Selective Solid Phase Synthesis of Ureas and Hydantoins from Common Phenyl Carbamate Intermediates

Xiao-yi Xiao,[†] Khehyong Ngu,[‡] Corinne Chao, and Dinesh V. Patel*[,‡]

Affymax Research Institute, 3410 Central Expressway, Santa Clara, California 95051

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An efficient method for selective, solid phase synthesis of unsymmetrical ureas and hydantoins from a common phenyl carbamate dipeptide intermediate is decribed. Reaction of phenyl carbamate **6** with primary or secondary amines (R_3R_4NH) in THF results in selective formation of ureas **8**, whereas its treatment with a tertiary amine base (iPr_2NEt or DBU) in DMF affords clean conversion to hydantoins **10**.

Introduction

In the era of rational drug design, it has become relatively easy to discover peptidic leads for therapeutically important enzyme or receptor targets. While such compounds by themselves may usually find limited utility because of poor metabolic stability, bioavailability, and absorption, they do provide a good starting point for drug discovery projects. The next critical step in *de novo* drug design is to transform such peptidic leads into more stable and bioavailable nonpeptidic molecules. This strategy has been extensively persued in the last decade and has led to the culmination of a wide variety of nonpeptidic replacements for peptide amide bonds and secondary structures of peptides.[1]

In this paper, we would like to describe an efficient and practical solid phase synthesis (SPS) of ureas and hydantoins from a common intermediate. The urea functionality has attracted considerable attention as a stable, nonhydrolyzable replacement for amide bonds of peptides.[2] The five-membered hydantoins represent a cyclic scaffold displaying conformationally constrained dipeptide motifs.[3] An obvious advantage with the solid phase methodology for these peptidomimetic motifs is their potential utility in the area of combinatorial chemistry.[4] In order to effectively utilize the "split and pool" protocol in a combinatorial format, it has become increasingly necessary to develop equivalent solid phase chemistries of various traditional solution phase reactions.[5]

Ureas are typically prepared in solution or solid phase by treatment of isocyanates[6] or *p*-nitrophenyl carbamates (PNP)[7] with amines. This relatively simple method works well for single amino esters but is inappropriate for insertion of urea linkages as amide bond isosteres in a peptidic framework. This is because of the susceptibility of reactive isocyanate or PNP carbamate intermediates to nucleophilic attack by adjacent amide group resulting in formation of hydantoin as a side product. Hydantoins have been independently prepared on solid support from α-urea esters which in turn are derived from α-amino esters and isocyanates. The final step involves N-cyclization of ureas to the immobilized ester group, resulting in simultaneous cleavage from the resin to generate hydantoins in solution.[8] This strategy is well suited for synthesis of individual hydantoins, but not appropriate for their inclusion as nonpeptidic surrogates in a peptide framework because of the mandatory requirement of an ester linker adjacent to the urea group.

Herein, we report an efficient method for selective, SPS of both unsymmetrical ureas or hydantoins from common linear dipeptide intermediates **6**. Phenyl carbamate **7** derived from dipeptide **6** on solid support serves as the activated intermediate which can be treated with primary or secondary amines (R_3R_4NH) to form unsymmetrical ureas **8**, or alternatively with a tertiary amine base (iPr_2NEt or DBU) to form hydantoins **10**. Phenyl carbamates have been occasionally used as intermediates for solution synthesis of ureas.[9] They are more stable than *p*-nitrophenyl carbamates or isocyanates, and at the same time, they are reactive enough and more prone to nucleophilic attack by primary or secondary amines than simple alkyl carbamates. Thus, they may offer the right balance of stability and reactivity for selective conversion to either ureas or hydantoins by appropriate choice of reagents and reaction conditions. This study represents the first example of SPS of ureas or hydantoins from common phenyl carbamate intermediates.

[†] Current address: IRORI Quantum Microchemistry, 11025 N. Torrey Pines Rd., #100 La Jolla, CA 92037.

[‡] Current address: VERSICOR Inc., 34790 Ardentech Ct., Ardenwood Business Park, Fremont, CA 94555. e-mail: dpatel@versicor.com.

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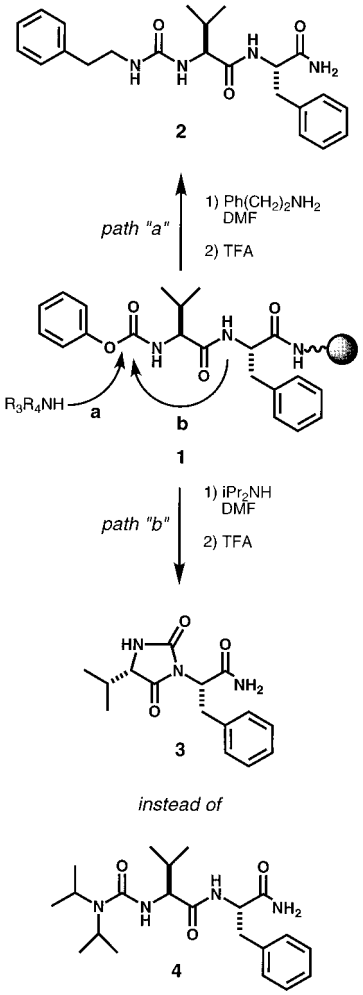
Scheme 1. Unsymmetrical Ureas and Hydantoins from Phenyl Carbamates



Results and Discussion

Resin-bound phenyl carbamate dipeptide PhOCONH-Val-Phe-NH-resin **1** was designed to be the substrate for initial studies (Scheme 1). The valine residue provides a sterically demanding situation for the reaction, while the chromophoric phenylalanine group facilitates HPLC identification of the final cleavage product. Additionally, UV absorption of the released phenol (288 nm, e_{max} = 2600 M^{-1} cm^{-1}) provides a convenient and reliable tool to monitor the progress of these displacement reactions. Dipeptide NH_2-Val-Phe-NH-resin was synthesized on TentaGel S AM resin (90 mmol)[10] using conventional Fmoc deprotection/HATU-coupling chemistry. It was treated with excess phenyl chloroformate (5−10-fold) and diisopropylethylamine (10−20-fold) in aqueous 1,4-dioxane at room temperature for 4 h.[11] The resulting phenyl carbamate intermediate **1** on resin is stable at room temperature and can be stored dry for several weeks without any noticeable decomposition. Resin-bound phenyl carbamate **1** was treated separately with either excess phenethylamine or diisopropylamine in DMF (0.2−0.5 M) at room temperature. Within 1 h, measurement of the released phenol in the supernatant (diluted in 0.1 N aqueous KOH) indicated completion of reaction. Standard TFA cleavage of the resulting resin yielded predominantly the anticipated urea product **2** for the phenethylamine reaction. However, only the internally cyclized hydantoin **3** and none of the urea **4** was obtained from the diisopropylamine reaction. In retrospect, this result is not surprising because more nucleophilic and less hindered amines such as phenethylamine will be more likely to attack the activated carbamate to yield ureas (path a), whereas a relatively more basic and more hindered amine such as iPr_2NH, especially under conditions unoptimized for urea formation, is more likely to act as a general base (path b) and yield hydantoins (Scheme 1). These observations prompted us to thoroughly investigate the factors influencing formation of ureas and hydantoins from common peptidic phenyl carbamate intermediates on solid support.

Table 1. Effect of Solvent on Urea vs Hydantoin Formation

solvent	$Ph(CH_2)_2NH_2$[a]	iPr_2NEt[b]
CH_2Cl_2	36%	44%
THF	100%	1%
1,4-dioxane	31%	0.3%
CH_3CN	100%	97%
DMF	100%	93%
DMSO	100%	90%

[a] Percentage of phenol release after 1 h of treatment of phenyl carbamate **1** with $Ph(CH_2)_2NH_2$ in a particular solvent. [b] Percentage of phenol release after 1 h of treatment of phenyl carbamate **1** with iPr_2NEt in a particular solvent.

Effect of Solvents on Hydantoin vs Urea Formation. A striking observation made during the early experiments was that phenyl carbamate **1** was formed from the corresponding dipeptide amine by treatment with phenyl isocyanate and iPr_2NEt in aqueous 1,4-dioxane and found to be stable. Thus, despite the fact that iPr_2NEt is a strong, non-nucleophilic tertiary amine, there was no hydantoin cyclization observed in 1,4-dioxane during the rather long reaction times (12 h). This is in sharp contrast to the smooth cyclization to hydantoin observed for the same intermediate **1** with iPr_2NH in DMF. This led us to speculate that, besides the steric nature of phenyl carbamate intermediate and basicity of amine, solvents may play an important role in directing the reaction of amines with phenyl carbamates on solid support. For example, the above observation suggested that DMF may strongly favor hydantoin formation, whereas 1,4-dioxane would tend to disfavor cyclization. This led us to investigate the effect of solvents on selective urea and hydantoin formation from phenyl carbamates on solid support (Table 1). Six different solvents (DCM, acetonitrile, THF, 1,4-dioxane, DMF, and DMSO) were included in the study. For each solvent, phenethylamine and iPr_2NEt were used at a 0.5 M concentration to react with resin-bound phenyl carbamate **1**. The rate of reaction was monitored by quantitative spectrophotometric measurement of the amount of phenol released after 1 h. Reaction with phenethylamine should give a measure of the extent of urea formation, whereas the phenol release from iPr_2NEt reaction should reflect the degree of hydantoin cyclization.[12]

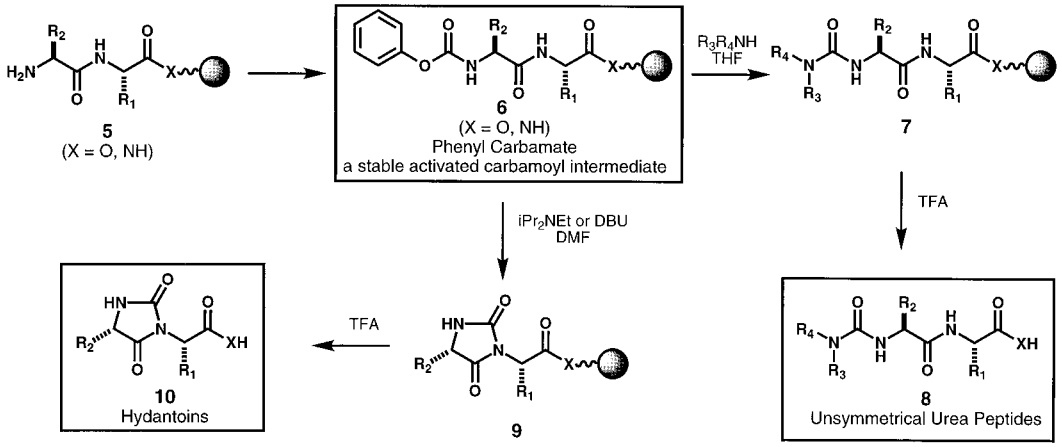
The resulting data provides us with good choice for selective urea or hydantoin transformations (Table 1). Thus, urea formation is sluggish in CH_2Cl_2 (36%) and

(10) TentaGel S resin is from RAPP Polymere: 90 μ. Initial loading: 0.23 mmol/g. AM: acid cleavable linker.

(11) The reaction was usually continued until the resin became ninhydrin negative, signifying the disappearance of starting amine. Later experiments suggested that the carbamate formation was usually complete in 1 h.

(12) Simple hydrolysis of phenyl carbamate **1** would also result in the release of phenol accompanied by the formation of corresponding free amine of **1**. This possibility was ruled out because the final resin was ninhydrin negative. Therefore, it was appropriate to view

Scheme 2. Solid Phase Synthesis of Unsymmetrical Ureas and Hydantoins



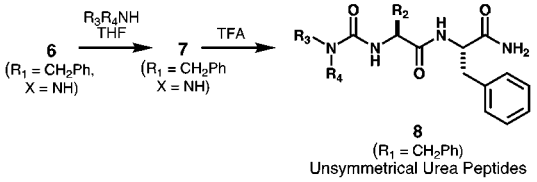
1,4-dioxane (31%) but proceeds very efficiently in THF, CH_3CN, DMF, and DMSO (100%), whereas hydantoin cyclization is observed to proceed very poorly in THF (1%) and 1,4-dioxane (0.3%). This makes THF the most discriminatory and ideal solvent for selective urea formation, whereas a choice of several different solvents (CH_3CN, DMF, and DMSO) is available for preparing hydantoins. In the latter case, DMF was chosen for effecting cyclizations based on convenience, toxicity, and resin-swelling ability. With THF as the optimum solvent for urea and DMF for hydantoin formation, structurally diverse dipeptide phenyl carbamate intermediates on resin were treated with a series of primary, secondary, and tertiary amines under the above established conditions to investigate the scope and selectivity of these transformations (Scheme 2, Table 2).

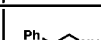
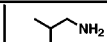
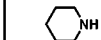
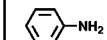
Solid Phase Synthesis of Unsymmetrical Ureas 8 from Phenyl Carbamates 7. Formation of unsymmetrical ureas **8** vs competing internal cyclization to hydantoins **10** from common phenyl carbamate intermediate **6** can be expected to be influenced by the steric and electronic nature of the two reacting partners, i.e. the incoming nucleophilic reagent R_3R_4NH and the R_2 substituents on carbamate **6** (Scheme 2, Table 2). Starting with phenethylamine as a representative example of a simple primary amine, the urea reaction was studied with various phenyl carbamates **6** bearing different R_2 groups (Table 2). Resin-bound dipeptides **5** were converted to phenyl carbamates **6** and individually treated with phenethylamine (entry a−e, Table 2) and iPr_2NEt in THF for 1 h. The crude products **8a**−**8e** obtained after TFA cleavage were reasonably pure as judged by HPLC (72−94%), and analysis of the ^1H NMR spectra confirmed that urea formation proceeded with high selectivity (>14:1). The tolerance for sterically hindered (**8b**, R_2 = iPr), acidic (**8d**, $R_2 = (CH_2)_2CO_2H$), and basic (**8e**, $R_2 = (CH_2)_4NH_2$) substituents serves to illustrate the structural flexibility for the R_2 site afforded by this route for preparing ureas.

Next, we investigated the scope of substituents on the other nitrogen of urea moiety (R_3 and R_4) by treating phenyl carbamates **6** with more sterically demanding amines (R_3R_4NH). The reaction of a primary amine such as isobutylamine proceeds with excellent conversion and selectivity (**8f**, 93%, 25:1 urea vs hydantoin). The selectivity is slightly compromised with secondary amines such as cyclohexylamine (**8g**, 79%, 8:1 urea vs hydantoin) and the highly hindered diisopropylamine (**8h-j**, 83−97%, 7 to 9:1 urea vs hydantoin). These results highlight the anticipated trend that as the incoming amine R_3R_4NH gets sterically demanding, the dipeptide phenyl carbamate intermediate **6** becomes more susceptible to cyclizing to the hydantoin side product. Nevertheless, even worse case combinations of having bulky substituents on both nitrogens in urea products such as **8j** ($R_2 = R_3 = R_4$ = iPr) can be achieved in excellent yields with adequate selectivity (97%, 7:1 urea vs hydantoin).

Solid Phase Synthesis of Hydantoins 10 from Phenyl Carbamates 6. In hydantoin synthesis, the

Table 2. Solid Phase Synthesis of Unsymmetrical Ureas

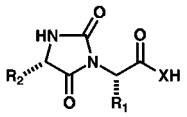


Entry	Amine R_3R_4NH	Carbamate, R_2	Product Ratio[a] (Urea 8/hydantoin)	HPLC purity[b] Crude 8
a			32:1	86%
b			20:1	72%
c			32:1	94%
d			14:1[c]	85%
e			15:1[c]	87%
f			25:1	93%
g			8:1	79%
h			NR[d]	-
i			9:1	83%
j			7:1	91%
k			7:1	97%

a) Ratios are calculated by comparison of integrations of the α-proton of the phenylalanine residue.
b) Percentages are sum of ureas and hydantoins. c) Th acid labile side chain protecting groups were deprotected during TFA cleavage. d) N.R. means no reaction.

the amount of phenol release from **1** upon DIEA treatment as an indication of the extent of cyclization to hydantoin. Similarly, since phenyl carbamate **1** was reasonably stable to storage, phenol release upon reaction with phenethylamine was used as a measure of urea formation.

Table 3. Solid Phase Synthesis of Hydantoins 10



Entry	R_2	R_1	X	Time[a]	HPLC
a	Me	Ph	NH	1 h	95%
b	iPr	Ph	NH	1 h	89%
c	iPr	Ph	O	24 h	93%
d	Ph	iPr	O	1 h	92%
e	iPr	Me	O	24 h 1 h[b]	<50% 92%[b]
f	Ph	Ph	O	2 h	95%[b]

a: Phenylcarbamate **6** was treated with DIEA in DMF for the indicated period of time.

b: DBU was employed instead of DIEA as a base.

possibility of competetive urea formation is eliminated by choosing a tertiary base such as DIEA or DBU for effecting the cyclization reaction. The normal protocol is to treat the immobilized dipeptide phenyl carbamate **6** with DIEA in DMF and monitor the course of reaction by spectrophotometric measurement of the released phenol. Typically, cyclization was found to be complete within 1 h for the amide-linked products derived from Tentagel S Resin (X = NH), whereas much longer reaction times (24 h) were required for ester-linked products from hydroxyl Wang resin (X = O). The reasons for such an influence of linker and nature of immobilized support are not clear, and these examples serve to highlight the importance of such commonly ignored physical parameters in solid phase organic synthesis. In all instances, the crude products were obtained in almost quantitative yields and good purity (89−95%). In the case of **10e** (R_2 = iPr, R_1 = Me), incomplete cyclization was observed even after prolonged treatment (<50% yield after 24 h) under standard conditions, but a dramatic enhancement in efficiency and extent of conversion was realized by employing DBU in place of DIEA as a base (essentially quantitative mass recovery of crude product with 92% purity after 1 h).[13] The possibility of epimerization during DBU treatment was eliminated on the basis of ^{1}H NMR and HPLC analysis of the hydantoin product **10e**. Similarly, **10f** (R_2 = R_1 = CH_2Ph) underwent smooth cyclization with DBU. These results (**10e** and **10f**) point to the possibility of DBU as being a more effective base than DIEA for preparing hydantoins.

Conclusion

In summary, we have described the first examples of a simple and efficient method for selectively synthesizing either unsymmetrical ureas or hydantoins from common phenyl carbamate intermediates. Phenyl carbamate is an activated carbamoyl intermediate with the right balance of stability and chemical reactivity such that it can be selectively converted to either ureas or hydantoins by the appropriate choice of nucleophile/base and solvents. Thus, reaction of dipeptide derived phenyl carbamate **6** with primary or secondary amines (R_3R_4NH) in THF leads to selective formation of ureas **8**, whereas its treatment with a tertiary amine base (iPr_2NEt or DBU) in DMF affords clean conversion to hydantoins **10**. Since a wide variety of substituents are well tolerated in both instances, it permits the syntheses of hydantoins and ureas with an adequate degree of structural diversity. The current method should facilitate the utility of ureas and hydantoins as peptide amide-bond surrogates and dipeptidomimetic scaffolds respectively in the field of drug discovery. In general, maneuvering the outcome of common reactive intermediates to different products in a predictable manner is a very useful chemical strategy. It can be expected to facilitate the application of solid phase methodologies to combinatorial preparation of structurally diverse chemical libraries of various scaffolds and pharmacophores.

Experimental Section

General. TentaGel S AM resin was from RAPP Polymere, Germany. Wang hydroxy resin was from Advanced ChemTech. All reagents and solvents were from either Aldrich Chemical Co. or VWR and were used as received without any additional treatment. ^{1}H and ^{13}C NMR spectra were obtained on a 400 MHz Varian spectrometer, with $CDCl_3$ or CD_3OD as the solvent and internal reference. Low-resolution mass spectra were obtained on an Electron Spray mass spectrometer. Final TFA cleavage products were normally lyophilized from benzene (if solubility was a problem, 5−10% methanol was added). Fmoc numbers and phenol concentrations were measured on a HP8452A diode array spectrophotometer.

Preparation of Dipeptide Phenyl Carbamate 1. TGS AM resin (2.10 g, 0.48 mmol) was suspended in DMF (10 mL). DIEA (0.84 mL, 4.83 mmol, 10 equiv), L-Fmoc-Phe-OH (0.94 g, 2.42 mmol, 5 equiv), and PyBOP (1.26 g, 2.42 mmol, 5 equiv) were added. The reaction mixture was shaken at room temperature for 1 h and washed with DMF (10 mL × 4). The resin was subjected to a second coupling under identical conditions. Kaiser test of the resin was negative. The resulting resin (400 mg) was treated with 20% piperidine/DMF (4 mL) at room temperature for 30 min, giving an Fmoc number of 192. The resin was then washed with DMF (5 mL × 3), MeOH (5 mL × 3), and ether (5 mL × 3) and coupled with L-Fmoc-Val-OH under the above standard conditions. The final resin was negative to Kaiser test. The Fmoc protecting group (400 mg) was removed under the standard conditions described above. The resulting dipeptide amine H_2N-Val-Phe-NH-TGS was treated with DIEA (0.28 mL, 1.6 mmol, 20 equiv) and phenyl chloroformate (0.10 ml, 0.8 mmol, 10 equiv) in 9:1 1,4-dioxane/water at room temperature for 1 h. Kaiser test indicated completion of reaction. The resin was washed with 1,4-dioxane (5 mL × 4) and ether (5 mL × 4) and dried under vacuum to give **1**.

Preparation of Urea 2. Immobilized phenyl carbamate dipeptide **1** (200 mg) was treated with 0.5 M phenethylamine/DMF at room temperature for 1 h. Measurement of the released phenol indicated that the reaction was 99% complete. Standard TFA cleavage (room temperature, 30 min) yielded urea **2** as a white solid (14 mg, quantitative): ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.62 (d, J = 8.0 Hz, 3 H), 0.74 (d, J = 6.9 Hz, 3 H), 1.86−1.95 (m, 1 H), 2.65 (t, J = 7.1 Hz, 2 H), 2.88 (dd, J = 8.0, 14.1 Hz, 1 H), 3.08 (dd, J = 6.0, 14.1 Hz, 1 H), 3.20−3.32 (m, 2 H), 4.64 (dd, J = 6.0, 8.0 Hz, 1 H), 5.79 (br d, J = 6.2 Hz, 1 H), 7.06−7.38 (m, 10 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.17, 19.09, 30.17, 36.25, 37.36, 41.22, 53.76, 59.97, 70.34, 126.36, 126.86, 128.52, 128.74, 129.12, 136.50, 139.20, 173.05,

(13) Other organic bases like triethylamine and *N*-methylmorpholine were also tested and and found to give less satisfactory results.

173.20, 190.05; LRMS calcd for $C_{23}H_{31}N_4O_3$ (M + H) 411.5, found 411.2.

Preparation of Hydantoin 3. Immobilized phenyl carbamate dipeptide **1** (200 mg) was suspended in DMF (2 mL) and treated with diisopropylamine (0.5 M) at room temperature for 1 h. Measurement of the released phenol indicated that the reaction was 99% complete. Standard TFA cleavage (room temperature, 30 min) yielded hydantoin **3** as a white solid (15 mg, quantitative): ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.38 (d, J = 6.8 Hz, 3 H), 0.75 (d, J = 7.0 Hz, 3 H), 1.80−1.92 (m, 1 H), 3.34 (dd, J = 5.2, 14.0 Hz, 1 H), 3.48 (dd, J = 12.0, 14.1 Hz, 1 H), 3.74 (d, J = 3.8 Hz, 1 H), 4.86 (dd, J = 5.2, 12.0 Hz, 1 H), 7.09−7.22 (m, 5 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.45, 18.52, 29.95, 34.31, 55.48, 70.45, 127.10, 128.77, 129.06, 136.50, 171.80, 173.90, 213.00; LRMS calcd for $C_{14}H_{21}N_3O_2Na$ (M + Na) 312.3, found 311.9.

General Procedure for Synthesis of Ureas on Solid Supports. Immobilized dipeptide phenyl carbamate **6** was prepared in the same manner as described for **1** and treated overnight with 0.5 M primary or secondary amine in THF at room temperature, at which time the phenol release was essentially found to be complete. The resulting intermediate resin **7** was subjected to standard TFA cleavage treatment described above to yield the desired ureas **8**.

***N*-(Phenethylcarbamoyl)-L-Gly-L-Phe-NH$_2$ (8a):** ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.55 (t, J = 7.3 Hz, 2 H), 2.78 (dd, J = 7.9, 13.9 Hz, 1 H), 2.94 (dd, J = 5.8, 13.9 Hz, 1 H), 3.15 (t, J = 7.3 Hz, 2 H), 3.50 (s, 2 H), 4.41 (dd, J = 5.8, 7.9 Hz, 1 H), 6.95−7.10 (m, 5 H); ^{13}C NMR (100 MHz, CD_3OD) δ 37.57, 38.88, 42.90, 44.61, 55.59, 127.41, 127.93, 128.80, 129.62, 129.98, 130.44, 138.39, 140.90, 161.00, 173.10, 176.05; HRMS ($C_{20}H_{24}N_4O_3$ + H)$^+$ calcd 369.1927, found 369.1923.

***N*-(Phenethylcarbamoyl)-L-Val-L-Phe-NH$_2$ (8b):** ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.49 (d, J = 6.3 Hz, 3 H), 0.62 (d, J = 6.2 Hz, 3 H), 1.75−1.84 (m, 1 H), 2.53 (t, J = 7.0 Hz, 2 H), 2.75 (dd, J = 8.2, 13.0 Hz, 1 H), 2.97 (dd, J = 5.3, 13.0 Hz, 1 H), 3.04−3.20 (m, 2 H), 3.65 (d, J = 4.4 Hz, 1 H), 4.42 (dd, J = 5.3, 8.2 Hz, 1 H), 6.95−7.25 (m, 10 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.52, 18.44, 29.78, 35.83, 36.94, 40.85, 53.49, 59.75, 125.84, 126.34, 128.02, 128.26, 128.66, 136.50, 138.80, 160.20, 173.00, 174.00; HRMS ($C_{23}H_{30}N_4O_3$ + H)$^+$ calcd 411.2396, found 411.2394.

***N*-(Phenethylcarbamoyl)-L-Phe-L-Phe-NH$_2$ (8c):** ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.50 (t, J = 7.2 Hz, 2 H), 2.61 (dd, J = 8.0, 14.0 Hz, 1 H), 2.70−2.83 (m, 2 H), 2.90 (dd, J = 5.8, 14.0 Hz, 1 H), 3.10−3.20 (m, 2 H), 4.16 (dd, J = 5.8, 8.0 Hz, 1 H), 4.40 (dd, J = 5.8, 7.6 Hz, 1 H), 6.90−7.13 (m, 15 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 35.67, 36.77, 37.37, 40.76, 53.41, 55.20, 125.65, 126.19, 126.24, 127.84, 127.92, 128.12, 128.59, 128.65, 136.30, 138.70, 158.50, 172.80, 173.90; HRMS ($C_{27}H_{30}N_4O_3$ + H)$^+$ calcd 459.2396, found 459.2391.

***N*-(Phenethylcarbamoyl)-L-Glu-L-Phe-NH$_2$ ammonium salt (8d):** ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.50−1.70 (m, 1 H), 1.70−1.80 (m, 1 H), 2.08 (t, J = 7.3 Hz, 2 H), 2.59 (t, J = 7.3 Hz, 2 H), 2.82 (dd, J = 8.3, 14.0 Hz, 1 H), 3.03 (dd, J = 5.7, 14.0 Hz, 1 H), 3.10−3.25 (m, 3 H), 3.91 (dd, J = 5.7, 8.3 Hz, 1 H), 7.00−7.18 (m, 10 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 26.89, 29.72, 35.96, 37.07, 41.08, 53.50, 53.68, 126.03, 126.50, 128.71, 128.31, 128.42, 128.70, 128.75, 128.86, 136.50, 138.86, 158.65, 172.76, 173.76, 174.22; HRMS ($C_{23}H_{28}N_4O_5$ + H)$^+$ calcd 441.2138, found 441.2146.

***N*-(Phenethylcarbamoyl)-L-Lys-L-Phe-NH$_2$ (8e):** ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.05−1.15 (m, 2 H), 1.30−1.53 (m, 4 H), 2.62 (t, J = 7.0 Hz, 2 H), 2.70 (t, J = 7.0 Hz, 2 H), 2.86 (dd, J = 8.6, 14.2 Hz. 1 H), 3.09 (dd, J = 5.5, 14.2 Hz, 1 H), 3.21 (t, J = 7.3 Hz, 2 H), 3.85 (dd, J = 5.1, 7.9 Hz, 1 H), 4.48 (dd, J = 5.5, 8.6 Hz, 1 H), 7.05−7.20 (m, 10 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.76, 26.51, 30.91, 36.33, 37.12, 39.10, 41.42, 54.08, 54.45, 126.36, 126.89, 128.50, 128.56, 128.71, 129.01, 129.06, 129.16, 136.69, 139.14, 159.25, 173.96, 174.69; HRMS ($C_{24}H_{33}N_5O_3$ + H)$^+$ calcd 440.2662, found 440.2663.

***N*-(Isobutylcarbamoyl)-L-Ala-L-Phe-NH$_2$ (8f):** ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.77 (d, J = 6.6 Hz, 6 H), 1.11 (d, J = 7.2 Hz, 3 H), 1.56 (m, 1 H), 2.75−2.85 (m, 2 H), 2.97 (dd, J = 7.6, 14.0 Hz, 1 H), 3.07 (dd, J = 5.9, 14.0 Hz, 1 H), 3.95 (q, J = 7.2 Hz, 1 H), 4.49 (dd, J = 5.9, 7.6 Hz, 1 H), 7.11−7.20 (m, 5 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.64, 19.88, 28.86, 37.20, 47.49, 50.35, 53.76, 126.89, 128.52, 129.22, 136.66, 159.01, 174.30, 174.43; HRMS ($C_{17}H_{26}N_4O_3$ + H)$^+$ calcd 335.2083, found 335.2085.

(Piperidylcarbamoyl)-Ala-L-Phe-NH$_2$ (8g): ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.29 (d, J = 7.1 Hz, 3 H), 1.44−1.64 (m, 6 H), 3.08−3.38 (m, 6 H), 4.14 (q, J = 7.1 Hz, 1 H), 4.66 (dd, J = 6.3, 14.2 Hz, 1 H), 6.65 (br s, 1 H), 6.96 (br s, 1 H), 7.15−7.35 (m, 5 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.86, 24.26, 25.63, 37.08, 37.51, 45.27, 50.16, 51.60, 54.01, 127.36, 128.95, 129.42, 136.29, 157.57, 174.46, 175.66; LRMS calcd for $C_{18}H_{27}N_4O_3$ (M + H) 347.4, found 347.2.

***(N,N′*-Diisopropylcarbamoyl)-L-Gly-L-Phe-NH$_2$ (8i):** ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.98 (d, J = 6.8 Hz, 6 H), 1.00 (d, J = 6.9 Hz, 6 H), 2.84−3.00 (m, 4 H), 3.50−3.58 (m, 2 H), 4.43 (dd, J = 5.8, 7.2 Hz, 1 H), 6.95−7.12 (m, 5 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.20, 33.31, 36.98, 43.69, 45.56, 53.40, 126.38, 128.03, 128.68, 136.20, 157.50, 171.28, 174.30; HRMS ($C_{18}H_{28}N_4O_3$ + H)$^+$ calcd 349.2240, found 349.2232.

***(N,N′*-Diisopropylcarbamoyl)-Ala-L-Phe-NH$_2$ (8j):** ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.14 (d, J = 6.8 Hz, 6 H), 1.16 (d, J = 6.9 Hz, 6 H), 1.35 (d, J = 7.2 Hz, 3 H), 3.03 (dd, J = 5.9, 14.0 Hz, 1 H), 3.37 (dd, J = 5.9, 14.0 Hz, 1 H), 3.65−3.80 (m, 2 H), 4.08 (dq, J = 3.5, 7.2 Hz, 1 H), 4.42 (br d, J = 3.5 Hz, 1 H), 4.74 (dt, J = 5.9, 8.8 Hz, 1 H), 5.33 (br s, 1 H), 6.46 (br d, J = 8.8 Hz, 1 H), 7.10 (br s, 1 H), 7.16−7.30 (m, 5 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.14, 21.37, 21.54, 39.96, 45.88, 51.80, 53.15, 127.20, 128.90, 129.54, 136.40, 157.10, 173.30, 173.83; HRMS ($C_{19}H_{30}N_4O_3$ + H)$^+$ calcd 363.2396, found 363.2394.

***(N,N′*-Diisopropylcarbamoyl)-L-Val-L-Phe-NH$_2$ (8k):** ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.79 (d, J = 6.9 Hz, 3 H), 0.86 (d, J = 6.8 Hz, 3 H), 1.13 (d, J = 6.8 Hz, 6 H), 1.15 (d, J = 6.8 Hz, 6 H), 1.98−2.08 (m, 1 H), 3.06 (t, J = 6.6 Hz, 2 H), 3.75−3.84 (m, 2 H), 3.92−3.96 (m, 1 H), 4.57−4.65 (m, 1 H), 7.12−7.22 (m, 5 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.15, 19.70, 21.39, 21.51, 30.89, 37.45, 45.62, 53.74, 60.47, 127.20, 128.86, 129.47, 136.78, 157.51, 172.79, 174.26; HRMS ($C_{21}H_{34}N_4O_3$ + H)$^+$ calcd 391.2709, found 391.2713.

General Procedure for Synthesis of Hydantoins on Solid Supports. Immobilized dipeptide phenyl carbamate **6** was treated with 0.5 M DIEA or DBU in DMF at room temperature for the indicated time (Table 2) to give resin **9**. Standard TFA treatment of resin **9** yielded the desired hydantoins **10**.

(5*S*)-5-Methyl-3-[(2*S*)-1-amino-1-oxo-3-phenylprop-2-yl-]hydantoin (10a): ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.95 (d, J = 7.0 Hz, 3 H), 3.35−3.48 (m, 2 H), 3.86 (q, J = 7.0 Hz, 3 H), 4.84 (dd, J = 5.8, 11.6 Hz, 1 H), 7.10−7.23 (m, 5 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.58, 34.99, 52.88, 56.38, 127.38, 128.91, 129.31, 136.20, 156.60, 174.10, 177.50; HRMS ($C_{13}H_{15}N_3O_3$ + H)$^+$ calcd 262.1192; found 262.1192.

(5*S*)-5-Isopropyl-3-[(2*S*)-1-amino-1-oxo-3-phenylprop-2-yl]hydantoin (10b): ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.38 (d, J = 6.8 Hz, 3 H), 0.75 (d, J = 7.0 Hz, 3 H), 1.80−1.92 (m, 1 H), 3.34 (dd, J = 5.2 14.0 Hz, 1 H), 3.48 (dd, J = 12.0, 14.0 Hz, 1 H), 3.75 (d, J = 3.8 Hz, 1 H), 4.86 (dd, J = 5.2, 12.0 Hz, 1 H), 7.09−7.21 (m, 5 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.45, 18.52, 29.95, 34.30, 55.48, 62.44, 127.10, 128.7, 129.06, 136.30, 157.80, 171.90, 173.80; HRMS ($C_{15}H_{19}N_3O_3$ + H)$^+$ calcd 290.15047, found 290.15115.

(5*S*)-5-Isopropyl-3-[(1*S*)-1-carboxy-2-phenylethyl]hydantoin (10c): ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.66 (d, J = 8.1 Hz, 3 H), 0.98 (d, J = 8.0 Hz, 3 H), 2.09−2.18 (m, 1 H), 3.62−3.65 (m, 2 H), 3.96 (d, J = 5.3 Hz, 1 H), 5.11 (dd, J = 9.1, 12.1 Hz, 1 H), 7.25−7.38 (m, 5 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.57, 18.70, 30.08, 34.08, 53.41, 126.95, 128.71, 129.12, 136.80, 162.50, 170.90, 173.20; HRMS ($C_{15}H_{18}N_2O_4$ + H)$^+$ calcd 291.13448, found 291.13443.

(5*S*)-5-Benzyl-3-[(1*S*)-1-carboxy-2-methylpropyl]-hydantoin(10d): ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.78 (d, J = 8.0 Hz, 3 H), 1.16 (d, J = 7.0 Hz, 3 H), 2.61−2.71 (m, 1 H), 3.01−3.08 (m, 1 H), 3.38 (dd, J = 5.0, 15.0 Hz, 1 H), 4.40 (d, J = 11.5 Hz, 1 H), 4.48 (dd, J = 5.0, 11.6 Hz, 1 H), 7.31−7.47 (m, 5 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.15, 20.93, 28.03, 36.83, 37.80, 58.47, 127.48, 128.89, 129.68, 135.10, 163.21,

170.80, 173.30; HRMS ($C_{15}H_{18}N_2O_4$ + H)$^+$ calcd 291.13448, found 291.13405.

(5*S*)-5-Isopropyl-3-[(1*S*)-1-carboxyethyl]Hydantoin (10e): ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.08 (d, J = 8.1 Hz, 3 H), 1.21 (d, J = 7.9 Hz, 3 H), 1.77 (d, J = 7.5 Hz, 3 H), 2.36−2.45 (m, 1 H), 4.13 (d, J = 4.0 Hz, 1 H), 4.95 (q, J = 7.5 Hz, 1 H), 6.63 (br d, 10.5 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.99, 16.27, 19.11, 30.70, 48.09, 158.10, 164.00, 172.95; LRMS calcd for $C_9H_{15}N_2O_4$ (M + H)$^+$ 215.1, found 215.0.

(5*S*)-5-Benzyl-3-[(1*S*)-1-carboxy-2-phenylethyl]hydantoin (10f): ^{1}H NMR (400 MHz, CD_3OD) δ 2.37(dd, J = 5.5, 8.6 Hz, 1H), 2.88 (dd, J = 4.5, 9.5 Hz, 1H), 3.31 (m, 3H), 4.17 (dd, J = 3.85, 4.67, Hz, 1H), 7.22 (m, 10H); HRMS ($C_{19}H_{18}N_2O_4$ + H)$^+$ calcd 339.13448, found 339.13353.

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