Stereoselective Backbone Modifications of Peptides via Chelate Enolate Claisen Rearrangement

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Unnatural amino acids are quite common in nature, often found in peptides and cyclopeptides produced by marine organisms.[1] Many of these peptides show antibiotic activity[2] and are therefore highly interesting from a pharmaceutical perspective.[3] For efficient target screening and optimization of lead structures, flexible synthetic concepts are necessary, such as peptide modifications. These modifications can be carried out at the side chain or directly on the peptide backbone.[4] Side chain modifications are straightforward, but require suitable derivatives.[5] In contrast, achiral glycine subunits can be used for backbone modifications, because the whole side chain is transferred on request.[6] But the control of the stereochemical outcome of these reactions is not a trivial issue. In general this is true for modifications of linear peptides via glycine cation equivalents[7] and glycine anions (glycine enolates) as well.[8] Better results are obtained in enolate alkylation of cyclic peptides, presumably since one face of the enolate is shielded by the peptide ring.[9]

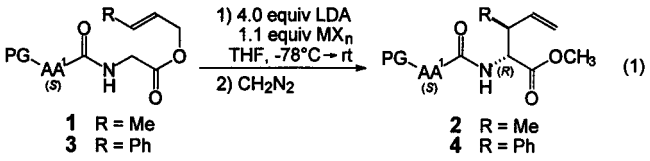
For quite some time we have been investigating syntheses of γ,δ-unsaturated amino acids.[10] One approach toward these structures is based on a variation of the Claisen rearrangement, proceeding via chelated amino acid ester enolates.[11] If esters of chiral allylic alcohols are used, the corresponding enantiomerically pure amino acids are obtained.[12]

This protocol is not limited to the rearrangement of amino acid esters but can also be applied to peptides. Therefore, we thought to use the chiral information of the peptide chain as a stereocontrolling element. In our first attempts, we investigated the rearrangement of various peptide methallylic esters, with only moderate success. The poor yields, however, could be increased in the presence of Pd(0)-complexes,[13] or by using MnO_2 for chelation,[14] but without significant diastereoselectivity.

Table 1. Chelate Claisen Rearrangement of Dipeptide Allylic Esters

entry	substrate	PG	AA[1]	MXn	% yield	% ds
1	**1a**	Boc	Phe	$Ti(O^iPr)_4$	57	82
2	**1a**	Boc	Phe	$NiCl_2$	86	77
3	**1b**	Boc	Val	$Ti(O^iPr)_4$	65	89
4	**1b**	Boc	Val	$NiCl_2$	69	81
5	**1b**	Boc	Val	CuBr	78	78
6	**1c**	Cbz	Val	CuBr	82	90
7	**1d**	Ts	Val	$Ti(O^iPr)_4$	60	96
8	**1d**	Ts	Val	$NiCl_2$	66	93
9	**1d**	Ts	Val	−	55	92
10	**1e**	Ts	Leu	$Ti(O^iPr)_4$	86	90
11	**1e**	Ts	Leu	$NiCl_2$	80	93
12	**1e**	Ts	leu	−	90	90
13	**1f**	Ts	Ile	−	88	95
14	**1g**	Ts	Phe	−	74	90
15	**1h**	Ts	Met	−	69	90
16	**3a**	Ts	Val	$Ti(O^iPr)_4$	60	96
17	**3a**	Ts	Val	$NiCl_2$	57	96
18	**3a**	Ts	Val	−	60	95
19	**3b**	Boc	Val	−	60	91

Herein we describe our attempts to use the chiral backbone of a given peptide to control the stereochemical outcome of its modification by chelate Claisen rearrangement. We were interested to see if it is possible to coordinate a deprotonated peptide chain not only twice (like amino acid ester enolates) but several times toward the chelating metal. We hoped to obtain peptide metal complexes in which one face of the enolate is shielded by the complex. Although manganese chloride obviously is not the best choice, other metal salts could be more suitable for this purpose.[15] Therefore, we investigated the rearrangement of several dipeptide crotyl esters **1** (R = CH_3) (eq 1).[16] The results



(1)

obtained are shown in Table 1.

Starting with the Boc-protected phenylalanine derivative **1a,** we found good selectivities in the presence of $Ti(O^iPr)_4$ and $NiCl_2$ as well. Although the selectivity observed in the presence of $NiCl_2$ was a little lower, the yield was much better.[17] Replacing phenylalanine by the sterically more bulky valine (**1b**) resulted in an increase of selectivity. Other metal salts such as CuBr gave comparable results. Switching to other carbamate protecting groups such as Cbz had no significant effect on the diastereoselectivity (ds). Introduction of the tosyl group, however, increased the ds from 89% to 96%. Tosyl-protected peptides are therefore the substrates

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(16) The crotyl esters were chosen, because they allow the generation of two stereogenic centers in a highly diastereoselective fashion (95% ds), as determined by HPLC or GC.
(17) Titanium compounds are known to catalyze transesterifications. This can explain the lower yields obtained in some cases (see also ref 11).

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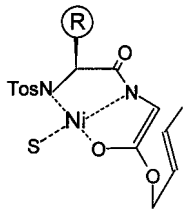


Figure 1.

Table 2. Chelate Claisen Rearrangement of Tripeptide Allylic Esters 5

entry	ester	PG	AA^1	AA^2	R	MXn	% yield	% ds
1	**5a**	Ts	Val	Gly	Me	–	59	62
2	**5a**	Ts	Val	Gly	Me	$SnCl_2$	82	88
3	**5b**	Ts	Val	β-Ala	Me	$SnCl_2$	89	85
4	**5c**	Ts	Val	Leu	H	$SnCl_2$	85	85
5	**5d**	Boc	Val	Leu	H	$SnCl_2$	74	84

of choice; in all examples investigated so far, the selectivites were in the range of 90 to 96 ds, with yields up to 90%. Cinnamyl esters **3** gave especially good selectivites.[18] Most surprising was the fact that even the lithium enolates showed these excellent results. This is in sharp contrast to our observations with amino acid esters. In general, the chelate Claisen rearrangement takes place during the warm-up at about −20 °C, and lithium enolates normally decompose before they reach this rearrangement temperature. Presumably this is not the case with tosylated peptides. This can probably be explained by the formation of lithium complexes,[19] which have a stabilizing effect comparable to the chelate formation with other metal salts. This may also explain the *unlike*[20] (*S*/*R*) diastereoselectivities observed. In all examples investigated so far, an (*R*)-amino acid was formed during the Claisen rearrangement, if an (*S*)-amino acid was placed in the peptide chain. The (*R*)-configurations of the new formed stereogenic centers were confirmed by HPLC[21] analyses and comparison with peptides obtained by classical peptide couplings. The unnatural γ,δ-unsaturated amino acids required were obtained via stereoselective Claisen rearrangement in the presence of quinine,[22] which gave the (*R*) amino acids (80−87% ee, 98% ds).

For the reactions with $NiCl_2$, this stereochemical outcome can be rationalized by the formation of a square planar chelate complex (Figure 1), in which one face of the enolate is shielded by the R side chain of the (*S*)-amino acid. The rearrangement occurs on the sterically less-hindered opposite (*unlike*) face of the enolate, giving rise to the (*R*)-amino acid. This rational can also explain the excellent selectivites obtained with the sterically most-demanding amino acids, valine and isoleucine. Similar complexes are probably involved in rearrangements of other metal enolates, including lithium enolates.

(18) Using cinnamyl esters, elimination of cinnamyl alcohol was observed as a side reaction.

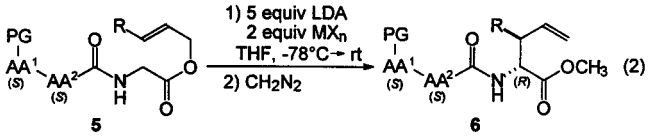
(19) Comparable lithium chelate complexes were proposed by Seebach et al. to explain the solubilization of peptides in the presence of lithium salts (ref 4).

(20) Seebach, D.; Prelog, V. *Angew. Chem.* **1982**, *94*, 696−702; *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 654- 662.

(21) HPLC analyses were performed on the corresponding methyl esters using a achiral column (silica gel) and a chiral column (Daicel OD-H) as well.

(22) Kazmaier, U.; Krebs, A. *Angew. Chem.* **1995**, *107*, 2213; *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2012.

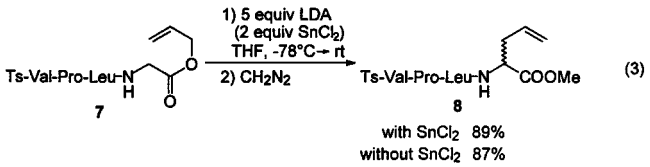
If this assumption is correct, one might expect an induction not only from amino acids adjacent to the *C*-terminal amino acid like in the investigated dipeptides, but also from amino acids "further away" in the peptide chain, e.g., in tri- or tetrapeptides. The results obtained with several allylic esters of tripeptides **5** containing valine as a stereocontrolling element (eq 2) are shown in Table 2.



(2)

In contrast to the results obtained in the rearrangement of dipeptides, lithium enolates of **5** showed no significant diastereoselectivity (entry 1). Tin chloride is the chelating agent of choice for the rearrangement of these larger peptides. The tosyl-protected derivatives gave excellent yields and also very high diastereoselectivities. This is quite surprising with respect to the fact that five atoms are between the stereocontrolling valine and the newly formed chiral center of the *C*-terminal amino acid. Even increasing the distance to six atoms by incorporation of a β-amino acid (entry 3) had no significant negative influence on the rearrangement. On the other hand, attempts to increase the diastereoselectivity by introduction of a second chiral amino acid into the peptide chain were unsuccessful (entries 4, 5). The side chains of the amino acids AA^1 and AA^2 probably interact with each other in such a way that the overall shielding effect of these side chains is not increased in comparison with the single side chains. The selectivities obtained are not limited to tosylated tripeptides, comparable results are also obtained with Boc-protected derivatives such as **5d**, although the yields are lower in these cases.

Incorporation of secondary amino acids, such as sarcosine or proline, into the peptide chain should interupt the successive coordination of the peptide chain toward the chelating metal ion. Therefore, one might expect and does observe a dramatic drop in the selectivity obtained with these derivatives. Rearrangement of tetrapeptide **7** gave high yields of the expected amino acid **8** as a nearly 1:1 diastereomeric mixture (eq 3), independent of the presence of $SnCl_2$.



(3)

These results also support our hypothesis on the intermediates of this peptide Claisen rearrangement. Further examples and applications of these asymmetric rearrangements are currently under investigation.

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Supporting Information Available: General experimental procedures and analytical and spectroscopic data of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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