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Enantioselective synthesis of stimulus-responsive amino acid via asymmetric α-amination of aldehyde

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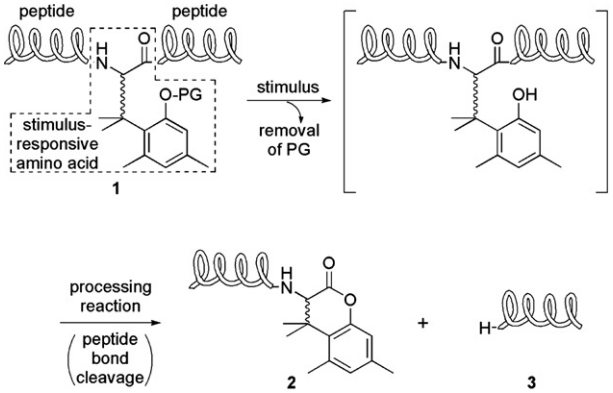
ABSTRACT

Development of a methodology to control the function of peptides and proteins is an indispensable task in the field of chemical biology and drug delivery. Recently, we reported synthesis of racemic stimulus-responsive amino acids and their application for controlling peptidyl function. In this study, we report enantioselective synthesis of a key intermediate of stimulus-responsive amino acids via asymmetric α-amination reaction of an aldehyde. The obtained chiral intermediate was converted to an Fmoc protected UV-responsive amino acid with (*S*)-configuration, and it was successfully incorporated into a model peptide by Fmoc solid phase peptide synthesis.

1. Introduction

Development of a methodology to control the function of peptides/proteins is an indispensable task in the field of chemical biology and drug delivery. Photo-responsive processing (peptide bond cleavage)[1a–i] or conformational change[1j] has been successfully applied for controlling peptide/protein function. Previously, we reported a stimulus-responsive amino acid[2] including a photo-responsive one[2a,c,d] and its application for controlling peptidyl function in living cells[2d] (Scheme 1). Peptide **1**, possessing the stimulus-responsive amino acid, was converted to processing products **2** and **3** by stimulus-induced removal of PG (protective group removable by a stimulus) followed by lactonization of the trimethyl lock moiety.[3] In previous reports, the racemic material was used as a stimulus-responsive amino acid;[2] therefore, its incorporation into a peptide afforded a diastereomeric mixture of the peptide. Consequently, it has been desirable to synthesize a chiral stimulus-responsive amino acid for ease of purifying synthetic peptides. In this paper, we report enantioselective synthesis of a key intermediate of the stimulus-responsive amino acid and its application for preparing the Fmoc protected UV-responsive amino acid with (*S*)-configuration identical to that of naturally occurring amino acids. Incorporation of the UV-responsive amino acid into a model peptide is also reported.



Scheme 1. Stimulus-responsive processing system (PG: protective group removable by a stimulus).

2. Results and discussion

2.1. Enantioselective α-amination of aldehyde 4

An enantioselective α-amination of an aldehyde with a dialkyl azodicarboxylate in the presence of proline[4,5] or its derivatives[4,6] is one of the most attractive methods for preparing chiral amino acid derivatives. Therefore, we applied these systems for enantioselective α-amination of aldehyde **4**[2d] (Table 1). Aldehyde **4** was

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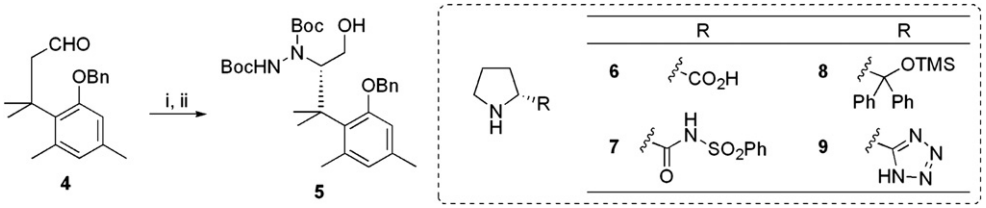
Table 1
Asymmetric α-amination of aldehyde **4**



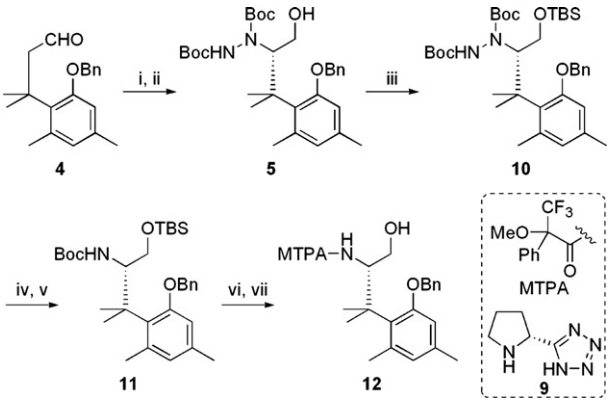
Entry	Catalyst (equiv)	Solvent	Time	Yield of **5** (%)	ee of **5** (%)
1	**6** (0.5)	DMSO	7 days	—[a]	20
2	**6** (0.1)[b]	CH_2Cl_2	7 days	—[a]	2[c]
3	**6** (0.1)[b]	Acetonitrile	7 days	—[a]	10[c]
4	**7** (0.2)[b]	CH_2Cl_2	7 days	—[a]	—
5	**7** (0.2)[b]	Acetonitrile	7 days	—[a]	—
6	**8** (0.1)	Toluene	3 days	22	>99[c]
7	**9** (0.1)	CH_2Cl_2	3 days	67	>99
8	**9** (0.1)	CH_2Cl_2	7 days	42	98
9	**9** (0.1)	Acetonitrile	1.5 days	42	78
10	**9** (0.1)	Acetonitrile[d]	4 days	—[a]	18
11	**9** (0.5)	CH_2Cl_2	3 days	85	>99
12	**9** (0.5)	CH_2Cl_2[d]	3 days	37	84
13	**9** (0.5)	Acetonitrile	1.5 days	54	78
14	**9** (0.5)	DMF	1 days	56	63
15	**9** (0.5)	THF	3 days	70	79

Reagents and conditions. (i) di-*tert*-butyl azodicarboxylate, catalyst, solvent, rt. (ii) $NaBH_4$, MeOH.
[a] Almost all starting material was recovered.
[b] An enantiomer of the catalyst was used.
[c] An enantiomer of alcohol **5** was obtained as a major product.
[d] Water (10% (v/v)) was added.

treated with di-*tert*-butyl azodicarboxylate in the presence of proline or its derivatives, and the resulting mixture was immediately reduced to alcohol **5** with sodium borohydride to prevent a racemization reaction. An enantiomeric excess was determined by chiral HPLC analysis of alcohol **5**. Determination of the absolute configuration of alcohol **5** will be mentioned later. When proline **6** or sulfonamide **7**[6n,7] was used as a catalyst, almost all starting material was recovered after a week of reaction (entries 1–5). In the presence of 0.1 equiv of silyl ether **8**,[6j,7] an enantiomer of **5** was obtained enantioselectively (>99% ee); however, the chemical yield after 72 h of reaction was not sufficient (entry 6). A moderate chemical yield and high enantioselectivity were achieved using 0.1 equiv of tetrazole **9**[6m,7] in CH_2Cl_2 (entry 7). Prolonged reaction time decreased the chemical yield and enantioselectivity presumably due to side reactions of the generated aldehyde (entries 7 and 8). After optimization of reaction conditions (entries 7–15), alcohol **5** with high enantiomeric purity was obtained in high yield using 0.5 equiv of tetrazole **9** in CH_2Cl_2 (entry 11, 85% yield, >99% ee).

2.2. Determination of absolute configuration

Next, we attempted to determine the absolute configuration of alcohol **5** using Kusumi's method, also known as a modified Mosher's method (Scheme 2).[8] Aldehyde **4** was converted to alcohol **5** under the reaction conditions of entry 11 in Table 1. According to the previous report,[2d] crude alcohol **5** was derivatized to protected amino alcohol **11**. Briefly, the hydroxyl group of **5** was protected with a *tert*-butyldimethylsilyl (TBS) group. Then, trifluoroacetylation of the terminal nitrogen of **10** and subsequent reductive cleavage of the activated N–N bond afforded protected amino alcohol **11**. Deprotection of the Boc group and the TBS group of **11** under acidic conditions followed by acylation with (*R*) or (*S*)-1-methoxy-1-phenyl-1-trifluoromethylacetic acid afforded (*R*) or (*S*)-MTPA amide **12**, respectively. For calculation of Δδ values, which was obtained by subtracting the chemical shift of (*R*)-MTPA derivative from that of (*S*)-MTPA derivative ($\Delta\delta = \delta_{(S)\text{-MTPA}} - \delta_{(R)\text{-MTPA}}$), H_a, H_b, H_c, and H_d were assigned on the basis of NOE experiment (Fig. 1a). Then, the Δδ values were calculated and the absolute configuration of amide **12** was ascertained as (*S*) (Fig. 1b).[8b] It is



Scheme 2. Reagents and conditions: (i) di-*tert*-butyl azodicarboxylate, **9** (0.5 equiv), CH_2Cl_2. (ii) $NaBH_4$, MeOH. (iii) TBSOTf, Et_3N, CH_2Cl_2, 0 °C, 75% (three steps). (iv) Trifluoroacetic anhydride, Et_3N, CH_2Cl_2. (v) SmI_2, *t*-BuOH, HMPA, THF, 64% (two steps). (vi) HCl, 1,4-dioxane. (vii) (*S*) or (*R*)-1-methoxy-1-phenyl-1-trifluoromethylacetic acid, EDC·HCl, Et_3N, CH_2Cl_2, 36% (two steps) for (*R*)-MTPA derivative, 38% (two steps) for (*S*)-MTPA derivative.

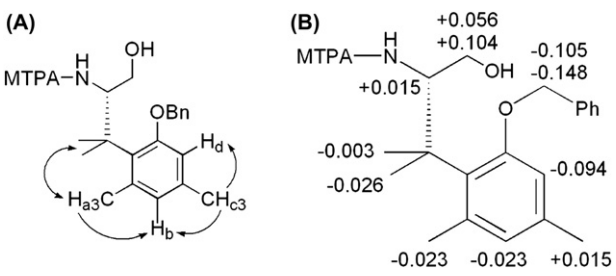


Figure 1. Determination of the absolute configuration using Kusumi's method. (a) Observed NOEs (arrows) with MTPA amide **12**. (b) Δδ values ($\delta_{(S)\text{-MTPA}} - \delta_{(R)\text{-MTPA}}$) obtained for (*S*)- and (*R*)-MTPA amide **12** in $CDCl_3$ with 5% (v/v) D_2O.

widely accepted that tetrazole **9**-mediated α-amination of an aldehyde proceeds via hydrogen bonding of a tetrazole moiety of an enamine intermediate to a dialkyl azodicarboxylate to generate an aminated product with (*S*)-configuration (Fig. 2).[4a,6m] Therefore, the enantioselectivity observed in our experiments agrees well with that of the previous report.

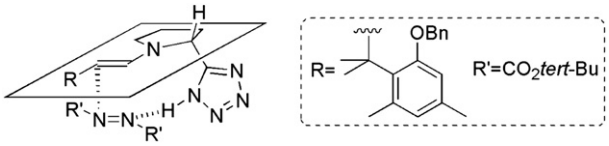
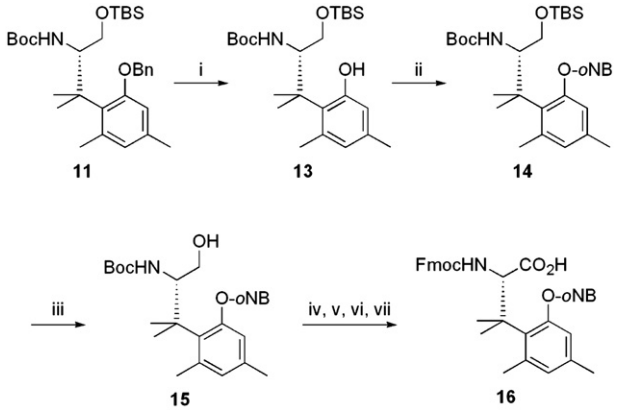


Figure 2. Proposed transition state for the α-amination of aldehyde **4**.

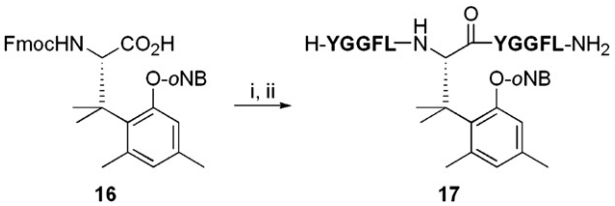
2.3. Synthesis of chiral stimulus-responsive amino acid derivative

Having chiral intermediate **11** with (*S*)-configuration, we then attempted to synthesize a chiral UV-responsive amino acid possessing an *o*-nitrobenzyl group as a phenolic protective group (Scheme 3).[2d] The benzyl group of **11** was removed by hydrogenolysis to afford phenol **13**. In this reaction, accidental removal of the TBS group was sometimes observed;[9] however, it was suppressed by the addition of sodium bicarbonate. Phenol **13** is a key synthetic intermediate of stimulus-responsive amino acids.[2a,b,d] Therefore, an enantiomeric excess of **13** was ascertained by chiral HPLC and was determined as >99% ee. To demonstrate the applicability of chiral synthetic intermediate **13** for synthesis of the stimulus-responsive amino acids, it was converted to UV-responsive amino acid derivative **16**. Phenol **13** was alkylated with *o*-nitrobenzyl bromide to afford ether **14** (*o*-NB: *o*-nitrobenzyl). Then, the silyl group of **14** was removed under acidic conditions to generate alcohol **15**. Oxidation of alcohol **15** using pyridinium dichromate (PDC) in DMF was examined; however, a mixture of corresponding aldehyde and a small amount of the carboxylic acid was obtained. The use of PDC in DMF for oxidation of primary alcohols has been well documented to afford corresponding carboxylic acids.[10] However in our case, the second step for the carboxylic acid did not proceed well, presumably due to the presence of a sterically hindered side chain functionality. Therefore, the obtained crude material was subjected to subsequent oxidation with $NaClO_2$, followed by deprotection of the Boc group and protection of the generated amine with an Fmoc group to yield Fmoc amino acid **16** in 84% yield over four steps.



Scheme 3. Reagents and conditions: (i) H_2, Pd/C, $NaHCO_3$, MeOH, 83%, >99% ee (ii) *o*-nitrobenzyl bromide, K_2CO_3, DMF, 84%. (iii) AcOH, H_2O, THF, 93%. (iv) PDC, DMF. (v) $NaClO_2$, 2-methyl-2-butene, NaH_2PO_4, acetonitrile, acetone, H_2O. (vi) HCl, AcOEt. (vii) FmocOSu, Na_2CO_3, acetonitrile, H_2O, 84% (four steps). (*o*-NB: *o*-nitrobenzyl).

Unfortunately, attempts to determine the enantiomeric excess of **16** using chiral HPLC (ChiralPak IA, *i*-PrOH/hexane system) were unsuccessful. In the previous report, we noted that peptide **17** and its diastereomer **17′** derived from racemic **16** can be easily separated by reverse phase HPLC (Scheme 4).[2d] Therefore, we decided to estimate an enantiomeric excess of amino acid derivative **16** on the basis of a diastereomeric excess of the peptide. Peptide **17** was synthesized by Fmoc solid phase peptide synthesis according to the previous report. The obtained crude material was analyzed by reverse phase HPLC, and peptide **17** was eluted at 21.0 min (Fig. 3a). When racemic **16** was incorporated in the peptide, **17** and its diastereomer **17′** were eluted separately (retention time of **17′**: 22.6 min) (Fig. 3b). Based on these results, a diastereomeric excess of the peptide derived from **16** was calculated as >99% de. Therefore, an enantiomeric excess of Fmoc amino acid **16** was estimated as >99% ee.



Scheme 4. Reagents and conditions: (i) Fmoc solid phase peptide synthesis on a NovaSyn TGR resin. (ii) TFA/triethylsilane/H_2O=95/2.5/2.5 (v/v/v). (*o*-NB: *o*-nitrobenzyl; **F**: phenylalanine; **G**: glycine; **L**: leucine; **Y**: tyrosine).

3. Conclusions and summary

In conclusion, enantioselective synthesis of a key intermediate of stimulus-responsive amino acids via asymmetric α-amination reaction of the aldehyde was reported. An absolute configuration of the intermediate was ascertained as (*S*) using Kusumi's method. The obtained chiral intermediate was applied for preparing the Fmoc protected UV-responsive amino acid with (*S*)-configuration and was successfully incorporated into a model peptide by Fmoc solid phase peptide synthesis. These results enable us to prepare chiral stimulus-responsive amino acids, not just the UV-responsive compound. Its application in synthesizing other stimulus-responsive amino acids is in progress.

4. Experimental section

4.1. General methods

All reactions were carried out under a positive pressure of argon unless otherwise noted. For column chromatography, silica gel (KANTO KAGAKU N-60) was employed. NMR spectra were measured using a JEOL GSX400, a Bruker AV400 N, or a JEOL JNM-AL300 spectrometer. Exact mass spectra were recorded on a Waters MICROMASS® LCT PREMIER™ or a Bruker Esquire200 T. Enantiomeric excesses were estimated by HPLC on a ChiralPak IA (Daicel Chiral Industries, Ltd., 4.6×250 mm, detection at 220 nm). For reverse phase HPLC analysis, a Cosmosil $5C_{18}$-AR-II analytical column (Nacalai Tesque, 4.6×250 mm) was employed and eluting products were detected by UV at 220 nm. Optical rotations were measured using a JASCO P-2200 polarimeter (concentration in g/100 mL).

4.2. Typical procedure of α-amination reaction described in Table 1 (entry 11)

To a solution of aldehyde **4**[2d] (50.0 mg, 169 μmol) in CH_2Cl_2 (250 μL) were added di-*tert*-butyl azodicarboxylate (54.3 mg, 236 μmol) and tetrazole **9**[6m,7] (11.7 mg, 84.0 μmol), and the reaction mixture was stirred at room temperature for 72 h. After addition of saturated aqueous solution of NH_4Cl, the resulting mixture was

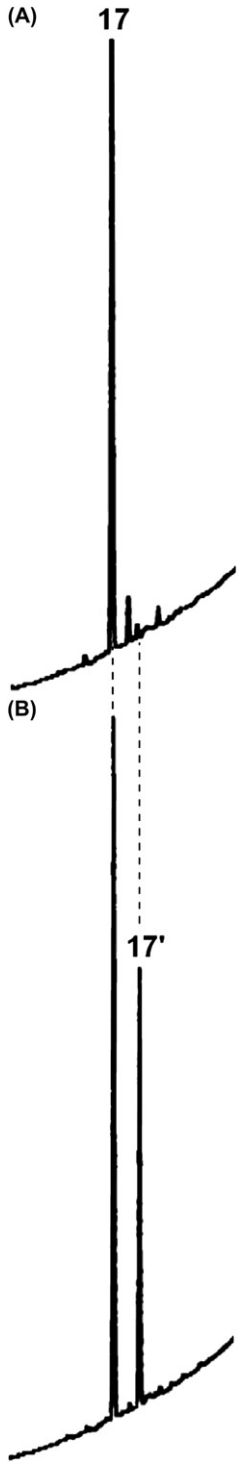


Figure 3. HPLC profiles of a crude material of the peptide derived from (a) **16**, or (b) racemic **16**. Peptide **17′** is a diastereomer of peptide **17**. Retention times, **17**: 21.0 min; **17′**: 22.6 min. Only a critical retention time region of the HPLC charts was enlarged. HPLC conditions: Cosmosil $5C_{18}$-AR-II column (4.6×250 mm) with a linear gradient of 0.1% (v/v) TFA in acetonitrile/0.1% (v/v) aqueous TFA solution (20–80% over 30 min) at a flow rate of 1.0 mL/min, detection at 220 nm.

stirred for 30 min and then extracted with diethyl ether. The organic phase was washed with brine, dried over Na_2SO_4, and concentrated in vacuo. To the obtained crude material were successively added MeOH (2.00 mL) and sodium borohydride (8.0 mg, 210 μmol) at 0 °C. The resulting suspension was stirred at room temperature for 30 min. After addition of saturated aqueous solution of NH_4Cl, the reaction mixture was stirred for 30 min and then extracted with AcOEt. The combined organic layer was washed with 5% (w/v) aqueous solution of $KHSO_4$ followed by brine, dried over Na_2SO_4, and concentrated in vacuo. The crude product was purified by preparative TLC (SiO_2, hexane/AcOEt=2/1 (v/v)), and 75.7 mg of alcohol **5** (143 μmol, 85%, >99% ee) was obtained as a white powder. ^{1}H NMR spectrum was identical with that of the racemic one.[2d] HPLC conditions: ChiralPak IA (hexane/*i*-PrOH=95/5 (v/v), 0.25 mL/min). Retention times: 36.3 min (minor) and 57.6 min (major).

4.3. Asymmetric synthesis of Fmoc protected UV-responsive amino acid derivative

*4.3.1. (S)-3-(2-Benzyloxy-4,6-dimethylphenyl)-2-(1,2-di-tert-butoxycarbonylhydrazinyl)-3,3-dimethylpropanol (**5**).* Aldehyde **4**[2d] (1.33 g, 4.47 mmol) was converted to corresponding alcohol **5** according to the experiment in the Section 4.2. The crude product was reprecipitated from hexane, and 2.34 g of alcohol **5** was obtained as a white powder. It was used for a subsequent reaction without further purification. $[\alpha]_D^{19}$ +5.47 (*c* 1.45, $CHCl_3$); ^{1}H NMR spectrum was identical with that of the racemic one.[2d]

*4.3.2. (S)-3-(2-Benzyloxy-4,6-dimethylphenyl)-2-(1,2-di-tert-butoxycarbonylhydrazinyl)-3,3-dimethylpropanol tert-butyldimethylsilyl ether (**10**).* Alcohol **5** (2.34 g) was converted to corresponding silyl ether **10** (2.16 g, 3.36 mmol, 75% over three steps) according to the previous report.[2d] $[\alpha]_D^{19}$ +17.1 (*c* 1.03, $CHCl_3$); ^{1}H NMR spectrum was identical with that of the racemic one.

*4.3.3. (S)-3-(2-Benzyloxy-4,6-dimethylphenyl)-2-tert-butoxycarbonylamino-3,3-dimethylpropanol tert-butyldimethylsilyl ether (**11**).* Hydrazine derivative **10** (2.16 g, 3.36 mmol) was converted to corresponding amine **11** (1.14 g, 2.16 mmol, 64% over two steps) according to the previous report.[2d] $[\alpha]_D^{21}$ −29.3 (*c* 1.06, $CHCl_3$); ^{1}H NMR spectrum was identical with that of the racemic one.

*4.3.4. (S)-2-tert-Butoxycarbonylamino-3,3-dimethyl-3-(4,6-dimethyl-2-hydroxyphenyl)propanol tert-butyldimethylsilyl ether (**13**).* Benzyl ether **11** (1.14 g, 2.16 mmol) was converted to corresponding phenol **13** (0.782 g, 1.79 mmol, 83%) according to the previous report.[2d] When desilylation had been observed, sodium bicarbonate (50 mg/MeOH 1.0 mL) was added to the reaction mixture. The enantiomeric excess was estimated as >99% ee. HPLC conditions: ChiralPak IA (hexane/*i*-PrOH=99/1 (v/v), 0.25 mL/min). Retention times: 32.4 min (minor) and 37.4 min (major). $[\alpha]_D^{20}$ −36.7 (*c* 0.95, $CHCl_3$); ^{1}H NMR spectrum was identical with that of the racemic one.

*4.3.5. (S)-2-tert-Butoxycarbonylamino-3,3-dimethyl-3-[2,4-dimethyl-6-(2-nitrobenzyloxy)phenyl]propanol tert-butyldimethylsilyl ether (**14**).* Phenol **13** (0.770 g, 1.76 mmol) was converted to corresponding nitrobenzyl ether **14** (0.840 g, 1.47 mmol, 84%) according to the previous report.[2d] $[\alpha]_D^{20}$ −35.5 (*c* 1.02, $CHCl_3$); ^{1}H NMR spectrum was identical with that of the racemic one.

*4.3.6. (S)-2-tert-Butoxycarbonylamino-3,3-dimethyl-3-[2,4-dimethyl-6-(2-nitrobenzyloxy)phenyl]propanol (**15**).* Silyl ether **14** (0.840 g, 1.47 mmol) was converted to corresponding alcohol **15** (0.623 g, 1.36 mmol, 93%) according to the previous report.[2d] $[\alpha]_D^{19}$ −18.9 (*c* 0.93, $CHCl_3$); ^{1}H NMR spectrum was identical with that of the racemic one.

*4.3.7. (S)-3,3-Dimethyl-3-[2,4-dimethyl-6-(2-nitrobenzyloxy)phenyl]-2-(9-fluorenylmethoxycarbonylamino)propionic acid (**16**).* Pyridinium dichromate (1.93 g, 5.13 mmol) was added to a solution of alcohol **15** (470 mg, 1.02 mmol) in DMF (5.20 mL). The reaction

mixture was stirred overnight. After addition of 5% (v/v) aqueous solution of $KHSO_4$, the obtained mixture was extracted with diethyl ether. The combined organic layer was washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The obtained crude material was subjected to subsequent reactions without purification according to the literature.[2d] Fmoc protected amino acid derivative **16** was obtained as a pale yellow amorphousness (514 mg, 84% over four steps). $[\alpha]_D^{23}$ −6.69 (*c* 1.12, $CHCl_3$); ^1H NMR spectrum was identical with that of the racemic one.

4.4. Determination of absolute configuration using Kusumi's method

4.4.1. General procedure for synthesis of MTPA derivatives. Hydrogen chloride in 1,4-dioxane (4 M, 1.0 mL) was added to substrate **11** (51 mg, 95 μmol) and the resulting mixture was stirred for 6 h. After being quenched with 1 M aqueous NaOH, the reaction mixture was extracted with CH_2Cl_2. The organic phase was dried over Na_2SO_4, and concentrated in vacuo to give a crude product. To the crude product in CH_2Cl_2 (1.0 mL) were added 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (EDC·HCl, 1.2 equiv), (*R*) or (*S*)-1-methoxy-1-phenyl-1-trifluoromethylacetic acid (1.2 equiv) and triethylamine (1.0 equiv), and the reaction mixture was stirred overnight. After being quenched with saturated aqueous solution of NH_4Cl, the reaction mixture was extracted with AcOEt. The organic phase was washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The obtained product was purified by column chromatography (hexane/AcOEt=6/1 (v/v)), and MTPA amide (*R*)-**12** or (*S*)-**12** was obtained, respectively, as a yellow oil.

*4.4.2. (R)-MTPA derivative ((R)-**12**).* $[\alpha]_D^{28}$ −9.89 (*c* 2.17, $CHCl_3$); ^1H NMR ($CDCl_3$ with 5% (v/v) D_2O, 400 MHz) δ=1.495 (3H, s), 1.566 (3H, s), 2.228 ($3H_c$, s), 2.507 ($3H_a$, s), 3.17 (3H, s), 3.533 (1H, dd, *J*=11.6 and 8.0 Hz), 3.687 (1H, dd, *J*=11.6 and 2.8 Hz), 4.912 (1H, td, *J*=8.0 and 2.8 Hz), 5.060 (1H, d, *J*=11.8 Hz), 5.133 (1H, d, *J*=12.0 Hz), 6.594 ($1H_b$, s), 6.673 ($1H_d$, s), 7.25–7.45 (8H, m), 7.54 (2H, m); ^{13}C NMR ($CDCl_3$, 75 MHz) δ=20.7 (CH_3), 25.9 (CH_3), 27.9 (CH_3), 29.0 (CH_3), 43.3 (C), 54.8 (CH_3), 58.9 (CH), 64.7 (CH_2), 71.1 (CH_2), 112.9 (CH), 127.6 (CH), 127.7 (CH), 127.9 (CH), 127.9 (CH), 128.5 (CH), 128.6 (CH), 129.4 (CH), 129.5 (C), 132.8 (C), 136.8 (C), 137.0 (C), 138.1 (C), 158.4 (C), 168.0 (C); HRMS (ESI-TOF) calcd for $C_{30}H_{34}F_3NNaO_4$ ($[M+Na]^+$): 552.2338, found: 552.2357.

*4.4.3. (S)-MTPA derivative ((S)-**12**).* $[\alpha]_D^{28}$ +11.3 (*c* 1.19, $CHCl_3$); ^1H NMR ($CDCl_3$ with 5% (v/v) D_2O, 400 MHz) δ=1.492 (3H, s), 1.540 (3H, s), 2.243 ($3H_c$, s), 2.484 ($3H_a$, s), 3.27 (3H, s), 3.589 (1H, dd, *J*=11.2 and 8.0 Hz), 3.791 (1H, dd, *J*=11.2 and 2.4 Hz), 4.927 (1H, td, *J*=8.0 and 2.4 Hz), 4.955 (1H, d, *J*=12.4 Hz), 4.985 (1H, d, *J*=12.4 Hz), 6.571 ($1H_b$, s), 6.579 ($1H_d$, s), 7.09 (2H, d, *J*=7.8 Hz), 7.21 (2H, t, *J*=7.8 Hz), 7.28–7.46 (6H, m); ^{13}C NMR ($CDCl_3$, 75 Hz) δ=20.8 (CH_3), 25.8 (CH_3), 28.4 (CH_3), 28.7 (CH_3), 43.3 (C), 54.8 (CH_3), 58.8 (CH), 64.4 (CH), 71.2 (CH_2), 100.5 (C), 112.9 (CH), 127.5 (CH), 127.8 (CH), 128.0 (CH), 128.3 (CH), 128.6 (CH), 129.2 (CH), 129.8 (C), 1323 (C), 136.8 (C), 136.8 (C), 137.8 (C), 158.4 (C), 167.9 (C); HRMS (ESI-TOF) calcd for $C_{30}H_{34}F_3NNaO_4$ ($[M+Na]^+$): 552.2338, found: 552.2321.

4.5. Synthesis of peptide 17

Peptide **17** was synthesized on NovaSyn TGR resin using Fmoc solid phase peptide synthesis reported in the previous report.[2d] The resulting crude material was analyzed by reverse phase HPLC. HPLC conditions: Cosmosil $5C_{18}$-AR-II analytical column (0.1% (v/v) TFA in acetonitrile/0.1% (v/v) aqueous TFA solution=20–80% over 30 min, 1.0 mL/min). Retention times, **17**: 21.0 min; **17′**: 22.6 min. MS (ESI-IT) calcd for $C_{76}H_{96}N_{13}O_{16}$ ($[M+H]^+$): 1446.7, **17**: found 1446.5, **17′**: found 1446.4.

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Supplementary data

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.tet.2010.07.033.

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