The *trans*-dimethyl diketone (**30**) may exist in either of two conformers, steroidal (A) and non-steroidal (B) (Fig. 1a). Conformer (A) may be formed in the first step on the catalytic reduction of enone (**23**). In a conformer (A), 4-methyl group possesses axial bond and should be affected by considerable steric compression of ring B and furan ring moiety, whereas a conformer (B) has equatorial 4-methyl group and are cosidered sterically more stable than a conformer (A). If the diketone (**30**) takes conformer (A), the chemical shift of 4-methyl group should be expected uperfield (δ 0.9 under) due to aromatic anisotropic effect of furan ring and steric compression of the ring moiety. However, the chemical shift of 4-methyl group of diketone (**30**) appeared in the farthest downfield (δ 1.38) than the other eremophilane-type compounds which is shown in Table I (δ 0.85—1.09).

Geminal protons (9-Ha and 9-Hb) of **30** are coupled by 10-proton as ABX type which appeared in double doublet singnals with J=5.6 and 18 Hz and J=2.8 and 18 Hz, respectively.

Table I. The Chemical Shifts of C-4 and C-5 Methyl Groups of Furanoeremophilanes (ppm, at 100 MHz)

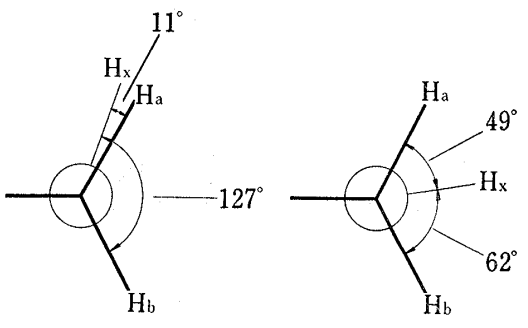
Compound	**30**	**28**	**34**	**36**	**23**	**24**	**3**
4-CH_3	1.38	0.92	1.09	0.85	0.92	1.14	0.87
5-CH_3	1.42	1.12	1.45	1.21	1.30	1.19	1.11



A B

28: R_1=H, R_2=CH_3
30: R_1=CH_3, R_2=H

Fig. 1a. Conformation of **28** and **30** in Steroidal (A) and *non*-Steroidal (B)



28-A: J_{ax} 9.6 Hz; J_{bx} 5.8 Hz

30-B: J_{ax} 5.6 Hz; J_{bx} 2.8 Hz

Fig. 1b. Dihedral Angles between C–10 H_x and C–9 H_a and C–10 H_x and C–9 H_b for **28-A** and **30-B**

15) K. Naya, M. Nakagawa, M. Hayashi, K. Tsuji, and M. Naito, *Tetrahedron Lett.*, **1971**, 2961.

The bond angles are calculated from these coupling constants by the modified Karplus equation[16] as illustrated in Fig. 1b.

Consequently, from these NMR data and conformational analysis a preferred conformation of diketone (**30**) should be shown by a non-steroidal conformation (B) as shown in Fig. 1a. The procedures just described can be applied in cases of conformation (A) and (B) of diketone (**28**) as well. A preferred conformation of cis-dimethyldiketone(**28**) should be considered to be steroidal conformation (A) than non-steroidal (B), which is also supported by means of NMR coupling constants of 9-geminal protons, J=9.6 and 18 Hz and J=5.8 and 18 Hz, as illustrated in Fig. 1b.

Treatment of diketone (**28**) with 1,2-ethanedithiol in presence of borontrifluoride–ether complex gave thioketal (**32**). Reductive desulfurization of **32** with W-2 Raney nickel yielded a mixture of olefin (**33**) and ketone (**3**) in a ratio of 2: 1, which was catalytically reduced with palladium charcoal to afford (±)-ligularone (**3**), mp 68—70°, quantitatively. All spectral data of (±)-ligularone (**3**) were identified with those of (+)-ligularone isolated from *Ligularia sibirica* Cass reported by Ishii, *et al.*[7] and Takahashi, *et al.*[17]

Furthermore, an alternative synthesis of (±)-ligularone (**3**) from the diene adduct (**17**) and 10α-H epimer (**20**) was investigated. Hydrolysis of the adduct (**17**) and (**20**) with aqueous acetic acid at room temperature gave triketone (**34**), mp 129—131°, and (**35**), mp 150—153°, respectively. The IR and NMR spectral data of **34** and **35** were identified with those of Bohlmann's compound,[18] respectively. Both triketones (**34** and **35**) were refluxed in

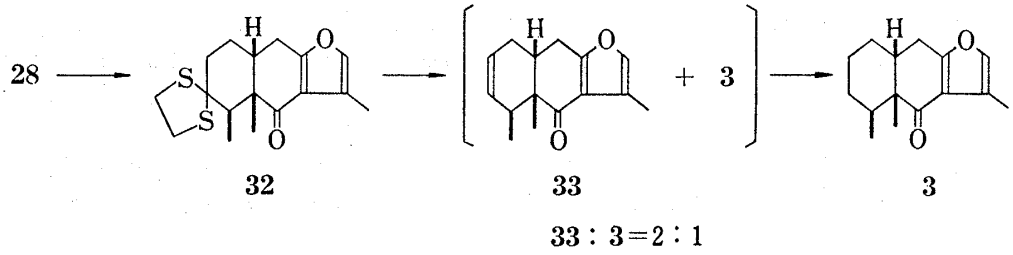


Chart 4

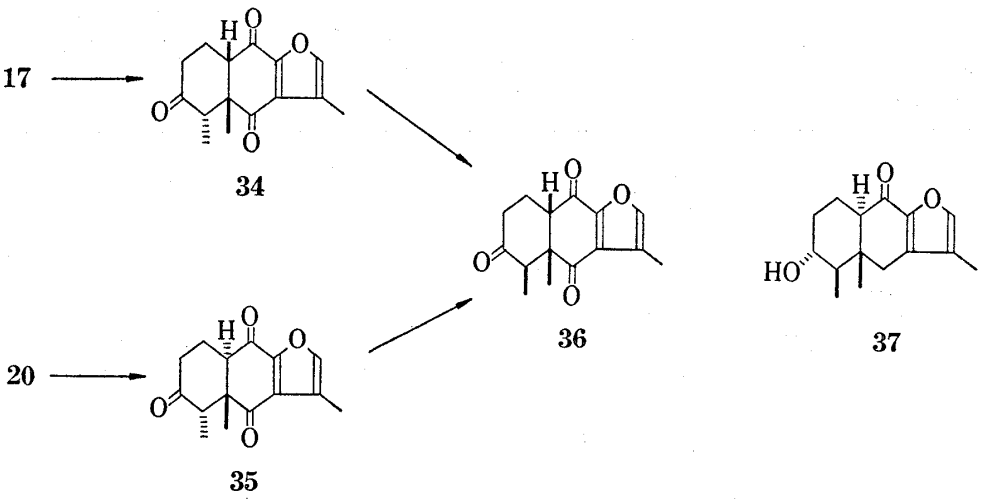


Chart 5

16) K.L. Williamson and W.S. Johnson, *J. Am. Chem. Soc.*, **83**, 4623 (1961); R.J. Abraham and J.S.E. Holker, *J. Chem. Soc.*, **1963**, 806.

17) M. Tada, Y. Moriyama, Y. Tanahashi, and T. Takahashi, *Bull. Chem. Soc. Jpn.*, **47**, 1999 (1974).

18) The authors are indebted to Professor Bohlmann, Technischen Universitat Berlin, for his kind identification of the samples and sending us the manuscript (ref. 19) before the publication.

benzene containing catalytic amount of *p*-toluenesulfonic acid to give 4*β*-methyl triketone (**36**), mp, 204—205.5°, in good yield. During the course of this study, independently, Bohlmann, *et al.*[19] reported successful conversion of the triketone (**36**) into some sesquiterpenes, (±)-ligularone (3) and (±)-euryopsonol (**37**).

Experimental

All melting points were determined on a Yanagimoto micro melting points apparatus and are uncorrected. NMR spectra are for solution in $CDCl_3$ unless otherwise cited and they were measured with a Jeol JNM-4H-100 spectrometer at 100 MHz and a Hitachi R-24 spectrometer at 60 MHz using Me_4Si as the internal standard. IR spectra were measured for KBr disk with a Hitachi Perkin-Elmer 225 and a Hitachi 215 grating spectrophotometer. UV spectra were measured with a Hitachi 323 and 200 spectrophotometer. Mass spectra were measured on a Hitachi RMU-7M double focusing mass spectrometer at 70 eV by using direct insertion. High-resolution mass spectral data were determined by a Hitachi datalyzer 002 connected on line with the mass spectrometer.

Wako silica gel C-200 (200 mesh) containing 2% fluorescence reagent 254 and quartz column were used in column chromatography. Preparative thin-layer chromatography (TLC) was carried out using Merk silica gel HF_{254}.

3-Methyl-4-oxo-4,5,6,7-tetrahydrobenzofuran (**9**)——To a solution of 2-acetylcyclohexanedione (**8**)[9] (16.5 g) in ether was added diazomethane ethereal solution (prepared from 107 g of N-methyl-N-nitroso-*p*-toluenesulfonamide with aq-KOH) in ice bath and the solution was allowed to stand for 1 hr at room temperature. After completed the reaction, the ether was evaporated. The residue was dissolved in dioxane (60 ml) and to the solution was added 60% $HClO_4$ (3 ml) under cooling in an ice bath and allowed to stand for 30 min at room temperature. Excess amounts of saturated aq-$NaHCO_3$ was added to the reaction mixture and dioxane was evaporated *in vacuo*. After addition of 10% NaOH into the residue, the mixture was extracted with benzene. The benzene layer was washed with 2% aq-NaOH and then was purified with a silica gel chromatography to give a solid compound (**9**) (5.10 g; 32% yield). Recrystallization from hexane afforded colorless prism of **9**, mp 61—61.5° [reported,[10] mp 61.5—62.5°]. IR cm^{-1}: 1675 (CO); UV λ_{max}^{EtOH} 265 nm; NMR δ: 2.18 (3H, d, J=1 Hz), 7.08 (1H, m, $W1/2$=4 Hz); MS *m/e* (rel. intensity): 150 (M^+, 81), 122 ($[M-C_2H_4]^+$, 100).

5-Formyl-3-methyl-4-oxo-4,5,6,7-tetrahydrobenzofuran (**10**)——A benzene solution of **9** (3.41 g) was added dropwise to a stirring suspension of NaH (50% in mineral oil, 3.27 g) and 10 g of HCO_2Et in anhydrous benzene in an ice bath under N_2 gas stream, and allowed to stand over night at room temperature. To the reaction mixture was added 5% H_2SO_4 (50 ml) and then the solution was extracted with benzene. After evaporation of benzene, the residue was chromatographed on silica gel to give **10** (3.91 g; 96% yield), mp 32—33.5°. MS *m/e* (rel. intensity): 178 (M^+, 100), 149 (47), 121 (44); IR cm^{-1}: 1645 (CO); UV λ_{max}^{EtOH} 301.5 nm (ε 7800); NMR δ: 2.22 (3H, d, J=1 Hz), 7.10 (1H, m, $W1/2$=3 Hz), 7.24 (1H, m, $W1/2$=5 Hz).

Copper(II) chelate derivative of **10**, it had mp 220° (dec.) as pale green needles. *Anal.* Calcd. for $C_{20}H_{18}CuO_6$: C, 57.48; H, 4.34. Found: C, 57.49; H, 4.33. IR cm^{-1}: 1625, 1600 (CO).

3,5-Dimethyl-4-oxotetrahydrobenzofuran (**11**)——A THF solution of **10** (3.38 g) was added dropwise to a stirring suspension of NaH (50% mineral oil, 1.1 g) in anhydrous THF (50 ml) at 0° and then the solution was stirred for 30 min. CH_3I (4.0 g) was added to the above solution and stirred for 24 hr at room temperature. To the reaction mixture was added 5% aq-NaOH (50 ml) with stirring for 30 min. The solvent was evaporated *in vacuo* to leave crude product, which was extracted with benzene and then benzene was evaporated. The residue was chromatographed on silica gel to give **11** (1.98 g; 64% yield) as colorless prism, mp 36—38°. IR cm^{-1}: 1670 (CO); UV λ_{max}^{EtOH} nm: 243, 264. NMR δ: 1.20 (3H, d, J=7 Hz), 2.17 (3H, d, J=1 Hz), 7.05 (1H, m, $W1/2$=3 Hz). MS *m/e* (rel. intensity): 164 (M^+, 53), 149 ($[M-CH_3]^+$, 53), 122 ($[M-C_3H_6]^+$, 100).

3,5-Dimethyl-4-hydroxybenzofuran (**12**)——A mixture of **11** (2.07 g), 10% Pd-charcoal (1.5 g) in *p*-cymene (6 ml) in a sealed tube was heated at 200° for 3 hr, and the reaction mixture was filtrated and washed with acetone. The filtrate and washed solvent was combined, and the solvent was evaporated *in vacuo*. The product, in part, was separated by preparative TLC on silica gel and then recrystallization from hexane yielded **12** as colorless needles, mp 74—75°. High-resolution MS: Mol. Wt. 162.0680 for $C_{10}H_{10}O_2$: Observed M^+, 162.0669. IR cm^{-1}: 3450 (OH); UV λ_{max}^{EtOH} nm: 249, 256, 284, 293; NMR δ: 2.31 (3H, s), 2.42 (3H, d, J=1 Hz), 4.85 (1H, br. s), 7.01 (2H, s), 7.28 (1H, m): MS *m/e* (rel. intensity): 162 (M^+, 100), 161 ($[M-H]^+$, 72).

3,5-Dimethylbenzofuran-4,7-quinone (**14**)——(a) According to the procedure of Moser and Howie,[20] Fremy's salt was prepared starting from 17.2 g of $NaNO_2$. To a slurry of freshly prepared Fremy's salt in

19) F. Bohlmann, H. -J. Forster, and C. -H. Fischer, *Ann. Chem.*, **1976**, 1487.
20) W. Moser and R.A. Howie, *J. Chem. Soc.* (*A*), **1968**, 3039.

H_2O (200 ml) was added with stirring a solution of the above obtained phenol (**12**) in MeOH in ice bath. The reaction mixture was stirred at 0° for 30 min and allowed to stand at room temperature for 1 hr. After saturation with NaCl, the reaction mixture was extracted with benzene. Evaporation of the benzene and the residue was chromatographed over silica gel to give predominantly 3,5-dimethylbenzofuran-4,7-quinone (**14**) (1.2 g; 54% yield, recrystallized from hexane) as yellow needles, mp 100—102°, together with a small amount of 3,5-dimethyl-2,3-dihydrobenzofuran-4,7-quinon (**15**) as orange-red prism, mp 79—80°. **14**: *Anal.* Calcd. for $C_{10}H_8O_3$: C, 68.18; H, 4.58. Found: C, 67.96; H, 4.87. IR cm^{-1}: 1685, 1675; UV λ_{max}^{EtOH} nm (ε): 253.5 (15700), 260 (14500), 298.5 (2500), 396 (1350); NMR δ: 2.07 (3H, d, $J=1$ Hz), 2.25 (3H, d, $J=1$ Hz), 6.45 (1H, m, $W1/2=5$ Hz), 7.37 (1H, m, $W1/2=5$ Hz). MS *m/e* (rel. intensity): 176 (M^+, 100), 148 ($[M-CO]^+$, 18), 108 ($[M-C_4H_4O]^+$, 50). **15**: *Anal.* Calcd. for $C_{10}H_{10}O_3$: C, 67.41; H, 5.66. Found: C, 67.24; H, 5.80. IR cm^{-1}: 1680, 1650, 1605; UV λ_{max}^{EtOH} nm (ε): 270 (15100), 418 (850); NMR δ: 1.32 (3H, d, $J=7$ Hz), 2.03 (3H, d, $J=1$ Hz), 3.30—2.80 (1H, m, $W1/2=30$ Hz), 4.22 (1H, dd, $J=7$, 10 Hz), 4.73 (1H, t, $J=10$ Hz), 6.33 1H, m, $W1/2=3$ Hz); MS *m/e* (rel. intensity); 178 (M^+, 86), 163 ($[M-CH_3]^+$, 88), 150 ($[M-CO]^+$, 44), 95 (100).

(b) Conversion of **15** into **14**: A solution of dihydro compound (**15**) (535 mg) and DDQ (1.02 g) in diphenyl ether (10 g) was heated at 180° (bath temperature) for 1.5 hr and allowed to stand at room temperature. Dichlorodicyano-*p*-hydroquinone was filtrated and washed with benzene. The filtrate was evaporated *in vacuo* to left an residue which was purified by chromatography and recrystallized from hexane. Furanoquinone (**14**) (503 mg; 95% yield) was confirmed with above authentic specimen.

The Diels-Alder Reaction of Quinone (14) and 3-Ethoxy-1,3-pentadiene (16)——(a) To a solution of **14** (704 mg) in abs. benzene (60 ml) was added 3-ethoxy-1,3-pentadiene (**16**)[11] (2.24 g) and the reaction mixture was refluxed for 48 hr. Evaporation of the benzene and the residue was added with a small amount of hexane, and allowed to stand at room temperature to give colorless crystal. Recrystallization from benzene–hexane gave colorless prisms (805 mg; 70% yield) of the adduct (**17**), mp 136—138°. *Anal.* Calcd. for $C_{17}H_{20}O_4$: C, 70.81; H, 6.99. Mol. Wt. 288.1360 Found: C, 70.52; H, 6.98. M^+, 288.1371. IR cm^{-1}: 1700, 1680; UV λ_{max}^{EtOH} nm (ε): 243.5 (4700), 310.5 (6800); NMR (CCl_4) δ: 0.68 (3H, d, $J=7$ Hz), 1.22 (3H, t, $J=7$ Hz), 1.41 (3H, s), 2.26 (3H, d, $J=1$ Hz), 2.80 (1H, d, $J=7$ Hz), 3.65 (2H, q, $J=7$ Hz), 4.43 (1H, dd, $J=2.5$, 5 Hz), 7.39 (1H, m, $W1/2=3$ Hz). MS *m/e* (rel. intensity): 288 (M^+, 100), 273 ($[M-CH_3]^+$, 46), 259 (48).

(b) The reaction product from **14** (529 mg) and **16** (2.0 g) under the same condition as described above was absorbed over silica gel column (70 g) and allowed to stand for 1 hr. Elution with hexane–EtOAc (30 :1) gave a crystal, which was recrystallized from hexane–EtOAc to give the adduct (**20**) (475 mg; 55% yield) as colorless prisms, mp 150—152°. *Anal.* Calcd. for $C_{17}H_{20}O_4$: C, 70.81; H, 6.99. Mol. Wt. 288.1360. Found: C, 70.74; H, 6.87. M^+, 288.1373. IR cm^{-1}: 1685, 1670; UV λ_{max}^{EtOH} nm (ε): 243.5 (5100), 301.5 (7000). NMR δ: 1.15 (3H, d, $J=7$ Hz), 1.23 (3H, s), 2.26 (3H, d, $J=1$ Hz), 4.50 (1H, dd, $J=2.5$, 5 Hz), 7.39 (1H, m, $W1/2=3$ Hz). MS *m/e* (rel. intensity): 288 (M^+, 100), 273 ($[M-CH_3]^+$, 58), 259 (67).

Reduction of Adduct (20) with $NaBH_4$——To a solution of the adduct (**20**) (311 mg) in benzene (2 ml) and MeOH (20 ml) was added $NaBH_4$ (25 mg) with stirring at room temperature and stirring was continued for 30 min. NH_4Cl was added to the reaction mixture and then the solution was evaporated *in vacuo*. The residue was extracted with benzene, washed with H_2O and dried. Evaporation of the solvent and was added with 75% aq-AcOH (10 ml) and allowed to stand at room temperature for 2.5 hr. Removal of AcOH *in vacuo*, the residue was chromatographed on silica gel (40 g). Elution with hexane–EtOAc (4: 1) gave the first fraction of 9β-OH (**21**) as colorless needles (78 mg; 28% yield), mp 234—235.5°, and second fraction 9α-OH (**22**) as colorless brock (181 mg; 64% yield), mp 214—216°. The both compounds were recrystallized from EtOAc–hexane. **21**: *Anal.* Calcd. for $C_{15}H_{18}O_4$: C, 68.68; H, 6.92. Found: C, 68.40; H, 6.75. IR cm^{-1}: 3450, 3350 (OH), 1720, 1700, 1675 (CO); UV λ_{max}^{EtOH} 267.5 nm (ε 3200); NMR δ: 1.13 (3H, d, $J=7$ Hz), 1.26 (3H, s), 2.22 (3H, d, $J=1$ Hz), 4.91 (1H, t, $J=5$ Hz; after added D_2O, d, $J=5$ Hz), 7.17 (1H, m, $W1/2=4$ Hz); MS *m/e* (rel. intensity): 262 (M^+, 41), 244 ($[M-H_2O]^+$, 13), 138 ($[M-C_8H_{12}O]^+$, 100). **22**: *Anal.* Calcd. for $C_{15}H_{18}O_4$: C, 68.68; H, 6.92. Found: C, 68.43; H, 7.01. IR cm^{-1}: 3475 (OH), 1710, 1685 (CO); UV λ_{max}^{EtOH} 268 nm (ε 3400); NMR δ: 1.06 (3H, s), 1.17 (3H, d, $J=7$ Hz), 2.19 (3H, d, $J=1$ Hz), 4.69 (1H, dd, $J=5$, 10 Hz; after added D_2O, d, $J=10$ Hz), 7.16 (1H, m, $W1/2=4$ Hz); MS (rel. intensity): 262 (M^+, 82), 244 ($[M-H_2O]^+$, 13), 138 ($[M-C_8H_{12}O]^+$, 100).

9,10-Dehydro-4-epifuranoeremophilan-3,6-dione (23)——(a) From 9β-OH (**21**): A solution of 9β-OH (**21**) (51 mg) and *p*-toluenesulfonic acid monohydrate (25 mg) in benzene (15 ml) was refluxed for 20 min. Evaporation of the benzene, the residue was purified by preparative TLC over silica gel and developed with benzene–EtOAc (10: 1). Recrystallization from hexane afforded (**23**) as fine yellow needles (43 mg; 90% yield), mp 149—150°. *Anal.* Calcd. for $C_{15}H_{16}O_3$: C, 73.75; H, 6.60. Found: C, 73.90; H, 6.62. IR cm^{-1}: 1715, 1670 (CO); UV λ_{max}^{EtOH} nm (ε): 241 (8260), 336 (5730); NMR δ: 0.92 (3H, d, $J=7$ Hz), 1.30 (3H, s), 2.23 (3H, d, $J=1$ Hz), 6.67 (1H, d, $J=2$ Hz), 7.10 (1H, m, $W1/2=3$ Hz); MS *m/e* (rel. intensity): 244 (M^+, 98), 239 ($[M-CH_3]^+$, 24), 189 ($[M-C_3H_3O]^+$, 100).

(b) From 9α-OH (**22**): To a solution of 9α-OH (**22**) (180 mg) in THF (3 ml) and benzene (20 ml) was added a freshly prepared methyl(carboxysulfamoyl)triethylammonium hydroxide inner salt[13] (330 mg) in benzene and then the reaction mixture was warmed at 50° for 20 min. After completion of the reaction, H_2O was added to the solution and was extracted with benzene. The organic layer was washed with saturated

aq-NaCl and dried. Removal of solvent left crude crystal which was purified by silica gel column chromatography to give **23** (93 mg; 56% yield). This compound (**23**) was identical with an above authentic specimen (**23**) in all respects.

9,10-Dehydrofuranoeremophilan-3,6-dione (24)——A solution of **23** (257 mg) and *p*-toluenesulfonic acid monohydrate (180 mg) in benzene (70 ml) was refluxed for 2 hr. Evaporation of the solvent left the crude product which was chromatographed over silica gel column (30 g). Elution with hexane–EtOAc (20: 1) gave a first fraction (**24**) (23 mg; 9% yield) and second fraction an unchanged material (**23**) (229 mg; 89% recovery). Recrystallization from pentane afforded colorless needles (**24**), mp 119—120°. High-resolution MS Mol. Wt. 244.1099 for $C_{15}H_{16}O_3$: Observed M$^+$, 244.1122. IR cm^{-1}: 1720, 1660; UV λ_{max}^{EtOH} nm (ε): 240 (8030), 337 (5530); NMR δ: 1.14 (3H, d, J=7 Hz), 1.19 (3H, s), 2.21 (3H, d, J=1 Hz), 6.54 (1H, d, J=1 Hz), 7.07 (1H, m, $W1/2$=3 Hz); MS *m/e* (rel. intensity): 244 (M$^+$, 100), 239 ([M–CH_3]$^+$, 24), 189 ([M–C_3H_3O]$^+$, 97).

3,3-Ethylenedithio-9,10-dehydrofuranoeremophilan-6-one (25)——To a solution of diketone (**24**) (12 mg), ethanedithiol (200 mg) in abs. ether (3 ml) was added, dropwise, 10 drops of $BF_3 \cdot OEt_2$ at room temperature. The solution was allowed to stand for 24 hr and then was added 10 drops of $BF_3 \cdot OEt_2$ and the reaction time was prolonged to 48 hr. The reaction mixture was shaked with saturated $NaHCO_3$ and then was extracted with benzene–ether. Evaporation of solvent left an oily residue which was purified by silica gel column chromatography to give an oily product (**25**) (10 mg; 63% yield). High-resolution MS: Mol. Wt. 320.0903 for $C_{17}H_{20}O_2S_2$: Observed, 320.0895. IR cm^{-1} 1660 (CO); UV λ_{max}^{EtOH} nm: 217, 241.5, 339; NMR δ: 1.28 (3H, s), 1.44 (3H, d, J=7 Hz), 2.21 (3H, d, J=1 Hz), 3.10—3.40 (4H, m, $W1/2$=15 Hz), 6.38 (1H, d, J=1 Hz), 7.02 (1H, m, $W1/2$=4 Hz).

Desulfurization of thioketal (25) with Raney Nickel——A solution of thioketal (**25**) (10 mg) in EtOH (6 ml) was added W-2 Raney Ni (100 mg) and the reaction mixture was refluxed with stirring for 50 min. The catalyst was filtrated out and EtOH was evaporated. The reaction product was purified by preparative TLC to give a furanophenol (**27**) (4.5 mg; 62% yield) as colorless oil. IR cm^{-1}: 3580 (OH); UV λ_{max}^{EtOH} nm: 253.5, 258, 283, 292.5; NMR δ: 1.60 (3H, m, $W1/2$=13 Hz), 2.18 (3H, d, J=2 Hz), 2.35 (3H, d, J=1 Hz), 5.35—5.55 (2H, m, $W1/2$=12 Hz), 6.83 (1H, d, J=2 Hz), 7.12 (1H, m, $W1/2$=3 Hz); MS *m/e* (rel. intensity): 230 (M$^+$, 18), 175 ([M–C_4H_7]$^+$, 100).

4-Epifuranoeremophilan-3,6-dione (30)——Catalytic reduction of **23** (15 mg) with 10%Pd-charcoal (10 mg) in EtOH at room temperature for 45 min was carried out. After the catalyst was filtrated out, evaporation of the solvent left an oily residue. The residue was purified by preparative TLC (benzene–EtOAc (10: 1) as developing solvent) to give an oily product (**30**) (12 mg; 79% yield) together with small amount of **31**. **30**: IR cm^{-1}: 1730, 1690 (CO); UV λ_{max}^{EtOH} 270 nm; NMR δ: 1.38 (3H, d, J=7 Hz), 1.42 (3H, s), 2.72 (1H, dd, J=2.8, 18 Hz), 3.29 (1H, dd, J=5.6, 18 Hz), 7.09 (1H, m, $W1/2$=4 Hz); MS *m/e* (rel. intensity): 246 (M$^+$, 33), 122 ([M–$C_8H_{12}O$]$^+$, 100). **31**: IR cm^{-1}: 1720, 1640 (CO); UV λ_{max}^{EtOH} 272.5 nm; MS *m/e* (rel. intensity): 248 (M$^+$, 8), 124 ([M–$C_8H_{12}O$]$^+$, 100).

Furanoeremophilan-3,6-dione (28)——(a) Catalytic reduction of **24** (16 mg) in EtOAc (10 ml) with 10% Pd-charcoal (10 mg) was carried out. After work-up, the crude product was purified by preparative TLC over silica gel and recrystallized from hexane–EtOAc to afford **28** (14 mg; 87% yield), mp 176—178°, together with small amount of **29**, mp 150—153°. **28**: *Anal.* Calcd. for $C_{15}H_{18}O_3$: C, 73.15; H, 7.37; Mol. Wt. 246.1255. Found: C, 72.92; H, 7.43; M$^+$, 246.1236. IR cm^{-1}: 1725, 1675 (CO); UV λ_{max}^{EtOH} 269 nm (ε 3300); NMR δ: 0.92 (3H, d, J=7 Hz), 1.12 (3H, s), 2.19 (3H, d, J=1 Hz), 2.99 (1H, dd, J=5.8, 18 Hz), 3.25 (1H, dd, J=9.6, 18 Hz), 7.14 (1H, m, $W1/2$=4 Hz); MS *m/e* (rel. intensity): 246 (M$^+$, 31), 122 ([M–$C_8H_{12}O$]$^+$, 100). **29**: IR cm^{-1}: 1720, 1710, 1640 (CO); UV λ_{max}^{EtOH} 271.5 nm; MS *m/e* (rel. intensity): 248 (M$^+$, 7), 124 ([M–$C_8H_{12}O$]$^+$, 100).

(b) A solution of 4-epi compound (**30**) (16 mg), *p*-toluenesulfonic acid (16 mg) in benzene was refluxed for 10 min. After work-up, a colorless needles **28**, mp 176—178°, were obtained, quantitatively. It had mixed mps, IR and NMR spectra were identical with those of above authentic diketone (**28**), respectively.

Conversion of 28 into (±)-Ligularone (3)——To a solution of **28** (14 mg), ethanedithiol (140 mg) in abs. ether was added, dropweise, $BF_3 \cdot OEt_2$ (15 drops) with stirring at room temperature. The reaction mixture was allowed to stand at room temperature for 24 hr. After addition of saturated $NaHCO_3$ to the reaction mixture and was extracted with ether. Evaporation of solvent, the residue was chromatographed over silica gel to give thioketal (**32**) (15 mg) as colorless crystal (82% yield). To a solution of crude **32** in EtOH (6 ml) was added W-2 Raney Ni catalyst (100 mg) and the reaction mixture was refluxed with stirring for 20 min. Removal of the catalyst, the filtrate was evaporated and purified with preparative TLC on silica gel to afford a mixture of **3** and dehydro compound (**33**) [8 mg; 74% over all yield from **28**] which were indicated by NMR spectroscopy.

The above reaction product (7 mg) was dissolved in EtOAc (4 ml), and catalytically reduced with 10% Pd-charcoal (7 mg) at room temperature for 2.5 hr. After work-up the crude product was purified by preparative TLC on silica gel to afford colorless crystals (**3**), quantitatively. Purification by sublimation method afforded (±)-ligularone (**3**), mp 68—70°. High-resolution MS Mol. Wt. 232.1462 for $C_{15}H_{20}O_2$: Observed M$^+$, 232.1464. IR cm^{-1}: 1665 (CO); UV λ_{max}^{EtOH} 268 nm; NMR δ: 0.87 (3H, d, J=7 Hz), 1.11 (3H, s), 2.18 (3H, s, J=1 Hz), 2.74 (1H, dd, J=6, 18 Hz), 2.90 (1H, dd, J=6, 18 Hz), 7.00 (1H, m, $W1/2$=3 Hz); MS *m/e* (rel. intensity): 232 (M$^+$, 24), 122 ([M–C_8H_{14}]$^+$, 100). All spectral data of ±-(**3**) were identical with an

reported in authentic natural (+)-ligularone by Ishii, *et al.*[7] and Takahashi, *et al.*[17]

4-Epifuranoeremophilan-3,6,9-trione (**34**)——According to the procedure as described for **17**, the diene adduct (**17**) was prepared from **14** (352 mg) and **16** (1.35 g). The crude adduct was dissolved in AcOH–H_2O (3: 1) (10 ml) and allowed to stand at room temperature for 1.5 hr. Evaporation of solvent *in vacuo* left crude product which was chromatographed over silica gel to give **34** (566 mg). Recrystallization from EtOAc–hexane gave **34** as colorless rhombic prisms (342 mg; 66% yield), mp 129—131°. *Anal.* Calcd. for $C_{15}H_{16}O_4$: C, 69.22; H, 6.20. Mol. Wt. 260.1047. Found: C, 69.11; H, 6.24; M^+, 260.1032. IR cm^{-1}: 1720, 1695, 1675; UV λ_{max}^{EtOH} nm (ε): 216.5 (11900), 244 (5300), 304 (7300); NMR δ: 1.09 (3H, d, J=7 Hz), 1.45 (3H, s), 2.20 (3H, d, J=1 Hz), 3.02 (1H, t, J=6 Hz), 7.48 (1H, m, $W1/2$=3 Hz); MS *m/e* (rel. intensity): 260 (M^+, 100), 245 ($[M-CH_3]^+$, 17), 232 ($[M-CO]^+$, 52).

4-Epi-10αH-furanoeremophilan-3,6,9-trione (**35**)——According to the procedure as described for **20**, the crude diene adduct (**20**) was prepared from **14** (352 mg) and **16** (1.35 g). The crude (**20**) was dissolved in AcOH–H_2O (3: 1) (10 ml) and allowed to stand at room temperature for 1 hr. After work-up as usual manner, recrystallization from EtOAc–hexane gave **35** (231 mg; 45% yield) as colorless needles, mp 150—153° (reported,[19] mp 151°). *Anal.* Calcd. for $C_{15}H_{16}O_4$: C, 69.22; H, 6.20; Mol. Wt. 260.1047. Found: C, 69.17; H, 6.40; M^+, 260.1031. IR cm^{-1}: 1725, 1700, 1685 (CO); UV λ_{max}^{EtOH} nm (ε): 217 (12500), 244 (5400), 304 (7400); NMR δ: 1.15 (3H, s), 1.24 (3H, d, J=7 Hz), 2.25 (3H, d, J=1 Hz), 2.88 (1H, q, J=7 Hz), 3.51 (1H, dd, J=4, 12 Hz), 7.48 (1H, m, $W1/2$=3 Hz); MS *m/e* (rel. intensity): 260 (M^+, 100), 245 ($[M-CH_3]^+$, 7), 232 ($[M-CO]^+$, 13).

Furanoeremophilan-3,6,9-trione (**36**)——A solution of **35** (10 mg) in benzene (6 ml) containing *p*-toluenesulfonic acid monohydrate (10 mg) was refluxed for 3 hr. Evaporation of solvent left crude crystal which was chromatographed for purification. Recrystallization from EtOAc–hexane afforded **36** (9 mg; 90% yield) as colorless prisms, mp 204—205.5° (reported,[19] mp 203°). *Anal.* Calcd. for $C_{15}H_{16}O_4$: C, 69.22; H, 6.20; Mol. Wt. 260.1047. Found: C, 69.47; H, 6.37; M^+, 260.1047. IR cm^{-1}: 1730, 1700, 1695 (CO); UV λ_{max}^{EtOH} nm (ε): 238 (11900), 244 (5400), 305 (7500); NMR δ: 0.85 (3H, d, J=7 Hz), 1.21 (3H, s), 2.25 (3H, d, J=1 Hz), 2.67 (1H, q, J=7 Hz), 3.01 (1H, m, $W1/2$=12 Hz), 7.48 (1H, m, $W1/2$=3 Hz); MS *m/e* (rel. intensity): 260 (M^+, 100), 245 ($[M-CH_3]^+$, 14), 232 ($[M-CO]^+$, 29).

Treatment of 4-epi compound (**34**) under same condition as described above **35** also gave **36** in 90% yield.

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