CHEMISTRY LETTERS, pp. 1189-1192, 1981.

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

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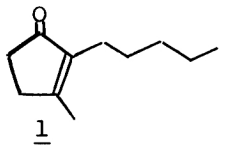
Dihydrojasmone and *cis*-jasmone were synthesized in high yields by the Michael addition of lithium di-*n*-butylcuprate and bromomagnesium di-1-butenylcuprate, respectively, to 2-methylene-3-methyl-3-methoxymethyloxycyclopentanone. (±)-Jasmololone was also synthesized by the Michael addition of dialkenylcuprate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

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).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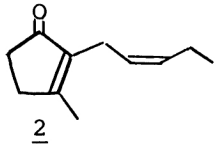
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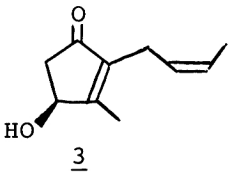
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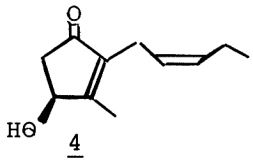
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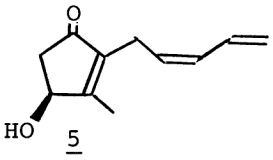
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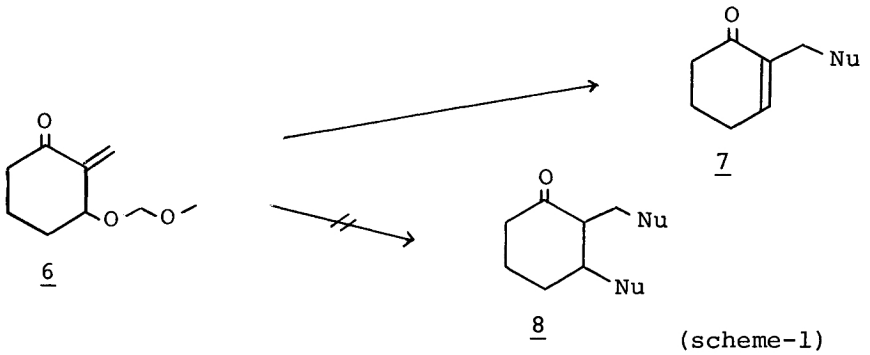
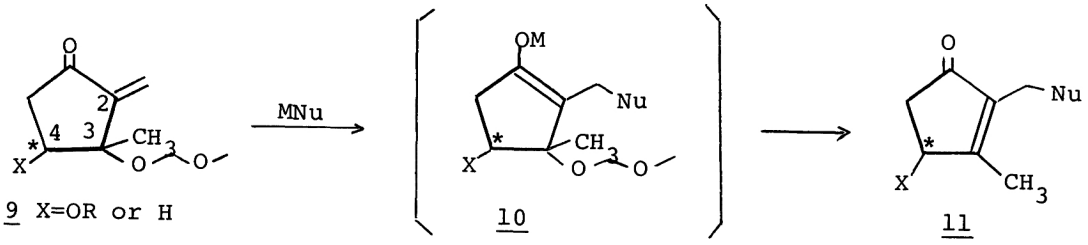
For the construction of these molecules, the inter- or intramolecular aldol condensation of the corresponding keto aldehydes is widely used.[1] However, in the synthesis of these five-membered keto alcohol moieties present in 3 — 5, generation of the labile β-ketol system with the correct absolute configuration 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).[2] This reactive exocyclic enone undergoes 1,4-addition of various nucleophiles to give only monoalkylated 2-cyclohexenone 7 without forming the dialkylated product 8, since the exocyclic enone 6 is much more reactive than the resulting endocyclic enone 7 [3] (Scheme 1).



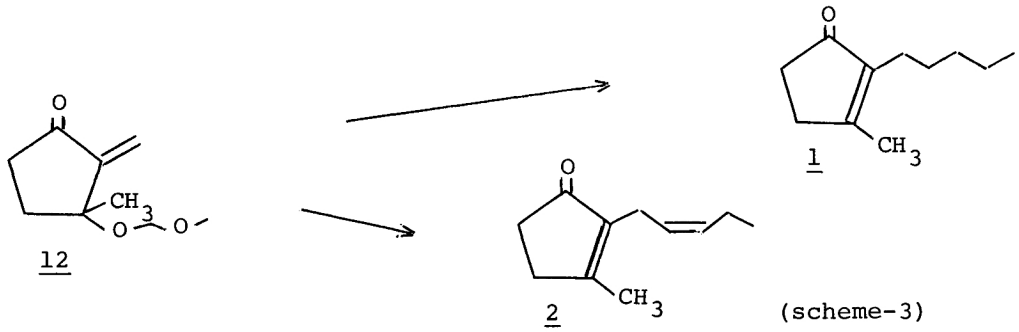
(scheme-1)

As an extention 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 methoxymethyloxy 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.



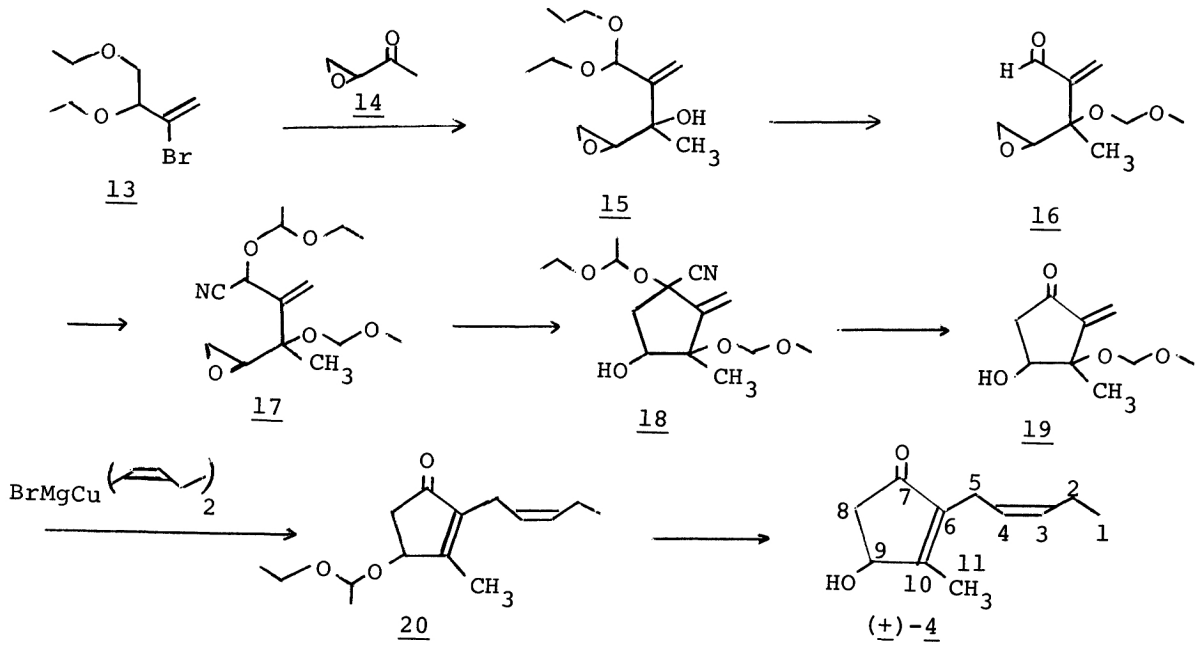
(scheme-2)

At first 1,4-conjugate addition of organometallic reagents to the enone 12 was conducted (Scheme 3). Addition of the enone 12 [4] (120 mg, 0.71 mmol) in ether at -78°C under nitrogen to 1.2 equiv of lithium di-*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°C under nitrogen) to a solution of CuI (1.3 mmol) in THF-Me_2S (9 : 1), was followed by passage at -70°C of dry acetylene (excess, bubbling for 1 min).[5] To this reaction mixture a solution of the enone 12 (1 mmol) in THF was added over 20 min at -70°C. Acidification (3 N-HCl) at 0°C and purification by column chromatography gave, in 73% yield, *cis*-jasmone (2): NMR (CCl_4) δ 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 cm^{-1}. The cis configuration of the double bond was fully confirmed by its NMR spectrum.



(scheme-3)

Next we attempted to synthesize (±)-jasmololone (4) (Scheme 4) in order to examine whether the β-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 [6] (21.8 g, 105 mmol) in THF at -78°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 ($ClCH_2OMe$ in diisopropylethylamine at 0°C → room temp for 12 h) and removal of diethyl acetal [$CuSO_4$ in $MeOH/H_2O$ (4/1) at room temp for 1 h] gave 16 in 45% overall yield from the epoxy ketone 14: NMR (CCl_4) δ 1.34 (s, 3 H, $-CH_3$), 2.47-2.76 (m, 2 H), 2.85 (dd, 1 H, J = 3 & 4 Hz), 3.33 (s, 3 H, $-OCH_3$), 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, -CHO); IR (neat) 1700, 1625 cm^{-1}. Cyclization of the protected cyanohydrin 17 (712.5 mg, 2.5 mmol), prepared from the enal 16 (Me_3SiCN-KCN/18-crown-6,[7] $PhCH_2N^+Me_3F^-$, ethyl vinyl ether/H^+), gave only five membered ring 18 [8] in 70% yield by refluxing for 1.5 h in THF with five equiv of sodium bistrimethylsilylamide.



(scheme-4)

Acid treatment (pyridinium *p*-toluenesulfonate[9] 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_4) δ 1.45, 1.51 (s, 3 H, $-CH_3$), 3.38, 3.41 (s, 3 H, $-OCH_3$), 5.59 (br s, 1 H, olefinic), 6.28 (br s, 1 H, olefinic); IR (neat) 3450, 1730, 1645 cm^{-1}. 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, $CDCl_3$) δ 0.91 (t, 3 H, J = 7.4 Hz, $-CH_3$), 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, $-CH_2CH=CH-$), 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^{-1}; mass spectrum m/e 180 (M^+). ^{13}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.

Acknowledgement: We thank Mr. Y. Nakamura of Tokyo Institute of Technology and JEOL Co. for measurement of the NMR spectra. This research was supported by grant-in-aids administered by the Ministry of Education, Japanese Government (No. 56550602 and 00585218) and the Asahi Glass Foundation for Industrial Technology.

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(Received June 20, 1981)