Pergamon

Tetrahedron Letters, Vol. 37, No. 30, pp. 5351-5354, 1996

0040-4039/96 $15.00 + 0.00

PII: S0040-4039(96)01104-5

Synthesis of Quaternary Amino Acids Containing β,γ- as well as γ,δ-Unsaturated Side Chains *via* Chelate-Enolate Claisen Rearrangement

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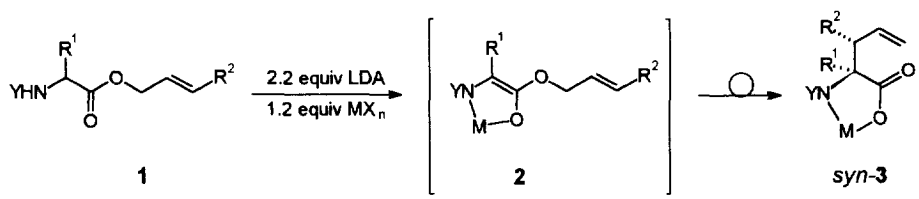
Abstract: Ester enolate Claisen rearrangement of chelated *N*-protected α,β-unsaturated amino acid allylic esters results in a migration of the double bond and the formation of highly unsaturated amino acids in good yields and in a highly diastereoselective fashion.

Among the amino acids containing quaternary carbon centers, the α-alkylated amino acids are an especially interesting class of nonproteinogenic amino acids,[1] particularly in view of their activity as enzyme inhibitors.[2] α-Vinyl amino acids are known to inhibit pyridoxal phosphate-dependent enzymes, and especially, amino acid decarboxylases.[3] Four different types of synthetic approaches to α-vinylic amino acids[4] can be differentiated: a) Oxidation of the corresponding vinylic amino alcohols;[5] b) Direct or indirect introduction of the vinylic side chain onto an amino acid;[6] c) Generation of the vinylic double bond by elimination from suitable precursors like methionine or related compounds;[7] d) Regioselective α-alkylation of α,β–unsaturated amino acid ester enolates with migration of the double bond.[8] γ,δ-Unsaturated amino acids are also of great interest not only as naturally occurring amino acids,[9] but also as intermediates for the synthesis of complex amino acids and peptides.[10] While various methods are known for the synthesis of the α-alkylated amino acids, the sigmatropic rearrangement processes are well suited for the introduction of the unsaturated side chains.[4]

In a previous communication we described a new variation of the ester enolate Claisen rearrangement, one that is especially suitable for α-amino acid synthesis.[11] Deprotonation of *N*-protected amino acid allylic esters (Scheme 1) such as **1** with LDA at -78 °C and subsequent addition of a metal salt (MX_n) presumably results in the formation of a chelated metal enolate **2**, which undergoes Claisen rearrangement upon warming to room temperature, giving rise to unsaturated amino acid **3**.

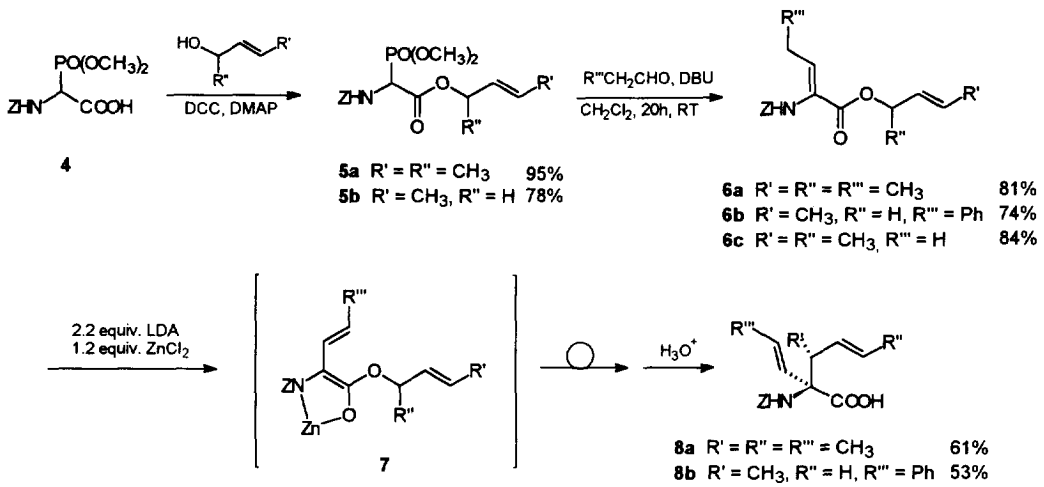


1 **2** ***syn*-3**

Scheme 1

Due to the fixed enolate geometry, as a result of chelate formation, the rearrangement proceeds with a high degree of diastereoselectivity, independent of the substitution pattern and the protecting groups Y used. This method is suitable for the synthesis of sterically highly demanding amino acids containing quaternary carbon centers in the α- as well as in the β-position[12] and can also be applied to peptides.[13]

If this rearrangement procedure is applied not to normal amino acid esters but to allylic esters of α,β-unsaturated amino acids **6**, the di-unsaturated amino acids **8** are obtained, which contain a vinylic as well as an allylic side chain. The corresponding α,β-unsaturated amino acid esters **6** are easily obtained from the dimethoxyphosphinylglycine **4**[14] *via* phosponate condensation as reported by Schmidt *et al.* (Scheme 2).[15]



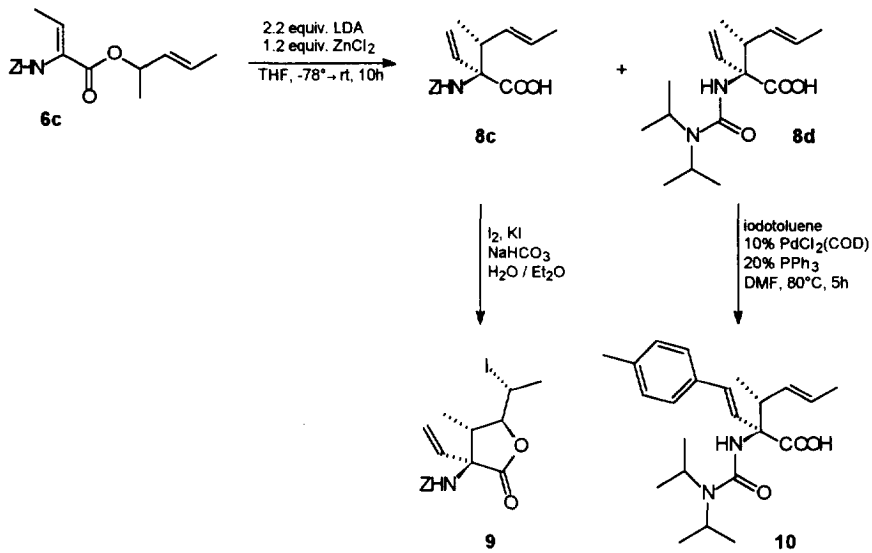
Scheme 2

Especially when diazabicycloundecene (DBU) is used as a base, the *Z*-configurated didehydroamino acid esters **6** (88 - 96% *Z*) are formed preferentially, although the olefin geometry is not relevant for our purpose. Deprotonation with an excess of LDA probably results in the formation of the chelate bridged dienolate **7** which undergoes the Claisen rearrangement during warming. Because the rearrangement proceeds with a high preference for the *chairlike* transition state, the *syn*-product is formed with a high degree of diastereoselectivity (94 - 96 %ds) and with a clean *trans* olefin geometry in the allylic side chain. In the case of rearrangement products with a substituted vinylic side chain (R''' ≠ H), the configuration of the olefin, resulting from the double bond migration, is also preferentially *trans* (88 - 93%), as indicated by typical *trans* couplings of 15.6 - 17.6 Hz for the vinylic hydrogen atoms in the ^{1}H nmr spectra.[16]

An interesting observation is made in the rearrangement of allylic ester **6c** (Scheme 3). Besides the normal rearrangement product **8c**, **8d** is obtained as a side product, resulting from a unusual cleavage of the benzyloxycarbonyl group (Z) under the reaction conditions used.[16] This side reaction can be suppressed if

lithiumhexamethyldisilazide (LiHMDS) is used as a base, while prolonged reaction times in the reaction using LDA leads to **8d** nearly exclusively.

The products obtained by these chelate enolate Claisen rearrangements are not only interesting because of their potential biological activity, but also as intermediates for the synthesis of even more complex amino acids *via* regioselective modifications of the different unsaturated side chains. Two examples are shown in Scheme 3. Iodolactonization of the *normal* rearrangement product **8c** to the corresponding iodolactone **9** occurs in a highly diastereoselective fashion[17] and exclusively in an 5-*exo*-*trig*-mode[18] at the allylic double bond. On the other hand, Heck reaction[19] of **8d** with iodotoluene proceeds regioselectively at the sterically least hindered position of the unsubstituted vinylic double bond,[20] giving rise to the *all-trans* configurated amino acid **10**.[21]



Scheme 3

In conclusion, it has been shown that the ester enolate Claisen rearrangement of chelated *N*-protected α,β-unsaturated amino acid allylic esters gives rise to highly unsaturated amino acids in good yields and in a highly diastereoselective fashion. Further investigations, especially of an asymmetric version, are in progress.

Acknowledgments:

I thank Prof. Dr. G. Helmchen for his generous support of this work. Financial support by the Deutsche Forschungsgemeinschaft, the Fonds der Chemischen Industrie as well as the Otto Röhm Gedächtnisstiftung is gratefully acknowledged.

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16. **8c**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.34 (s, 5H), 6.37 (dd, *J* 17.3, 10.7 Hz, 1H), 5.52 (dq, *J* 15.1, 6.4 Hz, 1H), 5.32 - 5.04 (m, 7H), 3.73 (s, 3H), 2.51 (m_{br}, 1H), 1.66 (dd, *J* 6.4, 1.4 Hz, 3H), 0.97 (d, *J* 6.9 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.8, 153.9, 136.4, 135.3, 130.4, 128.7, 128.5, 128.2, 128.1, 114.8, 66.9, 66.3, 52.2, 45.7, 18.0, 15.3. **8d**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.58 (dd, *J* 17.6, 10.3 Hz, 1H), 5.58 (dq, *J* 15.1, 6.4 Hz, 1H), 5.38 (ddq, *J* 15.1, 9.8, 1.5 Hz, 1H), 5.17 (dd, *J* 17.6, 1.4 Hz, 1H), 5.15 (dd, *J* 10.3, 1.4 Hz, 1H), 4.97 (s_{br}, 1H), 3.89 (sep, *J* 6.9 Hz, 2H), 3.71 (s, 3H), 2.44 (dq, *J* 9.8, 7.0 Hz, 1H), 1.69 (dd, *J* 6.4, 1.5 Hz, 3H), 1.21 (d, *J* 6.9 Hz, 6H), 1.20 (d, *J* 6.9 Hz, 6H), 0.98 (d, *J* 7.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.8, 156.1, 137.9, 132.3, 128.4, 113.5, 65.7, 51.8, 47.2, 45.0, 21.5, 21.0, 17.9, 15.6.
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21. **9**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35 (s, 5H), 5.77 (dd, *J* 17.4, 10.8 Hz, 1H), 5.47 (d, *J* 10.8 Hz, 1H), 5.37 (d, *J* 17.4 Hz, 1H), 5.20 (s_{br}, 1H), 5.09 (s, 2H), 4.33 (m_{br}, 1H), 4.11 (m_{br}, 1H), 3.11 (m_{br}, 1H), 1.98 (d_{br}, 3H), 1.19 (d, *J* 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.6, 154.8, 135.6, 129.9, 128.63, 128.58, 128.4, 128.3, 119.9, 86.9, 67.4, 66.4, 41.6, 22.9, 22.5, 12.4. **10**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.29 (d, *J* 8.0 Hz, 2H), 7.08 (d, *J* 8.0 Hz, 2H), 6.93 (d, *J* 16.1 Hz, 1H), 6.45 (d, *J* 16.1 Hz, 1H), 5.63 (dq, *J* 15.1, 6.2 Hz, 1H), 5.43 (ddd, *J* 15.1, 9.4, 1.4 Hz, 1H), 5.03 (s_{br}, 1H), 3.88 (sep, *J* 6.9 Hz, 2H), 3.74 (s, 3H), 2.55 (dq, *J* 9.0, 7.0 Hz, 1), 2.31 (s, 3H), 1.72 (dd, *J* 6.2, 1.4 Hz, 3H), 1.25 (d, *J* 6.9 Hz, 12H), 1.03 (d, *J* 7.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.0, 156.0, 136.8, 134.7, 132.5, 130.3, 129.2, 129.0, 128.8, 126.6, 65.6, 51.9, 47.6, 45.2, 21.4, 21.1, 17.9, 15.8.

(*Received in Germany* 3 *May* 1996; *revised* 31 *May* 1996; *accepted* 4 *June* 1996)