Pummerer-type Cyclization of Arnstein Tripeptide Analogues Induced by *O*-Silylated Ketene Acetals: Studies of Penicillin Biosynthesis

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Abstract: We report the first biomimetic conversion of Arnstein tripeptide analogues (**1a** and **1b**) into *cis* β-lactams (**2a** and **2b**) using *O*-silylated ketene acetal (**3**) involving asymmetric induction from the sulfoxide sulfur to the α-carbon. The peptide **1** was treated with **3** at room temperature in the presence of a catalytic amount of ZnI_2 in MeCN to give *cis*-**2**, *trans*-**2**, and α-siloxysulfide (**7**). Reaction of *R*-**1** with **3** gave *cis*-**2** predominantly, and *S*-**1** gave a mixture of *cis*-**2** and *trans*-**2**. High *cis* selectivity was obtained by the use of a large volume of solvent and was strongly influenced by the absolute stereochemistry of the sulfoxide, the cysteinyl amino group, and the volume of solvent. The *cis* β-lactams (**2a,b**) were obtained preferentially from *R*-**1a,b**. These chemical transformations strongly support Baldwin's mechanism which involves the initial formation of the *cis* β-lactam by the Pummerer-type cyclization of the Arnstein tripeptide in penicillin biosynthesis and provide useful information on the first key step in penicillin biosynthesis.

Introduction

The mechanism of penicillin biosynthesis from the Arnstein tripeptide has been studied extensively by many chemists and reviewed.[1] Most of the biosynthetic mechanisms have been ascertained by Baldwin et al. using an excellent enzymatic technique.[2] However, the first step in the biosynthesis of penicillin, conversion of the Arnstein tripeptide to a *cis* β-lactam intermediate still is a fascinating mechanistic problem. Earlier, two hypothetical intermediates involving 2,3-dehydrocysteinyl structures (**A** and **B**) were ruled out by studies with radioactive primary metabolite precursors.[1] Other proposed intermediates including thiazepine (**C**)[3] and hydroxamic acid (**D**)[4] have also been eliminated by incorporating experiments into penicillin under incubation conditions, and two general mechanisms remain: (i) hydroxylation at the C-3 of the cysteinyl residue (activated alcohol **E** as the intermediate)[1] and (ii) dehydration of the carbon–sulfur bond (thioaldehyde **F** as the intermediate) (Scheme 1).[5] Although Baldwin et al. recently proposed the latter type of mechanism involving a thioaldehyde formation route via the Pummerer-type cyclization (Scheme 2),[2] the intermediate for this mechanism has not been identified yet. The type of enzyme involved has of course also been unknown. Previously, we reported the first silicon-induced Pummerer-type cyclization[6] and applied it to a biomimetic conversion of an Arnstein tripeptide analogue (**1a**) into *cis* β-lactam (**2a**) involving an asymmetric induction from the chiral sulfoxide to the α-carbon of sulfur.[7] The chemical transformation strongly supports Baldwin's mechanism which involves the initial formation of *cis* β-lactam by the Pummerer-type reaction of the Arnstein tripeptide in penicillin biosynthesis.[8] We now describe a full account of this work and a mechanistic study of the Pummerer-type cyclization[9] of a more closely related Arnstein tripeptide analogue (**1b**) (Scheme 3).

Pummerer-type Cyclization of the Arnstein Peptide Analogues (1a and 1b) Using *O*-Silylated Ketene Acetal (3). Preparation of the Arnstein-type dipeptide (**1a**) is shown in Scheme 4. Treatment of the sulfide (**4**)[8l] with (benzyloxy)carbonyl chloride followed by coupling with D-valine methyl ester using DCC in *N,N*-dimethylformamide (DMF) afforded the dipeptide (**6**), which was oxidized with $NaIO_4$ in methanol to furnish **1a** as a

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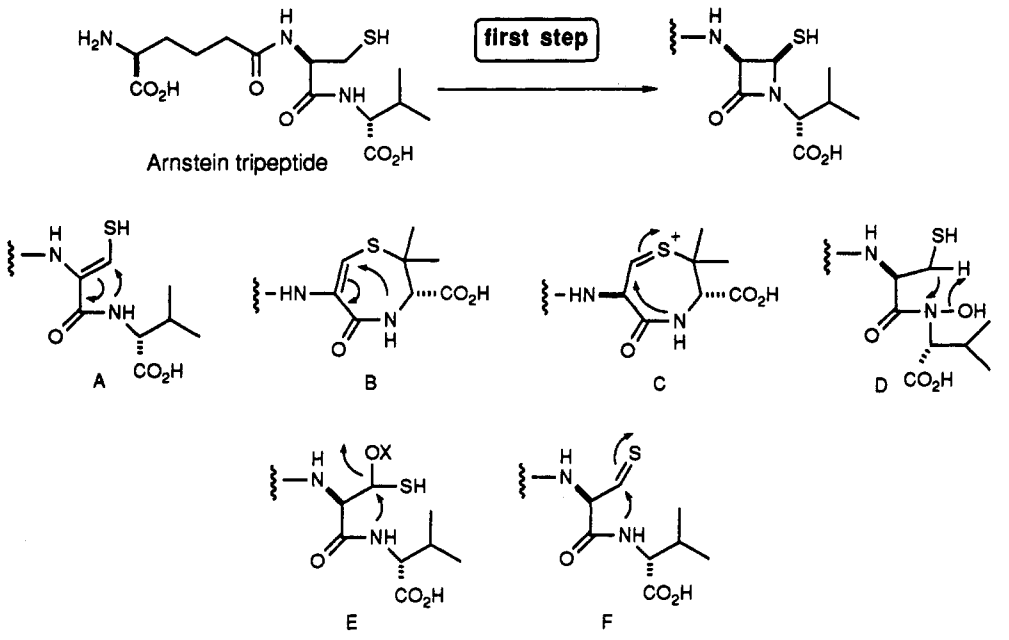
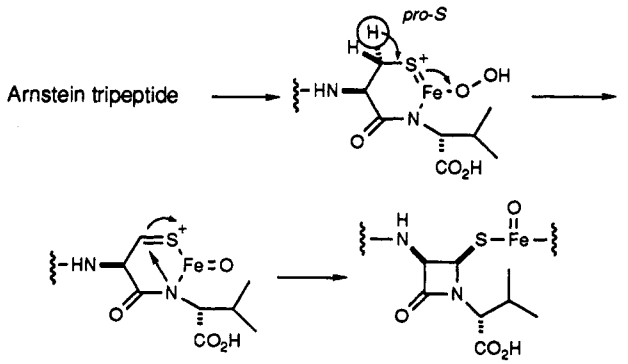
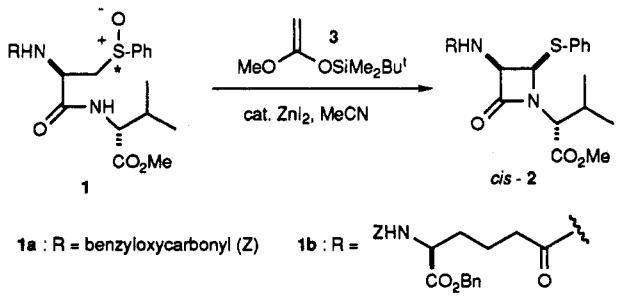
Scheme 1



Scheme 2



Scheme 3



Scheme 4

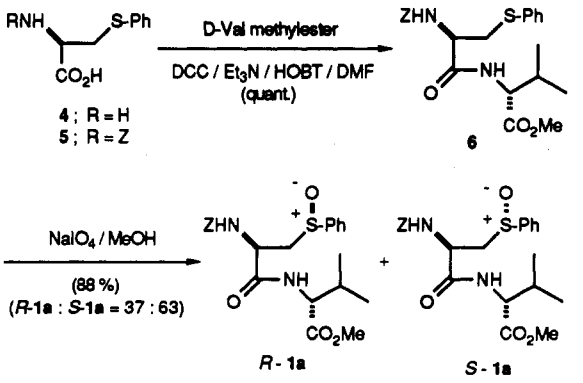
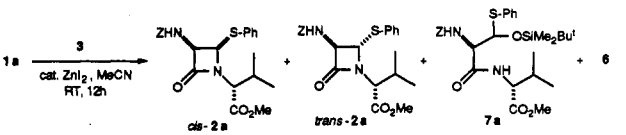


Table 1. Reaction of Dipeptide (**1a**) with *O*-Silylated Ketene Acetal (**3**)



run	sulfoxide	conc (M/L)	% yield of **2a** (*cis*:*trans*)[a]	% yield of **7a** (polar:less polar)[a]	% yield of **6**
1	*R*-**1a**	0.017	69 (5.2:1)	3 (1.4:1)	6
2	*S*-**1a**	0.044	50 (1:2.2)	6 (6.1:1)	23

[a] Determined from their ^{1}H-NMR and HPLC data.

mixture of diastereomers. The diastereomers could be separated by column chromatography on silica gel with AcOEt–hexanes. The polar isomer was *R*-sulfoxide (*R*-**1a**), and the less polar isomer was *S*-sulfoxide (*S*-**1a**) (*vide infra*).

Dipeptide **1a** was treated with **3** at room temperature in the presence of a catalytic amount of ZnI_2 in MeCN to give *cis*-**2a**, *trans*-**2a**, α-siloxysulfide (**7**), and the deoxygenated sulfide (**6**). The ratios of the *cis*/*trans* of **2a** and the sulfides varied slightly under the reaction conditions used. By the use of a large volume of solvent, the *cis* selectivity was increased. However, the total reaction rate was slowed down. The reaction conditions were optimized, and the use of 0.017 M/L solution in MeCN for *R*-**1a** and 0.044 M/L solution in MeCN for *S*-**1a** was found to give good results (Table 1). *R*-**1a** was treated with **3** to give *cis*-**2a** predominantly and *S*-**1a** with **3** to give a mixture of *cis*-**2a** and *trans*-**2a**. It should be noted that *cis* β-lactam was obtained preferentially from *R*-**1a** compared with the fact that the naturally occurring 3-amino-β-lactams involving penicillin have a complete *cis* orientation.

Next, we examined the reaction of more closely related Arnstein tripeptide analogues (*R*-**1b** and *S*-**1b**) with **3**. The synthesis of the fully protected tripeptide (**10**) was accomplished by a modification of Baldwin's method.[10] Treatment of the 2-α-aminoadipic acid derivative (**8**)[11] with isobutyl chloroformate in the presence of Et_3N gave a mixed anhydride, which was coupled with **4** to give dipeptide (**9**). Reaction of crude **9** with D-valine methyl ester in the presence of DCC and Et_3N in DMF gave **10**, which was oxidized by $NaIO_4$ in methanol to give a mixture of diastereomers of *R*-**1b** and *S*-**1b**. The mixture was separated by

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Scheme 5

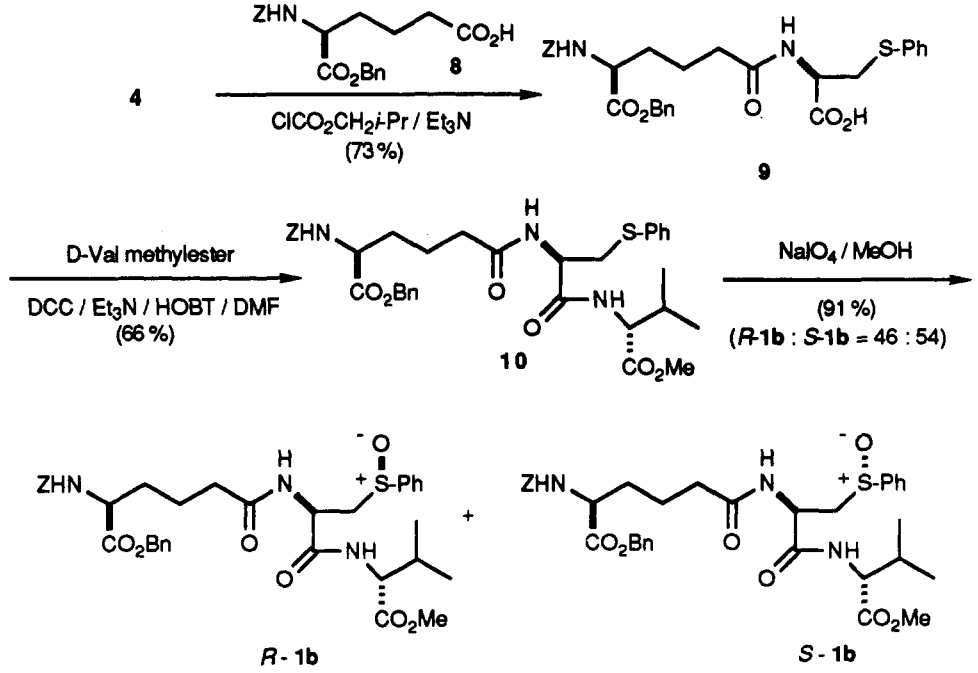
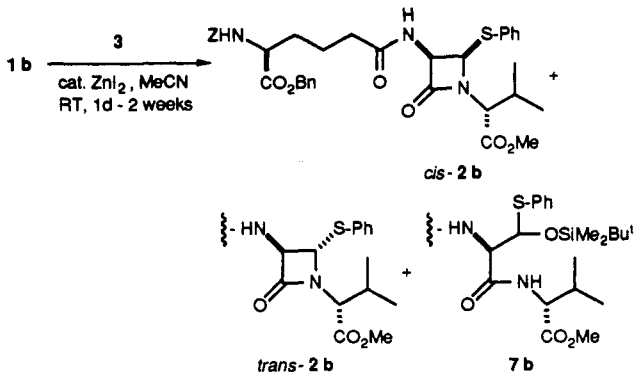


Table 2. Reaction of Tripeptide (**1b**) with *O*-Silylated Ketene Acetal (**3**)



run	sulfoxide	conc (M/L)	% yield of **2b** (*cis*:*trans*)[a]	% yield of **7b** (polar:less polar)[a]	% yield of recoverd **1b**
1	*R*-**1b**	0.3	42 (3.4:1)	54 (1:3.5)	0
2	*S*-**1b**	0.3	16 (1:1.1)	81 (10:1)	0
3	*R*-**1b**	0.04	26 (4.4:1)	54 (1:4.1)	19
4	*R*-**1b**	0.004	9 (11:1)	43 (1:4.2)	40

[a] Determined from their ^{1}H-NMR and HPLC data.

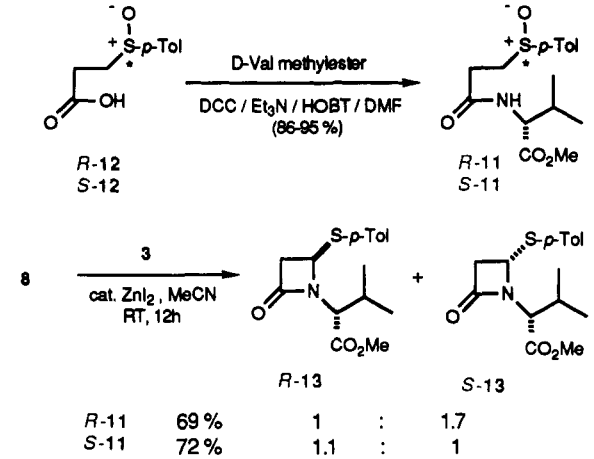
column chromatography on silica gel with MeOH–CH_2Cl_2 to give pure *R*-**1b** and *S*-**1b** (Scheme 5).

The silicon-induced Pummerer-type reaction of **1b** was carried out under conditions similar to those described for the reaction of **1a** with **3** and summarized in Table 2. Reaction of *R*-**1b** with **3** gave *cis*-**2b** predominantly and *S*-**1b** gave a mixture of *cis*-**2b** and *trans*-**2b**. Dilution of the reaction with solvent gave nearly the same effect observed in the case of **1a**, and high *cis* selectivity (*cis*:*trans* = 11:1) was obtained using 0.004 M/L conditions (Table 2).

In order to ascertain the effect of the amino group of cysteine, we finally examined the reaction of the chiral 2-deaminosulfoxide (**11**) (2-deamino derivative of **1**). The Pummerer-type cyclization of *R*- and *S*-**11**, which were prepared from the known chiral carboxylic acid[12] (**12**) with D-valine methyl ester, gave a mixture of *R*- and *S*-β-lactams (**13**),[13] respectively (*R*-**13**: *S*-**13** = 1:1.7 from *R*-**11**; 1.1:1 from *S*-**11**) (Scheme 6). There is no *cis* (4*R*) selectivity in these 2-deaminosulfoxides.

(12) Albinati, A.; Bravo, P.; Ganazzoli, F.; Resnati, G.; Viani, F. *J. Chem. Soc., Perkin Trans. 1*, **1986**, 1405.

Scheme 6



R-11	69%	1	:	1.7
S-11	72%	1.1	:	1

In the synthesis of 3-alkyl-4-phenylthioazetidin-2-ones using our silicon-induced Pummerer-type cyclization,[9b,d-f] the ratio of the energetically favorable 3,4-*trans* isomers tends to increase because of the bulkiness of the 3-alkylsubstitutes. These results explain that the *cis* selectivity of **2a,b** from **1a,b** was strongly influenced by the cysteinyl amino group as well as the absolute stereochemistry of the sulfoxide.

Determination of the Stereochemistry of Sulfoxides (1a and 1b). The absolute configuration of the sulfur center of **1a** and **1b** was assigned from the CD spectrum. Mislow reported that alkyl phenyl sulfoxides which exhibited a negative Cotton effect at about 235–255 nm tend to have an *R*-configuration and those which exhibited a positive one tend to have the *S*-configuration.[14] Therefore, (+)-sulfoxides have the *R*-configuration and (–)-ones have the *S*-configuration (Table 3).

Finally, the stereochemistry of *S*-**1a** was confirmed by X-ray analysis (Figure 1).

Transition-State Model. Although the details of the *cis* selectivity of the reaction of *R*-**1** with **3** remain unknown, a working

(13) The absolute stereochemistry at the newly generated chiral center of the β-lactams was ascertained by the CD spectrum, which had a strong positive or negative Cotton effect at 210–220 nm (octant rule) in good agreement with the value from monocyclic β-lactams reported by Reling and Jensen: Rehling, H.; Jensen, H. *Tetrahedron Lett.* **1972**, 2793.

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Scheme 7

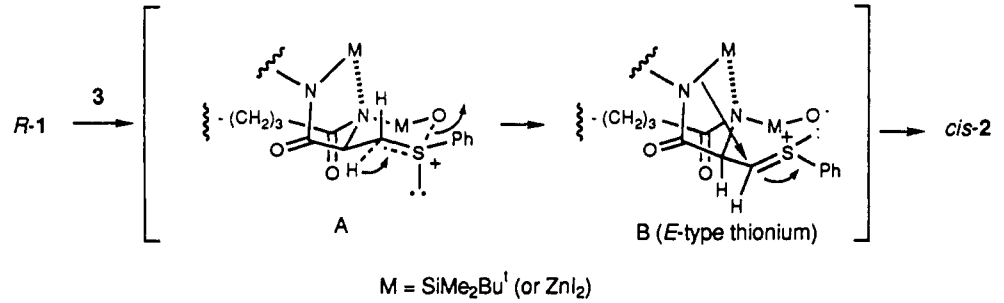

Table 3. $[\alpha]_D$ and CD Spectrum of Sulfoxides (**1**)

run	sulfoxide	$[\alpha]_D$ (c, $CHCl_3$)	CD (MeOH) (17 °C) λ ext
1	*R*-**1a**	+66.5° (0.87)	242 (–6.3), 227 (0.0), 215 (+8.7) ($c' = 0.0522 \times 10^{-3}$ M/L)
2	*S*-**1a**	–144° (0.41)	241 (+6.5), 230 (0.0), 216 (–7.7) ($c' = 0.0337 \times 10^{-3}$ M/L)
3	*R*-**1b**	+39.0° (0.805)	242 (–87.2), 226 (0.0), 213 (+124.6) ($c' = 0.007\,783 \times 10^{-3}$ M/L)
4	*S*-**1b**	–107° (0.965)	243 (+25.7), 228 (0.0), 216 (–37.8) ($c' = 0.046\,84 \times 10^{-3}$ M/L)

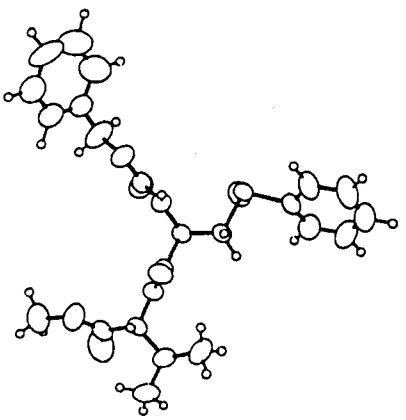

Figure 1. X-Ray crystallographic structure of *S*-**1a**.

model is given in Scheme 7. Initial silicon transfer from **3** to *R*-**1** resulted in the chelated structure **A**.[15] Subsequent abstraction of the α-hydrogen by the generated ester enolate anion and elimination of the siloxy ligand would lead to the *E*-type thionium intermediate **B**. The β-amido moiety may be forced to attack the α-position to result in *cis*-**2**.

Although the effect of dilution of the reaction mixture with solvent also remains unclear, it seems to be an effect similar to the temperature effect in the reaction selectivity. In general, the selectivity of the reaction at low temperature is higher than that at high temperature, although the reaction rate is slowed down. As the volume of the solvent is increased, the *cis* selectivity is gradually increased and the reaction rate is slowed down in the present cyclization reactions.

Conclusions

We have reported the first biomimetic conversion of Arnstein tripeptide analogues (**1a** and **1b**) into *cis* β-lactams (**2a** and **2b**) using *O*-silylated ketene acetal (**3**) involving asymmetric induction from the sulfoxide sulfur to the α-carbon. Although, in penicillin biosynthesis, IPNS were shown to catalyze the completely stereospecific β-lactam ring formation with deprotonation of the *pro-S* hydrogen and retention of the configuration at the cysteinyl C-3 position (Scheme 1), the deprotonation step cannot be discussed on the basis of the present results. Very recently, we were able to clarify the relationship between stereospecfic α-deprotonation and asymmetric induction of the α-carbon of sulfur in the silicon-induced Pummerer-type rearrangement in acyclic sulfoxides.[7b] Although further investigation of the deprotonation of the *pro-S* hydrogen in the Pummerer-type cyclization of **1a** and **1b** using an isotope labeling technique is currently in progress, the present results provide useful information on the first key step in penicillin biosynthesis.

(15) Chelated structures involving penta- and hexacoordinated silicon species have been proposed in aldol and Michael reactions with *O*-silylated ketene acetals in the presence of a fluoride anion; for review see: Chuit, C.; Corriu, R. J. P.; Reye, C.; Young, J. C. *Chem. Rev.* **1993**, *93*, 1371. In the absence of a catalyst: Myers, A. G.; Widdowson, K. L. *J. Am. Chem. Soc.* **1990**, *112*, 9672. Myers, A. G.; Widdowson, K. L.; Kukkola, P. J. *J. Am. Chem. Soc.* **1992**, *114*, 2765. Myers, A. G.; Kephart, S. E.; Chen, H. *J. Am. Chem. Soc.* **1992**, *114*, 7922.

Experimental Section

All melting points are uncorrected. IR spectra were recorded on JASCO HPIR-102 and Shimadzu FTIR-8100 spectrophotometers with $CHCl_3$ as a solvent. ^{1}H-NMR spectra were measured on JEOL JNM-FX90Q (90 MHz), JEOL JNM-EX270 (270 MHz), and JEOL JNM-GX500 (500 MHz) spectrometers with $CDCl_3$ as a solvent and TMS as an internal standard, unless otherwise noted. MS and HRMS were obtained on ESCO EMD-05A and JEOL JMS-D300 mass spectrometers. Optical rotations were measured in 1-dm cells of 1-mL capacity with a Perkin-Elmer 241 instrument. E. Merck silica gel 60 (70–230 mesh ASTM) for column chromatography and E. Merck precoated TLC plates (silica gel F_{254}) were used for preparative (prep.) TLC. Organic layers were dried with anhydrous Na_2SO_4.

***N*-(Benzyloxycarbonyl)-*S*-phenyl-L-cysteine (5).** (Benzyloxy)carbonyl chloride (1.318 g, 7.72 mmol) and an aqueous solution of NaOH (NaOH, 0.281 g, 7.02 mmol, water, 28 mL) were added dropwise from separate syringes to a vigorously stirred solution of **4**[8l] (1.385 g, 7.02 mmol) and NaOH (0.281 g, 7.02 mmol) in water (70 mL) at 0 °C. After being stirred for 3 h at 0 °C, the reaction mixture was washed with ether (70 mL). The aqueous layer was acidified with 5 N HCl and then extracted with AcOEt (100 mL × 3). The organic layer was washed with brine, dried over Na_2SO_4, and concentrated. The residue was purified by column chromatography on silica gel with 5% MeOH in CH_2Cl_2 to give **5** as colorless crystals: mp 85–88 °C (hexane/benzene); $[\alpha]_D^{25}$ +6.3° (c 0.75, $CHCl_3$); IR, 3450, 3050, 1720 cm^{-1}; ^{1}H NMR δ 3.44 (m, 2H, CH_2SPh), 4.50–4.82 (m, 1H, >CHCO), 5.10 (s, 2H, CH_2Ph), 5.58–5.79 (brs, 1H, NH), 7.10–7.47 (m, 10H, ArH). Anal. Calcd for $C_{17}H_{17}NO_4S$: C, 61.60; H, 5.18; N, 4.23; S, 9.68. Found: C, 61.26; H, 5.18; N, 4.33; S, 9.36. HRMS Calcd for $C_{17}H_{17}NO_4S$: 331.0879. Found: 331.0891.

***N*-(Benzyloxycarbonyl)-*S*-phenyl-L-cysteinyl-D-valine Methyl Ester (6).** DCC (2.241 g, 11 mmol), a solution of HOBT (1.468 g, 11 mmol) in DMF (37 mL), a solution of D-valine methyl ester hydrochloride (2.015 g, 12 mmol), and Et_3N (1.100 g, 11 mmol) in DMF (37 mL) were added to a solution of **5** (3.60 g, 11 mmol) in DMF (37 mL) at –5 °C and stirred at room temperature for 2 d. The white precipitate was removed by filtration, and the filtrate was concentrated on a rotary evaporator to give a crude oil, which was purified by column chromatography on silica gel, eluting with 25% AcOEt in hexane to give **6** (5.082 g, quant.) as colorless crystals: mp 123–125 °C ($CHCl_3$/hexane); $[\alpha]_D^{25}$ –27.7° (c 0.58, $CHCl_3$); IR, 3430, 1735, 1680 cm^{-1}; ^{1}H NMR δ 0.88, 0.93 (each d, each 3H, J = 6.7 Hz, Me_2), 2.12–2.18 (m, 1H, C*H*Me_2), 3.24 (dd, 1H, J = 7.3, 14.0 Hz, C*H*HS), 3.39 (brd, 1H, J = 14.0 Hz, CH*H*S), 3.72 (s, 3H, MeO), 4.33 (br, 1H, >CHNZ), 4.49 (dd, 1H, J = 4.8, 8.5 Hz, >C*H*CO_2), 5.11, 5.12 (AB-q, 2H, J = 12.2 Hz, CH_2Ph), 5.61, 6.66 (each brs, each 1H, NH × 2), 7.20-7.42 (m, 10H, ArH). Anal. Calcd for $C_{23}H_{28}N_2O_5S$: C, 62.13; H, 6.36; N, 6.30; S, 7.21. Found: C, 61.98; H, 6.32; N, 6.33; S, 7.20. HRMS Calcd for $C_{23}H_{28}N_2O_5S$: 444.1719. Found: 444.1719.

***N*-(Benzyloxycarbonyl)-*S*-phenyl-L-cysteinyl-D-valine Methyl Ester *S*-Oxide (*R*-1a, *S*-1a).** A mixture of **6** (80.5 mg, 0.181 mmol) and $NaIO_4$

(81.4 mg, 0.380 mmol) in MeOH (2 mL) was stirred at room temperature for 2 d. The reaction mixture was diluted with CH_2Cl_2 and washed with water, and brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel, eluting with 50% AcOEt in hexane to give **1a** (73.7 mg, 88%, *R*-**1a**:*S*-**1a** = 37:63) as colorless crystals. Anal. Calcd for $C_{23}H_{28}N_2O_6S$: C, 59.98; H, 6.13; N, 6.08; S, 6.96. Found: C, 59.71; H, 6.19; N, 5.92; S, 6.86.

1a was purified by column chromatography on silica gel, eluting with 40% AcOEt in hexane to give pure *R*-**1a** and *S*-**1a**, respectively. *R*-**1a**: mp 123–125 °C (CH_2Cl_2/hexane); $[\alpha]_D^{28}$ +66.5° (*c* 0.87, $CHCl_3$); IR, 3450, 1730, 1645, 1040 cm^{-1}; ^{1}H NMR δ 0.90, 0.95 (each d, each 3H, *J* = 6.7 Hz, Me_2), 2.19 (m, 1H, C*H*Me_2), 3.16 (m, 1H, C*H*HS(O)), 3.39 (dd, 1H, *J* = 6.7, 14.0 Hz, CH*H*S(O)), 3.72 (s, 3H, MeO), 4.44 (dd, 1H, *J* = 4.9, 8.5 Hz, >C*H*CO_2), 4.67 (q, 1H, *J* = 6.7 Hz, >C*H*NZ), 5.05, 5.09 (AB-q, 2H, *J* = 12.2 Hz, CH_2Ph), 5.98 (br, 1H, NH), 7.33–7.65 (m, 11H, ArH, NH). HRMS Calcd for $C_{23}H_{28}N_2O_6S$–HOSPh: 334.1529. Found: 334.1530. *S*-**1a**: mp 156–157 °C (CH_2Cl_2/hexane); $[\alpha]_D^{30}$ −114.3° (*c* 0.41, $CHCl_3$); IR, 3430, 1720, 1670, 1040 cm^{-1}; ^{1}H NMR δ 0.91, 0.95 (each d, each 3H, *J* = 6.7 Hz, Me_2), 2.22 (m, 1H, C*H*Me_2), 3.09 (dd, 1H, *J* = 4.9, 13.4 Hz, C*H*HS(O)), 3.30 (br, 1H, CH*H*S(O)), 3.74 (s, 3H, MeO), 4.49 (dd, 1H, *J* = 4.9, 8.5 Hz, >C*H*CO_2), 4.77 (m, 1H, >C*H*NZ), 5.13, 5.20 (AB-q, 2H, *J* = 12.2 Hz, CH_2Ph), 6.60 (br, 1H, NH), 7.29-7.52 (m, 11H, ArH, NH). HRMS Calcd for $C_{23}H_{28}N_2O_6S$–HOSPh: 334.1529. Found: 334.1529.

Pummerer-type Reaction of *R*-1a with 3. To a stirred solution of *R*-**1a** (56.1 mg, 0.122 mmol) and ZnI_2 (3.9 mg, 0.0122 mmol) in dry MeCN (7.2 mL, 0.017 M) was added **3** (229.4 mg, 1.22 mmol) dropwise at room temperature for 12 h under nitrogen. MeOH (1 mL) and silica gel were added to the mixture with stirring. After 12 h, the silica gel was removed by filtration and the reaction mixture was poured into saturated sodium bicarbonate and repeatedly extracted with CH_2Cl_2. The organic layer was washed with brine, dried, and evaporated. The residue was purified by prep. TLC, eluting with 30% AcOEt in hexane to give a mixture of **2** and **6** (40.4 mg; *cis*-**2a**:*trans*-**2a**:**6** = 5.2:1:0.57; *cis*-**2a**, 58%; *trans*-**2a**, 11%; **6**, 6%) and **7a** (2.1 mg, 3.1%, polar:less polar = 1.38:1). Each *cis*-**2a**, *trans*-**2a**, **6**, polar-**7a**, and less polar-**7a** was purified by prep. TLC, eluting with 20% AcOEt in hexane and 1% MeOH in CH_2Cl_2 to give the pure state.

***cis*-2a**: a colorless oil; $[\alpha]_D^{20}$ −134.7° (*c* 0.39, $CHCl_3$); IR, 3450, 1770, 1735 cm^{-1}; ^{1}H NMR (C_6D_6) δ 0.77, 1.02 (each d, each 3H, *J* = 6.7 Hz, Me_2), 2.51–2.60 (m, 1H, C*H*Me_2), 3.23 (s, 3H, MeO), 4.00 (d, 1H, *J* = 9.2 Hz, >C*H*CO_2), 4.92, 4.98 (AB-q, 2H, *J* = 12.2 Hz, CH_2Ph), 5.14 (d, 1H, *J* = 4.3 Hz, 4-H), 5.20 (dd, 1H, *J* = 4.3, 9.2 Hz, 3-H), 5.25 (d, 1H, *J* = 9.2 Hz, NH), 6.89–7.36 (m, 10H, ArH). Anal. Calcd for $C_{23}H_{26}N_2O_5S$: C, 62.41; H, 5.93; N, 6.33; S, 7.25. Found: C, 62.22; H, 5.93; N, 6.23; S, 7.29. HRMS Calcd for $C_{23}H_{26}N_2O_5S$: 442.1563. Found: 442.1564.

***trans*-2a**: a colorless oil; $[\alpha]_D^{27}$ +19.9° (*c* 0.096, $CHCl_3$); IR, 3450, 1770, 1725 cm^{-1}; ^{1}H NMR δ 1.01, 1.07 (each d, each 3H, *J* = 6.7 Hz, Me_2), 2.68 (m, 1H, C*H*Me_2), 3.74 (s, 3H, MeO), 3.81 (d, 1H, *J* = 8.5 Hz, >C*H*CO_2), 4.64 (brd, 1H, *J* = 9.0 Hz, 3-H), 4.79 (brs, 1H, 4-H), 5.29 (s, 2H, CH_2Ph), 5.42 (brd, 1H, *J* = 9.0 Hz, NH), 7.34 (m, 10H, ArH). HRMS Calcd for $C_{23}H_{26}N_2O_5S$: 442.1559. Found: 442.1549.

polar-7a: $[\alpha]_D^{25}$ −20.3° (*c* 0.198, $CHCl_3$); IR, 3404, 3020, 2957, 2929, 1736, 1682, 1491 cm^{-1}; ^{1}H NMR δ 0.0023, 0.013 (each s, each 3H, $SiMe_2$), 0.83 (s, 9H, *t*-Bu), 0.97, 0.99 (each d, each 3H, *J* = 6.4 Hz, Me_2), 2.23 (br octet, 1H, *J* = 6.4 Hz, C*H*Me_2), 3.75 (s, 3H, MeO), 4.46 (brs, 1H, C*H*CHSPh), 4.59 (dd, 1H, *J* = 4.6, 8.3 Hz, >C*H*CO_2Me), 5.09 (s, 2H, CH_2Ph), 5.59, 5.98 (each brs, each 1H, CHSPh, NH), 7.22–7.55 (m, 11H, ArH, NH). HRMS Calcd for $C_{25}H_{33}N_2O_6SSi$ (M-*t*-Bu): 517.1826. Found: 517.1821.

less polar-7a: $[\alpha]_D^{25}$ +5.01° (*c* 0.200, $CHCl_3$); IR, 3412, 3022, 2957, 1736, 1680, 1495 cm^{-1}; ^{1}H NMR δ 0.022, 0.055 (each s, each 3H, $SiMe_2$), 0.89 (s, 9H, *t*-Bu), 0.95, 1.01 (each d, each 3H, *J* = 6.4 Hz, Me_2), 2.19 (br m, 1H, C*H*Me_2), 3.72 (s, 3H, MeO), 4.48 (brs, 1H, C*H*CHSPh), 4.60 (dd, 1H, *J* = 4.6, 8.2 Hz, >C*H*CO_2Me), 5.13 (s, 2H, CH_2Ph), 5.60, 5.89 (each brs, each 1H, CHSPh, NH), 7.21–7.41 (m, 11H, ArH, NH). HRMS Calcd for $C_{25}H_{33}N_2O_6SSi$ (M-*t*-Bu): 517.1825. Found: 517.1813.

Pummerer-type Reaction of *S*-1a with 3. To a stirred solution of *S*-**1a** (54.9 mg, 0.119 mmol) and ZnI_2 (3.8 mg, 0.0119 mmol) in dry MeCN (2.7 mL, 0.044 M) was added **3** (223.7 mg, 1.19 mmol) dropwise at room temperature for 12 h under nitrogen. MeOH (1 mL) and silica gel were added to the mixture with stirring. After 12 h, the silica gel was removed by filtration and the reaction mixture was poured into saturated sodium bicarbonate and repeatedly extracted with CH_2Cl_2. The organic layer was washed with brine, dried, and evaporated. The residue was purified by prep. TLC, eluting with 30% AcOEt in hexane to give a mixture of **2** and **6** (38.6 mg; *cis*-**2a**:*trans*-**2a**:**6** = 1:2.2:1.5; *cis*-**2a**, 16%; *trans*-**2a**, 34%; **6**, 23%) and **7a** (3.5 mg, 3.1%, polar:less polar = 6.1:1) as colorless oils. Each *cis*-**2a**, *trans*-**2a**, **6**, polar-**7a**, and less polar-**7a** was purified by prep. TLC, eluting with 20% AcOEt in hexane and 1% MeOH in CH_2Cl_2 to give the pure state.

[*N*-(Benzyloxycarbonyl)-α-benzyl-δ-(L-α-aminoadipoyl)]-*S*-phenyl-L-cysteine (9). This was prepared by a modification of Baldwin's method.[10] Et_3N (131.3 mg, 1.30 mmol) was added to a solution of *N*-(benzyloxycarbonyl)-α-benzyl-δ-L-α-aminoadipic acid[11] (**8**, 500 mg, 1.30 mmol) in dry THF (25 mL) under nitrogen, and the solution was cooled at −15 °C for 30 min. Isobutyl chloroformate (177.6 mg, 1.30 mmol) was added, and the mixture was stirred at −15 °C for 30 min. A solution of **4**[8l] (256 mg, 1.30 mmol) in water (15 mL) and Et_3N (0.25 mL) was cooled to 0 °C and added in one portion to the cold vigorously stirred reaction mixture; the resulting solution was stirred at room temperature for 1 h. The reaction mixture was diluted with water (20 mL) and washed with ether (20 mL × 2). The aqueous layer was acidified to pH 2 by 1 N HCl and then extracted with AcOEt (50 mL × 3). The organic layer was washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure to give crude **9** (537 mg, 73%) as a yellow oil, which was used without further purification: IR, 3430, 2960, 1719, 1665, 1510 cm^{-1}; ^{1}H NMR δ 1.96–2.35 (m, 6H, $CH_2CH_2CH_2$), 3.28 (dd, 1H, *J* = 6.1, 14 Hz, C*H*HSPh), 3.46 (dd, 1H, *J* = 4.0, 14 Hz, CH*H*SPh), 4.37 (m, 1H, C*H*CO_2Bn), 4.78 (brq, 1H, *J* = 5.5 Hz, C*H*CH_2SPh), 5.05, 5.10 (AB-q, 2H, *J* = 12 Hz, CH_2Ph), 5.07, 5.15 (AB-q, 2H, *J* = 12 Hz, CH_2Ph), 5.67 (brd, 1H, *J* = 7.9 Hz, NH), 6.60 (brd, 1H, *J* = 6.7 Hz, NH), 7.12-7.39 (m, 15H, ArH), 8.09 (brs, 1H, CO_2H). HRMS Calcd for $C_{12}H_{17}N_2O_7$ (M^+–SPh–Ph–Ph): 301.1036. Found: 301.1063.

[*N*-(Benzyloxycarbonyl)-α-benzyl-δ-(L-α-aminoadipoyl)]-*S*-phenyl-L-cysteinyl-D-valine Methyl Ester (10). DCC (56.0 mg, 0.272 mmol), a solution of HOBT (38.0 mg, 0.282 mmol) in DMF (1 mL), a solution of D-valine methyl ester hydrochloride (52.0 mg, 0.130 mmol), and Et_3N (31.0 mg 0.310 mmol) in DMF (1 mL) were added to a solution of **9** (145.0 mg, 0.257 mmol) in DMF (1 mL) at −5 °C and stirred at room temperature for 12 h. The reaction mixture was diluted with CH_2Cl_2 and washed with 1% aqueous HCl, saturated aqueous $NaHCO_3$, and brine, dried over Na_2SO_4, and concentrated on a rotary evaporator to give a crude oil, which was purified by column chromatography on silica gel, eluting with 2% MeOH in CH_2Cl_2 to give **10** (114 mg, 66%) as colorless powder: mp 108–109 °C (hexane/CH_2Cl_2); $[\alpha]_D^{22}$ −26.1° (*c* 0.811, $CHCl_3$); IR, 3430, 2960, 1730, 1500 cm^{-1}; ^{1}H NMR δ 0.89, 0.94 (each d, each 3H, *J* = 6.7 Hz, Me_2), 1.66-1.87 (m, 4H, CH_2CH_2), 2.11–2.55 (m, 3H, CH_2CON, C*H*Me_2), 3.19 (dd, 1H, *J* = 7.3, 14 Hz, C*H*HSPh), 3.36 (dd, 1H, *J* = 6.1, 14 Hz, CH*H*SPh), 3.66 (s, 3H, MeO), 4.38 (m, 1H, >C*H*CO_2Bn), 4.46 (dd, 1H, *J* = 4.9, 8.9 Hz, >C*H*CO_2-Me), 4.57 (br qu, 1H, *J* = 6.7 Hz, >C*H*CH_2SPh), 5.07, 5.12 (AB-q, 2H, *J* = 12 Hz, CH_2Ph), 5.16 (s, 2H, CH_2Ph), 5.59 (d, 1H, *J* = 7.9 Hz, NH), 6.34 (d, 1H, *J* = 6.7 Hz, NH), 6.76 (d, 1H, *J* = 8.6 Hz, NH), 7.18–7.43 (m, 15H, ArH). Anal. Calcd for $C_{36}H_{43}N_3O_8S$: C, 63.84; H, 6.40; N, 6.20; S, 4.73. Found: C, 63.77; H, 6.44; N, 6.08; S, 4.53. HRMS Calcd for $C_{36}H_{43}N_3O_8S$: 677.2768. Found: 677.2758.

[*N*-(Benzyloxycarbonyl)-α-benzyl-δ-(L-α-aminoadipoyl)]-*S*-phenyl-L-cysteinyl-D-valine Methyl Ester *S*-Oxide (1b). This product (158 mg, 91%, *R*-**1b**:*S*-**1b** = 46:54) was prepared from **10** (169.7 mg, 0.25 mmol) and $NaIO_4$ (320.8 mg, 1.50 mmol) in MeOH (20 mL) in a manner similar to that used in the preparation of **1a** as colorless needles. **1b** was purified by column chromatography on silica gel, eluting with 0.5% MeOH in CH_2Cl_2 to give pure *R*-**1b** and *S*-**1b** as colorless crystals.

***R*-1b**: mp 147 °C (hexane/CH_2Cl_2); $[\alpha]_D^{23}$ +39.0° (*c* 0.805, $CHCl_3$); IR, 3420, 3010, 2960, 1715, 1675, 1505, 1080, 1050 cm^{-1}; ^{1}H NMR δ 0.91, 0.95 (each d, each 3H, *J* = 6.7 Hz, Me_2), 1.62–1.88 (m, 4H, CH_2-CH_2), 2.13–2.24 (m, 3H, CH_2CON, C*H*Me_2), 3.15 (dd, 1H, *J* = 7.3, 14 Hz, C*H*HSPh), 3.35 (dd, 1H, *J* = 6.7, 14 Hz, CH*H*SPh), 3.65 (s, 3H, MeO), 4.36 (m, 1H, >C*H*CO_2Bn), 4.36 (br dd, 1H, *J* = 4.9, 7.9 Hz, >C*H*CO_2Me), 4.86 (br qu, 1H, *J* = 6.7 Hz, >C*H*CH_2SPh), 5.06, 5.11 (AB-q, 2H, *J* = 12 Hz, CH_2Ph), 5.15 (s, 2H, CH_2Ph), 5.71 (d, 1H, *J* = 7.9 Hz, NH), 6.76 (d, 1H, *J* = 6.1 Hz, NH), 7.29–7.67 (m, 15H, ArH), 7.57 (d, 1H, *J* = 7.9 Hz, NH). Anal. Calcd for $C_{36}H_{43}N_3O_9S$: C, 62.32; H, 6.25; N, 6.06; S, 4.62. Found: C, 62.17; H, 6.44; N, 5.94; S, 4.57. HRMS Calcd for $C_{36}H_{43}N_3O_9S$: 693.2720. Found: 693.2727.

***S*-1b**: mp 146 °C (hexane/CH_2Cl_2); $[\alpha]_D^{23}$ −107° (*c* 0.965, $CHCl_3$); IR, 3430, 3320, 3010, 2960, 1725, 1679, 1510, 1080, 1050 cm^{-1}; ^{1}H NMR δ 0.90, 0.94 (each d, each 3H, *J* = 6.7 Hz, Me_2), 1.73–2.02 (m, 4H, CH_2CH_2), 2.16–2.38 (m, 3H, CH_2CON, C*H*Me_2), 3.04 (dd, 1H, *J* = 4.6, 13 Hz, C*H*HSPh), 3.26 (dd, 1H, *J* = 5.5, 13 Hz, CH*H*SPh),

3.63 (s, 3H, MeO), 4.40 (m, 1H, >C*H*CO_2Bn), 4.45 (br dd, 1H, J = 4.9, 7.9 Hz, >C*H*CO_2Me), 4.89 (br qu, 1H, J = 5.5 Hz, >C*H*CH_2SPh), 5.06, 5.11 (AB-q, 2H, J = 12 Hz, CH_2Ph), 5.15 (s, 2H, CH_2Ph), 5.79 (d, 1H, J = 7.9 Hz, NH), 7.29–7.64 (m, 15H, ArH), 7.59 (d, 1H, J = 6.1 Hz, NH), 7.67 (d, 1H, J = 7.9 Hz, NH). Anal. Calcd for $C_{36}H_{43}N_3O_9S$: C, 62.32; H, 6.25; N, 6.06; S, 4.62. Found: C, 62.18; H, 6.28; N, 6.07; S, 4.53. HRMS Calcd for $C_{36}H_{43}N_3O_9S$: 693.2717. Found: 693.2711.

Pummerer-type Reaction of *R*-1b with 3. (i) To a stirred solution of ***R*-1b** (100 mg, 0.144 mmol) and ZnI_2 (4.6 mg, 0.0144 mmol) in dry MeCN (0.5 mL, 0.3 M) was added **3** (270 mg, 1.44 mmol) dropwise at room temperature for 1 d under nitrogen. The reaction mixture was poured into saturated sodium bicarbonate and repeatedly extracted with CH_2Cl_2. The organic layer was washed with brine, dried, and evaporated. The residue was purified by prep. TLC, eluting with 30–50% AcOEt in hexane to give **2** (40.4 mg, 42%, ***cis*-2b**:***trans*-2b** = 3.4:1) and **7b** (62.8 mg, 54%, polar:less polar = 1.38:1) as colorless oils. The ***cis*-2b**, ***trans*-2b**, polar-**7b**, and less polar-**7b** were purified by prep. TLC, eluting with Et_2O and 1% MeOH in CH_2Cl_2 to give the pure state. (ii) ***R*-1b** (60.9 mg, 0.088 mmol); **3** (165 mg, 0.88 mmol); ZnI_2 (2.8 mg, 0.0088 mmol); MeCN (2 mL, 0.04 M); 1 week; **2** (15.6 mg, 26%, ***cis*-2b**:***trans*-2b** = 4.4:1); **7b** (37.7 mg, 54%, polar:less polar = 1:4.2); ***R*-1b** (11.5 mg, 19%). (iii) ***R*-1b** (30.0 mg, 0.043 mmol); **3** (81.3 mg, 0.43 mmol); ZnI_2 (1.4 mg, 0.0043 mmol); MeCN (10 mL, 0.004 M); 2 weeks; **2** (2.6 mg, 9%, ***cis*-2b**:***trans*-2b** = 11:1); **7b** (15.1 mg, 43%, polar:less polar = 1:4.2); ***R*-1b** (12.1 mg, 40%).

***cis*-2b**: colorless crystals; mp 130–131°C (hexane/CH_2Cl_2); $[\alpha]_D^{21}$ –47.8° (c 0.333, $CHCl_3$); IR, 3420, 2910, 1760, 1730, 1500 cm^{-1}; ^1H NMR δ 0.95, 1.08 (each d, each 3H, J = 6.7 Hz, Me_2), 1.67–1.85 (m, 4H, CH_2CH_2), 2.17 (m, 1H, C*H*HCON), 2.33 (m, 1H, CH*H*CON), 2.51 (d heptet, 1H, J = 6.7, 9.2 Hz, C*H*Me_2), 3.72 (s, 3H, MeO), 4.00 (d, 1H, J = 9.2 Hz, >C*H*CO_2Me), 4.39 (m, 1H, >C*H*CO_2Bn), 5.07, 5.12 (AB-q, 2H, J = 12 Hz, CH_2Ph), 5.13 (s, 2H, CH_2Ph), 5.39 (d, 1H, J = 4.9 Hz, 4-H), 5.40 (d, 1H, J = 8.6 Hz, NH), 5.62 (dd, 1H, J = 4.9, 9.2 Hz, 3-H), 6.61 (d, 1H, J = 9.2 Hz, NH), 7.21–7.35 (m, 15H, ArH). Anal. Calcd for $C_{36}H_{41}N_3O_8S$: C, 63.97; H, 6.13; N, 6.22; S, 4.74. Found: C, 63.92; H, 6.07; N, 6.25; S, 4.67. HRMS Calcd for $C_{36}H_{41}N_3O_8S$: 675.2612. Found: 675.2612.

***trans*-2b**: $[\alpha]_D^{23}$ +22.3° (c 0.476, $CHCl_3$); IR, 3400, 2910, 1760, 1720 cm^{-1}; ^1H NMR δ 1.01, 1.08 (each d, each 3H, J = 6.7 Hz, Me_2), 1.63–2.00 (m, 4H, CH_2CH_2), 2.17 (m, 1H, C*H*HCON), 2.31 (m, 1H, CH*H*CON), 2.67 (d heptet, 1H, J = 6.7, 8.5 Hz, C*H*Me_2), 3.73 (s, 3H, MeO), 3.82 (d, 1H, J = 8.5 Hz, >C*H*CO_2Me), 4.41 (m, 1H, >C*H*CO_2Bn), 4.71 (d, 1H, J = 2.4 Hz, 4-H), 4.79 (dd, 1H, J = 2.4, 7.9 Hz, 3-H), 5.08, 5.13 (AB-q, 2H, J = 12 Hz, CH_2Ph), 5.17 (s, 2H, CH_2Ph), 5.47 (d, 1H, J = 6.7 Hz, NH), 6.49 (d, 1H, J = 7.9 Hz, NH), 7.26–7.53 (m, 15H, ArH). HRMS Calcd for $C_{36}H_{41}N_3O_8S$: 675.2614. Found: 675.2629.

polar-7b: $[\alpha]_D^{23}$ –10.3° (c 1.06, $CHCl_3$); IR, 3400, 2950, 2929, 2850, 1720, 1660, 1490 cm^{-1}; ^1H NMR δ 0.01, 0.05 (each s, each 3H, $SiMe_2$), 0.84 (s, 9H, t-Bu), 0.98, 1.00 (each d, each 3H, J = 6.7 Hz, Me_2), 1.68–1.86 (m, 4H, CH_2CH_2), 2.17–2.25 (m, 3H, CH_2CON, C*H*Me_2), 3.72 (s, 3H, MeO), 4.38 (m, 1H, >C*H*CO_2Bn), 4.57 (dd, 1H, J = 4.9, 8.6 Hz, >C*H*CO_2Me), 4.61 (dd, 1H, J = 3.1, 6.1 Hz, >C*H*CHSPh), 5.08, 5.13 (AB-q, 2H, J = 12 Hz, CH_2Ph), 5.14, 5.17 (AB-q, 2H, J = 12 Hz, CH_2Ph), 5.53 (d, 1H, J = 7.9 Hz, NH), 5.55 (d, 1H, J = 3.1 Hz, C*H*SPh), 6.71 (d, 1H, J = 6.1 Hz, NH), 7.28–7.58 (m, 16H, ArH, NH); FAB-MASS m/z 808 (M^+ + 1). HRMS Calcd for $C_{36}H_{52}N_3O_9Si$ (M^+–SPh): 698.3472. Found: 698.3472. HRMS Calcd for $C_{32}H_{42}N_3O_9Si$ (M^+–SPh–t–Bu): 642.2690. Found: 640.2690.

less polar-7b: $[\alpha]_D^{22}$ +32.2° (c 0.829, $CHCl_3$); IR, 3400, 2950, 2929, 2850, 1720, 1660, 1490 cm^{-1}; ^1H NMR δ 0.01, 0.10 (each s, each 3H, $SiMe_2$), 0.92 (s, 9H, t-Bu), 0.93, 1.05 (each d, each 3H, J = 6.7 Hz, Me_2), 1.65–1.86 (m, 4H, CH_2CH_2), 2.06–2.24 (m, 3H, CH_2CON, C*H*Me_2), 3.72 (s, 3H, MeO), 4.39 (m, 1H, >C*H*CO_2Bn), 4.62 (dd, 1H, J = 4.9, 8.5 Hz, >C*H*CO_2Me), 4.66 (dd, 1H, J = 3.1, 6.1 Hz, >C*H*CHSPh), 5.08, 5.12 (AB-q, 2H, J = 12 Hz, CH_2Ph), 5.16 (s, 2H, CH_2Ph), 5.52 (d, 1H, J = 7.9 Hz, NH), 5.61 (d, 1H, J = 3.1 Hz, C*H*SPh), 6.55 (d, 1H, J = 6.1 Hz, NH), 7.23–7.40 (m, 16H, ArH, NH); FAB-MASS m/z 808 (M^+ + 1). HRMS Calcd for $C_{36}H_{52}N_3O_9Si$ (M^+ – SPh): 698.3470. Found: 698.3468. Anal. Calcd for $C_{42}H_{56}N_3O_9SSi$: C, 62.41; H, 7.12; N, 5.20; S, 3.97. Found: C, 62.13; H, 7.13; N, 5.13; S, 4.07. HRMS Calcd for $C_{32}H_{42}N_3O_9Si$ (M^+–SPh–t–Bu): 642.2689. Found: 640.2684.

Pummerer-type Reaction of *S*-1b with 3. To a stirred solution of ***S*-1b** (100 mg, 0.144 mmol) and ZnI_2 (4.6 mg, 0.0144 mmol) in dry MeCN (0.5 mL, 0.3 M) was added **3** (270 mg, 1.44 mmol) dropwise at room temperature for 1 d under nitrogen. The reaction mixture was poured into saturated sodium bicarbonate and repeatedly extracted with CH_2Cl_2. The organic layer was washed with brine, dried, and evaporated. The residue was purified by prep. TLC, eluting with 30–50% AcOEt in hexane to give **2** (16.0 mg, 16%, ***cis*-2b**:***trans*-2b** = 1:1.1) and **7b** (81 mg, 54%, polar:less polar = 10:1) as colorless oils. The ***cis*-2b**, ***trans*-2b**, polar-**7b**, and less polar-**7b** were purified by prep. TLC, eluting with Et_2O and 1% MeOH in CH_2Cl_2 to give the pure state.

***N*-[(1*R*)-1-(Methoxycarbonyl)-2-methylpropyl]-(*p*-tolylthio)butanamide S_R-Oxide (*R*-11).** This product (291 mg, 95%) was prepared from ***R*-12** [12] {$[\alpha]_D^{15}$ +171° (c 0.703, MeOH), 200 mg, 0.943 mmol}, DCC (204 mg, 0.990 mmol), HOBT (140 mg, 1.04 mmol), D-valine methyl ester hydrochloride (190 mg, 1.13 mmol), and Et_3N (0.16 mL, 1.13 mmol) in DMF in a manner similar to that used in the preparation of **6** as a pale yellow oil: $[\alpha]_D^{26}$ +130.4° (c 0.708, $CHCl_3$); IR, 3430, 2900, 1740, 1680, 1090, 1040 cm^{-1}; ^1H NMR δ 0.92, 0.95 (each d, each 3H, J = 6.7 Hz, Me_2), 2.16 (m, 1H, C*H*Me_2), 2.42 (s, 3H, Me-Ar), 2.50 (ddd, J = 6.7, 7.3, 15 Hz, C*H*HCH$_2$S), 2.80 (td, 1H, J = 7.3, 15 Hz, CH*H*CH$_2$S), 2.95 (td, 1H, J = 6.7, 14 Hz, C*H*HS), 3.26 (td, 1H, J = 7.3, 14 Hz, C*H*HS), 3.73 (s, 3H, MeO), 4.50 (dd, 1H, J = 4.9, 8.5 Hz, >CHCO$_2$), 6.50 (brd, 1H, J = 8.5 Hz, NH), 7.33, 7.50 (each d, each 2H, J = 8.5 Hz, ArH). HRMS Calcd for $C_{16}H_{23}NO_4S$: 325.1346. Found: 325.1341.

***N*-[(1*R*)-1-(Methoxycarbonyl)-2-methylpropyl]-(*p*-tolylthio)butanamide S_S-Oxide (*S*-11).** This product (132 mg, 86%) was prepared from ***S*-12** [12] {$[\alpha]_D^{15}$ –172° (c 0.793, MeOH), 100 mg, 0.472 mmol}, DCC (102 mg, 0.496 mmol), HOBT (70.1 mg, 0.519 mmol), D-valine methyl ester hydrochloride (95.5 mg, 0.566 mmol), and Et_3N (57.3 mg, 0.566 mmol) in DMF in a manner similar to that used in the preparation of **6** as a pale yellow oil: $[\alpha]_D^{23}$ –139.3° (c 0.432, $CHCl_3$); IR, 3420, 2910, 1735, 1670, 1080, 1030 cm^{-1}; ^1H NMR δ 0.90, 0.91 (each d, each 3H, J = 6.7 Hz, Me_2), 2.14 (m, 1H, C*H*Me_2), 2.42 (s, 3H, Me–Ar), 2.51 (ddd, J = 6.1, 7.9, 16 Hz, C*H*HCH$_2$S), 2.78 (td, J = 7.9, 16 Hz, CH*H*CH$_2$S), 2.97 (ddd, 1H, J = 6.1, 7.9, 14 Hz, C*H*HS), 3.27 (td, 1H, J = 7.9, 14 Hz, C*H*HS), 3.74 (s, 3H, MeO), 4.48 (dd, 1H, J = 4.9, 8.6 Hz, >CHCO$_2$), 6.52 (brd, 1H, J = 8.6 Hz, NH), 7.33, 7.50 (each d, each 2H, J = 8.6 Hz, ArH). Anal. Calcd for $C_{16}H_{23}NO_4S$: C, 59.04; H, 7.14; N, 4.30; S, 9.85. Found: C, 58.74; H, 7.13; N, 4.22; S, 9.61. HRMS Calcd for $C_{16}H_{23}NO_4S$: 325.1345. Found: 325.1339.

Pummerer-type Reaction of 11 with 3. (i) To a stirred solution of ***R*-11** (24.5 mg, 0.075 mmol) and ZnI_2 (2.4 mg, 0.0075 mmol) in dry MeCN (4 mL) was added **3** (70.9 mg, 0.375 mmol) dropwise at room temperature for 12 h under nitrogen. The reaction mixture was poured into saturated sodium bicarbonate and repeatedly extracted with CH_2Cl_2. The organic layer was washed with brine, dried, and evaporated. The residue was purified by prep. TLC, eluting with 20% AcOEt in hexane to give **13** (15.8 mg, 69%, ***R*-13**:***S*-13** = 1:1.7) as a colorless oil: ^1H NMR δ 0.94, 1.09 (each d, each 1/2.7 × 3H, J = 6.8 Hz, Me_2), 0.94, 1.07 (each d, each 1.7/2.7 × 3H, J = 6.8 Hz, Me_2), 2.35 (s, 3H, Me-Ar), 2.39 (m, 1/2.7 × 1H, C*H*Me_2), 2.64 (m, 1.7/2.7 × 1H, C*H*Me_2), 2.86 (dd, 1.7/2.7 × 1H, J = 2.4, 15 Hz, 3-H), 2.97 (dd, 1/2.7 × 1H, J = 2.4, 15 Hz, 3-H), 3.30 (dd, 1.7/2.7 × 1H, J = 5.1, 15 Hz, 3-H), 3.38 (dd, 1/2.7 × 1H, J = 5.1, 15 Hz, 3-H), 3.72 (s, 1/2.7 × 3H, MeO), 3.73 (s, 1.7/2.7 × 3H, MeO), 3.80 (d, 1.7/2.7 × 1H, J = 8.4 Hz, >CHCO$_2$), 3.94 (d, 1/2.7 × 1H, J = 8.4 Hz, >CHCO$_2$), 4.81 (dd, 1.7/2.7 × 1H, J = 2.4, 5.1 Hz, 4-H), 5.12 (dd, 1/2.7 × 1H, J = 2.4, 5.1 Hz, 4-H), 7.13–7.39 (m, 4H, ArH). Anal. Calcd for $C_{16}H_{21}NO_3S$: C, 62.50; H, 6.90; N, 4.56; S, 10.43. Found: C, 62.70; H, 6.94; N, 4.74; S, 10.02.

Each ***R*-13** and ***S*-13** were purified by prep. TLC to give the pure state. ***R*-13**: $[\alpha]_D^{26}$ –78.4° (c 0.198, $CHCl_3$); CD (MeOH, 26 °C) λ_{ext} 253 nm ($\Delta\epsilon$ +6.2), 239 (0.0), 219 (–22.2); IR, 3010, 2950, 1760, 1735 cm^{-1}. HRMS Calcd for $C_{16}H_{21}NO_3S$: 307.1240. Found: 307.1240. ***S*-13**: $[\alpha]_D^{26}$ +156.7° (c 0.334, $CHCl_3$); CD (MeOH, 26 °C) λ_{ext} 255 nm ($\Delta\epsilon$ –3.4), 245 (0.0), 216 (+30.7); IR, 3010, 2950, 1760, 1740 cm^{-1}. HRMS Calcd for $C_{16}H_{21}NO_3S$: 307.1239. Found: 307.1222.

(ii) To a stirred solution of ***S*-11** (28.6 mg, 0.088 mmol) and ZnI_2 (2.8 mg, 0.0088 mmol) in dry MeCN (4 mL) was added **3** (82.7 mg, 0.44 mmol) dropwise at room temperature for 12 h under nitrogen. The reaction mixture was poured into saturated sodium bicarbonate and repeatedly extracted with CH_2Cl_2. The organic layer was washed with brine, dried, and evaporated. The residue was purified by prep. TLC, eluting with 20% AcOEt in hexane to give **13** (19.5 mg, 72%, ***R*-13**:***S*-13** = 1.1:1) as a colorless oil.

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