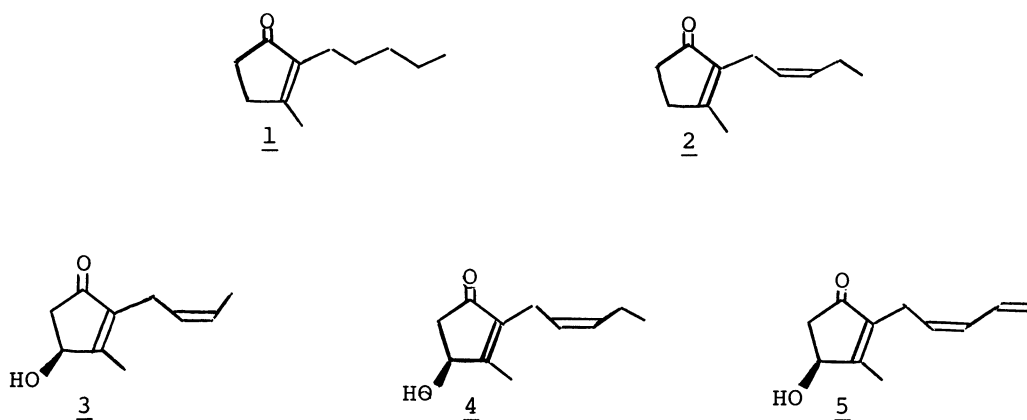


2-METHYLENE-3-ALKOXYCYCLOPENTANONES AS REACTIVE INTERMEDIATES AND THEIR APPLICATION TO THE SYNTHESES OF DIHYDROJASMONE, *CIS*-JASMONE, AND (±)-JASMOLOLONE

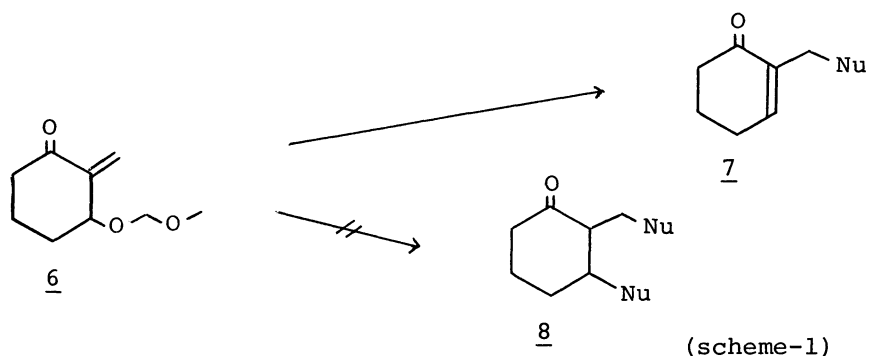
Takashi TAKAHASHI, Kimihiko HORI, and Jiro TSUJI\*  
 Tokyo Institute of Technology, Meguro, Tokyo 152

Dihydrojasmone and *cis*-jasmone were synthesized in high yields by the Michael addition of lithium di-*n*-butylcuprate and bromomagnesium di-1-butenylcuprate, respectively, to 2-methylene-3-methyl-3-methoxymethoxycyclopentanone. (±)-Jasmololone was also synthesized by the Michael addition of dialkenylcuprate to 2-methylene-3-methyl-3-methoxymethoxy-4-ethoxyethoxycyclopentanone.

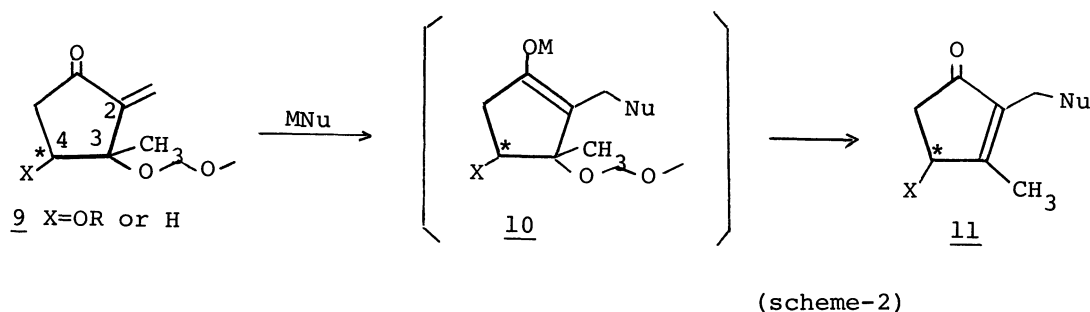
2,3-Dialkyl-2-cyclopenten-1-one is an important partial structure of some natural products, such as dihydrojasmone (1), *cis*-jasmone (2), cinerolone (3), jasmololone (4) and pyrethrolone (5).



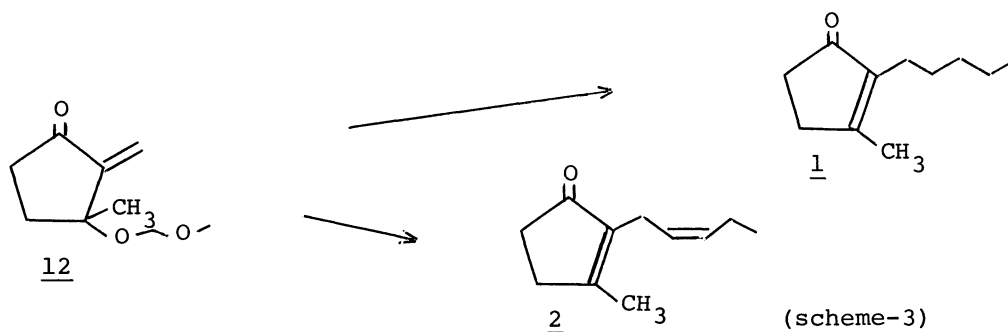
For the construction of these molecules, the inter- or intramolecular aldol condensation of the corresponding keto aldehydes is widely used.<sup>1)</sup> However, in the synthesis of these five-membered keto alcohol moieties present in 3 — 5, generation of the labile  $\beta$ -ketol system with the correct absolute configuration of the secondary hydroxy group by aldol condensation is extremely difficult. We have recently reported the synthesis of very reactive 2-methylene-3-alkoxycyclohexanone (6).<sup>2)</sup> This reactive exocyclic enone undergoes 1,4-addition of various nucleophiles to give only mono-alkylated 2-cyclohexenone 7 without forming the dialkylated product 8, since the exocyclic enone 6 is much more reactive than the resulting endocyclic enone 7.<sup>3)</sup> (Scheme 1).



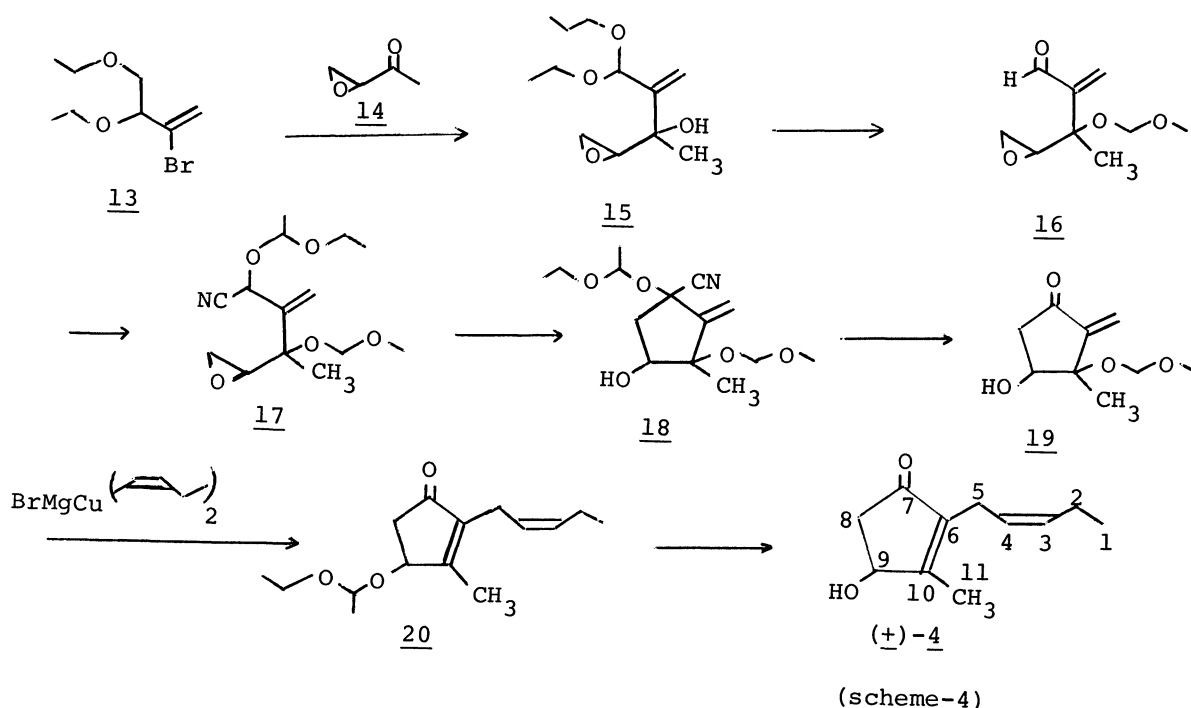
As an extension of this methodology to five-membered ketones, we describe here effective syntheses of 1, 2, and 4 by the 1,4-conjugate addition of *cis*-dialkenyl cuprate to 2-methylene-3-methyl-3-alkoxycyclopentanone 9 (Scheme 2). Michael addition to this enone 9 completed within 10 to 20 min and the resulting enolate 10 caused elimination of the methoxymethoxy group selectively to give the desired endocyclic enones 11. Therefore, if the enone 9 bears an optically active hydroxy group at C(4) position, the chirality of the keto alcohol can be kept intact.



At first 1,4-conjugate addition of organometallic reagents to the enone 12 was conducted (Scheme 3). Addition of the enone 12 <sup>4)</sup> (120 mg, 0.71 mmol) in ether at  $-78^{\circ}\text{C}$  under nitrogen to 1.2 equiv of lithiumdi-*n*-butylcuprate, prepared in ether in the usual manner, gave 2-pentyl-3-methyl-2-cyclopenten-1-one (1) in 94% yield. The introduction of *cis*-1-butenyl chain was carried out in the following way. Addition of ethylmagnesium bromide (2.6 mmol in THF, dropwise over 10 min at  $-30^{\circ}\text{C}$  under nitrogen) to a solution of CuI (1.3 mmol) in THF- $\text{Me}_2\text{S}$  (9 : 1), was followed by passage at  $-70^{\circ}\text{C}$  of dry acetylene (excess, bubbling for 1 min). <sup>5)</sup> To this reaction mixture a solution of the enone 12 (1 mmol) in THF was added over 20 min at  $-70^{\circ}\text{C}$ . Acidification (3 N-HCl) at  $0^{\circ}\text{C}$  and purification by column chromatography gave, in 73% yield, *cis*-jasmonone (2): NMR ( $\text{CCl}_4$ )  $\delta$  2.02 (br s, 3 H, vinyl methyl), 5.11 (dt, 1 H,  $J = 10$  & 6 Hz, olefinic), 5.36 (dt, 1 H,  $J = 10$  & 6 Hz, olefinic); IR (neat) 1690, 1640  $\text{cm}^{-1}$ . The *cis* configuration of the double bond was fully confirmed by its NMR spectrum.



Next we attempted to synthesize ( $\pm$ )-jasmololone (4) (Scheme 4) in order to examine whether the  $\beta$ -ketol system can survive or not in this method. The exocyclic enone 19 was prepared in the following way. Metalation of the vinyl bromide 13 <sup>6)</sup> (21.8 g, 105 mmol) in THF at  $-78^{\circ}\text{C}$  with *n*-butyllithium, followed by addition of the epoxy ketone 14 (6 g, 70 mmol) gave the alcohol 15. The protection of the resulting tertiary alcohol ( $\text{ClCH}_2\text{OME}$  in diisopropylethylamine at  $0^{\circ}\text{C}$  — room temp for 12 h) and removal of diethyl acetal [ $\text{CuSO}_4$  in  $\text{MeOH}/\text{H}_2\text{O}$  (4/1) at room temp for 1 h] gave 16 in 45% overall yield from the epoxy ketone 14: NMR ( $\text{CCl}_4$ )  $\delta$  1.34 (s, 3 H,  $-\text{CH}_3$ ), 2.47–2.76 (m, 2 H), 2.85 (dd, 1 H,  $J = 3$  & 4 Hz), 3.33 (s, 3 H,  $-\text{OCH}_3$ ), 6.15 (d, 1 H,  $J = 1.5$  Hz, olefinic), 6.65 (d, 1 H,  $J = 1.5$  Hz, olefinic), 9.60 (s, 1 H,  $-\text{CHO}$ ); IR (neat) 1700, 1625  $\text{cm}^{-1}$ . Cyclization of the protected cyanohydrin 17 (712.5 mg, 2.5 mmol), prepared from the enal 16 ( $\text{Me}_3\text{SiCN-KCN}/18\text{-crown-6}$ , <sup>7)</sup>  $\text{PhCH}_2\text{N}^+\text{Me}_3\text{F}^-$ , ethyl vinyl ether/ $\text{H}^+$ ), gave only five membered ring 18 <sup>8)</sup> in 70% yield by refluxing for 1.5 h in THF with five equiv of sodium bistrimethylsilylamide.



Acid treatment (pyridinium *p*-toluenesulfonate<sup>9</sup>) at 40°C; 74% yield) of the cyclized product 18, followed by base treatment (diisopropylethylamine at 40°C; 83% yield) gave the exocyclic enone 19: NMR (CCl<sub>4</sub>) δ 1.45, 1.51 (s, 3 H, -CH<sub>3</sub>), 3.38, 3.41 (s, 3 H, -OCH<sub>3</sub>), 5.59 (br s, 1 H, olefinic), 6.28 (br s, 1 H, olefinic); IR (neat) 3450, 1730, 1645 cm<sup>-1</sup>. The Michael addition of *cis*-1-butenyl chain to the exocyclic enone 19, after the protection of secondary alcohol with ethyl vinyl ether, was carried out as above (12 → 2) to give 20 in 70% yield. Hydrolysis of the ethoxyethyl group gave (±)-jasmololone (4); NMR (200 MHz, CDCl<sub>3</sub>) δ 0.91 (t, 3 H, *J* = 7.4 Hz, -CH<sub>3</sub>), 2.02 (s, 3 H, vinyl methyl), 2.19 (dd, 1 H, *J* = 1.9 & 17.8 Hz), 2.69 (dd, 1 H, *J* = 6.4 & 18.7 Hz), 2.85 (d, 2 H, *J* = 6.8 Hz, -CH<sub>2</sub>CH=CH-), 4.34-4.69 (m, 1 H, -CH(OH)-), 5.00-5.44 (m, 2 H, olefinic); IR (neat) 3400, 1700, 1645, 1090, 1050 cm<sup>-1</sup>; mass spectrum *m/e* 180 (M<sup>+</sup>). <sup>13</sup>C NMR δ 13.5, 20.4, 132.7, 123.9, 21.0, 140.4, 205.2, 44.1, 71.2, 169.2, 13.9 for carbons 1 through 11, respectively.

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