Application of the chelate enolate Claisen rearrangement to the modification of dipeptides

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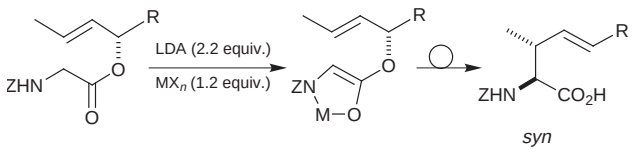
Manganese enolates of allylic esters of dipeptides are suitable to undergo Claisen rearrangements, giving rise to unsaturated peptides in excellent yield.

Peptides and cyclopeptides containing unnatural amino acids are quite common in nature, and are often found in marine organisms.[1] Many of these peptides show antibiotic activity,[2] and are therefore highly interesting from a pharmaceutical point of view.[3] For straightforward approaches towards these targets, efficient target screening and optimization of lead structures, flexible synthetic concepts are necessary. In addition to classical peptide coupling of commercially available or synthesized amino acids, the modification of existing peptides is especially suitable for this purpose. These modifications can be carried out in the side chain or directly on the peptide backbone.[4] The great advantage of side chain modifications results from the fact that the chiral center in the newly formed amino acid can be taken over from the precursor amino acid.[5] On the other hand, suitable precursors are necessary. In contrast, achiral glycine subunits can be used for backbone modifications, because the whole side chain is transferred.[6] As reactive intermediates, glycine cation equivalents[7] as well as glycine anions (glycine enolates) can be used.[8] The major drawback of this concept results from the difficulty of controlling the stereochemical outcome of the C–C coupling step.

For quite some time we have been investigating syntheses of γ,δ-unsaturated amino acids.[9] One approach towards these structures is based on a variation of the Claisen rearrangement, proceeding *via* chelated amino acid ester enolates (Scheme 1).[10]

Because of the fixed enolate geometry given by chelation, and the high preference of the Claisen rearrangement for the *chair like* transition state, the *syn* configured rearranged products are formed in a highly stereoselective fashion. If esters of chiral allylic alcohols are used, the corresponding enantiomerically pure amino acids are obtained. [11]

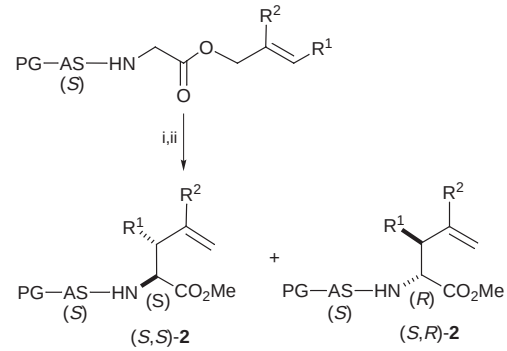
Therefore we were interested to see if it was also possible to transfer this Claisen protocol to peptides, and to use it for backbone modifications. Our early attempts were carried out with zinc enolates, which generally give the best results in the rearrangement of amino acids.[12] But with peptides the yields obtained were modest (20%), although they could be increased (70–80%) by addition of Pd^0 catalysts. However, under these conditions the allylation of the peptide chains proceeds *via* π-allyl–palladium intermediates. This intermolecular process results in significantly lower diastereoselectivities, and also the formation of regioisomers if substituted allylic esters are used. Therefore we undertook an intensive metal tuning to find suitable chelate complexes which undergo Claisen rearrangement without assistance from a palladium catalyst. By far the best results are obtained if manganese salts are used for chelation.[13] We investigated the rearrangement of various esters of dipeptides (Scheme 2) and the results obtained are shown in Table 1.†



Scheme 1

Independent of the protecting groups (PG) used,‡ the yields obtained with these manganese enolates were always excellent, with both esters of terminal allylic alcohols (entries 1–3) and *trans* configured substituted alcohols (entries 4–11).§ These are especially interesting, because in their rearrangement two new stereogenic centers are formed. Therefore we investigated preferentially the rearrangement of crotyl esters, because the results obtained with these esters in general can be transferred to other *trans* configured esters without problems. In all examples investigated so far, the simple diastereoselectivity of the rearrangement was very high (≥95%) and comparable to the results obtained with amino acids.¶ No significant induced diastereoselectivity was observed. Obviously the *N*-terminal amino acid has no notable influence on the rearrangement. This is also reflected in the high yields obtained, which are also nearly independent on the peptide used.

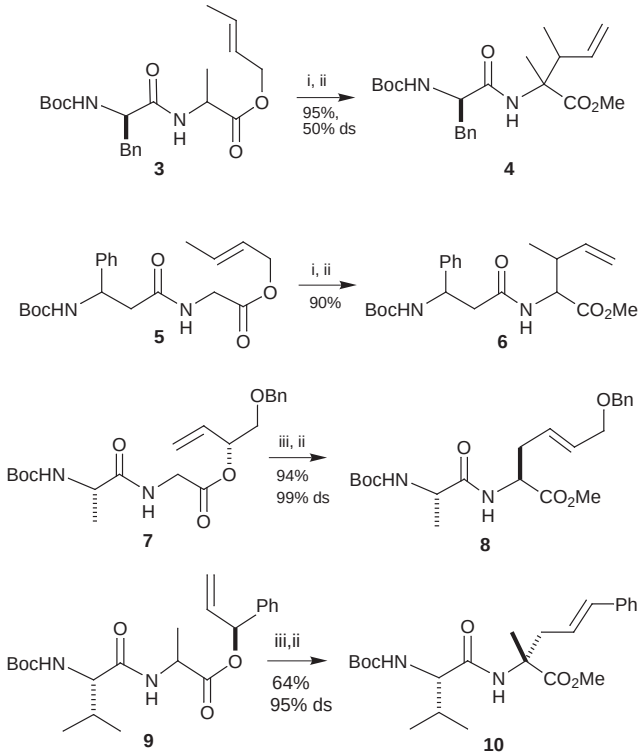
This protocol is also suitable for the direct introduction of α-alkylated amino acids into peptides (Scheme 3). These derivatives show higher resistances towards proteases, and therefore they are interesting for the development of peptide



Scheme 2 *Reagents and conditions*: i, LDA (4.0 equiv.), $MnCl_2$ (1.2 equiv.), THF, −78 °C→room temp.; ii, CH_2N_2.

Table 1 Chelate enolate Claisen rearrangement of peptides

Entry	Ester	PG	AS	R^1	R^2	Yield (%)	Selectivity *SS*:*SR*
1	**1a**	Boc	Val	H	Me	88	51:49
2	**1b**	Boc	Phe	H	Me	90	63:37
3	**1c**	Z	Phe	H	Me	88	66:34
4	**1d**	Z	Val	Me	H	92	61:39
5	**1e**	Boc	Val	Me	H	93	37:63
6	**1f**	Boc	Phe	Me	H	93	62:38
7	**1g**	CF_3CO	Phe	Me	H	98	47:53
8	**1h**	Ts	Phe	Me	H	92	35:65
9	**1i**	Ts	Ile	Me	H	83	35:65
10	**1k**	Boc	Met	Me	H	88	33:67
11	**1m**	Boc	Lys(Boc)	Me	H	78	42:58



Scheme 3 *Reagents and conditions*: i, LDA (4.0 equiv.), $MnCl_2$ (1.2 equiv.), THF, −78 °C→room temp.; ii, CH_2N_2; iii, LHMDS (4.0 equiv.), $MnCl_2$ (1.2 equiv.), THF, −78 °C→room temp.

based pharmaceuticals.[14] Because of the steric hindrance of these amino acids, their introduction into peptides by classical peptide coupling reactions often causes problems, and therefore special coupling reagents and methods have to be applied.[15] Using the peptide Claisen rearrangement even sterically hindered peptides such as **4** and **10** can be obtained. This procedure is also suitable for the rearrangement of peptides containing β-amino acids (**5**).[16] Since the influence of the adjacent amino acid on the rearrangement can be neglected, this allows for the stereoselective synthesis of peptides if esters of chiral allylic alcohols such as **7** and **9** are used.[17] The corresponding dipeptides **8** and **10** were obtained not only in good to excellent yields but also in a highly diastereoselective fashion.

These unsaturated peptides obtained by backbone modification are suitable substrates for subsequent reactions on the double bond (side chain modifications). These reactions are currently under investigation. We are also looking for chelate complexes which allow chirality transfer from the peptide chain to the new stereogenic center formed during the rearrangement.

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Notes and references

† General procedure for the peptide Claisen rearrangement: 0.2 mmol of peptide ester **1** was dissolved in 3 ml of THF, before 0.24 mmol of $MnCl_2$ was added. The mixture was cooled to −78 °C. A freshly prepared solution of 0.8 mmol LDA in 2 ml of THF was added slowly and the reaction mixture was allowed to warm to room temperature overnight. The resulting brown solution was hydrolyzed by vigorous stirring with 5 ml 1 M HCl solution, until a clear solution was obtained. After separation of the aqueous layer the rearrangement product was extracted three times with 10 ml of 1 M NaOH solution. The combined basic aqueous layers were acidified with 1 M HCl solution (pH 1) and the peptide was extracted twice with CH_2Cl_2 (15 ml each). After evaporation of the solvent, the crude product was purified by flash chromatography. For analytical purposes the rearrangement products were converted into the corresponding methyl esters with CH_2N_2.

‡ If a trifluoroacetyl group is used as protecting group, LHMDS should be applied instead of LDA.

§ The yields and selectivities obtained with *cis*-configured esters are generally lower, depending on the substituent. This can be explained by an increased rearrangement *via* the *boat like* transition state (ref. 18).

¶ Determined by NMR and/or HPLC analysis

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