JOC The Journal of Organic Chemistry

A Strategy for O-Alkylation of Serine and Threonine from Serinyl and Threoninyl Acetic Acids by Photoinduced Decarboxylative Radical Reactions: Connection between Serine/Threonine and Carbohydrates/Amino Acids at the Side Chain

Takashi Yamamoto, Tomoya Iwasaki, Toshio Morita, and Yasuharu Yoshimi

J. Org. Chem., **Just Accepted Manuscript** • DOI: 10.1021/acs.joc.8b00061 • Publication Date (Web): 09 Mar 2018

Just Accepted

ACS Publications

is published by the American Chemical Society. 1155 Sixteenth Street N.W., Washington, DC 20036

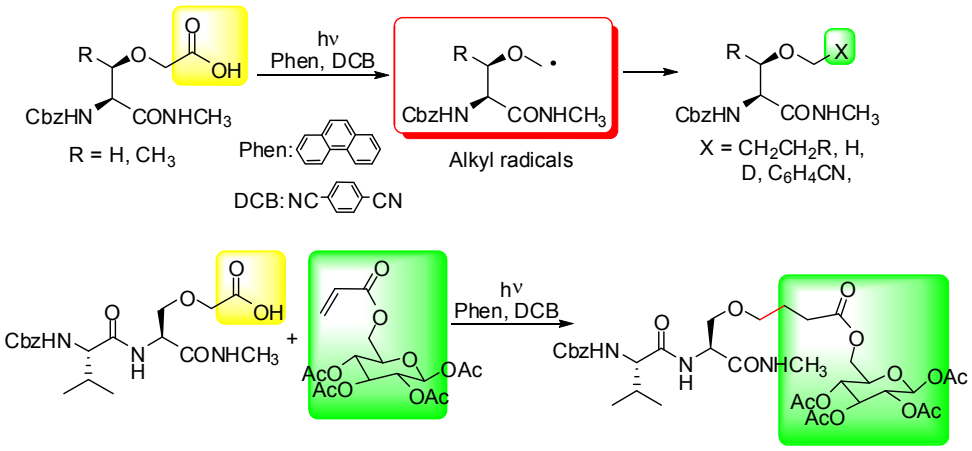
A Strategy for *O*-Alkylation of Serine and Threonine from Serinyl and Threoninyl Acetic Acids by Photoinduced Decarboxylative Radical Reactions: Connection between Serine/Threonine and Carbohydrates/Amino Acids at the Side Chain

Takashi Yamamoto, Tomoya Iwasaki, 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

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

Table of Contents



Abstract

O-Alkylations of serine and threonine derivatives at the hydroxy group were achieved using photoinduced decarboxylative radical reactions of serinyl and threoninyl acetic acids with an organic photocatalyst without racemization under mild conditions. Photoinduced decarboxylative radical additions of serinyl and threoninyl acetic acids to electron-deficient

alkenes provided linked serine and threonine with carbohydrates and amino acids at the side chain. In addition, *O*-methylations containing deuterium and *O*-benzylation of serine were performed under similar photochemical conditions.

Introduction

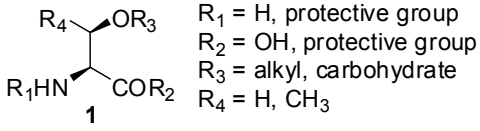
O-Alkylated-serine and -threonine **1** have high bioactivities[1] and are used as precursors for synthesis of high-value designer peptides[2] (Scheme 1a). Therefore, *O*-alkylations of serine and threonine at the hydroxy group are important processes for the preparation of modified serine and threonine. In particular, connections (*O*-alkylations) of serine and threonine with carbohydrates at the hydroxy group provide glyco-amino acids and -peptides, which are of pharmaceutical interest in many areas, including juvenile human growth hormone and tissue plasminogen activator studies.[3] A large effort in the past several decades has been devoted to the study of introducing alkyl groups at the hydroxy group in serine and threonine; however, the reactant is limited to high reactive electrophiles such as methyl iodide, allyl bromide, and benzyl bromide.[4] When the usual electrophile, such as alkyl halide, is used, the formation of undesired products is observed. In the case of serine, the alkoxide formed by the reaction with a base does not attack alkyl halide, but rather intramolecularly attacks to an *N*-protecting group such as Boc (R = *t*-Bu) and Cbz (R = Bn) groups (Scheme 1b). This primarily yields an

oxazolidinone derivative **2**.[5] Furthermore, the hindering alkoxide of threonine leads to the formation of the corresponding oxazolidinone **3** and dehydrothreonine **4** via proton abstraction at the α-position by the alkoxide (Scheme 1c).[6] Thus, a method for the preparation of alkylated-serine and –threonine without racemization and hydrolysis under mild conditions is a desirable goal.

Recently, we reported a general method for generating alkyl radicals from aliphatic carboxylic acids via decarboxylation by using organic photoredox catalyst such as phenanthrene (Phen) and 1,4-dicyanobenzene (DCB) (Scheme 2).[7] Decarboxylative radical reactions of carboxylic acids have recently attracted increasing attention as a synthetic method, because they offer several advantages, for example, carboxylic acids are easy to store and handle, and decarboxylation releases only CO_2, which is nonflammable, nontoxic, and easily removed from the reaction medium.[8] The process is initiated by photoinduced electron transfer from Phen to DCB, generating the radical cation of Phen, which oxidizes the carboxylate ions to form carboxy radicals. Carboxy radicals smoothly decarboxylate to generate the corresponding alkyl radicals. The generated alkyl radicals reacted with a variety of reagents such as electron-deficient alkenes, oxime ethers, thiols, and radical anions of dicyanobenzenes to provide the respective addition,[7d,f,g] reduction,[7b,e] and substitution[7c] products in high yields. This finding encouraged us to apply photoinduced decarboxylation to *O*-alkylation of serine and threonine employing

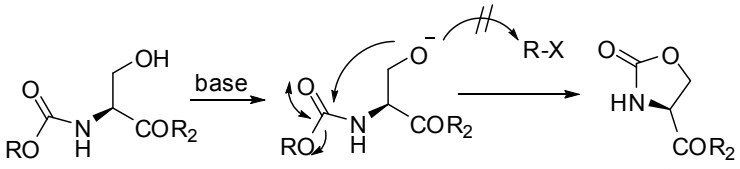
serinyl and threoninyl acetic acids **5** as a substrate (Scheme 1d). The results of this effort, which led to a facile access to introduce alkyl group in serine and threonine without racemization through the formation of alkyl radicals, are described below.

a. *O*-Alkylated serine and threonine



1

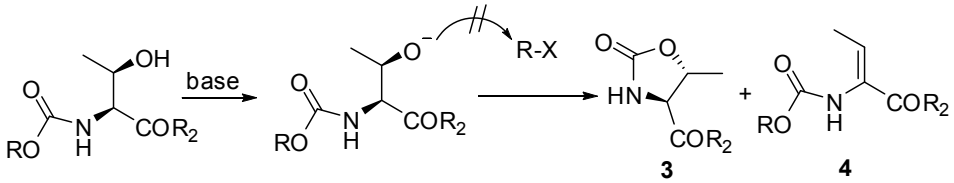
b. *O*-Alkylation of serine with usual alkyl halide



R = *t*-Bu or Bn

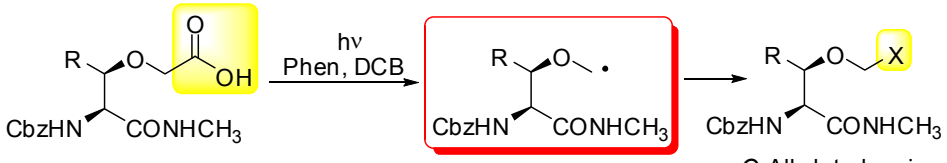
2

c. *O*-Alkylation of threonine with usual alkyl halide



3 **4**

d. This work



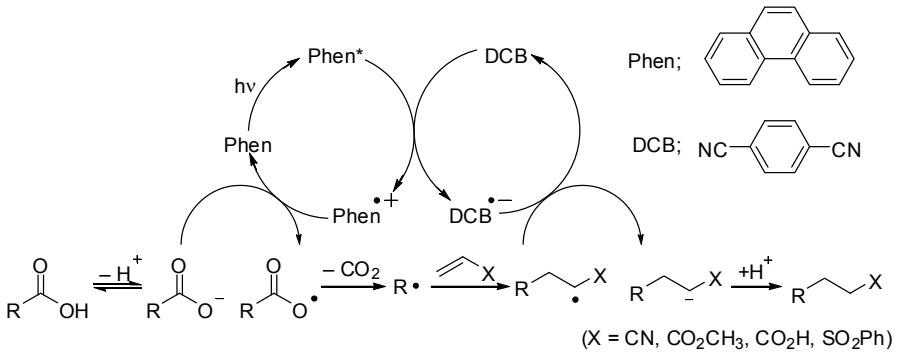
R = H, CH_3

5

Alkyl radicals

O-Alkylated serine and threonine

Scheme 1. *O*-Alkylation of serine and threonine.



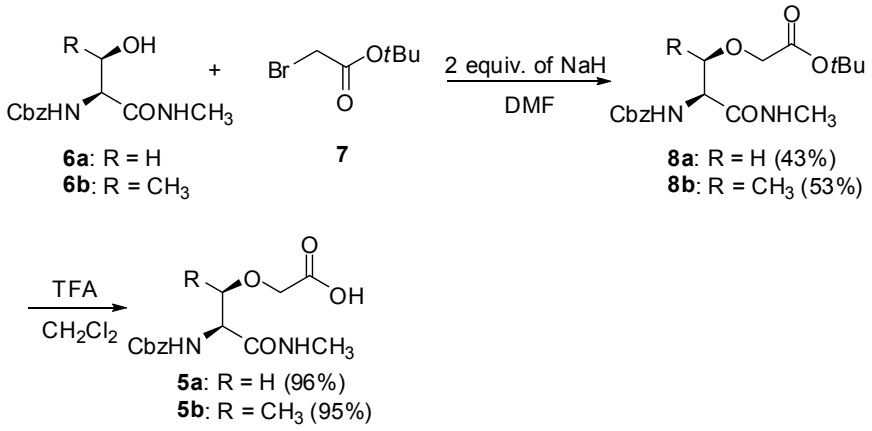
Scheme 2. Photoinduced decarboxylative radical addition of carboxylic acids to electron-deficient alkenes.

Results and Discussion

Preparation of serinyl and threoninyl acetic acids 5a,b

Initially, the preparation of L-serinyl and L-threoninyl acetic acids **5a**,**b** from *N*-Cbz L-serine and L-threonine amides **6a**,**b** and the high reactive electrophile **7** for the photoreaction substrate to avoid the formation of undesired products was examined by the modified method[9] (Scheme 3). A THF solution containing **6a** and 3 equiv. of α-bromo *t*-butyl acetate **7** was slowly added to the THF solution with 1.2 equiv. of NaH at 0 °C and stirred for 3 h at room temperature to afford **8a** in a low yield (22%). Instead of amide **6a**, the use of an ester such as *N*-Cbz serine methyl ester and *N*-Boc serine methyl ester with **7** yielded a complex mixture. An attempt to carry out a reaction involving **6a** with α-bromo ethyl acetate in the place of **7** failed. Thus, *N*-Cbz L-serine *N'*-methyl amide **6a** and **7** are found to be suitable for etherification of serine by NaH. When the effects of NaH concentration, solvent (THF or DMF), base (NaH or LDA or *t*-BuOK or $NaNH_2$),

and synthetic procedure were assessed (Table S1 in SI), ethers **8a**,**b** formed optimally in DMF containing **6a**,**b**, 3 equiv. of **7**, and 2 equiv. of NaH for 3 h at room temperature. This was followed by deprotection of the *t*-butyl group in **8a**,**b** by TFA to yield the corresponding carboxylic acids **5a**,**b**. In order to verify α-chirality retention in **8** during etherification using NaH, the corresponding D-**8a** was synthesized by the same method from D-**6a**. Chiral HPLC analysis of **8a**, D-**8a**, and a 1:1 mixture of **8a** and D-**8a** showed that the retention of the chirality was observed (Figure S1 in SI).



Scheme 3. Preparation of **5a**,**b** from **6a**,**b**.

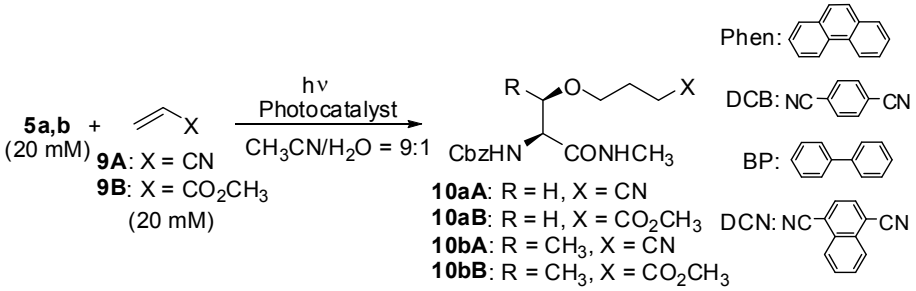
Photoinduced decarboxylative radical additions of 5 or 12 to electron-deficient alkenes 9 for the preparation of *O*-alkylated serine and threonine derivatives 10 or13

An initial photochemical experiment was carried out by the photoinduced decarboxylative

radical addition of **5** to electron-deficient alkene **9** such as acrylonitrile **9A** and methyl acrylate **9B** for the preparation of *O*-alkylated serine and threonine **10**. Table 1 shows the effects of concentrations of photocatalyst, irradiation time, base, and the nature of electron-deficient alkene in photoinduced reactions of **5a**,**b** to **9A**,**B**. An aqueous acetonitrile solution (CH_3CN/H_2O = 9:1) containing **5a** (20 mM) and **9A** (20 mM) was mixed with catalytic amounts of Phen (1 mM, 5 mol%) and DCB (1 mM, 5 mol%) in 15 × 180 mm Pyrex vessels. The mixture was irradiated for 9 h in an Ar atmosphere at room temperature (100 W, high-pressure mercury lamp ($\lambda > 280$ nm)). Irradiation resulted in the formation of *O*-alkylated serine amide **10aA** in high yield (83%) through the decarboxylative radical addition (Entry 1, Table 1). Addition of NaOH (1 equiv.) to the reaction mixture shortens the irradiation time (6 h) in a similar yield (79%, Entry 1); however, photoreactions in the absence of a base were preferred, due to the possibility of base-promoted racemization and hydrolysis in the sensitive amino acids and carbohydrates. Instead of Phen and DCB, the use of biphenyl (BP) and 1,4-dicyanonaphthalene (DCN) under the same photochemical conditions provided the similar yield of **10aA** (86%, Entry 2). As reported by us,[10] the use of relatively poorly electron-deficient alkenes such as **9B** in the place of **9A** led to a significantly lower yield of adduct, along with formation of polymeric materials[11]. When higher concentrations of BP and DCN were used as photocatalyst, the yield of adduct slightly improved. In fact, the photoreaction of **5a** with **9B** for

6 h using Phen (4 mM, 20 mol%) and DCB (4 mM, 20 mol%) led to a lower yield of **10aB** (35%, Entry 3), and an improved yield of **10aB** (66%) was obtained in the photoreaction of **5a** with **9B** using BP (4 mM, 20 mol%) and DCN (4 mM, 20 mol%) (Entry 4). In addition, these photochemical conditions enabled the efficient photoinduced decarboxylative radical addition of a threonine derivative **5b** with **9A**,**B** to afford high and moderate yields of **10bA** and **10bB**, respectively (Entries 5 and 6). Thus, the photoinduced decarboxylative radical addition of **5** to a poorly electron-deficient alkene in the absence of a base was optimized for the use of BP (4 mM) and DCN (4 mM) with 6 h irradiation time. Similar yield of D-**10aA** was obtained in the photoreaction of D-**5a** with **9A** (Entry 7), and the chirality retention of **10aA** in the photoreaction was confirmed by chiral HPLC analysis of **10aA**, D-**10aA**, and a 1:1 mixture of **10aA** and D-**10aA** (Figure S2 in SI).

Table 1 Photoinduced decarboxylative radical addition of **5a**,**b** to **9A**,**B**.



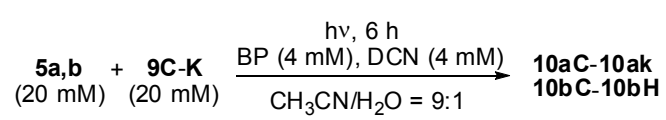
Entry	**5**	**9**	Photocatalyst	Irrad. time/h	Yield of **10**/%[a]
1	**5a**	**9A**	Phen (1 mM), DCB (1 mM)	9 (6)[b]	83 (79)[b]
2	**5a**	**9A**	BP (1 mM), DCN (1 mM)	9	86

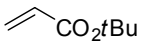
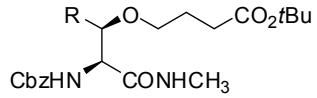
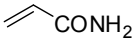
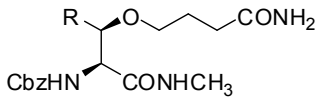
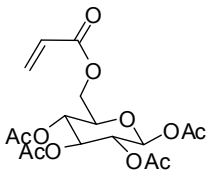
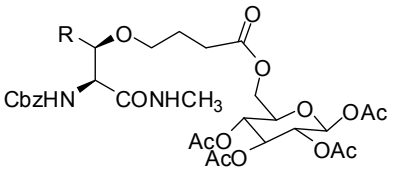
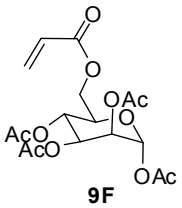
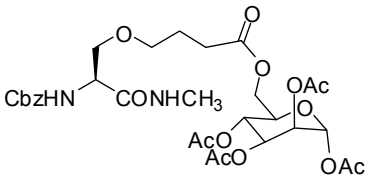
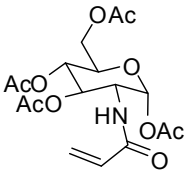
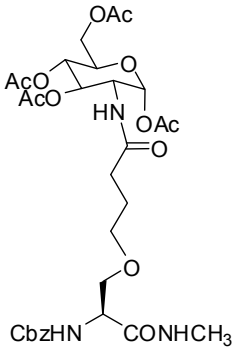
3	**5a**	**9B**	Phen (4 mM), DCB (4 mM)	6	35
4	**5a**	**9B**	BP (4 mM), DCN (4 mM)	6	66
5	**5b**	**9A**	BP (4 mM), DCN (4 mM)	6	87
6	**5b**	**9B**	BP (4 mM), DCN (4 mM)	6	68
7	D-**5a**	**9A**	BP (4 mM), DCN (4 mM)	6	85

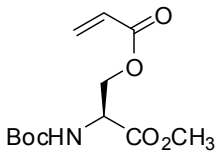
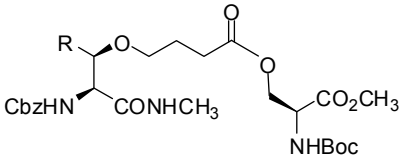
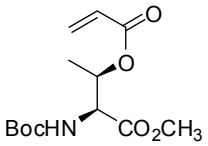
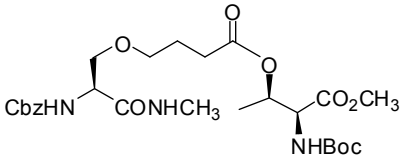
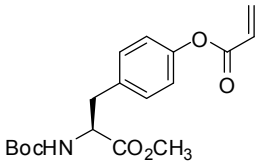
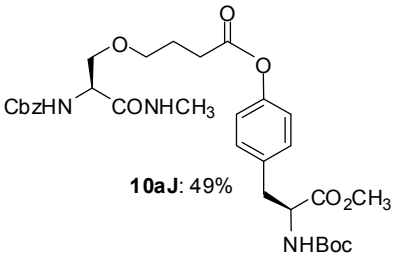
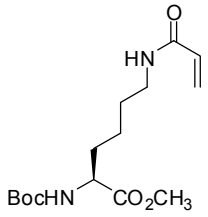
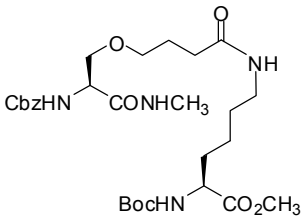
[a]Isolated yield. [b]Addition of 1 equiv. of NaOH.

To demonstrate the utility of the photoinduced radical addition of **5**, electron-deficient alkenes **9C**–**K** were subjected to this photoreaction (Table 2). Similarly, the photoreactions of **5a**,**b** with *t*-butyl acrylate **9C** and acrylamide **9D** provided adducts **10aC**–**bD** in moderate yields, respectively (Entries 1 and 2). It is notable that the protected carbohydrate-acrylate and -acrylamide, such as β-D-glucosyl acrylate **9E**, α-D-mannosyl acrylate **9F**, and α-D-glucosaminyl acrylamide **9G**, can be employed in the photoreaction to yield the connected products **10aE**–**aG** between **5** and carbohydrates by alkyl chain (Entries 3–5). In addition, the linked amino acids **10aH**–**aK** at the side chain were obtained in the photoreactions of **5a**,**b** with L-serinyl acrylate **9H**, L-threoninyl acrylate **9I**, L-tyrosyl acrylate **9J**, and L-lisinyl acrylamide **9K** (Entries 6–9). Other diastereomers of **10** were not observed in these photoreactions. Thus, this photochemical radical addition can provide the connected serine and threonine with carbohydrates and amino acids at the side chain without racemization.

Table 2 Photoinduced decarboxylative radical addition of **5a**,**b** to **9C**–**K**.

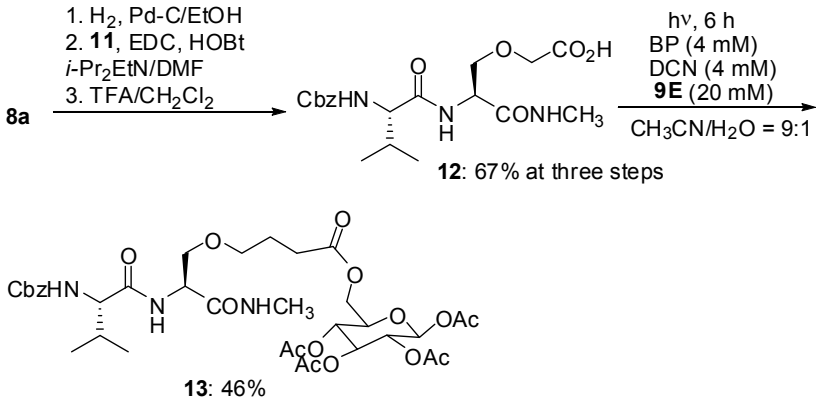


Entry	Electron-deficient alkene **9**	Product **10**[a]
1	 **9C**	 **10aC**: 67% **10bC**: 65%
2	 **9D**	 **10aD**: 55% **10bD**: 52%
3	 **9E**	 **10aE**: 47% **10bE**: 45%
4	 **9F**	 **10aF**: 44%
5	 **9G**	 **10aG**: 44%

6	 **9H**	 **10aH**: 66% **10bH**: 63%
7	 **9I**	 **10aI**: 66%
8	 **9J**	 **10aJ**: 49%
9	 **9K**	 **10aK**: 66%

[a]Isolated yield.

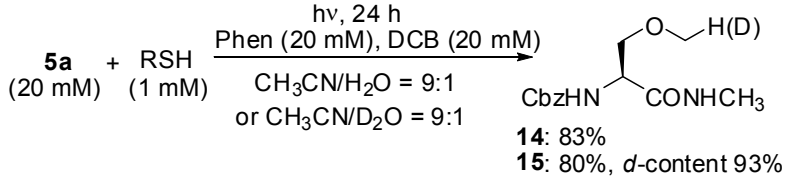
This methodology can also apply to the modification of dipeptide **12** with **9E**, which was prepared from **8a** coupling with *N*-Cbz L-valine **11** at three steps, to provide the connected dipeptide **13** with the carbohydrate at the side chain (Scheme 4).



Scheme 4 Photoinduced decarboxylative radical addition of dipeptide **12** to **9E**.

Photoinduced decarboxylative reduction and deuteration of 5a

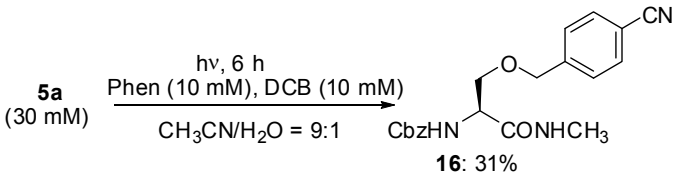
To further prepare another type of *O*-alkylated serine, photoinduced reduction[7b] and deuteration[7e] of **5a** were investigated (Scheme 5). The photoreaction of **5a** with Phen (20 mM), DCB (20 mM), and *t*-dodecanethiol (RSH, 1 mM, 5 mol%) for 24 h led to the high yield of reduction product **14** (83%) through hydrogen abstraction in the thiol by the generated radical. As reported by us,[7e] the use of D_2O instead of water in the solvent causes exchange of SH to SD in the thiol, and the generated radicals by photoinduced decarboxylation abstract D atom from SD to yield deuterated products. In fact, a high yield and deuterium-content of **15** was obtained in the photoreaction of **5a** in CH_3CN/D_2O = 9:1. Thus, *O*-methylation containing a deuterium of serine is achieved by photoreaction of **5** using thiol and D_2O.



Scheme 5 Photoinduced decarboxylative reduction and deuteration of **5a**.

Photoinduced substitution of DCB with 5a via decarboxylation

Finally, substitution of DCB by **5a** via photoinduced decarboxylation was demonstrated (Scheme 6).[7c] The photoreaction of **5a** (30 mM), Phen (10 mM), and DCB (10 mM) in the absence of alkene and thiol provided *O*-benzylated serine amide **16** via the sequent decarboxylative radical addition to the radical anion of DCB and decyanation.

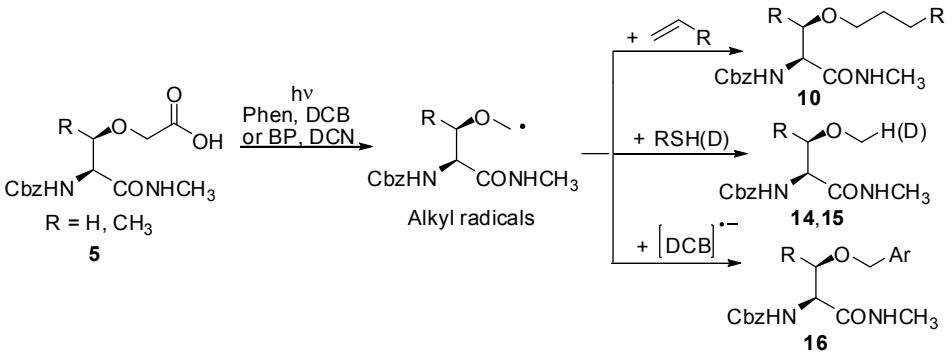


Scheme 6 Photoinduced substitution of DCB with **5a** via decarboxylation

Conclusion

Photoinduced decarboxylative radical reactions of **5** were found to be a useful method for the preparation of *O*-alkylated serine and threonine (Scheme 7). In particular, photoinduced decarboxylative radical additions of **5** to **9** are proven to connect serine and threonine with

carbohydrates and amino acids at the side chain through the similar reaction mechanism to Scheme 2. *O*-Alkylation by using this photochemical method proceeded with complete retention of α-chirality of serine and threonine, because base, heating, and metal are not used in the photoreaction. Further investigation into modification of peptides at the side chain using this photochemical method is in progress.



Scheme 7 Photoinduced decarboxylative radical reactions for the preparation of *O*-alkylated serine and threonine **10**, **14**, **15**, **16**

Experimental Section

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 $CDCl_3$ or CD_3OD containing tetramethylsilane as an internal standard, and were acquired on either a 500 or a 600 MHz spectrometer. ^{13}C NMR spectra were acquired on either a 125 or a 150 MHz spectrometer. High-resolution mass spectra were obtained using double-focusing magnetic sector mass spectrometer coupled with FAB. The light source was a high-pressure (100 W) mercury arcs.

Column chromatography was performed on Wakogel C-300, particle size 45-75 μm.

Procedure for the synthesis of *N*-Cbz serine and threonine amides 5a,b

Benzylchloroformate (9.38 g, 55 mmol) was added dropwise to serine or threonine (5.25 or 5.96 g, 50 mmol) in an aq. $NaHCO_3$ (10.5 g, 125 mmol) solution (100 mL) at 0 °C. The mixture was stirred overnight at room temperature and washed with EtOAc. The aqueous solution was acidified by the slow addition of 1M HCl until the pH decreased to 1 and was then extracted with EtOAc. The organic layer was dried over Na_2SO_4 and concentrated *in vacuo*. The crude product was recrystallized by hexane/EtOAc = 1:1 to give the corresponding *N*-Cbz serine or threonine as a white solid (10.9g, 91% or 12.0g, 95%).

EDC hydrochloride (2.74 g, 14 mmol) and HOBt (2.18 g, 14 mmol) were added to solutions of *N*-Cbz serine or threonine (3.00 or 3.29 g, 13 mmol), methylammonium hydrochloride (0.93 g, 14 mmol), and *i*-Pr_2NEt (3.24 g, 25 mmol) in DMF (50 mL) at 0 °C. The mixture was stirred for 2 h at 0 °C and overnight at room temperature, and then concentrated *in vacuo*. The residue was dissolved in EtOAc, and sequentially washed with 4% $NaHCO_3$, 1M HCl, and water. The organic layer was dried over Na_2SO_4 and concentrated *in vacuo*. The crude product was purified by silica-gel column chromatography using chloroform/acetone = 20:1–10:1 as the eluent to give the corresponding *N*-Cbz serine and threonine amides **6a**,**b** as a white solid in 79 or 73%

yield (2.59 or 2.53g), respectively.

6a: white solid, mp 120–121°C; IR (KBr, cm^{-1}) 3391, 3367, 2968, 2928, 1685, 1656, 1554, 1515; ^1H NMR (500 MHz, CD_3OD) δ 7.36–7.29 (m, 5H), 5.13–5.06 (m, 2H), 4.17–4.14 (m, 1H), 3.76–3.74 (m, 2H), 2.73 (s, 3H); ^{13}C NMR (125 MHz, CD_3OD) δ 172.1, 157.1, 137.0, 128.1, 127.8, 127.7, 66.5, 61.9, 57.3, 25.1; HRMS (FAB, *m/z*) calcd for $(M+H)^+$ $C_{12}H_{17}N_2O_4$: 253.1188, found: 253.1180.

6b: white solid, mp 160–161°C; IR (KBr, cm^{-1}) 3395, 3301, 2974, 2923, 1693, 1636, 1577, 1523; ^1H NMR (500 MHz, CD_3OD) δ 7.38–7.29 (m, 5H), 5.15–5.06 (m, 2H), 4.16–4.03 (m, 2H), 2.71 (s, 3H), 1.16 (d, J = 6.3 Hz, 3H); ^{13}C NMR (125 MHz, CD_3OD) δ 172.2, 157.3, 136.7, 128.2, 127.8, 127.6, 67.0, 66.6, 60.7, 25.1, 18.9; HRMS (FAB, *m/z*) calcd for $(M+H)^+$ $C_{13}H_{19}N_2O_4$: 267.1345, found: 267.1346.

DMF solution (5 mL) containing **6** (**6a**,**b** and D-**6a**, 1.19 mmol, 0.300g, 0.317g, and 0.300g) and 3 equiv. of α-bromo *t*-butyl acetate **7** (0.53 mL, 3.57 mmol) was slowly added to DMF solution (5 mL) of 2 equiv. of 60% NaH (0.10 g, 2.38 mmol) at 0 °C and stirred for 3 h at room temperature. Then, water was added to the mixture and extracted with EtOAc. The organic layer was dried over Na_2SO_4 and concentrated *in vacuo*. The crude product was purified by silica-gel column chromatography using hexane/EtOAc = 4:1–1:1 as the eluent to give **8a**,**b** and D-**8a** (43, 53%, 0.187g, 0.240g, and 0.187g).

8a: white solid, mp 78–79°C; IR (KBr, cm^{-1}) 3303, 2975, 2923, 1743, 1692, 1650, 1575, 1542; ^1H NMR (500 MHz, $CDCl_3$) δ 7.44–7.24 (m, 5H), 6.95 (s (br), 1H), 6.24 (s (br), 1H), 5.13 (s, 2H), 4.30–4.27 (m, 1H), 4.12–3.88 (m, 3H), 3.65–3.61 (m, 1H), 2.84 (d, J = 4.0 Hz, 3H), 1.47 (s,

9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.4, 170.3, 156.5, 136.3, 128.6, 128.3, 128.1, 82.5, 71.5, 68.9, 67.1, 54.3, 28.1, 26.5; HRMS (FAB, *m/z*) calcd for $(M+H)^+$ $C_{18}H_{27}N_2O_6$: 367.1869, found: 367.1891.

8b: colorless oil; IR (neat, cm^{-1}) 3340, 2979, 2931, 1726, 1669, 1522, 1508; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.41 (s (br), 1H), 7.35–7.29 (m, 5H), 6.14 (s (br), 1H), 5.11–5.05 (m, 2H), 4.27–4.01 (m, 3H), 3.92–3.85 (m, 1H), 2.83 (d, *J* = 4.6 Hz, 3H), 1.44 (s, 9H), 1.09 (d, *J* = 6.3 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.2, 169.0, 156.2, 136.3, 128.6, 128.2, 128.0, 82.5, 68.2, 67.0, 56.6, 28.1, 26.4, 15.5; HRMS (FAB, *m/z*) calcd for $(M+H)^+$ $C_{19}H_{29}N_2O_6$: 381.2026, found: 381.2013.

D-**8a**: white solid, mp 78–79°C; IR (KBr, cm^{-1}) 3306, 2923, 1739, 1692, 1650, 1577, 1545; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.41–7.29 (m, 5H), 6.93 (s (br), 1H), 6.22 (s (br), 1H), 5.14 (s, 2H), 4.30–4.27 (m, 1H), 4.12–3.89 (m, 3H), 3.65–3.61 (m, 1H), 2.85 (d, *J* = 4.1 Hz, 3H), 1.48 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 170.4, 170.3, 156.5, 136.3, 128.6, 128.3, 128.1, 82.5, 71.5, 68.9, 67.1, 54.4, 28.1, 26.5; HRMS (FAB, *m/z*) calcd for $(M+H)^+$ $C_{18}H_{27}N_2O_6$: 367.1869, found: 367.1891.

CH_2Cl_2/TFA= 1:1 (5 mL : 5 mL) solution containing **8** (**8a**,**b** and D-**8a**, 2.06 mmol, 0.755g, 0.784g, and 0.755g) was stirred overnight at room temperature, and concentrated *in vacuo*. Purification by column chromatography on silica gel using hexane/EtOAc = 2:1–1:2 as eluents gave *N*-Cbz serinyl and threoninyl acetic acids **5a**,**b** and D-**5a** as a white solid (96, 95, 96%, 0.614g, 0.653g, and 0.614g).

5a: white solid, mp 126–128°C; IR (KBr, cm^{-1}) 3377, 3274, 2969, 2939, 1755, 1716, 1642, 1524; ^{1}H NMR (500 MHz, CD_3OD) δ 7.40–7.26 (m, 5H), 5.13–5.06 (m, 2H), 4.29–4.20 (m,

1H), 4.09–4.07 (m, 2H), 3.86–3.81 (m, 1H), 3.74–3.71 (m, 1H), 2.74 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.9, 171.7, 157.2, 136.7, 128.1, 127.7, 127.6, 70.7, 67.4, 66.6 55.4, 25.1; HRMS (FAB, *m/z*) calcd for $(M+H)^+$ $C_{14}H_{19}N_2O_6$: 311.1243, found: 311.1243.

5b: white solid, mp 146–147°C; IR (KBr, cm^{-1}) 3305, 2969, 2936, 1743, 1686, 1651, 1554; ^{1}H NMR (500 MHz, CD_3OD) δ 7.45–7.19 (m, 5H), 5.15–5.07 (m, 2H), 4.23–3.95 (m, 4H), 2.74 (s, 3H), 1.16 (d, J = 6.3 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.5, 171.9, 157.4, 136.7, 128.1, 127.7, 127.6, 75.7, 66.6, 66.0, 59.6, 25.1, 15.1; HRMS (FAB, *m/z*) calcd for $(M+H)^+$ $C_{15}H_{21}N_2O_6$: 325.1400, found: 325.1408.

D-**5a**: white solid, mp 126–128°C; IR (KBr, cm^{-1}) 3373, 3271, 2969, 2939, 1753, 1716, 1644, 1527; ^{1}H NMR (500 MHz, CD_3OD) δ 7.41–7.26 (m, 5H), 5.14–5.06 (m, 2H), 4.29–4.20 (m, 1H), 4.09–4.07 (m, 2H), 3.86–3.81 (m, 1H), 3.74–3.70 (m, 1H), 2.73 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.9, 171.7, 157.2, 136.7, 128.1, 127.7, 127.6, 70.7, 67.4, 66.6, 55.4, 25.1; HRMS (FAB, *m/z*) calcd for $(M+H)^+$ $C_{14}H_{19}N_2O_6$: 311.1243, found: 311.1243.

Procedure for the synthesis of dipeptide 12

Debenzylation of **8a** (0.961 g, 2.62 mmol) was performed by treatment with 10 % Pd/C (0.1 g) and H_2 in EtOH (50 mL) with TLC monitoring. After complete consumption of the starting material, the mixture was filtered through celite, and the filtrate was evaporated. The following coupling with **11** was carried out without further purification.

EDC hydrochloride (0.550 g, 2.88 mmol), HOBt (0.480 g, 3.14 mmol), and *i*-Pr_2EtN (0.560 mL, 3.14 mmol) were added to a solution containing the corresponding debenzylated serine

amide and *N*-Cbz valine **11** (0.660 g, 2.62 mmol) in DMF (20 mL) at 0 °C. The mixture was stirred at 0 °C for 2 h and overnight at room temperature, and then concentrated *in vacuo*. The residue was dissolved in EtOAc, and sequentially washed with 1 M HCl, 4% $NaHCO_3$, and water. The organic layer was dried over Na_2SO_4 and concentrated *in vacuo*. The crude product was purified by silica-gel column chromatography using hexane/EtOAc = 4:1–1:1 as the eluent to give the corresponding dipeptide as a white solid (79%, 0.9661g).

The *t*-butyl group in the peptide (0.960 g, 2.06 mmol) was removed by the abovementioned method using TFA/CH_2Cl_2 = 1:1 solution to give dipeptide **12** (85%, 0.822g).

12: white solid, mp 187–188°C; IR (KBr, cm^{-1}) 3297, 2962, 2873, 1696, 1643, 1538; ^{1}H-NMR (500 MHz, CD_3OD) δ 7.36–7.28 (m, 5H), 5.17–5.07 (m, 2H), 4.43 (s (br), 1H), 4.12–3.88 (m, 4H), 3.68–3.66 (m, 1H), 2.67 (s, 3H), 2.17–2.13 (m, 1H), 1.00–0.95 (m, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.0, 170.8, 157.9, 136.9, 128.2, 127.7, 127.4, 70.4, 67.2, 66.5, 61.4, 53.6, 30.2, 25.0, 18.3, 17.0; HRMS (FAB, *m/z*) calcd for $(M+H)^+$ $C_{19}H_{28}N_3O_7$: 410.1927, found: 410.1924.

General Procedure for the synthesis of alkenes 9E–K

Acryloyl chloride (0.17 g, 2.2 mmol) was slowly added to solution of alcohol or amine (1.9 mmol) and Et_3N (2 mL) in THF (30 mL) at 0 °C under Ar atmosphere, and stirred for 2 h at room temperature. Water (50 ml) was added to the mixture, and extracted with EtOAc, and dried over Na_2SO_4, and concentrated under reduced pressure. Purification by column

chromatography on silica gel using hexane/EtOAc = 10:1 as eluents gave the corresponding acrylate or acrylamide **9E**–**K**.

9E: white solid, mp 144–145°C; IR (KBr, cm^{-1}) 2966, 2950, 1751, 1635; ^1H NMR (500 MHz, $CDCl_3$) δ 6.45 (d, *J* = 17.2 Hz, 1H), 6.15 (dd, *J* = 17.2, 10.4 Hz, 1H), 5.89 (d, *J* = 10.4 Hz, 1H), 5.73 (d, *J* = 8.0 Hz, 1H), 5.27 (t, *J* = 9.5 Hz, 1H), 5.16–5.12 (m, 2H), 4.32–4.26 (m, 2H), 3.91–3.89 (m, 1H), 2.14 (s, 3H), 2.12–1.99 (m, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ170,2. 169.4, 169.3, 169.0, 165.7, 131.9, 127.7, 91.7, 72.9, 72.7, 70.3, 68.0, 61.8, 20.9, 20.6; HRMS (FAB, *m/z*) calcd for $(M+Na)^+$ $C_{17}H_{22}NaO_{11}$: 425.1060, found: 425.1069.

9F; white solid, mp 106–107°C; IR (KBr, cm^{-1}) 2989, 2870, 1750, 1637, 1545; ^1H NMR (500 MHz, $CDCl_3$) δ 6.46 (d, *J* = 17.8 Hz, 1H), 6.16 (dd, *J* = 17.8, 10.3 Hz, 1H), 5.89–5.87 (m, 2H), 5.49 (d, *J* = 2.9 Hz, 1H), 5.31 (t, *J* = 9.7 Hz, 1H), 5.15 (dd, *J* = 9.7, 3.4 Hz, 1H), 4.31 (s, 2H), 3.88–3.85 (m, 1H), 2.23 (s, 3H), 2.09–2.01 (m, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.3, 169.9, 169.6, 168.5, 165.7, 131.8, 127.8, 90.4, 73.3, 70.7, 68.2, 65.6, 62.4, 20.9, 20.8, 20.7, 20.6; HRMS (FAB, *m/z*) calcd for $(M+Na)^+$ $C_{17}H_{22}NaO_{11}$: 425.1060, found: 425.1079.

9G: white solid, mp 110–111°C; IR (KBr, cm^{-1}) 3383, 2952, 2925, 1751, 1662, 1630, 1544; ^1H NMR (500 MHz, $CDCl_3$) δ 6.28 (d, *J* = 17.2 Hz, 1H), 6.22 (d, *J* = 4.0 Hz, 1H), 6.04 (dd, *J* = 17.2, 10.3 Hz, 1H), 5.89 (d, *J* = 9.2 Hz, 1H), 5.70 (d, *J* = 10.3 Hz, 1H), 5.30–5.24 (m, 2H), 4.59–4.55 (m, 1H), 4.27 (dd, *J* = 12.6, 4.0 Hz, 1H), 4.09–4.02 (m, 2H), 2.22 (s, 3H), 2.10–2.01 (m, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.9, 170.8, 169.2, 168.7, 165.4, 129.8, 128.1, 90.7, 70.7, 69.8, 67.5, 61.6, 51.2, 21.0, 20.8, 20.6; HRMS (FAB, *m/z*) calcd for $(M+H)^+$ $C_{17}H_{24}NO_{10}$: 402.1400, found: 402.1389.

9H: white solid, mp 57–58°C; IR (KBr, cm^{-1}) 3342, 2969, 2928, 1738, 1707, 1637, 1531; ^1H NMR (600 MHz, $CDCl_3$) δ 6.42 (d, *J* = 17.2 Hz, 1H), 6.11 (dd, *J* = 17.2, 10.3 Hz, 1H), 5.87 (d,

J = 10.3 Hz, 1H), 5.33 (d (br), *J* = 7.6 Hz, 1H), 4.65–4.59 (m, 1H), 4.55–4.40 (m, 2H), 3.78 (s, 3H), 1.46 (s, 9H); ^{13}CNMR (150 MHz, $CDCl_3$) δ 170.3, 165.6, 155.2, 131.9, 127.7, 80.4, 64.5, 53.0, 52.9, 28.3; HRMS (FAB, *m/z*) calcd for $(M+H)^+$ $C_{12}H_{20}NO_6$: 274.1291, found: 274.1287.

9I: colorless oil; IR (neat, cm^{-1}) 3362, 2979, 1748, 1722, 1636, 1509; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.39 (d, *J* = 17.2 Hz, 1H), 6.07 (dd, *J* = 17.2, 10.3 Hz, 1H), 5.85 (d, *J* = 10.3 Hz, 1H), 5.46 (s (br), 1H), 5.30–5.21 (m, 1H), 4.51–4.45 (m, 1H), 3.73 (s, 3H), 1.47 (s, 9H), 1.35 (d, *J* = 6.3 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.7, 164.9, 155.9, 131.6, 128.0, 80.3, 70.9, 57.2, 52.7, 28.3, 17.0; HRMS (FAB, *m/z*) calcd for $(M+H)^+$ $C_{13}H_{22}NO_6$: 288.1447, found: 288.1436.

9J: white solid, mp 66–67°C; IR (KBr, cm^{-1}) 3384, 2982, 1743, 1688, 1632, 1504; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.18 (d, *J* = 8.6 Hz, 2H), 7.09 (d, *J* = 8.6 Hz, 2H), 6.62 (d, *J* = 17.2 Hz, 1H), 6.34 (dd, *J* = 17.2, 10.3 Hz, 1H), 6.04 (d, *J* = 10.3 Hz, 1H), 5.01 (d (br), *J* = 8.0 Hz, 1H), 4.62–4.55 (m, 1H), 3.74 (s, 3H), 3.24–2.87 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.3, 164.6, 155.2, 149.7 133.8, 132.7, 130.5, 130.2, 127.9, 121.9, 121.5, 80.1, 54.5, 52.4, 37.8, 28.4; HRMS (FAB, *m/z*) calcd for $(M+H)^+$ $C_{18}H_{24}NO_6$: 350.1604, found: 350.1606.

9K: colorless oil; IR (neat, cm^{-1}) 3307, 3289, 2976, 2941, 2871, 1743, 1710, 1664, 1626, 1536; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.29 (d, *J* = 16.9, 1H), 6.16–6.02 (m, 2H, NH and $CH=CH_2$), 5.63 (d, *J* = 10.0 Hz, 1H), 5.20 (d (br), *J* = 8.0 Hz, 1H), 4.32–4.23 (m, 1H), 3.74 (s, 3H), 3.33 (q, *J* = 6.7 Hz, 2H), 1.88–1.75 (m, 1H), 1.73–1.51 (m, 3H), 1.48–1.36 (m, 11H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.4, 165.8, 155.7, 130.9, 126.4, 80.0, 53.2, 52.4, 39.1, 32.5, 28.9, 28.4, 22.6; HRMS (FAB, *m/z*) calcd for $(M+H)^+$ $C_{15}H_{27}N_2O_5$: 315.1920, found: 315.1910.

Photoreactions of 5a,b or 12

An aqueous CH_3CN solution (CH_3CN 90 mL, H_2O 10 mL) of **5** (20 mM), **9** (20 mM), BP (4

mM), and DCN (4 mM) 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 as the eluents to give adducts **10**. The photoinduced decarboxylative reduction, deuteration, and substitution of **5** or photoinduced decarboxylative radical addition of dipeptide **12** were also carried out in a similar manner.

10aA: mp 107–108°C; IR (KBr, cm^{-1}) 3298, 2934, 2875, 2244, 1686, 1653, 1545; ^1H NMR (500 MHz, $CDCl_3$) δ 7.62–7.30 (m, 5H), 6.41 (s (br), 1H), 5.73 (s (br), 1H), 5.15 (s, 2H), 4.35–4.27 (m, 1H), 3.93–3.84 (m, 1H), 3.58–3.44 (m, 3H), 2.85 (d, J = 4.6 Hz, 3H), 2.43 (t, J = 6.9 Hz, 2H), 1.98–1.79 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.3, 156.2, 136.1, 128.7, 128.4, 128.3, 119.9, 70.5, 69.4, 67.4, 54.6, 26.5, 25.4, 14.5; HRMS (FAB, *m/z*) calcd for $(M+H)^+$ $C_{16}H_{22}N_3O_4$: 320.1610, found: 320.1616.

D-**10aA**: white solid, mp 106–107°C; IR (KBr, cm^{-1}) 3302, 2935, 2878, 2244, 1685, 1654, 1545; ^1H NMR (500 MHz, $CDCl_3$) δ 7.60–7.28 (m, 5H), 6.38 (s (br), 1H), 5.71 (s (br), 1H), 5.13 (s, 2H), 4.35–4.27 (m, 1H), 3.93–3.84 (m, 1H), 3.58–3.47 (m, 3H), 2.83 (d, J = 4.6 Hz, 3H), 2.40 (t, J = 6.9 Hz, 2H), 2.00–1.77 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.3, 156.2, 136.1, 128.7, 128.4, 128.3, 119.9, 70.5, 69.4, 67.4, 54.6, 26.5, 25.4, 14.5; HRMS (FAB, *m/z*) calcd for $(M+H)^+$ $C_{16}H_{22}N_3O_4$: 320.1610, found: 320.1624.

10bA: white solid, mp 127–128°C; IR (KBr, cm^{-1}) 3294, 2970, 2939, 2896, 2244, 1686, 1652, 1547, 1458; ^1H NMR (500 MHz, $CDCl_3$) δ 7.43–7.28 (m, 5H), 6.46 (s (br), 1H), 5.78–5.71 (m, 1H), 5.13 (s, 2H), 4.35–4.23 (m, 1H), 4.17–4.01 (m, 1H), 3.77–3.68 (m, 1H), 3.63–3.45 (m, 1H), 2.83 (d, J = 5.2 Hz, 3H), 2.40 (t, J = 6.9 Hz, 2H), 1.98–1.76 (m, 2H), 1.13 (d, J = 6.3 Hz, 3H);

^{13}C NMR (125 MHz, $CDCl_3$) δ 170.1, 156.5, 136.1, 128.7, 128.4, 128.2, 120.1, 74.9, 67.5, 67.3, 58.7, 26.4, 25.7, 15.4, 14.6; HRMS (FAB, *m/z*) calcd for $(M+H)^+$ $C_{17}H_{24}N_3O_4$: 334.1767, found: 334.1770.

10aB: white solid, mp 86–87°C; IR (KBr, cm^{-1}) 3302, 2946, 2871, 1737, 1687, 1656, 1544; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.46–7.26 (m, 5H), 6.39 (s (br), 1H), 5.72 (s (br), 1H), 5.11 (s, 2H), 4.29–4.18 (m, 1H), 3.88–3.77 (m, 1H), 3.65 (s, 3H), 3.56–3.38 (m, 3H), 2.82 (d, J = 4.1 Hz, 3H), 2.35 (t, J = 6.9 Hz, 2H), 1.91–1.80 (m, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 174.1, 170.5, 156.2, 136.1, 128.7, 128.4, 128.3, 70.5, 70.3, 67.3, 54.3, 51.8, 31.0, 26.5, 24.9; HRMS (FAB, *m/z*) calcd for $(M+H)^+$ $C_{17}H_{25}N_2O_6$: 353.1713, found: 353.1721.

10bB: colorless oil; IR (neat, cm^{-1}) 3302, 2930, 2898, 1736, 1690, 1652, 1551; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37–7.33 (m, 5H), 6.55 (s (br), 1H), 5.81 (s (br), 1H), 5.12 (s, 2H), 4.24–4.15 (m, 1H), 4.03–3.90 (m, 1H), 3.66 (s, 3H), 3.60–3.51 (m, 2H), 2.83 (d, J = 4.6 Hz, 3H), 2.36 (t, J = 6.9 Hz, 2H), 1.91–1.86 (m, 2H), 1.07 (d, J = 6.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.2, 170.0, 156.3, 136.2, 128.6, 128.3, 128.2, 74.8, 68.6, 67.2, 58.0, 51.7, 31.1, 26.3, 25.3, 15.3; HRMS (FAB, *m/z*) calcd for $(M+H)^+$ $C_{18}H_{27}N_2O_6$: 367.1869, found: 367.1880.

10aC: white solid, mp 58–59°C; IR (KBr, cm^{-1}) 3300, 2969, 2933, 1728, 1686, 1656, 1551; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37–7.31 (m, 5H), 6.55 (s (br), 1H), 5.79 (s (br), 1H), 5.12 (s, 2H), 4.31–4.20 (m, 1H), 3.89–3.72 (m, 1H), 3.50–3.47 (m, 3H), 2.83 (d, J = 5.2 Hz, 3H), 2.26 (t, J = 7.2 Hz, 2H), 1.85–1.82 (m, 2H), 1.44 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.0, 170.6, 156.2, 136.2, 128.6, 128.3, 128.2, 80.5 70.5, 70.3, 67.2, 54.2, 32.6, 28.2, 26.4, 25.1; HRMS (FAB, *m/z*) calcd for $(M+H)^+$ $C_{20}H_{31}N_2O_6$: 395.2182, found: 395.2202.

10bC: white solid, mp 58–59°C; IR (KBr, cm^{-1}) 3294, 2973, 2929, 1729, 1694, 1650, 1542; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37–7.32 (m, 5H), 6.62 (s (br), 1H), 5.85 (s (br), 1H), 5.12 (s, 2H), 4.27–4.15 (m, 1H), 4.05–3.91 (m, 1H), 3.57–3.51 (m, 2H), 2.84 (d, J = 4.6 Hz, 2H), 2.27 (t, J =

7.2 Hz, 2H), 1.84–1.82 (m, 2H), 1.44 (s, 9H), 1.08 (d, J = 6.3 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.1, 170.0, 156.3, 136.2, 128.6, 128.3, 128.2, 80.5 74.8, 68.7, 67.2, 57.9, 32.6, 28.2, 26.3, 25.5, 15.4; HRMS (FAB, *m/z*) calcd for $(M+H)^+$ $C_{21}H_{33}N_2O_6$: 409.2339, found: 409.2315.

10aD: white solid, mp 149-150°C; IR (KBr, cm^{-1}) 3303, 2961, 2884, 1687, 1647, 1554; ^{1}H NMR (500 MHz, CD_3OD) δ 7.38–7.29 (m, 5H), 5.14–5.06 (m, 2H), 4.30–4.18 (m, 1H), 3.69–3.60 (m, 2H), 3.47–3.44 (m, 2H), 2.73 (s, 3H), 2.23 (t, J = 7.4 Hz, 2H), 1.85–1.80 (m, 2H); ^{13}C NMR (125 MHz, CD_3OD) δ 177.5, 172.0, 157.1, 136.7, 128.2, 127.8, 127.7, 70.1 70.0, 66.6, 55.4, 31.8, 25.4, 25.1; HRMS (FAB, *m/z*) calcd for $(M+H)^+$ $C_{16}H_{24}N_3O_5$: 338.1716, found: 338.1703.

10bD: white solid, mp 172–173°C; IR (KBr, cm^{-1}) 3312, 3195, 2973, 2875, 1688, 1646, 1541; ^{1}H NMR (500 MHz, CD_3OD) δ 7.39–7.30 (m, 5H), 5.16–5.07 (m, 2H), 4.12–4.01 (m, 1H), 3.97–3.88 (m, 1H), 3.59–3.50 (m, 1H), 3.34–3.29 (m, 1H), 2.74 (s, 3H), 2.22 (t, J = 7.6 Hz, 2H), 1.81–1.75 (m, 2H), 1.14 (d, J = 6.3 Hz, 3H); ^{13}CNMR (125 MHz, CD_3OD) δ 177.6, 172.3, 157.3, 136.7, 128.2, 127.8, 127.7, 75.0, 68.1, 66.7, 59.8, 31.8, 25.8, 25.1, 15.2; HRMS (FAB, *m/z*) calcd for $(M+H)^+$ $C_{17}H_{26}N_3O_5$: 352.1872, found: 352.1895.

10aE: white solid, mp 90–91°C; IR (KBr, cm^{-1}) 3383, 3327, 2962, 2884, 1758, 1658, 1531; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37–7.29 (m, 5H), 6.55 (s (br), 1H), 5.78 (s (br), 1H), 5.72 (d, J = 8.0 Hz, 1H), 5.26 (t, J = 9.5 Hz, 1H), 5.15–5.09 (m, 4H), 4.27 (dd, J = 12.6, 4.6 Hz, 2H), 4.12 (d, J = 10.9 Hz, 1H), 3.83–3.81 (m, 2H), 3.53–3.49 (m, 3H), 2.83 (d, J = 4.6 Hz, 3H), 2.40 (t, J = 7.2 Hz, 2H), 2.10–1.98 (m, 12H), 1.89–1.86 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.1, 170.6, 170.1, 169.5 169.3, 169.0, 156.2, 136.2, 128.6, 128.3, 128.2, 91.7, 72.8, 72.7, 70.3, 70.2, 67.8, 67.2, 61.5, 54.4, 30.8, 26.4, 24.7, 20.8, 20.6; HRMS (FAB, *m/z*) calcd for $(M+H)^+$ $C_{30}H_{41}N_2O_{15}$: 669.2507, found: 669.2491.

10bE: white solid, mp 75–76°C; IR (KBr, cm^{-1}) 3392, 2971, 2935, 1759, 1672, 1543, 1508; ^{1}H

NMR (600 MHz, $CDCl_3$) δ 7.37–7.28 (m, 5H), 6.55 (s (br), 1H), 5.78–5.72 (m, 2H), 5.26 (t, *J* = 8.9 Hz, 1H), 5.14–5.09 (m, 4H), 4.25–4.14 (m, 3H), 4.01–3.99 (m, 1H), 3.85–3.82 (m, 1H), 3.59–3.55 (m, 1H), 3.53–3.49 (m, 1H), 2.84 (d, *J* = 4.1 Hz, 3H), 2.43–2.40 (m, 2H), 2.10 (s, 3H), 2.05–2.01 (m, 9H), 1.89–1.86 (m, 2H), 1.09 (d, *J* = 5.5 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 173.2, 170.1, 170.0, 169.5, 169.3, 169.0, 156.3, 136.3, 128.6, 128.3, 128.2, 91.7, 74.8, 72.8, 72.7 70.3, 68.5, 67.8, 67.2, 61.5, 58.0, 31.0, 26.3, 25.1, 20.9, 20.6, 15.3; HRMS (FAB, *m/z*) calcd for $(M+H)^+$ $C_{31}H_{43}N_2O_{15}$: 683.2663, found: 683.2668.

10aF: colorless oil; IR (neat, cm^{-1}) 3395, 3322, 2940, 2876, 1752, 1669, 1516; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37–7.30 (m, 5H), 6.58 (s (br), 1H), 5.87 (s, 1H), 5.80 (s (br), 1H), 5.49 (d, *J* = 2.9 Hz, 1H), 5.27 (t, *J* = 9.7 Hz, 1H), 5.18–5.12 (m, 3H), 4.30–4.27 (m, 2H), 4.15 (d, *J* = 10.9 Hz, 1H), 3.83–3.81 (m, 2H), 3.52–3.49 (m, 3H), 2.83 (d, *J* = 4.6 Hz, 3H), 2.41 (t, *J* = 6.9 Hz, 2H), 2.20 (s, 3H), 2.10–2.00 (m, 9H), 1.92–1.88 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.2, 170.6, 170.2, 169.9, 169.8, 168.5, 156.2, 136.2, 128.6, 128.3, 128.2, 90.4, 73.2, 70.7, 70.3, 70.2, 68.3, 67.2, 65.5 62.1, 54.3, 30.8, 26.4, 24.7, 20.8, 20.8, 20.7, 20.6 ; HRMS (FAB, *m/z*) calcd for $(M+Na)^+$ $C_{30}H_{40}N_2NaO_{15}$: 691.2326, found: 691.2325.

10aG: white solid, mp 130–131°C; IR (KBr, cm^{-1}) 3310, 2956, 2870, 1749, 1685, 1659, 1537; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.29–7.22 (m, 5H), 6.59 (s (br), 1H), 6.38 (d (br), *J* = 8.6 Hz, 1H), 6.13 (s (br), 1H), 5.78 (d (br), *J* = 6.9 Hz, 1H), 5.24 (t, *J* = 10.0 Hz, 1H), 5.14–5.06 (m, 3H), 4.50–4.45 (m, 1H), 4.21–4.17 (m, 2H), 4.00–3.96 (m, 2H), 3.75–3.72 (m, 1H), 3.39–3.32 (m, 3H), 2.73 (d, *J* = 4.6 Hz, 3H), 2.22–1.95 (m, 14H), 1.75–1.71 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.2, 170.4, 169.7, 169.6, 168.2, 168.1, 155.3, 135.0, 127.6, 127.3, 127.1, 89.6, 69.8, 69.0, 68.7, 68.5, 66.8, 66.2, 60.6, 53.6, 49.7, 31.5, 25.3, 24.3, 20.0, 19.8, 19.7, 19.6; HRMS (FAB, *m/z*) calcd for $(M+Na)^+$ $C_{30}H_{41}N_3NaO_{14}$: 690.2486, found: 690.2474.

10aH: colorless oil; IR (neat, cm^{-1}) 3351, 2966, 2881, 1729, 1724, 1674, 1524; ^{1}H NMR (500

MHz, $CDCl_3$) δ 7.41–7.30 (m, 5H), 6.49 (s (br), 1H), 5.76 (s (br), 1H), 5.53 (s (br), 1H), 5.13 (s, 2H), 4.58–4.50 (m, 1H), 4.45–4.26 (m, 3H), 3.89–3.81 (m, 1H), 3.76 (s, 3H), 3.60-3.42 (m, 3H), 2.83 (d, *J* = 4.0 Hz, 3H), 2.36 (t, *J* = 6.6 Hz, 2H), 1.92–1.81 (m, 2H), 1.46 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.2, 170.6, 170.5, 156.3, 155.3, 136.1, 128.7, 128.6, 128.3, 80.4, 70.4, 70.2, 67.3, 64.3, 54.4, 52.9, 31.0, 28.4, 28.3, 26.3, 24.8; HRMS (FAB, *m/z*) calcd for $(M+H)^+$ $C_{25}H_{38}N_3O_{10}$: 540.2557, found: 540.2549.

10bH: colorless oil; IR (neat, cm^{-1}) 3359, 2974, 1740, 1711, 1672, 1512, 1454; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.48–7.29 (m, 5H), 6.52 (s (br), 1H), 5.78 (s (br), 1H), 5.52 (s (br), 1H), 5.15–5.10 (m, 2H), 4.59–4.56 (m, 1H), 4.47–4.30 (m, 2H), 4.21–4.18 (m, 1H), 4.01–3.95 (m, 1H), 3.76 (s, 3H), 3.64–3.41 (m, 2H), 2.84 (d, *J* = 4.6 Hz, 3H), 2.44–2.27 (m, 2H), 1.92–1.79 (m, 2H), 1.45 (s, 9H), 1.09 (d, *J* = 6.3 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.2, 170.4, 170.0, 156.4, 155.3, 136.2, 128.7, 128.4, 128.2, 80.4, 74.8, 68.3, 67.2, 64.3, 58.2, 53.0, 52.8, 30.9, 28.4, 26.4, 25.1, 15.4; HRMS (FAB, *m/z*) calcd for $(M+H)^+$ $C_{26}H_{40}N_3O_{10}$: 554.2714, found: 554.2717.

10aI: colorless oil; IR (neat, cm^{-1}) 3352, 2974, 2879, 1739, 1718, 1675, 1512; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.41–7.28 (m, 5H), 6.62 (s (br), 1H), 5.84 (s (br), 1H), 5.50–5.39 (m, 2H), 5.12 (s, 2H), 4.51–4.37 (m, 1H), 4.32 (s, 1H), 3.91–3.78 (m, 1H), 3.71 (s, 3H), 3.59–3.38 (m, 3H), 2.82 (d, *J* = 4.6 Hz, 3H), 2.42–2.23 (m, 2H), 1.91–1.76 (m, 2H), 1.45 (s, 9H), 1.29 (d, *J* = 6.3 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.4, 171.1, 170.6, 156.3, 156.0, 136.2, 128.6, 128.3, 128.2, 80.3, 70.5, 70.4, 70.1, 67.2, 57.1, 54.4, 52.7, 31.1, 28.3, 26.4, 24.8, 17.1; HRMS (FAB, *m/z*) calcd for $(M+H)^+$ $C_{26}H_{40}N_3O_{10}$: 554.2714, found: 554.2708.

10aJ: white solid, mp 123–124°C; IR (KBr, cm^{-1}) 3304, 2975, 2876, 1752, 1714, 1690, 1654, 1533, 1511; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.46–7.30 (m, 5H), 7.12 (d, *J* = 8.0 Hz, 2H), 7.01 (d, *J* = 8.0 Hz, 2H), 6.42 (s (br), 1H), 5.74 (s (br), 1H), 5.12 (s, 2H), 5.02 (s (br), 1H), 4.61–4.52 (m, 1H), 4.33–4.21 (m, 1H), 3.96–3.80 (m, 1H), 3.70 (s, 3H), 3.65–3.45 (m, 3H), 3.20–2.96 (m, 2H),

2.77 (d, J = 4.6 Hz, 3H), 2.67–2.53 (m, 2H), 2.09–1.93 (m, 2H), 1.42 (s, 9H) ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.3, 172.1, 170.5, 156.2, 155.2, 149.7, 136.1, 133.8, 130.4, 128.7, 128.4, 128.2, 121.6, 80.1, 70.4, 70.3, 67.3, 54.4, 54.3, 52.4, 37.8, 31.4, 28.4, 26.4, 24.9; HRMS (FAB, *m/z*) calcd for $(M+H)^+$ $C_{31}H_{42}N_3O_{10}$: 616.2870, found: 616.2875.

10aK: colorless oil; IR (neat, cm^{-1}) 3304, 2957, 2878, 1709, 1688, 1653, 1540; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35 (s, 5H), 6.81 (s (br), 1H), 6.29 (s (br), 1H), 5.93 (s (br), 1H), 5.31 (s (br), 1H), 5.12 (s, 2H), 4.45–4.15 (m, 2H), 3.90–3.78 (m, 1H), 3.72 (s, 3H), 3.55–3.38 (m, 3H), 3.25–3.20 (m, 2H), 2.82 (d, J = 4.6 Hz, 3H), 2.25–2.14 (m, 2H), 1.94–1.71 (m, 3H), 1.71–1.59 (m, 1H), 1.59–1.33 (m, 13H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.5, 173.1, 170.9, 156.4, 155.7, 136.1, 128.6, 128.4, 128.2, 80.0, 70.3, 69.8, 67.3, 54.6, 53.4, 52.4, 39.1, 33.1, 32.2, 29.0, 28.4, 26.5, 25.7, 22.7; HRMS (FAB, *m/z*) calcd for $(M+H)^+$ $C_{28}H_{45}N_4O_9$: 581.3200, found: 581.3193.

13: white solid, mp 122–123°C; IR (KBr, cm^{-1}) 3300, 2963, 2874, 1760, 1692, 1645, 1540; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35–7.32 (m, 5H), 6.95 (d (br), J = 7.4 Hz, 1H), 6.71 (s (br), 1H), 5.72 (d, J = 8.6 Hz, 2H), 5.32–5.27 (m, 1H), 5.16–5.10 (m, 4H), 4.51 (s, 1H), 4.26–4.23 (m, 1H), 4.15–4.06 (m, 2H), 3.91–3.83 (m, 2H), 3.56–3.41 (m, 3H), 2.79 (s, 3H), 2.39–2.35 (m, 2H), 2.23–1.86 (m, 15H), 1.01–0.88 (m, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.2, 171.3, 170.2, 170.1, 169.7, 169.4, 169.1, 157.0, 136.2, 128.7, 128.4, 128.2, 91.7, 72.8, 72.6, 70.2, 70.0, 69.8, 67.8, 67.2, 61.5, 61.0, 52.4, 30.9, 30.8, 26.4, 24.7, 20.9, 20.6, 19.3, 17.6; HRMS (FAB, *m/z*) calcd for $(M+H)^+$ $C_{35}H_{50}N_3O_{16}$: 768.3191, found: 768.3162.

14: white solid, mp 141–142°C; IR (KBr, cm^{-1}) 3302, 2991, 2926, 1684, 1655, 1577, 1550; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.47–7.23 (m, 5H), 6.39 (s (br), 1H), 5.65 (s (br), 1H), 5.10 (s, 2H), 4.29–4.20 (m, 1H), 3.83–3.77 (m, 1H), 3.46–3.39 (m, 1H), 3.34 (s, 3H), 2.81 (d, J = 5.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.5, 156.2, 136.1, 128.7, 128.4, 128.3, 72.0, 67.3, 59.2, 54.2, 26.5; HRMS (FAB, *m/z*) calcd for $(M+H)^+$ $C_{13}H_{19}N_2O_4$: 267.1345, found: 267.1324.

15: white solid, mp 141-142°C; IR (KBr, cm^{-1}) 3305, 2982, 2902, 1684, 1651, 1576, 1546; ^1H NMR (600 MHz, $CDCl_3$) δ 7.43–7.26 (m, 5H), 6.39 (s (br), 1H), 5.67 (s (br), 1H), 5.11 (s, 2H), 4.29–4.20 (m, 1H), 3.84–3.76 (m, 1H), 3.49–3.40 (m, 1H), 3.35 (s, 2H), 2.81 (d, *J* = 5.0 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 170.5, 156.2, 136.1, 128.7, 128.4, 128.3, 72.0, 67.3, 59.2 (t, *J* = 21.7 Hz), 54.2, 26.5; HRMS (FAB, *m/z*) calcd for $(M+H)^+$ $C_{13}H_{18}DN_2O_4$: 268.1408, found: 268.1411.

16: white solid, mp 172–173°C; IR (KBr, cm^{-1}) 3299, 2961, 2227, 1685, 1647, 1536; ^1H NMR (500 MHz, $CDCl_3$) δ 7.62 (d, *J* = 8.0 Hz, 2H), 7.38–7.27 (m, 7H), 6.37 (s (br), 1H), 5.66 (s (br), 1H), 5.12 (s, 2H), 4.58 (s, 2H), 4.41–4.30 (m, 1H), 3.99–3.91 (m, 1H), 3.67–3.58 (m, 1H), 2.83 (d, *J* = 4.6 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.2, 156.1, 143.0, 136.0, 132.4, 128.7, 128.5, 128.3, 127.8, 118.8, 111.7, 72.5, 70.3, 67.5, 54.5, 26.5; HRMS (FAB, *m/z*) calcd for $(M+H)^+$ $C_{20}H_{22}N_3O_4$: 368.1610, found:368.1613.

Supporting Information

^1H and ^{13}C NMR spectra data for all compounds. This material is available free of charge via Internet at http://pubs.acs.org/.

Acknowledgments

This work was partially supported by the Japan Society for the Promotion of Science (JSPS), Grant-in-Aid no. 17K05779, for scientific research. Y. Y. thanks Prof. S. H. Gellman at UW Madison. This method was inspired while visiting his lab.

References

(1) (a) Maruyama W.; Naoi M.; Narabayashi H.; *J. Neurol. Sci.*, **1996**, *139*, 141–148.(b) Andurkar, S. V.; Stables, J. P.; Kohn, H. *Tetrahedron: Asymmetry*, **1998**, *9*, 3841–3854. (c) Wang, Z.; Liu, J.; Xu, L.; Zhang, H.; Liu, Q.; Jiao, Q. *Chem. Res. Chin. Univ.* **2013**, 29, 95–98. (d) Kekulandara, D. N.; Samarasinghe, K. T. G.; Godage, D. N. P. M.; Ahn, Y.-H. *Org. Biomol. Chem.* **2016**, *14*, 10886–10893.

(2) (a) Okada Y., *Curr. Org. Chem.*, **2001**, *5*, 1–43. (b) Cochrane, S. A.; Huang, Z.; Vederas, J. C. *Org. Biomol. Chem.* **2013**, *11*, 630–639. (c) Nomura, W.; Aikawa, H.; Ohashi, N.; Urano, E.; Metifiot, M.; Fujino, M.; Maddali, K.; Ozaki, T.; Nozue, A.; Narumi, T.; Hashimoto, C.; Tanaka, T.; Pommier, Y.; Yamamoto, N.; Komano, J. A.; Murakami, T.; Tamamura, H. *ACS Chem. Biol.* **2013**, *8*, 2235–2244. (d) Maynard, S. H.; Almeida, A. M.; Yoshimi, Y.; Gellman, S. H. *J. Am. Chem. Soc.* **2014**, *136*, 16683–16688. (e) Rojas-Ocáriz, V.; Compañón, I.; Aydillo, C.; Castro-Lopez, J.; Jiménez-Barbero, J.; Hurtado-Guerrero, R.; Avenoza, A.; Zurbano, M. M.; Peregrina, J. M.; Busto, J. H.; Corzana, F. *J. Org. Chem.*, **2016**, *81*, 5929–5941.

(3) (a) Horwell, D. C. *Trends Biotechnol*, **1995**, *13*, 132. (b) 6.3 Glycopeptide in "*Peptides: Chemistry and Biology, 2nd*", ed. by Sewald, N.; Jakubke, H. 2009, Wiley-VCH, pp386–395.

(4) (a) Wong C. H., Ho M. F., Wang K. T., *J. Org. Chem.*, **1978**, *18*, 3604. (b) Deechongkit, S.;

You, S.; Kelly, J. W. *Org. Lett.*, **2004**, *P*, 497–500. (c) Besada, P.; Mamedova, L.; Thomas, C. J.; Costanzia, S.; Jacobson. K. A. *Org. Biomol. Chem.* **2005**, *3*, 2016–2025.

(5) (a) Kano, S.; Yokomatsu, T.; Iwasawa, H.; Shibuya, S. *Tetrahedron Lett.* **1987**, *28*, 6331–6334. (b) Curran, T. P.; Pollastri, M. P.; Abelleira, S. M.; Messier, R. J.; McCollum, T. A.; Rowe, C. G. *Tetrahedron Lett.* **1994**, *35*, 5409–5412.

(6) (a) Somlai, C.; Lovas, S.; Forgo, P.; Murphy, R. F.; Penke, B. *Synthetic Commun.* **2001**, *31*, 3633–3640. (b) Naidu, B. N.; Sorenson, M. E.; Connolly, T. P.; Ueda, Y. *J. Org. Chem.*, **2003**, *68*, 10098–10102. (c) Dinda, B. K.; Basak, S.; Ghosh, B.; Mal, D. *Synthesis*, **2016**, *48*, 1235–1245.

(7) (a) Review; Yoshimi, Y. *J. Photochem. Photobiol. A* **2017**, *342*, 116–130. (b) Yoshimi ,Y.; Itou, T.; Hatanaka, M. *Chem. Commun.* **2007**, 5244–5246. (c) Itou, T.; Yoshimi, Y.; Morita, T.; Tokunaga, Y.; Hatanaka, M. *Tetrahedron* **2009**, *65*, 263–269. (d) Yoshimi, Y.; Masuda, M.; Mizunashi, T.; Nishikawa, K.; Maeda, K.; Koshida, N.; Itou, T.; Morita, T.; Hatanaka, M. *Org. Lett.* **2009**, *11*, 4652–4655. (e) Itou, T.; Yoshimi, Y.; Nishikawa, K.; Morita, T.; Okada, Y.; Ichinose, N.; Hatanaka, M. *Chem. Commun*. **2010**, 6177–6179. (f) Nishikawa, K.; Yoshimi, Y.; Maeda, K.; Morita, T.; Takahashi, I.; Itou, T.; Inagaki, S.; Hatanaka, M. *J. Org. Chem.* **2013**, *78*, 582–589. (g) Maeda, K.; Saito, H.; Osaka, K.; Nishikawa, K.; Sugie, M.; Morita, T.; Takahashi, I.; Yoshimi, Y. *Tetrahedron* **2015**, *71*, 1117–1123.

(8) (a) Cassani, C.; Bergonzini, G.; Wallentin, C. *Org. Lett.* **2014**, *16*, 4228–4231. (b) Chu, L.; Ohta, C.; Zuo, Z.; MacMillan, D. W. C. *J. Am. Chem. Soc*. **2014**, *136*, 10886–10889. (c) Liu, Z.; Wang, L.; Liu, D.; Wang, Z. *Synlett* **2015**, 26, 2849–2852. (d) Xuan, J.; Zhang, Z.-G.; Xiao, W. *Angew. Chem., Int. Ed.* **2015**, *54*, 15632–15641. (e) Zhou, C.; Li, P.; Zhu, X.; Wang, L. *Org. Lett.* **2015**, *17*, 6198−6201. (f) Liu, P.; Zhang, G.; Sun, P. *Org. Biomol. Chem.* **2016**, *14*, 10763–10777. (g) Cai, S.; Xu, Y.; Chen, D.; Li, L.; Chen, Q.; Huang, M.; Weng, W. *Org. Lett*. **2016**, *18*, 2990−2993. (h) Ramirez, N. P.; Gonzalez-Gomez, J. C. *Eur. J. Org. Chem.* **2017**, 2154–2163.

(9) Sawa, N.; Wada, T.; Inoue, Y. *Tetrahedron* **2010**, *66*, 344–349.

(10) Yoshimi, Y.; Washida, S.; Okita, Y.; Nishikawa, K.; Maeda, K.; Hayashi, S.; Morita, T. *Tetrahedron Lett.* **2013**, *54*, 4324–4326.

(11) Yamawaki, M.; Ukai, A.; Kamiya, Y.; Sugihara, S.; Sakai, M.; Yoshimi, Y. *ACS Macro Lett.* **2017**, *6*, 381−385.