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Application of the Peptide Claisen Rearrangement toward the Synthesis of Cyclic Peptides

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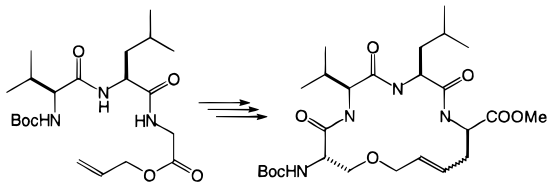
ABSTRACT



Allylic esters of peptides undergo Claisen rearrangement after deprotonation in the presence of tin chloride, giving rise to allylated peptides. Subsequent *N*-allylation and ring-closing metathesis provides the corresponding cyclic peptides. The yields in the last step strongly depend on the ring size formed.

Cyclic peptides are widely found in marine organisms and fungi.[1] Many of these peptides show significant biological activities[2] and are therefore highly interesting from a pharmaceutical point of view.[3] In higher organisms, cyclic structures can be formed by oxidation of two cysteine subunits, a process which is generally used to stabilized secondary and tertiary structures of peptides. Cystine-containing peptides are also found preferentially in peptide hormones and in a number of redox-active proteins (**1**).[4] In these last examples the disulfide bridge locks a tetrapeptide fragment of the protein chain into a β-turn type structure.[5] Frequently, loops and turn in peptides and proteins are responsible for their biological activity, and therefore these structures are highly interesting from a pharmaceutical point of view, and as targets for peptidomimetics.[6] Cyclizations of peptides, in general, results in an increased stability toward proteases, also in cystine peptides the disulfide bonds are sensitive to reduction. The metabolic stability of these compounds can dramatically be increased by replacing the critical disulfide bond by a noncleavable C−C bonds.[7] Therefore a lot of investigations have been carried out toward the synthesis of carba analogues of cystine, such as 2,7-diaminosuberic acid.[8] Very recently Williams[9] and Grubbs[10] described syntheses based on a dimerization of tethered allyl glycines via ring closing metathesis.[11] As shown by Grubbs

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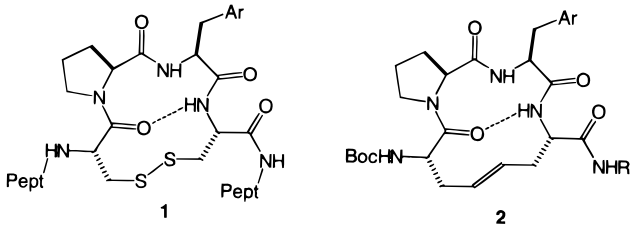
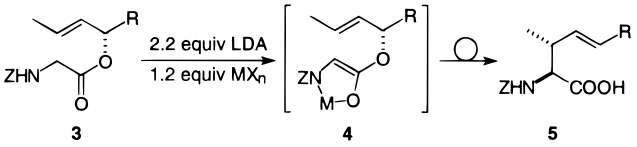
et al. this ring-closing approach can directly be used for the synthesis of cyclic peptides, such as **2**, a carba analogue of the glutaredoxin active site **1**.[12] This is an extremely straightforward approach toward these β-turn mimetics, but also smaller and larger ring systems can be obtained by this protocol.[13]



For quite some time we have been investigating syntheses of γ,δ-unsaturated amino acids.[14] One approach toward these structures is based on a variation of the Claisen rearrangement, proceeding via chelated amino acid ester enolates **4** (Scheme 1).[15] If esters of chiral allylic alcohols **3** are used,

Scheme 1

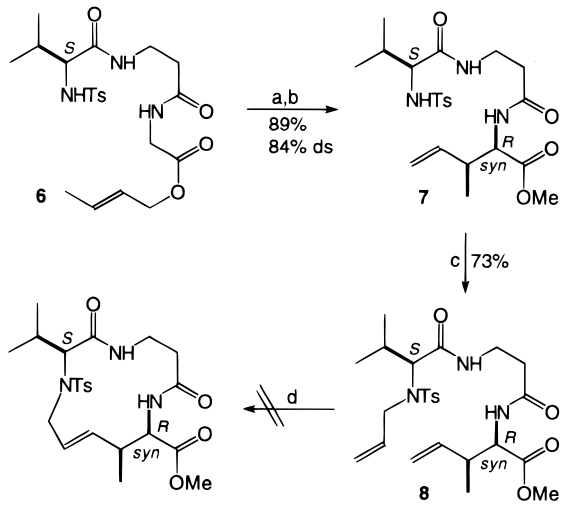


the corresponding enantiomerically pure amino acids **5** are obtained.[16]

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 methyl allylic esters, with only moderate success.[17] To improve the yield and also the selectivity of the rearrangement, we carried out an extensive screening with regard to the N^{α}-protecting group, the substitution pattern in the allylic ester moiety, and also the metal salt used for chelation. $MnCl_2$ was found to give excellent yields in the rearrangement of various types of peptide esters, but without any selectivity.[18] The peptide chain has no influence on the rearrangement of these manganese enolates, and therefore this approach is only suitable for the stereoselective introduction of allylic side chains onto peptides if esters of chiral allylic alcohols are used. On the other hand, if allylic esters of tosylated peptides were subjected to Claisen rearrangement, the rearrangement products are obtained in a highly diastereoselective fashion.[19] Tosyl-protected amino acids are also suitable substrates for palladium-catalyzed allylic alkylations, giving rise to *N*-allylated derivatives under very mild conditions.[20]

Herein we describe applications of these protocols to the synthesis of cyclic peptides. We started our investigations with the rearrangement of peptide ester **6** (Scheme 2).[21] In

Scheme 2[a]



[a] Conditions: (a) 5.0 equiv of LHMDS, 2.0 equiv of $SnCl_2$, THF, −78 °C → room temperature, 16 h; (b) CH_2N_2, ether, 10 min; (c) 1 mol % $(allylPdCl)_2$, 4.5 mol % PPh_3, allyl carbonate, THF, room temperature, 16 h; (d) 10−15 mol % $RuCl_2(PCy_3)_2$(=CHPh), toluene, room temperature → 90 °C, 8 h.

the presence of tin chloride, used for chelation, the rearranged product **7** was obtained in excellent yield and highly stereoselective. An induced diastereoselectivity of 84% was remarkable, especially with respect that the only chiral center in the peptide **6** was seven atoms away from the newly formed chiral center.[19] The (*R*)-configured amino acid was formed preferentially with high *syn* selectivity (>95%).[22] The subsequent *N*-allylation gave rise to the *N*-allylated product

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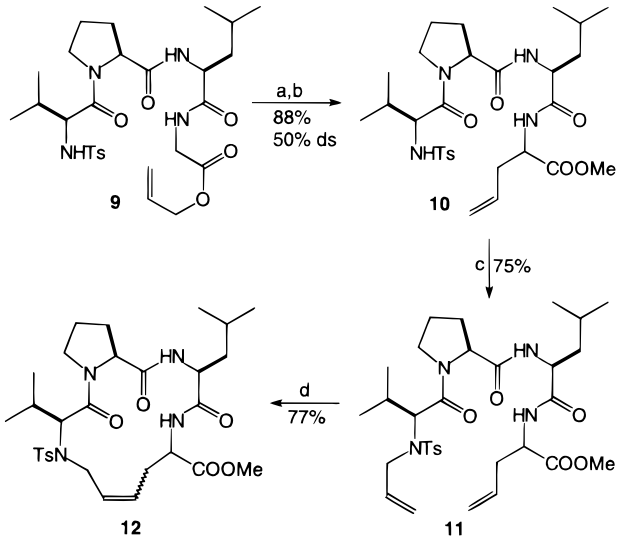
(21) **General Procedure for Peptide Claisen Rearrangements:** A total of 0.2 mmol of the corresponding peptide ester were dissolved in 4 mL of THF, before 0.4 mmol (380 mg) of tin chloride were added. The mixture was cooled to −70 °C. A freshly prepared solution of 1 mmol LHMDS in 2.5 mL of THF was added slowly, and the reaction mixture was allowed to warm to room temperature overnight. The resulting solution was hydrolyzed by vigorous stirring for 1 h with 5 mL of 1 N HCl solution. After separation of the aqueous layer the rearrangement product was extracted three times with 10 mL of 1 N NaOH solution. The combined basic aqueous layers were acidified with 1 N HCl solution (pH 1), and the peptide was extracted twice with methylene chloride (15 mL each). After evaporation of the solvent, the crude product was converted into the corresponding methyl esters with diazomethane and purified by flash chromatography.

8 without any racemization.[23] This can be explained by the extremely mild reaction conditions. The base required for the deprotonation of the tosylamide is generated in situ (EtO^-) from the allylic carbonate, and therefore this approach is suitable even for the allylation of sensitive amino acids and peptides. Unfortunately all attempts to cyclize the diallylated substrate **8** under different reaction conditions and various amounts of Grubbs's catalyst were unsuccessful.[24]

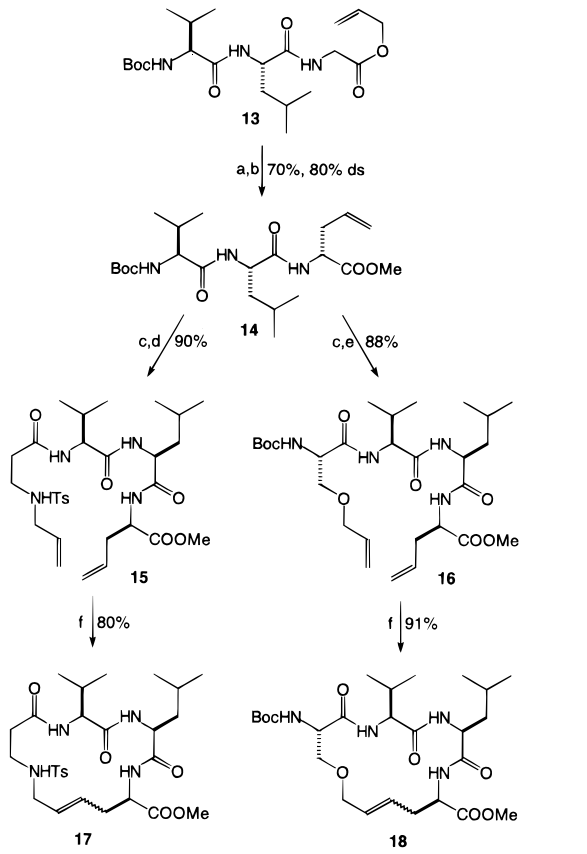
Scheme 3[a]



[a] Conditions: (a) 5.0 equiv of LHMDS, 2.0 equiv of $SnCl_2$, THF, −78 °C → room temperature, 16 h; (b) CH_2N_2, ether, 10 min; (c) 1 mol % $(allylPdCl)_2$, 4.5 mol % PPh_3, allyl carbonate, THF, room temperature, 16 h; (d) 10 mol % $RuCl_2(PCy_3)_2(=CHPh)$, CH_2Cl_2, reflux, 14 h.

What are the reasons? We focused on three parameters: (a) the unsaturated amino acid, (b) the ring size; and (c) the amino acid sequence. In all ring closing metatheses described in the literature so far, only unbranched allylglycines, or related amino acids, were used as substrates. Probably the methyl group of the C terminal amino acid caused the troubles. Unfortunately exchanging this amino acid by allylglycine was just as fruitless as reducing the ring size by replacing the β-amino acid by an α-amino acid such as leucine. Obviously 12- and 13-membered peptide rings are not the best targets for this strategy. The problems with these medium-sized rings may result from an unsuitable conformation of the linear peptide chain. Probably *trans* amide bonds avoid the approximation of the allyl termini. Therefore we decided to enlarge the ring size and to introduce one proline, which is suitable to form *cis* amide bonds and turn structures.

Scheme 4[a]



[a] Conditions: (a) 5.0 equiv of LHMDS, 2.0 equiv of $SnCl_2$, THF, −78 °C → room temperature, 16 h; (b) CH_2N_2, ether, 10 min; (c) HCl, dioxane, 0 °C, 30 min; (d) 1 equiv *N*-tosyl-*N*-allyl-β-Ala, 1.1 equiv TBTU,[30] 5 equiv, NEt_3, CH_2Cl_2, 10h; (e) 1 equiv of Boc-Ser(Oall), 1.1 equiv of TBTU, 5 equiv of NEt_3, CH_2Cl_2, 8 h; (f) 10 mol % $RuCl_2(PCy_3)_2(=CHPh)$, CH_2Cl_2, reflux, 15 h.

Rearrangement of the tetrapeptide ester **9** gave the desired allylated tetrapeptide **10** in excellent yield (Scheme 3).[25] *N*-Allylation provided the substrate **11** for the subsequent ring-closing metathesis,[26] which now resulted in the formation of the desired cyclic peptide **12** (15-membered ring) in high yield.[27] This is in good agreement with the results described by Grubbs et al. for comparable peptides such as **2** (14-membered ring).

(22) The stereochemical outcome of this reaction probably can be explained by a 4-fold coordination of the deprotonated peptide chain toward the chelating metal ion. In such a complex, one face of the enolate is shielded by the isopropyl side chain of the (*S*)-valine. Claisen rearrangement obviously occurs from the "opposite" face giving rise to an (*R*)-amino acid. See also ref 19.

(23) **General Procedure for the *N*-Allylations of Peptides.** To a stirred solution of the Ts-protected peptide (1 mmol) in 2 mL of dry THF a solution of π-allylpalladium chloride dimer (0.01 mmol), triphenylphosphine (0.045 mmol), and the allyl carbonate (2 mmol) was added at room temperature. The solution was stirred overnight. After evaporation of the solvent, the residue was purified by flash chromatography.

(24) No reaction was observed, even at temperatures up to 90 °C. These conditions only resulted in decomposition of the catalyst.

(25) The newly generated amino acid was formed in racemic form, because proline containing peptides do not undergo stereoselective Claisen rearrangements (see ref 19).

(26) **General Procedure for Ring Closing Metatheses of Peptides.** A solution of 17 mg (0.02 mmol, 10 mol %) of $RuCl_2(PCy_3)_2(=CHPh)$ in 10 mL of CH_2Cl_2 was added to a solution of 0.2 mmol of the diallylated peptide in 40 mL of CH_2Cl_2 under argon. The clear solution was refluxed overnight. The solvent was removed in vacuo, and the residue was purified by flash chromatography.

(27) The double bond was obtained as an inseparable (*E*/*Z*) mixture, with a predominant amount of the (*Z*) isomer, as indicated by a typical 10.5 Hz coupling for the vinylic protons in the ^1H NMR spectrum.

To prove if the proline plays a significant role for the cyclization, we came back to our allylated tripeptides such as **14** (Scheme 4), which could not by cyclized previously after *N*-allylation. Cleavage of the *N*-protecting group and coupling with allylated amino acids provided the prolonged peptides **15** and **16**. Subsequent ring-closing metathesis yielded the corresponding 16-membered cyclic peptides **17**[28] and **18**[29] in even higher yields in comparison to the smaller proline peptide. Obviously ring size plays a major role for the success of this reaction, and the amino acid sequence and conformational issues are less important, at least for peptides with more than 14 ring members.

In conclusion we have shown, that the peptide Claisen rearrangement is a versatile tool for the allylation of peptides. The combination of this approach with the palladium-catalyzed *N*-allylation and the ring-closing metathesis provides and straightforward access to cyclic peptides.

Acknowledgment. We thank the Deutsche Forschungsgemeinschaft (SFB 247) and the Fonds der Chemischen Industrie for generous financial support.

Supporting Information Available: Analytical and spectroscopic data of all described peptides. This material is available free of charge via the Internet at http://pubs.acs.org.

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(28) The (*E*) isomer was formed preferentially ($J = 15.4$ Hz), which could be purified by crystallization.

(29) Unfortunately, the olefin geometry could not be determined from the NMR spectra.

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