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Sequential Intermolecular Radical Addition and Reductive Radical Cyclization of Tyrosine and Phenylalanine Derivatives with Alkenes via Photoinduced Decarboxylation: Access to Ring-constrained γ-Amino Acids

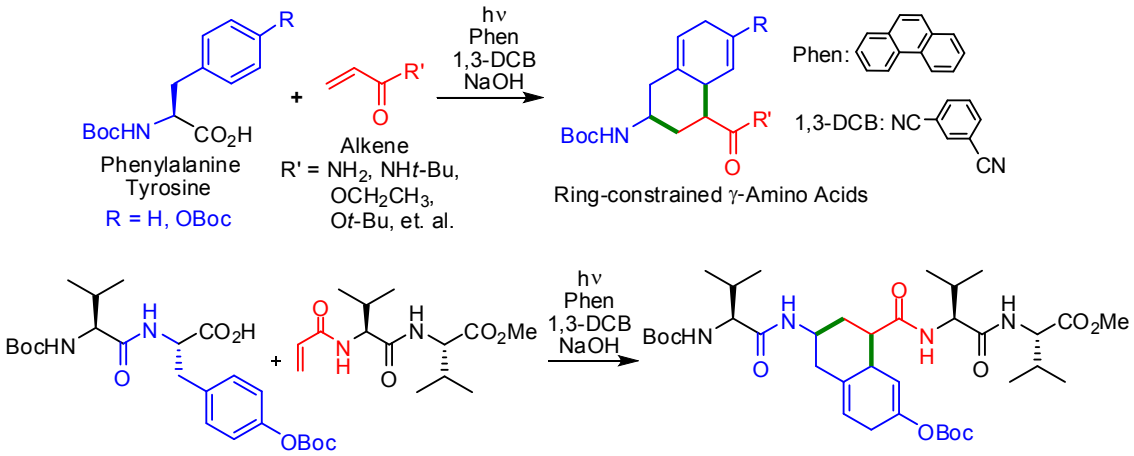
Kazuyuki Osaka, Ayuka Usami, Tomoya Iwasaki, Mugen Yamawaki, Toshio Morita, Yasuharu Yoshimi*

Department of Applied Chemistry and Biotechnology, Graduate School of Engineering, University of Fukui, 3-9-1 Bunkyo, Fukui 910-8507, Japan

Corresponding author; Y. Yoshimi Tel: +81-776-27-8633, Fax: +81-776-27-8747

E-mail of corresponding author: yyoshimi@u-fukui.ac.jp

TOC



▪Abstract

Sequential radical addition to alkenes and reductive radical cyclization of phenylalanine and tyrosine derivatives via photoinduced decarboxylation furnished ring-constrained γ-amino acids under mild conditions. A variety of alkenes such as acrylamides and acrylic esters could be

employed in the photoinduced radical cascade cyclization. The yields of the ring-constrained γ-amino acids are dependent on the electron-accepting ability and steric hindrance of the alkene used. The proposed sequential reaction can also be applied for direct tethering of dipeptides to yield unique ring-constrained tetrapeptides.

·Introduction

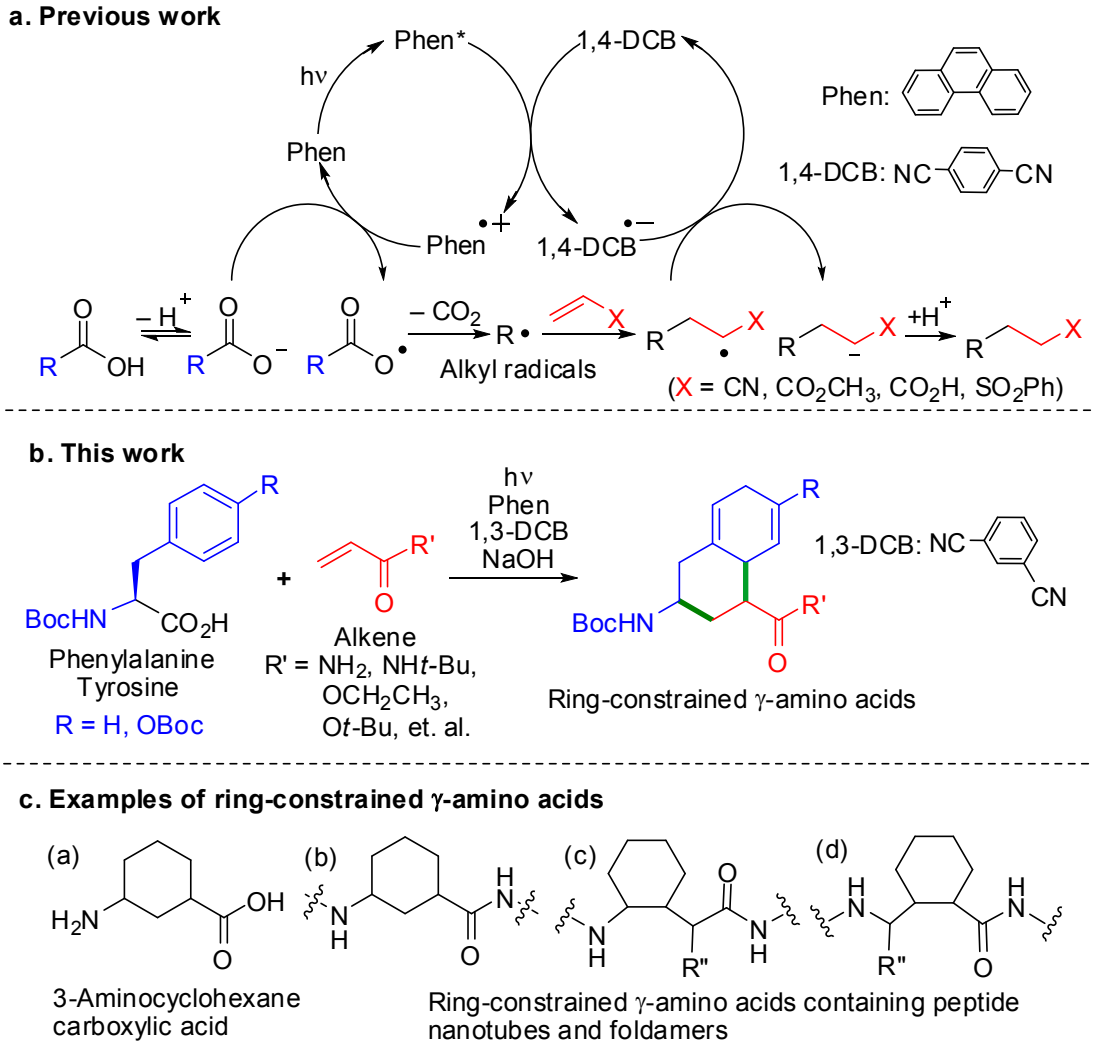
Radical cascade (tandem) reactions have been considered as powerful and facile tools for the preparation of complex organic molecules.[1] This sequential radical reaction has been applied to synthesize numerous valuable heterocycles and fused structures,[2] especially, some natural products such as (*S*)-mappicine and (+)-strychnine.[3] In this protocol, alkyl radicals are generated by the reaction of an organic halide (RX where X = Br or I) with AIBN as the radical initiator and Bu_3SnH as the halogen and/or hydrogen transfer agent. However, the utility of this method is limited by the toxicity of the substrates and reagents, as well as the difficulties associated with the removal of tin containing byproducts (Bu_3SnX).

Recently, photoindued decarboxylative radical reactions of aliphatic carboxylic acids in the presence of a photoredox catalyst have been established as an effective and environmentally-friendly method for the generation of alkyl radicals.[4-7] This is because carboxylic acids occur widely in nature and are easy to handle; moreover, decarboxylation

releases the nonflammable and nontoxic product CO_2 under mild conditions (e.g., at room temperature), and light is a traceless reagent. According to our previous report,[5] decarboxylation of aliphatic carboxylic acids by the radical cation of phenanthrene (Phen) via photoinduced electron transfer (PET) between the excited state of Phen and 1,4-dicyanobenzene (1,4-DCB) furnished alkyl radicals (Scheme 1a). These radicals reacted with a variety of radical acceptors to provide the corresponding products in high yields. In particular, the addition of alkyl radicals to electron-deficient alkenes proceeds efficiently to generate the addition-radical, even with the use of only 1 eq. of alkene.[6] Subsequently, back electron transfer (BET) from the radical anion of 1,4-DCB to the resulting radical generates an anion, which is protonated to generate the adduct in high yields. This finding encouraged us to explore the intermolecular radical addition of carboxylic acids to *N*-acryloyl amino acid esters and peptides as radical acceptors via PET-promoted decarboxylation, because *N*-alkylcarbonyl amino acids and peptides are potential pharmaceutical agonists and inhibitors.[7] During this investigation, it was unexpectedly revealed that sequential radical addition and reductive cyclization of phenylalanine and tyrosine derivatives with acrylamides onto the benzene ring occurred to afford ring-constrained γ-amino acids (Scheme 1b). To the best of our knowledge, this is the first example of sequential intermolecular radical addition to alkenes and reductive radical cyclization onto the benzene ring. Furthermore, the ring-constrained γ-amino acids are

structurally similar to 3-aminocyclohexane carboxylic acid (Scheme 1c (a)), which is used as the building block for peptide nanotubes[8] (Scheme 1c (b)) and "foldamers"[9] (Scheme 1c (b), (c), and (d)). Herein, we report a facile and metal-free route to ring-constrained γ-amino acids via a new radical cascade reaction of tyrosine and phenylalanine with acrylamides and acrylic esters, initiated by PET-promoted decarboxylation under mild photoredox catalyst conditions.

Scheme 1. a. PET-promoted Decarboxylative Radical Addition of Carboxylic Acids to Alkenes, **b.** Sequential Intermolecular Radical Addition and Reductive Radical Cyclization of Phenylalanine and Tyrosine Derivatives with Alkenes via PET-promoted Decarboxylation, and **c.** Examples of Ring-constrained γ-Amino Acids.



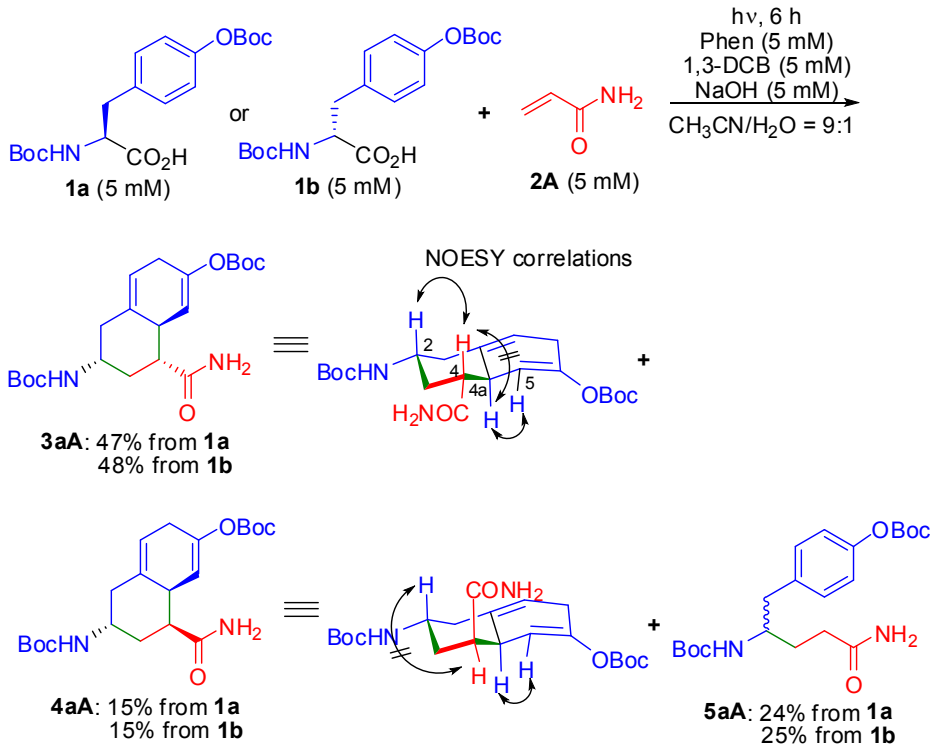
▪Results and Discussion

Initially, we attempted to optimize the photochemical reaction conditions by using *N*-Boc-L-tyrosine(OBoc) **1a** (Boc = *t*-butoxycarbonyl) and acrylamide **2A** (Scheme S1 and Table S1 in SI). The use of 1,3-dicyanobenzene (1,3-DCB) instead of 1,4-DCB as an electron acceptor resulted in improved product yields because substitution between the radical generated

via photoinduced decarboxylation and the radical anion of 1,3-DCB suppressed the formation of alkylcyanobenzene, as reported by us.[10] Irradiation (100 W high-pressure mercury lamp with a Pyrex glass filter; $\lambda > 280$ nm) of **1a** (5 mM) in an aqueous acetonitrile solution (CH_3CN/H_2O = 9:1, v/v) containing Phen (5 mM), 1,3-DCB (5 mM), and **2A** (5 mM) under the optimized conditions in an argon atmosphere for 6 h at room temperature afforded major ring-constrained γ-amino acid **3aA** (47%), minor ring-constrained γ-amino acid **4aA** (15%), and adduct **5aA** (24%) as all-racemic mixtures (Scheme 2). The structure and stereochemistry of cyclized product **3aA** was confirmed by measurement of NOESY (as shown in SI) and X-ray crystallographic analysis (Figure 1), and Boc-protected amino group, carbamoyl group, and ring junction part in **3aA** are in equatorial positions. Measurement of NOESY of the minor product **4aA** (as shown in SI) suggested that **4aA** which the carbamoyl group occupies an axial position is diastereomer of **3aA**, even though stereochemistry of **4aA** was not confirmed at present, and further investigation about stereochemistry of **4aA** is underway. When the corresponding D-tyrosine derivative **1b** was subjected to the photochemical conditions, almost identical product yields were observed, indicating that the chirality at the α-position in **1a**,**b** did not affect the photoreaction. The radical at the α-position generated from chiral *N*-Boc-L-α-amino acids via photoinduced decarboxylation lost its chirality to yield a racemic mixture of the products due to the generation of the planar radical by hyperconjugation (π-radical).[6] Moreover,

all-racemic mixtures of **3aA**, **4aA**, and **5aA** in the photoreaction with **1a** or **1b** were observed even though chiral **1a** and **1b** were used as the substrates. As reported by us earlier,[11] the unprotected phenolic OH group of tyrosine prevented PET-induced decarboxylation, and protection of the phenolic OH by the Boc group in **1** is essential for the promoting photoinduced decarboxylative reactions.

Scheme 2. Photoreactions of *N*-Boc-L-tyrosine(OBoc) **1a** or *N*-Boc-D-tyrosine(OBoc)**1b** with Acrylamide **2A**.



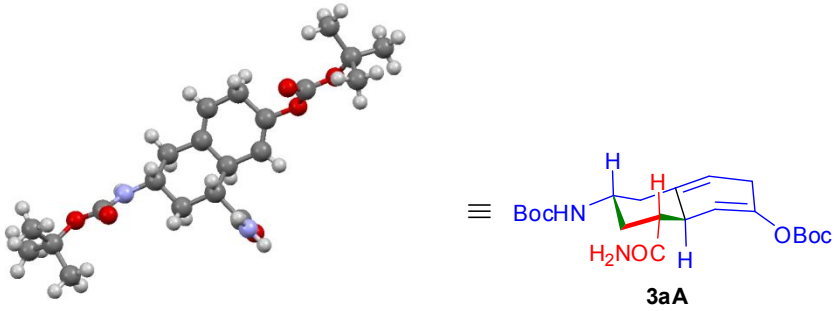
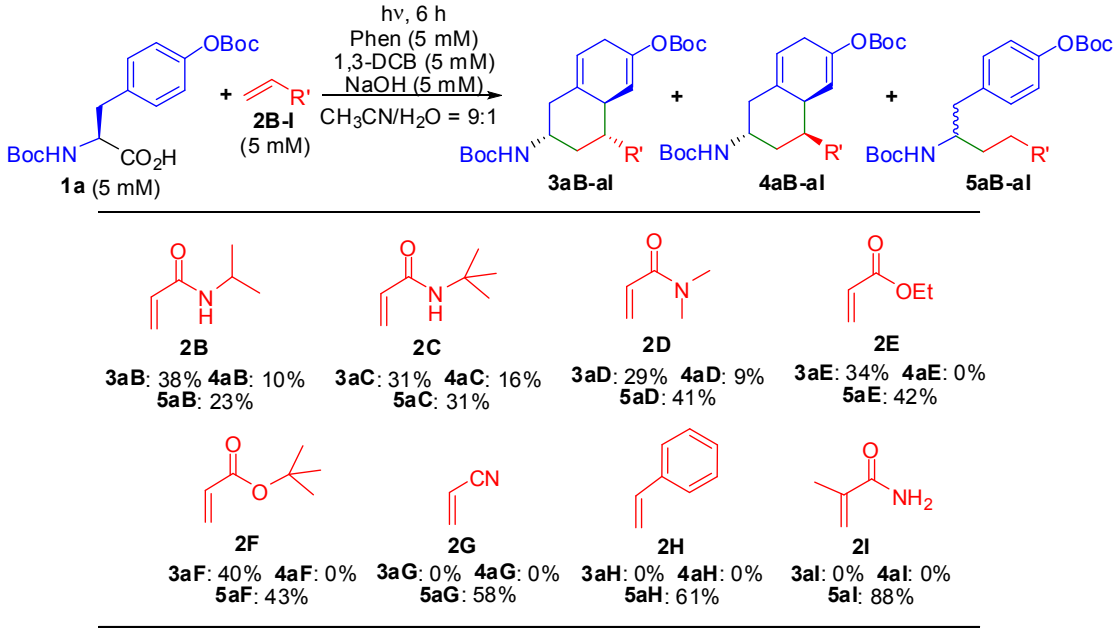


Figure 1. X-ray Crystallographic Analysis of **3aA**.

Next, the effect of alkenes **2B–I** in the photoinduced decarboxylative radical reactions of **1a** was evaluated (Table 1). Photoreactions of **1a** with slightly bulky *N*-alkyl substituted acrylamides such as *N*-isopropyl acrylamide **2B** and *N*-*tert*-butyl acrylamide **2C** marginally decreased the yields of cyclized products **3aB–aC** and **4aB–aC**. The use of the bulkier acrylamide such as *N,N*-dimethyl acrylamide **2D** decreased the yields of cyclized products **3aD** and **4aD**, but increased the yield of adduct **5aD**. These results indicated that reductive cyclization onto benzene rings with acrylamides was weakly dependent on the steric hindrance of the acrylamide. Interestingly, the use of acrylic esters such as ethyl acrylate **2E** and *t*-butyl acrylate **2F** instead of acrylamide exclusively afforded major ring-constrained γ-amino acids **3aE** (34%) and **3aF** (40%) without minor product **4**, along with adducts **5aE** (42%) and **5aF** (43%). The strong electron-accepting ability of alkenes such as acrylonitrile **2G** and styrene **2H,** and the high steric hindrance of alkene such as methacrylamide **2I** at the position of radical generation prevented the formation of cyclized products **3** and **4**, and exclusively yielded

adducts (**5aG**: 58%, **5aH**: 61%, **5aI**: 88%). Thus, the ratio of the photoreaction products was strongly dependent on the electron-accepting ability and steric hindrance of the alkene used.

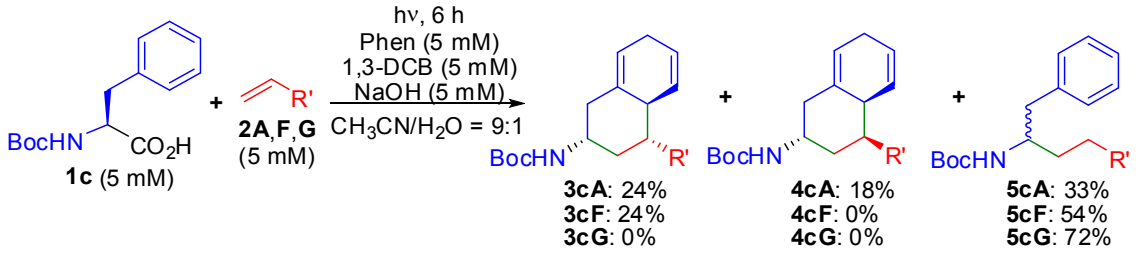
Table 1. Effect of Alkenes **2A–I** in Photoreaction of **1a**.



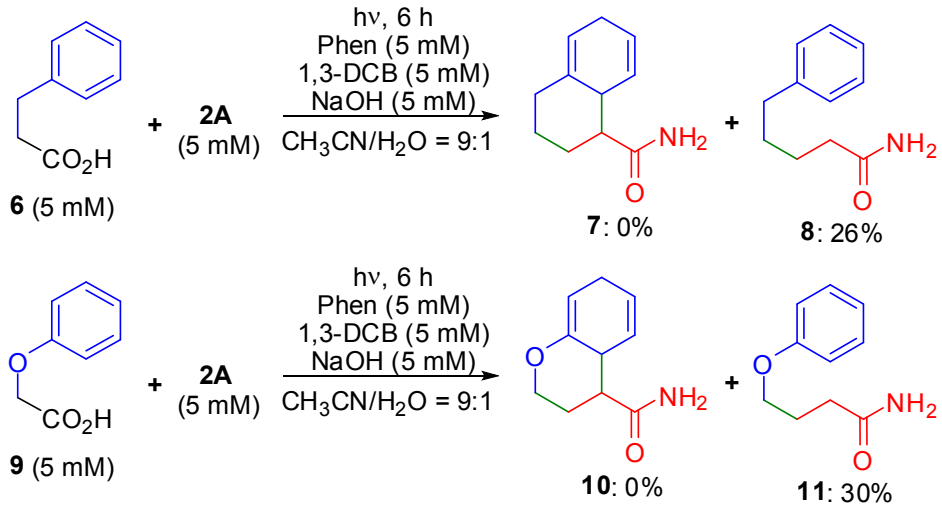
Next, the substrate scope of the radical cascade reaction was investigated using *N*-Boc-L-phenylalanine **1c** and 3-phenylpropionic acid derivatives **6** and **9**. The weaker electron-donating ability of the benzene ring of **1c** compared to that of **1a** decreased the yields of major cyclized products **3cA**,**3cF** and minor product **4cA**, while slightly increased the yields of adducts **5cA**,**5cF**,**5cG** (Scheme 3). Similar trends in the product ratio were observed for **1c**. The use of 3-phenylpropionic acid **6** and phenoxyacetic acid **9**, which lack the amine unit bearing the *N*-Boc group in **1a**–**c**, did not lead to the formation of the desired cyclized products

7 and **10**, and only adducts **8** and **11** were obtained (Scheme 4). Thus, we conclude that radical cyclization via photoinduced decarboxylation requires tyrosine and phenylalanine derivatives as the substrates.

Scheme 3. Photoreactions of *N*-Boc-L-Phenylalanine **1c** with **2A**,**F**,**G**.



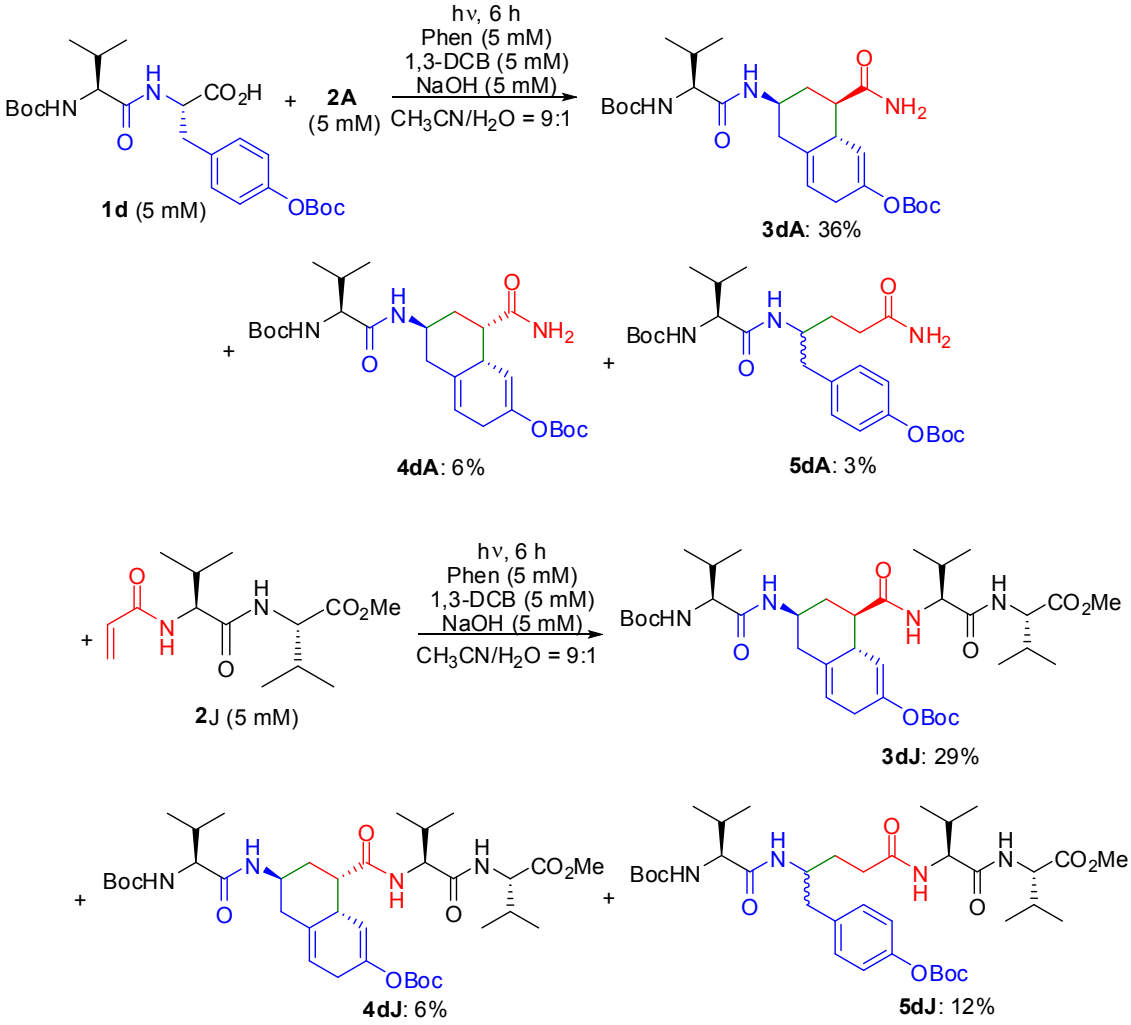
Scheme 4. Photoreactions of **6** and **9** with **2A**.



Finally, the sequential photoinduced decarboxylative radical cascade reaction of dipeptide **1d** (*N*-Boc-ValTyr(OBoc)OH) having a tyrosine residue was demonstrated (Scheme 5). A similar

photoreaction of dipeptide **1d** with **2A** led to the formation of dipeptides **3dA** (36%) and **4dA** (6%) containing the ring-constrained γ-amino acid along with adduct **5dA** (3%). The connection between **1d** and *N*-acryloyl dipeptide **2J** with the ring-constrained γ-amino acid in the photoinduced decarboxylative radical reaction was successfully achieved to yield ring-constrained tetrapeptides **3aJ** (29%) and **4aJ** (6%). Although the low solubility of the resulting peptides decreased the yields of the ring-constrained peptides, the photochemical method can allow for the direct tethering of peptides containing a ring-constrained γ-amino acid.

Scheme 5. Photoreactions of **1d** with **2A**,**J**.

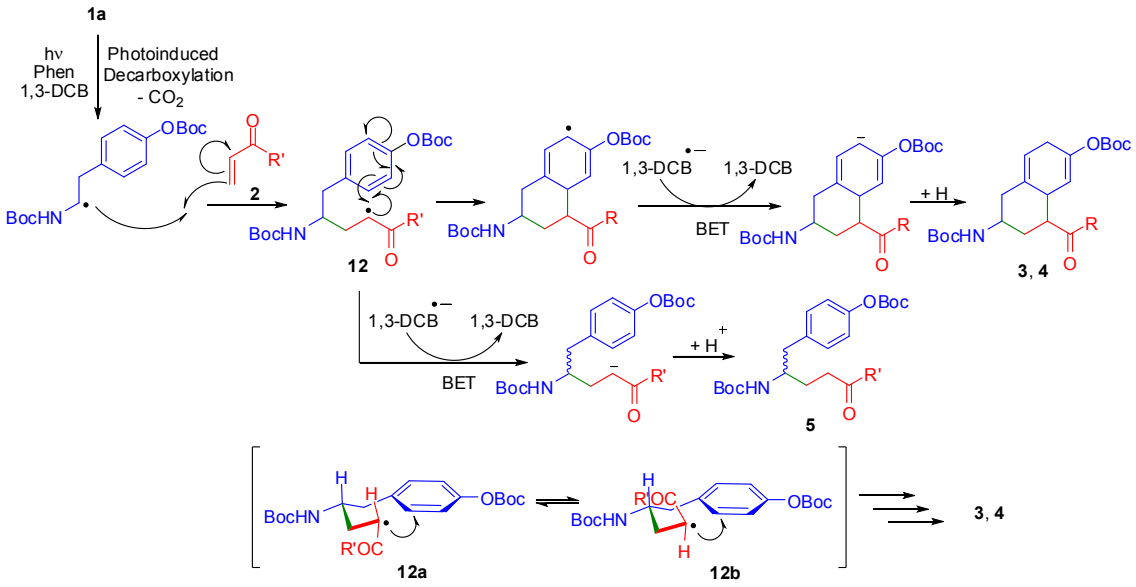


A plausible mechanism for the sequential radical addition and reductive radical cyclization of **1a** by PET-promoted decarboxylation is shown in Scheme 6. The alkyl radical generated by photoinduced decarboxylation adds to electron-deficient alkene **2** to form radical intermediate **12**. As shown in Scheme 4, the presence of the amine unit bearing a Boc group in radical **12** promotes radical cyclization onto the benzene ring at the closed-space position. The resulting

radical is reduced through BET from the radical anion of 1,3-DCB to yield ring-constrained γ-amino acids **3** and **4**, similar to Birch reduction, after protonation. We have previously reported a similar reductive cyclization of alicyclic α-amino acids onto the benzene ring at the *ipso*-position via photoinduced decarboxylation under photoredox catalyst conditions.[12] The rate of radical cyclization onto the benzene ring is dependent on both the electron-donating ability of the benzene ring of **1** and the steric hindrance of alkene **2**. The photoreaction of **1a** having a strongly electron-donating benzene ring (C_6H_4OBoc) with **2A** having low steric hindrance gave the best yields of ring-constrained γ-amino acids **3aA** and **4aA**. A very bulky alkene such as **2I** restricted the radical cyclization to exclusively yield adduct **5aI**. In addition to the radical cyclization of **12**, BET from the radical anion of 1,3-DCB to radical **12** proceeded to yield adduct **5**. In the cases of acrylonitrile **2G** and styrene **2H**, the strong electron-accepting ability of radical **12** accelerated BET from the radical anion of 1,3-DCB to yield mainly adducts **5aG** and **5aH**. Thus, the ratio of two competitive processes between the radical cyclization and BET is determined by the electron-donating ability of the benzene ring in **1**, steric hindrance of alkene **2**, and electron-accepting ability of radical **12**. Although the difference in the product ratio and stereochemistry between the acrylamide and the acrylic ester is not clear at present, two six-membered transition states of radicals **12a** and **12b** in which the Boc-protected amino group is in the equatorial position as shown in Scheme 6 led to the respective formation of **3** and

4.

Scheme 6. A Plausible Mechanism for Radical Cascade Reaction of **1** with **2**.



Conclusion

Sequential inter- and intramolecular radical cascade reactions of tyrosine and phenylalanine derivatives **1** onto aromatic rings with acrylamides and acrylic esters **2** via PET-promoted decarboxylation under mild conditions proceed efficiently to yield ring-constrained γ-amino acids **3** and **4** in moderate yields. The product ratio is dependent on the electron-donating ability of the benzene ring in **1**, steric hindrance of alkene **2**, and electron-accepting ability of radical **12**. This organic photoredox catalyst method provides a facile and environmentally-friendly route to unique ring-constrained γ-amino acids from simple starting materials such as

phenylalanine, tyrosine, acrylamide, and acrylic ester. Further, our protocol allows for direct tethering of peptides with ring-constrained γ-amino acids.

Experimental Section

General Information. All reagents and solvents were used as received from commercial suppliers. IR spectra were recorded on an FT-IR spectrometer. ^{1}H NMR spectra were recorded in $CDCl_3$ containing tetramethylsilane as an internal standard, and were acquired on either a 300 or 500 MHz spectrometers. $^{13}C\{^{1}H\}$ NMR spectra were acquired on a 125 MHz spectrometer. High-resolution mass spectra were obtained using double-focusing magnetic sector mass spectrometer coupled with FAB. The light source was a Riko UV-100HA high-pressure (100 W) mercury arc, and Pyrex vessels (18 mm x 180 mm) were directly attached to the light source ($\lambda > 280$ nm, Phen mainly absorbed at 313 nm light). Column chromatography was performed on Wakogel C-300, particle size 45-75 μm. Further purification by GPC was conducted for **3aB**, **4aB**, **3aC**, **4aC**, **3aD**, **4aD**, **3cG**, **4dA**, **5dA**, **3dJ**, and **4dJ**.

General procedure for synthesis of *N*-Boc tyrosine(OBoc) 1a,b

Benzyl alcohol (90 mmol, 14 mL) was added to a solution of L-tyrosine (30 mmol, 5.40 g) and *p*-TsOH (5.70 g, 1.0 eq) in toluene (90 mL). The mixture was refluxed for 27 h using Dean-Stark trap, and white solids was formed. The mixture was filtered to yield the desired benzyl protected L-tyrosine *p*-toluenesulfonate as a white solid (8.44 g, 64%).

K_2CO_3 (0.871 g, 2.5 eq) and DMAP (0.0301 g, 0.10 eq) were added to the solution of benzyl protected L-tyrosine *p*-toluenesulfonate (2.5 mmol, 1.10 g) and $(Boc)_2O$ (7.5 mmol, 1.7 mL) in DMF (8.4 mL). The mixture was stirred at room temperature for 4 h, and quenched by water.

The aqueous layer was acidified (1M HCl) to a pH 2–3 and then extracted with EtOAc, and washed with brine. The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by silica-gel column chromatography using hexane/EtOAc = 20:1 as the eluent to yield *N*,*O*-bisBoc benzyl protected L-tyrosine as a colorless liquid (1.10 g, quant.).

Debenzylation of *N*,*O*-bisBoc benzyl protected L-tyrosine (1.5 mmol, 0.700 g) was carried out by 10 % Pd/C (0.0427 g) and H_2 in MeOH (3.0 mL) with TLC monitoring. After complete consumption of starting material (about 1.5 h), the mixture was filtered through a celite, and then concentrated under reduced pressure. The crude product was purified by silica-gel column chromatography using hexane/EtOAc = 5:1 to 1:1 as the eluent to yield **1a** as a white solid (0.460 g, 83%).

Similar procedure from D-tyrosine (30 mmol, 5.40 g) provided **1b** in the similar yield (0.460 g, 53%). Compounds **1a–c** have been previously reported.

N-Boc-L-tyrosine(OBoc) 1a[4b]: ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 9.09 (br, 1H), 7.19 (d, J = 8.4 Hz, 2H), 7.11 (d, J = 8.4 Hz, 2H), 6.64 (br, 0.3H), 5.01 (br, 0.7H), 4.64–4.58 (m, 0.7H), 4.39 (br, 0.3H), 3.27–2.85 (m, 2H), 1.55 (s, 9H), 1.42 (s, 6H), 1.28 (s, 3H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ_C 175.9, 175.5, 155.4, 151.9, 150.0, 133.4, 130.3, 121.3, 83.6, 81.6, 80.4, 54.1, 37.0, 28.2, 27.9, 27.6.

N-Boc-D-tyrosine(OBoc) 1b[4b]: ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 9.35 (br, 1H), 7.19 (d, J = 8.6 Hz, 2H), 7.11 (d, J = 8.6 Hz, 2H), 6.66 (br, 0.3H), 5.01 (br, 0.7H), 4.58–4.65 (m, 0.7H), 4.38 (br, 0.3H), 3.27–2.86 (m, 2H), 1.55 (s, 9H), 1.42 (s, 6H), 1.28 (s, 3H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ_C 175.9, 175.1, 155.4, 151.9, 150.1, 133.4, 130.3, 121.3, 83.6, 81.7, 80.4, 54.1, 37.0, 28.2, 27.9, 27.6.

N-Boc-L-phenylalanine 1c[6a]: ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 9.88 (br, 1H), 7.33–7.17 (m, 5H), 6.64 (br, 0.3H), 4.98 (br, 0.7H), 4.65–4.59 (m, 0.7H), 4.41 (br, 0.3H), 3.27–2.88 (m, 2H), 1.42 (s, 6H), 1.27 (s, 3H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ_C 176.6, 175.9, 155.3, 135.8, 129.5, 129.3, 128.6, 127.1, 126.9, 80.3, 56.0, 54.2, 37.7, 28.2, 27.9.

General procedure for synthesis of dipeptides *N*-BocValTyr(OBoc)OH 1d and *N*-Acryloyl ValValOMe 7

EDC hydrochloride (1.2 eq, 0.732 g) and HOBt· H_2O (1.4 eq, 0.681 g) were added to solution of *N*-BocValOH (3.2 mmol, 0.690 g), benzyl protected tyrosine *p*-toluenesulfonate (3.2 mmol, 1.41 g), and *i*-Pr_2NEt (1.2 eq, 0.66 mL) in DMF (22 mL) at 0 °C. This mixture was stirred for 2 h at 0 °C, and overnight at room temperature, quenched by water, and then extracted with EtOAc. The combined organic layer was washed with 0.1 M H_2SO_4, water, and brine. The organic layer was dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification of a crude product was conducted by silica gel column chromatography using hexane/ EtOAc = 2:1 as an eluent to yield *N*-BocValTyr(OH)CO_2Bn as a white solid (1.18 g, 79%).

K_2CO_3 (1.5 eq, 0.260 g) and $(Boc)_2O$ (2.0 eq, 0.58 mL) were added to the solution of *N*-BocValTyr(OH)CO_2Bn (1.2 mmol, 0.601 g) in acetone (8.1 mL). The mixture was stirred at room temperature for 2.5 h, quenched by water, and extracted with EtOAc. The combined organic layer was washed with water and brine, and dried over Na_2SO_4, and concentrated under reduced pressure. The crude product was purified by silica-gel column chromatography using hexane/EtOAc = 2:1 as the eluent to yield *N*-BocValTyr(OBoc)CO_2Bn as a white solid (0.688 g, 94%).

Similar debenzylation of *N*-BocValTyr(OBoc)CO_2Bn (0.52 mmol, 0.300 g) with 10% Pd/C (0.0456 g) in MeOH (1.0 mL) and purification by silica-gel column chromatography using hexane/EtOAc = 2:1 to 0:1 as the eluent yielded *N*-BocValTyr(OBoc)CO_2H **1d** as a white solid (0.218 g, 84%). Synthesis of *N*-acryloyl dipeptide **2J** has been previously reported by us.[7]

N-BocValTyr(OBoc)OH 1d: white solid, mp 86–87 °C; IR (KBr, cm^{-1}) 3401, 2980, 1740, 1535, 1397; ^1H NMR (300 MHz, $CDCl_3$) δ_H 9.25 (br, 1H), 7.17 (d, J = 8.6 Hz, 2H), 7.06 (d, J = 8.6 Hz,

2H), 6.90 (br, 1H), 5.37 (br, 1H), 4.84 (br, 1H), 4.04–3.86 (m, 1H), 3.21–2.98 (m, 2H), 2.08–1.96 (m, 1H), 1.53 (s, 9H), 1.44 (s, 9H), 0.89–0.85 (m, 6H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ_C 173.6, 171.8, 156.1, 151.8, 150.0, 133.4, 130.4, 121.2, 83.5, 80.4, 60.0, 53.0, 36.7, 30.6, 28.3, 27.6, 19.1, 17.8; HRMS (FAB) calcd for $(M+H)^+$ $C_{24}H_{37}N_2O_8$: 481.2550, found 481.2544.

***N-Acryloyl ValValOMe 2J'*:** ^1H NMR (300 MHz, $CDCl_3$) δ_H 7.82 (br, 1H), 7.57 (br, 1H), 6.35–6.19 (m, 2H), 5.59 (dd, J = 9.4, 2.5 Hz, 1H), 4.81–4.65 (m, 1H), 4.55–4.42 (m, 1H), 3.74 (s, 3H), 2.20–2.03 (m, 2H), 1.01–0.83 (m, 12H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ_C 172.3, 172.2, 165.6, 130.7, 126.6, 58.3, 57.5, 51.9, 31.5, 30.6, 19.1, 19.0, 18.6, 17.9.

General procedure for the photoreaction of 1 with 2. An aqueous CH_3CN solution (CH_3CN 45 mL, H_2O 5 mL) of **1** (5 mM), **2** (5 mM), NaOH (5 mM, 0.0100g), Phen (5 mM, 0.0455g), and 1,3-DCB (5 mM, 0.0320g) in Pyrex vessels (18 mm x 180 mm) was purged with Ar for 10 min. The mixture was irradiated with a 100 W high-pressure mercury lamp for 6 h, and then the solvent was removed under reduced pressure. The crude product was purified by silica-gel column chromatography using hexane/EtOAc = 4:1 to 1:2 as the eluent to yield cyclized products **3** and **4** along with adduct **5**. Photoreactions of **6** and **9** with **2A** were carried out under the same conditions to yield **8** and **11**. Compounds **5cG** and **11** have been previously reported.

rac-(2S, 4R, 4aS) and (2R, 4S, 4aR)-2-N-Boc-amino-4-carbamoyl-6-O-Boc-oxy-1,2,3,4,4a,7-hexahydronaphthalene (3aA): 0.0480 g, 47%, white solid, mp 218–219 °C; IR (KBr, cm^{-1}) 3352, 2977, 1754, 1672, 1522; ^1H NMR (300 MHz, $CDCl_3$) δ_H 5.81 (br, 1H), 5.62 (br, 1H), 5.50–5.44 (br, 2H), 4.62 (br, 1H), 3.53 (br, 1H), 3.04 (br, 1H), 2.85 (br, 1H), 2.60–2.56 (m, 1H), 2.20–2.09 (m, 2H), 1.91–1.82 (m, 2H), 1.49 (s, 9H), 1.43 (s, 9H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ_C 175.3, 155.1, 151.3, 146.7, 133.1, 118.5, 112.8, 83.0, 79.4, 50.3, 49.3, 41.1, 39.8, 36.7, 29.7, 28.4, 27.9, 27.6; HRMS (FAB) calcd for $(M+H)^+$ $C_{21}H_{33}N_2O_6$: 409.2338, found 409.2320.

rac-(2S, 4S, 4aS) and (2R, 4R, 4aR)-2-N-Boc-amino-4-carbamoyl-6-O-Boc-oxy-1,2,3,4,4a,7-hexahydronaphthalene (4aA): 0.0153 g, 15%, white solid, mp 195–196 °C; IR (KBr, cm^{-1}) 3447, 2978, 1710, 1672, 1502; ^1H NMR (300 MHz, $CDCl_3$) δ_H 5.52 (br, 3H), 5.45 (br, 1H), 4.56 (br, 1H), 4.03 (br, 1H), 3.12 (br, 1H), 2.98–2.81 (m, 2H), 2.40–2.06 (m, 4H), 1.94–1.84 (m, 1H), 1.50 (s, 9H), 1.40 (s, 9H);

$^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$) δ_C 175.6, 154.8, 151.4, 146.5, 132.0, 119.7, 113.1, 83.1, 79.5, 47.5, 46.1, 40.1, 39.0, 34.3, 28.4, 28.0, 27.6; HRMS (FAB) calcd for $(M+H)^+$ $C_{21}H_{33}N_2O_6$: 409.2338, found 409.2320.

4-N-Boc-amino-5-(4'-O-Boc-phenoxy)pentylamide (5aA): (using hexane/EtOAc = 4:1 to 1:2, and then chloroform/acetone = 3:1 as the eluent), 0.0245 g, 24%, white solid, mp 162–163 °C; IR (KBr, cm^{-1}) 3418, 3369, 2981, 1756, 1680, 1448; ^{1}H NMR (300 MHz, $CDCl_3$) $\delta_{H;}$ 7.17 (d, J = 8.7 Hz, 2H), 7.08 (d, J = 8.7 Hz, 2H), 6.23 (br, 1H), 5.66 (br, 1H), 4.64 (br, 1H), 3.84 (br, 1H), 2.83–2.71 (m, 2H), 2.30–2.20 (m, 2H), 1.96–1.60 (m, 2H), 1.55 (s, 9H), 1.39 (s, 9H); $^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$) δ_C 175.2, 156.0, 151.9, 149.5, 135.1, 130.1, 121.1, 83.5, 79.5, 51.0, 41.1, 32.5, 30.4, 28.2, 27.6; HRMS (FAB) calcd for $(M+H)^+$ $C_{21}H_{33}N_2O_6$:409.2338, found 409.2326.

rac-(2S, 4R, 4aS) and (2R, 4S, 4aR)-2-N-Boc-amino-4-N-isopropylcarbamoyl-6-O-Boc-oxy-1,2,3,4,4a,7-hexahydronaphthalene (3aB): (using hexane/EtOAc = 5:1 to chloroform/acetone = 10:1 as the eluent), 0.0428 g, 38%, white solid, mp 205–206 °C; IR (KBr, cm^{-1}) 3284, 2974, 1758, 1686, 1550; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 5.63 (br, 1H), 5.46 (br, 1H), 5.35 (br, 1H), 4.75 (br, 1H), 4.01–4.12 (m, 1H), 3.50–3.48 (br, 1H), 3.03–2.99 (m, 1H), 2.81 (br, 2H), 2.57–2.53 (br, 1H), 2.11–1.83 (m, 3H), 1.70–1.56 (m, 1H), 1.49 (s, 9H), 1.43 (s, 9H), 1.16–1.11 (m, 6H); $^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$) δ_C 171.6, 155.0, 151.3, 146.4, 133.5, 118.2, 112.8, 82.9, 79.4, 51.6, 49.4, 41.2, 40.2, 36.5, 28.4, 28.0, 27.6, 22.6; HRMS (FAB) calcd for $(M+H)^+$ $C_{24}H_{39}N_2O_6$: 451.2807, found 451.2798.

rac-(2S, 4S, 4aS) and (2R, 4R, 4aR)-2-N-Boc-amino-4-N-isopropylcarbamoyl-6-O-Boc-oxy-1,2,3,4,4a,7-hexahydronaphthalene (4aB): (using hexane/EtOAc = 5:1 to chloroform/acetone = 10:1 as the eluent), 0.0113 g, 10%, white solid, mp 222–223 °C; IR (KBr, cm^{-1}) 3363, 2978, 1747, 1631, 1528; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 5.49 (br, 1H), 5.40–5.33 (m, 2H), 4.55 (br, 1H), 4.13–4.01 (m, 2H), 3.13–3.11 (br, 1H), 2.87 (br, 2H), 2.39–2.35 (br, 1H), 2.21–1.87 (m, 4H), 1.50 (s, 9H), 1.45 (s, 9H), 1.14–1.07 (m, 6H); $^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$) δ_C 171.9, 155.0, 151.3, 146.3, 130.6, 119.0, 112.8, 83.0, 79.1, 52.2, 51.4, 49.4, 40.3, 36.6, 28.6, 28.3, 28.0, 27.6; HRMS (FAB) calcd for $(M+H)^+$ $C_{24}H_{39}N_2O_6$: 451.2807, found 451.2798.

4-N-Boc-amino-5-(4'-O-Boc-phenoxy)-N-isopropyl-pentylamide (5aB): (using hexane/EtOAc = 5:1 to chloroform/acetone = 10:1 as the eluent), 0.0259 g, 23%, white solid, mp 106–107 °C; IR (KBr, cm^{-1}) 3349, 2930, 1758, 1684, 1456; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 7.17 (d, J = 8.7 Hz, 2H), 7.08 (d, J = 8.7 Hz, 2H), 5.83 (br, 1H), 4.59–4.56 (br, 1H), 4.13–3.98 (m, 1H), 3.78 (br, 1H), 2.85–2.63 (m, 2H), 2.18–2.11 (m, 2H), 1.85–1.64 (m, 2H), 1.55 (s, 9H), 1.39 (s, 9H), 1.15–1.12 (m, 6H); $^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$) δ_C 171.9, 156.1, 152.1, 149.7, 135.5, 130.4,

121.3, 83.7, 79.5, 51.5, 41.5, 33.7, 30.2, 28.5, 27.8, 22.9; HRMS (FAB) calcd for $(M+H)^+$ $C_{24}H_{39}N_2O_6$: 451.2807, found 451.2810.

rac-(2S, 4R, 4aS) and (2R, 4S, 4aR)-2-N-Boc-amino-4-N-t-butylcarbamoyl-6-O-Boc-oxy-1,2,3,4,4a,7-hexahydronaphthalene (3aC): (using hexane/EtOAc = 10:1 to chloroform/acetone = 10:1 as the eluent), 0.0360 g, 31%, white solid, mp 237–238 °C; IR (KBr, cm^{-1}) 3383, 2927, 1753, 1685, 1547; ^1H NMR (300 MHz, $CDCl_3$) δ_H 5.47 (br, 1H), 5.40–5.37 (m, 2H), 4.58–4.55 (br, 1H), 3.54–3.46 (m, 1H), 3.04–2.94 (m, 1H), 2.83–2.81 (m, 2H), 2.58–2.53 (m, 1H), 2.17–2.05 (m, 1H), 1.92–1.77 (m, 2H), 1.66–1.55 (m, 1H), 1.50 (s, 9H), 1.43 (s, 9H), 1.34 (s, 9H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ_C 171.9, 155.0, 151.3, 146.3, 119.0, 112.8, 83.0, 52.2, 51.4, 49.4, 40.3, 36.6, 28.6, 28.0, 27.6; HRMS (FAB) calcd for $(M+H)^+$ $C_{25}H_{41}N_2O_6$: 465.2965, found 465.2988.

rac-(2S, 4S, 4aS) and (2R, 4R, 4aR)-2-N-Boc-amino-4-N-t-butylcarbamoyl-6-O-Boc-oxy-1,2,3,4,4a,7-hexahydronaphthalene (4aC): (using hexane/EtOAc = 10:1 to chloroform/acetone = 10:1 as the eluent), 0.0186 g, 16%, white solid, mp 219–220 °C; IR (KBr, cm^{-1}) 3356, 2930, 1751, 1635, 1537; ^1H NMR (300 MHz, $CDCl_3$) δ_H 5.49 (br, 1H), 5.38–5.33 (m, 2H), 4.57–4.55 (br, 1H), 4.03 (br, 1H), 3.12–3.07 (m, 1H), 2.87 (br, 2H), 2.39–2.31 (m, 1H), 2.02–2.16 (m, 1H), 2.00–1.88 (m, 3H), 1.51 (s, 9H), 1.46 (s, 9H), 1.34 (s, 9H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ_C 172.3, 151.6, 146.2, 132.6, 119.3, 113.4, 83.2, 79.5, 51.5, 49.5, 46.3, 40.6, 39.2, 34.2, 28.5, 28.1, 27.7; HRMS (FAB) calcd for $(M+H)^+$ $C_{25}H_{41}N_2O_6$: 465.2965, found 465.2975 .

4-N-Boc-amino-5-(4'-O-Boc-phenoxy)-N-t-butyl-pentylamide (5aC): (using hexane/EtOAc = 10:1 to chloroform/acetone = 10:1 as the eluent), 0.0360 g, 31 %, white solid, mp 60 °C; IR (KBr, cm^{-1}) 3373, 2925, 1751, 1685, 1456; ^1H NMR (300 MHz, $CDCl_3$) δ_H 7.17 (d, J = 8.7 Hz, 2H), 7.08 (d, J = 8.7 Hz, 2H), 5.63 (br, 1H), 4.59–4.56 (br, 1H), 3.75 (br, 1H), 2.81–2.66 (m, 2H), 2.12–2.08 (m, 2H), 1.84–1.63 (m, 2H), 1.55 (s, 9H), 1.39 (s, 9H), 1.33 (s, 9H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ_C 172.0, 155.8, 151.9, 149.5, 130.3, 121.1, 83.5, 79.2, 51.5, 51.1, 41.4, 34.3, 29.7, 28.7, 28.3, 27.6; HRMS (FAB) calcd for $(M+H)^+$ $C_{25}H_{41}N_2O_6$: 465.2965, found 465.2990.

rac-(2S, 4R, 4aS) and (2R, 4S, 4aR)-2-N-Boc-amino-4-N,N-dimethylcarbamoyl-6-O-Boc-oxy-1,2,3,4,4a,7-hexahydronaphthalene (3aD): (using hexane/EtOAc = 4:1 to chloroform/acetone = 3:1 as the eluent), 0.0316 g, 29%, white solid, mp 88–89 °C; IR (KBr, cm^{-1}) 3365, 2978, 1752, 1634, 1523; ^1H NMR (300 MHz, $CDCl_3$) δ_H 5.50 (br, 1H), 5.29–5.28 (br, 1H), 4.53–4.51 (br, 1H), 3.53 (br, 1H), 3.17–3.05 (m, 1H), 3.02 (s, 3H), 2.97 (s, 3H), 2.86–2.84 (m, 2H), 2.66–2.57 (m, 2H), 2.08–2.03 (m, 1H), 1.92–1.83 (m, 1H), 1.69–1.57 (m, 1H), 1.48 (s, 9H), 1.43 (s, 9H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ_C 173.0, 155.0, 151.2, 146.8, 133.5, 118.3, 113.1, 82.9, 79.4, 49.4, 45.5, 41.3, 40.4,

37.5, 36.1, 35.7, 28.4, 28.0, 27.6; HRMS (FAB) calcd for $(M+H)^+$ $C_{23}H_{37}N_2O_6$: 437.2652, found 437.2671.

rac-(2S, 4S, 4aS) and (2R, 4R, 4aR)-2-N-Boc-amino-4-N,N-dimethylcarbamoyl-6-O-Boc-oxy-1,2,3,4,4a,7-hexahydronaphthalene (4aD): (using hexane/EtOAc = 4:1 to chloroform/acetone = 3:1 as the eluent), 0.00982 g, 9%, white solid, mp 161–162 °C; IR (KBr, cm^{-1}) 3351, 2979, 1751, 1628, 1534; ^1H NMR (300 MHz, $CDCl_3$) δ_H 5.51 (br, 1H), 5.34 (br, 1H), 4.58–4.56 (br, 1H), 3.96 (br, 1H), 3.28–3.18 (m, 1H), 2.97 (s, 3H), 2.95 (s, 3H), 2.90–2.83 (m, 1H), 2.74–2.67 (m, 1H), 2.43–2.38 (m, 1H), 2.20–2.10 (m, 2H), 1.79–1.65 (m, 2H), 1.49 (s, 9H), 1.45 (s, 9H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ_C 173.3, 154.9, 151.4, 146.3, 132.5, 119.9, 113.9, 83.0, 79.4, 46.4, 42.5, 40.3, 39.0, 37.0, 35.7, 33.3, 28.3, 28.0, 27.6; HRMS (FAB) calcd for $(M+H)^+$ $C_{23}H_{37}N_2O_6$: 437.2652, found 437.2648.

4-N-Boc-amino-5-(4'-O-Boc-phenoxy)-N,N-dimethyl-pentylamide (5aD): (using hexane/EtOAc = 4:1 to chloroform/acetone = 3:1 as the eluent), 0.0447 g, 41%, white solid, mp 84–85 °C; IR (KBr, cm^{-1}) 3432, 2930, 1757, 1684, 1507; ^1H NMR (300 MHz, $CDCl_3$) δ_H 7.19 (d, J = 8.4 Hz, 2H), 7.07 (d, J = 8.4 Hz, 2H), 4.69–4.66 (br, 1H), 3.77 (br, 1H), 2.95 (s, 3H), 2.92 (s, 3H), 2.77–2.61 (m, 2H), 2.38–2.28 (m, 2H), 1.89–1.66 (m, 2H), 1.55 (s, 9H), 1.40 (s, 9H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ_C 172.6, 155.6, 151.9, 149.4, 135.5, 130.3, 121.0, 83.4, 79.0, 51.8, 41.3, 37.1, 35.4, 29.9, 28.8, 28.2, 27.5; HRMS (FAB) calcd for $(M+H)^+$ $C_{23}H_{37}N_2O_6$: 437.2652, found 437.2628.

rac-(2S, 4R, 4aS) and (2R, 4S, 4aR)-2-N-Boc-amino-4-ethoxycarbonyl-6-O-Boc-oxy-1,2,3,4,4a,7-hexahydronaphthalene (3aE): (using hexane/EtOAc = 10:1 to 5:1 as the eluent), 0.0372 g, 34%, white solid, mp 99–100 °C; IR (KBr, cm^{-1}) 3373, 2946, 1751, 1725, 1688, 1522; ^1H NMR (300 MHz, $CDCl_3$) δ_H 5.50 (br, 1H), 5.37 (br, 1H), 4.61–4.52 (m, 1H), 4.15 (q, J = 7.1 Hz, 2H), 3.51 (br, 1H), 3.13–2.99 (m, 1H), 2.90–2.84 (m, 2H), 2.61–2.56 (m, 1H), 2.37–2.17 (m, 2H), 1.89–1.70 (m, 2H), 1.49 (s, 9H), 1.43 (s, 9H), 1.26 (t, J = 7.1 Hz, 3H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ_C 173.7, 154.9, 151.1, 146.9, 132.5, 118.9, 112.5, 83.1, 79.4, 60.6, 49.0, 41.3, 40.4, 36.5, 28.3, 27.9, 14.2; HRMS (FAB) calcd for $(M+H)^+$ $C_{23}H_{36}NO_7$: 438.2493, found 438.2480.

ethyl 4-N-Boc-amino-5-(4'-O-Boc-phenoxy)pentanoate (5aE): (using hexane/EtOAc = 10:1 to 5:1 as the eluent), 0.0459 g, 42%, white solid, mp 85–86 °C; IR (KBr, cm^{-1}) 3332, 2930, 1760, 1681, 1457; ^1H NMR (300 MHz, $CDCl_3$) δ_H 7.18 (d, J = 8.6 Hz, 2H), 7.09 (d, J = 8.6 Hz, 2H), 4.11 (q, J = 7.1 Hz,, 2H), 3.80 (br, 1H), 2.84–2.69 (m, 2H), 2.35 (t, J = 7.3 Hz, 2H), 1.90–1.62 (m, 2H), 1.55 (s, 9H), 1.39 (s, 9H), 1.24 (t, J = 7.1 Hz, 3H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ_C 173.5, 155.4, 151.9, 149.5, 135.3, 130.3, 121.1, 83.5, 79.2, 60.5, 51.3, 41.0, 31.2, 28.3, 27.6, 14.1; HRMS (FAB) calcd for $(M+H)^+$ $C_{23}H_{36}NO_7$: 438.2493, found 438.2495.

rac-(2S, 4R, 4aS) and (2R, 4S,

4aR)-2-N-Boc-amino-4-t-butoxycarbonyl-6-O-Boc-oxy-1,2,3,4,4a,7-hexahydronaphthalene (3aF): (using hexane/EtOAc = 10:1 to 6:1 as the eluent), 0.0466 g, 40%, white solid, mp 80–81 °C; IR (KBr, cm^{-1}) 2984, 1756, 1718, 1692, 1523; ^1H NMR (300 MHz, $CDCl_3$) δ_H 5.49 (br, 1H), 5.39 (br, 1H), 4.44 (br, 1H), 3.55 (br, 1H), 3.09–2.83 (m, 3H), 2.61–2.55 (m, 1H), 2.36–2.14 (m, 2H), 1.87–1.58 (m, 2H), 1.49 (s, 9H), 1.45 (s, 9H), 1.44 (s, 9H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ_C 173.0, 154.9, 151.2, 146.7, 132.7, 118.7, 112.5, 82.6, 80.9, 79.4, 49.9, 49.2, 41.3, 39.8, 36.6, 28.3, 28.0, 27.6; HRMS (FAB) calcd for $(M+H)^+$ $C_{25}H_{40}NO_7$: 466.2805, found 466.2805.

t-butyl 4-N-Boc-amino-5-(4'-O-Boc-phenoxy)pentanoate (5aF): (using hexane/EtOAc = 10:1 to 6:1 as the eluent), 0.0500 g, 43%, colorless oil; IR (neat, cm^{-1}) 3356, 2806, 1762, 1723, 1510, 1392; ^1H NMR (300 MHz, $CDCl_3$) δ_H 7.16 (d, J = 8.4 Hz, 2H), 7.08 (d, J = 8.4 Hz, 2H), 4.41–4.30 (m, 1H), 3.78 (br, 1H), 2.26–2.14 (m, 2H), 1.83–1.64 (m, 2H), 1.55 (s, 9H), 1.43 (s, 9H), 1.39 (s, 9H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ_C 172.1, 155.0, 151.9, 149.6, 135.3, 130.3, 121.0, 83.4, 80.3, 51.1, 49.7, 43.1, 42.1, 32.8, 28.3, 28.1, 27.6, 14.1; HRMS (FAB) calcd for $(M+H)^+$ $C_{25}H_{40}NO_7$: 466.2805, found 466.2811.

4-N-Boc-amino-5-(4'-O-Boc-phenoxy)pentanitrile (5aG): (using hexane/EtOAc = 5:1 to 2:1 as the eluent), 0.0566 g, 58%, white solid, mp 68 °C; IR (KBr, cm^{-1}) 3385, 2933, 2243, 1759, 1456; ^1H NMR (300 MHz, $CDCl_3$) δ_H 7.20–7.09 (m, 4H), 4.44 (d, J = 9.2 Hz, 1H), 3.91–3.76 (m, 1H), 2.89–2.71 (m, 2H), 2.48–2.29 (m, 2H), 1.95–1.76 (m, 2H), 1.55 (s, 9H), 1.40 (s, 9H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ_C 155.5, 152.0, 149.9, 134.6, 130.3, 121.5, 119.6, 83.7, 79.9, 51.2, 40.6, 30.3, 28.3, 27.7, 14.4; HRMS (FAB) calcd for $(M+H)^+$ $C_{21}H_{31}N_2O_5$: 391.2234, found 391.2220.

2-N-Boc-amino-4-phenyl-1-(4'-O-Boc-phenoxy)butane (5aH): (using hexane/EtOAc = 20:1 as the eluent), 0.0673 g, 61%, white solid, mp 112–113 °C; IR (KBr, cm^{-1}) 3393, 2930, 1760, 1456; ^1H NMR (300 MHz, $CDCl_3$) δ_H 7.24–7.06 (m, 9H), 4.36–4.33 (br, 1H), 3.87 (br, 1H), 2.80–2.65 (m, 4H), 1.86–1.74 (m, 2H), 1.55 (s, 9H), 1.42 (s, 9H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ_C 155.4, 152.0, 149.6, 141.7, 135.5, 130.4, 128.4, 125.9, 121.1, 83.5, 79.2, 51.3, 40.7, 36.0, 32.5, 28.4, 27.7; HRMS (FAB) calcd for $(M+H)^+$ $C_{26}H_{36}NO_5$: 442.2594, found 442.2599.

4-N-Boc-amino-5-(4'-O-Boc-phenoxy)-2-methylpentylamide (5aI): (diastereomer mixture, using hexane/EtOAc = 10:1 to 3:1 as the eluent), 0.0930 g, 88%, white solid, mp 90 °C; IR (KBr, cm^{-1}) 3420, 2933, 1757, 1684, 1457; ^1H NMR (300 MHz, $CDCl_3$) δ_H 7.16–7.08 (m, 4H), 6.98 (br, 1H), 5.56 (br, 1H), 4.50–4.45 (m, 1H), 3.99 (br, 1H), 2.84–2.61 (m, 2H), 2.39–2.34 (m, 1H), 1.97–1.76 (m, 2H), 1.55 (s, 9H), 1.38 (s, 9H), 1.12 (d, J = 6.8 Hz, 3H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ_C 179.2, 155.7, 151.9, 149.5, 135.4, 130.3, 121.1, 83.5, 79.3, 50.7, 41.6, 38.3, 37.9, 28.3, 28.2, 27.6, 18.4; HRMS (FAB) calcd for $(M+H)^+$ $C_{22}H_{35}N_2O_6$: 423.2496, found 423.2498.

rac-(2S, 4R, 4aS) and (2R, 4S, 4aR)-2-N-Boc-amino-4-carbamoyl-1,2,3,4,4a,7-hexahydronaphthalene (3cA): (using hexane/EtOAc = 10:1 to 1:3 as the eluent), 0.0175 g, 24%, white solid, mp 232–233 °C; IR (KBr, cm^{-1}) 3336, 2974, 1661, 1615, 1525; ^1H NMR (300 MHz, $CDCl_3$) δ_H 5.76–5.70 (m, 1H), 5.66–5.60 (m, 1H), 5.54–5.40 (m, 3H), 4.49 (br, 1H), 3.57–3.46 (m, 1H), 2.88–2.80 (m, 1H), 2.67–2.65 (m, 2H), 2.56–2.50 (m, 1H), 2.22–2.17 (m, 1H), 2.09–2.00 (m, 1H), 1.92–1.81 (m, 1H), 1.64–1.59 (m, 1H), 1.44 (s, 9H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ_C 175.6, 155.1, 133.2, 125.3, 120.2, 79.5, 50.6, 49.4, 41.9, 38.4, 37.1, 28.3, 26.7; HRMS (FAB) calcd for $(M+H)^+$ $C_{16}H_{25}N_2O_3$: 293.1866, found 293.1846.

rac-(2S, 4S, 4aS) and (2R, 4R, 4aR)-2-N-Boc-amino-4-carbamoyl-1,2,3,4,4a,7-hexahydronaphthalene (4cA): (using hexane/EtOAc = 10:1 to 1:3 as the eluent), 0.0132 g, 18%, white solid, mp 197–198 °C; IR (KBr, cm^{-1}) 3410, 2926, 1712, 1662, 1500; ^1H NMR (300 MHz, $CDCl_3$) δ_H 5.77–5.73 (m, 1H), 5.64–5.57 (m, 2H), 5.34–5.36 (m, 2H), 4.59 (br, 1H), 4.01 (br, 1H), 2.96–2.90 (m, 1H), 2.72 (br, 2H), 2.42–2.32 (m, 1H), 2.17–2.04 (m, 1H), 1.93–1.83 (m, 1H), 1.45 (s, 9H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ_C 176.0, 154.8, 132.9, 124.8, 121.4, 81.2, 47.5, 46.1, 39.9, 38.7, 34.6, 29.7, 28.4, 26.7; HRMS (FAB) calcd for $(M+H)^+$ $C_{16}H_{25}N_2O_3$: 293.1866, found 293.1851.

4-N-Boc-amino-5-phenylpentylamide (5cA): (using hexane/EtOAc = 10:1 to 3:1 as the eluent), 0.0241 g, 33%, white solid, mp 162 °C; IR (KBr, cm^{-1}) 3414, 3353, 2923, 1684, 1653, 1456; ^1H NMR (300 MHz, $CDCl_3$) δ_H 7.32–7.16 (m, 5H), 6.25 (br, 1H), 5.47 (br, 1H), 4.52 (d, J = 9.0 Hz, 1H), 3.91–3.85 (m, 1H), 2.80–2.74 (m, 2H), 2.30–2.23 (m, 2H), 1.94–1.59 (m, 2H), 1.39 (s, 9H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ_C 175.5, 156.3, 137.7, 129.4, 128.5, 126.6, 79.6, 51.2, 42.0, 32.8, 30.8, 28.4; HRMS (FAB) calcd for $(M+H)^+$ $C_{16}H_{25}N_2O_3$: 293.1866, found 293.1871.

rac-(2S, 4R, 4aS) and (2R, 4S, 4aR)-2-N-Boc-amino-4-t-butoxycarbonyl-1,2,3,4,4a,7-hexahydronaphthalene (3cF): (using hexane/EtOAc = 9:1 as the eluent), 0.0210 g, 24%, white solid, mp 87–88 °C; IR (KBr, cm^{-1}) 3383, 2972, 1719, 1689, 1522; ^1H NMR (300 MHz, $CDCl_3$) δ_H 5.74–5.70 (m, 1H), 5.58–5.53 (m, 2H), 4.46–4.43 (br, 1H), 3.51 (br, 1H), 2.81–2.64 (m, 4H), 2.55–2.50 (m, 1H), 2.24–2.11 (m, 2H), 1.87–1.79 (m, 1H), 1.45 (s, 9H), 1.44 (s, 9H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ_C 173.5, 154.9, 133.0, 125.3, 125.0, 120.1, 80.6, 79.3, 50.3, 49.2, 42.1, 38.6, 36.9, 28.4, 28.0, 26.6; HRMS (FAB) calcd for $(M+H)^+$ $C_{20}H_{32}NO_4$: 350.2331, found 350.2312.

t-butyl 4-N-Boc-amino-5-phenylpentanoate (5cF): (using hexane/EtOAc = 9:1 to 6:1 as the eluent), 0.0472 g, 54%, colorless oil; IR (neat, cm^{-1}) 3471, 2958, 1706, 1505, 1445; ^1H NMR (300 MHz, $CDCl_3$) δ_H 7.30–7.16 (m, 5H), 4.46–4.44 (br, 1H), 3.85–3.78 (m, 1H), 2.85–2.68 (m, 2H), 2.27 (t, J = 7.2 Hz, 2H), 1.84–1.73 (m, 1H), 1.64–1.54 (m, 1H), 1.42 (s, 9H), 1.39 (s, 9H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ_C 173.3, 155.4, 137.9, 129.4, 128.3, 126.3, 80.3, 79.0, 51.6,

41.8, 32.4, 29.7, 28.8, 28.3, 27.9; HRMS (FAB) calcd for $(M+H)^+$ $C_{20}H_{32}NO_4$: 350.2331, found 350.2316.

4-N-Boc-amino-5-phenylpentanitrile (5cG)[6a]: (using hexane/EtOAc = 10:1 to 2:1 as the eluent), 0.0494 g, 72%, white solid, mp 107 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 7.34–7.15 (m, 5H), 4.38–4.32 (m, 1H), 3.91–3.79 (m, 1H), 2.89–2.72 (m, 2H), 2.48–2.29 (m, 2H), 1.97–1.86 (m, 1H), 1.75–1.61 (m, 1H), 1.40 (s, 9H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ_C 155.4, 137.0, 129.3, 128.6, 126.8, 119.5, 79.7, 51.2, 41.3, 30.4, 28.3, 14.3; HRMS (FAB) calcd for $(M+H)^+$ $C_{16}H_{22}N_2O_2$: 275.1759, found 275.1776.

5-phenylpentanitrile (8): (using hexane/EtOAc = 10:1 to 2:1 as the eluent), 0.0115 g, 26%, white solid, mp 98 °C; IR (KBr, cm^{-1}) 3403, 2944, 1684, 1456; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 7.31–7.23 (m, 2H), 7.20–7.16 (m, 3H), 5.45 (br, 2H), 2.66–2.61 (m, 2H), 2.29–2.22 (m, 2H), 1.73–1.64 (m, 4H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ_C 175.3, 142.0, 128.5, 128.3, 125.7, 35.7, 35.6, 31.0, 25.0; HRMS (FAB) calcd for $(M+H)^+$ $C_{11}H_{16}NO$: 178.1233, found 178.1215.

4-phenoxybutylnitrile (11)[4b]: (using hexane/EtOAc = 10:1 to 2:1 as the eluent), 0.0134 g, 30%, white solid, ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 7.32–7.24 (m, 2H), 7.00–6.83 (m, 3H), 5.52 (br, 2H), 4.13–3.96 (m, 2H), 2.53–2.39 (m, 2H), 2.18–2.09 (m, 2H); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ_C 174.7, 158.7, 129.4, 120.7, 114.4, 66.60, 32.13, 24.95.

rac-(2S, 4R, 4aS) and (2R, 4S, 4aR)-2-N-(N'-Boc-Val)-amino-4-carbamoyl-6-O-Boc-oxyo-1,2,3,4,4a,7-hexahydronaphthalene (3dA): (using hexane/EtOAc = 4:1 to 1:3 as the eluent), 0.0457 g, 36%, white solid, mp 256–257 °C; IR (KBr, cm^{-1}) 3332, 2952, 1763, 1662, 1516; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 7.05 (br, 1H), 6.38 (br, 1H), 5.69 (br, 1H), 5.51–5.43 (m, 2H), 5.24–5.17 (m, 1H), 3.98–3.93 (m, 1H), 3.84 (br, 1H), 3.03 (br, 1H), 2.86 (br, 2H), 2.64–2.53 (m, 1H), 2.17–1.70 (m, 5H), 1.50 (s, 9H), 1.43 (s, 9H), 0.97–0.88 (m, 6H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ_C 175.5, 171.2, 155.9, 151.3, 146.9, 132.9, 118.7, 112.8, 83.0, 79.8, 59.8, 50.5, 47.8, 40.8, 39.8, 35.5, 31.4, 30.8, 28.3, 27.6, 19.3, 18.2; HRMS (FAB) calcd for $(M+H)^+$ $C_{26}H_{42}N_3O_7$: 508.3023, found 508.3017.

rac-(2S, 4S, 4aS) and (2R, 4R, 4aR)-2-N-(N'-Boc-Val)-amino-4-carbamoyl-6-O-Boc-oxy-1,2,3,4,4a,7-hexahydronaphthalene (4dA): (using hexane/EtOAc = 4:1 to 1:3 as the eluent), 0.00761 g, 6%, white solid, mp 114–115 °C; IR (KBr, cm^{-1}) 3373, 2916, 1745, 1667, 1539; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 6.02 (br, 1H), 5.79 (br, 1H), 5.46–5.41 (m, 2H), 5.19 (br, 1H), 5.00–4.97 (br, 1H), 4.24 (br, 1H), 3.63–3.57 (m, 1H), 3.11–3.06 (m, 1H), 2.85–2.82 (m, 2H), 2.39–2.21 (m, 2H), 2.13–1.77 (m, 4H), 1.43 (s, 9H), 1.35 (s, 9H), 0.91–0.87 (m, 6H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ_C 180.0, 170.9, 151.3, 146.3, 139.0, 132.2, 120.1, 113.2, 83.1, 80.3, 54.8, 47.0, 45.1, 39.9, 38.8, 34.0, 30.4, 28.3, 27.6, 19.3, 18.4; HRMS (FAB) calcd for $(M+H)^+$ $C_{26}H_{42}N_3O_7$: 508.3023, found 508.3011.

4-N-(N'-Boc-Val)-amino-5-(4'-O-Boc-phenoxy)pentylamide (5dA): (using hexane/EtOAc =

4:1 to 0:1 as the eluent), 0.00381 g, 3%, white solid, mp 199–200 °C; IR (KBr, cm^{-1}) 3409, 2950, 1744, 1556, 1409; ^1H NMR (300 MHz, $CDCl_3$) δ_H 7.17 (d, J = 8.7 Hz, 2H), 7.07 (d, J = 8.7 Hz, 2H), 6.36 (br, 1H), 6.00 (br, 1H), 5.37 (br, 1H), 5.00–4.97 (br, 1H), 4.23 (br, 1H), 3.86–3.64 (m, 1H), 2.83–2.74 (m, 2H), 2.26–2.13 (m, 3H), 2.00– 1.76 (m, 2H), 1.55 (s, 9H), 1.42 (s, 9H), 0.89–0.73 (m, 6H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ_C 176.7, 175.4, 156.0, 151.8, 149.9, 134.9, 130.0, 121.3, 83.5, 80.0, 60.5, 56.1, 50.2, 40.9, 32.3, 30.9, 30.3, 28.2, 27.6, 19.1, 17.7; HRMS (FAB) calcd for $(M+H)^+$ $C_{26}H_{42}N_3O_7$: 508.3023, found 508.3017.

rac-(2S, 4R, 4aS) and (2R, 4S, 4aR)-2-N-(N'-Boc-Val)-amino-4-carbonyl[ValVal(OMe)]-6-O-Boc-oxy-1,2,3,4,4a,7-hexahydronaphthalene (3dJ)): (using chloroform/acetone = 1:0 to 3:1 as the eluent), 0.0523 g, 29%, white solid, mp 244–245 °C; IR (KBr, cm^{-1}) 3381, 2940, 1753, 1643, 1547; ^1H NMR (300 MHz, $CDCl_3$) δ_H 6.63 (br, 2H), 5.51 (br, 1H), 5.35 (br, 1H), 5.17 (br, 1H), 4.50–4.46 (m, 1H), 4.30–4.25 (m, 1H), 4.00 (br, 1H), 3.84 (br, 1H), 3.71 (s, 3H), 3.06–3.02 (m, 1H), 2.83 (br, 2H), 2.63–2.57 (m, 1H), 2.24–1.87 (m, 7H), 1.47 (s, 9H), 1.43 (s, 9H), 0.86–0.99 (m, 18H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ_C 173.2, 172.0, 171.6, 171.0, 156.0, 151.1, 146.8, 133.0, 118.6, 112.4, 82.8, 79.5, 59.2, 59.0, 57.4, 51.8, 50.7, 47.5, 41.4, 40.1, 35.6, 32.0, 30.6, 30.5, 28.4, 27.6, 19.1, 18.9, 18.1, 18.0; HRMS (FAB) calcd for $(M+H)^+$ $C_{37}H_{61}N_4O_{10}$: 721.4387, found 721.4374.

rac-(2S, 4S, 4aS) and (2R, 4R, 4aR)-N-2-(N'-Boc-Val)-amino-4-carbonyl[ValVal(OMe)]-6-O-Boc-oxy-1,2,3,4,4a,7-hexahydronaphthalene (4dJ): (using chloroform/acetone = 1:0 to 3:1 as the eluent), 0.0108 g, 6%, white solid, mp 222–223 °C; IR (KBr, cm^{-1}) 3385, 2950, 1748, 1647, 1528; ^1H NMR (300 MHz, $CDCl_3$) δ_H 6.96 (br, 1H), 6.35–6.30 (m, 1H), 5.50–5.44 (m, 2H), 5.18–5.12 (m, 1H), 4.60–4.52 (m, 1H), 4.25–4.18 (m, 1H), 4.01–3.90 (m, 2H), 3.71 (s, 3H), 2.95 (br, 1H), 2.82 (br, 2H), 2.52–2.47 (m, 1H), 2.25–1.92 (m, 7H), 1.49 (s, 9H), 1.43 (s, 9H), 0.98–0.86 (m, 18H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ_C 172.1, 171.1, 170.8, 155.8, 151.5, 146.8, 132.7, 119.0, 112.7, 82.9, 79.8, 59.4, 57.0, 51.9, 50.7, 47.3, 40.7, 36.4, 31.7, 30.6, 30.3, 28.3, 27.6, 19.3, 17.8, 19.1, 19.0, 18.1; HRMS (FAB) calcd for $(M+H)^+$ $C_{37}H_{61}N_4O_{10}$: 721.4387, found 721.4380.

4-N-(N'-Boc-Val)-amino-5-(4'-O-Boc-phenoxy)-N-[ValVal(OMe)]pentylamide (5dJ): (using chloroform/acetone = 1:0 to 3:1 as the eluent), 0.0216 g, 12%, white solid, mp 201–202 °C; IR (KBr, cm^{-1}) 3376, 2936, 1757, 1523, 1423; ^1H NMR (300 MHz, $CDCl_3$) δ_H 7.40–7.37 (br, 1H), 7.20–7.16 (m, 2H), 7.07–7.02 (m, 2H), 6.70–6.55 (m, 2H), 5.13–5.10 (br, 1H), 4.58–4.54 (m, 1H), 4.29–4.16 (m, 2H), 3.83–3.69 (m, 4H), 2.79–2.70 (m, 2H), 2.22–1.83 (m, 7H), 1.54 (s, 9H), 1.43 (s, 9H), 1.00–0.74 (m, 18H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ_C 173.6, 172.6, 172.3, 171.9, 151.7, 149.6, 135.6, 130.1, 121.1, 83.4, 79.9, 60.4, 59.5, 57.1, 52.2, 50.1, 41.0, 32.2, 31.1, 30.3, 29.5, 28.3, 27.6, 19.3, 19.1, 18.9, 18.5, 18.2, 17.8; HRMS (FAB) calcd for $(M+H)^+$ $C_{37}H_{61}N_4O_{10}$: 721.4387, found 721.4377.

Supporting Information

^{1}H and ^{13}C NMR spectra for all compounds and CIF file for X-ray crystallographic analysis of **3aA**. This material is available free of charge via Internet at http://pubs.acs.org/.

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