

Nonracemic *Syn*-Selective Aldol Reactions with a Second-Generation Vinylogous Urethane Lithium Enolate

Richard H. Schlessinger,* Yu-Jang Li,¹ and Derek J. Von Langen²

Department of Chemistry, University of Rochester, Rochester, New York 14626

Received February 16, 1996

We reported the reaction of aldehydes with the lithium enolate derived from the vinylogous urethane **1**, substituted with the C_2 -symmetric *trans*-2,5-dimethylpyrrolidine auxiliary of *R,R* stereochemistry, to afford *syn*-lactone products **2** with good *de* values (>90%) (Scheme 1).³ The problems associated with preparation of large amounts of the nonracemic auxiliary contained in **1** discouraged us from using this enolate within the context of total synthesis.⁴ As a result, we set out to develop a more available analogue of **1**, which from our perspective obviated use of a C_2 -symmetric auxiliary.

An X-ray study of the racemic form of the lithium enolate derived from the racemic analogue of the vinylogous urethane **1** gave us the necessary structural information to develop a new and readily available vinylogous urethane enolate system carrying a single chiral arm on the pyrrolidine ring.⁵ This X-ray study shows that the lithium enolate derived from racemic **1** exists as a highly organized structure in which the lithium atom is bonded to the sp^3 -hybridized nitrogen atom contained in the pyrrolidine ring system. This in turn causes the carbon backbone of the enolate (C_1 – C_4) to be significantly twisted about the C_2 , C_3 bond of the enolate. Additionally, the racemic enolate organizes, in the crystalline state, as a dimer consisting of one part of the *R,R* form of the pyrrolidine ring and one part of the *S,S* form of the pyrrolidine ring, as depicted in the monomeric structures **3** and **4**, respectively (Figure 1).

It is important to note that neither the alternative twist structure, **5**, for the *R,R* form of the enolate nor the alternative twist structure, **6**, for the *S,S* form of the enolate was found. As indicated in structures **5** and **6**, a severe nonbonded interaction occurs between the C_4 vinyl hydrogen atom and the equatorial and proximal methyl group held on the pyrrolidine ring—precluding the existence of these species.

From the above observations, we felt that a system such as the vinylogous urethane **7**, which contains a readily available nonracemic auxiliary, should afford *syn*-lactone products on condensation with aldehydes.⁶ We held this notion to be valid, since we felt that on deprotonation **7** would likely organize into the enolate structure **8** (depicted as a monomer) and that its alternative twist structure **9** would not exist, again due to a severe nonbonded interaction between the C_4 vinyl hydrogen atom and the equatorial and proximal chiral

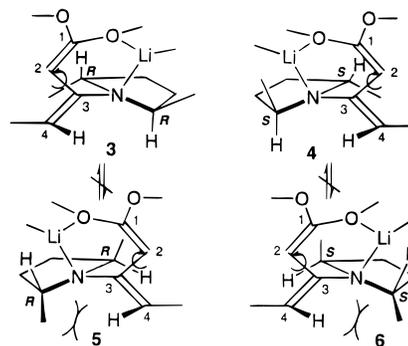
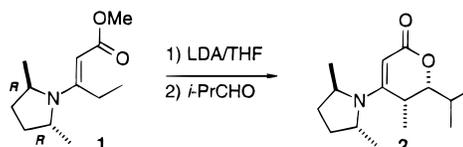
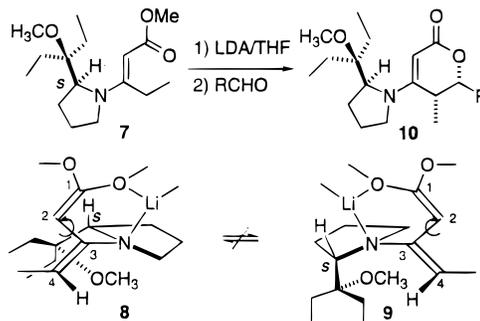


Figure 1.

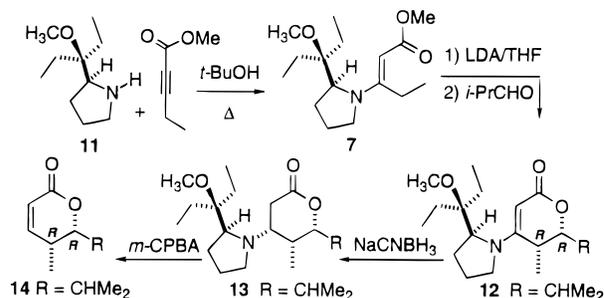
Scheme 1



Scheme 2



Scheme 3



arm held on the pyrrolidine ring. Herein, we wish to report that the lithium enolate derived from the vinylogous urethane **7** undergoes condensation with a variety of aldehydes to yield *syn*-lactone products, **10**, possessing very high *de* values (>96%) (Scheme 2).

Vinylogous urethane **7** was prepared by condensing the L-proline-derived amine **11**⁶ with methyl 2-pentynoate in *tert*-butyl alcohol (76%). Deprotonation of **7** with LDA in THF at -78 °C followed by treatment with isobutyraldehyde gave the *syn*-vinylogous urethane lactone **12** (89%) (Scheme 3). The stereoselectivity for this reaction was determined in the following manner. Reduction of **12** with NaCNBH_3 in (1 N HCl/THF) gave the β -amino lactone **13** (100%). Elimination of the amine residue of **13** using *m*-CPBA in pyridine gave rise to the unsaturated lactone **14** (82% from **12**).

Both the *de* and *ee* of lactone **14**, and hence of the vinylogous urethane lactone **12**, were determined by

(1) Current address: Department of Chemistry, Rensselaer Polytechnic Institute, Troy, NY 12180.

(2) Current address: Merck Research Laboratories, P.O. Box 2000, Rahway, NJ 07065.

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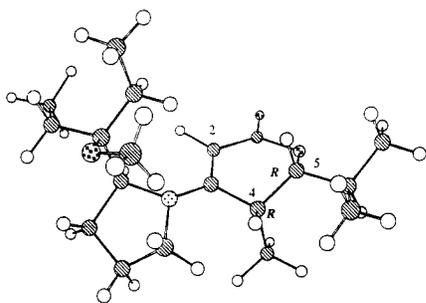
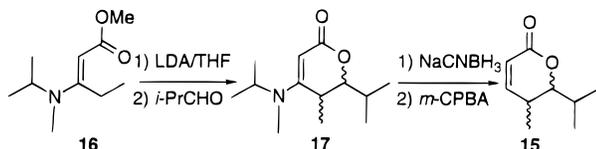


Figure 2.

Scheme 4



comparison with a racemic mixture of the *syn* and *anti* forms of the lactones **15**. These lactones were obtained by condensation of the lithium enolate generated from the vinylogous urethane **16** and isobutyraldehyde, followed by serial treatment of the product mixture, **17**, with NaCNBH₃ and *m*-CPBA (Scheme 4).⁷ Comparative HPLC analysis of lactones **15**, and the lactone **14**, showed the latter substance to have formed with 99% de (Spherisorb 3 μm normal phase silica gel) and 97% ee (Chiralcel OD or Chiralcel OJ).

The absolute stereochemistry of **12**, and therefore **14**, was determined by single-crystal X-ray analysis of the former. This analysis (Figure 2, Chem 3D Cartesian coordinates regenerated from the X-ray data) reveals the stereochemistry at C₄ and C₅ to be *R,R*. The C₄ methyl residue of **12** occupies a pseudoaxial position on the lactone ring, while the C₅ isopropyl group resides in a pseudoequatorial position. The chiral arm of the amine residue is disposed toward the C₂ position of the lactone ring, while the methoxy group of the chiral arm is positioned over the pyrrolidine ring.

Knowing the absolute configuration of the nonracemic auxiliary of **7** and the absolute configuration of the lactone product **12** provides us with an optical trace of this reaction. In this instance, the *Re* face of the enolate **8**, generated from **7**, reacts with the *Si* face of isobutyraldehyde to give **12**. The same reactive orientation obtains for the conversion of **1** into the lactone product **2** via the enolate species **3**. Thus, in both cases, **8** and **3** appear to react *antiperiplanar* to the lithium nitrogen bond—precluding coordination of the aldehyde to the lithium counterion of these enolates (Figure 3).⁸ The question then arises as to whether species such as **3** or **8**, in terms

(7) Under typical conditions, the vinylogous urethane derived from isopropylmethylamine **16** provides **17** with 3:1 *syn:anti* selectivity. This experimental observation is consistent with the structural findings (X-ray) found for the enolate derived from vinylogous urethane **1**, as well as for the observation that the vinylogous urethane derived from pyrrolidine is exclusively *anti*-selective, whereas the vinylogous urethanes derived from *tert*-butylmethylamine and diisopropylamine are exclusively *syn*-selective.

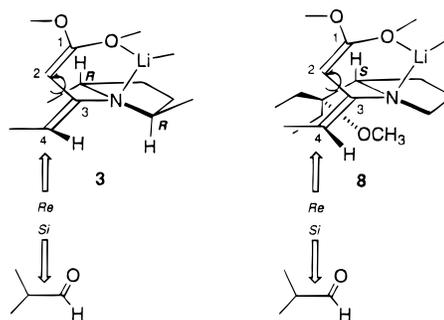
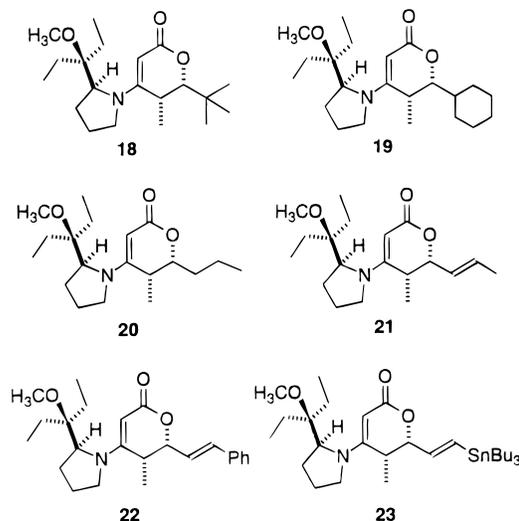


Figure 3.

Scheme 5



of their reaction with aldehydes, should be classified as enolates or as hyperactive enamines. A variety of orientational possibilities for reaction of the *Si* face of aldehydes with the *Re* face of these enolates can be imagined; however, since pertinent experimental evidence is lacking we prefer not to speculate on this point.⁹

Several other vinylogous urethane lactones have been prepared and their chemical yields, de's, and ee's determined. These include vinylogous urethane lactones **18** (83%, de 99%, ee 97%) **19** (83%, 96%, 97%), **20** (57%, 92%, 95%), **21** (74%, 99%, 97%), **22** (74%, 92%, 96%), and **23** (68%, 98%, 97%) (Scheme 5).

Acknowledgment. Financial support of this work by Grant CA-28544 (NIH), by a Sherman Clarke Fellowship (to Y.-J.L.), and by a Merck Sharp and Dohme fellowship (to Y.-J.L.) is gratefully acknowledged.

Supporting Information Available: General experimental procedures and spectral details are provided for vinylogous urethane lactones **10** and **17–23** and lactones **13–15** (4 pages).

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(8) This, of course, assumes that the reactive species in solution is that depicted in structures **8** and **3**. The validity of these enolate structures as the reactive intermediates in solution, particularly as aggregated species, is currently being examined.

(9) For a leading reference on the consideration of transition states for the aldol condensation, see: Bernardi, A.; Gennari, C.; Goodman, J. M.; Volker, L.; Paterson I. *Tetrahedron* **1995**, *51*, 4853.