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# A Versatile Preparation of α,β-Unsaturated Lactones from Homoallylic Alcohols

**Gary E. Keck,* Xiang-Yi Li, and Chad E. Knutson**

*Department of Chemistry, University of Utah, 315 South 1400 East RM Dock, Salt Lake City, Utah 84112-0850*

*keck@chemistry.chem.utah.edu*

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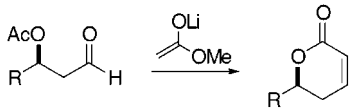
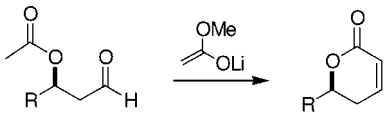
## ABSTRACT




**A new method for the synthesis of α,β-unsaturated lactones from β-acetoxy aldehydes by reaction with the lithium enolate of methyl acetate was developed. The reaction is relatively insensitive to structural changes in the aldehyde substrates. The process was extended to the synthesis of five-ring lactones from α-acetoxy aldehydes. Experimental evidence regarding the mechanism of this one-pot transformation was obtained. The observations are consistent with a pathway involving an initial aldol condensation with subsequent acyl migration, lactonization, and β-elimination and not an enolate equilibration–aldol mechanism.**

The addition of various allylmetals to aldehydes is now well established as an important and useful synthetic method. Stereoselectivity in such reactions has been achieved using "substrate controlled" processes,[1] chiral reagents,[2] and most recently via catalytic enantioselective reactions.[3] Our interest in these reactions and the structures of certain natural products of interest to us has led us to investigate general methods for the conversion of the products of such reactions to α,β-unsaturated lactones. We report herein a general method for accomplishing this transformation as outlined in Scheme 1.

**Scheme 1**




The actual substrates for the reaction are β-acetoxy aldehydes, which are readily available by acetylation of the homoallylic alcohols, followed by processing of the homoallylic acetates to yield the corresponding aldehyde. For most of the cases described herein, this was accomplished by ozonolysis of the olefin followed by reductive workup with either $Me_2S$/MeOH or triphenylphosphine.[4] As expected, the β-acetoxy aldehydes proved to be very labile with respect to β-elimination and decomposed upon attempts at chromatography (Scheme 2).

Reaction of the β-acetoxy aldehydes with the lithium enolate of methyl acetate,[5] initially at −78 °C followed by

(1) For a review on the use of allylmetals, see: Yamamoto, Y.; Asao, N. *Chem. Rev.* **1993**, *93*, 2207. (a) Evans, D. A.; Dart, M. J.; Duffy, J. L.; Yang, M. G.; Livingston, A. B. *J. Am. Chem. Soc.* **1995**, *117*, 6619. (b) Keck, G. E.; Boden, E. P. *Tetrahedron Lett.* **1984**, *25*, 265. (c) Keck, G. E.; Abbott, D. E.; Boden, E. P.; Enholm, E. J. *Tetrahedron Lett.* **1984**, *25*, 3927. (d) Keck, G. E.; Abbott, D. E.; Wiley M. R. *Tetrahedron Lett.* **1987**, *28*, 139. (e) Keck, G. E.; Savin, K. A.; Cressman, E. N. K.; Abbott, D. E. *J. Org. Chem.* **1994**, *59*, 7889.

(2) (a) Brown, H. C.; Vara Prasad, J. V. N.; Zee. S.-H. *J. Org. Chem.* **1986**, *51*, 432. (b) Corey, E. J.; Yu, C.-M.; Kim, S.-S. *J. Am. Chem. Soc.* **1989**, *111*, 5495. (c) Roush, W. R.; Park, J. C. *J. Org. Chem.* **1990**, *55*, 1143. (d) Hafner, A.; Duthaler, R. O.; Marti, R.; Rihs, G.; Rothe-Streit, P.; Schwarzenbach, F. *J. Am. Chem. Soc.* **1992**, *114*, 2321. (e) Marshall, J. A.; Gung, W. Y. *Tetrahedron* **1989**, *45*, 1043.

(3) (a) Keck, G. E.; Tarbet, K. H.; Geraci, L. S. *J. Am. Chem. Soc.* **1993**, *115*, 8467. (b) Keck, G. E.; Geraci, L. S. *Tetrahedron Lett.* **1993**, *34*, 7827. (c) Keck, G. E.; Krishnamurthy, D.; Grier, M. C. *J. Org. Chem.* **1993**, *58*, 6543. (d) Mikami, K.; Terada, M.; Nakai, T. *J. Am. Chem. Soc.* **1989**, *111*, 1940. (e) Costa, A. L.; Piazza, M. G.; Tagliavini, E.; Trombini, C.; Umani-Ronchi, A. *J. Am. Chem. Soc.* **1993**, *115*, 7001. (f) Keck, G. E.; Krishnamurthy, D. *Org. Synth.* **1998**, *62*, 12.

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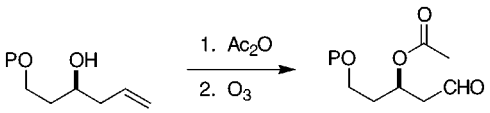
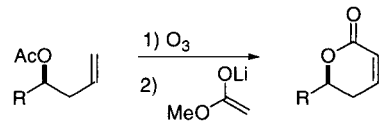
**Scheme 2**

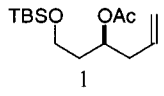
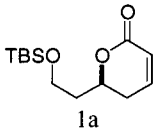
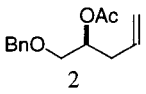
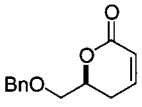
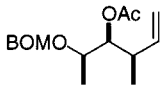
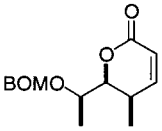
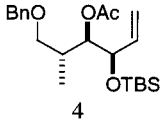
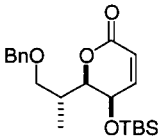
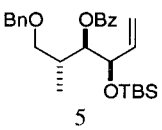
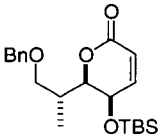
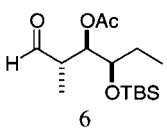
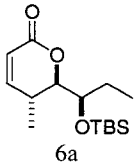



warming to −20 °C and allowing the mixture to stand at that temperature for several hours, afforded the α,β-unsaturated lactones in the isolated yields shown in Table 1. Since the β-acetoxy aldehydes could not be purified without decomposition, these represent overall yields for the two-step process including the aldehyde-forming step of ozonolysis or oxidation, respectively.[4]

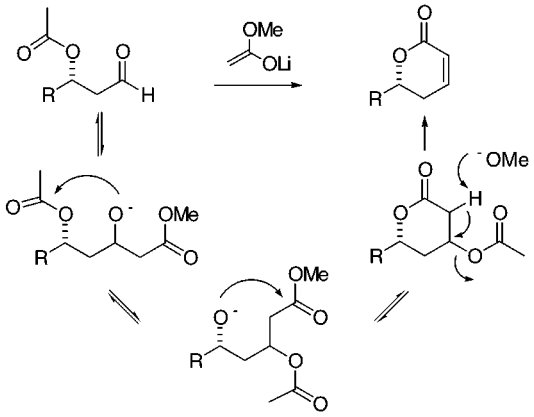
Mechanistically, we envisioned these reactions as proceeding via initial addition of the lithium enolate to the aldehyde carbonyl, followed by acetate migration and subsequent lactonization and β-elimination (Scheme 3). An alternative possibility involving an intramolecular condensation of an acetate enolate generated by a proton transfer−equilibration process is considered extremely unlikely on the basis of the following evidence.

**Table 1.** Preparation of Lactone Products



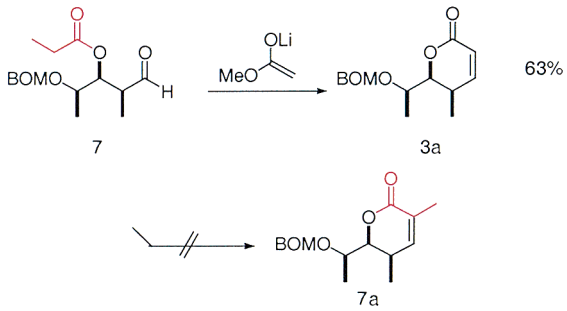

| Entry | Substrate | Product | % Yield |
|---|---|---|---|
| 1 |  1 |  1a | 89 |
| 2 |  2 |  2a | 69 |
| 3 |  3 |  3a | 62 |
| 4 |  4 |  4a | 73 |
| 5 |  5 |  4a | 46 |
| 6 |  6 |  6a | 75 |

**Scheme 3**




First of all, with substrate **5**, conversion to **4a** was found to occur (albeit in lower yield) when the benzoate derivative was used in place of the acetate (Table 1, entries 4 and 5). This is consistent with the suggested pathway, and also with the expectation that the benzoate would undergo the critical migration step less readily than the acetate. Second, when the propionate (**7**) rather than the acetate derivative of substrate **3** was employed in a reaction with the enolate of methyl acetate, **3a** was again obtained in essentially the same yield, demonstrating that the propionate group was lost in the reaction (Scheme 4). This result is compatible with the proposed overall pathway, but not with one involving ester enolate equilibration followed by intramolecular aldol condensation, which would have led to a different product (**7a**) containing an additional methyl group.

**Scheme 4**

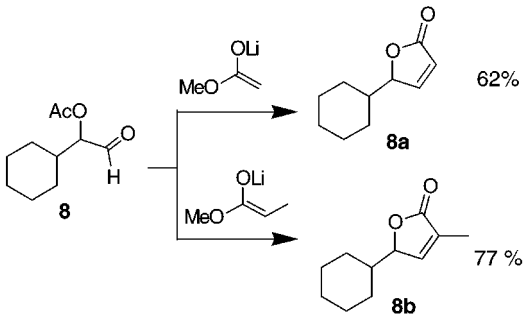



(4) The exceptions were substrate **6**, which was prepared by hydrogenation of **5**, and substrates **10** and **11**. These materials were prepared by deprotection (DDQ) of the corresponding primary PMB ethers, followed by oxidation using the TPAP/NMO protocol of Ley. It should be noted that this approach to the preparation of β-acetoxy aldehydes for use in these reactions is complicated by the very acetate migration which makes the overall reaction possible. The only deprotection/oxidation sequences which we have been able to carry out successfully to date involve either

Attempts to extend this reaction to more highly substituted enolates have not as yet been successful with $\beta$-acetoxy aldehydes as substrates. For example, reaction of substrate **2** with the lithium enolate of methyl *propionate* led largely to $\beta$-elimination with very little of the desired lactone observed. Apparently, nucleophilic addition is retarded sufficiently by the additional steric demand of the substituted enolate that proton transfer from the aldehyde methylene and subsequent elimination competes. Likewise, reaction of the aldehyde substrate **4** (with an α-OTBS group) with the enolate of methyl *propionate* did not afford the desired annulation product. Although $\beta$-elimination was not observed in this case, consistent with the expectation that $\beta$-elimination would be slowed by the presence of the bulky α-substituent, starting material was recovered along with a complex mixture of diasteromeric hydroxy acetates.

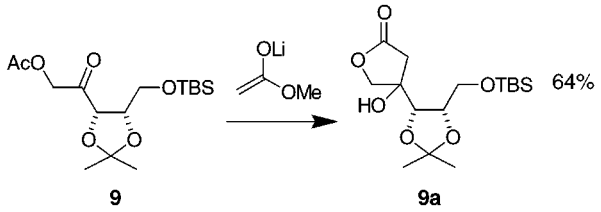
As expected, this pathway for the production of α,$\beta$-unsaturated lactones is not limited to $\beta$-acetoxy aldehydes but can be carried out with α-acetoxy aldehydes as well. Thus substrate **8** was converted to the five-ring lactone **8a** using this protocol in 62% overall yield. With such α-acetoxy aldehydes, the use of more substituted enolates proved viable since competing $\beta$-elimination is not possible. Thus, reaction of aldehyde **8** with the lithium enolate of methyl propionate provided the α-substituted lactone **8b** in 77% yield (Scheme 5).

**Scheme 5**



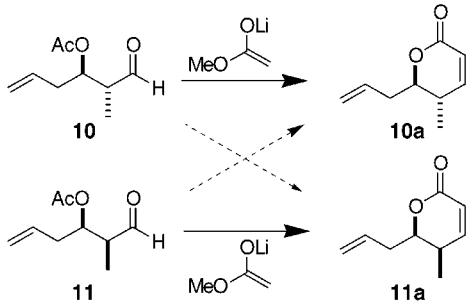

One attempt has been made toward extending this method to the use of an α-acetoxy ketone. Treatment of **9** under the typical reaction conditions resulted in the formation of tertiary alcohol **9a**. Apparently in this particular instance base-induced cleavage of the acetate is faster than $\beta$-elimination. It is presently unclear whether the use of less sterically encumbered ketone substrates will provide unsaturated lactone products (Scheme 6).

**Scheme 6**




Given the ready availability of a variety of homoallylic alcohols via the addition of a diverse array of allyl reagents to aldehydes, we anticipate that the simple method described herein will prove to be of considerable utility in synthesis. In this regard, it is noteworthy that no epimerization of potentially sensitive stereocenters α to the aldehyde was detected in the reactions described herein. To further test for epimerization, the diastereomeric substrates **10** and **11** were each subjected to the reaction conditions and led cleanly to the diastereomeric products **10a** and **11a** with no crossover detected by $^1$H NMR (Scheme 7).

**Scheme 7**

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**Supporting Information Available:** Experimental procedures, characterization data, and NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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hydrogenolysis of benzyl ethers or removal of PMB ethers using DDQ, followed by either TPAP or Dess−Martin oxidation. It is interesting to note that, although the removal of benzyl ethers using DDQ is also well established, the conditions (time and temperature) required are such that adventitious acetate migration complicates these reactions as well.

(5) The enolate of methyl acetate was generated by dropwise addition of methyl acetate to a stirred solution of LDA (typically 0.1 M) maintained at −78 °C and used 15−30 min after addition was completed.