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Synthetic Approach to the Synthesis of Eudesmane Type of Sesquiterpenes by Using Furan Derivatives as a Starting Material

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3-(1′,4′-Dioxopentyl)-3-methylcyclohexanone (V) was transformed to the compounds (VIa, VIb, and VII) under acidic conditions. 2-Isopropyl-4,9-dimethyl-$\Delta^{2(3)}$-1,5-octadione 5-ethylenethioketal (XIII) was synthesized from compounds (VIa and VIb). 6-Isopropyl-3-methyl-3-(5′-methylfuryl-2′)cyclohexanone (XVIII) was obtained from compound (III).

Although the furan derivatives have been used for the synthesis of some alicyclic natural products,[2] there are no reports concerned with its use as a starting point in the synthesis of the eudesmane class of sesquiterpenes. We have been exploring the possibility of using 2-methylfuran as a starting material for the synthesis of some sesquiterpenes. This paper describes the synthesis of 4,9-dimethyloctalone derivatives which have basic substituents already besides a substituent at C-6.

Metalation of 2-methylfuran with *n*-butyllithium in ethereal solution yielded 2-lithio-5-methylfuran (I)[3] which on reaction with 3-ethoxy-2-cyclohexenone (II) followed by treatment with 10% sulfuric acid gave 3-(5′-methylfuryl-2′)-2-cyclohexenone (III). The nuclear magnetic resonance (NMR) spectrum (δ) ($CDCl_3$) showed the signals for methyl protons at 2.34, two aromatic protons at 6.08 (d, $J=3.0$ Hz) and 6.61 (d, $J=3.0$ Hz), and olefinic proton at 6.35. The infrared (IR) spectrum ($CHCl_3$) showed a carbonyl absorption at 1640 cm^{-1} and the molecular formula, $C_{11}H_{12}O_2$, was verified by microanalysis and mass spectrum (*m/e* 176, M^+). An ethereal solution of III was added to a mixture of methyl copper and tri-*n*-butylphosphine in ether[4] at −30°, and then allowed to stand for 3 hr at room temperature to give the methylated furanoketone (IV). The NMR spectrum (δ) ($CDCl_3$) showed methyl resonances at 1.30 due to C_3–CH_3 and 2.24 due to $C_{5'}$–CH_3. The signals due to aromatic protons appeared at 5.83 as a broad singlet. The IR spectrum ($CHCl_3$) showed the carbonyl absorption at 1695 cm^{-1}. These facts and mass spectrum (*m/e* 192, M^+) revealed the compound (IV) to be 3-methyl-3-(5′-methylfuryl-2′)cyclohexanone. The furan ring of compound (IV) was surprisingly easy to be hydrolyzed with concentrated hydrochloric acid in methanol at room temperature to give the triketone (V) in high yield. Its structure was confirmed by spectral data and was subjected to acid-catalyzed cyclization. A solution of compound (V) in concentrated hydrochloric acid and methanol was heated under reflux. The crude product was chromatographed to give three compounds.

The first one, mp 92—93°, showed the molecular formula, $C_{12}H_{16}O_2$, by microanalysis and mass spectrum (*m/e* 192, M^+). The NMR (δ) ($CDCl_3$) showed methyl signals at 1.00 as singlet and 1.11 as doublet ($J=7$ Hz). The signals due to C_2–H and C_3–H appeared at 5.79 (q, $J=3$ and 10 Hz) and 6.58 (q, $J=3$ and 10 Hz). The IR spectrum ($CHCl_3$) showed the

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1) Location: *Aobayama, Sendai.*

2) *a*) G. Büchi and H. Wüest, *J. Org. Chem.*, 31, 977 (1966); *b*) G. Büchi and E. Demole, *ibid.*, 38, 123 (1973); *c*) R. Robinson, *J. Chem. Soc.*, 1938, 1390; *d*) A. Koebner and R. Robinson, *ibid.*, 1938, 1944; *e*) A.J. Birch, R. Jaeger, and R. Robinson, *ibid.*, 1945, 582; *f*) A.J. Birch and G.S.R. Subba Rao, *Tetrahedron Letters*, 1967, 2763; *idem*, *Austral. J. Chem.*, 23, 547 (1970).

3) *cf.* V. Ramanathan and R. Levine, *J. Org. Chem.*, 27, 1216 (1962).

4) *cf.* Recent review on organo-copper compounds, J.F. Normant, *Synthesis*, 1972, 63.

carbonyl absorption at 1670 and 1701 cm^{-1}. These facts revealed the first compound to be 4,9-dimethyl-Δ^2-1,5-octadione (VIa).

The second one showed the molecular ion peak at m/e 192 in its mass spectrum. The NMR spectrum (δ) ($CDCl_3$) showed methyl signals at 1.13 as singlet and at 1.10 as doublet ($J=7$ Hz). The signals due to C_2–H and C_3–H appeared at 5.88 (q, $J=3$ and 10 Hz) and 6.65 (q, $J=3$ and 10 Hz). The IR spectrum ($CHCl_3$) showed the carbonyl absorption at 1675 and 1705 cm^{-1}. These facts revealed the second one to be a stereoisomer of compound (VIa), the result of which was confirmed by transformation of compounds (VIa) and (VIb) into the compound (VIII).

The third one, mp 79—80°, showed the molecular formula, $C_{12}H_{16}O_2$, by microanalysis and mass spectrum (m/e 192, M^+). The NMR spectrum (δ) ($CDCl_3$) showed methyl signals at 1.19 and 1.88. The IR spectrum ($CHCl_3$) showed the carbonyl absorption at 1670 and 1705 cm^{-1}. These facts revealed the third one to be 4,9-dimethyl-$\Delta^{4(10)}$-1,5-octadione (VII).

On the other hand, compound (VIa) was treated with ethylene glycol and *p*-toluenesulfonic acid in benzene to afford compound (VIII) which showed the molecular formula, $C_{14}H_{20}O_3$, by microanalysis and mass spectrum (m/e 236, M^+). The NMR spectrum (δ) ($CDCl_3$) showed methyl signals at 1.08 and 1.90. The signals due to C_2-methylene protons, C_3-vinylic proton, and C_5-ethylenedioxy protons appeared at 2.75 as a broad singlet, 5.53 as a broad singlet, and 3.80, respectively. The presence of the coupling among C_2-protons, C_3-vinylic proton and C_4-vinyl methyl protons was confirmed by double irradiation studies in each signal. The IR spectrum ($CHCl_3$) showed the carbonyl absorption at 1705 cm^{-1}. These facts revealed the compound (VIII) to be 5,5-ethylenedioxy-4,9-dimethyl-Δ^3-1-octalone.[5] The compound (VIII) was also obtained from compound (VIb) by the same treatment described above. The identity of these two compounds was confirmed by mixed melting point test and comparison of spectroscopic data. These facts revealed that compounds VIa and VIb were the stereoisomers each other at C_4-position.

Secondly we tried to introduce an isopropyl substituent at C_2-position. Compound (VIII) was treated with ethyl formate and sodium hydride to give hydroxymethylene compound (IX). The signals due to ethylenedioxy protons, C_3-vinylic proton, and hydroxymethylene protons appeared at 3.75, 5.75, and 6.7—7.2, respectively. The IR spectrum ($CHCl_3$) showed the α-hydroxymethylene carbonyl absorption at 1660 and 1640 cm^{-1}. The mass spectrum showed the molecular ion peak at m/e 264. The hydroxymethylene compound (IX) was treated with 1-butanethiol to give thioether derivative (X), which was treated with lithium dimethylcuprate to afford compound (XI) which showed the molecular ion peak at m/e 278 in the mass spectrum. The NMR spectrum (δ) (CCl_4) showed two doublets ($J=6$ Hz) at 0.76 and 1.00 due to isopropyl group and a singlet at 0.93 due to C_9-methyl protons. The signals due to C_4-methyl, ethylenedioxy, and C_3-vinylic proton appeared at 1.95, 3.80, and 5.55, respectively. The IR spectrum ($CHCl_3$) showed the carbonyl absorption at 1700 cm^{-1}. These facts showed the compound (XI) to be 5,5-ethylenedioxy-2-isopropyl-4,9-dimethyl-Δ^3-1-octalone. This was treated with trifluoroacetic acid to afford compound XII, whose treatment with ethanedithiol and boron trifluoride etherate gave compound (XIII). This showed the molecular formula, $C_{17}H_{26}OS_2$, by microanalysis and mass spectrum (m/e 310, M^+). The NMR spectrum (δ) (CCl_4) showed two doublets due to isopropyl group ($J=6$ Hz) at 1.00 and 1.08 and a singlet due to C_9-methyl protons at 1.17. The signals due to C_4-methyl protons, ethylene thioketal, and C_3-vinylic proton appeared at 1.37 as doublet ($J=8$ Hz), 3.20 as singlet and 6.20 as doublet ($J=4$ Hz), respectively. The IR spectrum ($CHCl_3$) showed the carbonyl absorption at 1660 cm^{-1}. These facts revealed that the migration of double

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5) We previously assigned this compound as 1,1-ethylenedioxy-4,9-dimethyl-Δ^3-5-octalone, but this assignment is now shown to be incorrect by transformation of this compound to XIII.[6] .

6) T. Kametani, H. Nemoto, and K. Fukumoto, *Heterocycles*, 2, 639 (1974).

bond occurred under the reaction condition and the compound (XIII) was found to be 2-isopropyl-4,9-dimethyl-$\Delta^{2(3)}$-1,5-octadione-5-ethylene thioketal.

From the experiment described above, it was found that the furan derivative (IV) was extremely easy to be hydrolized to give triketone (V) which was cyclized under acidic condition and the carbonyl group at C_5 position of compounds (VIa and VIb) could be protected selectively as shown in a formation of the ketal (VIII).

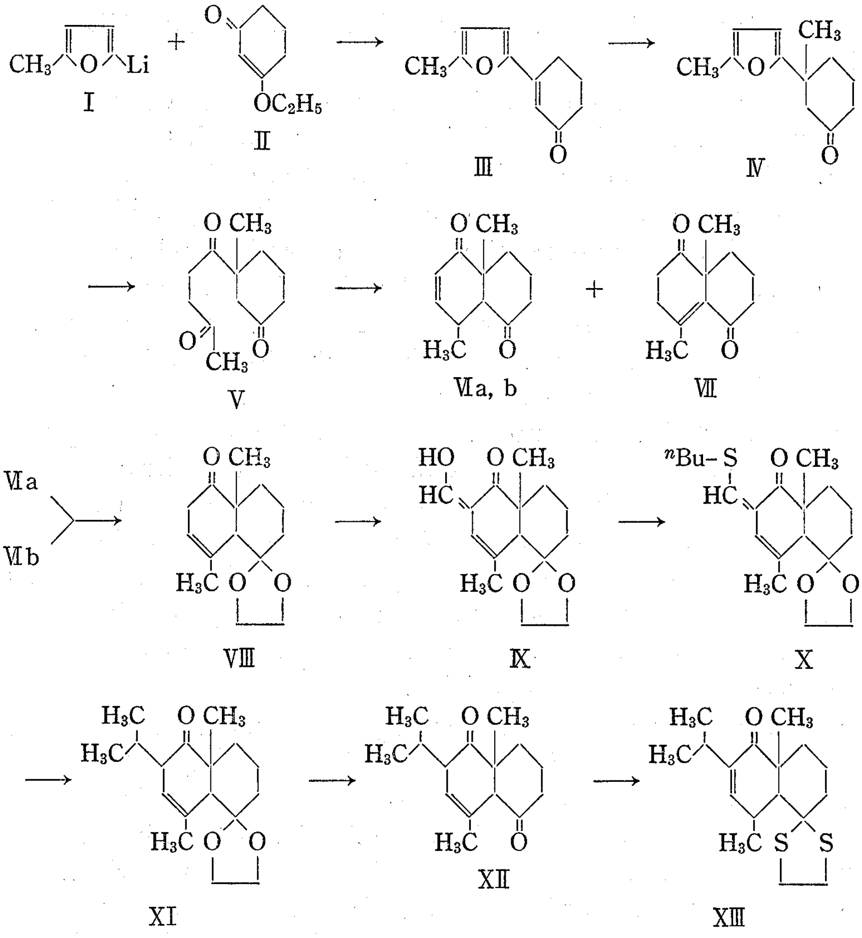

Chart 1

Thirdly, the synthesis of compound (XVIII) which has all the necessary carbon units for the eudesmane class of sesquiterpene was investigated. The same reaction sequence as described above was used for introducing an isopropyl group at the C_6-position of compound (III). The compound (III) was treated with ethyl formate and sodium hydride to give hydroxymethylene compound (XIV) which was reacted with 1-butanethiol and *p*-toluenesulfonic acid to give compound (XV) which showed the molecular formula, $C_{16}H_{20}O_2S$, by microanalysis and mass spectrum (m/e 276, M^+). The NMR spectrum (δ) ($CDCl_3$) showed methyl signal at 2.35 as singlet. The signals due to $C_{4'}$–H, C_2–H, and $C_{3'}$–H appeared at 6.05 (doublet, $J=$ 3 Hz), 6.38 (singlet) and 6.55 (doublet, $J=3$ Hz), respectively. The IR spectrum ($CHCl_3$) showed the absorptions due to carbonyl and double bonds at 1630 and 1605 cm^{-1}. The compound (XV) was treated with lithium dimethylcuprate to afford compound (XVI) which showed the molecular formula, $C_{14}H_{18}O_2$, by microanalysis of its 2,4-dinitrophenylhydrazone derivative and mass spectrum (m/e 218, M^+). The NMR spectrum (δ) (CCl_4) showed two methyl signals due to isopropyl group at 0.88 (doublet, $J=6$ Hz) and 0.99 (doublet, $J=6$ Hz). The signals due to $C_{5'}$–CH_3, $C_{4'}$–H, C_2–H, and $C_{3'}$–H appeared at 2.35 (singlet), 6.02 (doublet, $J=3$ Hz), 6.25 (singlet), and 6.5 (doublet, $J=3$ Hz), respectively. The IR spectrum ($CHCl_3$) showed the absorption due to carbonyl and double bonds at 1650 and 1610 cm^{-1}, respectively.

Thus, the compound (XVI) was synthesized from compound (III) in high yield but there was some possibility that the isopropyl group was introduced at C_4 in place of C_6-position.

Therefore we tried to synthesize compound (XVI) by using alternative reaction sequences. 4-Acetyl-5-methylhexanoic acid (XVIII)⁷⁾ was treated with sodium borohydride and the reduced product was lactonized with acid to give compound (XIX) which showed the molecular formula, $C_9H_{16}O_2$, by microanalysis and mass spectrum (*m/e* 156, M^+). The NMR spectrum (δ) ($CDCl_3$) showed methyl signals due to isopropyl group and C_5–CH_3 at 0.97 (doublet, J=4 Hz) and 1.9 (doublet, J=6 Hz), respectively. The IR spectrum ($CHCl_3$) showed carbonyl absorption at 1720 cm^{-1}. The compound (XIX) was reacted with 2-lithio-5-methylfuran to give compound (XX) which showed the molecular formula, $C_{14}H_{20}O_2$, by microanalysis of its 2,4-dinitrophenylhydrazone derivative and mass spectrum (*m/e* 220, M^+). The NMR spectrum (δ) (CCl_4) showed methyl signals due to isopropyl group at 0.98 (doublet, J=6 Hz) and 1.15 (doublet, J=6 Hz). The signals due to C_2–CH_3 and $C_{5'}$–CH_3 appeared at 1.35 (doublet, J=6.5 Hz) and 2.28 (singlet). The signals due to C_5–H, $C_{4'}$–H, and $C_{3'}$–H appeared at 5.05—5.30 (multiplet), 5.85 (doublet, J=3 Hz) and 6.10 (doublet, J=3 Hz), respectively. The IR spectrum ($CHCl_3$) showed an enol ether absorption at 1700 cm^{-1}. The compound (XX) was used directly without isolation of hydroxyketone derivative (XXI) because the compound (XXI) was easily cyclized to give compound (XX) and very difficult for its isolation. Thus, the compound (XX) was treated with sulfuric acid at first and then oxidized with Jones reagent to give compound (XXII) which showed the molecular formula, $C_{14}H_{20}O_3$, by microanalysis of its 2,4-dinitrophenylhydrazone derivative and mass spectrum (*m/e* 236, M^+). The NMR spectrum (δ) (CCl_4) showed methyl signals due to isopropyl group at 0.95 (doublet, J=6 Hz) and 0.98 (doublet, J=6 Hz). The signals due to C_5–CH_3 and acetyl group appeared at 2.10 (singlet) and 2.40 (singlet), respectively. Furthermore, the signals due to C_4–H and C_3–H appeared at 6.10 (doublet, J=3 Hz) and 6.97 (doublet, J=3 Hz), respectively. The IR spectrum ($CHCl_3$) showed carbonyl absorption at 1700 cm^{-1}. The compound (XXII) was

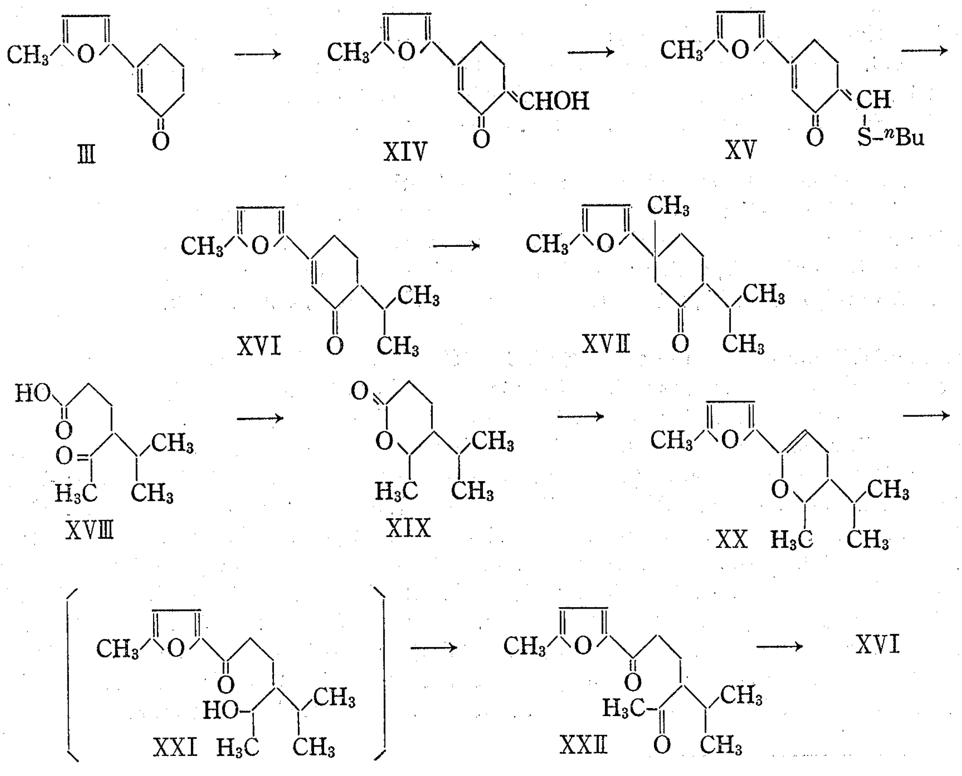

Chart 2

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7) G. Mukherji, B.K. Ganguly, R.C. Banerjee, D. Mukherji, and J.C. Bardhan, *J. Chem. Soc.*, **1963**, 2402.

treated with sodium hydroxide to give compound (XVI) which was identical with the authentic sample prepared as above. Thus, we could confirm the isopropyl group of compound (XVI) to be introduced at C_6-position. Furthermore, the compound (XVI) was treated with methylcopper and tri-*n*-butylphosphine to give compound (XVII) which showed the molecular ion peak at *m/e* 234. The NMR spectrum (δ) ($CDCl_3$) showed methyl signals due to isopropyl group, C_3–CH_3, and $C_{5'}$–CH_3 at 0.8—1.1 as multiplet, 1.3 as singlet, and 2.25 as singlet, respectively. The signals due to $C_{3'}$–H appeared at 5.75 as singlet. The IR spectrum ($CHCl_3$) showed carbonyl absorption at 1700 cm^{-1}.

Thus we could demonstrate the possible use of 2-methylfuran as a starting material for the synthesis of 4,9-dimethyloctalone derivatives and the compound (XVII) which might be a useful intermediate for the synthesis of eudesmane class of sesquiterpenes. The acid-catalyzed cyclization of compound XVII is now under investigation.

Experimental[8]

3-(5′-Methylfuryl-2′)-2-cyclohexenone (III)——To a solution of 2.5 g of 2-methylfuran in 50 ml of dry ether was added 30 ml of a solution of *n*-butyllithium (1 mole) in dry ether at 0°. After the stirring had been continued for 1.5 hr at 0°, a solution of 4.2 g of 3-ethoxy-2-cyclohexenone in 20 ml of dry ether was added dropwise to the above solution and the stirring was continued for 3 hr at 0°. To the resulting mixture was added water, which was acidified with 10% H_2SO_4. The ethereal layer was separated and the aqueous layer was extracted with ether. The combined ethereal layers were washed with water and saturated NaCl solution, dried over Na_2SO_4 and evaporated to give a yellowish oil, which was triturated with ether to give 2.7 g of III as colorless needles, mp 78.5—79°. NMR($CDCl_3$) δ: 2.34 (3H, s, CH_3), 6.08 (1H, d, $J=3.0$ Hz, aromatic proton), 6.35 (1H, s, olefinic proton), 6.61 (1H, d, $J=3.0$ Hz, aromatic proton). IR($CHCl_3$) cm^{-1}: 1640, 1600. Mass Spectrum *m/e*: 176 (M^+). *Anal.* Calcd. for $C_{11}H_{12}O_2$: C, 74.97; H, 6.86. Found: C, 74.84; H, 6.86.

3-Methyl-3-(5′-methylfuryl-2′)cyclohexanone (IV)——To a solution of 1.3 g of cuprous iodide and 4 g of tri-*n*-butylphosphine in 40 ml of ether was added 10 ml of a solution of methyllithium (1.28 mole) in ether at −30°. After the stirring had been continued for 30 min at −30°, a solution of 880 mg of compound (III) in 10 ml of ether was added dropwise at −30° and the stirring was continued for 1 hr at −30° and then for 3 hr at room temperature. A saturated NH_4Cl solution was then added and ethereal layer was separated. The aqueous layer was extracted with ether and the combined ethereal layers were washed with water and saturated NaCl solution, dried over Na_2SO_4 and evaporated to afford a pale yellowish oil, which was chromatographed on silica gel. Elution with benzene afforded 600 mg of IV as a colorless oil, bp 75—80° (3 mmHg). NMR($CDCl_3$) δ: 1.30 (3H, s, C_3-CH_3), 2.24 (3H, s, $C_{5'}$-CH_3), 5.83 (2H, broad s, aromatic proton). IR($CHCl_3$) cm^{-1}: 1695. Mass Spectrum *m/e*: 192 (M^+). *Anal.* Calcd. for $C_{12}H_{16}O_2$: C, 74.97; H, 8.39. Found: C, 74.45; H, 8.53.

3-(1′,4′-Dioxopentyl)-3-methylcyclohexanone (V)——A mixture of 1.2 g of compound (IV), 5 ml of conc. HCl, and 10 ml of MeOH was stirred for 12 hr at room temperature. The mixture was then basified with sat. $NaHCO_3$ solution and extracted with $CHCl_3$. The extract was washed with water, dried over Na_2SO_4 and evaporated to give a brownish oil, which was distilled to give 1.21 g of colorless oil, bp 138—140° (3 mmHg). NMR($CDCl_3$) δ: 1.26 (3H, s, C-CH_3), 2.14 (3H, s, $COCH_3$). IR($CHCl_3$) cm^{-1}: 1700. Mass spectrum *m/e*: 210 (M^+).

The Reaction of Triketone (V) with conc. HCl in MeOH——A solution of 800 mg of triketone (V) in 20 ml of conc. HCl and 20 ml of MeOH was refluxed for 16 hr. After an addition of 50 ml of water the resulting mixture was extracted with ether. The extract was washed with water, dried over Na_2SO_4 and evaporated to leave a brownish oil, which was chromatographed on silica gel using ether–hexane (1:10) as an eluant. The first fraction gave 120 mg of compound (VIa) as colorless prisms, mp 92—93° (from ether–hexane). NMR ($CDCl_3$) δ: 1.00 (3H, s, C_9-CH_3), 1.11 (3H, d, $J=7$ Hz, C_4-CH_3), 5.79 (1H, q, $J=3$ and 10 Hz, C_2-H), 6.58 (1H, q, $J=3$ and 10 Hz, C_3-H). IR($CHCl_3$) cm^{-1}: 1670, 1701. Mass Spectrum *m/e*: 192 (M^+). *Anal.* Calcd. for $C_{12}H_{16}O_2$: C, 74.97; H, 8.39. Found: C, 74.94; H, 8.88. The second fraction gave 115 mg of compound (VIb) as a colorless oil. NMR($CDCl_3$) δ: 1.13 (3H, s, C_9-CH_3), 1.10 (3H, d, $J=7$ Hz, C_4-CH_3), 5.88 (1H, q, $J=3$ and 10 Hz, C_2-H), 6.65 (1H, q, $J=3$ and 10 Hz, C_3-H). IR($CHCl_3$) cm^{-1}: 1675, 1705. Mass Spectrum *m/e*: 192 (M^+). The third fraction gave 40 mg of compound (VII) as colorless needles, mp 79—80° (from MeOH). NMR($CDCl_3$) δ: 1.19 (3H, s, C_9-CH_3), 1.88 (3H, s, C_4-CH_3). IR($CHCl_3$) cm^{-1}: 1670, 1705. Mass Spectrum *m/e*: 192 (M^+). *Anal.* Calcd. for $C_{12}H_{16}O_2$: C, 74.97; H, 8.39. Found: C, 74.67; H, 8.39.

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8) Melting points are uncorrected and were determined with a Yanagimoto microapparatus (MP-S2). IR spectra were measured with a Hitachi EPI-3 spectrophotometer. Mass spectra were measured with a Hitachi RMU-7 spectrometer. NMR spectra were taken with JNM-PMX spectrophotometer using tetramethylsilane as internal reference.

4,9-Dimethyl-5,5-ethylenedioxy-Δ^3-1-octalone (VIII)——A solution of 700 mg of compound (VIa), 372 mg of ethylene glycol and 50 mg of *p*-toluenesulfonic acid in 30 ml of benzene was refluxed for 12 hr with a water separator. Saturated $NaHCO_3$ solution was added to the cooled mixture as above and the benzene layer was separated. The organic layer was washed with H_2O, dried over Na_2SO_4 and evaporated to give a pale brownish oil, which was chromatographed on silica gel. Elution with benzene gave 280 mg of VIII as colorless prisms, mp 86—87° (from hexane). NMR($CDCl_3$) δ: 1.08 (3H, s, C_9-CH_3), 1.90 (3H, m, C_4-CH_3), 2.75 (2H, broad s, C_2-H_2), 3.80 (4H, s, O-$C\underline{H}_2$-$C\underline{H}_2$-O), 5.53 (1H, s, C_3-H). IR($CHCl_3$) cm^{-1}: 1705. Mass Spectrum *m/e*: 236 (M^+). *Anal.* Calcd. for $C_{14}H_{20}O_3$: C, 71.16; H, 8.53. Found: C, 71.29; H, 8.83.

A mixture of 230 mg of compound (VIb), 110 mg of ethylene glycol, 20 mg of *p*-toluenesulfonic acid and 20 ml of benzene was worked up as described above and chromatographed on silica gel to give 76 mg of colorless prisms, mp 86—87° (from hexane), which was identical with the compound obtained above by mixed mp and comparison of spectroscopic data.

4,9-Dimethyl-5,5-ethylenedioxy-2-hydroxymethylene-Δ^3-1-octalone (IX)——A mixture of 90 mg of compound (VIII), 200 mg of ethyl formate, 200 mg of sodium hydride and 10 ml of benzene was stirred for 1 hr at room temperature, to a cooled mixture of which 10 ml of water was added and then the aqueous layer was separated. The aqueous layer was acidified with 10% HCl and extracted with ether. The extract was washed with water, dried over Na_2SO_4 and evaporated to afford a brownish oil, which was chromatographed on silica gel. Elution with hexane–ether (9: 1) gave 86 mg of IX as a colorless oil. NMR(CCl_4) δ: 1.1 (3H, s, C_9-CH_3), 1.95 (3H, s, C_4-CH_3), 3.75 (4H, s, O-$C\underline{H}_2$-$C\underline{H}_2$-O), 5.75 (1H, broad s, C_3-H), 6.7—7.2 (2H, broad s, =$C\underline{H}$-OH). IR($CHCl_3$) cm^{-1}: 1640, 1660. Mass Spectrum *m/e*: 264 (M^+).

4,9-Dimethyl-5,5-ethylenedioxy-2-isopropyl-Δ^3-1-octalone (XI)——A mixture of 86 mg of compound (IX), 43 mg of 1-butanethiol, 10 mg of *p*-toluenesulfonic acid and 20 ml of benzene was refluxed for 1.5 hr, to the cooled reaction mixture of which 10 ml of 10% NaOH solution was added and the benzene layer was separated. The organic layer was washed with water, dried over Na_2SO_4 and evaporated to afford 80 mg of a pale brownish oil, which was used for the next reaction without further purification.

A solution of 70 mg of the compound (X) obtained above in 5 ml of ether was added at −30° to a suspension of lithium dimethyl cuprate which was prepared by adding 10 ml of a solution of methyl lithium (1 mole) in ether to a suspension of 800 mg of cuprous iodide in 20 ml of ether. After the stirring had been continued for 2 hr at −30°, 30 ml of saturated NH_4Cl solution was added and the ethereal layer was separated. The ethereal layer was washed with saturated NH_4Cl solution, water, and saturated NaCl solution, dried over Na_2SO_4 and evaporated to afford a yellowish oil, which was chromatographed on silica gel. Elution with benzene gave 40 mg of colorless oil. NMR(CCl_4) δ: 0.76 (3H, d, $J=6$ Hz, $-CH{<}^{C\underline{H}_3}_{CH_3}$), 0.93 (3H, s, C_9-CH_3), 1.00 (3H, d, $J=6$ Hz, $-CH{<}^{CH_3}_{C\underline{H}_3}$), 1.95 (3H, m, C_4-CH_3), 3.80 (4H, s, $OC\underline{H}_2C\underline{H}_2O$), 5.55 (1H, broad s, C_3-H). IR ($CHCl_3$) cm^{-1}: 1700. Mass Spectrum *m/e*: 278 (M^+).

4,9-Dimethyl-2-isopropyl-$\Delta^{2(3)}$-1,5-octadione 5-Ethylenethioketal (XIII)——A solution of 640 mg of compound (XI) in 2 ml of trifluoroacetic acid was stirred for 3 hr at room temperature. The reaction mixture was poured into water and extracted with ether. The extract was washed with water, saturated $NaHCO_3$ solution, and water, dried over Na_2SO_4 and evaporated to give a brownish oil, which was chromatographed on silica gel. Elution with benzene afforded 281 mg of XII as a colorless oil. NMR ($CDCl_3$) δ: 0.75 (3H, d, $J=6$ Hz, $-CH{<}^{C\underline{H}_3}_{CH_3}$), 1.00 (3H, d, $J=6$ Hz, $-CH{<}^{CH_3}_{C\underline{H}_3}$), 1.05 (3H, s, C_9-CH_3), 1.80 (3H, m, C_4-CH_3), 5.60 (1H, broad s, C_3-H). IR ($CHCl_3$) cm^{-1}: 1700. Mass Spectrum *m/e*: 234 (M^+).

A mixture of 200 mg of compound (XII), 100 mg of ethanedithiol, 1 ml of boron trifluoride etherate, and 2 ml of acetic acid was stirred for 14 hr at room temperature. The reaction mixture was then poured into 5 ml of water and extracted with ether. The extract was washed with 10% NaOH, water and saturated $NaHCO_3$ solution, dried over Na_2SO_4 and evaporated to afford a pale yellowish oil, which was chromatographed on silica gel. Elution with benzene gave 98 mg of XIII as colorless prisms, mp 79—80° (from MeOH). NMR (CCl_4) δ: 1.00 (3H, d, $J=6$ Hz, $-CH{<}^{C\underline{H}_3}_{CH_3}$), 1.08 (3H, d, $J=6$ Hz, $-CH{<}^{CH_3}_{C\underline{H}_3}$), 1.17 (3H, s, C_9-CH_3), 1.37 (3H, d, $J=8$ Hz, C_4-CH_3), 3.20 (4H, s, S-$C\underline{H}_2$-$C\underline{H}_2$-S), 6.2 (1H, d, $J=4$ Hz, C_3-H). IR ($CHCl_3$) cm^{-1}: 1660. Mass Spectrum *m/e*: 310 (M^+). *Anal.* Calcd. for $C_{17}H_{26}OS_2$: C, 65.78; H, 8.44. Found: C, 65.63; H, 8.73.

3-(5′-Methylfuryl-2′)-6-hydroxymethylene-2-cyclohexenone (XIV)——A mixture of 3.42 g of compound (III), 2.57 g of ethyl formate, 0.8 g of NaH and 50 ml of benzene was stirred for 1 hr at room temperature. The reaction mixture was then diluted with 20 ml of water, acidified with 10% HCl solution and extracted with benzene. The extract was washed with water, dried over Na_2SO_4 and evaporated to give a yellowish oil, which was distilled to give 3 g of XIV as a colorless oil, bp 160—161° (3 mmHg). NMR ($CDCl_3$) δ: 2.40 (3H, s, $C_{5'}$-CH_3), 6.1 (1H, d, $J=3$ Hz, $C_{4'}$-H), 6.4 (1H, s, C_2-H), 6.56 (1H, d, $J=3$ Hz, $C_{3'}$-H), 7.6 (1H, broad s, =$C\underline{H}$-OH). IR ($CHCl_3$) cm^{-1}: 1600, 1630. Mass Spectrum *m/e*: 204 (M^+). *Anal.* Calcd. for $C_{12}H_{12}O_3$: C, 70.57; H, 5.92. Found: C, 70.43; H, 5.93.

The Reaction of Compound (XIV) with 1-Butanethiol——A mixture of 1.5 g of compound (XIV), 0.5 g of 1-butanethiol, 30 mg of *p*-toluenesulfonic acid, and 30 ml of benzene was refluxed for 1 hr, and 10 ml of

10% NaOH solution was then added to the above cooled reaction mixture and the benzene layer was separated. The organic layer was washed with water, dried over Na_2SO_4, and evaporated to afford a brownish oil, which was distilled to give 1 g of XV as a colorless oil, bp 205—206° (0.03 mmHg). NMR ($CDCl_3$) δ: 2.35 (3H, s, $C_{5'}$-CH_3), 6.05 (1H, d, $J=3$ Hz, $C_{4'}$-H), 6.38 (1H, s, C_2-H), 6.55 (1H, d, $J=3$ Hz, $C_{3'}$-H), 7.28 (1H, broad s, =CH-S-^{n}Bu). IR ($CHCl_3$) cm^{-1}: 1605, 1630. Mass spectrum *m/e*: 276 (M^+). *Anal.* Calcd. for $C_{16}H_{20}O_2S$: C, 69.52; H, 7.29. Found: C, 69.80; H, 7.23.

6-Isopropyl-3-(5′-methylfuryl-2′)-2-cyclohexenone (XVI)——A solution of 2.5 g of compound (XV) in 20 ml of ether was added at −30° to a suspension of lithium dimethyl cuprate which was prepared by adding 50 ml of a solution of methyllithium (0.9 mole) in ether to a suspension of 6 g of cuprous iodide in 50 ml of ether. After the stirring had been continued for 1 hr at −30°, 50 ml of saturated NH_4Cl solution was added to the resulting mixture and the solvent was separated. The ethereal layer was washed with saturated NH_4Cl solution, water, and saturated NaCl solution, dried over Na_2SO_4 and evaporated to give a yellowish oil, which was distilled to afford 1.3 g of XVI as a colorless oil, bp 145—146° (3 mmHg). NMR (CCl_4) δ: 0.88 (3H, d, $J=6$ Hz, $-\mathrm{CH}{<}^{\mathrm{CH_3}}_{\mathrm{CH_3}}$), 0.99 (3H, d, $J=6$ Hz, $-\mathrm{CH}{<}^{\mathrm{CH_3}}_{\mathrm{CH_3}}$), 2.35 (3H, s, $C_{5'}$-CH_3), 6.02 (1H, d, $J=3$ Hz, $C_{4'}$-H), 6.25 (1H, s, C_2-H), 6.5 (1H, d, $J=3$ Hz, $C_{3'}$-H). IR ($CHCl_3$) cm^{-1}: 1600, 1650. Mass Spectrum *m/e*: 218 (M^+). The 2,4-dinitrophenylhydrazone of XVI yielded reddish needles, mp 176—177° (from MeOH). *Anal.* Calcd. for $C_{20}H_{22}O_5N_4$: C, 60.29; H, 5.57; N, 14.06. Found: C, 60.19; H, 5.65; N, 14.03.

6-Isopropyl-3-methyl-3-(5′-methylfuryl-2′) cyclohexanone (XVII)——To a solution of 1.14 g of cuprous iodide and 3.6 g of tri-*n*-butylphosphine in 40 ml of ether was added 10 ml of a solution of methyllithium (1.28 mole) in ether at −30°. After the stirring had been continued for 30 min at −30°, a solution of 526 mg of compound (XVI) in 10 ml of ether was added dropwise to the above mixture at −30° and stirring was continued for 5 hr at −30°. Afterwards, saturated NH_4Cl solution was added to the above mixture and the ethereal layer was separated. The aqueous layer was extracted with ether and the combined ethereal layers were washed with water and saturated NaCl solution, dried over Na_2SO_4 and evaporated to afford a yellowish oil, which was chromatographed on silica gel. Elution with hexane–benzene (2:1) afforded 25 mg of XVII as a colorless oil. NMR ($CDCl_3$) δ: 0.8—1.1 (6H, m, $-\mathrm{CH}{<}^{\mathrm{CH_3}}_{\mathrm{CH_3}}$), 1.3 (3H, s, C_3-CH_3), 2.25 (3H, s, $C_{5'}$-CH_3), 5.75 (2H, s, $C_{3'}$-H, $C_{4'}$-H). IR ($CHCl_3$) cm^{-1}: 1700. Mass Spectrum *m/e*: 234 (M^+).

4-Isopropyl-5-methyl-5-pentanolide (XIX)——To a solution of 10 g of 4-acetyl-5-methylhexanoic acid in 100 ml of MeOH was added 7.6 g of $NaBH_4$ at 40—50°. After stirring had been continued for 1 hr at room temperature, solvent was evaporated off and acidified with 10% HCl solution. The aqueous solution was extracted with ether. The ethereal layer was washed with water, dried over Na_2SO_4 and evaporated to leave 9.5 g of colorless oil. A mixture of 9.5 g of colorless oil prepared as above, 300 mg of *p*-toluenesulfonic acid, and 150 ml of benzene was refluxed for 16 hr with a water separator. Saturated $NaHCO_3$ solution was added to the cooled reaction mixture and the benzene layer was separated. The organic layer was washed with water, dried over Na_2SO_4 and evaporated to afford a brownish oil, which was distilled to give 6 g of XIX as a colorless oil, bp 112—114° (6 mmHg). NMR ($CDCl_3$) δ: 0.97 (6H, d, $J=4$ Hz, $-\mathrm{CH}{<}^{\mathrm{CH_3}}_{\mathrm{CH_3}}$), 1.9 (3H, d, $J=6$ Hz, $-\mathrm{OCH}$-$\mathrm{C\underline{H}_3}$), 4.3—4.8 (1H, m, $\mathrm{CH_3}$-$\mathrm{C\underline{H}}$-O-). IR ($CHCl_3$) cm^{-1}: 1720. Mass Spectrum *m/e*: 156 (M^+). *Anal.* Calcd. for $C_9H_{16}O_2$: C, 69.14; H, 10.32. Found: C, 68.74; H, 9.82.

3,4-Dihydro-3-isopropyl-2-methyl-6-(5′-methylfuryl-2′)-α-pyran (XX)——To a solution of 10.3 g of 2-methylfuran in 200 ml of ether was added 200 ml of *n*-butyllithium solution of ether (prepared from 7 g of *n*-butyl bromide and 2 g of lithium in ether) at 0°. After the stirring had been continued for 1.5 hr at 0°, a solution of 6 g of compound (XIX) in 100 ml of ether was added dropwise and stirring was continued for 3 hr at −30°. To the reaction mixture was added 50 ml of water and acidified with 10% H_2SO_4. The ethereal layer was separated and the aqueous layer was extracted with ether. The combined ethereal layer was washed with water and saturated NaCl solution, dried over Na_2SO_4 and evaporated to give a yellowish oil, which was distilled to give 6.7 g of XX as a colorless oil, bp 120—122° (3 mmHg). NMR (CCl_4) δ: 0.98 (3H, d, $J=6$ Hz, $-\mathrm{CH}{<}^{\mathrm{CH_3}}_{\mathrm{CH_3}}$), 1.15 (3H, d, $J=6$ Hz, $-\mathrm{CH}{<}^{\mathrm{CH_3}}_{\mathrm{CH_3}}$), 1.35 (3H, d, $J=6.5$ Hz, $>\mathrm{CH}$-$\overset{|}{\mathrm{C}}\mathrm{H}$-$\mathrm{C\underline{H}_3}$), 2.28 (3H, s, $C_{5'}$-CH_3), 5.05—5.30 (1H, m, C_5-H), 5.85 (1H, d, $J=3$ Hz, $C_{4'}$-H), 6.10 (1H, d, $J=3$ Hz, $C_{3'}$-H). IR ($CHCl_3$) cm^{-1}: 1700. Mass Spectrum *m/e*: 220 (M^+). The 2,4-dinitrophenylhydrazone of XX afforded reddish needles, mp 164—165° (from MeOH). *Anal.* Calcd. for $C_{20}H_{26}O_6N_4$: C, 57.40; H, 6.26; N, 13.39. Found: C, 57.37; H, 6.13; N, 13.35.

2-(4-Acetyl-5-methylhexanoyl)-5-methylfuran (XXII)——To a solution of 2 g of compound (XX) in 30 ml of acetone was added dropwise 6 ml of 10% H_2SO_4 solution and the mixture was stirred for 30 min at room temperature. After 10 ml of Jones reagent had been added to the reaction mixture at room temperature and the stirring had been continued for 1 hr at room temperature, the reaction mixture was poured into 100 ml of water and extracted with ether. The ethereal layer was washed with water and saturated NaCl solution, dried over Na_2SO_4 and evaporated to give a yellowish oil, which was distilled to afford 1.5 g of XXII as a colorless oil, bp 149—150° (3 mmHg). NMR (CCl_4) δ: 0.95 (3H, d, $J=6$ Hz, $-\mathrm{CH}{<}^{\mathrm{CH_3}}_{\mathrm{CH_3}}$), 0.98 (3H, d, $J=6$ Hz,

$-CH\left\langle{}^{CH_3}_{CH_3}\right.$), 2.10 (3H, s, C_5-CH_3), 2.40 (3H, s, -CO-CH_3), 6.10 (1H, d, $J=3$ Hz, C_4-H), 6.97 (1H, d, $J=3$ Hz, C_3-H). IR ($CHCl_3$) cm^{-1}: 1700. Mass Spectrum m/e: 236 (M^+). The mono-2,4-dinitrophenylhydrazone derivative afforded pale reddish needles, mp 144—145° (from MeOH). *Anal.* Calcd. for $C_{20}H_{24}O_6N_4$: C, 57.68; H, 5.81; N, 13.46. Found: C, 57.27; H, 5.65; N, 13.61.

Base-catalyzed Cyclization of 2-(4-Acetyl-5-methylhexanoyl)-5-methylfuran (XXII)——A mixture of 600 mg of compound (XXII), 1 ml of 10% NaOH aqueous solution and 20 ml of MeOH was stirred for 14 hr at room temperature. To the above reaction mixture 50 ml of H_2O was added and extracted with ether. The ethereal layer was washed with water, dried over Na_2SO_4 and evaporated to give a yellowish oil, which was distilled to afford 530 mg of XXII as a colorless oil, identical with 6-isopropyl-3-(5′-methylfuryl-2′)-2-cyclohexenone prepared as above.

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