

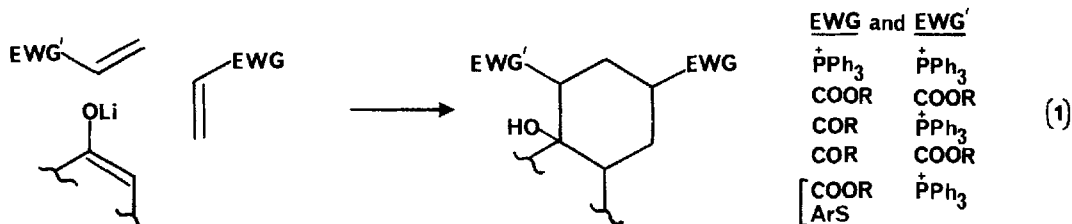
**SEQUENTIAL MICHAEL-MICHAEL-RING CLOSURE REACTIONS FOR 3-DIFFERENT-COMPONENT,
 ONE-POT, 2+2+2 CONSTRUCTION OF ACYLCYCLOHEXENES AND AN ACYLCYCLOHEXANOL.**

Gary H. Posner* and Shu-Bin Lu, and Edward Asirvatham

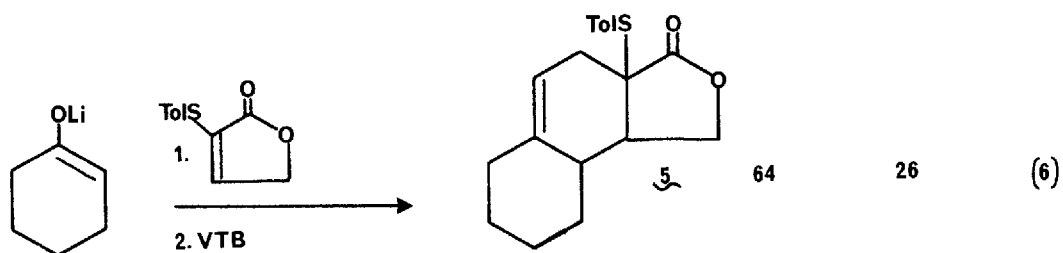
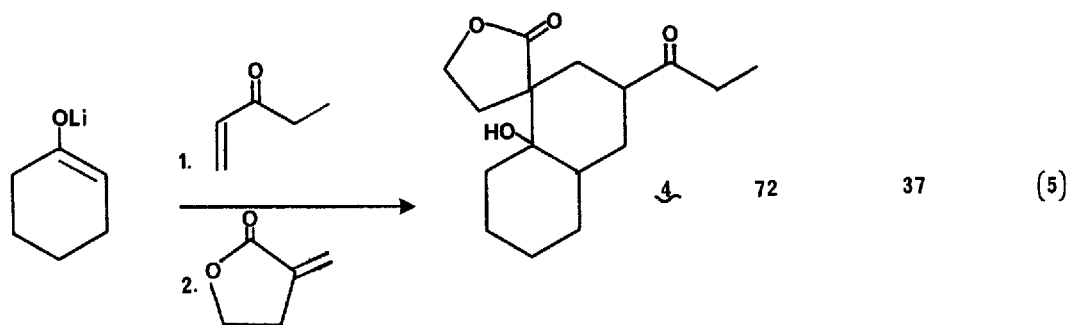
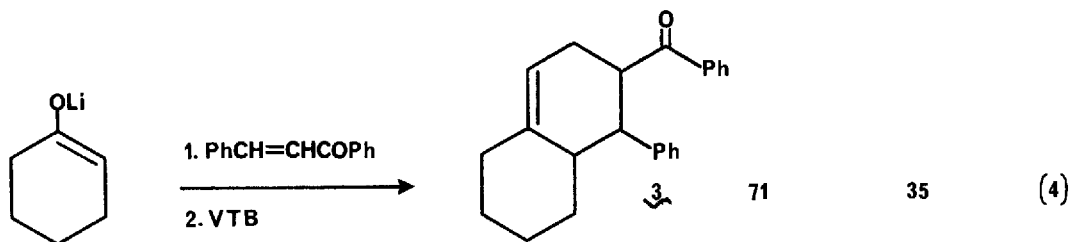
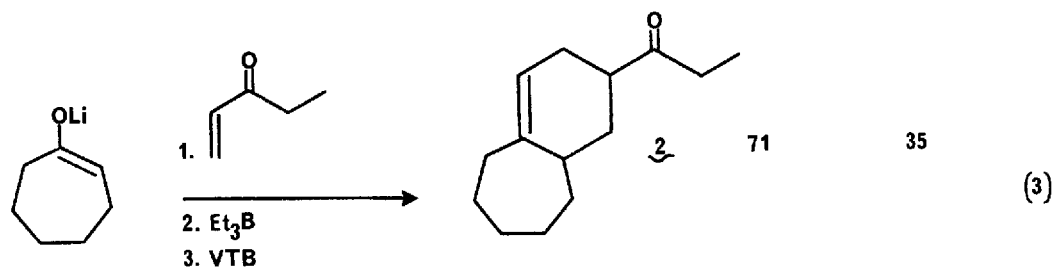
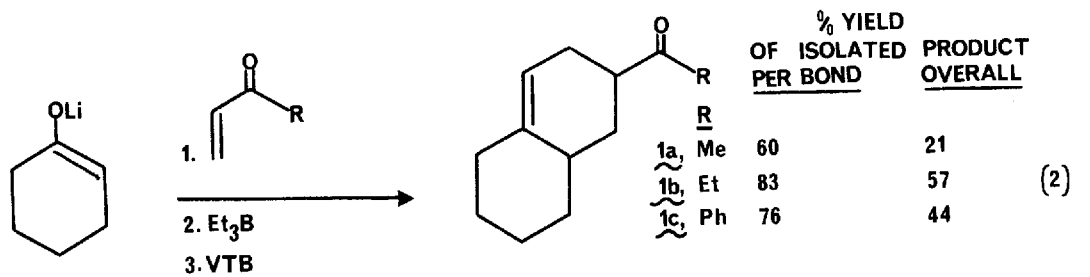
Department of Chemistry, The Johns Hopkins University, Baltimore, Maryland 21218.

Summary: Two different ketones and a vinylphosphonium salt, separately two different ketones and an acrylate-type ester, and separately a ketone, an unsaturated lactone and a vinylphosphonium salt are linked together in one pot to form new 6-membered carbocycles with average yields of 60-83% per each of three new carbon-carbon bonds (eqs. 2-6).

Controlled formation of several carbon-carbon bonds in one reaction vessel is an efficient and rapid way of converting simpler molecules into structurally more complex molecules. We have recently reported such a procedure involving sequential Michael-Michael-Ring Closure (MIMIRC) reactions for one-pot, 2+2+2 construction of phosphorus-substituted cyclohexenes¹ and of alkoxycarbonyl-substituted cyclohexanols.² In both cases, as represented in eq. 1, a ketone lithium enolate added to two equivalents of the same Michael acceptor, $\text{CH}_2=\text{CHEWG}$, in which the electron-withdrawing group (EWG) was either $-\text{P}^+\text{Ph}_3$ or $-\text{COOR}$ and in which the culminating ring closure step was either a Wittig olefination or an aldol condensation. We have now succeeded in applying this type of MIMIRC sequence to the coupling of three different components: two different ketones and a vinylphosphonium bromide, separately two different ketones and an acrylate-type ester, and separately a ketone, a 2-arylthio-4-butenolide and a vinylphosphonium salt (eq. 1).



Conventional wisdom indicates that Michael addition of a ketone lithium enolate to a vinyl ketone under aprotic conditions leads to a polymer.³ To circumvent this problem, Stork and Ganem introduced α -silylenones as tamed Michael acceptors which could be used effectively



in Robinson annulations involving single Michael additions.⁴ Recently, however, Ziegler and Hwang showed that some reactive vinyl ketones undergo single Michael additions by ketone lithium enolates in aprotic media often without serious undersirable polymerization.⁵ We found that cyclohexanone lithium enolate in tetrahydrofuran (THF) at -78°C underwent a single Michael addition to methyl, ethyl, and phenyl vinyl ketones⁶ to give a new enolate ion which, in the presence of triethylboron,¹ added to vinyltriphenylphosphonium bromide (VTB) to give, after intramolecular Wittig cyclization, acylcyclohexene annulation products 1a-1c with average yields of 60-83% per new carbon-carbon bond (eq. 2).^{7,8} Only in the case of methyl vinyl ketone was polymer observed in significant quantity; somewhat better results were obtained using methyl α -trimethylsilylvinyl ketone (70% average yield per each new carbon-carbon bond). In a similar 2+2+2 MIMIRC sequence, cycloheptanone lithium enolate reacted with one equivalent of ethyl vinyl ketone, with triethylboron, and then with VTB to give acylcyclohexene annulation product 2 with an average yield of 71% per new carbon-carbon bond (eq. 3).⁸ Even a β -substituted vinyl ketone could be used successfully as the first Michael acceptor in this sequence: cyclohexanone, chalcone, and VTB gave regiospecifically tetra-substituted cyclohexene 3 with an average yield of 71% per new carbon-carbon bond (eq. 4).⁸

This one-pot multiple carbon-carbon bond-forming process can be achieved also by combining one equivalent each of two different ketones and an acrylate-type ester. Cyclohexanone lithium enolate added to ethyl vinyl ketone in THF at -78°C and the resultant acyclic enolate intermediate added to α -methylene γ -butyrolactone to produce acylcyclohexanol annulation product 4 with an average yield of 72% per new C-C bond (eq. 5).⁸ Adduct 4 represents the kind of synthetically useful, richly-functionalized, tetra-oxygenated molecule which can be assembled efficiently, rapidly, and conveniently by this three-different-component coupling process. Each of the three functional groups in adduct 4 (ketone, lactone, and hydroxyl group) can be manipulated chemospecifically, and formation of the third C-C bond in adduct 4 via an aldol condensation represents construction of a hindered spiro-fused β -hydroxycarbonyl system.²

The preliminary results reported here indicate that 2+2+2 MIMIRC sequences can be interrupted after only one Michael addition occurs when vinyl ketones are used as the initial Michael acceptors. Finally, equation 6 represents one example in which a 2+2+2 MIMIRC sequence was interrupted after initial Michael addition to 2-toluenethio-4-butenolide; com-

pletion of the MIMIRC process with VTB led to acylcyclohexene 5 with an average yield of 64% per new carbon-carbon bond.⁸ Further examples of this 3-different-component, 2+2+2, MIMIRC coupling process will add to the already clear, high synthetic potential of this procedure.^{9,10}

ACKNOWLEDGEMENT

We thank the donors of the Petroleum Research Fund, administered by the American Chemical Society, for generous financial support.

REFERENCES

1. Posner, G. H. and Lu, S.-B. J. Am. Chem. Soc., **1985**, 107, 1424.
2. Posner, G. H., Lu, S.-B., Asirvatham, E., Silversmith, E. F. and Shulman, E. M., J. Am. Chem. Soc., in press.
3. (a) Gawley, R. E., Synthesis, **1976**, 777;
(b) Wakselman, C. and Mondon, M., Tetrahedron Lett., **1973**, 4285.
(c) Dionne, G. and Engel Ch. R., Can. J. Chem., **1978**, 56, 419.
4. Stork, G. and Ganem, B., J. Am. Chem. Soc., **1973**, 95, 6152.
5. Ziegler, F. E. and Hwang, K.-J., J. Org. Chem., **1983**, 48, 3349.
6. Floyd, J. C., Tetrahedron Lett., **1974**, 2877.
7. A typical procedure is as follows: To a dry 100 ml flask fitted with a magnetic stirring bar, an argon inlet, and a serum cap and charged with 1-trimethylsilyloxycyclohexene (272 mg, 1.6 mmol) in 2.5 ml of dry THF was added MeLi in Et₂O (1.1 ml, 1.55 M, 1.7 mmol) over 2 minutes at 0°C. The reaction mixture was warmed to 25°C with stirring. After 1 hour, the reaction mixture was cooled to -78°C followed by the addition of ethyl vinyl ketone (0.18 ml, 1.8 mmol) over 1 minute. Stirring was continued for 3 hours at -78°C followed by the addition of Et₃B in THF (1.6 ml, 1 M, 1.6 mmol) over 1 minute. Stirring was continued for another 1.5 hour at -78°C. Dilution was achieved by the addition of 57 ml of dry THF. VTB (0.915 g, 97%, 2.4 mmol) in 4 ml of dry DMF was added via syringe pump over 22 hours while maintaining the reaction mixture at -46°C. Stirring was continued at this temperature overnight. Quenching was achieved by adding saturated NaH₂PO₄ and 5 ml of Et₂O. The organic phase was separated and the aqueous phase was extracted with 2 x 100 ml Et₂O. The combined organic solution was dried (anhydrous MgSO₄), filtered, and concentrated. After preparative TLC (40% Et₂O/hexanes) 176.2 mg (57%) of desired product 1b was obtained: NMR (CDCl₃, 80 MHz) δ: 1.04 (3H, t, J=7.3 Hz), 2.49 (2H, g, J=7.3 Hz), 1.0-2.4 (14H) 5.29 (1H, m); IR (CCl₄, cm⁻¹): 1700; High resolution mass spectrum (M⁺): Calcd., 192.1514, Found: 192.1509.
8. Yields are reported for pure products isolated by preparative TLC; all new compounds were fully characterized spectroscopically and by combustion microanalysis and/or high resolution mass spectra.
9. See the following Letter: Posner, G. H. and Asirvatham, E., Tetrahedron Lett., **1986**, 27, 000.
10. cf. Danishefsky, S.; Chackalamannil, S., Harrison, P.; Silvestri, M. and Cole, P., J. Am. Chem. Soc., **1985**, 107, 2474.

(Received in USA 24 October 1985)