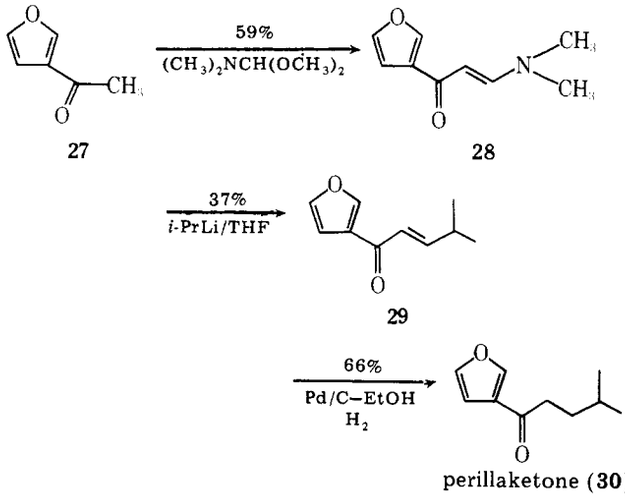
Scheme II. A Total Synthesis of Perillaketone



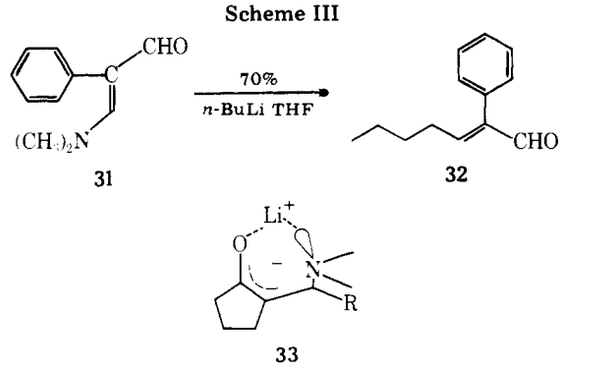
***trans*-3-[3-(Dimethylamino)acryloyl]furan (28).** A mixture of 3.30 g (0.03 mol) of 3-acetylfuran (**27**) and 25.0 mL of *N,N*-dimethylformamide dimethyl acetal was heated under reflux for 12 h. The mixture was evaporated in vacuo and the residue was crystallized under pentane. Recrystallization 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



Acknowledgments. We thank Professor Leo A. Paquette of Ohio State University for critical evaluation of the work. Professors Jack E. Baldwin of M.I.T. and Edward C. Taylor of Princeton University are thanked for helpful discussions. We thank Mr. Paul L. Unger for providing spectrographic support and Mr. George M. Maciak for combustion analyses.

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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(8) *E* stereochemistry is assigned to the enamino ketones by analogy with 1-dimethylamino-2-benzoylethylene derived from acetophenone, in which $J_{H_\alpha H_\beta}$ = 11.5 Hz. *E* stereochemistry is assigned on the same basis to the α,β-unsaturated ketones. See H. Meerwein, W. Florian, G. Schön, and G. Stopp, *Justus Liebigs Ann. Chem.*, **641,** 1 (1961), for use of DMF acetals as formylating agents.
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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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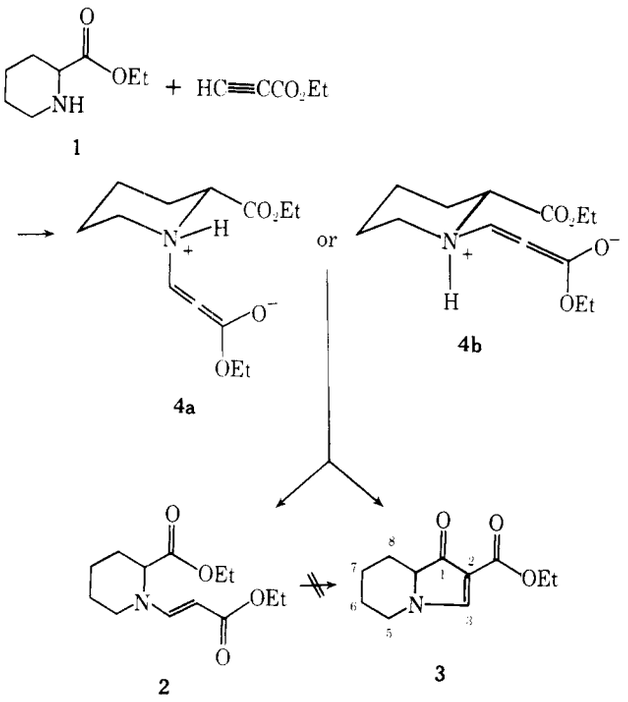
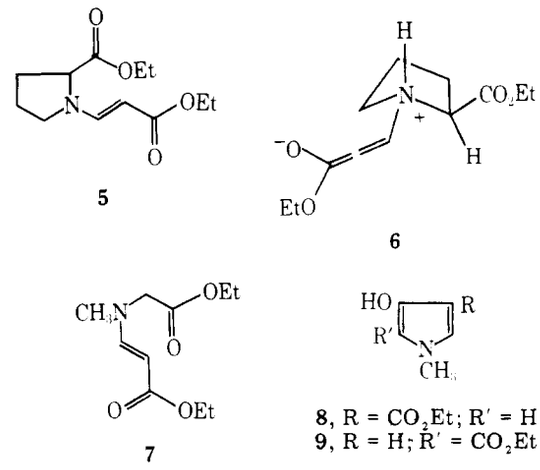
Scheme I



temperature, the NMR spectrum showed, in addition to **2**, a substantial amount of a second product having a vinyl proton singlet at 6.75 ppm. Integration indicated the molar ratio of **2** and the new compound in the product mixture to be 63:37. When refuxing hexane (~70 °C) was employed as the solvent, the latter compound represented 54% of the product mixture; with refluxing heptane (~100 °C) it reached 74%. GLC showed only the two products being formed and these compounds were separated by preparative GLC although substantial losses, particularly of **3**, were experienced during the process due to air-oxidation and thermal degradation. The new compound was identified as **3** on the basis of spectral data and elemental analyses. Compounds **2** and **3** are both formed by pathways which are irreversible under the reaction conditions, the relative yields being independent of reaction times. Moreover, **2** when resubmitted to refluxing heptane was not converted into **3**, proving that it is not a precursor of **3** in the condensation reaction.

Attack of ethyl propiolate on ethyl pipecolate probably occurs axially to give cis zwitterion **4a** having the two substituents on the same face of the piperidine ring, although trans zwitterion **4b** arising by equatorial attack would also be capable of cyclization. In ethanol, proton transfer from solvent intercepts **4** before intramolecular acylation can occur but in hydrocarbon solvents, where the zwitterion is the only source of protons, acylation competes effectively with inter- and intramolecular proton transfer.

The structure of the zwitterionic intermediate appears to be crucial to this annelation reaction. Only Michael adduct **5** was obtained from the condensation of ethyl propiolate with the ethyl ester of proline, probably because eclipsing interactions hinder cis attack of ethyl propiolate on the proline ester. Trans zwitterion **6**, which forms instead, is structurally incapable of cyclization and consequently undergoes a proton transfer to give **5**. Cyclization is unlikely with zwitterionic intermediates which are conformationally mobile. Although the condensation of methyl ethylaminoacetate with dimethyl acetylenedicarboxylate was carried out by Winterfeldt and Dillinger in *tert*-butyl alcohol which precluded cyclization, we have obtained a similar result from the condensation of ethyl methylaminoacetate with ethyl propiolate in refluxing



heptane. The latter reaction gave predominantly Michael adduct **7**; a trace of a second component, possibly pyrrole **8** or **9**, was obtained but the compound was unstable and was not fully characterized.

Experimental Section

NMR spectra were obtained with a JEOL MH-100 100 MHz spectrometer operating in the external lock mode. Spectra were obtained in dilute solution in $CDCl_3$ or CCl_4. Mass spectra (70 eV) were obtained with an LKB-9000 spectrometer using the direct inlet. Elemental analyses were performed by Galbraith Laboratories, Inc., Knoxville, Tenn.

Condensations of Ethyl Propiolate with Esters of Amino Acids. Ethyl Pipecolate. A solution of ethyl propiolate (0.4 g, 4.1 mmol) in 2 mL of heptane was added dropwise to 0.64 g (4.1 mmol) of ethyl pipecolate in refluxing heptane (10 mL) under N_2. After 15 min, a sample was removed and added to $CDCl_3$; the NMR spectrum showed the reaction was essentially complete and had given a 24:76 mixture of **2** and **3**. Heptane was removed under a stream of N_2 and the residue was partitioned by GLC on a column of 3% OV-17 (Chromosorb W) at 240 °C. Compound **3**, ethyl 1-oxo-1,5,6,7,8,8a-hexahydroindolizine-2-carboxylate, eluted first: NMR δ 1.3 (t) and 4.3 (q, C_2H_5), 6.75 (s, not exchangeable with D_2O, 3-CH), the remaining protons appeared in unresolved multiplets at 3.9, 2.7, and 2.0–1.6; MS *m/e* 209 (parent), 163, 135, 107. The compound was sensitive to oxygen and had to be stored under N_2 at −10 °C.

Anal. Calcd for $C_{11}H_{15}NO_3$: C, 63.16; H, 7.18,; N, 6.70. Found: C, 62.93; H, 7.11; N, 6.63.

Compound **2** was retained 35% longer than **3**: NMR δ 1.3 (2 × t) and 4.3 (2 × q, 2 × C_2H_5), 4.61 (d, J = 13 Hz, -CH=CHCO-), 7.68 (d, J = 13 Hz, -CH=CHCO-), the remaining protons appeared in unresolved multiplets at 3.18, 2.22, 2.12, and 1.9–1.5 (the proton at 4.61 underwent exchange ($t_{1/2}$ ~ 20 min) with D_2O; the doublet at 7.68 collapsed simultaneously to a singlet.); MS *m/e* 255 (parent). The compound was sensitive to oxygen and was stored under N_2 at −10 °C.

Anal. Calcd for $C_{13}H_{21}NO_4$: C, 61.18; H, 8.24; N, 5.49. Found: C, 61.31; H, 8.12; N, 5.44.

Proline Ethyl Ester. Similar treatment of the ethyl ester of proline gave exclusively Michael adduct **5**: NMR δ 1.25 (2 × t) and 4.15 (2 × q, 2 × C_2H_5), 4.61 (d, J = 13 Hz, -CH=CHCO-), 7.65 (d, J = 13 Hz, -CH=CHCO-), the remaining protons appeared in unresolved multiplets at 3.7–3.2 and 2.3–1.8; MS *m/e* 241 (parent). The compound was air sensitive.

Anal. Calcd for $C_{12}H_{19}NO_4$: C, 59.75; H, 7.88. Found: C, 59.49; H, 7.80.

Ethyl Methylaminoacetate. Similar treatment of the ethyl ester of methylaminoacetic acid gave 90% of Michael adduct **7**: NMR δ 1.27 (2 × t) and 4.19 (2 × q, 2 × C_2H_5), 2.96 (s, NCH_3), 3.89 (s, CH_2), 4.64 (d, J = 13 Hz, -CH=CHCO-), 7.43 (d, J = 13 Hz, -CH=CHCO-); MS *m/e* 215 (parent).

Anal. Calcd for $C_{10}H_{17}NO_4$: C, 55.81; H, 7.91. Found: C, 55.62; H, 7.81.

A more volatile component was obtained from the reaction in very low yield and is provisionally assigned as cycloadduct **8** or **9**: NMR δ 1.3 (t) and 4.3 (q, C_2H_5), 3.6 (s, NCH_3), 6.2 (d) and 6.9 (d, ring CH's, J = 2.8 Hz); MS *m/e* 169 (parent). The compound was highly air sensitive and was not characterized further.

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Registry No.—**1**, 15862-72-3; **2**, 67425-79-0; **3**, 67425-80-3; **5**, 67425-81-4; **7**, 67425-82-5; **8**, 65172-11-4; **9**, 65171-90-6; ethyl propiolate, 623-47-2; proline ethyl ester, 5817-26-5; methylaminoacetic acid ethyl ester, 13200-60-7.

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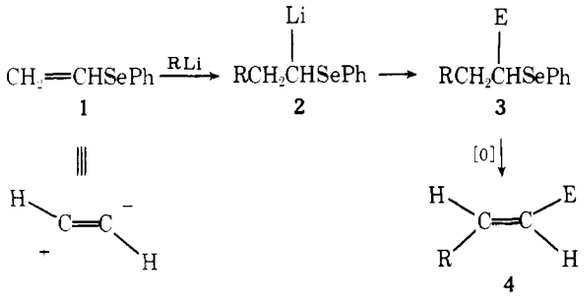
Communications

Vinyl Phenyl Selenide: A $^{+}CH{=}CH^{-}$ Synthon[1]

Summary: Vinyl phenyl selenide (1) may be utilized as a $^{+}CH{=}CH^{-}$ synthon by reaction with alkyllithiums, trapping of the resulting α-lithioalkyl phenyl selenides **2** with electrophiles to give **3**, and oxidative elimination of phenylselenenic acid to produce the disubstituted alkenes **4**.

Sir: The use of a variety of synthons for the formation of new carbon to carbon bonds is a well-established strategy in synthetic organic chemistry. In this communication we wish to report the use of vinyl phenyl selenide (1) as a $^{+}CH{=}CH^{-}$ synthon (Scheme I).[2]

Scheme I



The addition of alkyllithiums to a number of vinyl derivatives of second-row elements in their lower oxidation states has been reported.[3] We felt that such additions to vinyl phenyl selenides would be particularly useful for the following reasons: (1) the ability of a phenylseleno group to stabilize an adjacent carbanion and the reaction of these carbanions with a variety of electrophiles has been demonstrated;[4] (2) subsequent to performing its function, the phenylseleno group may be easily removed via oxidative elimination of phenylselenenic acid to generate alkenes, often regio- and stereospecifically;[5] and (3) the requisite vinyl phenyl selenides are readily available.[6]

Although vinyl phenyl selenide (1) is unreactive toward both *n*-Bu_2CuLi and *n*-BuMgBr, alkyllithiums readily add to 1[7] in dimethoxymethane or diethyl ether at 0 °C to give the α-lithioalkyl phenyl selenides **2**, which may be trapped by electrophiles to give the substituted alkyl phenyl selenides **3**; oxidative elimination of phenylselenenic acid for instances in which the regiospecificity is unambiguous (e.g., E = > C=O or >COH) leads to the formation of the *E*-disubstituted alkenes **4** in good overall yield (Table I).[8]

Since the reaction of alkyllithiums with 1 can also lead to α-deprotonation[9] or carbon–selenium bond cleavage,[10] the proper choice of reaction conditions is essential for the success of the desired addition reaction (Scheme II). In particular,

Table I. Alkyllithium Addition–Electrophile Trapping with Vinyl Phenyl Selenide[a]

entry	RLi	electrophile	E	% yield 3	% yield 4
a	*n*-BuLi	D_2O	D–	97	
b	*n*-BuLi	CH_3I[b]	CH_3–	95	
c	*n*-BuLi	*n*-$C_{10}H_{11}Br$[b]	*n*-$C_{10}H_{21}$–	80	
d	*n*-BuLi	PhSeBr	PhSe–	84	*c*
e	*n*-BuLi	$(CH_3)_3SiCl$	$(CH_3)_3Si$–	90	*d*
f	*n*-BuLi	PhCHO	PhCH(OH)–	71	75[h]
g	*n*-BuLi	CH_3COCH_3	$(CH_3)_2C(OH)$–	60	83[h]
h	*n*-BuLi	$PhCOCH_3$	$PhC(CH_3)(OH)$–	*e*	50[f,h]
i	*n*-BuLi	PhCN	PhCO–	*e*,*g*	61[f,h]
j	*i*-PrLi	D_2O	D–	92	
k	*i*-PrLi	CH_3COCH_3	$(CH_3)_2C(OH)$–	72	81[h]
l	*i*-PrLi	$(CH_3)_3SiCl$	$(CH_3)_3Si$–	86	*d*
m	*t*-BuLi	D_2O	D–	85	

[a] Yields refer to isolated, purified products. See ref 8. All reactions utilize 1.2 equiv of alkyllithium and 1.2–1.5 equiv of electrophile (except D_2O quenches). Reactions with *n*-BuLi were run in dimethoxymethane; reactions with *i*-PrLi and *t*-BuLi were run in diethyl ether. [b] 1 equiv of HMPA was added with the electrophile. [c] Bis(phenylseleno) acetals may be hydrolyzed to the corresponding aldehydes; thus, 1 is also a $^{+}CH_2CHO$ synthon. [d] Oxidation of (α-trimethylsilyl)alkyl phenyl selenides affords the corresponding aldehydes: K. Sachdev and H. S. Sachdev, *Tetrahedron Lett.*, 4223 (1976). [e] Intermediate not isolated. [f] Overall yield from 1. [g] Hydrolyzed with 5% HCl (75 °C, 15 min) prior to oxidation–elimination. [h] Only the *E* isomer was produced.

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