Synthesis of Cyclic Peptides by Ring-Closing Metathesis

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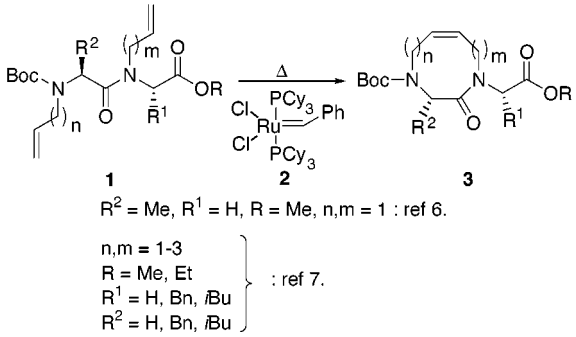
Received May 18, 2000

The synthesis of a series of "amide to amide" cyclized peptides by ring-closing metathesis (RCM) as well as a convenient synthesis for the linear precursors is described. In addition, the influence of the length of the alkene substituents and the influence of the peptide sequence is investigated, leading to a set of general rules to obtain "amide to amide" cyclized peptides by RCM.

Introduction

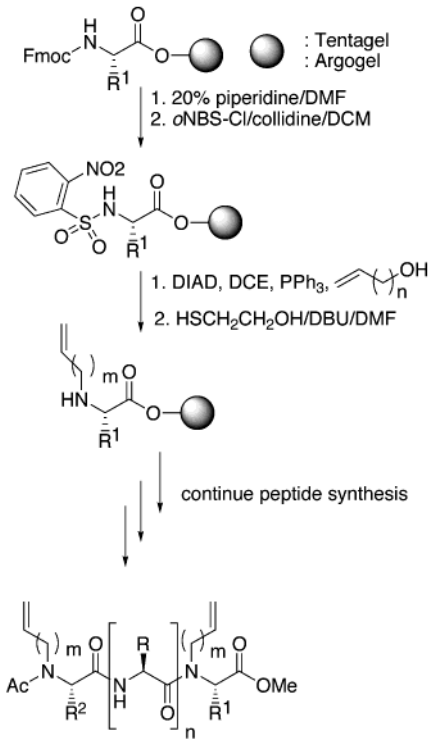
Cyclization of peptides is an appropriate way to reduce the flexibility of a peptide and—among others—to increase the affinity toward a receptor.[1] Methods for cyclization can be divided into cyclizations involving C and N termini,[2] the so-called "backbone to backbone" cyclization,[3] and methods involving the side chains of individual amino acids.[2] Examples of the latter method include the formation of disulfide bridges between cysteine residues and the formation of lactam bridges between glutamic/aspartic acid and lysine residues.

Scheme 1



In our approach denoted 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 by RCM were reported[5] but so far only one cyclic peptide **3** involving *N*-substituted amino acids was prepared from **1** using Grubbs ruthenium catalyst **2** (Scheme 1).[6] Recently, we

Scheme 2



synthesized a number of cyclic dipeptides derived from the cyclization of amide substituents in bis-*N*-alkylated dipeptides[7] (Scheme 1) as well as a number of cyclic Leu-Enkephalin derivatives originating from the cyclization of bis amide substituted peptides in a rolling loop scan.[8]

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(1) See e.g. Adang, A. E. P.; Hermkens, P. H. H.; Linders, J. T. M.; Ottenheijm, H. C. J.; van Staveren, C. J. *Recl. Trav. Chim. Pays-Bas* **1994**, *113*, 63−78.

(2) See, for example, Hruby, V. J.; Al-Obeidi, F.; Kazmierski, W. *Biochem. J.* **1990**, *268*, 249−262.

(3) See, for example, Gilon, C.; Halle, D.; Chorev, M.; Selinger, Z.; Byk, G. *Biopolymers* **1991**, *31*, 745−750.

(4) For recent reviews, see Grubbs, R. H.; Miller, S. J.; Fu, G. C. *Acc. Chem. Res.* **1995**, *28*, 446−452. Schmalz, H.-G. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 1833−1836. Schuster, M.; Blechert, S. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2036−2056. Grubbs, R. H.; Chang, S. *Tetrahedron* **1998**, *54*, 4413−4450. Armstrong, S. K. *J. Chem. Soc., Perkin Trans. 1* **1998**, 371−388.

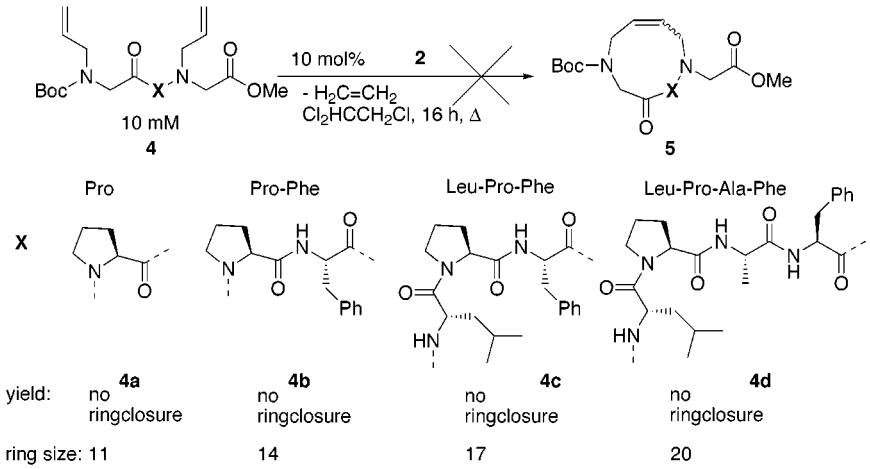
(5) Piscopio, A. D.; Miller, J. F.; Koch, K. *Tetrahedron Lett.* **1998**, *39*, 2667−2670. Piscopio, A. D.; Miller, J. F.; Koch, K. *Tetrahedron Lett.* **1997**, *38*, 7143−7146. Piscopio, A. D.; Miller, J. F.; Koch, K. *Tetrahedron* **1999**, *55*, 8189−8198. Jarvo, E. R.; Copeland, G. T.; Papaioannou, N.; Bonitatebus, P. J., Jr.; Miller, S. J. *J. Am. Chem. Soc.* **1999**, *121*, 11638−11643. Pernerstorfer, J.; Schuster, M.; Blechert, S. *Chem. Commun.* **1997**, 1949−1950. Fink, B. E.; Kym, P. R.; Katzenellenbogen, J. A. *J. Am. Chem. Soc.* **1998**, *120*, 4334−4344. Ripka, A. S.; Bohacek, R. S.; Rich, D. H. *Bioorg., & Med. Chem. Lett.* **1998**, *8*, 357−360. Grubbs, R. H.; Blackwell H. E. *Angew. Chem., Int. Engl.* **1998**, *37*, 3281−3284. Clark, T. D.; Ghadiri, M. R. *J. Am. Chem. Soc.* **1995**, *117*, 12364−12365.

(6) Miller, S. J.; Blackwell, H. E.; Grubbs, R. H. *J. Am. Chem. Soc.* **1996**, *118*, 9606−9614. Miller, S. J.; Grubbs, R. H. *J. Am. Chem. Soc.* **1995**, *117*, 5855−5856.

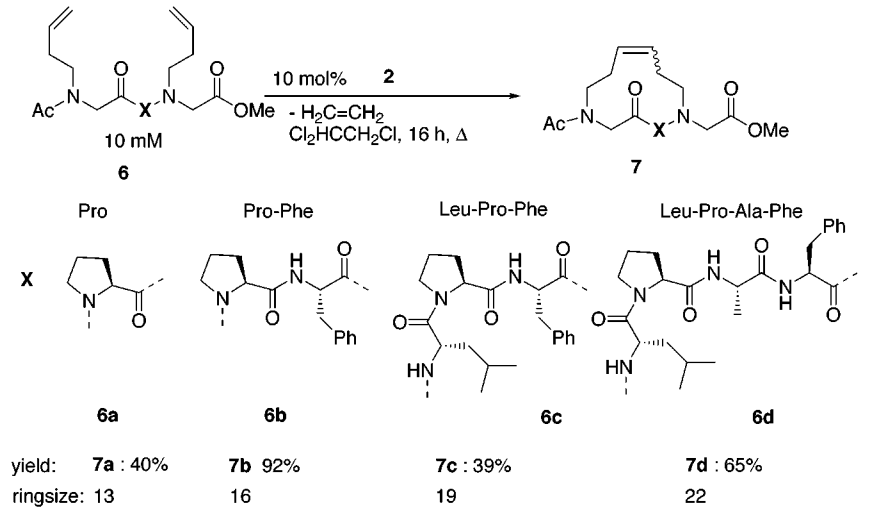
(7) Reichwein, J. F.; Liskamp, R. M. J. *Eur. J. Org. Chem.* **2000**, *65*, 2335−2344.

10.1021/jo000759t CCC: $19.00
Published on Web 08/25/2000

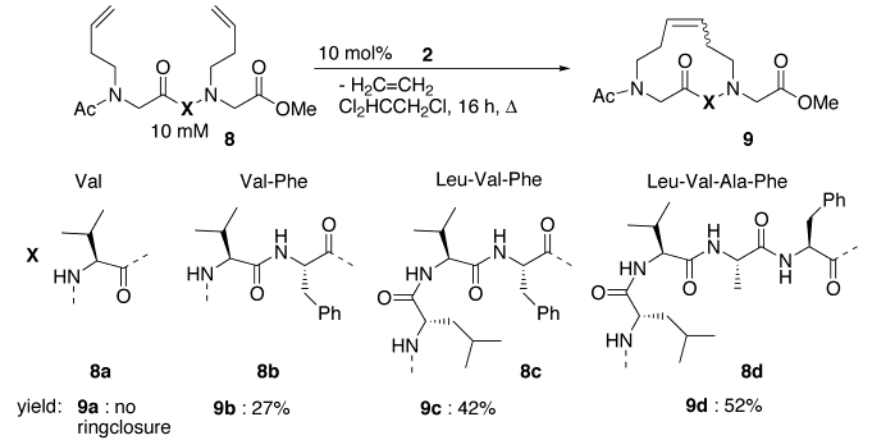
Scheme 3



Scheme 4



Scheme 5



We were interested to investigate the preparation of larger cyclic peptides. One of the restrictions found so far was the synthesis of the appropriate starting building blocks (*N*-substituted amino acids) for synthesis of bis-*N*-alkene peptides. The previously required relatively simple bis-*N*-alkylated dipeptides were prepared by different methods. However, a few peptides were prepared according to our earlier method for site-specific alkylation,[9] which enabled the introduction of a substituent onto every desired peptide bond nitrogen.

In this procedure the Fmoc group of the first amino acid was removed and replaced by an *o*-nitrobenzene sulfonyl (*o*NBS) group, which increases the acidity of the N−H proton enough for a Mitsunobu reaction using an

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(9) Reichwein, J. F.; Liskamp, R. M. J. *Tetrahedron Lett.* **1998**, *39*, 1243−1246.

appropriate unsaturated alcohol for introduction of the alkene substituent. After removal of the *o*NBS group by application of a thiolate, peptide synthesis was continued until the site for introduction of the required second alkene side chain was reached, which was carried out as just described. All cyclization precursors used for these studies could be prepared according to this general and versatile protocol (Scheme 2).[9] RCM was carried out after cleavage of the bis-*N*-alkylated peptides from the resin, leading to the cyclized peptide.[10]

Results and Discussion

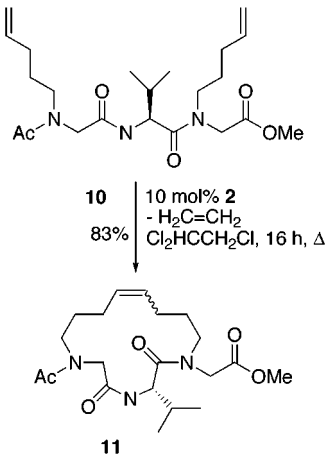
Tri- up to hexapeptides containing *N*-allyl substituents **4a**−**d** both on the first and last amide bond were prepared. A proline residue was incorporated in order to favor ring closure by facilitating rotation (of the peptide bond) within the peptide backbone. Unfortunately, all attempts to cyclize these compounds using the Grubbs ruthenium catalyst **2** failed (Scheme 3). Despite the presence of a proline residue, it is likely that these peptides cannot adopt the proper conformation for ring-closure. The only products obtained were either isomers, in which the double bond had migrated one carbon atom,[11] or dimers.

Increasing the distance between the *N*-allyl groups by the introduction of even more amino acids between them did not lead to any ring-closure product by RCM. The only parameter which still could be varied was the length of the alkenyl substituent. For this purpose one carbon atom homologation to a homoallyl group was chosen and synthesized. Remarkably, after subjection to RCM conditions the corresponding peptides **6a**−**d** all underwent ring closure in moderate to very good yields affording **7a**−**d** (Scheme 4). Apparently, the length of the alkene chain has a tremendous effect on formation of the ring, which cannot be fully explained by the increased ring size (compare Schemes 3 and 4). However, the increase in length will allow the existence of more conformations that have the proper geometry for ring closure. The ^{1}H and ^{13}C NMR spectra showed the presence of many (seven for **7d**) conformers which originated from mixtures of *E* and *Z* isomers and from rotations around the tertiary amide bonds.

Thus, it seemed that the length of the alkene substituents was crucial for ring closure. Therefore, at this point it was important to investigate if the originally introduced proline was still required for cyclization to occur. To study this, proline was replaced by valine. It was suspected that this change in the backbone would have a significant effect on the ring-closure results. The number of rotamers is reduced as is clear from the ^{1}H and ^{13}C NMR spectra which show sharper and more defined signals. The absence of proline is reflected in the lower yields of cyclized peptides **9a**,**b** obtained from the smaller peptides **8a**,**b**. Not quite unexpectedly, the larger peptides **8c**,**d** gave comparable results (Scheme 5) as the corresponding peptides **6c**,**d** containing proline (Scheme 4), showing that in larger sequences proline is no longer required for a "cis" like backbone conformation which is favorable for cyclization.

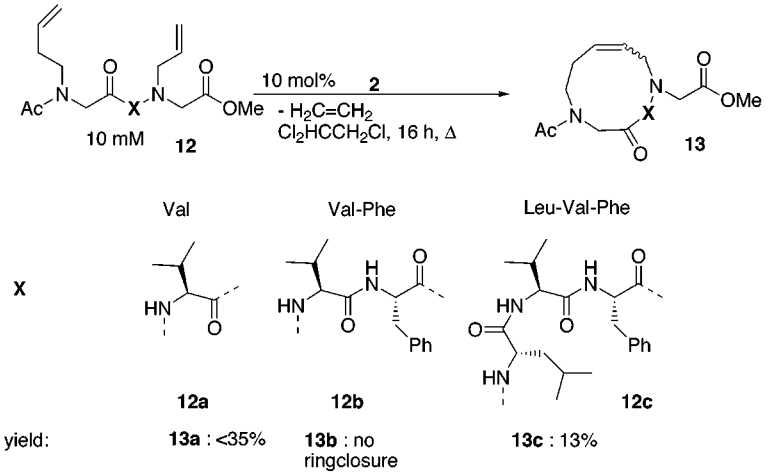
Although tripeptide **8a** could not be cyclized, we were interested in cyclic structures based on tripeptides without a proline residue. We reasoned that the only way this could be achieved is by further elongation of the *N*-alkene substituents. Therefore an analogue of **8a** was synthesized, i.e., **10** containing 4-pentenyl substituents instead of the homoallyl group. This tripeptide **10** was ring-closed to **11** in a very good yield of 83% (Scheme 6). However, ^{1}H and ^{13}C NMR spectra revealed the presence of several conformers.

Scheme 6

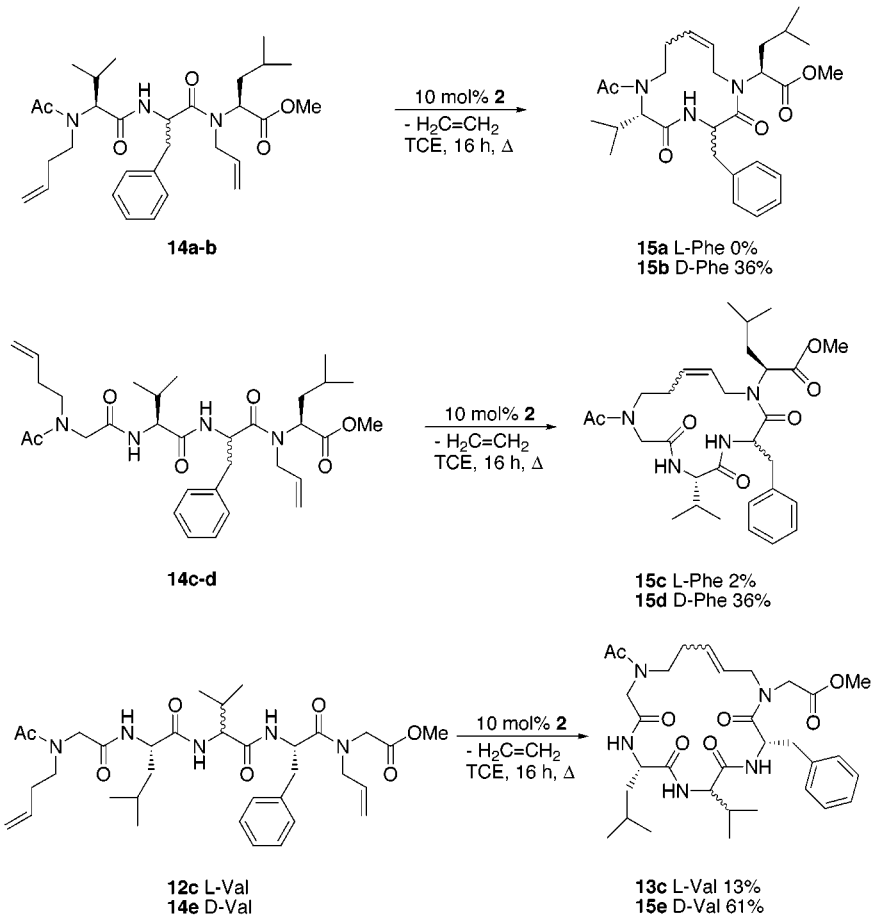


As was clearly demonstrated above, the length of the two alkene substituents was important for the success of the ring closure. So far only peptides were used having two *N*-alkene substituents of equal length, and it was interesting to investigate if also alkene substituents of unequal length could be employed. In addition, peptides con-

Scheme 7



Scheme 8



taining, for example, a homoallyl and an allyl substitu--ent as in **12**, will lead to "identical size mimetics" of head to tail cyclic peptides. Fortunately, peptides **12** could be ring-closed, albeit in low yields, to obtain **13** (Scheme 7).

The role of proline with respect to successfully obtaining cyclic peptides has been discussed above. Another way to preorganize the backbone toward a cyclic structure is the introduction of a D-amino acid which will supposedly induce a β-turn like structure.[12] The presence of D-amino acids, is also an essential requirement for the cyclization of small peptides.[13] The effect of the presence of a D-amino acid was investigated in peptides **14**. These were subjected to RCM using **2** and the all-L peptide barely gave ring closure except for the tetra- and pentapeptide. In contradistinction the peptides containing a D-amino acid all gave the cyclic peptides in moderate to high yields (Scheme 8). It is noteworthy to mention that the cyclic tetrapeptide **15d** consisted of only one conformation according to ^{1}H, ^{13}C, and NOESY NMR spectra. It is possible that the formation of **15c** was accomplished by racemization because this peptide is identical to **15d** as judged by its NMR spectra and retention time on HPLC.

Conclusion

Based on the above-described results, "rules" for cyclization of bis *N*-alkylated peptides by RCM can be inferred (Figure 1). Cyclic dipeptides—involving two amide bonds—can be obtained starting from bis *N*-allyl (or longer) alkene substituents. Cyclic tripeptides—involving three amide bonds—can be obtained starting from bis *N*-4-pentenyl (or longer) alkene substituents. Cyclic tetra-, penta-, and hexapeptides—involving four, five, or six amide bonds, respectively—can be obtained starting from bis *N*-homoallyl (or longer) alkene substituents. Introduction of either a proline residue or one D-amino acid residue as part of the ring increases the yield of the cyclization.

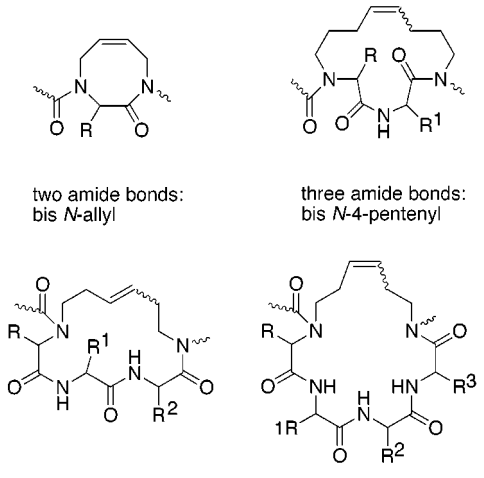


Figure 1.

In conclusion, we have prepared a variety of cyclic peptides employing ring-closing metathesis. The results

(10) Although RCM can be carried out on the solid phase, so far higher yields were obtained if RCM was carried out in solution: see ref 7.

(11) Based on the presence of the ω-CH_3 signals at 1.8 ppm in ^{1}H NMR spectra; see also ref 7.

were used to define a set of rules with respect to the length of the alkene substituents which have to be obeyed for ring closure to take place. We have demonstrated that the length of the alkene substituent has a tremendous influence on the cyclization results. Incorporation of proline-facilitated ring closure probably due to the presence of a "cis" rotamer. A β-turn structure favored by introduction of a D-amino acid residue also led to a large increase of the ring closure yield.

Experimental Section

General. Unless otherwise stated, chemicals were obtained from commercial sources and used without further purification. TEA[14] and DiPEA were distilled subsequently 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 on molecular sieves (4 Å). THF was distilled from $LiAlH_4$. Reactions were run at ambient temperature unless stated otherwise. ^{1}H NMR spectra were also recorded using the COSY sequence. ^{13}C spectra were recorded using the attached proton test (APT) sequence. 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).[15] Solvents were evaporated under reduced pressure at 40 °C. Column chromatography was performed on silica 60. Analytical and preparative HPLC was performed on a automated HPLC system with an auto sampler and a 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, resectively), or a UV detector operating at 254 and 220 nm, at a flow of 1 mL/min (11.5 mL/min 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 a nitrogen atmosphere with dry peptide-grade solvents.

For the synthesis of Fmoc-(*N*all)Gly-OH, see ref 7.

Typical Procedure for RCM. A 10 mM solution of the linear peptide in TCE was purged with nitrogen for 15 min, followed by the addition of 10 mol % of $Cl_2(PCy_3)_2Ru$=CHPh **2** and refluxed for 16 h under a nitrogen atmosphere. After concentrating in vacuo, the crude cyclic peptide was obtained and was purified by column chromatography.

Boc-(*N*all)Gly-Pro-(*N*all)Gly-OMe 4a was prepared as described for **4d** (vide infra). Crude **4a** was purified by chromatography (2.5% MeOH/DCM) and obtained as a colorless oil (0.187 mmol 79 mg) in 75% yield. R_f 0.43 (10% MeOH/DCM). The purity according to HPLC was 98%. ^{1}H NMR ($CDCl_3$): δ 1.40 (s, 9H, CH_3 Boc), 1.94−2.13 (m, 4H, $^\beta CH_2$ and $^\gamma CH_2$ Pro), 3.42−4.28 (m, 9H, CH_2 *N*all, Gly and $^\delta CH_2$ Pro), 3.67 and 3.71 (two s, 3H, OCH_3), 4.43, 4.49, 4.86, and 4.92 (four lines, 1H, CH_2 Gly), 4.51−4.55 and 4.81−4.84 (m, 1H, $^\alpha$CH Pro), 5.05−5.31 (m, 4H, =CH_2), 5.67−5.91 (m, 2H, =CH). ^{13}C NMR ($CDCl_3$): δ 21.9, 24.6, 25.0, 28.7, 29.1, and 31.5 ($^\beta CH_2$ and $^\gamma CH_2$ Pro), 28.1 (CH_3 Boc), 46.3, 46.4, 46.9, 47.2, 47.5, 47.7, 47.9, 48.8, 49.8, 49.9, 50.1, 50.9, and 51.4 (CH_2), 51.9, 52.1, and 52.2 (OCH_3), 56.2, 56.5, and 56.8 ($^\alpha$CH Pro), 79.8 and 80.0 (C Boc), 116.3, 116.4, 117.1, 117.9, and 118.3 (=CH_2), 132.1, 132.3, 132.6, 133.6, and 134.0 (=CH), 155.4 and 155.9 (CO Boc), 167.5, 167.6, 169.4, 169.9, 170.6, 172.6, 172.7, and 173.4 (CO). MS-MS (FAB) *m*/*z*: 869 [2M + Na]$^+$, 847 [2M + H]$^+$, 446 [M + Na]$^+$, 424 [M + H]$^+$, 368 [M − *t*Bu + H]$^+$, 324 [M − Boc + H]$^+$, 227 [(H-Pro-(*N*all)Gly-OMe) + H]$^+$.

Boc-(*N*all)Gly-Pro-Phe-(*N*all)Gly-OMe 4b was prepared as described for **4d** (vide infra). Crude **4b** was purified by chromatography (2.5% MeOH/DCM) and obtained as a colorless oil (0.198 mmol, 113 mg) in 88% yield. R_f 0.53 (10% MeOH/DCM). The purity according to HPLC was 95%. ^{1}H NMR ($CDCl_3$): δ 1.42 (s, 9H, CH_3 Boc), 1.78−2.16 (m, 4H, $^\beta CH_2$ and $^\gamma CH_2$ Pro), 2.86−3.13 (m, 2H, $^\beta CH_2$ Phe), 3.33 (br m, 1H, $^\delta CH_2$ Pro) 3.52−4.15 (m, 9H, CH_2 (*N*all)Gly 8H and $^\delta CH_2$ Pro 1H), 3.68 (s, 3H, OCH_3), 4.48 (br m, 1H, $^\alpha$CH Pro), 4.80−5.12 (m, 5H, =CH_2 and $^\alpha$CH Phe), 5.56−5.82 (m, 2H, =CH), 7.16−7.22 (m, 5H, ArH), 7.35−7.39 (m, 1H, NH). ^{13}C NMR ($CDCl_3$): δ 24.8 and 27.3 ($^\beta CH_2$ and $^\gamma CH_2$ Pro), 38.9 ($^\beta CH_2$ Phe), 46.3, 47.1, 48.0, 50.6 and 51.1 (CH_2), 28.3 (CH_3 Boc), 50.1, 50.4, 52.0, 52.4, and 60.0 ($^\alpha$CH and OCH_3), 80.2 (C Boc), 116.4, 118.2, and 118.5 (=CH_2), 126.7, 128.0.2, 128.5, 129.5, and 129.7 (CH Ar), 132.3 and 134.0 (=CH), 136.6 (C Ar), 155.9 (CO Boc), 168.9, 169.4, 170.5, 170.7, 171.5, and 171.8 (CO). MS-MS (FAB) *m*/*z*: 1163 [2M + Na]$^+$, 1141 [2M + H]$^+$, 593 [M + Na]$^+$, 571 [M + H]$^+$, 471 [M − Boc + H]$^+$, 442 [(Boc-(*N*all)Gly-Pro-Phe) + H]$^+$, 374 [(H-Pro-Phe-(*N*all)Gly-OMe) + H]$^+$, 295 [(Boc-(*N*all)Gly-Pro) + H]$^+$, 277 [(H-Phe-(*N*all)Gly-OMe) + H]$^+$, 130 [(H-(*N*all)Gly-OMe) + H]$^+$.

Boc-(*N*all)Gly-Leu-Pro-Phe-(*N*all)Gly-OMe 4c was prepared as described for **4d** (vide infra). Crude **4c** was purified by chromatography (2.5% MeOH/DCM) and obtained as a colorless oil (0.204 mmol, 140 mg) in 91% yield. R_f 0.60 (10% MeOH/DCM). The purity according to HPLC was 93%. ^{1}H NMR ($CDCl_3$): δ 0.90−0.96 (m, 6H, CH_3 Leu), 1.31−1.49 (m, 2H $^\beta CH_2$ Leu), 1.43 (s, 9H, CH_3 Boc), 1.63−1.66 (m, 1H, $^\gamma$CH Leu), 1.91−2.16 (m, 4H, $^\beta CH_2$ and $^\gamma CH_2$ Pro), 2.86−3.13 (m, 2H, $^\beta CH_2$ Phe), 3.46−3.47 (m, H, $^\delta CH_2$ Pro), 3.60−4.11 (m, 9H, CH_2 (*N*all)Gly 8H and $^\delta CH_2$ Pro 1H), 3.66 and 3.68 (s, 3H, OCH_3), 4.46−4.48 (m, 1H, $^\alpha$CH Pro), 4.78−4.83 (m, 1.25H, $^\alpha$CH Leu and Phe 0.25H), 4.99−5.14 (m, 4.75H, =CH_2 and $^\alpha$CH Phe 0.75 H), 5.46−5.78 (m, 2H, =CH), 6.60 (m, 1H, NH Leu), 7.17−7.27 (m, 6H, ArH and NH Phe). ^{13}C NMR ($CDCl_3$): δ 21.7, 23.4, and 24.7 ($^\gamma$CH and CH_3 Leu), 24.9, 27.7, 27.8, 39.1, 41.9, 47.0, 47.1, 47.9, 49.6, 50.2, and 51.1 CH_2), 28.2 (CH_3 Boc), 48.7, 50.2, 50.6, 52.0, 52.4, 59.8, and 59.9 ($^\alpha$CH and OCH_3), 80.8 (C Boc), 118.3 and 118.5 (=CH_2), 126.9, 126.9, 128.4, 129.4, and 129.6 (CH Ar), 132.1, 132.2 and 133.0 (=CH), 136.2 and 136.4 (C Ar), 155 (CO Boc), 169.2, 169.3, 169.5, 170.4, 170.5, 171.6, 171.8, and 172.1 (CO). MS-MS (FAB) *m*/*z*: 706 [M + Na]$^+$, 684 [M + H]$^+$, 584 [M − Boc + H]$^+$, 374 [(H-Pro-Phe-(*N*all)-Gly-OMe) + H]$^+$, 130 [(H-(*N*all)Gly-OMe) + H]$^+$, 555.3 [(Boc-(*N*all)Gly-Leu-Pro-Phe) + H]$^+$.

Boc-(*N*all)Gly-Leu-Pro-Ala-Phe-(*N*all)Gly-OMe 4d. Fmoc-(*N*all)Gly-OH was coupled to TentaGel-OH according to the method of Sieber.[16] The Fmoc group was removed from Fmoc-(*N*all)Gly-O-TentaGel (0.224 mmol, 995 mg) by treatment with 20% piperidine in NMP for 30 min, followed by washings with NMP (3×) and DCM (3×). The resulting amine was treated with Boc-Phe-OH (0.896 mmol, 237 mg), PyBroP (0.896 mmol, 418 mg), and DiPEA (1.79 mmol, 312 μL) in NMP for 1 h, followed by washings with NMP (3×) and DCM (3×). Removal of the Boc-group was achieved by treatment (twice) with 4 N HCl in Dioxane for 15 min, followed by washings with DCM (6×). The hydrochloride salt was treated with Fmoc-Ala-OH (0.896 mmol, 295 mg), HATU (0.896 mmol, 340 mg), and DiPEA (1.79 mmol, 312 μL) in NMP for 1 h, followed by washings with NMP (3×) and DCM (3×). The Fmoc group was removed by treatment with 20% piperidine in NMP for 30 min, followed by washings with NMP (3×) and DCM (3×). This procedure was repeated for the introduction of the proline, leucine and *N*-allyl-glycine residues. Treatment of the resin with a catalytic amount of NaCN in MeOH for 16 h afforded

(12) See, for example, Kessler, H.; Gratias, R.; Gurrath, M.; Muller. *Pure Appl. Chem.* **1996**, *68*, 1201−1205.

(13) See, for example, Schmidt, U.; Langner, J. *J. Pept. Res.* **1997**, *49*, 67−73.

(14) Abbreviations used: (*N*all)Aaa: *N*-allyl amino acid; all: allyl; (*N*hal)Aaa: *N*-homoallyl amino acid; hal: homo allyl; (*N*pen)Aaa: *N*-4-pentenyl amino acid; pen: 4-pentenyl; DCE: 1,2-dichloroethane; TCE: 1,1,2-trichloroethane; DCM: dichloromethane; DMF: *N*,*N*′-dimethylformamide; PyBroP, bromotripyrrolidinophosphonium hexafluorophosphate; BOP, (1*H*-benzotriazol-1-yloxy)tris(dimethyl)phosphonium hexafluorophosphate; HOAt, 1-hydroxy-7-azabenzotriazole; HATU, *O*-(7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate; TEA: triethylamine; DiPEA: *N*,*N*-diisopropylethylamine: DEAD: diethyl azodicarboxylate; DIAD: diisopropyl azodicarboxylate; NMP: 1-methyl-2-pyrrolidinone.

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(16) Sieber, P. *Tetrahedron Lett.* **1987**, *28*, 6147−6150.

crude **4d**. Column chromatography (gradient: 2.5% MeOH/DCM to 5% MeOH/DCM) afforded **4d** (0.218 mmol, 165 mg) as a colorless oil in 97% yield. R_f 0.61 (10% MeOH/DCM). The purity according to HPLC was 96%. ^{1}H NMR ($CDCl_3$): δ 0.92−0.98 (m, 6H, CH_3 Leu), 1.25−1.28 (m, 3H, CH_3 Ala), 1.46 (s, 9H, CH_3 Boc), 1.46−1.51 (m, 1H, $^{\gamma}$CH Leu), 1.53−1.65 (m, 2H $^{\beta}CH_2$ Leu), 1.87−2.31 (m, 4H, $^{\beta}CH_2$ and $^{\gamma}CH_2$ Pro), 2.92−3.15 (m, 2H, $^{\beta}CH_2$ Phe), 3.51−3.58 (m, 1H, $^{\delta}CH_2$ Pro), 3.65−4.16 (m, 9H, CH_2 (*N*all)Gly 8H and $^{\delta}CH_2$ Pro 1H), 3.71 and 3.72 (s, 3H, OCH_3), 4.30−4.35 (m, 1H, $^{\alpha}$CH Ala), 4.46−4.50 (m, 1H, $^{\alpha}$CH Pro), 4.81−4.86 (m, 1.20H, $^{\alpha}$CH Leu and Phe 0.20H), 5.04−5.18 (m, 4.8H, $=CH_2$ and $^{\alpha}$CH Phe 0.8 H), 5.53−5.79 (m, 2H, =CH), 6.74−6.77 (m, 2H, NH Leu and Phe), 7.08 (m, 1H, NH Phe), 7.16−7.30 (m, 5H, ArH). ^{13}C NMR ($CDCl_3$): δ 17.9, 21.8, 23.3, and 24.7 ($^{\gamma}$CH and CH_3), 28.3 (CH_3 Boc), 25.1, 27.6, 39.1, 41.9, 47.1, 47.3, 48.1, 49.6, 50.1, and 51.2 (CH_2), 48.9, 50.1, 50.5, 52.1, 52.5, and 59.8 ($^{\alpha}$CH and OCH_3), 80.7 (C Boc), 118.4 and 118.5 ($=CH_2$), 126.9, 128.4, 129.4, and 129.6 (CH Ar), 132.1 and 133.1 (=CH), 136.1 and 136.4 (C Ar), 169.2, 169.5, 170.9, 171.4, 171.6, 171.9, and 172.3 (CO). MS-MS (FAB) *m*/*z*: 1532 $[2M + Na]^+$, 777 $[M + Na]^+$, 755 $[M + H]^+$, 655 [M − Boc + H]$^+$, 558 [(H-Leu-Pro-Ala-Phe-(*N*all)Gly-OMe) + H]$^+$, 445 [(H-Pro-Ala-Phe-(*N*all)Gly-OMe) + H]$^+$, 277 [(H-Phe-(*N*all)Gly-OMe) + H]$^+$, 130 [(H-(*N*all)Gly-OMe) + H]$^+$, 626 [(Boc-(*N*all)Gly-Leu-Pro-Ala-Phe-H) + H]$^+$, 379 [(Boc-(*N*all)-Gly-Leu-Pro-Ala-H) + H]$^+$, 408 [(Boc-(*N*all)Gly-Leu-Pro-H) + H]$^+$.

Ac-(*N*hal)Gly-Pro-(*N*hal)Gly-OMe 6a was prepared as described for **6d** (vide infra). Crude **6a** was purified by chromatography (gradient: 2.5% MeOH/DCM to 10% MeOH/DCM) and obtained as a colorless oil (108 μmol, 41 mg) in 46% yield. R_f 0.60 (10% MeOH/DCM). ^{1}H NMR ($CDCl_3$): δ 1.95−2.07 (m, 4H, $^{\beta}CH_2$ and $^{\gamma}CH_2$ Pro), 2.14 and 2.16 (s, 3H, CH_3 Ac), 2.18−2.47 (m, 4H, $^{\beta}CH_2$ hal), 3.36−3.75 (m, 7H, $^{\alpha}CH_2$ hal, $^{\delta}CH_2$ Pro and $^{\alpha}CH_2$ Gly 1H), 3.70 (s, 3H, OCH_3), 3.71−4.05 (m, 2H, CH_2 Gly), 4.50−4.58 (m, 1.5H, CH_2 Gly 1H and $^{\alpha}$CH Pro 0.8H), 4.89−5.14 (m, 4.5H, $=CH_2$ and $^{\alpha}$CH Pro 0.2H), 5.70−5.82 (m, 1H, =CH). ^{13}C NMR ($CDCl_3$): δ 21.0 (CH_3 Ac), 24.7, 25.1, 28.8, 29.3, 31.8, 32.7, 33.0, 46.4, 46.6, 46.8, 47.3, 48.1, 48.2, 48.3, 48.7, 49.1, 49.5, 50.3, and 51.1 (CH_2), 52.0, 52.3, 56.3, and 56.6 ($^{\alpha}$CH Pro and OCH_3), 116.8, 117.6, and 117.7 ($=CH_2$), 134.2, 134.5, and 135.2 (=CH), 167.0, 171.1, and 172.7 (CO). MS (ESI) *m*/*z*: 416 $[M + Na]^+$.

Ac-(*N*hal)Gly-Pro-Phe-(*N*hal)Gly-OMe 6b was prepared as described for **6d** (vide infra). Crude **6b** was purified by chromatography (gradient: 2.5% MeOH/DCM to 5% MeOH/DCM) and obtained as a colorless oil (78 μmol, 41 mg) in 33% yield. R_f 0.55 (10% MeOH/DCM). ^{1}H NMR ($CDCl_3$): δ 1.68−2.12 (m, 4H, $^{\beta}CH_2$ and $^{\gamma}CH_2$ Pro), 2.14 and 2.17 (s, 3H, CH_3 Ac), 2.20−2.35 (m, 4H, $^{\beta}CH_2$ hal), 2.89−3.16 (m, 2H, $^{\beta}CH_2$ Phe), 3.20−3.36 (m, 2H, $^{\delta}CH_2$ Pro), 3.39−3.54 (m, 4H, $^{\alpha}CH_2$ hal), 3.70 (s, 3H, OCH_3), 3.70−4.41 (m, 4H CH_2 Gly), 4.44−4.49 (m, 1H, $^{\alpha}$CH Pro), 4.78−4.83 (0.2H, $^{\alpha}$CH Phe), 4.98−5.13 (m, 4.8H, $=CH_2$ and $^{\alpha}$CH Phe 0.8H), 5.58−5.84 (m, 1H, =CH), 6.91−6.94 (m, 1H, NH), 7.16−7.34 (m, 5H, ArH). MS (ESI) *m*/*z*: 563 $[M + Na]^+$.

Ac-(*N*hal)Gly-Leu-Pro-Phe-(*N*hal)Gly-OMe 6c was prepared as described for **6d** (vide infra). Crude **6c** was purified by chromatography (gradient: 2.5% MeOH/DCM to 5% MeOH/DCM) and obtained as a colorless oil (0.165 mmol, 108 mg) in 66% yield. R_f 0.54 (10% MeOH/DCM). ^{1}H NMR ($CDCl_3$): δ 0.91−0.99 (m, 6H, CH_3 Leu), 1.35−1.66 (m, 3H, $^{\beta}CH_2$ and $^{\gamma}$CH Leu), 1.87−2.12 (m, 4H, $^{\beta}CH_2$ and $^{\gamma}CH_2$ Pro), 2.16 (s, 3H, CH_3 Ac), 2.26−2.39 (m, 4H, $^{\beta}CH_2$ hal), 2.87−3.18 (m, 2H, $^{\beta}CH_2$ Phe), 3.23 (t, 2H, J = 7.3 Hz, $^{\delta}CH_2$ Pro), 3.36−3.56 (m, 4H, $^{\alpha}CH_2$ hal), 3.69 and 3.71 (s, 3H, OCH_3), 3.76−4.17 (m, 4H CH_2 Gly), 4.49 (br m, 1H, $^{\alpha}$CH Pro), 4.69−4.82 (m, 1H, $^{\alpha}$CH Leu), 4.95−5.13 (m, 5H, $=CH_2$ and $^{\alpha}$CH Phe), 5.54−5.80 (m, 1H, =CH), 6.62−6.77 (m, 1H, NH), 7.08−7.26 (m, 6H, ArH and NH). MS (ESI) *m*/*z*: 676 $[M + Na]^+$.

Ac-(*N*hal)Gly-Leu-Pro-Ala-Phe-(*N*hal)Gly-OMe 6d. Fmoc-Gly-OH was coupled to TentaGel-OH according to the method of Sieber.[16] The Fmoc group was removed from Fmoc-Gly-O−TentaGel (0.236 mmol, 1.00 g) by treatment with 20% piperidine in DMF for 30 min, followed by washings with DMF (3×) and DCM (3×). The amine group was treated with *o*NBS-Cl (1.25 mmol, 278 mg) and DiPEA (1.29 mmol, 224 μL) in DMF for 30 min, followed by washings with DCM (6×). Mitsunobu reaction of the sulfonamide was carried out using PPh_3 (1.25 mmol, 328 mg), 3-butene-1-ol (2.35 mmol, 202 μL), and DIAD (1.18 mmol, 232 μL) in DCM for 30 min, followed by washings with DCM (3×) and DMF (6×). The *o*NBS group was removed by DBU (1.21 mmol, 180 μL) in 0.50 M 2-mercaptoethanol/DMF for 30 min, followed by washings with 25% HOAc/DMF (1×), DMF (3×), 2.5% DiPEA/DMF (3×), and DMF (3×). Now the secondary amine was treated with Boc-Phe-OH (0.706 mmol, 187 mg), PyBroP (0.706 mmol, 329 mg), and DiPEA (1.45 mmol, 252 μL) in DMF for 1 h, followed by washings with DMF (3×) and DCM (3×). Removal of the Boc-group was achieved with 4 N HCl in dioxane for 15 min, this step was repeated once, followed by washings with DCM (6×). The amine group was treated with Fmoc-Ala-OH (0.706 mmol, 232 mg), HATU (0.706 mmol, 268 mg), and DiPEA (1.45 mmol, 252 μL) in DMF for 1 h, followed by washing with DMF (3×) and DCM (3×). The Fmoc group was removed by treatment with 20% piperidine in DMF for 30 min, followed by washings with DMF (3×) and DCM (3×). The amine group was treated with Fmoc-Pro-OH (0.706 mmol, 302 mg), BOP (0.706 mmol, 396 mg), and DiPEA (1.45 mmol, 252 μL) in DMF for 1 h, followed by washings with DMF (3×) and DCM (3×). The leucine and glycine residues were introduced as described for the proline residue. Introduction of the *o*NBS-group, the Mitsunobu reaction, and removal of the *o*NBS-group were carried out as described above. Now the secondary amine was treated with Ac-Cl (1.25 mmol, 89 μL) and DiPEA (1.25 mmol, 217 μL) in DCM for 30 min, followed by washings with DCM (6×). Treatment of the resin with a catalytic amount of NaCN in MeOH for 16 h afforded crude **6d**. Column chromatography (gradient: 2.5% MeOH/DCM to 10% MeOH/DCM) afforded **6d** (76 μmol, 54 mg) as a colorless oil in 32% yield. R_f 0.36 (10% MeOH/DCM). ^{1}H NMR ($CDCl_3$): δ 0.88−0.94 (m, 6H, CH_3 Leu), 1.16−1.23 (m, 3H, CH_3 Ala), 1.46−1.63 (m, 3H, $^{\beta}CH_2$ and $^{\gamma}$CH Leu), 1.88−2.11 (m, 4H, $^{\beta}CH_2$ and $^{\gamma}CH_2$ Pro), 2.02 and 2.13 (s, 3H, CH_3 Ac), 2.18−2.34 (m, 4H, $^{\beta}CH_2$ hal), 2.87−3.12 (m, 2H, $^{\beta}CH_2$ Phe), 3.21−3.48 (m, 4H $^{\alpha}CH_2$ hal), 3.51−4.13 (m, 6H, $^{\delta}CH_2$ Pro and CH_2 Gly), 3.68 and 3.69 (s, 3H, OCH_3), 4.34−4.48 (m, 2H, $^{\alpha}$CH Pro and $^{\alpha}$CH Ala), 4.73−4.83 (m, 1H, $^{\alpha}$CH Leu), 4.95−5.14 (m, 5H, $=CH_2$ and $^{\alpha}$CH Phe), 5.57−5.77 (m, 1H, =CH), 7.04−7.29 (m, 8H, ArH and NH). MS (ESI) *m*/*z*: 747 $[M + Na]^+$.

Cyclo [Ac-(*N*hal)Gly-Pro-(*N*hal)Gly-OMe] 7a was prepared as described in the typical procedure for RCM. Column chromatography (gradient 2.5% MeOH/DCM to 10% MeOH/DCM) afforded **7a** (137 μmol, 48 mg) as a brownish oil in 46% yield. R_f 0.32 (10% MeOH/DCM). The purity according to HPLC was 95%. MS (FAB) *m*/*z*: 388 $[M + Na]^+$, 366 $[M + H]^+$.

Cyclo [Ac-(*N*hal)Gly-Pro-Phe-(*N*hal)Gly-OMe] 7b was prepared as described in the typical procedure for RCM. Column chromatography (gradient 2.5% MeOH/DCM to 5% MeOH/DCM) afforded **7b** (72.3 μmol, 36 mg) as a brownish oil in 92% yield. R_f 0.51 (10% MeOH/DCM). The purity according to HPLC was >99%. MS (FAB) *m*/*z*: 1074 $[2M + Na]^+$, 1025 $[2M + H]^+$, 535 $[M + Na]^+$, 513 $[M + H]^+$.

Cyclo [Ac-(*N*hal)Gly-Leu-Pro-Phe-(*N*hal)Gly-OMe] 7c was prepared as described in the typical procedure for RCM. Column chromatography (gradient 2.5% MeOH/DCM to 10% MeOH/DCM) afforded crude **7c**. After a second purification by column chromatography (gradient 2.5% MeOH/DCM to 5% MeOH/DCM) **7c** (64.0 μmol, 40 mg was obtained) as a white solid in 39% yield. R_f 0.38 (10% MeOH/DCM). Preparative HPLC afforded pure (99+%) **7c** in a recovery of 41%. MS (FAB) *m*/*z*: 648 $[M + Na]^+$, 626 $[M + H]^+$.

Cyclo [Ac-(*N*hal)Gly-Leu-Pro-Ala-Phe-(*N*hal)Gly-OMe] 7d was prepared as described in the typical procedure for RCM. Column chromatography (gradient 2.5% MeOH/DCM to 10% MeOH/DCM) afforded **7d** (50.0 μmol, 34 mg) as a brownish solid in 65% yield. R_f 0.48 (10% MeOH/DCM). The purity according to HPLC was 98%. MS (FAB) *m*/*z*: 719 $[M + Na]^+$, 697 $[M + H]^+$.

Ac-(*N*hal)Gly-Val-(*N*hal)Gly-OMe 8a was prepared as described for **6d**. Crude **8a** was purified by chromatography (gradient: 2.5% MeOH/DCM to 5% MeOH/DCM) and obtained as a colorless oil (116 μmol, 46 mg) in 46% yield. The purity according to HPLC was 93%. R_f 0.53 (10% MeOH/DCM). ^{1}H NMR ($CDCl_3$): δ 0.85−0.91 and 0.97−1.01 (m, 6H, CH_3 Val), 2.04 and 2.15 (s, 3H, CH_3 Ac), 1.93−2.15 (m, 1H, $^{\beta}$CH Val), 2.22−2.39 (m, 4H, $^{\beta}CH_2$ hal), 3.38−3.48 (m, 4H, $^{\alpha}CH_2$ hal), 3.20−4.40 (m, 4H, CH_2 Gly), 3.70 and 3.74 (s, 3H, OCH_3), 4.45−4.50 and 4.75−4.87 (m, 1H $^{\alpha}$CH Val), 5.00−5.14 (m, 4H, $=CH_2$), 5.66−5.82 (m, 1H, =CH), 6.70−6.80 (m, 1H, NH). MS-MS (FAB) *m*/*z*: 813 [2M + Na]$^+$, 791 [2M + H]$^+$, 418 [M + Na]$^+$, 396 [M + H]$^+$, 253 [(Ac-(*N*hal)Gly-Val) + H]$^+$, 154 [(Ac-(*N*hal)Gly) + H]$^+$, 144 [(H-(*N*hal)Gly-OMe) + H]$^+$.

Ac-(*N*hal)Gly-Val-Phe-(*N*hal)Gly-OMe 8b was prepared as described for **6d**. Crude **8b** was purified by chromatography (gradient: 2.5% MeOH/DCM to 5% MeOH/DCM) and obtained as a white solid (161 μmol, 87 mg) in 64% yield. R_f 0.57 (10% MeOH/DCM). ^{1}H NMR ($CDCl_3$): δ 0.71−0.88 (m, 6H, CH_3 Val), 1.98−2.18 (m, 3H $^{\beta}$CH Val and $^{\beta}CH_2$ hal), 2.12 and 2.18 (s, 3H, CH_3 Ac), 2.21−2.37 (m, 2H, $^{\beta}CH_2$ hal), 2.81−3.11 (m, 4H, $^{\alpha}CH_2$ hal and $^{\beta}CH_2$ Phe) 3.17−3.51 (m, 2H, $^{\alpha}CH_2$ hal), 3.68 (s, 3H, OCH_3), 3.83−4.10 (m, 4H, CH_2 Gly), 4.22−4.37 (m, 1H, $^{\alpha}$CH Val), 4.82−5.16 (m, 5H, $^{\alpha}$CH Phe and $=CH_2$), 5.54−5.80 (m, 1H, =CH), 6.63−6.66 and 6.85−6.98 (m, 2H, NH), 7.16−7.27 (m, 5H, ArH). MS (ESI) *m*/*z*: 565 [M + Na]$^+$.

Ac-(*N*hal)Gly-Leu-Val-Phe-(*N*hal)Gly-OMe 8c was prepared as described for **6d**. Crude **8c** was purified by chromatography (gradient: 2.5% MeOH/DCM to 5% MeOH/DCM) and obtained as a colorless oil (145 μmol, 93 mg) in 61% yield. R_f 0.26 (10% MeOH/DCM). ^{1}H NMR ($CDCl_3$): δ 0.84−0.93 (m, 12H, CH_3 Val and Leu), 1.50−1.62 (m, 3H, $^{\gamma}$CH and $^{\beta}CH_2$ Leu), 1.93−2.15 (m, 3H, $^{\beta}$CH Val and $^{\beta}CH_2$ hal), 2.15 (s, 3H, CH_3 Ac), 2.24−2.36 (m, 2H, $^{\beta}CH_2$ hal), 2.89−3.13 (m, 2H, $^{\beta}CH_2$ Phe), 3.17−3.50 (m, 4H, $^{\alpha}CH_2$ hal), 3.60−3.76 (m, 1H, CH_2 Gly), 3.67 (s, 3H, OCH_3), 3.83−4.06 (m, 3H, CH_2 Gly), 4.41−4.44 and 4.46−4.73 (m, 2H, $^{\alpha}$CH Leu and Val), 4.82−5.26 (m, 5H, $^{\alpha}$CH Phe and $=CH_2$), 5.54−5.80 (m, 2H, =CH), 6.67−6.83 (m, 1H, NH), 7.08−7.27 (m, 6.1H, ArH and NH), 7.37−7.43 and 7.59−7.62 (m, 0.8H, NH), 8.15−8.18 (m, 1H, 0.1H). ^{13}C NMR ($CDCl_3$): δ 18.0, 18.3, 18.7, 18.8, 18.9, 21.1, 21.5, 21.8, 22.9, 24.7, 24.8, 31.2, 31.7 (CH_3 and CH), 31.4, 31.8, 32.7, 32.8, 32.9, 39.3, 39.6, 40.8, 41.6, 46.9, 47.4, 47.9, 48.0, 48.2, 49.4, 49.7, and 50.0 (CH_2), 49.9, 50.1, 51.7, 52.0, 52.5, 58.0, and 58.1 ($^{\alpha}$CH and OCH_3), 116.7, 117.0, 117.9, 118.0, and 118.1 ($=CH_2$), 127.0, 128.6, 129.3, 129.4, 129.5, and 129.6 (CH Ar), 133.8, 134.1, 134.8, and 135.4 (=CH), 136.3 and 136.4 (C Ar), 168.8, 169.2, 169.5, 170.4, 170.5, 171.4, 171.7, 172.0, 172.2, and 172.3 (CO). MS (ESI) *m*/*z*: 678 [M + Na]$^+$.

Ac-(*N*hal)Gly-Leu-Val-Ala-Phe-(*N*hal)Gly-OMe 8d was prepared as described for **6d**. Crude **8d** was purified by chromatography (gradient: 2.5% MeOH/DCM to 5% MeOH/DCM) and obtained as a colorless oil (86 μmol, 61 mg) in 65% yield. R_f 0.23 (10% MeOH/DCM). ^{1}H NMR (DMSO-d_6): δ 0.80−0.90 (m, 12H, CH_3 Val and Leu), 1.11−1.17 (m, 3H, CH_3 Ala), 1.48−1.63 (m, 3H, $^{\gamma}$CH and $^{\beta}CH_2$ Leu), 1.92−2.32 (m, 5H, $^{\beta}$CH Val and $^{\beta}CH_2$ hal), 1.92 and 2.05 (s, 3H, CH_3 Ac), 2.76−3.04 (m, 2H, $^{\beta}CH_2$ Phe), 3.24−3.58 (m, 6H, $^{\alpha}CH_2$ hal and CH_2 Gly 2H), 3.62 and 3.66 (s, 3H, OCH_3), 3.86−4.07 (m, 2H, CH_2 Gly), 4.13−4.18 (m, 2H, $^{\alpha}$CH Val), 4.26−4.48 (m, 2H, $^{\alpha}$CH Leu and Ala), 4.60 (br m, 0.1H, $^{\alpha}$CH Phe), 4.91−5.14 (m, 4.9H, $^{\alpha}$CH Phe 0.9 H and $=CH_2$), 5.64−5.83 (m, 2H, =CH), 7.18−7.30 (m, 5H, ArH), 7.72−7.75, 7.86−7.92, 8.03−8.06 and 8.23−8.32 (m, 4H, NH). ^{13}C NMR (DMSO, d6): δ 18.7, 18.8, 19.1, 19.2, 20.0, 21.9, 22.2, 22.3, 23.8, 24.9, 25.1, 31.1, and 31.3 (CH_3 and CH), 32.0, 32.3, 33.2, 33.4, 38.7, 41.3, 41.4, 46.6, 48.5, 48.8, 49.4, and 51.8 (CH_2), 48.6, 50.4, 50.6, 52.0, 52.1, 52.5, 52.9, 58.2, and 58.4 ($^{\alpha}$CH and OCH_3), 117.1, 117.4, 118.0, and 118.1 ($=CH_2$), 127.3, 127.4, 129.1, 129.2, 130.0, and 130.1 (CH Ar), 135.8, 136.4, 136.5, and 136.9 (=CH), 138.2 and 138.4 (C Ar), 169.4, 169.5, 170.5, 171.0, 171.2, 171.4, 172.2, 172.6, 172.7, and 172.9 (CO). MS (ESI) *m*/*z*: 749 [M + Na]$^+$.

Cyclo [Ac-(*N*hal)Gly-Val-Phe-(*N*hal)Gly-OMe] 9b was prepared as described in the typical procedure for RCM. Column chromatography (gradient 2.5% MeOH/DCM to 10% MeOH/DCM) afforded **9b** (42.8 μmol, 22 mg) as an off white solid in 27% yield. R_f 0.52 (10% MeOH/DCM). The purity according to HPLC was 99+%. MS (FAB) *m*/*z*: 1051 [2M + Na]$^+$, 1027 [2M + H]$^+$, 537 [M + Na]$^+$, 515 [M + H]$^+$.

Cyclo [Ac-(*N*hal)Gly-Leu-Val-Phe-(*N*hal)Gly-OMe] 9c was prepared as described in the typical procedure for RCM. Column chromatography (gradient 2.5% MeOH/DCM to 10% MeOH/DCM) afforded **9c** (60.4 μmol, 37 mg) as a brownish solid in 42% yield. R_f 0.45 (10% MeOH/DCM). Preparative HPLC afforded pure (99+%) **9c** in a recovery of 15%. MS (FAB) *m*/*z*: 1277 [2M + Na]$^+$, 1255 [M + H]$^+$, 650 [M + Na]$^+$, 628 [M + H]$^+$.

Cyclo [Ac-(*N*hal)Gly-Leu-Val-Ala-Phe-(*N*hal)Gly-OMe] 9d was prepared as described in the typical procedure for RCM. Column chromatography (gradient 2.5% MeOH/DCM to 10% MeOH/DCM) afforded **9d** (48.2 μmol, 33 mg) as a brownish oil in 54% yield. R_f 0.37 (10% MeOH/DCM). Preparative HPLC afforded pure (99+%) **9d** in a recovery of 30%. MS (FAB) *m*/*z*: 1420 [2M + Na]$^+$, 1398 [M + H]$^+$, 721 [M + Na]$^+$, 699 [M + H]$^+$.

Ac-(*N*pen)Gly-Val-(*N*pen)Gly-OMe 10 was prepared as described for **6d**. Crude **10** was purified by chromatography (2.5% MeOH/DCM) and obtained as a colorless oil (260 μmol, 107 mg) in 52% yield. R_f 0.58 (10% MeOH/DCM). ^{1}H NMR ($CDCl_3$): δ 0.76−0.97 (m, 6H, CH_3 Val), 1.52−1.72 (m, 4H, $^{\beta}CH_2$ pen), 1.92−2.17 (m, 8H, CH_3 Ac and $^{\gamma}CH_2$ pen and $^{\beta}$CH Val), 3.21−3.49 (m, 4H, $^{\alpha}CH_2$ pen), 3.60−4.43 (m, 4H, CH_2 Gly), 3.66 and 3.70 (s, 3H, OCH_3), 4.70−4.83 (m, 1H, $^{\alpha}$CH Val), 4.89−5.04 (m, 4H, $=CH_2$), 5.65−5.81 (m, 1H, =CH), 6.71−6.82 (m, 1H, NH). ^{13}C NMR ($CDCl_3$): δ 17.2, 17.5, 19.4 ($^{\gamma}CH_3$ Val), 21.0 and 21.5 (CH_3 Ac), 26.2, 26.5, 27.4, 27.6, 30.4, 30.5, 30.8, 46.9, 47.2, 47.5, 48.3, 49.4, 49.6, 49.9, 50.0, and 52.1 (CH_2), 31.3, 31.5, and 31.6 ($^{\beta}$CH Val), 52.0, 52.4, 53.3, 53.4, and 53.8 ($^{\alpha}$CH Val and OCH_3), 114.9, 115.1, 115.7, 115.8, and 115.9 ($=CH_2$), 136.7, 136.9. 137.5, and 137.6 (=CH), 168.0, 168.7, 169.3, 169.5, 171.2, and 171.9 (CO). MS (ESI) *m*/*z*: 446 [M + Na]$^+$.

Cyclo [Ac-(*N*pen)Gly-Val-(*N*pen)Gly-OMe] 11 was prepared as described in the typical procedure for RCM. Column chromatography (gradient 2.5% MeOH/DCM to 5% MeOH/DCM) afforded **11** (152 μmol, 58 mg) as a brownish oil in 76% yield. R_f 0.49 (10% MeOH/DCM). Preparative HPLC afforded pure (99+%) **12** in a recovery of 25%. MS (ESI) *m*/*z*: 418 [M + Na]$^+$, 396 [M + H]$^+$.

Ac-(*N*hal)Gly-Val-(*N*al)Gly-OMe 12a was prepared as described for **6d**. Crude **12a** was purified by chromatography (2.5% MeOH/DCM) and obtained as a colorless oil (320 μmol, 117 mg) in 64% yield. R_f 0.67 (10% MeOH/DCM). ^{1}H NMR ($CDCl_3$): δ 0.84−0.95 (m, 6H, CH_3 Val), 1.94−2.13 (m, 4H, CH_3 Ac and $^{\beta}$CH Val), 2.17−2.38 (m, 2H, $^{\beta}CH_2$ hal), 3.32−3.44 (m, 2H, $^{\alpha}CH_2$ hal), 3.58−4.37 (m, 6H, CH_2 Gly and $^{\alpha}CH_2$ all), 3.65 and 3.69 (s, 3H, OCH_3), 4.70−4.83 (m, 1H $^{\alpha}$CH Val), 4.95−5.22 (m, 4H, $=CH_2$), 5.62−5.81 (m, 2H, =CH), 6.85−6.88 (m, 1H, NH). ^{13}C NMR ($CDCl_3$): δ 17.2, 17.6, 19.5 (CH_3 Val), 21.1 and 21.5 (CH_3 Ac), 31.2, 31.3, and 31.4 ($^{\beta}$CH Val), 31.8, 32.7, 46.6, 46.8, 48.1, 49.2, 49.6, 49.8, 49.9, 51.3 and 52.3 (CH_2), 51.9, 53.4, 53.5, and 53.9 ($^{\alpha}$CH Val and OCH_3), 116.8, 117.7, 118.1, 118.5, and 118.7 ($=CH_2$), 132.1, 132.2, 133.8, and 135.0 (=CH), 168.1, 168.7, 169.3, 169.4, 171.2, 171.8, 172.0, and 172.1 (CO). MS (ESI) *m*/*z*: 404 [M + Na]$^+$.

Ac-(*N*hal)Gly-Val-Phe-(*N*all)Gly-OMe 12b was prepared as described for **6d**. Crude **12b** was purified by chromatography (gradient 2.5% MeOH/DCM to 5% MeOH/DCM) and obtained as a colorless oil (154 μmol, 83 mg) in 61% yield. R_f 0.58 (10% MeOH/DCM). ^{1}H NMR ($CDCl_3$): δ 0.71−0.88 (m, 6H, CH_3 Val), 2.00−2.17 (m, 1H, $^{\beta}$CH Val), 2.15 and 2.17 (s, 3H, CH_3 Ac), 2.26−2.36 (m, 2H, $^{\beta}CH_2$ hal), 2.88−3.09 (m, 2H, $^{\beta}CH_2$ Phe), 3.36−3.48 (m, 2H, $^{\alpha}CH_2$ hal), 3.60−4.06 (m, 6H, CH_2 Gly and $^{\alpha}CH_2$ all), 3.66 and 3.67 (s, 3H, OCH_3), 4.11−4.29 (m, 1H $^{\alpha}$CH Val), 4.84−5.13 (m, 5H, $=CH_2$ and $^{\alpha}$CH Phe), 5.46−5.79 (m, 2H, =CH), 6.69−6.72 and 6.93−7.08 (m, 2H, NH), 7.16−7.26 (m, 5H, ArH). MS (ESI) *m*/*z*: 551 [M + Na]$^+$, 529 [M + H]$^+$, 400 [M − ((*N*all)Gly-OMe) + H]$^+$.

Ac-(*N*hal)Gly-Leu-Val-Phe-(*N*all)Gly-OMe 12c was prepared as described for **6d**. Crude **12c** was purified by chromatography (gradient: 2.5% MeOH/DCM to 5% MeOH/DCM)

and obtained as a white solid (77 μmol, 50 mg) in 31% yield. R_f 0.56 (10% MeOH/DCM). ^{1}H NMR ($CDCl_3$): δ 0.83−0.92 (m, 12H, CH_3 Val and Leu), 1.49−1.70 (m, 3H, $^{\gamma}$CH and $^{\beta}CH_2$ Leu), 1.93−2.18 (m, 1H, $^{\beta}$CH Val), 1.98 and 2.14 (s, 3H, CH_3 Ac), 2.23−2.36 (m, 2H, $^{\beta}CH_2$ hal), 2.89−3.12 (m, 2H, $^{\beta}CH_2$ Phe), 3.37−3.48 (m, 2H, $^{\alpha}CH_2$ hal), 3.59−4.08 (m, 6H, CH_2 Gly and $^{\alpha}CH_2$ all), 3.64, 3.66 and 3.67 (s, 3H, OCH_3), 4.43−4.51 and 4.62−4.74 (m, 2H $^{\alpha}$CH Val and Leu), 4.91−5.25 (m, 5H, $=CH_2$ and $^{\alpha}$CH Phe), 5.44−5.80 (m, 2H, =CH), 6.75−6.86, 7.53−7.70 and 8.28−8.31 (m, 3H, NH), 7.15−7.30 (m, 5H, ArH). MS (ESI) *m*/*z*: 664 $[M + Na]^+$.

Cyclo [Ac-(*N*hal)Gly-Val-(*N*al)Gly-OMe] 13a was prepared as described in the typical procedure for RCM. Column chromatography (gradient: 2.5% MeOH/DCM to 5% MeOH/DCM) afforded **13a** (2 μmol, 7 mg) as a brownish oil in 35% yield. R_f 0.41 (10% MeOH/DCM). Preparative HPLC afforded pure (99+% according to HPLC) **13a** in a recovery of 42%. MS (ESI) *m*/*z*: 375 $[M + Na]^+$.

Cyclo [Ac-(*N*hal)Gly-Leu-Val-Phe-(*N*all)Gly-OMe] 13c was prepared as described in the typical procedure for RCM. Column chromatography (gradient 2.5% MeOH/DCM to 5% MeOH/DCM) afforded **13c** (1 μmol, 6 mg) as a white solidl in 13% yield. R_f 0.41 (10% MeOH/DCM). Preparative HPLC afforded pure (99+%) **13c** in a quant. recovery. MS (FAB) *m*/*z*: 632 $[M + Na]^+$, 614 $[M + H]^+$.

Ac-(*N*hal)Val-Phe-(*N*all)Leu-OMe 14a was prepared as described for **6d**. Crude **14a** was purified by chromatography (gradient: 2.5% MeOH/DCM to 5% MeOH/DCM) and obtained as a colorless oil (63 μmol, 33 mg) in 24% yield. R_f 0.54 (10% MeOH/DCM). ^{1}H NMR ($CDCl_3$): δ 0.67−0.98 (m, 12H, CH_3 Val and Leu), 1.33−1.47 (m, 1H, $^{\gamma}$CH Leu), 1.50−2.12 (m, 4H, $^{\beta}CH_2$ hal and $^{\beta}CH_2$ Leu), 1.98, 2.00, 2.03 and 2.06 (s, 3H, CH_3 Ac), 2.20−2.32 (m, 1H, $^{\beta}$CH Val), 2.82−3.19 (m, 4H, $^{\beta}CH_2$ Phe and $^{\alpha}CH_2$ hal), 3.62, 3.64, 3.65 and 3.67 (s, 3H, OCH_3), 3.71−3.95 (m, 1H, $^{\alpha}CH_2$ all), 4.10−4.38 (m, 2H, $^{\alpha}CH_2$ all and $^{\alpha}$CH Val), 4.77−5.26 (m, 6H, $^{\alpha}$CH Leu, $^{\alpha}$CH Phe and $=CH_2$), 5.49−5.96 (m, 2H, =CH), 6.06−6.09, 6.65−6.57 and 7.03−7.12 (m, 1H, NH), 7.17−7.26 (m, 5H, ArH). ^{13}C NMR ($CDCl_3$): δ 18.0, 18.7, 18.8, 19.5, 21.7, 21.8, 21.9, 22.8, 23.0, 23.2, 24.6, 24.7, 26.1, 26.2, and 31.4 (CH_3 and CH), 33.2, 37.8, 38.4, 38.7, 39.3, 45.5, 48.9, 49.7 (CH_2), 50.5, 51.6, 51.7, 53.0, 55.1, 55.9, and 58.1 ($^{\alpha}$CH and OCH_3), 116.9, 117.0, 117.2, 117.8 ($=CH_2$), 126.7, 127.0, 128.4, 128.5, 128.6, 129.3, 129.5, and 129.5 (CH Ar), 133.8, 134.3, 134.4, 134.5 (=CH), 135.9 and 136.7 (C Ar), 169.8, 180.4, 170.5, 171.6, 171.9, 172.0, 172.1, and 172.7 (CO). MS (ESI) *m*/*z*: 550 $[M + Na]^+$.

Ac-(*N*hal)Val-D-Phe-(*N*all)Leu-OMe 14b was prepared as described for **6d**. Crude **14b** was purified by chromatography (gradient 2.5% MeOH/DCM to 5% MeOH/DCM) and obtained as a colorless oil (25 μmol, 13 mg) in 10% yield. R_f 0.68 (10% MeOH/DCM). ^{1}H NMR ($CDCl_3$): δ 0.72−0.98 (m, 12H, CH_3 Val and Leu), 1.27−1.43 (m, 1H, $^{\gamma}$CH Leu), 1.46−1.80 (m, 2H, $^{\beta}CH_2$ Leu), 1.99−2.21 (m, 2H, $^{\beta}CH_2$ hal), 2.11 and 2.14 (s, 3H, CH_3 Ac), 2.43 (m, 1H, $^{\beta}$CH Val), 2.84−3.09 (m, 2H, $^{\beta}CH_2$ Phe), 3.19−3.25 (m, 2H, $^{\alpha}CH_2$ hal), 3.56−3.76 (m, 1H $^{\alpha}CH_2$ all), 3.62 and 3.65 (s, 3H, OCH_3), 4.19−4.37 (m, 1H, $^{\alpha}CH_2$ all), 4.83−4.88 (m, 1H, $^{\alpha}$CH Leu), 5.00−5.25 (m, 6H, $^{\alpha}$CH Val, $^{\alpha}$CH Phe and $=CH_2$), 5.57−5.74 (m, 2H, =CH), 7.18−7.26 (m, 5H, ArH), 7.40−7.50 (m, 1H, NH). ^{13}C NMR ($CDCl_3$): δ 19.0, 19.5, 22.0, 22.7, 24.7, 26.3 (CH_3 and CH), 33.4, 37.9, 39.0 and 48.6 (CH_2), 50.6, 52.0, and 55.8 ($^{\alpha}$CH and OCH_3), 117.2 and 117.5 ($=CH_2$), 126.7, 128.3, and 129.5 (CH Ar), 134.3 (=CH), 136.6 (C Ar), 170.6, 171.7, 172.1, and 172.5 (CO). MS (ESI) *m*/*z*: 550 $[M + Na]^+$.

Ac-(*N*hal)Gly-Val-Phe-(*N*all)Leu-OMe 14c was prepared as described for **6d**. Crude **14c** was purified by chromatography (2.5% MeOH/DCM) and obtained as a colorless oil (101 μmol, 59 mg) in 46% yield. R_f 0.36 (10% MeOH/DCM). ^{1}H NMR ($CDCl_3$): δ 0.75−0.87 (m, 12H, CH_3 Val and Leu), 1.40−1.48 (m, 1H, $^{\gamma}$CH Leu), 1.51−1.77 (m, 2H, $^{\beta}CH_2$ Leu), 2.05−2.18 (m, 1H, $^{\beta}$CH Val), 2.17 and 2.18 (s, 3H, CH_3 Ac), 2.30−2.45 (m, 2H, $^{\beta}CH_2$ hal), 2.87−3.07 (m, 2H, $^{\beta}CH_2$ Phe), 3.38−3.50 (m, 2H, $^{\alpha}CH_2$ hal), 3.61 and 3.62 (s, 3H, OCH_3), 3.67−4.04 (m, 4H, $^{\alpha}CH_2$ all and CH_2 Gly), 4.19−4.24 (m, 1H, $^{\alpha}$CH Val), 4.74−4.79 (m, 1H, $^{\alpha}$CH Leu), 5.06−5.15 (m, 5H, $^{\alpha}$CH Phe and $=CH_2$), 5.60−5.78 (m, 2H, =CH), 6.68−6.71 and 6.92−6.95 (d, 2H, NH), 7.16−7.27 (m, 5H, ArH). ^{13}C NMR ($CDCl_3$): δ 14.8, 21.6, 21.8, 22.1, 22.2, 22.5, 22.6, 24.2, 24.5, and 24.6 (CH_3 and CH), 24.6, 27.1, 27.5, 37.7, 38.9, 46.6, 46.7, 46.8, and 48.4 (CH_2), 49.7, 50.4, 51.9, 52.2, 55.6, 57.9, 59.6, and 59.8 ($^{\alpha}$CH and OCH_3), 116.1, 116.5, 117.6, and 117.7 ($=CH_2$), 126.8, 128.3, 129.2, and 129.5 (CH Ar), 133.9 and 134.8 (=CH), 136.3 and 136.5 (C Ar), 170.2, 170.6, 171.6, 171.9, and 172.4 (CO). MS (ESI) *m*/*z*: 607 $[M + Na]^+$, 585 $[M + H]^+$, 400 [M − ((*N*all)-Leu-OMe) + $H]^+$.

Ac-(*N*hal)Gly-Val-D-Phe-(*N*all)Leu-OMe 14d was prepared as described for **6d**. Crude **14d** was purified by chromatography (2.5% MeOH/DCM) and obtained as a colorless oil (101 μmol, 59 mg) in 46% yield. R_f 0.36 (10% MeOH/DCM). ^{1}H NMR ($CDCl_3$): δ 0.69−0.94 (m, 12H, CH_3 Val and Leu), 1.27−1.36 (m, 1H, $^{\gamma}$CH Leu), 1.42−1.80 (m, 2H, $^{\beta}CH_2$ Leu), 1.97−2.22 (m, 1H, $^{\beta}$CH Val), 2.04, 2.14, 2.16 and 2.22 (s, 3H, CH_3 Ac), 2.28−2.39 (m, 2H, $^{\beta}CH_2$ hal), 2.88−3.11 (m, 2H, $^{\beta}CH_2$ Phe), 3.36−3.50 (m, 2H, $^{\alpha}CH_2$ hal), 3.52−4.11 (m, 4H, $^{\alpha}CH_2$ all and CH_2 Gly), 3.62, 3.63 and 3.65 (s, 3H, OCH_3), 4.26−4.32 (m, 1H, $^{\alpha}$CH Val), 4.81−4.87 (m, 1H, $^{\alpha}$CH Leu), 5.00−5.20 (m, 5H, $^{\alpha}$CH Phe and $=CH_2$), 5.44−5.81 (m, 2H, =CH), 6.57−6.60, 6.66−6.69, 6.81−6.85 and 6.88−6.99 (m, 2H, NH), 7.13−7.27 (m, 5H, ArH). ^{13}C NMR ($CDCl_3$): δ 16.9, 19.1, 21.0, 21.8, 22.6, 24.5, and 30.2 (CH_3 and CH), 31.8, 32.8, 37.6, 39.1 48.4, 50.0, and 51.0 (CH_2), 50.8, 52.0, 55.6, and 58.0 ($^{\alpha}$CH and OCH_3), 117.8 and 118.0 ($=CH_2$), 127.0, 128.5, and 129.7 (CH Ar), 134.0 (=CH), 136.4 (C Ar), 169.7, 170.3, 171.8, 172.0, and 172.7 (CO). MS (ESI) *m*/*z*: 607 $[M + Na]^+$.

Ac-(*N*hal)Gly-Leu-Val-D-Phe-(*N*all)Gly-OMe 14e was prepared as described for **6d**. Crude **14f** was purified by chromatography (2.5% MeOH/DCM) and obtained as a white solid (134 μmol, 86 mg) in 54% yield. R_f 0.54 (10% MeOH/DCM). ^{1}H NMR ($CDCl_3$): δ 0.58−0.84 (m, 6H, CH_3 Val), 0.88−0.93 (m, 6H, CH_3 Leu), 1.47−1.77 (m, 3H, $^{\gamma}$CH Leu and $^{\beta}CH_2$ Leu), 1.86−2.06 (m, 1H, $^{\beta}$CH Val), 2.00, 2.12 and 2.13 (s, 3H, CH_3 Ac), 2.45−2.35 (m, 2H, $^{\beta}CH_2$ hal), 2.91−3.13 (m, 2H, $^{\beta}CH_2$ Phe), 3.39−3.44 (m, 2H, $^{\alpha}CH_2$ hal), 3.64, 3.65 and 3.72 (s, 3H, OCH_3), 3.68−5.21 (m, 13H, $^{\alpha}CH_2$ all and CH_2 Gly, $^{\alpha}$CH and $=CH_2$), 5.57−5.76 (m, 2H, =CH), 7.14−7.26 (m, 5H, ArH), 6.8−8.3 (m, 3H, NH). ^{13}C NMR ($CDCl_3$): δ 17.6, 17.7, 18.8, 18.9, 19.1, 21.1, 21.6, 21.9, 22.3, 22.8, 24.8, 30.9, 31.2, and 31.7 (CH_3 and CH), 31.9, 32.8, 38.7, 41.0, 47.4, 48.4, and 49.9 (CH_2), 49.8, 50.2, 50.4, 51.4, 51.9, 52.0, 52.5, 57.5, and 58.0 ($^{\alpha}$CH and OCH_3), 116.5, 117.6, 117.7, 118.2, 118.4, and 118.5 ($=CH_2$), 126.8, 128.4, 129.3, and 129.4 (CH Ar), 131.9, 132.2, 134.0, and 135.3 (=CH), 136.2, 136.3, and 136.8 (C Ar), 168.6, 169.1, 169.2, 169.3, 169.9, 170.3, 170.5, 171.3, 171.5, 171.6, 172.2, and 172.6 (CO). MS (ESI) *m*/*z*:664 $[M + Na]^+$.

Cyclo [Ac-(*N*hal)Val-D-Phe-(*N*all)Leu-OMe] 15b was prepared as described in the typical procedure for RCM. Column chromatography (gradient: 2.5% MeOH/DCM to 5% MeOH/DCM) afforded **15b** (2 μmol, 8 mg) as a brownish oil in 36% yield. R_f 0.50 (10% MeOH/DCM). MS (ESI) *m*/*z*: 522 $[M + Na]^+$, 500 $[M + H]^+$.

Cyclo [Ac-(*N*hal)Gly-Val-Phe-(*N*all)Leu-OMe] 15c was prepared as described in the typical procedure for RCM. Column chromatography (gradient: 1% MeOH/DCM to 10% MeOH/DCM) afforded **15c** (40 μmol, 22 mg) as a brownish oil in low purity. R_f 0.30 (10% MeOH/DCM). Preparative HPLC afforded pure (99+%) **16c** in 5% recovery, overall 2% yield. MS (FAB) *m*/*z*: 579 $[M + Na]^+$, 557 $[M + H]^+$.

Cyclo [Ac-(*N*hal)Gly-Val-D-Phe-(*N*all)Leu-OMe] 15d was prepared as described in the typical procedure for RCM. Column chromatography (gradient: 2.5% MeOH/DCM to 5% MeOH/DCM), followed by another purification by column chromatography (gradient: EtOAc:hexanes, 1:1 to EtOAc) afforded **15d** (68 μmol, 38 mg) as a colorless oil in 90% yield. R_f 0.30 (10% MeOH/DCM). Preparative HPLC afforded pure (99+%) **15d** in 39% recovery. ^{1}H NMR ($CDCl_3$): δ 0.69−0.74 (m, 6H, CH_3 Val), 0.77−0.88 (m, 6H, CH_3 Leu), 1.31−1.36 (m, 1H, $^{\gamma}$CH Leu), 1.51−1.59 (m, 1H, $^{\beta}CH_2$ Leu), 1.60−1.74 (m, 1H, $^{\beta}$CH Val), 1.77−1.86 (m, 1H, $^{\beta}CH_2$ Leu), 2.04 (s, 3H, CH_3 Ac), 2.06−2.19 (m, 1H, $^{\beta}CH_2$ hal), 2.44−2.49 (m, 1H, $^{\beta}CH_2$ hal), 2.88−2.96 (m, 1H, CH_2 Phe), 3.00 and 3.05 (s, 1H, CH_2 Gly),

3.20 and 3.26−3.25 (s, 1H, $^{\alpha}CH_2$ hal), 3.27−3.44 (m, 2H, CH_2 Phe and $^{\alpha}CH_2$ all), 3.59 (s, 3H, OCH_3), 3.55−3.69 (m, 1H, $^{\alpha}CH_2$ hal), 4.05−4.09 (m, 1H, $^{\alpha}$CH Val), 4.35 and 4.41 (s, 1H, $^{\alpha}CH_2$ all), 4.75−4.80 (m, 1H, $^{\alpha}$CH Leu), 4.85 and 4.90 (s, 1H, CH_2 Gly), 5.06−5.14 (m, 1H, =CH (*N*all)Gly), 5.32−5.42 (m, 2H, =CH (*N*hal)Gly and $^{\alpha}$CH Phe), 6.26 (d, 1H, J = 10.2 Hz, NH Phe), 7.16−7.26 (m, 5H, ArH), 8.04 (d, 1H, J = 8.4 Hz, NH Val). ^{13}C NMR ($CDCl_3$): δ 18.0, 18.8, 21.5, 21.6, 22.8, 24.6, and 31.4 (CH_3 and CH), 31.4, 36.3, 38.2, 47.2, 51.5, and 53.1 (CH_2), 49.9, 51.9, 54.6 and 58.3 ($^{\alpha}$CH and OCH_3), 126.7, 128.4, 128.8, 129.6, and 130.9 (CH Ar and =CH), 136.9 (C Ar), 169.7, 170.3, 170.5, 172.2, and 172.4 (CO). MS (FAB) *m*/*z*: 579 $[M + Na]^+$, 557 $[M + H]^+$.

Cyclo [Ac-(*N*hal)Gly-Leu-Val-D-Phe-(*N*all)Gly-OMe] 15e was prepared as described in the typical procedure for RCM. Column chromatography (gradient: 2.5% MeOH/DCM to 5% MeOH/DCM) afforded **15f** (82 μmol, 50 mg) as a white solid in 61% yield. R_f 0.40 (10% MeOH/DCM). MS (ESI) *m*/*z*: 636 $[M + Na]^+$, 614 $[M + H]^+$.

Acknowledgment. These investigations were supported by the Council for Chemical Sciences of The Netherlands Organization for Scientific Research (CW-NWO) with financial aid from The Netherlands Technology foundation.

Supporting Information Available: Copies of ^{1}H NMR spectra of compounds **4a**−**d**, **6a**−**d**, **7a**−**d**, **8a**−**d**, **9b**−**e**, **10**, **11**, **12a**−**c**, **13a**, **13c**, **14a**−**e**, and **15b**−**e.** Copies of ^{13}C NMR spectra of compounds **4a**−**d**, **6a**, **7b**−**d**, **8c**−**d**, **9b**−**d**, **10**−**11**, **12a**, **14a**−**e**, and **15b**−**e**. HPLC traces of compounds **4a**−**d**, **7a**−**d**, **8a**, **9b**−**d**, **11**, **13a**, **15b**−**e**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO000759T