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Remarkable Diastereomeric Rearrangement of an α-Acyloxy *β*-Ketosulfide to an α-Acyloxy Thioester: A Novel Approach to the Synthesis of Optically Active (2*S*,3*S*) *β*-Amino α-Hydroxy Acids

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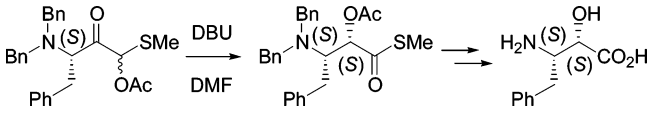

A novel and efficient synthetic method is described for (2*S*,3*S*)-3-amino-2-hydroxy-4-phenyl butyric acid derivatives, which are useful intermediates of enzyme inhibitors. This involves a Pummerer rearrangement of a *β*-ketosulfoxide derived from L-phenylalanine followed by highly stereoselective acyl migration. From these studies, it appears that nitrogen-protecting groups exert a substantial influence over stereoselectivity. The mechanism of the rearrangement is discussed. *β*-Amino α-hydroxy carboxylic acids are important pharmaceutical intermediates, and this method may provide a versatile synthesis from various amino acids in a few steps.

Introduction

Optically active *β*-amino α-hydroxy carboxylic acids are well known as useful intermediates for various drugs and drug candidates.[1] Ubenimex (Bestatin), an anticancer agent launched in Japan, is a peptide mimetic composed of (2*S*,3*R*)-3-amino-2-hydroxy-4-phenyl butyric acid and L-leucine.[2] The side chain of paclitaxel (Taxol) similarly consists of (2*R*,3*S*)-3-amino-2-hydroxy-3-phenyl propionic acid.[3] The structures of these compounds are characterized by *threo* amino alcohols configured at the α and *β* positions. Various synthetic approaches to these *threo* amino alcohols have been reported.[4] On the other hand, compounds with opposite relative configurations such as *erythro*-(2*S*,3*S*) are found in some enzyme inhibitors, particularly in HIV protease inhibitors. The technologies required to produce the intermediates for these drugs economically on an industrial scale are becoming ever more important. (2*S*,3*S*)-3-Amino-2-hydroxy-4-phenyl butyric acid ((*S*,*S*)-AHPBA) is used as the core building block of HIV protease inhibitors such as KNI-272, AG-1859, etc (Figure 1).[5,6] One efficient synthetic approach, reported by Reetz et al. in 1988,[7] is the transformation

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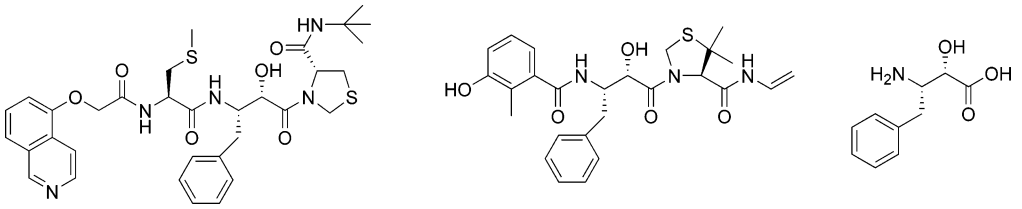
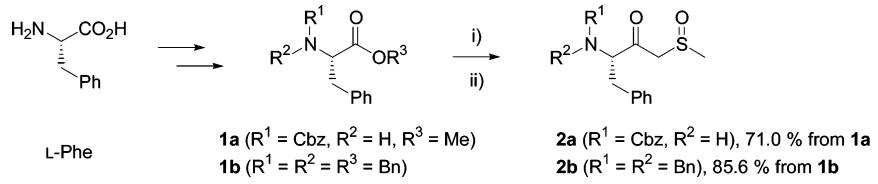


FIGURE 1. HIV protease inhibitors and (*S*,*S*)-AHPBA **6c**.

SCHEME 1. Preparation of a *β*-Ketosulfoxide[a]



[a] Reagents and conditions: (i) DMSO, $NaNH_2$, THF, 0 °C; (ii) 10 % citric acid aq.

of L-phenylalanine to the corresponding *N*,*N*-dibenzylamino aldehyde followed by the diastereoselective nucleophilic addition of trimethylsilyl cyanide to produce the synthetically equivalent cyanohydrin. Since then, the strategy of stereoselective addition to *N*-protected amino aldehydes has gained wide recognition and several different approaches to AHPBA have been reported.[8,9] Although some of these methods appear to hold promise on an industrial scale, the preparation of aldehydes by multistep transformations from amino acids and the use of highly toxic trimethylsilyl cyanide, which must necessarily be purified by distillation, are problematic from the point of view of commercial manufacturing. Accordingly, one-carbon homologation directly from amino acids or their esters is of great interest in terms of developing truly practical industrial processes.

Previously, we focused our attention on the synthesis of α-aminoalkyl α′-halomethyl ketones from amino acid esters, which are also versatile intermediates for enzyme inhibitors.[10] In the present study, our goal was the synthesis of another class of common intermediates, *β*-amino α-hydroxy carboxylic acids, especially (*S*,*S*)-AHPBA from L-phenylalanine. Our approach involves a Pummerer rearrangement and the subsequent α,*β* rearrangement of the acylated hydroxy group; the controlled stereochemistry of the latter rearrangement, to our present knowledge, being hitherto unreported in the literature. This paper summarizes our studies by describing a new synthetic approach to (*S*,*S*)-AHPBA and discussing the stereochemistry at the key rearrangement reaction.[11]

Results and Discussion

β-Ketosulfoxides **2a** and **2b** were prepared by the conventional method, namely, the nucleophilic addition of a dimsyl anion to an *N*-protected amino acid ester (Scheme 1). *N*-benzyloxycarbonyl L-phenylalanine methyl ester **1a** and *N*,*N*-dibenzyl L-phenylalanine benzyl ester **1b** were each reacted at 0 °C with the anion generated by heating dimethyl sulfoxide (DMSO) with sodium amide. Use of an excess amount of the nucleophile gave a high yield of ketosulfoxides **2a** and **2b** by virtue of their acidity. The ketosulfoxides were converted to α-hydroxy sulfides through a Pummerer rearrengement.[12,13] The rearrangement readily took place under acidic conditions, e.g., hydrochloric acid/DMSO, to afford the corresponding α-hydroxy sulfides **3a** and **3b**, followed by acetylation to give **4a** and **4b** (Scheme 2). These were mixtures of stereoisomers at the α-acetoxy group, with diastereomeric ratios determined by ^{1}H NMR being about 1:1 for **4a** and 20:1 for **4b**. A one-pot rearrangement/acetylation reaction was also achieved easily such that **2a** (**2b**) was converted directly to **4a** (**4b**) in one step by reaction with acetic anhydride and pyridine in the presence of catalytic amount of 4-dimethylamino pyridine (DMAP). The subsequent α,*β*-rearrangement of **4a** (**4b**) was then studied,

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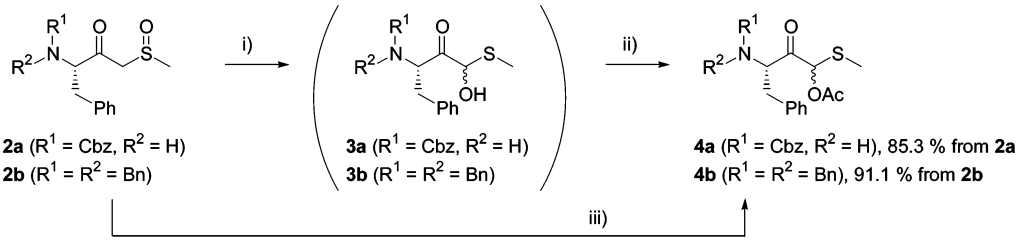
SCHEME 2. Preparation of an α-Acyloxy Sulfide via a Pummerer Rearrangement[a]



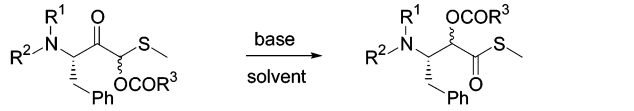
[a] Reagents and conditions: (i) 2 M HCl, DMSO, ambient temperature; (ii) AcCl, Pyridine, CH_2Cl_2, ambient temperature; (iii) Ac_2O, pyridine, DMAP, CH_2Cl_2, ambient Temperature.

TABLE 1. Acyl Migration of 4 to 5

entry	substrate	base	solvent	temp/°C	time	yield/%	diastereomeric ratio[a] (2*S*,3*S*)/(2*R*,3*S*)
1	4a	DMAP	toluene	reflux	20.5 h	<30	not measured
2	4a	Et_3N	toluene	60	28 h	0	NA
3	4a	DBU	toluene	ambient	2 h 20 min	97.5	42/58
4	4a	DBU	DMF	0	30 min	quant.	46/54
5	4b	DBU	toluene	ambient	50 min	quant.	59/41
6	4b	DBU	toluene	−30	50 min	quant.	58/42
7	4b	DBU	DMF	−30	1 h 15 min	88.2	92/8
8	4c	DBU	DMF	−30	30 min	92.7	87/13
9	4d	DBU	DMF	−30	3 h	89.0	90/10

[a] The ratio of (3*S*,2*S*)/(3*S*,2*R*) was indicated by peak area % in HPLC.

SCHEME 3. Preparation of an α-Acyloxy Thioester via Acyl Rearrangement[a]



[a] Reagents and conditions Shown in Table 1

with acyl migration to an α-acetoxy thioester as an equivalent of an α-hydroxy carboxylic acid (Scheme 3).[14] The rearrangement reaction of the *N*-Cbz derivative **4a** occurred slowly in pyridine above 100 °C but was incomplete and accompanied by decomposition in 4 days under reflux conditions. Reactions in toluene with some typical bases were then attempted (Table 1). No reaction proceeded with triethylamine, and with DMAP only a low yield was obtained. However, it was found that the use of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) significantly accelerated the rearrangement. The reaction in the case of the *N*-Cbz derivative **4a** gave poor diastereoselectivity with (2*R*,3*S*)-**5a** being slightly more predominant as the major isomer in dimethyl formamide (DMF) than toluene as a solvent. In contrast, the opposite isomer (2*S*,3*S*)-**5b** was obtained from the *N*,*N*-dibenzyl derivative **4b** and the selectivity was influenced by the solvent, being considerably higher in DMF than toluene. At −30 °C in DMF, the selectivity increased to 92:8. To the best of our knowledge, this is the first example of a stereoselective α,β acyl migration to a β-keto α-acyloxy sulfide. Other acylated substrates showed similar selectivities, the best being those that were the least hindered. Turning to the possible mechanism of the stereoselective rearrangement from **4b** to **5b**, we speculate that the base deprotonates the most acidic methine position of **4b** furnishing the enol or enolate species. Acyl migration may reasonably be expected to furnish the cyclic ortho ester **7**, and only the enol (*E*)-**4b** can contribute to the formation of **7** (Figure 2).

By this reasoning, the original configuration of the acyloxy group of **4b** would not influence the stereochemistry of the product **5b**. The relative configuration of the hemi-ortho ester stereogenic center could not be expected to play a significant role during the facial selectivity of the proton-transfer step. Simple MM2 energy minimization supports the suggested conformation of protonation from the less hindered β-face leading to the observed (2*S*)-stereochemistry (Figure 3).

However, a more detailed analysis of the conformation of **7** reveals two minima as shown in Figure 4. The two lowest energy conformations appear to be **7A** and **7B**, both of which would lead to the observed (*S*, *S*)-**5b**. On the basis of steric considerations, conformation **7B** is expected to be the lowest-energy conformer due to 1,3-torsional strain induced between the thiomethyl residue and the benzyl group. It is worthy of note that the protonation to **7B** took place from the more hindered face. This might be rationally explained by assuming that conformation **7B** can be involved in a hydrogen-bonded delivery of the proton from protonated DBU (DBU−H^+) from the more hindered face (as shown) which leads to the (2*S*)-stereochemistry.

On the other hand, poor diastereoselectivity was observed in the reaction of **4a**. It is considered that the lower basicity of the nitrogen at *N*-benzyloxycarbonyl group can hardly contribute to hydrogen bonding.

We further examined some reactions with the *N*,*N*-dibenzyl substrate **4b**. By consideration of the mechanism

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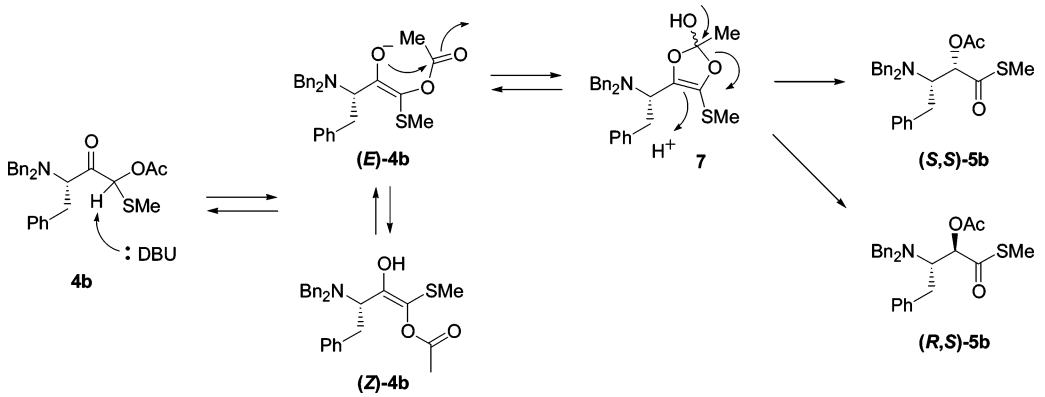


FIGURE 2. Proposed mechanism for the acyl migration.

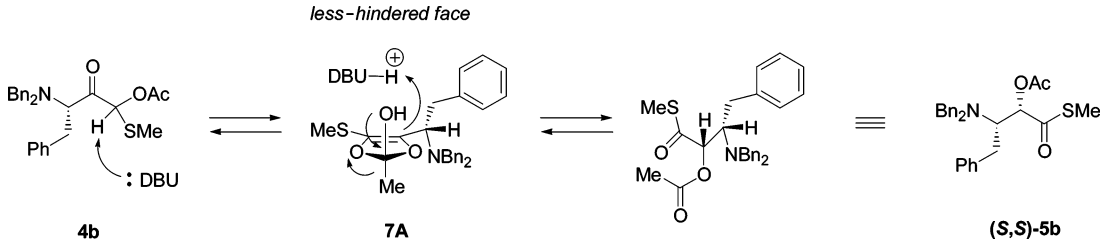


FIGURE 3. A possible mechanism for the stereoselective acyl migration to produce (*S*,*S*)-**5b**.

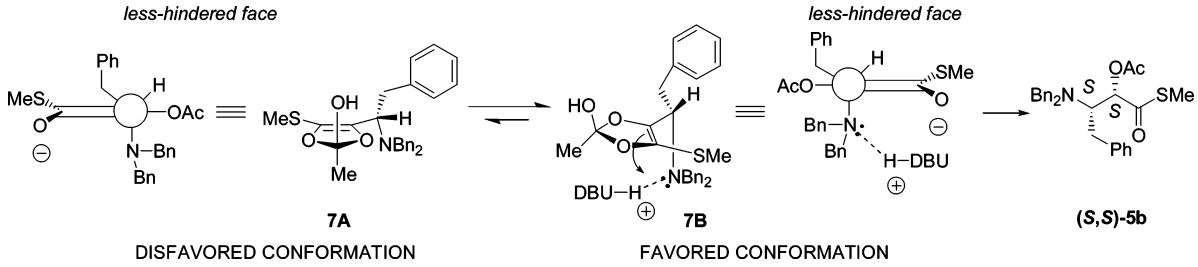


FIGURE 4. Detailed conformational analysis and H-bonded proton delivery from **7B**.

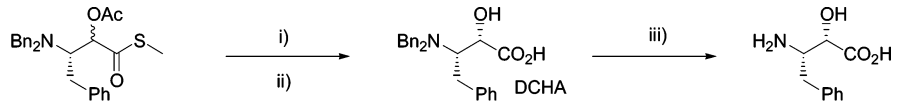
above, our supposition was that the reaction would not stoichiometrically consume the base, and therefore we added only catalytic amounts of DBU. Although the rearrangement reaction proceeded slowly with slightly lower selectivity, (2*S*,3*S*)/(2*R*,3*S*) = 89/11, it ran smoothly to completion suggesting the same reaction mechanism was in play. When the diastereo mixture, (2*S*,3*S*)/(2*R*,3*S*) = 55/45 of **5b**, that had been prepared in toluene was again treated under the rearrangement conditions in DMF, no change was detected in the ratio of diastereomers. This suggests that the protonation of **7A** and **7B** would be an irreversible step forming the thermodynamically stable product **5b**.

Thioester **5b** was successfully converted to the desired carboxylic acid **6b** by hydrolysis with sodium hydroxide in a methanol−water solution, and then **6b** was isolated as a crystalline dicyclohexylamine (DCHA) salt. The diastereomeric impurity (2*R*,3*S*)-**6b** could be efficiently removed by crystallization to give pure crystals of the (2*S*,3*S*)-**6b** DCHA salt. No epimerization at the C3 position was evident by chiral high-performance liquid chromatography (HPLC) analysis. The dibenzyl group of the (2*S*,3*S*)-**6b** DCHA salt was then removed by hydrogenation (Pd−C) to afford (2*S*,3*S*)-3-amino-2-hydroxy-4-phenyl butyric acid (2*S*,3*S*)-**6c** (Scheme 4). Last, an example of stereoselective acyl migration of another amino acid derivative is shown in Scheme 5. The Pummerer product from the *N*,*N*-dibenzyl L-leucine derivative **4e** was converted with high stereoselectivity to (2*S*,3*S*)-**5e** in a high yield in DMF with a catalytic amount of DBU. Compound **5e** can be similarly hydrolyzed to give the corresponding *β*-amino α-hydroxy carboxylic acid.

Conclusion

Optically active *N*-protected AHPBA, an important intermediate for the synthesis of enzyme inhibitors, was obtained in five steps from L-phenylalanine by a diastereoselective rearrangement that controls the stereochemistry of the α-hydroxy group. A *β*-ketosulfoxide prepared from *N*,*N*-dibenzyl L-phenylalanine benzyl ester with dimsyl carbanion was converted to the α-acetoxy sulfide by a Pummerer rearrangement. Acyl migration of the α-acetoxy sulfide took place in the presence of DBU, stereoselectively forming the *erythro* configuration to produce the hydroxy thioester, a stereoselective, kinetically controlled protonation from a H-bonded DBU complex with a basic, *N*,*N*-dibenzylated nitrogen has been invoked. The target compound was successfully obtained by hydrolysis of the thioester. To our knowledge, this is the first report of a synthesis of AHPBA employing

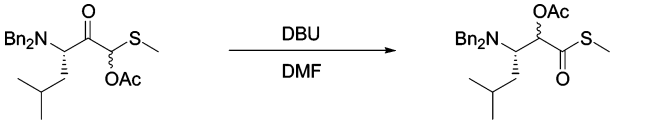
SCHEME 4. Transformation of 5b to (*S*,*S*)-AHPBA-6[a]



5b (2*S*,3*S*) / (2*R*,3*S*) = 89 / 11 (2*S*,3*S*)-**6b** DCHA salt (2*S*,3*S*)-**6c**

[a] Reagents and conditions: (i) 2 M NaOH, MeOH, ambient temperature; (ii) DCHA, 85% from (2*S*,3*S*)-**5b**; (iii) H_2/Pd−C, AcOH, MeOH, ambient temperature, 97 % from (2*S*,3*S*)-**6b**.

SCHEME 5. Acyl Rearrangement of the L-Leucine Derivative 4e[a]



4e **5e** (2*S*,3*S*) / (2*R*,3*S*) = 95 / 5

[a] Reagents and conditions: DBU, DMF, −30 °C, 15.5 h, 98 % from **4e**.

stereoselective acyl migration. By overcoming the problems with existing methods, this approach may have potential as a versatile method for the industrial-scale production of *erythro* β-amino α-hydroxy carboxylic acids.

Experimental Section

(3*S*)-3-(*N*-Benzyloxycarbonyl)amino-1-methylsulfinyl-2-oxo-4-phenylbutane (2a).

To a mixture of L-phenylalanine methyl ester hydrochloride (20.0 g, 92.73 mmol) suspended in toluene (93 mL) was added benzyl chloroformate (15.82 g, 92.73 mmol) with cooling in an ice bath, and 1 M Na_2CO_3 aqueous solution (130 mL) was added dropwise with vigorous stirring at 7 °C or lower. After this addition was complete, the mixture was stirred for 3 h. The organic layer was separated, washed with 0.1 M HCl (60 mL) and saturated $NaHCO_3$ aqueous solution (60 mL), and then dried over anhydrous Na_2SO_4. Concentration of the solution under reduced pressure provided Cbz-L-Phe-OMe (**1a**) (28.75 g, 96.8 wt%, 88.81 mmol, 95.8% from L-phenylalanine methyl ester) as a colorless oil.

Sodium amide (4.98 g, 127.7 mmol) was added to dimethyl sulfoxide (40 mL) at ambient temperature, and the suspended mixture was heated with stirring for 50 min at 72−76 °C. Tetrahydrofuran (50 mL) was added to the mixture that was cooled to 0 °C. To the resulting mixture was added dropwise a solution of **1a** (10.33 g, 96.8 wt%, 31.91 mmol) in tetrahydrofuran (20 mL) with stirring cooled at 0 °C, then the reaction was continued with stirring for 1 h at 0 °C. 10% Citric acid aqueous solution (120 mL) and dichloromethane (100 mL) was added to the reaction mixture and extracted, then the aqueous layer was extracted again with dichloromethane (60 mL). The combined organic layers were washed with saturated NaCl aqueous solution, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The resulting residue was crystallized in dichloromethane/*n*-hexane to obtain **2a** (8.14 g, 22.65 mmol, 71.0% from **1a**) as colorless crystals. The diastereomeric ratio was about 3:1 by the integral ratio in ^{1}H NMR.

^{1}H NMR (400 MHz, $CDCl_3$) (mixture of about 3:1 of diastereomeric isomers) δ = 2.63 (s, 3/4H), 2.66 (s, 9/4H), 2.94−3.11 (m, 1H), 3.12−3.21 (m, 1H), 3.57 (d, 3/ 4H, J = 14.0 Hz), 3.69 (d, 1/4H, J = 14.0 Hz), 3.89 (d, 1/4H, J = 14.2 Hz), 4.04 (d, 3/4H, J = 14.2 Hz), 4.45−4.59 (m, 1H), 5.07 (m, 2H), 5.44 (bd, 1/4H), 5.64 (bs, 3/ 4H), 7.14−7.39 (m, 10H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 36.3, 39.0, 39.5, 61.0, 62.1, 67.3, 127.3, 128.1, 128.6, 128.9, 129.3, 135.7, 156.0, 201.8; IR (neat) 1019, 1104, 1246, 1524, 1700, 1719 cm^{-1}; mp = 127−129 °C; $[\alpha]^{20}_D$ −68.8 (*c* 1.0, CH_3OH); MS (+FAB) *m/z* 360 (MH^+); HRMS (+FAB) calcd for $C_{19}H_{22}NO_4S$ (MH^+) 360.1270, found 360.1281.

(3*S*)-3-(*N*,*N*-Dibenzyl)amino-1-methylsulfinyl-2-oxo-4-phenylbutane (2b).

To a solution of L-phenylalanine (25.0 g, 151.3 mmol) and Na_2CO_3 (66.67 g, 482.4 mmol) dissolved in water (100 mL) was added benzyl chloride (57.51 g, 454.3 mmol), and the mixture was heated at 95 °C with stirring for 19 h. After the reaction mixture was cooled at ambient temperature, water (50 mL) and *n*-heptane (67 mL) were added and extracted. The organic layer was separated and washed twice with a mixed solution of methanol/water (1/2) (50 mL) and then dried over anhydrous Na_2SO_4. Concentration of the solution under reduced pressure provided Bn_2-L-Phe-OBn (**1b**) (61.64 g, 90.5 wt%, 121.8 mmol, 84.7% from L-phenylalanine) as a colorless oil.

Sodium amide (3.76 g, 96.39 mmol) was added to dimethyl sulfoxide (40 mL) at ambient temperature, and the suspended mixture was heated with stirring for 30 min at 74−75 °C. Tetrahydrofuran (40 mL) was added to the mixture that was cooled to 0 °C. To the resulting mixture was added dropwise a solution of **1b** (15.47 g, 90.5 wt%, 32.14 mmol) in tetrahydrofuran (20 mL) with stirring cooled at 0 °C, then the reaction was continued with stirring for 30 min at 0 °C. Citric acid aqueous solution (10%, 120 mL) and ethyl acetate (100 mL) were added to the reaction mixture and extracted; then the aqueous layer was extracted again with ethyl acetate (50 mL). The combined organic layers were washed with saturated NaCl aqueous solution, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The resulting residue was purified through silica gel column chromatography (*n*-hexane/ethyl acetate = 2/1 to 1/3) and then crystallized in toluene/*n*-hexane to obtain **2b** (11.16 g, 27.54 mmol, 85.6% from **1b**) as slightly yellowish crystals. The diastereomeric ratio was about 1:1 by the integral ratio in ^{1}H NMR.

^{1}H NMR (400 MHz, $CDCl_3$) (mixture of about 1:1 of diastereomeric isomers) δ = 2.27 (s, 3/2H), 2.35 (s, 3/2H), 2.97 (dd, 1H, J = 3.4, 13.4 Hz), 3.14 (dd, 1H, J = 9.5, 13.4 Hz), 3.19 (dd, 1H, J = 9.7, 13.3 Hz), 3.55−3.65 (m, 7/2H), 3.75 (d, 1/2H, J = 14.3 Hz), 3.85 (d, 2H, J = 13.4 Hz), 4.01 (d, 1/2H, J = 14.4 Hz), 4.07 (d, 1/2H, J = 14.4 Hz), 7.10−7.40 (m, 15H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 28.6, 39.6, 55.3, 63.5, 70.1, 126.7, 128.1, 128.9, 129.1, 129.3, 129.5, 129.9, 138.7, 201.5; IR (neat) 963, 1052, 1374, 1453, 1493, 1602, 1715 cm^{-1}; mp = 58−59 °C; $[\alpha]^{20}_D$ −46.9 (*c* 1.0, CH_3OH); MS (+FAB) *m/z* 406 (MH^+); HRMS (+FAB) calcd for $C_{25}H_{28}NO_2S$ (MH^+) 406.1841, found 406.1862.

(3*S*)-3-(*N*-Benzyloxycarbonyl)amino-1-hydroxy-1-methylthio-2-oxo-4-phenylb utane (3a).

To a solution of **2a** (708.6 mg, 1.971 mmol) in a mixed solvent of dimethyl sulfoxide (15 mL) and tetrahydrofuran (6 mL) was added 2 M HCl (7.5 mL). After the mixture was stirred for 18 h at ambient temperature, it was cooled in an ice bath and neutralized with saturated $NaHCO_3$ aqueous solution (15 mL). Water (50 mL) and ethyl acetate (50 mL) were added to the mixture and extracted. After the organic layer was separated, the resulting aqueous layer was extracted twice with ethyl acetate (25 mL). The combined organic layers were washed with water (50 mL) and saturated NaCl aqueous solution (30 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The resulting residue was crystallized in *n*-hexane/ethyl acetate to give crude **3a** (659.7 mg, 1.835 mmol, 93.2% from **2a**) as colorless crystals.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 1.50 (bd, 1H), 1.78 (s, 3H), 2.97 (dd, 1H, J = 8.8, 14.0 Hz), 3.24 (dd, 1H, J = 5.7, 14.0 Hz), 4.86 (m, 1H), 5.05 (m, 2H), 5.55 (bd, 1H), 7.18−7.39 (m, 10H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 9.9, 36.9, 56.1, 68.7, 127.6, 128.6, 128.8, 129.0, 129.1, 129.3, 129.6, 129.7, 136.3, 202.5; IR (neat) 1032, 1194, 1250, 1522, 1694 cm^{-1}; MS (+FAB) m/z 360 (MH^+); HRMS (+FAB) calcd for $C_{19}H_{22}NO_4S$ (MH^+) 360.1270, found 360.1269.

(3*S*)-1-Acetoxy-3-(*N*-benzyloxycarbonyl)amino-1-methylthio-2-oxo-4-phenylbutane (4a).

To a solution of **3a** (404.5 mg, 1.125 mmol) in a mixture of dichloromethane (11 mL) and pyridine (0.27 mL) was added dropwise acetyl chloride (0.12 mL, 1.69 mmol) with cooling in an ice bath, and the resulting mixture was stirred for 3 h at ambient temperature. HCl (0.5 M, 20 mL) and dichloromethane (15 mL) were added to the mixture and extracted. The organic layer was separated and washed with saturated $NaHCO_3$ aqueous solution (12 mL) and saturated NaCl aqueous solution (15 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The resulting residue was purified through silica gel column chromatography (*n*-hexane/ethyl acetate = 5/1 to 4/1) to obtain **4a** (413.3 mg, 1.029 mmol, 91.5% from **3a**) as colorless crystals. The diastereomeric ratio was about 1:1 by the integral ratio in ^{1}H NMR.

^{1}H NMR (400 MHz, $CDCl_3$) (mixture of about 1:1 of diastereomeric isomers) δ = 1.75 (s, 3/2H), 1.98 (s, 3/2H), 2.14 (s, 3/2H), 2.17 (s, 3/2H), 2.99 (m, 1H), 3.17 (m, 1H), 4.97−5.29 (m, 4H), 6.01 (s, 1/2H), 6.15 (s, 1/2H), 7.17−7.37 (m, 10H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 10.8, 20.6, 36.5, 56.0, 67.3, 126.9, 127.3, 128.1, 128.2, 128.5, 128.7, 129.4, 129.5, 136.1, 169.8, 196.4; IR (neat) 1044, 1108, 1212, 1264, 1524, 1692, 1750 cm^{-1}; MS (+FAB) m/z 402 (MH^+); HRMS (+FAB) calcd for $C_{21}H_{24}NO_5S$ (MH^+) 402.1375, found 402.1365.

(3*S*)-1-Acetoxy-3-(*N*-benzyloxycarbonyl)amino-1-methylthio-2-oxo-4-phenylbutane (4a), One-Pot Reaction from 2a.

2a (166.2 mg, 0.462 mmol) was dissolved in a mixture of dichloromethane (4.6 mL), pyridine (0.5 mL), and acetic anhydride (0.5 mL); then 4-dimethylamino pyridine (3 mg) was added to the solution. The resulting mixture was stirred for 17.5 h at ambient temperature. HCl (1 M, 10 mL) and ethyl acetate (15 mL) were added to the mixture and extracted. The organic layer was separated and washed with saturated $NaHCO_3$ aqueous solution (10 mL) and saturated NaCl aqueous solution (10 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The resulting residue was purified through preparative silica gel thin-layer chromatography to obtain **4a** (124.5 mg, 0.310 mmol, 67.1% from **2a**) as a colorless solid.

(3*S*)-3-(*N*,*N*-Dibenzyl)amino-1-hydroxy-1-mehtylthio-2-oxo-4-phenylbutane (3b).

To a solution of **2b** (309.6 mg, 0.763 mmol) in dimethyl sulfoxide (6 mL) was added 2 M HCl (1.5 mL). After the mixture was stirred for 16 h at ambient temperature, it was cooled in an ice bath and neutralized with saturated $NaHCO_3$ aqueous solution (5 mL). Water (10 mL) and ethyl acetate (20 mL) was added to the mixture and extracted. After the organic layer was separated, the resulting aqueous layer was extracted twice with ethyl acetate (10 mL). The combined organic layers were washed with water (20 mL) and saturated NaCl aqueous solution (20 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The resulting residue was crystallized in *n*-hexane/ethyl acetate to give crude **3b** (371.5 mg) as a slightly yellowish solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 1.71 (s, 3H), 3.04 (dd, 1H, J = 11.3, 12.8 Hz), 3.24−3.30 (m, 1H), 3.83−3.94 (m, 1H), 4.04 (bd, 1H), 4.31 (br, 1H), 4.65 (m, 2H), 4.77 (s, 1H), 5.03 (dd, 1H, J = 3.4, 11.3 Hz), 6.90−7.82 (m, 15H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 13.3, 49.2, 56.4, 61.0, 80.6, 129.4, 129.5, 129.6, 129.7, 129.7, 129.8, 129.8, 130.5, 201.5; IR (neat) 974, 1125, 1428, 1569, 1713 cm^{-1}; MS (+FAB) m/z 406 (MH^+); HRMS (+FAB) calcd for $C_{25}H_{28}NO_2S$ (MH^+) 406.1841, found 406.1865.

(3*S*)-1-Acetoxy-3-(*N*,*N*-Dibenzyl)amino-1-methylthio-2-oxo-4-phenylbutane (4b).

To a solution of crude **3b** (173.0 mg, prepared above) in a mixture of dichloromethane (4 mL) and pyridine (0.1 mL) was added dropwise acetyl chloride (0.05 mL, 0.703 mmol) with cooling in an ice bath, and the resulting mixture was stirred for 30 min at ambient temperature. HCl (0.5 M, 5 mL) and dichloromethane (10 mL) were added to the mixture and extracted. The organic layer was separated and washed with saturated $NaHCO_3$ aqueous solution (5 mL) and saturated NaCl aqueous solution (8 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The resulting residue was purified through preparative silica gel thin-layer chromatography to obtain **4b** (144.8 mg, 0.324 mmol, 91.1% from **2b** in two steps) as colorless crystals. The diastereomeric ratio was about 20:1 by the integral ratio in ^{1}H NMR.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 1.22 (s, 3H), 2.11 (s, 3H), 3.25 (dd, 1H, J = 12.2, 12.2 Hz), 3.70−3.80 (m, 1H), 4.21 (bd, 2H), 4.44 (bd, 2H), 4.85 (bd, 1H), 6.53 (bd, 1H), 6.94−7.85 (m, 15H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 10.6, 20.8, 56.3, 62.6, 63.3, 68.8, 77.6, 127.7, 128.9, 129.5, 129.8, 130.0, 130.8, 131.5, 170.5, 194.7; IR (neat) 967, 1081, 1212, 1372, 1428, 1725 cm^{-1}; MS (+FAB) m/z 448 (MH^+); HRMS (+FAB) calcd for $C_{27}H_{30}NO_3S$ (MH^+) 448.1946, found 448.1938.

(3*S*)-1-Acetoxy-3-(*N*,*N*-Dibenzyl)amino-1-methylthio-2-oxo-4-phenylbutane (4b). One-Pot Reaction from 2b.

2b (102.4 mg, 0.252 mmol) was dissolved in a mixture of dichloromethane (2 mL), pyridine (0.2 mL), and acetic anhydride (0.2 mL); then 4-dimethylamino pyridine (3 mg) was added to the solution. The resulting mixture was stirred for 10 days at ambient temperature. HCl (1 M, 10 mL) and ethyl acetate (10 mL) was added to the mixture and extracted. The organic layer was separated and washed with water (6 mL), saturated $NaHCO_3$ aqueous solution (7 mL), and saturated NaCl aqueous solution (7 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The resulting residue was purified through preparative silica gel thin-layer chromatography to obtain **4b** (86.6 mg, 0.193 mmol, 76.8% from **2b**) as a colorless solid.

Methylthio (2*S*,3*S*)- and (2*R*,3*S*)-2-acetoxy-3-(*N*-benzyloxycarbonyl)amino-4-phenylbutylate (5a).

To a solution of **4a** (124.5 mg, 0.310 mmol) in toluene (3 mL) was added 1,8-diazabicyclo [5.4.0] uncec-7-ene (0.05 mL, 0.334 mmol), and the mixture was stirred for 1 h 55 min at ambient temperature. HCl (1 M, 7 mL) and ethyl acetate (15 mL) was added to the mixture and extracted. The organic layer was separated and washed with saturated $NaHCO_3$ aqueous solution (7 mL) and saturated NaCl aqueous solution (7 mL), and then dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The resulting residue was purified through preparative silica gel thin-layer chromatography to obtain **5a** (121.4 mg, 0.302 mmol, 97.5% from **4a**) as a colorless solid. The diastereomeric ratio was about 6:4 by the integral ratio in ^{1}H NMR. For determination of the absolute configuration, the analyses of **6c** that had been obtained by the following experiments conformed to the referential sample of (*S*,*S*)-**6c** prepared by the known reaction via cyanation to dibenzylamino aldehyde.[7]

^{1}H NMR (400 MHz, $CDCl_3$) (mixture of about 3:2 of diastereomeric isomers) δ = 2.18 (s, 3H), 2.25 (s, 6/5H), 2.31 (s, 9/5H), 2.77−2.99 (m, 2H), 4.53 (m, 1H), 4.81 (bd, 2/5H, −NH), 5.04 (d, 2H, J = 2.6 Hz), 5.11 (bd, 3/5H, −NH), 5.21 (d, 3/5H,, J = 2.4 Hz), 5.43 (d, 2/5H, J = 4.0 Hz), 7.16−7.38 (m, 10H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 11.6, 21.0, 38.9, 54.1, 67.3, 78.1, 127.4, 128.5, 128.9, 129.0, 129.2, 129.6, 136.8, 155.9, 170.1, 197.9; IR (neat) 1042, 1214, 1524, 1690, 1754 cm^{-1}; MS (+FAB) m/z 402 (MH^+); HRMS (+FAB) calcd for $C_{21}H_{24}NO_5S$ (MH^+) 402.1375, found 402.1388.

Methylthio (2*S*,3*S*)- and (2*R*,3*S*)-2-Acetoxy-3-(*N*,*N*-dibenzyl)amino-4-phenylbutylate (5b).

To a solution of **4b** (50.6 mg, 0.113 mmol) in dimethyl formamide (1.1 mL) cooled to −30 °C was added 1,8-diazabicyclo[5.4.0]uncec-7-ene (0.02 mL, 0.134 mmol), and the

mixture was stirred for 1 h 15 min at −30 °C. HCl (0.2 M, 6 mL) and ethyl acetate (10 mL) were added to the mixture and extracted. The organic layer was separated and washed with water (6 mL) and saturated NaCl aqueous solution (8 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The resulting residue was purified through preparative silica gel thin-layer chromatography to obtain **5b** (44.6 mg, 0.100 mmol, 88.2% from **4b**) as a colorless solid. The diastereomeric ratio of (2*S*, 3*S*):(2*R*, 3*S*) was about 92:8 by the integral ratio in ^{1}H NMR.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 1.82 (s, 3H), 2.42 (s, 3H), 3.18 (dd, 1H, J = 11.3, 13.0 Hz), 4.00 (br, 2H), 4.08 (bd, 1H), 4.37 (bd, 2H), 4.51 (bd, 1H), 6.18 (s, 1H), 7.13−7.80 (m, 15H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 11.8, 21.5, 31.9, 55.8, 63.6, 74.2, 77.6, 125.4, 127.7, 128.6, 129.7, 130.3, 130.7, 131.7, 170.0, 195.6; IR (neat) 1046, 1206, 1368, 1459, 1663, 1764 cm^{-1}; mp = 137−138 °C; $[\alpha]^{20}_D$ −41.3 (*c* 1.0, CH_3OH); MS (+FAB) *m/z* 448 (MH^+); HRMS (+FAB) calcd for $C_{27}H_{30}NO_3S$ (MH^+) 448.1946, found 448.1964.

(2*S*,3*S*)- and (2*R*,3*S*)-3-(*N*,*N*-Dibenzyl)amino-2-hydroxy-4-phenyl Butyric Acid (6b).

To a solution of **5b** (87.1 mg, 0.171 mmol) in tetrahydrofuran (1.7 mmol) was added 1 M NaOH aqueous solution (0.68 mL), and the mixture was stirred for 2 days at ambient temperature. After concentration of the reaction mixture under reduced pressure, water (2 mL) and dichloromethane (7 mL) were added thereto and extracted. The organic layer was separated, and the resulting aqueous layer was extracted twice with dichloromethane (4 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The resulting residue was purified through preparative silica gel thin-layer chromatography to obtain **6b** (44.9 mg, 0.120 mmol, 69.9% from **5b**) as a colorless solid. Most of analysis data were collected as (2*S*,3*S*)-**6b** DCHA salt in the following experiment.

(2*S*,3*S*)-3-(*N*,*N*-Dibenzyl)amino-2-hydroxy-4-phenyl Butyric Acid Dicyclohexylamine Salt ((2*S*,3*S*)-6b DCHA).

To a solution of **4b** (9.398 g, 20.99 mmol) in dimethyl formamide (45 mL) cooled to −31 °C was added a solution of 1,8-diazabicyclo[5.4.0]uncec-7-ene (641 mg, 4.21 mmol) in dimethyl formamide (3 mL) for 10 min, and the mixture was stirred for 16 h at −30 °C. Citric acid aqueous solution (10%, 50 mL) and ethyl acetate (77 mL) were added to the mixture and extracted. The organic layer was separated and washed with water (50 mL) and saturated NaCl aqueous solution (10 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to give crude **5b**. By HPLC analysis, the ratio of (2*S*, 3*S*):(2*R*, 3*S*), was about 89:11, and (2*S*, 3*S*)-**5b** (8.101 g, 18.10 mmol, 86.2% as the (2*S*, 3*S*)-isomer) was obtained.

The crude **5b** as obtained above was dissolved in methanol (90 mmol), and 2 M NaOH aqueous solution (36 mL) was added to the mixture with stirring at ambient temperature. The reaction was continued for 3.5 h at ambient temperature. After concentration of the reaction mixture under reduced pressure to remove methanol, 6 M HCl (12 mL) and dichloromethane (50 mL) were added to the residue, adjusting pH to 1.9, and then extracted. The organic layer was separated and washed with saturated NaCl aqueous solution (30 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The resulting residue was dissolved in acetone (50 mL). After filtration to remove the insoluble matter and washing it with acetone (30 mL), to the filtrate was added dropwise dicyclohexylamine (4.43 g, 24.43 mmol) to give slurry. The resulting crystals were filtered and washed with acetone (30 mL) and dried in vacuo to obtain (2*S*, 3*S*)-**6b** DCHA salt (9.02 g, 95 *wt*% 15.38 mmol, 85% from (2*S*, 3*S*)-**5b**) as colorless crystals.

^{1}H NMR (400 MHz, DMSO-d_6) δ = 0.90−1.30 (m, 10H), 1.52−1.80 (m, 6H), 1.85−2.02 (m, 4H), 2.37 (dd, 1H, J = 3.1, 14.5 Hz), 2.87 (dd, 1H, J = 11.0, 14.5 Hz), 2.91 (m, 2H), 3.37 (m, 2H), 3.53 (d, 2H, J = 14.6 Hz), 3.82 (d, 2H, J = 14.6 Hz), 4.16 (s, 1H), 6.95−7.30 (m, 15H); ^{13}C NMR (100 MHz, DMSO-d_6) δ = 24.4, 25.3, 29.6, 32.6, 52.2, 53.9, 62.0, 69.6, 125.7, 126.6, 127.9, 128.1, 128.5, 129.8, 141.0, 141.5, 176.4; IR (neat) 1046, 1127, 1358, 1455, 1576 cm^{-1}; mp = 196−197 °C; $[\alpha]^{20}_D$ 10.24 (*c* 1.0, CH_3OH); MS (+FAB) *m/z* 376(MH^+), 557 (M+DCHAH^+); HRMS (+FAB) calcd for $C_{24}H_{26}NO_3$ (MH^+) 376.1913, found 376.1926.

(2*S*,3*S*)-3-Amino-2-hydroxy-4-phenylButyric Acid ((2*S*,3*S*)-6c) and (2*S*,3*S*)-6c Sodium Salt).

To a solution of (2*S*, 3*S*)-**6b** DCHA (2.784 g, 5.0 mmol) dissolved in a mixture of methanol (25 mL) and acetic acid (2.4 mL) was added 5% palladium on carbon (water content 53.3%) (1.139 g, 0.23 mmol Pd). The resulting mixture was stirred for 25 h under hydrogen at atmospheric pressure at ambient temperature. NaOH (2 M) aqueous solution (about 20 mL) was added to the reaction mixture in a water bath to adjust pH to5.1 at 30 °C. After the mixture was stirred for 40 min at ambient temperature, it was filtered to remove the catalyst. HPLC analysis of the filtrate detected (2*S*,3*S*)-**6c** (949 mg, 4.86 mmol, 97.2% from (2*S*, 3*S*)-**6b** DCHA). The filtrate was concentrated under reduced pressure to remove methanol, and then ethyl acetate (50 mL) was added to the concentrate with stirring at ambient temperature. The resulting crystals were filtered and dried in vacuo to obtain (2*S*,3*S*)-**6c** sodium salt (602.0 mg, 2.77 mmol, 57.0% as a recovery yield in crystallization).

^{1}H NMR (400 MHz, DMSO-d_6) δ = 2.75 (dd, 1H, J = 9.4, 14.2 Hz), 3.07 (dd, 1H, J = 4.0, 14.2 Hz), 3.21 (ddd, 1H, J = 4.0, 7.4, 9.4 Hz), 3.61 (d, 1H, J = 7.4 Hz), 7.23−7.36 (m, 5H); ^{13}C NMR (100 MHz, DMSO-d_6) δ = 35.9, 55.5, 70.0, 127.0, 128.9, 129.8, 137.2; IR (neat) 749, 801, 1063, 1154, 1343, 1422, 1600 cm^{-1}; mp = 251−252 °C; $[\alpha]^{20}_D$ −5.83 (*c* 0.86, 1 M HCl); MS (+FAB) *m/z* 196 (MH^+), 217 (MNa^+); HRMS (+FAB) calcd for $C_{10}H_{14}NO_3$ (MH^+) 196.0974, found 196.0990.

Methylthio (2*S*,3*S*)- and (2*R*,3*S*)-2-Acetoxy-3-(*N*,*N*-dibenzyl)amino-5-methylhexanoate (5e).

(3*S*)-1-Acetoxy-3-(*N*,*N*-dibenzyl)amino-1-methylthio-5-methy-2-oxolhexane (**4e**) was obtained from L-leucine by the same procedure used for the preparation of **4b**. To a solution of **4e** (0.61 g, 1.48 mmol) in dimethyl formamide (7.5 mL) cooled to −30 °C was added 1,8-diazabicyclo[5.4.0]uncec-7-ene (0.066 mL), and the mixture was stirred for 15.5 h at −30 °C. Citric acid aqueous solution (10%, 20 mL) and ethyl acetate (30 mL) were added to the mixture and extracted. The organic layer was separated and washed with saturated $NaHCO_3$ aqueous solution (20 mL) and saturated NaCl aqueous solution (20 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The resulting residue was purified through silica gel column chromatography to obtain **5e** (0.6 g, 1.45 mmol, 98% from **4e**) as a colorless oil. The diastereomeric ratio of (2*S*, 3*S*):(2*R*, 3*S*), was about 95:5 by the integral ratio in ^{1}H NMR.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 0.37 (d, 3H, J = 6.4 Hz), 0.87 (d, 3H, J = 6.7 Hz), 1.01 (m, 1H), 1.76−1.86 (m, 2H), 2.23 (s, 3H), 2.26 (s, 3H), 3.25 (m, 1H), 3.31 (d, 2H, J = 13.5 Hz), 3.92 (d, 2H, J = 13.5 Hz), 5.83 (d, 1H, J = 1.6 Hz), 7.21−7.33 (m, 10H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 11.2, 20.8, 21.2, 23.9, 24.0, 36.1, 53.9, 57.1, 127.1, 128.2, 129.2, 139.4, 170.1, 199.3; IR (neat) 1044, 1216, 1368, 1453, 1683, 1752 cm^{-1}; MS (ESI) *m/z* 414 (MH^+); HRMS (+FAB) calcd for $C_{24}H_{32}NO_3S$ (MH^+) 414.2103, found 414.2106.

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Supporting Information Available: Characterization data for compounds **2**−**5**. This material is available free of charge via the Internet at http://pubs.acs.org.

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