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Artificial model for cystathionine β-synthase: efficient β-replacement reaction with thiols employing a novel pyridoxal model compound having an imidazole function

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Abstract—As a second-generation pyridoxal model compound for cystathionine β-synthase, we designed a novel model compound having an ionophore function and an imidazole function, application of which to the β-replacement reaction with various thiols smoothly took place to give *S*-substituted cysteines. Peptides having a serine-*O*-carbonate residue at the N-terminal position were also converted to the corresponding peptides having an *S*-substituted cysteine residue under the catalytic conditions of the novel pyridoxal model compound.

1. Introduction

A β-replacement reaction of the serine hydroxyl group with a nucleophile catalyzed by pyridoxal plays an important role in a biological system.[1] Although this reaction system is expected to be of great use for the synthesis of various unnatural amino acids by artificial mimicking, only a limited number of examples mimicking tryptophane synthase, in which the nucleophile is indole, have been reported.[2] In a preceding paper, we have described catalytic transformation of serine-*O*-carbonate **3** into *S*-substituted cysteines **4** employing pyridoxal model compound **1** (Fig. 1), which is the first example mimicking cystathionine β-synthase as shown in Figure 2.[3] However, there still remains a problem in that compound **1** is a good catalyst for the reaction with aryl thiols, but is less effective for that with alkane thiols. In order to extend the reaction system to a general method, it is necessary to solve this problem. For the purpose, we designed a novel second-generation model compound of pyridoxal derivative **1**.

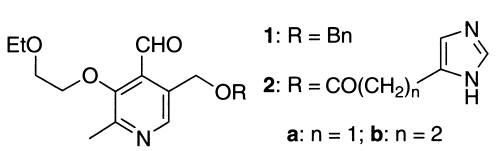

Figure 1. Structures of pyridoxal model compounds **1** and **2**.

As, in general, alkane thiols are more nucleophilic than aromatic thiols because of the electron-donating property of an alkyl group, the phenomenum appears to be strange. This result could indicate that, as aromatic thiols are less nucleophilic but are more acidic than alkane thiols, the formation of thiolate from thiol and/or the protonation procedure to an enolate species might be important to finish the reaction. In order to overcome this problem, we designed model compounds **2** which have an imidazole function. Introduction of the imidazole function was expected to introduce activation of the elimination of the carbonate moiety of **5** (Step 1) as well as activation of the 1,4-addition of alkane thiols to **6** (Step 2) as shown in Fig. 3. Taking into account the distance between the imidazole moiety and the reaction site, two model compounds **2a** and **2b** having different methylene lengths were designed.

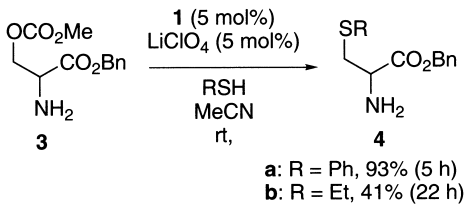

Figure 2. Pyridoxal **1** catalyzed β-replacement reaction of serine-*O*-carbonate **3** with thiols.

On the other hand, we previously described regio- and stereoselective α-alkylation of peptides at the N-terminal position, employing a pyridoxal derivative.[4] This is a unique and useful method to synthesize peptides including unnatural amino acids without preparing the corresponding unnatural amino acids,[5] and would be of great use for construction of an unnatural peptide library.[6] Accordingly, we utilized the novel model compounds **2** to β-replacement

Keywords: amino acids and derivatives; coenzymes; pyridines; substitution.

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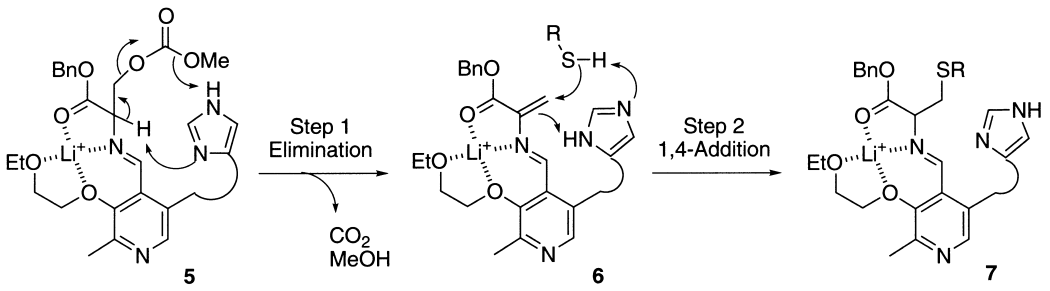


Figure 3. Expected effect of the imidazole moiety on the β-replacement reaction.

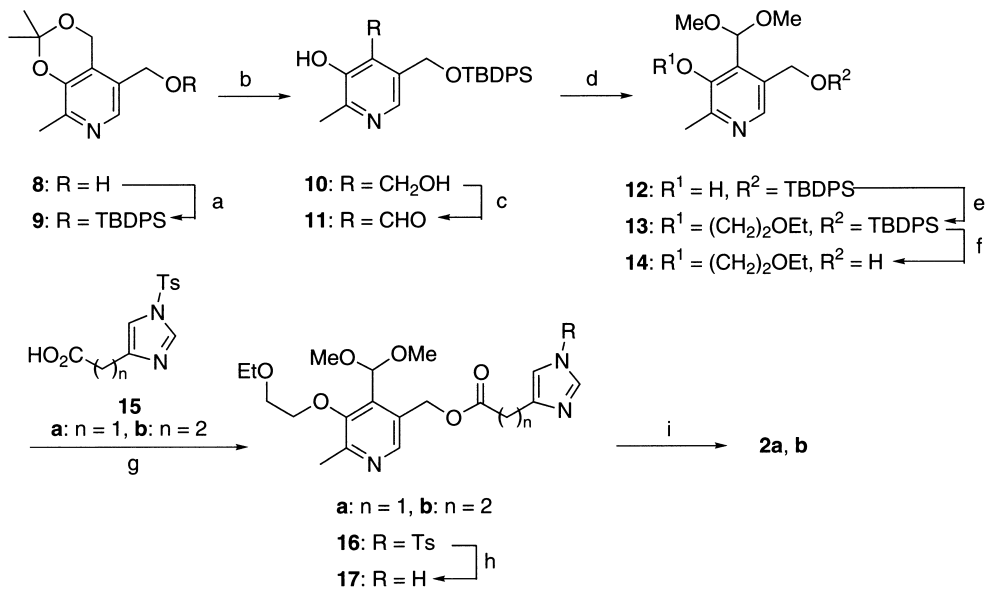
reaction of peptides having a serine-*O*-carbonate residue at the N-terminal position as well. In this paper, we would like to describe the synthesis of pyridoxal model compounds **2** and their ability for β-replacement reaction of serine-*O*-carbonate derivatives including peptides with thiols.[7]

2. Results and discussion

Synthesis of the model compounds **2** was achieved as shown in Scheme 1. Alcohol **8**[8] was protected with a *tert*-butyldiphenylsilyl (TBDPS) group to give **9**, the acetonide group of which was removed by acidic treatment, affording diol **10**. Oxidation of **10** with MnO_2 afforded aldehyde **11**, which was protected as dimethyl acetal **12**. An ethoxyethyl goup was introduced to **12**, affording **13**. In order to couple with an imidazole moiety, the silyl group of **13** was removed under conventional fluoride treatment to yield **14**. Esterification of **14** with *N*-tosylimidazolecarboxylic acids **15a** and **15b** smoothly took place to afford **16a** and **16b**, respectively. Removal of the *N*-protecting group, a tosyl group, afforded **17a** and **17b**, the dimethyl acetal group of which was then hydrolyzed under the usual conditions to give the desired model compounds **2a** and **2b**.

Employing **2a** and **2b**, we examined the β-replacement reaction of serine-*O*-carbonate **3** with thiols, and the results are summarized in Table 1. Novel model compounds **2a** and **2b** efficiently catalyzed the β-replacement reactions with benzyl and ethyl mercaptans, both of which were ineffective substrates in the reactions catalyzed by the basic compound **1** (entries 1 and 2 vs entries 4–7).[3] Particularly in the reaction with ethyl mercaptan, **2a** and **2b** were about two times as effective as **1** (entry 2 vs entries 5 and 7). These results clearly show the effectiveness of the imidazole function. Although no significant difference in reactivity between **2a** and **2b** was observed (entries 4 and 5 vs entries 6 and 7), the proximity effect of the imidazole function in the reactions with **2a** and **2b** is also evident from the result that the yield for the reaction with **1** in the presence of 5 mol% of imidazole was almost the same as that without imidazole (entry 1 vs entry 3). Namely, the existence of the imidazole function close to the aldehyde moiety is suggested to play an important role in the present reactions. Other thiols also reacted smoothly under the catalytic conditions of **2b** (entries 8 and 9).

Encouraged by the results described above, we planned to apply the reaction to peptides having a serine-*O*-carbonate residue at the N-terminal position. At first, we applied **2b** to the β-replacement reaction of serine amide **18a**. The reaction, as expected, required longer time due to lower reactivity of an amide group than that of an ester group, but proceeded to give *S*-benzylcysteine amide **19a** in almost the



Scheme 1. (a) TBDPSCI, imidazole, DMF, rt, 96%; (b) 60% AcOH, reflux, 72%; (c) MnO_2, pyridine, rt, 65%; (d) $HC(OMe)_3$, *p*-TsOH, MeOH, reflux, 94%; (e) NaH, $EtO(CH_2)_2Br$, DMF, rt, 73%; (f) *n*-Bu_4NF, THF, rt, 91%; (g) **15a** or **b**, DCC, DMAP, CH_2Cl_2, rt, **16a**: 74%, **16b**: 60%; (h) Ac_2O, pyridine, rt, **17a**: quant., **17b**: 89%; (i) 60% AcOH, reflux, **2a**: 58%, **2b**: 81%.

Table 1. β-Replacement reaction of **3** with thiols (RSH) catalyzed by pyridoxal **1** or **2**

Entry	Pyridoxal	R	Time (h)	Product **4**	Yield (%) of **4** Based on **3**	Yield (%) of **4** Based on **1** or **2**
1	**1**	Bn	19	**c**	61	1220
2	**1**	Et	22	**b**	41	820
3[a]	**1**	Bn	19	**c**	63	1260
4	**2a**	Bn	19	**c**	83	1660
5	**2a**	Et	22	**b**	76	1520
6	**2b**	Bn	19	**c**	84	1680
7	**2b**	Et	22	**b**	80	1600
8	**2b**	$HO(CH_2)_3$	72	**d**	49	980
9	**2b**	$HS(CH_2)_3$[b]	25	**e**[c]	60	1200

[a] Reaction was carried out in the presence of 5 mol% of imidazole.
[b] Thiol (0.6 equiv.) was employed.
[c] Both thiol groups were alkylated.

Table 2. β-Replacement reaction of amide and peptides **18** with thiols catalyzed by pyridoxal **2b**

18 **19**

Entry	**18**: AA	R	Product **19**	Yield (%) of **19** Based on **18**	Yield (%) of **19** Based on **2b**
1	**a**: NHBn	Bn	**a**	81	1620
2	**b**: Gly-OBn	Bn	**b**	77	1540
3	**c**: L-Ala-OBn	Bn	**c**	76	1520
4	**d**: L-Val-OBn	Bn	**d**	70	1400
5	**e**: L-Ala-L-Ala-OBn	Bn	**e**	68	1360
6	**c**: L-Ala-OBn	Ph	**f**	81	1620
7	**c**: L-Ala-OBn	Et	**g**	70	1400
8	**c**: L-Ala-OBn	$HO(CH_2)_3$	**h**	44	880

same yield as that for the ester **3** (entry 1 in Table 2 vs entry 6 in Table 1). Peptides **18b–e** having a serine-*O*-carbonate residue at the N-terminal position were also transformed into those having an *S*-substituted cysteine residue under the same conditions. Steric bulkiness of the neighboring amino acid residue did not affect the reaction so much (entries 2–4), and the products **19c** and **19d** were obtained as a diastereomeric mixture in a ratio of ca. 1:1 (entries 3 and 4).

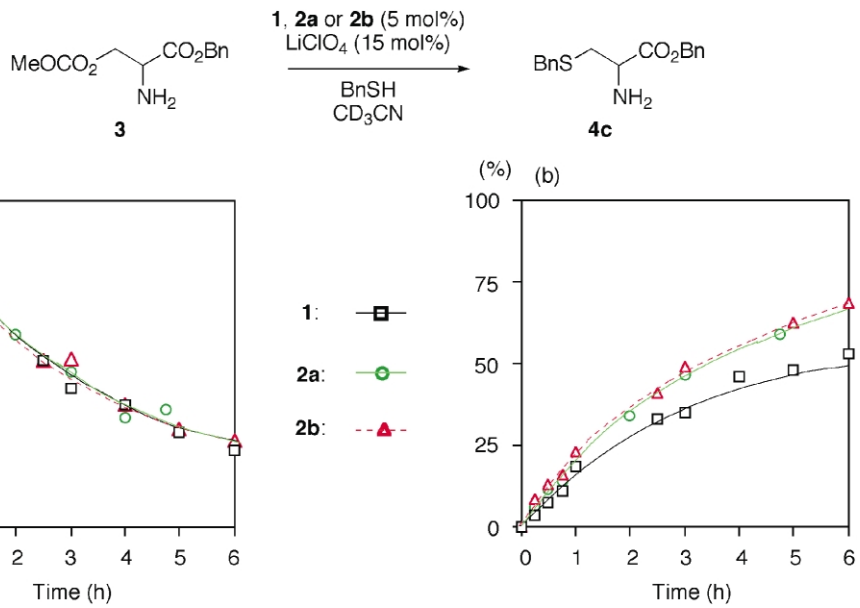


Figure 4. β-Replacement reaction of **3** catalyzed by pyridoxals **1**, **2a** or **2b**.

Tripeptide **18e** also reacted to give **19e** in almost the same yield (entry 5). Concerning the kind of thiols, the reaction with thiophenol smoothly took place as expected (entry 6), while those with alkane thiols also proceeded to give the desired products (entries 7 and 8).

In order to clarify the role of the imidazole function, we traced the reactions of **1**, **2a** and **2b** by ^{1}H NMR spectrum, and the results are shown in Fig. 4. Comparing the results of **1** and **2**, it is obvious that the imidazole function does not activate the elimination of the carbonate moiety (Step 1 in Fig. 3), but activates the addition of the thiol. As described in our preceding paper,[3] it is obvious that the acidity of thiol is highly related with the reactivity. Although the detailed function of the imidazole moiety is not clear, hydrogen transfer from thiol to the α-position, that involves deprotonation of the thiol hydrogen and/or protonation to the enolate, appears to be activated by the imidazole function as indicated by Step 2 in Fig. 3.

In conclusion, we have designed and synthesized novel pyridoxal derivatives **2** having an ionophore function and an imidazole moiety, which were clearly shown to be effective for catalytic β-replacement reaction of serine-*O*-carbonate with various thiols to *S*-substituted cysteines. This reaction was also applied to peptides having a serine-*O*-carbonate residue at the N-terminal position, and consequently various *S*-substituted cysteine residues were directly introduced without preparing the respective *S*-substituted cysteines alternatively, which would be of great use for construction of a peptide library in the field of combinatorial chemistry. Applications of the present reaction system to the β-replacement reaction with other nucleophiles than the sulfur nucleophile and to a chiral system would be of great use for the synthesis of unnatural amino acids, which is under progress in our laboratory.

3. Experimental

3.1. General

Melting points (mps) were taken on a Yanagimoto micro-melting point apparatus and are uncorrected. Infrared spectra were measured on a JASCO FT/IR-200 Fourier-transfer infrared spectrometer. ^{1}H NMR spectra were measured on a JEOL EX-270 (270 MHz) spectrometer and tetramethylsilane (TMS) was used as an internal standard. ^{13}C NMR spectra were measured on the same instrument (67.8 MHz) with $CDCl_3$ as an internal standard (77.0 ppm). Low and High resolution mass spectra (EI-MS and HR-MS) were obtained by use of a JEOL D-300 mass spectrometer. For silica gel column chromatography, E. Merck Kieselgel 60 (0.063–0.200 mm) was used.

3.1.1. 5-[(*tert*-Butyldiphenylsilyloxy)methyl]-2,2,8-trimethyl-4*H*-1,3-dioxino[4,5-*c*]pyridine (9). To a stirred solution of alcohol **8** (9.13 g, 43.7 mmol) in DMF (50 ml) was added imidazole (7.43 g, 109 mmol) and *tert*-butyldiphenylsilyl chloride (13.2 g, 48.0 mmol), and the whole was stirred at room temperature for 15 h. After concentration under reduced pressure, the resultant residue was partitioned with ether and H_2O. The ethereal layer was separated, and the aqueous phase was extracted with ether. Combined ethereal layers were washed with H_2O and saturated NaCl solution, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was passed through a silica gel short column with ethyl acetate/hexane (1:3) as an eluant to give the title compound **9** (18.8 g, 96%) as a colorless oil. IR ν_{max} (KBr): 2935, 2858, 1599, 1419 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ: 1.04 (9H, s, $C(CH_3)_3$), 1.55 (6H, s, $C(CH_3)_2$), 2.41 (3H, s, 2-CH_3), 4.58 (2H, s, 5-CH_2), 4.88 (2H, s, 4-CH_2), 7.36–7.45 (6H, m, aromatic H), 7.64–7.68 (4H, m, aromatic H), 7.88 (1H, s, 6-H). ^{13}C NMR ($CDCl_3$) δ_C: 18.4, 19.2, 24.7, 26.7, 58.7, 61.6, 99.6, 125.5, 127.8, 128.3, 128.9, 129.9, 132.8, 135.5, 138.4, 147.3. EI-MS *m*/*z* (%): 447 (M^+, 3.1). High-resolution MS Calcd for $C_{27}H_{33}NO_3Si$ (M^+) 447.2230. Found: 447.2232.

3.1.2. 5-[(*tert*-Butyldiphenylsilyloxy)methyl]-3-hydroxy-4-(hydroxymethyl)-2-methylpyridine (10). A solution of **9** (18.7 g, 41.7 mmol) in acetic acid– H_2O (3:2, 100 ml) was refluxed for 4 h. After concentration under reduced pressure, the resultant residue was dried by azeotropic evaporation with benzene, and recrystallized from methanol to give **10** (12.2 g, 72%) as colorless crystals, mp 206–208°C (MeOH). IR ν_{max} (KBr): 2952, 2637, 1467, 1423 cm^{-1}. ^{1}H NMR (DMSO-d_6) δ: 1.00 (9H, s, $C(CH_3)_3$), 2.35 (3H, s, 2-CH_3), 4.70 (2H, s, 5-CH_2), 4.79 (2H, s, 4-CH_2), 5.70 (1H, br s, 4′-OH), 7.40–7.57 (6H, m, aromatic H), 7.62–7.65 (4H, m, aromatic H), 7.92 (1H, s, 6-H), 9.24 (1H, br s, 3-OH). ^{13}C NMR (DMSO-d_6) δ_C: 18.8, 19.4, 26.6, 56.2, 61.4, 128.0, 130.0, 131.0, 131.7, 132.7, 135.0, 138.2, 146.3, 149.4. EI-MS *m*/*z* (%): 408 ($M+H^+$, 0.3). Anal. Calcd for $C_{24}H_{29}NO_3Si$: C, 70.73; H, 7.17; N, 3.44. Found: C, 70.67; H, 7.13; N, 3.42.

3.1.3. 5-[(*tert*-Butyldiphenylsilyloxy)methyl]-3-hydroxy-2-methylpyridine-4-carbaldehyde (11). To a stirred solution of **10** (10.0 g, 24.6 mmol) in pyridine (200 ml) was added MnO_2 (6.4 g, 73.6 mmol), and the whole was stirred at room temperature for 55 h. The reaction mixture was filtered through a cerite pad, and the cerite pad was washed with pyridine. After concentration under reduced pressure, the resultant residue was purified by silica gel column chromatography (ethyl acetate/hexane=1:3) to give **11** (6.52 g, 65%) as pale yellow crystals, mp 77–78°C (AcOEt/hexane). IR ν_{max} (KBr): 3325, 2932, 2857, 1561 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ:1.03 (9H, s, $C(CH_3)_3$), 2.53 (3H, s, 2-CH_3), 4.93 (2H, s, 5-CH_2), 7.39–7.46 (6H, m, aromatic H), 7.62–7.65 (4H, m, aromatic H), 7.81 (1H, s, 6-H), 10.54 (1H, s, CHO), 11.44 (1H, br s, 3-OH). ^{13}C NMR ($CDCl_3$) δ_C: 18.8, 19.1, 26.7, 61.2, 120.2, 127.9, 130.1, 132.1, 132.5, 135.5, 138.6, 151.9, 153.8, 197.3. EI-MS *m*/*z* (%): 405 (M^+, 0.5), 348 (M^+-tBu, 100). Anal. Calcd for $C_{24}H_{27}NO_3Si$: C, 69.18; H, 7.32; N, 3.10. Found: C, 69.15; H, 7.25; N, 3.11.

3.1.4. 5-[(*tert*-Butyldiphenylsilyloxy)methyl]-3-hydroxy-2-methylpyridine-4-carbaldehyde dimethyl acetal (12). To a stirred solution of **11** (6.00 g, 14.8 mmol) in methanol (100 ml) and trimethyl orthoformate (50 ml) was added *p*-toluenesulfonic acid (ca. 100 mg), and the whole was refluxed for 30 h. After cooling, the reaction mixture was neutralized with saturated $NaHCO_3$ solution, and concentrated under reduced pressure. The resultant residue was

partitioned with ethyl acetate and H_2O, and extracted with ethyl acetate. The combined organic layers were washed with H_2O and saturated NaCl solution, dried over Na_2SO_4, and concentrated under reduced pressure. The resultant residue was purified by silica gel column chromatography (ethyl acetate/hexane=1:2) to give **12** (6.25 g, 94%) as colorless crystals, mp 77.5–79°C (ether/hexane). IR ν_{max} (KBr): 3071, 2931, 2858, 1661 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 1.06 (9H, s, $C(CH_3)_3$), 2.47 (3H, s, 2-CH_3), 3.35 (6H, s, $CH(OCH_3)_2$), 4.71 (2H, s, 5-CH_2), 5.84 (1H, s, $CH(OCH_3)_2$), 7.36–7.44 (6H, m, aromatic H), 7.66–7.69 (4H, m, aromatic H), 7.97 (1H, s, 6-H), 8.74 (1H, br s, 3-OH). ^{13}C NMR ($CDCl_3$) δ_C: 19.2, 26.8, 53.6, 61.5, 96.1, 102.6, 124.1, 127.8, 129.9, 131.1, 133.1, 135.6, 139.4, 148.5, 150.2. EI-MS *m/z* (%): 451 (M^+, 1.0), 150 (M^+-tBu, 100). Anal. Calcd for $C_{26}H_{33}NO_4Si$: C, 71.11; H, 6.67; N, 3.46; O, 11.85; Si, 6.91. Found: C, 70.88; H, 6.60; N, 3.44.

3.1.5. 5-[(*tert*-Butyldiphenylsilyloxy)methyl]-3-(2-ethoxyethoxy)-2-methylpyridine-4-carbaldehyde dimethyl acetal (13). To a stirred suspension of NaH (60% in oil, 293 mg, 7.33 mmol), which had been washed with hexane, in DMF (7 ml) was added dropwise a solution of **12** (3.00 g, 6.65 mmol) in DMF (13 ml) under ice-cooling, and the whole was stirred at room temperature for 30 min. 2-Bromoethyl ethyl ether (0.9 ml, 7.98 mmol) was added dropwise to the reaction mixture at room temperature, and stirring was continued at room temperature for 20 h. The reaction mixture was diluted with H_2O, and extracted with ether. The combined ethereal layers were washed with 1 M NaOH solution, H_2O and saturated NaCl solution, dried over Na_2SO_4, and concentrated under reduced pressure. The resultant residue was purified by silica gel column chromatography (ethyl acetate/hexane=1:3) to give **13** (2.55 g, 73%) as a colorless oil. IR ν_{max} (KBr): 2931, 2858, 1590 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 1.10 (9H, s, $C(CH_3)_3$), 1.26 (3H, t, J=7 Hz, OCH_2CH_3), 2.54 (3H, s, 2-CH_3), 3.24 (6H, s, $CH(OCH_3)_2$), 3.60 (2H, q, J=7 Hz, OCH_2CH_3), 3.73–3.76 (2H, m, OCH_2CH_2OEt), 3.92–3.95 (2H, m, OCH_2CH_2OEt), 5.07 (2H, s, 5-CH_2), 5.64 (1H, s, $CH(OCH_3)_2$), 7.32–7.41 (6H, m, aromatic H), 7.69–7.73 (4H, m, aromatic H), 8.79 (1H, s, 6-H). ^{13}C NMR ($CDCl_3$) δ_C: 15.2, 19.2, 19.3, 26.8, 55.3, 60.9, 66.8, 69.38, 73.9, 101.2, 127.6, 129.5, 133.6, 133.9, 135.5, 135.6, 144.1, 150.4, 151.0. FAB-MS *m/z*: 524 ($M+H^+$). High-resolution MS Calcd for $C_{30}H_{42}NO_5Si$ ($M+H^+$) 524.2832. Found: 524.2847.

3.1.6. 3-(2-Ethoxyethoxy)-5-(hydroxymethyl)-2-methylpyridine-4-carbaldehyde dimethyl acetal (14). To a stirred solution of **13** (2.41 g, 4.61 mmol) in THF (10 ml) was added dropwise tetrabutylammonium fluoride (1 M in THF, 11.5 ml, 11.5 mmol), and the whole was stirred at room temperature for 5 h. After concentration, the resultant residue was partitioned with ethyl acetate and H_2O, and extracted with ethyl acetate. The combined organic layers were washed with H_2O and saturated NaCl solution, dried over Na_2SO_4, and concentrated under reduced pressure. Purification by silica gel column chromatography (ethyl acetate) afforded **14** (1.16 g, 91%) as colorless crystals, mp 66–67°C (AcOEt/Hexane). IR ν_{max} (KBr): 3241, 2932 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 1.29 (3H, t, J=7 Hz, OCH_2CH_3), 2.54 (3H, s, 2-CH_3), 3.52 (6H, s, $CH(OCH_3)_2$), 3.63 (2H, q, J=7 Hz, OCH_2CH_3), 3.76–3.79 (2H, m, OCH_2CH_2OEt), 3.94–3.97 (2H, m, OCH_2CH_2OEt), 4.75 (2H, br d, J=6 Hz, 5-CH_2), 5.88 (1H, s, $CH(OCH_3)_2$), 8.27 (1H, s, 6-H). ^{13}C NMR ($CDCl_3$) δ_C: 15.2, 19.3, 56.3, 60.6, 66.7, 69.3, 74.0, 101.8, 133.3, 137.4, 146.5, 150.7, 152.7. EI-MS *m/z* (%): 285 (M^+, 20.5), 253 (M^+-MeOH, 100). Anal. Calcd for $C_{14}H_{23}NO_5$: C, 58.79; H, 7.96; N, 4.90. Found: C, 58.95; H, 8.07; N, 4.91.

3.1.7. 3-(2-Ethoxyethoxy)-2-methyl-5-{[*N*-(*p*-toluenesulfonyl)imidazol-4(5)-yl]acetoxy}methylpyridine-4-carbaldehyde dimethyl acetal (16a). To a stirred solution of **14** (232 mg, 0.815 mmol) and (*N*-tosylimidazolyl)acetic acid (274 mg, 0.979 mmol) in CH_2Cl_2 (8 ml) were added DCC (202 mg, 0.981 mmol) and DMAP (ca. 10 mg) at room temperature, and the whole was stirred at room temperature for 40 h. After being diluted with CH_2Cl_2, the reaction mixture was filtered, washed with saturated $NaHCO_3$ solution, H_2O and saturated NaCl solution, and dried over Na_2SO_4. After concentration under reduced pressure, the resultant residue was purified by silica gel column chromatography (ethyl acetate/acetone=5:1) to give **16a** (330 mg, 74%) as a colorless oil. IR ν_{max} (KBr): 3842, 3631, 3119, 2932, 1739, 1594 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 1.28 (3H, t, J=7 Hz, OCH_2CH_3), 2.43 (3H, s, Ar-CH_3), 2.54 (3H, s, 2-CH_3), 3.41 (6H, s, $CH(OCH_3)_2$), 3.62 (2H, q, J=7 Hz, OCH_2CH_3), 3.67 (2H, s, $OCOCH_2$), 3.75–3.79 (2H, m, OCH_2CH_2OEt), 3.95–3.98 (2H, m, OCH_2CH_2OEt), 5.45 (2H, s, 5-CH_2), 5.75 (1H, s, $CH(OCH_3)_2$), 7.31 (1H, d, J=1 Hz, imidazole H), 7.35, 7.81 (each 2H, AA′BB′, J=8 Hz, aromatic H), 7.94 (1H, d, J=1 Hz, imidazole H), 8.30 (1H, s, 6-H). ^{13}C NMR ($CDCl_3$) δ_C: 15.2, 19.3, 21.6, 34.0, 55.9, 61.9, 66.8, 69.3, 74.0, 101.1, 115.2, 127.3, 128.4, 130.4, 134.8, 136.1, 137.4, 137.6, 145.5, 146.2, 150.7, 152.9, 169.6. FAB-MS *m/z*: 548 ($M+H^+$). High-resolution MS Calcd for $C_{26}H_{34}N_3O_8$ ($M+H^+$): 548.2066. Found: 548.0264.

3.1.8. 3-(2-Ethoxyethoxy)-2-methyl-5-{[imidazol-4(5)-yl]acetoxy}methylpyridine-4-carbaldehyde dimethyl acetal (17a). To a solution of **16a** (50 mg, 0.091 mmol) in acetic anhydride (0.4 ml) was added pyridine (8 μl) and the whole was stirred at room temperature for 3 h. After concentration, the residue was dissolved in methanol (0.8 ml) and stirred at room temperature for 2 h. The methanol was evaporated off under reduced pressure, and H_2O was added to the residue, which was adjusted pH 8 with $NaHCO_3$ and extracted with $CHCl_3$. The organic layers were washed with H_2O and saturated NaCl solution, dried over Na_2SO_4, and concentrated under reduced pressure to give **17a** (35.9 mg, quant.) as a colorless oil. IR ν_{max} (KBr): 3128, 2935, 1739 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 1.28 (3H, t, J=7 Hz, OCH_2CH_3), 2.53 (3H, s, 2-CH_3), 3.43 (6H, s, $CH(OCH_3)_2$), 3.62 (2H, q, J=7 Hz, OCH_2CH_3), 3.75 (2H, s, $OCOCH_2$), 3.77–3.79 (2H, m, OCH_2CH_2OEt), 3.95–3.98 (2H, m, OCH_2CH_2OEt), 5.46 (2H, s, 5-CH_2), 5.76 (1H, s, $CH(OCH_3)_2$), 6.94 (1H, s, imidazole H), 7.53 (1H, s, imidazole H), 8.26 (1H, s, 6-H). ^{13}C NMR ($CDCl_3$) δ_C: 15.2, 19.2, 33.3, 55.9, 61.9, 66.8, 69.3, 74.1, 96.1, 101.2, 117.5, 128.8, 135.1, 137.6, 145.0, 150.8, 152.7, 170.8. EI-MS *m/z* (%): 393 (M^+, 35.2), 81 (imidazole–CH_2^+, 100). High-resolution MS Calcd for $C_{19}H_{27}N_3O_6$ (M^+): 393.1899. Found: 393.1899.

3.1.9. 3-(2-Ethoxyethoxy)-2-methyl-5-{[imidazol-4(5)-yl]acetoxy}methylpyridine-4-carbaldehyde (2a). A solution of **17a** (35.5 mg, 0.090 mmol) in acetic acid–H_2O (3:2, 5 ml) was refluxed for 3 h. After being neutralized with saturated $NaHCO_3$ solution, the reaction mixture was extracted with ethyl acetate. The organic layers were washed with saturated $NaHCO_3$ solution, H_2O and saturated NaCl solution, dried over Na_2SO_4, and concentrated under reduced pressure. The resultant residue was purified by silica gel column chromatography ($CHCl_3$/MeOH=10:1) to give **2a** (18.2 mg, 58%) as a colorless oil. IR ν_{max} (KBr): 3133, 2876, 1739, 1698 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 1.20 (3H, t, J=7 Hz, OCH_2CH_3), 2.60 (3H, s, 2-CH_3), 3.54 (2H, q, J=7 Hz, OCH_2CH_3), 3.75 (2H, s, $OCOCH_2$), 3.69–3.76 (2H, m, OCH_2CH_2OEt), 4.13–4.16 (2H, m, OCH_2CH_2OEt), 5.46 (2H, s, 5-CH_2), 6.95 (1H, s, imidazole H), 7.55 (1H, s, imidazol H), 8.38 (1H, s, 6-H), 10.60 (1H, s, CHO). ^{13}C NMR ($CDCl_3$) δ_C: 15.0, 19.3, 33.2, 62.0, 66.8, 69.2, 75.1, 96.1, 117.2, 128.3, 132.1, 135.1, 144.4, 155.0, 155.11, 170.6, 192.3. EI-MS m/z (%): 347 (M^+, 0.2), 81 (imidazole–CH_2^+, 100). High-resolution MS Calcd for $C_{17}H_{21}N_3O_5$ (M^+): 347.1481. Found: 347.1492.

3.1.10. 3-(2-Ethoxyethoxy)-2-methyl-5-{3-[*N*-(*p*-toluenesulfonyl)imidazol-4(5)-yl]propanoyloxy}methylpyridine-4-carbaldehyde dimethyl acetal (16b). Compound **16b** was obtained as a colorless oil in 60% yield by the same method as that for **16a**. IR ν_{max} (KBr): 2931, 1737, 1379 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 1.28 (3H, t, J=7 Hz, OCH_2CH_3), 2.43 (3H, s, Ar-CH_3), 2.54 (3H, s, 2-CH_3), 2.69, 2.87 (each 2H, t, J=8 Hz $COCH_2CH_2$imidazole), 3.42 (6H, s, $CH(OCH_3)_2$), 3.62 (2H, q, J=7 Hz, OCH_2CH_3), 3.75–3.78 (2H, m, OCH_2CH_2OEt), 3.95–3.98 (2H, m, OCH_2CH_2OEt), 5.40 (2H, s, 5-CH_2), 5.75 (1H, s, $CH(OCH_3)_2$), 7.02 (1H, d, J=1 Hz, imidazole H), 7.34, 7.80 (each 2H, AA′BB′, J=8 Hz, aromatic H), 7.91 (1H, d, J=1 Hz, imidazole H), 8.28 (1H, s, 6-H). ^{13}C NMR ($CDCl_3$) δ_C: 15.2, 19.3, 21.7, 23.4, 33.1, 55.9, 61.4, 66.8, 69.4, 74.0, 101.2, 113.3, 127.3, 128.3, 128.8, 130.3, 136.2, 137.5, 143.7, 145.4, 146.0, 150.7, 152.8, 172.2. EI-MS m/z: 561 (M^+, 4.4), 277 [M^+–$COCH_2CH_2$imidazole(Tos), 100]. High-resolution MS Calcd for $C_{27}H_{35}N_3O_8S$ (M^+): 561.2144. Found: 561.2155.

3.1.11. 3-(2-Ethoxyethoxy)-2-methyl-5-{3-[imidazol-4(5)-yl]propanoyloxy}methylpyridine-4-carbaldehyde dimethyl acetal (17b). Compound **17b** was obtained as a colorless oil in 89% yield by the same method as that for **17a**. IR ν_{max} (KBr): 3091, 2932, 1736, 1447 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 1.28 (3H, t, J=7 Hz, OCH_2CH_3), 2.54 (3H, s, 2-CH_3), 2.73, 2.96 (each 2H, t, J=7 Hz, $COCH_2CH_2$-imidazole), 3.42 (6H, s, $CH(OCH_3)_2$), 3.62 (2H, q, J=7 Hz, OCH_2CH_3), 3.75–3.79 (2H, m, OCH_2CH_2OEt), 3.94–3.98 (2H, m, OCH_2CH_2OEt), 5.43 (2H, s, 5-CH_2), 5.76 (1H, s, $CH(OCH_3)_2$), 6.79 (1H, s, imidazole H), 7.52 (1H, s, imidazole H), 8.27 (1H, s, 6-H). ^{13}C NMR ($CDCl_3$) δ_C: 15.2, 19.3, 21.8, 34.1, 55.9, 61.5, 66.8, 69.3, 74.1, 77.2, 96.1, 101.2, 128.8, 134.7, 137.6, 145.4, 150.8, 152.8, 173.1. EI-MS m/z: 407 (M^+, 42.9), 123 (imidazole $CH_2CH_2CO^+$, 100). High-resolution MS Calcd for $C_{20}H_{29}N_3O_6$ (M^+): 407.2056. Found: 407.2056.

3.1.12. 3-(2-Ethoxyethoxy)-2-methyl-5-{3-[imidazol-4(5)-yl]propanoyloxy}methylpyridine-4-carbaldehyde (2b). Compound **2b** was obtained as a colorless oil in 81% yield by the same method as that for **2a**. IR ν_{max} (KBr): 3103, 2871, 1738, 1697, 1448 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 1.20 (3H, t, J=7 Hz, OCH_2CH_3), 2.61 (3H, s, 2-CH_3), 2.74, 2.95 (each 2H, t, J=7 Hz, $COCH_2CH_2$imidazole), 3.54 (2H, q, J=7 Hz, OCH_2CH_3), 3.75–3.77 (2H, m, OCH_2CH_2OEt), 4.13–4.16 (2H, m, OCH_2CH_2OEt), 5.42 (2H, s, 5-CH_2), 6.80 (1H, s, imidazole H), 7.55 (1H, s, imidazole H), 8.38 (1H, s, 6-H), 10.61 (1H s CHO). ^{13}C NMR ($CDCl_3$) δ_C: 15.0, 19.4, 21.9, 34.0, 61.6, 66.8, 69.2, 75.1, 77.2, 117.6, 128.2, 132.1, 134.7, 144.6, 155.1, 155.2, 172.9, 192.3. EI-MS m/z: 361 (M+, 0.9), 123 (imidazole $CH_2CH_2CO^+$, 100). High-resolution MS Calcd for $C_{18}H_{23}N_3O_5$ (M^+): 361.1637. Found: 361.1624.

3.2. General procedure for β-replacement reaction

β-Replacement reactions with **2** were carried out according to the same procedure described in a preceding paper, and the results are summarized in Tables 1 and 2. Spectral properties of the products **4a**–**e** are also shown in a preceding paper. Spectral properties of amide **19a** and peptides **19b**–**h** are as follows. Peptides **19c**–**h** were obtained as a diastereomeric mixture (ca. 1:1).

3.2.1. *S*-Benzylcysteine benzylamide (19a). A colorless oil. IR ν_{max} (KBr): 3374, 1668, 1587 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 1.55 (2H, m, NH_2), 2.42 (1H, dd, J=7, 14 Hz, CH_2S), 2.81 (1H, dd, J=5, 14 Hz, CH_2S), 3.56 (1H, dd, J=5, 7 Hz, α-H), 3.68 (2H, s, SCH_2Ph), 4.22–4.41 (2H, m, $NHCH_2Ph$), 7.20–7.36 (10H, m, aromatic H), 7.98 (1H, m, amide NH). ^{13}C NMR ($CDCl_3$) δ_C: 36.0, 38.6, 55.0, 66.3, 126.7, 127.2, 127.8, 128.5, 129.0, 129.7, 135.4, 137.9, 170.6. EI-MS m/z: 300 (M^+, 38). High-resolution MS Calcd for $C_{17}H_{20}N_2OS$ (M^+): 300.1296. Found: 300.1301.

3.2.2. (*S*-Benzylcysteinyl)glycine benzyl ester (19b). A colorless oil. IR ν_{max} (KBr): 3370, 1741, 1650, 1592 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 1.48 (2H, br s, NH_2), 2.35 (1H, dd, J=7, 14 Hz, α-CH_2S), 2.83 (1H, dd, J=5, 14 Hz, α-CH_2S), 3.56 (1H, dd, J=5, 7 Hz, N-terminal α-H), 3.68 (2H, s, SCH_2Ph), 4.13–4.37 (2H, AB in ABX, J=5, 13 Hz, C-terminal α-H), 5.10–5.16 (2H, AB type, J=11 Hz, CO_2CH_2Ph), 7.20–7.48 (10H, m, aromatic H), 8.01 (1H, br s, amide NH). ^{13}C NMR ($CDCl_3$) δ_C: 39.1, 42.0, 55.0, 58.2, 65.3, 124.9, 125.9, 127.8, 128.0, 128.5, 129.3, 133.3, 138.8, 169.5, 172.1. EI-MS m/z (%): 372 (M^+, 7.6), 91 (Bn^+, 100). High-resolution MS Calcd for $C_{20}H_{24}N_2O_3S$ (M^+): 372.1508. Found: 372.1510.

3.2.3. (*S*-Benzylcysteinyl)-L-alanine benzyl ester (19c, ca 1:1 diastereomeric mixture). A colorless oil. IR ν_{max} (KBr): 3376, 1737, 1652, 1593 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 1.33 (3/2H, d, J=7 Hz, α-CH_3), 1.36 (3/2H, d, J=7 Hz, α-CH_3), 1.49 (2H, br s, NH_2), 2.30 (1/2H, dd, J=7, 14 Hz, α-CH_2S), 2.36–2.87 (2/2H, AB in ABX, α-CH_2S), 2.93 (1/2H, dd, J=5, 14 Hz, α-CH_2S), 3.58 (1/2H, dd, J=5, 7 Hz, N-terminal α-H), 3.62 (1/2H, dd, J=5, 7 Hz, N-terminal α-H), 3.68 (2/2H, s, SCH_2Ph), 3.70 (2/2H, s, SCH_2Ph), 4.37 (1H, qn, J=7 Hz, C-terminal α-H), 5.11–5.16 (2H, AB type, CO_2CH_2Ph), 7.20–7.48 (10H, m, aromatic H), 7.92 (1H, br s, amide NH). ^{13}C NMR ($CDCl_3$) δ_C: 17.2, 38.4, 40.1, 53.0, 55.6, 66.9, 126.8, 127.1, 127.5, 128.0, 128.4,

129.0, 134.8, 138.4, 171.8, 172.9. EI-MS *m/z* (%): 386 (M^+, 5.2), 91 (Bn^+, 100). High-resolution MS Calcd for $C_{21}H_{26}N_2O_3S$ (M^+): 386.1664. Found: 386.1666.

3.2.4. (*S*-Benzylcysteinyl)-L-valine benzyl ester (19d, ca 1:1 diastereomeric mixture). A colorless oil. IR ν_{max} (KBr): 3366, 1747, 1669, 1508 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 0.73, 0.75 (each 3/2H, each d, J=7 Hz, $CH(CH_3)_2$), 0.88, 0.91 (each 3/2H, each d, J=7 Hz, $CH(CH_3)_2$), 1.50 (2H, br s, NH_2), 2.11–2.20 (1H, m, $CH(CH_3)_2$), 3.13 (1/2H, dd, J=7, 11 Hz, α-CH_2S), 3.15–3.53 (2/2H, AB in ABX, α-CH_2S), 3.61 (1/2H, dd, J=5, 11 Hz, α-CH_2S), 3.59–3.63 (1H, m, N-terminal α-H), 3.67 (2/2H, s, SCH_2Ph), 3.70 (2/2H, s, SCH_2Ph), 4.48 (1/2H, dd, J=5, 9 Hz, C-terminal α-H), 4.53 (1/2H, dd, J=5, 9 Hz, C-terminal α-H), 5.11–5.14 (2H, AB type, CO_2CH_2Ph), 7.30–7.45 (10H, m, aromatic H), 8.12 (1H, br s, amide NH). ^{13}C NMR ($CDCl_3$) δ_C: 17.2, 19.4, 31.2, 37.3, 38.4, 56.81, 59.6, 67.6, 126.0, 127.1, 128.0, 128.3, 128.6, 129.0, 135.1, 138.4, 171.7, 172.8. EI-MS *m/z* (%): 414 (M^+, 13), 91 (Bn^+, 100). High-resolution MS Calcd for $C_{23}H_{30}N_2O_3S$ (M^+): 414.1977. Found: 414.1973.

3.2.5. (*S*-Benzylcysteinyl)-L-alanyl-L-alanine benzyl ester (19e, ca 1:1 diastereomeric mixture). A colorless oil. IR ν_{max} (KBr): 3363, 1741, 1668, 1506 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 1.21 (3H, d, J=7 Hz, C-terminal α-CH_3), 1.34 (3/2H, d, J=7 Hz, α-CH_3), 1.37 (3/2H, d, J=7 Hz, α-CH_3), 1.48 (2H, br s, NH_2), 3.22–3.38 (1H, m, α-CH_2S), 3.55–3.70 (1H, m, α-CH_2S), 3.70 (2/2H, s, SCH_2Ph), 3.73 (2/2H, s, SCH_2Ph), 3.88 (1H, m, N-terminal α-H), 4.22 (1H, qn, J=7 Hz, α-H), 4.42 (1H, qn, J=7 Hz, C-terminal α-H), 5.04–5.12 (2H, AB type, CO_2CH_2Ph), 6.96 (1H, br s, amide NH), 7.28–7.45 (10H, m, aromatic H), 8.12 (1H, br s, amide NH). ^{13}C NMR ($CDCl_3$) δ_C: 17.0, 17.8, 36.5, 38.4, 47.5, 52.6, 55.2, 66.9, 126.8, 127.1, 128.2, 129.0, 135.0, 138.4, 170.6, 171.8, 173.1. EI-MS *m/z* (%): 443 (M^+, 3.4), 91 (Bn^+, 100). High-resolution MS Calcd for $C_{23}H_{30}N_3O_4S$ (M^+): 443.1879. Found: 443.1884.

3.2.6. (*S*-Phenylcysteinyl)-L-alanine Benzyl Ester (19f, ca 1:1 diastereomeric mixture). A colorless oil. IR ν_{max} (KBr): 3373, 1737, 1665, 1590 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 1.39 (3/2H, d, J=7 Hz, α-CH_3), 1.42 (3/2H, d, J=7 Hz, α-CH_3), 1.55 (2H, br s, NH_2), 3.22 (1/2H, dd, J=7, 14 Hz, α-CH_2S), 3.25–3.60 (2/2H, AB in ABX, α-CH_2S), 3.62 (1/2H, dd, J=5, 14 Hz, α-CH_2S), 3.66 (1H, m, N-terminal α-H), 4.42 (1H, qn, J=7 Hz, C-terminal α-H), 5.04–5.12 (2H, AB type, CO_2CH_2Ph), 7.30–7.45 (10H, m, aromatic H), 8.12 (1H, br s, amide NH). ^{13}C NMR ($CDCl_3$) δ_C: 17.0, 39.0, 56.1, 57.9, 66.9, 125.9, 126.8, 127.2, 128.0, 128.5, 129.0, 129.7, 135.5, 138.8, 171.8, 172.7. EI-MS *m/z* (%): 354 (M^+, 19), 263 (32), 91 (Bn^+, 100). High-resolution MS Calcd for $C_{17}H_{26}N_2O_4S$ (M^+): 354.1613. Found: 354.1610.

3.2.7. (*S*-Ethylcysteinyl)-L-alanine benzyl ester (19g, ca 1:1 diastereomeric mixture). A colorless oil. IR ν_{max} (KBr): 3381, 1756, 1653, 1500 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 1.13 (3H, d, J=7 Hz, SCH_2CH_3), 1.31 (3/2H, d, J=7 Hz, α-CH_3), 1.32 (3/2H, d, J=7 Hz, α-CH_3), 1.55 (2H, br s, NH_2), 2.51 (2H, q, J=7 Hz, SCH_2CH_3), 2.73–3.11 (2/2H, AB in ABX, α-CH_2S), 2.81–2.96 (2/2H, AB in ABX, α-CH_2S), 3.68 (1H, m, N-terminal α-H), 4.40 (1H, m, C-terminal α-H), 5.21 (2H, s, CO_2CH_2Ph), 7.30–7.45 (5H, m, aromatic H), 7.98 (1H, br s, amide NH). ^{13}C NMR ($CDCl_3$) δ_C: 17.1, 39.1, 53.6, 56.1, 67.8, 124.3, 125.6, 128.0, 128.5, 128.9, 132.1, 138.8, 171.07, 172.2. EI-MS *m/z* (%): 324 (M^+, 5.3), 91 (Bn^+, 100). High-resolution MS Calcd for $C_{16}H_{34}N_2O_3S$ (M^+): 324.1508. Found: 324.1511.

3.2.8. *S*-(3-Hydroxypropyl)cysteinyl]-L-alanine benzyl ester (19h, ca 1:1 diastereomeric mixture). A colorless oil. IR ν_{max} (KBr): 3368, 3033, 1737, 1661 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 1.36 (3/2H, d, J=7 Hz,** α-CH_3), 1.38 (3/2H, d, J=7 Hz, α-CH_3), 1.61 (2H, br, NH_2), 1.76 (2H, qn, J=7 Hz, $SCH_2CH_2CH_2OH$), 2.59 (2H, t, J=7 Hz, $SCH_2CH_2CH_2$-OH), 2.90–2.95 (2/2H, m, α-CH_2S), 2.98–3.06 (2/2H, m, α-CH_2S), 3.68 (1H, m, N-terminal α-H), 3.72 (2H, t, J=7 Hz, $SCH_2CH_2CH_2OH$), 4.40 (1H, m, C-terminal α-H), 5.08 (2H, br s, CO_2CH_2Ph), 7.24–7.42 (5H, m, aromatic H), 8.09 (1H, br s, amide NH). ^{13}C NMR (67.8 MHz, $CDCl_3$) δ_C: 17.0, 31.2, 36.8, 36.8, 38.8, 53.9, 54.3, 56.0, 67.3, 125.9, 126.8, 128.0, 134.1, 171.8, 172.7. EI-MS *m/z* (%): 355 ($M+H^+$, 1.0), 91 (Bn^+, 100). High-resolution MS Calcd for $C_{16}H_{34}N_2O_3S$ ($M+H^+$): 355.1615. Found: 355.1610.

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References

1. For example: Davis, L.; Metzler, D. E. *The Enzymes*; Boyer, P. D., Ed.; Academic: New York, 1972; Vol. VII, pp 1–22.
2. (a) Weinre, W.; Winkler, J.; Zimmerman, S. C.; Czarnil, A. W.; Breslow, R. *J. Am. Chem. Soc.* **1985**, *107*, 4093. (b) Murakami, Y.; Kikuchi, J.; Kitazaki, T. *J. Chem. Soc., Chem. Commun.* **1998**, 143. (c) Murakami, Y.; Kikuchi, J.; Hisaeda, Y.; Nakamura, K.; Kitazaki, T.; Kaya, H. *Bull. Chem. Soc. Jpn* **1990**, *63*, 2339. (d) Murakami, Y.; Hisaeda, Y.; Nakamura, K.; Kikuchi, J. *Chem. Lett.* **1990**, 1765. (e) Murakami, Y.; Hisaeda, Y.; Miyajima, T.; Sakata, H.; Kikuchi, J. *Chem. Lett.* **1993**, 645. (f) Murakami, Y.; Hisaeda, Y.; Miyajima, T.; Kikuchi, J. *Chem. Lett.* **1993**, 2093.
3. Miyashita, K.; Murafuji, H.; Iwaki, H.; Yoshioka, E.; Imanishi, T., *Tetrahedron*, **2003**, *59*, 4867.
4. (a) Miyashita, K.; Iwaki, H.; Tai, K.; Murafuji, H.; Imanishi, T. *Chem. Commun.* **1998**, 1987. (b) Miyashita, K.; Iwaki, H.; Tai, K.; Murafuji, H.; Sasaki, N.; Imanishi, T. *Tetrahedron* **2001**, *57*, 5773.
5. Examples for direct modification of peptides: (a) Bossler, H. G.; Seebach, D. *Angew. Chem. Int. Ed. Engl.* **1993**, *33*, 439. (b) Seebach, D.; Beck, A. K.; Bossler, H. G.; Gerber, C.; Ko, S. Y.; Murtiashaw, C. W.; Nerf, R.; Shoda, S.; Thaler, A.; Krieger, M.; Wenger, R. *Helv. Chim. Acta* **1993**, *76*, 1564. (c) Bossler, H. G.; Seebach, D. *Helv. Chim. Acta* **1994**, *77*, 1124. (d) Ager, D. J.; Froen, D. E.; Klix, R. C.; Zhi, B. *Tetrahedron* **1994**, *50*, 1975. (e) Kazmaier, U. *J. Org. Chem.* **1994**, *59*, 6667.
6. (a) Scott, W. L.; Zhou, C.; O'Donnell, M. J. *J. Am. Chem. Soc.* **1996**, *116*, 6070. (b) Scott, W. L.; Zhou, C.; Fang, Z.; O'Donnell, M. J. *Tetrahedron Lett.* **1997**, *38*, 3695.
7. A part of this work appeared in a prelimanary communication: Miyashita, K.; Murafuji, H.; Iwaki, H.; Yoshioka, E.; Imanishi, T. *Chem. Commun.* **2002**, 1922.
8. Baddiley, J.; Mathias, A. P. *J. Chem. Soc.* **1952**, 2583.