(cooling with an ice bath was required). After 2 h, the upper layer was separated and the aqueous phase was extracted with ether (2 × 50 mL). The combined organic extracts were washed with saturated sodium bicarbonate and brine and dried ($MgSO_4$). Removal of the solvent under reduced pressure yielded 9.0 g (96%) of **7**: NMR (CCl_4) δ 1.05–1.85 (12 H, broad m, $6CH_2$), 2.06–2.50 (6 H, m, $3CH_2$), 3.60 (3 H, s, CO_2CH_3), 4.72–5.18 (2 H, m, vinyl CH_2), 5.45–6.12 (1 H, m, vinyl CH).

Anal. Calcd for $C_{14}H_{24}O_3$: C, 69.96; H, 10.06. Found: C, 70.24; H, 10.23.

Methyl 9-Oxo-12-dodecanaloate (8). A three-neck round-bottom flask fitted with a mechanical stirrer was charged with *tert*-butyl alcohol (60 mL), water (20 mL), **5** (4.32 g, 17.8 mmol), and osmium tetroxide (45.2 mg, 0.17 mmol in *tert*-butyl alcohol). The resulting solution was stirred for 5 min. A temperature of 24–26 °C was maintained with ice bath cooling during the addition of sodium metaperiodate (8.24 g, finely divided) in small portions over a period of 30 min. The tan-colored slurry was stirred at ambient temperature for an additional 4 h. At the end of this period the precipitate was white. The reaction mixture was extracted thoroughly with ether (3 × 100 mL), and the combined organic layers were washed with saturated sodium sulfite, saturated $NaHCO_3$, and brine and dried (Na_2SO_4). Removal of the solvent under reduced pressure yielded 3.9 g (91%) of product: NMR (CCl_4) δ 1.04–1.83 (10 H, broad m, $5CH_2$), 2.10–2.55 (4 H, m, $2CH_2$), 2.61 (4 H, s, $COCH_2CH_2CO$), 3.61 (3 H, s, CO_2CH_3), 9.60 (1 H, s, CHO).[10]

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Registry No.—**1**, 533-87-9; **2**, 1931-63-1; **4**, 34546-57-1; **6**, 67237-57-4; **7**, 67237-58-5; **8**, 50266-44-9; 1-bromo-3-butene, 5162-44-7.

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An Efficient Conversion of Ketones to α,β-Unsaturated Ketones

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The C-alkylation of a terminal carbon in conjugated enamino ketones may be achieved through reaction with alkyl halides in the presence of *n*-butyllithium,[1] hydroxymethylation of acylated enamines with formaldehyde and an alkyllithium,[2] or through use of enamino ketones as nucleophilic acylating agents.[3,4]

We have now found that the reaction of structurally related β-acylenamines with alkyllithium reagents follows an alternative course to yield α,β-unsaturated carbonyl compounds. The problems associated with the synthesis of such compounds have been documented[5,6] and some particularly efficient methods have been developed for their preparation.[7] The work reported herein affords a practical, efficient route to α,β-unsaturated ketones in 60–85% yield based on starting ketone.

Condensation of ketones **1–7** with *N,N*-dimethylformamide dimethyl acetal at 110 °C for 12 h under nitrogen gave enamino ketones **8–14**, respectively.[8] When the enamino ketones were treated with 1.1 equiv of *n*-butyllithium in anhydrous tetrahydrofuran at −30 to 0 °C and then allowed to warm to room temperature, the corresponding α,β-unsaturated ketones **15–24** were obtained (Table I).

In order to demonstrate the versatility of this synthetic method, we have applied the sequence to prepare several natural products of which dihydrojasmone (**26**) and perillaketone (**30**), originally isolated from *Perilla frutescens* Brit.,[13] are representative examples.

The conversion of *N,N*-dimethylatropaldehyde (**31**)[12] to the unsaturated aldehyde (**32**) in 70% yield without any concomitant carbinol formation would serve to indicate that the course of these reactions is not sterically determined. Furthermore, the absence of any additional attack on the α,β-unsaturated carbonyl compounds by alkyllithium is believed due to the intervention of intermediates such as **33** which have no propensity for additional attack by nucleophiles.

The generality of the process is demonstrated by successful extension to methyllithium and *tert*-butyllithium reagents

Scheme I. A Total Synthesis of Dihydrojasmone

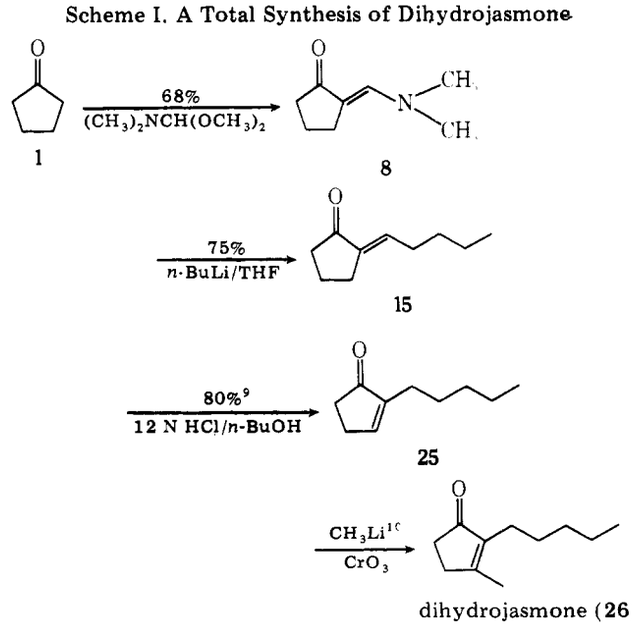

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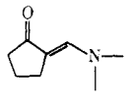
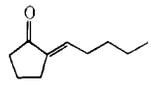
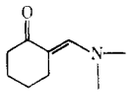
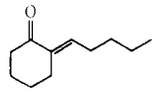
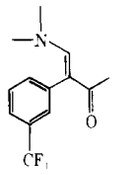
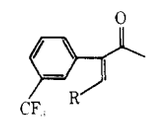
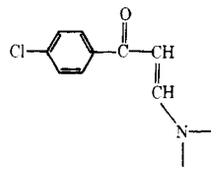
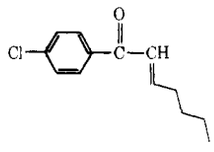
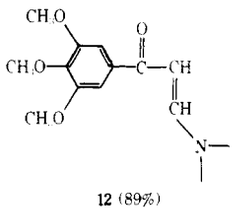
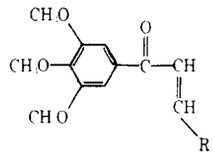
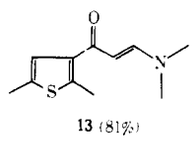
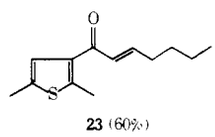
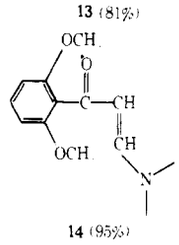
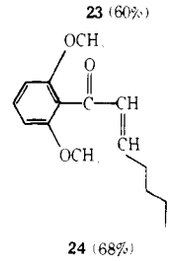
Table I. Two-Step Conversion of Ketones to α,β-Unsaturated Ketones

ketones	registry no.	enamines (yield, %)[a]	registry no.	α,β-unsaturated ketones (yield, %)	registry no.
cyclopentanone (1)	120-92-3	 8 (68%)	67382-33-6	 15 (75%)	67382-39-2
cyclohexanone (2)	108-94-1	 9 (66%)	28467-36-9	 16 (73%)	67382-40-5
m-trifluoromethylphenylacetone (3)	349-76-8	 10 (83%)	67382-34-7	 17, R = *n*-C_4H_9 (65%) 18, R = *t*-C_4H_9 (55%) 19, R = CH_3 (75%)	67382-41-6 67382-42-7 67382-43-8
p-chloroacetophenone (4)	99-91-2	 11 (85%)	67382-35-8	 20 (68%)	67382-44-9
3,4,5-trimethoxyacetophenone (5)	1136-86-3	 12 (89%)	67382-36-9	 21, R = *n*-C_4H_9 (60%) 22, R = CH_3 (64%)	67382-45-0 67382-46-1
3-acetyl-2,5-dimethylthiophene (6)	2530-10-1	 13 (81%)	67382-37-0	 23 (60%)	67382-47-2
2,6-dimethoxyacetophenone (7)	2040-04-2	 14 (95%)	67382-38-1	 24 (68%)	67382-48-3

[a] These refer to isolated yields of chromatographically homogeneous materials. All intermediates and products were characterized by IR, NMR, and mass spectroscopy and afforded satisfactory combustion analyses.

(Table I), and the data show that these conversions are comparable in efficiency.

In view of the capriciousness of 1,4 vs. 1,2 addition of organometallic reagents[14] to unsaturated carbonyl compounds, the consistency of our results provides a useful route to substituted, conjugated enones.

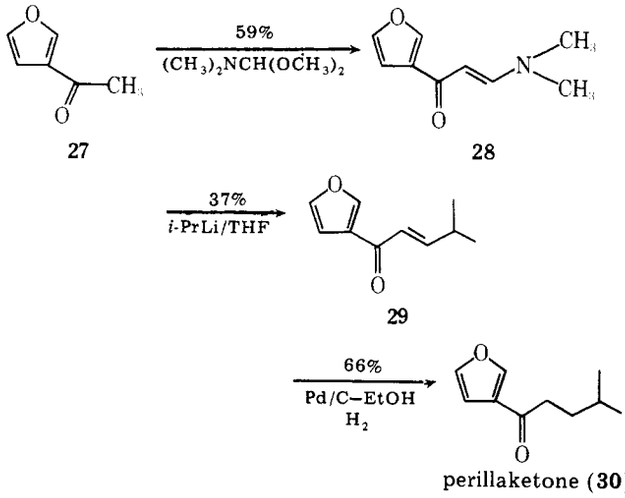
Experimental Section

2-[(Dimethylamino)methylene]cyclopentanone (8). To 8.4 g (0.1 mol) of cyclopentanone was added 11.9 g (0.1 mol) of *N,N*-dimethylformamide dimethyl acetal and the mixture was refluxed under nitrogen at 110 °C for 12 h. The resulting mixture was stripped of methanol and distilled in a Kugelrohr apparatus at 90 °C/30 μm to afford 12.2 g (88%) of the title compound as an amber oil which was used without further purification [$n^{25}D$ 1.5795; $\bar{\nu}_{CO}$ 1685 cm^{-1}; NMR ($CDCl_3$, Me_4Si) δ 1.5–3.0 (m, 6 H, cyclopentanone ring protons), 3.08 (s, 6 H, $N(CH_3)_2$), 7.1 (t, J = 0.75 Hz, =CH; M^+ *m/e* 139).

2-Pentylidenecyclopentanone (15). To 11.12 g of 8 in 350 mL of tetrahydrofuran at −30 °C (N_2) was added 57.2 mL (1.1 equiv) of 1.6 M *n*-butyllithium reagent, dropwise over 30 min. The reaction mixture was stirred to room temperature over 2 h. The excess *n*-butyllithium was destroyed with water (5.0 mL) and the solvent was removed in vacuo. The oily residue was treated with 100 mL of water and extracted five times with 100-mL portions of ether. The ether was washed with water, dried ($MgSO_4$), and evaporated in vacuo (40 °C (10 mm)) to give 9.4 g (75%) of the title compound 15: bp 100–102 °C (8 mm); $n^{25}D$ 1.4756, lit.[7c] $n^{20}D$ 1.4743; $\bar{\nu}_{CO}$ = 1660, 1730 cm^{-1} (lit.[9] 1653, 1709 cm^{-1}); NMR ($CDCl_3$, Me_4Si) δ 0.50–1.33 (m, 15 H), 6.30–6.73 (m, 1 H, vinyl). Anal. Calcd: 78.95; H, 10.53. Found: C, 78.73; H, 10.49.

2-Pentyl-2-cyclopenten-1-one (25). To 1.0 g of 15 dissolved in 10.0 mL of *n*-butyl alcohol was added 2.0 mL of 12 N hydrochloric acid and the mixture was stirred at 100 °C for 1 h.[9] The mixture was poured into water and extracted with ether. The ether solution was dried over anhydrous magnesium sulfate and stripped to give 0.8 g (80%) of 25 as a mobile, colorless, fragrant liquid whose obtention comprises a synthesis of dihydrojasmone[10] (26): $n^{25}D$ 1.4687; $\bar{\nu}_{CO}$ 1715, 1638; NMR ($CDCl_3$, Me_4Si) δ 0.33–3.00 (m, 15 H), 7.26–7.5 (m, 1 H, vinyl). Anal. Calcd: C, 78.90; H, 10.59. Found: C, 78.65; H, 10.44.

Scheme II. A Total Synthesis of Perillaketone



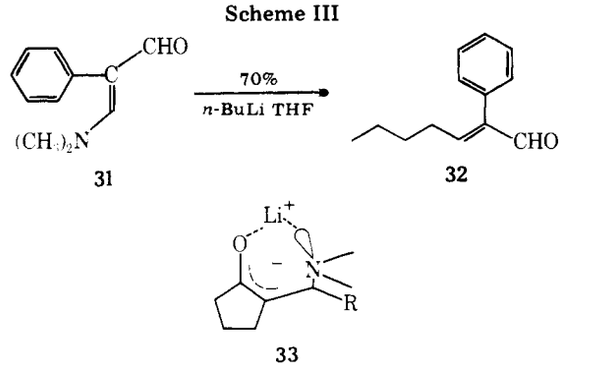
***trans*-3-[3-(Dimethylamino)acryloyl]furan (28).** A mixture of 3.30 g (0.03 mol) of 3-acetylfuran (**27**) and 25.0 mL of *N,N*-dimethylformamide dimethyl acetal was heated under reflux for 12 h. The mixture was evaporated in vacuo and the residue was crystallized under pentane. Recrystallization from diisopropyl ether/dichloromethane gave 2.9 g (59%) of *trans*-3-[3-(dimethylamino)acryloyl]-furan (**28**): mp 103–105 °C; NMR ($CDCl_3$, Me_4Si) δ 2.95 (s, 6 H, $N(CH_3)_2$), 5.42 (d, 1 H), 7.68 (d, 1 H, J = 13.5 Hz, *trans*-vinyl), 6.68, 7.41, 8.0 (m, 3 H, furan). Anal. Calcd: C, 65.44; H, 6.71; N, 8.48. Found: C, 65.55; H, 6.42; N, 8.63.

***trans*-3-Furyl 3-Methyl-1-butenyl Ketone (29).** To 1.65 g (0.01 mol) of the *trans*-enamino ketone (**28**) in 100 mL of dry (Linde 4A Sieves) tetrahydrofuran under nitrogen was added 5.5 mL of 1.85 M isopropyllithium reagent in pentane. After stirring at −30 °C for 0.5 h, the solution was stirred to room temperature and 5.0 mL of water was added. The solution was stripped dry, and the residue was extracted with dichloromethane. The organic layer was washed with saturated sodium chloride solution, dried ($MgSO_4$), and evaporated in vacuo to give an oil which was purified by chromatography (325 g of silica gel, gradient elution with dichloromethane and ethyl acetate/dichloromethane) to give 0.6 g (37%) of the trans-α,β-unsaturated ketone (**29**): NMR ($CDCl_3$, Me_4Si) δ 1.13 [d, 6 H, J = 6.2 Hz, $(CH_3)_2C$], 2.55 (m, 1 H, CH(C)(C)), 6.4 (d, 1 H, J = 14 Hz, *trans*-vinyl), 7.0 (m, 1 H, vinyl), 7.0 (m, 1 H, vinyl), 8.0, 7.4, 6.8 (m, 3 H, furan). Anal. Calcd: C, 73.15; H, 7.37. Found: C, 73.41; H, 7.14.

Synthesis of Perillaketone (30). To a solution of 0.6 g of **29** in 100 mL of ethanol was added 60 mg of 5% palladium on carbon and the mixture was hydrogenated for 1 h. The solution was filtered through celite and evaporated in vacuo to give 0.4 g (66%) of perillaketone (30) identical with authentic material: NMR ($CDCl_3$, Me_4Si) δ 2.71 (t, 2 H, J = 8 Hz, $-COCH_2-$), 0.7–2 (m, 7 H, aliphatic), 6.7–8.1 (m, 3 H, furan).

2-Phenyl-*trans*-2-heptenal (32). To 3.5 g of *N,N*-dimethylatropaldehyde (**31**)[12] was added 150 mL of dry tetrahydrofuran (Linde 4A Sieves) and the solution was cooled to −30 °C. Under nitrogen was added 9.0 mL of 2.4 M *n*-BuLi reagent in 2 min and the reaction mixture was stirred to room temperature over 2 h. To the solution was added 100 mL of 1 N HCl followed by 500 mL of ether. The ether extract was dried (magnesium sulfate) and removed in vacuo to give 1.3 g (35%) of **32** as an amber oil. The analytical sample was obtained by column chromatography over 45 g of silica gel (Woelm Act. 1) using dichloromethane as the eluant: NMR ($CDCl_3$, Me_4Si) δ 0.6–1.65 (m, 7 H, $CH_3(CH_2)_2$), 2.33 (q, 2 H, J = 8 Hz, $-CH_2C=C-$), 6.67 (t, 1 H, J = 8 Hz, $-CH=C<$), 6.85–7.5 (m, 5 H, aromatic), 9.50 (s, 1 H, CH=O); M^+ *m/e* 188; n^{25}_D 1.5247.

Scheme III



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Registry No.—**25,** 25564-22-1; **27,** 14313-09-8; **28,** 67382-49-4; **29,** 34348-59-9; **30,** 553-84-4; **31,** 67382-50-7; **32,** 67382-51-8; *N,N*-dimethylformamide dimethyl acetal, 4637-24-5.

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Annelation of Ethyl Propiolate with Ethyl Pipecolate

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In conjunction with studies of the alkaloid slaframine[1] we undertook a search for routes to Δ^2 derivatives of 1-oxooctahydroindolizines. The cycloaddition of ethyl propiolate to ethyl pipecolate (**1**) was formally attractive for this purpose although an earlier attempt by Winterfeldt and Dillinger to effect a similar condensation of dimethyl acetylenedicarboxylate with methyl ethylaminoacetate had met with failure, only an uncyclized Michael adduct being obtained.[2,3] Nevertheless, we were encouraged by molecular model studies which suggested that the geometry of the zwitterionic intermediate resulting from addition of **1** to the acetylenic ester would be particularly conducive to annelation.

Treatment of ethyl pipecolate with ethyl propiolate in refluxing ethanol gave Michael adduct **2** in yield >90%. Examination of the NMR spectrum of the crude reaction mixture revealed no more than a trace of a signal that might represent the vinyl proton of the desired 1-oxohexahydroindolizine **3** but when the reaction was repeated in hexane at ambient

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