Solid-Phase Synthesis of Peptides Containing Reverse-Turn Mimetic Bicyclic Lactams

Cesare Gennari,*[a,b] Antonia Mielgo,[a] Donatella Potenza,[a] Carlo Scolastico,*[a,b] Umberto Piarulli,[c] and Leonardo Manzoni[a]

Keywords: Solid-phase synthesis / Reverse-turns / FMOC strategy / Peptidomimetics

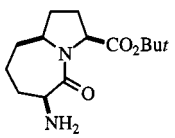
The solid-phase synthesis and characterization of a series of peptides (**4**–**15**) containing reverse-turn mimetic bicyclic lactams is reported. The bicyclic lactams (**1a**, **1b**) possess high structural similarity to the two central residues of a β-turn. Amino acid conjugates of these bicyclic lactams were synthesized on solid supports following a 9-fluorenylmethoxycarbonyl (FMOC) protection strategy on Wang-Merrifield resin. Coupling between amino acids was accomplished by means of diisopropylcarbodiimide (DIC)/hydroxyazabenzotriazole (HOAt). Coupling between amino acids and the mimics was performed with the potent Carpino's reagent *O*-(7-azabenzotriazol-1-yl)-*N*,*N*,*N*′,*N*′-tetramethyluronium hexafluorophosphate (HATU). The final compounds were cleaved from the resin and obtained as *N*-acetylated methyl esters or benzyl amides.

Introduction

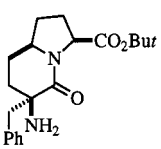
The synthesis of artificial peptides containing pre-determined structural motifs is one of the most interesting and promising areas for the construction of bioactive molecules. The typical structural motifs of natural proteins such as α-helix, β-sheet, and reverse-turn, provide a clear basis for the design of synthetic peptidomimetics. β-Turns, with their ten-membered-ring H-bond, are an important motif in natural proteins for folding and generating compact structures, and their structural mimics have been extensively investigated.[1] γ-Turns, with their seven-membered-ring H-bond, have also attracted significant attention as turn elements that may induce a more compact and rigid structure in proteins compared to β-turns.[2] However, among the common protein secondary structures, the β-sheet is the least well-understood, despite the fact that many biological processes are connected with the creation of a β-sheet structure in peptides and proteins. The synthesis of small, soluble model compounds represents an area of intense research with the aim of improving the understanding of these important secondary structures. To investigate the thermodynamic and kinetic features of β-sheets, model systems have been devised that enhance the probability of β-sheet formation by using designed templates that bring two polypeptide chains into close proximity. A β-sheet structure can be induced in different ways: with the aid of a template like Kemp's diacylaminoepindolidione derivative,[3] of a turn mimetic compound enforcing chain reversal,[4] or by attaching peptide chains to a molecular scaffold possessing the required geometric parameters to induce a β-sheet.[5][6] Several β-turn mimics and β-sheet nucleators have been designed, synthesized, and tested for nucleation of antiparallel β-sheets,[4][5] while only a few have been designed for the induction of parallel β-sheets.[5x,6]

On the other hand, the physical basis for the β-sheet forming propensity of the various amino acids is not clearly established. In 1993 and 1994, three teams of researchers reported studies on the propensities of different amino acids to form antiparallel β-sheets.[7a−7d] These studies involved systematically varying amino acids within small β-sheet-containing proteins and quantifying the effects of the mutations upon the thermodynamic stabilities of the proteins. Recently, Nowick and co-workers reported on the propensities of four different amino acids to form parallel β-sheets, and found that leucine and valine are relatively good, alanine is moderate, while glycine is poor.[7e] Although other contributions such as conformational entropy, steric factors, and hydrophobic interactions are also likely to be involved, the influence of the amino acid side-chains on electrostatic interactions and hydrogen bonding appears to be the most important factor in determining β-sheet forming propensities.

Recently, the design and synthesis of two bicyclic lactams (**1a**, **b**) (Figure 1) possessing high structural similarity to the two central residues of a β-turn was reported by researchers



1a



1b

Figure 1. Reverse-turn mimetic bicyclic lactams **1a** and **1b**

[a] Dipartimento di Chimica Organica e Industriale, Università degli Studi di Milano,
[b] Centro CNR per lo Studio delle Sostanze Organiche Naturali, via G. Venezian 21, I-20133 Milano, Italy
Fax: (internat.) 39-02/2364369
E-mail: cesare@iumchx.chimorg.unimi.it
[c] Istituto di Scienze Mat. Fis. e Chimiche, Università dell'Insubria, via Lucini 3, I-22100 Como, Italy

Supporting information for this article is available on the WWW under http://www.wiley-vch.de/home/eurjoc or from the author.

  1434−193X/99/0202−0379 $ 17.50+.50/0

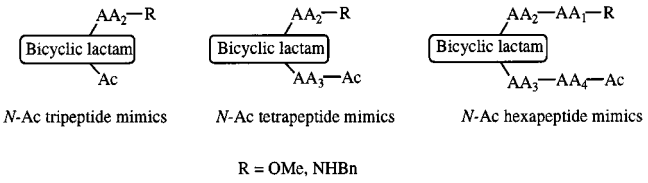


Figure 2. General structure of the constrained *N*-acetylated tripeptide, tetrapeptide, and hexapeptide mimics

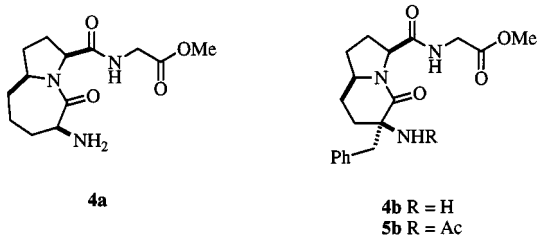


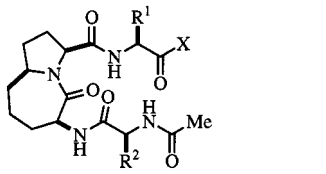
Figure 3. Tripeptide mimics incorporating both (5,7)- and (5,6)-bicyclic lactams

in Milan.[8a−8c] Peptides incorporating these lactams would be capable of adopting intramolecular hydrogen-bonded conformations. The conformational preferences of the resulting constrained peptides would offer the opportunity of investigating in detail the secondary structures (γ- vs. β-turns) and the propensity to adopt an antiparallel β-sheet conformation (β-hairpin).

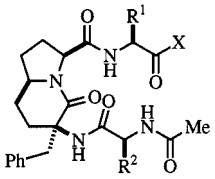
In this paper, we report the solid-phase synthesis of a number of peptides containing reverse-turn mimetic bicyclic lactams (**1a**, **b**). The general structures of these constrained *N*-acetylated tripeptide, tetrapeptide, and hexapeptide mimics, with methyl ester or benzyl amide functions as carboxy terminal groups, are shown in Figure 2. In order to study the influence of the bicyclic lactam, of the amino acid sequence, and of the type of carboxy terminal group on the preferred folding pattern, the constrained peptides **4**−**15** were prepared (Figures 3, 4, and 5). Among the proteinogenic amino acids, Val and Ala were specifically chosen because of their propensity to appear in β-sheet regions.[7] Other natural amino acids such as Phe, Gly, Met, and Cys were also selected. Investigation of the conformational preferences of the peptide derivatives by the use of NMR spectroscopy, IR spectroscopy, and computational methods is discussed in the accompanying paper.[8d]

Results and Discussion

The synthesis and structural characterization of bicyclic lactams **1a** and **1b** has been reported previously.[8a−8c] Amino acid conjugates of these bicyclic lactams were synthesized on solid-phase supports following a 9-fluorenylmethoxycarbonyl (FMOC) protection strategy on Wang−-Merrifield resin.[9] For this purpose, the free amino group in compounds **1a** and **1b** was first protected with the FMOC group employing FMOC−O−succinimide (FMOC−O−NSu) with 2,6-lutidine as base. Subsequent trifluoroacetic acid treatment afforded the *N*-FMOC−-[bicyclic lactam]−OH compounds (**3a**, **b**, 90% overall yield

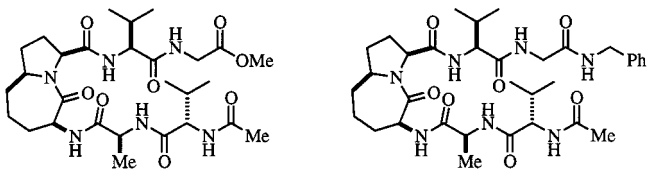


6a X = OMe, R^1 = H, R^2 = CH_2Ph
7a X = NHBn, R^1 = CH_2CH_2SMe, R^2 = CH_2StBu
8a X = OMe, R^1 = CH_2Ph, R^2 = H
9a X = OMe, R^1 = *i*Pr, R^2 = H
10a X = NHBn, R^1 = *i*Pr, R^2 = CH_2Ph
11a X = OMe, R^1 = *i*Pr, R^2 = CH_2Ph
12a X = OMe, R^1 = *i*Pr, R^2 = Me



6b X = OMe, R^1 = H, R^2 = CH_2Ph
7b X = NHBn, R^1 = CH_2CH_2SMe, R^2 = CH_2StBu
12b X = OMe, R^1 = *i*Pr, R^2 =Me
13b X = NHBn, R^1 = *i*Pr, R^2 = Me

Figure 4. *N*-Acetylated tetrapeptide mimics incorporating both the (5,7)- and the (5,6)-bicyclic lactams



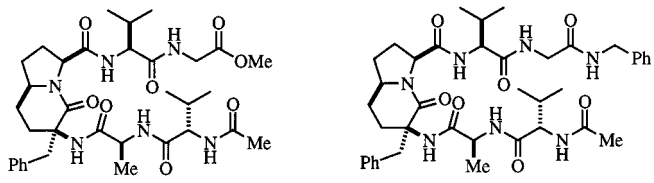
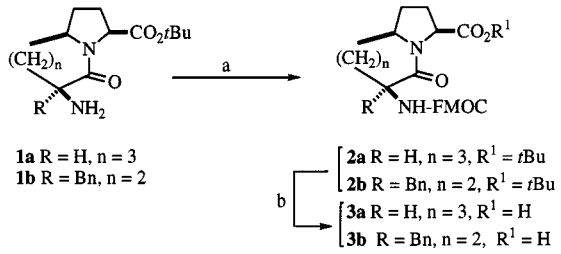


Figure 5. *N*-Acetylated hexapeptide mimics incorporating both the (5,7)- and the (5,6)-bicyclic lactams



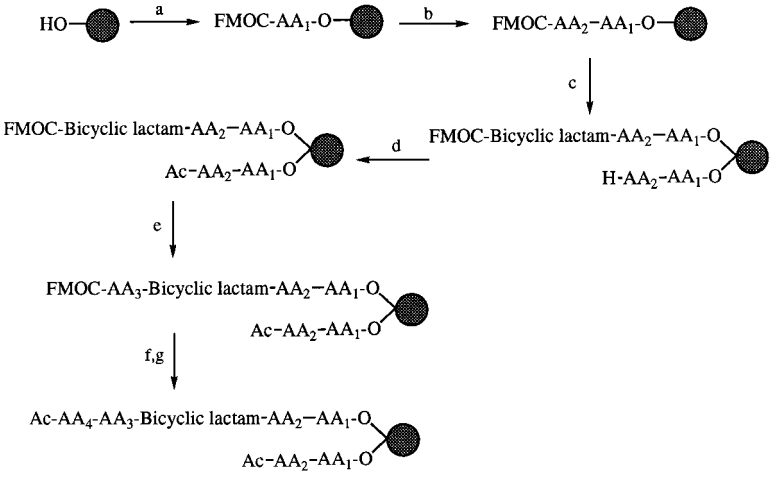
Scheme 1. Synthesis of the *N*-FMOC−[bicyclic lactam]−OH compounds **3a** and **3b** starting from H−[bicyclic lactam]−O*t*Bu compounds **1a** and **1b**; a: FMOC−ONSu (1.5 equiv.), 2,6-lutidine (1.5 equiv.), THF, 0°C, 6.7 h; b: TFA, DCM, 1.5 h, room temp.

for the two steps) ready for use in solid-phase chemistry (Scheme 1).

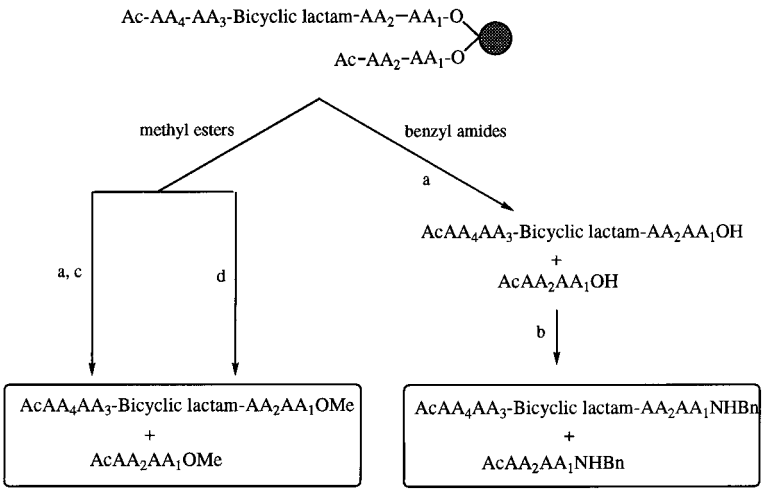
A representative sequence for the solid-phase synthesis of the constrained peptides is outlined in Scheme 2. *N*-FMOC−glycine was attached to the Wang−Merrifield resin by means of the diisopropylcarbodiimide (DIC)/1-hydroxybenzotriazole (HOBt)/4-dimethylaminopyridine (DMAP) protocol,[10] while attachment of other *N*-FMOC-amino acids was accomplished following the Sieber procedure,[11] which employs 2,6-dichlorobenzoyl chloride and pyridine in dichloromethane. The final loadings of these resins were established using the quantitative picric acid test[12] and the possibly present hydroxy groups (not reacted) were capped with Ac_2O or PhCOCl. Deprotection of the amino groups was effected with a 20% piperidine solution in dimethylformamide. Coupling between amino acids was performed with DIC/hydroxyazabenzotriazole (HOAt) and that the reaction had reached completion was verified by performing a TNBS test.[13]

For incorporation of the bicyclic lactams into the growing peptide chains, a 1.0:1.2 ratio lactam **3a**,**b**/H−AA_2−O−resin (or H−AA_2−AA_1−O−resin) was used, and the couplings were performed with the potent Carpino's reagent *O*-(7-azabenzotriazol-1-yl)-*N*,*N*,*N*′,*N*′-tetramethyluronium hexafluorophosphate (HATU).[14] This reagent, often used in the presence of HOAt, is highly efficient for difficult couplings of hindered substrates and has been extensively used for coupling *N*-methyl amino acids.[15] It requires the presence of a base: diisopropylethylamine (DIPEA) is usually employed, but in long coupling cycles epimerization as well as FMOC deprotection have been reported, and 2,4,6-collidine has been proposed as a better alternative.[14b] After extensive optimization, we found that the best conditions for attachment of peptidomimetics **3** to the growing peptide chain were HATU/HOAt/2,4,6-collidine/*N*-FMOC−[bicyclic lactam]−OH/H−AA_2−AA_1−O−resin (or H−AA_2−O−resin) in a ratio 2:2:2:1:1.2 for 15 h at room temperature.

Once the FMOC-peptidomimetic bicyclic lactam had been inserted into the peptide chain, excess free NH_2 groups were capped by means of acetylimidazole, which proved to be the most effective capping method. After deprotection of the FMOC group, incorporation of the subsequent amino acid on the H−[bicyclic lactam]−AA_2−AA_1−O−resin {or H−[bicyclic lactam]−AA_2−O−resin} (1 equiv.) was accomplished with HATU/HOAt/2,4,6-collidine/*N*-FMOC−AA_3−OH (4 equiv.:4 equiv.:4 equiv.:4 equiv.). At this stage, the use of a double amount of 2,4,6-collidine (8 equiv.) led to a mixture of compounds, presumably due to partial deprotection of the FMOC group of the newly attached *N*-FMOC-amino acid, resulting in double incorporation of the same amino acid. When DIPEA was used instead of 2,4,6-collidine, some epimerization was observed. The coupling efficiency was checked by performing a TNBS test,[13] which proved effective only in the case of the amino



Scheme 2. General scheme for the solid-phase synthesis of the constrained peptides **4**−**15**; a: *N*-FMOC−AA_1−OH (2 equiv.), Py (3.3 equiv.), 2,6-dichlorobenzoyl chloride (2 equiv.), DMF, 20 h; followed by PhCOCl (3.5 equiv.), Py (5 equiv.), DCM, 2 h [alternatively: *N*-FMOC−Gly−OH (3 equiv.), HOBt (3 equiv.), DIC (3 equiv.), DMAP (cat.), DMF, 16 h; followed by Ac_2O (2 equiv.), DMAP (1 equiv.), DCM, 2 h]; b: 20% piperidine/DMF followed by *N*-FMOC−AA_2−OH (3 equiv.), DIC (3 equiv.), HOAt (3 equiv.), DCM/DMF, 2.5 h; c: 20% piperidine/DMF followed by *N*-FMOC−[bicyclic lactam]−OH (1 equiv.), HATU (2 equiv.), HOAt (2 equiv.), 2,4,6-collidine (2 equiv.), DCM/DMF, 15 h; d: acetyl imidazole (10 equiv.), DCM, 2 h; e: 20% piperidine/DMF followed by *N*-FMOC−AA_3−OH (4 equiv.), HATU (4 equiv.), HOAt (4 equiv.), 2,4,6-collidine (4 equiv.), DCM/DMF, 15 h; f: 20% piperidine/DMF followed by *N*-FMOC−AA_4−OH (3 equiv.), DIC (3 equiv.), HOAt (3 equiv.), DCM/DMF, 2.5 h; g: 20% piperidine/DMF followed by acetyl imidazole (10 equiv.), DCM, 2 h.



Scheme 3. General scheme for the cleavage of the constrained peptides from the Wang−Merrifield resin; a: TFA/H_2O, 95:5; b: $BnNH_2$ (1 equiv.), HATU (2 equiv.), 2,4,6-collidine (2 equiv.), DMF; c: CH_2N_2, AcOEt/Et_2O; d: MeOH/TEA/DMF, 50°C, 24 h.

group of the (5,7)-bicyclic lactam (type **a**), showing that 1 cycle was sufficient for quantitative coupling. The TNBS test failed with the (5,6)-bicyclic lactam (type **b**) because of the reduced reactivity of the more hindered amino group. In this case, after extensive optimization of the conditions, it was established (by cleavage from the resin) that two cycles were required for quantitative coupling of the *N*-FMOC−amino acid to the type-**b** lactam. After incorporation of the final *N*-FMOC−amino acid, the resulting constrained peptides were subjected to 20% piperidine/DMF treatment to deprotect the FMOC group, and subsequent acetylation with acetyl imidazole in dichloromethane to give the desired *N*-acetylated resin-bound peptides. Attempts to directly acetylate the amino group of the (5,6)-bicyclic lactam with acetylimidazole (synthesis of compound **5b**) were unsuccessful. In this case, acetylation was successfully achieved with Ac_2O/TEA in dichloromethane.

Final cleavage of the peptides from the resin was effected by acid treatment (TFA/H_2O, 95:5) with subsequent esterification of the resulting acids with diazomethane, or by direct synthesis of the methyl esters using a TEA/MeOH/DMF solution at 50°C.[5w] For the preparation of the benzyl amides, after the acidic cleavage (TFA/H_2O) the resulting acids were coupled with benzylamine in the presence of HATU and 2,4,6-collidine. For peptide derivatives containing methionine (compounds **7a** and **7b**) a TFA/H_2O/EtSMe solution (95:5:1) was used for the acidic cleavage, and after the usual work-up Ph_3P was added in order to prevent methionine oxidation. The desired final compounds (overall yields 20−50%) were easily separated from small amounts of mono- and dipeptides ($AcAA_2AA_1R$ or $AcAA_2R$; R = OMe, NHBn) by flash chromatography on silica gel (Scheme 3).

Conclusions

We have developed a solid-phase synthesis of the peptide mimics **4**−**15** incorporating the reverse-turn mimics **1a** and **1b**. This methodology renders these bicyclic lactams particularly attractive as building blocks for combinatorial chemistry. On the other hand, the conformational preferences of the synthesized peptides offer the possibility of investigating the secondary structures (β-turns, γ-turns and β-hairpins). Investigation of the conformational preferences of the peptide derivatives using NMR spectroscopy, IR spectroscopy, and computational methods is discussed in the accompanying paper.[8d] Further work on the preparation of combinatorial libraries of constrained peptides is in progress and will be reported in due course.

Experimental Section

General: Wang−Merrifield resin was purchased from Fluka and Novabiochem (100−200 mesh, 0.6−0.8 mmol/g). All products were purified by flash chromatography using 230−400 mesh silica gel (Merck). TLC analyses were performed with 0.25 mm 60 F_{254} silica plates (Merck). All the solvents used for the solid-phase synthesis were of HPLC quality or Analytical Reagent grade. Dichloromethane (DCM), diisopropylethylamine (DIPEA), triethylamine (TEA), *N*,*N*-dimethylformamide (DMF), and methanol (MeOH) were distilled from CaH_2 under nitrogen. 2,4,6-Collidine and 2,6-lutidine were purchased from Fluka and used without further purification. Organic extracts were dried with Na_2SO_4. All solid-phase reactions were carried out on a wrist shaker (Lab-Line multi-wrist shaker). − NMR: Bruker AC-200, Bruker AC-300. − Optical rotations: Perkin-Elmer 141 polarimeter. − UV: Perkin-Elmer Lambda 6 UV/Vis spectrophotometer. − Elemental analyses are available as Supporting Information on the www under http://www.wiley.vch.de/home/eurjoc or from the author.

Preparation of *N*-FMOC−[bicyclic lactam]−O*t*Bu (2)

General Procedure: FMOC−ONSu (1.5 equiv.) and 2,6-lutidine (1.5 equiv.) were added to a solution of H−[bicyclic lactam]−O*t*Bu (**1**) (0.17 mmol) in THF (1.7 ml) at 0°C, and the resulting mixture was stirred at this temperature for 6−7 h. Consumption of the starting material was monitored by TLC. The solvent was then evaporated under reduced pressure without heating and the resulting residue was purified by flash chromatography on silica gel.

(3*S*,7*S*,10*S*)-1-Aza-10-*tert*-butyloxycarbonyl-3-(9′-fluorenylmethoxycarbonylamino)-2-oxobicyclo[5,3,0]decane, *N*-FMOC−[(5,7)-bicyclic lactam]−O*t*Bu (2a): The general procedure was followed using **1a** and the crude reaction mixture was purified by flash column chromatography on silica gel (acetone/*n*-hexane, 25:75, R_f = 0.35). White solid, low melting point; yield 90%. − $[\alpha]_D$ = −27.3 (*c* = 0.56, $CHCl_3$). − ^{1}H NMR (300 MHz, $CDCl_3$, 300 K): δ = 7.75 (d, 2 H, *J* = 7.5 Hz, aromatic H), 7.60 (d, 2 H, *J* = 7.5 Hz, aromatic H), 7.40−7.23 (m, 4 H, aromatic H), 6.28 (d, 1 H, *J* = 7.5 Hz, N*H*FMOC), 4.52 (t, 1 H, *J* = 7.5 Hz, C*H*CO_2*t*Bu), 4.38−4.18 (m, 4 H, C*H*NHFMOC, NHCO_2CH_2, NHCO_2CH_2C*H*), 3.88−3.75 (m, 1 H, C*H*NCO), 2.29−1.40 (m, 10 H, CH_2), 1.49 (s, 9 H, *t*Bu). − ^{13}C NMR (50 MHz, $CDCl_3$, 300 K): δ = 170.9, 170.7, 155.4, 143.9, 141.2, 127.5, 126.9, 125.1, 119.8, 81.4, 66.8, 61.3, 59.1, 54.7, 47.1, 34.2, 32.8, 31.5, 27.9, 27.6.

(3*S*,6*S*,9*S*)-1-Aza-3-benzyl-9-*tert*-butyloxycarbonyl-3-(9′-fluorenylmethoxycarbonylamino)-2-oxobicyclo[4,3,0]nonane, *N*-FMOC−[(5,6)-bicyclic lactam]−O*t*Bu (2b): The general procedure was followed using **1b** and the resulting residue was purified by flash chromatography on silica gel (ethyl acetate/*n*-hexane, 30:70, R_f = 0.33). At room temperature, the ^{1}H-NMR spectrum in $CDCl_3$ showed the presence of two conformational isomers. A variable-temperature NMR study was carried out, in which the two rotamers became resolved at 323K ([D_6]benzene). White solid, low melting point; yield 90%. − $[\alpha]_D$ = +55.0 (*c* = 0.5, MeOH). − ^{1}H NMR (300 MHz, [D_6]benzene, 323 K): δ = 7.61 (d, 2 H, *J* = 7.1 Hz, aromatic H), 7.52 (t, 2 H, *J* = 7.1 Hz, aromatic H), 7.29−7.02 (m, 9 H, aromatic H), 6.13 (s, 1 H, N*H*FMOC), 4.50−4.30 (m, 2 H, NHCO_2CH_2), 4.28 (d, 1 H, *J* = 7.1 Hz, C*H*CO_2*t*Bu), 4.12 (t, 1 H, *J* = 7.1 Hz, NHCO_2CH_2C*H*), 3.51 (d, 1 H, *J* = 14.2 Hz, *H*CHPh), 3.31 (d, 1 H, *J* = 14.2 Hz, HC*H*Ph), 2.88 (br. s, 1 H, C*H*NCO), 2.68−2.53 (m, 1 H, CH), 2.12−2.03 (m, 1 H, CH), 1.70−1.28 (m, 6 H, CH_2), 1.42 (s, 9 H, *t*Bu). − ^{13}C NMR (75 MHz, [D_6]benzene, 323 K): δ = 171.5, 170.6, 155.7, 145.4, 142.5, 137.8, 131.9, 129.2, 129.0, 128.7, 128.5, 128.2, 128.0, 127.7, 126.3, 120.8, 81.9, 67.5, 61.3, 59.6, 48.6, 43.9, 32.5, 31.1, 29.9, 28.8, 27.6.

General Procedure for the Preparation of *N*-FMOC−[bicyclic lactam]−OH (3): A solution of the starting *N*-FMOC−[bicyclic lactam]−O*t*Bu (**2**) (0.14 mmol) in trifluoroacetic acid (1.08 mL) and dichloromethane (1.08 mL) was stirred at room temperature for 1.5 h. The solvents were then evaporated under reduced pressure and the crude residue thus obtained was used directly in the following steps.

General Procedure for *N*-FMOC−Amino Acid Loading onto Wang−Merrifield Resin

General Method A: Loading of *N*-FMOC−Gly−OH:[10] A mixture of *N*-FMOC−Gly−OH (0.84 mmol), HOBt (0.84 mmol), DIC (0.84 mmol), and DMAP (0.08 mmol) in DMF (3 mL) was added to a suspension of Wang−Merrifield resin (400 mg, 0.6−0.8 mmol/g, 0.28 mmol) in DMF (1.4 mL). After shaking for 16 h at room temperature, the resin was washed with DMF (5 × 5 mL) and DCM (5 × 5 mL). A quantitative picric acid test[12,16] indicated a loading of 0.62 mmol/g. Then, acetic anhydride (2 equiv., 0.56 mmol, 53 μL), DMAP (1 equiv., 0.28 mmol, 10 mg) and DCM (4 mL) were added and the resulting mixture was shaken for a further 2 h at room temperature. The solution was drained, the resin was washed with DMF (5 × 5 mL) and DCM (5 × 5 mL), and dried in vacuo.

General Method B: Loading of Other *N*-FMOC−Amino Acids:[11] 1.5 g of Wang−Merrifield resin (0.6−0.8 mmol/g, 1.05 mmol) and the corresponding *N*-FMOC−amino acid (2 equiv.) were shaken in DMF (13 mL) at room temperature for 15 min. Pyridine (3.3 equiv., 276 μL), and then 2,6-dichlorobenzoyl chloride (2 equiv., 297 μL) were added, and the suspension was shaken for 20 h at room temperature. It was then washed with DMF (5 × 10 mL) and DCM (5 × 10 mL), and dried in vacuo. The final loading was determined by performing a quantitative picric acid test (found loadings: 0.70 mmol/g for *N*-FMOC−Phe−OH, 0.62 mmol/g for *N*-FMOC−Val−OH and 0.64 mmol/g for *N*-FMOC−Met−OH). Capping was performed with benzoyl chloride (3.5 equiv., 420 μL) and pyridine (5 equiv., 417 μL) in DCM (13 mL) for 2 h. The solution was drained, the resin was rinsed with DCM (5 × 10 mL), and dried in vacuo.

General Procedure for the Preparation of the Resin-Bound Peptide Mimics

General Procedure 1: H−[Bicyclic lactam]−Gly−*O*−Wang-Merrifield Resin: A 5-mL solid-phase reaction vessel was charged with *N*-FMOC−Gly−O−Wang-Merrifield resin (0.62 mmol/g, 1.2 equiv.), which was treated with a 20% piperidine/DMF solution (2.7 mL, 1 × 3 min, 2 × 17 min). The solution was drained and the resin was washed with DMF (3 × 2 mL), MeOH (2 × 2 mL), and DCM (3 × 2 mL). Then, HATU (2 equiv.), HOAt (2 equiv.), the corresponding *N*-FMOC−[bicyclic lactam]−OH (1 equiv.), DCM/DMF (1:3, 2.4 mL/0.1 mmol of amino groups), and 2,4,6-collidine (2 equiv.) were successively added and the resulting mixture was shaken for 15 h at room temperature. The solution was drained and the resin was washed with DMF (3 × 2 mL), MeOH (2 × 2 mL), and DCM (3 × 2 mL). The unreacted amino groups possibly present were capped by treatment with a 0.33 M solution (10 equiv.) of acetylimidazole in DCM for 2 h. The solution was drained and the resin was washed with DCM (5 × 2 mL). At this stage, a TNBS test[13,17] indicated that the capping was complete. The FMOC group was deprotected following the same procedure as described above. The resulting resin was dried in vacuo and the title compounds were cleaved from it following one of the cleavage procedures outlined below.

General Procedure 2: Ac−[Bicyclic lactam]−Gly−*O*−Wang-Merrifield Resin: A 5-mL solid-phase reaction vessel was charged with *N*-FMOC−Gly−O−Wang-Merrifield resin (0.62 mmol/g, 1.2 equiv.), which was treated with a 20% piperidine/DMF solution (2.7 mL, 1 × 3 min, 2 × 17 min). The solution was drained and the resin was washed with DMF (3 × 2 mL), MeOH (2 × 2 mL), and DCM (3 × 2 mL). Then, HATU (2 equiv.), HOAt (2 equiv.), the corresponding *N*-FMOC−[bicyclic lactam]−OH (1 equiv.), DCM/DMF (1:3, 2.4 mL/0.1 mmol of amino groups), and 2,4,6-collidine (2 equiv.) were successively added and the mixture was shaken for 15 h at room temperature. The solution was drained and the resin was washed with DMF (3 × 2 mL), MeOH (2 × 2 mL), and DCM (3 × 2 mL). The unreacted amino groups possibly present were capped by treatment with a 0.33 M solution (10 equiv.) of acetylimidazole in DCM for 2 h. The solution was drained and the resin was rinsed with DCM (5 × 2 mL). At this stage, a TNBS test indicated that the capping was complete. The FMOC group was then deprotected following the same procedure as described above and the resulting free amino groups were acetylated using acetic anhydride (10 equiv.) and TEA (10 equiv.) in DCM (2.7 mL) for 2 h. After the usual washings with DCM (5 × 2 mL), the resin was dried in vacuo and the resulting compounds were cleaved from it following one of the cleavage procedures outlined below.

General Procedure 3: Ac−AA_3−[Bicyclic lactam]−AA_2−*O*−Wang-Merrifield Resin: A solid-phase reaction vessel was charged with *N*-FMOC−AA_2−O−Wang-Merrifield resin (1.2 equiv.), which was treated with a 20% piperidine/DMF solution (2 mL/100 mg of resin, 1 × 3 min., 2 × 17 min.). The solution was drained and the

resin was washed with DMF (3 × 2 mL), MeOH (2 × 2 mL), and DCM (3 × 2 mL). Then, HATU (2 equiv.), HOAt (2 equiv.), the corresponding *N*-FMOC−[bicyclic lactam]−OH (1 equiv.), DCM/DMF (1:3, 2.4 mL/0.1 mmol of amino groups), and 2,4,6-collidine (2 equiv.) were successively added and the mixture was shaken for 15 h at room temperature. The solution was drained and the resin was washed with DMF (3 × 2 mL), MeOH (2 × 2 mL), and DCM (3 × 2 mL). The unreacted amino groups possibly present were capped by treatment with a 0.33 M solution of acetylimidazole (10 equiv.) in DCM for 2 h. The solution was drained and washed with DCM (5 × 2 mL). The capping efficiency was assessed by performing a TNBS test and in the event of incomplete capping a second cycle was carried out. A solution of 20% piperidine in DMF was then used to deprotect the FMOC group following the same procedure as described above. *N*-FMOC−AA_3−OH (4 equiv.), HATU (4 equiv.), HOAt (4 equiv.), DCM/DMF (1:3, 4.38 mL/0.1 mmol of amino groups), and 2,4,6-collidine (4 equiv.) were successively added and the mixture was shaken at room temperature for 15 h. The solution was drained and the resin was rinsed with DMF (3 × 2 mL), MeOH (2 × 2 mL), and DCM (3 × 2 mL). This coupling reaction was followed by a TNBS test for the (5,7)-bicyclic lactam derivatives (**a** series), which showed that 1 cycle was sufficient for quantitative coupling. In the case of the (5,6)-bicyclic lactam (**b** series), this test failed and two coupling cycles were run in all cases. The FMOC group was again deprotected and a solution of acetylimidazole in DCM (10 equiv., 0.33 M) was used to acetylate the amino group (2 h cycles). The resin was rinsed with DCM (5 × 2 mL) and the acetylation was assessed by performing a TNBS test. The title compounds were cleaved from the resin following one of the cleavage procedures outlined below.

General Procedure 4: Ac−AA_4−AA_3−[Bicyclic lactam]−AA_2−AA_1−*O*−Wang-Merrifield Resin: A solid-phase reaction vessel was charged with *N*-FMOC−AA_1−O−Wang-Merrifield resin (1.2 equiv.), which was treated with a 20% piperidine/DMF solution [2 mL/100 mg of resin, 1 × 3 min., 2 × 17 min., washings with DMF (3 × 2 mL), MeOH (2 × 2 mL), DCM (3 × 2 mL)]. *N*-FMOC−AA_2−OH (3.6 equiv.) and HOAt (3.6 equiv.) were dissolved in anhydrous DCM and anhydrous DMF (DCM/DMF, 4:1, 0.062 M) under nitrogen. At 0°C, DIC (3.6 equiv.) was added dropwise to this solution. The resulting mixture was stirred for 10 min at this temperature and for a further 10 min at room temperature, then added to the aforementioned H−AA_1−O−Wang-Merrifield resin. This mixture was shaken at room temperature for 2.5 h. The solution was then drained and the resin was rinsed with DMF (3 × 2 mL) and DCM (3 × 2 mL). The success of the coupling was assessed by performing a TNBS test, which showed that 1 cycle was sufficient for quantitative coupling in all cases. A 20% piperidine/DMF solution was then used to deprotect the FMOC group (same procedure as above). Then, HATU (2 equiv.), HOAt (2 equiv.), the corresponding *N*-FMOC−[bicyclic lactam]−OH (1 equiv.), DCM/DMF (1:3, 2.4 mL/0.1 mmol of amino groups), and 2,4,6-collidine (2 equiv.) were successively added and the mixture was shaken for 15 h at room temperature. The solution was drained and the resin was washed with DMF (3 × 2 mL), MeOH (3 × 2 mL), and DCM (3 × 2 mL). The unreacted amino groups possibly present were capped by treatment with a 0.33 M solution of acetylimidazole (10 equiv.) in DCM for 2 h. The solution was drained and the resin was washed with DCM (5 × 2 mL). The capping efficiency was assessed by performing a TNBS test and in the event of incomplete capping a second cycle was carried out. After deprotection of the FMOC group following the usual procedure, *N*-FMOC−AA_3−OH (4 equiv.), HATU (4 equiv.), HOAt (4 equiv.), DCM/DMF (1:3, 4.38 mL/0.1 mmol of amino groups), and 2,4,6-collidine (4 equiv.) were successively added and the mixture was shaken at room temperature for 15 h. The solution was drained and the resin was rinsed with DMF (3 × 2 mL), MeOH (2 × 2 mL), and DCM (3 × 2 mL). The success of the coupling reaction was assessed by performing a TNBS test for the (5,7)-bicyclic lactam derivatives (**a** series), which showed that 1 cycle was sufficient for quantitative coupling. In the case of the (5,6)-bicyclic lactam (**b** series), this test failed and two coupling cycles were run in all cases. The FMOC group was again deprotected and a solution of *N*-FMOC−AA_4−OH (3 equiv.) in DCM/DMF (4:1, 0.062 M), preactivated with DIC (3 equiv.) and HOAt (3 equiv.) in the same manner as described above, was then added and the suspension was shaken for 2.5 h at room temperature. The solution was then drained and the resin was rinsed with DMF (3 × 2 mL) and DCM (3 × 2 mL). In all cases, TNBS tests showed that 1 coupling cycle was sufficient for completion of the reaction. The FMOC group was then deprotected and the resulting free amino groups were acetylated with a solution of acetylimidazole in DCM (10 equiv., 0.33 M) (2 h cycles). The resin was washed with DCM (5 × 2 mL) and the acetylation was assessed by performing a TNBS test. The title compounds were cleaved from the resin following one of the cleavage procedures outlined below.

Cleavage of the Peptide Mimics from the Resin

Cleavage as Methyl Esters. − General Procedure A: Acidic Cleavage: The appropriate resin was treated with TFA/H_2O solution (95:5, v/v) (5.2 mL/0.1 mmol, 1 × 3 min, 1 × 2 h, and 3 × 5 min). The solutions were drained, combined, and concentrated under reduced pressure to yield a residue, which was subsequently dissolved in AcOEt/Et_2O, 3:1 (3 mL). To this solution, cooled to 0°C, a freshly prepared and distilled solution of CH_2N_2 in Et_2O containing 2−3 mmol was added dropwise. After stirring for 10 min at 0°C and for 1 h at room temperature, the excess diazomethane was destroyed by the addition of a few drops of glacial acetic acid. Evaporation of the solvents under reduced pressure afforded a residue, which was subsequently purified by flash column chromatography on silica gel.

General Procedure B: Basic Cleavage:[5w] The appropriate resin was treated with an anhydrous TEA/MeOH/DMF solution (8.5 mL/0.1 mmol, 1:2:2, v/v/v) under nitrogen. The mixture was stirred (magnetic stirring bar) at 50°C (2 cycles, 24 h). After each cycle, the solution was transferred via a cannula (leaving the beads in the solid-phase reaction vessel for another cycle) to a flask, and the resin was washed twice with anhydrous methanol. Evaporation of the solvents under reduced pressure afforded a residue, which was subsequently purified by flash chromatography on silica gel.

Cleavage as Benzyl Amides. − General Procedure C: The appropriate resin was treated with TFA/H_2O solution (95:5, v/v) (5.2 mL/0.1 mmol, 1 × 3 min, 1× 2 h, and 3 × 5 min). The solutions were drained, combined, and concentrated under reduced pressure. A solution of benzylamine (1 equiv.) and 2,4,6-collidine (2 equiv.) in anhydrous DMF (10 mL/mmol of substrate) was added to the resulting residue under nitrogen. At 0°C, HATU (2 equiv.) was added to this solution and the mixture was stirred for 1 h at 0°C and for 17 h at room temperature. DCM, acetic acid (4 equiv.), and water were then added and the aqueous layer was extracted with DCM (3 times). The combined organic layers were dried with Na_2SO_4 and concentrated to yield a residue, which was subsequently purified by flash column chromatography on silica gel. In the case of compounds **7a**, **7b**, **15a**, and **15b**, after completion of the reaction the solvents were evaporated without heating and the residue was purified directly by flash column chromatography without any initial work-up.

Tripeptide Mimics

H−[(5,7)-Bicyclic lactam]−GlyOMe (4a): General Procedure 1 was followed. Cleavage from the resin using the basic method (General Procedure B) led to the isolation of the title compound after purification by flash column chromatography on silica gel (DCM/MeOH, 80:20, R_f = 0.16). Overall yield 37%. − $[\alpha]_D$ = +2.5 (*c* = 0.4, MeOH). − ^{1}H NMR (300 MHz, 20 mM, $CDCl_3$, 300 K): δ = 7.64 (br. s, 1 H, CON*H*CH_2CO_2Me), 4.78 (d, 1 H, *J* = 7.5 Hz, C*H*CONH), 4.15 (dd, 1 H, *J* = 7.5 Hz, *J′* = 22.5 Hz, *H*CHCO$_2$Me), 3.82 (dd, 1 H, *J* = 7.5 Hz, *J′* = 22.5 Hz, HC*H*CO$_2$Me), 3.80−3.68 (m, 2 H, C*H*NCO, C*H*NH$_2$), 3.72 (s, 3 H, OMe), 2.52 (br. s, 2 H, NH$_2$), 2.39−2.15 (m, 2 H, CH_2), 2.09−1.38 (m, 8 H, CH_2).

H−[(5,6)-Bicyclic lactam]−GlyOMe (4b): General Procedure 1 was followed. Cleavage from the resin using the basic method (General Procedure B) led to the isolation of the title compound after purification by flash column chromatography on silica gel (DCM/MeOH, 95:5, R_f = 0.23). Overall yield 63%. − $[\alpha]_D$ = −104.5 (*c* = 1.1, MeOH). − ^{1}H NMR (300 MHz, 65 mM, $CDCl_3$, 300 K): δ = 7.35−7.10 (m, 6 H, aromatic H, CON*H*CH_2CO_2Me), 4.42 (d, 1 H, *J* = 7.5 Hz, C*H*CONH), 4.08 (dd, 1 H, *J* = 7.5 Hz, *J′* = 22.5 Hz, *H*CHCO$_2$Me), 3.97 (dd, 1 H, *J* = 7.5 Hz, *J′* = 22.5 Hz, HC*H*CO$_2$Me), 3.72 (s, 3 H, OMe), 3.24 (part A of AB system, 1 H, *J* = 15.0 Hz, *H*CHPh), 3.18−3.03 (m, 2 H, NH$_2$), 2.79 (part B of AB system, 1 H, *J* = 15.0 Hz, HC*H*Ph), 2.28−2.15 (m, 1 H, C*H*NCO), 2.07−1.58 (m, 8 H, CH_2). − ^{13}C NMR (50 MHz, $CDCl_3$, 300 K): δ = 171.4, 170.3, 136.8, 130.5, 128.0, 126.5, 60.7, 59.5, 57.2, 52.2, 45.9, 41.1, 31.5, 29.6, 27.8, 25.9.

Ac−[(5,6)-Bicyclic lactam]−GlyOMe (5b): General Procedure 2 was followed. Cleavage from the resin using the acidic method (General Procedure A) led to the isolation of the title compound after purification by flash column chromatography on silica gel (DCM/MeOH, 95:5, R_f = 0.33). Overall yield 28%. − $[\alpha]_D$ = −75.0 (*c* = 0.4, MeOH). − ^{1}H NMR (300 MHz, $CDCl_3$, 20 mM, 300 K): δ = 7.60 (part X of ABX system, 1 H, *J* = 7.5 Hz, CON*H*CH_2CO_2Me), 7.33−7.16 (m, 5 H, aromatic H), 6.32 (s, 1 H, N*H*Ac), 4.41 (d, 1 H, *J* = 7.5 Hz, C*H*CONH), 4.21 (part A of ABX system, 1 H, *J* = 7.5 Hz, *J′* = 22.5 Hz, *H*CHCO$_2$Me), 3.72 (part B of ABX system, 1 H, *J* = 7.5 Hz, *J′* = 22.5 Hz, HC*H*CO$_2$Me), 3.70 (s, 3 H, OMe), 3.32 (part A of AB system, 1 H, *J* = 15.0 Hz, *H*CHPh), 2.93 (part B of AB system, 1 H, *J* = 15.0 Hz, HC*H*Ph), 2.58−2.48 (m, 1 H, C*H*NCO), 2.35−1.55 (m, 8 H, CH_2), 1.90 (s, 3 H, Ac). − ^{13}C NMR (75 MHz, $CDCl_3$, 300 K): δ = 173.5, 172.5, 170.4, 169.5, 135.5, 130.7, 128.3, 127.5, 60.6, 59.6, 56.5, 44.5, 41.1, 33.4, 31.1, 28.9, 27.5, 23.6.

***N*-Acetylated Tetrapeptide Mimics**

Ac−Phe−[(5,7)-Bicyclic lactam]−GlyOMe (6a): General Procedure 3 was followed, with the modification that DIPEA (8 equiv.) was used for the incorporation of *N*-FMOC−Phe−OH during 1 coupling cycle. Cleavage from the resin using the acidic method (General Procedure B) led to the isolation of the title compound after purification by flash column chromatography on silica gel (DCM/MeOH, 95:5, R_f = 0.29). Overall yield 9%. − $[\alpha]_D$ = −56.7 (*c* = 0.6, MeOH). − ^{1}H NMR (300 MHz, $CDCl_3$, 13 mM, 300 K): δ = 7.38−7.05 (m, 7 H, aromatic H, CON*H*CH_2CO_2Me, N*H*COCHBn), 5.96 (d, 1 H, *J* = 7.5 Hz, N*H*Ac), 4.72 (q, 1 H, *J* = 7.5 Hz, C*H*NHAc), 4.72−4.60 (m, 1 H, C*H*CONHCH$_2$-CO$_2$Me), 4.40 (dd, 1 H, *J* = 7.5 Hz, *J′* = 6.0 Hz, C*H*NHCOCHBn), 4.11 (dd, 1 H, *J* = 7.5 Hz, *J′* = 22.5 Hz, *H*CHCO$_2$Me), 3.81 (dd, 1 H, *J* = 7.5 Hz, *J′* = 22.5 Hz, HC*H*CO$_2$Me), 3.81−3.68 (m, 1 H, C*H*NCO), 3.70 (s, 3 H, OMe), 3.10 (dd, 1 H, *J* = 7.5 Hz, *J′* = 15.0 Hz, *H*CHPh), 3.02 (dd, 1 H, *J* = 7.5 Hz, *J′* = 15.0 Hz, HC*H*Ph), 2.42−2.20 (m, 2 H, CH_2), 2.08−1.35 (m, 8 H, CH_2), 1.95 (s, 3 H, Ac). − ^{13}C NMR (75 MHz, $CDCl_3$, 300 K): δ = 174.5, 172.1, 171.2, 169.9, 136.3, 129.2, 128.6, 127.0, 60.9, 59.6, 54.1, 53.4, 52.2, 41.0, 38.5, 34.7, 33.3, 31.0, 27.5, 25.9, 23.2.

Ac−Cys(*t*Bu)−[(5,7)-Bicyclic lactam]−Met−NHBn (7a): General Procedure 3 was followed. Cleavage from the resin was effected according to General Procedure C, with the modification that a TFA/H_2O/EtSMe (95:5:1, v/v/v) solution was used. After the usual work-up, Ph_3P (1 equiv.) was added to prevent methionine oxidation and the resulting crude material was purified by flash column chromatography on silica gel (first DCM and then DCM/MeOH, 95:5; R_f = 0.30 for the latter eluent). Overall yield 29%. − $[\alpha]_D$ = −17.7 (*c* = 0.6, MeOH). − ^{1}H NMR (300 MHz, $CDCl_3$, 10 mM, 300 K): δ = 7.49 [d, 1 H, *J* = 7.5 Hz, CON*H*CH(CH$_2$)$_2$SMe], 7.38−7.18 (m, 6 H, aromatic H, N*H*COCHNHAc), 6.78 (t, 1 H, *J* = 7.5 Hz, CON*H*Bn), 6.32 (d, 1 H, *J* = 7.5 Hz, N*H*Ac), 4.67−4.50 [m, 3 H, C*H*CONHCH(CH$_2$)$_2$SMe, C*H*NHCOCHN-HAc, C*H*NHAc], 4.50−4.38 [m, 3 H, CONHC*H*$_2$Ph, C*H*(CH$_2$)$_2$SMe], 3.85−3.70 (m, 1 H, C*H*NCO), 2.95 (dd, 1 H, *J* = 7.5 Hz, *J′* = 15.0 Hz, *H*CHS*t*Bu), 2.80 (dd, 1 H, *J* = 7.5 Hz, *J′* = 15.0 Hz, HC*H*S*t*Bu), 2.60−2.40 (m, 2 H, CH$_2$C*H*$_2$SMe), 2.30−1.75 (m, 10 H, C*H*$_2$CH$_2$SMe, CH_2), 2.06 (s, 3 H, Ac), 2.02 (s, 3 H, SMe), 1.58−1.18 (m, 2 H, CH_2), 1.32 (s, 9 H, S*t*Bu).

Ac−Gly−[(5,7)-Bicyclic lactam]−PheOMe (8a): General Procedure 3 was followed. Cleavage from the resin using the acidic method (General Procedure A) led to the isolation of the title compound after purification by flash column chromatography on silica gel (DCM/MeOH, 95:5, R_f = 0.20). Overall yield 24%. − $[\alpha]_D$ = − 37.5 (*c* = 0.40, MeOH). − ^{1}H NMR (300 MHz, $CDCl_3$, 30 mM, 300 K): δ = 7.30−7.10 (m, 7 H, aromatic H, CON*H*CHCO$_2$Me, N*H*COCH$_2$), 6.25 (br. s, 1 H, N*H*Ac), 4.82 (dd, 1 H, *J* = 7.5 Hz, *J′* = 15.0 Hz, C*H*CO$_2$Me), 4.65 (d, 1 H, *J* = 7.5 Hz, C*H*CONHCHBn), 4.40 (dd, 1 H , *J* = 7.5 Hz, *J′* = 15.0 Hz, C*H*NHCOCH$_2$), 4.01−3.88 (m, 2 H, C*H*$_2$NHAc), 3.78−3.52 (m, 1 H, C*H*NCO), 3.72 (s, 3 H, OMe), 3.22 (dd, 1 H, *J* = 7.5 Hz, *J′* = 15.0 Hz, *H*CHPh), 3.02 (dd, 1 H, *J* = 7.5 Hz, *J′* = 15.0 Hz, HC*H*Ph), 2.40−2.20 (m, 1 H, CH_2), 2.20−2.08 (m, 1 H, CH_2), 2.05 (s, 3 H, Ac), 1.90−1.55 (m, 6 H, CH_2), 1.30−0.78 (m, 2 H, CH_2). − ^{13}C NMR (50 MHz, $CDCl_3$, 300 K): δ = 171.9, 170.6, 170.2, 167.4, 135.9, 128.9, 128.5, 126.9, 61.3, 59.5, 53.2, 53.1, 52.4, 42.8, 37.5, 34.5, 33.1, 30.9, 27.2, 25.9, 22.9.

Ac−Gly−[(5,7)-Bicyclic lactam]−ValOMe (9a): General Procedure 3 was followed. Cleavage from the resin using the acidic method (General Procedure A) led to the isolation of the title compound after purification by flash column chromatography on silica gel (DCM/MeOH, 95:5, R_f = 0.25). Overall yield 28%. − $[\alpha]_D$ = −2.4 (*c* = 0.80, MeOH). − ^{1}H NMR (300 MHz, $CDCl_3$, 20 mM, 300 K): δ = 7.33 (d, 1 H, *J* = 7.5 Hz, NH), 7.28 (d, 1 H, *J* = 7.5 Hz, NH), 6.25 (br. s, 1 H, N*H*Ac), 4.72 (d, 1 H, *J* = 7.5 Hz, C*H*CONHC*i*Pr), 4.52−4.40 (m, 2 H, C*H*NHCOCH$_2$, C*H*CO$_2$Me), 4.10−3.88 (m, 2 H, C*H*$_2$NHAc), 3.85−3.68 (m, 1 H, C*H*NCO), 3.75 (s, 3 H, OMe), 2.40−1.60 (m, 9 H, MeC*H*Me, CH_2), 2.02 (s, 3 H, Ac), 1.53−1.20 (m, 2 H, CH_2), 0.90 (d, 3 H, *J* = 7.5 Hz, *Me*CHMe), 0.88 (d, 3 H, *J* = 7.5 Hz, MeCH*Me*). − ^{13}C NMR (75 MHz, $CDCl_3$, 300 K): δ = 172.3, 171.9, 171.0, 61.4, 59.6, 57.4, 53.3, 52.1, 49.0, 34.9, 33.3, 31.0, 29.6, 27.3, 26.0, 18.9, 18.5, 17.6.

Ac−Phe−[(5,7)-Bicyclic lactam]−Val−NHBn (10a): General Procedure 3 was followed. Cleavage from the resin according to General Procedure C led to the isolation of the title compound after purification by flash column chromatography on silica gel (DCM/

MeOH, 95:5, R_f = 0.28). Overall yield 44%. − $[\alpha]_D$ = − 63.2 (*c* = 0.76, MeOH). − ^{1}H NMR (300 MHz, $CDCl_3$, 50 mM, 300 K): δ = 7.88 (br. s, 1 H, N*H*COCHBn), 7.48 (d, 1 H, *J* = 7.5 Hz, CON*H*-CH*i*Pr), 7.38−7.00 (m, 5 H, aromatic H), 6.64 (t, 1 H, *J* = 7.5 Hz, CON*H*Bn), 6.25 (d, 1 H, *J* = 7.5 Hz, N*H*Ac), 4.98 (q, 1 H, *J* = 7.0 Hz, C*H*NHAc), 4.70 (d, 1 H, *J* = 7.5 Hz, C*H*CONHCH*i*Pr), 4.55−4.32 (m, 3 H, C*H*NHCOCHBn, CONHCH_2Ph), 4.26 (dd, 1 H, *J* = 7.5 Hz, *J′* = 8.0 Hz, C*Hi*Pr), 3.87−3.52 (m, 1 H, C*H*NCO), 3.00 (dd, 1 H, *J* = 7.5 Hz, *J′* = 15.0 Hz, *H*CHPh), 2.90 (dd, 1 H, *J* = 7.5 Hz, *J′* = 15.0 Hz, HC*H*Ph), 2.30−2.12 (m, 1 H, MeC*H*Me), 2.12−2.03 (m, 1 H, CH_2), 2.03−1.20 (m, 9 H, CH_2), 1.88 (s, 3 H, Ac), 0.9 (d, 3 H, *J* = 7.5 Hz, *Me*CHMe), 0.82 (d, 3 H, *J* = 7.5 Hz, MeCH*Me*). − ^{13}C NMR (50 MHz, $CDCl_3$, 300 K): δ = 171.7, 171.5, 170.8, 170.3, 170.1, 138.2, 136.4, 129.0, 128.5, 128.3, 127.5, 127.3, 126.9, 61.4, 59.7, 58.7, 53.6, 53.4, 43.2, 39.4, 34.6, 33.2, 31.6, 30.0, 27.4, 26.8, 22.9, 19.6, 17.6.

Ac−Phe−[(5,7)-Bicyclic lactam]−ValOMe (11a): General Procedure 3 was followed. Cleavage from the resin using the acidic method (General Procedure A) led to the isolation of the title compound after purification by flash column chromatography on silica gel (DCM/MeOH, 95:5, R_f = 0.34). Overall yield 40%. − $[\alpha]_D$ = −52.3 (*c* = 0.58, MeOH). − ^{1}H NMR (300 MHz, $CDCl_3$, 50 mM, 300 K): δ = 7.65 (br. s, 1 H, N*H*COCHBn), 7.38 (d, 1 H, *J* = 7.5 Hz, CON*H*CH*i*Pr), 7.25−7.02 (m, 5 H, aromatic H), 6.12 (d, 1 H, *J* = 7.5 Hz, N*H*Ac), 4.95−4.82 (m, 1 H, C*H*Bn), 4.75 (d, 1 H, *J* = 7.5 Hz, C*H*CONHCH*i*Pr), 4.50−4.40 (m, 2 H, C*H*NHCOCHBn, C*H*CO_2Me), 3.88−3.72 (m, 1 H, C*H*NCO), 3.71 (s, 3 H, OMe), 3.05 (dd, 1 H, *J* = 7.5 Hz, *J′* = 15.0 Hz, *H*CHPh), 2.92 (dd, 1 H, *J* = 7.5 Hz, *J′* = 15.0 Hz, HC*H*Ph), 2.32−2.18 (m, 2 H, CH_2), 2.18−2.05 (m, 1 H, MeC*H*Me), 2.05−1.38 (m, 8 H, CH_2), 1.91 (s, 3 H, Ac), 0.90 (d, 3 H, *J* = 7.5 Hz, *Me*CHMe), 0.85 (d, 3 H, *J* = 7.5 Hz, MeCH*Me*). − ^{13}C NMR (75 MHz, $CDCl_3$, 300 K): δ = 172.1, 171.7, 171.1, 170.2, 169.8, 136.3, 129.2, 128.5, 126.9, 61.3, 59.7, 57.3, 53.9, 53.5, 52.0, 39.2, 34.8, 33.3, 31.4, 30.9, 27.4, 26.4, 23.1, 19.2, 17.7.

Ac−Ala−[(5,7)-Bicyclic lactam]−ValOMe (12a): General Procedure 3 was followed. Cleavage from the resin using the acidic method (General Procedure A) led to the isolation of the title compound after purification by flash column chromatography on silica gel (DCM/MeOH, 95:5, R_f = 0.20). Overall yield 20%. − $[\alpha]_D$ = −85.5 (*c* = 0.4, MeOH). − ^{1}H NMR (300 MHz, $CDCl_3$, 20 mM, 300 K): δ = 7.45−7.32 (m, 2 H, CON*H*CH*i*Pr, N*H*COCHMe), 6.25 (d, 1 H, *J* = 7.5 Hz, N*H*Ac), 4.78 (d, 1 H, *J* = 7.5 Hz, C*H*CONHCHCO_2Me), 4.58 (quint, 1 H, *J* = 7.5 Hz, C*H*NHAc), 4.50−4.40 (m, 2 H, C*H*NHCOCHMe, C*H*CO_2Me), 3.85−3.68 (m, 1 H, C*H*NCO), 3.73 (s, 3 H, OMe), 2.39−1.70 (m, 9 H, MeC*H*Me, CH_2), 2.00 (s, 3 H, Ac), 1.52−1.28 (m, 2 H, CH_2), 1.35 (d, 3 H, *J* = 7.5 Hz, *Me*CHNHAc), 1.0−0.8 (m, 6 H, *Me*CH*Me*). − ^{13}C NMR (75 MHz, $CDCl_3$, 300 K): δ = 172.2, 170.7, 170.2, 167.6, 61.4, 59.7, 57.3, 53.4, 52.1, 35.1, 33.4, 31.3, 31.1, 27.4, 25.9, 23.0, 19.2, 17.7.

Ac−Phe−[(5,6)-Bicyclic lactam]−GlyOMe (6b): General Procedure 3 was followed, with the modification that 2,4,6-collidine (8 equiv. instead of 4 equiv.) was used for the incorporation of *N*-FMOC−Phe−OH during two coupling cycles. Cleavage from the resin using the acidic method (General Procedure A) led to the isolation of the title compound, together with 5% of another epimer, after purification by flash column chromatography on silica gel (DCM/MeOH, 95:5, R_f = 0.31). Overall yield 45%. Data for the major compound: − ^{1}H NMR (300 MHz, $CDCl_3$, 50 mM, 300 K): δ = 7.72 (t, 1 H, *J* = 6.0 Hz, CON*H*CH_2), 7.32−7.10 (m, 10 H, aromatic H), 7.00 (s, 1 H, N*H*COCHBn), 6.61 (d, 1 H, *J* = 8.0 Hz, N*H*Ac), 4.70 (q, 1 H, *J* = 7.0 Hz, C*H*NHAc), 4.40 (d, 1 H, *J* = 7.5 Hz, C*H*CONHCH_2), 4.10−3.95 (m, 2 H, CH_2CO_2Me), 3.70 (s, 3 H, OMe), 3.15 (part A of AB system, 1 H, *J* = 13.0 Hz, *H*CHPh), 3.04 (dd, 1 H, *J* = 7.0 Hz, *J′* = 14.0 Hz, *H*CHPh), 2.95 (dd, 1 H, *J* = 7.0 Hz, *J′* = 14.0 Hz, HC*H*Ph), 2.77 (part B of AB system, 1 H, *J* = 13.0 Hz, HC*H*Ph), 2.48−2.32 (m, 1 H, C*H*NCO), 2.22−1.50 (m, 8 H, CH_2), 1.99 (s, 3 H, Ac). − ^{13}C NMR (50 MHz, $CDCl_3$, 300 K): δ = 171.5, 171.2, 170.9, 169.6, 136.7, 134.4, 130.6, 129.2, 128.5, 128.3, 127.5, 126.8, 60.7, 59.7, 58.9, 53.9, 52.1, 44.9, 41.2, 37.2, 33.5, 30.9, 29.0, 27.4, 23.0.

Ac−Cys(*t*Bu)−[(5,6)-Bicyclic lactam]−Met−NHBn (7b): General Procedure 3 was followed. Cleavage from the resin was effected according to General Procedure C, with the modification that a TFA/H_2O/EtSMe (95:5:1, v/v/v) solution was used. After the usual work-up, Ph_3P (1 equiv.) was added to prevent methionine oxidation and the resulting crude material was purified by flash column chromatography on silica gel (DCM/MeOH, 97:3, R_f = 0.29). Overall yield 30%. − $[\alpha]_D$ = −80.0 (*c* = 0.8, MeOH). − ^{1}H NMR (300 MHz, $CDCl_3$, 40 mM, 300 K): δ = 7.79 [d, 1 H, *J* = 7.5 Hz, CON*H*CH$(CH_2)_2$SMe], 7.38 (t, 1 H, *J* = 7.5 Hz, CON*H*Bn), 7.33−7.12 (m, 10 H, aromatic H), 6.88 (d, 1 H, *J* = 7.5 Hz, N*H*Ac), 4.58−4.49 [m, 1 H, C*H*(CH_2)SMe], 4.49−4.30 [m, 4 H, C*H*NHAc, C*H*CONHCH$(CH_2)_2$SMe, CONHCH_2Ph], 3.22 (d, 1 H, *J* = 15.0 Hz, *H*CHPh), 2.88−2.78 (m, 3 H, HC*H*Ph, CH_2S*t*Bu), 2.59−1.73 (m, 12 H, CH_2CH_2SMe, C*H*NCO, CH_2), 2.10 (s, 3 H, SMe), 1.92 (s, 3 H, Ac), 1.55−1.41 (m, 1 H, CH_2), 1.30 (s, 9 H, S*t*Bu). − ^{13}C NMR (50 MHz, $CDCl_3$, 300 K): δ = 172.1, 171.3, 171.2, 170.5, 169.4, 138.0, 134.0, 130.7, 128.6, 128.4, 128.1, 127.6, 127.4, 60.9, 60.0, 58.5, 53.3, 52.4, 45.3, 43.3, 34.9, 31.5, 31.3, 30.9, 30.1, 29.5, 29.0, 27.5, 22.7, 15.4.

Ac−Ala−[(5,6)-Bicyclic lactam]−ValOMe (12b): General Procedure 3 was followed. Cleavage from the resin using the basic method (General Procedure B) led to the isolation of the title compound after purification by flash column chromatography on silica gel (DCM/MeOH, 97:3, R_f = 0.34). Overall yield 26%. − $[\alpha]_D$ = −123.6 (*c* = 0.5, MeOH). − ^{1}H NMR (300 MHz, $CDCl_3$, 5 mM, 300 K): δ = 7.32−7.11 (m, 8 H, aromatic H, CON*H*CH*i*Pr, N*H*COCHMe, N*H*Ac), 4.68−4.50 (m, 1 H, C*H*NHAc), 4.45−4.32 (m, 2 H, C*H*CONHCH*i*Pr, C*H*CO_2Me), 3.73 (s, 3 H, OMe), 3.23 (part A of AB system, 1 H, *J* = 15.0 Hz, *H*CHPh), 2.88 (part B of AB system, 1 H, *J* = 15.0 Hz, HC*H*Ph), 2.45−1.53 (m, 8 H, CH_2, C*H*NCO), 2.12 (s, 3 H, Ac), 1.53−1.32 (m, 1 H, CH_2), 1.28 (d, 3 H, *J* = 7.5 Hz, *Me*CHNHAc), 1.04−0.85 (m, 6 H, *Me*CH*Me*). − ^{13}C NMR (75 MHz, $CDCl_3$, 300 K): δ = 174.5, 173.0, 170.0, 135.5, 130.8, 128.2, 127.4, 60.9, 59.5, 58.0, 51.9, 47.9, 45.1, 33.4, 31.3, 30.3, 29.4, 27.5, 23.1, 19.2, 18.9, 16.1.

Ac−Ala−[(5,6)-Bicyclic lactam]−Val−NHBn (13b): General Procedure 3 was followed. Cleavage from the resin according to General Procedure C led to the isolation of the title compound after purification by flash column chromatography on silica gel (DCM/MeOH, 97:3, R_f = 0.30). Overall yield 30%. − $[\alpha]_D$ = −60.0 (*c* = 0.6, MeOH). − ^{1}H NMR (300 MHz, $CDCl_3$, 5 mM, 300 K): δ = 7.51 (d, 1 H, *J* = 7.5 Hz, CON*H*CH*i*Pr), 7.39−7.15 (m, 12 H, aromatic H, N*H*COCHMe, N*H*Ac), 6.92 (t, 1 H, *J* = 7.5 Hz, CON*H*Bn), 4.50 (q, 1 H, *J* = 7.5 Hz, NHCOC*H*Me), 4.43−4.30 (m, 3 H, CONHCH_2Ph, C*H*CONHCH*i*Pr), 3.97 (t, 1 H, *J* = 7.5 Hz, C*Hi*Pr), 3.18 (part A of AB system, 1 H, *J* = 15.0 Hz, *H*CHPh), 2.75 (part B of AB system, 1 H, *J* = 15.0 Hz, HC*H*Ph), 2.62−1.70 (m, 9 H, MeC*H*Me, C*H*NCO, CH_2), 1.92 (s, 3 H, Ac), 1.52−1.32 (m, 1 H, CH_2), 1.31 (d, 3 H, *J* = 7.5 Hz, *Me*CHNHAc), 1.05−0.92 (m, 6 H, *Me*CH*Me*).

***N*-Acetylated Hexapeptide Mimics**

Ac−Val−Ala−[(5,7)-Bicyclic lactam]−Val−GlyOMe (14a): General Procedure 4 was followed. Cleavage from the resin using the acidic method (General Procedure A) led to the isolation of the title compound after purification by flash column chromatography on silica gel (DCM/MeOH, 95:5, R_f = 0.14). Overall yield 23%. − $[\alpha]_D$ = −77.3 (*c* = 0.4, MeOH). − ^{1}H NMR (300 MHz, $CDCl_3$, 10 mM, 300 K): δ = 7.35 (d, 1 H, *J* = 7.5 Hz, N*H*COCHMe), 7.25 (d, 1 H, *J* = 7.5 Hz, CON*H*CH*i*Pr), 6.57 (part X of ABX system, 1 H, *J* = 7.5 Hz, CON*H*CH_2CO_2Me), 6.51 (d, 1 H, *J* = 7.5 Hz, N*H*COCH*i*Pr), 6.14 (d, 1 H, *J* = 9.0 Hz, N*H*Ac), 4.70 (d, 1 H, *J* = 7.5 Hz, C*H*CONHCH*i*Pr), 4.58−4.43 (m, 2 H, NHCOC*H*Me, C*H*NHCOCHMe), 4.35−4.23 (m, 2 H, C*H*iPr, C*H*NHAc), 4.10 (part A of ABX system, 1 H, *J* = 7.5 Hz, *J′* = 22.5 Hz, *H*$CHCO_2$Me), 4.00 (part B of ABX system, 1 H, *J* = 7.5 Hz, *J′* = 22.5 Hz, HC*H*CO_2Me), 3.88−3.70 (m, 1 H, C*H*NCO), 3.75 (s, 3 H, OMe), 2.40−2.22 (m, 2 H, MeC*H*Me, CH_2), 2.12−1.75 (m, 8 H, MeC*H*Me, CH_2), 2.04 (s, 3 H, Ac), 1.53−1.18 (m, 2 H, CH_2), 1.38 (d, 3 H, *J* = 7.5 Hz, NHCOCH*Me*), 1.00−0.88 (m, 12 H, *Me*CH*Me*, *Me*CH*Me*). − ^{13}C NMR (50 MHz, $CDCl_3$, 300 K): δ = 172.5, 170.9, 170.7, 169.9, 61.8, 59.7, 58.3, 53.4, 52.3, 48.8, 41.0, 35.2, 33.4, 31.3, 30.1, 29.6, 27.3, 25.9, 23.2, 19.4, 19.1, 18.6, 18.1, 17.4.

Ac−Val−Ala−[(5,7)-Bicyclic lactam]−Val−GlyNHBn (15a): General Procedure 4 was followed. Cleavage from the resin according to General Procedure C led to the isolation of the title compound after purification by flash column chromatography on silica gel (first DCM/MeOH, 95:5, and then DCM/MeOH, 90:10, R_f = 0.14 for the first eluent). Overall yield 50%. − $[\alpha]_D$ = −26.5 (*c* = 0.4, MeOH). − ^{1}H NMR (300 MHz, $CDCl_3$, 10 mM, 300 K): δ = 7.89 (d, 1 H, *J* = 7.5 Hz, N*H*COCHMe), 7.55 (t, 1 H, *J* = 7.5 Hz, CON*H*Bn), 7.45−7.18 (m, 7 H, aromatic H, CON*H*CH*i*Pr, N*H*Ac), 7.12 (br. s, 1 H, CON*H*CH_2CONHBn), 7.02 (d, 1 H, *J* = 7.5 Hz, MeCHN*H*CO), 4.60 (d, 1 H, *J* = 7.5 Hz, C*H*CONHCH-*i*Pr), 4.50−4.35 (m, 4 H, NHCOC*H*Me, C*H*NHCOCHMe, NHC*H*$_2$Ph), 4.25 (dd, 1 H, *J* = 7.5 Hz, *J′* = 9.0 Hz, C*H*iPr), 4.18−4.03 (m, 1 H, C*H*NAc), 3.90−3.70 (m, 3 H, C*H*$_2$CONHBn, C*H*NCO), 2.38−1.68 (m, 8 H, CH_2), 2.00 (s, 3 H, Ac), 1.50−1.17 (m, 2 H, CH_2), 1.38 (d, 3 H, *J* = 7.5 Hz, NHCOCH*Me*), 0.97−0.80 (m, 12 H, *Me*CH*Me*, *Me*CH*Me*). − ^{13}C NMR (75 MHz, $CDCl_3$, 300 K): δ = 173.1, 172.9, 171.2, 170.7, 139.0, 128.9, 128.5, 127.7, 62.1, 59.7, 59.3, 58.4, 53.6, 49.0, 43.0, 35.3, 33.3, 31.2, 31.0, 30.8, 29.6, 27.3, 25.9, 22.7, 19.1, 18.7, 17.5, 16.6.

Ac−Val−Ala−[(5,6)-Bicyclic lactam]−Val−GlyOMe (14b): General Procedure 4 was followed. Cleavage from the resin using the basic method (General Procedure B) led to the isolation of the title compound after purification by flash column chromatography on silica gel (first DCM/MeOH, 97:3; then DCM/MeOH, 95:5; R_f = 0.27 for the latter eluent). Overall yield 25%. − $[\alpha]_D$ = −26.0 (*c* = 0.3, MeOH). − ^{1}H NMR (300 MHz, $CDCl_3$, 10 mM, 300 K): δ = 7.53 (d, 1 H, *J* = 7.5 Hz, MeCHN*H*CO), 7.39 (d, 1 H, *J* = 7.5 Hz, CON*H*CH*i*Pr), 7.31−7.10 (m, 7 H, aromatic H, CON*H*CH_2, N*H*COCHMe), 6.12 (d, 1 H, *J* = 7.5 Hz, N*H*Ac), 4.60 (q, 1 H, *J* = 7.5 Hz, NHCOC*H*Me), 4.32−4.20 (m, 3 H, *H*$CHCO_2$Me, C*H*NHAc, C*H*CONHCH*i*Pr), 4.10 (t, 1 H, *J* = 7.5 Hz, C*H*iPr), 3.82 (s, 3 H, OMe), 3.72 (dd, 1 H, *J* = 7.5 Hz, *J′* = 18.1 Hz, HC*H*CO_2Me), 3.20 (part A of AB system, 1 H, *J* = 15.0 Hz, *H*CHPh), 2.72 (part B of AB system, 1 H, *J* = 15.0 Hz, HC*H*Ph), 2.52−2.37 (m, 1 H, MeC*H*Me), 2.37−1.97 (m, 3 H, CH_2), 2.03 (s, 3 H, Ac), 1.88−1.11 (m, 6 H, MeC*H*Me, CH_2), 1.30 (d, 3 H, *J* = 7.5 Hz, NHCOCH*Me*), 1.04−0.94 (m, 12 H, *Me*CH*Me*, *Me*CH*Me*). − ^{13}C NMR (75 MHz, $CDCl_3$, 300 K): δ = 172.3, 171.7, 134.8, 130.7, 128.3, 127.7, 61.0, 60.2, 58.7, 52.6, 47.8, 45.4, 41.5, 34.8, 31.3, 31.1, 29.7, 29.4, 28.5, 27.6, 23.3, 19.7, 17.9, 15.4.

Ac−Val−Ala−[(5,6)-Bicyclic lactam]−Val−GlyNHBn (15b): General Procedure 4 was followed. Cleavage from the resin according to General Procedure C led to the isolation of the title compound after purification by flash column chromatography on silica gel (DCM/MeOH, 95:5, R_f = 0.35). Overall yield 45%. − $[\alpha]_D$ = −53.3 (*c* = 0.6, MeOH). − ^{1}H NMR (300 MHz, $CDCl_3$, 40 mM, 300 K): δ = 7.80 (t, 1 H, *J* = 7.5 Hz, CON*H*Bn), 7.75 (d, 1 H, *J* = 7.5 Hz, MeCHN*H*CO), 7.53 (t, 1 H, *J* = 7.5 Hz, CON*H*CH_2), 7.45 (s, 1 H, N*H*COCHMe), 7.35 (d, 1 H, *J* = 7.5 Hz, CON*H*-CH*i*Pr), 7.32−7.03 (m, 10 H, aromatic H), 6.57 (d, 1 H, *J* = 7.5 Hz, N*H*Ac), 4.53 (quint, 1 H, *J* = 7.5 Hz, NHCOC*H*Me), 4.53−4.30 (m, 3 H, CONHC*H*$_2$Ph, C*H*CONNCH*i*Pr), 4.21 (t, 1 H, *J* = 7.5 Hz, C*H*NHAc), 4.18−3.95 (m, 2 H, *H*CHCONHBn, C*H*iPr), 3.78 (dd, 1 H, *J* = 7.5 Hz, *J′* = 22.5 Hz, HC*H*CONHBn), 3.25 (part A of AB system, 1 H, *J* = 15.0 Hz, *H*CHPh), 2.83 (part B of AB system, 1 H, *J* = 15.0 Hz, HC*H*Ph), 2.48−1.88 (m, 7 H, C*H*NCO, MeC*H*Me, MeC*H*Me, CH_2), 2.03 (s, 3 H, Ac), 1.88−1.62 (m, 2 H, CH_2), 1.50−1.20 (m, 2 H, CH_2), 1.12 (d, 3 H, *J* = 7.5 Hz, NHCOCH*Me*), 1.09−0.92 (m, 12 H, *Me*CH*Me*, *Me*CH*Me*). − ^{13}C NMR (75 MHz, $CDCl_3$, 300 K): δ = 173.3, 172.4, 172.3, 171.6, 171.0, 170.3, 138.8, 135.5, 130.8, 128.5, 128.2, 127.5, 127.4, 127.3, 77.2, 61.1, 60.1, 59.5, 47.9, 45.2, 44.4, 43.4, 40.4, 34.8, 31.5, 30.3, 29.1, 28.8, 27.9, 23.2, 19.7, 19.5, 18.2, 15.9.

Acknowledgments

We thank the Commission of the European Union (Fixed Contribution Contract for Training through Research ERB FMB ICT 960586) for financial support and for a postdoctoral fellowship to A. M.; N.A.T.O. (Collaborative Research Grant CRG-951194 to C. G. and H. P. N., Cold Spring Harbor Laboratory, N.Y., U.S.A.), Merck (Merck's Academic Development Program Award to C. G., 1996−1997), and MURST COFIN 1998−99 (Rome) for financial support.

[1] [1a] A. Giannis, T. Kolter, *Angew. Chem.* **1993**, *105*, 1303−1326; *Angew. Chem. Int. Ed. Engl.* **1993**, *32*, 1244−1267. − [1b] G. L. Olson, D. R. Bolin, M. P. Bonner, M. Bös, C. M. Cook, D. C. Fry, B. J. Graves, M. Hatada, D. E. Hill, M. Kahn, V. S. Madison, V. K. Rusiecky, R. Sarabu, J. Sepinwall, G. P. Vincent, M. E. Voss, *J. Med. Chem.* **1993**, *36*, 3039−3049. − [1c] R. M. J. Liskamp, *Recl. Trav. Chim. Pays-Bas* **1994**, *113*, 1−19. − [1d] U. Slomczynska, D. K. Chalmers, F. Cornille, M. L. Smythe, D. D. Beusen, K. D. Moeller, G. R. Marshall, *J. Org. Chem.* **1996**, *61*, 1198−1204. − [1e] S. Hanessian, G. McNaughton-Smith, H.-G. Lombart, W. D. Lubell, *Tetrahedron* **1997**, *38*, 12789−12854.

[2] [2a] L. G. Pease, C. Watson, *J. Am. Chem. Soc.* **1978**, *100*, 1279−1286. − [2b] A. F. Spatola, M. K. Anwer, A. L. Rockwell, L. M. Gierasch, *J. Am. Chem. Soc.* **1986**, *108*, 825−831. − [2c] A.-M. Sapse, L. Mallah-Levy, S. B. Daniels, B. W. Erickson, *J. Am. Chem. Soc.* **1987**, *109*, 3256. − [2d] K. Burgess, K.-K. Ho, *J. Am. Chem. Soc.* **1994**, *116*, 799−800. − [2e] R. Haubner, R. Gratias, B. Diefenbach, S. L. Goodman, A. Jonczyk, H. Kessler, *J. Am. Chem. Soc.* **1996**, *118*, 7461−7472.

[3] [3a] D. S. Kemp, B. R. Bowen, *Tetrahedron Lett.* **1988**, *29*, 5077−5080. − [3b] D. S. Kemp, B. R. Bowen, *Tetrahedron Lett.* **1988**, *29*, 5081−5082. − [3c] D. S. Kemp, B. R. Bowen, C. C. Muendel, *J. Org. Chem.* **1990**, *55*, 4650−4657.

[4] [4a] D. S. Kemp, P. McNamara, *Tetrahedron Lett.* **1982**, *23*, 3761−3764. − [4b] D. S. Kemp, W. E. Stites, *Tetrahedron Lett.* **1988**, *29*, 5057−5060. − [4c] U. Nagai, K. Sato, R. Nakamura, R. Kato, *Tetrahedron* **1993**, *49*, 3577−3592. − [4d] J.-P. Dumas, J. P. Germanas, *Tetrahedron Lett.* **1994**, *35*, 1493−1496. − [4e] W. F. Michne, J. D. Schoroeder, *Int. J. Protein Res.* **1996**, *47*, 2. − [4f] T. S. Haque, J. C. Little, S. H. Gellman, *J. Am. Chem.*

Soc. **1996**, *118*, 6975−6985. − [4g] K. Kyonghee, J. P. Germanas, *J. Org. Chem.* **1997**, *62*, 2847−2852. − [4h] K. Kyonghee, J. P. Germanas, *J. Org. Chem.* **1997**, *62*, 2853−2860. − [4i] C. Strässler, A. Linden, H. Heimgartner, *Helv. Chim. Acta* **1997**, *80*, 1528−1551. − [4j] T. S. Haque, S. H. Gellman, *J. Am. Chem. Soc.* **1997**, *119*, 2303−2304. − [4k] S. Krauthäuser, L. A. Christianson, D. R. Powell, S. H. Gellman, *J. Am. Chem. Soc.* **1997**, *119*, 11719−11720. − [4l] T. Kayashi, T. Asai, H. Ogoshi, *Tetrahedron Lett.* **1997**, *38*, 3039−3042. − [4m] S. Hanessian, H. Yang, *Tetrahedron Lett.* **1997**, *38*, 3155−3158.

[5] [5a] M. Feigel, *J. Am. Chem. Soc.* **1986**, *108*, 181−182. − [5b] M. Feigel, *Liebigs Ann. Chem.* **1989**, 459−468. − [5c] V. Brandmeier, M. Feigel, *Tetrahedron* **1989**, *45*, 1365−1376. − [5d] V. Brandmeier, M. Feigel, *Angew. Chem.* **1989**, *102*, 466−468; *Angew. Chem. Int. Ed. Engl.* **1989**, *28*, 486−488. − [5e] H. Díaz, J. R. Espina, J. W. Kelly, *J. Am. Chem. Soc.* **1992**, *114*, 8316−8318. − [5f] B. Gardner, H. Nanashi, M. Khan, *Tetrahedron* **1993**, *49*, 3433−3448. − [5g] H. Díaz, K. Y. Tsang, D. Choo, J. W. Kelly, *Tetrahedron* **1993**, *49*, 3533−3545. − [5h] W. C. Ripka, G. V. De Lucca, A. C. Bach II, R. S. Pottorf, J. M. Blaney, *Tetrahedron* **1993**, *49*, 3609−3628. − [5i] H. Díaz, K. Y. Tsang, D. Choo, J. R. Espina, J. W. Kelly, *J. Am. Chem. Soc.* **1993**, *115*, 3790−3793. − [5j] K. Y. Tsang, H. Diaz, N. Graciani, J. W. Kelly, *J. Am. Chem. Soc.* **1994**, *116*, 3988−4005. − [5k] V. Brandmeier, W. H. B. Sauer, M. Feigel, *Helv. Chim. Acta* **1994**, *77*, 70−85. − [5l] D. S. Kemp, Z. Q. Li, *Tetrahedron Lett.* **1995**, *36*, 4175−4178. − [5m] D. S. Kemp, Z. Q. Li, *Tetrahedron Lett.* **1995**, *36*, 4179−4180. − [5n] S. R. Labrenz, J. W. Kelly, *J. Am. Chem. Soc.* **1995**, *117*, 1655−1656. − [5o] J. P. Schneider, J. W. Kelly, *J. Am. Chem. Soc.* **1995**, *117*, 2533−2546. − [5p] R. R. Gardner, G.-B. Liang, S. H. Gellman, *J. Am. Chem. Soc.* **1995**, *117*, 3280−3281. − [5q] K. C. L. Nesloney, J. W. Kelly, *J. Org. Chem.* **1996**, *61*, 3127−3137. − [5r] K. McWilliams, J. W. Kelly, *J. Org Chem.* **1996**, *61*, 7408−7414. − [5s] J. S. Nowick, D. L. Holmes, G. Mackin, G. Noronha, A. J. Shaka, E. M. Smith, *J. Am. Chem. Soc.* **1996**, *118*, 2764−2765. − [5t] C. L. Nesloney, J. W. Kelly, *J. Am. Chem. Soc.* **1996**, *118*, 5836−5845. − [5u] E. M. Smith, D. L. Holmes, A. J. Shaka, J. S. Nowick, *J. Org. Chem.* **1997**, *62*, 7906−7907. − [5v] J. S. Nowick, M. Pairish, I. Q. Lee, D. L. Holmes, J. W. Ziller, *J. Am. Chem. Soc.* **1997**, *119*, 5413−5420. − [5w] D. L. Holmes, E. M. Smith, J. S. Nowick, *J. Am. Chem. Soc.* **1997**, *119*, 7655−7669. − [5x] I. G. Jones, W. Jones, M. North, *J. Org. Chem.* **1998**, *63*, 1505−1513.

[6] [6a] G. Wagner, M. Feigel, *Tetrahedron* **1993**, *49*, 10831−10841. − [6b] M. J. Winningham, D. Y. Sogah, *J. Am. Chem. Soc.* **1994**, *116*, 11173−11174. − [6c] S. Nowick, E. M. Smith, G. Noronha, *J. Org. Chem.* **1995**, *60*, 7386−7387. − [6d] A. B. Gretchikhine, M. Y. Ogawa, *J. Am. Chem. Soc.* **1996**, *118*, 1543−1544. − [6e] M. L. Skar, J. S. Svendsen, *Tetrahedron* **1997**, *53*, 17425−17440. − [6f] M. J. Winningham, D. Y. Sogah, *Macromolecules* **1997**, *30*, 862−876 .

[7] [7a] C. A. Kim, J. M. Berg, *Nature* **1993**, *362*, 267−270. − [7b] D. L. Minor Jr., P. S. Kim, *Nature* **1994**, *371*, 264−268. − [7c] D. L. Minor Jr., P. S. Kim, *Nature* **1994**, *367*, 660−662. − [7d] C. K. Smith, J. M. Withka, L. Regan, *Biochemistry* **1994**, *33*, 5510−5517. − [7e] J. S. Nowick, S. Insaf, *J. Am. Chem. Soc.* **1997**, *119*, 10903−10908.

[8] [8a] L. Colombo, M. Di Giacomo, L. Belvisi, L. Manzoni, C. Scolastico, A. Salimbeni, *Gazz. Chim. Ital.* **1996**, *126*, 543−554. − [8b] A. Salimbeni, F. Paleari, R. Canevotti, M. Criscuoli, A. Lippi, M. Angiolini, L. Belvisi, C. Scolastico, L. Colombo, *Bioorg. Med. Chem. Lett.* **1997**, *7*, 2205−2210. − [8c] L. Colombo, M. Di Giacomo, G. Brusotti, N. Sardone, M. Angiolini, L. Belvisi, S. Maffioli, L. Manzoni, C. Scolastico, *Tetrahedron* **1998**, *54*, 5325−5326. − [8d] L. Belvisi, C. Gennari, A. Mielgo, D. Potenza, C. Scolastico, *Eur. J. Org. Chem.* **1999**, 389−400.

[9] S. S. Wang, *J. Am. Chem. Soc.* **1973**, *95*, 1328−1333.

[10] [10a] M. Pàtek , Z. Flegilovà, *J. Org. Chem.* **1996**, *61*, 6735−6738. − [10b] R. Athernon, R. C. Sheppard, *Solid-Phase Peptide Synthesis*, Oxford University Press, **1989**, p. 136.

[11] P. Sieber, *Tetrahedron Lett.* **1987**, *28*, 6147−6150.

[12] B. Gisin, *Anal. Chim. Acta* **1972**, *58*, 248−249.

[13] W. S. Hancock, J. E. Battersby, *Anal. Biochem.* **1976**, *71*, 260−264.

[14] [14a] L. A. Carpino, *J. Am. Chem. Soc.* **1993**, *115*, 4397−4398. − [14b] L. A. Carpino, A. El-Faham, *J. Org. Chem.* **1994**, *59*, 695−698. − [14c] L. A. Carpino, A. El-Faham, C. A. Minor, F. Albericio, *J. Chem. Soc., Chem. Commun.* **1994**, 201−203. − [14d] L. A. Carpino, A. El-Faham, F. Albericio, *Tetrahedron Lett.* **1994**, *35*, 2279−2282. − [14e] L. A. Carpino, A. El-Faham, *J. Org. Chem.* **1995**, *60*, 3561−3564.

[15] [15a] J. M. Humphrey, J. B. Aggen, A. R. Chamberlin, *J. Am. Chem. Soc.* **1996**, *118*, 11759−11770. − [15b] C. L. Wysong, T. S. Yokum, G. A. Morales, R. L. Gundry, M. L. McLaughlin, R. P. Hammer, *J. Org. Chem.* **1996**, *61*, 7650−7651. − [15c] A. Virgilio, S. C. Schürer, J. A. Ellman, *Tetrahedron Lett.* **1996**, *37*, 6961−6964. − [15d] T. Y. Chan, A. Chen, N. Allanson, R. Chen, D. Liu, M. J. Sofia, *Tetrahedron Lett.* **1996**, *37*, 8097−8100. − [15e] A. A. Virgilio, A. A. Bray, W. Zhang, L. Trinh, M. Snyder, M. M. Morrissey, J. A. Ellman, *Tetrahedron* **1997**, *53*, 6635−6644. − [15f] S. L. Mellor, C. McGuire, W. C. Chan, *Tetrahedron Lett.* **1997**, *38*, 3311−3314. − [15g] A. Nefzi, J. M. Ostresh, R. A. Houghten, *Tetrahedron Lett.* **1997**, *38*, 4943−4946. − [15h] S. C. Miller, T. S. Scalan, *J. Am. Chem. Soc.* **1997**, *119*, 2301−2302. − [15i] R. A. Goodnow, S. Tam, D. L. Pruess, W. W. McComas, *Tetrahedron Lett.* **1997**, *38*, 3199−3202. − [15j] R. T. Pon, S. Yu, *Tetrahedron Lett.* **1997**, *38*, 3331−3334. − [15k] I. R. Marsh, M. Bradley, *J. Org. Chem.* **1997**, *62*, 6199−6203. − [15l] A. K. Szardenings, T. S. Burkoth, *Tetrahedron* **1997**, *53*, 6573−6593.

[16] The original procedure was slightly modified: A sample of the dried resin was taken and weighed. After deprotection of the FMOC group following the usual procedure, the resulting resin (free amino groups) was treated with a 0.1 M solution of picric acid in DCM (2 × 1 min) and then repeatedly washed with DCM until the washings were no longer yellow. The picrate was then eluted with a 5% (v/v) solution of DIPEA in DCM (2 × 1 min) and after careful washing with DCM (again until the disappearance of the yellow colour in the washings), the collected eluates were pooled. DCM was evaporated in vacuo and the resulting picrate was then diluted with absolute EtOH so as to give a suitable UV/Vis absorbance. The absorbance was measured at 358 nm. DIPEA picrate has $\varepsilon = 14500$ (a 10^{-5} M solution has $A = 0.145$). For further details, see ref.[12]

[17] Procedure: A few resin beads were sampled and washed several times with ethanol. The sample was then placed in a vial and 1 drop of a 10% solution of DIPEA in DMF and 1 drop of 1% 2,4,6-trinitrobenzenesulfonic acid (TNBS) in DMF were added. The sample was then viewed under a microscope and colour changes were noted. The TNBS test is considered to be positive (presence of free amino groups) when the resin beads turn orange or red within 1 min and negative (no free amino groups) when the beads remain colourless. For further details, see ref.[13]

Received September 2, 1998
[O98399]