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Succinimidyl Carbamate Derivatives from *N*-Protected α-Amino Acids and Dipeptides−Synthesis of Ureidopeptides and Oligourea/Peptide Hybrids

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The preparation of succinimidyl (1-{[(alkyloxy)carbonyl]-amino}-1-X-methyl)carbamates (**4**) and succinimidyl [1-(acyl-amino)-1-X-methyl] carbamates (**5**) from a variety of *N*-Boc-, -Z- or -Fmoc-protected α-amino acids and dipeptides as well as the carbamate structural characterization are described. We have previously shown that succinimidyl carbamates **5**, derived from *N*-Boc dipeptides, can serve as direct precursors of 1,3,5-triazepan-2,6-diones, a novel class of conformationally constrained dipeptide mimetics. Herein, we have evaluated the use of these building blocks for the synthesis of ureido-peptides (in solution and on solid support), peptidyl hydantoins, oligoureas and some oligo(urea/amide) hybrids. Conformational investigations by NMR of ureidotripeptide **6i** and pentamer **10**, consisting of alternating amides and ureas, suggested that folded conformations (i.e. a urea turn) characterized by a *cis*,*trans* (*E*,*Z*) geometry of the urea linkage are populated in both [D_5]pyridine and [D_6]DMSO solutions.

Introduction

Intense research has been focused over the past 25 years on chemical modifications of the peptide backbone (i.e. backbone chemistry). The introduction of peptide bond surrogates (denoted ψ[...], according to Spatola's nomenclature for pseudopeptides)[1a] is long recognized as a powerful strategy to enhance biological lifetime of peptides, to improve biological activity or selectivity, to design enzyme inhibitors as well as to induce particular conformational features.[1] An exiting focus of backbone chemistry is the design and synthesis of oligomeric molecules with unnatural backbones for the creation of novel secondary structures[2] and for applications in biology.[3] In the field of peptide mimetics, the urea moiety as a non-peptide linkage has attracted much attention in recent years. Several families of peptide mimetics with a urea backbone, including *N*,*N*-linked oligoureas [N(CONHR)–$(CH_2)_m$–]$_n$,[4] *N*,*N*′-linked oligoureas [NH–CHR–CH_2–NH–CO–]$_n$,[5] ureidopeptoids [NR–CH_2–CH_2–NH–CO–]$_n$[6] and oligomeric imidazolidinones[7] have been described. The urea fragment is promising for drug discovery and biomedical applications because of its expected resistance to protease degradation and interesting H-bonding properties.[8–10] In the solid state, *N*,*N*′-disubstituted ureas are often involved in self-complementary bidirectional intermolecular H-bonds because of the *trans* geometry of the two amide bonds (*Z*,*Z* conformer).[11–13] Self-organization at the molecular level has also been documented. *N*,*N*-linked oligoureas have be used by Nowick and coworkers to generate intramolecular H-bonded structures that mimic protein secondary structural elements such as β-sheets and hairpin turns.[4] Moreover, we have shown, with a combination of NMR spectroscopy and circular dichroism, that enantiopure *N*,*N*′-linked oligourea strands bearing proteinogenic side-chains [NH–CHR–CH_2–NH–CO–]$_n$ as short as seven residues adopt a stable helical fold stabilized by remote intrastrand bifurcated H-bonds, which is reminiscent of the 14-helix described for the corresponding γ^4-peptides [NH–CHR–CH_2–CH_2–CO–]$_n$.[14] The predictability of folding of these oligourea strands can be integrated with the diversity of available side-chain appendages to develop molecules with specific functions (e.g. antibacterial, amphiphilic, cationic oligoureas[15]).

In this context, modification of peptides by introducing a ureido linkage ψ[NH–CO–NH] between two neighbouring α-amino acids is of particular interest. The insertion of a urea fragment between two amino acids has long been seen as a side reaction resulting from an unwanted Curtius

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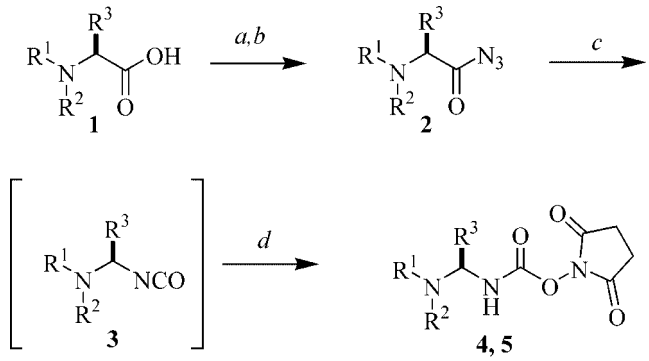
rearrangement occurring even at low temperature during peptide coupling with peptidyl–and aminoacyl azide derivatives.[16] Thirty years ago, Chipens and coworkers first synthesized ureido analogues of biologically active peptides to study their activity.[17] They prepared a number of angiotensin analogues containing a urea fragment at various positions in the sequence by direct condensation in solution of a peptidyl isocyanate with the free amino group of a second peptide fragment. Other applications of ureidopeptides to biology include the synthesis of Leu-enkephalin analogues,[18] gastrin antagonists,[19] protease inhibitors[20] and a growth hormone secretagogue with strong in vivo activity in the rat.[21] However, little is known about the conformational preferences of pseudopeptides incorporating one or several ureido unit(s).[22,23] We have recently started to investigate the intramolecular H-bonding propensities and conformational behaviour of model ureidopeptides in solution.[23] As a result of competitive conjugation, the barriers of rotation of substituted ureas are lower than those of corresponding amides, and one might expect greater flexibility of the urea linkage in solution. Accordingly, we found that the urea moiety in simple *N*-acyl-*N′*-carbamoyl-*gem*-diaminolalkyl residues bearing proteinogenic side-chains adopts a *cis,trans* (*E,Z*) geometry that can be further stabilized by an intramolecular H-bond in nonpolar organic solvent. The resulting eight-membered (C_8) H-bonded ring has been termed a "urea turn".[23]

With the aim to study in more detail the propensity for urea turn formation in a more comprehensive set of ureidopeptides, including previously unreported oligourea/peptide hybrids (made of alternating urea and amide moieties), as well as to incorporate ureido moieties into bioactive peptide segments,[24] we have now investigated the preparation and reactivity of a variety of succinimidyl carbamates derived from *N*-protected α-amino acids and dipeptides. Succinimidyl carbamates, which combine both excellent reactivity and stability[5f,5g,14b] are useful substitutes for the corresponding isocyanates, which may degrade upon prolonged storage. In addition, we previously reported that linear diamino derivatives (e.g. derived from *N,N′*-linked oligoureas [NH–CHR–CH_2–NH–CO–]$_n$, or dipeptides) activated at one end as a succinimidyl carbamate and protected at the other end by a Boc group are useful intermediates in the synthesis of cyclic urea-based systems (e.g. macrocyclic oligoureas[13b] and 1,3,5-triazepan-2,6-dione dipeptidomimetics[13c,25]).

Results and Discussion

Succinimidyl Carbamates from α-Amino Acids and Dipeptides

The reaction sequence we employed for the preparation of succinimidyl (1-{[(alkyloxy)carbonyl]amino}-1-X-methyl)carbamates (**4**) and succinimidyl [1-(acylamino)-1-X-methyl] carbamates (**5**) starting from *N*-protected α-amino acids and dipeptides, respectively, is outlined in Scheme 1.



Scheme 1. *a*: EtOCOCl, NMM, THF, –20 °C; *b*: NaN_3, H_2O; *c*: toluene, 65 °C; *d*: *N*-hydroxysuccinimide, pyridine.

It is analogous to that developed by Goodman and coworkers for the synthesis of *N,N′*-diacylated 1,1-diaminoalkanes en route to partially modified retro-inverso peptides (PMRI).[26–28] *N*-protected α-amino acids and dipeptides **1** were first converted into the corresponding acyl azides **2** by reaction of their mixed anhydrides [formed with EtOCOCl/*N*-methylmorpholine (NMM) in THF] with NaN_3. Isocyanates **3**, generated in situ upon heating acyl azides **3** in toluene, were treated with *N*-hydroxysuccinimide to give carbamates **4** and **5**. In most cases, succinimidyl carbamates **4** and **5** precipitated directly from the toluene solution at room temperature or upon cooling and were recovered by filtration. Analytically pure samples were usually obtained either directly by trituration with a CH_2Cl_2/iPr_2O solution after an aqueous workup or after purification by preparative C_{18} RP-HPLC with a gradient of solvent A (0.1% aqueous TFA) and solvent B (MeCN containing 0.08% TFA).[29] Overall, succinimidyl carbamates **5** derived from differentially functionalized *N*-Boc, -Z and -Fmoc dipeptides were recovered in higher yields than carbamates derived from *N*-Boc amino acids (Table 1).

These results are in agreement with those previously reported by Goodman and coworkers in a study on diacylated *gem*-diaminoalkyl residues derived from Boc-, Z- and acetyl phenylalanine.[30] They found that side reactions associated with MeOH or benzyl alcohol addition to the corresponding isocyanate vary with the nature of the N protecting group, and that the acyl group gives consistently better results than alkyloxycarbonyl-type protections (Ac > Z > Boc).

Although it is well known that the Curtius rearrangement proceeds with complete retention of configuration,[31] epimerization might still occur either during the formation of the acyl azide or during the reaction of the isocyanate with *N*-hydroxysuccinimide.[32] The stereoselectivity of the series of steps leading to the succinimidyl carbamate (e.g. **5d**) from the corresponding dipeptide was investigated with RP-HPLC on a C_{18} column. HPLC analysis of a crude sample of **5d** (Figure 1, a) and comparison with an equimolar mixture of **5d** and its epimer Boc-L-Ile-D-*g*Val-CO-OSu[33] (*epi*-**5d**) (Figure 1, b) revealed that no epimerization occurred at the α-CH of the *g*Val residue (**5d**/*epi*-**5d** > 200:1).

Table 1. Succinimidyl carbamates **4** and **5** generated from *N*-protected α-amino acids and dipeptides **1**.

Entry	Compd.	R^1	R^2	R^3	% Yield[a]
1	**4a**	Boc	H	Bn	88
2	**4b**	Boc	H	CH_2OBn	60
3	**4c**	Boc	H	Me	58
4	**4d**	Boc	H	H	50
5	**4e**	Boc	H	*i*Bu	55
6	**4f**	Boc		$-(CH_2)_3-$	51
7	**4g**	Z	H	*i*Bu	82
8	**4h**	Z	H	Bn	76
9	**5a**	Boc-Gly	H	*s*Bu	87
10	**5b**	Boc-Ala	H	Bn	91
11	**5c**	Boc-Phe	H	*i*Bu	82
12	**5d**	Boc-Ile	H	*i*Pr	62
13	***epi*-5d**	Boc-Ile	H	*i*Pr	85
14	**5e**	Boc-Lys	H	*i*Pr	69
15	**5f**	Boc-Pro	H	*i*Pr	72
16	**5g**	Boc-Pro	H	*i*Bu	76
17	**5h**	Boc-Pro	H	Me	43
18	**5i**	Boc-Pro	H	Bn	79
19	**5j**	Boc-Glu(-O*t*Bu)	H	*i*Bu	83
20	**5k**	Boc-Ser(Bn)	H	*i*Bu	73
21	**5l**	Fmoc-Gly	H	*s*Bu	52
22	**5m**	Fmoc-Ala	H	*i*Pr	82
23	**5n**	Fmoc-Leu	H	Me	94
24	**5o**	Fmoc-Ile	H	H	52
25	**5p**	Fmoc-Ile	H	*i*Bu	93
26	**5q**	Fmoc-Phe	H	Me	86
27	**5r**	Z-Val	H	Me	96
28	**5s**	Z-Ala	H	*i*Bu	83
29	**5t**	Z-Leu	H	*i*Pr	83

[a] Isolated yield from **1** after precipitation or crystallisation.

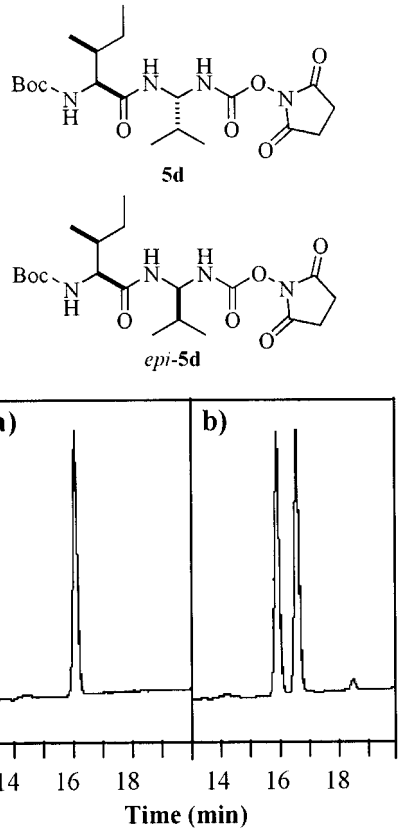


Figure 1. C_{18} RP-HPLC traces of crude **5d** (left panel) and an equimolar mixture of **5d** and ***epi*-5d** (right panel).

Monocrystals of **4f** and **5f**, suitable for X-ray diffraction studies were obtained by slow evaporation of dichloromethane/diisopropyl ether solutions. The two molecules adopt characteristic folded conformations [i.e. a tail biter-type shape stabilized by a weak C(2)–H···O(5) H-bond (D = 3.44 Å, θ = 160°)] for **4f** (Figure 2, a) and an S-like shape for **5f** (Figure 3, a).

Main torsional angle (&πηι;, ψ) values for the 1,1-diaminoalkyl residue of (–73°, 131°) and (–113°, +76°) were observed for **4f** and **5f**, respectively.[34] Carbamates **4f** and **5f** self-assemble into highly organized H-bonded networks of chains and sheets, respectively (Figure 2, b and Figure 3, b). The crystal structure of **4f** is composed of infinite chains running parallel to the [010] direction with the N(2)H engaged in continuous H-bonds with the carbonyl of the Boc protecting group (D = 2.90 Å, θ = 173°). Carbamate **5f** self-assembles to form an infinite, parallel, sheet-like arrangement with both the N(2)H and N(3)H of the 1,1-diaminoalkyl residue engaged in H-bonding with the carbonyls of the Boc protecting group and of the Pro residue, respectively (D_1 = 3.00 Å, θ_1 = 174° and D_2 = 2.84 Å, θ_2 = 161°). Infinite sheets are held together two-by-two through extensive van der Waals contacts between *tert*-butyl groups.

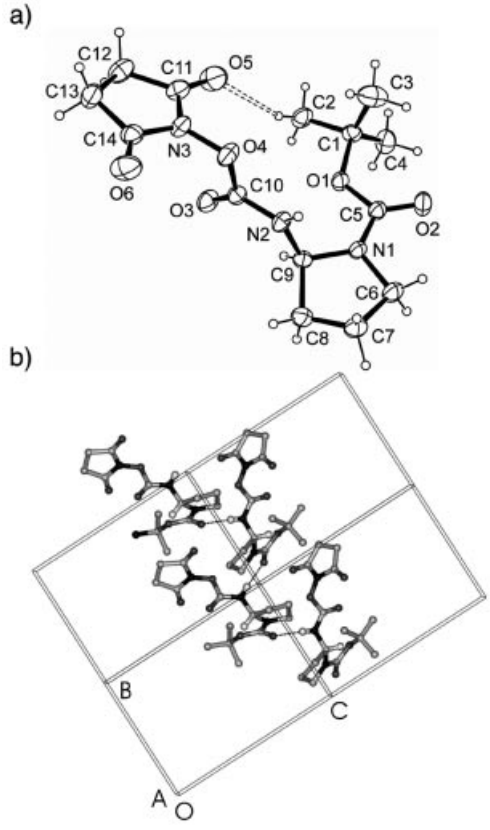


Figure 2. Ortep diagram (a) and partial crystal packing (b) of **4f**.

Reactivity of Succinimidyl Carbamates

As expected, carbamates **4** and **5** react rapidly and cleanly with simple primary and secondary amines includ-

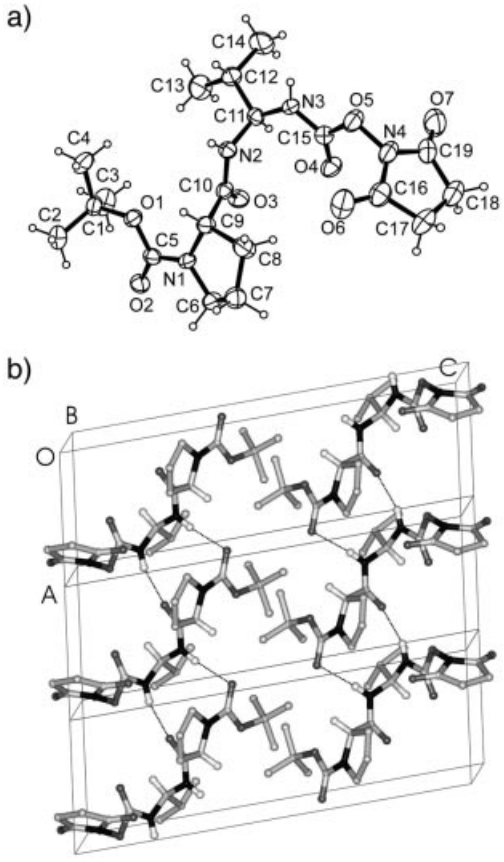
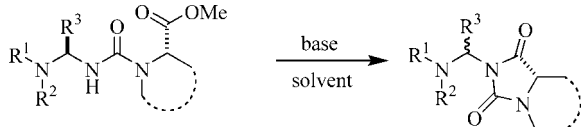


Figure 3. Ortep diagram (a) and partial crystal packing (b) of **5f**.

ing amino acid derivatives to give the corresponding ureidopeptides **6** in good yields ranging from 70% to 97% (Table 2).

Ureidopeptide esters **6** generated by coupling **4** or **5** to an α-amino ester can be further transformed to novel peptidyl hydantoins.[35] Ureidopeptides **6f** and **6i** were quantitatively converted into the corresponding hydantoins **7a** and **7b**, respectively, by treatment with 10% Et_3N in MeOH for 12 h, as previously reported by Liskamp and coworkers for the solid-phase synthesis of hydantoins.[36] In all cases, cyclization was accompanied by epimerization at the *gem*-diamino residue, as evidenced by comparison of NMR spectra of peptidyl hydantoins generated from **6f** (*g*Val) and **6k** (D-*g*Val). The use of lower amounts of Et_3N proved less satisfactory with much slower or incomplete conversion. Alternatively, KF/Al_2O_3 (40 wt.-%) was also found to be effective in promoting clean hydantoin formation from **6f** and **6a** but did not suppress epimerization at the *gem*-diaminoalkyl residue (Table 3).

Table 3. Hydantoins **7**.

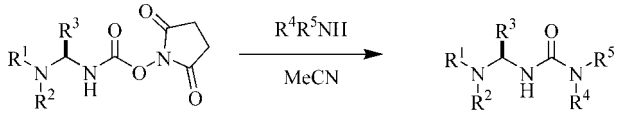


6a, 6f, 6k, 6i **7**

Entry	Compd. **6**	Base	Solvent	Hydantoin	% Yield
1	**6f**	Et_3N	MeOH	**7a**	quant.[a]
2	**6i**	Et_3N	MeOH	**7b**	quant.[a]
3	**6k**	Et_3N	MeOH	**7a**	quant.[a]
4	**6f**	KF/Al_2O_3	THF	**7a**	32[b]
5	**6a**	KF/Al_2O_3	MeCN	**7c**	65[b]

[a] Isolated yield from **6** after precipitation or crystallisation. [b] Isolated yield after purification by column chromatography.

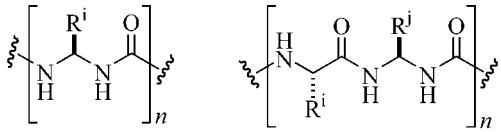
Table 2. Synthesis of ureidopeptides **6** from carbamates **4** and **5**.



4, 5 **6**

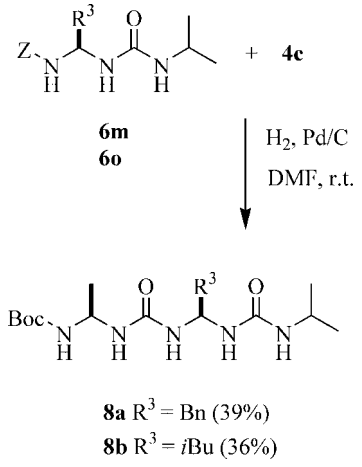
Entry	Carbamates **4**, **5**	Amine (R^4R^5NH)	Urea **6**	% Yield
1	**4a**	H-Val-OMe	Boc-*g*Phe-CO-Val-OMe (**6a**)	85
2	**4b**	$(Bn)_2NH$	Boc-*g*Ser(Bn)-CON$(Bn)_2$ (**6b**)	95
3	**5e**	*i*PrNH$_2$	Boc-Lys(2-Cl-Z)-*g*Val-CONH*i*Pr (**6c**)	74
4	**5e**	$(Bn)_2NH$	Boc-Lys(2-Cl-Z)-*g*Val-CON$(Bn)_2$ (**6d**)	70
5	**5g**	$(Me)_2NH$	Boc-Pro-*g*Leu-CON$(Me)_2$ (**6e**)	79
6	**5d**	H-Pro-OMe	Boc-Ile-*g*Val-CO-Pro-OMe (**6f**)	93
7	**5d**	H-Val-OBn	Boc-Ile-*g*Val-CO-Val-OBn (**6g**)	81
8	***epi*-5d**	H-Val-OBn	Boc-Ile-D-*g*Val-CO-Val-OBn (**6h**)	93
9	**5h**	H-Leu-OMe	Boc-Pro-*g*Ala-CO-Leu-OMe (**6i**)	74
10	**5g**	H-Ala-Phe-OMe	Boc-Pro-*g*Leu-CO-Ala-Phe-OMe (**6j**)	70
11	***epi*-5d**	H-Pro-Ome	Boc-Ile-D-*g*Val-CO-Pro-OMe (**6k**)	80
12	**5b**	*i*PrNH$_2$	Boc-Ala-*g*Phe-CONH*i*Pr (**6l**)	96
13	**4h**	*i*PrNH$_2$	Z-*g*Phe-CONH*i*Pr (**6m**)	92
14	**4h**	H-Val-OMe	Z-*g*Phe-CO-Val-OMe (**6n**)	86
15	**4g**	*i*PrNH$_2$	Z-*g*Leu-CONH*i*Pr (**6o**)	97
16	**5s**	*i*PrNH$_2$	Z-Ala-*g*Leu-CONH*i*Pr (**6p**)	88

Sequential coupling and deprotection steps with succinimidyl carbamates derived from α-amino acids (**4**) and dipeptides (**5**) should, in principle, lead to the formation of novel *N*,*N*′-linked oligoureas **A** and oligourea/peptide hybrids **B**, respectively. It is noteworthy that oligomers of type **A** belong to the β-peptide lineage and can be viewed as the aza[2]-analogues of 14-helical β[3]-peptides.[2] Sequences of type **B** consisting of alternating amide and urea bonds are isosteres of mixed α,β-peptide foldamer[37] sequences. The consequence of substituting a N for an α-C in ω-amino acid constituents of ω-peptides is to fix the "ψ" angle to a value close to 170–180°. For example, the 14-helical fold of γ-peptides has been shown previously to be stabilized by substitution of a urea for the CH_2–CO–NH units in the γ[4]-peptide backbone.[14]



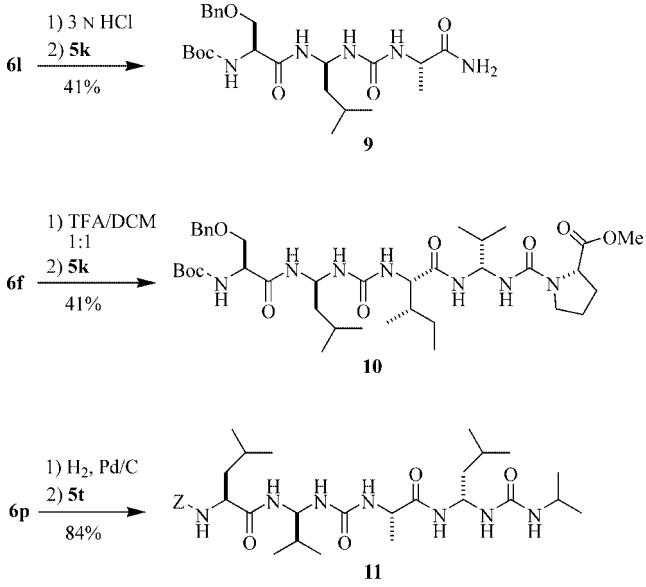
A **B**

In the case of carbamates **4** derived from α-amino acids, removal of the *N*-protecting group following urea formation generates an 1-acylamino-1-aminoalkane of the general formula GP–NH–CHR[2]–NH_2 (GP = R^1NHCO–). Although monoacylated *gem*-diamines are masked forms of aldehydes—they hydrolyse to amides, aldehydes and ammonia—they can be surprisingly stable depending on the nature of the GP group (electron-withdrawing substituents substantially increase the rate of hydrolysis).[38] Acyl-protected (GP = R^1CO–) and to a lower extent urethane-protected (GP = R^1OCO–) *gem*-diamines have been used with success in the synthesis of PMRI peptides.[28] However, we found only one report in the literature dealing with monoprotected *gem*-diaminoalkyl derivatives derived from protected ureidopeptides.[18] Our initial attempts to isolate *gem*-diamines derived from **6b** and **6m** by acidolysis (TFA/CH_2Cl_2 (1:1) or 3 M HCl in dioxane) and hydrogenolysis (in MeOH or DMF in the presence or absence of 1 equiv. of 1 M HCl) of the Boc and Z protecting groups, respectively, were unsuccessful. Complete decomposition of the *gem*-diamine was rapidly observed under these conditions. However, when hydrogenation of **6m** and **6o** was performed in the presence of Boc-*g*Ala-COOSu (**4c**), we were able to isolate the bisureido compounds **8a** and **8b** resulting from the coupling of **4c** to H-*g*Phe-CONH*i*Pr and H-*g*Leu-CONH*i*Pr, respectively, in 30–40% yield (Scheme 2). Hydrogenolysis of the Z group at a lower temperature was investigated in order to decrease the rate of hydrolysis of the formed *N*-carbamoyl-*gem*-diaminoalkyl residue and to allow sequential deprotection/coupling procedures to be performed. However, our attempts to form diurea Z-Phe-ψ[NHCONH]-Phe-ψ[NHCONH]-Val-OMe (**8c**) by hydrogenolysis of **6n** at –10 °C and immediate coupling with **4h** were not satisfactory. While this manuscript was in preparation, an alternative synthesis of short oligoureas of type **A** by C-terminal elongation was proposed by Sureshbabu.[24]



Scheme 2.

We also evaluated the synthesis of oligourea/peptide hybrids of type **B** (Scheme 3).



Scheme 3. Solution-phase synthesis of oligo(amide/urea) hybrids.

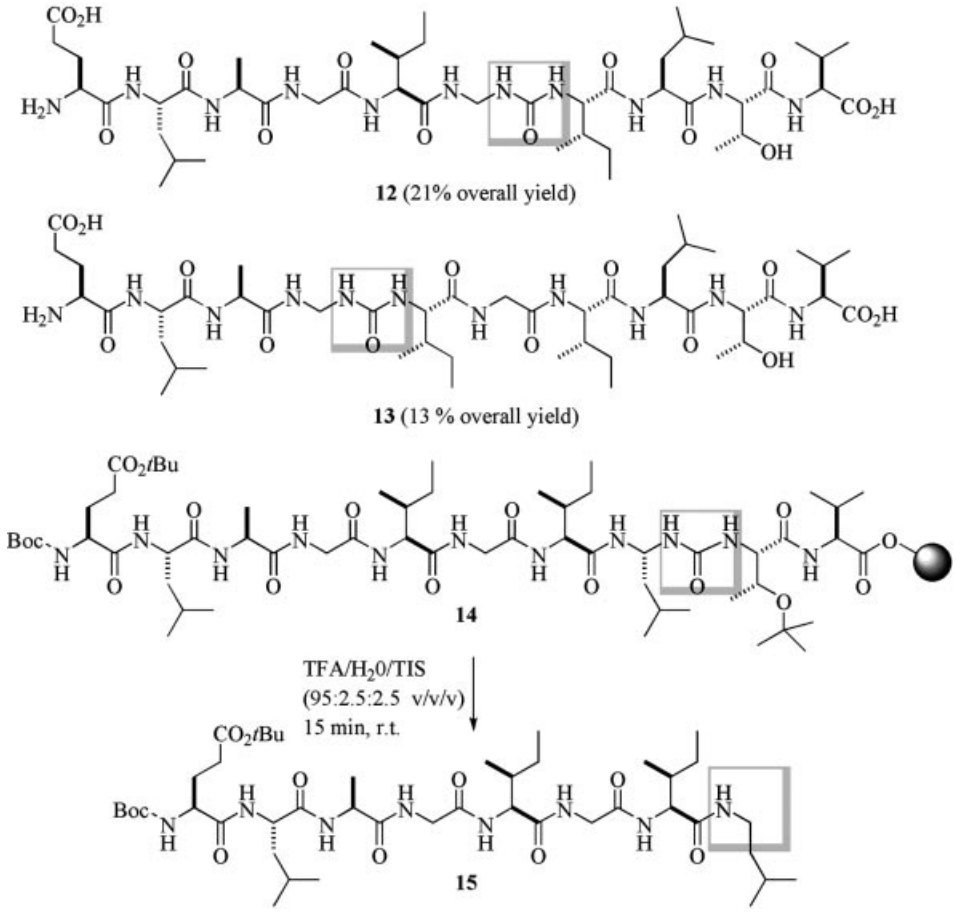
Sequential coupling and deprotection steps with *N*-Boc-protected derivatives was attempted first. Boc deprotection of **6l** by treatment with 3 M HCl in dioxane and immediate coupling with **5k** did not afford the expected hybrid tetramer because of extensive hydrolysis of the *gem*-diaminoalkyl residue. Instead, ureidotripeptide Boc-Ser(Bn)-*g*Leu-CO-Ala-NH_2 (**9**), which lacks *g*Phe-CONH*i*Pr, was recovered in 41% yield. In contrast, treatment of Boc-Ile-*g*Val-CO-Pro-OMe (**6f**) with TFA/CH_2Cl_2 at 0 °C gave the expected TFA salt which upon reaction with **5k**, yielded pentameric Boc-Ser(Bn)-*g*Leu-CO-Ile-*g*Val-CO-Pro-OMe (**10**) with alternating amide and urea bonds. The stability of the *gem*-diaminoalkyl moiety to TFA was found to be variable and sequence dependent. An attempt to synthesize hexameric Boc-Val-*g*Ala-CO-Leu-*g*Val-CO-Ala-*g*Leu-CONH*i*Pr under the same conditions was not successful because of extensive hydrolysis of *gem*-diaminoalkyl resi-

dues during successive TFA treatments, even when performed at low temperature. This is in contrast to diacylated *gem*-dimainoalkyl moieties in PMRI peptides, which were found to be stable to TFA treatments.[28] Alternatively, the solution-phase synthesis of oligourea/peptide hybrids was readily achieved by employing Z-protected building blocks, mixed tetramer **11** being synthesized in 84% yield (Scheme 3).

Solid-phase Synthesis of Ureidopeptides and Oligo-(amide/urea) Hybrids

The Fmoc/*tert*-butyl strategy associated with solid-phase methodology was also considered for the synthesis of ureidopeptides. Six analogues of the tumour-associated-antigen-derived peptide [Leu^{27}]MART-1(26–35)[39] (H-Glu^{26}-Leu-Ala-Gly-Ile-Gly-Ile-Leu-Thr-Val^{35}-OH), incorporating one ureido linkage between residues Leu^{27} and Ala^{28}, Gly^{30}and Ile^{31}, Ile^{31} and Gly^{32}, Gly^{32}and Ile^{33}, Ile^{33}and Leu^{34} or Leu^{34} and Thr^{35} were selected as targets. They were assembled on a home-made multichannel synthesizer with a semi-automatic mode[40] on a 40 μmol scale starting from Fmoc-Val Wang resin. The formation of the urea linkage was achieved by coupling succinimidyl carbamates **5l**, **5p** and **5o**, derived from *N*-Fmoc-protected dipeptides and **5j** (4 equiv.) to the free amino group of the resin-bound peptide in DMF (2 mL) in the presence of Hünig's base (DIEA, 4 equiv.) twice for 120 min.[41] At the end of that time the Kaiser ninhydrin test[42] was negative. The Fmoc group was deprotected with 20% piperidine in DMF, and the last amino acids were introduced with standard solid-phase peptide synthesis procedures. Side-chain deprotection and cleavage of the oligomers from the resin were performed simultaneously by treatment with TFA/H_2O/triisopropylsilane (95:2.5:2.5) for 60 min at 20 °C. After precipitation in cold ether and centrifugation, crude compounds were purified by RP-HPLC on a C_{18} column and analyzed by high resolution mass spectrometry. Again, differential sensitivity of the *N*-acyl-*N*′-carbamoyl-*gem*-diaminolalkyl moiety towards acid-catalyzed hydrolysis, depending on the presence or absence of an alkyl side chain, was observed, in agreement with the expectations of Loudon and coworkers for monoacylated *gem*-diamino compounds.[38a] Ureidopeptides **12** and **13** incorporating a *gem*-Gly moiety were recovered in 21% and 13% overall yield (17 steps) after purification, respectively (Scheme 4). Purities of the crude products based on RP-HPLC were 58% and 75%, respectively. ^{1}H NMR spectroscopic data for compound **12** in [D_6]DMSO are given in the supporting information.

However, in the four other cases (containing an alkyl side chain at the *gem*-diamino moiety), the conditions employed for the cleavage from the resin and protecting groups re-



Scheme 4.

sulted in extensive hydrolysis of the *N*-acyl-*N′*-carbamoyl-*gem*-diaminolalkyl moiety and precluded isolation of the expected ureidopeptides.[43] For example, cleavage of resin-bound ureidopeptide **14** by TFA treatment (Scheme 4) afforded the truncated ureidopeptide **15** as the major product, resulting from breakdown of the *gem*-diaminoalkyl moiety (65% purity based on HPLC analysis of the crude cleavage mixture; see the supporting information for ^{1}H NMR and HRMS data of purified **15** in [D_6]DMSO). These results suggest that milder conditions should be employed for safely removing ureidopeptides and oligo(amide/urea) hybrids from the solid supports.

Conformational Features of Ureidopeptides 6i and 10

The conformational preference of ureidopeptides **6i** and **10** was investigated by a combination of X-ray crystallography and ^{1}H NMR spectroscopy. Similar to what was observed in earlier work for monomeric *N*-Boc- and *N*-acetyl-*N′*-carbamoyl-*gem*-diaminoalkyl derivatives with *i*Bu, *i*Pr and Bn side chains,[22,23] the geometry of the *N*,*N′*-disubstituted urea motif in the crystal structure of **6i** is nearly *trans*,*trans* planar with a maximum deviation of 17° for the urea N–CO bond in one of the two molecules of the asymmetric unit (Figure 4, a).

The &πηι; and ψ torsion angles for the *gem*-diaminoalkyl residue in the two independent molecules of the asymmetric unit are negative [–109° for **6i**(I) and –132° for **6i**(II)] and positive [+74° for **6i**(I) and +100° for **6i**(II)], respectively. In the solid-state structure of **6i**, the molecules are organized in long stacks of polar sheets with all three amide/urea NH groups oriented in the same direction (Figure 4, b). The sheet alignment consists of a complex network of complementary H-bonds between non-equivalent alternating antiparallel and parallel molecules with N···O distances ranging from 2.84 Å to 3.03 Å. In solution, the situation is quite different, and the urea fragment recovers some conformational freedom. Information about the local conformation induced by the urea fragment in **6i** was gained from ROESY experiments in [D_5]pyridine. An intense ROE correlation was observed between the protons of the Leu NH and the α-C of the preceding *g*Ala residue (Figure 5, a).

A short interproton distance is possible only if one assumes that the urea adopts a *cis*,*trans* (*E*,*Z*) geometry as shown in Figure 6.

In the *Z*,Z (*trans*,*trans*) conformation adopted by **6i** in the solid state, this distance is above 4 Å (4.23 Å and 4.18 Å in molecules I and II, respectively). These observations are in line with previous IR and ^{1}H NMR spectroscopic investigations of model *N*-Boc-*N′*-carbamoyl-*gem*-diaminoalkyl derivatives in low-polarity solvents, which showed that the urea moiety adopts a stable *cis*,*trans* conformation that can be stabilized by an intramolecular H-bond (i.e. a urea turn). Molecular modelling of the turn conformation revealed that when the urea fragment adopts the *cis*,*trans* conformation, the interproton distance between the α-CH(*i*) and NH(*i*+1) protons is close to 2.0 Å. Interestingly, when analyzing ureidopeptide **10** by NMR in [D_6]DMSO, a similar NOE pattern was observed, suggesting that the (*E*,*Z*) geometry can be at least partially retained in a polar solvent (Figure 5, b).

Conclusions

A series of succinimidyl carbamate derivatives has been prepared starting from diversely substituted *N*-protected α-amino acids and dipeptides, and their reactivity with external amines has been studied. We have shown previously that succinimidyl [1-(acylamino)-1-X-methyl] carbamates (**5**), generated from *N*-Boc-protected dipeptides, can be readily converted into the 1,3,5-triazepan-2,6-dione skeleton, a novel, conformationally constrained, peptide-derived scaffold.[13c,25] With the aim to study the propensity of the urea linkage in linear segments to promote local folded conformations (i.e. a urea turn[23]), we have investigated the use of carbamates **5** in the synthesis of ureidopeptides and oligo-

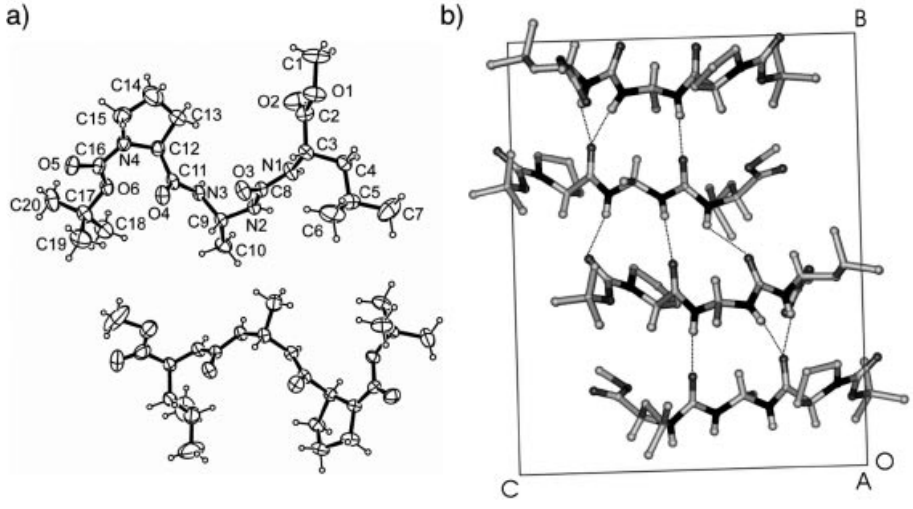


Figure 4. Ortep diagram (a) and partial crystal packing (b) of **6i**.

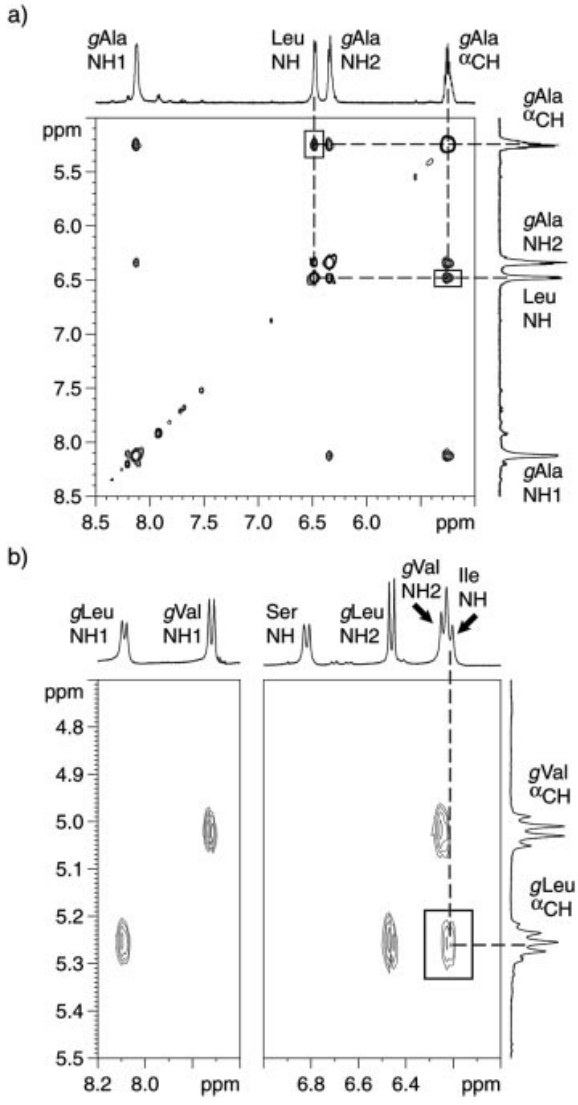


Figure 5. Parts of the ROESY spectra demonstrating the *cis*,*trans* conformation of the *N*,*N*′-disubstituted urea fragment in a) **6i** and b) **10**, at 298 K in [D_5]pyridine and [D_6]DMSO, respectively.

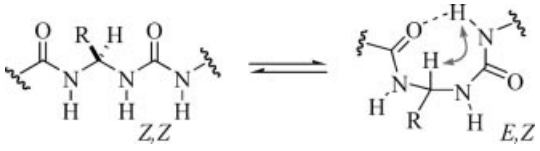


Figure 6. Representation of the extended (*trans*,*trans*) and folded (*cis*,*trans*) conformations adopted by the urea linkage in ureidopeptides. The strong NOE connectivity between the α-CH(*i*) and NH(*i*+1), characterisitic of the (*cis*,*trans*) conformation observed in solution, is shown by an arrow.

urea/peptide hybrids consisting of alternating urea and amide moieties. The preparation of ureidopeptides was also attempted with solid-phase techniques. Under the acidic conditions required for Boc-removal in solution or resin cleavage in the Fmoc/*t*Bu strategy, the stability of the *N*-acyl-*N*′-carbamoyl-*gem*-diamino moiety was found to be substantially decreased by the presence of an alkyl side chain.

Spectroscopic conformational studies suggested a common propensity of the urea linkage in both ureidopeptides and oligo(amide/urea) hybrids to promote C_8 folded conformations by populating *cis*,*trans* (*E*,*Z*) geometry. The folding behaviour of longer oligo(amide/urea) hybrids is currently under investigation in our laboratories.

Experimental Section

General Remarks: Amino acid derivatives were purchased from NeoMPS or Novabiochem. THF was freshly distilled from sodium/benzophenone under an inert atmosphere of Ar. Toluene was distilled from P_2O_5 and stored over 4 Å molecular sieves. The reactions were carried out under an excess pressure of Ar. HPLC analysis was performed on a Nucleosil C_{18} column (5 μm, 3.9 × 150 mm) with a linear gradient of solvent A (0.1% TFA in H_2O) and solvent B (0.08% TFA in MeCN) at a flow rate of 1.2 mL/min with UV detection at 214 nm.

General Procedure for the Preparation of Succinimidyl Carbamates 4, 5. Procedure A: The *N*-protected α-amino acid or *N*-protected dipeptide (usually about 10 mmol) was dissolved in THF (30 mL) under Ar and cooled to –20 °C. After addition of EtOCOCl (1.1 equiv.) and NMM (1.1 equiv.), the mixture was stirred at –20 °C for 20 min. The resulting white suspension was warmed to –5 °C and treated with an aqueous solution of NaN_3 (5 mL, 2.5 equiv.). The mixture was stirred for 5 min, diluted with EtOAc, washed with brine, dried with $MgSO_4$ and concentrated under reduced pressure to give the acyl azide **2**, which was used without further purification. Toluene was added under Ar, and the resulting solution was heated to 65 °C whilst stirring. After the gas evolution had stopped (ca. 10 min), *N*-hydroxysuccinimide (1 equiv.) and pyridine (1 equiv.) were added. The mixture was stirred for 5 min at 65 °C and then cooled to room temperature. In most cases the title compound crystallised from the toluene solution and was collected by filtration. Recrystallisation from toluene afforded the pure succinimidyl carbamate **4** or **5**, respectively. Otherwise, the solvent was removed in vacuo, and the residue was purified by recrystallisation from the appropriate solvent.

Succinimidyl *N*-[1-(*tert*-Butoxycarbonylamino)-2-phenylethyl]carbamate (Boc-*g*Phe-COOSu, 4a): Boc-Phe-OH (2.65 g, 10 mmol) was transformed according to the general procedure A. Recrystallisation from toluene yielded **4a** (3.32 g, 88%): white solid, m.p. 141 °C. $[a]_D^{25}$ = +4.0 (*c* = 1.4, DMF). HPLC: t_R = 10.94 min (linear gradient, 20–80% solvent B, 20 min). ^{1}H NMR ([D_6]DMSO, 200 MHz): δ = 1.33 (s, 9 H, $(CH_3)_3$), 2.77 (s, 4 H, CH_2CH_2), 2.94 (br. d, *J* = 6.7 Hz, 2 H, CH_2Ph), 5.03–5.12 (m, 1 H, NHC*H*NH), 7.15–7.35 (m, 5 H, arom. H), 7.52 (br. d, *J* = 7.7 Hz, 1 H, N*H*$CO_2(CH_3)_3$), 8.79 (br. d, *J* = 7.4 Hz, 1 H, N*H*CO_2Su) ppm. ^{13}C NMR ([D_6]DMSO, 50 MHz): δ = 25.2 (CH_2), 28.0 (CH_3), 39.6 (CH_2), 61.3 (CH), 78.2 (C), 126.3 (CH), 128.1 (CH), 129.2 (CH), 137.0 (C), 150.5 (C), 154.2 (C), 170.7 (C), 172.7 (C) ppm. MALDI-TOF MS: *m*/*z* 400.8 [M + Na]$^+$, 417.0 [M + K]$^+$.

Succinimidyl *N*-[2-Benzyloxy-1-(*tert*-butoxycarbonylamino)ethyl]-carbamate (Boc-*g*Ser(Bn)-COOSu, 4b): Boc-Ser(Bzl)-OH (11.8 g, 40 mmol) was transformed according to the general procedure A. Recrystallisation from toluene yielded **4b** (12.14 g, 60%): white solid, m.p. 142 °C. $[a]_D^{25}$ = –4.5 (*c* = 1.9, DMF). HPLC: t_R = 12.88 min (linear gradient, 20–80% solvent B, 20 min). ^{1}H NMR ([D_6]DMSO, 200 MHz): δ = 1.35 [s, 9 H, $C(CH_3)_3$], 2.73 (s, 4 H, CH_2CH_2), 3.46 (d, *J* = 6.6 Hz, 2 H, CH_2OCH_2Ph), 4.46 (s, 2 H, CH_2OCH_2Ph), 5.07–5.21 (m, 1 H, NHC*H*NH), 7.19–7.36 (m, 5 H,

arom. H), 7.38 [br. d, 1 H, N*H*$CO_2C(CH_3)_3$], 8.67 (br. d, J = 7.6 Hz, 1 H, N*H*CO_2Su) ppm. ^{13}C NMR ([D$_6$]DMSO, 50 MHz): δ = 25.2 (CH_2), 28.0 (CH_3), 59.0 (CH), 69.8 (CH_2), 72.0 (CH_2), 78.4 (C), 127.5 (CH), 128.1 (CH), 138.0 (C), 150.8 (C), 154.4 (C), 170.7 (C) ppm. MALDI-TOF MS: m/z 430.2 [M + Na]$^+$, 446.3 [M + K]$^+$.

***tert*-Butyl 2-(Succinimidylcarbonylamino)pyrrolidine-1-carboxylate (Boc-*g*Pro-COOSu, 4f):** Boc-Pro-OH (2.15 g, 10 mmol) was transformed according to the general procedure A. Recrystallisation from toluene yielded **4f** (1.66 g, 51%): white solid, m.p. 114 °C. HPLC: t_R = 5.37 min (linear gradient, 30–100% solvent B, 20 min). ^{1}H NMR ([D$_6$]DMSO, 300 MHz): δ = 1.37, 1.41 [s, 9 H, $C(CH_3)_3$], 1.70–2.04 (m, 4 H, CHC*H*$_2$C*H*$_2$), 2.76 (s, 4 H, C*H*$_2$C*H*$_2$), 3.12–3.17 (m, 1 H, NC*H*$_2$), 3.30–3.37 (m, 1 H, NC*H*$_2$), 5.30 (m, 1 H, NC*H*NH), 8.71 (d, J = 8.4 Hz, 1 H, N*H*CO_2Su) ppm. ^{13}C NMR ([D$_6$]DMSO, 50 MHz): δ = 21.9 (CH), 25.7 (CH_3), 28.4 (CH_2), 28.5 (CH_2), 33.8 (CH), 45.8 (CH), 65.8 (CH_2), 79.6 (C), 150.8 (C), 153.4 (C), 171.3 (C) ppm. MALDI-TOF MS: m/z 350.15 [M + Na]$^+$, 366.19 [M + K]$^+$.

Succinimidyl *N*-[1-(Benzyloxycarbonylamino)-3-methylbutyl]carbamate (Z-*g*Leu-COOSu, 4g): Z-Leu-OH (2.65 g, 10 mmol) was transformed according to the general procedure A. Recrystallisation from toluene yielded **4g** (3.08 g, 82%): white solid, m.p. 121 °C. $[a]_D^{25}$ = +11.8 (c = 1.0, DMF). HPLC: t_R = 8.82 min (linear gradient, 30–100% solvent B, 20 min). ^{1}H NMR ([D$_6$]DMSO, 200 MHz): δ = 0.82 [d, J = 5.8 Hz, 6 H, CH(C*H*$_3$)$_2$], 1.40–1.62 [m, 3 H, C*H*$_2$C*H*$(CH_3)_2$], 2.72 (s, 4 H, CH_2CH_2), 4.92–5.10 (m, 3 H, NHC*H*NH, OC*H*$_2$Ph), 7.22–7.41 (m, 5 H, arom. H), 7.80 (br. d, J = 8.1 Hz, 1 H, N*H*CO_2CH_2Ph), 8.61 (br. d, J = 7.5 Hz, 1 H, N*H*CO_2Su) ppm. ^{13}C NMR ([D$_6$]DMSO, 50 MHz): δ = 21.9 (CH_3), 22.1 (CH_3), 23.9 (CH), 25.2 (CH_2), 42.8 (CH_2), 58.9 (CH), 65.3 (CH_2), 127.7 (CH), 128.3 (CH), 136.8 (CH), 150.6 (C), 155.0 (C), 170.8 (C) ppm. MALDI-TOF MS: m/z 400.1 [M + Na]$^+$, 416.8 [M + K]$^+$.

Boc-Gly-*g*Ile-COOSu (5a): Boc-Gly-Leu-OH (865 mg, 3 mmol) was transformed according to the general procedure A. Recrystallisation from toluene yielded **5a** (1.04 g, 87%): white solid, m.p. 134 °C. $[a]_D^{25}$ = +7.2 (c = 1.1, DMF). HPLC: t_R = 9.13 min (linear gradient, 20–80% solvent B, 20 min). ^{1}H NMR ([D$_6$]DMSO, 200 MHz): δ = 0.79–0.95 (m, 6 H, C*H*$_3$CHCH$_2$C*H*$_3$), 0.96–1.14 (m, 2 H, CH_3CHC*H*$_2$CH$_3$), 1.38 [s, 9 H, C(C*H*$_3$)$_3$], 1.60–1.78 (m, 1 H, CH_3C*H*CH$_2$CH$_3$), 2.77 (s, 4 H, C*H*$_2$C*H*$_2$), 3.50–3.68 (m, 2 H, NHC*H*$_2$CO), 5.00–5.20 (m, 1 H, NHC*H*NH), 6.90–7.00 [m, 1 H, N*H*$CO_2C(CH_3)_3$], 7.99 (d, J = 8.6 Hz, 1 H, N*H*CO_2Su), 8.54 (d, J = 8.0 Hz, 1 H, N*H*COCH$_2$) ppm. ^{13}C NMR ([D$_6$]DMSO, 50 MHz): δ = 10.7 (CH_3), 14.2 (CH_3), 24.3 (CH_2), 25.2 (CH_2), 28.0 (CH_3), 38.1 (CH), 43.0 (CH_2), 61.4 (CH), 78.0 (C), 150.8 (C), 155.7 (C), 168.7 (C), 170.7 (C) ppm. HRMS: calcd. for $C_{17}H_{29}N_4O_7$ [M + H]$^+$ 401.2031; found 401.2047.

Boc-Phe-*g*Leu-COOSu (5c): Boc-Phe-Leu-OH (1.503 g, 3 mmol) was transformed according to the general procedure A. Recrystallisation from toluene yielded **5c** (1.21 g, 82%): white solid, m.p. 156 °C (dec.). $[a]_D^{25}$ = +15.8 (c = 1.0, DMF). HPLC: t_R = 14.01 min (linear gradient, 20–80% solvent B, 20 min). ^{1}H NMR ([D$_6$]-DMSO, 200 MHz): δ = 0.87 (d, J = 5.4 Hz, 3 H, CH_3), 0.88 (d, J = 5.4 Hz, 3 H, CH_3), 1.29 [s, 9 H, C(C*H*$_3$)$_3$], 1.50–1.73 [m, 3 H, CHC*H*$_2$C*H*$(CH_3)_2$], 2.64–2.98 (m, 2 H, C*H*$_2$Ph), 2.76 (s, 4 H, C*H*$_2$C*H*$_2$), 4.04–4.21 (m, 1 H, C*H*CO), 5.32 (m, 1 H, NHC*H*NH), 6.85 [d, J = 8.6 Hz, 1 H, N*H*$CO_2C(CH_3)_3$], 7.10–7.30 (m, 5 H, arom. H), 8.25 (d, J = 8.3 Hz, 1 H, N*H*CO_2Su), 8.65 (d, J = 7.5 Hz, 1 H, N*H*COCH) ppm. ^{13}C NMR ([D$_6$]DMSO, 50 MHz): δ = 21.9 (CH_3), 22.2 (CH_3), 23.8 (CH), 25.2 (CH_2), 28.0 (CH_3), 37.1 (CH_2), 42.9 (CH_2), 55.5 (CH), 56.4 (CH), 77.9 (C), 126.1 (CH), 127.9 (CH), 129.2 (CH), 138.1 (C), 150.2 (C), 155.2 (C), 170.7 (C), 171.0 (C) ppm. HRMS: calcd. for $C_{24}H_{35}N_4O_7$ [M + H]$^+$ 491.2500; found 491.2509.

Boc-Ile-L-*g*Val-COOSu (5d): Boc-Ile-Val-OH (2.50 g, 7.57 mmol) was transformed according to the general procedure A. Recrystallisation from toluene yielded **5d** (2.08 g, 62%): white solid, no defined m.p. (dec.). $[a]_D^{25}$ = +4.5 (c = 1.0, DMF). HPLC: t_R = 16.00 min (linear gradient, 20–65% solvent B, 30 min). ^{1}H NMR ([D$_6$]DMSO, 200 MHz): δ = 0.64–0.91 [m, 12 H, CH(C*H*$_3$)$_2$, C*H*$_3$CHCH$_2$C*H*$_3$], 0.97–1.05 (m, 1 H, CH_3CHC*H*$_2$CH$_3$) 1.27–1.37 [s, 11 H, C(C*H*$_3$)$_3$, CH_3CHC*H*$_2$CH$_3$], 1.56–1.63 (m, 1 H, CH_3C*H*CH$_2$CH$_3$), 1.80–1.94 [m, 1 H, CHC*H*$(CH_3)_2$], 2.70 (s, 4 H, C*H*$_2$C*H*$_2$), 3.71–3.79 (m, 1 H, NHC*H*CO), 4.87–4.99 (m, 1 H, NHC*H*NH), 6.66 [d, J = 8.9 Hz, 1 H, N*H*$CO_2C(CH_3)_3$], 7.98 (d, J = 8.7 Hz, 1 H, N*H*CO_2Su), 8.53 (d, J = 8.1 Hz, 1 H, N*H*COCH) ppm. ^{13}C NMR ([D$_6$]DMSO, 50 MHz): δ = 10.7 (CH_3), 15.2 (CH_3), 18.1 (CH_3), 18.3 (CH_3), 24.3 (CH_2), 25.2 (CH_2), 28.1 (CH_3), 31.7 (CH), 36.1 (CH), 58.6 (CH), 62.7 (CH), 77.9 (C), 150.8 (C), 155.3 (C), 170.6 (C), 171.0 (C) ppm. HRMS: calcd. for $C_{20}H_{35}N_4O_7$ [M + H]$^+$ 443.2500; found 443.2486.

Boc-Lys(2-Cl-Z)-*g*Val-COOSu (5e): Boc-Lys(2-Cl-Z)-Val-OH (1.59 g, 2.9 mmol) was transformed according to the general procedure A. Recrystallisation from toluene yielded **5e** (1.29 g, 69%): white solid, m.p. 141 °C (dec.). $[a]_D^{25}$ = +2.2 (c = 1.0, DMF). HPLC: t_R = 14.98 min (linear gradient, 20–80% solvent B, 20 min). ^{1}H NMR ([D$_6$]DMSO, 200 MHz): δ = 0.84 (d, J = 6.2 Hz, 3 H, CH_3), 0.87 (d, J = 5.4 Hz, 3 H, CH_3), 1.15–1.57 (m, 6 H, CHC*H*$_2$C*H*$_2$C*H*$_2$), 1.34 [s, 9 H, C(CH$_3$)$_3$], 1.72–1.98 [m, 1 H, C*H*$(CH_3)_2$], 2.72 (s, 4 H, C*H*$_2$CO), 2.85–3.08 (m, 2 H, C*H*$_2$NH), 3.78–3.92 (m, 1 H, NHC*H*CO), 4.87–4.99 (m, 1 H, NHC*H*NH), 5.06 (s, 2 H, OC*H*$_2$), 6.82 [d, J = 8.2 Hz, 1 H, N*H*CO_2(C(CH$_3$)$_3$)], 7.24–7.50 (m, 4 H, arom. H), 7.93 (d, J = 8.7 Hz, 1 H, N*H*CO_2Su), 8.54 (d, J = 7.9 Hz, 1 H, CHCON*H*CH) ppm. ^{13}C NMR ([D$_6$]-DMSO, 50 MHz): δ = 18.0 (CH_3), 18.2 (CH_3), 22.7 (CH_2), 25.2 (CH_2), 28.1 (CH_3), 29.0 (CH_2), 31.2 (CH_2), 31.8 (CH), 40.0 (CH_2), 54.1 (CH), 62.4 (CH_2), 62.8 (CH), 77.9 (C), 127.2 (CH), 129.2 (CH),129.6 (CH), 132.0 (C), 134.5 (C), 150.8 (C), 155.3 (C), 155.3 (C), 155.8 (C), 170.6 (C), 171.6 (C) ppm. HRMS: calcd. for $C_{28}H_{41}ClN_5O_9$ [M + H]$^+$ 626.2587; found 626.2646.

Boc-Pro-*g*Val-COOSu (5f): Boc-Pro-Val-OH (2.60 g, 8.27 mmol) was transformed according to the general procedure A. Recrystallisation from toluene yielded **5f** (2.54 g, 72%): white solid, m.p. 148 °C. $[a]_D^{25}$ = –18.1 (c = 1.0, DMF). HPLC: t_R = 8.98 min (linear gradient, 20–80% solvent B, 20 min). ^{1}H NMR ([D$_6$]DMSO, 200 MHz): δ = 0.87 [d, J = 6.4 Hz, 6 H, CH(C*H*$_3$)$_2$], 1.31, 1.37 [s, 9 H, C(C*H*$_3$)$_3$], 1.74–2.07 [m, 5 H, CHC*H*$(CH_3)_2$, CHC*H*$_2$C*H*$_2$CH$_2$], 2.74 (s, 4 H, C*H*$_2$C*H*$_2$), 3.17–3.32 (m, 2 H, NC*H*$_2$CH$_2$), 4.10–4.13 (m, 1 H, NC*H*CO), 4.88–5.04 (m, 1 H, NHC*H*NH), 8.08 (d, J = 8.5 Hz, 1 H, N*H*CO_2Su), 8.49 (d, J = 7.8 Hz, 1 H, N*H*COCH) ppm. ^{13}C NMR ([D$_6$]DMSO, 50 MHz): δ = 18.2 (CH_3), 22.8 (CH_2), 25.2 (CH_2), 28.0 (CH_3), 31.0 (CH_2), 31.6(CH), 46.4 (CH_2), 59.2 (CH), 62.9 (CH), 78.3 (C), 150.8 (C), 153.3 (C), 170.7 (C), 171.8 (C) ppm. HRMS: calcd. for $C_{19}H_{31}N_4O_7$ [M + H]$^+$ 427.2187; found 427.2193.

Boc-Ser(Bn)-*g*Leu-COOSu (5k): Boc-Ser(Bn)-Leu-OH (4.52 g, 11.07 mmol) was transformed according to the general procedure A. Precipitation from toluene yielded **5k** (4.21 g, 73%): white solid, m.p. 121 °C. $[a]_D^{20}$ = +10.6 (c = 0.5, DMF). HPLC: t_R = 10.50 min (linear gradient, 30–100% solvent B, 20 min). ^{1}H NMR ([D$_6$]-DMSO, 300 MHz): δ = 0.83–0.86 (m, 6 H, CH_3), 1.39 [s, 9 H, C(CH$_3$)$_3$], 1.50–1.60 [m, 3 H, C*H*$_2$C*H*$(CH_3)_2$], 2.75 (s, 4 H,

CH_2CH_2), 3.54–3.57 (m, 1 H, CH_2OBn), 4.19–4.26 (m, 1 H, CHCO), 4.46 (d, J = 2.5 Hz, 2 H, OCH_2Ph), 5.26–5.36 (m, 1 H, NHC*H*NH), 6.91 (d, J = 8.5 Hz, 1 H, N*H*CHCO), 7.27–7.37 (m, 5 H, H-arom), 8.19 (d, J = 8.3 Hz, 1 H, N*H*CO_2Su), 8.66 (d, J = 7.6 Hz, 1 H, CHCON*H*) ppm. ^{13}C NMR ([D$_6$]DMSO, 75 MHz): δ = 22.4 (CH_3), 22.7 (CH_3), 24.3 (CH), 25.7 (CH_2), 28.6 (CH_3), 31.8 (CH_2), 43.3 (CH_2), 54.8 (CH), 56.9 (CH), 70.5 (CH_2), 72.5 (CH_2), 78.7 (C), 127.8 (CH), 127.9 (CH), 128.6 (CH), 138.7 (C), 151.0 (C), 155.6 (C), 169.6 (C), 171.2 (C), 173.2 (C) ppm. MALDI-TOF MS: m/z 543.198 [M + Na]$^+$.

Fmoc-Leu-*g*Ala-COOSu (5n): Fmoc-Leu-*g*Ala-OH (1.80 g, 4.24 mmol) was transformed according to the general procedure A. Recrystallisation from toluene yielded **5n** (2.13 g, 94%): white solid, m.p. 181 °C. $[\alpha]_D^{20}$ = +5.6 (c = 0.5, DMF). HPLC: t_R = 10.82 min (linear gradient, 30–100% solvent B, 20 min). ^{1}H NMR ([D$_6$]-DMSO, 300 MHz): δ = 0.84–0.89 [m, 6 H, CH(CH_3)$_2$], 1.30 (d, J = 6.49 Hz, 3 H, CHCH_3), 1.33–1.52 (m, 2 H, CHCH_2CH), 1.55–1.68 [m, 1 H, C*H*(CH$_3$)$_2$], 2.75 (s, 4 H, CH_2CH_2), 3.99–4.07 (m, 1 H, NHC*H*CH$_2$), 4.18–4.30 (m, 3 H, CH_2O, C*H*CH$_2$O), 5.24–5.36 (m, 1 H, NHC*H*NH), 7.32 (t, J = 6.77 Hz, 2 H, arom. H), 7.39–7.47 (m, 3 H, arom. H, N*H*CO_2Fm), 7.71–7.75 (m, 2 H, arom. H), 7.89 (d, J = 7.44 Hz, 2 H, arom. H), 8.36 (d, J = 7.61 Hz, 1 H, N*H*CO_2Su), 8.69 (d, J = 6.92 Hz, 1 H, N*H*COCH) ppm. ^{13}C NMR ([D$_6$]DMSO, 75 MHz): δ = 21.0 (CH_3), 21.8 (CH_3), 23.6 (CH_3), 24.7 (CH), 25.7 (CH_2), 41.1 (CH_2), 47.1 (CH), 53.2 (CH), 54.9 (CH), 66.0 (CH_2), 120.5 (2 CH), 125.8 (2 CH), 127.5 (2 CH), 128.1 (2 CH), 141.2 (2 C), 144.2 (C), 144.4 (C), 150.8 (C), 156.4 (C), 171.2 (2 C), 172.1 (C) ppm. HRMS: calcd. for $C_{28}H_{32}N_4O_7$ [M + Na]$^+$ 559.2163; found 559.2041.

Fmoc-Ile-*g*Gly-COOSu (5o): Fmoc-Ile-Gly-OH (2.70 g, 4.66 mmol) was transformed according to the general procedure A. Recrystallisation from toluene yielded **5o** (1.31 g, 52%): white solid, m.p. 220 °C. $[\alpha]_D^{25}$ = +2.0 (c = 1.0, DMF). HPLC: t_R = 10.94 min (linear gradient, 30–100% solvent B, 20 min). ^{1}H NMR ([D$_6$]DMSO, 200 MHz): δ = 0.80 (t, J = 7.0 Hz, 3 H, CH_3), 0.83 (d, J = 6.6 Hz, 3 H, CH_3), 1.01–1.23 (m, 1 H, CH_2CH$_3$), 1.34–1.50 (m, 1 H, CH_2CH$_3$), 1.59–1.82 (m, 1 H, C*H*CH$_3$), 2.76 (s, 4 H, CH_2CO), 3.91 (t, J = 8.0 Hz, 1 H, C*H*CH$_2$O), 4.22–4.30 (m, 3 H, CHCH_2O, NHC*H*), 4.35–4.55 (m, 2 H, NHCH_2), 7.28–7.46 (m, 5 H, arom. H, N*H*CO_2Fm), 7.75 (d, J = 6.9 Hz, 2 H, arom. H), 7.89 (d, J = 7.0 Hz, 2 H, arom. H), 8.69 (br. t, J = 5.6 Hz, 1 H, N*H*CO_2Su), 9.00 (br. t, J = 8.0 Hz, 1 H, CHCON*H*CH$_2$) ppm. ^{13}C NMR ([D$_6$]-DMSO, 50 MHz): δ = 10.7 (CH_3), 15.2 (CH_3), 24.3 (CH_2), 25.2 (CH_2), 36.3 (CH), 45.6 (CH_2), 46.6 (CH), 58.8 (CH), 65.6 (CH_2), 120.0 (CH), 125.3 (CH), 126.9 (CH), 127.5 (CH), 140.6 (C), 143.7 (C), 151.9 (C), 155.8 (C), 170.6 (C), 171.7 (C) ppm. HRMS: calcd. for $C_{27}H_{31}N_4O_7$ [M + H]$^+$ 523.2187; found 523.2149.

Z-Val-*g*Ala-COOSu (5r): Z-Val-Ala-OH (1.90 g, 5.89 mmol) was transformed according to the general procedure A. Recrystallisation from toluene yielded **5r** (2.47 g, 96%): white solid, m.p. 170 °C. $[\alpha]_D^{20}$ = +26.9 (c = 0.5, DMF). HPLC: t_R = 6.54 min (linear gradient, 30–100% solvent B, 20 min). ^{1}H NMR ([D$_6$]DMSO, 300 MHz): δ = 0.81 [d, J = 7.01 Hz, 3 H, CH(CH_3)$_2$], 0.83 [d, J = 7.01 Hz, 3 H, CH(CH_3)$_2$], 1.31 (d, J = 6.55 Hz, 3 H, CHCH_3), 1.86–1.96 [m, 1 H, C*H*(CH$_3$)$_2$], 2.75 (s, 4 H, CH_2CH_2), 3.86 (dd, J = 8.77, 6.80 Hz, 1 H, NHC*H*CO), 5.00 (d, J = 12.66 Hz, 1 H, CH_2Phe), 5.05 (d, J = 12.69 Hz, 1 H, CH_2Phe), 5.26–5.38 (m, 1 H, NHC*H*NH), 7.20 (d, J = 8.92 Hz, 1 H, N*H*CHCO), 7.28–7.40 (m, 5 H, arom. H), 8.36 (d, J = 7.83 Hz, 1 H, N*H*CHNH), 8.75 (d, J = 7.32 Hz, 1 H, NHCHN*H*) ppm. ^{13}C NMR ([D$_6$]DMSO, 75 MHz): δ = 18.5 (CH_3), 19.7 (CH_3), 21.0 (CH_3), 25.7 (2 CH_2), 30.9 (CH), 54.7 (CH), 60.2 (CH), 65.8 (CH_2), 128.1 (2 CH), 128.2 (CH), 128.8 (2 CH), 137.5 (C), 150.8 (C), 156.5 (C), 170.7 (C), 171.2 (2 C) ppm. MALDI-TOF MS: m/z 457.137 [M + Na]$^+$, 473.115 [M + K]$^+$.

General Procedure for the Preparation of Ureas 6. Procedure B: To a stirred solution of the amine (1.1 equiv.) in MeCN or DMF (10 mL), were successively added succinimidyl carbamate **4** or **5** (usually about 1 mmol) and Hünig's base (1.2 equiv.). After 10–30 min, the mixture was diluted with saturated $NaHCO_3$ and extracted with EtOAc. The organic layer was washed with 1 N $KHSO_4$, brine, saturated $NaHCO_3$ and brine, dried ($MgSO_4$), and the solvents were evaporated. Flash chromatography and/or recrystallisation afforded pure urea **6**.

Boc-*g*Ser(Bn)-CON(Bn)$_2$ (6b): Carbamate **4b** (428 mg, 1.05 mmol) was treated with dibenzylamine (202 μL, 1.05 mmol) according to the general procedure B to yield **6b** (489 mg, 95%): white solid, m.p. 74 °C. $[\alpha]_D^{25}$ = –15.7 (c = 1.2, DMF). HPLC: t_R = 14.46 min (linear gradient, 30–100% solvent B, 20 min). ^{1}H NMR ([D$_6$]-DMSO, 200 MHz): δ = 1.37 [s, 9 H, C(CH$_3$)$_3$], 3.48 (d, J = 6.4 Hz, 2 H, CH_2OCH$_2$Ph), 4.30 (d, J = 16.2 Hz, 2 H, NCH_2Ph), 4.42 (d, J = 16.2 Hz, 2 H, NCH_2Ph), 4.48 (s, 2 H, CH$_2$OCH_2Ph), 5.30–5.45 (m, 1 H, NHC*H*NH), 6.65 (d, J = 7.9 Hz, 1 H, NHCHN*H*), 6.81 (d, J = 7.9 Hz, 1 H, N*H*CHNH), 7.10–7.71 (m, 15 H, arom. H) ppm. ^{13}C NMR ([D$_6$]DMSO, 50 MHz): δ = 28.1 (CH_3), 48.6 (CH_2), 71.0 (CH_2), 71.9 (CH_2), 78.1 (C), 126.9 (CH), 127.2 (CH), 127.3 (CH), 127.4 (CH), 128.1 (CH), 128.1 (CH), 138.1 (CH), 138.4 (CH), 154.4 (C), 156.7 (C) ppm. MALDI-TOF MS: m/z 512.4 [M + Na]$^+$, 528.6 [M + K]$^+$.

Boc-Lys(2-Cl-Z)-*g*Val-CONH*i*Pr (6c): Carbamate **5d** (0.3 g, 0.463 mmol) was treated with isopropylamine (47 μL, 0.556 mmol) according to the general procedure B to yield **6c** (0.193 g, 74%): white solid, m.p. 166 °C. $[\alpha]_D^{25}$ = –16.2 (c = 0.9, DMF). HPLC: t_R = 11.33 min (linear gradient, 30–100% solvent B, 20 min). ^{1}H NMR (CD$_3$OD, 200 MHz): δ = 0.89 (d, J = 6.7 Hz, 3 H, CH_3CHCH$_3$), 0.91 (d, J = 6.7 Hz, 3 H, CH$_3$CHCH_3), 1.04 [d, J = 6.5 Hz, 6 H, NHCH(CH_3)$_2$], 1.20–1.69 (m, 6 H, CHCH_2CH_2CH_2), 1.38 [s, 9 H, C(CH$_3$)$_3$], 1.72–1.98 [m, 1 H, CHC*H*(CH$_3$)$_2$], 3.00–3.14 (m, 2 H, CH_2NH), 3.73 [h, 1 H, J = 6.5 Hz, NHC*H*(CH$_3$)$_2$], 3.89 (m, 1 H, NHC*H*CO), 4.99 (d, J = 7.8 Hz, 1 H, NHC*H*NH), 5.12 (s, 2 H, OCH_2), 7.23–7.43 (m, 4 H, H arom.) ppm. ^{13}C NMR ([D$_6$]DMSO, 75 MHz): δ = 18.2 (CH_3), 18.3 (CH_3), 22.7 (CH_2), 23.0 (CH_3), 23.1 (CH_3), 28.1 (CH_3), 29.1 (CH_2), 31.5 (CH2), 32.0 (CH), 40.1 (CH2), 40.7 (CH), 54.37 (CH), 61.3 (CH), 62.5 (CH2), 127.2 (CH), 129.2 (CH), 129.6 (CH), 132.2 (C), 134.6 (C), 155.2 (C), 155.7 (C), 156.4 (C), 171.5 (C) ppm. HRMS: calcd. for $C_{27}H_{45}ClN_5O_6$ [M + H]$^+$ 570.3053; found 570.3037.

Boc-Pro-*g*Leu-CON(Me)$_2$ (6e): Carbamate **5f** (500 mg, 1.14 mmol) was treated with HCl·N(Me)$_2$ (111 mg, 1.36 mmol) and Hünig's base (395 μL, 2.27 mmol) according to the general procedure B to yield **6e** (0.33 g, 79%): white solid, m.p. 180 °C. $[\alpha]_D^{25}$ = –54.2 (c = 1.0, DMF). HPLC: t_R = 6.97 min (linear gradient, 30–100% solvent B, 20 min). ^{1}H NMR ([D$_6$]DMSO, 200 MHz): δ = 0.87–0.92 [m, 6 H, CH(CH_3)$_2$], 1.36, 1.44 [s, 10 H, C(CH_3)$_3$, C*H*(CH$_3$)$_2$], 1.48–1.65 [m, 2 H, CH_2CH(CH$_3$)$_2$], 1.70–2.20 (m, 4 H, CH$_2$CH_2CH_2CH), 2.80 [s, 6 H, N(CH_3)$_2$], 3.14–3.45 (m, 2 H, NCH_2CH$_2$), 3.98–4.15 (m, 1 H, NC*H*CO), 5.28–5.48 (m, 1 H, NHC*H*NH), 6.41 [d, J = 8.3 Hz, 1 H, N*H*CON(CH$_3$)$_2$], 7.74 (d, J = 7.8 Hz, 1 H, N*H*COCH) ppm. ^{13}C NMR ([D$_6$]DMSO, 50 MHz): δ = 22.4 (CH_3), 23.0 (CH_2), 24.2 (CH), 27.8 (CH_3), 30.9 (CH_2), 35.6 (CH_3), 44.0 (CH_2), 46.4 (CH_2), 55.9 (CH), 59.7 (CH), 78.4 (C), 153.1 (C), 156.8 (C), 171.0 (C) ppm. HRMS: calcd. for $C_{18}H_{35}N_4O_4$ [M + H]$^+$ 371.2653; found 371.2660.

Boc-Ile-*g*Val-CO-Val-OBn (6g): Carbamate **5c** (170 mg, 0.384 mmol) was treated with HCl·H-Val-OBn (103 mg, 0.423 mmol) and Hünig's base (80 μL, 0.461 mmol) according to the general procedure B to yield **6g** (180 mg, 81%): white solid, m.p. 180 °C (dec.). $[\alpha]_D^{25} = -5.5$ (c = 1.0, DMF). HPLC: t_R = 13.24 min (linear gradient, 30–100% solvent B, 20 min). ^{1}H NMR ([D$_6$]DMSO, 200 MHz): δ = 0.65–0.95 (m, 18 H, CH_3CHCH_3, CH_3CHCH$_2$CH_3), 0.95–1.18 (m, 1 H, CH$_3$CHCH_2CH$_3$), 1.18–1.49 [m, 10 H, C(CH_3)$_3$, CH$_3$CHCH_2CH$_3$], 1.49–1.71 (m, 1 H, CH$_3$CHCH$_2$CH$_3$), 1.75–2.10 (m, 2 H, CH$_3$CHCH$_3$), 3.78 [br. t, J = 7.3 Hz, 1 H, CHCH(CH$_3$)CH$_2$CH$_3$], 4.04–4.11 [m, 1 H, COCHCH(CH$_3$)$_2$], 4.99–5.23 [m, 3 H, OCH_2OPh, NHCHNH), 6.38 [br. d, J = 9 Hz, 1 H, NHCO$_2$C(CH$_3$)$_3$], 6.46–6.57 (m, 2 H, CONHCHNHCONH), 7.22–7.44 (m, 5 H, arom. H), 8.01 (br. d, J = 7.3 Hz, 1 H, CONHCHNHCONH) ppm. ^{13}C NMR ([D$_6$]-DMSO, 50 MHz): δ = 10.9 (CH$_3$), 15.2 (CH$_3$), 17.6 (CH$_3$), 18.1 (CH$_3$), 18.9 (CH$_3$), 24.1 (CH$_2$), 28.0 (CH$_3$), 30.2 (CH), 31.8 (CH), 36.7 (CH), 57.2 (CH) 57.7 (CH), 58.6 (CH), 65.6 (CH$_2$), 77.8 (C), 127.8 (CH), 128.3 (CH), 135.9 (C), 155.1 (C), 156.8 (C), 170.3 (C), 172.3 (C) ppm. HRMS: calcd. for C$_{28}$H$_{47}$N$_4$O$_6$ [M + H]$^+$ 535.3490; found 535.3483.

Boc-Pro-*g*Ala-CO-Leu-OMe (6i): Carbamate **5g** (1.0 g, 2.508 mmol) was treated with HCl·H-Leu-OMe (501 mg, 2.76 mmol) and Hünig's base (640 μL, 3.67 mmol) according to the general procedure B to yield **6i** (790 mg, 74%): white solid, m.p. 167 °C. $[\alpha]_D^{25} = -32.5$ (c = 0.9, DMF). HPLC: t_R = 7.57 min (linear gradient, 30–100% solvent B, 20 min). ^{1}H NMR ([D$_6$]DMSO, 300 MHz): δ = 0.79 (d, J = 6.1 Hz, 3 H, CH$_3$), 0.83 (d, J = 6.5 Hz, 3 H, CH$_3$), 1.21 (d, J = 6.5 Hz, 3 H, CH$_3$), 1.27–1.61 [m, 12 H, C(CH_3)$_3$, CH_2CH(CH$_3$)$_2$], 1.55–1.84 (m, 3 H, CH$_2$CH_2CH_2CH), 1.91–2.10 (m, 3 H, CH$_2$CH_2CH_2CH), 3.15–3.42 (m, 2 H, NCH_2CH$_2$), 3.56 (s, 3 H, OCH_3), 3.87–4.01 (m, 1 H, NHCHCO), 4.08–4.21 (m, 1 H, NHCHCO), 5.11–5.28 (m, 1 H, NHCHNH), 6.31 (br. d, J = 7.7 Hz, 1 H, NHCONH), 6.44 (br. d, J = 8.0 Hz, 1 H, NHCONH), 8.16 (br. d, J = 7.4 Hz, 1 H, NHCOCH) ppm. ^{13}C NMR ([D$_6$]DMSO, 75 MHz): δ = 21.4 (CH$_3$), 21.6 (CH$_3$), 22.6 (CH$_3$), 23.1 (CH$_2$), 24.2 (CH), 27.9 (CH), 28.1 (CH$_3$), 30.9 (CH$_2$), 41.1 (CH$_2$), 46.4 (CH$_2$), 50.6 (CH$_2$), 51.6 (CH), 53.1 (CH), 59.5 (CH$_3$), 78.3 (C), 153.2 (C), 156.0 (C), 171.7 (C), 173.8 (C) ppm. MALDI-TOF MS: m/z 451.08 [M + Na]$^+$, 467.51 [M + K]$^+$.

Boc-Pro-*g*Leu-CO-Ala-Phe-OMe (6j): Carbamate **5f** (300 mg, 0.68 mmol) was treated with TFA·H-Ala-Phe-OMe (273 mg, 0.75 mmol) and Hünig's base (142 μL, 0.82 mmol) in MeCN according to the general procedure B to yield **6j** (274 mg, 70%): white solid, m.p. 185 °C. $[\alpha]_D^{25} = -15.9$ (c = 1.0, DMF). HPLC: t_R = 7.57 min (linear gradient, 30–100% solvent B, 20 min). ^{1}H NMR ([D$_6$]DMSO, 500 MHz): δ = 0.83–0.86 [m, 7 H, CH(CH_3)$_2$, CH(CH$_3$)$_2$], 1.11 (d, J = 6.86 Hz, 3 H, CHCH_3), 1.26 [s, 9 H, C(CH_3)$_3$], 1.36–1.41 [m, 1 H, CH_2CH(CH$_3$)$_2$], 1.48–1.57 [m, 1 H, CH_2CH(CH$_3$)$_2$], 1.68–1.79 (m, 3 H, CHCH_2CH$_2$, CHCH$_2$CH_2), 1.94–2.10 (m, 1 H, CHCH_2CH$_2$), 2.90 (dd, J = 13.85, 9.37 Hz, 1 H, CH_2Ph), 3.02 (dd, J = 13.90, 5.35 Hz, 1 H, CH_2Ph), 3.21–3.26 (m, 1 H, NCH_2), 3.30–3.36 (m, 1 H, NCH_2), 3.58 (s, OCH_3), 3.99 (dd, J = 25.19, 7.97 Hz, 1 H, NCH), 4.15–4.21 (m, 1 H, NHCHCH$_3$), 4.41–4.45 (m, 1 H, CHCOOMe), 5.21 (quint, J = 7.60 Hz, 1 H, NHCHNH), 6.25 (br. s, 1 H, NHCHCH$_3$), 6.43 (d, J = 8.44 Hz, 1 H, NHCONHCHCH$_3$), 7.18–7.29 (m, 5 H, arom. H), 7.97 (br. s, 1 H, NCHCONH), 8.35 (d, J = 7.37 Hz, 1 H, NHCHCOOMe) ppm. ^{13}C NMR ([D$_6$]DMSO, 125 MHz): δ = 21.9 (CH$_3$), 22.2 (CH$_3$), 22.7 (CH$_2$), 23.9 (CH$_3$), 27.6 (3 CH$_3$), 27.9 (CH), 30.8 (CH$_2$), 36.3 (CH$_2$), 43.5 (CH$_2$), 46.2 (CH$_2$), 47.8 (CH$_3$), 51.6 (CH), 53.4 (CH), 54.9 (CH), 59.3 (CH), 78.1 (C), 126.3 (CH), 128.0 (2 CH), 128.8 (2 CH), 136.9 (C), 153.1 (C), 155.6 (C), 171.6 (C), 172.9 (C) ppm. MALDI-TOF MS: m/z 598.46 [M + Na]$^+$, 614.68 [M + K]$^+$.

Boc-Ile-D-*g*Val-CO-Pro-OMe (6k): Carbamate *epi*-**5c** (603 mg, 1.36 mmol) was treated with HCl·H-Pro-OMe (248 mg, 1.50 mmol) and Hünig's base (278 μL, 1.64 mmol) in MeCN according to the general procedure B to yield **6k** (497 mg, 80%): white solid, m.p. 170 °C. $[\alpha]_D^{20} = -20.6$ (c = 1.0, DMF). HPLC: t_R = 8.86 min (linear gradient, 30–100% solvent B, 20 min). ^{1}H NMR ([D$_6$]DMSO, 500 MHz): δ = 0.76–0.81 (m, 12 H, 4 CH$_3$), 1.01–1.10 (m, 1 H, CHCHCH_2), 1.36 [s, 9 H, C(CH_3)$_3$], 1.32–1.40 (m, 1 H, CHCHCH_2), 1.61–1.69 (m, 1 H, CHCHCH$_2$), 1.76–1.82 (m, 1 H, CHCH_2CH$_2$), 1.82–1.88 (CHCH$_2$CH_2), 1.88–1.94 [m, 1 H, CHCH(CH$_3$)$_2$], 2.05–2.12 (m, 1 H, CHCHCH$_2$), 3.20–3.25 (m, 1 H, NCH_2), 3.32–3.38 (m, 1 H, NCH_2), 3.56 (s, 3 H, OMe), 3.71 (t, J = 7.47 Hz, 1 H, CHCHCH$_2$), 4.21 (dd, J = 8.60, 3.69 Hz, 1 H, NCH), 5.00 [q, J = 8.12 Hz, 1 H, CH(CH$_3$)$_2$], 6.25 (d, J = 8.31 Hz, 1 H, NHCON), 6.64 (d, J = 8.34 Hz, 1 H, BocNH), 7.68 (d, J = 8.39 Hz, 1 H, CHCONH) ppm. ^{13}C NMR ([D$_6$]DMSO, 125 MHz): δ = 10.9 (CH$_3$), 15.1 (CH$_3$), 18.1 (CH$_3$), 18.3 (CH$_3$), 23.8 (CH$_2$), 24.0 (CH2), 27.9 (3 CH$_3$), 28.9 (CH$_2$), 31.9 (CH), 36.2 (CH), 45.2 (CH$_2$), 51.3 (CH$_3$), 58.2 (CH), 58.8 (CH), 61.6 (CH), 77.8 (C), 154.8 (C), 155.1 (C), 170.0 (C), 173.0 (C) ppm. HRMS: calcd. for C$_{22}$H$_{40}$N$_4$O$_6$ [M + Li]$^+$ 463.3103; found 463.3106.

Z-*g*Phe-CO-Val-OMe (6n): Carbamate **4h** (520 mg, 1.26 mmol) was treated with HCl·H-Val-OMe (317 mg, 1.89 mmol) and Hünig's base (324 μL, 1.89 mmol) according to the general procedure B to yield **6n** (467 mg, 86%): white solid, m.p. 181 °C. $[\alpha]_D^{25} = -3.6$ (c = 1.0, DMF). HPLC: t_R = 10.74 min (linear gradient, 30–100% solvent B, 20 min). ^{1}H NMR ([D$_6$]DMSO, 300 MHz): δ = 0.76 [d, J = 6.8 Hz, 3 H, CH(CH_3)$_2$], 0.77 [d, J = 6.8 Hz, 3 H, CH(CH_3)$_2$], 1.78–2.01 [m, 1 H, CH(CH$_3$)$_2$], 2.87 (d, J = 5.9 Hz, 2 H, CHCH_2Ph), 3.58 (s, 3 H, OCH$_3$), 4.00–4.06 [m, 1 H, CHCH(CH$_3$)$_2$], 4.95 (s, 2 H, OCH_2Ph), 5.15 (br. t, J = 7.5 Hz, 1 H, CHCH$_2$Ph), 6.39 (br. d, J = 8.6 Hz, 1 H, NHCO), 6.52 (br. d, J = 8.1 Hz, 1 H, NHCO), 7.14–7.32 (m, 10 H, arom. H), 7.74 (br. d, J = 7.2 Hz, 1 H, NHCO) ppm. ^{13}C NMR ([D$_6$]DMSO, 75 MHz): δ = 17.7 (CH$_3$), 18.9 (CH$_3$), 30.5 (CH), 40.9 (CH$_2$), 51.5 (CH$_3$), 57.3 (CH), 65.0 (CH$_2$), 126.2 (C), 127.6(C), 127.7 (C), 128.0 (C), 128.3 (C), 129.1 (C), 129.2 (C), 137.0 (C), 137.6 (C), 155.0 (C), 156.2 (C), 173.0 (C) ppm. MALDI-TOF MS: m/z 378.1 [M + Na]$^+$, 394.0 [M + K]$^+$.

Z-Ala-*g*Leu-CONH*i*Pr (6p): Carbamate **5s** (0.50 g, 1.11 mmol) was treated with isopropylamine (0.28 mL, 3.35 mmol) according to the general procedure B to yield **6p** (0.38 g, 88%): white solid, m.p. 172 °C. $[\alpha]_D^{20} = +6.0$ (c = 0.5, DMF). HPLC: t_R = 8.67 min (linear gradient, 30–100% solvent B, 20 min). ^{1}H NMR ([D$_6$]DMSO, 300 MHz): δ = 0.84 [d, J = 5.88 Hz, 6 H, CH$_2$CH(CH_3)$_2$], 0.98–1.02 [m, 6 H, NHCH(CH_3)$_2$], 1.17 (d, J = 7.14 Hz, 3 H, CHCH_3), 137–1.59 [m, 3 H, CH_2CH(CH$_3$)$_2$, CH$_2$CH(CH$_3$)$_2$], 3.56–3.72 [m, 1 H, NHCH(CH$_3$)$_2$], 3.97 [quint., J = 7.12 Hz, 1 H, NHCH-(CH$_3$)$_2$], 4.98 (d, J = 12.46 Hz, 1 H, CH_2Phe), 5.03 (d, J = 12.47 Hz, 1 H, CH_2Phe), 5.14–5.23 (m, 1 H, NHCHNH), 5.94 [d, J = 7.51 Hz, 1 H, NHCH(CH$_3$)$_2$], 6.07 [d, J = 8.53 Hz, 1 H, NHCONHCH(CH$_3$)$_2$], 7.29–7.35 (m, 5 H, arom. H), 7.39 (d, J = 7.78 Hz, 1 H, NHCHCO), 8.10 (d, J = 7.82 Hz, 1 H, NHCHNH) ppm. ^{13}C NMR ([D$_6$]DMSO, 75 MHz): δ = 23.4 (CH$_3$), 27.4 (CH$_3$), 27.6 (CH$_3$), 28.3 (CH$_3$), 28.4 (CH$_3$), 29.4 (CH), 46.0 (CH), 48.9 (CH), 55.2 (CH), 60.4 (CH), 70.5 (CH$_2$), 132.9 (2 CH), 133.0 (CH), 133.5 (2 CH), 142.2 (C), 160.8 (C), 161.4 (C), 177.2 (C) ppm. HRMS: calcd. for C$_{20}$H$_{32}$N$_4$O$_4$ [M + Li]$^+$ 399.2579; found 399.2572.

Peptidyl Hydantoin (7a): Ureidopeptide ester **6f** (100 mg, 0.22 mmol) was stirred with a solution of 10% Et$_3$N in MeOH.

The reaction was monitored by HPLC. The organic mixture was concentrated. Recrystallization afforded **7a** (93 mg, quantitative): white solid, m.p. 104 °C (dec.). $[\alpha]_D^{25}$ = –32.2 (*c* = 1.0, DMF). HPLC: t_R = 9.96 min (linear gradient, 30–100% solvent B, 20 min). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 0.85–0.90 [m, 9 H, CH(C*H*$_3$)$_2$, CH(CH$_3$)CH$_2$C*H*$_3$, CH(C*H*$_3$)CH$_2$CH$_3$], 0.99 [dd, *J* = 6.71, 2.51 Hz, 3 H, CH(C*H*$_3$)$_2$], 1.03–1.14 [m, 1 H, CH(CH$_3$)C*H*$_2$CH$_3$], 1.36–1.46 [m, 1 H, CH(CH$_3$)C*H*$_2$CH$_3$], 1.43 [s, 9 H, C(C*H*$_3$)$_3$], 1.58–1.71 (m, 1 H, NCHC*H*$_2$), 1.79–1.88 [m, 1 H, C*H*(CH$_3$)-CH$_2$CH$_3$], 1.99–2.10 (m, 2 H, NCH$_2$C*H*$_2$), 2.20–2.28 (m, 1 H, NCHC*H*$_2$),2.29–2.39 [m, 1 H, C*H*(CH$_3$)$_2$], 3.16–3.23 (m, 1 H, NCH$_2$), 3.61–3.72 (m, 1 H, NCH$_2$), 3.93 (dd, *J* = 13.86, 6.24 Hz, 1 H, NHC*H*CO), 4.02 (dt, *J* = 7.71, 2.08 Hz, 1 H, NC*H*CO), 4.98 (br. s, 1 H, OCON*H*), 5.59 (dt, *J* = 9.95, 2.28 Hz, 1 H, NHC*H*N), 7.02 (dd, *J* = 9.21, 6.67 Hz, 1 H, N*H*CHN) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz, chemical shift of rotamers in italics): δ = 11.4/*11.5* (CH$_3$), 15.6/*15.7* (CH$_3$), 18.6/*18.7* (CH$_3$), 18.8/*18.9* (CH$_3$), 24.7 (CH$_2$), 26.8/*26.9* (CH$_2$), 27.7/*27.8* (CH$_2$), 30.7 (CH), 31.2 (CH), 37.1/*37.3* (3 CH$_3$), 45.5/*45.6* (CH$_2$), 59.2/*59.3* (CH), 62.1/*62.3* (CH), 62.9/*63.0* (CH), 80.0 (C), 155.8 (C), 159.7/*159.9* (C), 171.1/*171.2* (C), 172.8/*173.0* (C) ppm. MALDI-TOF MS: *m*/*z* 447.7 [M + Na]$^+$, 463.8 [M + K]$^+$.

Peptidyl Hydantoin (7c): KF/Al_2O_3 (74 mg, 1.27 mmol) was added to a solution of ureidopeptide ester **6a** (100 mg, 0.25 mmol) in MeCN (4 mL), and the mixture was stirred at room temperature for 4 h. After the completion of the reaction, the precipitate was filtered through Celite©, washed with MeCN, and the filtrate was dried under reduced pressure. The residue was purified by column chromatography with cyclohexane/EtOAc (9:1) and afforded **7c** (60 mg, 65%): white solid, m.p. 170 °C. HPLC: t_R = 10.51 min (linear gradient, 30–100% solvent B, 20 min). ^{1}H NMR ([D$_6$]DMSO, 300 MHz): δ = 0.67 (d, *J* = 6.70 Hz, 3 H, CH$_3$), 0.87 (d, *J* = 6.96 Hz, 3 H, CH$_3$), 1.33 [s, 9 H, C(CH$_3$)$_3$], 1.86–1.97 [m, 1 H, C*H*(CH$_3$)$_2$], 3.17 (d, *J* = 7.82 Hz, 2 H, C*H*$_2$Phe), 3.71 (d, *J* = 2.47 Hz, 1 H, CHC*H*NH), 5.57 (q, *J* = 7.88 Hz, 1 H, NHC*H*N), 7.16–7.29 (m, 5 H, arom H), 7.61 (d, *J* = 6.79 Hz, 1 H, N*H*CHN), 8.09 (s, 1 H, NCON*H*) ppm. ^{13}C NMR ([D$_6$]DMSO, 75 MHz): δ = 15.8 (CH$_3$), 18.8 (CH$_3$), 28.4 (CH$_3$), 30.1 (CH$_3$), 37.8 (CH$_2$), 59.4 (CH), 61.2 (CH), 78.9 (C), 127.0 (CH), 128.7 (CH), 129.5 (CH), 137.1 (C), 154.6 (C), 156.8 (C), 172.9 (C). HRMS: calcd. for $C_{19}H_{27}N_3O_4$ [M + Na]$^+$ 384.1894; found 384.1871.

Boc-*g*Ala-CO-*g*Phe-CONH*i*Pr (8a): Carbamate **4c** (76 mg, 0.25 mmol) was treated with Z-*g*Phe-CONH*i*Pr (**6l**, 100 mg, 0.28 mmol) with 10% Pd/C under H_2 in DMF. After 3 h, the mixture was diluted with saturated $NaHCO_3$ and extracted with EtOAc. The organic layer was washed with saturated $NaHCO_3$ and brine, dried ($MgSO_4$), and the solvents were evaporated. Recrystallization afforded **8a** (40 mg, 39%): white solid, m.p. 134 °C. $[\alpha]_D^{25}$ = –18.9 (*c* = 0.5, DMF). HPLC: t_R = 10.44 min (linear gradient, 0–100% solvent B, 20 min). ^{1}H NMR ([D$_6$]DMSO, 400 MHz): δ = 0.99 [dd, *J* = 10.6, 5.2 Hz, 6 H, NHCH(C*H*$_3$)$_2$], 1.16 [d, *J* = 5.2 Hz, 3 H, CH(C*H*$_3$)], 1.37 [s, 9 H, (C*H*$_3$)$_3$], 2.90 (d, *J* = 6.2 Hz, 2 H, C*H*$_2$Ph), 3.60 [sext, *J* = 5.4 Hz, 1 H, NHC*H*-(CH$_3$)$_2$], 5.02–5.14 [m, 2 H, NHC*H*CH$_3$NH, NHC*H*(CH$_2$Ph)NH], 5.92–6.08 (br. s, 1 H), 6.18 (br. d, *J* = 7.4 Hz, 1 H), 6.42–6.53 (br. s, 1 H), 7.07–7.15 [br. s, 1 H, NHCO$_2$C(CH$_3$)$_3$], 7.17–7.29 (m, 5 H, arom. H) ppm. ^{13}C NMR ([D$_6$]DMSO, 100 MHz): δ = 21.8 (CH$_3$), 23.0 (CH$_3$), 23.2 (CH$_3$), 28.2 (CH$_3$), 40.8 (CH), 41.1 (CH$_2$), 54.2 (CH), 58.8 (CH), 77.7 (C), 126.1 (CH), 128.1 (CH), 129.2 (CH), 138.1 (C), 154.2 (C), 155.9 (C), 156.5 (C) ppm. MALDI-TOF MS: *m*/*z* 430.5 [M + Na]$^+$, 446.6 [M + K]$^+$.

Boc-Ser(Bn)-*g*Leu-CO-Ala-NH$_2$ (9): 6l (100 mg, 0.25 mmol) was treated with 3 N HCl in dioxane for 30 min at room temp. The oily residue, which separated upon addition of Et_2O/n-hexane (3:1), was collected and dried under vacuo. The resulting crude HCl salt (66 mg) was dissolved in DMF whilst stirring and treated with **5k** (Boc-Ser(Bn)-*g*LeuCOOSu) (114 mg, 0.22 mmol) and Hünig's base (75 μL, 0.44 mmol), according to general procedure B. The crude product was purified by flash column chromatography (CH_2Cl_2/MeOH, 20:1.5) to yield pure **9** (44 mg, 41%) as a white solid, m.p. 212 °C. $[\alpha]_D^{20}$ = +11.4 (*c* = 0.5, DMF). HPLC: t_R = 8.37 (linear gradient, 30–100% B, 20 min). ^{1}H NMR ([D$_5$]pyridine, 400 MHz): δ = 0.82 (d, *J* = 5.4 Hz, 3 H, CH$_3$), 0.83 (d, *J* = 5.3 Hz, 3 H, CH$_3$), 1.46 [s, 9 H, C(C*H*$_3$)$_3$], 1.64 (d, *J* = 7.0 Hz, 3 H, CH$_3$), 1.76–1.81 [m, 1 H, C*H*(CH$_3$)$_2$], 1.83–193 [m, 2 H, C*H*$_2$CH(CH$_3$)$_2$], 4.01 (dd, *J* = 5.6, 9.3 Hz, 1 H, C*H*$_2$O), 4.07 (dd, *J* = 5.7, 9.4 Hz, 1 H, C*H*$_2$O), 4.52 (q, *J* = 11.8 Hz, 2 H, OCH$_2$Ph), 4.96–5.00 (m, 4 H), 5.98–6.04 (m, 1 H, NHC*H*NH), 7.21–7.40 (m, 6 H, arom. H, α-CHAla), 7.58–7.61 (d, 2 H, N*H*CHN*H*), 7.95 (br. s., 1 H, CON*H*$_2$), 8.16 (d, *J* = 7.9 Hz, 1 H, BocN*H*), 8.29 (br. s., 1 H, CON*H*$_2$) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz) 22.13(CH$_3$), 22.44 (CH$_3$), 24.85 (CH$_3$), 28.26 (CH$_3$), 43.86 (CH$_2$), 50.11 (CH), 55.49 (CH), 56.93 (CH), 71.14 (CH$_2$), 73.11 (CH$_2$), 78.74 (C), 127.7 (CH), 127.9 (CH), 128.51 (CH), 138.6 (C), 156.34 (C), 157.91 (C), 171.38 (C), 176.47 (C) ppm. HRMS: calcd for $C_{24}H_{39}N_5O_6$ [M + Li]$^+$ 500.3055; found 500.3044.

Boc-Ser(Bn)-*g*Leu-CO-Ile-*g*Val-CO-Pro-OMe (10): 6f (40 mg, 0.088 mmol) was placed in a round-bottom flask and dissolved in CH_2Cl_2 (1 mL) and cooled to 0 °C. TFA (1 mL) was then added dropwise to the solution. The solution was stirred for 20 min at 0 °C and checked by TLC (EtOAc). TFA was co-evaporated with cyclohexane, and the residue was dried under vacuum. The crude trifluoroacetate salt was dissolved in DMF (0.5 mL). **5k** (42 mg, 0.080 mmol) and Hünig's base (27 μL, 0.159 mmol) were added. The solution was stirred 30 min at room temp. After being checked by TLC, the mixture was diluted with saturated $NaHCO_3$ and extracted with EtOAc. The organic layer was washed with 1 N $KHSO_4$, brine, saturated $NaHCO_3$ and brine, dried with Na_2SO_4 and concentrated in vacuo. The crude product was purified by flash column chromatography (CH_2Cl_2/MeOH, 97:3) to yield pure **10** (27 mg, 41%) as a white solid, m.p. 208 °C. HPLC: t_R = 18.20 min (linear gradient, 5–65% B, 20 min). ^{1}H NMR ([D$_6$]DMSO, 400 MHz): δ = 0.76–0.83 [m, 15 H, 2 CH(C*H*$_3$)$_2$, CHCH$_3$CH$_2$C*H*$_3$], 0.96–1.04 (m, 2 H, CHCH$_3$C*H*$_2$CH$_3$), 1.24–1.26 (m, 3 H, CHC*H*$_3$CH$_2$CH$_3$), 1.38 [s, 9 H, (C*H*$_3$)$_3$], 1.41–1.59 [m, 3 H, CHC*H*$_2$CH(CH$_3$)$_2$, CHCH$_2$C*H*(CH$_3$)$_2$], 1.63–1.69 (m, 1 H, C*H*CH$_3$CH$_2$CH$_3$), 1.78–1.94 [m, 3 H, NCH$_2$C*H*$_2$, CHC*H*(CH$_3$)$_2$], 2.08–2.13 (m, 2 H, NCO$_2$MeC*H*$_2$), 3.26–3.28 (m, 2 H, NC*H*$_2$), 3.53–3.55 (m, 2 H, NHCHC*H*$_2$OBn), 3.58 (s, 3 H, CO$_2$C*H*$_3$), 3.98 (dd, *J* = 8.82, 6.43 Hz 1 H, NHC*H*secButyl), 4.13–4.18 (m, 1 H, NHC*H*CH$_2$OBn), 4.22 (dd, *J* = 8.65, 3.02 Hz 1 H, NC*H*CO$_2$Me), 4.45 (d, *J* = 2.65 Hz, 2 H, OC*H*$_2$Ph), 5.02 [q, *J* = 8.21 Hz, 1 H, NHC*H*CH(CH$_3$)$_2$], 5.25 (quint, *J* = 7.65 Hz, 1 H, NHC*H*CH$_2$CH), 5.25 (quint, *J* = 7.65 Hz, 1 H, NHC*H*CH$_2$CH), 6.22 (d, *J* = 10.07 Hz, 1 H, NHCON*H*), 6.24 (d, *J* = 8.82 Hz, 1 H, NHCHN*H*), 6.46 (d, *J* = 8.43 Hz, 1 H, NHCHN*H*), 6.82 (d, *J* = 8.47 Hz, 1 H, BocN*H*), 7.24–7.34 (m, 6 H, arom H), 7.72 (d, *J* = 8.44 Hz, 1 H, N*H*CHNH), 8.09 (d, *J* = 7.70 Hz, 1 H, N*H*CHNH) ppm. ^{13}C NMR ([D$_5$]pyridine, 75 MHz): δ = 12.58 (CH$_3$), 16.92 (CH$_3$), 20.39 (2 CH$_3$), 23.34 (CH$_3$), 23.48 (CH$_3$), 25.57 (CH$_2$), 25.95 (CH), 26.20 (CH$_2$), 29.31 (3 CH$_3$), 30.79 (CH$_2$), 33.14 (CH), 39.39 (CH), 45.26 (CH$_2$), 47.22 (CH$_2$), 52.68 (CH$_3$), 56.44 (CH), 57.86 (CH), 59.77 (CH), 60.31 (CH), 65.11 (CH), 72.22 (CH$_2$), 74.10 (CH$_2$), 79.72 (C), 124.05 (CH), 124.38 (CH), 124.71 (CH), 136.40 (C), 139.69 (C), 157.36 (C), 157.44 (C), 159.08 (C), 173.90 (C), 174.96 (C). MALDI-TOF MS: *m*/*z* 784.92 [M + Na]$^+$, 801.19 [M + K]$^+$.

Z-Leu-*g*Val-CO-Ala-*g*Leu-CONH*i*Pr (11): Compound **6p** (380 mg, 0.97 mmol) was dissolved in MeOH (60 mL) and hydrogenated for 3 h in the presence of 10% Pd/C as a catalyst at room temperature and under an atmospheric pressure of H_2. The catalyst was removed by filtration through Celite©, and the solution was concentrated to yield pure H-Ala-*g*Leu-CONH*i*Pr (240 mg, 96%). Carbamate **5t** (200 mg, 0.43 mmol) was treated with H-Ala-*g*Leu-CONH*i*Pr (100 mg, 0.39 mmol) and Hünig's base (66 μL, 0.39 mmol) in DMF (10 mL). The mixture was stirred at room temperature for 2 h, and after completion of the reaction, the product was precipitated by the addition of saturated aqueous Na_2CO_3. The precipitate was collected and washed with H_2O, 1 N $KHSO_4$ and H_2O. Further washing with MeOH removed impurities to yield pure product **11** (202 mg, 84%) as a white solid, m.p. 240 °C. HPLC: t_R = 10.10 min (linear gradient, 30–100% solvent B, 20 min). ^{1}H NMR ([D$_6$]-DMSO, 500 MHz): δ = 0.80–0.85 [m, 18 H, CHCH(CH_3)$_2$, 2 CH$_2$CH(CH_3)$_2$], 1.00 [dd, J = 8.31, 6.55 Hz, 6 H, NHCH(CH_3)$_2$], 1.10 (d, J = 6.90 Hz, 3 H, CHCH_3), 1.31–1.37 (m, 1 H, CHCH_2), 1.40–1.47 (m, 3 H, CHCH_2, CHCH_2), 1.48–1.54 [m, 1 H, CH$_2$CH(CH$_3$)$_2$], 1.57–1.63 [m, 1 H, CH$_2$CH(CH$_3$)$_2$], 1.82–1.89 [m, 1 H, CHCH(CH$_3$)$_2$], 3.60–3.66 [m, 1 H, NHCH(CH$_3$)$_2$], 3.96–4.00 (m, 1 H, OCONHCH), 4.07–4.13 (m, 1 H, NHCHCH$_3$), 4.98–5.04 [m, 1 H, NHCHCH(CH$_3$)$_2$], 5.01 (s, 2 H, CH_2Ph), 5.16–5.22 (m, 1 H, NHCHCH$_2$), 5.92 (d, J = 6.98 Hz, 1 H, NH*i*Pr), 6.03 (d, J = 8.50 Hz, 1 H, NHCONH*i*Pr), 6.31 (d, J = 7.95 Hz, 1 H, NHCHCH$_3$), 6.36 (d, J = 8.83 Hz, 1 H, NHCONHCHCH$_3$), 7.28–7.37 (m, 6 H, arom. H, OCONH), 7.93 [d, J = 6.99 Hz, 1 H, NHCHCH(CH$_3$)$_2$], 8.17 (d, J = 8.00 Hz, 1 H, NHCHNHCONH*i*Pr) ppm. ^{13}C NMR ([D$_6$]DMSO, 125 MHz): δ = 18.1 (CH$_3$), 21.3 (CH$_3$), 22.0 (CH$_3$), 22.1 (CH$_3$), 22.8 (CH$_3$), 22.9 (CH$_3$), 23.0 (CH), 23.9 (CH$_3$), 24.0 (CH$_3$), 24.9 (CH), 31.9 (CH), 40.5 (CH$_2$), 40.6 (CH$_2$), 43.5 (CH), 48.1 (CH$_2$), 48.4 (CH$_2$), 53.0 (CH), 54.9 (CH), 61.0 (CH), 65.1 (CH), 66.8 (CH$_2$), 127.4 (C), 127.5 (C), 128.1 (C), 136.9 (C), 155.6 (C), 155.9 (C), 156.0 (C), 171.3 (C), 172.3 (C) ppm. HRMS: calcd for C$_{31}$H$_{53}$N$_7$O$_6$ [M + Li]$^+$ 626.4212; found 626.4200.

General Procedure for Solid-Phase Syntheses. Procedure C: Ureidopeptides were synthesized on Wang resin or on 2-chlorotrityl resin[44] with a home-made semi-automatic peptide synthesizer.[40] For each coupling step, the reactants were introduced manually as a solution in dry DMF (2.0 mL). *Nα*-Fmoc amino acids (5.0 equiv.) with standard side-chain protecting groups were coupled 2 times with BOP (5.0 equiv.), HOBt (5.0 equiv.) and Hünig's base (10.0 equiv.) in dry DMF for 20 min. Succinimidyl carbamates **5** (4.0 equiv.) were coupled 2 times in dry DMF in the presence of NMM (4.0 equiv.) or Hünig's base (4.0 equiv.) for 120 min. The washing of the resin as well as the Fmoc deprotection (with a freshly prepared solution of 20% piperidine in DMF) were performed automatically. The coupling and deprotection steps were monitored by the Kaiser test.[42] At the end of the elongation of the peptidic chain, the resin was washed with CH_2Cl_2 and dried with Et_2O before the next step.

General Procedure for Cleavage from the Wang Resin. Procedure D: A mixture of TFA/H_2O/Triisopropylsilane [95:2.5:2.5 (v/v/v); 10.0 mL] was added to the resin. The mixture was gently shaken for 60 min, and the resulting solution was flushed through a frit in cold Et_2O. The precipitate was recovered by centrifugation, dissolved in H_2O, and freeze-dried.

Ureidopeptide 12. The synthesis of **12** was performed with building block **5o** on resin (40 μmol) according to the general procedures C and D. The purity of the crude ureidopeptide was 58% (determined by C_{18} RP-HPLC). Purification by semi-preparative C_{18} RP-HPLC gave pure **12** (8.5 mg, 21% yield and >99% purity): HPLC: t_R = 12.83 min (linear gradient, 20–80% solvent B, 20 min). MS: calcd. for [M]$^+$ 1000.2; found [M + Na]$^+$ 1022.8, [M + K]$^+$ 1039.2.

Ureidopeptide 13. The synthesis of **13** was performed with building block **13** on resin (40 μmol) according to the general procedures C and D. The purity of the crude ureidopeptide was 75% (determined by C_{18} RP-HPLC). Purification by semi-preparative C_{18} RP-HPLC gave pure **13** (5 mg, 13% yield and >99% purity): HPLC: t_R = 12.50 min (linear gradient, 20–80% solvent B, 20 min). MS: calcd. for [M]$^+$ 1000.2; found [M + H]$^+$ 1001.5, [M + Na]$^+$ 1022.4, [M + K]$^+$ 1038.6.

X-ray Crystal Structure Determination of Boc-*g*Pro-COOSu (4f), Boc-Pro-*g*Val-COOSu (5f), Boc-Pro-*g*Ala-CO-Leu-OMe (6i): X-ray data were collected at room temperature on a NoniusKappa-CCD diffractometer with graphite-monochromatized Mo-K_α radiation (λ = 0.71073 Å). Reflections were indexed, integrated and reduced with the HKL2000[45] package. No absorption correction was applied. The structures were solved by direct methods (SIR92)[46] and refined by full-matrix least-squares methods against F^2 (SHELXL-97)[47] The WinGX[48] suite was used to analyze and prepare the data for publication. The figures were prepared with Ortep3[49] and WebLabViewer.[50]

Boc-*g*Pro-COOSu (4f): $C_{14}H_{21}N_3O_6$, M = 327.34, monoclinic, space group $P2_1$, Z = 2, a = 8.2844(3) Å, b = 8.5651(4) Å, c = 12.2094(6) Å, β = 104.752(2), V = 837.78(6) Å^3, ρ_c = 1.298 Mg·m^{-3}, 7395 reflections measured, 1631 unique, R_{int} = 0.035, R_1 [$I > 2\sigma(I)$] = 0.038, wR_2 (all data) = 0.093 for 208 parameters, GooF = 1.021, residual density (max./min.) = 0.11/–0.135 e.A^{-3}.

Boc-Pro-*g*Val-COOSu (5f): $C_{19}H_{30}N_4O_7$, M = 426.47, monoclinic, space group $P2_1$, Z = 2, a = 6.3317(3) Å, b = 9.9550(5) Å, c = 18.9409(12) Å, β = 98.311(2), V = 1181.35(11) Å^3, ρ_c = 1.199 Mg·m^{-3}, 8743 reflections measured, 1772 unique, R_{int} = 0.063, R_1 [$I > 2\sigma(I)$] = 0.0504, wR_2 (all data) = 0.125 for 271 parameters, GooF = 0.976, residual density (max./min.) = 0.141/–0.171 e.A^{-3}.

Boc-Pro-*g*Ala-CO-Leu-OMe (6i): $C_{20}H_{36}N_4O_6$, M = 428.53, monoclinic, space group $P2_1$, Z = 4, a = 8.8689(1) Å, b = 18.6361(3) Å, c = 15.4116(3) Å, β = 103.001(1), V = 2481.96(7) Å^3, ρ_c = 1.147 Mg·m^{-3}, 23527 reflections measured, 4761 unique, R_{int} = 0.051, R_1 [$I > 2\sigma(I)$] = 0.055, wR_2 (all data) = 0.138 for 541 parameters, GooF = 1.036, residual density (max./min.) = 0.255/–0.226 e·A^{-3}.

Because of the lack of any significant anomalous dispersion effects, the absolute configuration could not be determined from the diffraction experiment. Bijvoet pairs have been merged prior to refinement. The absolute stereochemistry of Boc-*g*Pro-COOSu, Boc-Pro-*g*Val-COOSu and Boc-Pro-*g*Ala-CO-Leu-OMe were based on the known configuration of L-Pro, Boc-L-Pro-L-Val and Boc-L-Pro-*g*Ala-COOSu/H-L-Leu-OMe, respectively. All H atoms were placed at calculated positions and refined with a riding model, with C–H distances of 0.93–0.97 Å and with an N–H distance of 0.86 Å. The H-atom U_{iso} parameters were fixed at 1.2 U_{eq}(C) for ethane and methylene groups, at 1.2 U_{eq}(N) for the N–H group and at 1.5 U_{eq}(C) for methyl groups.

CCDC-623589 (for **4f**), -623587 (for **5f**) and -623588 (for **6i**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Supporting Information (see also the footnote on the first page of this article): Analytical data for compounds **4c**, **4d**, **4e**, **4h**, ***epi*-5d**,

5g, **5h**, **5i**, **5j**, **5m**, **5p**, **5q**, **5s**, **5t**, **6a**, **6d**, **6f**, **6h**, **6l**, **6m**, **6o** and **7**, ^{1}H NMR chemical shifts for ureidopeptide **12** and compound **15** in [D_6]-DMSO after C_{18} RP-HPLC purification, Part of the COSY and TOCSY spectra of **15** in [D_6]DMSO and the high-resolution ESI spectrum of compound **15** are included.

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