

HETEROCYCLES, Vol. 97, No. 2, 2018, pp. 1269 - 1287. © 2018 The Japan Institute of Heterocyclic Chemistry  
Received, 14th March, 2018, Accepted, 19th April, 2018, Published online, 18th May, 2018  
DOI: 10.3987/COM-18-S(T)86

## DIRECT ENANTIOSELECTIVE INDOLYLATION OF PEPTIDYL IMINE FOR THE SYNTHESIS OF INDOLYL GLYCINE-CONTAINING PEPTIDES\*\*

**Tsubasa Inokuma, Kodai Nishida, Akira Shigenaga, Ken-ichi Yamada, and Akira Otaka\***

Institute of Biomedical Sciences and Graduate School of Pharmaceutical Sciences, Tokushima University, Tokushima, 770-8505, Japan; E-mail: aotaka@tokushima-u.ac.jp

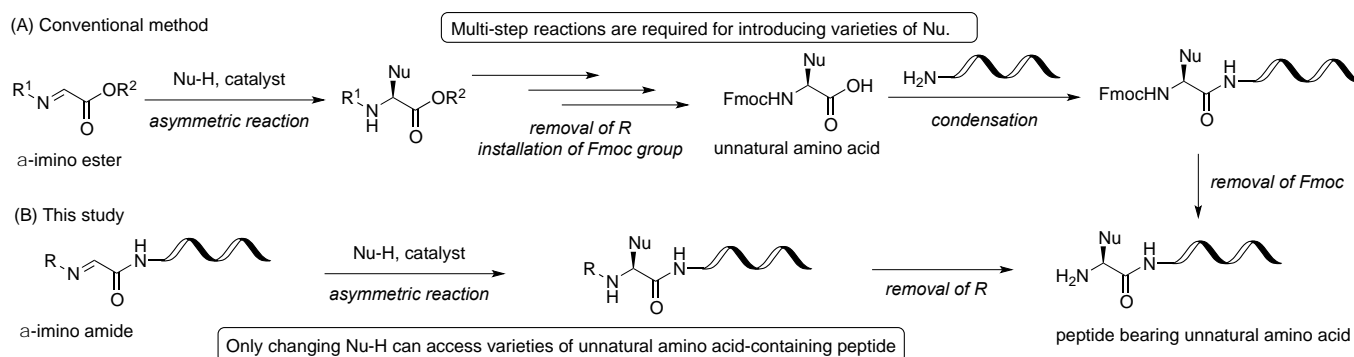
**Abstract** – A novel synthetic method involving the direct application of a catalytic asymmetric reaction to peptides was developed. The conditions optimized for the model asymmetric reaction of a simple  $\alpha$ -imino amide with an indole derivative were successfully applied to an asymmetric Friedel–Crafts reaction of  $\alpha$ -imino peptide possessing a hydrophobic anchor to afford the indolyl glycine-containing peptide. This novel strategy will be of great value for the synthesis of the biologically important peptides bearing varieties of unnatural amino acids.

Peptides have recently gained interest for the development of novel pharmaceuticals.<sup>1</sup> In particular, peptides containing unnatural amino acids are attractive novel drug candidates because they often exhibit better biological activity and/or proteolytic stability than those of the peptides consisting of only proteinogenic amino acids.<sup>2</sup> The preparation of these peptides has traditionally relied on (1) asymmetric construction of unnatural amino acid units,<sup>3</sup> and (2) installation of the units into the peptide elongation process (Scheme 1-A). As a method for the synthesis of unnatural amino acids, 1,2-addition to  $\alpha$ -imino esters is a powerful tool because it can access diverse derivatives by changing only the nucleophiles.<sup>4</sup> Because *N*-Fmoc amino acids are usually utilized as the units in chain elongation process, however, multi-step reactions, including deprotection of the amino and carboxy groups and installation of an Fmoc group into the amine moiety, are required for generating such synthetic intermediates before its application to peptide synthesis. This process has hampered the diversity-oriented synthesis of peptides

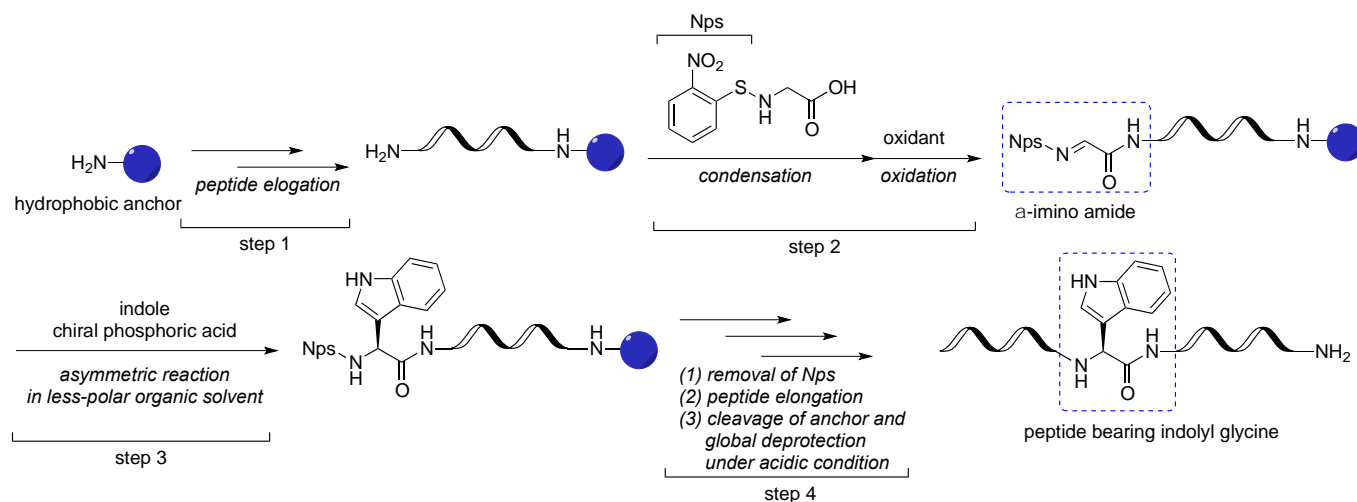
---

\*\* Dedicated to Prof. Kiyoshi Tomioka on the occasion of his 70th birthday

bearing unnatural amino acids. To address this problem, we envisioned an asymmetric construction of unnatural amino acid units in a growing peptide chain (Scheme 1-B). If an  $\alpha$ -imino amide moiety could be installed onto the N-terminus of an elongating peptide, asymmetric 1,2-addition of the nucleophiles into the imino moiety would yield a peptide containing an unnatural amino acid in its N-terminus. Although chemical installation of unnatural side chains into a peptidic substrate in an achiral manner has been demonstrated,<sup>5</sup> an asymmetric reaction has yet to be reported. In this protocol, changing the nucleophiles in the 1,2-addition enables easy access to a diverse range of unnatural amino acid-containing peptides. We planned to incorporate a hydrophobic anchor that makes the peptidic substrate soluble in less-polar solvents<sup>6</sup> because peptidic compounds are basically insoluble in the less-polar organic solvents, such as toluene, chloroform, and dichloromethane, which are often most suitable for asymmetric catalytic reactions. As an unnatural unit of the target peptide, we chose  $\alpha$ -indolyl glycine. This unit is a promising analog to proteinogenic aromatic amino acids such as phenylalanine, tyrosine and tryptophan, and extensive effort has been directed toward its asymmetric synthesis.<sup>7</sup> For example, Hiemstra *et al.* reported an asymmetric Friedel–Crafts reaction of *N*-2-nitrophenylsulfenyl (Nps)  $\alpha$ -imino ester and indole to construct this motif,<sup>7f</sup> and this reaction is the basis of the present work (Scheme 2). The first step is peptide elongation on the amine moiety of a hydrophobic anchor using liquid-phase peptide synthesis (step 1). Next, condensation of *N*-Nps glycine on the growing peptide chain followed by oxidation of the N-terminal residue to the corresponding imine provides the site at which a wide range of unnatural amino acid residues can be incorporated (step 2). Next, asymmetric 1,2-addition of indole on the resulting imine is performed (step 3). Subsequent removal of the Nps group followed by the usual manipulations for peptide elongation, anchor cleavage, and global deprotection by acidic treatment afford the desired peptides bearing indolyl glycine (step 4).



Scheme 1. Strategies for the synthesis of peptides bearing unnatural amino acids

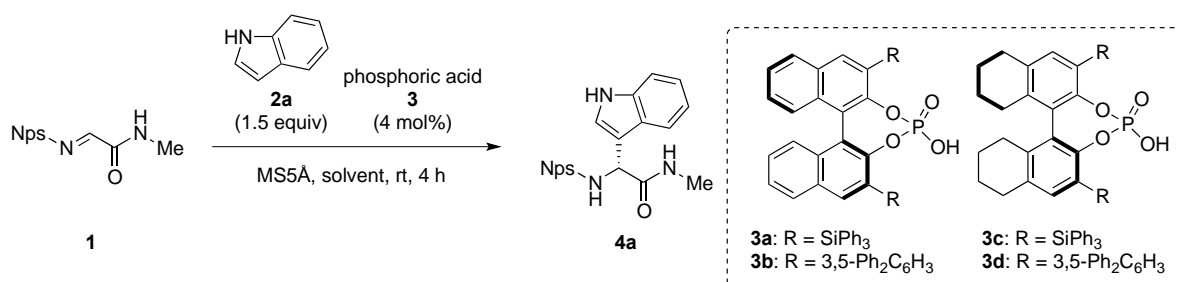


Scheme 2. Outline of this study: Synthesis of a peptide bearing  $\alpha$ -indolyl glycine

We initially screened the conditions of the asymmetric Friedel–Crafts reaction using simple methyl amide **1** as a model substrate and non-substituted indole **2a** as a nucleophile (Table 1). When we employed the conditions reported for the synthesis of the ester analog of **4a**<sup>7f</sup> in the model reaction, the corresponding adduct **4a** was obtained in moderate stereoselectivity (entry 1). In our reaction, catalyst **3b**, reported by Terada's group as the optimal catalyst for asymmetric 1,2-addition of indole to *N*-Boc imine,<sup>8</sup> gave better enantioselectivity than **3a** (entry 2). Hydrogenated catalysts **3c** and **3d** were also tested and **3c** provided higher enantioselectivity (entries 3 and 4). When  $\text{CHCl}_3$  was used as a solvent, the reaction with **3b** gave slightly lower enantioselectivity than that employed in toluene (entry 5) whereas the reaction with **3c** proceeded in improved enantioselectivity (entry 6). Other chlorinated solvents or THF gave poorer results (entries 7–9). Therefore, we concluded that the optimal catalyst and solvent were **3c** and  $\text{CHCl}_3$ , respectively. The absolute configuration of adduct **4a** was determined to be *R* based on comparison of the the specific rotation with those of (*R*)-**4a** derived from a known compound.<sup>9</sup>

Next, the scope of the indole nucleophiles was examined (Table 2). Both electron-donating and electron-withdrawing substituents at the 4-positions of indole were tolerated (entries 1-3). The enantiomeric excess of adducts **4e-i** varied depending on the position of the indole substituents. 2-Methylindole **2e** gave an unsatisfactory result while the reactions of 4-, 5-, 6-, or 7-methyl-substituted indoles **2f-i** proceeded in good to excellent selectivity (entries 4-8).

Table 1. Screening of the reaction conditions

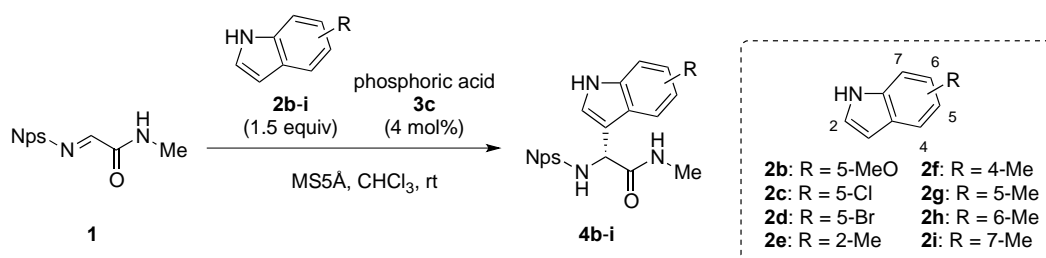


| Entry          | phosphoric acid | solvent                              | yield (%) <sup>a</sup> | ee (%) <sup>b</sup> |
|----------------|-----------------|--------------------------------------|------------------------|---------------------|
| 1 <sup>c</sup> | <b>3a</b>       | toluene                              | 64                     | 67                  |
| 2              | <b>3b</b>       | toluene                              | 92                     | 76                  |
| 3              | <b>3c</b>       | toluene                              | 71                     | 78                  |
| 4              | <b>3d</b>       | toluene                              | 88                     | 69                  |
| 5              | <b>3b</b>       | CHCl <sub>3</sub>                    | 78                     | 71                  |
| 6              | <b>3c</b>       | CHCl <sub>3</sub>                    | 82                     | 80                  |
| 7              | <b>3c</b>       | CH <sub>2</sub> Cl <sub>2</sub>      | 70                     | 65                  |
| 8              | <b>3c</b>       | ClCH <sub>2</sub> CH <sub>2</sub> Cl | 49                     | 62                  |
| 9              | <b>3c</b>       | THF                                  | 8                      | 9                   |

<sup>a</sup> Isolated yield. <sup>b</sup> Determined by chiral HPLC analysis. <sup>c</sup> The reaction was performed for 6 h.

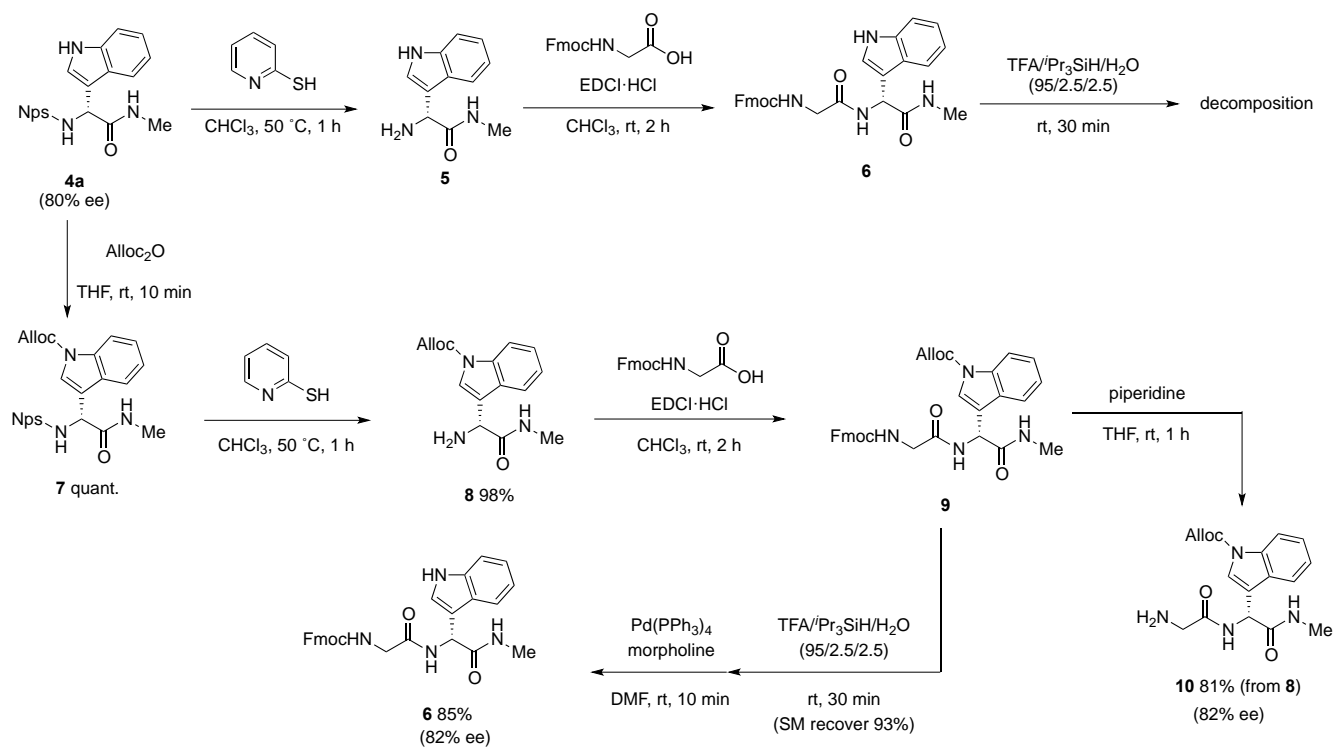
The conditions for deprotection and peptide-elongation were investigated using model compound **4a** (Scheme 3). Deprotection of the amino group of **4a** was achieved with aid of 2-mercaptopyridine<sup>10</sup> and Fmoc-Gly-OH was connected to **5** as the next amino acid residue without any problems. The resulting dipeptide **6**, however, was unstable against the acidic treatment required to remove the hydrophobic anchor, due to the lability of the unnatural amino acid moiety bearing an electron-rich aryl group indole.<sup>11</sup> To overcome this problem, we introduced an electron-withdrawing group on the nitrogen atom of the indole ring to diminish the electron-density. An electron-withdrawing allyloxycarbonyl (Alloc) group was successfully introduced to **4a** using diallyl dicarbonate in THF at room temperature to afford **7** in quantitative yield. Removal of the Nps group, condensation of another amino acid, and removal of the Fmoc group were performed using standard procedures without loss of enantiomeric excess. As expected, dipeptide **9** survived under the acidic condition, and retainment of the enantiomeric excess was confirmed at the stage of dipeptide **6** after removal of the Alloc group. The Fmoc group of **9** was readily removed under standard conditions to give **10**, which was ready for further peptide elongation. In these transformations, no racemization was observed and each step proceeded in high chemical yield.

Table 2. Scope of the indole



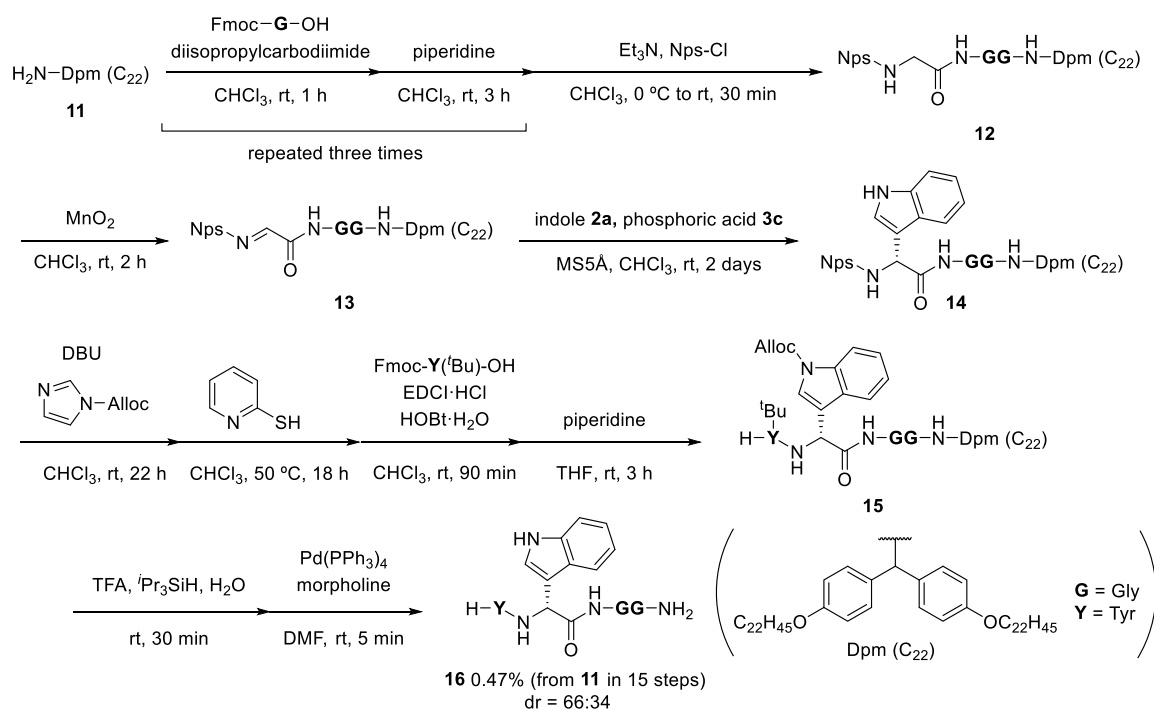
| entry | <b>2</b>  | time (h) | <b>4</b>  | yield (%) <sup>a</sup> | ee (%) <sup>b</sup> |
|-------|-----------|----------|-----------|------------------------|---------------------|
| 1     | <b>2b</b> | 4        | <b>4b</b> | 76                     | 77                  |
| 2     | <b>2c</b> | 24       | <b>4c</b> | 52                     | 85                  |
| 3     | <b>2d</b> | 4        | <b>4d</b> | 70                     | 81                  |
| 4     | <b>2e</b> | 18       | <b>4e</b> | 72                     | 45                  |
| 5     | <b>2f</b> | 4        | <b>4f</b> | 92                     | 77                  |
| 6     | <b>2g</b> | 4        | <b>4g</b> | 65                     | 70                  |
| 7     | <b>2h</b> | 4        | <b>4h</b> | 99                     | 79                  |
| 8     | <b>2i</b> | 4        | <b>4i</b> | 95                     | 93                  |

<sup>a</sup> Isolated yield. <sup>b</sup> Determined by chiral HPLC analysis.



Scheme 3. Model study for deprotection and peptide elongation

Having established the conditions for dipeptide synthesis, synthesis of tetrapeptide-bearing indolyl glycine was conducted via direct asymmetric reaction of peptides using a hydrophobic anchor (Scheme 4). We selected the bis(4-docosyloxyphenyl)methyl (Dpm (C<sub>22</sub>)) group reported by Takahashi *et al.* as the anchor moiety.<sup>6a</sup> First, three glycine residues were installed into anchor **11** and the N-terminal amino group was protected with an Nps group. Next, oxidation of **12** was realized under our previously established conditions to give  $\alpha$ -imino peptide **13**.<sup>12</sup> An asymmetric Friedel–Crafts reaction of indole and **13** successfully afforded indolyl glycine-containing adduct **14**. The Alloc protection of the indole moiety by Alloc-imidazole<sup>13</sup> followed by removal of the Nps group, condensation of Fmoc-Tyr(O<sup>t</sup>Bu)-OH, and deprotection of the N-terminal amino group by the treatment of piperidine afforded tetrapeptide precursor **15**. Cleavage of the hydrophobic anchor and the protecting group of the side chain under acidic condition followed by removal of the Alloc group afforded unprotected tetrapeptide **16** containing an unnatural indolyl glycine residue in 0.47% overall yield (70% average yield in each step) from **11**. Both diastereomers of the products were obtained in a ratio of 66:34. The stereochemistry of the major diastereomer was tentatively assigned to be *R* on the basis of the model reaction using **1**.



Scheme 4. Application to peptide synthesis using a hydrophobic anchor

In conclusion, we here presented the unprecedented version of an asymmetric Friedel–Craft reaction for producing unnatural amino acid-containing peptides. Presented method features the use of peptidyl imine on a hydrophobic anchor. The conditions optimized by the model reaction using simple  $\alpha$ -imino amide **1**

as the substrate were applied to the catalytic asymmetric reaction of a peptide with a hydrophobic anchor, and this process successfully afforded the indolyl glycine-containing peptide. Further optimization of this system to develop a practical process applicable to the synthesis of biologically important peptides bearing a variety of unnatural amino acids is currently underway.

## EXPERIMENTAL

**General Procedure:** All reactions were carried out under a positive pressure of argon. Analytical thin-layer chromatography was performed on Merck TLC silica gel 60F<sub>254</sub> silica gel plates. Visualization was accomplished with molibdenum phosphate, *p*-anisaldehyde, Hannessian's cocktail or ninhydrin. For column chromatography, silica gel (KANTO KAGAKU N-60) was employed. NMR spectra were recorded using a Bruker AV400N at 400 MHz frequency for <sup>1</sup>H, and JEOL JNM-AL300 at 75 MHz frequency for <sup>13</sup>C in the stated solvents using tetramethylsilane as an internal standard. Chemical shifts were reported in parts per million (ppm) on the  $\delta$  scale from an internal standard (NMR descriptions: s, singlet; d, doublet; t, triplet; q, quartet; hept, heptet; m, multiplet; br, broad). Coupling constants, *J*, are reported in Hertz. For chiral HPLC analysis, a chiralpak IA (DAICEL, 4.6 × 250 mm), a chiralpak IB-3 (DAICEL, 4.6 × 250 mm) or a chiralpak IC-3 (DAICEL, 4.6 × 250 mm) were employed and eluting products were detected by UV at 254 nm. A solvent system consisting of HPLC grade of hexane and 2-propanol was used for HPLC analysis. Mass spectra were recorded on a Waters MICROMASS<sup>®</sup> LCT PREMIERTM (ESI-TOF). Optical rotations were measured using a JASCO P-2200 polarimeter (concentration in g dL<sup>-1</sup>). IR was measured using a JEOL FT-IR 6200. Melting point was determined on YANAGIMOTO micro melting point apparatus. For analysis and separation of the peptidic products, a Cosmosil 5C<sub>18</sub>-AR-II analytical column (Nacalai Tesque, 4.6 × 250 mm, flow rate 1.0 mL/min) or a Cosmosil 5C<sub>18</sub>-AR-II semi-preparative column (Nacalai Tesque, 10 × 250 mm, flow rate 3.0 mL/min) was employed, respectively, and eluting products were detected by UV at 220 nm. A solvent system consisting of 0.1% TFA aqueous solution (v/v, solvent A), 0.1% TFA in MeCN (v/v, solvent B) or 0.1% HCO<sub>2</sub>NH<sub>4</sub> aqueous solution (w/v, solvent C), MeCN (solvent D) were used for HPLC elution. Materials were purchased from Tokyo Chemical Industry Co., Ltd., Aldrich Inc., Wako Pure Chemical Industries Ltd., Nacalai tesque Inc., Kanto Chemical Co., Inc. commercial suppliers and were used without purification. For manganese (IV) oxide, CMD-100 (NIPPON DENKO Co., Ltd. Japan) was used. The catalysts **3b** and **3d** were prepared according to the literature procedure.<sup>14</sup>

### Preparation of the starting material 1

#### *N*-Methyl-2-(((2-nitrophenyl)thio)amino)acetamide (Nps-Gly-NHMe)

To a solution of H-Gly-NHMe<sup>15</sup> (2.08 g, 23.6 mmol) in CHCl<sub>3</sub> (50 mL) were added Et<sub>3</sub>N (4.94 mL, 35.4

mmol) and Nps-Cl (3.84 g, 20.3 mmol) at 0 °C and stirred at rt. After 12 h, the reaction mixture was quenched with 5% KHSO<sub>4</sub> aq, extracted with CH<sub>2</sub>Cl<sub>2</sub>, dried over Na<sub>2</sub>SO<sub>4</sub>, evaporated *in vacuo* and purified by recrystallization from hexane and EtOAc to afford Nps-Gly-NHMe as a yellow powder (2.68 g, 55%). mp 166–168 °C (hexane/EtOAc); <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ 8.26 (dd, *J*<sub>1</sub> = 8.3 Hz, *J*<sub>2</sub> = 1.2 Hz, 1H), 7.90 (dd, *J*<sub>1</sub> = 8.3 Hz, *J*<sub>2</sub> = 1.2 Hz, 1H), 7.88 (s, 1H), 7.81 (ddd, *J*<sub>1</sub> = *J*<sub>2</sub> = 8.3 Hz, *J*<sub>3</sub> = 1.2 Hz, 1H), 7.39 (ddd, *J*<sub>1</sub> = *J*<sub>2</sub> = 8.3 Hz, *J*<sub>3</sub> = 1.2 Hz, 1H), 5.20 (t, *J* = 5.6 Hz, 1H), 3.45 (d, *J* = 5.6 Hz, 2H), 2.62 (d, *J* = 4.6 Hz, 3H); <sup>13</sup>C NMR (75.0 MHz, DMSO-*d*<sub>6</sub>) δ 170.3, 145.4, 142.1, 134.4, 125.8, 125.2, 124.7, 53.4, 25.5; IR (KBr) ν 3359, 3273, 1648, 1632, 1546 cm<sup>-1</sup>; MS-ESI *m/z* 264 (M + Na<sup>+</sup>, 100); Anal. Calcd for C<sub>9</sub>H<sub>11</sub>N<sub>3</sub>O<sub>3</sub>S: C, 44.81; H, 4.60; N, 17.42. Found: C, 44.60; H, 4.50; N, 17.21.

### (*E*)-*N*-Methyl-2-(((2-nitrophenyl)thio)imino)acetamide (1)

To a solution of Nps-Gly-NHMe (500 mg, 2.07 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (40 mL) was added MnO<sub>2</sub> (3.60 g, 41.4 mmol) at rt and stirred at the same temperature for 1 h. Then, the insoluble manganese reagent was removed by filtration through Celite<sup>®</sup>. The residue was evaporated *in vacuo* and purified by silica gel column chromatography (CHCl<sub>3</sub>/acetone = 4/1) to afford **1** as a yellow powder (437 g, 88%). mp 134–135 °C (hexane/EtOAc); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 8.34 (dd, *J*<sub>1</sub> = 8.3 Hz, *J*<sub>2</sub> = 1.3 Hz, 1H), 8.26 (dd, *J*<sub>1</sub> = 8.3 Hz, *J*<sub>2</sub> = 8.3 Hz, 1H), 8.22 (s, 1H), 7.75 (ddd, *J*<sub>1</sub> = *J*<sub>2</sub> = 8.3 Hz, *J*<sub>3</sub> = 1.3 Hz, 1H), 7.42 (ddd, *J*<sub>1</sub> = *J*<sub>2</sub> = 8.3 Hz, *J*<sub>3</sub> = 1.3 Hz, 1H), 6.79 (s, 1H), 3.00 (d, *J* = 5.3 Hz, 3H); <sup>13</sup>C NMR (75.0 MHz, CDCl<sub>3</sub>) δ 162.1, 154.4, 142.7, 137.9, 134.3, 126.1, 125.7, 26.1; IR (KBr) ν 3224, 3074, 1658, 1590, 1566, 1514 cm<sup>-1</sup>; MS-ESI *m/z* 262 (M + Na<sup>+</sup>, 100); HRMS-ESI (*m/z*): [M + Na<sup>+</sup>] calcd for C<sub>9</sub>H<sub>9</sub>N<sub>3</sub>NaO<sub>3</sub>S; 262.0262, found, 262.0257.

### Preparation of the catalysts **3a** and **3c**

#### (*S*)-4-Hydroxy-2,6-bis(triphenylsilyl)dinaphtho[2,1-*d*:1',2'-*f*][1,3,2]dioxaphosphepine 4-oxide (**3a**)

To a solution of (*S*)-3,3'-bis(triphenylsilyl)-[1,1'-binaphthalene]-2,2'-diol<sup>16</sup> (538 mg, 0.670 mmol) in pyridine (1.55 mL, 19.3 mmol) was added POCl<sub>3</sub> (157 μL, 1.68 mmol) at rt and stirred at 95 °C for 12 h. After that, H<sub>2</sub>O (1000 μL) was added at 0 °C and stirred at 95 °C for 6 h. Then, the reaction mixture was diluted with CH<sub>2</sub>Cl<sub>2</sub>, washed with 1 M HCl, dried over Na<sub>2</sub>SO<sub>4</sub>, evaporated *in vacuo* and purified by silica gel column chromatography (CHCl<sub>3</sub>/MeOH = 100/1 to 20/1). The collected residue was dissolved in CH<sub>2</sub>Cl<sub>2</sub> and washed with 1 M HCl to afford **3a** (382 mg, 66%) as a white powder. mp >300 °C (hexane/EtOAc); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 8.08 (s, 2H), 7.78 (d, *J* = 8.1 Hz, 2H), 7.67-7.61 (m, 12H), 7.45-7.27 (m, 22H), 7.24-7.16 (m, 2H); <sup>13</sup>C NMR (75.0 MHz, CDCl<sub>3</sub>) δ 151.2, 141.9, 136.7, 134.2, 133.9, 130.8, 129.6, 128.7, 127.8, 127.5, 126.9, 126.0, 125.5, 121.4; IR (KBr) ν 3068, 3047, 1826, 1585, 1429, 1280, 1212 cm<sup>-1</sup>; MS-ESI *m/z* 887 (M + Na<sup>+</sup>, 100); HRMS-ESI (*m/z*): [M + Na<sup>+</sup>] calcd for

C<sub>56</sub>H<sub>41</sub>NaO<sub>4</sub>PSi<sub>2</sub>; 887.2179, found, 887.2179; [ $\alpha$ ]<sub>D</sub><sup>15</sup> +155.4 (*c* 1.00, CHCl<sub>3</sub>).

**(S)-4-Hydroxy-2,6-bis(triphenylsilyl)-8,9,10,11,12,13,14,15-octahydrodinaphtho[2,1-*d*:1',2'-*f*][1,3,2]-dioxaphosphepine 4-oxide (3c)**

To a solution of 3,3'-bis(triphenylsilyl)-5,5',6,6',7,7',8,8'-octahydro-[1,1'-binaphthalene]-2,2'-diol<sup>17</sup> (186 mg, 0.229 mmol) in pyridine (1.83 mL, 22.7 mmol) was added POCl<sub>3</sub> (42.8  $\mu$ L, 0.459 mmol) at rt and stirred at 95 °C for 20 h. Additional POCl<sub>3</sub> (428  $\mu$ L, 4.59 mmol) was added at rt and the mixture was stirred at 95 °C for 34 h. After that, H<sub>2</sub>O (1.83 mL) was added and stirred at 95 °C for 6 h. Then, the reaction mixture was diluted with CH<sub>2</sub>Cl<sub>2</sub>, washed with 1 M HCl, dried over Na<sub>2</sub>SO<sub>4</sub>, evaporated *in vacuo* and purified by silica gel column chromatography (CHCl<sub>3</sub>/MeOH = 20/1). The collected residue was dissolved in CH<sub>2</sub>Cl<sub>2</sub> and washed with 1 M HCl to afford **3c** (119 mg, 60%) as a white powder. mp 183–184 °C (hexane/EtOAc); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  7.61-7.53 (m, 12H), 7.39-7.27 (m, 18H), 7.13 (s, 2H), 3.07-2.83 (m, 4H), 2.79-2.56 (m, 6H), 2.32-2.22 (m, 2H), 1.83-1.71 (m, 2H), 1.67-1.56 (m, 2H); <sup>13</sup>C NMR (75.0 MHz, CDCl<sub>3</sub>)  $\delta$  151.3, 140.6, 139.2, 136.6, 134.4, 129.4, 129.0, 128.2, 127.6, 122.2, 29.1, 28.0, 22.6, 22.4; IR (KBr)  $\nu$  1821, 1568, 1490, 1309, 1106 cm<sup>-1</sup>; MS-ESI *m/z* 871 (M - H<sup>-</sup>, 100); HRMS-ESI (*m/z*): [M + Na<sup>+</sup>] calcd for C<sub>56</sub>H<sub>49</sub>NaO<sub>4</sub>PSi<sub>2</sub>; 895.2805, found, 895.2775; [ $\alpha$ ]<sub>D</sub><sup>15</sup> +107.6 (*c* 1.00, CHCl<sub>3</sub>).

**Typical procedure for the asymmetric Friedel-Crafts reaction**

To a mixture of the *N*-Nps imine **1** (100 mg, 0.418 mmol), catalyst **3c** (14.6 mg, 0.0167 mmol), and MS5Å (62.5 mg) in CHCl<sub>3</sub> (4.2 mL) was added indole **2a** (73.5 mg, 0.627 mmol) at rt and stirred at the same temperature for 4 h. The resulting mixture was purified by silica gel column chromatography (CHCl<sub>3</sub>/acetone = 20/1) to afford the adduct **4a** (123 mg, 82%).

**(R)-2-(1*H*-Indol-3-yl)-*N*-methyl-2-(((2-nitrophenyl)thio)amino)acetamide (4a)**

Yellow powder; mp 163–165 °C (hexane/EtOAc); <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>)  $\delta$  11.09 (s, 1H), 8.26 (dd, *J*<sub>1</sub> = 8.3 Hz, *J*<sub>2</sub> = 1.3 Hz, 1H), 8.05-7.97 (m, 2H), 7.74 (ddd, *J*<sub>1</sub> = *J*<sub>2</sub> = 8.3 Hz, *J*<sub>3</sub> = 1.3 Hz, 1H), 7.67 (d, *J* = 8.0 Hz, 1H), 7.37 (dd, *J*<sub>1</sub> = *J*<sub>2</sub> = 8.0 Hz, 1H), 7.38-7.34 (m, 2H), 7.10 (dd, *J*<sub>1</sub> = *J*<sub>2</sub> = 7.0 Hz, 1H), 7.02 (dd, *J*<sub>1</sub> = *J*<sub>2</sub> = 7.0 Hz, 1H), 5.40 (d, *J* = 6.5 Hz, 1H), 4.62 (d, *J* = 6.5 Hz, 1H), 2.61 (d, *J* = 4.5 Hz, 3H); <sup>13</sup>C NMR (75.0 MHz, DMSO-*d*<sub>6</sub>)  $\delta$  172.0, 145.5, 142.2, 136.1, 134.2, 125.83, 125.78, 125.1, 125.0, 124.3, 121.3, 119.1, 118.8, 112.5, 111.6, 60.4, 25.7; IR (KBr)  $\nu$  3309, 3089, 1649, 1590, 1543, 1491, 1335 cm<sup>-1</sup>; MS-ESI *m/z* 379 (M + Na<sup>+</sup>, 100); HRMS-ESI (*m/z*): [M + Na<sup>+</sup>] calcd for C<sub>17</sub>H<sub>16</sub>N<sub>4</sub>NaO<sub>3</sub>S; 379.0841, found, 379.0822; HPLC [Chiralpak IC-3, hexane/2-propanol = 75/25, 1.0 mL/min,  $\lambda$  = 254 nm, retention times: (major) 32.4 min, (minor) 42.3 min, 80% ee]; [ $\alpha$ ]<sub>D</sub><sup>17</sup> -66.0 (*c* 1.00, CHCl<sub>3</sub>).

**(R)-2-(5-Methoxy-1H-indol-3-yl)-N-methyl-2-(((2-nitrophenyl)thio)amino)acetamide (4b)**

Yellow powder; mp 114–116 °C (hexane/EtOAc);  $^1\text{H}$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$  10.95 (s, 1H), 8.26 (dd,  $J_1 = 7.8$  Hz,  $J_2 = 1.0$  Hz, 1H), 8.07–8.00 (m, 2H), 7.75 (dd,  $J_1 = J_2 = 7.8$  Hz, 1H), 7.37 (ddd,  $J_1 = J_2 = 7.8$  Hz,  $J_3 = 1.0$  Hz, 1H), 7.30 (d,  $J = 2.5$  Hz, 1H), 7.27 (d,  $J = 8.8$  Hz, 1H), 7.16 (d,  $J = 2.5$  Hz, 1H), 6.75 (dd,  $J_1 = 8.8$  Hz,  $J_2 = 2.5$  Hz, 1H), 5.37 (d,  $J = 6.5$  Hz, 1H), 4.59 (d,  $J = 6.5$  Hz, 1H), 3.75 (s, 3H), 2.63 (d,  $J = 4.8$  Hz, 3H);  $^{13}\text{C}$  NMR (75.0 MHz, DMSO- $d_6$ )  $\delta$  172.1, 153.3, 145.5, 142.2, 134.2, 131.2, 126.3, 125.8, 125.1, 125.0, 124.9, 112.34, 112.26, 111.5, 100.8, 60.5, 55.4, 25.7; IR (KBr)  $\nu$  3305, 1658, 1589, 1564, 1509, 1336, 1305  $\text{cm}^{-1}$ ; MS-ESI  $m/z$  409 ( $\text{M} + \text{Na}^+$ , 100); HRMS-ESI ( $m/z$ ): [ $\text{M} + \text{Na}^+$ ] calcd for  $\text{C}_{18}\text{H}_{18}\text{N}_4\text{NaO}_4\text{S}$ ; 409.0946, found, 409.0961; HPLC [Chiralpak IC-3, hexane/2-propanol = 75/25, 1.0 mL/min,  $\lambda = 254$  nm, retention times: (major) 47.4 min, (minor) 72.1 min, 77% ee];  $[\alpha]^{17}_{\text{D}} -39.7$  ( $c$  1.00,  $\text{CHCl}_3$ ).

**(R)-2-(5-Chloro-1H-indol-3-yl)-N-methyl-2-(((2-nitrophenyl)thio)amino)acetamide (4c)**

Yellow powder; mp 131–134 °C (hexane/EtOAc);  $^1\text{H}$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$  11.29 (s, 1H), 8.25 (dd,  $J_1 = 8.3$  Hz,  $J_2 = 1.3$  Hz, 1H), 8.03 (q,  $J = 4.8$  Hz, 1H), 7.96 (dd,  $J_1 = 8.3$  Hz,  $J_2 = 1.3$  Hz, 1H), 7.74 (s, 1H), 7.73 (ddd,  $J_1 = J_2 = 8.3$  Hz,  $J_3 = 1.3$  Hz, 1H), 7.42 (d,  $J = 2.0$  Hz, 1H), 7.39 (d,  $J = 8.0$  Hz, 1H), 7.37 (ddd,  $J_1 = J_2 = 8.3$  Hz,  $J_3 = 1.3$  Hz, 1H), 7.09 (dd,  $J_1 = 8.0$  Hz,  $J_2 = 2.0$  Hz, 1H), 5.48 (d,  $J = 6.5$  Hz, 1H), 4.60 (d,  $J = 6.5$  Hz, 1H), 2.60 (d,  $J = 4.8$  Hz, 3H);  $^{13}\text{C}$  NMR (75.0 MHz, DMSO- $d_6$ )  $\delta$  171.7, 145.4, 142.2, 134.7, 134.1, 126.8, 126.3, 125.8, 125.1, 125.0, 123.5, 121.2, 118.6, 113.1, 112.5, 60.2, 25.7; IR (KBr)  $\nu$  3632, 3277, 1659, 1592, 1565  $\text{cm}^{-1}$ ; MS-ESI  $m/z$  413 ( $\text{M} (^{35}\text{Cl}) + \text{Na}^+$ , 100); HRMS-ESI ( $m/z$ ): [ $\text{M} + \text{Na}^+$ ] calcd for  $\text{C}_{17}\text{H}_{15}^{35}\text{ClN}_4\text{NaO}_3\text{S}$ ; 413.0451, found, 413.0448; HPLC [Chiralpak IC-3, hexane/2-propanol = 75/25, 1.0 mL/min,  $\lambda = 254$  nm, retention times: (major) 15.1 min, (minor) 21.0 min, 85% ee];  $[\alpha]^{17}_{\text{D}} -39.7$  ( $c$  1.00,  $\text{CHCl}_3$ ).

**(R)-2-(5-Bromo-1H-indol-3-yl)-N-methyl-2-(((2-nitrophenyl)thio)amino)acetamide (4d)**

Yellow powder; mp 142–144 °C (hexane/EtOAc);  $^1\text{H}$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$  11.30 (s, 1H), 8.26 (dd,  $J_1 = 8.3$  Hz,  $J_2 = 1.0$  Hz, 1H), 8.03 (q,  $J = 4.5$  Hz, 1H), 7.97 (d,  $J = 8.3$  Hz, 1H), 7.89 (s, 1H), 7.73 (ddd,  $J_1 = J_2 = 8.3$  Hz,  $J_3 = 1.0$  Hz, 1H), 7.41 (d,  $J = 2.5$  Hz, 1H), 7.37 (ddd,  $J_1 = J_2 = 8.3$  Hz,  $J_3 = 1.0$  Hz, 1H), 7.36 (d,  $J = 8.5$  Hz, 1H), 7.21 (dd,  $J_1 = 8.5$  Hz,  $J_2 = 2.5$  Hz, 1H), 5.48 (d,  $J = 6.3$  Hz, 1H), 4.61 (d,  $J = 6.3$  Hz, 1H), 2.61 (d,  $J = 4.5$  Hz, 3H);  $^{13}\text{C}$  NMR (75.0 MHz, DMSO- $d_6$ )  $\delta$  171.7, 145.4, 142.2, 134.9, 134.1, 127.6, 126.1, 125.8, 125.1, 125.0, 123.7, 121.7, 113.6, 112.4, 111.6, 60.2, 25.7; IR (KBr)  $\nu$  3319, 1661, 1633, 1516, 1339  $\text{cm}^{-1}$ ; MS-ESI  $m/z$  457 ( $\text{M} (^{79}\text{Br}) + \text{Na}^+$ , 96), 459 ( $\text{M} (^{81}\text{Br}) + \text{Na}^+$ , 100); HRMS-ESI ( $m/z$ ): [ $\text{M} (^{79}\text{Br}) + \text{Na}^+$ ] calcd for  $\text{C}_{17}\text{H}_{15}^{79}\text{BrN}_4\text{NaO}_3\text{S}$ ; 456.9946, found, 456.9947; HPLC [Chiralpak IC-3, hexane/2-propanol = 75/25, 1.0 mL/min,  $\lambda = 254$  nm, retention times: (major) 15.0 min,

(minor) 20.6 min, 81% ee];  $[\alpha]_D^{20}$   $-43.3$  ( $c$  1.00,  $\text{CHCl}_3$ ).

**(R)-N-Methyl-2-(2-methyl-1H-indol-3-yl)-2-(((2-nitrophenyl)thio)amino)acetamide (4e)**

Yellow powder; mp 159–161 °C (hexane/EtOAc);  $^1\text{H}$  NMR (400 MHz,  $\text{DMSO-}d_6$ )  $\delta$  10.96 (s, 1H), 8.24 (dd,  $J_1 = 8.5$  Hz,  $J_2 = 1.0$  Hz, 1H), 7.88 (q,  $J = 4.8$  Hz, 1H), 7.85 (dd,  $J_1 = 8.5$  Hz,  $J_2 = 1.0$  Hz, 1H), 7.70 (ddd,  $J_1 = J_2 = 8.5$  Hz,  $J_3 = 1.0$  Hz, 1H), 7.62 (d,  $J = 7.8$  Hz, 1H), 7.36 (ddd,  $J_1 = J_2 = 8.5$  Hz,  $J_3 = 1.0$  Hz, 1H), 7.24 (d,  $J = 7.8$  Hz, 1H), 7.00 (dd,  $J_1 = 7.8$  Hz,  $J_2 = 1.2$  Hz, 1H), 6.93 (ddd,  $J_1 = J_2 = 7.8$  Hz,  $J_3 = 1.0$  Hz, 1H), 5.35 (d,  $J = 4.8$  Hz, 1H), 4.53 (d,  $J = 4.8$  Hz, 1H), 2.59 (d,  $J = 4.8$  Hz, 3H), 2.32 (s, 3H);  $^{13}\text{C}$  NMR (75.0 MHz,  $\text{DMSO-}d_6$ )  $\delta$  165.9, 136.6, 134.9, 127.6, 126.4, 125.2, 118.6, 117.1, 116.9, 116.4, 112.4, 110.7, 110.1, 102.1, 99.3, 52.2, 17.0, 2.4; IR (KBr)  $\nu$  3311, 1630, 1512, 1339, 1305  $\text{cm}^{-1}$ ; MS-ESI  $m/z$  393 ( $\text{M} + \text{Na}^+$ , 100); HRMS-ESI ( $m/z$ ):  $[\text{M} + \text{Na}^+]$  calcd for  $\text{C}_{18}\text{H}_{18}\text{N}_4\text{NaO}_3\text{S}$ ; 393.0997, found, 393.0995; HPLC [Chiralpak IC-3, hexane/2-propanol = 50/50, 1.0 mL/min,  $\lambda = 254$  nm, retention times: (major) 51.2 min, (minor) 27.0 min, 45% ee];  $[\alpha]_D^{17}$   $-17.3$  ( $c$  1.00,  $\text{CHCl}_3$ ).

**(R)-N-Methyl-2-(4-methyl-1H-indol-3-yl)-2-(((2-nitrophenyl)thio)amino)acetamide (4f)**

Yellow powder; mp 180–182 °C (hexane/EtOAc);  $^1\text{H}$  NMR (400 MHz,  $\text{DMSO-}d_6$ )  $\delta$  11.09 (d,  $J = 2.2$  Hz, 1H), 8.23 (dd,  $J_1 = 8.5$  Hz,  $J_2 = 1.2$  Hz, 1H), 8.04 (dd,  $J_1 = 8.5$  Hz,  $J_2 = 1.2$  Hz, 1H), 7.89 (q,  $J = 4.5$  Hz, 1H), 7.67 (ddd,  $J_1 = J_2 = 8.5$  Hz,  $J_3 = 1.2$  Hz, 1H), 7.34 (d,  $J = 2.2$  Hz, 1H), 7.33 (ddd,  $J_1 = J_2 = 8.5$  Hz,  $J_3 = 1.2$  Hz, 1H), 7.20 (d,  $J = 8.0$  Hz, 1H), 6.96 (dd,  $J_1 = J_2 = 8.0$  Hz, 1H), 6.75 (d,  $J = 8.0$  Hz, 1H), 5.28 (d,  $J = 6.3$  Hz, 1H), 4.90 (d,  $J = 6.3$  Hz, 1H), 2.60 (d,  $J = 4.5$  Hz, 3H), 2.57 (s, 3H);  $^{13}\text{C}$  NMR (75.0 MHz,  $\text{DMSO-}d_6$ )  $\delta$  172.7, 145.5, 142.1, 136.2, 133.9, 129.4, 125.6, 125.4, 125.0, 124.8, 124.7, 121.2, 120.8, 113.1, 109.6, 60.7, 25.8, 20.3; IR (KBr)  $\nu$  3306, 1647, 1491, 1336, 1306  $\text{cm}^{-1}$ ; MS-ESI  $m/z$  393 ( $\text{M} + \text{Na}^+$ , 100); HRMS-ESI ( $m/z$ ):  $[\text{M} + \text{Na}^+]$  calcd for  $\text{C}_{18}\text{H}_{18}\text{N}_4\text{NaO}_3\text{S}$ ; 393.0997, found, 393.0994; HPLC [Chiralpak IC-3, hexane/2-propanol = 75/25, 1.0 mL/min,  $\lambda = 254$  nm, retention times: (major) 34.5 min, (minor) 56.7 min, 77% ee];  $[\alpha]_D^{17}$   $-45.2$  ( $c$  1.00,  $\text{CHCl}_3$ ).

**(R)-N-Methyl-2-(5-methyl-1H-indol-3-yl)-2-(((2-nitrophenyl)thio)amino)acetamide (4g)**

Yellow powder; mp 184–187 °C (hexane/EtOAc);  $^1\text{H}$  NMR (400 MHz,  $\text{DMSO-}d_6$ )  $\delta$  11.95 (d,  $J = 1.8$  Hz, 1H), 8.26 (dd,  $J_1 = 8.3$  Hz,  $J_2 = 1.3$  Hz, 1H), 8.01 (dd,  $J_1 = 8.3$  Hz,  $J_2 = 1.3$  Hz, 1H), 7.97 (q,  $J = 3.8$  Hz, 1H), 7.74 (ddd,  $J_1 = J_2 = 8.3$  Hz,  $J_3 = 1.3$  Hz, 1H), 7.44 (s, 1H), 7.38 (dd,  $J_1 = 8.3$  Hz,  $J_2 = 1.3$  Hz, 1H), 7.28 (d,  $J = 1.5$  Hz, 1H), 7.26 (d,  $J = 8.5$  Hz, 1H), 6.93 (dd,  $J_1 = 8.5$  Hz,  $J_2 = 1.5$  Hz, 1H), 5.34 (d,  $J = 6.3$  Hz, 1H), 4.58 (d,  $J = 6.3$  Hz, 1H), 2.61 (d,  $J = 3.8$  Hz, 3H), 2.38 (s, 3H);  $^{13}\text{C}$  NMR (75.0 MHz,  $\text{DMSO-}d_6$ )  $\delta$  172.0, 145.5, 142.2, 134.5, 134.1, 127.2, 126.1, 125.8, 125.1, 125.0, 124.3, 122.8, 118.6,

112.0, 111.3, 60.4, 25.7, 21.4; IR (KBr)  $\nu$  3297, 1659, 1508, 1336, 1305  $\text{cm}^{-1}$ ; MS-ESI  $m/z$  393 ( $M + \text{Na}^+$ , 100); HRMS-ESI ( $m/z$ ): [ $M + \text{Na}^+$ ] calcd for  $\text{C}_{18}\text{H}_{18}\text{N}_4\text{NaO}_3\text{S}$ ; 393.0997, found, 393.1012; HPLC [Chiralpak IC-3, hexane/2-propanol = 75/25, 1.0 mL/min,  $\lambda$  = 254 nm, retention times: (major) 29.2 min, (minor) 44.3 min, 70% ee];  $[\alpha]^{17}_{\text{D}}$   $-32.3$  ( $c$  1.00,  $\text{CHCl}_3$ ).

**(R)-N-Methyl-2-(6-methyl-1H-indol-3-yl)-2-(((2-nitrophenyl)thio)amino)acetamide (4h)**

Yellow powder; mp 117–120 °C (hexane/EtOAc);  $^1\text{H}$  NMR (400 MHz,  $\text{DMSO}-d_6$ )  $\delta$  10.92 (s, 1H), 8.26 (dd,  $J_1 = 7.8$  Hz,  $J_2 = 1.3$  Hz, 1H), 7.99 (dd,  $J_1 = 7.8$  Hz,  $J_2 = 1.3$  Hz, 1H), 7.98 (q,  $J = 4.8$  Hz, 1H), 7.75 (ddd,  $J_1 = J_2 = 7.8$  Hz,  $J_3 = 1.3$  Hz, 1H), 7.53 (d,  $J = 8.3$  Hz, 1H), 7.37 (ddd,  $J_1 = J_2 = 7.8$  Hz,  $J_3 = 1.3$  Hz, 1H), 7.25 (d,  $J = 2.2$  Hz, 1H), 7.16 (s, 1H), 6.85 (dd,  $J_1 = 8.3$  Hz,  $J_2 = 2.2$  Hz, 1H), 5.34 (d,  $J = 6.3$  Hz, 1H), 4.57 (d,  $J = 6.3$  Hz, 1H), 2.60 (d,  $J = 4.8$  Hz, 3H), 2.39 (s, 3H);  $^{13}\text{C}$  NMR (75.0 MHz,  $\text{DMSO}-d_6$ )  $\delta$  172.0, 145.5, 142.1, 136.6, 134.2, 130.3, 125.8, 125.1, 125.0, 123.8, 123.6, 120.6, 118.8, 112.4, 111.3, 60.5, 25.7, 21.4; IR (KBr)  $\nu$  3297, 1659, 1508, 1336, 1305  $\text{cm}^{-1}$ ; MS-ESI  $m/z$  393 ( $M + \text{Na}^+$ , 100); HRMS-ESI ( $m/z$ ): [ $M + \text{Na}^+$ ] calcd for  $\text{C}_{18}\text{H}_{18}\text{N}_4\text{NaO}_3\text{S}$ ; 393.0997, found, 393.1007; HPLC [Chiralpak IC-3, hexane/2-propanol = 75/25, 1.0 mL/min,  $\lambda$  = 254 nm, retention times: (major) 36.8 min, (minor) 61.1 min, 79% ee];  $[\alpha]^{17}_{\text{D}}$   $-52.2$  ( $c$  1.00,  $\text{CHCl}_3$ ).

**(R)-N-Methyl-2-(7-methyl-1H-indol-3-yl)-2-(((2-nitrophenyl)thio)amino)acetamide (4i)**

Yellow powder; mp 192–195 °C (hexane/EtOAc);  $^1\text{H}$  NMR (400 MHz,  $\text{DMSO}-d_6$ )  $\delta$  11.07 (s, 1H), 8.26 (dd,  $J_1 = 7.7$  Hz,  $J_2 = 1.2$  Hz, 1H), 7.99 (dd,  $J_1 = 7.7$  Hz,  $J_2 = 1.2$  Hz, 1H), 7.98 (q,  $J = 4.5$  Hz, 1H), 7.74 (ddd,  $J_1 = J_2 = 7.7$  Hz,  $J_3 = 1.2$  Hz, 1H), 7.49 (d,  $J = 6.8$  Hz, 1H), 7.37 (ddd,  $J_1 = J_2 = 7.7$  Hz,  $J_3 = 1.2$  Hz, 1H), 7.34 (d,  $J = 2.5$  Hz, 1H), 6.96–6.88 (m, 2H), 5.37 (d,  $J = 6.5$  Hz, 1H), 4.60 (d,  $J = 6.5$  Hz, 1H), 2.60 (d,  $J = 4.5$  Hz, 3H), 2.45 (s, 3H);  $^{13}\text{C}$  NMR (75.0 MHz,  $\text{DMSO}-d_6$ )  $\delta$  172.0, 145.5, 142.2, 135.6, 134.2, 125.8, 125.6, 125.1, 125.0, 124.0, 121.7, 120.7, 119.0, 116.6, 113.0, 60.5, 25.7, 16.7; IR (KBr)  $\nu$  3313, 1644, 1492, 1336, 1305  $\text{cm}^{-1}$ ; MS-ESI  $m/z$  393 ( $M + \text{Na}^+$ , 100); HRMS-ESI ( $m/z$ ): [ $M + \text{Na}^+$ ] calcd for  $\text{C}_{18}\text{H}_{18}\text{N}_4\text{NaO}_3\text{S}$ ; 393.0997, found, 393.0995; HPLC [Chiralpak IC-3, hexane/2-propanol = 75/25, 1.0 mL/min,  $\lambda$  = 254 nm, retention times: (major) 36.4 min, (minor) 52.1 min, 93% ee];  $[\alpha]^{16}_{\text{D}}$   $-52.1$  ( $c$  1.00, MeCN).

**Model study for deprotection and peptide elongation**

**Allyl (R)-3-(2-(methylamino)-1-(((2-nitrophenyl)thio)amino)-2-oxoethyl)-1H-indole-1-carboxylate (7)**

To a solution of **4a** (60.0 mg, 0.168 mmol) and DMAP (3.9 mg, 0.0319 mmol) in THF (1.7 mL) was added  $\text{Alloc}_2\text{O}$  (56.0  $\mu\text{L}$ , 0.209 mmol) at rt and stirred at the same temperature for 10 min. Then the

reaction mixture was purified by silica gel column chromatography (CHCl<sub>3</sub>/acetone = 30/1) to afford the Alloc-protected indolyl glycine **7** (74.5 mg, quant). Yellow powder; mp 170–171 °C (hexane/EtOAc); <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ 8.25 (dd, *J*<sub>1</sub> = 8.3 Hz, *J*<sub>2</sub> = 1.2 Hz, 1H), 8.14 (q, *J* = 4.5 Hz, 1H), 8.11 (d, *J* = 8.3 Hz, 1H), 7.97 (dd, *J*<sub>1</sub> = 8.3 Hz, *J*<sub>2</sub> = 1.2 Hz, 1H), 7.81 (s, 1H), 7.77 (d, *J* = 8.3 Hz, 1H), 7.74 (ddd, *J*<sub>1</sub> = *J*<sub>2</sub> = 8.3 Hz, *J*<sub>3</sub> = 1.2 Hz, 1H), 7.38 (dd, *J*<sub>1</sub> = *J*<sub>2</sub> = 8.3 Hz, 1H), 7.37 (dd, *J*<sub>1</sub> = *J*<sub>2</sub> = 8.3 Hz, 1H), 7.29 (ddd, *J*<sub>1</sub> = *J*<sub>2</sub> = 8.3 Hz, *J*<sub>3</sub> = 1.2 Hz, 1H), 6.11 (dddd, *J*<sub>1</sub> = 17.3 Hz, *J*<sub>2</sub> = 10.4 Hz, *J*<sub>3</sub> = *J*<sub>4</sub> = 4.8 Hz, 1H), 5.72 (d, *J* = 7.0 Hz, 1H), 5.49 (ddd, *J*<sub>1</sub> = 17.3 Hz, *J*<sub>2</sub> = 3.2 Hz, *J*<sub>3</sub> = 1.6 Hz, 1H), 5.36 (ddd, *J*<sub>1</sub> = 10.4 Hz, *J*<sub>2</sub> = 2.8 Hz, *J*<sub>3</sub> = 1.6 Hz, 1H), 4.98-4.91 (m, 2H), 4.69 (d, *J* = 7.0 Hz, 1H), 2.61 (d, *J* = 4.5 Hz, 3H); <sup>13</sup>C NMR (75.0 MHz, DMSO-*d*<sub>6</sub>) δ 170.8, 149.9, 145.1, 142.1, 134.9, 134.3, 132.0, 128.5, 125.8, 125.2, 124.8, 124.4, 123.0, 120.2, 119.3, 119.0, 114.7, 67.4, 59.8, 25.8; IR (KBr) ν 3280, 3119, 1727, 1645, 1510, 1456, 1402, 1342, 1306 cm<sup>-1</sup>; MS-ESI *m/z* 463 (M + Na<sup>+</sup>, 100); HRMS-ESI (*m/z*): [M + Na<sup>+</sup>] calcd for C<sub>21</sub>H<sub>20</sub>N<sub>4</sub>NaO<sub>5</sub>S; 463.1052, found, 463.1044; [α]<sup>16</sup><sub>D</sub> -91.0 (*c* 1.00, CHCl<sub>3</sub>).

#### Allyl (*R*)-3-(1-amino-2-(methylamino)-2-oxoethyl)-1*H*-indole-1-carboxylate (**8**)

To a solution of **7** (47.0 mg, 0.107 mmol) in CHCl<sub>3</sub> (1.3 mL) was added 2-mercaptopyridine (119 mg, 1.07 mmol) at rt and stirred at 50 °C for 1 h. Then the reaction mixture was purified by silica gel column chromatography (CHCl<sub>3</sub>/MeOH = 50/1) to afford the primary amine **8** (30.0 mg, 98%). Colorless oil; <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ 8.08 (d, *J* = 7.5 Hz, 1H), 8.05 (q, *J* = 4.8 Hz, 1H), 7.77 (d, *J* = 7.5 Hz, 1H), 7.63 (s, 1H), 7.34 (dd, *J*<sub>1</sub> = *J*<sub>2</sub> = 7.5 Hz, 1H), 7.25 (dd, *J*<sub>1</sub> = *J*<sub>2</sub> = 7.5 Hz, 1H), 6.10 (dddd, *J*<sub>1</sub> = 17.2 Hz, *J*<sub>2</sub> = 10.4 Hz, *J*<sub>3</sub> = *J*<sub>4</sub> = 5.5 Hz, 1H), 5.47 (ddd, *J*<sub>1</sub> = 17.2 Hz, *J*<sub>2</sub> = *J*<sub>3</sub> = 1.5 Hz, 1H), 5.35 (ddd, *J*<sub>1</sub> = 10.4 Hz, *J*<sub>2</sub> = *J*<sub>3</sub> = 1.5 Hz, 1H), 4.92 (ddd, *J*<sub>1</sub> = 5.5 Hz, *J*<sub>2</sub> = *J*<sub>3</sub> = 1.5 Hz, 2H), 4.59 (s, 1H), 2.61 (d, *J* = 4.8 Hz, 3H), 2.30 (s, 2H); <sup>13</sup>C NMR (75.0 MHz, DMSO-*d*<sub>6</sub>) δ 173.1, 150.0, 135.0, 132.1, 128.8, 124.5, 123.2, 122.8, 122.7, 120.6, 118.9, 114.6, 67.2, 52.1, 25.6; IR (NaCl) ν 3363, 3308, 1738, 1660, 1455, 1394 cm<sup>-1</sup>; MS-ESI *m/z* 310 (M + Na<sup>+</sup>, 100); HRMS-ESI (*m/z*): [M + Na<sup>+</sup>] calcd for C<sub>15</sub>H<sub>17</sub>N<sub>3</sub>NaO<sub>3</sub>; 310.1168, found, 310.1180; [α]<sup>14</sup><sub>D</sub> -9.8 (*c* 1.00, CHCl<sub>3</sub>).

#### Allyl (*R*)-3-(1-(2-aminoacetamido)-2-(methylamino)-2-oxoethyl)-1*H*-indole-1-carboxylate (**10**)

To a solution of **8** (30.0 mg, 0.104 mmol) and Fmoc-Gly-OH (37.3 mg, 0.125 mmol) in CHCl<sub>3</sub> (5.2 mL) was added EDCI·HCl (24.0 mg, 0.125 mmol) at rt and stirred at the same temperature for 2 h. After that, the reaction was diluted with CHCl<sub>3</sub>, washed with H<sub>2</sub>O, dried over Na<sub>2</sub>SO<sub>4</sub> and evaporated *in vacuo*. To the residue was added Et<sub>2</sub>O to precipitate the product. Resulting white precipitate was collected by filtration to obtain the amide **9** containing small amount of impurities.

To a suspension of above obtained amide **9** in THF (3.0 mL) was added piperidine (193 μL, 2.01 mmol)

at rt. After stirring at the same temperature for 1 h, the reaction mixture was evaporated *in vacuo* and purified by silica gel column chromatography (THF/MeOH = 2/1) to afford the **10** (28.0 mg, 81% in two steps). White powder; mp 183–185 °C (hexane/EtOAc); <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ 8.57 (s, 1H), 8.30 (q, *J* = 4.4 Hz, 1H), 8.09 (d, *J* = 8.3 Hz, 1H), 7.75 (d, *J* = 8.3 Hz, 1H), 7.67 (s, 1H), 7.37 (dd, *J*<sub>1</sub> = *J*<sub>2</sub> = 8.3 Hz, 1H), 7.28 (dd, *J*<sub>1</sub> = *J*<sub>2</sub> = 8.3 Hz, 1H), 6.11 (dddd, *J*<sub>1</sub> = 17.1 Hz, *J*<sub>2</sub> = 10.5 Hz, *J*<sub>3</sub> = *J*<sub>4</sub> = 4.8 Hz, 1H), 5.69 (s, 1H), 5.47 (ddd, *J*<sub>1</sub> = 17.1 Hz, *J*<sub>2</sub> = *J*<sub>3</sub> = 1.5 Hz, 1H), 5.35 (ddd, *J*<sub>1</sub> = 10.5 Hz, *J*<sub>2</sub> = *J*<sub>3</sub> = 1.2 Hz, 1H), 4.97-4.090 (m, 2H), 3.32 (s, 2H), 2.61 (d, *J* = 4.4 Hz, 3H), 2.30 (s, 2H); <sup>13</sup>C NMR (75.0 MHz, DMSO-*d*<sub>6</sub>) δ 172.5, 169.5, 149.9, 134.9, 132.0, 128.3, 124.9, 123.8, 123.0, 120.1, 119.2, 119.1, 114.7, 67.4, 48.5, 44.5, 25.7; IR (KBr) ν 3284, 3055, 1740, 1648, 1536, 1456, 1394 cm<sup>-1</sup>; MS-ESI *m/z* 367 (M + Na<sup>+</sup>, 100); HRMS-ESI (*m/z*): [M + Na<sup>+</sup>] calcd for C<sub>17</sub>H<sub>20</sub>N<sub>4</sub>NaO<sub>4</sub>; 367.1382, found, 367.1393; [α]<sup>16</sup><sub>D</sub> - 53.2 (*c* 1.00, acetone).

To determine the enantiomeric excess of **10**, the primary amino group of **10** was protected by Fmoc group again and converted to less polar compound **6**.

### Allyl

#### (*R*)-3-(1-(9*H*-fluoren-9-yl)-3,6,9-trioxo-2-oxa-4,7,10-triazaundecan-8-yl)-1*H*-indole-1-carboxylate (**9**)

To a solution of **10** (28.0 mg, 0.0813 mmol) in THF (2.7 mL) was added Fmoc-OSu (30.2 mg, 0.0895 mmol) at rt and stirred at the same temperature. After 20 min, Fmoc-OSu (10.0 mg, 0.0296 mmol) was added and stirred for another 30 min. After that, the reaction mixture was purified by preparative TLC (CHCl<sub>3</sub>/acetone = 2/1) to afford Fmoc-protected dipeptide **9** (42.4 mg, 92%). White powder; mp 189–191 °C (hexane/EtOAc); <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>, 80 °C) δ 8.25 (d, *J* = 7.7 Hz, 1H), 8.07 (d, *J* = 8.0 Hz, 1H), 7.98 (q, *J* = 4.6 Hz, 1H), 7.85 (d, *J* = 7.5 Hz, 2H), 7.73 (d, *J* = 7.7 Hz, 1H), 7.70-7.62 (m, 3H), 7.48-7.16 (m, 8H), 6.10 (dddd, *J*<sub>1</sub> = 17.2 Hz, *J*<sub>2</sub> = 10.4 Hz, *J*<sub>3</sub> = *J*<sub>4</sub> = 5.5 Hz, 1H), 5.71 (d, *J* = 7.9 Hz, 1H), 5.46 (d, *J* = 17.2 Hz, 1H), 5.34 (d, *J* = 10.4 Hz, 1H), 4.93 (d, *J* = 5.5 Hz, 2H), 4.36-4.14 (m, 3H), 3.74 (d, *J* = 6.0 Hz, 2H), 2.63 (d, *J* = 4.6 Hz, 3H); <sup>13</sup>C NMR (75.0 MHz, DMSO-*d*<sub>6</sub>, 80 °C) δ 172.0, 169.2, 149.6, 143.5, 142.4, 140.3, 139.1, 137.1, 134.7, 131.6, 128.4, 128.2, 127.1, 126.8, 126.6, 124.7, 124.3, 123.5, 122.5, 120.8, 119.7, 119.53, 119.45, 119.0, 118.6, 114.3, 108.7, 67.0, 48.8, 48.5, 46.4, 44.3, 25.2; IR (KBr) ν 3289, 3067, 1737, 1693, 1540, 1456, 1395 cm<sup>-1</sup>; MS-ESI *m/z* 589 (M + Na<sup>+</sup>, 100); HRMS-ESI (*m/z*): [M + Na<sup>+</sup>] calcd for C<sub>32</sub>H<sub>30</sub>N<sub>4</sub>NaO<sub>6</sub>; 589.2063, found, 589.2092; [α]<sup>16</sup><sub>D</sub> -4.1 (*c* 1.00, DMF).

A mixture of **9** (35.4 mg, 0.0625 mmol), TFA (6.24 mL), <sup>1</sup>Pr<sub>3</sub>SiH (156 μL) and H<sub>2</sub>O (156 μL) was stirred at rt for 30 min. After that, TFA was evaporated and the residue was added Et<sub>2</sub>O. Resulting white precipitate was collected by filtration and the reaction mixture was purified by silica gel column chromatography (CHCl<sub>3</sub>/acetone = 4/1) to recover the starting material **9** (33.0 mg, 93%).

**(9H-Fluoren-9-yl)methyl****(R)-2-(((1-(1H-indol-3-yl)-2-(methylamino)-2-oxoethyl)amino)-2-oxoethyl)carbamate (6)**

To a solution of above recovered **9** (33.0 mg) in DMF (0.58 mL) were added Pd(PPh<sub>3</sub>)<sub>4</sub> (6.7 mg, 5.8 μmol) and morpholine (10.1 μL, 0.116 mmol) at rt and stirred at the same temperature for 10 min. Then the reaction mixture was diluted with EtOAc, washed with sat. NH<sub>4</sub>Cl<sub>aq</sub>, dried over Na<sub>2</sub>SO<sub>4</sub>, evaporated *in vacuo* and purified by silica gel column chromatography (CHCl<sub>3</sub>/acetone = 2/1) to afford **6** (23.8 mg, 85%). Colorless amorphous; <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ 11.0 (s, 1H), 8.27 (d, *J* = 7.1 Hz, 1H), 8.08 (q, *J* = 4.6 Hz, 1H), 7.89 (d, *J* = 7.6 Hz, 2H), 7.71 (d, *J* = 7.6 Hz, 2H), 7.62 (d, *J* = 7.8 Hz, 1H), 7.55 (t, *J* = 5.9 Hz, 1H), 7.42 (dd, *J*<sub>1</sub> = *J*<sub>2</sub> = 7.6 Hz, 2H), 7.34 (dd, *J*<sub>1</sub> = *J*<sub>2</sub> = 7.6 Hz, 2H), 7.31 (d, *J* = 7.1 Hz, 1H), 7.24 (d, *J* = 2.4 Hz, 1H), 7.01 (dd, *J*<sub>1</sub> = *J*<sub>2</sub> = 7.1 Hz, 1H), 6.97 (dd, *J*<sub>1</sub> = *J*<sub>2</sub> = 7.1 Hz, 1H), 5.63 (d, *J* = 4.8 Hz, 1H), 4.31-4.19 (m, 3H), 3.69 (d, *J* = 5.9 Hz, 2H), 2.59 (d, *J* = 4.6 Hz, 3H); <sup>13</sup>C NMR (75.0 MHz, DMSO-*d*<sub>6</sub>) δ 170.6, 168.4, 156.5, 143.8, 140.7, 136.1, 127.6, 127.1, 125.7, 125.2, 123.9, 121.2, 120.1, 119.1, 118.7, 112.0, 111.4, 65.7, 49.7, 46.6, 43.2, 25.6; IR (KBr) ν 3062, 2545, 1705, 1659, 1524, 1452 cm<sup>-1</sup>; MS-ESI *m/z* 505 (M + Na<sup>+</sup>, 100); HRMS-ESI (*m/z*): [M + Na<sup>+</sup>] calcd for C<sub>28</sub>H<sub>26</sub>N<sub>4</sub>NaO<sub>4</sub>; 505.1852, found, 505.1849; HPLC [Chiralpak IC-3, hexane/2-propanol = 50/50, 1.0 mL/min, λ = 254 nm, retention times: (major) 16.6 min, (minor) 9.9 min, 82% ee]; [α]<sup>16</sup><sub>D</sub> -28.1 (*c* 0.82, DMF).

**Application to peptide synthesis using hydrophobic anchor****(E)-N-(Bis(4-(docosyloxy)phenyl)methyl)-2-(2-(((2-nitrophenyl)thio)imino)acetamido)acetamido)-acetamide (13)**

<Condensation> To a solution of **11**<sup>6a</sup> (2.00 g, 2.40 mmol), HOBt·H<sub>2</sub>O (441 mg, 2.88 mmol) and Fmoc-Gly-OH (856 mg, 2.88 mmol) in CHCl<sub>3</sub> (100 mL) was added diisopropylcarbodiimide (446 μL, 2.88 mmol) at rt and stirred at the same temperature for 1 h. After that, small amount of MeOH was added and CHCl<sub>3</sub> was evaporated *in vacuo*. Then, MeOH was added and the white precipitate was washed with MeOH. The collected white solid was used for next step without further purifications.

<Removal of Fmoc group> To a solution of above obtained white solid in CHCl<sub>3</sub> (40 mL) was added piperidine (8.00 mL, 80.9 mmol) at rt and stirred at the same temperature for 3 h. After that, small amount of MeOH was added and CHCl<sub>3</sub> was evaporated *in vacuo*. Then, MeOH was added and the white precipitate was washed with MeOH. The collected white solid was used for next step without further purifications.

The processes of condensation and removal of Fmoc group were repeated three times to yield H-Gly-Gly-Gly-NHDpm (C<sub>22</sub>) (2.18 g).

To a solution of H-Gly-Gly-Gly-NHDpm (C<sub>22</sub>) (2.18 g) in CHCl<sub>3</sub> (80 mL) were added Et<sub>3</sub>N (0.502 mL,

3.59 mmol) and Nps-Cl (683 mg, 3.60 mmol) at rt and stirred at the same temperature for 30 min. After that, small amount of MeOH was added and CHCl<sub>3</sub> was evaporated *in vacuo*. Then, MeOH was added and the yellow precipitate was washed with MeOH to yield **12** (2.27 g). 500 mg of thus obtained product was used for next step without further purifications.

To a solution of crude **12** (500 mg) in CHCl<sub>3</sub> (8.6 mL) was added MnO<sub>2</sub> (563 mg, 6.48 mmol) at rt and stirred at the same temperature for 2 h. After that, the manganese reagent was removed by filtration through Celite<sup>®</sup> and the filtrate was purified by silica gel column chromatography (CHCl<sub>3</sub>/acetone = 10/1) to yield the imine containing hydrophobic anchor **13** (210.7 mg). Yellow powder: <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 8.30 (d, *J* = 7.3 Hz, 1H), 8.28 (d, *J* = 7.3 Hz, 1H), 8.04 (s, 1H), 7.69 (dd, *J*<sub>1</sub> = *J*<sub>2</sub> = 7.3 Hz, 1H), 7.54 (s, 1H), 7.37 (dd, *J*<sub>1</sub> = *J*<sub>2</sub> = 7.3 Hz, 1H), 7.16 (s, 1H), 7.08 (d, *J* = 8.6 Hz, 4H), 6.88 (s, 1H), 6.79 (d, *J* = 8.6 Hz, 4H), 6.07 (d, *J* = 7.8 Hz, 1H), 4.03 (d, *J* = 5.4 Hz, 2H), 3.98 (d, *J* = 5.4 Hz, 2H), 3.87 (t, *J* = 6.6 Hz, 4H), 1.76-1.70 (m, 4H), 1.43-1.37 (m, 4H), 1.33-1.21 (m, 72H), 0.88 (t, *J* = 6.6 Hz, 6H). 200 mg of thus obtained product was used for next step.

**(*R*)-*N*-(2-((2-((Bis(4-(docosyloxy)phenyl)methyl)amino)-2-oxoethyl)amino)-2-oxoethyl)-2-(1*H*-indol-3-yl)-2-(((2-nitrophenyl)thio)amino)acetamide (14)**

To a solution of **13** (200 mg, *ca.* 0.17 mmol) in CHCl<sub>3</sub> (3.64 mL) were added MS5Å (250 mg), catalyst **3c** (75.5 mg, 0.086 mmol) and indole **2a** (30.4 mg, 0.259 mmol) at rt and stirred at the same temperature for 2 days. After that, small amount of MeOH was added and CHCl<sub>3</sub> was evaporated *in vacuo*. Then, MeOH was added and the yellow precipitate was washed with MeOH and purified by silica gel column chromatography (CHCl<sub>3</sub>/acetone = 4/1) to yield **14** (92.5 mg) containing impurities. 91.6 mg of thus obtained product was used for next step.

**3-(((10*R*,13*S*)-13-Amino-14-(4-(*tert*-butoxy)phenyl)-1,1-bis(4-(docosyloxy)phenyl)-3,6,9,12-tetraoxo-2,5,8,11-tetraazatetradecan-10-yl)-1*H*-indole-1-carboxylate (15)**

To a solution of **14** (91.6 mg) in THF (3.6 mL) were added *N*-Alloc imidazole (219 mg, 1.44 mmol) and DBU (21.5 μL, 0.144 mmol) at rt and stirred at the same temperature for 22 h. After that, small amount of MeOH was added and THF was evaporated *in vacuo*. Then, MeOH was added and the yellow precipitate was washed with MeOH to yield Alloc-protected product (99.3 mg) as yellow powder. Thus obtained product was used for next step without further purifications.

To a solution of above obtained product in CHCl<sub>3</sub> (2.4 mL) was added 2-mercaptopyridine (118 mg, 14.8 mmol) at rt and stirred at 50 °C for 18 h. After that, small amount of MeOH was added and CHCl<sub>3</sub> was evaporated *in vacuo*. Then, MeOH was added and the white precipitate was washed with MeOH to yield primary amine product (91.2 mg) as white powder. Thus obtained product was used for next step without

further purifications.

To a solution of above obtained product, HOBt·H<sub>2</sub>O (28.3 mg, 0.185 mmol) and Fmoc-Tyr(<sup>t</sup>Bu)-OH (36.2 mg, 0.0788 mmol) in CHCl<sub>3</sub> (2.4 mL) was added EDCI·HCl (15.6 mg, 0.0814 mmol) at rt and stirred at the same temperature for 90 min. After that, small amount of MeOH was added and CHCl<sub>3</sub> was evaporated *in vacuo*. Then, MeOH was added and the white precipitate was washed with MeOH to yield tetrapeptide product (92.3 mg) as white powder. Thus obtained product was used for next step without further purifications.

To a solution of above obtained product in THF (2.4 mL) was added piperidine (142 μL, 1.44 mmol) at rt and stirred at the same temperature for 3 h. After that, small amount of MeOH was added and THF was evaporated *in vacuo*. Then, MeOH was added and the white precipitate was washed with MeOH to yield the product (39.7 mg) including **15** as white powder. Thus obtained product was used for next step without further purifications.

**(S)-2-Amino-N-((R)-2-((2-((2-amino-2-oxoethyl)amino)-2-oxoethyl)amino)-1-(1H-indol-3-yl)-2-oxoethyl)-3-(4-hydroxyphenyl)propanamide (16)**

A mixture of above obtained product, TFA (3.8 mL), <sup>i</sup>Pr<sub>3</sub>SiH (0.1 mL) and H<sub>2</sub>O (0.1 mL) was stirred at rt for 30 min. After that, MeCN was added. The precipitated hydrophobic anchor was removed by filtration and washed with TFA. Then, the amount of TFA in the filtrate was reduced to *ca.* 5 mL by evaporation and the resulting residue was poured into cold Et<sub>2</sub>O (250 mL). After stirring the suspension for 5 min, the supernatant was discarded by decantation and precipitated peptide was collected (1.91 mg). To a solution of above obtained peptide (1.91 mg) in DMF (0.3 mL) were added morpholine (8.63 μL, 99.1 μmol) and Pd(PPh<sub>3</sub>)<sub>4</sub> (4.0 mg, 3.46 μmol) at rt and incubated at the same temperature for 5 min. The reaction mixture was passed through Wakogel<sup>®</sup> 50C18 (eluent: H<sub>2</sub>O/MeOH = 50/50) and the collected filtrate was lyophilized. Then, the crude product was purified by semipreparative HPLC (Preparative HPLC condition: linear gradient of solvent D in solvent C, 10 to 30% over 30 min) to afford **16** (0.85 mg, 0.47% from **11**). Colorless amorphous powder; retention times = 12.5 min for major diastereomer and 10.2 min for minor diastereomer (Analytical HPLC condition: linear gradient of solvent B in solvent A, 10 to 40% over 30 min); LRMS (ESI-TOF) *m/z* calcd for C<sub>23</sub>H<sub>27</sub>N<sub>6</sub>O<sub>5</sub> ([M + H]<sup>+</sup>): 467.2, found: 467.1; HRMS (ESI-TOF) *m/z* calcd for C<sub>23</sub>H<sub>26</sub>N<sub>6</sub>NaO<sub>5</sub> ([M + Na]<sup>+</sup>): 489.1862, found: 489.1884.

## ACKNOWLEDGEMENTS

This research was supported in part by a Grant-in-Aid for Young Scientist (B) (JP16K18845) from Japan Society for the Promotion of Science (JSPS), a research program for the development of an intelligent Tokushima artificial exosome (iTEX) from Tokushima University, and Shionogi & Co., Ltd. Award in

Synthetic Organic Chemistry, Japan from Shionogi & Co., Ltd.. We also thank NIPPON DENKO Co., Ltd. for providing the MnO<sub>2</sub>.

## REFERENCES AND NOTES

- (a) K. Fosgerau and T. Hoffmann, *Drug Discov. Today*, 2015, **20**, 122; (b) L. Otvos and J. D. Wade, *Front. Chem.*, 2014, **2**, 62; (c) A. A. Kasper and J. M. Reichert, *Drug Discov. Today*, 2013, **18**, 807; (d) D. J. Craik, D. P. Fairlie, S. Liras, and D. Price, *Chem. Biol. Drug Des.*, 2013, **81**, 136.
- (a) W. Kang, H. Liu, L. Ma, M. Wang, S. Wei, P. Sun, M. Jiang, M. Guo, C. Zhou, and J. Dou, *Eur. J. Pharm. Sci.*, 2017, **105**, 169; (b) M. Arias, K. V. Jensen, L. T. Nguyen, D. G. Storey, and H. J. Vogel, *Biochim. Biophys. Acta*, 2015, **1848**, 277; (c) C. J. Vickers, G. E. González-Páez, K. M. Litwin, J. C. Umotoy, E. A. Coutsiás, and D. W. Wolan, *ACS Chem. Biol.*, 2014, **9**, 2194; (d) R. P. Hicks, J. J. Abercrombie, R. K. Wong, and K. P. Leung, *Bioorg. Med. Chem.*, 2013, **21**, 205.
- For reviews, see: (a) K. Maruoka, T. Ooi, and T. Kano, *Chem. Commun.*, 2007, 1487; (b) K. Maruoka and T. Ooi, *Chem. Rev.*, 2003, **103**, 3013. For recent examples, see: (c) S. S. M. Spoehrle, T. H. West, J. E. Taylor, A. M. Z. Slawin, and A. D. Smith, *J. Am. Chem. Soc.*, 2017, **139**, 11895; (d) X.-Z. Zhang, Y.-H. Deg, X. Yan, K.-Y. Yu, F.-X. Wang, X.-Y. Ma, and C.-A. Fan, *J. Org. Chem.*, 2016, **81**, 5655; (e) J.-X. Guo, T. Zhou, B. Xu, S.-F. Zhu, and Q.-L. Zhou, *Chem. Sci.*, 2016, **7**, 1104; (f) X.-H. Wei, G.-W. Wang, and S.-D. Yang, *Chem. Commun.*, 2015, **51**, 832; (g) C. Molinaro, J. P. Scott, M. Shevlin, C. Wise, A. Ménard, A. Gibb, E. M. Junker, and D. Lieberman, *J. Am. Chem. Soc.*, 2015, **137**, 999.
- For reviews, see: (a) B. Eftekhari-Sis and M. Zirak, *Chem. Rev.*, 2017, **117**, 8326; (b) A. E. Taggi, A. M. Hafez, and T. Leckta, *Acc. Chem. Res.*, 2003, **36**, 10; (c) S. Perera, D. Sinha, N. K. Rana, V. Trieu-Do and J. C.-G. Zhao, *J. Org. Chem.*, 2013, **78**, 10947; (d) J. Jiang, X. Ma, S. Liu, Y. Qian, F. Lv, L. Qiu, X. Wu, and W. Hu, *Chem. Commun.*, 2013, **49**, 4238; (e) S. Kobayashi, M. M. Salter, Y. Yamazaki, and Y. Yamashita, *Chem. Asian J.*, 2010, **5**, 493; (f) T. Kano, Y. Yamaguchi, and K. Maruoka, *Chem. Eur. J.*, 2009, **15**, 6678; (g) M. Rueping and A. P. Antonchick, *Org. Lett.*, 2008, **10**, 1731.
- (a) M. S. Segundo, I. Guerrero, and A. Correa, *Org. Lett.*, 2017, **19**, 5288; (b) L. Zhao, O. Basle, and C.-J. Li, *Proc. Natl. Acad. Sci. USA*, 2009, **106**, 4106.
- (a) D. Takahashi, T. Yano, and T. Fukui, *Org. Lett.*, 2012, **14**, 4514; (b) G. Tana, S. Kitada, S. Fujita, Y. Okada, S. Kim, and K. Chiba, *Chem. Commun.*, 2010, **46**, 8219.
- (a) X.-W. Wang, Y.-Z. Hua, and M.-C. Wang, *J. Org. Chem.*, 2016, **81**, 9227; (b) D. Lin, J. Wang, X. Zhang, S. Zhou, J. Lian, H. Jiang, and H. Liu, *Chem. Commun.*, 2013, **49**, 2575; (c) K. Goswami, I. Duttagupta, and S. Sinha, *J. Org. Chem.*, 2012, **77**, 7081; (d) Q. Kang, Z.-A. Zhao and S.-L. You,

- [Tetrahedron, 2009, 65, 1603](#); (e) T. Andreassen, L-K. Hansen, and O. R. Gautun, [Eur. J. Org. Chem., 2008, 4871](#); (f) M. J. Wanner, P. Hauwert, H. E. Schoemaker, R. de Gelder, J. H. van Maarseveen, and H. Hiemstra, [Eur. J. Org. Chem., 2008, 180](#).
8. M. Terada, S. Yokoyama, K. Sorimachi, and D. Uruguchi, [Adv. Synth. Catal., 2007, 349, 1863](#).
  9. See supporting information for detail.
  10. R. G. Lovey and A. B. Cooper, [Synlett, 1994, 167](#).
  11. The acidic treatment of **6** resulted in complex mixture including Fmoc-Gly-NH<sub>2</sub>. We presume that the degraded product was produced by (1) protonation of indole to form cationic species (2) liberation of indole moiety to form Fmoc-Gly-N=CHC(O)NHMe (3) hydrolysis of imine.
  12. T. Inokuma, T. Jichu, K. Nishida, A. Shigenaga, and A. Otaka, [Chem. Pharm. Bull., 2017, 65, 573](#).
  13. S. T. Heller, E. E. Schultz, and R. Sarpong, [Angew. Chem. Int. Ed., 2012, 51, 8304](#).
  14. T. Kano, T. Yurino, D. Asakawa, and K. Maruoka, [Angew. Chem. Int. Ed., 2013, 52, 5532](#).
  15. J. H. Rowley, S. C. Yau, B. M. Kariuki, A. R. Kennedy, and N. C. O. Tomkinson, [Org. Biomol. Chem., 2013, 11, 2198](#).
  16. R. B. Benford, Y.-N. Chang, M. F. Haddow, and C. L. McMullin, [Dalton Trans., 2011, 40, 9034](#).
  17. N. V. Sewgobind, M. J. Wanner, S. Ingemann, R. de Gelder, J. H. van Maarseveen, and H. Hiemstra, [J. Org. Chem., 2008, 73, 6405](#).