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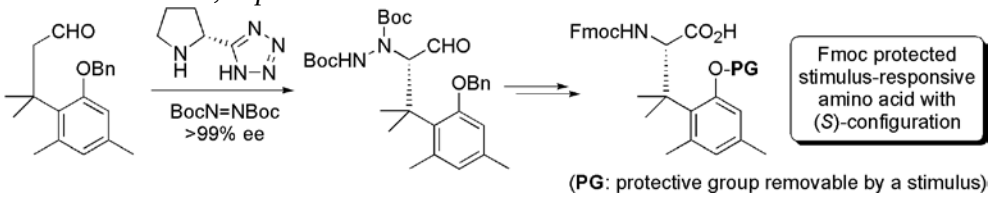

(**PG**: protective group removable by a stimulus)

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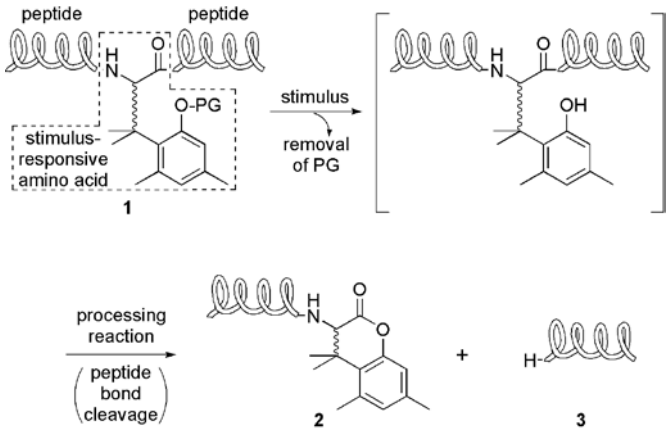
ABSTRACT

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]

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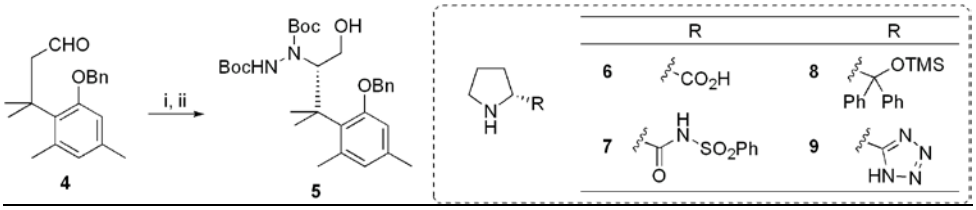


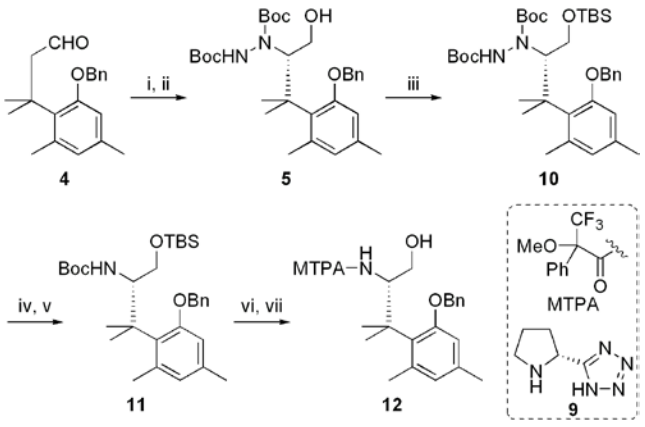
entry	catalyst (eq.)	solvent	time	yield of **5** (%)	ee of **5** (%)
1	**6** (0.5)	DMSO	7 d	-[a]	20
2	**6** (0.1)[b]	CH_2Cl_2	7 d	-[a]	2[c]
3	**6** (0.1)[b]	acetonitrile	7 d	-[a]	10[c]
4	**7** (0.2)[b]	CH_2Cl_2	7 d	-[a]	-
5	**7** (0.2)[b]	acetonitrile	7 d	-[a]	-
6	**8** (0.1)	toluene	3 d	22	>99[c]
7	**9** (0.1)	CH_2Cl_2	3 d	67	>99
8	**9** (0.1)	CH_2Cl_2	7 d	42	98
9	**9** (0.1)	acetonitrile	1.5 d	42	78
10	**9** (0.1)	acetonitrile[d]	4 d	-[a]	18
11	**9** (0.5)	CH_2Cl_2	3 d	85	>99
12	**9** (0.5)	CH_2Cl_2[d]	3 d	37	84
13	**9** (0.5)	acetonitrile	1.5 d	54	78
14	**9** (0.5)	DMF	1 d	56	63
15	**9** (0.5)	THF	3 d	70	79

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

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 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 equivalents 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 equivalents 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 equivalents 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 $\Delta\delta$ 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 (Figure 1a). Then, the $\Delta\delta$ values were calculated and the absolute configuration of amide **12** was ascertained as (*S*) (Figure 1b).[8b] It is 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 (Figure 2).[4a,6m] Therefore, the enantioselectivity observed in our experiments agrees well with that of the previous report.



Scheme 2. Reagents and conditions: (i) di-*tert*-butyl azodicarboxylate, **9** (0.5 eq.), CH_2Cl_2. (ii) $NaBH_4$, MeOH. (iii) TBSOTf, Et_3N, CH_2Cl_2, 0 °C, 75% (3 steps). (iv) trifluoroacetic anhydride, Et_3N, CH_2Cl_2. (v) SmI_2, *tert*-BuOH, HMPA, THF, 64% (2 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% (2 steps) for (*R*)-MTPA derivative, 38% (2 steps) for (*S*)-MTPA derivative.

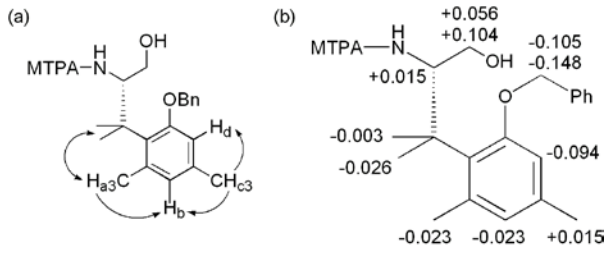


Figure 1. Determination of the absolute configuration using Kusumi's method. (a) Observed NOEs (arrows) with MTPA amide **12**. (b) $\Delta\delta$ values ($\delta_{(S)\text{-MTPA}} - \delta_{(R)\text{-MTPA}}$) obtained for (*S*)- and (*R*)-MTPA amide **12** in $CDCl_3$ with 5% (v/v) D_2O.

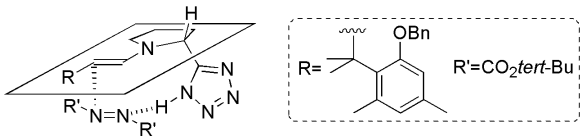


Figure 2. Proposed transition state for the α-amination of aldehyde **4**.

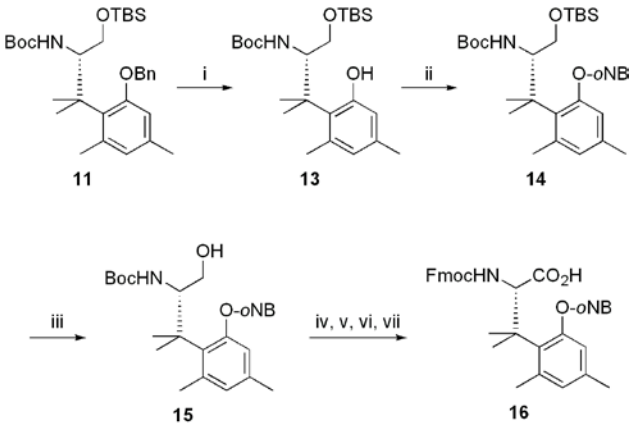
2.3. Synthesis of chiral stimulus-responsive amino acid derivative

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 4 steps.

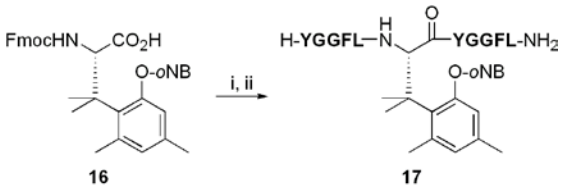
Unfortunately, attempts to determine the enantiomeric excess of **16** using chiral HPLC (ChiralPak IA, *i*PrOH/hexane system) were unsuccessful. In the previous report, we noted that peptide **17** and its diastereomer **17′** derived from racemic **16** can be easily separated by reverse phase HPLC (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 (Figure 3a). When racemic **16** was incorporated in the peptide, **17** and its diastereomer **17′** were eluted separately (retention time of **17′**: 22.6 min) (Figure 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.

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.



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% (4 steps). (*o*NB: *o*-nitrobenzyl)



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)

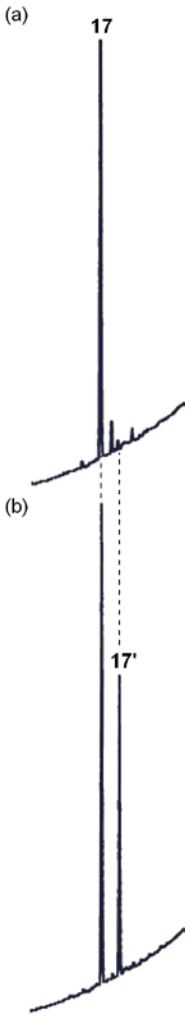


Figure 3. HPLC profiles of a crude material of the peptide derived from (a) **16**, or (b) racemic **16**. Peptide **17′** is a diastereomer of peptide **17**. Retention times, **17**: 21.0 min; **17′**: 22.6 min. Only a critical retention time region of the HPLC charts was enlarged. HPLC conditions: 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% to 80% over 30 min) at a flow rate of 1.0 mL/min, detection at 220 nm.

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 AV400N, or a JEOL JNM-AL300 spectrometer. Exact mass spectra were recorded on a Waters MICROMASS® LCT PREMIER™ or a Bruker Esquire200T. 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 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 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. $[\alpha]^{19}_D$ +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 3 steps) according to the previous report.[2d] $[\alpha]^{19}_D$ +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 2 steps) according to the previous report.[2d] $[\alpha]^{21}_D$ -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). $[\alpha]^{20}_D$ -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] $[\alpha]^{20}_{D}$ -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] $[\alpha]^{19}_{D}$ -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 4 steps). $[\alpha]^{23}_{D}$ -6.69 (*c* 1.12, $CHCl_3$); ^{1}H 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 eq.), (*R*) or (*S*)-1-methoxy-1-phenyl-1-trifluoromethylacetic acid (1.2 eq.) and triethylamine (1.0 eq.), 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**)*

$[\alpha]^{28}_{D}$ -9.89 (*c* 2.17, $CHCl_3$); ^{1}H 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) calc. for $C_{30}H_{34}F_3NNaO_4$ ([*M*+Na]$^+$): 552.2338, found: 552.2357.

*4.4.3. (S)-MTPA derivative ((S)-**12**)*

$[\alpha]^{28}_{D}$ +11.3 (*c* 1.19, $CHCl_3$); ^{1}H 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) calc. 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 to 80% over 30 min, 1.0 mL/min). Retention times, **17**: 21.0 min; **17′**: 22.6 min. MS (ESI-IT) calc. 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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References and notes

1. (a) Li, H.; Hah, J.-M.; Lawrence, D. S. *J. Am. Chem. Soc.* **2008**, *130*, 10474-10475. (b) Toebes, M; Coccoris, M.; Bins, A.; Rodenko, B.; Gomez, R.; Nieuwkoop, N. J.; Kasteele, W. v. d.; Rimmelzwaan, G. F.; Haanen, J. B. A. G.; Schumacher, T. N. M. *Nat. Med.* **2006**, *12*, 246-251. (c) Parker, L. L.; Kurutz, J. W.; Kent, S. B. H.; Kron, S. J. *Angew. Chem. Int. Ed.* **2006**, *45*, 6322-6325. (d) Sohma, Y.; Kiso, Y. *ChemBioChem* **2006**, *7*, 1549-1557. (e) Pellois, J.-P.; Muir, T. W. *Angew. Chem. Int. Ed.* **2005**, *44*, 5713-5717. (f) Dos Santos, S.; Chandravarkar, A.; Mandal, B.; Mimna, R.; Murat, K.; Saucede, L.; Tella, P.; Tuchscherer, G.; Mutter, M. *J. Am. Chem. Soc.* **2005**, *127*, 11888-11889. (g) Endo, M.; Nakayama, K.; Kaida, Y.; Majima, T. *Angew. Chem. Int. Ed.* **2004**, *43*, 5643-5645. (h) Bosques, C. J.; Imperiali, B. *J. Am. Chem. Soc.* **2003**, *125*, 7530-7531. (i) England, P. M.; Lester, H. A.; Davidson, N.; Dougherty, D. A. *Proc. Natl. Acad. Sci. USA* **1997**, *94*, 11025-11030. (j) Renner, C.; Moroder, L. *ChemBioChem* **2006**, *7*, 868-878, and references therein.
2. (a) Shigenaga, A.; Yamamoto, J.; Sumikawa, Y.; Furuta, T.; Otaka, A. *Tetrahedron Lett.* **2010**, *51*, 2868-2871. (b) Shigenaga, A.; Yamamoto, J.; Hirakawa, H.; Ogura, K.; Maeda, N.; Morishita, K.; Otaka, A. *Tetrahedron Lett.* **2010**, *51*, 2525-2528. (c) Shigenaga, A.; Yamamoto, J.; Hirakawa, H.; Yamaguchi, K.; Otaka, A. *Tetrahedron* **2009**, *65*, 2212-2216. (d) Shigenaga, A.; Tsuji, D.; Nishioka, N.; Tsuda, S.; Itoh, K.; Otaka, A. *ChemBioChem* **2007**, *8*, 1929-1931.
3. (a) Jung, M. E.; Piizzi, G. *Chem. Rev.* **2005**, *105*, 1735-1766, and references therein. (b) Amsberry, K. L.; Borchardt, R. T. *J. Org. Chem.* **1990**, *55*, 5867-5877. (c) Caswell, M.; Schmir, G. L.; *J. Am. Chem. Soc.* **1980**, *102*, 4815-4821. (d) Milstien, S.; Cohen, L. A. *J. Am. Chem. Soc.* **1972**, *94*, 9158-9165. (e) Borchardt, R. T.; Cohen, L. A. *J. Am. Chem. Soc.* **1972**, *94*, 9166-9174. (f) Milstien, S.; Cohen, L. A. *Proc. Natl. Acad. Sci. USA* **1970**, *67*, 1143-1147.
4. Recent reviews: (a) Bertelsen, S.; Jørgensen, K. A. *Chem. Soc. Rev.* **2009**, 38, 2178-2189. (b) Mukherjee, S.; Yang, J. W.; Hoffmann, S.; List, B. *Chem. Rev.* **2007**, *107*, 5471-5569. (c) Erkkilä, A.; Majander, I.; Pihko, P. M. *Chem. Rev.* **2007**, *107*, 5416-5470. (d) Notz, W.; Tanaka, F.; Barbas, C. F., III. *Acc. Chem. Res.* **2004**, *37*, 580-591. (e) Duthaler, R. O. *Angew. Chem. Int. Ed.* **2003**, *42*, 975-978.

5. (a) Blackmond, D. G.; Moran, A.; Hughes, M.; Armstrong, A. *J. Am. Chem. Soc.* **2010**, *132*, 7598-9599. (b) Simmons, B.; Walji, A. M.; MacMillan, D. W. C. *Angew. Chem. Int. Ed.* **2009**, *48*, 4349-4353. (c) Alba, A.-N.; Companyo, X.; Moyano, A.; Rios, R. *Chem. Eur. J.* **2009**, *15*, 7035-7038. (d) Hartmanna, C. E.; Grossa, P, J.; Niegerb, M.; Bräse, S. *Org. Biomol. Chem.* **2009**, *7*, 5059-5062. (e) Makino, K.; Kubota, S.; Hara, S.; Sakaguchi, M.; Hamajima, A.; Hamada, Y. *Tetrahedron* **2009**, *65*, 9468-9473. (f) Nuzzi, A.; Massi, A.; Dondoni, A. *Org. Lett.* **2008**, *10*, 4485-4488. (g) George, S.; Suryavanshi, G. S.; Sudalai, A. *Tetrahedron Lett.* **2008**, *49*, 6791-6793. (h) Lim, A.; Choi, J. H.; Tae, J. *Tetrahedron Lett.* **2008**, *49*, 4882-4885. (i) Baumann, T.; Vogt, H.; Bräse, S. *Eur. J. Org. Chem.* **2007**, 266-282. (j) Talluri, S. K.; Sudalai, A. *Tetrahedron* **2007**, *63*, 9758-9763. (k) Umbreen, S.; Brockhaus, M.; Ehrenberg, H.; Schmidt, B. *Eur. J. Org. Chem.* **2006**, 4585-4595. (l) Kotkar, S. P.; Sudalai, A. *Tetrahedron Asymmetry* **2006**, *17*, 1738-1742. (m) Miao, W.; Xu, W.; Zhang, Z.; Ma, R.; Chen, S.-H.; Li, G. *Tetrahedron Lett.* **2006**, *47*, 6835-6837. (n) Suri, J. T.; Steiner, D. D.; Barbas, C. F., III. *Org. Lett.* **2005**, *7*, 3885-3888. (o) Iwamura, H.; Mathew, S. P.; Blackmond, D. G. *J. Am. Chem. Soc.* **2004**, *126*, 11770-11771. (p) Iwamura, H.; Wells, D. H., Jr.; Mathew, S. P.; Klussmann, M.; Armstrong, A.; Blackmond, D. G. *J. Am. Chem. Soc.* **2004**, *126*, 16312-16313. (q) Chowdari, N. S.; Ramachary, D. B.; Barbas, C. F., III. *Org. Lett.* **2003**, *5*, 1685-1688. (r) Bøgevig, A.; Juhl, K.; Kumaragurubaran, N.; Zhuang, W.; Jørgensen, K. A. *Angew. Chem. Int. Ed.* **2002**, *41*, 1790-1793. (s) List, B. *J. Am. Chem. Soc.* **2002**, *124*, 5656-5657.

6. (a) Baumann, T.; Bächle, M.; Hartmann, C.; Bräse, S. *Eur. J. Org. Chem.* **2008**, 2207-2212. (b) Ait-Youcef, R.; Sbargoud, K.; Moreau, X.; Greck, C. *Synlett* **2009**, 3007-3010. (c) Nishikawa, Y.; Kitajima, M.; Kogure, N.; Takayama, H. *Tetrahedron* **2009**, *65*, 1608-1617. (d) Kalch, D.; De Rycke, N.; Moreau, X.; Greck, C. *Tetrahedron Lett.* **2009**, *50*, 492-494. (e) Hayashi, Y.; Aratake, S.; Imai, Y.; Hibino, K.; Chen, Q.-Y.; Yamaguchi, J.; Uchimaru, T. *Chem. Asian J.* **2008**, *3*, 225-232. (f) Nishikawa, Y.; Kitajima, M.; Takayama, H. *Org. Lett.* **2008**, *10*, 1987-1990. (g) Jiang, H.; Nielsen, J. B.; Jørgensen, K. A. *Chem. Eur. J.* **2007**, *13*, 9068-9075. (h) Thomassigny, C.; Prim, D.; Greck, C. *Tetrahedron Lett.* **2006**, *47*, 1117-1119. (i) Franzen, J.; Marigo, M.; Fielenbach, D.; Wabnitz, T. C.; Kjærsgaard, A.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2005**, *127*, 18296-18304. (j) Marigo, M.; Schulte, T.; Franzen, J.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2005**, *127*, 15710-15711. (k) Kotrusz, P.; Alemayehu, S.; Toma, S.; Schmalz, H.-G.; Adler, A. *Eur. J. Org. Chem.* **2005**, 4904-4911. (l) Chowdari, N. S.; Barbas, C. F., III. *Org. Lett.* **2005**, *7*, 867-870. (m) Dahlin, N.; Bøgevig, A.; Adolfsson, H. *Adv. Synth. Catal.* **2004**, *346*, 1101-1105. (n) Henmi, Y.; Makino, K.; Yoshitomi, Y.; Hara, O.; Hamada, Y. *Tetrahedron Asymmetry* **2004**, *15*, 3477-3481. (o) Vogta, H.; Vanderheidena, S.; Bräse, S. *Chem. Commun.* **2003**, 2448-2449.

7. Preparation of sulfonamide **7** and tetrazole **9**, see: Cobb, A. J. J.; Shaw, D. M.; Longbottom, D. A.; Gold, J. B.; Ley, S. V. *Org. Biomol. Chem.* **2005**, *3*, 84-96. Toluene solution of silyl ether **8** was purchased from SIGMA-ALDRICH.

8. (a) Kusumi, T.; Ooi, T.; Ohkubo, Y.; Yabuuchi, T. *Bull. Chem. Soc. Jpn.* **2006**, *79*, 965-980, and references therein. (b) Kusumi, T.; Fukushima, T.; Ohtani, I.; Kakisawa, H. *Tetrahedron Lett.* **1991**, *32*, 2939-2942. (c) Ohtani, I.; Kusumi, T.; Kashman, Y.; Kakisawa, H. *J. Am. Chem. Soc.* **1991**, *113*, 4092-4096.

9. Hattori, K.; Sajiki, H.; Hirota, K. *Tetrahedron Lett.* **2000**, *41*, 5711-5714.

10. Corey, E. J.; Schmidt, G. *Tetrahedron Lett.* **1979**, *20*, 399-402.