Synthesis of New Chiral Sulfinyldiacetic Acid Derivatives and Attempt at Chemoselective Asymmetric Pummerer Reaction

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(R_S)-1 (85% ee) was prepared by utilizing a porcin pancreatic lipase-promoted hydrolysis of sulfinyldiacetic acid dimethyl ester (8) which was derived from thiodiacetic acid (7). (R_S)-1 (99% ee) and (S_S)-1 (99% ee) were readily obtained by methanolysis of (R_S,*S*)-12 and (S_S,*S*)-12 with MeONa in MeOH. (R_S,*S*)-12 and (S_S,*S*)-12 were furnished by chromatographic separation of the diastereomeric mixture, obtained by oxidation of thiodiacetic mono-carboxylic acid (11) with 30% H_2O_2 followed by dehydrative condensation of the resultant sulfinyldiacetic mono-carboxylic acid with 4(*S*)-isopropyl-1,3-thiazolidine-2-thione. (R_S)-1 (99% ee) was successively treated with $(TMS)_2NLi$, Ac_2O, and TMSOTf to give a major *chiral*-3 product in 75% ee and in a highly chemoselective manner (*chiral*-3 : *chiral*-2 = 93 : 7).

Key words chiral sulfoxide; asymmetric Pummerer reaction; enzymatic hydrolysis; optical resolution; crystallographic structure; close contact

We had previously reported highly chemoselective Pummerer reactions of sulfinyldiacetic acid amide ester *rac*-(**1**) with acetic anhydride (Ac_2O) and trimethylsilyl triflate (TMSOTf) in CH_2Cl_2 at −40 °C or in *N*,*N*-dimethylformamide (DMF) at room temperature affording α-acetoxy sulfides *rac*-(**2**) and *rac*-**3** in a 91 : 9 or 3 : 97 ratio and in high yields, as summarized in Chart 1.[1] In the report, the structure of *rac*-**2** and *rac*-**3** was successfully determined by their alkaline hydrolysis to give glyoxylic amide (**4**) and mercaptoacetic amide (**5**), respectively.[1]

The asymmetric Pummerer reaction of the dicarboxylic acid derivatives (**A**) bearing a chiral sulfinyl group must be intriguing in regard to the development of new enzyme inhibitors; chiral α-acetoxy sulfides (**B**) having particularly designed D- or L-amino acid amide group(s).[2] Chemical conversion of **A** to **B** can be achieved by the Pummerer reaction. In general, the Pummerer reactions of chiral sulfoxides using Ac_2O resulted in poor optical yields probably due to the generation of an achiral sulfrane or a sulfonium acetate intermediate through the reaction process.[3] Therefore, some interesting improved methods were developed by using Ac_2O and 1,3-dicyclohexylcarbodiimide (DCC) for trapping the acetate ion[4] or using ethoxy vinyl acetate without releasing acetate ion.[5] *O*-Methyl-*O*-*tert*-butyldimethylsilyl ketene acetal was exploited for highly stereoselective silicon-induced Pummerer-type reaction.[6] We anticipated a new type of Pummerer reaction of chiral sulfoxide (**1**) without participation of acetate ion by utilizing a possible chiral sulfrane intermediate (**C**) *in situ*. There have been many reports on the intramolecular nonbonded S···O interaction (close contact) in the X-ray crystallographic structures of sulfoxides.[7] Such nonbonded S···O interactions must be possible in the molecule of chiral sulfoxide (**1**) as well as those in the crystallographic structure of chiral sulfoxide (S_S,*S*)-(**6**).[8] Thus, treatment of chiral sulfoxide (**1**) with a base would readily generate the chiral sulfrane intermediate **C** by assistance of this S···O interaction.

In the present report, we describe the synthesis of chiral sulfinyldiacetic acid amide esters (R_S)-(**1**) and (S_S)-(**1**) and then discuss our attempts to perform chemoselective asymmetric Pummerer reactions. The purpose of these preliminary experiments is to aid in the development of new enzyme inhibitors.

The synthesis of (R_S)-**1** was done by exploiting the known enzymatic hydrolysis[8] of a prochiral σ-symmetric dicarboxylic dimethyl ester, as shown in Chart 2. Namely, sulfinyldiacetic acid dimethyl ester (**8**),[8] derived from thiodiacetic

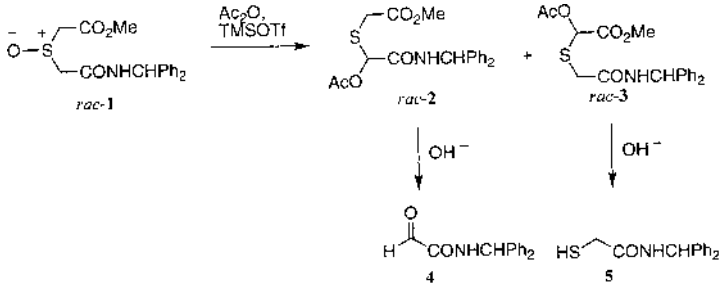
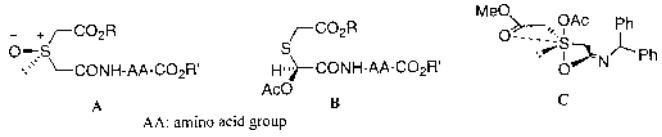


Chart 1



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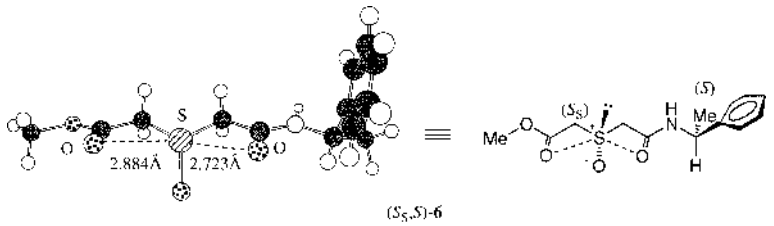
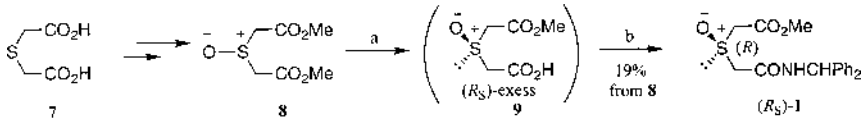
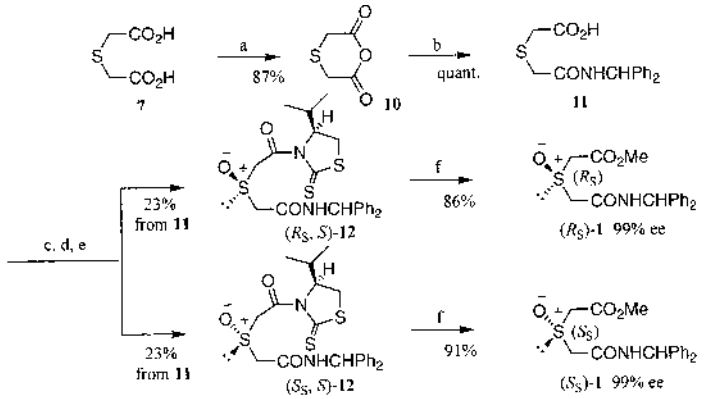


Fig. 1. Computer-Generated Drawing of (S_S,*S*)-**6** Derived from the X-Ray Coordinates



Reagents and conditions: (a) PPL (10^4 units/mmol), 0.1 M phosphate buffer (pH 8.0), rt, 12 h; (b) EDC·HCl (0.6 mol eq.), H_2NCHPh_2 (1.0 mol eq.), DMAP (0.3 mol eq.), CH_2Cl_2–DMF, rt, 12 h.

Chart 2



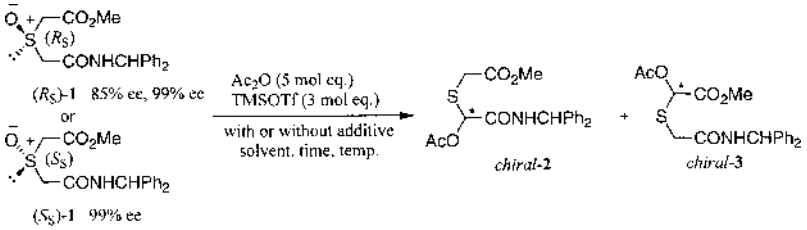
Reagents and conditions: (a) Ac_2O (2.0 mol eq.), reflux, 3 h; (b) Ph_2CHNH_2 (1.1 mol eq.), pyridine (0.1 mol eq.), Et_2O, reflux, 45 min; (c) 30% H_2O_2 (2.0 mol eq.), HFIP, rt, 3 h; (d) EDC·HCl (1.5 mol eq.), 4(*S*)-IPTT (1.2 mol eq.), DMAP (0.1 mol eq.), CH_2Cl_2, 0 °C/1 h, rt/1 h; (e) silica gel column (*n*-hexane/AcOEt=1 : 1); (f) MeONa (1.1 mol eq.), MeOH, 0 °C, 40 min.

Chart 3

acid (**7**), was treated with porcin pancreatic lipase (PPL) in 0.1 M phosphate buffer solution (pH 8.0) to give the known (R_S)-excess mono-carboxylic acid (**9**).[8] The crude compound (**9**) without purification, was submitted to dehydrative condensation with aminodiphenylmethane in the presence of 1-ethyl-3-(3-dimethylaminopropyl)-carbodiimide hydrochloride (EDC·HCl) and *N*,*N*-dimethylaminopyridine (DMAP) to yield (R_S)-**1** in 85% ee. The synthesis of (R_S)-**1** and (S_S)-**1** was performed by utilizing the optical resolution of a diastereomeric mixture with the use of 4(*S*)-isopropyl-1,3-thiazolidine-2-thione [4(*S*)-IPTT] amides,[9] as shown in Chart 3. After dehydration of **7** in acetic anhydride (Ac_2O) under heating, the resultant thiodiacetic anhydride (**10**) was treated with aminodiphenylmethane in the presence of a catalytic amount of pyridine in Et_2O under reflux to obtain a mono-amide (**11**). Oxidation of **11** with 30% H_2O_2 in 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP) gave a crude sulfoxide, which was submitted to dehydrative condensation with 4(*S*)-IPTT in the presence of EDC·HCl and DMAP in CH_2Cl_2. The resultant diastereomeric mixture of 4(*S*)-IPTT amides without purification was chromatographed on a silica gel column with *n*-hexane–AcOEt (1 : 1) to furnish desired pure (R_S,*S*)-(**12**) and (S_S,*S*)-(**12**). Methanolysis of (R_S,*S*)-**12** and (S_S,*S*)-**12** with MeONa in MeOH gave (R_S)-**1** and (S_S)-**1** in high yields and in 99% ee, respectively.

Subsequently, chemoselective asymmetric Pummerer reactions of (R_S)-**1** (85% ee) and (S_S)-**1** (99% ee) were attempted by using 5 mol eq of Ac_2O and 3 mol eq of TMSOTf. All experimental results are summarized in Table 1. In CH_2Cl_2 at −40 °C or MeCN at room temperature without the use of an additive, the reaction of (R_S)-**1** (85% ee) proceeded chemoselectively to give *rac*-**2** or *rac*-**3** as a major product in a ratio of 93 : 7 or 2 : 98 (entries 1 and 2). Interestingly, a tentative similar reaction of (S_S)-**1** (99% ee) in DMF afforded 53% ee of *chiral*-**3** as a major product (entry 3). In all of the reactions, the low yield of the minor products led to an inability to determine the exact ee (%) of these products. Similar treatment of (R_S)-**1** (85% ee) in CH_2Cl_2 at −40 °C in the presence of DCC gave 29% ee of *chiral*-**3** as a major product with a high chemoselectivity (entry 4); however, the direction of the reaction was the opposite of that observed without the use of DCC (entry 1).

Table 1. Chemoselective Asymmetric Pummerer Reaction of (R_S)-**1** or (S_S)-**1**



Entry	Solvent	Additive	Time	Temp. (°C)	Yield (%)[a]	Ratio[b] **2** : **3**	ee (%)[c] of major product
1[d]	CH_2Cl_2	none	24 h	−40	74	93 : 7	0
2[d]	MeCN	none	5 min	rt	37	2 : 98	0
3[e]	DMF	none	3 h	rt	85	4 : 96	53[f]
4[d]	CH_2Cl_2	DCC (4.0 mol eq)	24 h	−40	57	4 : 96	29[f]
5[d]	CH_2Cl_2	$(TMS)_2NLi$ (1.0 mol eq)	17.5 h	−40	39	8 : 92	63
6[g]	CH_2Cl_2	$(TMS)_2NLi$ (1.0 mol eq)	14 h	−78→−40	47	7 : 93	75[f]

a) Total yield of **2** and **3**. *b*) Determined by ^{1}H-NMR (200 MHz, $CDCl_3$) analysis. *c*) Determined by HPLC (CHIRALCEL OD, *n*-hexane–propan-2-ol) analysis. *d*) (R_S)-**1** (85% ee) was employed. *e*) (S_S)-**1** (99% ee) was employed. *f*) Determined by ^{1}H-NMR (300 MHz, $CDCl_3$) analysis using a chiral shift reagent, Eu(hfc)$_3$. *g*) (R_S)-**1** (99% ee) was employed.

Finally, a new type of Pummerer reaction was examined by using (R_S)-**1** (85% and 99% ee) in the following manner. After reaction of (R_S)-**1** with lithium bis(trimethylsilyl)amide [$(TMS)_2NLi$] in CH_2Cl_2 at −40 °C or −78 °C, the resultant solution was treated with Ac_2O at −40 °C or −78 °C and then the mixture was allowed to react with TMSOTf at −40 °C. The desired reaction proceeded to furnish a major product, *chiral*-**3** in 63% or 75% ee and in a highly chemoselective manner, as shown in Table 1 (entries 5 and 6), respectively. However, it was difficult to completely separate both *chiral*-**2** and *chiral*-**3** compounds on a silica gel column. Although the absolute configuration of newly formed chiral carbon atom of *chiral*-**3** ("major product," entries 3—6 in Table 1) has not been determined, it depended on the corresponding sulfinyl chirality of (R_S)- or (S_S)-**1**.

In conclusion, we achieved the syntheses of (R_S)-**1** and/or (S_S)-**1** by utilizing the PPL hydrolysis method and an optical resolution procedure with the use of 4(*S*)-IPTT amides, (R_S,*S*)-**12** and (S_S,*S*)-**12**. Based on their facile aminolyses,[10] both compounds, (R_S,*S*)-(**12**) and (S_S,*S*)-(**12**), are expected to be useful for the syntheses of various chiral sulfoxides bearing amino acid derivatives. We have also demonstrated a new method using $(TMS)_2NLi$ to perform an asymmetric Pummerer reaction with high chemoselectivity. However, further improvement of this method, which relies on the participation of a basic reagent, must be investigated with respect to both optical and chemical yields.

Experimental

All melting points were determined on a Yanagimoto micro melting point apparatus and are uncorrected. IR spectra were obtained on a Perkin-Elmer 1720 IR Fourier transform spectrometer. ^{1}H-NMR (200 and 300 MHz) spectra were recorded on a JEOL JNM-FX 200 or JEOL JNM-AL 300 spectrometer. Chemical shifts are given in δ values (ppm) using tetramethylsilane (TMS) as an internal standard. All mass spectra (EI-MS or FAB-MS) were recorded on a JEOL JMSSX-102A spectrometer. Elementary combustion analyses were performed by a Yanagimoto CHN CORDER and are within 0.4% of the theoretical values. All reactions were monitored by TLC employing 0.25 mm silica gel plates (E. Merck 5715, 60 F_{254}). Preparative TLC (PTLC) was performed on 0.5 mm silica gel plates (E. Merck 5744, 60 F_{254}). The column chromatography was carried out on silica gel [Katayama Chemical K070 (70—300 mesh) and E. Merck 9385 (230—400 mesh)]. Optical rotations were measured on a JASCO DIP-370 polarimeter. HPLC analyses were performed by using a JASCO (PU-980, UV-970, 807-IT) instrument. The typical workup includes washing an organic portion with brine, drying it over anhydrous $MgSO_4$, followed by filtration and concentration *in vacuo*.

Methyl (+)-(*R*)-[(Diphenylmethylcarbamoyl)methylsulfinyl]acetate [(R_S)-1] To a mixture of methyl methoxycarbonylmethylsulfinylacetate (**8**)[8] (25.2 g, 0.13 mol) in 0.1 M phosphate buffer solution (pH 8.0, 1 l) was added porcine pancreatic lipase (PPL) (Sigma Type II, 24.6 g, 10^4 units/mmol). The entire mixture was stirred at room temperature for 12 h. After adjusting to pH 2.0 with 1 N HCl, the acidic reaction mixture was filtered through a celite bed. The filtrate was evaporated *in vacuo* to give an oily residue. After addition of MeOH to the residue, the solution was filtered through a celite bed and then the resultant filtrate was evaporated *in vacuo*. The crude carboxylic acid (**9**)[8] (15.2 g, 0.084 mol) was dissolved in a solution of CH_2Cl_2 (500 ml) and DMF (100 ml). After addition of DMAP (3.1 g, 0.025 mol), aminodiphenylmethane (14.6 ml, 0.085 mol), and EDC·HCl (10.1 g, 0.053 mol), the entire mixture was stirred at room temperature for 12 h. The reaction mixture was treated with 1 N HCl and then submitted to the typical workup to give an oily residue. The residue was chromatographed on a silica gel column with AcOEt–$CHCl_3$ (5 : 1) to afford (R_S)-**1** (5.4 g, 19% from **8**, 85% ee) as colorless needles (acetone–*n*-hexane). The enantiomeric excess (85%) was determined by HPLC using a CHIRALCEL OD column with *n*-hexane–2-propanol (2 : 1). mp 120—121 °C. $[\alpha]_D^{23}$ +6.6° (c=1.06, $CHCl_3$). ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 3.56 (1H, d, J=13.9 Hz), 3.66 (1H, d, J=14.7 Hz), 3.83 (1H, d, J=14.7 Hz), 3.84 (1H, d, J=13.9 Hz), 3.78 (3H, s), 6.28 (1H, d, J=8.3 Hz), 7.23—7.31 (10H, m) 7.67 (1H, d, J=8.3 Hz). IR (KBr) cm^{-1}: 1724, 1650, 1052. FAB-MS *m/z* 346.1108 (Calcd for $C_{18}H_{20}NO_4S$: 346.1113). *Anal.* Calcd for $C_{18}H_{19}NO_4S$: C, 62.59; H, 5.54; N, 4.06. Found: C, 62.46; H, 5.60; N, 4.02.

Thiodiacetic Anhydride (10) A mixture of thiodiacetic acid (**7**) (25.0 g, 166.5 mmol) and Ac_2O (31 ml) was refluxed under N_2 for 3 h. After evaporation *in vacuo*, the resultant residue was crystallized in AcOEt to give compound (**10**) (19.2 g, 87%) as colorless needles. mp 92—95 °C. ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 3.63 (4H, s). IR (KBr) cm^{-1}: 1752, 602. EI-MS *m/z*: 131.9889 (Calcd for $C_4H_4O_3S$: 131.9881). *Anal.* Calcd for $C_4H_4O_3S$: C, 36.36; H, 3.05. Found: C, 36.36; H, 3.06.

[(Diphenylmethylcarbamoyl)methylsulfanyl]acetic Acid (11) To a solution of thiodiacetic anhydride (**10**) (1.06 g, 8.03 mmol) in Et_2O (40 ml) were added aminodiphenylmethane (1.53 ml, 8.88 mmol) and pyridine (0.07 ml, 0.87 mmol). The mixture was refluxed under N_2 for 45 min and then treated with 1 N HCl (50 ml). The acidic aqueous solution was extracted with AcOEt (80 ml×3 times). The extract was submitted to the typical workup to give a crude product, which was purified on a silica gel column with $CHCl_3$–MeOH (9 : 1) to furnish compound (**11**) (2.58 g, 100%) as colorless needles. mp 115—117 °C (AcOEt). ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 3.25 (2H, s), 3.41 (2H, s), 6.24 (1H, d, J=8.3 Hz), 7.21—7.37 (11H, m), 8.0 (1H, bs). IR (KBr) cm^{-1}: 3337, 1718, 1625, 698. EI-MS *m/z*: 315.0930 (Calcd for $C_{17}H_{17}NO_3S$: 315.0929). *Anal.* Calcd for $C_{17}H_{17}NO_3S$: C, 64.74; H, 5.43; N, 4.44. Found: C, 64.76; H, 5.51; N, 4.38.

(R_S,*S* or S_S,*S*)-*N*-Diphenylmethyl-2-[2-(4-isopropyl-2-thioxothiazolidin-3-yl)-2-oxo-ethylsulfinyl]acetamide [(R_S,*S*)-12] or [(S_S,*S*)-12] To a solution of **11** (208.1 mg, 0.66 mmol) in 1,1,1,3,3,3-hexafluoro-2-propanol (1.6 ml) was added 30% H_2O_2 (0.15 ml, 1.37 mmol), and then the mixture was stirred at room temperature under N_2 for 3 h. After treating with 10% Na_2SO_3, the resultant solution was evaporated *in vacuo* to give an oily residue. To a solution of the residue in CH_2Cl_2 (6.6 ml) were successively added 4(*S*)-isopropyl-1,3-thiazolidine-2-thione (127.3 mg, 0.79 mmol), EDC·HCl (191.1 mg, 1.00 mmol), and DMAP (8.2 mg, 0.07 mmol). The entire mixture was stirred at room temperature under N_2 for 1 h and then treated with 1 N HCl (10 ml). The acidic solution was extracted with $CHCl_3$ (10 ml× 3 times) and the extract was submitted to the usual workup to give a yellow residue. The residue was chromatographed on a silica gel column with AcOEt–*n*-hexane (1 : 1) to give (R_S,*S*)-**12** (70.7 mg, 23%) and (S_S,*S*)-**12** (72.3 mg, 23%) as yellow needles (AcOEt), respectively. (R_S,*S*)-**12**: mp 133.5—135 °C (dec.). $[\alpha]_D^{25}$ +244.8° (*c*=1.00, $CHCl_3$). ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 0.96 (3H, d, *J*=6.8 Hz), 1.04 (3H, d, *J*=6.8 Hz), 2.04—2.37 (1H, m), 3.03 (1H, d, *J*=11.5 Hz), 3.53—3.67 (1H, m), 3.56 (1H, d, *J*=13.9 Hz), 3.79 (1H, d, *J*=13.9 Hz), 4.69 (1H, d, *J*=16.4 Hz), 4.88 (1H, d, *J*=16.4 Hz), 5.03 (1H, t, *J*=6.6 Hz), 6.26 (1H, d, *J*=8.3 Hz), 7.23—7.31 (10H, m), 7.6 (1H, d, *J*=8.3 Hz). IR (KBr) cm^{-1}: 1666, 1244, 1044. FAB-MS *m*/*z*: 475.1136 (Calcd for $C_{23}H_{27}N_2O_3S_3$: 475.1184). *Anal.* Calcd for $C_{23}H_{26}N_2O_3S_3$: C, 58.20; H, 5.52; N, 5.90. Found: C, 58.08; H, 5.53; N, 5.76. (S_S,*S*)-**12**: mp 143—144.5 °C (dec.). $[\alpha]_D^{25}$ +153.8° (*c*=1.02, $CHCl_3$). ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 0.97 (3H, d, *J*=6.8 Hz), 1.04 (3H, d, *J*=6.6 Hz), 2.29—2.35 (1H, m), 3.06 (1H, d, *J*=11.7 Hz), 3.50—3.63 (1H, m), 3.60 (1H, d, *J*=13.9 Hz), 3.84 (1H, d, *J*=13.9 Hz), 4.60 (1H, d, *J*=16.4 Hz), 4.91 (1H, d, *J*=16.4 Hz), 5.10 (1H, t, *J*=6.6 Hz), 6.29 (1H, d, *J*=8.3 Hz), 7.26—7.32 (10H, m), 7.68 (1H, d, *J*=8.3 Hz). IR (KBr) cm^{-1}: 1674, 1245, 1036. FAB-MS *m*/*z*: 475.1162 (Calcd for $C_{23}H_{27}N_2O_3S_3$: 475.1184). *Anal.* Calcd for $C_{23}H_{26}N_2O_3S_3$: C, 58.20; H, 5.52; N, 5.90. Found: C, 58.53; H, 5.55; N, 6.09.

Conversion of (R_S,*S*)-12 to Methyl (+)-(*R*)-[(Diphenylmethylcarbamoyl)methylsulfinyl]acetate [(R_S)-1] To a solution of (R_S,*S*)-**12** (2.98 g, 6.27 mmol) in MeOH (6.9 ml) was added MeONa (1 M MeOH solution 6.9 ml, 6.9 mmol). The mixture was stirred at 0 °C under N_2 for 40 min and then treated with 1 N HCl (10 ml). The acidic solution was extracted with AcOEt (50 ml×3 times), and the extract was submitted to the usual workup to give an oily residue. Chromatographic purification of the residue on a silica gel column was carried out using AcOEt–*n*-hexane (1 : 2 to 3 : 1) to give (R_S)-**1** (1.85 g, 86%, 99% ee) as a white powder (acetone–*n*-hexane). The enantiomeric excess (99%) was determined by HPLC using a CHIRALCEL OD column with *n*-hexane–2-propanol (2 : 1). All spectroscopic data were identical to those of the (R_S)-**1** compound, which was prepared by the enzymatic procedure described above. mp 124—126 °C. $[\alpha]_D^{22}$ +8.1° (*c*=1.05, $CHCl_3$).

Conversion of (S_S,*S*)-12 to Methyl (−)-(*S*)-[(Diphenylmethylcarbamoyl)methylsulfinyl]acetate [(S_S)-1] This reaction was carried out similarly, according to the conversion of (R_S,*S*)-**12** to (R_S)-**1** by using (S_S,*S*)-**12** (3.03 g, 6.83 mmol) and MeONa (1 M MeOH solution 7 ml, 7.0 mmol); (S_S)-**1** (2.0 g, 91%, 99% ee) was obtained as a white powder (acetone–*n*-hexane). mp 124—124.5 °C. $[\alpha]_D^{22}$ −8.1° (*c*=1.07, $CHCl_3$). All spectroscopic data of (S_S)-**1** were identical to those of (R_S)-**1**.

Pummerer Reaction of (R_S)-1 and (S_S)-1 Entry 1 in Table 1: To a solution of (R_S)-**1** (85% ee, 139 mg, 0.4 mmol) in CH_2Cl_2 (10 ml) were added Ac_2O (190 ml, 2.0 mmol) and TMSOTf (232 ml, 1.3 mmol). The mixture was stirred at −40 °C under N_2 for 24 h and then treated with an aqueous solution saturated with $NaHCO_3$. The resultant solution was extracted with AcOEt. The extract was submitted to the usual workup to give an oily residue. The residue was purified by a PTLC method with AcOEt–*n*-hexane (1 : 2) to give a mixture (115.4 mg) of *rac*-**2** and *rac*-**3** in a 74% total yield. The product ratio, *rac*-**2** : *rac*-**3** (93 : 7) was detrmined by a ^{1}H-NMR (200 MHz, $CDCl_3$) analysis based on the AcO signals (δ 2.17 for *rac*-**2** and δ 1.88 for *rac*-**3**). The enantiomeric excess of the major product was determined to be 0% by the HPLC analysis using a CHIRALCEL OD column with *n*-hexane–2-propanol (5 : 1). Pure *rac*-**2** was obtained by recrystallization of the crude compound in *n*-hexane–$CHCl_3$. Colorless needles; mp 111—112 °C. ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 2.17 (3H, s), 3.39 (1H, d, *J*=13.4 Hz), 3.66 (1H, d, *J*=13.4 Hz), 3.69 (3H, s), 6.24 (1H, d, *J*=8.3 Hz), 7.26—7.34 (11H, m). IR (KBr) cm^{-1}: 1746, 1657, 700. EI-MS *m*/*z*: 387.1138 (Calcd for $C_{20}H_{21}NO_5S$: 387.1140). *Anal.* Calcd for $C_{20}H_{21}NO_5S$: C, 62.00; H, 5.46; N, 3.62. Found: C, 61.88; H, 5.51; N, 3.51.

Entry 2 in Table 1: The Pummerer reaction of (R_S)-**1** (85% ee, 50 mg, 0.14 mmol) was similarly carried out using Ac_2O (71 μl, 0.72 mmol) and TMSOTf (81 μl, 0.45 mmol) in MeCN (2 ml) to give a mixture (20.7 mg, 37% total yield) of *rac*-**2** and *rac*-**3** in a ratio of 2 : 98. Pure *rac*-**3** was obtained by recrystallization of the crude compound in *n*-hexane–$CHCl_3$. Colorless crystals; mp 94—96 °C. ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 1.88 (3H, s), 3.45 (1H, d, *J*=16.1 Hz), 3.56 (1H, d, *J*=16.1 Hz), 3.67 (3H, s), 6.26 (1H, d, *J*=8.1 Hz), 7.28—7.31 (11H, m). IR (KBr) cm^{-1}: 1746, 1640, 699. EI-MS *m*/*z*: 387.1184 (Calcd for $C_{20}H_{21}NO_5S$: 387.1140). *Anal.* Calcd for $C_{20}H_{21}NO_5S$: C, 62.00; H, 5.46; N, 3.62. Found: C, 61.93; H, 5.61; N, 3.56.

Entry 3 in Table 1: The Pummerer reaction of (S_S)-**1** (99% ee, 35 mg, 0.1 mmol) was similarly carried out using Ac_2O (48 μl, 0.5 mmol) and TMSOTf (59 μl, 0.3 mmol) in DMF (1 ml) to give a mixture (33.3 mg, 85% total yield) of *chiral*-**2** and *chiral*-**3** in a ratio of 4 : 96. The enantiomeric excess of the major product, *chiral*-**3**, was determined to be 53% by ^{1}H-NMR (300 MHz, $CDCl_3$) analysis using a chiral shift reagent, Eu(hfc)$_3$.

Entry 4 in Table 1: The Pummerer reaction of (R_S)-**1** (85% ee, 50 mg, 0.14 mmol) with Ac_2O (71 μl, 0.72 mmol) and TMSOTf (81 μl, 0.45 mmol) in the presence of 1,3-dicyclohexylcarbodiimide (120 mg, 0.58 mmol) in CH_2Cl_2 (2 ml) gave a mixture (31.9 mg, 57% total yield) of *chiral*-**2** and, *chiral*-**3**, in a ratio of 4 : 96. The enantiomeric excess of the major product, *chiral*-**3**, was determined to be 29% by ^{1}H-NMR (300 MHz, $CDCl_3$) analysis using a chiral shift reagent, Eu(hfc)$_3$.

Entry 5 in Table 1: To a solution of (R_S)-**1** (85% ee, 50 mg, 0.14 mmol) in CH_2Cl_2 (2 ml) was added lithium bis(trimethylsilyl)amide [$(TMS)_2NLi$] (1 M *n*-hexane solution 145 μl, 0.14 mmol) at −40 °C under N_2, and then the mixture was stirred at −40 °C under N_2 for 30 min. After successive addition of Ac2O (71 μl, 0.72 mmol) and TMSOTf (81 μl, 0.45 mmol), the entire mixture was stirred at −40 °C for 17 h, followed by treatment with an aqueous solution saturated with $NaHCO_3$. The resultant solution was extracted with AcOEt, and the extract was submitted to the typical workup to give an oily residue. PTLC purification of the residue, as described above, gave a mixture (22.0 mg, 39% total yield) of *chiral*-**2** and *chiral*-**3** in a ratio of 8 : 92. The enantiomeric excess of the major product, *chiral*-**3**, was determined to be 63% by HPLC analysis, as described above.

Entry 6 in Table 1: To a solution of (R_S)-**1** (99% ee, 50 mg, 0.14 mmol) in CH_2Cl_2 (2 ml) was added $(TMS)_2NLi$ (1 M *n*-hexane solution 145 μl, 0.14 mmol) at −78 °C under N_2. After being stirred at −78 °C for 1 h, Ac_2O (71 μl, 0.72 mmol) was added, and then the mixture was stirred at −78 °C for 1 h. To the mixture was added TMSOTf (81 μl, 0.45 mmol) at −78 °C. The entire mixture was warmed to −40 °C, and stirred at −40 °C for 12 h. The same treatment of the reaction mixture, as described in entry 5, afforded a mixture (26.4 mg, 47% total yield) of *chiral*-**2** and *chiral*-**3** in a ratio of 7 : 93. The enantiomeric excess of the *chiral*-**3** was determined to be 75% by ^{1}H-NMR (300 MHz, $CDCl_3$) analysis using a chiral shift reagent, Eu(hfc)$_3$.

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References and Notes

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