Synthesis of Cyclic Dipeptides by Ring-Closing Metathesis

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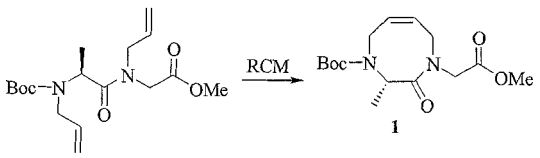
Several cyclic dipeptides (**4a–g** and **9a–c**) have been synthesized by "amide-to-amide" cyclization of **2a–g** and **8a–c**, respectively, by means of ring-closing metathesis employing the Grubbs ruthenium catalyst. The influence of additives as well as the length of the amide substituent were studied. Best yields were obtained by cyclization in solution with either lithium fluoroacetate or α,α-dichlorotoluene as an additive.

Introduction

Cyclization of peptides is an appropriate way to reduce the flexibility and to increase the affinity of the peptides towards a receptor.[1] Methods for cyclization can be divided into two categories: cyclizations involving C and N termini,[2] the so called "backbone-to-backbone" cyclization[3] and methods involving the side chains of individual amino acids.[2] The latter method involves in particular cysteine in the formation of disulfide bridges and glutamine/aspartic acid and lysine in the formation of lactam bridges.

In our method referred to as "amide-to-amide" cyclization, we wanted to use *N*-substituted amides in such a way that we could perform cyclization by ring-closing metathesis (RCM).[4] Several cyclic peptides obtained by RCM were reported[5] but to the best of our knowledge there is only one example involving *N*-substituted amino acids in the literature of a cyclic peptide **1** obtained by RCM (Scheme 1).[6]

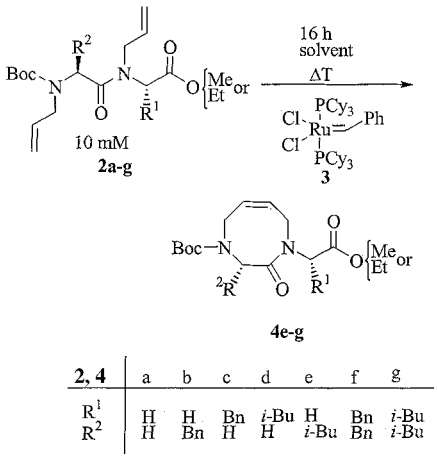


Scheme 1

Since this cyclization involved a dipeptide consisting merely of an *N*-allyl-substituted alanine and glycine, we were interested in investigating: (1) whether this method could be extended to other amino acids; (2) the optimal conditions for ring closure of the bis(*N*-substituted) dipeptides; and (3) the influence of the length of the *N*-alkene substituent. One of the limitations so far was the synthesis of the appropriate *N*-substituted amino acids, and peptides. However, we recently published a method by which we were able to introduce by a "site-specific *N*-alkylation" procedure a substituent on any desired amide moiety in a peptide.[7]

Results and Discussion

Dipeptides containing *N*-allyl substituents on both amide bonds were prepared from *N*-alkylated amino acids **2a**−**2e**[7,8] or by peralkylation of dipeptides **2f**−**2g**.[9] The dipeptides **2** obtained in this manner were subjected to RCM using Grubbs catalyst (Scheme 2) and the results are given in Table 1. TCE (1,1,2-trichloroethane)[10] gave better yields than DCE (1,2-dichloroethane), probably because a higher reflux temperature can be reached. A higher temperature is favorable for rotation about the tertiary amide bond and a "*cis*"-like conformation is probably necessary for cyclization, according to Miller et al.[11] Indeed, ^{1}H NMR temperature experiments showed that coalescence temperatures range from 80°C to 100°C for **2a**−**2c** and **2f**, i.e., mostly above the reflux temperature of DCE. As expected, all possible rotamers seem to be present in the ^{1}H and ^{13}C NMR spectra at room temperature. When TCE was replaced by toluene, poor results were obtained, probably because of a less active catalyst.



2, 4	a	b	c	d	e	f	g
R^1	H	H	Bn	*i*-Bu	H	Bn	*i*-Bu
R^2	H	Bn	H	H	*i*-Bu	Bn	*i*-Bu

Scheme 2

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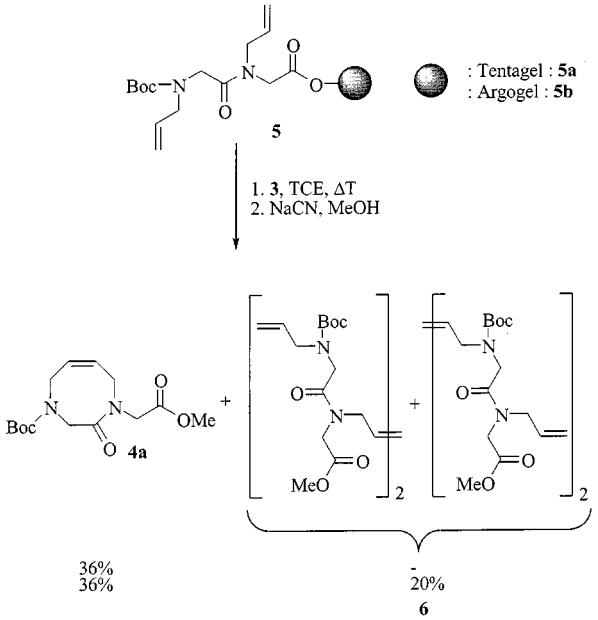
Table 1. RCM of bis(*N*-allyl)dipeptides

Entry	Peptide **2**[a][b]	Solvent[c]	T [°C]	Yield **4** (%)	
1	Boc-(*N*all)Gly-(*N*all)Gly-OEt (**2a**)	DCE	81−85	39	**4a**
2	Boc-(*N*all)Gly-(*N*all)Gly-OEt (**2a**)	Toluene	110	3	**4a**
3	Boc-(*N*all)Gly-(*N*all)Gly-OEt (**2a**)	TCE	110−115	73	**4a**
4	Boc-(*N*all)Phe-(*N*all)Gly-OEt (**2b**)	DCE	81−85	25	**4b**
5	Boc-(*N*all)Phe-(*N*all)Gly-OEt (**2b**)	TCE	110−115	51	**4b**
6	Boc-(*N*all)Gly-(*N*all)Phe-OMe (**2c**)	DCE	81−85	20	**4c**
7	Boc-(*N*all)Gly-(*N*all)Phe-OMe (**2c**)	TCE	110−115	59	**4c**
8	Boc-(*N*all)Gly-(*N*all)Leu-OMe (**2d**)	TCE	110−115	35	**4d**
9	Boc-(*N*all)Leu-(*N*all)Gly-OEt (**2e**)	TCE	110−115	50	**4e**
10	Boc-(*N*all)Phe-(*N*all)Phe-OMe (**2f**)	TCE	110−115	27	**4f**
11	Boc-(*N*all)Leu-(*N*all)Leu-OMe (**2g**)	TCE	110−115	53	**4g**

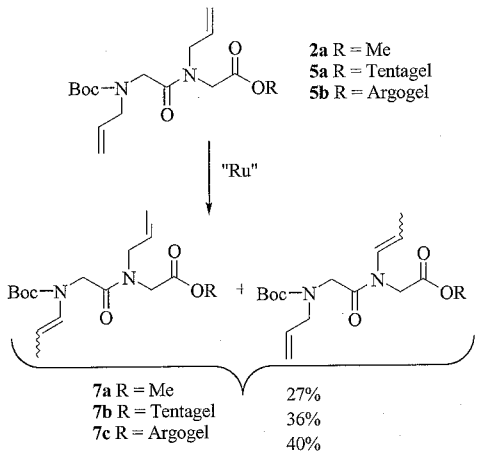
[a] The concentration of dipeptides was 10 mM. − [b] (*N*all): *N*-allyl. − [c] DCE: 1,2-dichloroethane; TCE: 1,1,2-trichloroethane.

It has been shown that RCM can be carried out on the solid phase.[5a,6a] Since we were interested in an all solid phase synthesis including RCM of cyclic peptides, the dipeptide Boc-(*N*all)Gly-(*N*all)Gly (**5**) was prepared on Tentagel®−OH and Argogel®−OH resin using our method for solid phase synthesis of peptoids.[8] Tentagel gave a low recovery, probably because of the instability of the resin at high temperatures: The weight of the resin was significantly decreased (by at least 25%). Argogel resin is believed to be stable up to 200°C[12] and no significant loss of either the peptide or the resin was observed. However, the yield of the desired eight-membered cyclic peptide **4a** was not the same, but much lower than in solution, presumably due to a faster degradation of the catalyst by the resin. On Argogel, dimers **6** were also formed by metathesis (Scheme 3) The low yields relative to yields obtained by cyclization in solution made this route unacceptable as an alternative.



Scheme 3

Close examination of the products obtained after RCM on the solid support as well as products resulting from RCM in solution led to the isolation of linear dipeptides **7a**−**c** with a migrated double bond (Scheme 4). A similar observation was reported recently.[13] Migration of the double bond is dependent on the temperature at which RCM was carried out. Increasing the temperature led to increasing amounts of dipeptides **7a**−**c**. It is not believed that the Grubbs ruthenium catalyst itself is not responsible for this double bond migration but rather a ruthenium hydride species formed by the degradation of the catalyst. Indeed, ruthenium hydride species are reported as effective catalysts for migration of terminal double bonds.[14]



Scheme 4

The use of additives in an RCM reaction has proved to be successful in several cases.[15−18] This inspired us to investigate the role of several additives in this reaction especially with respect to prevention of migration of the double bond. The investigated additives were PCy_3,[15] styrene,[16] CuCl,[15] α,α-dichlorotoluene,[17] $Ti(OiPr)_4$,[18] and F_3CCO_2Li (Table 2). Each of these additives has a different mechanism of action in combination with the catalyst. Addition of PCy_3 resulted in an inactive catalyst with no migration of the double bond (Table 2, Entry 2). Styrene led to recycling of the more stable benzylidene ruthenium species, thereby stabilizing the catalyst (Table 2, Entry 3). Although styrene was not expected to be a substrate for cross metathesis we detected some by-products by mass spectrometry, presumably from this cross metathesis reaction. The role of CuCl on Grubb's catalyst in RCM is not completely understood. It is believed that a complex with the ruthenium species was formed, resulting in a new and more stable active complex[15] which led to an increase of the

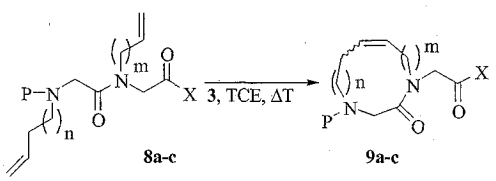
Table 2. Influence of additives on the RCM reaction of dipeptides **2a** (nd: not determined)

Entry	Additive	Amount (mol-%)	**2a** (%)[a]	**4a** (%)[a]	**7a** (%)[a]
1	none		< 5	> 66	< 29
2	PCy_3	500	> 50	nd	nd
3	styrene	100	< 18	> 72	< 10
4	CuCl	15	< 17	> 78	< 5
5	α,α-dichlorotoluene	100	< 22	> 65	< 13
6	$Ti(OiPr)_4$	100	nd	> 88[b]	nd
7	F_3CCO_2Li	100	nd	> 88	nd

[a] Based on ^1H NMR spectroscopy. – [b] Quantitative transesterification to the *i*Pr ester.

yield (Table 2, Entry 4). Use of CuCl was hampered by a more tedious workup necessary for removal of all (paramagnetic) Cu^I. α,α-Dichlorotoluene is a scavenger specific for hydride species and therefore only migration of the double bond was diminished (Table 2, Entry 5). α,α-Dichlorotoluene seemed to be a promising additive in combination with larger amounts of catalyst. $Ti(OiPr)_4$ could coordinate the carbonyl functions of the peptide, thereby preventing them from interacting with the catalyst. As a result, the catalyst could be stabilized, which indeed led to an increased yield (Table 2, Entry 6). However, a disadvantage of the use of $Ti(OiPr)_4$ was that it also acted as a transesterfication catalyst,[19] which in this case led to the *i*Pr ester. This problem was avoided by using F_3CCO_2Li, Li^+ which also coordinated to the carbonyl moieties, and identical results were obtained (Table 2, compare Entries 6 and 7). A disadvantage was the poor solubility of the lithium salts in chlorinated solvents which made it less suitable for the RCM of larger peptides.

Migration of the double bond could be dependent on the distance between this double bond and the carbonyl function. Use of a longer olefinic substituent would make the coordination between the catalyst and the carbonyl moiety less favorable, thereby preventing migration of the double bond. To investigate this, three dipeptides were prepared bearing one homoallyl and one allyl substituent (**8a**), two homoallyl (3-butenyl) substituents (**8b**) or 4-pentenyl substituents (**8c**) instead of two allyl substituents. All dipeptides did undergo RCM to form a nine-membered ring compound **9a**, ten-membered ring compound **9b** and twelve-membered ring compound **9c**, respectively (Scheme 5), but surprisingly all these dipeptides also gave rise to the migration of the double bond. Apparently, migration of the



8, 9	n	m	P	X	yield of 9 (%)
a	1	1	Ac	Phe-OMe	26
b	1	2	Boc	OMe	26
c	2	3	Ac	Phe-OMe	26

Scheme 5

double bond is not entirely dependent on the distance between the double bond and the carbonyl functionality but is merely a competing reaction of RCM. The easier the formation of the cyclic peptide, the less the competing migration occurred.

Conclusion

We have successfully prepared "amide-to-amide" cyclic peptides by ring-closing metathesis in acceptable yields. So far RCM on the solid phase gave poor results owing to a faster formation of by-products such as dimers, and migration of the double bond. The migration of the double bond seemed to be catalyzed by a ruthenium degradation product, probably a ruthenium hydride species. This phenomenon also occurred in solution and seemed not to be dependent on the distance between the double bond and the carbonyl moiety of the amide functionality. The use of additives improved the yield of the RCM reaction in a number of cases, probably by stabilizing the catalyst rather than by eliminating the formed ruthenium hydride. The best additives, $Ti(OiPr)_4$ and F_3CCO_2Li, have the major disadvantages of transesterfication and poor solubility, respectively. Therefore the use of α,α-dichlorotoluene (which removes any ruthenium hydride formed) with larger amounts of catalyst seemed to be the most suitable combination in the RCM of these (di)peptides. The application of RCM in the synthesis of larger cyclic peptides is the subject of other studies.[20,21]

Experimental Section

General: Unless otherwise stated, chemicals were obtained from commercial sources and used without further purification. DiPEA were distilled consecutively from ninhydrin and KOH. 2,4,6-Collidine was distilled from CaH_2. "Dry solvents" were obtained as peptide grade solvents from Biosolve and stored over molecular sieves (4 Å). Reactions were run at ambient temperature unless noted otherwise. – ^1H NMR spectra were recorded with a Varian G-300 (300 MHz) spectrometer and chemical shift values are reported in ppm relative to TMS (δ = 0.00). ^1H NMR spectra were also recorded using the COSY sequence. – ^{13}C NMR spectra were recorded with a Varian G-300 (75 MHz) spectrometer and chemical shift values are reported in ppm relative to $CDCl_3$ (δ = 77.0). ^{13}C NMR spectra were recorded using the attached proton test (APT) sequence. – Fast atom bombardment (FAB) mass spectrometry was carried out using a Jeol JMS SX/SX 102A four-sector mass spectrometer, coupled with an HP-9000 data system. Electron Spray Ionisation (ESI) mass spectrometry was carried out using a Shimadzu LCMS QP-8000 single quadrupole benchtop mass spectrometer, coupled with a QP-8000 data system. – Microanalyses were carried out at Leiden University using a Perkin–Elmer Series II 2400 CNH S/O analyzer. – R_f values were determined by thin-layer chromatography (TLC) on Merck precoated silica gel 60F-254 (0.25 mm) plates. Spots were visualized with I_2, UV light, or Cl_2/TDM (*N*,*N*,*N*′,*N*′-tetramethyl-4,4′-diaminodiphenylmethane).[22] Solvents were evaporated under reduced pressure at 40 °C. – Column chromatography was performed on silica gel 60 (70–230 mesh). Analytical and preparative HPLC was performed with a Gilson automated HPLC system 205 with a 233XL auto

sampler and a 119 UV/Vis detector with either an analytical or preparative reverse-phase column (Alltech Adsorbosphere C8, 5 μm, 250×4.6 mm; Alltech Adsorbosphere C8, 10 μm, 250×22 mm, resp.), a UV detector operating at 254 and 220 nm, at a flow of 1 mL min^{-1} (11.5 mL min^{-1} for preparative HPLC). Elution was effected using a gradient from 0.1% TFA in water to 0.085% TFA in acetonitrile/water (95:5, v/v) in 20 min. All solid-phase reactions were run under nitrogen with dry peptide grade solvents. All compounds were homogenous on TLC unless stated otherwise.

Compound **2a** was prepared from H-(*N*all)Gly-OEt and Boc-(*N*all)Gly-OH.

H-(*N*all)Gly-OEt: To a cooled (ice bath) solution of allylamine (0.1 mol, 8.0 mL) in THF (130 mL), ethyl bromoacetate (50 mmol, 5.5 mL) in THF (80 mL) was added dropwise. After stirring for 2 h, the reaction mixture was concentrated in vacuo and suspended in Et_2O. The suspension was filtered, the residue washed with Et_2O and the filtrate concentrated in vacuo. Column chromatography (eluent: Et_2O) afforded H-(*N*all)Gly-OEt (33.0 mmol, 4.7 g) as an oil in 66% yield. − R_f = 0.25 (eluent: Et_2O). − ^{1}H NMR ($CDCl_3$): δ = 1.28 (t, 3 H, *J* = 7.2 Hz, CH_3 from OEt), 1.66 (br. s, 1 H, NH), 3.27 (d, 2 H, *J* = 2.9 Hz, CH_2 from all), 3.39 (s, 2 H, CH_2 from Gly), 4.19 (q, 2 H, *J* = 7.2 Hz, CH_2 from OEt), 5.09−5.22 (m, 2 H, =CH_2), 5.80−5.93 (m, 1 H, =CH). − ^{13}C NMR ($CDCl_3$): δ = 14.0 (CH_3 from OEt), 49.8 (CH_2 from all), 51.6 (CH_2 from Gly), 60.4 (CH_2 from OEt), 116.1 (=CH_2), 136.0 (=CH), 172.2 (CO).

Boc-(*N*all)Gly-OH: To a solution of H-(*N*all)Gly-OEt (10 mmol, 1.5 g) in dioxane (42 mL) was added Boc_2O (11 mmol, 2.4 g). After stirring for 16 h, MeOH (12 mL) and 4 N NaOH (12 mmol, 3.0 mL) was added. Stirring was continued for 2.5 h after which the reaction mixture was poured into water (60 mL) and the resulting mixture washed with Et_2O (2 × 50 mL). The pH of the aqueous layer was adjusted to pH ≈ 2−3 with 1 N $KHSO_4$. The aqueous layer was extracted with EtOAc (3 × 75 mL) and the combined organic layers were washed with brine, dried (Na_2SO_4) and concentrated in vacuo to give Boc-(*N*all)Gly-OH (9.6 mmol, 2.08 g) as a white solid in 96% yield. − ^{1}H NMR ($CDCl_3$): δ = 1.44 and 1.46 (s, 9 H, CH_3 from Boc), 3.89 (s, 2 H, CH_2 from Gly), 3.95−3.99 (m, 2 H, CH_2 from all), 5.14−5.18 (m, 2 H, =CH_2), 5.74−5.83 (m, 1 H, =CH). − ^{13}C NMR ($CDCl_3$): δ = 28.1 (CH_3 from Boc), 47.6 (CH_2 from all), 50.2 and 50.8 (CH_2 from Gly), 80.8 (C from Boc), 117.1 and 117.8 (=CH_2), 133.2 and 133.4 (=CH), 155.2 and 155.8 (CO from Boc), 175.2 and 175.5 (CO). − MS (FAB); *m/z*: 453 $[2 M + Na]^+$, 431 $[2 M + H]^+$, 375 $[2 M - tBu + H]^+$, 331 $[2 M - Boc+H]^+$, 238 $[M + Na]^+$, 216 $[M + H]^+$, 160 $[M - tBu + H]^+$, 116 $[M - Boc + H]^+$. − $C_{10}H_{17}NO_4$ (215.1): calcd. C 55.80, H 7.96, N 6.51; found C 55.86, H 7.84, N 6.51.

Boc-(*N*all)Gly-(*N*all)Gly-OEt (2a): To a cooled (ice bath) solution of H-(*N*all)Gly-OEt (4.86 mmol, 0.69 g), Boc-(*N*all)Gly-OH (5.3 mmol, 1.2 g) and PyBroP (5.4 mmol, 2.5 g) in dry DCM (40 mL) was added DiPEA (11 mmol, 1.9 mL). After stirring for 1 h, the reaction mixture was concentrated in vacuo and redissolved in EtOAc (75 mL). The organic layer was washed with 1 N $KHSO_4$ (3 × 50 mL), 1 N $NaHCO_3$ (3 × 50 mL), water (50 mL) and brine (50 mL), dried (Na_2SO_4) and concentrated in vacuo. Column chromatography (eluent: gradient of hexanes/EtOAc, 3:1 to hexanes/EtOAc, 2:1, v/v) afforded **2a** (4.28 mmol, 1.45 g) as a white solid in 88% yield. − R_f = 0.27 (eluent: hexanes/EtOAc, 2:1, v/v). − ^{1}H NMR ($CDCl_3$): δ = 1.26 (t, 3 H, *J* = 7.0 Hz, CH_3 from OEt), 1.45 (s, 9 H, CH_3 from Boc), 3.85−4.09 (m, 6 H, CH_2 from all and CH_2 Boc-*Gly*), 4.07 (s, 2 H, CH_2 from *Gly*-OEt), 4.18 (q, 2 H, *J* = 7.0 Hz, CH_2 from OEt), 5.07−5.21 (m, 4 H, =CH_2), 5.70−5.81 (m, 2 H, =CH). − ^{13}C NMR ($CDCl_3$): δ = 14.0 (CH_3 from OEt), 28.2 (CH_3 from Boc), 47.0 and 47.4 (CH_2 from all), 49.6 and 50.1 (CH_2 from *Gly*-OEt), 50.7 and 51.0 (CH_2 form Boc-*Gly*), 61.0 and 61.5 (CH_2 from OEt), 80.0 (C from Boc), 116.6, 117.4, 117.8 and 118.3 (=CH_2), 132.2, 132.6, 133.6 and 134.3 (=CH), 155 (CO from Boc), 169.1 and 169.4 (CO). − MS (ESI); *m/z*: 363 $[M + Na]^+$. − $C_{17}H_{28}N_2O_5$ (340.1): calcd. C 59.98, H 8.29, N 8.23; found C 59.71, H 7.70, N 8.20.

Compound **2b** was prepared from H-(*N*all)Gly-OEt and Boc-(*N*all)Phe-OMe. The latter compound was prepared from *p*NBS-Phe-OMe via *p*NBS-(*N*all)Phe-OMe[7] and H-(*N*all)Phe-OMe.

***p*NBS-Phe-OMe:** TEA (18.0 mmol, 2.5 mL) was added to a solution of HCl·H−Phe-OMe (5.2 mmol, 1.1 g) and *p*NBS-Cl (5.8 mmol, 1.3 g) in dry DCM (25 mL). After stirring for 16 h, the solution was washed with 2 N HCl (3 × 15 mL), 1 N $NaHCO_3$ (3 × 15 mL) and brine (15 mL), dried (Na_2SO_4) and concentrated in vacuo. The residue was crystallized from DCM/hexanes and afforded ***p*NBS-Phe-OMe** (4.02 mmol, 1.46 g) as a white crystalline solid in 78% yield. − ^{1}H NMR ($CDCl_3$): δ = 3.06 (m, 2 H, CH_2), 3.61 (br. s, 3 H, OCH_3), 4.24−4.31 (m, 1 H, CH), 5.25 and 5.22 (br. s, 1 H, NH), 7.04−7.07 (m, 2 H, ArH from Phe), 7.22−7.27 (m, 3 H, ArH from Phe), 7.83−7.87 (m, 2 H, ArH from *p*NBS), 8.21−8.25 (m, 2 H, ArH from *p*NBS). − ^{13}C NMR ($CDCl_3$): δ = 38.1 (CH_2), 51.7 (CH), 56.2 (OCH_3), 123.1, 126.4, 127.2, 127.7 and 128.3 (CH from Ar), 134.0 (C from Ph), 144.7 and 148.9 (C from *p*NBS) 170.2 (CO). − MS (ESI); *m/z*: 405 $[M + H]^+$.

***p*NBS-(*N*all)Phe-OMe:** To a solution of *p*NBS−Phe-OMe (4.0 mmol, 1.5 g) and K_2CO_3 (8.1 mmol, 1.1 g) in dry DMF (20 mL), allyl bromide (7.4 mmol, 0.64 mL) was added. After stirring for 16 h, the reaction mixture was poured into water (20 mL). The aqueous layer was extracted with Et_2O (3 × 25 mL) and the combined organic layers were washed with brine, dried (Na_2SO_4) and concentrated in vacuo to give *p*-NBS-(*N*all)Phe-OMe (4.02 mmol, 1.67 g) as a slightly green solid in quantitative yield. − ^{1}H NMR ($CDCl_3$): δ = 2.97 (dd, 1 H, *J* = 14.3 Hz and *J* = 8.8 Hz, CH_2 from all), 3.34 (dd, 1 H, *J* = 14.3 Hz and *J* = 6.3 Hz, CH_2 from all), 3.54 (s, 3 H, OCH_3), 3.86−3.94 (m, 2 H, CH_2 from Phe), 4.85−4.90 (m, 1 H, CH), 5.07−5.22 (m, 2 H, =CH_2), 5.60−5.66 (m, 1 H, =CH), 7.14−7.23 (m, 5 H, ArH from Phe), 7.68−7.72 (m, 2 H, ArH from *p*NBS), 8.11−8.15 (m, 2 H, ArH from *p*NBS). − ^{13}C NMR ($CDCl_3$): δ = 35.2 (CH_2 from Phe), 47.6 (CH_2 from all), 51.3 (CH), 60.5 (OCH_3), 118.0 (=CH_2), 122.9, 126.0, 127.7 and 128.3 (CH from Ar), 132.7 (=CH), 135.6 (C from Phe), 144.9 and 148.8 (C from *p*NBS) 169.5 (CO).

H-(*N*all)Phe-OMe: To a solution of *p*-NBS-(*N*all)Phe-OMe (4.02 mmol, 1.62 g) and K_2CO_3 (12 mmol, 1.7 g) in dry DMF (10 mL) was added PhSH (4.9 mmol, 0.5 mL). After stirring for 1 h, the reaction mixture was poured into water (20 mL). The aqueous layer was extracted with Et_2O (3 × 25 mL) and the combined organic layers were washed with 1 N $NaHCO_3$ (3 × 15 mL), brine, dried (Na_2SO_4) and concentrated in vacuo. Column chromatography (eluent: hexanes/EtOAc, 2:1, v/v) afforded H-(*N*all)-Phe-OMe (3.16 mmol, 697 mg) as a green oil in 79% yield. − R_f = 0.39 (eluent: hexanes/EtOAc, 2/1, v/v). − ^{1}H NMR ($CDCl_3$): δ = 1.63 (br. s, 1 H, NH), 2.97 (d, 2 H, *J* = 6.6 Hz, CH_2 from Phe), 3.19 (m, 2 H, CH_2 from all), 3.56 (t, 1 H, *J* = 7.0 Hz, CH), 3.64 (s, 3 H, OCH_3) 5.04−5.16 (m, 2 H, =CH_2), 5.74−5.85 (m, 1 H, =CH), 7.17−7.32 (m, 5 H, CH Ar). − ^{13}C NMR ($CDCl_3$): δ = 38.8 (CH_2 from Phe), 49.6 (CH_2 from all), 50.6 (CH), 61.1 (OCH_3), 115.3 (=CH_2), 125.7, 127.4 and 128.2 (CH from Ar), 135.2 (=CH), 136.3,

(C from Ar) 174.0 (CO). − MS (ESI); *m/z*: 220 [M + H]$^+$, 160 [M − CO_2Me + H]$^+$.

Boc-(*N*all)Phe-OH: To a solution of H-(*N*all)Phe-OMe (0.53 mmol, 012 g) and Boc_2O (1.0 mmol, 0.23 g) in dioxane (10 mL) was added TEA (1.0 mmol, 0.15 mL). The reaction mixture was heated at reflux for 4 h and stirred for another 16 h at room temperature. MeOH (3.5 mL) and 4 N NaOH (2.8 mmol, 0.7 mL) were added to the reaction mixture. After stirring for 5 h, the reaction mixture was poured into water (10 mL). The aqueous layer was washed with Et_2O (2 × 25 mL). The pH of the aqueous layer was adjusted to pH ≈ 2−3 with 1 N $KHSO_4$. The aqueous layer was extracted with EtOAc (3 × 25 mL) and the combined organic layers were washed with brine, dried (Na_2SO_4) and concentrated in vacuo. Column chromatography (eluent: 10% MeOH/DCM, v/v) afforded Boc-(*N*all)Phe-OH (0.368 mmol, 117 mg) as a greenish oil in 70% yield. − R_f = 0.57 (eluent: 10% MeOH/DCM, v/v). − ^{1}H NMR ($CDCl_3$): δ = 1.46 and 1.48 (s, 9 H, CH_3 from Boc), 3.07−3.36 (m, 3 H, CH_2 and CH from Phe), 3.70−4.28 (br. m, 2 H, CH_2 from all), 4.98−5.03 (m, 2 H, =CH_2), 5.48−5.73 (m, 1 H, =CH), 7.18−7.31 (m, 5 H, ArH). − ^{13}C NMR ($CDCl_3$): δ = 27.38 (CH_3 from Boc), 34.3 and 35.2 (CH_2 from Phe), 50.1 and 50.7 (CH_2 from all), 60.3 and 61.3 (CH), 79.9 and 80.0 (C from Boc), 115.9 and 116.6 (=CH_2), 125.4, 127.4 and 128.4 (CH from Ar), 133.3 (=CH), 137.3, (C from Ar), 153.8 and 154.8 (CO from Boc), 176.0 (CO).

Boc-(*N*all)Phe-(*N*all)Gly-Et (2b): Preparation as described above for the preparation of **2a** starting from H-(*N*all)Gly-OEt and Boc-(*N*all)Phe-OMe. The crude product was purified by chromatography (eluent: hexanes/EtOAc, 4:1, v/v) to afford **2b** (0.108 mmol, 42 mg) as a colorless oil in 53% yield. − R_f = 0.78 (eluent: hexanes/EtOAc, 4:1, v/v). − ^{1}H NMR ($CDCl_3$): δ = 1.16−1.67 (m, 12 H, CH_3 from Boc and OEt), 2.94−3.21 (m, 2 H, CH_2 from Phe), 3.71−4.29 (br. m, 8 h, CH_2 from all, Gly and OEt), 4.92−5.14 (m, 4 H, =CH_2), 5.28−5.36 (m, 1 H, CH from Phe), 5.66−5.75 (m, 2 H, =CH), 7.18−7.27 (m, 5 H, ArH). − ^{1}H NMR ([D_6]DMSO, 90 °C): δ = 1.20 (t, 3 H, *J* = 7.1 Hz, CH_3 from OEt), 1.29 (s, 9 H, CH_3 from Boc), 2.84−2.91 (m, 1 H, CH_2 from Phe), 3.04−3.10 (m, 1 H, CH_2 from Phe), 3.78−3.80 (m, 2 H, CH_2 from all), 3.90−3.91 (d, 2 H, CH_2 from all), 3.80−4.15 (m, 2 H, CH_2 from Gly), 4.11 (q, 2 H, *J* = 7.1 Hz, CH_2 from OEt), 5.01−5.14 (m, 5 H, =CH_2 and CH), 5.65−5.78 (m, 2 H, =CH), 7.15−7.28 (m, 5 H, ArH). − ^{13}C NMR ($CDCl_3$): δ = 13.1 (CH_3 from OEt), 26.8 and 27.2 (CH_3 from Boc), 35.3 and 35.5 (CH_2 from Phe), 44.5 and 45.2 (CH_2 from Gly), 46.3 and 471 (CH_2 from (*N*all)Gly), 48.4 and 49.9 (CH_2 from (*N*all)Phe), 54.3 and 56.4 (CH from Phe), 60.1 (CH_2 from OEt), 79.4 (C from Boc), 115.3 and 115.9 (=CH_2 from (*N*all)Gly), 116.4 and 117.0 (=CH_2 from (*N*all)Phe), 125.3, 127.2, 127.3 and 128.7 (CH from Ar), 131.5 and 131.7 (=CH from (*N*all)Gly), 133.7 and 134.4 (=CH from (*N*all)Phe), 136.5, (C from Ar), 154.1 (CO from Boc), 168.0, 168.2 and 169.7 (CO). − MS (ESI); *m/z*: 453 [M + Na]$^+$.

Boc-(*N*all)Gly-(*N*all)Phe-OMe (2c): To a solution of HCl·H-(*N*all)Phe-OMe (0.211 mmol, 54 mg), Boc-(*N*all)Gly-OH (0.23 mmol, 50 mg) and PyBroP (0.24 mmol, 0.11 g) in dry DMF (2 mL), DiPEA (0.59 mmol, 0.10 mL) was added. After stirring for 16 h, the reaction mixture was poured into water (5 mL) and the aqueous layer was extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with HCl (2 N, 3 × 10 mL), $NaHCO_3$ (1 N, 3 × 10 mL), brine (10 mL), dried (Na_2SO_4) and concentrated in vacuo. Column chromatography (eluent: gradient of hexanes/EtOAc, 4:1 to hexanes/EtOAc, 1:1, v/v) afforded **2c** (0.113 mmol, 47 mg) as a colorless oil in 54% yield. − R_f = 0.70 (eluent: hexanes/EtOAc, 1:1, v/v). − ^{1}H NMR ($CDCl_3$): δ = 1.44 and 1.46 (s, 9 H, CH_3 from Boc), 2.95−3.36 (m, 3 H, CH_2 from Phe and 1H CH_2 from all), 3.71 (s, 3 H, OCH_3), 3.64−4.08 (m, 5 H, 3H CH_2 from all and CH_2 from Gly), 4.41−4.51 (m, 1 H, CH), 5.05−5.18 (m, 4 H, =CH_2), 5.50−5.62 (m, 1 H, =CH), 5.74−5.85 (m, 1 H, =CH), 7.19−7.32 (m, 5 H, ArH Phe). − ^{1}H NMR ([D_6]DMSO, 80 °C): δ = 1.38 (s, 9 H, CH_3 from Boc), 2.98−3.13 (m, 1 H, CH_2 from Phe), 3.22−3.29 (m, 1 H, CH_2 from Phe), 3.62 (s, 3 H, OCH_3), 3.68−4.01 (m, 6 H, CH_2 from all and Gly), 4.63 (m, 1 H, CH), 5.04−5.19 (m, 4 H, =CH_2), 5.60 (m, 1 H, =CH), 5.73 (m, 1 H, =CH), 7.21−7.30 (m, 5 H, ArH). − ^{13}C NMR ($CDCl_3$): δ = 27.3 (CH_3 from Boc), 34.0 and 38.7 (CH_2 from Phe), 346.2 and 46.5 (CH_2 from Gly), 49.2 and 49.6 (CH_2 from all), 51.2 (CH), 60.1 (OCH_3), 79.1 (C from Boc), 115.4 and 115.6 (=CH_2 from (*N*all)Gly), 116.4 and 116.8 (=CH_2 from (*N*all)Phe), 125.7, 127.4, 127.5, 127.8, 128.2 and 128.3 (CH from Ar), 132.0 and 132.8 (=CH from (*N*all)Gly), 133.3 (=CH from (*N*all)Phe), 136.8, (C from Ar), 154.6 (CO from Boc), 168.0, 168.4 and 169.9 (CO). − MS (ESI); *m/z*: 439 [M + Na]$^+$.

Compound **2d** was prepared from H-(*N*all)Leu-OMe and Boc-(*N*all)Gly-OMe. The former compound was prepared from *p*NBS-Leu-OMe via *p*-NBS-(*N*all)Leu-OMe.

***p*NBS-Leu-OMe:** Preparation as described above for the preparation of *p*-NBS−Phe-OMe starting from H-Leu-OMe and obtained as a yellow solid (4.6 mmol, 1.5 g) in 89% yield. − ^{1}H NMR ($CDCl_3$): δ = 0.78 (d, 3 H, *J* = 6.6 Hz, $^{\delta}CH_3$), 0.81 (d, 3 H, *J* = 6.6 hz, $^{\delta}CH_3$), 1.46 (d, 1 H, *J* = 7.0 Hz, CH_2), 1.48 (d, 1 H, *J* = 7.3 Hz, CH_2), 1.66 (quintet, 1 H, *J* = 6.7 Hz, $^{\gamma}CH$), 3.42 (s, 3 H, OCH_3), 3.97 (t, 1 H, *J* = 7.3 hz, $^{\alpha}CH$), 5.95 (br. s, 1 H, NH), 8.00−8.03 (m, 2 H, ArH), 8.26−8.29 (m, 2 H, ArH). − ^{13}C NMR ($CDCl_3$): δ = 20.3 and 21.6 ($^{\delta}CH_3$), 23.3 ($^{\gamma}CH$), 40.8 (CH_2), 51.4 ($^{\alpha}CH$), 53.6 (OCH_3), 123.2 and 127.5 (CH from Ar), 144.9 and 149.0 (C from Ar) 171.4 (CO).

***p*NBS-(*N*all)Leu-OMe:** Preparation as described above for the preparation of *p*NBS-(*N*all)Phe-OMe starting from *p*NBS-Leu-OMe and obtained as an orange oil (4.55 mmol, 1.699 g) in quantitative yield. − ^{1}H NMR ($CDCl_3$): δ = 0.82 (d, 3 H, *J* = 6.2 Hz, $^{\delta}CH_3$), 0.86 (d, 3 H, *J* = 6.3 hz, $^{\delta'}CH_3$) 1.54−1.66 (m, 3 H, $^{\gamma}CH$ and $^{\beta}CH_2$), 3.40 (s, 3 H, OCH_3), 3.62−3.75 (m, 1 H, CH_2 from all), 3.86−3.93 (m, 1 H, CH_2 from all), 4.55−4.60 (m, 1 H, $^{\alpha}CH$), 5.01−5.14 (m, 2 H, =CH_2), 5.68−5.82 (m, 1 H, =CH), 7.91−7.96 (m, 2 H, ArH), 8.23−8.27 (m, 2 H, ArH). − ^{13}C NMR ($CDCl_3$): δ = 20.0 and 21.5 ($^{\delta}CH_3$), 23.1 ($^{\gamma}CH$), 37.7 ($^{\beta}CH_2$), 47.4 (CH_2 from all), 51.0 ($^{\alpha}CH$), 57.4 (OCH_3), 116.9 (=CH_2), 122.9 and 127.8 (CH from Ar), 133.8 (=CH),144.5 and 149.9 (C from Ar) 170.2 (CO).

H-(*N*all)Leu-OMe: Preparation as described above for the preparation of H-(*N*all)Phe-OMe starting from *p*NBS-(*N*all)Leu-OMe. Crude H-(*N*all)Leu-OMe was purified by chromatography (eluent: hexanes/EtOAc, 4:1, v/v) and gave H-(*N*all)Leu-OMe (0.368 mmol, 299 mg) as a greenish oil in 70% yield. R_f = 0.58 (eluent: hexanes/EtOAc, 2:1, v/v). − ^{1}H NMR ($CDCl_3$): δ = 0.79 (d, 3 H, *J* = 7.0 Hz, $^{\delta}CH_3$), 0.82 (d, 3 H, *J* = 6.9 hz, $^{\delta'}CH_3$) 1.35 and 1.37 (d, 2 H, *J* = 6.6 Hz and *J* = 7.3 Hz, $^{\beta}CH_2$), 1.46 (br. s, 1 H, NH), 1.58−1.65 (m, 1 H, $^{\gamma}CH$), 2.95−3.02 (m, 1 H, CH_2 from all), 3.11−3.19 (m, 1 H, CH_2 from all), 3.19 (t, 1 H, *J* = 7.3 Hz, $^{\alpha}CH$), 3.61 (s, 3 H, OCH_3), 4.94−5.09 (m, 2 H, =CH_2), 5.67−5.80 (m, 1 H, =CH_2). − ^{13}C NMR ($CDCl_3$): δ = 21.5 and 21.6 ($^{\delta}CH_3$), 23.8 ($^{\gamma}CH$), 41.8 ($^{\beta}CH_2$), 49.7 (CH_2 from all), 50.4 ($^{\alpha}CH$), 58.0 (OCH_3), 115.1 (=CH_2), 135.4 (=CH) 175.3 (CO).

Boc-(*N*all)Gly-(*N*all)Leu-OMe (2d): To a solution of H-(*N*all)Leu-OMe (0.43 mmol, 80 mg), Boc-(*N*all)Gly-OH (0.77 mmol, 0.14 g)

and TFFH[10] (2.2 mmol, 0.57 mg) in dry DCM (2 mL), DiPEA (1.3 mmol, 0.23 mL) was added. After stirring for 16 h, the reaction mixture was washed with HCl (2 N, 3 × 10 mL), $NaHCO_3$ (1 N, 3 × 10 mL), brine (10 mL), dried (Na_2SO_4) and concentrated in vacuo. Column chromatography (eluent: hexanes/EtOAc, 4:1, 1/1, v/v) afforded **2d** (0.15 mmol, 59 mg) as a colorless oil in 35% yield. − R_f = 0.58 (eluent: hexanes/EtOAc, 4:1, v/v). − ^{1}H NMR ($CDCl_3$): δ = 0.87−0.94 (m, 6 H, $^{\delta}CH_3$), 1.41 and 1.43 (s, 9 H, CH_3 from Boc), 1.24−1.87 (m, 3 H, $^{\beta}CH_2$ and $^{\gamma}CH$), 3.66 (s, 3 H, OCH_3), 3.82−4.06 (m, 6 H, CH_2 from all Gly), 4.99−5.25 (m, 5 H, $^{\alpha}CH$ and $=CH_2$), 5.76−5.84 (m, 2 H, =CH). − ^{13}C NMR ($CDCl_3$): δ = 21.0, 21.4, 21.6 and 21.8 ($^{\delta}CH_3$), 23.9 ($^{\gamma}CH$), 27.3 (CH_3 from Boc), 37.0 ($^{\beta}CH_2$), 46.8 (CH_2 from Gly), 49.4 and 49.8 (CH_2 from all), 51.0 and 51.5 ($^{\alpha}CH$), 54.7 (OCH_3), 79.0 (C from Boc), 115.6, 116.1 and 116.4 ($=CH_2$), 133.1 (=CH), 154.5 (CO from Boc), 171.2 (CO).). − MS (ESI) *m/z*: 405 $[M + Na]^+$.

Compound **2e** was prepared from H-(*N*all)Gly-OEt and Boc-(*N*all)Leu-OMe.

Boc-(*N*all)Leu-OH: Preparation as described above for the preparation of Boc-(*N*all)Phe-OH starting from H-(*N*all)Leu-OH. Crude Boc-(*N*all)Leu-OMe was purified by chromatography (eluent: 10% MeOH/DCM, v/v) and gave Boc-(*N*all)Leu-OMe (0.56 mmol, 0.17 g) as a greenish oil in 74% yield. − R_f = 0.52 (eluent: 10% MeOH/DCM, v/v). − ^{1}H NMR ($CDCl_3$): δ = 0.89 (d, 3 H, *J* = 6.3 Hz, $^{\delta}CH_3$), 0.91 (d, 3 H, *J* = 6.2 hz, $^{\delta'}CH_3$), 1.42 (s, 9 H, CH_3 from Boc), 1.63−1.77 (m, 3 H, $^{\beta}CH_2$ and $^{\gamma}CH$), 3.58−3.63 (m, 1 H, $^{\alpha}CH$), 3.91−4.19 (m, 2 H, CH_2 from all), 5.06−5.14 (m, 2 H, $=CH_2$), 5.82−5.83 (m, 1 H, =CH). − ^{13}C NMR ($CDCl_3$): δ = 20.7 and 21.9 ($^{\delta}CH_3$), 23.7 ($^{\gamma}CH$), 27.3 (CH_3 from Boc), 37.1 and 37.9 ($^{\beta}CH_2$), 48.0 and 48.6 (CH_2 from all), 56.5 ($^{\alpha}CH$), 79.8 (C from Boc), 115.3 and 116.0 ($=CH_2$), 134.0 (=CH), 155.2 (CO from Boc), 177.0 (CO). − MS (ESI); *m/z*: 294 $[M + Na]^+$, 238 $[M - t\text{Bu} + Na]^+$, 216 $[M + H]^+$, 194 $[M - \text{Boc} + Na]^+$, 172 $[M - \text{Boc} + H]^+$.

Boc-(*N*all)Leu-(*N*all)Gly-Et (2e): Preparation as described above for the preparation of **2a** starting from H-(*N*all)Gly-OEt and Boc-(*N*all)Leu-OMe. Crude **2e** was purified by chromatography (eluent: hexanes/EtOAc, 4:1, v/v) afforded **2e** (0.13 mmol, 52 mg) as a colorless oil in 42% yield. − R_f = 0.67 (eluent: hexanes/EtOAc, 4:1, v/v). − ^{1}H NMR ($CDCl_3$): δ = 0.87−0.93 (m, 6 H, $^{\delta}CH_3$), 1.25 (t, 3 H, *J* = 7.1 Hz, CH_3 from OEt), 1.43 and 1.46 (s, 9 H, CH_3 from Boc), 1.43−1.74 (m, 3 H, $^{\beta}CH_2$ and $^{\gamma}CH$), 3.68−4.78 (m, 2 H, CH_2 from all), 3.82−4.05 (m, 2 H, CH_2 from Gly), 4.09−4.11 (m, 2 H, CH_2 from all), 4.16 (q, 2 H, *J* = 7.1 Hz, CH_2 from OEt), 5.00−5.20 (m, 5 H, $^{\alpha}CH$ and $=CH_2$), 5.66−5.81 (m, 2 H, =CH). − ^{13}C NMR ($CDCl_3$): δ = 13.1 (CH_3 from OEt), 21.5 and 21.7 ($^{\delta}CH_3$), 23.4 ($^{\gamma}CH$), 27.3 and 27.3 (CH_3 from Boc), 38.0 ($^{\beta}CH_2$), 46.8 (CH_2 from Gly), 49.4 and 49.8 (CH_2 from all), 51.0 and 51.5 ($^{\alpha}CH$), 60.1 (OCH_2 from OEt), 79.2 (C from Boc), 111.6, 115.1 and 116.6 ($=CH_2$), 131.6, 132.1 and 134.6 (=CH), 154.4 (CO from Boc), 168.1 and 170.7 (CO). − MS (ESI); *m/z*: 419 $[M + Na]^+$.

Boc-(*N*all)Phe-(*N*all)Phe-OMe (2f): To a cooled solution (pentane/N_2 bath, −70 °C) of Boc−Phe−Phe-OMe[23] (0.66 mmol, 0.28 g) and allyl bromide (5.8 mmol, 0.50 mL) in dry THF (5 mL) was added P4 phosphazene base in hexanes (1 M, 2 mmol, 2.0 mL). After stirring for 16 h, the reaction mixture was diluted with ether/EtOAc (20 mL, 1:1), and washed with HCl/H_2O (2 N, 2 × 25 mL), dried (Na_2SO_4) and concentrated in vacuo. Column chromatography (silica, eluent: gradient of hexanes/EtOAc, 4:1 to hexanes/EtOAc, 2:1, v/v) afforded a mixture of mono- and dialkylated dipeptides. Column chromatography (silica, eluent: gradient of hexanes/EtOAc, 9:1 to hexanes/EtOAc, 4:1, v/v) afforded **2f** (0.48 mmol, 241 mg) as a white solid in 72% yield. − R_f = 0.54 (eluent: hexanes/EtOAc, 2:1, v/v). − ^{1}H NMR ($CDCl_3$): δ = 1.26−1.46 (m, 9 H, CH_3 from Boc), 2.32−2.45 (m, 1H $^{\beta}CH_2$), 2.65−4.89 (m, 10 H, 3H $^{\beta}CH_2$ and CH_2 from all OCH_3), 4.89−5.39 (m, 6 H, $^{\alpha}CH$ and $=CH_2$), 5.56−5.82 (m, 2 H, =CH), 6.55−6.96 (m, 1 H, ArH), 7.05−7.39 (m, 9 H, ArH). − ^{13}C NMR ($CDCl_3$): d 28.3 (CH_3 from Boc), 29.7, 34.3, 36.1 and 37.3 ($^{\beta}CH_2$), 45.7, 46.3, 46.7 and 51.9 (CH_2 from all), 51.9 and 52.0 (OCH_3), 56.9 and 61.4 ($^{\alpha}CH$), 80.5 (C from Boc), 116.3, 118.2 and 119.8 ($=CH_2$), 126.5, 126.9, 128.1, 128.3, 128.5, 129.2, 129.6, 129.9, 130.2 and 130.8 (CH from Ar), 131.6, 133.1, 135.1 and 135.6 (=CH), 136.4, 137.3, 137.8 and 137.9 (C from Ar), 155.0 (CO from Boc), 169.3, 170.6 and 172.5 (CO). − MS (ESI); *m/z*: 529 $[M + Na]^+$.

Boc-(*N*all)Leu-(*N*all)Leu-OMe (2g): Preparation as described above for the preparation of **2f** starting from Boc-Leu-Leu-OMe.[23] Crude **2g** was purified by chromatography (eluent: hexanes/EtOAc, 4:1, v/v) afforded a mixture of mono- and bis-alkylated dipeptide. Column chromatography (eluent: gradient of hexanes/EtOAc, 9:1, v/v) afforded **2g** (0.11 mmol, 48 mg) as a colorless oil in 27% yield. − R_f = 0.64 (eluent: hexanes/EtOAc, 2/1, v/v). − ^{1}H NMR ($CDCl_3$): δ = 0.90−0.96 (m, 12 H, $^{\delta}CH_3$), 1.46 (s, 9 H, CH_3 from Boc), 1.41−1.82 (m, 6 H, $^{\beta}CH_2$ and $^{\gamma}CH$), 3.71 (s, 3 H, OCH_3), 3.65−3.71 (m, 2 H, CH_2 from all), 4.00 (br. m, 2 H, CH_2 from all), 4.53−5.29 (m, 6 H, $^{\alpha}CH$ and $=CH_2$), 5.80 (br. m, 2 H, =CH). − ^{13}C NMR ($CDCl_3$): δ = 20.8, 21.0, 21.3, 21.5, 21.7 and 21.9 ($^{\delta}CH_3$), 23.4 and 24.0 ($^{\gamma}CH$), 27.3 (CH_3 from Boc), 37.0, 37.9, 38.1 and 38.3 ($^{\beta}CH_2$), 44.9, 46.2, 47.2 and 47.9 (CH_2 from all), 50.9 (OCH_3), 51.1, 51.3, 51.5, 53.1, 54.9, 56.5, 56.7, and 57.9 ($^{\alpha}CH$), 79.0, 79.2, 79.6 and 80.0 (C from Boc), 114.9, 115.1, 115.4 and 116.5 ($=CH_2$), 133.2, 133.4, 134.1, 134.6 and 134.8 (=CH), 154.2 and 154.5 (CO from Boc), 170.3, 170.6 and 170.9 (CO). − MS (ESI); *m/z*: 461 $[M + Na]^+$.

General RCM Procedure: A 10 mM solution of the linear bis(*N*-alkylated) peptide in 1,1,2-trichloroethane was purged with nitrogen for 15 min, followed by the addition of 10 mol-% of $Cl_2(PCy_3)_2Ru{=}CHPh$ (**3**) and heated at reflux for 16 h under a nitrogen flow. After concentrating in vacuo, the resulting crude cyclized peptide was purified by column chromatography.

Cyclic Peptide 4a: Preparation according to the general RCM procedure. Column chromatography (eluent: hexanes/EtOAc, 1:1, v/v) afforded **4a** (0.151 mmol, 47 mg) as a brownish oil in 73% yield and **7a** (56 μmol, 19 mg) as a brownish oil in 27% yield. When the RCM was carried out in toluene, **4a** and **7a** were obtained in 3% and 35%, respectively.

4a: R_f = 0.23 (eluent: hexanes/EtOAc, 1:1, v/v). − ^{1}H NMR ($CDCl_3$): δ = 1.23−1.29 (m, 3 H, CH_3 from OEt), 1.43 and 1.46 (s, 9 H, CH_3 from Boc), 3.91−3.93 (m, 2 H, CH_2 from all), 4.10 (d, 2 H, *J* = 2.2 Hz, CH_2 from all), 4.13 (s, 2 H, CH_2 from ^{1}Gly), 4.16−4.22 (m, 2 H, CH_2 from OEt), 3.98, 4.06, 4.14 and 4.37 (s, 2 H, CH_2 from ^{2}Gly), 5.84−5.88 (m, 2 H, =CH). − ^{1}H NMR ([D_6]DMSO, 90 °C): d 1.22 (t, 3 H, *J* = 7.1 Hz, CH_3 from OEt), 1.40 (s, 9 H, CH_3 from Boc), 3.80 (d, 2 H, *J* = 5.8 Hz, CH_2 from all), 3.97−4.01 (m, 6 H, CH_2 from all and Gly), 4.14 (q, 2 H, *J* = 7.1 Hz, CH_2 from OEt), 5.08−5.24 (m, 4 H, $=CH_2$), 5.73−5.86 (m, 2 H, =CH). − ^{13}C NMR ($CDCl_3$): δ = 13.2 (CH_3 from OEt), 27.3 (CH_3 from Boc), 44.0 and 44.3 (CH_2 from all), 45.2 and 45.5 (CH_2 from all), 49.4 and 50.0 (CH_2 from ^{2}Gly), 51.1, 51.5 (CH_2 from ^{1}Gly), 60.3 (CH_2 from OEt), 79.7, 80.2 (C from Boc), 124.1, 130.8, 132.4 (=CH), 153.7 (CO from Boc), 168.2, 169.1 (CO). − MS (FAB); *m/z*: 625 $[2\ M + H]^+$, 313 $[M + H]^+$, 257 $[M - t\text{Bu} + H]^+$.

7a: R_f = 0.60 (eluent: hexanes/EtOAc, 1:1, v/v). − ^{1}H NMR ($CDCl_3$): δ = 1.25 (t, 3 H, *J* = 7.2 Hz, CH_3 from OEt), 1.43, 1.45

and 1.49 (s, 9 H, CH_3 from Boc), 1.59−1.81 (m, 6 H, NCH=CHCH_3, 3.87−4.27 (m, 4 H, CH_2), 4.15, 4.16 and 4.17 (s, 2 H, CH_2 from OEt), 4.58−4.66 (m, 0.4 H, NCH=CHCH_3 *E*), 5.03−5.16 (0.8 H) and 5.54−5.66 (0.8 H) (m, 1.6 H, NCH=CHCH_3 *Z*, 5.8 (0.2) and 6.15−6.25 (1.4 H) (m, 1.6 H, NCH=CHCH_3 *Z*), 6.75−6.95 (m, 0.4 H, NCH=CHCH_3 *E*). − MS (ESI); *m/z*: 363 $[M + Na]^+$, 323 $[M - (CHCHCH_3) + Na]^+$, 263 $[M - Boc + Na]^+$, 223 $[M - (Boc-CHCHCH_3) + Na]^+$.

Cyclic Peptide 4b: Preparation according to the general RCM procedure. Column chromatography (eluent: hexanes/EtOAc, 2:1, v/v) afforded **4b** (50 μmol, 20 mg) as a brownish oil in 51% yield. − R_f = 0.44 (eluent: hexanes/EtOAc, 1:1, v/v). − ^{1}H NMR ($CDCl_3$): δ = 1.23−1.31 (m, 12 H, CH_3 Boc and OEt), 2.90−3.03 and 3.36−3.50 (m, 2 H, $^{\beta}CH_2$), 3.57−3.93 (m, 4 H, 3H CH_2 from all and 1H CH_2 from Gly), 4.14−4.44 (m, 4 H, 1 H CH_2 from all, 1 H CH_2 from Gly and CH_2 from OEt), 4.95 and 5.22−5.24 (m, 1 H, $^{\alpha}CH$), 5.74−5.87 (m, 2 H, =CH), 7.18−7.30 (m, 5 H, ArH). − ^{13}C NMR ($CDCl_3$): δ = 13.2 (CH_3 from OEt), 27.1 and 27.2 (CH_3 from Boc), 35.9 and 36.2 ($^{\beta}CH_2$), 43.0 and 44.6 (CH_2 from Gly), 49.1 and 49.3 (CH_2 from all), 58.7 and 59.9 ($^{\alpha}CH$), 60.3 (CH_2 from OEt), 79.3 and 79.9 (C from Boc), 123.5, 123.7, 125.1, 125.4, 127.0 and 127.4 (CH from Ar), 129.0 and 129.1 (=CH from (*N*all)Gly), 132.7 and 133.8 (=CH from (*N*all)Phe), 137.4, (C from Ar), 152.6 and 153.6 (CO from Boc), 168.0, 168.3, 169.8 and 170.1 (CO). − MS (FAB); *m/z*: 827 $[2 M + Na]^+$, 805 $[2 M + H]^+$, 425 $[M + Na]^+$, 403 $[M + H]^+$, 347 $[M - tBu + H]^+$.

Cyclic Peptide 4c: Preparation according to the general RCM procedure. Column chromatography (eluent: hexanes/EtOAc, 1:1, v/v) afforded **4c** (67 μmol, 26 mg) as a brownish oil in 59% yield. − R_f = 0.42 (eluent: hexanes/EtOAc, 1/1, v/v). − ^{1}H NMR ($CDCl_3$): δ = 1.41−1.44 (s, 9 H, CH_3 from Boc), 3.01−3.19 (m, 1 H, $^{\beta}CH_2$), 3.34−3.45 (m, 1.5 H, 1H $^{\beta}CH_2$, 0.5H CH_2 from Gly), 3.70 (s, 3 H, OCH_3), 3.66−3.74 (m, 1 H, CH_2 from all), 3.85−3.99 and 4.03−4.17 (m, 4 H, 3 H CH_2 from all and 1H CH_2 from Gly) 4.43−4.49 (m, 0.5 H, CH_2 from Gly), 4.75−4.80 and 5.19−5.24 (m, 1 H, $^{\alpha}CH$), 5.48−5.60 (m, 1 H, =CH), 5.68−5.72 (m, 1 H, =CH), 7.21−7.29 (m, 5 H, ArH). − ^{13}C NMR ($CDCl_3$): δ = 27.3 (CH_3 from Boc), 33.3 and 34.6 ($^{\beta}CH_2$), 41.0 and 42.2 (CH_2 from Gly), 45.4 (CH_2 from all), 51.2 ($^{\alpha}CH$), 51.4 and 51.8 (CH_2 from all), 59.6 and 60.6 (OCH_3), 79.6 and 80.1 (C from Boc), 124.0, 124.3, 125.7, 125.8, 127.6 and 128.1 (CH from Ar), 130.3 (=CH from (*Nall*)Gly), 132.2 (=CH from (*Nall*)Phe), 136.1 and 136.4 (C from Ar), 153.7 (CO from Boc), 168.6, 168.9, and 170.7 (CO). − MS (FAB); *m/z*: 799 $[2 M + Na]^+$, 777 $[2 M + H]^+$, 677 $[2 M - Boc + H]^+$, 411 $[M + Na]^+$, 389 $[M + H]^+$, 333 $[M - tBu + H]^+$, 289 $[M - Boc + H]^+$.

Cyclic Peptide 4d: Preparation according to the general RCM procedure. Column chromatography (eluent: hexanes/EtOAc, 2:1, v/v) afforded **4d** (48 μmol, 17 mg) as a brownish oil in 35% yield. − R_f = 0.15 (eluent: hexanes/EtOAc, 2/1, v/v). − ^{1}H NMR ($CDCl_3$): δ = 0.85−0.96 (m, 6 H, $^{\delta}CH_3$), 1.46 (s, 9 H, CH_3 from Boc), 1.39−1.58 (m, 1 H, $^{\gamma}CH$), 1.61−1.77 (m, 2 H, $^{\beta}CH_2$), 3.70 (s, 3 H, OCH_3), 3.80−4.26 (m, 6 H, CH_2 from all and Gly), 5.28−5.33 and 5.40−4.45 (m, 1 H, $^{\alpha}CH$), 5.80−5.84 (m, 2 H, =CH). − ^{13}C NMR ($CDCl_3$): δ = 20.7, 22.3 and 23.7 ($^{\delta}CH_3$), 27.3 (CH_3 from Boc), 29.9 ($^{\gamma}CH$), 37.4, 39.0, 39.4 ($^{\beta}CH_2$), 45.5, 45.7 and 51.7 (CH_2), 51.1 ($^{\alpha}CH$), 54.7 and 54.8 (OCH_3), 80.1 (C from Boc), 125.1, 125.4, 129.9 and 131.1 (=CH), 154.0 (CO from Boc), 169.0 and 171.5 (CO). − MS (FAB); *m/z*: 731 $[2 M + Na]^+$, 709 $[2 M + H]^+$, 609 $[2 M - Boc + H]^+$, 377 $[M + Na]^+$, 355 $[M + H]^+$, 329 $[M - tBu + H]^+$, 255 $[M - Boc + H]^+$.

Cyclic Peptide 4e: Preparation according to the general RCM procedure. Column chromatography (eluent: hexanes/EtOAc, 4:1, v/v) afforded **4e** (58 μmol, 22 mg) as a colorless oil in 50% yield. − R_f = 0.40 (eluent: hexanes/EtOAc, 2:1, v/v). − ^{1}H NMR ($CDCl_3$): δ = 0.92−0.97 (m, 6 H, $^{\delta}CH_3$ from Leu), 1.23−1.27 (m, 3 H, CH_3 from OEt), 1.42 and 1.48 (s, 9 H, CH_3 from Boc), 1.30−1.48 (m, 1 H, $^{\beta}CH_2$), 1.55−1.69 (m, 1 H, $^{\gamma}CH$), 1.99−2.09 (m, 1 H, $^{\beta}CH_2$), 3.38−3.78 (m, 3 H, CH_2 from all and Gly) 4.01−4.51 (m, 5 H, CH_2 from all, Gly and OEt), 4.74 and 5.05 (m, 1 H, $^{\alpha}CH$), 5.77−5.82 and 5.89−5.94 (m, 2 H, =CH). − ^{13}C NMR ($CDCl_3$): δ = 13.2 (CH_3 from OEt), 21.6, 21.8 and 22.1 ($^{\delta}CH_3$), 23.7 ($^{\gamma}CH$), 27.3 and 27.5 (CH_3 from Boc), 40.0, 40.1, 42.5, 42.7, 44.4 and 49.2 (CH_2), 55.6 and 56.5 ($^{\alpha}CH$), 60.2 (CH_2 from OEt), 79.3 and 80.1 (C from Boc), 123.7, 123.9, 132.7 and 134.0 (=CH), 152.9 and 154.0 (CO from Boc), 168.1, 168.3, 170.5 and 171.0 (CO). − MS (FAB); *m/z*: 759 $[2 M + Na]^+$, 737 $[2 M + H]^+$, 637 $[2 M - Boc + H]^+$, 391 $[M + Na]^+$, 369 $[M + H]^+$.

Cyclic Peptide 4f: Preparation according to the general RCM procedure. Column chromatography (eluent: hexanes/EtOAc, 4:1, v/v) afforded **4f** (23 μmol, 11 mg) as a brownish oil in 27% yield. − R_f = 0.44 (eluent: hexanes/EtOAc, 2:1, v/v). − ^{1}H NMR ($CDCl_3$): δ = 1.24 and 1.27 (s, 9 H, CH_3 from Boc), 2.67−2.75 (m, 1 H, CH_2 from all), 2.93−3.46 (m, 5 H, $^{\beta}CH_2$ and 1H CH_2 from all), 3.69 (s, 3 H, OCH_3), 3.61−3.75 (m, 1 H, CH_2 from all), 3.92−3.98 (m, 1 H, CH_2 from all), 4.08−4.13, 4.45, 4.81 and 5.06−5.10 (m, 2 H, $^{\alpha}CH$), 5.52−5.53 (m, 1 H, =CH), 5.75 (m, 1 H, =CH), 7.08−7.31 (m, 10 H, ArH). − ^{13}C NMR ($CDCl_3$): δ = 28.2 (CH_3 from Boc), 35.5 and 36.8 ($^{\beta}CH_2$), 44.0 and 45.6 (CH_2 from all), 52.2 (OCH_3), 60.1, 61.3 and 63.9 ($^{\alpha}CH$), 80.2 and 80.8 (C from Boc), 124.1, 124.4, 126.2, 126.7, 128.0, 128.3, 128.6, 129.1, 130.1 and 130.3 (CH from Ar), 133.9 and 135.3 (=CH), 137.8 and 138.2 (C from Ar), 154.6 (CO from Boc), 170.5 (CO). − MS (FAB); *m/z*: 501 $[M + Na]^+$, 479 $[M + H]^+$, 447 $[M - OMe + H]^+$, 423 $[M - tBu + H]^+$, 379 $[M - Boc + H]^+$.

Cyclic Peptide 4g: Preparation according to the general RCM procedure. Column chromatography (eluent: hexanes/EtOAc, 4:1, v/v) afforded **4g** (51 μmol, 21 mg) as a colorless oil in 53% yield. − R_f = 0.61 (eluent: hexanes/EtOAc, 2:1, v/v). − ^{1}H NMR ($CDCl_3$): δ = 0.82−0.94 (m, 12 H, $^{\delta}CH_3$), 1.42 and 1.47 (s, 9 H, CH_3 from Boc), 1.42−1.63 (m, 2 H, $^{\gamma}CH$), 1.72−1.81 (m, 2 H, $^{\beta}CH_2$), 2.02−2.11 (m, 2 H, $^{\beta}CH_2$), 3.68 and 3.70 (s, 3 H, OCH_3), 3.37−3.82 (m, 2 H, CH_2 from all), 3.98−4.35 (m, 2 H, CH_2 from all), 4.57, 4.93, 4.99−5.02 and 5.15−5.16 (m, 2 H, $^{\alpha}CH$), 5.79−5.80 and 5.89 (m, 2 H, =CH). − ^{13}C NMR ($CDCl_3$): δ = 22.0, 22.4, 22.6, 22.9, 23.3, 24.7 and 24.9 ($^{\gamma}CH$ and $^{\delta}CH_3$), 28.3 and 28.5 (CH_3 from Boc), 38.8, 41.0, 41.8, 42.4, 43.8 and 44.2 (CH_2), 52.2 (OCH_3), 56.9, 57.3 and 58.1 ($^{\alpha}CH$), 80.3 and 81.1 (C from Boc), 126.1, 126.4, 132.7 and 133.9 (=CH), 154.2 and 154.9 (CO from Boc), 171.6 and 172.0 (CO). − MS (FAB); *m/z*: 821 $[2 M + H]^+$, 721 $[2 M - Boc + H]^+$, 433 $[M + Na]^+$, 411 $[M + H]^+$, 379 $[M - OMe + H])^+$, 355 $[M - tBu + H]^+$, 311 $[M - Boc + H]^+$.

Fmoc-(*N*all)Gly-OH Required for the Preparation of 5: To a solution of H-(*N*all)Gly-OEt (10.1 mmol, 1.44 g) in dioxane (35 mL), were added MeOH (12.5 mL) and NaOH (4 N, 2.5 mL). Stirring was continued for 45 min. The pH was adjusted to ca. 9.5 with 2 N HCl, and FmocOSu[10] (9.53 mmol, 3.21 g) was added. The pH was maintained at 8.5−9.0 with 1 N NaOH. After stirring for 16 h, the reaction mixture was washed with Et_2O (2 × 50 mL). The pH of the aqueous layer was adjusted to 2−3 with 1 N $KHSO_4$. The aqueous layer was extracted with EtOAc (3 × 75 mL) and the combined organic layers were washed with brine, dried (Na_2SO_4) and concentrated in vacuo. Crystallization (hexanes/Et_2O) gave Fmoc-

(*N*all)Gly-OH (8.79 mmol, 3.21 g) as a white solid in 93% yield. − ^{1}H NMR ($CDCl_3$): δ = 3.86 and 4.05 (s, 2 H, CH_2 from Gly), 3.95−4.00 (m, 2 H, CH_2 from all), 4.21−4.30 (m, 1 H, CH from Fmoc), 4.49 (d, 2 H, *J* = 6.6 Hz, CH_2, from Fmoc) 5.11−5.20 (m, 2 H, =CH_2), 5.67−5.76 (m, 1 H, =CH), 7.27−7.43 (m, 4 H, ArH), 7.52−7.60 (m, 2 H, ArH), 7.75 (t, 2 H, *J* = 8.4 Hz, CH Ar). − ^{13}C NMR ($CDCl_3$):δ = 45.9 and 46.8 (CH_2 from all), 46.2 (CH from Fmoc), 49.5 and 49.8 (CH_2 from Gly), 66.7 and 67.0 (CH_2 from Fmoc), 116.9 and 117.4 (=CH_2), 119.0, 123.8, 124.0, 126.1 and 126.8 (CH from Ar), 131.7 and 131.9 (=CH), 140.4 and 142.8 (C from Ar), 154.8 and 155.5 (CO from Fmoc), 170.3, 173.5 and 173.6 (CO). − MS (FAB); *m*/*z*: 697 [2 M + Na]$^+$, 675 [2 M + H]$^+$, 360 [M + Na]$^+$, 338 [M + H]$^+$.

RCM on Tentagel 5a: Fmoc-(*N*all)Gly-OH was coupled to Tenta-Gel-OH® according to the method of Sieber.[24] The Fmoc group was removed from Fmoc-(*N*all)Gly-*O*-Tentagel (0.17 mmol, 0.60 g) by treatment with 20% piperidine in NMP for 30 min, followed by washing with NMP (3 ×) and DCM (3 ×). The resulting secondary amine was coupled to Boc-(*N*all)Gly-OH (0.49 mmol, 0.11 g), using PyBroP (0.50 mmol, 0.23 mg) and DiPEA (1.0 mmol, 0.18 mL) in NMP for 1 h. This was followed by washing with NMP (3 ×) and DCM (6 ×). Toluene or TCE (15 mL) was added to the resin and purged with nitrogen for 15 min, followed by the addition of Grubbs catalyst **3** (19 μmol, 16 mg) and heating at reflux for 16 h under nitrogen. The solvent was removed and the resin was washed with DCM (5 ×). Treatment of the resin with a catalytic amount of NaCN in EtOH for 16 h afforded crude **4a**. Column chromatography (eluent: hexanes/EtOAc, 1:1, v/v) afforded **4a** (59 μmol, 18 mg) as a brownish oil in 36% yield and **7a** (59 μmol, 20 mg) as a brownish oil in 36% yield.

RCM on Argogel 5b: The procedure was identical to RCM on Tentagel. In contrast, column chromatography (eluent: hexanes/EtOAc, 1:1, v/v) gave a mixture of **4a** and **6** [93 μmol, 28 mg, 9:5 ratio (based on olefinic signals in ^{1}H NMR spectrum)] as a brownish oil in 56% yield and **6a** (67 μmol, 22 mg) as a brownish oil in 40% yield.

Dimers 6: MS (FAB); *m*/*z*: 647 [M + Na]$^+$, 625 [M + H]$^+$, 525 [M − Boc + H]$^+$, 425 [M −2 Boc + H]$^+$.

Cyclic Peptide 4a as Its Corresponding *i*Pr Ester: Preparation as described in the typical procedure for RCM but with addition of $Ti(OiPr)_4$ (100 mol-% based on peptide). Column chromatography (eluent: hexanes/EtOAc, 1:1, v/v) afforded **4a** as its corresponding *i*Pr ester (0.22 mmol, 72 mg) as a brownish oil in 88% yield. − R_f = 0.40 (eluent: hexanes/EtOAc, 1:1, v/v). − ^{1}H NMR ($CDCl_3$): δ = 1.24 (dd, 6 H, *J* = 6.2 Hz and *J* = 2.2 Hz, CH_3 from O*i*Pr), 1.43 and 1.45 (s, 9 H, CH_3 from Boc), 3.90−4.36 (m, 8 H, CH_2 from all and Gly), 5.00−5.05 (m, 1 H, CH from O*i*Pr), 5.84−5.88 (m, 2 H, =CH). − ^{13}C NMR ($CDCl_3$): δ = 18.1 (CH_3 from O*i*Pr), 24.6 (CH_3 from Boc), 41.4 and 41.6 (CH_2 from all), 42.6 and 42.8 (CH_2 from all), 47.0 and 47.6 (CH_2 from ^{2}Gly), 48.5, 48.9 (CH_2 from ^{1}Gly), 65.3 (CH from O*i*Pr), 77.1, 77.6 (C from Boc), 121.6, 121.7, 128.2, 129.9 (=CH), 151.3 (CO from Boc), 165.1, 166.6 (CO). − MS (FAB); *m*/*z*: 675.4 [2 M + Na]$^+$, 653.5 [2 M + H]$^+$, 553.3 [2 M − Boc + H]$^+$, 349.2 [M + Na]$^+$, 327.2 [M + H]$^+$, 271.1 [M − *t*Bu + H]$^+$.

Ac-(*N*hal)Gly-(*N*all)Gly−Phe-OMe (8a): Fmoc−Phe-OH was coupled to ArgoGel-OH® according to the method of Sieber.[24] The Fmoc group was removed from Fmoc−Phe-*O*-Argogel (0.21 mmol, 1.0 g) by treatment with 20% piperidine in DMF for 30 min, followed by washing with DMF (3 ×) and DCM (3 ×). The amine was treated with Fmoc-Gly-OH (1.0 mmol, 0.30 g), BOP (1.0 mmol, 0.44 mg), collidine (2.5 mmol, 0.33 mL) in DMF for 1 h, followed by washing with DMF (3 ×) and DCM (3 ×). Next, the Fmoc group was removed by treatment with 20% piperidine in DMF for 30 min, followed by washing with DMF (3 ×) and DCM (3 ×). The liberated amine was sulfonated with *o*-NBS−Cl (1.25 mmol, 028 g) in the presence of collidine (2.5 mmol, 0.33 mL) in DCE for 2 h. This was followed by washing with DCM (6 ×). Mitsunobu reaction of the sulfonamide was carried out using PPh_3 (1.25 mmol, 0.33 mg), allyl alcohol (2.5 mmol, 0.17 mL), DiAD (1.25 mmol, 0.25 mL) in DCE for 30 min, followed by washing with DCM (3 ×) and repeated washing with DMF (6 ×). The *o*-NBS group was removed using DBU (1.25 mmol, 0.19 mL) in 2-thioethanol/DMF (0.50 M) for 30 min, followed by washing with DMF (6 ×), and DCM (3 ×). The resulting secondary amine was now treated with Fmoc-Gly-OH (1.0 mmol, 0.30 g), HATU (1.0 mmol, 0.38 g), collidine (2.5 mmol, 0.33 mL) in DMF for 1 h. the coupling was followed by washings with DMF (3 ×) and DCM (3 ×). Subsequent removal of the Fmoc group, introduction of the *o*NBS group, Mitsunobu reaction and removal of the *o*-NBS group was carried out as described above. Finally, the secondary amine was acetylated with AcCl (1.25 mmol, 89 μL), collidine (2.5 mmol, 0.33 mL) in DCE for 30 min, followed by washing with DCM (6 ×). Treatment of the resin with a catalytic amount of NaCN in MeOH for 16 h gave the crude **8a**. Column chromatography (eluent: gradient 2.5% MeOH/DCM to 5% MeOH/DCM v/v) afforded **8a** (119 μmol, 51 mg) as a colorless oil in 48% yield. R_f = 0.51 (eluent: 10% MeOH/DCM, v/v). − ^{1}H NMR ($CDCl_3$): δ = 2.10, 2.12 and 2.16 (3 s, 3 H, CH_3 from Ac), 2.30−2.37 (m, 2 H, $^{\beta}CH_2$ from hal), 2.99−3.19 (m, 2 H, CH_2 from Phe), 3.45 (t, 2 H, *J* = 7.3 Hz, $^{\alpha}CH_2$ from hal), 3.67 and 3.71 (2 s, 3 H, OCH_3), 3.59−4.15 (m, 6 H, CH_2 from Gly and all), 4.73−4.80 (m, 1 H, CH from Phe), 4.97−5.27 (m, 4 H, =CH_2), 5.50−5.84 (m, 2 H, =CH), 7.05−7.57 (m, 6 H, ArH and NH). − ^{13}C NMR ($CDCl_3$): δ = 21.0 and 21.5 (CH_3 from Ac), 32.0, 32.9, 36.8, 37.4, 37.6, 46.8, 47.0, 47.6, 49.4, 49.9, 50.0, 50.2, 50.3, 50.5 and 51.0 (CH_2), 52.2, 52.3, 53.1, 53.3 and 53.6 (CH and OCH_3), 116.5, 117.3, 117.5, 117.6 and 118.8 (=CH_2), 126.8, 127.1, 128.4, 128.5, 128.5, 129.1 and 129.2 (CH from Ar), 131.6, 131.8, 131.9, 134.2, 134.3 and 135.4 (=CH), 136.4 and 136.5 (C from Ar), 168.2, 168.4, 168.9, 169.7, 170.9, 171.3 171.7 and 171.8 (CO). − MS (ESI) *m*/*z*: 452 [M + Na]$^+$.

Cyclic Peptide 9a: Preparation according to the general RCM procedure. Column chromatography (eluent: gradient 2.5% MeOH/DCM to 10% MeOH/DCM v/v) afforded **9a** (30 μmol, 12 mg) as a brownish oil in 25% yield. − R_f = 0.42 (eluent: 10% MeOH/DCM, v/v). − Prep. HPLC afforded pure **9a** with a recovery of 93%. − ^{1}H NMR ($CDCl_3$): δ = 2.16 (s, 3 H, CH_3 from Ac), 2.17−2.48 (m, 2 H, $^{\beta}CH_2$ from hal), 3.03−3.24 (m, 2 H, CH_2 from Phe), 3.38−4.21 (m, 8 H, $^{\alpha}CH_2$ from hal, CH_2 from Gly and all), 3.70 (s, 3 H, OCH_3), 4.75−4.82 (m, 1 H, CH from Phe), 5.53−5.61 (m, 1 H, =CH from all), 5.81−5.87 (m, 1 H, =CH from hal), 7.17−7.33 (m, 6 H, ArH and NH). − ^{13}C NMR ($CDCl_3$): δ = 21.5 (CH_3 from Ac), 25.2, 29.7, 37.6, 47.8, 48.8 and 52.9 (CH_2), 52.3 and 53.4 (CH and OCH_3), 127.0, 127.9, 128.0, 128.5 and 129.2 (CH from Ar and =CH), 136.4 (C from Ar), 168.6, 170.3, 171.6 and 172.1(CO). − MS (ESI); *m*/*z*: 440 [M + K]$^+$, 424 [M + Na]$^+$.

Compound **8b** was prepared from H-(*N*hal)Gly-OEt and Boc-(*N*hal)Leu-OMe. Both compounds were prepared starting from *p*NBS-Gly-OMe

***p*NBS-Gly-OMe:** To a solution of HCl·H-Gly-OMe (10 mmol, 1.3 g) and *p*-NBS−Cl (11 mmol, 2.5 g) in dry DCM (50 mL) was added TEA (36 mmol, 5.0 mL). After stirring for 16 h, the organic layer was washed with HCl (2 N, 3 × 25 mL), $NaHCO_3$ (1 N, 3 ×

25 mL) and brine (25 mL), dried (Na_2SO_4) and concentrated in vacuo. Crystallization from DCM/hexanes afforded *p*-NBS-Gly-OMe (5.01 mmol, 1.37 g) as a yellow solid in 50% yield. − R_f = 0.59 (eluent: Et_2O). − ^1H NMR ($CDCl_3$): δ = 3.68 (s, 3 H, OCH_3), 3.89 (d, 2 H, *J* = 5.5 Hz, CH_2), 5.29 and 5.30 (m, 1 H, NH), 8.06−8.09 (m, 2 H, ArH), 8.35−8.39 (m, 2 H, ArH). − ^{13}C NMR ($CDCl_3$): δ = 43.0 (CH_2), 51.8 (OCH_3), 123.4, 126.9 and 127.5 (CH from Ar), 144.4 and 149.3 (C from Ar) 168.0 (CO).

***p*NBS-(*N*hal)Gly-OMe:** To a solution of *p*-NBS-Gly-OMe (4.50 mmol, 1.23 g), 3-buten-1-ol (5.9 mmol, 0.50 mL) and PPh_3 (5.8 mmol, 1.5 g) in dry DCM (25 mL), DEAD (5.9 mmol, 0.92 mL) was slowly added. After stirring for 1 h, the reaction mixture was concentrated in vacuo. Column chromatography (eluent: hexanes/EtOAc, 4:1, v/v) afforded *p*-NBS-(*N*hal)Gly-OMe (3.23 mmol, 1.06 g) as a white solid in 72% yield. − R_f = 0.47 (eluent: hexanes/EtOAc, 2:1, v/v). − ^1H NMR ($CDCl_3$): δ = 2.19−2.26 (m, 2 H, $^{\alpha}CH_2$ from hal), 3.25 (t, 2 H, *J* = 7.4 Hz, $^{\beta}CH_2$ from hal), 3.51 (s, 3 H, OCH_3), 4.06 (s, 2 H, CH_2 from Gly), 4.89−5.00 (m, 2 H, =CH_2), 5.52−5.72 (m, 1 H, =CH), 7.91−7.96 (m, 2 H, ArH), 8.21−8.26 (m, 2 H, ArH). − ^{13}C NMR ($CDCl_3$): δ = 31.3 ($^{\beta}CH_2$ from hal), 46.7 and 46.8 (CH_2), 51.2 (OCH_3), 116.5 (=CH_2), 123.1 and 127.6 (CH from Ar), 133.0 (=CH), 144.5 and 148.9 (C from Ar) 168.0 (CO).

HCl·H-(*N*hal)Gly-OMe: To a solution of *p*NBS-(*N*hal)Gly-OMe (3.2 mmol, 1.1 g) and K_2CO_3 (9.7 mmol, 1.3 g) in dry DMF (10 mL) was added PhSH (4.4 mmol, 0.45 mL). After stirring for 16 h, the reaction mixture was poured into water (20 mL) and the aqueous layer was extracted with Et_2O (3 × 25 mL). The combined organic layers were washed with $NaHCO_3$ (1 N, 3 × 15 mL) and brine, dried (Na_2SO_4) and concentrated in vacuo. The crude product was redissolved in Et_2O and HCl in Et_2O (6 N, 5 mL) was added. After stirring for 15 min, the reaction mixture was concentrated in vacuo. Crystallization from MeOH/Et_2O afforded HCl·H-(*N*hal)Gly-OMe (1.38 mmol, 229 mg) as an off-white solid in 43% yield. − ^1H NMR (D_2O): δ = 2.53−2.60 (m, 2 H, $^{\alpha}CH_2$ from hal), 3.29 (t, 2 H, *J* = 7.0 Hz, $^{\beta}CH_2$ from hal), 3.89 (s, 3 H, OCH_3), 4.09 (s, 2 H, CH_2 from Gly), 5.27−5.35 (m, 2 H, =CH_2), 5.81−5.92 (m, 1 H, =CH). − ^{13}C NMR (D_2O): δ = 29.0 ($^{\beta}CH_2$ from hal), 46.0 and 46.4 (CH_2), 52.7 (OCH_3), 118.3 (=CH_2), 131.9 (=CH), 166.9 (CO).

Boc-(*N*hal)Gly-OH: To a solution of HCl·H-*N*hal-OMe (0.74 mmol, 0.12 g) and Boc_2O (1.0 mmol, 0.22 g) in dioxane (6 mL) was added TEA (1.5 mmol, 0.21 mL). The reaction mixture was stirred for 16 h at room temperature. MeOH (2 mL) and NaOH (4 N, 1.6 mmol, 0.4 mL) were then added and after stirring for 3 h, the reaction mixture was poured into water (10 mL). The aqueous layer was washed with Et_2O (2 × 25 mL) followed by acidification with 1 N $KHSO_4$ and finally extraction with EtOAc (3 × 25 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), concentrated in vacuo and Boc-(*N*hal)Gly-OH (0.35 mmol, 80 mg) was obtained as a colorless oil in 47% yield. − ^1H NMR ($CDCl_3$): δ = 1.41 and 1.46 (s, 9 H, CH_3 from Boc), 2.24−2.30 (m, 2 H, $^{\beta}CH_2$ from hal), 3.28−3.37 (m, 2 H, $^{\alpha}CH_2$ from hal), 3.90 and 3.98 (s, 2 H, CH_2 from Gly), 5.00−5.09 (m, 2 H, =CH_2), 5.71−5.79 (m, 1 H, =CH), 9.31 (m, 1 H, CO_2 H).

Boc-(*N*hal)Gly-(*N*hal)Gly-OMe (8b): To a solution of HCl·H-(*N*hal)Gly-OMe (0.65 mmol, 0.11 g), Boc-(*N*hal)Gly-OH (0.35 mmol, 80 mg) and PyBroP (0.36 mmol, 0.17 g) in dry DCM (6 mL) was added DiPEA (1.4 mmol, 0.24 mL). After stirring for 16 h, the reaction mixture was washed with $NaHCO_3$ (1 N, 3 × 10 mL), brine (10 mL), dried (Na_2SO_4) and concentrated in vacuo. Column chromatography of the residue (eluent: gradient of hexanes/EtOAc, 4:1 to hexanes/EtOAc, 2:1, v/v) afforded **8b** (0.20 mmol, 69 mg) as a colorless oil in 58% yield. − R_f = 0.07 (eluent: hexanes/EtOAc, 4:1, v/v). − ^1H NMR ($CDCl_3$): δ = 1.44 and 1.47 (s, 9 H, CH_3 from Boc), 2.28−2.38 (m, 4 H, $^{\beta}CH_2$ from hal), 3.31−3.43 (m, 4 H, $^{\alpha}CH_2$ from hal), 3.72 and 3.77 (s, 3 H, OCH_3), 3.99−4.15 (m, 4 H, CH_2 from Gly), 5.00−5.16 (m, 4 H, =CH_2), 5.74−5.83 (m, 1 H, =CH). − ^{13}C NMR ($CDCl_3$): δ = 28.2 (CH_3 from Boc), 31.7, 32.4 and 32.7 ($^{\beta}CH_2$ from hal), 47.2, 47.4, 47.7, 47.8, 48.0, 48.7 and 49.3 (CH_2), 51.9 and 52.3 (OCH_3), 79.8 and 79.9 (C from Boc), 116.3, 116.7, 117.7 and 117.8 (=CH_2), 133.9, 134.9 and 135.5 (=CH), 155.7 (CO from Boc), 169.2 and 169.5 (CO). − MS (ESI); *m*/*z*: 377 $[M + Na]^+$.

Cyclic Peptide 9b: Preparation according to the general RCM procedure. Column chromatography (eluent: gradient hexanes/EtOAc, 1:1 to EtOAc, v/v) afforded **9b** (58.3 μmol, 19 mg) as a brownish oil in 33% yield. − R_f = 0.19 (eluent: hexanes/EtOAc, 1:1, v/v). Purity according to HPLC is 94%. − MS (FAB); *m*/*z*: 675 [2 M + Na]$^+$, 653 [2 M + H]$^+$, 349 [M + Na]$^+$, 327 [M + H]$^+$, 271 [M − *t*Bu + H]$^+$, 227 [M − Boc + H]$^+$.

Ac-(*N*pen)Gly-(*N*pen)Gly-Phe-OMe (8c): Preparation as described in the procedure for **8a**. Column chromatography (eluent: gradient 2.5% MeOH/DCM to 5% MeOH/DCM v/v) afforded **8a** (149 μmol, 70 mg) as a colorless oil in 59% yield. − R_f = 0.52 (eluent: 10% MeOH/DCM, v/v). − ^1H NMR ($CDCl_3$): δ = 1.42−1.75 (m, 4 H, $^{\gamma}CH_2$ from pen), 1.87−2.18 (m, 4 H, $^{\beta}CH_2$ from pen), 2.09 and 2.10 (s, 3 H, CH_3 from Ac), 2.96−3.40 (m, 6 H, CH_2 from Phe and $^{\alpha}CH_2$ from pen), 3.62−4.05 (m, 4 H, CH_2 from Gly), 3.66 and 3.70 (s, 3 H, OCH_3), 4.71−4.78 (m, 1 H, CH from Phe), 4.90−5.07 (m, 4 H, =CH_2), 5.64−5.83 (m, 2 H, =CH), 7.07−7.75 (m, 6 H, ArH and NH). − ^{13}C NMR ($CDCl_3$): δ = 20.9 (CH_3 from Ac), 26.0, 27.6, 30.5, 30.6, 30.9, 36.6, 37.4, 46.9, 47.2, 47.6, 48.5, 50.0, 50.1, 50.4 and 51.2 (CH_2), 52.1, 52.3, 53.4 and 53.7 (CH and OCH_3), 115.1, 115.6, 115.7 and 115.8 (=CH_2), 126.7, 126.8, 128.3, 128.4, 128.5, 129.0, 129.2 and 129.3 (CH from Ar), 136.5 and 136.6 (C from Ar), 136.8, 137.1 and 137.4 (=CH), 168.3, 168.4, 168.6, 169.3, 170.9, 171.2, 171.7 and 171.8 (CO). − MS (ESI); *m*/*z*: 494 $[M + Na]^+$.

Cyclic Peptide 9c: Preparation according to the general RCM procedure. Column chromatography (eluent: gradient 2.5% MeOH/DCM to 10% MeOH/DCM v/v) afforded **9c** (81 mg) as an impure brownish oil. − R_f = 0.33 (eluent: 10% MeOH/DCM, v/v). Prep. HPLC afforded pure **9c** in a overall yield of 24%. − ^1H NMR ($CDCl_3$): δ = 1.73 (br. m, 4 H, $^{\gamma}CH_2$ from pen), 2.01−2.20 (m, 4 H, $^{\beta}CH_2$ from pen), 2.17, 2.18 and 2.20 (s, 3 H, CH_3 from Ac), 2.95−3.48 (m, 6 H, CH_2 from Phe and $^{\alpha}CH_2$ from pen), 3.69, 3.70 and 3.73 (s, 3 H, OCH_3), 3.71−4.71 (m, 4 H, CH_2 from Gly), 4.80−4.82 (m, 1 H, CH from Phe), 5.28−5.48 (m, 2 H, =CH), 7.03−7.33 (m, 6 H, ArH and NH). − MS (ESI); *m*/*z*: 466 $[M + Na]^+$, 444 $[M + H]^+$.

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[10] Abbreviations used: (*N*all)Aaa: *N*-allyl amino acid; (*N*hal)Aaa: *N*-homoallyl amino acid; (*N*pen)Aaa: *N*-4-pentenyl amino acid; DCE: 1,2-dichloroethane; TCE: 1,1,2-trichloroethane; DCM: dichloromethane; PyBroP, bromotripyrrolidinophosphonium hexafluorophosphate; TFFH: tetramethylfluoroformamidinium hexafluorophosphate; BOP: (1*H*-benzotriazol-1-yloxy)tris(dimethyl)phosphonium hexafluorophosphate; HATU: *O*-(7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate; DiPEA: *N*,*N*-diisopropylethylamine; TEA: triethylamine; NMP:1-methyl-2-pyrrolidinone; DEAD: diethylazodicarboxylate; DiAD: diisopropylazodicarboxylate; FmocOSu: *N*-9-fluorenylmethoxycarbonyloxy)succinimide.

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