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# Direct modification of tripeptides using photoinduced decarboxylative radical reactions

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ABSTRACT

In order to explore the applicability of photoinduced electron transfer (PET) promoted decarboxylative reactions to the direct modification of peptides, a study was performed to assess the influence of amino acid side chains on photoreactions of *N*-terminal protected tripeptides. Photoinduced decarboxylation reactions of tripeptides, which are composed of central amino acids that possess alkyl, phenyl, thioether, hydroxy, and amide containing side chains, in the presence or absence of acrylonitrile and a thiol were found to proceed smoothly to give the corresponding radical addition, H-abstraction, and substitution products. Although photoreactions of tripeptides containing central amino acids with phenol and indole (Tyr and Trp) moieties do not take place efficiently, appropriate protection of these groups enables the substrates to undergo smooth photoinduced decarboxylative reactions.



## 1. Introduction

Peptides continue to receive attention owing to their importance in the fields of biochemistry, organic chemistry, and material science.[1] A large effort in the past several decades has been given to the study of peptide nanomaterials such as nanotubes.[2] Although a Click chemistry approach has been employed to modify peptides via the formation of 1,2,3-triazole moieties,[3] only a few other methods for directly introducing functionality into peptides have been uncovered. The main reason for this limitation is that a variety of different functional groups that are present in the individual amino acids, which mandates the use of highly specific and mild reaction conditions.

We believed that photoinduced electron transfer (PET) reactions, which take place in the absence of strong bases, heating, and metal catalysts, could serve as efficient methods to modify peptides. Of particular interest in this regard are studies carried out by Griesbeck[4] and Mariano,[5] which show that PET reactions of ω-carboxylate and ω-trialkylsilyl substituted *N*-phthalimido peptides take place efficiently through radical pathways to generate cyclic peptides containing 3-hydroxyphthalimidine group. Also, a photoinduced thiol-ene click reaction has been used to modify peptides.[6]

Recently, we reported an interesting decarboxylation reaction of carboxylic acids that is promoted by the radical cation of phenanthrene (Phen), formed by single electron transfer (SET) from the excited state of Phen (Phen*) to 1,4-dicyanobenzene (DCB) (Scheme 1).[7] The alkyl radicals, produced in this process by SET from carboxylates to the Phen radical cation followed by decarboxylation of the intermediate carboxy radicals, react with a variety of reagents such as electron-deficient alkenes, oxime ethers, and thiols, to produce addition,[7c–e,g–i] reduction,[7a,f] and substitution[7b] products in high yields. For example, alkyl radicals formed by irradiation of a mixture of carboxylic acids containing catalytic amounts of Phen and DCB undergo efficient addition to electron-deficient alkenes.[7i] The results of this early effort demonstrated that this photochemical process serves as an efficient method for generating alkyl radicals from aliphatic carboxylic acids under mild conditions.[8]

This finding encouraged us to investigate PET promoted reactions of peptides that contain *C*-terminal carboxylic acid groups. Below, the results of this effort, which led to the development of a new method for modifying tripeptides, are described.

## 2. Results and discussion

### 2.1. Photoinduced decarboxylation reactions of tripeptide: influence of amino acid side chains on the efficiency of the process

In the first phase of this study, PET induced decarboxylative addition reactions of radicals, formed from *N*-Boc tripeptides **1** (*N*-

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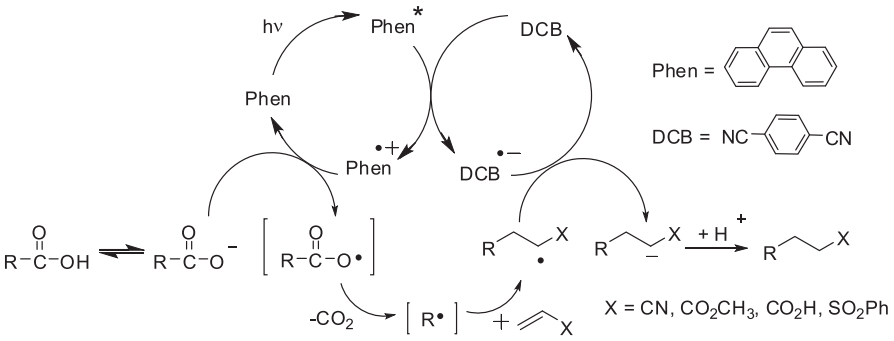
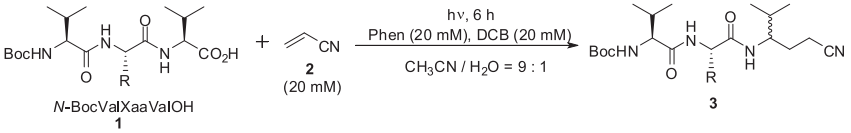


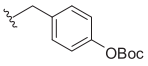
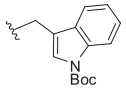
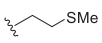
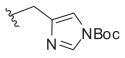
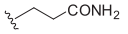
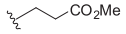
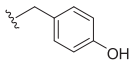
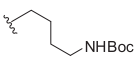
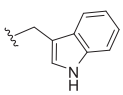
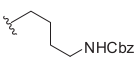

**Scheme 1.** The mechanistic pathway for PET promoted decarboxylative radical addition of carboxylic acids to alkenes.

BocValXaaValOH), which contain a variety of central amino acids (Xaa), to acrylonitrile **2** were examined in order to evaluate effect of peptide side chain on efficiencies (Table 1). The protected peptides are readily prepared starting with commercially available protected amino acids using liquid phase peptide synthetic protocols. Photoreactions of the tripeptides **1** (20 mM) were carried out by irradiating (100 W high-pressure mercury lamp through a Pyrex glass filter; $\lambda$ >280 nm) aqueous acetonitrile solutions ($CH_3CN/H_2O$=9:1) containing Phen (20 mM), DCB (20 mM) and acrylonitrile **2** (20 mM) under argon for 6 h at room temperature. In each case, the corresponding radical addition product **3** is produced as a 1:1 mixture of diastereomers. Interestingly, nearly all of the *N*-Boc tripeptides, containing central amino acids with alkyl (**1a**, Val, entry 1), phenyl (**1b**, Phe, entry 2), thioether (**1c**, Met, entry 3), hydroxy (**1d**, Ser, entry 4), and amide (**1e**, Gln, entry 5) side chains, undergo this addition reaction efficiently. In contrast, photoinduced decarboxylation of **1f** and **1g**, which possess the respective internal amino acids Tyr and Trp that contain electron rich phenol and indole moieties, do not take place (entries 6 and 7).[9] In these cases, starting materials are recovered after irradiation. A plausible reason for this result is that electron-donating arenes quench the photogenerated radical cation of Phen thus preventing PET promoted decarboxylation. As anticipated, introduction of Boc protecting groups on the phenolic hydroxy of **1f** giving **1h** and the indole nitrogen of **1g** giving **1i** enables the tripeptides to undergo efficient PET promoted radical addition to **2** (entries 8 and 9), although in the case of **1i** an uncharacterized byproduct is also formed.

**Table 1**
Photoinduced decarboxylative radical addition of tripeptides *N*-BocValXaaValOH **1** to acrylonitrile **2**[a]




*N*-BocValXaaValOH **1** (20 mM) + **2** (20 mM) → **3**

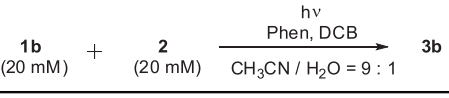
| Entry | Xaa | R | Yield of **3**[b] (%) | Entry | Xaa | R | Yield of **3**[b] (%) |
|---|---|---|---|---|---|---|---|
| 1 | **1a**, Val |  | 82 | 8 | **1h**, Tyr(Boc) |  | >99 |
| 2 | **1b**, Phe |  | 95 | 9 | **1i**, Trp(Boc) |  | 42 |
| 3 | **1c**, Met |  | 71 | 10 | **1j**, His(Boc) |  | 94 |
| 4 | **1d**, Ser |  | 88 | 11 | **1k**, Cys(Bn) |  | 73 |
| 5 | **1e**, Gln |  | 90 | 12 | **1l**, Glu(OMe) |  | 86 |
| 6 | **1f**, Tyr |  | 0 | 13 | **1m**, Lys(Boc) |  | 82 |
| 7 | **1g**, Trp |  | 0 | 14 | **1n**, Lys(Cbz) |  | 80 |

[a] The photoreactions of **1** (20 mM) were carried out in the presence of Phen (20 mM), DCB (20 mM), and acrylonitrile **2** (20 mM) using 100-W high-pressure mercury lamp under an argon atmosphere for 6 h.
[b] Isolated yields.

Similarly, *N*-BocVal(*N*-BocHis)ValOH (**1j**) containing a protected imidazole (entry 10), *N*-BocVal(BnCys)ValOH with an *S*-benzyl protected thiol (**1k**, entry 11), *N*-BocVal(GluOMe)ValOH (**1l**, entry 12) with an *O*-methyl protected carboxylate, and *N*-BocVal(*N*-Boc-Lys)ValOH (**1m**) and *N*-BocVal(*N*-CbzLys)ValOH (**1n**) with *N*-protected amines (entries 13 and 14) all participate in high yielding radical addition reactions.

In the next phase of this investigation, the effect of varying the amounts of the catalysts Phen and DCB on the efficiency of photoinduced decarboxylative radical addition of **1b** to **2** was explored (Table 2).[7i] Photoreaction of **1b** using catalytic amounts of Phen (5 mM) and DCB (5 mM) was found to produce a high yield of **3b** over a longer irradiation time (12 h) (entry 1). Addition of 1 equiv of NaOH to this photoreaction mixture leads to an acceleration (6 h) of the photoreaction giving **3b** in a similar high yield (entry 2). The observation that when the amounts of Phen and DCB are decreased to 1 mM a longer irradiation time is required to give a similar yield of the photoadduct, demonstrates that these substances function as a catalytic duo in the process. The results of additional studies show that biphenyl and 1,4-dicyanonaphthalene also act as a catalytic duo for the photoreaction of **1b** and **2** (entry 4).

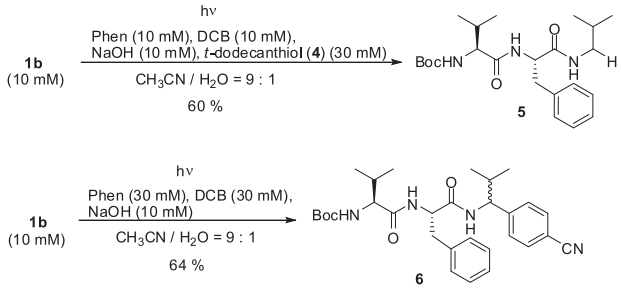
**Table 2**
Catalytic photoinduced decarboxylative radical addition of **1** to **2**[a]




| Entry | Phen (mM) | DCB (mM) | NaOH (mM) | Irradiation time (h) | Yield of **3b**[b] (%) |
|---|---|---|---|---|---|
| 1 | 5 | 5 | 0 | 12 | 94 |
| 2 | 5 | 5 | 20 | 6 | 93 |
| 3 | 1 | 1 | 20 | 24 | 74 |
| 4[c] | 1 | 1 | 20 | 24 | 50 |

[a] The photoreaction of **1b** (20 mM) was carried out in the presence of catalytic amounts of Phen and DCB.
[b] Isolated yield.
[c] Instead of Phen and DCB, biphenyl, and 1,4-dicyanonaphthalene were used.

An investigation was carried out to determine if the new PET promoted radical process could be used to promote reduction and substitution reactions of tripeptides (Scheme 2). We observed that photoreaction of tripeptide **1b** (10 mM) in the presence of *tert*-dodecanethiol (**4**) (30 mM) as a hydrogen atom source under similar conditions to those described above leads to formation of the reduction product **5** as a single stereoisomer in a moderate 60% yield.[7a,f] Photoreaction of **1b** conducted in the absence of a thiol and alkene leads to production of **6** (64%) as a 1:1 mixture of diastereomers, formed by addition of the intermediate radical to the radical anion of DCB.[7b]



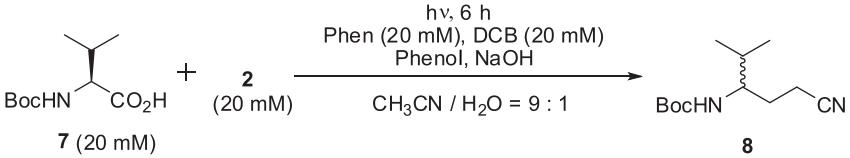

**Scheme 2.** Reduction and substitution of **1b** via photoinduced decarboxylation.

## 2.2. Effect of phenol and indole on the photoinduced decarboxylation

As mentioned above, tripeptides **1f** and **1g**, which contain electron-donating arene groups, do not undergo this PET promoted radical reaction. In order to better understand the reason for this phenomenon, we investigated the photoreaction of *N*-BocValOH **7** in the presence of phenol (Table 3) and indole (Table 4). We observed that Phen-DCB catalyzed photoreaction of **7** with **2** in the presence of 1 equiv of NaOH also generates a high yield of adduct **8** as a racemic mixture (entry 1, Table 3).[7c] The use of a small amount of phenol (2.5 mM) does not influence the efficiency of the photoreaction (entry 2), and use of a higher concentration of phenol (10 mM) leads to a significantly decrease in the yield of **8** (entry 3). When 1 equiv of phenol is present in the reaction mixture, the yield of **8** is markedly decreased (entry 4). On the other hand, the efficiency of the photoreaction in the presence of 1 equiv of *O*-Boc-phenol is not influenced (entry 5). An increase in the amount of NaOH to 2 equiv in the reaction mixture containing phenol (generating phenolate ion) significantly retards the photoreaction (entry 6).

A similar efficiency diminishing trend was observed when indole is added to the mixture containing Phen-DCB, **7**, and **2** (entries 1–4, Table 4). Also, the yield of **8** is not affected by the addition of 1 equiv of *N*-Boc-indole to the reaction mixture (entry 5). The combined results indicate that phenol, phenolate ion, and indole serve as quenchers of the PET promoted photoreaction. The respective oxidation potentials of the respective electron rich arenes, +0.62 V (vs SCE in $H_2O$, pH=7),[10] +0.35 V (vs SCE in $H_2O$, pH=12.5),[11] and +0.73 V (vs SCE in $H_2O$, pH=7)[10] are all lower than

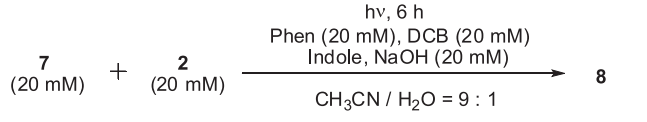
**Table 3**
Influence of phenol and phenolate ion on the photoinduced decarboxylation




| Entry | Phenol (mM) | NaOH (mM) | Yield of **8**[a] (%) | Recovery of **7**[a] (%) |
|---|---|---|---|---|
| 1 | 0 | 20 | 85 | 0 |
| 2 | 2.5 | 20 | 88 | 4 |
| 3 | 10 | 20 | 20 | 71 |
| 4 | 20 | 20 | 11 | 85 |
| 5[b] | 20 | 20 | 91 | 0 |
| 6 | 20 | 40 | 0 | 87 |

[a] Isolated yields.
[b] Instead of phenol, *O*-Boc-phenol was used.

**Table 4**
Influence of indole on the photoinduced decarboxylation




| Entry | Indole (mM) | Yield of **8**[a] (%) | Recovery of **7**[a] (%) |
|---|---|---|---|
| 1 | 20 | Trace | 92 |
| 2 | 10 | 9 | 85 |
| 3 | 5 | 58 | 32 |
| 4 | 2.5 | 70 | 28 |
| 5[b] | 20 | 88 | 0 |

[a] Isolated yields.
[b] Instead of indole, *N*-Boc-indole was used.

that of an aliphatic carboxylate ion such as hexanoate (+1.16 V vs SCE in $CH_3CN$).[12] Tyrosine and tryptophan both have oxidation potentials that are similar to those phenol and indole, respectively.[10] As a result, the rates of SET from phenol, phenolate ion, and indole to the radical cation of Phen (+1.50 V vs SCE in $CH_3CN$)[13] could be faster than that from the carboxylate ion. In this event, the presence of electron rich arenes would lead to reductive quenching of the Phen radical cation. Thus, the observation that introduction of Boc groups on the hydroxy and nitrogen of the respective phenol and indole leads to less efficient quenching is in full accord with the expected effects of these groups on arene oxidation potentials.

## 3. Conclusion

In the study described above, we found that the PET promoted decarboxylation reactions can be utilized for direct modification of appropriately protected peptides. The protected peptides are readily prepared starting with commercially available protected amino acids using solid or liquid phase peptide synthetic protocols. Photoreactions of the tripeptides utilizing the Phen–DCB dual catalytic system proceed through a pathway involving decarboxylative generation of radicals, which undergo addition, reduction, and substitution reactions. Investigations of applications of this photoreaction to peptide modification are currently in progress.

## 4. Experimental section

### 4.1. General experimental

All reagents and solvents were used as supplied commercially. $^1$H NMR spectra were recorded in $CD_3OD$ and $CDCl_3$ containing tetramethylsilane as an internal standard, and were acquired on either a 300 or a 500 MHz spectrometer. $^{13}$C NMR spectra were acquired on either a 75 or a 125 MHz spectrometer. High-resolution mass spectra were obtained using a time-of-flight mass spectrometer with a Fourier transform ion cyclotron resonance mass spectrometer with ESI positive mode. The light source was high-pressure mercury arc. Spectra data of **7** and **8** have been previously reported by us.[7c,d,j]

### 4.2. General procedure for synthesis of tripeptides 1

In order to avoid peptide solubility issues and side reaction with base, tripeptides **1** were synthesized by using three methods.

*4.2.1. Preparation of tripeptides* ***1a–d, f–g, k.*** EDC hydrochloride (1.1 equiv) and HOBt (1.2 equiv) were added to solutions of *N*-BocValOH (1.0 equiv), amino acid methyl ester hydrochlorides (Xaa=ValOMe, PheOMe, MetOMe, SerOMe, TyrOMe, TrpOMe, Csy(*S*-Bn)OMe, 1.0 equiv), and *i*-$Pr_2$NEt (1.1 equiv) in DMF at 0 °C. The mixtures were stirred for 2 h at 0 °C and overnight at room temperature, and concentrated in vacuo. The residues were dissolved in $CH_2Cl_2$, and washed with 4% $NaHCO_3$, 1 M HCl, and water. The organic layer was dried over $Na_2SO_4$ and concentrated in vacuo, giving residues that were subjected to silica gel column chromatography using hexane/AcOEt or $CH_2Cl_2$/AcOEt as eluents to give the desired protected dipeptides *N*-BocValXaaOMe (75–90%).

The dipeptides were hydrolyzed by using 1 M NaOH in MeOH until starting materials were consumed completely (by TLC monitoring). After each reaction is complete, 1 M $H_2SO_4$ was added until pH=3 and the solution was extracted with AcOEt or $CH_2Cl_2$. The organic layer was washed with $H_2O$ and brine, and dried over with $Na_2SO_4$, and concentrated in vacuo giving a residue that was subjected to silica gel column chromatography using hexane/AcOEt or $CH_2Cl_2$/AcOEt as eluents to give the desired dipeptide *N*-BocVal-XaaOH (85–99%). Similarly, the repetitive coupling–hydrolysis sequences with hydrochloride salt of ValOMe gave tripeptides *N*-BocValXaaValOH **1a–d**, **f–g**, **k** (two steps, 72–89%).

*4.2.2. N-BocValValValOH* ***1a.*** White solid, mp 131 °C; IR (KBr, $cm^{-1}$) 3327, 2967, 1646, 1526; $^1$H NMR (500 MHz, $CD_3OD$) $\delta_H$ 0.83–0.97 (m, 18H), 1.44 (s, 9H), 1.97–2.20 (m, 3H), 3.90 (d, *J*=6.7 Hz, 1H), 4.24–4.35 (m, 2H); $^{13}$C NMR (125 MHz, $CD_3OD$) $\delta_C$ 18.3, 18.6, 18.8, 19.6, 19.7, 19.8, 20.0, 28.7, 31.7, 31.8, 32.2, 58.9, 59.9, 61.7, 80.5, 157.9, 173.6, 174.4, 174.5; HRMS (FAB) calcd for $(M+H)^+$ $C_{20}H_{38}N_3O_6$: 416.2761, found 416.2715.

*4.2.3. N-BocValPheValOH* ***1b.*** White solid, mp 123–124 °C; IR (KBr, $cm^{-1}$) 3309, 3087, 1649; $^1$H NMR (500 MHz, $CD_3OD$) $\delta_H$ 0.76–0.95 (m, 12H), 1.43 (s, 9H), 1.90–1.94 (m, 1H), 2.10–2.17 (m, 1H), 2.91 (dd, *J*=13.9, 8.6 Hz, 1H), 3.12 (dd, *J*=13.9, 5.8 Hz, 1H), 3.83 (d, *J*=6.7 Hz, 1H), 4.29 (m, 1H), 4.75 (t, *J*=6.4 Hz, 1H), 7.16–7.26 (m, 5H); $^{13}$C NMR (125 MHz, $CD_3OD$) $\delta_C$ 18.3, 18.4, 19.5, 19.7, 28.7, 31.9, 32.1, 39.0, 55.5, 59.0, 61.6, 80.6, 127.7, 129.4, 129.5, 130.4, 138.2, 157.9, 173.3, 174.2, 174.3; HRMS (FAB) calcd for $(M+H)^+$ $C_{24}H_{38}N_3O_6$: 464.2760, found: 464.2777.

*4.2.4. N-BocValMetValOH* ***1c.*** White solid, mp 101–102 °C; IR (KBr, $cm^{-1}$) 3310, 2967, 1648; $^1$H NMR (500 MHz, $CD_3OD$) $\delta_H$ 0.91–1.02 (m, 12H), 1.44 (s, 9H), 1.90–2.21 (m, 7H), 2.49–2.60 (m, 2H), 3.87 (d, *J*=7.0 Hz, 1H), 4.32 (d, *J*=5.5 Hz, 1H), 4.59 (t, *J*=7.1 Hz, 1H); $^{13}$C NMR (125 MHz, $CD_3OD$) $\delta_C$ 15.2, 15.3, 18.3, 18.6, 18.7, 19.6, 19.8, 28.7, 30.7, 31.0, 31.6, 31.9, 33.1, 53.5, 53.6, 58.9, 59.0, 61.5, 80.5, 157.9, 173.6, 174.4; HRMS (FAB) calcd for $(M+H)^+$ $C_{20}H_{38}N_3O_6S$: 448.2481, found: 448.2520.

*4.2.5. N-BocValSerValOH* ***1d.*** White solid, mp 110–111 °C; IR (KBr, $cm^{-1}$) 3319, 2968, 1653; $^1$H NMR (500 MHz, $CD_3OD$) $\delta_H$ 0.91–0.98 (m, 12H), 1.43 (s, 9H), 2.04–2.08 (m, 1H), 2.16–2.21 (m, 1H), 3.74–3.83 (m, 2H), 3.91–3.95 (m, 1H), 4.34–4.37 (m, 1H), 4.50–4.57 (m, 1H); $^{13}$C NMR (125 MHz, $CD_3OD$) $\delta_C$ 18.2, 18.3, 18.4, 18.6, 19.5, 19.7, 19.8, 28.7, 31.7, 31.8, 31.9, 32.0, 56.3, 56.5, 58.9, 59.0, 61.4, 61.7, 63.0, 63.1, 80.5, 80.6, 158.0, 172.2, 174.5, 174.7; HRMS (FAB) calcd for $(M+H)^+$ $C_{18}H_{34}N_3O_7$: 404.2397, found: 404.2412.

*4.2.6. N-BocValTyrValOH* ***1f.*** Light yellow solid; mp 147–148 °C; IR (KBr, $cm^{-1}$) 3321, 2968, 1650; $^1$H NMR (500 MHz, $CD_3OD$) $\delta_H$ 0.78–0.97 (m, 12H), 1.44 (s, 9H), 1.91–1.99 (m, 1H), 2.01–2.12 (m, 1H), 2.81–2.85 (m, 1H), 3.00–3.04 (m, 1H), 3.83 (d, *J*=6.7 Hz, 1H), 4.29 (d, *J*=5.8 Hz, 1H), 4.68 (t, *J*=6.1 Hz, 1H), 6.67 (d, *J*=8.2 Hz, 2H), 7.05 (d, *J*=8.2 Hz, 2H); $^{13}$C NMR (125 MHz, $CD_3OD$) $\delta_C$ 16.8, 16.9, 18.1, 18.2, 27.2, 30.4, 30.6, 36.7, 54.3, 57.5, 60.2, 79.1, 114.7, 127.4, 129.9, 155.7, 156.4, 171.9, 172.7, 172.8; HRMS (FAB) calcd for $(M+H)^+$ $C_{24}H_{38}N_3O_7$: 480.2710, found: 480.2706.

*4.2.7. N-BocValTrpValOH* ***1g.*** Light yellow solid, mp 175–176 °C; IR (KBr, $cm^{-1}$) 3383, 2967, 1654; $^1$H NMR (500 MHz, $CD_3OD$) $\delta_H$ 0.78–0.90 (m, 12H), 1.41 (s, 9H), 1.94–1.98 (m, 1H), 2.08–2.12 (m, 1H),

3.14–3.28 (m, 2H), 3.85 (d, $J$=6.5 Hz, 1H), 4.26 (d, $J$=5.2 Hz, 1H), 4.78 (t, $J$=6.4 Hz, 1H), 7.00 (t, $J$=7.0 Hz, 1H), 7.07 (t, $J$=7.0 Hz, 1H), 7.12 (s, 1H), 7.30 (d, $J$=8.0 Hz, 1H), 7.60 (d, $J$=8.0 Hz, 1H); $^{13}$C NMR (125 MHz, $CD_3OD$) $\delta_C$ 18.3, 19.6, 19.7, 28.8, 32.1, 55.2, 59.4, 61.7, 80.7, 110.8, 112.3, 119.8, 121.2, 122.4, 124.7, 128.9, 138.1, 158.0, 173.8, 174.3; HRMS (FAB) calcd for $(M+H)^+$ $C_{26}H_{39}N_4O_6$: 503.2870, found: 503.2823.

*4.2.8. N-BocValCys(Bn)ValOH* ***1k***. White solid, mp 159–160 °C; IR (KBr, $cm^{-1}$) 3424, 3330, 2966, 1643; $^1$H NMR (500 MHz, $CD_3OD$) $\delta_H$ 0.90–0.97 (m, 12H), 1.42 (s, 9H), 2.02–2.20 (m, 2H), 2.68 (dd, $J$=13.9, 7.6 Hz, 1H), 2.87 (dd, $J$=13.9, 6.1 Hz, 1H), 3.73–3.79 (m, 2H), 3.92 (d, $J$=6.1 Hz, 1H), 4.24–4.27 (m, 1H), 4.65–4.68 (m, 1H), 7.18–7.33 (m, 5H); $^{13}$C NMR (125 MHz, $CD_3OD$) $\delta_C$ 18.3, 18.4, 18.5, 19.8, 19.9, 20.0, 28.7, 32.1, 32.3, 34.0, 34.2, 36.9, 37.1, 53.9, 60.1, 61.6, 61.7, 80.1, 128.0, 128.1, 129.4, 129.5, 130.1, 130.2, 139.4, 139.5, 157.9, 172.2, 174.4, 174.6; HRMS (FAB) calcd for $(M+H)^+$ $C_{25}H_{40}N_3O_6S$: 510.2638, found: 510.2616.

### 4.3. Preparation of tripeptides 1e, 1l, 1m, 1n

EDC hydrochloride (1.1 equiv) and HOBt (1.2 equiv) were added to the solution of *N*-BocXaaOH (Xaa=Gln, Glu(OMe), Lys(*N*-Cbz), 1.0 equiv), TsOH salt of ValOBn (1.0 equiv), and *i*-$Pr_2$NEt (1.1 equiv) in DMF at 0 °C. The mixture was stirred for 2 h at 0 °C and overnight at room temperature, and concentrated in vacuo. The residue was dissolved in $CH_2Cl_2$, and washed with 4% $NaHCO_3$, 1 M HCl, and water. The organic layer was dried over $Na_2SO_4$ and concentrated in vacuo giving a residue that was subjected to silica gel column chromatography using hexane/AcOEt or $CH_2Cl_2$/MeOH as eluents to give the desired protected dipeptide *N*-BocXaaValOBn (65–87%).

Boc group in this dipeptide was removed by using TFA in $CH_2Cl_2$ at 0 °C to room temperature until starting material was consumed completely (TLC monitoring). After reaction was complete, the mixture was evaporated to give the TFA salt of XaaValOBn. Similarly, using the repetitive peptide coupling sequence with *N*-BocValOH gave benzyl protected tripeptides *N*-BocValXaaValOBn (two steps, 64–82%). Debenzylation of the peptide was performed by treatment with 10% Pd/C and $H_2$ in MeOH (in the case of Xaa=Gln, use of MeOH and 1,4-dioxane as a solvent with heating because of difficult solubility) with TLC monitoring. After complete consumption of starting material, the mixture was filtered through Celite, and the filtrate was evaporated, and recrystallized with MeOH and diethyl ether to give **1e**, **1l**, **1n** (85–94%). In the case of **1m**, **1n** was debenzylated by 10% Pd/C and $H_2$ in MeOH and protected with Boc using $(Boc)_2O$ to give **1m** (89%).

*4.3.1. N-BocValGlnValOH* ***1e***. White solid, mp 204–205 °C; IR (KBr, $cm^{-1}$) 3320, 2968, 1649; $^1$H NMR (500 MHz, $CD_3OD$) $\delta_H$ 0.88–1.06 (m, 12H), 1.44 (s, 9H), 1.91–2.22 (m, 4H), 2.39–2.43 (m, 2H), 3.88 (d, $J$=7.1 Hz, 1H), 4.30 (d, $J$=5.5 Hz, 1H), 4.51 (t, $J$=6.9 Hz, 1H); $^{13}$C NMR (125 MHz, $CD_3OD$) $\delta_C$ 18.3, 18.5, 19.7, 19.8, 28.7, 31.3, 31.8, 31.9, 53.7, 59.4, 61.5, 80.6, 158.0, 173.5, 174.5, 175.2, 177.0; HRMS (FAB) calcd for $(M+H)^+$ $C_{20}H_{37}N_4O_7$ 445.2662, found: 445.2632.

*4.3.2. N-BocValGlu(OMe)ValOH* ***1l***. White solid, mp 104–105 °C; IR (KBr, $cm^{-1}$) 3320, 2968, 1722, 1529; $^1$H NMR (500 MHz, $CD_3OD$) $\delta_H$ 0.87–1.00 (m, 12H), 1.44 (s, 9H), 1.90–2.21 (m, 4H), 2.43–2.47 (m, 2H), 3.69 (s, 3H), 3.86 (d, $J$=7.0 Hz, 1H), 4.30 (d, $J$=5.5 Hz, 1H), 4.51 (t, $J$=6.8 Hz, 1H); $^{13}$C NMR (125 MHz, $CD_3OD$) $\delta_C$ 18.2, 18.6, 19.6, 19.8, 28.5, 28.7, 30.9, 31.7, 31.9, 52.2, 53.5, 59.1, 61.6, 80.6, 158.0, 173.4, 174.5, 174.6, 175.1; HRMS (FAB) calcd for $(M+H)^+$ $C_{21}H_{38}N_3O_8$: 460.2659, found: 460.2628.

*4.3.3. N-BocValLys(Boc)ValOH* ***1m***. White solid, mp 104–105 °C; IR (KBr, $cm^{-1}$) 3320, 3081, 1694, 1652; $^1$H NMR (500 MHz, $CD_3OD$) $\delta_H$ 0.88–0.97 (m, 12H), 1.39–1.57 (m, 22H), 1.63–1.70 (m, 1H), 1.77–1.83 (m, 1H), 1.99–2.04 (m, 1H), 2.14–2.21 (m, 1H), 3.02 (t, $J$=6.7 Hz, 2H), 3.89 (d, $J$=6.7 Hz, 1H), 4.30–4.43 (m, 1H), 4.45 (dd, $J$=13.7, 7.6 Hz, 1H); $^{13}$C NMR (125 MHz, $CD_3OD$) $\delta_C$ 14.5, 18.3, 18.4, 18.5, 19.6, 19.7, 19.9, 23.7, 24.0, 28.7, 28.8, 30.5, 31.7, 31.8, 32.0, 32.7, 32.9, 41.2, 54.3, 58.8, 58.9, 61.4, 79.8, 80.5, 157.9, 158.5, 174.1, 174.3, 174.5; HRMS (FAB) calcd for $(M+H)^+$ $C_{26}H_{49}N_4O_8$: 545.3550, found 545.3503.

*4.3.4. N-BocValLys(Cbz)ValOH* ***1n***. White solid, mp 165–166 °C; IR (KBr, $cm^{-1}$) 3424, 3327, 2965, 1690, 1645; $^1$H NMR (500 MHz, $CD_3OD$) $\delta_H$ 0.89–0.95 (m, 12H), 1.38–1.52 (m, 13H), 1.66–1.69 (m, 1H), 1.78–1.79 (m, 1H), 1.99–2.02 (m, 1H), 2.14–2.18 (m, 1H), 3.10 (t, $J$=6.8 Hz, 2H), 3.89 (d, $J$=6.7 Hz, 1H), 4.25 (d, $J$=5.5 Hz, 1H), 4.45 (m, 1H), 5.06 (s, 2H), 7.28–7.34 (m, 5H); $^{13}$C NMR (125 MHz, $CD_3OD$) $\delta_C$ 18.4, 18.5, 19.9, 23.9, 28.7, 30.4, 32.0, 32.8, 41.6, 54.4, 59.8, 61.5, 67.4, 80.6, 128.8, 128.9, 129.4, 138.4, 158.0, 158.9, 173.9, 174.4, 176.4; HRMS (FAB) calcd for $(M+H)^+$ $C_{29}H_{47}N_4O_8$: 579.3394, found 579.3385.

### 4.4. Preparation of tripeptides 1h–j

In a similar manner, reaction of *N*-BocValXaaOH (Xaa=Tyr, Trp, His, 1.0 equiv) with TsOH salt of ValOBn (1.0 equiv) gave the desired protected tripeptide *N*-BocValXaaValOBn (60–82%). $(Boc)_2O$ (1.2 equiv) was added to a $CH_2Cl_2$ solution of tripeptide, DMAP (0.1 equiv), and *i*-$Pr_2$NEt (1.2 equiv) at 0 °C. The mixture was stirred at room temperature (TLC monitoring). After reaction was complete, the mixture was concentrated in vacuo. AcOEt was added to the residue, which was washed with 4% $NaHCO_3$, 1 M HCl, and water. The organic layer was dried over $Na_2SO_4$ and concentrated in vacuo giving a residue that was subjected to silica gel column chromatography using $CH_2Cl_2$/AcOEt or $CH_2Cl_2$/MeOH as eluents to give the desired protected dipeptide *N*-BocValXaa(-Boc)ValOBn (63–81%). Debenzylation (see above) using 10% Pd/C and $H_2$ and recrystallization gave tripeptides **1h**–**j**, respectively (75–95%).

*4.4.1. N-BocValTyr(Boc)ValOH* ***1h***. White solid, mp 134–135 °C; IR (KBr, $cm^{-1}$) 3421, 2971, 1734, 1640; $^1$H NMR (500 MHz, $CD_3OD$) $\delta_H$ 0.79–0.93 (m, 12H), 1.39 (s, 9H), 1.61 (s, 9H), 1.93–1.97 (m, 1H), 2.12–2.16 (m, 1H), 3.06–3.22 (m, 2H), 3.84 (d, $J$=6.7 Hz, 1H), 4.30 (d, $J$=5.5 Hz, 1H), 7.19–7.28 (m, 2H), 7.62–7.64 (m, 1H), 8.06–8.07 (m, 1H); $^{13}$C NMR (125 MHz, $CD_3OD$) $\delta_C$ 18.3, 18.4, 19.6, 19.7, 28.5, 28.7, 31.9, 32.0, 54.1, 59.1, 61.6, 80.6, 84.7, 116.0, 117.1, 120.1, 123.6, 125.4, 131.8, 136.9, 150.9, 157.8, 173.3, 174.3, 174.4; HRMS (FAB) calcd for $(M+H)^+$ $C_{29}H_{46}N_3O_9$: 580.3234, found: 580.3215.

*4.4.2. N-BocValTrp(Boc)ValOH* ***1i***. White solid, mp 162–163 °C; IR (KBr, $cm^{-1}$) 3413, 3330, 2971, 1734, 1645; $^1$H NMR (500 MHz, $CDCl_3$) $\delta_H$ 0.81–0.89 (m, 12H), 1.37 (s, 9H), 1.63 (s, 9H), 2.08–2.19 (m, 2H), 3.11 (dd, $J$=13.9, 6.7 Hz, 1H), 3.26 (dd, $J$=13.9, 5.8 Hz, 1H), 4.02–4.04 (m, 1H), 4.37–4.39 (m, 1H), 4.85–4.89 (m, 1H), 5.05 (d, $J$=4.9 Hz, 1H), 6.81 (d, $J$=4.9 Hz, 1H), 7.21–7.31 (m, 3H), 7.50 (s, 1H), 7.61 (d, $J$=7.6 Hz, 1H), 8.10 (br, 1H); $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta_C$ 17.5, 17.8, 18.8, 19.2, 27.8, 30.6, 30.8, 53.3, 57.9, 59.9, 80.3, 83.7, 115.3, 119.0, 122.7, 124.5, 124.6, 130.2, 135.4, 149.6, 156.0, 171.1, 172.0, 173.6; HRMS (FAB) calcd for $(M+H)^+$ $C_{31}H_{47}N_4O_8$: 603.3394, found: 603.3394.

*4.4.3. N-BocValHis(Boc)ValOH* ***1j***. White solid, mp 165 °C; IR (KBr, $cm^{-1}$) 3326, 2971, 1654; $^1$H NMR (500 MHz, $CDCl_3$) $\delta_H$ 0.82–1.00 (m, 12H), 1.42 (s, 9H), 1.60 (s, 9H), 2.03–2.09 (m, 1H), 2.24–2.30 (m, 1H), 2.75–2.79 (m, 1H), 3.19–3.22 (m, 1H), 3.95–3.98 (m, 1H), 4.51–4.53 (m, 1H), 4.92–4.95 (m, 1H), 5.13 (d, $J$=8.2 Hz, 1H), 7.19 (s, 1H), 7.90 (m, 1H), 8.08 (s, 1H); $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta_C$ 17.4, 17.9, 18.6, 19.2, 27.8, 28.3, 31.0, 31.3, 31.4, 52.9, 57.9, 59.6, 79.7, 86.3,

115.4, 136.8, 138.0, 146.2, 155.8, 171.1, 171.4, 174.6; HRMS (FAB) calcd for $(M+H)^+$ $C_{26}H_{44}N_5O_8$: 554.3190, found: 554.3172.

### 4.5. General procedure for photoreaction of tripeptide 1

An aqueous $CH_3CN$ solution ($CH_3CN$ 36 ml, $H_2O$ 4 ml) of tripeptide **1** (20 mM), acrylonitrile **2** (0.052 ml, 20 mM), Phen (143 mg, 20 mM), and DCB (103 mg, 20 mM) in Pyrex vessels (18 mm×180 mm) was purged with argon for 10 min. The mixture was irradiated with 100 W high-pressure mercury lamp for 6 h. Removal of $CH_3CN$ gave an aqueous solution that was extracted with EtOAc, dried over $Na_2SO_4$, and concentrated in vacuo, giving a residue that was subjected to silica gel column chromatography using $CH_2Cl_2$/AcOEt or $CH_2Cl_2$/MeOH as eluents to give adduct **3**. Other photoreactions such as reduction and substitution were also performed by using a similar procedure.

*4.5.1. Procedure for catalytic photoreactions of **1b** with **2**.* An aqueous $CH_3CN$ solution ($CH_3CN$ 13.5 ml, $H_2O$ 1.5 ml) of tripeptide **1b** (138 mg, 20 mM), acrylonitrile **2** (0.02 ml, 20 mM), Phen (13.4 mg, 5 mM or 3 mg, 1 mM), and DCB (10 mg, 5 mM or 2 mg, 1 mM) in Pyrex vessels (18 mm×180 mm) was purged with argon for 10 min. Procedure for photoreaction and purification of **3b** is the same as the above mentioned method.

*4.5.2. Compound **3a** (1:1 mixture of diastereomers).* White solid, mp 198–200 °C; IR (KBr, $cm^{-1}$) 3443, 3330, 2964, 2248, 1637; $^1H$ NMR (500 MHz, $CD_3OD$) $\delta_H$ 0.85–1.00 (m, 18H), 1.42 (s, 9H), 1.66–1.78 (m, 2H), 1.90–2.07 (m, 3H), 2.33–2.46 (m, 2H), 3.72–3.75 (m, 1H), 3.86–3.89 (m, 1H), 4.07–4.13 (m, 1H); $^{13}C$ NMR (125.7 MHz, $CD_3OD$) $\delta_C$ 14.8, 14.9, 18.6, 18.7, 18.8, 19.0, 19.5, 19.6, 19.8, 19.9, 20.0, 28.6, 28.7, 29.2, 31.5, 31.6, 31.7, 31.8, 33.2, 33.3, 55.1, 60.7, 60.8, 61.6, 61.9, 80.6, 80.7, 120.8, 120.9, 158.0, 158.1, 173.6, 173.7, 174.4, 174.6; HRMS (FAB) calcd for $(M+H)^+$ $C_{22}H_{41}N_4O_4$: 425.3128, found: 425.3145.

*4.5.3. Compound **3b** (1:1 mixture of diastereomers).* White solid, mp 178–180 °C; IR (KBr, $cm^{-1}$) 3342, 3314, 2966, 2242, 1642; $^1H$ NMR (500 MHz, $CDCl_3$) $\delta_H$ 0.78–1.00 (m, 12H), 1.38 (s, 9H), 1.54–1.90 (m, 4H), 2.08–2.22 (m, 2H), 3.07–3.28 (m, 2H), 3.69–3.83 (m, 2H), 4.59–4.75 (m, 1H), 6.42–6.51 (m, 1H), 7.19–7.33 (m, 5H); $^{13}C$ NMR (125 MHz, $CDCl_3$) $\delta_C$ 14.0, 14.5, 17.2, 17.4, 17.9, 18.6, 18.9, 19.0, 19.2, 19.3, 29.8, 30.1, 31.9, 32.2, 37.0, 37.5, 54.0, 54.1, 54.6, 60.8, 61.0, 80.6, 80.8, 119.9, 120.0, 127.3, 127.4, 128.9, 129.0, 129.2, 136.3, 136.5, 156.4, 156.6, 170.6, 170.7, 170.8, 171.2, 171.5; HRMS (FAB) calcd for $(M+H)^+$ $C_{26}H_{41}N_4O_4$: 473.3128, found: 473.3109.

*4.5.4. Compound **3c** (1:1 mixture of diastereomers).* White solid, mp 139–141 °C; IR (KBr, $cm^{-1}$) 3306, 2966, 2247, 1642; $^1H$ NMR (500 MHz, $CD_3OD$) $\delta_H$ 0.87–0.97 (m, 12H), 1.45 (s, 9H), 1.70–1.76 (m, 2H), 1.91–2.11 (m, 5H), 2.36–2.57 (m, 4H), 3.71–3.85 (m, 2H), 4.40–4.45 (m, 1H), $^{13}C$ NMR (125 MHz, $CD_3OD$) $\delta_C$ 14.7, 14.8, 15.2, 18.5, 18.6, 18.9, 19.6, 19.7, 19.8, 28.8, 29.4, 31.1, 31.2, 31.6, 31.8, 32.5, 33.3, 33.4, 53.9, 54.2, 54.3, 55.2, 55.3, 55.4, 61.7, 62.1, 80.7, 80.8, 120.9, 121.0, 158.2, 158.3, 173.9, 174.6; HRMS (FAB) calcd for $(M+H)^+$ $C_{22}H_{41}N_4O_4S$: 457.2849, found: 457.2815.

*4.5.5. Compound **3d** (1:1 mixture of diastereomers).* White solid, mp 105–106 °C; IR (KBr, $cm^{-1}$) 3327, 3083, 2248, 1646; $^1H$ NMR (500 MHz, $CD_3OD$) $\delta_H$ 0.88–1.00 (m, 12H), 1.42 (s, 9H), 1.69–1.77 (m, 2H), 1.92–2.10 (m, 2H), 2.36–2.51 (m, 2H), 3.71–3.87 (m, 4H), 4.32–4.39 (m, 1H); $^{13}C$ NMR (125 MHz, $CD_3OD$) $\delta_C$ 14.4, 14.6, 14.7, 14.8, 15.5, 15.6, 18. 3, 18.4, 18.6, 18.7, 18.8, 19.0, 19.6, 19.7, 19.8, 28.8, 29.3, 29.3, 29.4, 29.6, 31.5, 32.7, 55.4, 55.6, 56.9, 57.1, 62.1, 62.7, 80.7, 80.9, 121.1, 121.2, 158.0, 158.5, 172.5, 172.6, 174.4, 174.5, 174.8; HRMS (FAB) calcd for $(M+H)^+$ $C_{20}H_{37}N_4O_5$: 413.2764, found: 413.2759.

*4.5.6. Compound **3e** (1:1 mixture of diastereomers).* White solid, mp 213 °C; IR (KBr, $cm^{-1}$) 3428, 3293, 3073, 2965, 2248, 1636; $^1H$ NMR (300 MHz, $CD_3OD$) $\delta_H$ 0.89–0.98 (m, 12H), 1.45 (s, 9H), 1.66–1.79 (m, 2H), 1.89–2.09 (m, 4H), 2.11–2.50 (m, 4H), 3.67–3.87 (m, 2H), 4.27–4.31 (m, 1H), $^{13}C$ NMR (75 MHz, $CD_3OD$) $\delta_C$ 14.8, 18.5, 18.6, 18.9, 19.6, 19.7, 19.8, 28.4, 28.8, 28.9, 29.4, 31.6, 31.8, 32.6, 33.4, 33.5, 54.8, 55.2, 55.4, 61.8, 62.4, 80.7, 80.8, 120.9, 121.0, 173.9, 174.7, 174.8, 177.7, 177.9; HRMS (FAB) calcd for $(M+H)^+$ $C_{22}H_{40}N_5O_5$: 454.3029, found: 454.3029.

*4.5.7. Compound **3h** (1:1 mixture of diastereomers).* White solid, mp 136–138 °C; IR (KBr, $cm^{-1}$) 3326, 2966, 2933, 2248, 1761, 1646; $^1H$ NMR (500 MHz, $CDCl_3$) $\delta_H$ 0.74–0.92 (m, 12H), 1.40–1.89 (m, 21H), 2.11–2.24 (m, 3H), 3.08–3.19 (m, 2H), 3.71–3.81 (m, 2H), 4.57–4.75 (m, 1H), 7.10–7.23 (m, 4H); $^{13}C$ NMR (125 MHz, $CDCl_3$) $\delta_C$ 14.0, 14.1, 14.6, 17.5, 18.0, 18.9, 19.0, 19.2, 19.3, 27.7, 28.0, 28.1, 28.2, 28.3, 29.9, 30.1, 31.9, 32.2, 36.5, 36.9, 54.1, 54.2, 54.6, 60.8, 61.0, 80.7, 80.8, 83.5, 83.6, 119.8, 120.0, 121.7, 121.8, 130.0, 130.1, 133.8, 134.1, 150.2, 150.3, 151.6, 151.7, 156.4, 156.6, 170.6, 170.7, 171.4; HRMS (FAB) calcd for $(M+H)^+$ $C_{31}H_{49}N_4O_7$: 589.3601, found: 589.3581.

*4.5.8. Compound **3i** (1:1 mixture of diastereomers).* White solid, mp 134–136 °C; IR (KBr, $cm^{-1}$) 3314, 2969, 2248, 1735, 1644; $^1H$ NMR (500 MHz, $CD_3OD$) $\delta_H$ 0.59–0.62 (m, 3H), 0.81–0.97 (m, 9H), 1.41 (s, 9H), 1.59–1.75 (m, 11H), 1.88–2.04 (m, 2H), 2.29–2.37 (m, 2H), 3.20–3.30 (m, 2H), 3.56–3.68 (m, 1H), 3.83–3.85 (m, 1H), 4.62–4.65 (m, 1H), 7.24–7.31 (m, 2H), 7.48–7.53 (m, 1H), 7.65–7.69 (m, 1H), 8.10–8.11 (m, 1H); $^{13}C$ NMR (125 MHz, $CD_3OD$) $\delta_C$ 14.1, 14.7, 18.3, 18.4, 18.9, 19.0, 19.5, 19.6, 28.0, 28.1, 28.4, 28.5, 28.6, 28.7, 31.9, 33.0, 33.3, 55.1, 55.2, 55.3, 61.7, 61.8, 80.7, 84.8, 85.0, 116.2, 116.3, 116.9, 117.1, 120.2, 120.3, 120.7, 121.0, 123.8, 123.9, 125.5, 125.6, 125.7, 131.4, 136.8, 136.9, 150.8, 158.2, 173.2, 173.3, 173.4, 174.2, 174.3; HRMS (FAB) calcd for $(M+H)^+$ $C_{33}H_{50}N_5O_6$: 612.3761, found: 612.3752.

*4.5.9. Compound **3j** (1:1 mixture of diastereomers).* Light yellow solid, mp 154–157 °C; IR (KBr, $cm^{-1}$) 3289, 2969, 2246, 1757, 1646; $^1H$ NMR (500 MHz, $CDCl_3$) $\delta_H$ 0.55–1.06 (m, 12H), 1.40–2.27 (m, 24H), 2.83–2.87 (m, 1H), 3.23–3.27 (m, 1H), 3.62–3.63 (m, 1H), 3.83–3.88 (m, 1H), 4.60–4.63 (m, 1H), 4.96 (d, $J$=3.95 Hz, 1H), 7.17–7.21 (m, 1H), 7.99–8.01 (m, 1H); $^{13}C$ NMR (125 MHz, $CDCl_3$) $\delta_C$ 14.1, 17.4, 17.6, 18.3, 18.9, 19.3, 19.5, 27.8, 27.9, 28.0, 28.3, 28.4, 28.5, 28.8, 29.9. 31.2, 31,8, 32.1, 32.4, 53.2, 54.0, 54.2, 61.3, 61.5, 80.6, 81.3, 85.9, 86.4, 115.1, 115.2, 119.5, 120.2, 136.7, 139.1, 139.4, 146.6, 146.7, 156.9, 170.7, 170.8, 171.6; HRMS (FAB) calcd for $(M+H)^+$ $C_{28}H_{47}N_6O_6$: 563.3557, found: 563.3533.

*4.5.10. Compound **3k** (1:1 mixture of diastereomers).* White solid, mp 150–152 °C; IR (KBr, $cm^{-1}$) 3429, 3318, 2965, 2247, 1644; $^1H$ NMR (500 MHz, $CD_3OD$) $\delta_H$ 0.87–0.98 (m, 12H), 1.44 (s, 9H), 1.73–1.78 (m, 2H), 1.94–2.03 (m, 2H), 2.37–2.88 (m, 4H), 3.70–3.81 (m, 4H), 4.46–4.49 (m, 1H), 7.21–7.34 (m, 5H); $^{13}C$ NMR (125 MHz, $CD_3OD$) $\delta_C$ 14.7, 14.8, 14.9, 18.5, 18.6, 18.8, 19.7, 28.7, 29.3, 31.9, 33.4, 33.5, 36.9, 54.2, 54.4, 55.4, 55.5, 61.9, 80.8, 121.0, 128.1, 129.6, 130.2, 139.4, 158.2, 172.6, 172.8, 174.2; HRMS (FAB) calcd for $(M+H)^+$ $C_{27}H_{43}N_4O_4S$: 519.3005, found: 519.2986.

*4.5.11. Compound **3l** (1:1 mixture of diastereomers).* White solid, mp 159 °C; IR (KBr, $cm^{-1}$) 3317, 2964, 2248, 1740, 1644; $^1H$ NMR (500 MHz, $CD_3OD$) $\delta_H$ 0.89–1.00 (m, 12H), 1.45 (s, 9H), 1.67–2.15 (m, 6H), 2.36–2.49 (m, 4H), 3.66–3.85 (m, 5H), 4.29–4.33 (m, 1H); $^{13}C$ NMR (125 MHz, $CD_3OD$) $\delta_C$ 14.7, 14.8, 18.5, 18.6, 18.8, 19.5, 19.6, 19.7, 19.8, 28.0, 28.1, 28.7, 28.8, 29.3, 29.4, 31.0, 31.1, 31.6, 31.8, 33.3, 33.4, 52.2, 52.3, 54.3, 54.4, 54.5, 55.1, 55.2, 55.3, 55.4, 61.7, 62.1, 80.6, 80.7,

120.9, 121.0, 158.1, 158.3, 173.6, 173.7, 173.8, 174.6, 174.9, 175.1; HRMS (FAB) calcd for $(M+H)^+$ $C_{23}H_{41}N_4O_6$: 469.3026, found: 469.3016.

*4.5.12. Compound* ***3m*** *(1:1 mixture of diastereomers).* White solid, mp 140–142 °C; IR (KBr, $cm^{-1}$) 3424, 2967, 2246, 1689, 1642; $^1H$ NMR (500 MHz, $CD_3OD$) $\delta_H$ 0.88–0.96 (m, 12H), 1.39–1.51 (m, 22H), 1.64–2.05 (m, 6H), 2.32–2.51 (m, 2H), 3.02 (t, *J*=6.5 Hz, 1H), 3.68–3.74 (m, 1H), 3.83–3.87 (m, 1H), 4.23–4.29 (m, 1H); $^{13}C$ NMR (125 MHz, $CD_3OD$) $\delta_C$ 14.8, 14.9, 18.6, 18.7, 18.8, 19.6, 19.7, 19.8, 24.2, 24.3, 28.7, 28.8, 29.4, 30.4, 31.8, 32.0, 32.6, 32.7, 33.3, 33.4, 41.1, 48.5, 48.7, 48.9, 49.0, 49.2, 49.4, 49.5, 55.1, 55.3, 61.5, 61.9, 79.8, 80.6, 80.7, 120.9, 121.0, 158.1, 158.2, 158.5, 174.4, 174.5; HRMS (FAB) calcd for $(M+H)^+$ $C_{28}H_{52}N_5O_6$: 554.3918, found: 554.3899.

*4.5.13. Compound* ***3n*** *(1:1 mixture of diastereomers).* White solid, mp 146–148 °C; IR (KBr, $cm^{-1}$) 3327, 2965, 2248, 1696, 1641; $^1H$ NMR (500 MHz, $CD_3OD$) $\delta_H$ 0.88–0.96 (m, 12H), 1.39–1.55 (m, 13H), 1.66–2.05 (m, 6H), 2.32–2.47 (m, 2H), 3.11 (t, *J*=6.1 Hz, 2H), 3.67–3.74 (m, 1H), 3.83–3.88 (m, 1H), 4.23–4.29 (m, 1H), 5.05–5.06 (m, 2H), 7.28–7.34 (m, 5H); $^{13}C$ NMR (125 MHz, $CD_3OD$) $\delta_C$ 14.7, 14.9, 18.4, 18.5, 18.7, 18.8, 19.6, 19.7, 19.8, 24.1, 24.2, 28.7, 28.8, 29.4, 30.4, 31.8, 32.0, 32.5, 32.6, 33.3, 33.4, 41.4, 55.1, 55.2, 61.4, 61.9, 67.3, 80.6, 80.7, 120.9, 121.0, 128.8, 128.9, 129.4, 138.3, 138.4, 158.0, 158.2, 158.9, 174.3, 174.4, 174.5; HRMS (FAB) calcd for $(M+H)^+$ $C_{31}H_{50}N_5O_6$: 588.3761, found 588.3712.

*4.5.14. Compound* ***5***. White solid, mp 177 °C; IR (KBr, $cm^{-1}$) 3309, 3087, 1686, 1640; $^1H$ NMR (300 MHz, $CD_3OD$) $\delta_H$ 0.77–0.84 (m, 12H), 1.42 (s, 9H), 1.63–1.72 (m, 1H), 1.90–1.97 (m, 1H), 2.78–2.87 (m, 4H), 3.80 (d, *J*=6.6 Hz, 1H), 4.61 (t, *J*=7.5 Hz, 1H), 7.15–7.28 (m, 5H); $^{13}C$ NMR (75 MHz, $CD_3OD$) $\delta_C$ 18.5, 19.6, 20.5, 38.9, 56.0, 62.0, 80.7, 127.8, 129.5, 130.3, 138.3, 158.2, 173.0, 174.1; HRMS (FAB) calcd for $(M+H)^+$ $C_{23}H_{38}N_3O_4$: 420.2862, found 420.2885.

*4.5.15. Compound* ***6*** *(1:1 mixture of diastereomers).* White solid, mp 136 °C; IR (KBr, $cm^{-1}$) 3305, 2966, 2229, 1646; $^1H$ NMR (300 MHz, $CDCl_3$) $\delta_H$ 0.69–0.94 (m, 12H), 1.36–1.63 (m, 9H), 1.91–2.22 (m, 2H), 3.00–3.16 (m, 2H), 3.65–3.90 (m, 1H), 4.62–4.71 (m, 2H), 7.12–7.33 (m, 7H), 7.54–7.60 (m, 2H); $^{13}C$ NMR (75 MHz, $CD_3OD$) $\delta_C$ 18.4, 18.5, 18.6, 19.2, 19.4, 19.5, 19.7, 20.1, 20.2, 28.7, 33.8, 34.1, 34.2, 55.9, 56.0, 56.1, 60.8, 61.2, 61.6, 111.6, 111.7, 119.7, 127.7, 127.8, 127.9, 129.3, 129.4, 129.5, 129.6, 130.2, 130.3, 130.4, 133.2, 138.1, 148.7, 149.1, 158.0, 172.6, 174.1; HRMS (FAB) calcd for $(M+H)^+$ $C_{30}H_{41}N_4O_4$: 521.3128, found 521.3138.

## Supplementary data

$^1H$ and $^{13}C$ NMR spectra data for all new compounds. This material is available free of charge via internet. Supplementary data associated with this article can be found in the online version, at http://dx.doi.org/10.1016/j.tet.2014.12.075.

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