A straightforward approach towards cyclic peptides *via* ring-closing metathesis—scope and limitations†‡

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N- and *C*-terminal diallylated peptides are obtained by several approaches, such as peptide Claisen rearrangement, *N*- and *O*- allylation, and the Ugi reaction of allyl-protected components. These diallylated peptides are suitable substrates for ring-closing metathesis and the success of this cyclisation was investigated with respect to the ring size, the position of the allyl moieties and the reaction parameters. In general, excellent yields are obtained for cyclisation of allyl glycine subunits and *N*-allylated amides, while allyl esters and allyl carbamates often presented serious problems. However, yields of up to 73% were obtained under optimised conditions, and the new generated double bond is formed with excellent *trans*-selectivity.

Introduction

Cyclic peptides are found in a wide variety of marine organisms and fungi.[1] Many of these peptides show significant biological activity,[2] and are therefore highly interesting from a pharmaceutical point of view.[3] In higher organisms, cyclic structures can be formed by the oxidation of two cysteine subunits, a process which is generally used to stabilise the secondary and tertiary structure of peptides. Cysteine-containing peptides are preferentially found in peptide hormones and a number of redox active proteins, such as glutaredoxin **1**.[4] Here, the disulfide bridge locks a tetrapeptide fragment of the protein chain into a β-turn type structure.[5] Frequently, loops and turns in peptides and proteins are responsible for their biological activity, making these structures are highly interesting from both a pharmaceutical point of view and as targets for peptidomimetics.[6] In general, cyclisation of peptides results in an increased stability towards proteases. Since in cysteine peptides the disulfide bonds are sensitive to reduction, the metabolic stability of these compounds can be dramatically increased by replacing the sensitive disulfide bond by a non-cleavable C–C bond.[7] Therefore, a lot of investigation has been carried out on the synthesis of carba analogues of cysteine, such as 2,7-diaminosuberic acid.[8] Very recently, Williams *et al.* and Grubbs *et al.* described syntheses based on the dimerisation of tethered allyl glycines *via* ring-closing metathesis.[9–11] As shown by Grubbs *et al.* this ring-closing approach can be directly used for the synthesis of cyclic peptides, such as **2**, a carba analogue of the glutaredoxin active site **1** (Fig. 1).[12] This is an extremely straightforward approach towards β-turn mimetics, and since the publication of this pioneering work, several examples of the synthesis of smaller and larger ring systems were reported, many of which featured interesting pharmaceutical properties.[13–15]

Ring-closing metathesis was not only used for the cyclisation of simple peptides to form cyclic peptidomimetics, but also for the fixation of helix structures and the interconnection of cyclic peptides.[16–17]

Peptides containing allyl glycines are very often used as precursors,[18] thus leading to surrogates for cysteine, as illustrated in Fig. 1. However, other unsaturated substrates can be cyclised, such as allylic ethers, esters or amides.[19–21] The yields in the
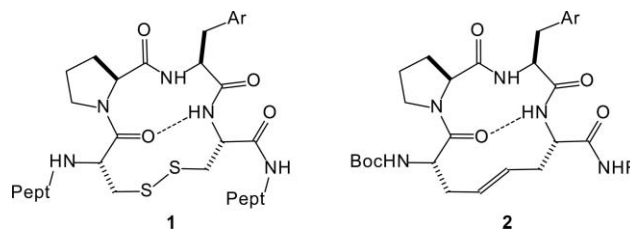

Fig. 1 Natural and artificial peptide loops.

cyclisation step depend on the ring size as well as on the distance between the double bonds and other functionalities. Liskamp *et al.* investigated the ring-closing metathesis of a wide range of peptides bearing the unsaturation on the amide functionality.[22] In this case, the introduced loops connect two amide nitrogens, leaving the amino acid sequence unaffected. Importantly, these macrocycles may be formed by connecting any two amide nitrogens, as long as the length of the alkene substituents is adjusted appropriately. It was established that the ring-closing metathesis can be conducted using *N*-alkylamides for a loop bridging two amides, *N*-pentenylamides for a loop spanning three amides and *N*-homoallylamides when four or more amides are involved in the ring. Libraries of cyclic peptides were obtained by this approach.

For quite some time we have been investigating syntheses of γ,δ-unsaturated amino acids.[23] Besides Pd-catalysed allylic alkylations of chelated amino acid ester enolates,[24] especially the Claisen rearrangement, proceeding *via* those chelated amino acid ester enolates is suitable for this purpose.[25] If esters of chiral allylic alcohols are used, the corresponding enantiomerically pure amino acids are obtained.[26] This protocol is not limited to the rearrangement of amino acid esters, but can also be applied to peptides.[27] In particular, allylic esters of tosylated peptides are suitable substrates for the Claisen rearrangement, yielding the products in a highly diastereoselective fashion, while the configuration of the newly formed stereogenic centre is controlled by the peptide chain.[28] Tosyl-protected amino acids are also appropriate substrates for palladium-catalysed allylic alkylations, giving rise to *N*-allylated derivatives under very mild conditions.[29] Therefore, these protocols open up an easy access to fully functionalised diallylic peptides, suitable precursors for ring-closing metathesis.[30]

Results and discussion

We started our investigations with the rearrangement of peptide ester **3** (Scheme 1). In the presence of tin chloride, used for

chelation, the rearranged product **4** was obtained with excellent yield and in a highly stereoselective manner. An induced diastereoselectivity of 84% was remarkable, especially with respect to the fact that the only chiral centre in the peptide **3** was 7 atoms away from the newly formed chiral centre. The (*R*)-configured amino acid was formed preferentially with high *syn* selectivity (>95%). Peptide **4** was subsequently subjected to a palladium-catalysed *N*-allylation, giving rise to the product **5** without any racemisation. Unfortunately, all attempts to cyclise this diallylated substrate **5** under different reaction conditions and various amounts of Grubbs' catalyst were unsuccessful.[31]
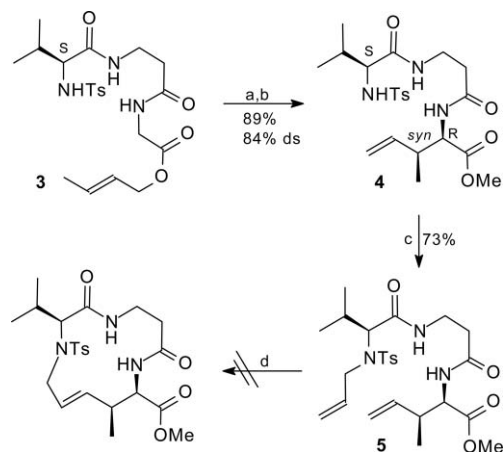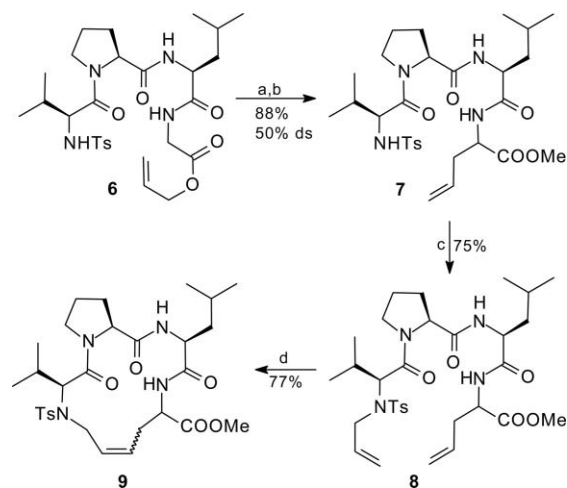

Scheme 1 Peptide Claisen rearrangement of crotyl ester **3**; (a) 5.0 equiv LHMDS, 2.0 equiv SnCl$_2$, THF, −78 °C → rt, 16 h; (b) CH$_2$N$_2$, ether, 10 min; (c) 1 mol% (allyl PdCl)$_2$, 4.5 mol% PPh$_3$, allyl carbonate, THF, rt, 16 h; (d) 10–15 mol% RuCl$_2$(PCy$_3$)$_2$(=CHPh), toluene, rt → 90 °C, 8 h.

Several factors influence the tendency of ring-closure metathesis, but we focused mainly on the following three parameters: (i) the unsaturated amino acid, (ii) the ring size and (iii) the amino acid sequence. In ring-closing metatheses described in the literature so far, unbranched allylglycines (or related amino acids) were generally used as substrates. Therefore, one might reason that the more steric demanding methyl group in α-position to the terminal olefin could inhibit the ring-closure.

Unfortunately, exchanging this amino acid with 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 were difficult to obtain by this strategy. Most likely, the problems with these medium sized rings result from an unsuitable conformation of the linear peptide chain in solution, with *trans* amide bonds inhibiting the allyl termini from coming within close proximity. Therefore we decided to enlarge the ring size and to introduce one proline, which is able to form *cis* amide bonds and turn structures.[32]

Rearrangement of the tetrapeptide ester **6** gave the desired allylated tetrapeptide **7** in excellent yield (Scheme 2).[33] *N*-allylation provided the substrate **8** for the subsequent ring-closing metathesis, which now resulted in the formation of the desired cyclic peptide **9** (15-membered ring) in high yield.[34] This was in good agreement with the results described by Grubbs *et al.* for comparable peptides such as **2** (14-membered ring).[12] The double bond was obtained as an inseparable *cis/trans*-mixture.

To determine if the proline plays a significant role in the cyclisation, we came back to our allylated tripeptides such as **10**, which could not by cyclised previously after *N*-allylation. Cleavage of the *N*-protecting group and coupling with allylated amino acids provided the elongated peptides **11** and **12**. Subsequent ring-closing metathesis yielded the corresponding 16-membered cyclic peptides **13** and **14** in even higher yields in comparison to the smaller proline peptide (Scheme 3). Obviously ring size played a major role for the success of this reaction; the amino

Scheme 2 Peptide Claisen rearrangement and subsequent ring-closing metathesis; (a) 5.0 equiv LHMDS, 2.0 equiv SnCl$_2$, THF, −78 °C → rt, 16 h; (b) CH$_2$N$_2$, ether, 10 min; (c) 1 mol% (allyl PdCl)$_2$, 4.5 mol% PPh$_3$, allyl carbonate, THF, rt, 16 h; (d) 10 mol% RuCl$_2$(PCy$_3$)$_2$(=CHPh), CH$_2$Cl$_2$, reflux, 14 h.
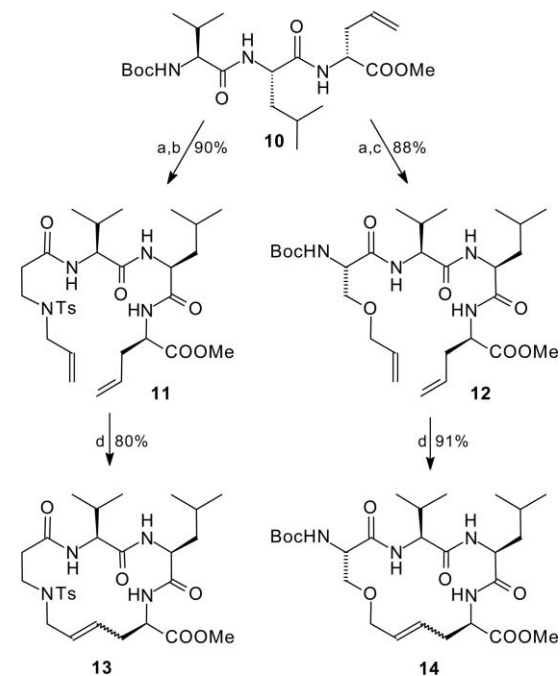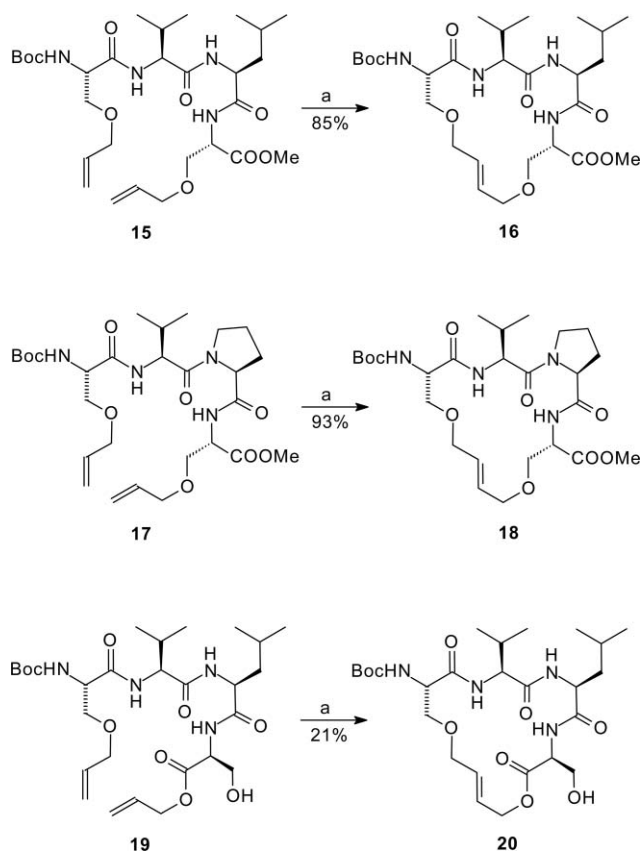

Scheme 3 Cyclisation of 16-membered rings; (a) HCl, dioxane, 0 °C, 30 min; (b) 1 equiv *N*-tosyl-*N*-allyl-β-Ala,[35] 5 equiv, 1.1 equiv TBTU, NEt$_3$, CH$_2$Cl$_2$, 10 h; (c) 1 equiv Boc-Ser(OAll), 1.1 equiv TBTU, 5 equiv, NEt$_3$, CH$_2$Cl$_2$, 8 h; (d) 10 mol% RuCl$_2$(PCy$_3$)$_2$(=CHPh), CH$_2$Cl$_2$, reflux, 15 h.

acid sequence and conformational issues were less important, at least for peptides with more than 14 ring members.

We further enlarged the ring size by replacing the allylglycine by an *O*-allylserine (Scheme 4, **15**). For comparison, the proline-containing peptide **17** was also prepared by conventional peptide synthesis. Both peptides **15** and **17** gave the expected 18-membered cyclisation products **16** and **18** in excellent yield, comparable to the 16-membered analogues. Product **18** was obtained as a separable 1 : 1 mixture of the *cis/trans*-isomers, while in the case of **16** the isomers could not be separated. An interesting observation was made after the *C*-terminal *O*-allylserine unit was replaced by the serine allyl ester **19**. In this case, the yield of the ring-closing metathesis dropped to 21%, although the ring size was the same as in **16** and **18**.

Ring strain should not be the problem, and therefore one might not expect higher yields at higher temperatures. Indeed, when the cyclisation is carried out in toluene at 60 °C,

Scheme 4 Cyclisation of 18-membered rings; (a) 10 mol% RuCl₂-(PCy₃)₂(=CHPh), CH₂Cl₂, reflux, 15 h.

Scheme 5 Multi component reactions and ring-closing metathesis; (a) 10 mol% RuCl₂(PCy₃)₂(=CHPh), CH₂Cl₂, reflux, 15 h.

only unreacted starting material **19** was recovered. Obviously, allylic esters are much less suited for ring-closing metathesis in comparison to allylic ethers or amides. This might be explained by a coordination of the carbonyl group to the ruthenium carbon complex formed in the first step of the metathesis, giving rise to a stable 6-membered chelate ring, which does not undergo further reactions.[36] This chelate formation can, in principle, be suppressed by addition of Ti(OⁱPr)₄, which coordinates more strongly to the carbonyl group.[37] Unfortunately, the addition of 5 equiv. of Ti(OⁱPr)₄ had no effect on the cyclisation. Another reason for the low yield might result from an interaction of the free hydroxy group on the C-terminal serine with the catalyst. We therefore protected this functionality by benzoylation, but the cyclisation yield was lower than with the free hydroxy group.

Because of our ongoing interest in stereoselective modifications of peptides we wanted to use cyclic peptides as templates for the stereoselective introduction of side chains, since stereoselective modifications of linear peptides are not a trivial issue.[38] The advantage of cyclisation *via* an allylic ester is that the latter can easily be cleaved after the modification under palladium catalysis. Most interesting from this point of view should be a fixation of peptide conformation by metathesis of two allylic protecting groups; an allyl ester on the C-terminus and an allyloxycarbonyl (Alloc)-protecting group on the N-terminus of the peptide. Sequential palladium-catalysed cleavage of both protecting groups in one step should provide fully unprotected modified peptides. We intensively investigated a ring-closure approach with these two allylic protecting groups. As substrates we chose N-allyl protected tripeptide allylic esters, since they lead to 16-membered rings, which has previously been reported to be a suitable size. To get rapid access to our substrates with a high potency of variation, the Passerini and Ugi multi-component reactions have been used, providing the required substrates in one step (Scheme 5).[39–40] With Alloc-protected valine as the acid component and the allylic ester of isocyanoacetic acid the depsipeptide, **21** was obtained as
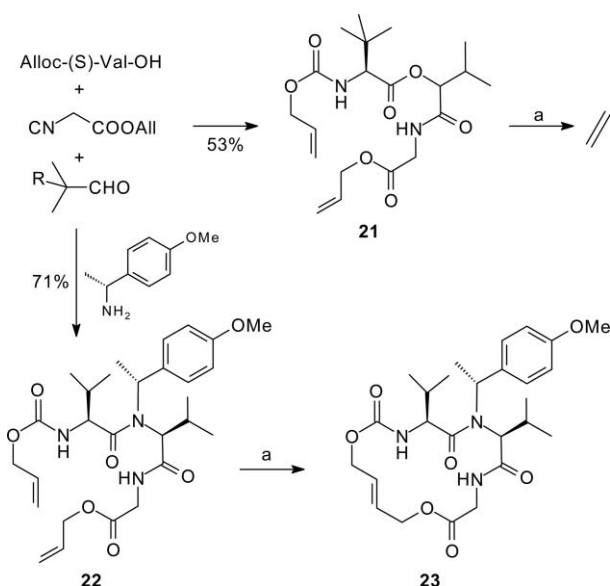
diastereomeric mixture in acceptable yield. In the presence of (R)-p-methoxy-1-phenylethylamine the corresponding peptide **22** could be obtained in a 3 : 1 diastereomeric ratio at rt. The selectivity could be increased to nearly 9 : 1 if the reaction was carried out at −30 °C. In this case the diastereomers could be separated by flash chromatography. The substrates were then subjected to ring-closing metathesis. No reaction was observed using depsipeptide **21** even with 10% catalyst, while the major diastereomer of **22** gave cyclisation product **23** in only 13% yield (Table 1, Entry 1).

Interestingly, only the *trans*-configured product was obtained (>95%) as determined by HPLC. The olefin geometry as well as the configuration of the newly formed stereogenic centre could be determined by X-ray structure analysis.[41]§ All amide and ester bonds showed *trans* configuration, even the N-alkylated amide bond. Therefore it is not obvious, why depsipeptide **21** did not undergo cyclisation.

Since the Ugi reaction turned out to be a valuable approach to the required substrates, we investigated the influence of several parameters on the outcome of the ring-closing metathesis (Scheme 6). One might expect an influence from the peptide sequence, especially if loop inducing amino acids such as prolines or N-alkylated amino acids are incorporated. Therefore we also varied the N-terminal amino acid using Alloc-protected alanine, proline and sterically demanding N-methyl valine as carbocyclic acids. With (S)-m-methoxy-1-phenylethylamine all peptides were obtained in high yield and especially with Alloc-alanine (**24**) in excellent diastereoselectivity. Unfortunately for the peptides **25** and **26** the diastereomeric ratio could not be determined because of the occurrence of several rotamers. Therefore the diastereomeric mixture was subjected to ring-closing metathesis and the yields are given in Table 1. None of the reactions ran to completion and in all cases the starting material was recovered. In agreement with the cyclisation of **22** only the all-(S)-substrates underwent cyclisation, while the other diastereomer was the major component of the recovered starting material. In all examples only the *trans* configured double bond (>95 *trans*) was obtained, as determined by X-ray structure analysis of **28** and comparison of the NMR spectra of the other cyclic peptides.†

Table 1 Ring-closing metathesis of peptides **22** and **24–26**

Entry	Peptide	Product	Catalyst	Reaction conditions	Yield/%	Comments
1	**22**	**23**	10% **A**	CH$_2$Cl$_2$, rt	13	Only *trans* double bond
2	**25**	**28**	5% **A**	CH$_2$Cl$_2$, rt	37	21% starting material recovered
3	**26**	**29**	10% **A**	Toluene, 60 °C	33	34% starting material recovered
4	**22**	**23**	10% **B**	CH$_2$Cl$_2$, rt	—	Polymerisation
5	**22**	**23**	5% **C**	Toluene, rt	—	Polymerisation
6	**25**	**28**	10% **B**	CH$_2$Cl$_2$, rt	—	Polymerisation
7	**25**	**28**	5% **C**	CH$_2$Cl$_2$, rt	5	Polymerisation
8	**24**	**27**	10% **A**	CH$_2$Cl$_2$, rt	15	21% starting material recovered
9	**24**	**27**	10% **A**	Toluene, 30 °C	16	—
10	**24**	**27**	10% **A**	Toluene, 90 °C or N$_2$ stream	27	—
11	**22**	**23**	10% **A**	CH$_2$Cl$_2$, rt, 0.3 eq. Ti(O^{i}Pr)$_4$	34	—
12	**22**	**23**	10% **A**	CH$_2$Cl$_2$, rt, 1 eq. Ti(O^{i}Pr)$_4$	26	—
13	**22**	**23**	10% **A**	CH$_2$Cl$_2$, rt, 4 eq. Ti(O^{i}Pr)$_4$	—	—
14	**22**	**23**	10% **B**	CH$_2$Cl$_2$, rt, 0.3 eq. Ti(O^{i}Pr)$_4$	—	Polymerisation
15	**22**	**23**	10% **A**	Catalyst added in 30 min to a 0.05 M solution of 25 in CH$_2$Cl$_2$ at rt	< 5	—
16	**25**	**28**	5% **A**	Catalyst added in 30 min to a 0.05 M solution of 28 in CH$_2$Cl$_2$ at rt	< 5	—
17	**22**	**23**	10% **A**	Catalyst added in 2 h to a 0.05 M solution of 25 in CH$_2$Cl$_2$ at rt	23	—
18	**25**	**28**	5% **A**	Catalyst added in 30 min to a 0.05 M solution (CH$_2$Cl$_2$) of 28 under N$_2$ stream at rt	34	—
19	**22**	**23**	5% **A**	Catalyst added in 30 min to a 0.05 M solution (CH$_2$Cl$_2$) of 28 under reflux–N$_2$ stream	38	—
20	**25**	**28**	10% **A**	Peptide (0.01 M solution) added to catalyst in CH$_2$Cl$_2$ under reflux–N$_2$ stream	51	Only *trans* double bond
21	**25**	**26**	10% **A**	Peptide (0.01 M solution) added to catalyst in CH$_2$Cl$_2$ under reflux–N$_2$ stream	73	Only *trans* double bond
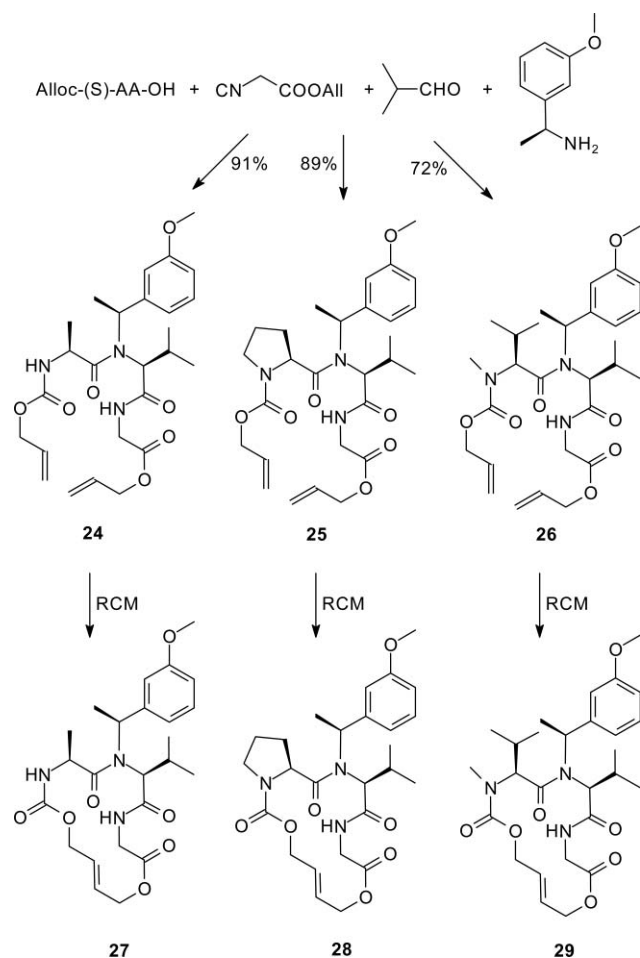
Scheme 6 Ugi reactions and ring-closing metathesis.

As expected, the best results were obtained with the proline peptide **25**. The isolated yield was better than **26**, for which more starting material was recovered.

With this substrate harsher reaction conditions were necessary. In comparison to **24** and **25** the reaction was rather slow at rt, but could be accelerated significantly by heating the reaction mixture to 60 °C. Since the pioneering work of Grubbs *et al.* using the 1st generation ruthenium catalyst **A**, several new catalysts have been developed such as the more reactive 2nd generation catalyst **B**, or the "boomerang catalyst" **C**, which allows regeneration of the metal complex (Fig. 2).[42–44]
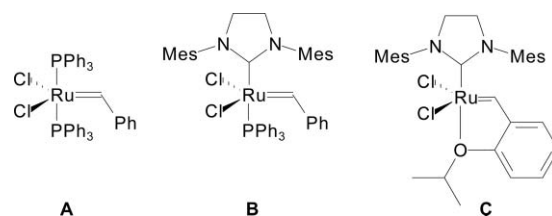
Fig. 2 Metathesis catalysts investigated.

We chose catalyst **A** for our investigations, because it is commercially available at a reasonable price and shows high tolerance towards functional groups. With respect to higher yields for cyclisations of our critical substrates, we also investigated the other catalysts, albeit without the desired effect. Both catalysts failed in the cyclisation of peptide **25** and **26**. Mainly, polymerisation was observed with catalyst **B**, while with catalyst **C** only traces of product (*ca.* 5%) were obtained in the reaction of **26**, and 50–60% of starting material could be recovered. Therefore, catalyst **A** was used for the further investigation of the influence of reaction conditions.

As illustrated with peptide **26**, higher temperatures are sometimes necessary for satisfying results. The combined influence of the reaction temperature and solvent was also investigated (entries 8–10). In the cyclisation of **24** the yield could be increased by switching from CH$_2$Cl$_2$ to toluene at higher temperatures (entry 10), while changing the solvent alone had no influence. An increase of yield was also observed if nitrogen was bubbled through the solution, to remove the ethylene that was formed.

Peptide **22** was used to investigate the influence of Lewis acids, such as Ti(O^{i}Pr)$_4$, on the outcome of the reaction. As

illustrated in entries 11–14, subequimolar ratios of Lewis acids can indeed increase the yield, while in higher ratios the reaction can be suppressed completely. Lewis acids only accelerated the metathesis reaction with catalyst **A**, but with the more reactive **B**, only homodimerisation and polymerisation occurred. The best results were obtained in a 0.01 M solution of substrate **22**, but the yield could not be increased to more than 35% under all conditions investigated so far; we thus presume that deactivation of the catalyst by the substrate occurs during the reaction.

Therefore, the mode of addition was thoroughly investigated with peptides **22** and **25** (entries 15–21). In both cases the yield of cyclisation product was below 5% if a solution of the catalyst was added over 30 min to a solution of the peptide in CH_2Cl_2 at rt (entries 15,16). If the catalyst solution was added more slowly, over 2 h *via* a syringe pump, a significant increase in the yield was observed (entry 17). The same results were obtained when the reaction mixture was degassed with N_2 to remove the ethylene liberated in the ring-closing step (entries 18–19). But by far the best results were obtained if the peptide solution was added to the catalyst solution in refluxing CH_2Cl_2 under an N_2 stream. Under these conditions the yield could be increased to 51 and 73%, respectively (entries 20 and 21). In both cases, only the product with the *trans*-configured double bond was obtained, no *cis* product could be determined by HPLC and NMR.

Conclusion

In conclusion, we have shown that not only the length and sequence of a peptide chain is responsible for the success of a ring-closing metathesis but also the synthetic protocol. While peptides containing amino acids with allylic side chains or with allylether side chains can be cyclised under "standard conditions", allylic esters and carbamates require optimised reaction conditions.

Experimental

All reactions were carried out in oven-dried glassware (100 °C) under argon. All solvents were dried before use. THF was distilled from sodium benzophenone, dichloromethane and diisopropylamine from calcium hydride. LHMDS solutions were prepared from freshly distilled hexamethyldisilazane and commercially available *n*-butyllithium solution (15% in hexane) in THF at −20 °C directly before use. The starting materials and the products were purified by flash chromatography on silica gel (32–63 μm). ^{1}H and ^{13}C NMR: Bruker AC 300, Bruker Advance 300, Bruker 400 MHz or Bruker DRX-500 spectrometer, respectively.

Diastereomeric ratios were determined by analytical HPLC using a Shimadzu workstation with an SPD-M10A diodearray detector and a Lichrosorb silicagel column (250 × 4 mm, 5 μm) or a Daicel "Chiralcel OD–H" column (250 × 4 mm, 5 μm). Optical rotations were measured using a Perkin-Elmer 241 polarimeter.

N-(4-Toluolsulfonyl)-(*S*)-valinyl-β-alaninyl-glycine crotylester (3)

To a solution of Tos-Val-β-Ala-OH (1.03 g, 3.0 mmol) in THF (15 ml) carbonyldiimidazole (0.49 g, 3.0 mmol) was added at rt. After evolution of CO_2 the reaction mixture was stirred for 10 min, before Gly-OAll·HCl (0.50 g, 3.0 mmol) was added as solid. After stirring for 10 h, the reaction mixture was diluted with Et_2O and washed with sat. $NaHCO_3$ and 1 N HCl. The aqueous layer was extracted with Et_2O. The combined organic layers were dried (Na_2SO_4) and evaporated *in vacuo* giving rise to a pale yellow solid. Crystallisation from MeOH–EtOAc–Et_2O gave 1.01 g (2.3 mmol, 75%) of **3** as colourless crystals, mp 171–172 °C. ^{1}H NMR (300 MHz, CDCl₃): δ 0.73 (3H, d, *J* 6.8), 0.76 (3H, d, *J* 6.8), 1.67 (3H, dd, *J* 6.5 and 1.0), 1.94 (1H, m), 2.32 (2H, dt, *J* 6.7 and 4.9), 2.40 (3H, s), 3.37 (1H, dd, *J* 8.3 and 5.9), 3.43 (2H, m), 3.84 (1H, dd, *J* 18.0 and 5.5), 4.03 (1H, dd, *J* 18.0

and 6.0), 4.54 (2H, d, *J* 6.7), 5.54 (1H, dtq, *J* 15.2 and 6.7, 1.6), 5.62 (1H, d, *J* 8.5), 5.78 (1H, dq, *J* 15.2 and 6.6), 6.64 (1H, t, *J* 5.5), 7.18 (1H, t, *J* 6.0), 7.23 (2H, d, *J* 8.9), 7.66 (2H, d, *J* 8.3). ^{13}C NMR (75 MHz, CDCl₃): δ 17.54, 17.74, 19.06, 21.50, 31.05, 36.04, 36.13, 41.48, 62.45, 66.36, 124.34, 127.36, 129.55, 132.38, 136.38, 143.74, 170.46, 171.06, 172.45. $C_{21}H_{31}N_3O_6S$ (453.56) calcd.: C 55.61 H 6.89 N 9.26 S 7.07; found: C 55.52 H 6.87 N 9.22 S 7.18.

N-(4-Toluolsulfonyl)-(*S*)-valinyl-β-alaninyl-(*R*)-γ,δ-dehydro-allo-isoleucine methylester (4)

Peptide **3** (227 mg, 0.5 mmol) and tin chloride (190 mg, 1.0 mmol) were placed in a Schlenk flask under argon. Abs. THF (10 ml) was added and the clear solution was cooled to −78 °C. A freshly prepared solution of LHMDS (from 3.13 mmol HMDS and 2.50 mmol BuLi) in THF (3 ml) was slowly added. The reaction mixture was warmed to rt overnight, diluted with Et_2O (20 ml) and hydrolysed with 1 N HCl (20 ml). Stirring was continued to destroy the peptide–metal complex. The layers were separated, the organic layer was washed again with 1 N HCl, dried (Na_2SO_4) and evaporated *in vacuo*. The crude product was esterified with diazomethane and purified by flash chromatography (hexane–EtOAc–EtOH 6 : 4 : 1) giving rise to **4** (190 mg, 0.44 mmol, 89%) as a colourless solid, mp 215–216 °C. Diastereomeric ratio: 16 : 84. HPLC (Daicel OD–H, hexane–isopropanol 90 : 10, 0.5 ml min⁻¹): t_{R1} = 28.17 min, t_{R2} = 35.35 min. ^{1}H NMR (300 MHz, CD₃OD): δ 0.81 (3H, d, *J* 6.4), 0.86 (3H, d, *J* 6.5), 1.03 (3H, bs), 1.84 (1H, m), 2.27 (2H, m), 2.40 (3H, s), 2.62 (1H, m), 3.15 (2H, m), 3.37 (1H, bs), 3.67 (3H, s), 4.42 (1H, bs), 5.03–5.09 (2H, m), 5.73 (1H, m), 7.33 (2H, d, *J* 8.4), 7.69 (2H, d, *J* 7.6). ^{13}C NMR (75 MHz, CD₃OD): δ 16.11, 18.56, 19.56, 21.45, 32.46, 35.92, 36.69, 41.33, 52.38, 58.17, 63.81, 116.14, 128.40, 130.53, 138.95, 140.36, 144.77, 173.17, 173.52. $C_{22}H_{33}N_3O_6S$ (467.58) calcd.: C 56.51 H 7.11 N 8.99; found: C 56.24 H 7.08 N 8.72.

[*N*-Allyl-*N*-(4-toluolsulfonyl)]-(*S*)-valinyl-β-alaninyl-(*R*)-γ,δ-dehydro-allo-isoleucin methylester (5)

A solution of allylpalladium chloride dimer (1.3 mg, 3.4 μmol, 1 mol%), triphenylphosphine (4 mg, 15.2 mmol, 4.5 mol%) and allyl ethyl carbonate (91 mg, 0.7 mmol) in abs. THF (2 ml) was added to a solution of **4** (165 mg, 0.35 mmol) in THF (5 ml). The reaction mixture was stirred overnight and the solvent was evaporated *in vacuo*. The crude product was purified by flash chromatography on silica (hexane–EtOAc 1 : 1) giving **5** (132 mg, 0.26 mmol, 73%) as a colourless oil. ^{1}H NMR (300 MHz, CDCl₃): δ 0.62 (3H, d, *J* 6.6), 0.81 (3H, d, *J* 6.5), 1.04 (3H, d, *J* 7.0), 2.15 (1H, m), 2.34–2.47 (2H, m), 2.38 (3H, s), 2.65 (1H, m), 3.33 (1H, m), 3.45 (1H, m), 3.64 (1H, d, *J* 10.8), 3.71 (3H, s), 3.86 (1H, dd, *J* 16.2 and 6.0), 4.13 (1H, dd, *J* 16.3 and 7.0), 4.60 (1H, dd, *J* 8.6 and 5.2), 5.01–5.18 (4H, m), 5.62–5.84 (2H, m), 6.03 (1H, d, *J* 8.2), 6.63 (1H, bs), 7.23 (2H, d, *J* 8.1), 7.67 (2H, d, *J* 8.2). ^{13}C NMR (75 MHz, CDCl₃): δ 15.54, 19.03, 19.45, 21.26, 27.00, 35.12, 35.26, 40.26, 47.08, 51.92, 55.79, 66.04, 116.23, 117.31, 127.23, 129.25, 134.86, 137.43, 138.21, 143.16, 169.49, 170.72, 171.51. $C_{25}H_{37}N_3O_6S$ (507.65) calcd.: C 59.15 H 7.35 N 8.28 S 6.32; found: C 59.11 H 7.44 N 8.13 S 6.54.

N-(4-Toluolsulfonyl)-(*S*)-valinyl-(*S*)-prolinyl-(*S*)-leucinyl-glycine allylester (6)

Tetrapeptide **6** was obtained by standard peptide coupling reactions in a 4 mmol scale. Crystallisation from EtOAc–Et_2O–hexane gave colourless needles, mp 158–159 °C. ^{1}H NMR (300 MHz, CDCl₃): δ 0.82 (3H, d, *J* 6.1), 0.84 (3H, d, *J* 6.0), 0.86 (3H, d, *J* 6.6), 0.91 (3H, d, *J* 6.8), 1.47–2.14 (8H, m), 2.39 (3H, s), 3.13 (1H, m), 3.38 (1H, m), 3.60 (1H, dd, *J* 9.9 and 6.5), 3.94 (1H, dd, *J* 18.2 and 5.4), 4.02 (1H, dd, *J* 18.2 and 5.3), 4.13 (1H, dd, *J* 8.4 and 2.6), 4.33 (1H, m), 4.58 (2H, dt,

J 6.2 and 1.3), 5.22 (1H, dt, *J* 10.4 and 1.3), 5.28 (1H, dt, *J* 17.2 and 1.4), 5.86 (1H, ddt, *J* 17.1, 10.4 and 6.3), 6.39 (1H, d, *J* 9.9), 6.76 (1H, t, *J* 5.4), 7.17 (1H, d, *J* 7.8), 7.26 (2H, d, *J* 8.1), 7.69 (2H, d, *J* 8.3). ^{13}C NMR (75 MHz, CDCl$_3$): δ 17.68, 19.07, 21.47, 21.77, 22.88, 24.57, 24.90, 27.14, 31.68, 40.60, 41.18, 47.24, 51.90, 59.34, 59.67, 65.87, 118.82, 127.41, 129.43, 131.48, 136.01, 143.59, 169.31, 170.92, 171.14, 172.06. C$_{28}$H$_{42}$N$_4$O$_7$S (578.73) calcd.: C 58.11 H 7.32 N 9.68 S 5.54; found: C 57.94 H 7.29 N 9.53 S 5.68.

N-(4-Toluolsulfonyl)-(*S*)-valinyl-(*S*)-prolinyl-(*S*)-leucinyl-allylglycine methylester (7)

According to the preparation of **4**, rearrangement product **7** was obtained from **6** (289 mg, 0.50 mmol) as a colourless foam in a diastereomeric ratio of 40 : 60. Yield: 275 mg (0.46 mmol, 93%). HPLC (Daicel OD–H, hexane–isopropanol 90 : 10, 0.5 ml min^{-1}): t_{R1} = 24.67 min, t_{R2} = 30.83 min. ^{1}H NMR (300 MHz, CDCl$_3$): δ 0.82 (3H, d, *J* 6.1), 0.86 (3H, d, *J* 6.2), 0.89 (3H, d, *J* 6.8), 0.94 (3H, d, *J* 6.7), 1.46–2.09 (8H, m), 2.39 (3H, s), 2.47 (2H, m), 3.12 (1H, m), 3.37 (1H, m), 3.64 (1H, dd, *J* 10.1 and 6.3), 3.69 (3H, s), 4.04 (1H, dd, *J* 8.4 and 2.7), 4.30 (1H, m), 4.56 (1H, m), 5.04 (1H, d, *J* 15.4), 5.05 (1H, d, *J* 11.6), 5.65 (1H, m), 6.06 (1H, d, *J* 10.0), 6.59 (1H, d, *J* 7.7), 7.00 (1H, d, *J* 7.7), 7.27 (2H, d, *J* 8.2), 7.69 (2H, d, *J* 8.3). ^{13}C NMR (75 MHz, CDCl3): δ 17.28, 18.99, 21.27, 21.66, 22.66, 24.42, 25.12, 26.85, 31.40, 36.04, 40.57, 46.99, 51.44, 51.66, 52.07, 59.13, 59.47, 118.79, 127.25, 129.18, 132.03, 136.61, 143.36, 170.47, 170.85, 171.17, 171.60. HMRS: calcd. for C$_{29}$H$_{45}$N$_4$O$_7$S ([M+H]$^+$), 593.2993; found, 593.3022. HMRS: calcd. for C$_{29}$H$_{44}$N$_4$O$_7$SNa ([M+Na]$^+$), 615.2812; found, 615.2847.

[*N*-(4-Toluolsulfonyl)-*N*-allyl]-(*S*)-valinyl-(*S*)-prolinyl-(*S*)-leucinyl-allylglycine methylester (8)

According to the preparation of **5**, *N*-allylated product **8** was obtained from **7** (260 mg, 0.440 mmol) as a pale yellow oil. Yield: 210 mg (0.33 mmol, 75%). ^{1}H NMR (300 MHz, CDCl$_3$): δ 0.83 (3H, d, *J* 6.1), 0.85 (3H, d, *J* 7.2), 0.88 (3H, d, *J* 6.7), 0.89 (3H, d, *J* 6.6), 1.39–1.49 (1H, m), 1.53–1.89 (2H, m), 1.89 (1H, m), 1.98–2.20 (4H, m), 2.38 (3H, s), 2.49 (2H, m), 3.52 (1H, m), 3.65–3.76 (1H, m), 3.69 (3H, s), 3.96 (1H, dd, *J* 16.6 and 5.3), 4.22–4.32 (3H, m), 4.39 (1H, dd, *J* 16.5 and 7.7), 4.56 (1H, m), 4.99–5.15 (4H, m), 5.63 (1H, m), 5.87 (1H, m), 6.70 (1H, d, *J* 7.7), 6.86 (1H, d, *J* 7.9), 7.23 (2H, d, *J* 7.9), 7.58 (2H, d, *J* 8.3). ^{13}C NMR (75 MHz, CDCl$_3$): δ 8.59, 19.75, 21.25, 21.78, 22.57, 24.50, 24.66, 27.32, 28.93, 36.06, 40.49, 47.31, 51.43, 51.70, 51.91, 52.07, 59.89, 62.16, 116.64, 118.78, 127.04, 129.18, 132.05, 135.71, 137.09, 143.30, 170.73, 170.84, 171.19, 171.61. C$_{32}$H$_{48}$N$_4$O$_7$S (632.82) calcd.: C 60.74 H 7.64 N 8.85 S 5.07; found: C 60.94 H 7.59 N 8.79 S 5.08. HMRS: calcd. for C$_{32}$H$_{49}$N$_4$O$_7$S ([M+H]$^+$), 633.3305; found, 633.3329. HMRS: calcd. for C$_{32}$H$_{48}$N$_4$O$_7$SNa ([M+Na]$^+$), 655.3124; found, 655.3154.

Cyclopeptide 9

Tetrapeptide **8** (85 mg, 0.134 mmol) was dissolved in CH$_2$Cl$_2$ (10 ml) in a Schlenk tube under argon. A solution of Grubbs' catalyst **A** (12 mg, 13.4 μmol, 10 mol%) in CH$_2$Cl$_2$ (15 ml) was added slowly to the peptide solution *via* a syringe. The mixture was refluxed for 2 h and allowed to stir overnight at rt. The solvent was evaporated *in vacuo* and the dark brown residue was purified by flash chromatography (hexane–EtOAc 6 : 4) giving rise to **9** (67 mg, 0.103 mmol, 77%) as a pale yellow oil. ^{1}H NMR (300 MHz, CDCl$_3$): δ 0.53 (3H, d, *J* 6.1), 0.83 (3H, d, *J* 6.4), 0.89 (3H, d, *J* 6.6), 0.94 (3H, d, *J* 6.6), 1.48–2.33 (8H, m), 2.40 (3H, s), 2.82 (2H, m), 3.67 (3H, s), 3.64–3.70 (3H, m), 3.82 (1H, dd, *J* 16.5 and 10.5), 3.96 (1H, m), 4.09 (1H, m), 4.23 (1H, d, *J* 10.5), 4.74 (1H, m), 5.19 (1H, t, *J* 10.5), 5.47 (1H, d, *J* 8.4), 5.55 (1H, t, *J* 10.9), 7.27 (2H, d, *J* 8.3), 7.70 (2H, d, *J* 8.3), 8.61 (1H, d, *J* 8.3). ^{13}C NMR (75 MHz, CDCl$_3$):

δ 19.11, 20.73, 21.50, 23.17, 24.34, 25.72, 27.68, 28.36, 28.63, 40.66, 40.81, 47.25, 52.36, 52.41, 54.79, 56.94, 61.52, 127.80, 128.56, 128.62, 129.52, 136.97, 143.73, 167.61, 171.35, 171.99, 172.71. HMRS: calcd. for C$_{30}$H$_{45}$N$_4$O$_7$S ([M+H]+), 605.2993; found, 605.3029. HMRS: calcd. for C$_{30}$H$_{44}$N$_4$O$_7$SNa ([M+Na]$^+$), 627.2812; found, 627.2820.

Cyclopeptide 13

According to the preparation of **9**, peptide **13** was obtained from **11** (61 mg, 0.10 mmol) as a pale yellow oil. Yield: 46 mg (0.08 mmol, 80%). ^{1}H NMR (500 MHz, d$_7$-DMF): δ 0.86 (3H, d, *J* 6.3), 0.88 (3H, d, *J* 6.4), 0.99 (3H, d, *J* 7.0), 1.00 (3H, d, *J* 7.0), 1.62–1.70 (2H, m), 1.76 (1H, m), 2.11 (1H, m), 2.43 (3H, s), 2.44–2.52 (3H, m), 2.69 (1H, m), 3.26 (1H, m), 3.51 (1H, m), 3.64 (3H, s), 3.75 (1H, dd, *J* 14.7 and 6.3), 3.81 (1H, dd, *J* 14.8 and 7.1), 3.97 (1H, dd, *J* 6.0 and 5.7), 4.43 (1H, m), 4.59 (1H, m), 5.43 (1H, dt, *J* 15.4, 6.7), 5.64 (1H, dt, *J* 15.4, 7.0), 7.47 (2H, d, *J* 8.0), 7.62 (1H, d, *J* 8.0), 7.71 (1H, d, *J* 8.3), 7.75 (2H, d, *J* 8.0), 8.15 (1H, d, *J* 6.1). ^{13}C NMR (125 MHz, d$_7$-DMF): δ 18.67, 19.50, 21.23, 21.35, 23.38, 25.13, 30.43, 33.88, 40.62, 43.28, 50.18, 51.94, 52.27, 52.39, 61.86, 127.81, 128.84, 130.42, 131.29, 137.32, 144.18, 171.89, 171.98, 172.50, 172.76. C$_{28}$H$_{42}$N$_4$O$_7$S (578.73) calcd.: C 58.11 H 7.32 N 9.68; found: C 58.15 H 7.38 N 9.27.

Cyclopeptide 14

According to the preparation of **9**, peptide **14** was obtained from **12** (80 mg, 0.14 mmol) as a colourless solid, mp 178–179 °C. Yield: 69 mg (0.13 mmol, 91%). ^{1}H NMR (300 MHz, CD$_3$OD): δ 0.92 (3H, d, *J* 6.2), 0.94 (3H, d, *J* 6.9), 0.96 (3H, d, *J* 6.0), 0.97 (3H, d, *J* 6.2), 1.42 (9H, s), 1.63 (2H, m), 1.69 (1H, m), 2.10 (1H, m), 2.35 (1H, m), 2.60 (1H, m), 1.57 (2H, m), 3.71 (3H, s), 3.84 (1H, d, *J* 11.8), 3.93 (1H, d, *J* 11.5), 4.26 (1H, m), 4.28 (1H, d, *J* 6.9), 4.37 (1H, m), 4.66 (1H, dd, *J* 9.8 and 3.3), 5.58 (2H, m). ^{13}C NMR (75 MHz, CD$_3$OD): δ 18.44, 19.75, 22.56, 22.97, 25.99, 28.65, 32.29, 34.88, 41.74, 52.80, 52.85, 53.70, 55.40, 62.07, 70.77, 72.19, 80.76, 128.18, 130.34, 157.42, 172.79, 173.04, 173.29, 173,69. HMRS: calcd. for C$_{26}$H$_{45}$N$_4$O$_8$ ([M+H]$^+$), 541.3222; found, 541.3256. HMRS: calcd. for C$_{26}$H$_{44}$N$_4$O$_8$Na ([M+Na]$^+$), 563.3041; found: 563.3052.

Cyclopeptide 16

According to the preparation of **9**, peptide **16** was obtained from **15** (80 mg, 0.134 mmol) using 5% catalyst (6 mg, 0.067 mmol). Purification of the crude product by flash chromatography (hexane–EtOAc 6 : 4 → 1 : 1) gave **16** as a colourless solid, mp 184–185 °C. Yield: 65 mg (0.144 mmol, 85%). The *cis/trans* ratio could not be determined. $[a]_D^{20}$ = −3.5 (*c* 1, CHCl$_3$). ^{1}H NMR (300 MHz, CDCl$_3$): δ 0.89–0.97 (12H, m), 1.43 (9H, s), 1.50–1.57 (3H, m), 2.20 (1H, m), 3.60–3.63 (2H, m), 3.75 (3H, s), 3.78–3.81 (2H, m), 4.10–4.15 (4H, m), 4.20–4.25 (2H, m), 4.44 (1H, m), 4.65 (1H, m), 5.30–5.43 (2H, m), 5.86 (1H, m), 6.06 (1H, d$_{br}$), 7.25 (1H, d$_{br}$), 7.35 (1H, d$_{br}$). ^{13}C NMR (75 MHz, CDCl$_3$): δ 16.47, 19.49, 21.84, 22.81, 24.83, 28.23, 31.05, 39.05, 52.46, 52.59, 52.75, 57.95, 69.63, 70.32, 71.29, 80.27, 127.81, 129.44, 155.73, 170.25, 170.95, 171.16, 171.32. C$_{27}$H$_{46}$O$_9$N$_4$ (570.684) calcd.: C 56.83 H 8.12 N 9.82; found: C 55.69 H 8.07 N 8.91. HMRS: calcd. for C$_{27}$H$_{47}$N$_4$O$_9$ ([M+H]$^+$), 571.3343; found, 571.3359. HMRS: calcd. for C$_{27}$H$_{46}$N$_4$O$_9$Na ([M+Na]$^+$), 593.3163; found, 593.3127.

Cyclopeptide 18

According to the preparation of **9**, peptide **18** was obtained from **17** (134 mg, 0.23 mmol) using 5% catalyst **A** (9 mg, 0.01 mmol). To remove traces of the catalyst, the products were dissolved in methanol and stirred vigorously after addition of 3% H$_2$O$_2$ solution. The mixture was diluted with CH$_2$Cl$_2$ and the phases were separated. The organic layer was nearly colourless.

In this case the *cis/trans* isomers could be separated by flash chromatography (hexane–EtOAc 2 : 8 → EtOAc) giving 66 mg (0.12 mmol, 52%) *trans*-**21** and 52 mg (0.09 mmol, 41%) *cis*-**21**. Overall yield: 118 mg (0.21 mmol, 93%). HPLC (Daicel OD-H, hexane–isopropanol 85 : 15, 0.5 ml min^{-1}): *trans*-**18**: t_{R1} = 28.14 min, *cis*-**18**: t_{R2} = 31.17 min. *trans*-**18**: $[a]_D^{22}$ = +11.7° (*c* 0.5, CHCl$_3$). ^{1}H NMR (300 MHz, CDCl$_3$): δ 0.70 (3H, d, *J* 6.8), 0.94 (3H, d, *J* 6.8), 1.40 (9H, s), 1.86–1.99 (2H, m), 2.06–2.13 (2H, m), 2.38 (1H, m), 3.46–3.65 (5H, m), 3.71 (3H, s), 3.72 (1H, m), 3.80 (1H, m), 3.96 (1H, m), 4.13–4.20 (2H, m), 4.29 (1H, s$_{br}$), 4.52 (1H, m), 4.59–4.66 (2H, m), 5.49 (1H, d, *J* 4.8), 5.90 (1H, d, *J* 15.5), 6.09 (1H, d, *J* 15.5), 7.81 (1H, d, *J* 7.9), 7.87 (1H, d, *J* 8.5). ^{13}C NMR (75 MHz, CDCl$_3$): δ 15.81, 20.16, 25.79, 26.31, 28.33, 30.15, 47.51, 52.31, 52.52, 52.91, 55.97, 60.31, 70.04, 70.46, 70.67, 71.42, 79.82, 127.10, 128.67, 154.94, 170.52, 170.70, 170.98, 171.15. *cis*-**18**: $[a]_D^{22}$ = −44.4° (*c* = 0.5, CHCl$_3$). ^{1}H NMR (300 MHz, CDCl$_3$): δ 0.84 (3H, d, J 6.7), 0.96 (3H, d, J 6.7), 1.43 (9H, s), 1.79 (1H, m), 1.94 (1H, m), 2.00 (1H, m), 2.11 (1H, m), 2.39 (1H, m), 3.51 (1H, m), 3.56–3.58 (2H, m), 3.63–3.69 (3H, m), 3.72 (3H, s), 3.90 (1H, m), 3.94–3.96 (2H, m), 3.99 (1H, m), 4.22 (1H, m), 4.49 (1H, d, J 7.7), 4.54 (1H, m), 4.76 (1H, dd, J 9.2 and 4.2), 5.53 (1H, d, J 5.7), 5.67 (1H, m), 5.75 (1H, m), 7.16 (1H, d, J 9.2), 7.70 (1H, d, J 7.4). ^{13}C NMR (75 MHz, CDCl$_3$): δ 16.45, 19.59, 24.61, 27.20, 28.04, 31.30, 47.06, 52.28, 52.67, 54.78, 59.91, 67.52, 69.51, 69.84, 70.69, 80.12, 126.85, 129.39, 154.94, 170.20, 170.51, 170.55, 170.85. HMRS: calcd. for C$_{26}$H$_{43}$N$_4$O$_9$ ([M+H]$^+$), 555.3030; found, 555.3036. HMRS: calcd. for C$_{26}$H$_{42}$N$_4$O$_9$Na ([M+Na]$^+$), 577.2849; found, 577.2839.

Cyclopeptide 20

According to the preparation of **9**, peptide **20** was obtained from **19** (88 mg, 0.15 mmol) using 5% catalyst **A** (7 mg, 0.008 mmol). Yield: 18 mg (32.4 μmol, 21%) of a grey–brown oil. ^{1}H NMR (300 MHz, CDCl$_3$): δ 0.88–0.94 (12H, m), 1.44 (9H, s), 1.50–1.60 (3H, m), 1.88 (1H, m), 3.74 (2H, m), 3.91–4.00 (2H, m), 4.09 (1H, m), 4.60–4.65 (7H, m), 5.57 (1H, d$_{br}$), 5.68–5.75 (2H, m), 6.75 (1H, d$_{br}$), 6.90 (1H, d$_{br}$), 7.05 (1H, d$_{br}$). ^{13}C NMR (75 MHz, CDCl$_3$): δ 18.41, 19.28, 20.89, 23.19, 24.83, 28.26, 30.51, 40.05, 51.57, 54.98, 63.41, 63.95, 69.95, 80.30, 127.74, 128.45, 155.71, 169.77, 171.21, 171.60, 172.34. HMRS: calcd. for C$_{26}$H$_{45}$N$_4$O$_9$ ([M+H]$^+$), 557.3187; found, 557.3173. HMRS: calcd. for C$_{26}$H$_{44}$N$_4$O$_9$Na ([M+Na]$^+$), 579.3006; found, 579.2990.

Depsipeptide 21

A solution of (*S*)-Aloc-ValOH (1.94 g, 5.00 mmol) in trifluoroethanol (5 ml) was added to a solution of pivalaldehyde (0.54 ml, 5.00 mmol) in the same solvent (5 ml) at 0 °C. Isocyanoacetic acid allylester (625 mg, 5.00 mmol) was added *via* a syringe over 20 min and the mixture was allowed to warm to rt overnight. Stirring at rt was continued for 24 h, before the solvent was removed *in vacuo*. The residue was dissolved in EtOAc (30 ml) and the organic layer was washed twice with sat. NaHCO$_3$ (30 ml) and 1 N KHSO$_4$ (30 ml). After drying (Na$_2$SO$_4$) and evaporation of the solvent the crude product was purified by flash chromatography (hexane–EtOAc 7 : 3 → 6 : 4). Subsequent crystallisation from ether gave **21** (1.10 g, 2.55 mmol, 53%) as a single diastereomer, mp 173–174 °C. The absolute configuration of the newly formed stereogenic centre was not determined. ^{1}H NMR (500 MHz, CDCl$_3$, HH-COSY): δ 0.88–0.98 (15H, m), 2.12 (1H, m), 3.82 (1H, dd, *J* 18.0 and 4.4), 4.11 (1H, m), 4.19 (1H, dd, *J* 18.0 and 5.8), 4.48–4.62 (5H, m), 5.15–5.32 (4H, m), 5.71 (1H, d, *J* 8.5), 5.84–5.88 (2H, m), 6.73 (1H, d, *J* 8.5). ^{13}C NMR (125 MHz, CDCl$_3$, HMBC, DEPT): δ 16.4, 18.4, 25.5, 25.6, 30.5, 33.7, 40.1, 59.1, 59.2, 64.7, 65.0, 116.8, 117.9, 130.5, 131.1, 156.8, 168.5, 169.7, 170.4. C$_{20}$H$_{32}$N$_2$O$_7$ (412.48) calcd.: C 58.24 H 7.82 N 6.79; found: C 58.17 H 7.75 N 6.83.

Allyloxycarbonyl-(*S*)-valyl-*N*-[(*R*)-1-methyl-*p*-methoxy-benzyl]-(*R,S*)-valyl-glycine allylester ((*S,R,R/S*)-22)

Isobutyraldehyde (360 mg, 5.0 mmol) was added to a solution of (*R*)-1-methyl-*p*-methoxy-benzylamine (755 mg, 5.0 mmol) in trifluoroethanol (5 ml). The solution was stirred for 15 min and subsequently cooled to −30 °C before (*S*)-Aloc-ValOH (1120 mg, 5.5 mmol) in trifluoroethanol (5 ml) was added. After a further 15 min, isocyanoacetic acid allylester (750 mg, 5.0 mmol) was added *via* a syringe over 20 min. The solution was kept at −30 °C for three days before the solvent was evaporated *in vacuo*. Workup was carried out as described for **21**. The diastereomers could be separated by flash chromatography (hexane–EtOAc 7 : 3 → 6 : 4) giving rise to (*S,R,R*)-**22** (196 mg, 0.4 mmol) and (*S,R,S*)-**22** (1589 mg, 3.1 mmol) as viscous aromatic oils. Overall yield: 1.785 g (3.6 mmol, 71%). The diastereomeric ratio was determined to 11 : 89 by HPLC (silica, hexane–EtOAc 73 : 27, 2 ml min^{-1}): t_R(*S,R,R*-**22**) = 7.40 min; t_R(*S,R,S*-**22**) = 10.71 min. (*S,R,R*)-**22**: $[a]_D^{22}$ = +44.5° (*c* 1, CHCl$_3$, >99% de). ^{1}H NMR (300 MHz, HH-COSY): δ 0.21 (3H, d, *J* 6.6), 0.70 (3H, d, *J* 6.6), 1.00 (3H, d, *J* 6.8,) 1.08 (3H, d, *J* 6.6), 1.54 (3H, d, *J* 7.0), 2.28 (1H, m), 2.81 (1H, m), 3.15 (1H, d, *J* 10.8), 3.75–3.85 (4H, m), 4.20 (1H, dd, *J* 18.0 and 7.0), 4.52–4.55 (4H, m), 4.80 (1H, m), 5.14–5.38 (5H, m), 5.58 (1H, d, *J* 9.6), 5.81–5.96 (2H, m), 6.88 (2H, d, *J* 8.5), 7.28 (2H, d, *J* 8.8), 8.50 (1H, m). ^{13}C NMR (75 MHz, HMBC): δ 17.0, 17.8, 19.6, 20.2, 20.8, 27.1, 27.1, 31.4, 41.0, 55.3, 57.2, 57.4, 65.8, 68.8, 113.8, 117.5, 118.8, 126.6, 132.8, 130.0, 130.2, 131.7, 156.2, 159.5, 169.6, 173.4, 173.6. HMRS: calcd. for C$_{28}$H$_{41}$N$_3$O$_7$ ([M]$^+$), 531.2944; found, 531.2951; calcd. for C$_{28}$H$_{42}$N$_3$O$_7$ ([M+H]$^+$), 532.3022; found, 532.2994. (*S,R,S*)-**22**, $[a]_D^{22}$ = −54.5° (*c* 1, CHCl$_3$, >98% de). ^{1}H NMR (300 MHz, HH-COSY): δ 0.79 (3H, d, *J* 6.3), 0.83 (3H, d, *J* 6.3), 1.04 (3H, d, *J* 7.0), 1.06 (3H, d, *J* 7.7), 1.64 (3H, d, *J* 6.8), 2.19 (1H, m), 2.80–2.94 (2H, m), 3.67 (1H, dd, *J* 18.2 and 4.7), 3.76 (3H, s), 3.93 (1H, dd, *J* 18.2 and 6.5), 4.54–4.61 (5H, m), 5.17–5.33 (5H, m), 5.45 (1H, d, *J* 9.4), 5.83–5.93 (2H, m), 6.78 (2H, d, *J* 8.8), 7.20 (2H, d, *J* 8.8), 8.38 (1H, bs). ^{13}C NMR (75 MHz, HMBC): δ17.2, 17.9, 19.9, 20.0, 20.4, 26.5, 31.6, 40.8, 55.2, 55.8, 57.2, 65.6, 65.9, 69.9, 113.9, 117.6, 118.6, 128.9, 129.9, 131.7, 132.6, 156.2, 159.3, 169.5, 171.4, 174.1. HMRS: calcd. for C$_{28}$H$_{41}$N$_3$O$_7$ ([M]$^+$), 531.2944; found, 531.2953; calcd. for C$_{28}$H$_{42}$N$_3$O$_7$ ([M+H]$^+$), 532.3022; found, 532.3036.

Cyclopeptide 26

In a 100 ml Schlenk flask peptide, (*S,R,S*)-**22** (531 mg, 1.00 mmol) was dissolved in CH$_2$Cl$_2$ (80 ml) under reflux and a constant stream of N$_2$ was bubbled through the solution. A solution of Grubbs' catalyst (81 mg, 0.10 mmol, 10 mol%) in CH$_2$Cl$_2$ (10 ml) was added slowly over a period of 2 h *via* a syringe. After 4 h when nearly all starting material was consumed (TLC), the solvent was removed *in vacuo* and the crude product was purified by flash chromatography (hexane–EtOAc 6 : 4 → 1 : 1 → 3 : 7) giving rise to **23** (367 mg, 0.73 mmol, 73%) as a colourless solid, mp 170–172 °C. In addition a small amount of **22** (80 mg, 0.15 mmol, 15%) was recovered. The *trans*-isomer was obtained with 95% selectivity as determined by HPLC. ^{1}H NMR (500 MHz, CDCl$_3$, HH-COSY): δ 0.28 (3H, d, *J* 6.6), 0.65 (3H, d, *J* 6.6), 0.99 (3H, d, *J* 7.0), 1.13 (3H, d, *J* 6.6), 1.63 (3H, d, *J* 6.9), 2.29 (1H, m), 2.74 (1H, m), 3.13 (1H, d, *J* 11.0), 3.60 (1H, dd, 1H, *J* 17.8 and 2.5), 3.78 (3H, s), 4.16 (1H, m), 4.47 (1H, dd, *J* 17.3 and 7.7), 4.51 (1H, dd, *J* 12.1 and 7.0), 4.68 (1H, dd, *J* 12.1 and 3.5), 4.80 (1H, dd, *J* 9.9 and 3.7), 4.95 (1H, dd, *J* 13.0 and 4.8), 5.31 (1H, q, *J* 6.6), 5.40 (1H, d, *J* 9.0), 5.78–5.96 (2H, m), 6.90 (2H, d, *J* 8.8), 7.30 (2H, d, *J* 8.8), 8.42 (1H, d, *J* 5.9). ^{13}C NMR (75 MHz, HMBC): δ 16.5, 18.7, 19.8, 20.6, 27.0, 31.0, 42.1, 55.3, 56.8, 57.8, 63.2, 64.6, 68.4, 113.9, 127.3, 130.9, 129.8, 130.2, 156.7, 159.6, 168.7, 173.3, 174.7. HMRS: calcd. for C$_{26}$H$_{38}$N$_3$O$_7$ ([M+H]$^+$), 504.2621; found, 504.2655; calcd. for C$_{26}$H$_{37}$N$_3$O$_7$Na ([M+Na]$^+$), 526.2532; found, 526.2482.

Allyloxycarbonyl-(S)-alanyl-N-[(S)-1-methyl-m-methoxy-benzyl]-(R,S)-valyl-glycine allylester ((S,S,R/S)-24)

According to the preparation of **22**, peptide **24** was obtained from (S)-Aloc-AlaOH (952 mg, 5.50 mmol), (S)-1-methyl-m-methoxy-benzyl amine (830 mg, 5.00 mmol), isobutyraldehyde (0.45 ml, 5.00 mmol) and isocyanoacetic acid allyl ester (625 mg, 5.00 mmol) in 91% yield. Flash chromatography (hexane–EtOAc 8 : 2 → 7 : 3→ 6 : 4) allowed the separation of the diastereomers giving rise to (S,S,R)-**24** (1.50 g, 2.98 mmol, 60%) and (S,S,S)-**24** (0.65 g, 1.29 mmol, 28%) as viscous oils. HPLC (silica, hexane–EtOAc 75 : 25, 2 ml min^{-1}): t_R(S,S,R-**27**) = 12.05 min; t_R(S,S,S-**24**) = 14.94 min. (S,S,R)-**24**: $[a]_D^{22} = -52.9°$ (c 0.8, CHCl$_3$). ^{1}H NMR (500 MHz, CDCl$_3$, HH-COSY): δ 0.16 (3H, d, J 6.4), 0.71 (3H, d, J 6.6), 1.42 (3H, d, J 6.7), 1.65 (3H, d, J 7.0), 2.78 (1H, m), 3.10 (1H, m), 3.75–3.80 (4H, m), 4.21 (1H, dd, J 18.1 and 7.0), 4.56–4.60 (4H, m), 5.11 (1H, t, J 7.3), 5.16–5.32 (5H, m), 5.58 (1H, d, J 8.3), 5.83–5.93 (2H, m), 6.84 (1H, dd, J 8.4 and 2.2), 7.05 (1H, d, J 8.6), 7.07 (1H, s), 7.26 (1H, t, J 8.0), 8.39 (1H, bs). ^{13}C NMR (75 MHz, CDCl$_3$): δ 17.0, 18.8, 19.6, 19.8, 27.5, 40.8, 48.4, 55.4, 56.5, 65.7, 68.2, 114.2, 114.4, 117.7, 118.8, 120.6, 129.4, 131.7, 132.6, 139.4, 155.7, 159.9, 169.4, 173.7, 174.5. HMRS: calcd. for C$_{26}$H$_{37}$N$_3$O$_7$ ([M]$^+$), 503.2632; found, 503.2632. (S,S,S)-**24**: $[a]_D^{22} = -6.9°$ (c 1.1, CHCl$_3$). ^{1}H NMR (500 MHz, CDCl$_3$, HH-Cosy): δ 0.85 (3H, d, J 6.7), 0.89 (3H, d, J 6.4), 1.35 (3H, d, J 6.7), 1.65 (3H, d, J 7.0), 2.85 (1H, m), 3.20 (1H, m), 3.68–3.79 (5H, m), 4.55–4.60 (4H, m), 4.83 (1H, m), 5.19 (1H, dd, J 10.4 and 1.2), 5.21 (1H, dd, J 10.6 and 1.2), 5.25–5.32 (3H, m), 5.67 (1H, d, J 6.7), 5.83–5.93 (2H, m), 6.78 (1H, dd, J 8.2 and 2.4), 6.83 (1H, s), 6.85 (1H, d, J 7.6), 7.19 (1H, t, J 7.9), 8.05 (1H, bs). ^{13}C NMR (75 MHz, CDCl$_3$): δ 17.4, 19.2, 19.9, 20.4, 26.8, 40.9, 48.3, 55.2, 59.5, 65.7, 65.7, 68.2, 113.2, 114.0, 117.7, 118.7, 119.5, 129.5, 131.7, 132.7, 139.6, 155.6, 159.7, 169.4, 171.1, 174.7. HMRS: calcd. for C$_{26}$H$_{37}$N$_3$O$_7$ ([M]$^+$), 503.2632; found, 503.2635. HMRS: calcd. for C$_{26}$H$_{38}$N$_3$O$_7$ ([M+H]$^+$), 504.2709; found, 504.2713.

Allyloxycarbonyl-(S)-prolinyl-N-[(S)-1-methyl-m-methoxy-benzyl]-(R,S)-valyl-glycine allylester ((S,S,R/S)-25)

According to the preparation of **22**, peptide **25** was obtained from (S)-Aloc-ProOH (995 mg, 5.00 mmol), (S)-1-methyl-m-methoxy-benzyl amine (830 mg, 5.50 mmol), isobutyraldehyde (0.45 ml, 5.00 mmol) and isocyanoacetic acid allyl ester (625 mg, 5.00 mmol) in 12 h at 4 °C. Flash chromatography (hexane–EtOAc 7 : 3 → 6 : 4) provided **25** (2.27 g, 4.38 mmol, 89%) as viscous colourless oil as a mixture of diastereomers and rotamers. ^{1}H NMR (500 MHz, CDCl$_3$, HH-COSY): δ 0.21 (1.8H, d, J 6.6), 0.37 (1.8H, d, J 6.6), 1.66 (1.8H, d, J 5.4), 1.93–2.33 (4H, m), 2.82–2.87 (1H, m), 3.04 (1H, m), 3.57–3.87 (6H, m), 4.33 (1H, dd, J 17.9 and 7.9), 4.30–4.78 (4H, m), 5.11–5.35 (6H, m), 6.84 (2H, m), 6.86 (1H, m), 7.15 (0.6H, d, J 7.7), 7.20 (0.6H, s), 7.30 (1H, m), 8.55 (1H, m). Selected signals of the minor isomer: δ = 0.71 (1.2H, d, J 6.3), 0.73 (1.2H, d, J 6.0), 1.70 (1.2H, d, J 5.6), 7.00 (0.4H, s), 7.06 (0.4H, d, J 7.5). ^{13}C NMR (125 MHz, CDCl$_3$, HMBC, DEPT): δ 16.8, 18.8, 18.8, 23.3, 27.8, 29.5, 30.6, 40.7, 46.8, 55.4, 55.9, 58.6, 65.7, 65.9, 69.8, 115.2, 117.3, 118.7, 120.6, 121.0, 129.8, 131.7, 133.0, 139.9, 154.8, 159.8, 169.6, 173.6, 174.2. Selected signals of the minor isomer: δ = 16.6, 24.3, 27.4, 30.6, 47.4, 55.2, 56.0, 58.9, 66.4, 69.3, 112.7, 114.2, 118.3, 121.0, 154.2, 174.3. HMRS: calcd. for C$_{28}$H$_{40}$N$_3$O$_7$ ([M+H]$^+$), 530.2801; found, 530.2861.

Allyloxycarbonyl-(S)-N-methyl-valyl-N-[(S)-1-methyl-m-methoxy-benzyl]-(R,S)-valyl-glycine allylester ((S,S,R/S)-26)

According to the preparation of **22**, peptide **26** was obtained from N-Aloc-N-Me-ValOH (1.07 g, 5.00 mmol), (S)-1-methyl-m-methoxy-benzyl amine (830 mg, 5.50 mmol), isobutyralde-

hyde (0.46 ml, 5.00 mmol) and isocyanoacetic acid allyl ester (625 mg, 5.00 mmol) in 12 h at 4 °C. Flash chromatography (hexane–EtOAc 7 : 3 → 6 : 4) provided **26** (1.96 g, 3.53 mmol, 72%) as viscous colourless oil as a mixture of diastereomers and rotamers. The diastereomers could in part be separated by a second flash chromatography. (S,S,R)-**26**: $[a]_D^{20} = -137.4°$ (c 1.1, CHCl$_3$). ^{1}H NMR (500 MHz, CDCl$_3$, HH-COSY, mixture of rotamers): δ 0.16–0.18 (2.1H, d, J 6.5), 0.87 (2.1H, d, J 6.5), 0.82–0.97 (7.8H, m), 1.59 (3H, d, J 7.1), 2.43 (1H, m), 2.79–3.18 (5H, m), 3.63 (3H, s), 4.31–4.63 (2H, m), 4.59–4.63 (4H, m), 4.94 (0.7H, d, J 10.5), 5.06 (0.3H, d, J 10.5), 5.20–5.27 (4H, m), 5.31 (0.3H, q, J 6.9), 5.42 (0.7H, q, J 7.2), 5.56–5.98 (2H, m), 6.79–6.89 (2H, m), 7.19–7.26 (2H, m), 8.32 (0.3H, bs), 8.40 (0.7H, bs). Coalescence was observed for the signals of the rotamers at 398 K in d$_6$-DMSO. ^{13}C NMR (125 MHz, CDCl$_3$, HMBC, DEPT): δ 17.1, 17.3, 17.9, 18.1, 19.4, 19.7, 19.8, 19.9, 20.1, 20.9, 25.8, 27.4, 28.5, 28.7, 29.2, 29.7, 40.8, 40.9, 53.2, 54.7, 55.0, 55.2, 60.6, 62.5, 63.2, 65.4, 65.6, 66.6, 68.5, 111.1, 111.9, 113.3, 113.6, 117.3, 117.7, 118.3, 118.6, 118.9, 120.0, 128.5, 129.5, 131.4, 131.8, 132.1, 132.5, 139.7, 144.7, 156.7, 159.3, 168.7, 171.2, 171.4. (S,S,S)-**26**: $[a]_D^{20} = -111.0°$ (c = 1, CHCl$_3$). ^{1}H NMR (500 MHz, CDCl$_3$, HH-COSY, mixture of rotamers): δ 0.84–1.04 (11.1H, m), 1.11 (0.9H, d, J 6.7), 1.56 (0.9H, d, J 7.1), 1.59 (2.1H, d, J 7.1), 2.59 (1H, m), 2.96–2.97 (2H, m), 3.07 (3H, s), 3.67–3.73 (3.7H, m), 3.80 (0.7H, dd, J 18.4 and 6.6), 3.82 (0.3H, dd, J 18.5 and 5.7), 3.95 (0.3H, dd, J 18.5 and 5.7), 4.46–4.75 (5H, m), 5.07 (0.3H, dd, J 10.3 and 1.0), 5.15 (0.7H, ddd, J 10.5, 1.2 and 1.0), 5.22–5.51 (3H, m), 5.42 (0.3H, q, J 6.8), 5.53 (0.7H, q, J 6.8), 5.74 (0.3H, m), 5.79–5.96 (1.7H, m), 6.59 (1H, m), 6.64 (0.3H, m), 6.65–6.81 (2H, m), 7.07 (0.3H, t, J 8.2), 7.20 (0.7H, t, J 9.0), 8.40 (0.3H, bs), 8.46 (0.7H, bs). ^{13}C NMR (125 MHz, CDCl$_3$, HMBC, DEPT): δ 17.2, 17.3, 17.9, 18.0, 19.4, 19.7, 19.8, 19.9, 20.1, 20.9, 25.9, 27.3, 28.5, 28.8, 29.2, 29.6, 40.85, 40.9, 53.4, 54.9, 55.0, 55.1, 60.7, 62.4, 63.0, 65.5, 65.8, 66.6, 70.2, 111.0, 111.7, 113.3, 113.8, 117.2, 117.5, 118.2, 118.6, 118.9, 119.9, 128.5, 129.3, 131.5, 131.7, 132.1, 132.6, 139.7, 144.6, 156.6, 159.6, 168.9, 171.2, 171.5. HMRS: calcd. for C$_{29}$H$_{43}$N$_3$O$_7$ ([M]$^+$), 545.3101; found, 545.3072. HMRS: calcd. for C$_{29}$H$_{44}$N$_3$O$_7$ ([M+H]$^+$), 546.3179; found, 546.3177.

Cyclopeptide 27

In a 250 ml Schlenk flask, peptide **24** (505 mg, 1.00 mmol) was dissolved in toluene (100 ml) at rt and a constant stream of N$_2$ was bubbled through the solution. A solution of Grubbs' catalyst (82 mg, 0.10 mmol, 10 mol%) in toluene (8 ml) was added slowly over a period of 2 h via a syringe. After stirring for 16 h, no starting material could be detected and the solution was concentrated to 20 ml. A 1% aqueous solution of H$_2$O$_2$ (to destroy the catalyst) was added and the mixture was stirred vigorously for 1 h, before charcoal was added. After 15 min the mixture was filtered through celite. The solvent was removed in vacuo and the crude product was purified by flash chromatography (hexane–EtOAc 6 : 4 → 3 : 7 → EtOAc) giving rise to **27** (129 mg, 0.27 mmol, 27%) as a colourless solid, mp 164–167 °C. Crystallisation from CH$_2$Cl$_2$–toluene–EtOAc provided crystals suitable for X-ray structure analysis.† ^{1}H NMR (500 MHz, CDCl$_3$, HH-COSY): δ 0.81 (3H, d, J 6.3), 0.83 (3H, d, J 6.3), 1.44 (3H, d, J 7.3), 1.60 (3H, d, J 7.3), 2.76 (1H, m), 2.94 (1H, d, J 11.2), 3.50 (1H, dd, J 17.6 and 2.4), 3.70 (3H, s), 3.85 (1H, dd, J 17.6 and 6.4), 4.19 (1H, d, J 13.7), 4.53 (1H, m), 4.66 (1H, m), 4.93–5.01 (2H, m), 5.41 (1H, d, J 8.8), 5.54 (1H, q, J 6.9), 5.90–5.92 (2H, m), 6.79 (1H, dd, J 8.2 and 2.4), 6.92 (1H, d, J 7.8), 6.98 (1H, s), 7.20 (1H, dd, J 8.3 and 7.8), 8.20 (1H, d, J 5.4). ^{13}C NMR (125 MHz, CDCl$_3$, HMBC): δ 16.7, 18.9, 19.8, 20.6, 26.2, 42.3, 48.2, 55.2, 55.8, 63.2, 64.7, 70.0, 113.7, 114.5, 119.5, 126.2, 131.2, 129.2, 139.4, 156.1, 159.7, 168.2, 170.3, 175.9. HMRS: calcd. for C$_{24}$H$_{33}$N$_3$O$_7$Na ([M+Na]$^+$), 498.2216; found, 498.2226.

Cyclopeptide 28

In a 250 ml Schlenk flask, peptide **25** (257 mg, 0.50 mmol) was dissolved in CH_2Cl_2 (50 ml) at rt and a constant stream of N_2 was bubbled through the solution. A solution of Grubbs' catalyst (20 mg, 0.025 mmol, 5 mol%) in CH_2Cl_2 (2.5 ml) was added slowly over a period of 90 min *via* a syringe. After all starting material was consumed, workup was carried out as described for **27**. The solvent was removed *in vacuo* and the crude product was purified by flash chromatography (hexane–EtOAc 6 : 4 → 1 : 1 → 3 : 7) giving rise to **28** (90 mg, 0.19 mmol, 38%) as a colourless solid. Crystallisation from EtOAc–heptane provided crystals suitable for X-ray structure analysis.† If the reaction was carried out in the presence of 10% Grubbs' catalyst under reflux according to the preparation of **23**, the yield could be increased to 51%. ^{1}H NMR (500 MHz, CDCl$_3$, HH-COSY): δ 0.85 (3H, d, *J* 6.7), 0.87 (3H, d, *J* 6.6), 1.60 (3H, d, *J* 7.1), 2.02 (2H, m,), 2.25 (2H, m,), 2.80 (1H, m), 2.91 (1H, d, *J* 11.0), 3.56–3.62 (2H, m), 3.76–3.79 (4H, m), 3.84 (1H, dd, *J* 17.8 and 6.1), 4.31 (1H, d, *J* 14.2), 4.43 (1H, dd, *J* 11.1 and 3.8), 4.88 (1H, dd, *J* 11.2 and 6.8), 4.92 (1H, dd, *J* 14.2 and 3.8), 5.03 (1H, dd, *J* 7.7 and 4.0), 5.63 (1H, q, *J* 6.9), 5.88–5.90 (2H, m), 6.82 (1H, dd, *J* 8.2 and 2.2), 6.98 (1H, d, *J* 7.6), 7.16 (1H, s), 7.24 (1H, t, *J* 8.0), 8.48 (1H, d, *J* 4.1). ^{13}C NMR (125 MHz, CDCl$_3$, HMQC, HMBC): δ 16.9, 19.7, 20.7, 24.7, 26.2, 30.6, 42.8, 46.5, 55.2, 55.9, 58.0, 63.7, 64.7, 70.4, 114.0, 114.4, 119.5, 125.7, 131.7, 129.2, 138.6, 154.2, 159.8, 168.0, 170.4, 175.6. $C_{26}H_{35}N_3O_7$ (501.58) calcd.: C 62.26 H 7.03 N 8.38; found: C 62.07 H 6.82 N 8.29. HMRS: calcd. for $C_{26}H_{35}N_3O_7$ ([M]$^+$), 501.2481; found, 501.2478.

Cyclopeptide 29

In a 100 ml Schlenk flask, peptide **26** (272 mg, 0.50 mmol) was dissolved in toluene (20 ml) at rt and a solution of Grubbs' catalyst (41 mg, 0.05 mmol, 10 mol%) in toluene was added slowly *via* a syringe. The solution was heated to 60 °C and the workup was carried out as described for **30**. The solvent was removed *in vacuo* and the crude product was purified by flash chromatography (hexane–EtOAc 6 : 4 → 1 : 1 → 3 : 7) giving rise to **29** (85 mg, 0.17 mmol, 33%) as a colourless solid and recovered **26** (93 mg, 0.18 mmol, 34%). ^{1}H NMR (500 MHz, CDCl$_3$): δ 0.79 (3H, d, *J* 6.6), 0.94 (3H, d, *J* 6.4), 1.01 (3H, d, *J* 6.6), 1.08 (3H, d, *J* 6.9), 1.59 (3H, d, *J* 7.1), 2.41 (1H, m), 2.83 (1H, m), 3.02 (1H, d, *J* 10.1), 3.20 (3H, s), 3.32 (1H, dd, *J* 16.7 and 3.0), 3.72 (3H, s), 4.25–4.31 (2H, m), 4.41 (1H, m), 4.48 (1H, d, *J* 10.3), 4.93 (1H, m), 5.09 (1H, dd, *J* 14.4 and 4.9), 5.89 (1H, m), 6.06 (1H, d, *J* 15.7), 6.16 (1H, q, *J* 7.1), 6.65–6.90 (3H, m), 7.13 (1H, t, *J* 8.2), 8.11 (1H, d, *J* 6.9). ^{13}C NMR (125 MHz, CDCl$_3$, DEPT, HSQC): δ 18.2, 19.7, 19.8, 20.1, 22.2, 25.5, 28.9, 30.5, 41.1, 55.1, 55.9, 61.1, 63.2, 64.8, 71.0, 111.3, 117.0, 121.1, 126.6, 128.9, 132.0, 139.5, 157.0, 159.5, 169.3, 170.3, 174.4. HMRS: calcd. for $C_{27}H_{40}N_3O_7$ ([M+H]$^+$), 518.2865; found, 518.2866.

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