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Synthesis of *dl*-Dehydroiridodiol

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Diethyl 3,6-dioxooctanedioate (**5**), which can be prepared readily from ethyl acetoacetate and ethyl γ-bromoacetoacetate, was utilized for a facile preparation of *dl*-dehydroiridodiol (**1**). Compound **5** was treated with sodium hydroxide to give ethyl 2-ethoxycarbonyl-3-oxo-1-cyclopenteneacetate (**6**), which was methylated, and then reduced to give ethyl 2-(2-ethoxycarbonyl-3-oxocyclopentyl)propionate (**8**). Compound **8** was transformed to the phosphate (**9**). On methylation with lithium dimethylcuprate, followed by reduction, the phosphate (**9**) was converted to *dl*-dehydroiridodiol (**1**) *via* ethyl 2-(2-ethoxycarbonyl-3-methyl-2-cyclopentenyl)propionate (**10**).

Keywords——*dl*-dehydroiridodiol; ethyl γ-bromoacetoacetate; diethyl 3,6-dioxooctanedioate; 3-oxo-1-cyclopenteneacetate; *Actinidia polygama* MIQ. (matatabi)

Dehydroiridodiol (**1**), isolated from dry leaves of the cat- and lacewing-attracting plant *Actinidia polygama* MIQ. (matatabi), is known to an attractant for the male adults of *Chrysopa septempunctata* WESMAEL and *Chrysopa japana* OKAMOTO, and shows activity in amounts as small as 10^{-4} μg.[1] Compound **1** was first synthesized from matabiether (**2**) which is a major terpene of *Actinidia polygama* MIQ., by treatment with formic acid, followed by lithium aluminum hydride reduction.[2] Sakan *et al.*[3] reported the reduction of dehydroiridodial (**3**) to give compound **1**, from which they also derived neonepetalactone (**4**). In the present paper, we wish to report the total synthesis of *dl*-dehydroiridodiol (**1**).

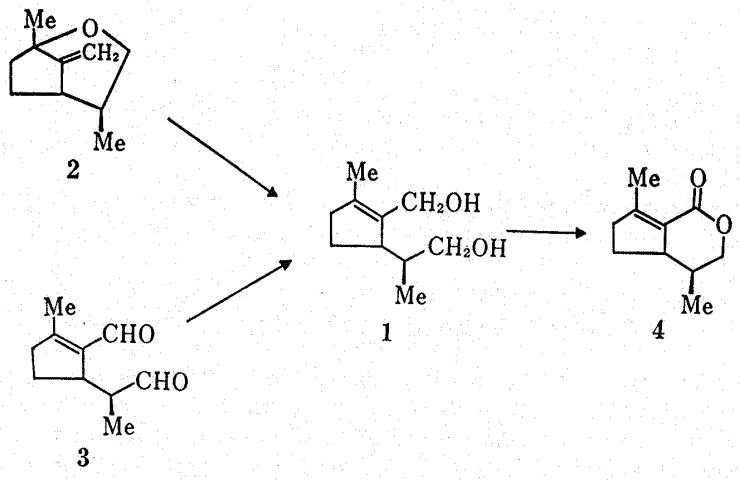

Chart 1

Ethyl acetoacetate was treated with sodium hydride and then with butyl lithium. The resulting dianion was allowed to react with the sodium salt of ethyl γ-bromoacetoacetate in tetrahydrofuran to give diethyl 3,6-dioxooctanedioate (**5**) in 70% yield. The dioate **5** was treated with sodium hydroxide in ethanol to give the cyclopentenone (**6**) in 94% yield. Reaction of compound **6** with methyl iodide in the presence of sodium ethoxide gave a 81% yield of the methylated derivative (**7**), which was reduced in the presence of platinum oxide to

give the cyclopentanone (**8**) in 91% yield. Applying the procedure reported by Weiler,[4] compound **8** was transformed into the phosphate (**9**), which was treated with lithium dimethylcuprate to give a mixture of the methylcyclopentene (**10**) and the cyclopentene (**11**) in a 2:1 ratio. A part of the mixture was subjected to preparative gas chromatography to obtain pure analytical samples of **10** and **11**. The mixture of **10** and **11** was reduced with lithium aluminum hydride, and the resulting products were subjected to silica gel column chromatography to afford *dl*-dehydroiridodiol (**1**) in a yield of 42% (from **8**). Structural assignment was made by comparison of spectral data with those reported in the literature.[3b]

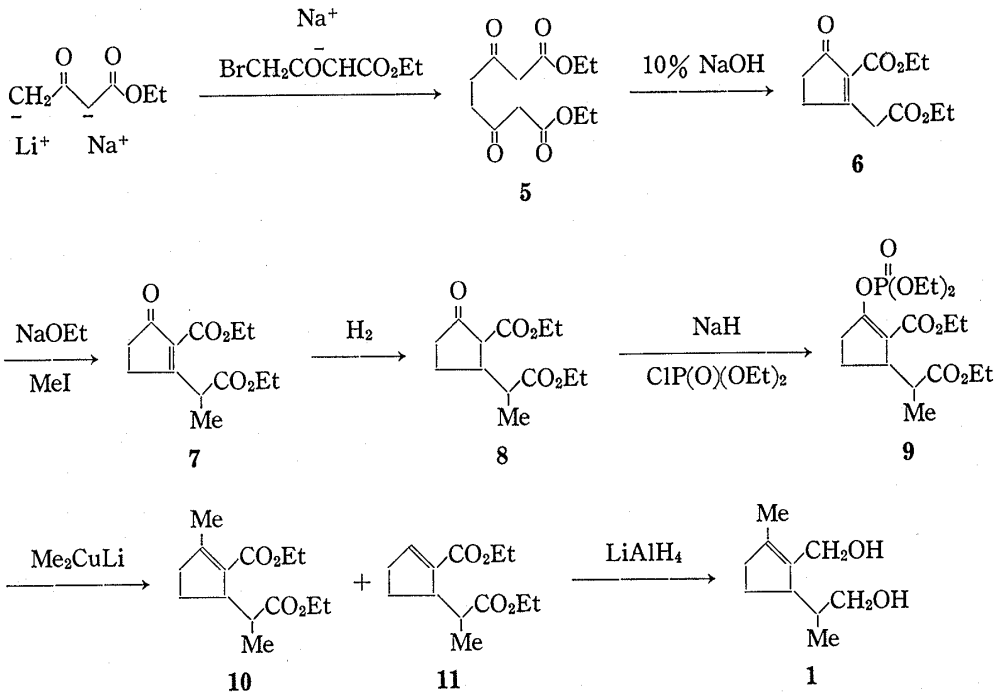

Chart 2

Experimental

Melting points and boiling points are uncorrected. IR spectra were taken on a JASCO IR-S spectrophotometer. NMR spectra were measured with a JEOL JNM-PMX 60 instrument using tetramethylsilane as an internal standard.

Diethyl 3,6-Dioxooctanedioate (**5**)——A solution of ethyl acetoacetate (5.2 g, 0.04 mol) in dry tetrahydrofuran (THF) (20 ml) was added dropwise to a suspension of sodium hydride (60% dispersion in mineral oil, 1.60 g, 0.04 mol) in dry THF (160 ml) under nitrogen at 0°C. After being stirred for an additional 20 min at the same temperature, the reaction mixture was cooled to −60°C. A solution of butyl lithium (10% w/v hexane solution, 28 ml, 0.044 mol) was added dropwise to this solution and the mixture was stirred for 20 min at −60°C. Separately, a solution of ethyl γ-bromoacetoacetate[5] (8.4 g, 0.04 mol) in dry THF (20 ml) was added dropwise to a suspension of sodium hydride (60% dispersion in mineral oil, 1.60 g, 0.04 mol) in dry THF (20 ml) with stirring at −10——15°C, and stirring was continued for 20 min at the same temperature. This solution of the sodium salt of ethyl γ-bromoacetoacetate was added dropwise to the dianion solution of ethyl acetoacetate at −60°C. After being stirred for 30 min at −60°C, the reaction mixture was neutralized with 10% hydrochloric acid (45 ml), and the mixture was extracted with ether. The ether solution was dried over magnesium sulfate, and concentrated *in vacuo*. The residual solid was recrystallized from hexane–ether (1:4) to give 7.2 g (70%) of the product **5** as colorless needles, mp 46°C (lit.[6] mp 47—48°C). IR ν_{max}^{KBr} cm^{-1}: 1745, 1710. NMR ($CDCl_3$) δ: 1.27 (6H, t, J=7 Hz, CH_3), 2.75 (4H, s, CH_2), 3.40 (4H, s, CH_2), 4.14 (4H, q, J=7 Hz, $CH_3\underline{CH_2}O$).

Ethyl 2-Ethoxycarbonyl-3-oxo-1-cyclopenteneacetate (**6**)——A solution of **5** (6.21 g, 0.024 mol) in 99% ethanol (50 ml) and 10% aqueous sodium hydroxide (10 ml, 0.024 mol) was stirred for 2 h at room temperature. The reaction mixture was neutralized with 10% hydrochloric acid (9.5 ml, 0.026 mol), and the solution was concentrated to dryness *in vacuo*. The residue was extracted with ether. The ether solution was concentrated to give a crystalline substance, which was recrystallized from ether–hexane (4:1) to yield 5.40 g

(94%) of the product **6** as colorless needles, mp 49—50°C. *Anal.* Calcd for $C_{12}H_{16}O_5$: C, 62.32; H, 6.54. Found: C, 61.95; H, 6.62. IR ν_{max}^{KBr} cm^{-1}: 1720, 1628. NMR ($CDCl_3$) δ: 1.27 (3H, t, J=7 Hz, CH_3), 1.33 (3H, t, J=7 Hz, CH_3), 2.30—2.95 (4H, m, $CH_2\times2$), 3.83 (2H, s, CH_2), 4.20 (2H, q, J=7 Hz, $CH_3C\underline{H}_2O$), 4.31 (2H, q, J=7 Hz, $CH_3C\underline{H}_2O$).

Ethyl 2-(2-Ethoxycarbonyl-3-oxo-1-cyclopentenyl)propionate (**7**)——Compound **6** (2.04 g, 0.008 mol) and methyl iodide (2.26 g, 0.016 mol) were added to a solution of sodium ethoxide prepared from sodium (0.23 g, 0.01 g atom) in absolute ethanol (50 ml). After being refluxed for 2 h, the reaction mixture was concentrated *in vacuo*, and the resulting residue was extracted with ether. The ether solution was dried, and concentrated to give an oily residue, which was distilled under reduced pressure to give 1.75 g (81%) of the product **7** as a pale yellow oil, bp 118—121°C (0.1 mmHg). *Anal.* Calcd for $C_{13}H_{18}O_5$: C, 61.40; H, 7.14. Found: C, 61.36; H, 7.20. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1720, 1625. NMR ($CDCl_3$) δ: 1.26 (3H, t, J=7 Hz, CH_3), 1.35 (3H, t, J=7 Hz, CH_3), 1.44 (3H, d, J=7 Hz, $C\underline{H}_3CH$), 2.37—2.90 (4H, m, CH_2), 4.18 (2H, q, J=7 Hz, $CH_3C\underline{H}_2O$), 4.23 (2H, q, J=7 Hz, $CH_3C\underline{H}_2O$), 4.47 (1H, q, J=7 Hz, $CH_3C\underline{H}$).

Ethyl 2-(2-Ethoxycarbonyl-3-oxocyclopentyl)propionate (**8**)——A mixture of **7** (6.49 g, 0.026 mol) and PtO_2 (100 mg) in ethanol (60 ml) was shaken in H_2 under atmospheric pressure at room temperature until absorption ceased (600 ml, 0.027 mol). The catalyst was filtered off, and the filtrate was concentrated *in vacuo*. The resulting oil was distilled under reduced pressure to give 5.93 g (91%) of the product **8** as a colorless oil, bp 108—110°C (0.2 mmHg). *Anal.* Calcd for $C_{13}H_{20}O_5$: C, 60.92; H, 7.87. Found: C, 60.60; H, 8.00. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1750, 1720. NMR ($CDCl_3$) δ: 1.10—1.53 (9H, m), 1.80—2.80 (5H, m), 2.91—3.20 (2H, m), 4.18 (2H, q, J=7 Hz), 4.24 (2H, q, J=7 Hz).

Ethyl 2-(2-Ethoxycarbonyl-3-diethoxyphosphoryl-2-cyclopentyl)propionate (**9**)——A solution of **8** (1.28 g, 5 mmol) in dry ether (10 ml) was added dropwise to a suspension of sodium hydride (60% dispersion in mineral oil, 0.20 g, 5 mmol) in dry ether (20 ml) under a nitrogen stream with stirring at room temperature. The mixture was stirred for an additional 30 min. A solution of diethyl chlorophosphate (0.95 g, 5.5 mmol) in dry ether (10 ml) was added dropwise to this mixture at room temperature with stirring. The whole was stirred for 2 h at room temperature, then ammonium chloride (0.50 g) was added. After being stirred for 30 min, the mixture was filtered through Celite, and the filtrate was concentrated to give the product **9** as a pale yellow oil. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1715, 1650, 1030. NMR ($CDCl_3$) δ: 1.20 (3H, d, J=7 Hz, $C\underline{H}_3CH$), 1.20—1.60 (12H, m), 1.70—3.30 (6H, m), 3.90—4.52 (8H, m).

Ethyl 2-(2-Ethoxycarbonyl-3-methyl-2-cyclopentenyl)propionate (**10**) **and Ethyl 2-(2-Ethoxycarbonyl-2-cyclopentenyl)propionate** (**11**)——A solution of lithium dimethylcuprate prepared from methyl lithium (1.5 M in ether, 20 ml, 30 mmol) and cuprous iodide (2.86 g, 15 mmol) was cooled to −40°C under nitrogen. To this solution was added dropwise an ether (20 ml) solution of crude **9** prepared from **8** (1.28 g, 5 mmol). The resulting mixture was stirred at −40°C for 30 min and poured into saturated aqueous ammonium chloride. The ether layer was separated and the aqueous layer was extracted with ether. The ether fraction was washed with 10% aqueous ammonia, dried over magnesium sulfate, filtered and concentrated. The resulting oil was distilled under reduced pressure to give a mixture (1.13 g) of **10** and **11** as a colorless oil, bp 82—86°C (0.1 mmHg). Compounds **10** and **11** were separated by gas chromatography (5% OV-17 on Chromosorb W). **10**: *Anal.* Calcd for $C_{14}H_{22}O_4$: C, 66.11; H, 8.72. Found: C, 66.14; H, 8.89. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1720, 1710, 1645. NMR ($CDCl_3$) δ: 1.08 (3H, d, J=7 Hz, $C\underline{H}_3CH$), 1.27 (6H, t, J=7 Hz, CH_3), 1.67—3.33 (6H, m), 2.02 (3H, t, J=1 Hz, CH_3–C=), 4.00 (2H, q, J=7 Hz, $CH_3C\underline{H}_2O$), 4.17 (2H, q, J=7 Hz, $CH_3C\underline{H}_2O$). MS *m/e*: 254 (M^+). **11**: *Anal.* Calcd for $C_{13}H_{20}O_4$: C, 64.98; H, 8.39. Found: C, 65.08; H, 8.53. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1720, 1710, 1645. NMR ($CDCl_3$) δ: 1.08 (3H, d, J=7 Hz, $C\underline{H}_3CH$), 1.27 (6H, t, J=7 Hz, CH_3), 1.67—3.33 (6H, m), 4.00 (2H, q, J=7 Hz, $CH_3C\underline{H}_2O$), 4.17 (2H, q, J=7 Hz, $CH_3C\underline{H}_2O$), 6.87 (1H, m, CH=). MS *m/e*: 240 (M^+).

***dl*-Dehydroiridodiol** (**1**)——A solution of the mixture (**10** and **11**) (1.13 g) in ether (10 ml) was added dropwise to a suspension of lithium aluminum hydride (230 mg, 6 mmol) in dry ether (30 ml) under nitrogen with stirring at 0°C. Stirring was continued for 30 min at 0°C, then water (0.1 ml) was added to the reaction mixture. The mixture was filtered through Celite, and the filtrate was dried over magnesium sulfate. The solvent was removed and the resulting oily residue was subjected to silica gel column chromatography (silica gel 40 g) using hexane–ethyl acetate (3:2) as an eluant to give 0.35 g (42% from **8**) of the product **1** as a colorless oil. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3520 (br), 1640. NMR ($CDCl_3$) δ: 0.88 (3H, d, J=7 Hz, $C\underline{H}_3CH$), 1.70 (3H, t, J=1 Hz, $C\underline{H}_3$–C=), 1.50—2.67 (6H, m), 2.86—3.20 (2H, br, OH×2), 3.40—3.67 (2H, m, –CH–$C\underline{H}_2$–OH), 4.20 (2H, s, $C\underline{H}_2OH$). MS *m/e*: 170 (M^+).

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