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A Straightforward Synthesis of Protected Isostatine from Achiral Precursors using the Asymmetric Chelate Claisen Rearrangement

Uli Kazmaier* and Achim Krebs

Organisch-Chemisches Institut der Universität, Im Neuenheimer Feld 270, D-69120 Heidelberg, Germany

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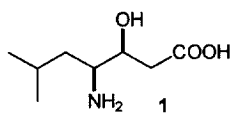
Abstract: Starting from achiral TFA-protected glycine crotyl ester (**3**) the interesting, suitable protected, enantiomerically pure β-hydroxy-γ-amino acid isostatine (**7**) was synthesized in only four steps. The amino acid obtained can directly be introduced into peptides.

Besides unnatural α-amino acids especially β-hydroxy-γ–amino acids like statine (**1**) or isostatine (**2**) are of great interest from a pharmaceutical point of view. They are part of various peptide mimetics, which can be used as renin- or HIV-protease inhibitors.[1] They are also very common in biologically active natural products such as pepstatine[2] and the dolastatines.[3] Isostatin is an essential amino acid of the didemnines,[4] a group of cyclic peptides which show strong antitumor, antiviral as well as immunosupressive activity.[5] Therefore a lot of investigations has been undertaken towards the synthesis of these interesting peptides,[6] and their building block isostatine as well.[7] The most common synthetic strategies towards β-hydroxy-γ-amino acids are based on aldol additions or Claisen condensations, followed by a reduction step.[8,9] These approaches are especially useful if the precursors required, amino aldehydes or amino acids, are commercially available. This is the case for most natural amino acids, which are relatively cheap. For the synthesis of isostatine and derivatives *D*-allo-isoleucine has to be used, which can also be obtained commercially, but is quite expensive. Therefore most syntheses of isostatine are comparatively long, including the preparation of *D*-allo-isoleucine.[7]



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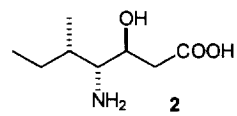

2

Recently, we have developed a new variation of the ester enolate Claisen rearrangement, proceeding *via* chelated allylic ester enolates.[10] Deprotonation of *N*-protected glycine allyl esters at -78 °C and subsequent addition of metal salts, presumably results in the formation of a chelated enolate, which undergoes Claisen rearrangement upon warming to room temperature (Scheme 1). Due to the fixed enolate geometry, as a result

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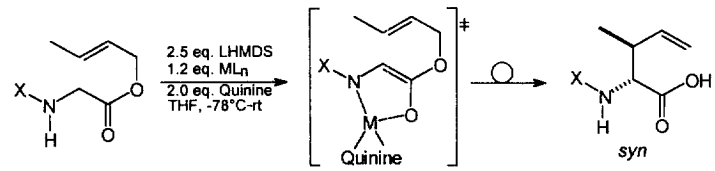
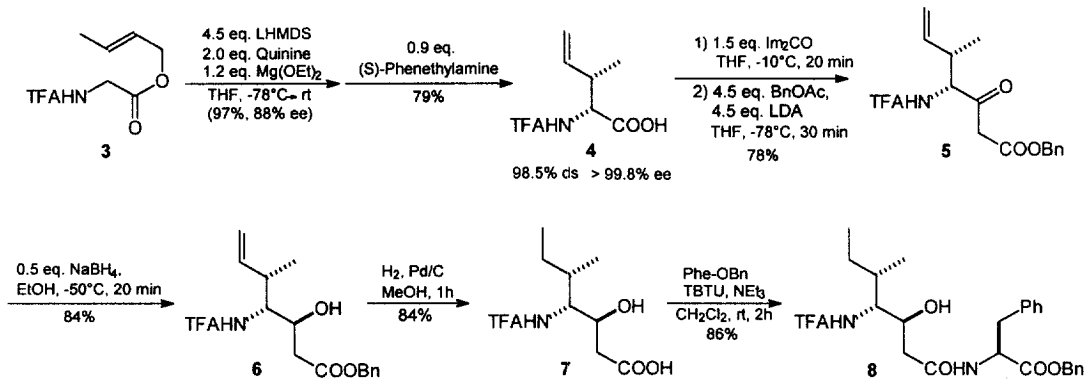
of chelate formation, the rearrangement proceeds with a high degree of *syn*-selectivity, independent of the substitution pattern and the protecting groups used.[11] If the reaction is carried out in the presence of chiral bidentate ligands, such as quinine, chiral γ,δ-unsaturated amino acids are obtained in high yields and in a highly stereoselective fashion.[12]



Scheme 1

This protocol allows the synthesis of *L*- and *D*- amino acids as well, depending on the ligand used. Quinidine gives rise to *L*-amino acids, while the *D*-configurated acids are obtained with quinine. Therefore this approach is especially suitable for the synthesis of *allo*-isoleucine and derivatives, with a *syn* relationship of the substituents. Based on this asymmetric chelate Claisen rearrangement we developed a short and very convenient synthesis of suitable protected isostatine (scheme 2), with *de novo* generation of all stereogenic centers.

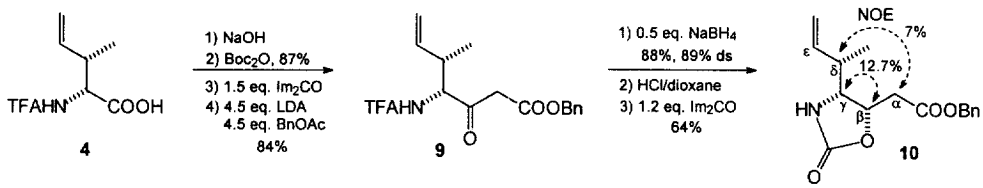


Scheme 2

Starting from achiral glycine crotyl ester **3**, the corresponding amino acid **4** was obtained by deprotonation with LHMDS[13] in the presence of $Mg(OEt)_2$[14] and quinine. The reaction mixture was allowed to warm up to room temperature overnight, giving rise to crude **4** in nearly quantitative yield. The enantiomerical purity was increased by single crystallization of the crude amino acid with (*S*)-phenethylamine. In general the trifluoroacetyl protecting group is used in this asymmetric Claisen rearrangement for several reasons: 1) TFA protected ester give the best selectivities; 2) The methyl ester of the TFA protected amino acids are volatile, and the selectivities (ds and ee) can easily be determined by GC;[15] 3). The TFA protecting group can easily be removed under very mild conditions.[16] This is especially interesting if the amino acids obtained have to be

introduced into peptides. For the prolongation of carbon chain a Claisen condensation *via* the corresponding imidazolide was chosen. The addition of carbonyldiimidazole[17] should be carried out at -10°C and the reaction mixture should be kept at this temperature, until the conversion into the imidazolide is complete (controlled by TLC). The reaction mixture was cooled to -78°C before a fresh prepared solution of the lithium enolate of benzyl acetate was added, giving rise to β-ketoester **5**. The subsequent reduction with sodium borohydride should also be carried out at low temperature, to avoid reductive cleavage of the TFA protecting group.[16a] Even at -50°C the reduction was very fast, and the reaction was quenched at this temperature with 1N $KHSO_4$ solution. The diastereoselectivity in the reduction step was very good (94% ds), and the amino acid **7** was obtained after catalytic hydrogenation.[18] The last three steps can be performed in one day. Therefore the whole synthesis of TFA isostatine, starting from achiral ester **3** takes only two days. The free amino acid should be obtained by saponification or reduction of the protecting group. But even more interesting is the direct introduction of **7** into peptides by coupling with other amino acids. E. g. reaction with phenylalanine benzyl ester under assistance of TBTU[19] gives rise to dipeptide **8**, which can selectively be prolonged on both sides, because of the orthogonality of the protecting groups.

The only critical step in the whole sequence is the activation of the TFA-protected amino acid **4**. If the reaction mixture is warmed to > 0°C it slowly turns yellow, caused from cyclization of the activated amino acid to the corresponding oxazole derivative. This oxazole formation results in an epimerization at the α-position. To avoid this problem one can easily switch to other *N*-protecting groups like Boc, which do not show this side reaction. The following steps can be performed in an analogues way, also the selectivity in the reduction step is a little lower (scheme 3). The higher selectivity obtained with the TFA protected derivative may result from a precoordination of the borohydride to the relatively acidic TFA amide moiety, and an intramolecular hydride transfer. Cleavage of the Boc group and reaction with carbonyldiimidazole gave rise to oxazolidinone **10**,[20] which was suitable for determination of the configuration *via* NOE difference spectroscopy.[21] Strong interactions were observed between the ring protons and also between the α- and δ-position of the side chains. This clearly indicates a *cis* orientation of these groups in **10**, corresponding to the *anti* configuration of isostatine.



Scheme 3

In summary, we have shown that the asymmetric chelate Claisen rearrangement is a powerful tool for the synthesis of natural amino acids. The sequence described allows the *de novo* generation of all stereogenic centers in only two stereoselective steps.

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13 LHMDS is superior to LDA in rearrangements of TFA protected esters, because of less side reactions.

14 In general $Al(O\mathit{i}Pr)_3$ is used for chelation, but $Mg(OEt)_2$ can also be applied in most cases.

15 A chiral column (Chira-Si-(*L*)-Val) was used.

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18 **7**: $[\alpha]_D^{20}$: -6.2 (c 0.15, methanol); ^{1}H NMR (300 MHz, CD_3OD): δ = 4.40 (s_{br}, 3H), 3.97 (m, 2H), 2.41 (m, 2H), 1.88 (m, 1H), 1.21 (sex, *J* = 6.9 Hz, 1H), 1.09 (sex, *J* = 7.0 Hz, 1H), 0.86 (d, *J* = 7.0 Hz, 3H), 0.82 (d, *J* = 6.7 Hz, 3H); ^{13}C NMR (75 MHz, CD_3OD): δ = 175.92, 157.72 (q, *J* = 31.2 Hz), 115.93 (q, *J* = 287.6 Hz), 67.61, 56.47, 49.80, 34.11, 26.91, 13.12, 11.27.

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20 ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.34 (s_{br}, 5H), 5.78 (s_{br}, 1H, NH), 5.62 (ddd, *J* = 17.5, 10.0, 7.3 Hz, $1H^{\varepsilon}$), 5.14 (d, *J* = 17.5 Hz, 1H), 5.13 (s, 2H), 5.07 (d, *J* = 10.0 Hz, 1H), 5.05 (m, 1H, H^{β}), 3.82 (t, *J* = 7.4 Hz, 1H, H^{γ}), 2.89 (dd, *J* = 16.4, 6.9 Hz, H^{α}), 2.80 (dd, *J* = 16.4, 6.1 Hz, H^{α}), 2.34 (sex, *J* = 6.9 Hz, H^{δ}), 1.06 (d, *J* = 6.7 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 169.47, 158.87, 138.99, 135.54, 128.64, 128.57, 128.44, 116.58, 75.97, 67.04, 58.81, 37.74, 34.53, 16.65.

21 NOE's observed: Irradiation at H^{α}: 7.0% H^{δ}, 7.7% H^{β}; Irradiation at H^{γ}: 12.7% H^{β}, 3.0% NH, 2.6% H^{ε}.