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Synthesis of Dihydrojasmone and *cis*-Jasmone

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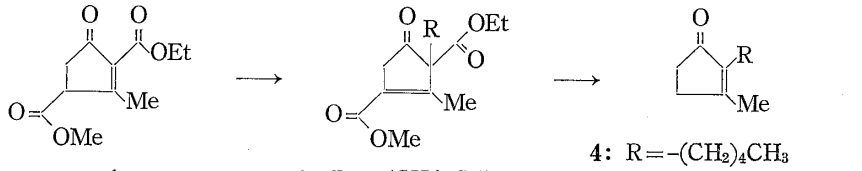
2-Ethoxycarbonyl-4-methoxycarbonyl-3-methyl-2-cyclopentenone (**1**), prepared readily from methyl acetoacetate, may be utilized for facile preparations of dihydro- and *cis*-jasmone. Compound **1** reacted with pentyl iodide and 1-bromo-2-pentyne in the presence of sodium hydride to give 2-ethoxycarbonyl-4-methoxycarbonyl-3-methyl-2-pentyl-3-cyclopentenone (**2**) and 2-ethoxycarbonyl-4-methoxycarbonyl-3-methyl-2-(2-pentynyl)-3-cyclopentenone (**3**), respectively. Decarbalkoxylations of compounds **2** and **3** afforded dihydrojasmone (**4**) and dehydrojasmone (**5**), respectively. Catalytic hydrogenation of dehydrojasmone (**5**) over a Pd–$CaCO_3$ catalyst gave *cis*-jasmone (**6**).

Keywords——methyl acetoacetate; ethyl γ-bromoacetoacetate; 2-cyclopentenone-2,4-dicarboxylate; dihydrojasmone; dehydrojasmone; *cis*-jasmone

Although considerable work has been done on syntheses of jasmone and jasmonoids,[2] there is still interest in new synthetic methodologies offering greater ease and economy. In the present paper, we report easy syntheses of dihydrojasmone (**4**) and *cis*-jasmone (**6**) using acetoacetate as a starting material.

In 1968, Dolby *et al.*[3] reported the reaction of ethyl acetoacetate with methyl γ-bromoacetoacetate in the presence of sodium hydride in 1,2-dimethoxyethane to give 4-ethoxycarbonyl-2-methoxycarbonyl-3-methyl-2-cyclopentenone in 48% yield. Applying this procedure, the reaction of methyl acetoacetate with ethyl γ-bromoacetoacetate in the presence of sodium hydride gave 2-ethoxycarbonyl-4-methoxycarbonyl-3-methyl-2-cyclopentenone (**1**) in 71% yield. Alkylation of compound **1** with pentyl iodide in 1,2-dimethoxyethane in the presence of sodium hydride gave 2-ethoxycarbonyl-4-methoxycarbonyl-3-methyl-2-pentyl-3-cyclopentenone (**2**) in 20% yield. A solution of compound **2** in a mixture of aqueous hydrobromic acid and acetic acid[4] was refluxed to give dihydrojasmone (**4**) in 80% yield.

Alkylation of compound **1** with 1-bromo-2-pentyne in 1,2-dimethoxyethane in the presence of sodium hydride at room temperature afforded 2-ethoxycarbonyl-4-methoxycarbonyl-3-methyl-2-(2-pentynyl)-3-cyclopentenone (**3**) in 46% yield. A mixture of compound **3** and sodium chloride in aqueous dimethylsulfoxide (DMSO)[5] was heated at 180° in a sealed



1

2: R=$-(CH_2)_4CH_3$
3: R=$-CH_2C{\equiv}CC_2H_5$

4: R=$-(CH_2)_4CH_3$
5: R=$-CH_2C{\equiv}CC_2H_5$
6: R=$-CH_2CH{=}CHC_2H_5$ (*cis*)

Chart 1

1) Location: *Aobayama, Sendai 980, Japan.*
2) W. Treff and H. Werner, *Chem. Ber.*, **68**, 640 (1935); T.-L. Ho, *Synth. Commun.*, **4**, 265 (1974).
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tube to give 3-methyl-2-(2-pentynyl)-2-cyclopentenone (dehydrojasmone) (**5**) in 33% yield. Catalytic hydrogenation of compound **5** over Pd–$CaCO_3$ catalyst gave *cis*-jasmone (**6**) in 65% yield.

Since the procedure is simple and requires few steps, this synthetic method should be practically useful for the preparation of these jasmonoids.

Experimental

Melting points and boiling points are uncorrected. IR spectra were taken on a Jasco IR-S spectrophotometer. NMR spectra were measured with a Hitachi R-20 instrument using tetramethylsilane as an internal standard.

2-Ethoxycarbonyl-4-methoxycarbonyl-3-methyl-2-cyclopentenone (**1**)——A 50% dispersion of sodium hydride in mineral oil (9.6 g, 0.2 mol) was washed by decantation with dry petroleum ether. When most of the mineral oil had been removed, dry tetrahydrofuran (THF) (500 ml) was added to the sodium hydride. The suspension was cooled with ice-salt at −10—0°, and a solution of methyl acetoacetate (23.2 g, 0.2 mol) in dry THF (20 ml) was added dropwise. Stirring was continued for an additional 1 hr at the same temperature, then the mixture was allowed to come to room temperature. Next, a solution of ethyl γ-bromoacetoacetate (20.9 g, 0.1 mol) in dry THF (20 ml) was added dropwise over a period of 30 min. After stirring for 2 hr, the reaction mixture was concentrated under reduced pressure. Separated crystals were collected by suction, washed with ether (30 ml×2), and dissolved in 10% HCl. The HCl solution was extracted with benzene (100 ml×2). The benzene extract was concentrated *in vacuo*, and the oily residue was distilled to give the product **1** as a pale yellow semi-solid, bp 135—145° (2 mmHg), 16 g (71%). *Anal.* Calcd for $C_{11}H_{14}O_5$: C, 58.40; H, 6.24. Found: C, 58.54; H, 6.44. enol: IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1695, 1658, 1610. NMR ($CDCl_3$) δ: 1.34 (3H, t, J=7 Hz, $\underline{CH_3}CH_2O$), 2.50 (3H, t, J=2.5 Hz, CH_3), 3.37 (2H, q, J=2.5 Hz, CH_2), 3.70 (3H, s, CH_3O), 4.20 (2H, q, J=7 Hz, $CH_3\underline{CH_2}O$), 11.35 (1H, br, OH). keto: IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1742, 1728, 1640. NMR ($CDCl_3$) δ: 1.31 (3H, t, J=7 Hz, $\underline{CH_3}CH_2O$), 2.35 (3H, s, CH_3), 2.70 (2H, d, J=5.5 Hz, CH_2), 3.74 (3H, s, CH_3O), 3.60—3.80 (1H, m, CH), 4.29 (2H, q, J=7 Hz, $CH_3\underline{CH_2}O$).

2-Ethoxycarbonyl-4-methoxycarbonyl-3-methyl-2-pentyl-3-cyclopentenone (**2**)——Following the procedure described above, a 50% dispersion of sodium hydride (0.96 g, 0.02 mol) was washed with dry petroleum ether. A solution of **1** (4.52 g, 0.02 mol) was added dropwise to a suspension of this sodium hydride in dry 1,2-dimethoxyethane (200 ml) with stirring at room temperature. The mixture was stirred for 1 hr, and pentyl iodide (8 g, 0.04 mol) was added dropwise. After refluxing for 24 hr, the reaction mixture was concentrated under reduced pressure. The residue was added to H_2O (50 ml), and the mixture was extracted with ether. The ether solution was dried over Na_2SO_4, and concentrated. The resulting residue was distilled to give a colorless oil (**2**), bp 130—132° (3 mmHg), 1.2 g (20%). *Anal.* Calcd for $C_{16}H_{24}O_5$: C, 64.84; H, 8.16. Found: C, 64.62; H, 8.26. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1760, 1720, 1640. NMR ($CDCl_3$) δ: 0.7—1.5 (14H, m), 2.15 (3H, t, J=2 Hz, CH_3), 3.10—3.30 (2H, m, CH_2), 3.75 (3H, s, CH_3O), 4.10 (2H, q, J=7 Hz, $CH_3\underline{CH_2}O$).

2-Ethoxycarbonyl-4-methoxycarbonyl-3-methyl-2-(2-pentynyl)-3-cyclopentenone (**3**)——Following the procedure described above, a 50% dispersion of sodium hydride (1.2 g, 0.025 mol) was washed with dry petroleum ether. A solution of **1** (5.65 g, 0.025 mol) in dry 1,2-dimethoxyethane (30 ml) was added dropwise to a suspension of this sodium hydride in dry 1,2-dimethoxyethane (250 ml) with stirring at room temperature. Stirring was continued for a further 2 hr, and a solution of 1-bromo-2-pentyne[6] (4.4 g, 0.03 mol) in dry 1,2-dimethoxyethane (20 ml) was added. After stirring for 24 hr, the reaction mixture was concentrated under reduced pressure to give oily residue to which H_2O (100 ml) was added. The mixture was extracted with ether. The ether solution was concentrated, and the residue was distilled to give a colorless oil (**3**), bp 105—107° (0.06 mmHg), 3.32 g (46%). *Anal.* Calcd for $C_{16}H_{20}O_5$: C, 65.74; H, 6.90. Found: C, 65.38; H, 6.91. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1765, 1720, 1640. NMR (CCl_4) δ: 1.00 (3H, t, J=6 Hz, $\underline{CH_3}CH_2C\equiv$), 1.20 (3H, t, J=7 Hz, $\underline{CH_3}CH_2O$), 2.09 (3H, t, J=2 Hz, 3-CH_3), 1.92—2.30 (2H, m, CH_2), 2.73 (2H, t, J=2 Hz, 2-$\underline{CH_2}C\equiv$), 3.10 (2H, m, 5-CH_2), 3.75 (3H, s, OCH_3), 4.10 (2H, q, J=7 Hz, $CH_3\underline{CH_2}O$).

3-Methyl-2-pentyl-2-cyclopentenone (Dihydrojasmone) (**4**)——A solution of compound **2** (0.9 g) in a mixture of acetic acid (18 ml), 47% HBr (12 ml), and H_2O (6 ml) was refluxed for 15 hr. After cooling, the reaction mixture was poured into 10% Na_2CO_3 (200 ml). The mixture was extracted with ether (50 ml×5), and the ether solution was dried over Na_2SO_4, then concentrated. The residue was distilled to give the product **4** as a pale yellow oil, bp 95—100° (15 mmHg) (lit.[4] bp 120—126° (16 mmHg)), 0.4 g (80%). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1690, 1645. NMR ($CDCl_3$) δ: 0.87 (3H, t), 1.0—1.7 (6H, m), 2.06 (3H, s, CH_3), 2.0—2.7 (6H, m). Semicarbazone, mp 174—175° (lit.[4] mp 176.5—177.5°).

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3-Methyl-2-(2-pentynyl)-2-cyclopentenone (Dehydrojasmone) (5)——A mixture of **3** (0.88 g) and NaCl (0.4 g) in DMSO (40 ml) and H_2O (0.7 g) was placed in a sealed tube. After heating at 180° for 7.5 hr, the reaction mixture was poured into a saturated NaCl solution (100 ml) and this solution was extracted with hexane. The hexane extract gave an oily substance (0.3 g), which was purified by silica gel (10 g) column chromatography, eluting with benzene, to give the product **5** as a colorless oil, 0.16 g (33%). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 2200, 1705, 1655. NMR (CCl_4) δ: 1.10 (3H, t, J=7 Hz, CH_3), 2.18 (3H, s, CH_3), 1.90—2.79 (6H, m), 2.98 (2H, s, 2-$CH_2C\equiv$). 2,4-Dinitrophenylhydrazone: mp 163—164° (EtOH) (lit.[7] mp 166°).

3-Methyl-2-(2-*cis*-pentenyl)-2-cyclopentenone (*cis*-Jasmone) (6)——A mixture of **5** (90 mg) and 5% Pd–$CaCO_3$[8] (50 mg) in ethanol (5 ml) was shaken in H_2 until absorption ceased (12 ml). The catalyst was filtered off, and the filtrate was concentrated. The residue (80 mg) was subjected to silica gel (2 g) column chromatography. Elution with $CHCl_3$ gave the product **6** as a pale yellow oil, 60 mg (65%). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1695, 1645, 760 (*cis* CH=CH). NMR (CCl_4) δ: 0.96 (3H, t, J=7 Hz, CH_3), 2.03 (3H, s, CH_3), 2.0—2.7 (6H, m), 2.85 (2H, d, J=6 Hz, CH_2), 5.2—5.55 (2H, m, olefinic protons). 2,4-Dinitrophenylhydrazone: mp 114—115° (EtOH) (lit.[9] mp 117.5°).

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Studies on the Metabolic Relationship between Alkyl Carbamates and Alkyl N-Hydroxycarbamates in Rats

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When methyl, ethyl or *n*-propyl N-hydroxycarbamate was administered to rats intraperitoneally, the corresponding alkyl carbamate was detected as a urinary metabolite by thin-layer chromatography. These alkyl N-hydroxycarbamates were also converted to the corresponding alkyl carbamates by rat liver slices, but not by rat liver 9000 ***g*** supernatant. This suggests that the reduction of alkyl N-hydroxycarbamates may be catalyzed by liver enzymes which are different in nature from aromatic hydroxylamine-reducing enzymes. Similarly, the metabolism of ethyl carbamate in rats was investigated *in vivo* and *in vitro*. However, no ethyl N-hydroxycarbamate could be detected in these experiments. Therefore, it appears unlikely that alkyl N-hydroxycarbamates are metabolites of the corresponding alkyl carbamates in rats.

Keywords——alkyl carbamates; alkyl N-hydroxycarbamates; metabolism; rats; thin-layer chromatography

The carbamate compounds are potentially dangerous from an environmental point of view. They have been widely used medicinally as sedatives, industrially as chemical raw materials, and agriculturally as herbicides, insecticides and fungicides. The simplest compounds among them, ethyl carbamate and ethyl N-hydroxycarbamate have almost equal

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