Synthesis of 1,3-Diene-Containing alpha-Amino Acids and Peptides via N-Acyliminium Ions

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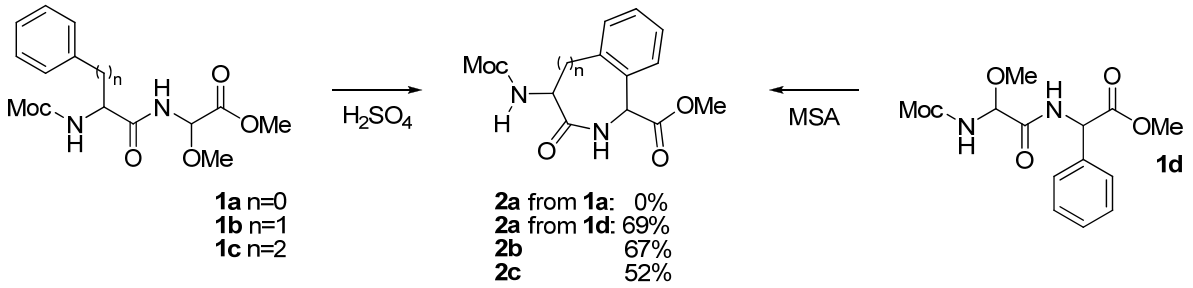
Chapter 3

N-Acyliminium ion chemistry in peptides

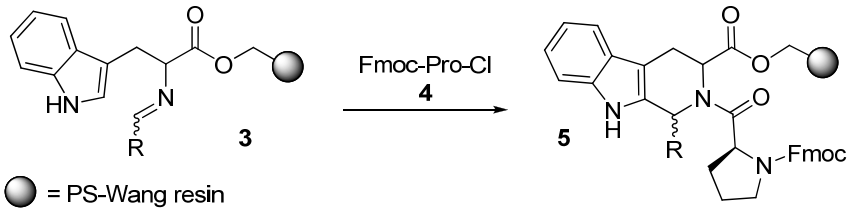
3.1 Introduction

Unlike *N*-acyliminium ion reactions in protected amino acids, not much is known about this reaction type in dipeptides or even larger systems. Most of the publications on this subject deal with intramolecular nucleophilic addition to an iminium ion.[1,2] The group of Ben-Ishai has conducted extensive studies on the intramolecular amidoalkylation of aromatic systems,[3] especially Phe-Gly(OMe) derivatives **1**.[4,5] Using this method several 7- and 8-membered benzolactams **2** have been synthesized (Scheme 3.1).[6] Formation of the 6-membered lactam **2a** was only successful for the reverse amino acid sequence Gly(OMe)-Phg **1d** (69% yield).



Scheme 3.1

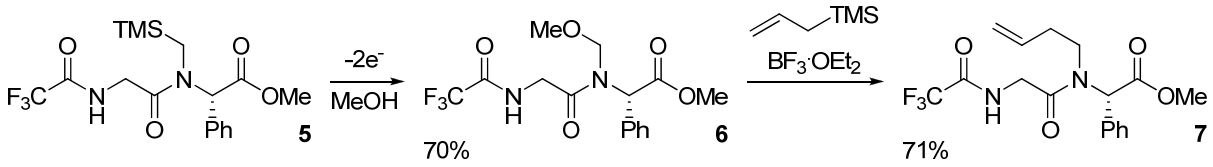
A different, but delicate system is the *N*-acyliminium Pictet-Spengler condensation in which Fmoc-protected proline acid chloride **4** is added to tryptophan imine **3** (Scheme 3.2). The resulting acyliminium ion then cyclizes onto the indole moiety to form a tetrahydro-*β*-carboline **5**.[7] Other applications of intramolecular *N*-acyliminium ion reactions are found in the synthesis of (-)-dysibetaine PP[8] and of bicyclic dipeptide mimetics.[9]



Scheme 3.2

The only intermolecular *N*-acyliminium ion reactions in dipeptides are published by Moeller and co-workers.[10-12] Selective generation of *N*-acyliminium ions in peptides by means

of an electrochemical oxidation of the *N*-substituted electroauxiliary methyltrimethylsilane (**5**, Scheme 3.3) allowed for peptide modifications via *N*-acyliminium ion chemistry at a late stage. Besides the intermolecular incorporation of an allyl group (**7**), this reaction was also successful with internal nucleophiles to form constrained (cyclized) peptide analogues.

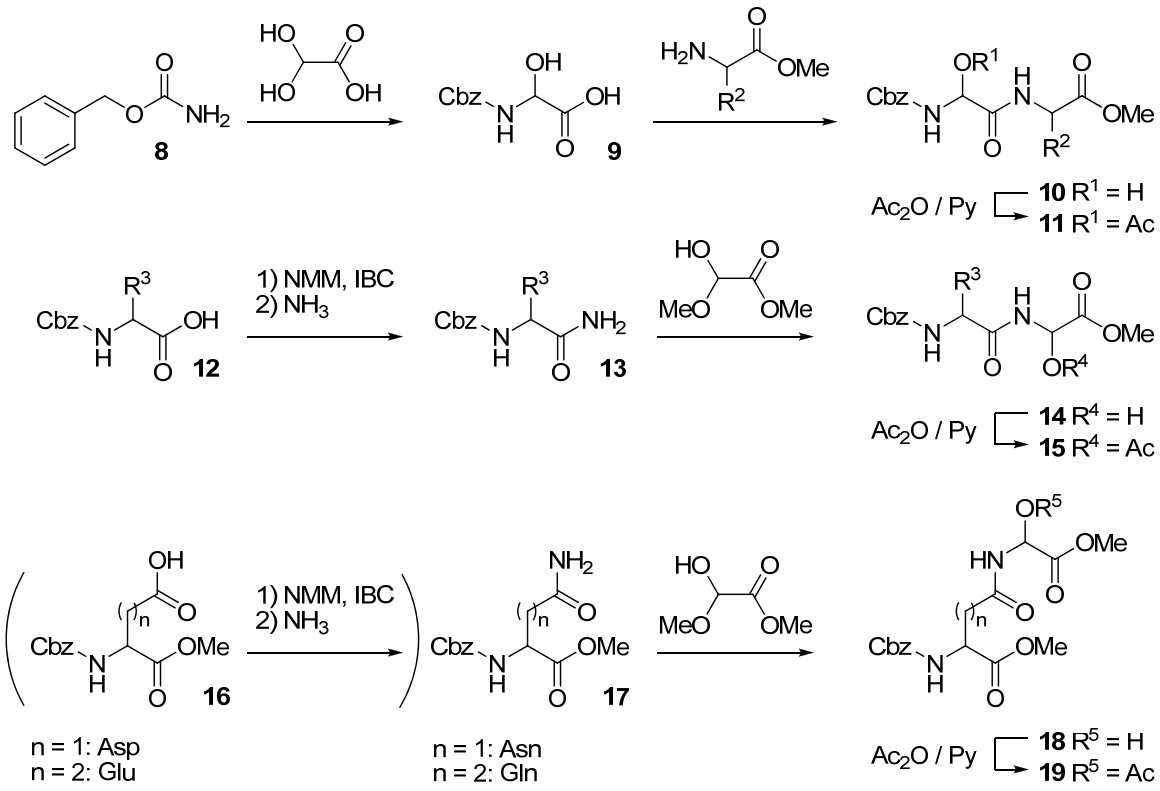


Scheme 3.3

Some amino acids with sensitive functional groups cannot be introduced in peptides via normal (solid phase) peptide chemistry as was shown for α-azidoglycine (Chapter 2.5). For this reason it would be useful to have tools in hand to install these delicate functionalities at the final stage of the synthesis of the peptide. Because very little is known about the introduction of substituents at the α-position of specific amino acids via *N*-acyliminium ion reactions in dipeptides or even larger systems, investigations were made to gain more insight into this field of research. This chapter describes our investigations into the scope and limitations of *N*-acyliminium ion chemistry in dipeptides.

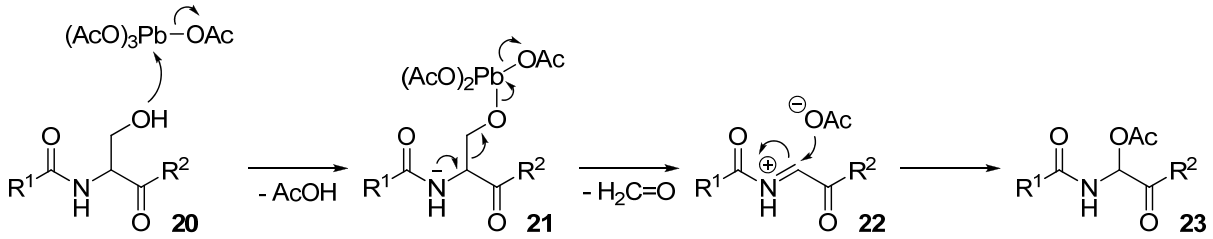
3.2 Synthesis of the precursors

In this chapter dipeptides of α-hydroxyglycine and a second amino acid will serve as *N*-acyliminium ion precursors. In chapter 2 it was shown that α-alkoxyglycines are valuable synthons for the synthesis of various unusual unsaturated amino acids. In dipeptides three sites for generation of the iminium ion can be distinguished. The α-hydroxyglycine unit can either be located on the *N*-terminus, the *C*-terminus or the side chain of the amino acid. This requires a slightly different synthetic sequence for each system. Synthesis of the *N*-terminal iminium precursor starts with condensation of the carbamate of choice (in this case Cbz-NH_2 **8**) with glyoxylic acid followed by an amino acid coupling[13] and finally acylation to arrive at the desired acyliminium precursor **11** (Scheme 3.4). The first step in the synthesis of the dipeptide having the α-acetoxyglycine located on the *C*-terminus or in the side chain was the transformation of *N*-protected amino acids **12** or **16**, respectively, into their corresponding amino amides **13** and **17**. Subsequent condensation with methyl glyoxylate methyl hemiacetal[14] followed by acylation gave the desired dipeptides **15** and **19** (Scheme 3.4). Also naturally derived amides such as the side chains in asparagine (**17**, n = 1) and glutamine (**17**, n = 2) can serve as starting material for the synthesis of *N*-acyliminium ion precursors.



Scheme 3.4

A shorter and more general method to synthesize these α-acetoxyglycine dipeptides was published by the group of Steglich.[15] Oxidative cleavage of the serine or threonine hydroxymethylene side chain moiety by lead tetraacetate under anhydrous conditions led to the direct formation of α-acetoxyglycines (Scheme 3.5). This principle was shown to be applicable for amino acids, di- and tripeptides without the need for protection of other oxidation sensitive amino acids such as cysteine, methionine and tryptophan.[16] The mechanism is proposed to consist of an exchange of an acetate group in $Pb(OAc)_4$ for the serine alcohol (**20**), followed by oxidative fragmentation (**21**, Scheme 3.5). Subsequent take up of an acetoxy anion by the intermediate *N*-acyliminium ion (**22**) furnishes the desired iminium ion precursor α-acetoxyglycine **23**.



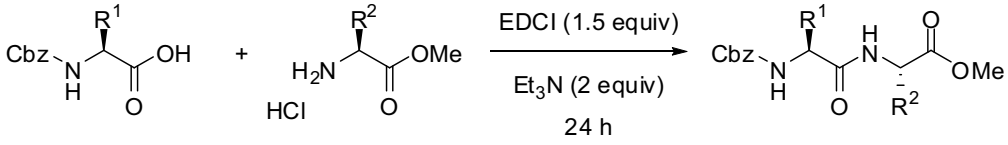
Scheme 3.5

The method using lead tetraacetate is shorter and starting materials are readily available. Furthermore, this method is easier to extend to larger systems such as peptides or even (small) enzymes. Incorporation of serine into an oligopeptides is easy to achieve using solid phase chemistry. The condensation with glyoxylic acid is more difficult, and the resulting hydroxyglycine may give problems during further build-up of the peptide chain. The important advantage of the lead tetraacetate method (despite its toxic properties) is that the introduction of the acetoxyglycine can be postponed to the last step of the synthesis, meanwhile working with a relatively uncomplicated serine derivative.

More recently Kita and co-workers described the oxidation of serine and threonine analogues using a hypervalent iodine reagent,[17] while a radical method was published by the group of Boto.[18] Because these methods lack the use of toxic metals, they could be a valuable alternative to the lead tetraacetate oxidation.

For reasons mentioned above, the oxidation method was chosen over the condensation method. Consequently, a small series of dipeptides was prepared via a peptide coupling strategy, with the serine either on the *N*-terminus, the *C*-terminus or on the side chain. The Cbz-group (benzyloxycarbonyl) was chosen as the protective group for the amine terminus because of the commercial availability of the protected amino acids and its resistance against the reagents used throughout the construction of the peptides.

Table 3.1



entry	R^1	R^2	product		yield (%)
1	CH_2OH	Me	Ser-Ala	**24**	58
2	CH_2OH	*i*-Pr	Ser-Val	**25**	70
3	CH_2OH	CH_2-2-indole	Ser-Trp	**26**	55
4	H	CH_2OH	Gly-Ser	**27**	57
5	Me	CH_2OH	Ala-Ser	**28**	54
6	*i*-Pr	CH_2OH	Val-Ser	**29**	59
7	$(CH_2)_2$-COOH [a]	CH_2OH	γ-Glu-Ser	**30**	85
8	CH_2OH	CH_2OH	Ser-Ser	**31**	53

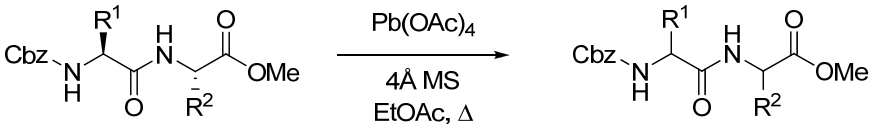
[a]) Cbz-Glu-OMe was used.

Coupling of the *N*-Cbz protected amino acids with amino methyl esters using EDCI and triethylamine gave the desired serine containing dipeptides in moderate yields (Table 3.1). The difficulty of this peptide coupling can be explained by the interaction of the serine alcohol with the coupling reagents. Later it was found that a peptide coupling with serine *tert*-butyl ethers using the mixed anhydride method gave a higher yield and greatly facilitated the

extraction of the product from the reaction mixture. Three *N*-terminal serine dipeptides were constructed (**24**-**26**, entry 1-3, Table 3.1), as well as three *C*-terminal serine dipeptides (**27**-**29** entry 4-6). To complete this series, Cbz-γ-Glu-Ser-OMe **30**, a γ-dipeptide and the serine-serine dipeptide **31** were prepared (entry 7 and 8).

Next, oxidation of the serine containing dipeptides to their α-acetoxyglycine derivatives with lead tetraacetate was investigated. It is important to run the reaction under anhydrous conditions because it is known that (traces of) water will result in formation of hydroxyglycine, instead of acetoxyglycine.[19] So the dipeptides were refluxed in EtOAc in the presence of 4 Å MS and $Pb(OAc)_4$ (1.5 equiv) until TLC showed complete conversion of the starting material. Prolonged exposure of **29** to the oxidation conditions resulted in a lower yield of the desired product **37** (entry 6, Table 3.2). As shown in Table 3.2, oxidation of the *N*-terminal α-acetoxy dipeptides **32** and **33** (entry 1 and 2) gave the desired products in near quantitative yields. The *C*-terminal dipeptides **35** and **36** and γ-acetoxyglycine **38** were obtained in good yields (entry 4, 5 and 7). Oxidation of the indole containing dipeptide **26** gave a mixture of unidentified products (entry 3). Degradation of the indole moiety is the most likely reason for this disappointing result. Protection of the indole nitrogen with a Boc- or Moc-group did not show an improvement of the yield. Also the results of the transformation of bis serine dipeptide **31** into its bis acetoxyglycine analogue **39** were unsatisfactory (entry 8). The negative result for both the tryptophan and bis-serine peptides are in contrast with the results reported by Apitz *et al*.[16] Nevertheless, with an appropriate set of acetoxyglycine dipeptides the stage was set for the exploration of the *N*-acyliminium ion reaction in dipeptides. The synthesized dipeptides were isolated as a 1:1 mixture of diastereomers, which is in agreement with the results of Apitz.

Table 3.2



entry	s.m.	R^1	R^2	Product	R^1	R^2	yield (%)
1	**24**	CH_2OH	Me	**32**	OAc	Me	99
2	**25**	CH_2OH	*i*-Pr	**33**	OAc	*i*-Pr	99
3	**26**	CH_2OH	CH_2-2-indole	**34**	OAc	CH_2-2-indole	0
4	**27**	H	CH_2OH	**35**	H	OAc	67
5	**28**	Me	CH_2OH	**36**	Me	OAc	84
6	**29**	*i*-Pr	CH_2OH	**37**	*i*-Pr	OAc	41[a]
7	**30**	Cbz-Glu(Ser-OMe)-OMe		**38**	Cbz-Glu(Gly(OAc)-OMe)-OMe		75
8	**31**	CH_2OH	CH_2OH	**39**	OAc	OAc	0

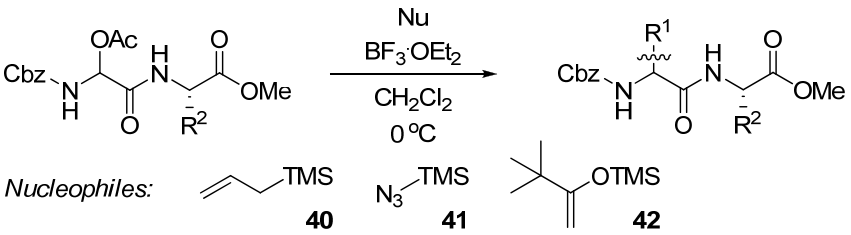
[a]) Reaction time is 24 h.

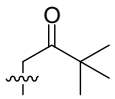
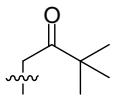
3.3 *N*-Acyliminium ion reactions in dipeptides

3.3.1 Cation formation at the *N*-terminus

The first *N*-acyliminium ion experiments were conducted on dipeptides having the acetoxy moiety on the α-position relative to the *N*-terminus. As a start dipeptide **32** was reacted with $BF_3{\cdot}OEt_2$ (4 equiv) and allyltrimethylsilane (**40**, 4 equiv) in dichloromethane at 0 °C. The desired allylglycine alanine dipeptide **43** was obtained in a promising 73% isolated yield. It appeared that this reaction was generally applicable to various nucleophiles. Reaction of both alanine and valine acetoxyglycine dipeptides **32** and **33** with allyltrimethylsilane (**40**), azidotrimethylsilane (**41**) and the silyl enol ether of *tert*-butyl methyl ketone (**42**) gave the allylglycine, azidoglycine and *tert*-butyl methyl ketoglycine containing dipeptides **43**-**48** in good yields (Table 3.3).

Table 3.3



entry	s.m.	R^2	nucleophile	product	R^1	R^2	yield (%)
1	**32**	Me	**40**	**43**		Me	73
2	**33**	*i*-Pr	**40**	**44**		*i*-Pr	86
3	**32**	Me	**41**	**45**		Me	72
4	**33**	*i*-Pr	**41**	**46**		*i*-Pr	60
5	**32**	Me	**42**	**47**		Me	65
6	**33**	*i*-Pr	**42**	**48**		*i*-Pr	68

Reaction conditions: dipeptide, Nu (4 equiv) and $BF_3{\cdot}OEt_2$ (4 equiv) in CH_2Cl_2 at 0 °C.

The isopropyl group in the valine dipeptides had hardly any influence on the stereochemical outcome of the reaction. For all three products **44**, **46** and **48** (entry 2, 4 and 6, Table 3.3) the products were isolated as near 1:1 mixtures of diastereomers. Due to the transoid configuration of the amide bond, the approach of the nucleophiles to the *N*-

acyliminium ion will not be effected by steric hindrance of the isopropyl group, which is quite remote from the reaction site.

In order to create shortcuts in the synthesis of the acetoxyglycine derivatives, *N*-Cbz serine methyl ester **49** was oxidized in the presence of an excess allyltrimethylsilane **40** (4 equiv). Instead of the desired allylglycine **51** a mixture of hydroxy- and acetoxyglycine and an unidentified byproduct were obtained (Figure 3.1). During the formation of **22** from **21** (Scheme 3.5), the leaving acetoxy anion is in close proximity to the *N*-acyliminium ion favoring formation of **50** over the desired product **51**. Oxidation of allyltrimethylsilane **40** by $Pb(OAc)_4$ might also be a reason for failure of this reaction.

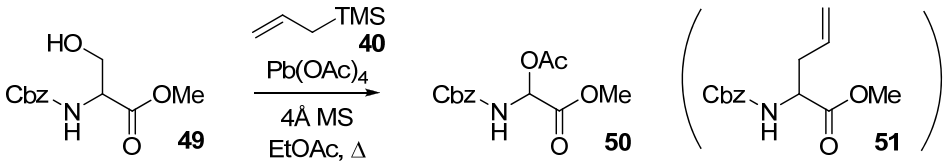
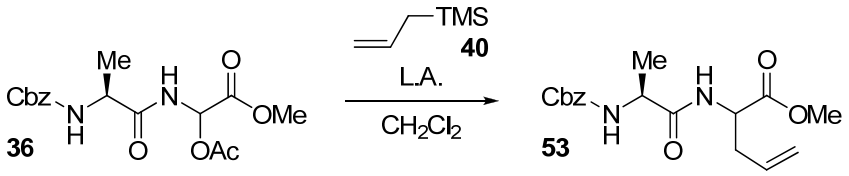


Figure 3.1

3.3.2 Cation formation at the *C*-terminus

When the *C*-terminal α-acetoxyglycine dipeptide **36** was reacted with allylsilane **40** under the same reaction conditions as used for the *N*-terminal α-acetoxyglycine dipeptides, hardly any product was obtained. Increasing the amounts of $BF_3{\cdot}OEt_2$ and the nucleophile to 8 and 12 equiv, respectively, resulted in a maximum isolated yield of 25% (entry 1-3, Table 3.4). Raising the reaction temperature to room temperature (entry 2) led to a substantial amount of unidentified side products, and was therefore not an option.

Table 3.4

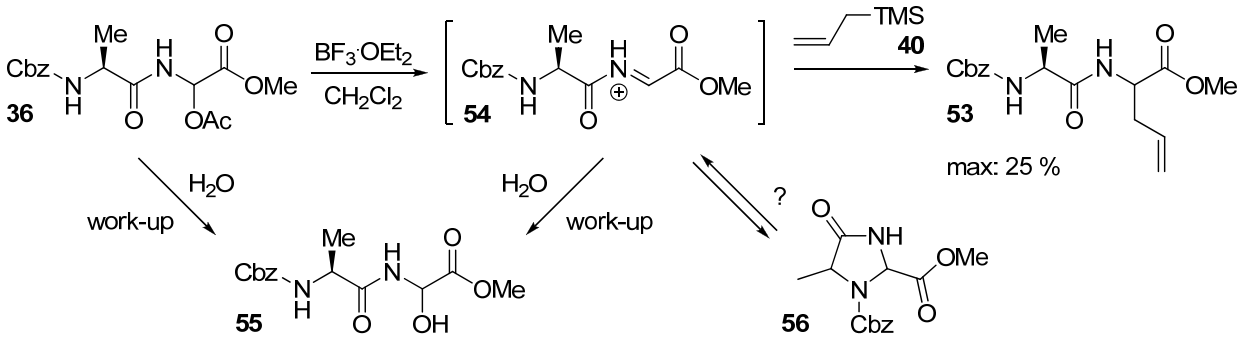


entry	equiv **40**	Lewis Acid	equiv L.A.	time at 0 °C	time at r.t.	yield (%)
1	4	$BF_3{\cdot}OEt_2$	4	60 h	-	18[a]
2	4	$BF_3{\cdot}OEt_2$	8	5 h	10 h	25
3	12	$BF_3{\cdot}OEt_2$	6	24 h	-	15
4	4	TIPSOTf	0.05	18 h	-	-
5	8	TIPSOTf	1	2 h	1 h	15
6	8	TIPSOTf	0.5	-	2 h	42[b]
7	8	$Sn(OTf)_2$	0.5	-	24 h	46

[a]) Hydroxyglycine containing dipeptide **55** isolated in 50% yield; [b]) many by-products formed (TLC).

One other aspect that could play a role in the cumbersome *C*-terminal α-acetoxy dipeptide iminium reaction is the Lewis acid. Until now $BF_3{\cdot}OEt_2$ was the Lewis acid of choice, mainly because of its low cost and ease of handling. For this part of the research, it was decided to look at other Lewis acids such as TIPSOTf and $Sn(OTf)_2$. When **36** was reacted with 5 mol % TIPSOTf at 0 °C for 18 h, no product was obtained (entry 4, Table 3.4). Increasing the amounts of Lewis acid (1 equiv) and nucleophile (8 equiv) did lead to formation of the desired allylglycine dipeptide **53** in 15% yield (entry 5) after 2 h at 0 °C and 1 h at room temperature. When the reaction was carried out for 2 h at room temperature with less TIPSOTf (0.5 equiv), the yield could be improved to 42% yield (entry 6). With $Sn(OTf)_2$ as Lewis acid the same reaction gave **53** in 46% yield after 24 h (entry 7). These results clearly show a decreased reactivity of the *C*-terminal dipeptide *N*-acyliminium ion compared to its *N*-terminal analogue.

In a few cases hydroxyglycine dipeptide **55** was isolated in about 50% yield (entry 1). Formation of this compound can either be explained by attack of water on the intermediate iminium ion **54**, or by hydrolysis of the unreacted acetoxyglycine **36**, both during work-up (Scheme 3.6). However, experiments with isotopically labeled H_2O should provide more insight in the formation of **55**.

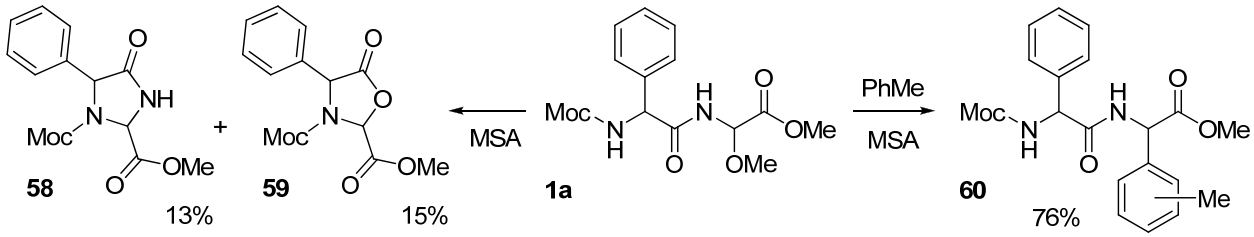


Scheme 3.6

In 1993, the group of Ben-Ishai reported their results on a similar reaction.[4] When Moc-Phg-Gly(OMe)-OMe **1a** (Scheme 3.7) was treated with methanesulphonic acid, instead of the desired benzolactam **2a** (Scheme 3.1), oxazolidinone **59** and imidazolidinone **58** were isolated in 15% and 13% respectively. Formation of **58** can be explained by addition of the carbamate nitrogen to the acyliminium ion. Oxazolidinone **59** is most likely the result of series of events which take place after the formation of **58**. These reactions involve the cleavage of the CH-NH bond, followed by attack of the amide carbonyl on the formed *N*-acyliminium ion and hydrolysis of the resulting imine.

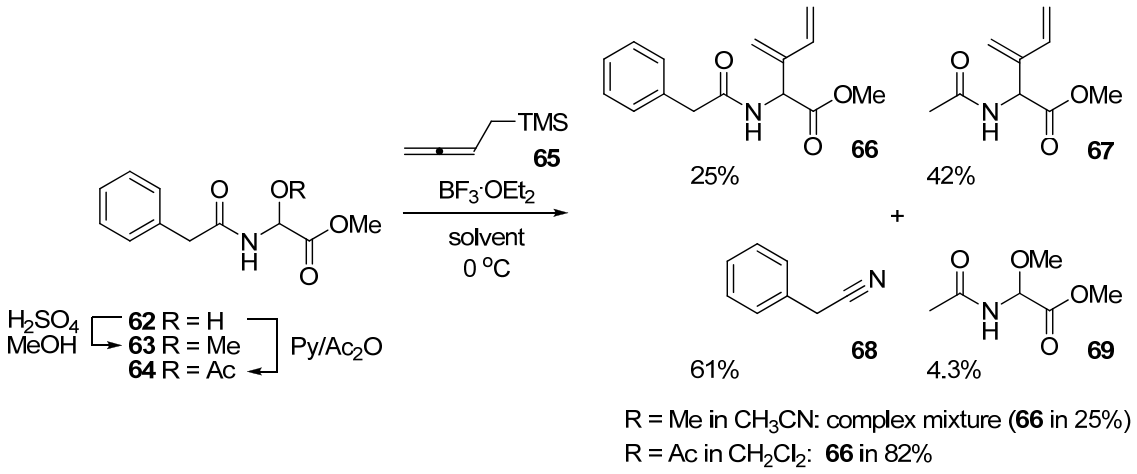
When the reaction was performed in the presence of toluene as the intermolecular nucleophile, addition product **60** could be isolated in 76% yield. In our case, the formation of imidazolidinone **56** was not observed, and not much is know about the stability of this class of compounds under acidic conditions. The results published by Ben-Ishai show that

intermolecular attack of a nucleophile is favored over the intramolecular addition of the carbamate nitrogen. Therefore in our case we expect that addition of allyltrimethylsilane **40** to iminium ion **54** is favored over the formation of **56**, leading to the desired dipeptide **53.**



Scheme 3.7

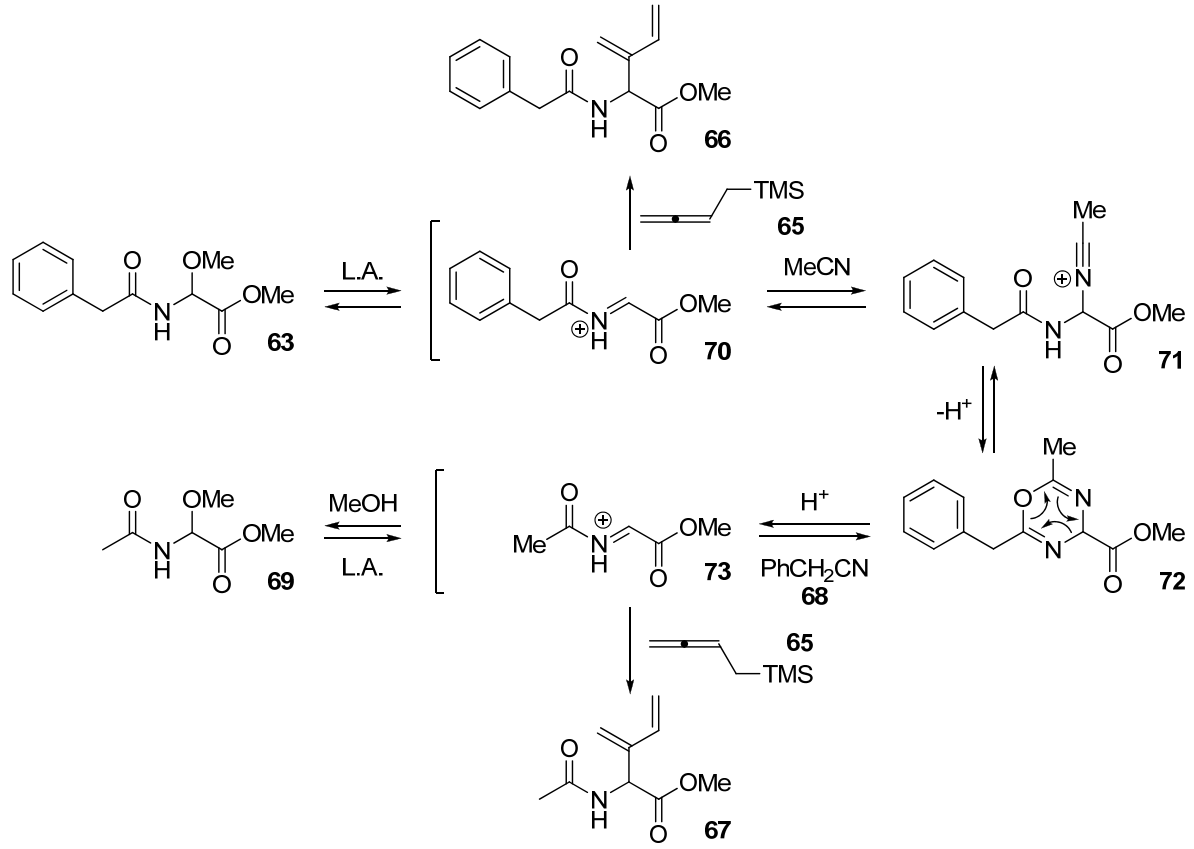
In order to obtain more information about the reactivity of amide-stabilized carbocations like **54**, (compared to the carbamate-stabilized carbocation ions described in Table 3.3) model substrate phenacetyl hydroxyglycine methyl ester **62** was prepared by the condensation of phenacetylacetamide and methyl glyoxylate methyl hemiacetal (see Chapter 2.2). Subsequent conversion into its methoxy- and acetoxyglycine derivatives **63** and **64** provided the desired *N*-acyliminium ion precursors (Scheme 3.8).



Scheme 3.8

When **63** was treated with allenylmethyltrimethylsilane **65** (See chapter 2.3) and $BF_3{\cdot}OEt_2$ in acetonitrile the reaction appeared to be sluggish. After 1 h at 0 °C still a large amount of starting material was present in the reaction mixture (TLC), whereas in the carbamate cases product formation would have been nearly complete (Chapter 2). After additional stirring at room temperature for 6 h a complex mixture, containing **66** (25%), **67** (42%), **68** (61%) and **69** (4%) was separated via column chromatography. Formation of all four products can be explained by a series of equilibrium reactions which take place after

formation of the *N*-acyliminium ion **70** (Scheme 3.9). First of all, addition of allenylmethyltrimethylsilane **65** to **70** gives phenacetyl diene product **66**. However, on addition of acetonitrile to **70**, nitrilium ion **71** is formed.[20] This species can cyclize to the six-membered intermediate **72** via a Ritter reaction,[21,22] which is facilitated by the transoid amide bond conformer. The reaction of *N*-acyliminium ion **70** with acetonitrile to give **72** can also be viewed as a reversible hetero Diels-Alder reaction.[23] The reverse reaction of **72** (retro-Diels-Alder) can equally well produce *N*-acyliminium ion **73** and phenylacetonitrile (**68**). Further reactions of **73** explain the formation of **67** and **69**. Taken this into account, the total yield of iminium ion adducts **66** and **67** depicted in Scheme 3.8 is 67%. From the product distribution (Scheme 3.8) it can be concluded that formation of the nitrilium ion **71** (Scheme 3.9) and further equilibration to iminium ion **73** is favored over direct addition of **65** to iminium ion **70**. A discussion on this observation will be given later.

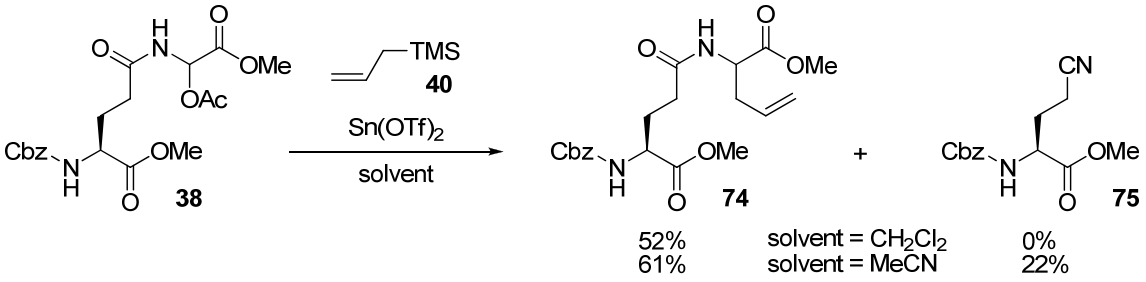


Scheme 3.9

When the solvent was replaced by dichloromethane and the acetoxy used as leaving group (**64**, Scheme 3.8), a four-fold decrease in reaction time was observed, and the desired phenacetyl diene product **66** was obtained in 82% yield without formation of the byproducts **67**-**69**. Again, the solvent was shown to play a crucial role in a reaction (see Chapter 2.5). But still, this does not explain the low yield for the reaction of *C*-terminal iminium ion precursor dipeptide **36** depicted in Table 3.4.

3.3.3 Cation formation in the side chain

To complete the series of iminium ion chemistry in dipeptides, γ-glutamyl dipeptide **38** was reacted at room temperature with allyltrimethylsilane **40** (4 equiv) and $Sn(OTf)_2$ (0.5 equiv) in both dichloromethane and acetonitrile. When the reaction was performed in CH_2Cl_2, the desired product **74** was obtained in 52% isolated yield, which is in agreement with the results obtained for the alanine dipeptide **36** (Table 3.4). When acetonitrile was used as the solvent, γ-glutamyl allylglycine **74** was obtained in 61% together with γ-glutanitrile[24] **75** in 22%. Remarkably, no other by-products of the Ritter reaction were isolated, or visible in the ^{1}H-NMR of the crude product. In the case of the glutamyl side-chain the equilibrium of the Ritter reaction between the dipeptide iminium ion (**70**-like) and *N*-acetyl iminium ion **73** lies apparently at the dipeptide side, instead of the acetyl side which is the case for the phenylacetamide (Scheme 3.9).



Scheme 3.10

3.3.4 Comparison of cations

From these results it can be concluded that there is a considerable difference in reactivity of the dipeptide between *N*-terminal carbamate stabilized iminium ions and *C*-terminal or γ-amide stabilized iminium ions. The key difference between the systems is the substitution pattern of the acyliminium ion. For the amino acid derivatives described in Chapter 2, the resulting iminium ion is a carbamate ester (**A**, Figure 3.2). In the case of the *N*-terminal dipeptides (**B**), the iminium ion is flanked by a carbamate and an amide. For the *C*-terminal and γ-dipeptides (**C**) the cation is located between an amide and an ester. These different substitution patterns exert different steric and electronic influences, resulting in different stability and reactivity of the acyliminium ions **A** - **C**.

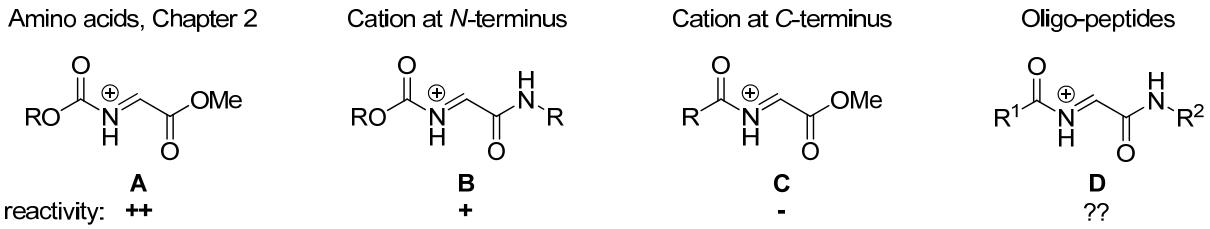
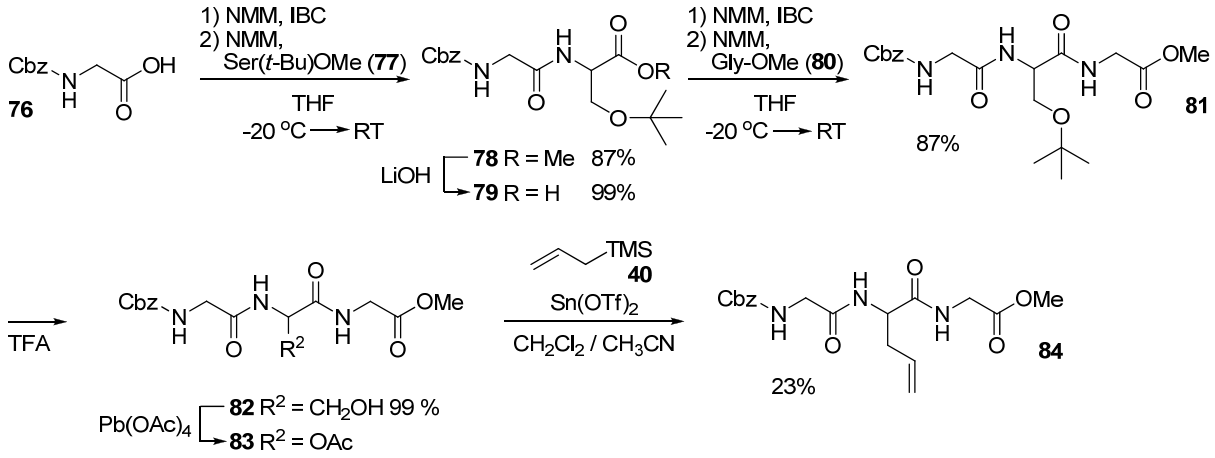


Figure 3.2

In the case where the cation is formed at the *C*-terminus, formation of hydroxyglycine containing dipeptide **55** (Scheme 3.6) suggests two possibilities. Either the acetoxyglycine is too stable, or the iminium ion is not reactive enough. Because the yield of allylglycine containing dipeptide **53** did not increase when the concentration nucleophile was raised, unreactivity of the iminium ion is probably not the reason. Apparently, a good electron withdrawing substituent on the nitrogen is a prerequisite for the reactivity of the iminium ion. In the case of phenylacetamide derivative **64** the benzyl group on the amide is just electron poor enough to allow for a smooth iminium ion reaction. When the amide is substituted with an alkyl chain, such as the isobutyl part of valine, or the propyl chain of glutamic acid, the electron withdrawing properties are insufficient for the iminium reaction to proceed, requiring relatively high temperatures and long reaction times. Because there is not much difference between the reactivity of iminium ions **A** and **B** (Figure 3.2), the electronic properties of the *C*-terminus (either an electron withdrawing ester or a neutral amide) do not seem to have a big effect when there is a good electron poor substituent on the nitrogen. Therefore it would be interesting to investigate the reactivity of iminium ions which are flanked by two amides (**D**, Figure 3.2), and compare the results with the **C**-type iminium ions.

Thus, a tripeptide was synthesized containing a serine as the second amino acid. To avoid difficulties due to diastereomeric mixtures and steric hindrance, the two other amino acids were chosen to be glycines. The tripeptide was built up from commercially available building blocks via solution phase peptide coupling methods. First, serine *tert*-butyl ether methyl ester **77** was coupled to *N*-Cbz-glycine **76** (Scheme 3.11).[25] Saponification of the resulting dipeptide **78**, and subsequent coupling with glycine methyl ester **80** gave the desired protected Gly-Ser-Gly tripeptide **81**. TFA-induced alcohol deprotection gave oxidation precursor **82** in 99% yield. Lead tetraacetate oxidation of **82** which should give *N*-acyliminium ion precursor **83** proved to be troublesome, as several byproducts were formed according to TLC. After work-up the crude α-acetoxyglycine containing tripeptide **83** was obtained in quantitative yield but with reduced purity (~75%, NMR). Purification appeared to be very difficult as it decomposed on the column.[26]



Scheme 3.11

The crude α-acetoxyglycine containing tripeptide **83** was subjected to conditions which gave the best results for the *C*-terminal iminium ion dipeptide reaction. Remarkably, **83** did not dissolve in dichloromethane. Therefore, acetonitrile was added as a co-solvent in a 5:1 ratio, running the risk of the occurrence of the Ritter reaction as one of the side reactions.[27] Nevertheless, after work-up and purification by column chromatography, the desired protected Gly-Allylglycine-Gly tripeptide **84** was isolated in an unoptimized 23% yield.

On the basis of this result, little can be said about the reactivity of the iminium ion located between two amides. However, the reaction does appear to be slow, and seems to resemble the *C*-terminal iminium ion cases.

3.4 Conclusion

Investigations into the intramolecular *N*-acyliminium ion reactions in di- and tripeptides are described in this chapter. The iminium ion precursors are prepared via a straightforward synthesis. Coupling of a suitably protected serine with an other amino acid, followed by a lead tetraacetate mediated oxidation of the serine provides the desired α-acetoxyglycine containing dipeptides in good yields.

The reactivity of the iminium ions located at the *N*-terminus of the dipeptide resemble the reactivity of *N*-acyliminium ions in amino acid. Addition of allylsilane, silyl enol ether and azidosilane to such iminium ions of several dipeptides proceed in satisfactory yields. Dipeptides with the iminium ion placed at the *C*-terminus proved to be less reactive. Reactions need higher temperature and longer time for completion and yields are significantly lower compared to the *N*-terminal iminium ions. It was discovered that when the reaction was performed in acetonitrile, the solvent interfered seriously. This side reaction could be avoided by performing the reaction in dichloromethane. Synthesis and reaction of a tripeptide iminium ion precursor proved to be equally successful.

From these results it can be concluded that the addition of nucleophiles works best on iminium ions with electron withdrawing acyl substituents on the nitrogen. These results provide a good starting point for further optimization of iminium ion reactions in oligopeptides.

3.5 Acknowledgements

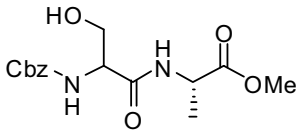
N. Dailly and L. Navío Marín are gratefully acknowledged for their large contributions to this chapter.

3.6 Experimental section

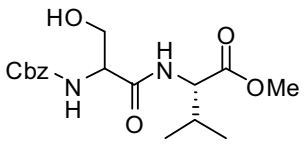
General remarks

For general remarks and the synthesis of **61**, **62**, **63** and **65**, see Chapter 2.

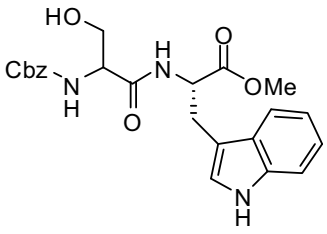
General procedure A: Synthesis of serine containing dipeptides. To a solution of Cbz-protected amino acid (1 g) in DCM (25 mL) were added the amino acid methyl ester (1 equiv) and EDCI (1.5 equiv) followed by Et_3N (2 equiv). The resulting solution was stirred at room temperature overnight. The reaction mixture was poured on saturated aqueous NH_4Cl solution and extracted with EtOAc three times. The organic layer was washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo* to give the crude product which was purified by column chromatography.



(2*S*)-Methyl 2-(2-(benzyloxycarbonylamino)-3-hydroxypropanamido)-propanoate (Cbz-Ser-Ala-OMe, 24). According to general procedure A, **24** (0.791 g, 2.43 mmol, 58%) was obtained as a white solid after column chromatography (PE/EtOAc 2:3). ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.37 (m, 5H), 6.83 (br s, 1H), 5.75 (br s, 1H), 5.16 (m, 2H), 4.59 (m, 1H), 4.28 (m, 1H), 4.10 (m, 1H), 3.78 (s, 3H), 3.69 (m, 1H), 3.00 (br s, 1H), 1.43 (d, *J* = 7.3 Hz, 3H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 173.61, 170.78, 156.65, 136.21, 128.75, 128.45, 128.26, 67.45, 63.23, 55.62, 52.88, 48.50, 17.89 ppm; R_f (PE/EtOAc 2:3) = 0.23.

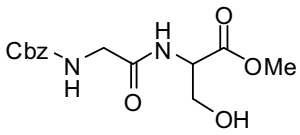


(2*S*)-Methyl 2-(2-(benzyloxycarbonylamino)-3-hydroxypropanamido)-3-methylbutanoate (Cbz-Ser-Val-OMe, 25). According to general procedure A, **25** (1.198 g, 3.40 mmol, 70%) was obtained as a white solid after column chromatography (PE/EtOAc 2:3). ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.37 (m, 5H), 6.89 (br s, 1H), 5.83 (br d, *J* = 6.9 Hz, 1H), 5.17 (m, 2H), 4.52 (dd, *J* = 8.8, 4.8 Hz, 1H), 4.29 (m, 1H), 4.15 (m, 1H), 3.77 (s, 3H), 3.68 (m, 1H), 3.09 (br s, 1H), 2.21 (m, 1H), 0.93 (d, *J* = 6.9 Hz, 3H), 0.89 (d, *J* = 6.9, 3H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 172.49, 171.22, 156.72, 136.19, 128.63, 128.30, 128.13, 67.31, 62.95, 57.62, 55.65, 52.41, 30.90, 19.08, 17.79 ppm; HRMS(FAB): calculated for $[C_{17}H_{25}N_2O_6+H]^+$: 353.1718, found: 353.1713; R_f (PE/EtOAc 2:3) = 0.36.

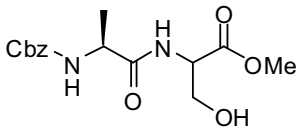


(2*S*)-Methyl 2-(2-(benzyloxycarbonylamino)-3-hydroxypropanamido)-3-(1H-indol-3-yl)propanoate (Cbz-Ser-Trp-OMe, 26). To a stirred solution of Cbz-Ser-OH (0.543 g, 2.29 mmol) and H-Trp-OMe (0.500 g, 2.29 mmol) in CH_2Cl_2 (20 mL) were added DCC (0.496 g, 2.41 mmol) and HOBt (0.325 g, 2.41 mmol), after 5 min, followed by Et_3N (0.463 g, 0.64 mL, 4.58 mmol). The white suspension was stirred at room temperature for another 16 h after which it was filtered over a glasfilter and extracted with EtOAc. The organic layer was washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by precipitation from CH_2Cl_2/MTBE/pentane to give **26** (0.552 g, 1.26 mmol, 55%) as a white solid. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.12 (br s, 1H), 7.52 (d, *J* = 7.6 Hz, 1H), 7.36 (m, 6H), 7.19 (t, *J* = 7.2 Hz, 1H), 7.12 (t, *J* = 7.4 Hz, 1H), 6.96 (d, *J* = 2.2 Hz, 1H), 6.93 (d, *J* = 7.6 Hz, 1H), 5.71 (br d, *J* = 7.2 Hz, 1H), 5.07 (s, 2H), 4.90 (dt, *J* = 5.6, 7.6 Hz, 1H), 4.22 (br s,

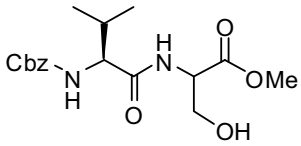
1H), 3.97 (br d, *J* = 10.8 Hz, 1H), 3.72 (s, 3H), 3.59 (dd, *J* = 5.7, 11.0 Hz, 1H), 3.32 (m, 2H), 2.97 (br s, 1H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 172.59, 171.00, 156.74, 136.27, 136.12, 128.56, 127.99, 127.30, 121.90, 119.32, 118.23, 111.58, 108.91, 67.17, 62.56, 56.27, 53.22, 50.18, 27.25 ppm; HRMS(FAB): calculated for $[C_{23}H_{25}N_3O_6+H]^+$: 440.1822, found: 440.1822.



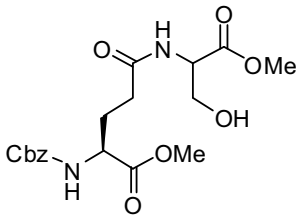
Methyl 2-(2-(benzyloxycarbonylamino)acetamido)-3-hydroxypropanoate (Cbz-Gly-Ser-OMe, 27). According to general procedure A, **27** (0.852 g, 2.75 mmol, 57%) was obtained as a white solid after column chromatography (EtOAc). ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.32 (m, 5H), 7.05 (br d, *J* = 7.2 Hz, 1H), 5.63 (br s, 1H), 5.14 (s, 2H), 4.67 (m, 1H), 3.95 (m, 4H), 3.79 (s, 3H), 3.00 (s, 1H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 171.06, 169.99, 157.06, 136.12, 128.55, 128.23, 128.05, 67.23, 62.44, 54.76, 52.74, 44.17 ppm; HRMS(FAB): calculated for $[C_{23}H_{25}N_3O_6+H]^+$: 311.1243, found: 311.1255; R_f (EtOAc) = 0.25.



Methyl 2-((*S*)-2-(benzyloxycarbonylamino)propanamido)-3-hydroxypropanoate (Cbz-Ala-Ser-OMe, 28). According to general procedure A, **28** (0.786 g, 3.42 mmol, 54%) was obtained as a white solid after column chromatography (PE/EtOAc 2:3). ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.37 (m, 5H), 6.84 (br s, 1H), 5.30 (br s, 1H), 5.13 (m, 2H), 4.66 (m, 1H), 4.25 (m, 1H), 3.98 (dd, *J* = 5.6, 3.4 Hz, 2H), 3.82 (s, 3H), 2.64 (s, 1H), 1.44 (d, *J* = 7.0 Hz, 3H) ppm; HRMS(FAB): calculated for $[C_{15}H_{20}N_2O_6+H]^+$: 325.1400, found: 325.1401; R_f (PE/EtOAc 2:3) = 0.25.

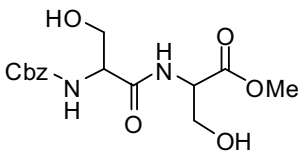


Methyl 2-((*S*)-2-(benzyloxycarbonylamino)-3-methylbutanamido)-3-hydroxypropanoate (Cbz-Val-Ser-OMe, 29). According to general procedure A, **29** (0.840 g, 2.38 mmol, 59%) was obtained as a white solid after column chromatography (PE/EtOAc 2:3). ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.36 (m, 5H), 6.71 (br d, *J* = 7.2 Hz, 1H), 5.35 (br d, *J* = 7.9 Hz, 1H), 5.13 (m, 2H), 4.68 (m, 1H), 3.99 (m, 3H), 3.87 (s, 3H), 2.58 (br s, 1H), 2.15 (m, 1H), 1.01 (dd, J = 12.3 Hz, 6.8 Hz, 6H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 171.94, 170.96, 157.03, 136.27, 128.74, 128.41, 128.26, 67.40, 62.97, 60.77, 54.84, 52.91, 31.37, 19.35, 18.22 ppm; HRMS(FAB): calculated for $[C_{17}H_{24}N_2O_6+H]^+$: 353.1713, found: 353.1718; R_f (PE/EtOAc 2:3) = 0.25.



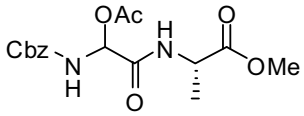
(2*S*)-Methyl 2-(benzyloxycarbonylamino)-5-(3-hydroxy-1-methoxy-1-oxopropan-2-ylamino)-5-oxopentanoate (Cbz-Glu(Ser-OMe)OMe, 30). To a stirred solution of Cbz-Ser-OH (5.00 g, 21.1 mmol) and H-Ser-OMe (3.28 g, 21.1 mmol) in CH_2Cl_2 (90 mL) were added EDCI (4.45 g, 23.2 mmol) and HOBt (3.13 g, 32.2 mmol), after 5 min followed by Et_3N (7.41 mL, 52.7 mmol). The white suspension was stirred at room temperature for another 72 h after which saturated aqueous NH_4Cl solution was added and the mixture was extracted with EtOAc three times. The organic layer was washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by column chromatography (CH_2Cl_2/IPA to give **30** (4.43 g, 11.2 mmol, 53%) as a white solid. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.32 (m, 5H), 6.91 (br s, 1H), 6.00 (br s, 1H), 5.06 (s, 2H), 4.63 (m, 1H), 4.34 (m, 1H), 1.91 (br s, 2H), 3.72 (s, 3H), 3.70 (s, 3H), 2.32 (m, 3H), 1.86 (m, 1H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 172.69, 172.13,

171.18, 156.63, 136.06, 128.61, 128.33, 128.16, 67.30, 62.66, 54.95, 53.18, 52.68, 52.65, 31.87, 28.28 ppm; HRMS(FAB): calculated for $[C_{18}H_{24}N_2O_8+H]^+$: 397.1611, found: 397.1617.

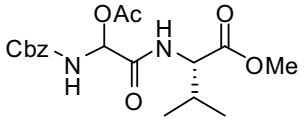


Methyl 2-(2-(benzyloxycarbonylamino)-3-hydroxypropanamido)-3-hydroxypropanoate (Cbz-Ser-Ser-OMe, 31). To a stirred solution of Cbz-Glu-OH (1.50 g, 5.08 mmol) and H-Ser-OMe (0.790 g, 5.08 mmol) in CH_2Cl_2 (30 mL) were added EDCI (1.07 g, 5.59 mmol) and HOBt (0.755 g, 5.59 mmol), after 5 min followed by Et_3N (1.30 g, 1.80 mL, 12.7 mmol). The white suspension was stirred at room temperature for another 72 h after which saturated aqueous NH_4Cl solution was added and the mixture was extracted with EtOAc three times. The organic layer was washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo* to give the crude product which was purified by precipitation from CH_2Cl_2/MTBE to give **31** (1.87 g, 4.31 mmol, 85%) as a white solid. ^{1}H-NMR (400 MHz, MeOD): δ = 7.34 (m, 5H), 5.14 (s, 2H), 4.57 (t, *J* = 3.6 Hz, 1H), 4.31 (t, *J* = 5.3 Hz, 1H), 3.93 (dd, *J* = 4.2, 11.3 Hz, 1H), 3.83 (m, 3H), 3.67 (s, 3H) ppm; ^{13}C-NMR (100 MHz, MeOD): δ = 171.32, 170.52, 156.93, 136.50, 127.91, 127.47, 127.32, 66.30, 61.69, 61.22, 56.77, 54.69, 51.31 ppm; IR (neat): ν = 3402, 2953, 2884, 1742, 1664, 1434, 1356, 1214, 1064 cm^{-1}; HRMS(FAB): calculated for $[C_{15}H_{20}N_2O_7+H]^+$: 341.1349, found: 341.1354; R_f (DCM/IPA 9:1) = 0.26.

General procedure B: Lead tetraacetate oxidation of serine containing dipeptides. To a solution of serine containing dipeptide in dry EtOAc (0.1 M) were added 4 Å MS (200-300% $^m/_m$) and $Pb(OAc)_4$ (1.5 equiv). The resulting purple-grey suspension was stirred at reflux until TLC showed complete consumption of s.m. (usually 3-6 h). After cooling to room temperature the reaction mixture was filtered over Celite® and the yellow filtrate was vigorously stirred with 5% aqueous citric acid solution (100% $^v/_v$) for 10 min. The layers of the colorless biphasic system were separated and the organic layer was washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product which used as such in the next reaction.

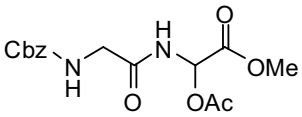


(2*S*)-Methyl 2-(2-acetoxy-2-(benzyloxycarbonylamino)acetamido)-propanoate (32). According to general procedure B, treatment of **24** (0.350 mg, 1.08 mmol) with $Pb(OAc)_4$ (0.665 g, 1.50 mmol) and 4 Å MS (1 g) in EtOAc (10 mL) for 4.5 h gave **32** as a colorless oil (~1:1 mixture of diastereomers, 0.378 g, 1.07 mmol, 99%). ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.38 (m, 5H), 7.06 (br s, 0.5H), 6.96 (br s, 0.5H), 6.46 (br s, 0.5H) 6.40 (br s, 0.5H), 5.16 (m, 3H), 4.58 (m, 1H), 3.78 (s, 3H), 2.17 (s, 3H), 1.45 (d, *J* = 7.2 Hz, 3H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 173.02, 172.53, 172.46, 164.98, 154.95, 135.62, 128.43, 128.21, 128.06, 75.15, 75.06, 67.42, 52.46, 48.35, 20.46, 17.69, 17.58 ppm; IR (neat): ν = 3398, 2965, 1735, 1682, 1523, 1456, 1221, 1057 cm^{-1}; R_f (PE/EtOAc 2:3) = 0.42.

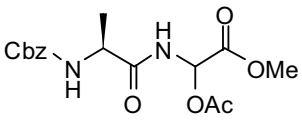


(2*S*)-Methyl 2-(2-acetoxy-2-(benzyloxycarbonylamino)acetamido)-3-methylbutanoate (33). According to general procedure B, treatment of **25** (0.350 mg, 0.993 mmol) with $Pb(OAc)_4$ (0.688 g, 1.55 mmol) and 4 Å MS (1 g) in EtOAc (10 mL) for 4.5 h gave **33** as a colorless oil (~1:1 mixture of diastereomers, 0.373 g, 0.981 mmol, 99%). ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.39 (m, 5H), 7.01 (br s, 0.5H), 6.89 (br s, 0.5H), 6.49 (m, 1H), 5.19 (m, 3H), 3.77 (s, 3H), 2.23, (m, 1H), 2.12 (s, 3H), 0.94 (m, 6H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 173.59, 167.16, 165.29, 154.77, 135.60, 128.56, 128.40, 128.21, 75.42, 75.24,

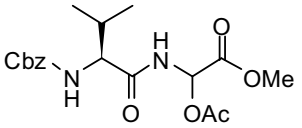
67.61, 57.60, 57.49, 52.35, 52.33, 31.05, 20.61, 18.85, 17.49 ppm; IR (neat): ν = 3417, 2965, 1740, 1681, 1520, 1218 cm^{-1}; HRMS(FAB): calculated for $[C_{18}H_{24}N_2O_7+H]^+$: 382.1662, found: 381.1659; R_f (PE/EtOAc 2:3) = 0.56.



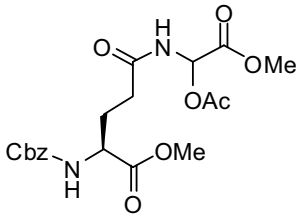
Methyl 2-acetoxy-2-(2-(benzyloxycarbonylamino)acetamido)acetate (35). According to general procedure B, **27** (0.400 g, 1.30 mmol) was treated with $Pb(OAc)_4$ (0.767 g, 1.73 mmol) and 4 Å MS (1 g) in EtOAc (12 mL) for 3 h to give **35** (~1:1 mixture of diastereomers, 0.295 g, 0.871 mmol, 67%) as a pink oil. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.38 (m, 6H), 6.44 (d, *J* = 9.0 Hz, 1H), 5.42 (br s, 1H), 5.16 (s, 2H), 3.99 (m, 2H), 3.82 (s, 3H), 2.13 (s, 3H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 170.43, 169.23, 167.12, 156.70, 136.14, 128.81, 128.55, 128.38, 72.04, 67.66, 53.65, 44.64, 20.81 ppm; HRMS(FAB): calculated for $[C_{15}H_{28}N_2O_7+H]^+$: 339.1192, found: 339.1189; R_f (PE/EtOAc 2:3) = 0.43.



Methyl 2-acetoxy-2-((*S*)-2-(benzyloxycarbonylamino)propanamido)-acetate (36). According to general procedure B, **28** (0.400 g, 1.23 mmol) was treated with $Pb(OAc)_4$ (0.737 g, 1.66 mmol) and 4 Å MS (1 g) in EtOAc (12 mL) for 4 h to give **36** (~1:1 mixture of diastereomers, 0.364 g, 1.03 mmol, 84%) as a colorless oil which solidified upon standing. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.59 (br s, 0.5H), 7.55 (br s, 0.5H), 7.30 (m, 5H), 6.42 (m, 1H), 5.34 (m, 1H), 5.15 (s, 2H), 4.35 (br s, 1H), 3.81 (s, 3H), 2.12 (s, 3H), 1.43 (d, *J* = 6.3 Hz, 3H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 172.65, 172.61, 170.17, 170.16, 167.03, 166.99, 156.07, 156.00, 136.07, 136.04, 128.55, 128.24, 128.06, 72.11, 72.08, 67.22, 67.18, 53.29, 50.39, 20.57, 18.38 ppm; IR (neat): ν = 3321, 3036, 2957, 1747, 1694, 1531, 1454, 1375, 1344, 1219, 1042 cm^{-1}; R_f (PE/EtOAc 2:3) = 0.45.



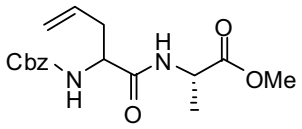
Methyl 2-acetoxy-2-((*S*)-2-(benzyloxycarbonylamino)-3-methylbutan-amido)acetate (37). According to general procedure B, **29** (0.400 g, 1.14 mmol) was treated with $Pb(OAc)_4$ (0.688 g, 1.55 mmol) and 4 Å MS (1 g) in EtOAc (12 mL) for 24 h to give **37** (~1:1 mixture of diastereomers, 0.180 g, 0.473 mmol, 41%) as a white solid after column chromatography (PE/EtOAc 2:3). ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.37 (m, 5H), 7.20 (br m, 1H), 6.41 (d, *J* = 8.9 Hz, H), 5.31 (br m, 1H), 5.15 (s, 2H), 4.16 (broad s, 1H), 3.83 (s, 3H), 2.20 (m, 1H), 2.13 (s, 3H), 1.01 (m, 3H), 0.94 (m, 3H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 171.64, 171.61, 170.23, 170.17, 167.07, 166.88, 156.50, 156.46, 136.15, 136.12, 128.55, 128,21, 128.04, 72.05, 72.00, 67.21, 59.88, 53.27, 53.26, 51.65, 31.41, 31.24, 20.54, 19.04, 19.02, 17.54 ppm; IR (KBr): ν = 3294, 2959, 1749, 1664, 1538, 1247, 1044 cm^{-1}; HRMS(FAB): calculated for $[C_{18}H_{24}N_2O_7+H]^+$: 381.1662, found: 381.1663; R_f (EtOAc/PE 3/2) = 0.71.



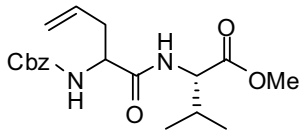
(2*S*)-Methyl 5-(1-acetoxy-2-methoxy-2-oxoethylamino)-2-(benzyloxy-carbonylamino)-5-oxopentanoate (38). According to general procedure B, **30** (0.100 g, 0.231 mmol) was treated with $Pb(OAc)_4$ (0.139 g, 0.314 mmol) and 4 Å MS (0.5 g) in EtOAc (10 mL) for 3 h to give **38** (~1:1 mixture of diastereomers, 74 mg, 0.174 mmol, 75%) as a colorless oil. ^{1}H-NMR (500 MHz, $CDCl_3$): δ = 7.36 (m, 5H), 7.16 (d, *J* = 9.0 Hz, 0.5H), 7.10 (d, *J* = 9.0 Hz, 0.5H), 6.41 (d, *J* = 9.0 Hz, 0.5H), 6.38 (d, *J* = 9.0 Hz, 0.5H), 5.55 (d, *J* = 7.6 Hz, 0.5H), 5.51 (d, *J* = 7.6 Hz, 0.5H), 5.11 (s, 2H), 4.41 (br s, 1H), 3.80 (s, 3H), 3.75 (s, 3H), 2.37 (m, 2H),

2.24 (m, 2H), 2.12 (s, 1.5H), 2.11 (s, 1.5H), 2.00 (m, 2H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 172.30, 171.83, 170.40 ,170.34, 167.18, 156.22, 136.09, 128.56, 128.26, 128.16, 128.13, 72.11, 67.18, 53.31, 53.22, 53.63, 31.87, 31.85, 28.15, 28.03, 20.63, 20.62 ppm; IR (neat): ν = 3328, 2956, 1747, 1703, 1529, 1218, 1044 cm^{-1}; HRMS(FAB): calculated for $[C_{19}H_{24}N_2O_9+H]^+$: 425.1560, found: 425.1564; R_f (PE/EtOAc 1:2) = 0.31.

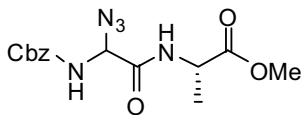
General procedure C: Nucleophilic addition to *N*-terminal iminium ion dipeptides. To a solution of acetoxyglycine containing dipeptide (0.100 g) and nucleophile (4 equiv) in CH_2Cl_2 (2 mL) at 0 °C was added $BF_3{\cdot}OEt_2$ (4 equiv). The resulting solution was stirred at 0 °C for 24 h after which it was poured on saturated aqueous $NaHCO_3$ solution and extracted with EtOAc two times. The organic layer was washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo* to give the crude product which was purified by column chromatography.



(2*S*)-Methyl 2-(2-(benzyloxycarbonylamino)pent-4-enamido)propanoate (43). According to general procedure C, **32** (0.122 g, 0.346 mmol) was treated with allyltrimethylsilane (0.122 g, 0.17 mL, 1.08 mmol) and $BF_3{\cdot}OEt_2$ (0.157 g, 0.14 mL, 1.08 mmol) to give **43** as a white solid (68 mg, 0.203 mmol, 73%)(~1:1 mixture of diastereomers) after column chromatography (PE/EtOAc 1:3). ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.38 (m, 5H), 6.54 (br s, 1H), 5.77 (m, 1H), 5.31 (br s, 1H), 5.15 (m, 4H), 4.57 (m, 1H), 4.27 (m, 1H), 3.77 (s, 3H), 2.56 (dd, *J* = 11.1, 6.0 Hz, 2H), 1.42 (d, *J* = 6.8 Hz, 3H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 173.19, 173.10, 170.67, 156.08, 136.17, 132.67, 128.53, 128.19, 128.06, 119.25, 67.34, 54.11, 52.49, 52.46, 48.09, 36.99, 18.18 ppm; IR (KBr): ν = 3317, 2954, 1748, 1668, 1538, 1455, 1217, 1054 cm^{-1}; HRMS(FAB): calculated for $[C_{17}H_{22}N_2O_5+H]^+$: 335.1607, found: 335.1610.

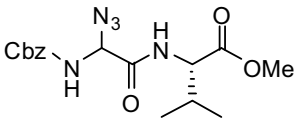


(2*S*)-Methyl 2-(2-(benzyloxycarbonylamino)pent-4-enamido)-3-methylbutanoate (44). According to general procedure C, **33** (0.105 g, 0.27 mmol) was treated with allyltrimethylsilane (0.110 g, 0.153 mL, 0.96 mmol) and $BF_3{\cdot}OEt_2$ (0.137 g, 0.122 mL, 0.96 mmol) to give **44** as a white solid (~1:1 mixture of diastereomers, 84 mg, 0.232 mmol, 86%) after column chromatography (PE/EtOAc 1:1). ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.35 (m, 5H), 6.52 (br s, 1H) 5.78 (m, 1H), 5.33 (br s, 1H) 5.15 (m, 4H), 4.55 (m, 1H), 4.30 (br s, 1H), 3.75 (s, 3H), 2.56 (m, 2H), 2.17 (m, 1H), 0.92 (m, 6H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 172.07, 172.00, 171.01, 155.97, 136.02, 132.64, 128.61, 128.34, 127.99, 127.89, 118.92, 66.87, 57.89, 57.03, 56.94, 52.01, 51.98, 36.67, 30.97, 18.74, 17.57 ppm; IR (KBr): ν = 3316, 2964, 1745, 1665, 1526, 1214, 1050, 919 cm^{-1}; HRMS(FAB): calculated for $[C_{19}H_{26}N_2O_5+H]^+$: 363.1920, found: 363.1913; R_f (PE/EtOAc 1:1) = 0.40.

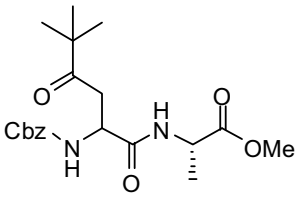


(2*S*)-Methyl 2-(2-azido-2-(benzyloxycarbonylamino)acetamido)-propanoate (45). According to general procedure C, **32** (0.100 g, 0.28 mmol) was treated with azidotrimethylsilane (0.131 g, 0.150 mL, 1.14 mmol) and $BF_3{\cdot}OEt_2$ (0.162 g, 0.145 mL, 1.14 mmol) to give **45** as a white solid (~1:1 mixture of diastereomers, 68 mg, 0.203 mmol, 72%) after column chromatography (PE/EtOAc 3:2). ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.35 (m, 5H), 6.90 (br s, 0.5H), 6.81 (br s, 0.5H), 6.12 (br s, 1H), 5.64 (br s, 1H), 5.20 (s, 2H), 4.58 (m, 1H), 3.80 (s, 3H), 1.47 (m, 3H) ppm; ^{13}C-NMR (100 MHz,

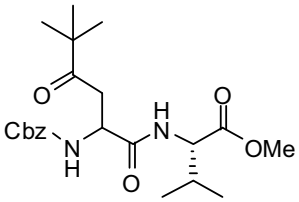
$CDCl_3$): δ = 172.69, 172.66, 164.96, 164.87, 156.02, 135.56, 128.60, 128.43, 128.24, 67.80, 67.43, 52.76, 52.73, 48.59, 18.08, 18.03 ppm; IR (KBr): ν = 3317, 2956, 2113, 1745, 1681, 1516, 1455, 1219, 1054 cm^{-1}; HRMS(FAB): calculated for $[C_{14}H_{17}N_5O_5+H]^+$: 336.1308, found: 336.1313; R_f (PE/EtOAc 2:3) = 0.30.



(2*S*)-Methyl 2-(2-azido-2-(benzyloxycarbonylamino)acetamido)-3-methylbutanoate (46). According to general procedure C, **33** (0.100 g, 0.263 mmol) was treated with azidotrimethylsilane (0.123 g, 0.140 mL, 1.05 mmol) and $BF_3{\cdot}OEt_2$ (0.151 g, 0.135 mL, 1.05 mmol) to give **46** as a white solid (~1:1 mixture of diastereomers, 64 mg, 0.176 mmol, 60%) after column chromatography (PE/EtOAc 3:2). ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.37 (m, 5H), 6.82 (br s, 0.5H), 6.72 (br s, 0.5H), 6.16 (br s, 1H), 5.67 (m, 1H), 5.20 (s, 2H), 4.54 (td, *J* = 8.7, 4.9 Hz, 1H), 3.79 (s, 1.5H), 3.78 (s, 1.5H), 2.23 (m, 1H), 0.95 (m, 6H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 171.83, 171.75, 165.44, 165.28, 156.07, 155.93, 135.56, 128.59, 128.41, 128.22, 67.78, 67.47, 67.36, 57.72, 57.61, 52.44, 52.41, 31.32, 31.27, 18.87, 18.82, 17.73, 17.65 ppm; IR (KBr): ν = 3321, 2965, 2112, 1736, 1677, 1509, 1216, 1056 cm^{-1}; HRMS(FAB): calculated for $[C_{16}H_{21}N_5O_5+H]^+$: 364.1621, found: 364.1616; R_f (PE/EtOAc 3:2) = 0.34.

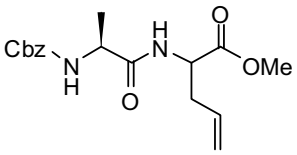


(2*S*)-Methyl 2-(2-(benzyloxycarbonylamino)-5,5-dimethyl-4-oxohexanamido)propanoate (47). According to general procedure C, **32** (0.110 g, 0.312 mmol) was treated with (3,3-dimethylbut-1-en-2-yloxy)trimethylsilane (0.200 g, 0.245 mL, 1.12 mmol) and $BF_3{\cdot}OEt_2$ (0.162 g, 0.145 mL, 1.12 mmol) to give **47** as a white solid (~1:1 mixture of diastereomers, 80 mg, 0.204 mmol, 65%) after column chromatography (PE/EtOAc 2:1). ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.38 (m, 5H), 6.97 (br s, 1H), 5.69 (br d, *J* = 7.2 Hz, 1H), 5.15 (s, 2H), 4.62 (m, 1H), 4.53 (m, 1H), 3.76 (m, 3H), 3.37 (m, 1H), 2.82 (m, 1H), 1.41 (m, 3H), 1.17 (s, 4.5H), 1.16 (s, 4.5H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 215.88, 170.50, 170.38, 168.36, 168.31, 155.97, 136.09, 128.55, 128.25, 128.10, 74.29, 74.21, 67.17, 66.9, 52.43, 52.47, 48.26, 48.22, 44.18, 44.15, 39.21, 26.30, 26.25, 18.05, 17.96 ppm; IR (KBr): ν = 3327, 2956, 1736, 1524, 1456, 1218, 1159, 1056 cm^{-1}; HRMS(FAB): calculated for $[C_{20}H_{28}N_2O_6+H]^+$: 393.2026, found: 393.2027; R_f (PE/EtOAc 2:1) = 0.20.

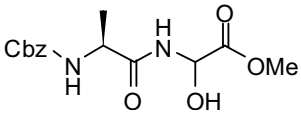


(2*S*)-Methyl 2-(2-(benzyloxycarbonylamino)-5,5-dimethyl-4-oxohexanamido)-3-methylbutanoate (48). According to general procedure C, **33** (80 mg, 0.21 mmol) was treated with (3,3-dimethylbut-1-en-2-yloxy)trimethylsilane (0.148 g, 0.185 mL, 0.84 mmol) and $BF_3{\cdot}OEt_2$ (0.123 g, 0.110 mL, 0.84 mmol) to give **48** as a white solid (~1:1 mixture of diastereomers, 60 mg, 0.144 mmol, 68%) after column chromatography (PE/EtOAc 2:1). ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.35 (m, 5H), 7.01 (br s, 1H), 5.99 (m, 1H), 5.15 (m, 2H), 4.65 (br s, 2H), 4.47 (m, 1H), 3.75 (s, 1.5H), 3.73 (s, 1.5H), 3.36 (br t, *J* = 17.04 Hz, 1H), 2.85 (m, 1H), 2.17 (m, 1H), 1.17 (s, 9H), 0.93 (m, 6H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 216.11, 171.86, 170.68, 155.97, 136.12, 128.56, 128.25, 128.12, 67.16, 57.44, 57.38, 52.13, 52.06, 50.85, 50.70, 44.22, 44.17, 39.27, 39.05, 31.13, 26.34, 18.94, 18.91, 17.64, 17.57 ppm; IR (KBr): ν = 3328,

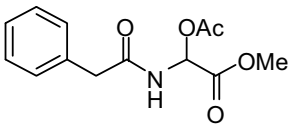
2965, 1713, 1531, 1368, 1213, 1151, 1052 cm^{-1}; HRMS(FAB): calculated for $[C_{22}H_{32}N_2O_6+H]^+$: 421.2339, found: 421.2336; R_f (PE/EtOAc 2:1) = 0.37.



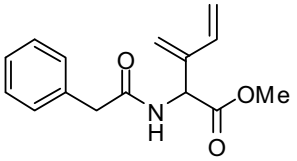
Methyl 2-((*S*)-2-(benzyloxycarbonylamino)propanamido)pent-4-enoate (53). To a solution of **36** (50 mg, 0.142 mmol) and allyltrimethylsilane (0.101 mg, 0.140 mL, 1.70 mmol) in CH_2Cl_2 (2 mL) at room temperature was added $Sn(OTf)_2$ (30 mg, 0.072 mmol). The resulting solution was stirred at room temperature for 24 h after which it was poured on saturated aqueous $NaHCO_3$ solution and extracted with EtOAc two times. The organic layer was washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification of the crude product by column chromatography (PE/EtOAc 1:2) gave **53** as a white solid (~1:1 mixture of diastereomers, 22 mg, 0.066 mmol, 46%). ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.37 (m, 5H), 6.60 (m, 1H), 5.65 (m, 1H), 5.40 (br s, 1H), 5.14 (m, 4H), 4.67 (m, 1H), 4.31 (m, 1H), 3.76 (s, 1.5H), 3.75 (s, 1.5H), 2.59 (m, 1H), 2.51 (m, 1H), 1.41 (d, *J* = 7.2 Hz, 3H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 171.94, 171.90, 171.85, 155.92, 136.19, 131.96, 131.94, 128.54, 128.21, 128.07, 119.36, 67.05, 52.44, 52.42, 51.65, 51.51, 50.48, 50.41, 36.35, 18.75, 18.44 ppm; IR (KBr): ν = 3312, 2953, 1718, 1669, 1524, 1455, 1246, 1070 cm^{-1}; HRMS(FAB): calculated for $[C_{17}H_{22}N_2O_5+H]^+$: 335.1607, found: 335.1610; R_f (PE/EtOAc 1:2) = 0.27.



Methyl 2-((*S*)-2-(benzyloxycarbonylamino)propanamido)-2-hydroxy-acetate (55). ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.38 (m, 6H), 5.58 (m, 1H), 5.25 (br t, *J* = 7.6 Hz, 1H), 5.15 (m, 2H), 4.31 (br t, *J* = 7.0 Hz, 1H), 4.08 (br s, 1H), 3.82 (s, 3H), 1.42 (d, *J* = 7.1 Hz, 3H) ppm; R_f (PE/EtOAc 1:2) = 0.18.

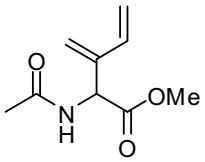


Methyl 2-acetoxy-2-(2-phenylacetamido)acetate (64). A solution of methyl 2-hydroxy-2-(2-phenylacetamido)acetate **62** (1.01 g, 4.52 mmol) and pyridine (10 drops) in Ac_2O/CH_2Cl_2 (15/5 mL) was stirred at room temperature for 17.5 h after which all volatiles were removed *in vacuo*. The crude product (brown oil which solidified upon standing) was purified by recrystallization from cyclohexane/EtOAc to afford **64** as an off white solid (0.882 g, 3.33 mmol, 74%). ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.26 (m, 5H), 6.72 (br d, *J* = 8.7 Hz, 1H), 6.37 (d, *J* = 8.9 Hz, 1H), 3.76 (s, 3H), 3.64 (s, 2H), 2.08 (s, 3H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 170.90, 170.39, 167.28, 133.75, 129.56, 129.27, 127.84, 72.32, 53.49, 43.51, 43.34, 20.78 ppm; HRMS(FAB): calculated for $[C_{13}H_{15}NO_5+H]^+$: 266.1028, found: 266.1038; R_f (EtOAc) = 0.60.

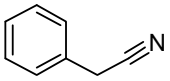


Methyl 3-methylene-2-(2-phenylacetamido)pent-4-enoate (66). *Method 1:* To a stirred solution of methoxyglycine **63** (1.91 g, 8.03 mmol) and allenylmethyltrimethylsilane (1.52 g, 12.1 mmol) in CH_3CN (40 mL) at 0 °C was added $BF_3{\cdot}OEt_2$ (2.27 g, 2.03 mL, 16.1 mmol). The resulting mixture was stirred at 0 °C for 1 h and additionally at room temperature for 6 h after which it was poured on saturated aqueous $NaHCO_3$ solution and extracted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified by column chromatography (PE/EtOAc 2:1) to give **66** (0.518 g, 2.00 mmol, 25%), **67** (0.615 g, 3.36 mmol, 42%), **68** (0.570 g, 4.87 mmol, 61%) and **69** (56 mg, 0.347 mmol, 4.3%).

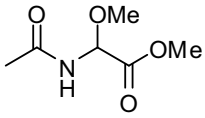
Method 2: To a stirred solution of acetoxyglycine **64** (50 mg, 0.186 mmol) and allenylmethyltrimethylsilane (48 mg, 0.377 mmol) in CH_2Cl_2 (1 mL) at 0 °C was added $BF_3{\cdot}OEt_2$ (53 mg, 48 μL, 0.377 mmol). The resulting mixture was stirred at 0 °C for 1.5 h before it was poured on saturated aqueous $NaHCO_3$ solution and extracted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4, filtered and concentrated *in vacuo* to give **66** (40 mg, 0.154 mmol, 82%) as a yellow solid. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.30 (m, 5H), 6.24 (dd, *J* = 10.9, 17.7 Hz, 1H), 6.11 (br d, *J* = 6.2 Hz, 1H), 5.35 (s, 1H), 5.31 (d, *J* = 8.8 Hz, 1H), 5.22 (s, 1H), 5.11 (m, 2H), 3.71 (s, 3H), 3.60 (s, 2H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 170.29, 170.15, 141.40, 134.93, 134.19, 129.19, 128.76, 127.20, 118.71, 115.66, 53.38, 52.78, 43.23 ppm; IR (neat): ν = 3290, 3030, 2953, 1749, 1650, 1531, 1202, 987, 913 cm^{-1}; R_f (EtOAc) = 0.62.



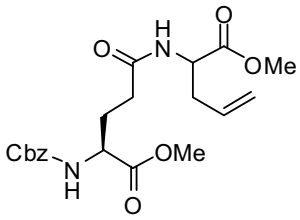
Methyl 2-acetamido-3-methylenepent-4-enoate (67). ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 6.30 (dd, *J* = 11.1, 17.7 Hz, 1H), 6.19 (br s, 1H), 5.43 (d, *J* = 17.7 Hz, 1H), 5.36 (d, *J* = 7.9 Hz, 1H), 5.28 (s, 1H), 5.21 (s, 1H), 5.17 (d, *J* = 11.1 Hz, 1H), 3.73 (s, 3H), 2.01 (s, 3H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 171.25, 169.33, 141.70, 135.06, 118.58, 115.71, 53.07, 52.46, 22.82 ppm; IR (neat): ν = 3287, 3049, 2955, 1748, 1659, 1538, 1204, 1004, 914 cm^{-1}; HRMS(FAB): calculated for $[C_9H_{13}NO_3+H]^+$: 184.0974, found: 184.0976; R_f (EtOAc) = 0.38.



2-Phenylacetonitrile (68). ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.35 (m, 5H), 3.70 (s, 2H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 129.94, 128.96, 127.83, 127.79, 117.90, 23.32 ppm; HRMS(EI): calculated for $[C_8H_7N]^+$: 117.0578, found: 117.0574; R_f (EtOAc) = 0.74.

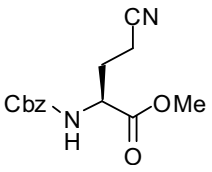


Methyl 2-acetamido-2-methoxyacetate (69). ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 6.88 (br d, *J* = 8.1 Hz, 1H), 5.49 (d, *J* = 9.3 Hz, 1H), 3.75 (s, 3H), 3.39 (s, 3H), 2.03 (s, 3H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 170.58, 168.37, 77.98, 56.34, 52.62, 22.88 ppm; R_f (EtOAc) = 0.26.

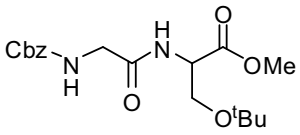


Methyl 2-((*S*)-4-(benzyloxycarbonylamino)-5-methoxy-5-oxopentanamido)pent-4-enoate (74). To a solution of **38** (50 mg, 0.118 mmol) and allyltrimethylsilane (54 mg, 75 μL, 0.471 mmol) in CH_3CN (0.6 mL) at room temperature was added $Sn(OTf)_2$ (25 mg, 0.059 mmol). The resulting solution was stirred at room temperature for 24 h after which it was poured on saturated aqueous $NaHCO_3$ solution and extracted with EtOAc three times. The organic layer was washed with brine, dried over Na_2SO_4, filtered and concentrated *in vacuo*. Purification by column chromatography (PE/EtOAc 1:2) gave **74** as a white solid (~1:1 mixture of diastereomers, 29 mg, 0.071 mmol, 61%) and **75** as a colorless oil (7 mg, 0.025 mmol, 22%). *Data for* **74**: ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.35 (m, 5H), 6.50 (d, *J* = 7.1 Hz, 0.5H), 6.32 (d, *J* = 7.3 Hz, 0.5H), 5.70 (m, 2H), 5.14 (m, 4H), 4.68 (m, 1H), 4.47 (td, *J* = 4.2, 8.4 Hz, 0.5H), 4.40 (td, *J* = 4.5, 8.3 Hz, 0.5H), 3.76 (s, 3H), 3.75 (s, 3H), 2.61 (m, 1H), 2.52 (m, 1H), 2.35 (m, 2H), 2.25 (m, 1H), 1.98 (m, 1H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 172.43, 172.39, 172.22, 172.16, 171.64, 171.43, 156.32, 156.22, 136.18, 136.16, 132.24, 128.53, 128.20, 128.12, 119.25, 119.18, 67.13, 67.11, 53.39, 52.55, 52.39, 51.81, 51.73, 36.43, 36.32, 32.25, 32.13, 28.71, 28.42 ppm; IR (neat): ν = 3326, 2954, 1745,

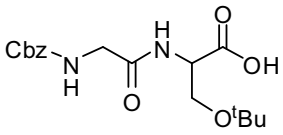
1628, 1531, 1439, 1215, 1057 cm^{-1}; HRMS(FAB): calculated for $[C_{20}H_{26}N_2O_7+H]^+$: 407.1818, found: 407.1813; R_f (PE/EtOAc 1:2) = 0.31.



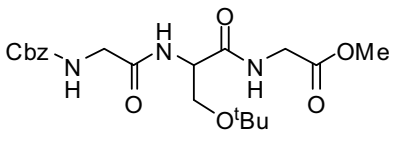
(*S*)-Methyl 2-(benzyloxycarbonylamino)-4-cyanobutanoate (75). ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.38 (m, 5H), 5.47 (br s, 1H), 5.15 (s, 2H), 4.48 (dd, *J* = 7.0, 12.5 Hz, 1H), 3.82 (s, 3H), 2.46 (m, 2H), 2.34 (m, 1H), 2.08 (m, 1H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 171.16, 155.86, 135.86, 128.62, 128.40, 128.22, 118.55, 67.41, 52.98, 52.84, 28.73, 13.55 ppm; IR (neat): ν = 3344, 2956, 2248, 1727, 1531, 1454, 1216, 1056 cm^{-1}; HRMS(FAB): calculated for $[C_{14}H_{16}N_2O_4+H]^+$: 277.1188, found: 277.1193; R_f (PE/EtOAc 1:2) = 0.60.



Methyl 11,11-dimethyl-3,6-dioxo-1-phenyl-2,10-dioxa-4,7-diazadodecane-8-carboxylate (Cbz-Gly-Ser(OtBu)OMe, 78). To a stirred solution of Cbz-Gly-OH (1.00 g, 4.78 mmol) in THF (12 mL) at -20 °C were added NMM (0.604 g, 0.67 mL, 6.98 mmol) and IBC (0.686 g, 0.65 mL, 5.02 mmol). The mixture was stirred at -20 °C for 10 min after which a solution of H-Ser(OtBu)-OMe·HCl (1.01 g, 4.78 mmol) in DMF (6 mL) was added followed by the drop wise addition of NMM (0.604 g, 0.67 mL, 6.98 mmol). The mixture was allowed to warm to room temperature overnight. After a total reaction time of 18.5 h the mixture was poured on saturated aqueous NH_4Cl solution and extracted with EtOAc four times. The organic layer was washed with brine, dried over Na_2SO_4, filtered and concentrated *in vacuo*. Purification by column chromatography (PE/EtOAc 1:1) gave **78** as a white oil (1.53 g, 4.17 mmol, 87%). ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.31 (m, 5H), 6.94 (br d, *J* = 7.4 Hz, 1H), 5.76 (br s, 1H), 5.11 (s, 2H), 4.71 (m, 1H), 3.95 (m, 2H), 3.79 (dd, *J* = 2.7, 9.1 Hz, 1H,), 3.71 (s, 3H), 3.54 (dd, *J* = 2.3, 8.9 Hz, 1H), 1.10 (s, 9H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 170.77, 168.95, 156.52, 136.28, 128.49, 128.12, 128.05, 73.49, 67.02, 61.83, 52.81, 52.40, 44.30, 27.22 ppm; HRMS(FAB): calculated for $[C_{18}H_{26}N_2O_6+H]^+$: 367.1869, found: 367.1860.

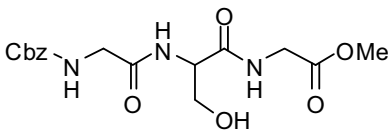


11,11-Dimethyl-3,6-dioxo-1-phenyl-2,10-dioxa-4,7-diazadodecane-8-carboxylic acid (Cbz-Gly-Ser(OtBu)OH, 79). To a stirred solution of **78** (1.31 g, 3.58 mmol) in THF (15 mL) at 0 °C was added slowly a solution of LiOH (0.172 g, 7.16 mmol) in H_2O (15 mL). The resulting solution was stirred at 0 °C for 1.5 h before it was poured on 5% aqueous $KHSO_4$ solution and extracted with EtOAc four times. The organic layer was washed with brine, dried over Na_2SO_4, filtered and concentrated *in vacuo* to give **79** as a white gel (1.24 g, 3.53 mmol, 99%). ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.35 (m, 5H), 6.88 (d, *J* = 7.2 Hz, 1H), 5.58 (br s, 1H), 5.15 (s, 2H), 4.70 (m, 1H), 3.97 (m, 3H), 3.57 (dd, *J* = 4.9, 8.4 Hz, 1H), 1.20 (s, 9H) ppm, COO*H* missing; ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 172.85, 170.08, 156.87, 136.17, 128.53, 128.19, 128.08, 74.11, 67.18, 61.52, 52.80, 44.21, 27.22 ppm; IR (neat): ν = 3318, 2974, 1719, 1671, 1526, 1237 cm^{-1}; HRMS(FAB): calculated for $[C_{17}H_{24}N_2O_6+H]^+$: 353.1713, found: 353.1718.

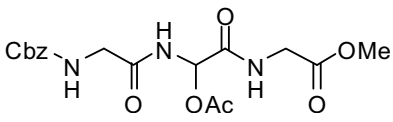


[2-(2-Benzyloxycarbonylamino-acetylamino)-3-*tert*-butoxy-propionylamino]-acetic acid methyl ester (Cbz-Gly-Ser(OtBu)-Gly-OMe, 81). To a stirred solution of **79** (1.23 g, 3.50 mmol) in THF (15 mL) at -20 °C were added NMM (0.443 g, 0.49 mL, 4.38

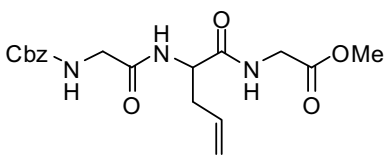
mmol) and IBC (0.502 g, 0.48 mL, 3.68 mmol). The mixture was stirred at -20 °C for 10 min after which a solution of H-Gly-OMe·HCl (0.440 g, 3.50 mmol) in DMF (5 mL) was added followed by the drop wise addition of NMM (0.443 g, 0.49 mL, 4.38 mmol). The mixture was allowed to warm to room temperature overnight. After a total reaction time of 17.5 h the mixture was poured on saturated aqueous NH_4Cl solution and extracted with EtOAc four times. The organic layer was washed with brine, dried over Na_2SO_4, filtered and concentrated *in vacuo*. Purification by column chromatography (PE/EtOAc 1:4) gave **81** as a colorless oil (1.29 g, 3.06 mmol, 87%) which solidified upon standing. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.35 (m, 6H), 6.89 (br d, *J* = 5.4 Hz, 1H), 5.44 (br s, 1H), 5.15 (m, 2H), 4.50 (br s, 1H), 4.13-3.85 (m, 5H), 3.78 (s, 3H), 3.37 (br t, *J* = 8.4 Hz, 1H), 1.24 (s, 9H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 170.36, 169.87, 168.95, 156.65, 136.09, 128.56, 128.25, 128.12, 74.50, 67.28, 61.05, 52.81, 52.37, 44.59, 41.38, 27.36 ppm; HRMS(FAB): calculated for $[C_{20}H_{29}N_3O_7+H]^+$: 424.2084, found: 424.2086; R_f (PE/EtOAc 1:4) = 0.24.



[2-(2-Benzyloxycarbonylamino-acetylamino)-3-hydroxy-propionylamino]-acetic acid methyl ester (Cbz-Gly-Ser-Gly-OMe 82). A solution of **81** (0.400 g, 0.945 mmol) in TFA/H_2O (7/0.14 mL) was stirred for 1.5 h at room temperature, after which all volatiles were co-evaporated with toluene 3 times to afford **82** as an off white solid (0.342 g, 0.931 mmol, 99%). ^{1}H-NMR (400 MHz, MeOD): δ = 7.33 (m, 5H), 5.13 (s, 2H), 4.52 (t, *J* = 5.2 Hz, 1H), 4.03-3.80 (m, 6H), 3.73 (s, 3H) ppm; ^{13}C-NMR (100 MHz, MeOD): δ = 171.19, 170.80, 170.14, 157.71, 136.50, 127.91, 127.47, 127.28, 66.36, 61.34, 55.02, 51.09, 43.48, 40.35 ppm; IR (neat): ν = 3340, 2950, 1755, 1659, 1452, 1220, 1052 cm^{-1}; HRMS(FAB): calculated for $[C_{16}H_{21}N_3O_7+H]^+$: 368.1458, found: 368.1461; R_f (EtOAc/MeOH 9:1) = 0.42.



[2-Acetoxy-2-(2-benzyloxycarbonylamino-acetylamino)-acetylamino]-acetic acid methyl ester (83). According to general procedure B, treatment of **82** (100 mg, 0.272 mmol) with $Pb(OAc)_4$ (0.181 g, 0.408 mmol) and 4 Å MS (0.300 g) in EtOAc (5 mL) for 3 h gave **83** as a colorless oil (0.378 g, 1.07 mmol, ~75%). ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.74 (br s, 1H), 7.36 (m, 5H), 7.21 (br s, 1H), 6.60 (d, *J* = 8.5 Hz, 1H), 5.62 (br s, 1H), 5.14 (s, 2H), 4.06 (d, *J* = 5.4 Hz, 2H), 3.98 (br s, 2H), 3.76 (s, 3H), 2.14 (s, 3H) ppm; ^{13}C-NMR (125 MHz, $CDCl_3$): δ = 171.20, 169.71, 165.97, 156.84, 136.32, 128.78, 128.47, 128.34, 72.85, 67.54, 52.77, 44.60, 41.54, 20.98 ppm, one *C*=O missing; IR (neat): ν = 3321, 3067, 2956, 1753, 1682, 1526, 1213, 1046 cm^{-1}; HRMS(FAB): calculated for $[C_{17}H_{21}N_3O_8+H]^+$: 396.1407, found: 396.1396; R_f (EtOAc/MeOH 9:1) = 0.56.



[2-(2-Benzyloxycarbonylamino-acetylamino)-pent-4-enoylamino]-acetic acid methyl ester (84). To a solution of **83** (50 mg, 0.127 mmol) and allyltrimethylsilane (58 mg, 80 µL, 0.506 mmol) in CH_2Cl_2/CH_3CN (0.5/0.1 mL) at room temperature was added $Sn(OTf)_2$ (26 mg, 0.063 mmol). The resulting solution was stirred at room temperature for 22 h after which it was poured on saturated aqueous $NaHCO_3$ solution and extracted with EtOAc three times. The organic layer was washed with brine, dried over Na_2SO_4, filtered and concentrated *in vacuo*. Purification by column chromatography (EtOAc) gave **84** as a colorless oil (11 mg, 0.029 mmol,

23%). ^{1}H-NMR (400 MHz, CD_3CN): δ = 7.37 (m, 5H), 7.10 (br s, 1H), 6.85 (br d, *J* = 7.2 Hz, 1H), 6.04 (br s, 1H), 5.78 (ddt, *J* = 7.2, 10.0, 14.3 Hz, 1H), 5.12 (m, 4H), 4.42 (td, *J* = 5.0, 8.0 Hz, 1H), 3.93 (m, 2H), 3.78 (m, 2H), 3.69 (s, 3H), 2.56 (m, 1H), 2.42 (m, 1H) ppm; ^{13}C-NMR (100 MHz, CD_3CN): δ = 172.37, 171.18, 170.43, 157.93, 138.13, 134.65, 129.57, 129.06, 128.89, 188.88, 67.46, 53.42, 52.71, 45.13, 41.73, 36.97 ppm; IR (neat): ν = 3311, 2953, 1750, 1666, 1531, 1215 cm^{-1}; HRMS(FAB): calculated for $[C_{17}H_{21}N_3O_8+H]^+$: 396.1407, found: 396.1396; R_f (CH_2Cl_2/IPA 9:1) = 0.48.

3.7 References

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25. Construction of the tripeptide starting from the C-terminus gave problems in the hydrogenation of Cbz-Ser(OtBu)-Gly-OMe in the presence of AcOH.
26. Formation of the tripeptide iminium ion precursor via the condensation route (Scheme 3.4) proved to be even more challenging.
27. A complicating factor is the overlap of starting material and product on TLC.