Total Synthesis of Furanoeremophilane and 14-Norfuranoeudesmane Derivatives by a Route Involving Alkylation of 2,4-Dimethyl-3-furoic Acid[1]

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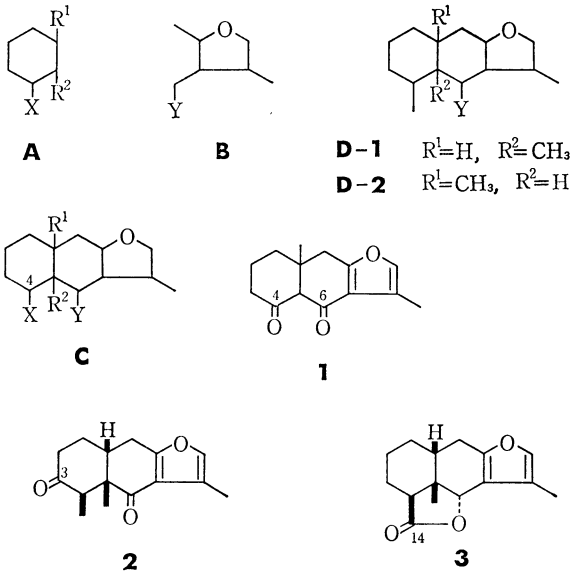
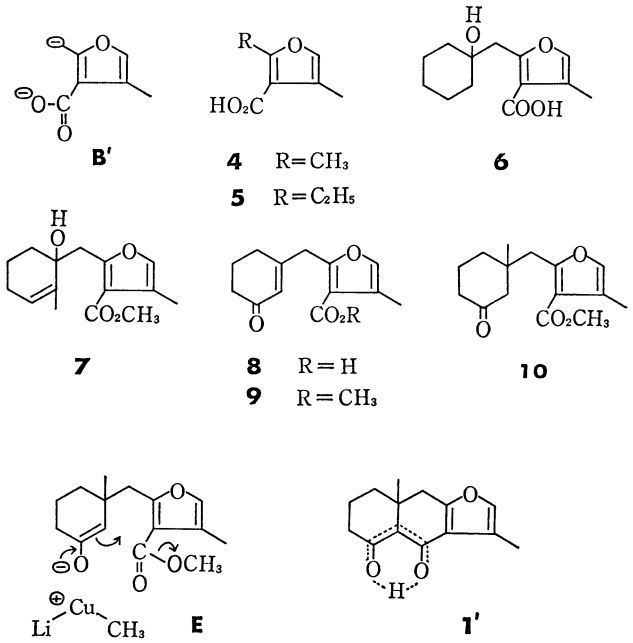
(±)-14-Norfuranoeudesmane-4,6-dione, (±)-furanoeremophilane-3,6-dione, and (±)-furanoeremophilan-14, 6α-olide were synthesized by a route involving alkylation of a dianion obtained from 2,4-dimethyl-3-furoic acid.

Various types of sesquiterpenes possessing a furan or γ-lactone moiety have been isolated from many species of higher and lower plants.[2] Although the true mechanism of biogenetical formation of a γ-lactone ring of sesquiterpenes is not clarified, furan ring is considered to be a possible precursor of the γ-lactone ring.[3] In fact oxidation of the furan ring with peracid[4] or oxygen[5] gives a γ-lactone ring. A number of syntheses of sesquiterpene lactones have been reported, but only a few of furanosesquiterpenes have been described.[6] We have undertaken the construction of furanoeremophilane- and furanoeudesmane-frameworks by combination of two moieties, **A** and **B**, to give **C**, successive transform ation of the substituent (X) into methyl group leading to furanoeremophilane- (**D-1**) and furanoeudesmane-skeletons (**D-2**), and the corresponding γ-lactones being derived from these furans. This paper deals with the synthesis of (±)-14-norfuranoeudesmane-4,6-dione (**1**), (±)-furanoeremophilane-3,6-dione (**2**),[7a] and (±)-furanoeremophilan-14,6α-olide (**3**).[8]



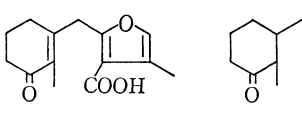
A dianion (**B'**) generated from 2,4-dimethyl-3-furoic acid (**4**) was used as a synthon corresponding to **B**. Treatment of 2,4-dimethyl-3-furoic acid (**4**)[9] with two equivalent mole of lithium diisopropylamide in a mixture of tetrahydrofuran and hexane (9: 2) at −78 °C gave an orange homogeneous solution. Alkylation of the dianion (**B'**) was then studied. The orange solution was quenched with one equivalent mole of methyl iodide at 0 °C and acidified with hydrochloric acid to give 2-ethyl-4-methyl-3-furoic acid (**5**) in 96% yield, suggesting a dianion nature for **B'**. Similar alkylation of **B'** with cyclohexanone gave a hydroxy acid (**6**) in 80% yield. Treatment of **B'** with 2-methyl-2-cyclohexen-1-one gave a 1,2-addition product in 70% yield, identified as its methyl ester (**7**). Although 1.1 or 2.5 equivalent moles of copper(I) iodide was added to **B'** before alkylation, the same 1,2-addition product was obtained as the main product.



(±)-14-Norfuranoeudesmane-4,6-dione. The dianion **B'** was treated with 3-methoxy-2-cyclohexen-1-one and then acidified with hydrochloric acid to give an acid (**8**) in 78% yield. The acid (**8**) should be formed by concomitant dehydration of the addition product. Treatment of an ester (**9**) derived from **8** with lithium dimethylcuprate(I) at 0 °C for 45 h gave (±)-14-norfuranoeudesmane-4,6-dione (**1**) in 73% yield, *via* an intermediate anion (**E**) which underwent cyclization. When the reaction was carried out for 3 h, a keto ester (**10**) and **1** were obtained in 71 and 26% yields, respectively. The ^{1}H-NMR spectrum of the diketone (**1**) shows that **1** in deuteriochloroform exists in equilibrium between **1** and an enol ketone (**1'**) in the ratio 3: 7.

(±)-Furanoeremophilane-3,6-dione. (±)-Furanoeremophilane-3,6,9-trione and (±)-furanoeremophilane-3,6-dione[7a] (**2**) have been synthesized from resorcinol by Yamakawa and Satoh,[6a] *via* a diene adduct of 3,5-dimethylbenzofuran-4,7-dione and 3-ethoxy-1,3-pentadiene in overall yields of *ca.* 5 and *ca.* 4%, respectively. Synthesis of **2** starting from **4** was carried out as follows.

Alkylation of the dianion (**B'**) with 3-methoxy-2-methyl-2-cyclohexen-1-one gave an acid (**11**) in 74% yield, which was hydrogenated over 5% palladium–charcoal in ethanol to afford its dihydro derivative (**12**) quantitatively. The acid (**12**) was cyclized by treatment with *p*-toluenesulfonic acid in diphenyl ether under reflux to give 14-norfuranoeremophilane-4,6-dione (**13**) in 44% yield as the sole product. A *cis* A/B ring juncture was observed for **13** by its conversion into **2**. Preferential attack of the intermediate cation produced from **12** should be accomplished from the side opposite to the hydrogen atom at C-10 to give **13** as depicted in **F**.



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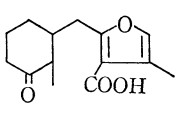

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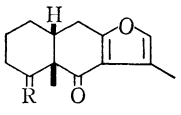
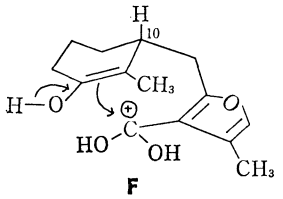


13 R=O
14 R=CH$_3$, OH
16 R=CH$_2$
18 R=β-CHO, α-H
19 R=α-CHO, β-H
20 R=β-COOH, α-H
21 R=α-COOH, β-H



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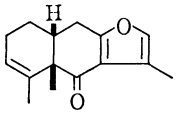

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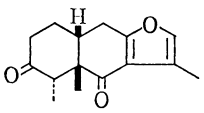

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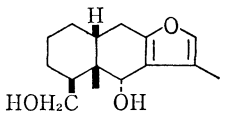

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The diketone (**13**) was methylated regioselectively with 1.2 equivalent moles of methyllithium in ether at −78 °C for 1 h, giving 4-hydroxy 4-methyl ketone (**14**) in 99% yield. Dehydration of **14** with phosphoryl chloride in pyridine under reflux gave a mixture of olefins, which was separated by preparative thin-layer chromatography to afford an *endo*-olefin (**15**) in 69% yield and an *exo*-olefin (**16**) in 12% yield. The *endo*-olefin (**15**) was subjected to hydroboration with diborane in tetrahydrofuran at 0 °C and then alkaline hydrogen peroxide oxidation to give a mixture of alcohols. This mixture was oxidized, without further purification, with pyridinium chlorochromate[10] in dichloromethane to give (±)-furanoeremophilane-3,6-dione (**2**)[6a,7a] in 4% yield and (±)-4β*H*-furanoeremophilane-3,6-dione (**17**)[6a] in 78% yield. Isomerization of **17** into **2** was effected in refluxing benzene containing a catalytic amount of *p*-toluenesulfonic acid in 94% yield.[6a] (±)-Furanoeremophilane-3,6-dione (**2**) was synthesized from **4** in 7 steps in an overall yield of 17%.

Since the dione (**2**) has been converted into (±)-ligularone[11] (furanoeremophilan-6-one), (±)-ligularol[11] (petasablin; furanoeremophilan-6β-ol), and (±)-furanofukinol[7] (furanoeremophilane-3β,6β-diol) by Yamakawa and Satoh,[6] the synthesis of **2** indicates the formal total synthesis of these furanoeremophilane derivatives.

(±)-Furanoeremophilan-14,6α-olide. Furanoeremophilan-14,6α-olide (**3**) has been isolated from *Ligularia Hodgsoni* Hook, f.[8] Synthesis of the furanoeremophilane with an extra γ-lactone ring was studied.

The Wittig reaction of (±)-14-norfuranoeremophilane-4,6-dione (**13**) with methylenetriphenylphosphorane in tetrahydrofuran at room temperature proceeded regioselectively to give the *exo*-olefin (**16**) in 45% yield besides unchanged **13**. The olefin (**16**) was subjected to hydroboration with diborane in tetrahydrofuran and then alkaline hydrogen peroxide oxidation. The product, without further purification, was oxidized with pyridinium dichromate (PDC)[12] in *N,N*-dimethylformamide at room temperature to give a mixture of aldehydes and carboxylic acids, which was separated by preparative thin-layer chromatography, giving 6-oxofuranoeremophilan-14-al (**18**) in 3% yield, 6-oxo-4β*H*-furanoeremophilan-14-al (**19**) in 46% yield, 6-oxofuranoeremophilan-14-oic acid (**20**) in 10% yield, and 6-oxo-4β*H*-furanoeremophilan-14-oic acid (**21**) in 7% yield.

The stereochemistry at C-4 of **18** and **20** was determined to be 4α*H* based on the formation of **18** and **20** on oxidation of known furanoeremophilane-14,6α-diol (**22**)[8] with PDC in *N,N*-dimethylformamide. This led to 4β*H*-configuration for **19** and **21**. A preferential attack of borane to the olefin (**16**) occurred from the less hindered β-side to give **19** and **21**. Both **19** and **21** were found to be stable on acid (*p*-TsOH–PhH, under reflux) and alkaline (KOH–MeOH, under reflux) treatment. On treatment with potassium hydroxide in methanol at room temperature, **18** isomerized into **19**. Thus the conversion of **19** (or **21**) into **18** (or **20**) with desired 4α*H*-configuration was unsuccessful. Finally, reduction of **20** with lithium borohydride in tetrahydrofuran followed by acidification with acetic acid afforded (±)-furanoeremophilan-14,6α-olide (**3**)[8] in 71% yield. The overall yield of **3** from **13** was 3%. This constitutes the first total synthesis of **3**.

In conclusion, two key intermediates, 14-norfuranoeudesmane-4,6-dione (**1**) and 14-norfuranoeremophilane-4,6-dione (**13**), were obtained from **4** in 56 and 32.5% yields, respectively; **2**, **15**, and **16** were derived from **13** in reasonable yields. This presents a useful route for the synthesis of sesquiterpene lactones and furans of an eudesmane- and an eremophilane-type with oxygenated functional groups on C-3, C-4, C-6, C-14, *etc.*

Experimental

Melting points were measured on a Mel-temp capillary melting point apparatus (Laboratory Devices) and are uncor-

rected. IR spectra were measured with a Hitachi EPI-G2 or a Hitachi 260-30 spectrometer, ^{1}H-NMR spectra with a Hitachi R-20B (60 MHz) or a Varian EM-390 (90 MHz) spectrometer in deuteriochloroform solution containing tetramethylsilane as an internal standard, low resolution mass spectra with a Hitachi RMU-6-Tokugata mass spectrometer at 70 eV with a direct inlet system and high resolution mass spectra with a JEOL JMS-D300 mass spectrometer; the relative peak intensities in the mass spectra are given in parentheses. Thin-layer chromatography was carried out on Kieselgel GF_{254} (E. Merck, Darmstadt) in 0.25 mm thickness for analytical use and 0.5 mm thickness for preparative use. Wakogel C-200 and Florisil "mesh 100—200" (Wako Pure Chemical Industries) were used for column chromatography. All experiments were carried out under nitrogen atmosphere.

Alkylation of 2,4-Dimethyl-3-furoic Acid (4) with Methyl Iodide, Cyclohexanone, and 2-Methyl-2-cyclohexen-1-one. Butyllthium (4.2 mmol) in hexane (2.8 ml) was added to a solution of diisopropylamine (0.6 ml; 4.2 mmol) in dry tetrahydrofuran (15 ml) with cooling in an ice-bath. After being stirred at room temperature for 20 min, the solution was cooled to −78 °C and then treated with 2,4-dimethyl-3-furoic acid (**4**; 280 mg, 2 mmol) in tetrahydrofuran for 30 min, the color of the solution turning to orange due to formation of the dianion (**B′**).

Methyl iodide (0.14 ml; 2.2 mmol) was added to the dianion solution, and the solution was stirred at 0 °C for 1 h. The orange color of the dianion solution disappeared almost immediately. After addition of water, the mixture was acidified with hydrochloric acid and extracted with ether. The ethereal solution was washed with brine, dried ($MgSO_4$) and evaporated. The residue was purified by sublimation (100 °C, 3 mmHg) to give **5** (296 mg) in 96% yield. 2-Ethyl-4-methyl-3-furoic acid (**5**): mp 69.5—70.5 °C; IR (Nujol) *ca.* 3000 (broad) and 1680 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 1.25 (3H, t, J=7 Hz), 2.15 (3H, d, J=1.5 Hz), 3.00 (2H, q, J=7 Hz), and 7.03 (1H, m). Found: *m/e* 154.0640. Calcd for $C_8H_{10}O_3$: M, 154.0630.

Cyclohexanone (0.23 ml) was added to a solution of dianion **B′** (2 mmol) (*vide supra*) at 0 °C. After being stirred for 30 min at 0 °C, a 10% sodium hydrogencarbonate solution was added to the reaction mixture and the mixture was extracted with ether. The ethereal solution was further treated with a 10% sodium hydrogencarbonate solution. The combined aqueous solution was acidified with hydrochloric acid and extracted with ether. The ethereal solution was treated in the usual way to give a residue which was chromatographed on a column of silica gel (20 g). Elution with hexane–ether gave **6** (380 mg) in 80% yield. 4-Methyl-2-(1-hydroxycyclohexylmethyl)-3-furoic acid (**6**): an oil; IR (neat) *ca.* 3500 (broad), *ca.* 3000 (broad), and 1680 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 2.12 (3H, d, J=1.2 Hz), 3.16 (2H, s), 7.14 (1H, m), and *ca.* 7.5 (2H, broad signal). Found: *m/e* 238.1224. Calcd for $C_{13}H_{18}O_4$: M, 238.1206.

The solution of dianion **B′** (2 mmol) (*vide supra*) was treated with 2-methyl-2-cyclohexen-1-one (2.1 mmol) at 0 °C for 20 min. The reaction mixture was treated as in the preparation of **6**, giving a carboxylic acid, which was methylated with diazomethane. The product was purified by column chromatography (silica gel) to give **7** (365 mg) in 70% yield. Methyl 4-methyl-2-(1-hydroxy-2-methyl-2-cyclohexenylmethyl)furan-3-carboxylate (**7**): an oil; IR (neat) *ca.* 3450 (broad) and 1710 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 1.83 (3H, broad signal), 2.13 (3H, d, J=1.2 Hz), 3.03 (1H, d, J=14.5 Hz), 3.53 (1H, d, J=14.5 Hz), 3.84 (3H, s), 5.50 (1H, m), and 7.11 (1H, m). Found: *m/e* 264.1350. Calcd for $C_{15}H_{20}O_4$: M, 264.1360.

When 1.1 equivalent mole (420 mg) or 2.5 equivalent mole (1 g) of copper(I) iodide was added to the solution of **B′** before the treatment with 2-methyl-2-cyclohexen-1-one, the same 1,2-addition product was obtained as the main product identified as its methyl ester (**7**).

Methyl 4-Methyl-2-(3-oxo-1-cyclohexenylmethyl)furan-3-carboxylate (9). 3-Methoxy-2-cyclohexen-1-one (1.8 g; 14 mmol) in tetrahydrofuran (5 ml) was added at 0 °C to a solution of dianion **B′**, prepared by treatment of **4** (1.96 g, 14 mmol) in tetrahydrofuran (15 ml) with lithium diisopropylamide (33 mmol) in tetrahydrofuran (90 ml)–hexane (22 ml) (*vide supra*). After being stirred at 0 °C for 1 h, water was added to the reaction mixture and the mixture was acidified with hydrochloric acid and extracted with ether. The ethereal solution was washed with brine, dried, and evaporated. The residue was chromatographed on a column of silica gel (100 g, elution with hexane–ether) to give **8** as yellow crystals (2.55 g) in 78% yield. Crystallization from hexane–ether gave pure **8**. 4-Methyl-2-(3-oxo-1-cyclohexenylmethyl)-3-furoic acid (**8**): mp 89—91 °C; IR ($CDCl_3$) *ca.* 3100 (broad), 1710, 1670, and 1615 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 2.18 (3H, d, J=1.2 Hz), 3.94 (2H, broad singlet), 5.85 (1H, m), 7.15 (1H, m), and *ca.* 10.2 (1H, broad signal). Found: *m/e* 234.0888. Calcd for $C_{13}H_{14}O_4$: M, 234.0891.

The carboxylic acid (**8**) was treated with diazomethane in ether to give a methyl ester (**9**). Methyl 4-methyl-2-(3-oxo-1-cyclohexenylmethyl)furan-3-carboxylate (**9**): an oil: IR (neat) 1725, 1670, 1625, and 1610 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 2.15 (3H, d, J=1.5 Hz), 3.82 (3H, s), 3.88 (2H, s), 5.78 (1H, m), and 7.12 (1H, m). Found: *m/e* 248.1057. Calcd for $C_{14}H_{16}O_4$: M, 248.1049.

14-Norfuranoeudesmane-4,6-dione (1). The ester (**9**) (310 mg; 1.25 mmol) in ether was added to a solution of lithium dimethycuprate (I) (3.8 mmol) in ether at 0 °C to form a yellow suspension. This was stirred at 0 °C for 45 h. The mixture was acidified with 2 M hydrochloric acid, stirred at room temperature for 1 h, and then extracted 6 times with ether. The combined ethereal solution was washed with a 5% sodium sulfite solution and brine, dried, and evaporated. The residue was purified by chromatography on a column of silica gel (20 g, elution with hexane–ether) to give **1** (213 mg) in 73% yield. Crystallization from hexane–ether gave pure **1**. (±)-14-Norfuranoeudesmane-4,6-dione (**1**): mp 91.5—93 °C; IR (KBr) *ca.* 2960 and 1612 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 1.18 (3H, s), 2.23 (3H, d, J=1.8 Hz), 2.69 (2H, s), 3.82 (0.3H, s), 7.07 (1H, m), and 15.26 (0.7H, s). Found *m/e* 232.1108. Calcd for $C_{14}H_{16}O_3$: M, 232.1100.

When the reaction was carried out for 3 h and interrupted by addition of hydrochloric acid, the reaction product from **9** (290 mg) gave, after separation by column chromatography, a keto ester (**10**, 220 mg) and **1** (70 mg) in 71 and 26% yields, respectively. Methyl 4-methyl-2-(1-methyl-3-oxocyclohexylmethyl)furan-3-carboxylate (**10**): an oil; IR (neat) 1720 (broad) cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 0.97 (3H, s), 2.15 (3H, d, J=1.2 Hz), 3.51 (2H, broad singlet), 3.83 (3H, s), and 7.16 (1H, m). Found: *m/e* 264.1348. Calcd for $C_{15}H_{20}O_4$: M, 264.1360.

4-Methyl-2-(2-methyl-3-oxo-1-cyclohexenylmethyl)-3-furoic Acid (11). 3-Methoxy-2-methyl-2-cyclohexen-1-one (1.80 g, 12.3 mmol) was added to the solution of dianion **B′** (14 mmol) (*vide supra*) at 0 °C and the mixture was stirred for 1 h. The reaction mixture was poured into water, acidified with hydrochloric acid and extracted with ether. The ethereal solution was treated in the usual way to give a residue, which was chromatographed on a column of silica gel (150 g). Elution with hexane–ether (1 : 1) afforded a carboxylic acid (**11**; 2.55 g) in 74% yield. 4-Methyl-2-(2-methyl-3-oxo-1-cyclohexenyl-

methyl)-3-furoic acid (**11**): mp 115—116 °C (crystallized from hexane–ether); IR (Nujol) 1670, 1602, and 1557 cm^{-1}; IR ($CHCl_3$) 1680 and 1660 cm^{-1}; ^1H-NMR ($CDCl_3$) δ 1.90 (3H, s), 2.00 (3H, d, J=2 Hz), 4.03 (2H, s), 6.85 (1H, broad signal), and 7.10 (1H, m); MS *m/e* 248 (M^+; 100), 175 (43), 149 (34), 109 (85), and 53 (60). Found: C, 67.47; H, 6.64%. Calcd for $C_{14}H_{16}O_4$: C, 67.73; H, 6.50%.

*Hydrogenation of the Carboxylic Acid (**11**).* The carboxylic acid (**11**; 1 g) in ethanol (50 ml) was hydrogenated in the presence of 5% palladium–charcoal (*ca.* 150 mg) at room temperature for 4 h. After filtration of the catalyst, the solvent was removed to give a dihydro derivative (**12**; 1 g) in quantitative yield. 4-Methyl-2-(2-methyl-3-oxocyclohexylmethyl)-3-furoic acid (**12**): mp 123—127 °C (crystallized from hexane–ether); IR (Nujol) 1700, 1678, 1598, and 1550 cm^{-1}; IR ($CHCl_3$) 1710 and 1680 cm^{-1}; ^1H-NMR ($CDCl_3$) δ 1.16 (3H, d, J=6 Hz), 2.17 (3H, d, J=2 Hz), 2.94 (1H, dd, J=18 and J=8 Hz), 3.31 (1H, dd, J=18 and J=5 Hz), 7.07 (1H, m), and 7.36 (1H, broad signal; disappeared on addition of D_2O); MS *m/e* 250 (M^+; 26), 178 (57), 122 (74), and 111 (100). Found: C, 67.11; H, 7.51%. Calcd for $C_{14}H_{18}O_4$: C, 67.18; H, 7.25%.

*Cyclization of the Dihydro Carboxylic Acid (**12**).* The dihydro carboxylic acid (**12**; 270 mg) was dissolved in diphenyl ether (20 ml) containing *p*-toluenesulfonic acid (*ca.* 50 mg), and the mixture was refluxed under a Dean-Stark water separator for 3.5 h. The reaction mixture was extracted with ether. The etheral solution was washed with a 5% aqueous sodium hydroxide solution and brine, dried, and evaporated to give an oil, which was chromatographed on a column of silica gel (20 g). Fractions eluted with hexane–ether (1 : 1) were combined and subjected to purification by chromatography under the same conditions as mentioned above to give **13** (111 mg) in 44% yield. (±)-14-Norfuranoeremophilane-4,6-dione (**13**): mp 105.5—106 °C (crystallized from ether); IR (Nujol) 1715, 1665, 1608, and 1565 cm^{-1}; ^1H-NMR ($CDCl_3$) δ 1.37 (3H, s), 2.19 (3H, d, J=2 Hz), 2.70 (1H, dd, J=18 and J=2 Hz), 3.22 (1H, dd, J=18 and J=6 Hz), and 7.18 (1H, m); MS *m/e* 232 (M^+; 16), 122 (100), and 94 (30). Found: C, 72.22; H, 7.04%. Calcd for $C_{14}H_{16}O_3$: C, 72.39; H, 6.94%.

*Methylation of 14-Norfuranoeremophilane-4,6-dione (**13**).* 14-Norfuranoeremophilane-4,6-dione (**13**; 127 mg) in ether (20 ml) was treated with methyllithium (0.6 mmol) in ether (1.2 ml) at −78 °C for 1 h. The reaction mixture was poured into water and extracted with ether. The ethereal solution was treated in the usual way to give a hydroxy ketone (**14**; 134 mg) in 99% yield. The product showed one spot on thin-layer chromatogram and ^1H-NMR methyl signals corresponding to one configurational isomer. However, the configuration at C-4 remained undetermined. 4ξ-Hydroxyfuranoeremophilan-6-one (**14**): mp 115—116.5 °C (crystallized from hexane); IR (Nujol) 3450, 1648, 1608, and 1565 cm^{-1}; ^1H-NMR ($CDCl_3$) δ 1.21 and 1.37 (each 3H, s), 2.18 (3H, d, J=2 Hz), 2.53 (1H, dd, J=18 and J=2 Hz), 3.16 (1H, dd, J=18 and J=6 Hz), 5.74 (1H, s-like; disappered on addition of D_2O), and 7.13 (1H, m); MS *m/e* 248 (M^+; 27), 205 (16), 163 (100), and 135 (30). Found: C, 72.35; H, 8.35%. Calcd for $C_{15}H_{20}O_3$: C, 72.55; H, 8.12%.

*Dehydration of the Hydroxy Ketone (**14**).* Phosphoryl chloride (0.3 ml) was added dropwise to a solution of the hydroxy ketone (**14**; 113 mg) in pyridine (5 ml) and the mixture was heated under reflux for 2 h. The reaction mixture was poured into ice water, and the product was extracted with ether. The ethereal solution was treated in the usual way to give a residue, which was subjected to separation by preparative thin-layer chromatography [developed with hexane–ether (4 : 1)] to give an *endo*-olefin (**15**; 73 mg; R_f 0.53) in 69% yield and an *exo*-olefin (**16**; 13 mg; R_f 0.47) in 12% yield. Furanoeremophil-3-en-6-one (**15**): mp 69—69.5 °C (crystallized from hexane); IR (Nujol) 1675, 1610, and 1565 cm^{-1}; ^1H-NMR ($CDCl_3$) δ 1.39 (3H, s), 1.73 (3H, d, J=2 Hz), 2.17 (3H, d, J=2 Hz), 2.74 and 2.98 (each 1H, dd, J=18 and J=6 Hz), 5.49 (1H, m), and 7.10 (1H, m); MS *m/e* 230 (M^+; 23), 122 (100), and 94 (31). Found: C, 78.14; H, 7.93%. Calcd for $C_{15}H_{18}O_2$: C, 78.23; H, 7.88%. Furanoeremophil-4(14)-en-6-one (**16**): an oil; IR (neat) 1675, 1615, 1568, and 902 cm^{-1}; ^1H-NMR ($CDCl_3$) δ 1.39 (3H, s), 2.20 (3H, d, J=2 Hz), 2.61 (1H, dd, J=18 and J=3 Hz), 3.14 (1H, dd, J=18 and J=6 Hz), 4.79 and 5.00 (each 1H, s), and 7.13 (1H, m); MS *m/e* 230 (M^+; 25), 122 (100), and 94 (41). Found: C, 78.50; H, 8.14%. Calcd for $C_{15}H_{18}O_2$: C, 78.23; H, 7.88%.

*(±)-Furanoeremophilane-3,6-dione (**2**).* A solution of diborane (0.8 mmol) in tetrahydrofuran (0.4 ml) was added to a solution of the *endo*-olefin (**15**; 67 mg) in tetrahydrofuran (10 ml) at 0 °C. The mixture was stirred at 0 °C for 1.5 h and then at room temperature for 30 min to complete the reaction. Excess of the reagent was destroyed by careful addition of water (0.5 ml). After addition of a 3 M aqueous sodium hydroxide solution (0.2 ml), hydrogen peroxide (30%, 0.2 ml) was added dropwise to the mixture with stirring at a rate such that the temperature of the reaction mixture did not exceed *ca.* 40 °C. The reaction mixture was then heated at 40—50 °C and maintained in this temperature range for 30 min to complete the oxidation reaction. The reaction mixture was treated in the usual way to give an oil, which, without further purification, was oxidized with pyridinuim chlorochromate (PCC,[10] 356 mg) in dichloromethane (1.5 ml) at room temperature for 5 h. After addition of 2-propanol (1 ml) in order to destroy excess of the oxidant, the reaction mixture was passed through a column of Florisil, the solvent being removed by evaporation. The residue was subjected to separation by preparative thin-layer chromatography [developed with hexane–ether (1: 9)] to give **2** (3.1 mg; R_f 0.54) in 4% yield and **17** (56.2 mg; R_f 0.45) in 78% yield. (±)-Furanoeremophilane-3,6-dione (**2**):[6a] mp 176—177 °C (crystallized from hexane–ether): IR (Nujol) 1710, 1660, 1605, and 1565 cm^{-1}; ^1H-NMR ($CDCl_3$) δ 0.92 (3H, d, J=7 Hz), 1.12 (3H, s), 2.18 (3H, d, J=2 Hz), 2.91 (1H, dd, J=18 and J=6 Hz), 3.27 (1H, dd, J=18 and J=10 Hz), and 7.11 (1H, m); MS *m/e* 246 (M^+; 31), 122 (100), and 94 (17). Found: C, 73.02; H, 7.52%. Calcd for $C_{15}H_{18}O_3$: C, 73.14; H, 7.37%. The compound was found to be identical with (±)-furanoeremophilane-3,6-dione (**2**) prepared by Yamakawa and Satoh.[6a] (±)-4β*H*-Furanoeremophilane-3,6-dione (**17**):[6a] mp 119.5—120 °C (crystallized from hexane–ether); IR (Nujol) 1705, 1665, 1604, and 1560 cm^{-1}; ^1H-NMR ($CDCl_3$) δ 1.37 (3H, d, J=7 Hz), 1.14 (3H, s), 2.12 (3H, d, J=2 Hz), 2.71 (1H, dd, J=18 and J=6 Hz), 3.30 (1H, dd, J=18 and J=5 Hz), and 7.07 (1H, m); *m/e* 246 (M^+; 22), 122 (100), and 94 (25). Found: C, 72.87; H, 7.55%. Calcd for $C_{15}H_{18}O_3$: C, 73.14; H, 7.37%.

*Isomerization of 4βH-Furanoeremophilane-3,6-dione (**17**).* According to the procedure of Yamakawa and Satoh,[6a] the diketone (**17**; 43.3 mg) dissolved in benzene (6 ml) containing *p*-toluenesulfonic acid (8 mg) was treated under reflux for 1 h. The crude product mixture was subjected to separation by preparative thin-layer chromatography [developed with hexane–ether (1 : 9)] to give **2** (40.5 mg) in 94% yield and unchanged **17** (2.2 mg).

*Wittig Reaction of 14-Norfuranoeremophilane-4,6-dione (**1**).* Butyllithium (7.3 mmol) in hexane (4.7 ml) was added to a solution of methyltriphenylphosphonium iodide (3.02 g; 7.5

mmol) in dry tetrahydrofuran (120 ml) at room temperature, and the mixture was stirred for 6.5 h. The diketone (**1**; 324 mg) in tetrahydrofuran (10 ml) was then added to this solution, the mixture being stirred for 11 h. The reaction mixture was treated in the usual way to give a residue, which was chromatographed on a column of silica gel (60 g). Elution with hexane–ether (4 : 1) gave furanoeremophil-4(14)-en-6-one (**16**; 146 mg) in 45% yield and the unchanged diketone (**1**; 56 mg).

Hydroboration and Successive Oxidation of Furanoeremophil-4(14)-en-6-one (16). The *exo*-olefin (**16**; 85 mg) in tetrahydrofuran (10 ml) was subjected to hydroboration with diborane (3.6 mmol) in tetrahydrofuran (3.6 ml) at room temperature for 1 h. Excess of the reagent was destroyed by addition of water (1 ml). After addition of a 3 M aqueous sodium hydroxide solution (0.4 ml) and hydrogen peroxide (30%, 0.4 ml), the mixture was heated at 40—50 °C for 30 min. The reactions mixture was treated in the usual way to give a residue, which was oxidized with pyridinium dichromate (PDC,[12] 1.0 g) in *N,N*-dimethylformamide at room temperature for 2 d. The reaction mixture was poured into water and extracted with ether. The ethereal solution was treated in the usual way to give a residue, which was subjected to separation by preparative thin-layer chromatography (developed with ether) to afford **18** (2.7 mg, R_f 0.89) in 3% yield, **19** (41.6 mg; R_f 0.79) in 46% yield, **20** (9.3 mg, R_f 0.71) in 10% yield, and **21** (7 mg; R_f 0.57) in 7% yield. 6-Oxofuranoeremophilan-14-al (**18**): an oil; IR (neat) 1720, 1670, and 1563 cm^{-1}; ^1H-NMR ($CDCl_3$) δ 1.38 (3H, s), 2.18 (3H, d, J=2 Hz), 2.57 (1H, dd, J=18 and J=3 Hz), 3.15 (1H, dd, J=18 and J=6 Hz), 3.23 (1H, t, J=4 Hz), 7.08 (1H, m), and 9.84 (1H, d, J=2 Hz); MS *m/e* 246 (M^+; 0.1), 122 (100), and 94 (42). Found: *m/e* 246.1257. Calcd for $C_{15}H_{18}O_3$: M, 246.1254. 6-Oxo-4βH-furanoeremophilan-14-al (**19**): an oil; IR (neat) 1715, 1662, 1608, and 1562 cm^{-1}; ^1H-NMR ($CDCl_3$) δ 1.50 (3H, s), 2.15 (3H, d, J=2 Hz), 2.54 (1H, dd, J=18 and J=1.5 Hz), 3.32 (1H, dd, J=18 and J=6 Hz), 3.44 (1H, t, J=7 Hz), 7.03 (1H, m), and 10.04 (1H, s); MS *m/e* 246 (M^+; 1), 232 (35), 218 (13), 122 (100), and 94 (16). Found: *m/e* 246.1249. Calcd for $C_{15}H_{18}O_3$: M, 246.1254. 6-Oxofuranoeremophilan-14-oic acid (**20**): an oil; IR (neat) 1705, 1670, 1610, and 1568 cm^{-1}; ^1H-NMR ($CDCl_3$) δ 1.30 (3H, s), 2.18 (3H, d, J=2 Hz), 2.52 (1H, dd, J=18 and J=2 Hz), 3.16 (1H, dd, J=18 and J=5 Hz), 3.46 (1H, t, J=4 Hz), 7.04 (1H, m), and 7.23 (1H, broad signal); MS *m/e* 262 (M^+; 22), 244 (11), 122 (100), and 94 (35). Found: *m/e* 262.1211. Calcd for $C_{15}H_{18}O_4$: M, 262.1205. 6-Oxo-4βH-furanoeremophilan-14-oic acid (**21**): an oil; IR (neat) 1712, 1663, 1615, and 1565 cm^{-1}; ^1H-NMR ($CDCl_3$) δ 1.43 (3H, s), 2.17 (3H, d, J=2 Hz), 2.54 (1H, dd, J=18 and J=1.5 Hz), 3.30 (1H, dd, J=18 and J=5 Hz), 3.38 (1H, t, J=4 Hz), 7.07 (1H, m), and 7.40 (1H, broad signal); MS *m/e* 262 (M^+; 0.3), 218 (37), 203 (27), and 122 (100). Found: *m/e* 262.1211. Calcd for $C_{15}H_{18}O_4$: M, 262.1205.

Oxidation of Furanoeremophilane-14,6α-diol (22). Furanoeremophilane-14,6α-diol[8] (**22**; 19.5 mg) was oxidized with PDC[12] (1 g) in *N,N*-dimethylformamide (1 ml) at room temperature for 8 h. After treatment in the usual way, the product mixture was separated by preparative tihn-layer chromatography [developed with hexane–ether (2: 3)] to afford 6-oxofuranoeremophilan-14-al (**18**; 8.3 mg) as a main product in 44% yield and 6-oxofuranoeremophilan-14-oic acid (**20**; 2.2 mg) in 11% yield.

(±)-Furanoeremophilan-14,6α-olide (3). Lithium borohydride (*ca.* 10 mg) was added to a solution of 6-oxofuranoeremophilan-14-oic acid (**20**; 6.4 mg) in tetrahydrofuran (10 ml) at room temperature, and the mixture was stirred for 45 min. After addition of acetic acid (8 ml), the mixture was stirred for 12 h at room temperature, and extracted with ether. The ethereal solution was treated in the usual way to give an oil, which was subjected to separation by preparative thin-layer chromatography [developed with hexane–ether (1: 1)] to give **3** (4.3 mg; R_f 0.47) in 71% yield and unchanged **20** (0.8 mg). (±)-Furanoeremophilan-14,6α-olide (**3**): mp 125—127 °C (crystallized from hexane–ether); IR (CCl_4) 1768, 1638, and 1562 cm^{-1}; ^1H-NMR ($CDCl_3$) δ 1.27 (3H, s), 2.02 (3H, d, J=2 Hz), 2.66 (2H, dd, J=18 and J=2 Hz), 5.07 (1H, m), and 7.06 (1H, m); MS *m/e* 246 (M^+; 100) 202 (28), and 95 (31). Found: *m/e* 246.1262. Calcd for $C_{15}H_{18}O_3$: M, 246.1257. The spectral data of (±)-**3** were found to be identical with those of natural (−)-**3**.[8]

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