Effective Preparation of *O*-Succinimidyl-2-(*tert*-butoxycarbonylamino)ethylcarbamate Derivatives from *β*-Amino Acids. Application to the Synthesis of Urea-Containing Pseudopeptides and Oligoureas†

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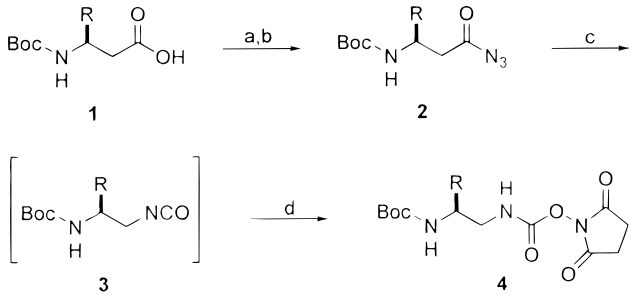
Introduction

In recent years, much attention has been paid to the syntheses and applications of substituted ureas. These are essential components of drug candidates including potent HIV protease inhibitors, CCK-B receptor antagonists, and endothelin antagonists.[1] Oligoureas have also been introduced as scaffolds for the creation of artificial *β*-sheets[2] and as peptide backbone mimetics.[3] Methods for the formation of unsymmetrically mono-, di-, tri-, and tetra-substituted ureas are well documented, and standard procedures involve the reaction of amines with carbonylation reagents,[4] isocyanates,[5] or carbamates.[6]

Scheme 1[a]



[a] Reagents: (a) EtOCOCl, NMM, THF, −20 °C; (b) NaN_3, H_2O; (c) toluene, 65 °C; (d) *N*-hydroxysuccinimide, pyridine.

As part of our ongoing efforts to develop peptide-derived immunomodulators, we needed a simple and safe access to urea-containing peptides and oligoureas. In 1995, Burgess and co-workers reported the use of diaminoethane-derived monophthalimide-protected isocyanates as building blocks for the solid-phase synthesis of oligoureas.[3a,b] This strategy requires the preparation of monophthalimide-protected diamines and is based on the use of triphosgene (bis(trichloromethyl)carbonate) as carbonylating reagent. In a related approach, Schultz and co-workers used azido 4-nitrophenyl carbamates as activated monomers.[3c,d] Similarly, 4-nitrophenyl carbamates obtained by reaction of Boc-protected *N*-substituted ethylenediamines with 4-nitrophenyl chloroformate have been reported as building blocks for the synthesis of ureapeptoids.[3e] Activated carbamates are typically prepared by reaction of amines with carbonates[4c] or chloroformates[3e,6b] or by reaction of isocyanates with alcohols.[6a] We now wish to report the application of Curtius rearrangement for the simple conversion of *N*-Boc-protected *β*-amino acids **1** into the corresponding *O*-succinimidyl-2-*(tert*-butoxycarbonylamino*)*ethylcarbamate derivatives **4**. *O*-succinimidyl carbamates **4** are stable, crystalline products that react readily with amines to form substitued ureas and then can be used as activated monomers in the synthesis of oligoureas.

Results and Discussion

N-Boc-protected *β*-amino acids **1** were first converted to the corresponding acyl azides **2** by reaction of their mixed anhydrides (formed with EtOCOCl/*N*-methylmorpholine (NMM)) with NaN_3. Isocyanates **3**, generated in situ upon heating acyl azides **2** in toluene at 65 °C, were trapped by *N*-hydroxysuccinimide (1 equiv) in the presence of pyridine (1 equiv) to give carbamate **4**. The reaction sequence from **1** was generally complete in less than 1 h (Scheme 1).

O-Succinimidyl carbamates **4**, which crystallized in most cases directly from the toluene solution at room temperature, were recovered simply by filtration in satisfactory yields. Recrystallization from toluene or from the appropriate solvent gave analytically pure samples.

† This paper is dedicated to the memory of our good friend and colleague, Marc Rodriguez, deceased August 17th, 1999.

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§ Neosystem.

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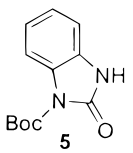
Table 1. Conversion of β-amino Acids 1 to the Correponding *O*-Succinimidyl Carbamates 4

R	compd 4	yield (%)[a]	mp (°C)	HPLC t_R (min)[b]
H	**4a**	55	132−134	6.95[c]
Me	**4b**	60	153−155	8.00[c]
i-Pr	**4c**	51	125−127	10.80[c]
Bn	**4d**	55	163−164	12.79[c]
CH_2CO_2(Bzl)	**4e**	58	115−117	13.47[c]
CH(Me)OBzl	**4f**	64	109−110	14.59[c]
$(CH_2)_4$NH(2-Cl-Z)	**4g**	60	114−115	10.66[d]

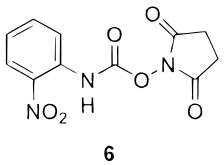
[a] Isolated yield from **1** after recrystallization. [b] Linear gradient of A (0.1% TFA in H_2O) and B (MeCN containing 0.08% TFA). [c] 20−80% B, 20 min. [d] 30−100% B, 20 min.

It is noteworthy that the mild conditions employed are compatible with the use of a number of functionalized side chains (Table 1).

We also applied this procedure to *N*-Boc-anthranilic acid, which is one of the simplest β-amino acids. However, attempts to convert the corresponding acyl azide to the desired *O*-succinimidyl carbamate failed. Instead, 2-oxo-2,3-dihydrobenzimidazole-1-carboxylic acid *tert*-butyl ester **5**[7] was recovered in 55% yield after recrystallization from ethyl acetate. The structure of **5** was assigned unambiguously by X-ray crystallography (A. Aubry, personnal communication). Alternatively, when starting from 2-nitrobenzoic acid,[8] the corresponding *O*-succinimidyl carbamate **6** could be isolated in 71% yield after recrystallization from ethyl acetate.



5

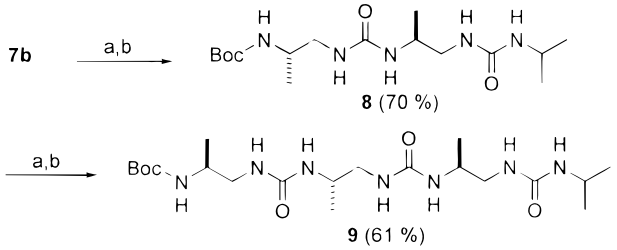


6

Carbamates **4** and **6** are stable crystalline solids that can be stored at 4 °C for months without any degradation. To study the scope and limitations of our activated monomers in the preparation of unsymmetrically substituted ureas, various amines and amino acids were allowed to react with carbamate **4**. The results are shown in Table 2.

We found that reacting carbamates **4** with primary amines or amino acids in the presence of Hunig's base at room temperature generated the corresponding urea derivatives **7** in good yields (Table 2; entries 1, 2). The reaction proceeds rapidly, and all starting material is generally consumed within 20 min. *N*-Hydroxysuccinimide is the only byproduct formed during the reaction and is easily removed by aqueous workup. Under the same conditions, aromatic amines such as aniline (entry 3) and a secondary amine (entry 4) also reacted very fast and

Scheme 2[a]



[a] Reagents: (a) TFA; (b) **4b**, Hunig's base, DMF.

in good yield with carbamate **4d** to give the expected ureas **7c** and **7d**, respectively.

Repetitive urea formation using carbamates **4** as activated monomers led to urea oligomers as exemplified by the facile synthesis of Boc-A^uCH_2-A^uCH_2-*i*-Pr (**8**) and Boc-A^uCH_2-A^uCH_2-A^uCH_2-*i*-Pr (**9**) (Scheme 2).[9]

Conclusion

In summary, *O*-succinimidyl-2-*(tert*-butoxycarbonylamino*)*ethylcarbamates **4** can be readily prepared from β-amino acids and react cleanly and in good yields with primary and secondary amines to form ureas. The mild conditions required for the preparations of carbamates **4** should be compatible with side chains of most proteinogenic amino acids, and therefore we anticipate that these stable activated intermediates will represent attractive building blocks for the solid-phase synthesis of urea-containing pseudopeptides and oligoureas.

Experimental Section

General Procedures. Amino acid derivatives were purchased from Neosystem or Novabiochem. THF was freshly distilled from Na/benzophenone under Ar before use. Toluene was distilled from P_2O_5 and stored over 4 Å molecular sieves. Aniline was passed through alumina before use. Boc-β^3-amino acids were prepared according to literature procedures[10] via Arndt-Eistert homologation of commercially available protected amino acids. The reactions were carried out under a positive pressure of Ar. HPLC analysis was performed on a Nucleosil C_{18} column (5 μm, 3.9 × 150 mm by using a linear gradient of A (0.1% TFA in H_2O) and 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 *O*-Succinimidyl Carbamates 4. The *N*-protected β-amino acid (10 mmol) was dissolved in THF (30 mL) under Ar and cooled to −20 °C. After addition of EtOCOCl (11 mmol) and NMM (11 mmol, 1.1 equiv), the mixture was stirred at −20 °C for 20 min. The resulting white suspension was allowed to warm to −5 °C and was treated with an aqueous solution (5 mL) of NaN_3 (25 mmol). The mixture was stirred for 5 min, diluted with EtOAc, washed with brine, dried over $MgSO_4$, 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 under stirring. After the gas evolution had stopped (ca. 10 min), *N*-hydroxysuccinimide (10

(7) 1,3-Dihydro-2*H*-benzimidazol-2-ones and related compounds represent attractive families of building blocks having interesting biochemical and pharmacological properties. Regioselective alkylation of 1,3-dihydro-2*H*-benzimidazol-2-one and structurally related cyclic urea analogues was reported by Meanwell et al. through the use of monoalkoxycarbonyl derivatives (including compound **5**). In this paper, **5** was synthesized by treatment of 1,3-dihydrobenzimidazol-2-one with NaH followed by an excess of di-*tert*-butyl dicarbonate. Meanwell, N. A.; Sit, S. Y.; Gao, J.; Wong, H. S.; Gao, Q.; St Laurent, D. R.; Balasubramanian, N. *J. Org. Chem.* **1995**, *60*, 1565.

(8) It is noteworthy that for the synthesis of oligoanthranilamides the group of Hamilton used 2-nitrobenzoic acid in place of *N*-benzoylanthranilic acid. In this case, the nitro group as a masked form of the amine was required to avoid the formation of azlactone: Hamuro, Y.; Geib, S. J.; Hamilton, A. D. *J. Am. Chem. Soc.* **1996**, *118*, 7529.

(9) We used the one-letter code nomenclature proposed by Burgess for oligourea sequences.[3b] Alternatively, we propose the following abbreviation that would allow the use of the three-letter code for amino acids: Boc(-β^3-HAla^u)$_2$-*i*-Pr (**8**) and Boc(-β^3-HAla^u)$_3$-*i*-Pr (**9**). According to Spatola's[11] nomenclature for pseudopeptides, we can also write Boc-(-β^3-HAla-Ψ[NHCONH])$_2$-*i*-Pr (**8**) and Boc(-β^3-HAla-Ψ[NHCONH])$_3$-*i*-Pr (**9**).

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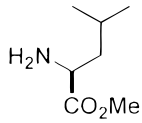
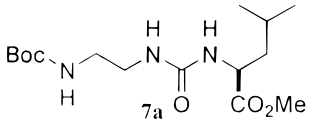
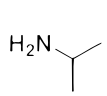
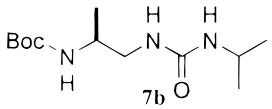
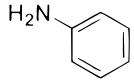
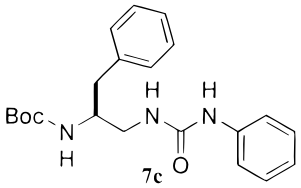
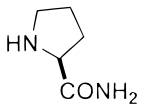
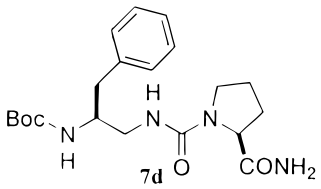
Table 2. Formation of Substituted Ureas 7 from Carbamates 4 and Various Amino Derivatives

Entry	Carbamate	Amine	Time (min)[a]	Urea 7	Yield (%)[b]
1	**4a**		20	 **7a**	78
2	**4b**		20	 **7b**	85
3	**4d**		20	 **7c**	87
4	**4d**		30	 **7d**	89

[a] Reaction conditions: carbamate (3 mmol), amine (3−4 mmol), Hunig's base (3 mmol), DMF (5 mL), rt. [b] Isolated yields.

mmol) and pyridine (10 mmol) were added. The mixture was stirred for 5 min at 65 °C and then cooled to room temperature. In most cases the title compound crystallized from the toluene solution and was collected by filtration. Recrystallization from toluene afforded the pure *O*-succinimidyl carbamate. Otherwise the solvent was removed in vacuo and the residue was purified by recrystallization from the appropriate solvent.

***O*-Succinimidyl-2-(*tert*-butoxycarbonylamino)ethylcarbamate (4a).** 3-(*tert*-Butoxycarbonylamino)propanoic acid (3.78 g, 20 mmol) was transformed according to the general procedure. Recrystallization from toluene yielded **4a** (3.3 g, 50%): colorless crystals; mp 132−134 °C; HPLC t_R 6.95 min (linear gradient, 20−80% B, 20 min); ^{1}H NMR (200 MHz, DMSO-d_6) δ 1.38 (s, 9H), 2.76 (s, 4H), 3.00−3.11 (m, 4H), 6.87 (br t, 1H); 8.27 (t, J = 5.1 Hz, 1H); ^{13}C NMR (50 MHz, CD_3CN) δ 171.7, 157.5, 153.1, 79.7, 42.7, 40.6, 28.6, 26.3; MS (MALDI-TOF) m/z 340 $[M + K]^+$, 324 $[M + Na]^+$. Anal. Calcd for $C_{12}H_{19}N_3O_6$: C, 47.84; H, 6.36; N, 13.95. Found: C, 48.09; H, 6.65; N, 14.00.

***(S)-O*-Succinimidyl-2-(*tert*-butoxycarbonylamino)propylcarbamate (4b).** Boc-β^3-HAla-OH (3.25 g, 16 mmol) was transformed according to the general procedure. Recrystallization from toluene yielded **4b** (3.05 g, 60%): white solid; mp 153−155 °C; $[\alpha]^{25}_D$ −14.4 (*c* 1.03, MeCN); HPLC t_R 8.00 min (linear gradient, 20−80% B, 20 min); ^{1}H NMR (200 MHz, CD_3CN) δ 1.07 (d, J = 6.8 Hz, 3H), 1.41 (s, 9H), 2.73 (s, 4H), 3.14−3.20 (m, 2H), 3.62−3.72 (m, 1H), 5.25 (br d, 1H), 6.54 (br t, 1H); ^{13}C NMR (50 MHz, CD_3CN) δ 171.7, 156.7, 153.3, 79.6, 47.7, 47.4, 28.7, 26.3, 18.4; MS (MALDI-TOF) m/z 355 $[M + K]^+$, 339 $[M + Na]^+$. Anal. Calcd for $C_{13}H_{21}N_3O_6$: C, 49.52; H, 6.71; N, 13.33. Found: C, 49.45; H, 6.57; N, 13.18.

***(S)-O*-Succinimidyl-2-(*tert*-butoxycarbonylamino)-3-methylpropylcarbamate (4c).** Boc-β^3-HVal-OH (1.27 g, 5.5 mmol) was transformed according to the general procedure. Recrystallization from toluene yielded **4c** (956 mg, 51%): white solid; mp 125−127 °C; $[\alpha]^{25}_D$ −41.2 (*c* 1.15, THF); HPLC t_R 10.80 min (linear gradient, 20−80% B, 20 min); ^{1}H NMR (200 MHz, CD_3CN) δ 0.89 (t, J = 7.0 Hz, 6H), 1.42 (s, 9H), 1.65−1.78 (m, 1H), 2.73 (s, 4H), 3.11−3.52 (m, 3H), 5.18 (br d, J = 8.5 Hz, 1H), 6.46 (br t, 1H); ^{13}C NMR (50 MHz, CD_3CN) δ 171.7, 157.7, 153.5, 79.3, 56.7, 44.8, 31.0, 28.7, 26.3, 19.8, 18.3. MS (MALDI-TOF) m/z 383 $[M + K]^+$, 367 $[M + Na]^+$. Anal. Calcd for $C_{15}H_{25}N_3O_6$: C, 52.47; H, 7.34; N, 12.24. Found: C, 52.26; H, 7.13; N, 11.92.

***(S)-O*-Succinimidyl-2-(*tert*-butoxycarbonylamino)-4-phenylpropylcarbamate (4d).** Boc-β^3-HPhe-OH (8.27 g, 29.5 mmol) was transformed according to the general procedure. Recrystallization from toluene yielded **4d** (6.6 g, 57%): white solid; mp 163−164 °C; $[\alpha]^{25}_D$ −15 (*c* 1.17, MeCN); HPLC t_R 12.79 min (linear gradient, 20−80% B, 20 min); ^{1}H NMR (200 MHz, CD_3CN) δ 1.33 (s, 9H), 2.68−2.90 (m, 6H), 3.16−3.37 (m, 2H), 3.78−3.93 (m, 1H), 5.26 (d, J = 8.0 Hz, 1H), 6.54 (br t, 1H); 7.16−7.34 (m, 5H); ^{13}C NMR (50 MHz, CD_3CN) δ 171.7, 157.3, 153.3, 139.4, 130.3, 129.4, 127.4, 79.6, 53.2, 46.3, 39.0, 28.6, 26.3; MS (MALDI-TOF) m/z 430 $[M + K]^+$, 414 $[M + Na]^+$. Anal. Calcd for $C_{19}H_{25}N_3O_6$: C, 58.30; H, 6.44; N, 10.74. Found: C, 58.17; H, 6.38; N, 10.69.

***(S)-O*-Succinimidyl-3-(benzyloxycarbonyl)-2-(*tert*-butoxycarbonylamino)propylcarbamate (4e).** Boc-β^3-HAsp(Bzl)-OH (2.53 g, 7.5 mmol) was transformed according to the general procedure. Recrystallization from toluene yielded **4e** (1.94 g, 58%): white solid; mp 115−117 °C; $[\alpha]^{25}_D$ −16.3 (*c* 1.3, THF); HPLC t_R 13.47 min (linear gradient, 20−80% B, 20 min); ^{1}H NMR (200 MHz, CD_3CN) δ 1.46 (s, 9H), 2.47−2.58 (m, 2H); 2.73 (s, 4H), 3.29 (t, J = 6.2 Hz, 2H), 3.96−4.08 (m, 1H), 5.10 (s, 2H), 5.45 (br d, J = 6.2 Hz, 1H); 6.54 (br t, 1H); 7.29−7.41 (m, 5H); ^{13}C NMR (50 MHz, CD_3CN) δ 171.7, 171.6, 156.5, 153.4, 137.4, 129.6, 129.4, 129.1, 118.3, 79.9, 67.2, 48.9, 45.8, 37.6, 28.6, 26.3; MS (MALDI-TOF) m/z 488 $[M + K]^+$, 472 $[M + Na]^+$. Anal. Calcd for $C_{21}H_{27}N_3O_8$: C, 56.12; H, 6.05; N, 9.35. Found: C, 55.89; H, 6.01; N, 9.32.

(2*R*,3*R*)-*O*-Succinimidyl-3-(benzyloxy)-2-(*tert*-butoxycarbonylamino)propylcarbamate (4f). Boc-β^3-HThr(Bzl)-OH (2.31 g, 7.14 mmol) was transformed according to the general procedure. Recrystallization from EtOAc/hexane yielded **4f** (2.0 g, 64%): white solid; mp 109−110 °C; $[\alpha]^{25}_D$ +8.6 (*c* 1.07, MeCN); HPLC t_R 14.59 min (linear gradient, 20−80% B, 20 min); ^{1}H NMR (200 MHz, CD_3CN) δ 1.16 (d, J = 6.1 Hz, 3H), 1.43 (s, 9H), 2.73 (s, 4H), 3.21−3.44 (m, 2H), 3.61−3.76 (m, 2H), 4.41 (d, J = 11.5 Hz, 1H), 4.60 (d, J = 11.5 Hz, 1H), 0.21 (br d, J = 9.1 Hz, 1H), 6.49 (br t, 1H), 7.25−7.39 (m, 5H); ^{13}C NMR (50 MHz, CD_3CN) δ 171.7, 157.2, 153.2, 139.9, 129.4, 129.3, 128.8, 128.5, 118.3, 79.7, 75.1, 71.5, 55.3, 44.2, 28.6, 26.3, 16.4; MS (MALDI-TOF) m/z 475 $[M + K]^+$, 459 $[M + Na]^+$. Anal. Calcd for $C_{21}H_{29}N_3O_7$: C, 57.92; H, 6.71; N, 9.65. Found: C, 58.02; H, 6.67; N, 9.81.

***(S)-O*-Succinimidyl-2-(*tert*-butoxycarbonylamino)-6-(2-chlorobenzyloxycarbonylamino)hexanoylcarbamate (4g).** Boc-β^3-HLys(2-Cl-Z)-OH (4.83 g, 11.26 mmol) was transformed according to the general procedure. Recrystallization from toluene yielded **4g** (3.67 g, 60%): white solid; mp 116−119 °C;

$[\alpha]^{25}_D$ −10.3 (*c* 1.0, MeCN); HPLC t_R 10.63 min (linear gradient, 30−100% B, 20 min); ^{1}H NMR (200 MHz, CD_3CN) δ 1.26−1.47 (m, 6H), 1.41 (s, 9H), 2.73 (s, 4H), 3.05−3.30 (m, 4H), 3.57−3.66 (m, 1H), 5.14 (s, 2H), 5.24 (br d, J = 8 Hz, 1H), 5.73 (br t, 1H), 6.52 (br t, 1H), 7.18−7.47 (m, 4H); ^{13}C NMR (50 MHz, CD_3CN) δ 171.7, 157.0, 153.1, 130.5, 130.4, 128.2, 118.3, 79.6, 64.1, 51.5, 46.6, 41.3, 32.4, 30.3, 28.7, 26.3, 23.6; MS (MALDI-TOF) *m*/*z* 579.9 $[M + K]^+$, 563.5 $[M + Na]^+$. Anal. Calcd for $C_{24}H_{33}ClN_4O_8$: C, 53.28; H, 6.15; N, 10.36. Found: C, 53.37; H, 6.12; N, 10.33.

***O*-Succinimidyl-(2-nitrophenyl)carbamate (6).** 2-Nitrobenzoic acid (1.17 g, 7 mmol) was transformed according to the general procedure for the preparation of **4**. The solvent was removed in vacuo, and recrystallization from EtOAc yielded **6** (1.39 g, 71%): light yellow crystals; mp 166−167 °C; HPLC t_R 9.45 min (linear gradient, 20−80% B, 20 min); ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.89 (s, 4H), 7.26 (dt, 1H), 7.69 (dt, 1H), 8.26 (dd, 1H), 8.40 (dd, 1H), 10.40 (br s); ^{13}C NMR (50 MHz, $CDCl_3$) δ 169.2, 148.5, 136.2, 133.1, 126.2, 124.1, 120.8, 25.6; MS (MALDI-TOF) *m*/*z* 318 $[M + K]^+$, 302 $[M + Na]^+$. Anal. Calcd for $C_{12}H_{10}N_2O_6$: C, 47.32; H, 3.25; N, 15.05. Found: C, 47.45; H, 3.26; N, 15.07.

Urea Formation: General Procedure. To a stirred solution of the amine (1.3 mmol) in 5 mL of DMF were successively added *O*-succinimidyl carbamate **4** (1 mmol) and Hunig's base (1 mmol). 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 evaporated. Flash chromatography and/or recrystallization afforded pure urea **7**.

Methyl (2*S*)-2-{[2-(*tert*-Butoxycarbonylamino)ethyl]ureido}-4-methylpentanoate (Boc-G^{u}CH$_2$-Leu-OMe, 7a). Carbamate **4a** (602 mg, 2 mmol) was reacted with HCl·H-Leu-OMe (436 mg, 2.4 mmol) according to the general procedure. Recrystallization from EtOAc/diisopropyl ether yielded **7a** (520 mg, 78%): colorless needles; mp 86−89 °C; $[\alpha]^{25}_D$ −10.8 (*c* 1.02, MeOH); HPLC t_R 11.39 min (linear gradient, 20−80% B, 20 min); ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.90 (d, J = 6.4 Hz, 3H), 0.91 (d, J = 6.2 Hz, 3H), 1.41 (s, 9H), 1.45−1.75 (m, 3H), 3.16−3.32 (m, 4H), 3.69 (s, 3H), 4.36−4.47 (m, 1H), 5.34 (br t, J = 5.2, 1H), 6.14 (d, J = 8.2, 1H), 6.76 (br t, J = 5.0, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 175.3, 158.5, 156.7, 79.4, 52.1, 51.7, 41.8, 41.3, 40.3, 28.4, 24.8, 22.9, 21.9; MS (MALDI-TOF) *m*/*z* 370 $[M + K]^+$, 354 $[M + Na]^+$, 332 $[M + 1]^+$. Anal. Calcd for $C_{15}H_{29}N_3O_5 \cdot 0.5H_2O$: C, 52.94; H, 8.82; N, 12.35. Found: C, 52.92; H, 8.68; N, 12.27.

(2*S*)-1-[2-(*tert*-Butoxycarbonylamino)propyl]-3-(1-methylethyl)urea (Boc-A^{u}CH$_2$-*i*-Pr, 7b). Carbamate **4b** (901 mg, 2.86 mmol) was reacted with *i*-$PrNH_2$ (511 μL, 6 mmol) according to the general procedure to yield **7b** (701 mg, 95%): white solid; mp 101 °C; $[\alpha]^{25}_D$ −7.4 (*c* 0.89, MeOH); HPLC t_R 8.71 min (linear gradient, 20−80% B, 20 min); ^{1}H NMR (200 MHz, CD_3CN) δ 1.03 (d, J = 6.6 Hz, 3H), 1.07 (d, J = 6.5 Hz, 6H), 1.40 (s, 9H), 3.02−3.08 (m, 2H), 3.47−3.60 (m, 1H), 3.65−3.81 (m, 1H), 4.92 (br d, 1H); 5.1 (br t, 1H), 5.66 (br, 1H); ^{13}C NMR (50 MHz, CD_3CN) δ 158.4, 156.4, 79.4, 47.7, 46.2, 42.2, 28.5, 23.4, 23.3, 18.6; MS (MALDI-TOF) *m*/*z* 298 $[M + K]^+$, 282 $[M + Na]^+$. Anal. Calcd for $C_{12}H_{25}N_3O_3$: C, 55.57; H, 9.72; N, 16.20. Found: C, 55.56; H, 9.82; N, 16.16.

(2*S*)-1-[2-(*tert*-Butoxycarbonylamino)-3-phenylpropyl]-3-phenylurea (Boc-F^{u}CH$_2$-Ph, 7c). Carbamate **4d** (500 mg, 1.28 mmol) was reacted with $PhNH_2$ (119 mg, 1.28 mmol) according to the general procedure. Recrystallization from CH_2Cl_2/hexane yielded **7c** (412 mg, 87%): white solid; mp 154 °C; $[\alpha]^{25}_D$ +10.3 (*c* 1.03, MeOH); HPLC t_R 15.23 min (linear gradient, 20−80% B, 20 min); ^{1}H NMR (200 MHz, CD_3OD) δ 1.35 (s, 9H), 2.70 (dd, J = 8.0, 13.7 Hz, 1H), 2.80 (dd, J = 7.8, 13.7 Hz, 1H), 3.16 (dd, J = 8.6, 13.6 Hz, 1H), 3.33 (dd, J = 4.6, 17.1 Hz, 1H), 3.81−3.85 (m, 1H), 7.16−7.34 (m, 10H); ^{13}C NMR (50 MHz, CD_3OD) δ 158.8, 158.6, 141.3, 140.1, 130.8, 130.2, 129.8, 127.7, 123.9, 120.7, 80.4, 54.6, 44.8, 40.3, 29.1, 28.8; MS (MALDI-TOF) *m*/*z* 408 $[M + K]^+$, 392 $[M + Na]^+$, 370 $[M + 1]^+$. Anal. Calcd for $C_{21}H_{27}N_3O_3$: C, 68.27; H, 7.37; N, 11.37. Found: C, 68.19; H, 7.32; N, 11.47.

Boc-F^{u}CH$_2$-Pro-NH$_2$, 7d. Carbamate **4d** (1.16 g, 3 mmol) was reacted with HCl·H-Pro-NH_2 (540 mg, 3.6 mmol) according to the general procedure. Flash chromatography ($CHCl_3$/MeOH 10:1) yielded **7d** (1.16 g, 88%): white solid; mp 96−98 °C; $[\alpha]^{25}_D$ −20.4 (*c* 1.02, MeOH); HPLC t_R 10.02 min (linear gradient, 20−80% B, 20 min); ^{1}H NMR (200 MHz, CD_3OD) δ 1.36 (s, 9H), 1.88−2.17 (m, 4H), 2.59−2.83 (m, 2H), 2.96 (dd, J = 9.4, 13.6 Hz, 1H), 3.21−3.50 (m, 3H), 3.89−3.99 (m, 1H), 4.29 (dd, J = 3.2, 8.1 Hz, 1H), 7.11−7.29 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.4, 157.8, 156.6, 137.4, 129.2, 128.6, 126.6, 79.6, 60.1, 51.6, 46.3, 45.7, 39.0, 28.8, 28.4, 24.7; MS (MALDI-TOF) *m*/*z* 429 $[M + K]^+$, 413 $[M + Na]^+$, 391 $[M + 1]^+$. Anal. Calcd for $C_{20}H_{30}N_4O_4$: C, 61.52; H, 7.74. Found: C, 61.78; H, 7.77.

Boc-A^{u}CH$_2$-A^{u}CH$_2$-*i*-Pr, 8. Compound **7b** (650 mg, 2.5 mmol) was dissolved in TFA (0.25M) at 0 °C. After stirring at room temperature for 30 min and concentration under reduced pressure, the crude trifluoroacetate salt was dried in vacuo over KOH and used without further purification. Carbamate **4b** was then reacted with a solution of the trifluoroacetate salt in DMF according to the general procedure. Recrystallization from EtOH/hexane yielded **8** (630 mg, 70%): white solid; mp 184−185 °C, $[\alpha]^{25}_D$ +9.3 (*c* 0.88, MeOH); HPLC t_R 8.52 min (linear gradient, 20−80% B, 20 min); ^{1}H NMR (200 MHz, CD_3OD) δ 1.05−1.12 (m, 12H), 1.42 (s, 9H), 2.92−3.24 (m, 4H), 3.56−3.84 (m, 2H); ^{13}C NMR (100 MHz, CD_3OD) δ 160.9, 160.7, 158.2, 80.0, 48.2, 47.8, 46.8, 46.4, 42.9, 28.5, 23.6, 23.5, 19.1, 18.6. Anal. Calcd for $C_{16}H_{33}N_5O_4$: C, 53.46; H, 9.25; N, 19.48. Found: C, 53.62; H, 9.29; N, 19.43.

Boc-A^{u}CH$_2$-A^{u}CH$_2$-A^{u}CH$_2$-*i*-Pr, 9. Compound **8** (440 mg, 1.22 mmol) was dissolved in TFA (0.25 M) at 0 °C. After stirring at room temperature for 30 min and concentration under reduced pressure, the crude trifluoroacetate salt that precipitated upon addition of Et_2O was collected by filtration, dried in vacuo over KOH, and used without further purification. To a solution of the trifluoroacetate salt in DMF were successively added **4b** and Hunig's base (637 μL, 3.66 mmol). The reaction mixture was stirred for 20 min, and saturated $NaHCO_3$ was added. The precipitate that formed was filtered, washed with saturated $NaHCO_3$, water, and Et_2O, and dried in vacuo over P_2O_5 to yield **9** (350 mg, 62%): white solid; mp 210−211 °C, $[\alpha]^{25}_D$ +63.6 (*c* 1.00, MeOH); HPLC t_R 8.53 min (linear gradient, 20−80% B, 20 min); ^{1}H NMR (200 MHz, CD_3OD) δ 1.03−1.12 (m, 15H), 1.44 (s, 9H), 2.55−2.85 (m, 3H), 3.21−3.39 (m, 3H), 3.61−3.95 (m, 4H); ^{13}C NMR (100 MHz, CD_3OD) δ 161.2, 161.1, 160.9, 158.7, 80.3, 48.2, 47.6, 47.5, 47.2, 47.1, 46.8, 43.0, 29.0, 23.8, 23.7, 19.5, 19.0, 18.7; MS (MALDI-TOF) *m*/*z* 499 $[M + K]^+$, 483 $[M + Na]^+$, 461 $[M + 1]^+$. Anal. Calcd for $C_{20}H_{41}N_7O_5$: C, 52.27; H, 8.99; N, 21.33. Found: C, 52.23; H, 9.00; N, 20.93.

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Supporting Information Available: Crystal data for compound **6**. This material is available free of charge via the Internet at http://pubs.acs.org.

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