MICHAEL ADDITION REACTIONS OF UNSATURATED ESTERS WITH LITHIUM ENOLATES DERIVED FROM VINYLOGOUS URETHANES

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Abstract—*The lithium enolate* 1 of vinylogous urethane 2 *undergoes highly diastereoselective conjugate addition reactions with unsaturated esters. The ester enolates arising from conjugate addition can be methylated with high diastereoselectivity.*

Recent reports of diastereoselective conjugate addition reactions of ester[2] and amide[3] enolates with unsaturated esters prompts us to describe our work on the conjugate addition behavior of lithium enolates derived from vinylogous urethanes.[4] For this study, we chose to examine the behavior of the lithium enolate **1** generated by lithium diisopropylamide (LDA) deprotonation of the vinylogous urethane **2**. Enolate **1**, and its analogues have been used in aldol-lactonization reactions that proceed with high diastereoselectivity.[5] The geometry of **1** has been determined, *via* ^{13}C nmr methods, in d_8THF solution; further, the aldol condensation products of **1** have been determined to arise *via* a kinetic process.[6] It was felt that **1** might exhibit the same behavior in conjugate addition reactions with unsaturated esters, and work was commenced to examine this possibility.

Dimethyl fumarate and dimethyl maleate were first examined with enolate **1**. Dimethyl fumarate reacts with **1** (THF/0.5M/15min/-78°C) to give a 9 : 1 ratio of the conjugate addition adducts **3** and **4** (R = methyl) in 90% yield.[7] Using vinylogous urethane enolate **5** (R = *t*-butyl) resulted only in formation of adduct **3** (R = *t*-butyl), again in 90% yield. Detailed ^1H nmr analysis of **3** (R=methyl) permitted a tentative assignment of its structure as *threo* about the C-4-C-5 bond. Dimethyl maleate gave a 9 : 1 ratio of **4** to **3** (R = methyl, 90% yield) respectively, on reaction with enolate **1** while only **4** (R = *t*-butyl, 90% yield)) was obtained with the enolate **5**. A comparison of the ^1H nmr spectra of **4** and **3** suggested that the maleate-derived adduct possessed *erythro* stereochemistry about the C-4-C-5 bond, but again this assignment was only tentative.

In order to unambiguously delineate the stereochemistry possessed by **3** and **4**, we resorted to X-ray analysis. Both **3** and **4** were isolated and found to be pure as viscous oils, hence they were treated with a mixture of $OsO_4/NaIO_4$ in aqueous *t*-butanol followed by treatment with CH_2N_2 to afford the amide diester substances **6** and **7**, respectively. Compound **7** proved to be a crystalline material, mp 68°C, and a single crystal X-ray analysis of it demonstrated it contained *erythro* stereochemistry around the C-4-C-5 bond (Figure 1).[8] Therefore,

compound **4** obtained from either enolate **1** or **5** (R = methyl or *t*-butyl) and dimethyl maleate must possess *erythro* stereochemistry.

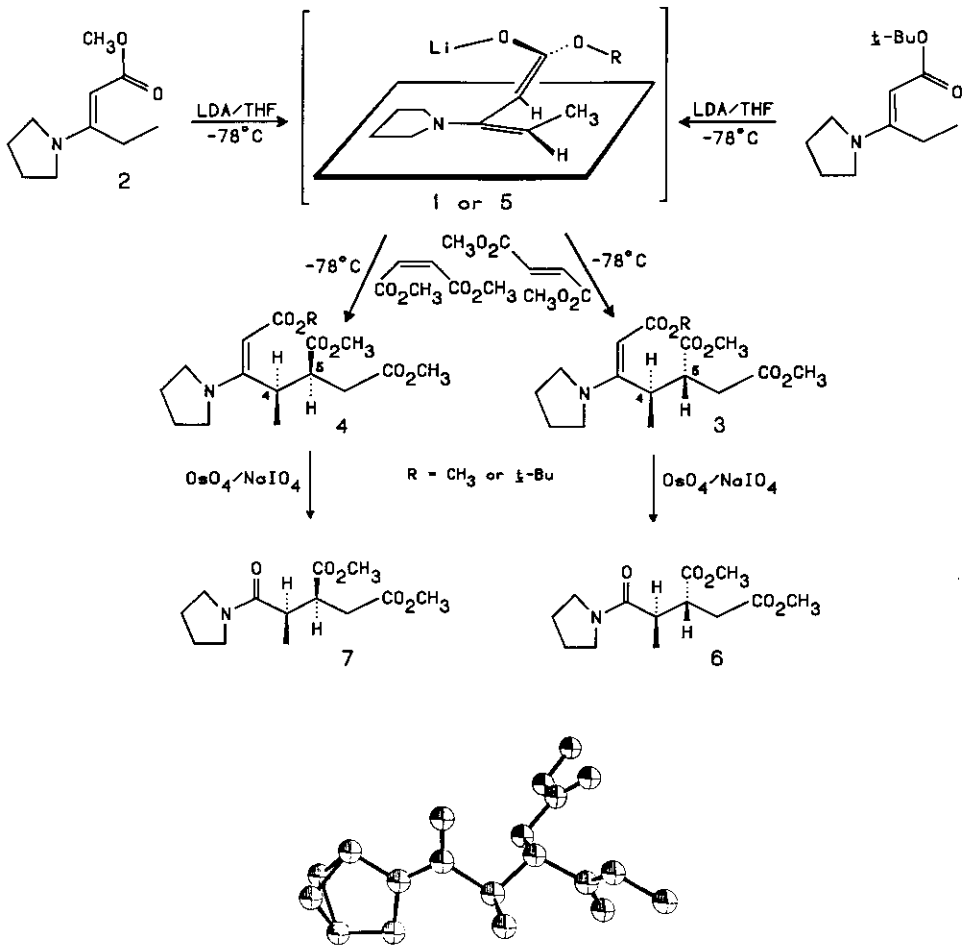
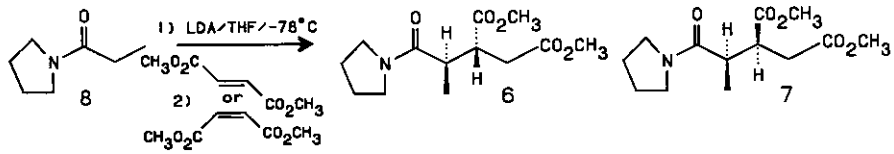
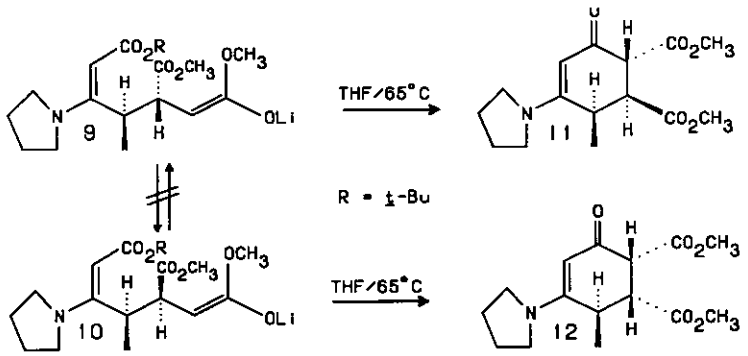


Figure 1

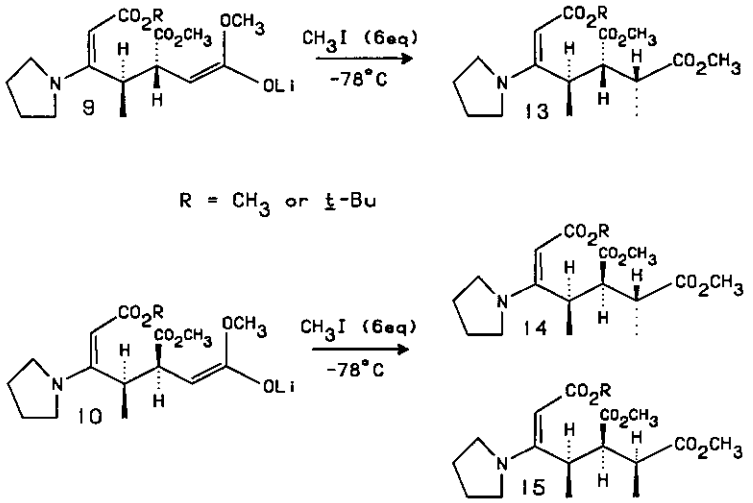
In view of the spectroscopic (^{1}H nmr, ^{13}C nmr, ms, and ir) similarity between adducts **3** and **4**, we assigned **3**, obtained from either **1** or **5** (R = methyl or *t*-butyl) and dimethyl fumarate, *threo* stereochemistry for the C-4-C-5 bond. Further confirmation of the structural interrelationship between adducts **3** and **4** and their degradation products **6** and **7** was obtained by reacting the lithium enolate of the pyrrolidine-derived amide of propionic acid, **8**, with dimethyl fumarate and dimethyl maleate.[9] In the fumarate case, a 1.9 : 1 ratio of **6** and **7** was isolated, while with maleate a 1 : 1.9 ratio of **6** and **7** was obtained. The conjugate addition adducts obtained in this manner were carefully separated by chromatography and found to be identical in all respects to the degradation products **6** and **7** obtained from the adducts **3** and **4**.



We presumed, that the conjugate addition adducts **3** and **4** (R = *t*-butyl) were initially generated at -78°C, *via* a kinetically controlled reaction manifold, as their ester-derived lithium enolate analogues **9** and **10**. By subjecting the enolates **9** and **10** to higher temperatures, we hoped to realize equilibration of their respective *threo* and *erythro* geometries, thereby confirming their kinetic origin. Much to our surprise, **9** and **10** did not show C-4-C-5 bond equilibration at temperatures as high as 22°C. However, at temperatures above 22°C (optimally 65°C), another reaction occurred, namely a Dieckmann condensation, and the products **11** and **12** were isolated from **9** and **10**, respectively. It was also possible to prepare **11** and **12** from the conjugate addition adducts **3** and **4** by deprotonation of the latter with LDA (1 eq/-78°C) followed by heating to 65°C for 12 h.[10] Since the Dieckmann products **11** and **12** formed at 65°C carry the same C-4-C-5 geometry as the conjugate addition adducts **3** and **4** formed at -78°C, we conclude that under the reaction conditions to which these systems were subjected equilibration of the C-4-C-5 bond which was initially formed on generation of the ester enolates **9** and **10**, does not occur. However, in view of the negative nature of these results (*i.e.* no C-4-C-5 bond equilibration), we cannot state with certainty that the conjugate addition geometry observed for adducts **3** and **4** is kinetic in origin.

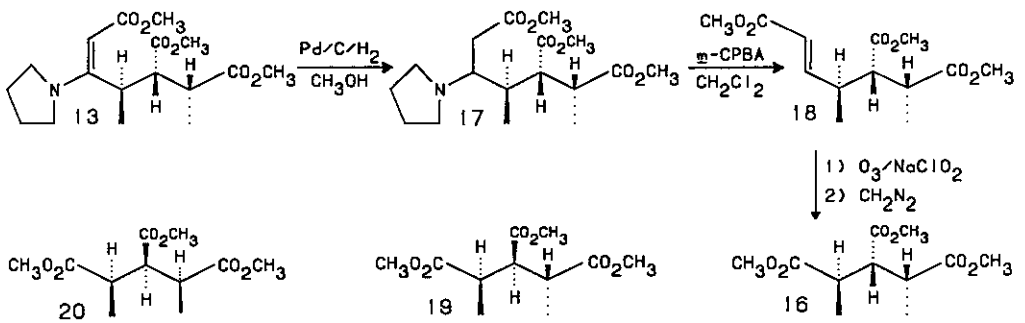


In view of the Dieckmann cyclization discovered for the enolates **9** and **10**, we became interested in utilizing these enolates for other reactions, in particular methylation. Thus, reaction of the vinylogous urethane enolate **1** with dimethyl fumarate at -78°C followed by quenching of the resultant ester enolate **9** with excess methyl iodide at -78°C gave rise to the alkylated adduct **13** in 80% yield.[11] Examination of the ^{1}H nmr spectrum of **13** suggested that methylation at C-6 was face selective to the extent of at least 95%. On the other hand, and somewhat to our surprise, the enolate **10** generated from **1** and dimethyl maleate, upon methylation at -78°C, afforded a 70 : 30 mixture of the products **14** and **15**, respectively.



9 13 10 14 15

The methylated adduct **13** was degraded to the glutarate derivative **16** in the following manner. Hydrogenation of **13** (10% Pd-C/CH_3OH/2200psi H_2/4h) gave the β-pyrrolidino ester **17** which on treatment with *m*-CPBA (CH_2Cl_2/0°C/12h) afforded the unsaturated **E**-ester system **18**. Ozonolysis of **18** followed by oxidation of the

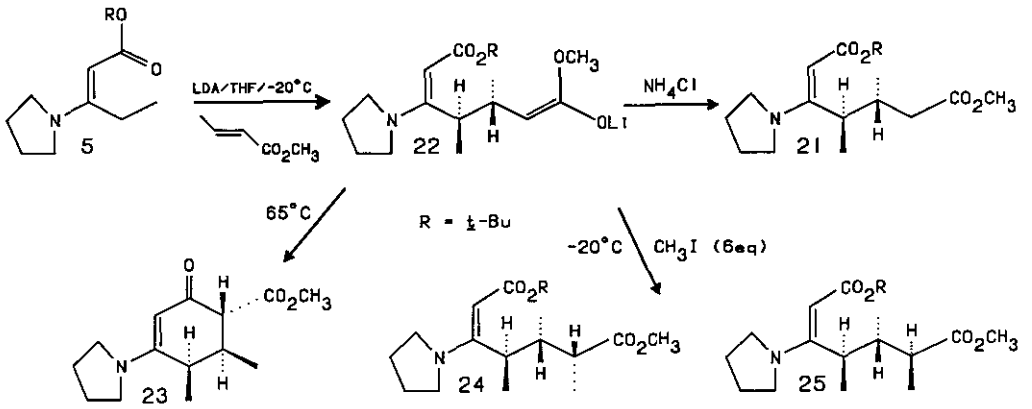


13 17 18 20 19 16

intermediate aldehyde with $NaClO_2$ in *t*-butanol/H_2O and treatment of the resulting acid with CH_2N_2 lead to formation of **16**. The same reaction sequence was applied to the mixture of **14** and **15** and resulted in formation of the glutarates **19** and **20**. After purification, the ^1H nmr spectrum of adducts **16**, **19**, and **20** were recorded, and the symmetry, or lack thereof, of these spectra definitively illuminated their respective structures.

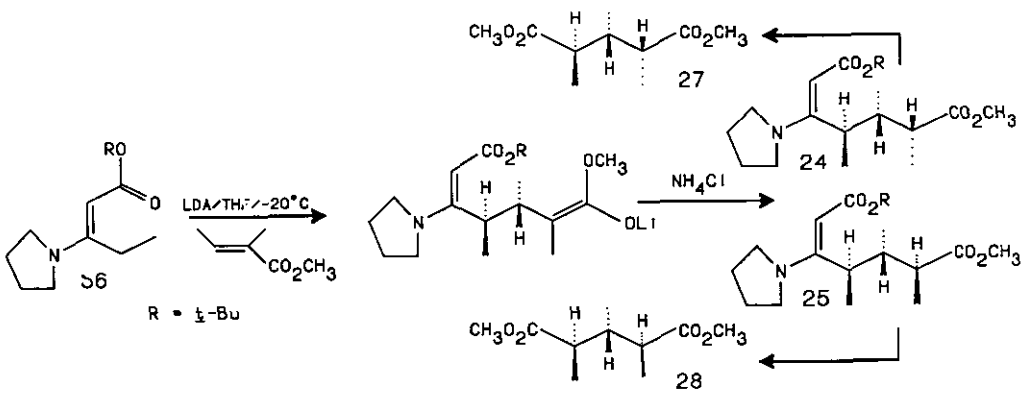
The behavior of **E**-methyl crotonate was also examined in essentially the same manner as the fumarate and maleate ester systems. Using the enolate **5**, rapid reaction with methyl crotonate occurred at -20°C, but not at -78°C. At -20°C, **5** and the crotonate ester gave rise to the conjugate addition adduct **21** as a single *threo* isomer in 80 to 85% yield. Upon warming the reaction mixture to 65°C, the intermediate ester enolate **22**, which arose from conjugate addition, underwent rapid intramolecular Dieckmann cyclization to give compound

23. Methylation of the enolate **22** at -20°C occurs with high facial selectivity giving a 19 : 1 mixture of the C-6 methylated substance **24** and its C-6 epimer **25**, respectively. The highly diastereoselective reaction of **5**



with crotonate and methyl iodide prompted us to study the reaction of **5** with methyl tiglate, the idea being to observe the diastereoselectivity of protonation of the ester enolate **26** which arises from this conjugate addition reaction. Methyl tiglate reacted smoothly with **5** at -20°C, and the conjugate addition-derived enolate, **26**, was quenched at this temperature with aqueous NH_4Cl. This protonation reaction proved remarkably face selective in that a 3 : 17 mixture of the adducts **24** and **25**, respectively, was isolated in 80% yield. The structures of **24** and **25** were demonstrated by conversion of them into their glutarate derivatives **27** and **28** using the reaction protocol previously described followed by ^1H nmr analysis.

The mechanism by which the enolates **1** and **5** undergo both the aldol and conjugate addition reactions is under active study with the major remaining conundrum of counterion involvement as yet unanswered.



ACKNOWLEDGMENT

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4. R. H. Schlessinger, and M. A. Poss, *J. Am. Chem. Soc.*, **1982**, *104*, 357.

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7. Satisfactory spectral and physical data were obtained for all new compounds.

8. It should be noted that the pyrrolidine ring in Figure 1 is disordered.

9. See reference 3.

10. The appropriate types of crossover experiments were not possible with either enolate system; and thus, this method of examining reversible conjugate addition was denied us.

11. For recent examples of conjugate addition reactions followed either by diastereoselective alkylation or by diastereoselective protonation, see a) M. Yamaguchi, M. Tsukamoto, and I. Hirao, *Tetrahedron Lett.*, **1985**, *26*, 1723. b) H. Kawasaki, K. Tomioka, and K. Koga, *Ibid.*, **1985**, *26*, 3031. c) I. Fleming, and J. J. Lewis, *J. Chem. Soc. Chem. Commun.*, **1985**, 149.

12. Work being carried out by Mr. J. R. Tata and Mr. E. J. Iwanowicz.

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