Stereospecific Amination by Dynamic Kinetic Resolution Utilizing 2-Oxoimidazolidine-4-carboxylate as a Novel Chiral Auxiliary

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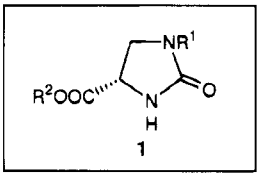
Received June 20, 1995®

A novel type of stereospecific amination by dynamic kinetic resolution using (4*S*)-2-oxoimidazolidine-4-carboxylate (**1**) as a chiral auxiliary was developed. A reaction of a diastereomeric mixture of (4*S*)-3-[(2*RS*)-2-bromoacyl]-2-oxoimidazolidine-4-carboxylates **4** with an amine in the presence of a base in HMPA predominantly afforded (4*S*)-3-[(2*R*)-2-(alkylamino)acyl]-2-oxoimidazolidine-4-carboxylates (*S,R*)-**7** in good yields. The reaction proceeded by stereospecific S_N2 type amination incorporated with rapid interconversion between the substrates (*S,S*)-**4** and (*S,R*)-**4**. Mechanistic study suggested that the unique stereoselectivity was induced through the interaction between an amine and the ester group of (*S,S*)-**4** in the transition state. The chiral auxiliary was easily removed with alkoxide anion to afford the α-amino acid synthon in good yields.

As part of our synthetic studies on angiotensin converting enzyme (ACE) inhibitors,[1] we have noticed the characteristics of (4*S*)-1-alkyl-2-oxoimidazolidine-4-carboxylates **1**, which are easily derived from L-asparagine. Namely, they have an asymmetric carbon originated from L-asparagine, functional groups like a urea and an ester, and a nearly planar 2-oxoimidazolidine ring. Moreover, conformational analysis of ACE inhibitors containing the 2-oxoimidazolidine-4-carboxylic acid moiety at the C-terminus elucidated that the amide bond at 3-position of 3-acyl derivative **2** was restricted exclusively to the *trans* geometry by the dipole–dipole repulsion of two carbonyl groups.[2] Further, this amide bond was anticipated to be scissile under mildly basic conditions. These structural and chemical characteristics prompted us to utilize **1** as a novel chiral auxiliary for an asymmetric synthesis.



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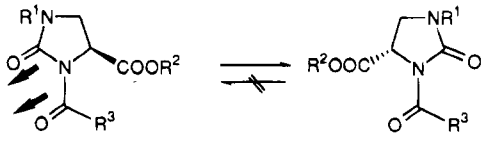
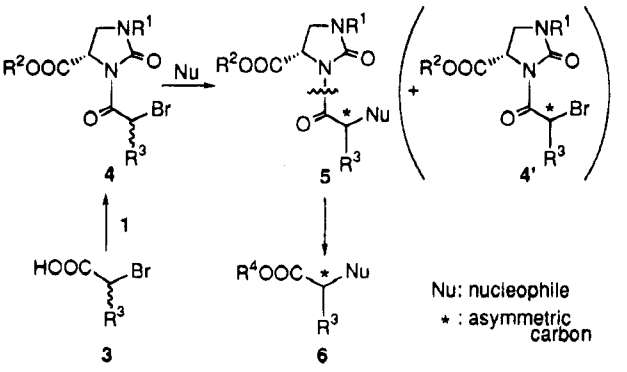


cis-**2** *trans*-**2**

Taking the above information into consideration, we designed a bimolecular substitution reaction of a diastereomeric mixture of **4**, that was composed of **1** and an acyl moiety having a racemic bromo group at 2-position, with a nucleophile as shown in Scheme 1. The substitution reaction rate was expected to be different for the diastereomers, due to the steric and/or electronic effects of the auxiliary, resulting in kinetic resolution. Furthermore, if the substrate rapidly epimerized under the reaction conditions, dynamic kinetic resolution was expected to proceed with exclusive formation of the chiral substituted product **5**. Dynamic kinetic resolution, in which rapid interconversion between optically isomeric substrates is incorporated with conventional kinetic resolution, has recently received much attention as a new methodology for asymmetric synthesis.[3] In this resolution, a single chiral product can theoretically be obtained in 100% yield, offering a tangible synthetic advantage.

Scheme 1



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® Abstract published in *Advance ACS Abstracts,* September 15, 1995.

(1) Hayashi, K.; Nunami, K.; Kato, J.; Yoneda, N.; Kubo, M.; Ochiai, T.; Ishida, R. *J. Med. Chem.* **1989**, *32*, 289.
(2) Shimizu, R.; Nunami, K.; Kubota, H.; Kinumaki, A.; Matsumoto, K. *Peptide Chemistry 1992*; Yanaihara, N., Ed.; ESCOM; Leiden, 1993; p 227.
(3) (a) Hayashi, T.; Konishi, M.; Fukushima, M.; Kanehira, K.; Hioki, T.; Kumada, M. *J. Org. Chem.* **1983**, *48*, 2195. (b) Stürmer, R. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 59. (c) Tai, A.; Watanabe, H.; Harada, T. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 1468. (d) Noyori, R.; Ikeda, T.; Ohkuma, T.; Widhalm, M.; Kitamura, M.; Takaya, H.; Akutagawa, S.; Sayo, N.; Saito, T.; Taketomi, T.; Kumobayashi, H. *J. Am. Chem. Soc.* **1989**, *111*, 9134. (e) Kitamura, M.; Ohkuma, T.; Tokunaga, M.; Noyori, R. *Tetrahedron Asymmetry* **1990**, *1*, 1. (f) Kitamura, M.; Tokunaga, M.; Noyori, R. *J. Am. Chem. Soc.* **1993**, *115*, 144. (g) Kitamura, M.; Tokunaga, M.; Noyori, R. *Tetrahedron* **1993**, *49*, 1853. (h) Koh, K.; Ben, R. N.; Durst, T. *Tetrahedron Lett.* **1993**, *34*, 4473. (i) Koh, K.; Ben, R. N.; Durst, T. *Tetrahedron Lett.* **1994**, *35*, 375. (j) Koh, K.; Durst, T. *J. Org. Chem.* **1994**, *59*, 4683. (k) Seebach, D. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 1320. (l) Inagaki, M.; Hiratake, J.; Nishioka, T.; Oda, J. *J. Am. Chem. Soc.* **1991**, *113*, 9360. (m) Fülling, G.; Sih, C. J. *J. Am. Chem. Soc.* **1987**, *109*, 2845. (n) Gu, R.; Lee, I.; Sih, C. J. *Tetrahedron Lett.* **1992**, *33*, 1953.

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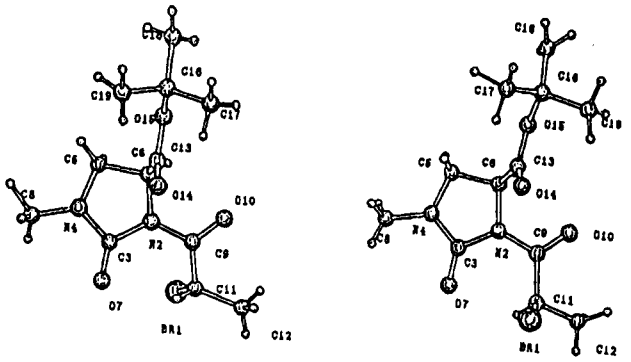


(S,S)-4a (S,R)-4a

Figure 1. X-ray structures of **4a**.

We selected an amine as a nucleophile, because the substituted products would provide optically active α-amino acid derivatives, which are useful chiral building blocks in organic synthesis,[4] by removal of the chiral auxiliary.

In this paper, we wish to report stereospecific amination through dynamic kinetic resolution utilizing **1** as a novel chiral auxiliary, which is applied to the preparation of a range of optically active α-amino acid synthons, and propose the reaction mechanism.[5,6]

Results and Discussion

Working Hypothesis. Our study began with the conformational analysis of *tert*-butyl (4*S*)-3-(2-bromopropionyl)-1-methyl-2-oxoimidazolidine-4-carboxylate ((*S,S*)-**4a** and (*S,R*)-**4a**) as typical substrates to examine the stereoselectivity of the reaction with an amine. Optically pure (*S,S*)-**4a** and (*S,R*)-**4a** were synthesized from L-asparagine according to the procedure previously reported[1] and separated by silica gel column chromatography. X-ray crystallographic analysis of each diastereomer was performed (Figure 1).[7] The results showed that these molecules have a nearly planar 2-oxoimidazolidine ring and a *trans* amide bond at the 3-position. Next we conducted molecular modeling of them, starting with the coordinates of their crystal structures. Thus, the *cis*- and *trans*-conformers of (*S,S*)-**4a** and (*S,R*)-**4a** were modeled, with full geometry optimization, using the CHARMm force field.[8] As shown in Table 1, the differences in potential energy between the *cis*- and *trans*-conformers were so large that the unstable *cis*-conformer would have an extremely low concentration. These results show that the amide bond at the 3-position of **4a** is restricted to the *trans* geometry, coplanar with the five-membered ring, and that the bulky ester group shields one side of that plane as shown in Figure 2. From the above

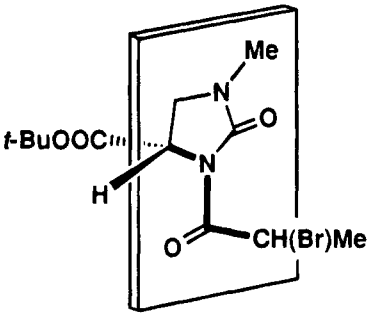
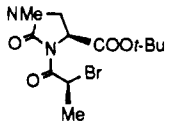
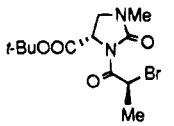
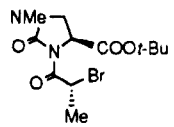
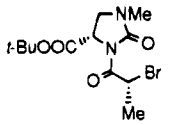
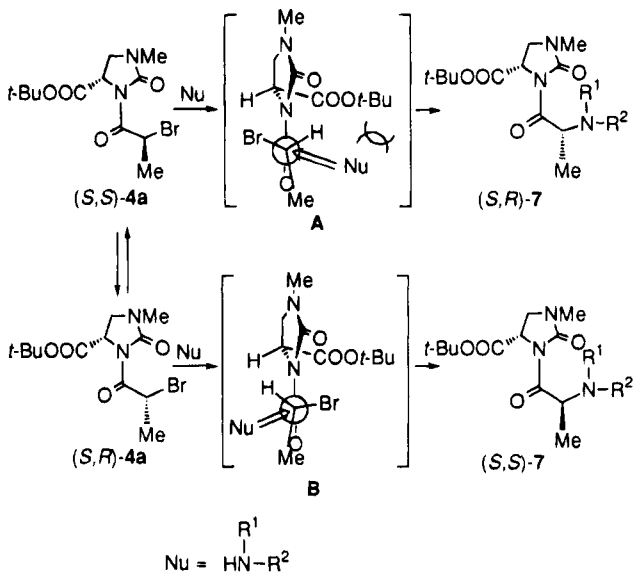


Figure 2. Schematic representation of the stable conformation of **4a**.

Table 1. Differences of Potential Energy between *cis*-4a and *trans*-4a

		$\Delta E_{cis\text{-}trans}$ (kcal/mol)
 *Cis*-(*S,S*)-**4a**	 *Trans*-(*S,S*)-**4a**	5.76
 *Cis*-(*S,R*)-**4a**	 *Trans*-(*S,R*)-**4a**	5.14

Scheme 2. Initial Proposal for Stereoselective Reactions of 4a



information, we proposed the working hypothesis shown in Scheme 2 for reaction of **4a** with an amine. Newman projections, having the lowest potential energy, are depicted as **A** and **B**. Taking into account the steric hindrance of the bulky ester group, it was predicted that an amine would attack the sterically less hindered site **B**, in preference to **A**, and kinetic resolution would result in the predominant formation of (*S,S*)-**7**. Further, since a rapid epimerization of **4a** at the asymmetric carbon attached to the electron-withdrawing amide carbonyl and bromo groups was expected under the reaction conditions, dynamic kinetic resolution became feasible by the re-

(4) Effenberger, F.; Burkard, U.; Willfahrt, J. *Angew. Chem., Int. Ed. Engl.* **1983**, *22*, 65.

(5) In our synthetic studies on ACE inhibitors, we have noticed that the reaction of a diastereomeric mixture of **4a** with amino acid esters gave one diastereomer in greater than 50% yield, and **4a** easily epimerized under substitution reaction conditions.[1]

(6) A part of this work has been reported in preliminary communication: Nunami, K.; Kubota, H.; Kubo, A. *Tetrahedron Lett.* **1994**, *35*, 8639.

(7) The author has deposited atomic coordinates for this structure with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK.

(8) Molecular Simulations Inc., 16 New England Executive Park Burlington, MA.

Scheme 3

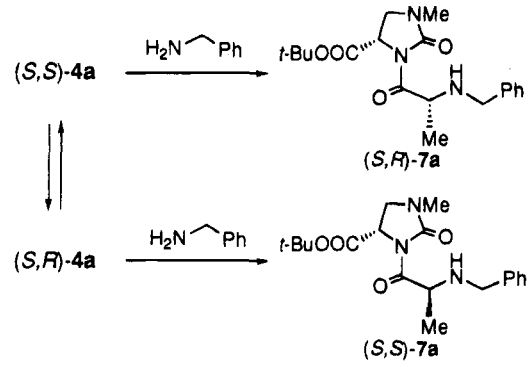


Table 2. Reaction of Bromide 4a with Benzylamine in a Polar Solvent

			7a	
run[a]	base[b]	solvent	yield (%)[c]	(S,R):(S,S)[d]
1	K_2CO_3	DMF	97	78:22
2	K_2CO_3	DMSO	94	82:18
3	K_2CO_3	HMPA	98	93:7
4	Et_3N	HMPA	96	94:6
5[e]	–	HMPA	98	89:11

[a] Reaction was carried out with 1 mol equiv of benzylamine at 25 °C for 14 h. [b] 1 mol equiv. [c] Isolated yield. [d] Determined by HPLC analysis. [e] 2 mol equiv of benzylamine was used.

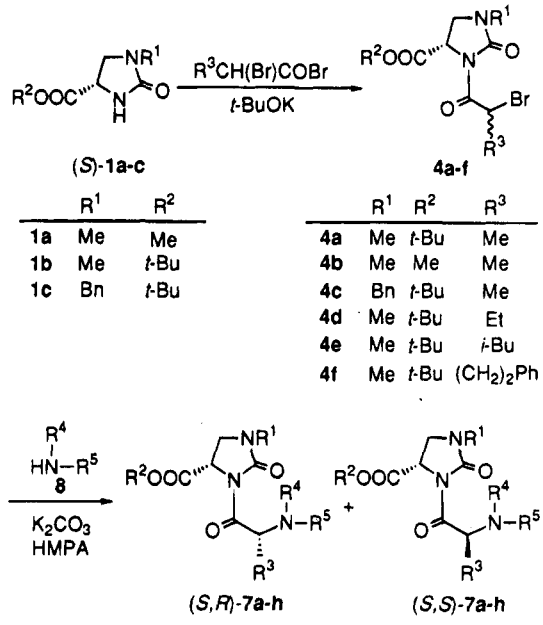
plenishment of the more reactive (*S,R*)-**4a** *via* epimerization of slower reacting substrate (*S,S*)-**4a**.

Dynamic Kinetic Resolution. First, kinetic resolution was examined as a basic reaction of dynamic kinetic resolution to verify the difference of the reaction rate between the substrates with an amine. Reaction of a diastereomeric mixture of **4a** with 1 equiv of benzylamine in CH_2Cl_2 at room temperature for 40 h proceeded stereospecifically to afford (*S,R*)-**7a** in an excellent yield, while (*S,R*)-**4a** was recovered almost quantitatively.[9] The reaction with 0.5 equiv of benzylamine in the presence of base such as K_2CO_3 or Et_3N also gave satisfactory results.[9] These results demonstrated that *tert*-butyl (4*S*)-1-methyl-2-oxoimidazolidine-4-carboxylate worked as an effective chiral auxiliary for kinetic resolution.

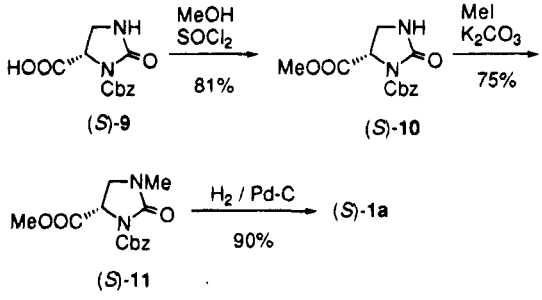
Next, epimerization of the diastereomers (*S,S*)- and (*S,R*)-**4a**, was examined for dynamic kinetic resolution as shown in Scheme 3. Epimerization of optically active **4a** was monitored as a function of the reaction solvent by periodically checking the change in the proportion of (*S,S*)-**4a** and (*S,R*)-**4a** in the presence of a base such as K_2CO_3 or Et_3N.[6] No epimerization was observed using CH_2Cl_2 or THF as a solvent but was observed in polar solvents such as DMF, DMSO, or HMPA. Extremely rapid epimerization was observed in HMPA. On the basis of these observations, reaction of **4a** with benzylamine in the presence of K_2CO_3 was examined in these polar solvents (Table 2, runs 1–3). All reactions afforded the product in 94–98% isolated yields, and the major product was (*S,R*)-**7a**, consistent with the observations in the kinetic resolution study. Stereoselectivity was greatly affected by the reaction solvent, and the highest selectivity in HMPA corresponded with the result from the epimerization study (run 3). The use of Et_3N instead of K_2CO_3 also afforded excellent results (run 4). On the other hand, the reaction using 2 equimolar amounts of benzylamine without any additional base resulted in inferior stereoselectivity (run 5). When each isolated product, (*S,R*)-**7a** or (*S,S*)-**7a**, was held in HMPA in the presence of 1 equimolar amount of K_2CO_3 and benzylamine at 25 °C for 24 h, they were recovered without any epimerization. From these results, it was apparent that effective dynamic kinetic resolution was performed in accordance with our synthetic strategy.

We examined the effects of substituents on the stereoselectivity of this unique dynamic kinetic resolution (Scheme 4). The substrates **4a–f** were synthesized by the reaction of the corresponding 2-bromoacyl bromides with the potassium salt of (*S*)-**1a**, prepared from (*S*)-**9**[1] according to the procedure in Scheme 5, or that of (*S*)-**1b** or (*S*)-**1c** previously reported.[1] The reaction of these substrates with amines **8** was carried out in the presence of K_2CO_3 in HMPA, and the results are shown in Table 3. The substrates with a bulky ester group gave better selectivity (entry 1 *vs* 2), while the effect of ranging R^1 and R^3 was minimal (entry 1 *vs* 3–6). Variations of the amine gave satisfactory yield and stereoselectivity results (entries 7 and 8). The stereochemistry of the major products of the reaction was established as follows. The major product obtained by the reaction of **4d** with benzylamine was converted to methyl (2*R*)-2-(benzylamino)butanoate ((*R*)-**12**) by treatment with MeONa in MeOH (85% yield, $[\alpha]^{25}_D$ +42.4) (Scheme 6). An authentic sample of methyl (2*S*)-2-(benzylamino)butanoate ((*S*)-**12**) was prepared from commercially available (2*S*)-2-aminobutanoic acid ((*S*)-**13**)[10] by esterification and reductive amination[11] using benzaldehyde. The optical rotation of (*S*)-**12** ($[\alpha]^{25}_D$ −42.1) showed that the major

Scheme 4



Scheme 5



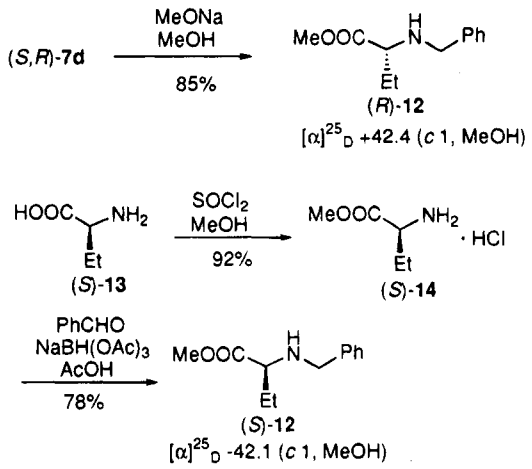
(9) Kubota, H.; Kubo, A.; Nunami, K. *Tetrahedron Lett.* **1994**, *35*, 3107.

Table 3. Reaction of Bromide 4a–f with Amine 8

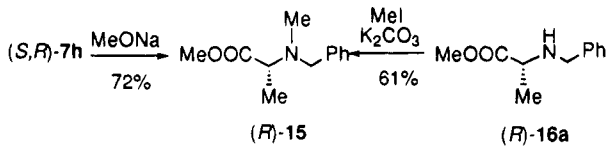
entry[a]	product	R^1	R^2	R^3	R^4	R^5	yield[b] (%)	(S,R):(S,S)[c]
1	**7a**	Me	*t*-Bu	Me	Bn	H	98	93:7
2	**7b**	Me	Me	Me	Bn	H	83	90:10
3	**7c**	Bn	*t*-Bu	Me	Bn	H	92	93:7
4	**7d**	Me	*t*-Bu	Et	Bn	H	90	94:6
5	**7e**	Me	*t*-Bu	*i*-Bu	Bn	H	85	93:7
6	**7f**	Me	*t*-Bu	$(CH_2)_2Ph$	Bn	H	94	95:5
7	**7g**	Me	*t*-Bu	Me	$CH(Ph)_2$	H	98	93:7
8	**7h**	Me	*t*-Bu	Me	Bn	Me	97	93:7

[a] Reaction was carried out in the presence of K_2CO_3 in HMPA at 25 °C for 14 h. [b] Isolated yield. [c] Determined by HPLC analysis.

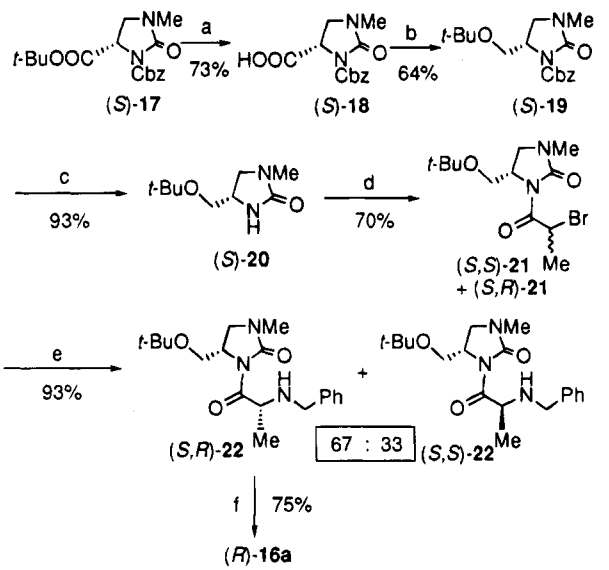
Scheme 6



Scheme 7



Scheme 8[a]



[a]Key: (a) HCl; (b) (1) BH_3-Me_2S, (2) isobutene, H_2SO_4 (cat.); (c) H_2 / Pd-C; (d) BrCOCH(Br)Me, *t*-BuOK; (e) benzylamine, K_2CO_3, HMPA; (f) NaOMe.

isomer of **7d** has (*S,R*) configuration.[12] In addition, the stereochemistry of the predominant isomer of **7f** was established to be (*S,R*) by X-ray crystallographic analysis.[7] Further, to determine the stereochemistry of the major isomer of **7h**, it was treated with MeONa in MeOH to afford (*R*)-**15** (Scheme 7), for which the absolute configuration was confirmed by comparison of its optical rotation ($[\alpha]^{24}_D$ +68.9) with that of methyl *N*-benzyl-*N*-methyl-D-alaninate ($[\alpha]^{24}_D$ +70.3) prepared by methylation of (*R*)-**16a**.[9] The stereochemistry of other products was assumed to have the same (*S,R*) configuration by the analogy with **7a,d,f,h**.

Mechanism of Dynamic Kinetic Resolution. The stereochemistry of the product formed in the kinetic resolution and dynamic kinetic resolution reactions by amination was completely opposite to that of our working hypothesis. Namely, we assumed that a nucleophile would attack from the sterically less hindered side of (*S,R*)-**4** resulting in the predominant formation of (*S,S*)-**7** (Scheme 2). We have reported that dynamic kinetic resolution of **4a** using malonic ester enolate as a nucleophile proceeded in accordance with this hypothesis.[13] But, in the case of amination, the product of the sterically disfavored approach, the (*S,R*)-product was exclusively isolated. These facts led us to propose that there is an interaction between the ester group and the amine nucleophile responsible for the stereoselectivity.

In order to examine whether the ester group is essential for the high stereoselectivity or not, the reaction of the ether derivative, instead of the ester derivative, with an amine was investigated. The reaction of (4*S*)-3-(2-bromopropionyl)-4-(*tert*-butoxymethyl)-1-methyl-2-oxoimidazolidine ((*S,R*)-**21** and (*S,S*)-**21**), synthesized from (*S*)-**17**[1] according to Scheme 8, with benzylamine gave amination products (*S,R*)-**22** and (*S,S*)-**22** with low stereoselectivity (67:33). The stereochemistry of the major product was confirmed by the conversion of it to (*R*)-**16a** with MeONa, according to the procedure previously described. Taking the low selectivity shown in Scheme 8 into consideration, we speculate that the transition state shown in Figure 3, in which an interaction between the amine and the ester group of (*S,S*)-**4** accelerates the formation of (*S,R*)-product, is responsible for the stereoselectivity of the amination.

Removal of the Chiral Auxiliary. Finally, we examined the removal of the chiral auxiliary from the amination products (Table 4). When (*S,R*)-**7a** was treated with less than 1 equiv of MeONa in MeOH at rt, optically

(10) A sample obtained from Tokyo Chemical Industry Co., Ltd. has the following optical rotation: $[\alpha]^{27}_D$ +20.4 (*c* 2, 6 N HCl).

(11) Abdel-Magid, A. F.; Maryanoff, C. A. *Synlett* **1990**, 537.

(12) After the publication of our communication,[6] Durst *et al.* reported a dynamic kinetic resolution of **4d** with benzylamine in the presence of $Bu_4N^+I^-$ (O'Meara, J. A.; Jung, M.; Durst, T. *Tetrahedron Lett.* **1995**, *36*, 2559). They described the exclusive formation of (*S,S*)-**7d**, and conversion of it to methyl (2*S*)-2-(benzylamino)butanoate by the removal of the auxiliary. However, the reported optical rotation ($[\alpha]_D$ +17.2 (*c* 0.36, MeOH)) is different from that of our authentic sample.

(13) Kubo, A.; Takahashi, M.; Kubota, H.; Nunami, K. *Tetrahedron Lett.* **1995**, *36*, 6251.

Table 4. Removal of Chiral Auxiliary from (*S,R*)-7a

					(*R*)-16			(*S*)-1				
run	reagent (equiv)	solvent	temp (°C)	time (h)	product	yield (%)[a]	ee (%)[b]	product	R^1	R^2	yield (%)[a]	ee (%)[b]
1	MeONa (1.0)	MeOH	r.t.	2	**16a**	90	>99	**1a**	Me	Me	72	0
2	MeONa (0.2)	MeOH	r.t.	20	**16a**	92	>99	**1a**	Me	Me	69	33
3	BnOLi (1.5)	THF	0	1	**16b**	60	>99	**1b**	Me	*t*-Bu	38	95
4	BnOLi (1.0)	Et_2O	0	0.5	**16b**	87	>99	**1b**	Me	*t*-Bu	76	>99

[a] Isolated yield. [b] Determined on the basis of optical rotation.

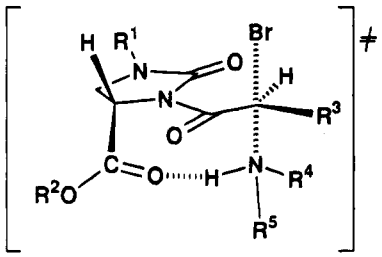
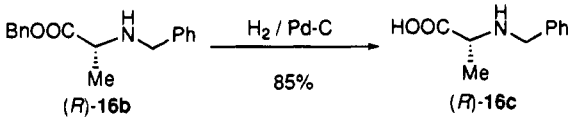


Figure 3. Proposed transition state for the reaction of bromide (*S,S*)-**4** with amine **8**.

Scheme 9



pure (*R*)-**16a** was isolated in 90–92% yield. However, serious racemization and transesterification of the recovered auxiliary **1** was observed under these conditions (runs 1 and 2). On the other hand, the use of $PhCH_2OLi$ in THF[14] resulted in the suppression of these undesirable side reactions (run 3). Further, by using Et_2O as a solvent, benzyl *N*-benzyl-D-alaninate ((*R*)-**16b**) was isolated in 87% yield, and (*S*)-**1b** was recovered in 76% yield without racemization (run 4). The optical purity of (*R*)-**16b** was determined by comparison of the optical rotation of (*R*)-**16c** ($[\alpha]^{25}_D$ −4.0) with that in the literature[15] after hydrogenation (Scheme 9).

Conclusion

We have developed a new category of dynamic kinetic resolution by stereospecific amination utilizing 2-oxoimidazolidine-4-carboxylate **1** as a novel chiral auxiliary. The reaction of the diastereomeric mixture **4** with an amine in the presence of K_2CO_3 or Et_3N in HMPA predominantly afforded (*S,R*)-**7** in nearly quantitative yield. The unique stereoselectivity of the reaction suggests the presence of the interaction between an amine and the ester group of **4** in the transition state. Since the chiral auxiliary of **7** can be easily removed without racemization, this methodology provides efficient access to a range of optically active α-amino acid synthons.[16] It is noteworthy that D-amino acid derivatives can be obtained with the chiral auxiliary derived from commercially available L-asparagine. Efforts to expand the utility of this method are under investigation in this laboratory.

Experimental Section

General. Melting points are uncorrected. ^1H NMR spectra were recorded at 200 MHz with TMS as an internal standard. HPLC analyses were performed with a Nucleosil $5C_{18}$ column (4.6 × 150 mm) using 0.05 N KH_2PO_4–CH_3CN solvent system as an eluent. Column chromatography was performed on silica gel (70–230 mesh). Preparative TLC was performed on silica gel precoated glass plate. All reactions with air- and moisture-sensitive compounds were conducted in oven-dried glassware under an atmosphere of dry nitrogen.

Separation of Diastereomers of 4a. Compound **4a** was synthesized by the procedure previously reported.[1] The diastereomers were separated by column chromatography on silica gel with hexane–AcOEt (1:1) as an eluent to give (*S,S*)-**4a** from the first fraction (R_f 0.76) and (*S,R*)-**4a** from the second fraction (R_f 0.57). Each of them was recrystallized from *i*-Pr_2O to afford colorless needles. (*S,S*)-**4a**: mp 81–83 °C; $[\alpha]^{28}_D$ −81.5 (*c* 1, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.47 (9H, s), 1.85 (3H, d, *J* = 6.8 Hz), 2.91 (3H, s), 3.32 (1H, dd, *J* = 3.7, 9.8 Hz), 3.72 (1H, t, *J* = 9.8 Hz), 4.64 (1H, dd, *J* = 3.7, 9.8 Hz), 5.93 (1H, q, *J* = 6.8 Hz); IR (KBr) 1750, 1737, 1677 cm^{-1}; SIMS *m/z* 337/335 (M^+ + 1), 281/279, 199, 145 (base), 99. Anal. Calcd for $C_{12}H_{19}BrN_2O_4$: C, 43.00; H, 5.71; N, 8.36. Found: C, 42.85; H, 5.79; N, 8.26. (*S,R*)-**4a**: mp 129–131 °C; $[\alpha]^{28}_D$ −63.7 (*c* 1, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.49 (9H, s), 1.82 (3H, d, *J* = 6.8 Hz), 2.91 (3H, s), 3.37 (1H, dd, *J* = 4.7, 9.7 Hz), 3.69 (1H, t, *J* = 9.7 Hz), 4.66 (1H, dd, *J* = 4.7, 9.7 Hz), 5.87 (1H, q, *J* = 6.8 Hz); IR (KBr) 1755, 1736, 1678 cm^{-1}; SIMS *m/z* 337/335 (M^+ + 1), 281/279, 199, 145 (base), 99. Anal. Calcd for $C_{12}H_{19}BrN_2O_4$: C, 43.00; H, 5.71; N, 8.36. Found: C, 42.81; H, 5.80; N, 8.25.

Molecular Modeling Analyses of 4a. The initial coordinates of **4a** were generated based on the energy minimization of the crystal structures by using CHARMm (Ver. 21.2) all-atom force field.[17] The length of C-H bonds was fixed by using SHAKE algorithm[18] to reduce the computation time. Molecular dynamics simulations were performed at 2000 K for 500 ps to search the conformational space. The distance dependent dielectric constant was used to approximate solvent effects. During the simulations, the structures were saved at every 0.5 ps, and were energy-minimized. The most stable *cis*- and *trans*- conformers of (*S,S*)-**4a** and (*S,R*)-**4a** were selected to investigate the energy differences.

Methyl (4*S*)-3-[(Benzyloxy)carbonyl]-2-oxoimidazolidine-4-carboxylate [(*S*)-10]. To a suspension of (*S*)-**9**[1] (15.0 g, 57 mmol) in MeOH (150 mL) was added $SOCl_2$ (4.6 mL, 63 mmol) at 0–5 °C under stirring. After stirring was continued for 5 h at the same temperature, the solution was concentrated in *vacuo*. The residue was dissolved in AcOEt, and the solution was washed successively with saturated aqueous $NaHCO_3$ and brine, dried over $MgSO_4$, and concentrated in *vacuo*. The resulting crystals were triturated with AcOEt to afford (*S*)-**10** (12.8 g, 81%) as colorless needles: mp 143–145 °C; $[\alpha]^{22}_D$ −78.2 (*c* 1, MeOH); ^1H NMR (DMSO-d_6) δ 3.26 (1H, dd, *J* = 3.4, 10.2 Hz), 3.65 (1H, t, *J* = 10.2 Hz), 3.66 (3H, s), 4.81 (1H, dd, *J* = 3.4, 10.2 Hz), 5.13, 5.22 (2H, ABq, *J* = 12.7 Hz), 7.25–7.44 (5H, m), 7.64 (1H, s); IR (KBr) 3255, 1759, 1707 cm^{-1}; SIMS *m/z* 279 (M^+ + 1), 91 (base). Anal. Calcd for $C_{13}H_{14}N_2O_5$: C, 56.11; H, 5.07; N, 10.07. Found: C, 56.07; H, 5.08; N, 10.13.

Methyl (4*S*)-3-[(Benzyloxy)carbonyl]-1-methyl-2-oxoimidazolidine-4-carboxylate [(*S*)-11]. A mixture of (*S*)-**10** (12.0 g, 43 mmol), K_2CO_3 (11.9 g), and methyl iodide (20.2

(14) Evans, D. A.; Ennis, M. D.; Mathre, D. J. *J. Am. Chem. Soc.* **1982**, *104*, 1737.
(15) Quitt, P.; Hellerbach, J.; Vogler, K. *Helv. Chim. Acta* **1963**, *32*, 327.
(16) For recent review, see: Duthaler, R. O. *Tetrahedron* **1994**, *50*, 1539.
(17) Brooks, B. R.; Bruccoleri, R. E.; Olafson, B. D.; States, D. J.; Swaminathan, S.; Karplus, M. *J. Comput. Chem.* **1983**, *4*, 1887.
(18) van Gunsteren, W. F.; Berendsen, H. J. C. *Mol. Phys.* **1977**, *34*, 1131.

g, 142 mmol) in Me_2CO (400 mL) was stirred at rt for 2 days. The insoluble materials were filtered off, and the filtrate was concentrated in *vacuo*. The residue was dissolved in AcOEt, and the solution was washed with brine, dried over $MgSO_4$, and concentrated in *vacuo*. The resulting residue was chromatographed on silica gel with AcOEt as an eluent to give (*S*)-**11** (9.5 g, 75%) as a colorless oil: $[\alpha]^{25}_D$ −59.9 (*c* 2, MeOH); ^{1}H NMR ($CDCl_3$) δ 2.85 (3H, s), 3.33 (1H, dd, *J* = 3.7, 9.6 Hz), 3.66 (1H, t, *J* = 9.6 Hz), 3.70 (3H, s), 4.69 (1H, dd, *J* = 3.7, 9.6 Hz), 5.22, 5.34 (2H, ABq, *J* = 12.4 Hz), 7.22−7.45 (5H, m); IR (film) 1785, 1752, 1710 cm^{-1}; EIMS *m*/*z* 292 (M^+), 189, 158, 91 (base). Anal. Calcd for $C_{14}H_{16}N_2O_5$: C, 57.53; H, 5.52; N, 9.58. Found: C, 57.29; H, 5.59; N, 9.70.

Methyl (4*S*)-1-Methyl-2-oxoimidazolidine-4-carboxylate [(*S*)-1a]. A mixture of (*S*)-**11** (8.0 g, 27 mmol) in MeOH (200 mL) was hydrogenolyzed in the presence of palladium black (0.1 g) under atmospheric pressure at rt for 3 h. After the catalyst was filtered off, the filtrate was concentrated to dryness in *vacuo*. The crystalline residue was recrystallized from *i*-Pr_2O−AcOEt to afford (*S*)-**1a** (3.9 g, 90%) as colorless prisms: mp 88−90 °C; $[\alpha]^{24}_D$ +26.9 (*c* 1, MeOH); ^{1}H NMR ($CDCl_3$) δ 2.79 (3H, s), 3.55−3.73 (2H, m), 3.79 (3H, s), 4.21 (1H, dd, *J* = 5.2, 8.7 Hz), 5.28 (1H, s); IR (KBr) 3260, 1750, 1715 cm^{-1}; EIMS *m*/*z* 158 (M^+), 115, 99 (base). Anal. Calcd for $C_6H_{10}N_2O_3$: C, 45.57; H, 6.37; N, 17.71. Found: C, 45.63; H, 6.54; N, 17.81.

Preparation of (4*S*)-1-Substituted-3-(2-bromoacyl)-2-oxoimidazolidine-4-carboxylic Acid Esters (4a−f). Compounds **4a,c,d** were synthesized by the procedure previously reported.[1]

Methyl (4*S*)-3-(2-Bromopropionyl)-1-methyl-2-oxoimidazolidine-4-carboxylate (4b). Potassium *tert*-butoxide (2.08 g, 19 mmol) was added portionwise to a solution of (*S*)-**1a** (2.93 g, 19 mmol) in THF (40 mL) at −50 °C. After being stirred at the same temperature for 20 min, 2-bromopropionyl bromide (4.00 g, 19 mmol) was added dropwise to the above mixture. Stirring was continued at −30 °C for 30 min, and then the reaction mixture was poured into a mixture of AcOEt (50 mL), AcOH (1.11 g), and brine (50 mL). The organic phase was separated and washed successively with brine, 5% aqueous K_2CO_3, and brine. The organic layer was dried over $MgSO_4$ and concentrated in *vacuo*. The residue was purified by column chromatography on silica gel with $CHCl_3$−AcOEt (1:1) as an eluent to afford a mixture of diastereomers of **4b** (4.38 g, 81%) as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 1.82 (d, *J* = 6.8 Hz) and 1.84 (d, *J* = 6.8 Hz) (total 3H), 2.91 (s) and 2.92 (s) (total 3H), 3.35−3.48 (1H, m), 3.65-3.87 (1H, m), 3.79 (s) and 3.80 (s) (total 3H), 4.72−4.87 (1H, m), 5.81−6.00 (1H, m); IR (KBr) 1744, 1680 cm^{-1}; EIMS *m*/*z* 294/292 (M^+), 235/233, 213, 159, 99 (base). Anal. Calcd for $C_9H_{13}BrN_2O_4$: C, 36.88; H, 4.47; N, 9.56. Found: C, 36.80; H, 4.50; N, 9.49.

Other compounds **4e** and **4f** were prepared similarly. The yields and the physical data are as follows:

***tert*-Butyl (4*S*)-3-(2-Bromo-4-methylvaleryl)-1-methyl-2-oxoimidazolidine-4-carboxylate (4e)**: yield 78%; colorless oil; ^{1}H NMR ($CDCl_3$) δ 0.85−1.07 (6H, m), 1.47 (s) and 1.49 (s) (total 9H), 1.60−2.10 (3H, m), 2.91 (3H, s), 3.25−3.41 (1H, m), 3.62−3.80 (1H, m), 4.60−4.75 (1H, m), 5.88−6.05 (1H, m); IR (KBr) 1747, 1685 cm^{-1}; SIMS *m*/*z* 379/377 (M^+ + 1), 323/321, 241, 199, 145 (base). Anal. Calcd for $C_{15}H_{25}BrN_2O_4$: C, 47.75; H, 6.68; N, 7.43. Found: C, 47.50; H, 6.73; N, 7.40.

***tert*-Butyl (4*S*)-3-(2-Bromo-4-phenylbutyryl)-1-methyl-2-oxoimidazolidine-4-carboxylate (4f)**: yield 84%; colorless oil; ^{1}H NMR ($CDCl_3$) δ 1.47 (s) and 1.48 (s) (total 9H), 2.20−2.98 (4H, m), 2.90 (s) and 2.91 (s) (total 3H), 3.29−3.42 (1H, m), 3.58−3.80 (1H, m), 4.53−4.74 (1H, m), 5.75−5.93 (1H, m), 7.07−7.36 (5H, m); IR (KBr) 1745, 1710, 1680 cm^{-1}; SIMS *m*/*z* 427/425 (M^+ + 1), 371/369, 289, 199, 145 (base). Anal. Calcd for $C_{19}H_{25}BrN_2O_4$: C, 53.66; H, 5.92; N, 6.59. Found: C, 53.79; H, 5.97; N, 6.49.

Typical Procedure for the Reaction of Bromide 4 with Amine 8. *tert*-Butyl (4*S*)-3-[2-(*N*-Benzylamino)propionyl]-1-methyl-2-oxoimidazolidine-4-carboxylate [(*S,R*)-7a and (*S,S*)-7a]. A mixture of **4a** (1.00 g, 3.0 mmol), benzylamine (0.32 g, 3.0 mmol), and K_2CO_3 (0.41 g) in HMPA (3 mL) was stirred at 25 °C for 14 h. The reaction mixture was diluted with AcOEt and water. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated in *vacuo*. The residue was purified by column chromatography on silica gel eluting with $CHCl_3$−AcOEt (1:2) to give a diastereomeric mixture of **7a** (1.06 g, 98%). The diastereomers were separated by preparative TLC (AcOEt) to afford (*S,R*)-**7a** (R_f 0.52) and (*S,S*)-**7a** (R_f 0.64), each as colorless needles. (*S,R*)-**7a**: mp 62−64 °C (AcOEt/hexane); $[\alpha]^{26}_D$ −33.0 (*c* 1, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.31 (3H, d, *J* = 6.9 Hz), 1.51 (9H, s), 1.91 (1H, br), 2.89 (3H, s), 3.34 (1H, dd, *J* = 4.2, 9.6 Hz), 3.60, 3.77 (2H, ABq, *J* = 12.0 Hz), 3.69 (1H, t, *J* = 9.6 Hz), 4.65 (1H, dd, *J* = 4.2, 9.6 Hz), 4.72 (1H, q, *J* = 6.9 Hz), 7.15−7.41 (5H, m); IR (KBr) 1730, 1718, 1673 cm^{-1}; SIMS *m*/*z* 362 (M^+ + 1), 306, 134 (base), 91. Anal. Calcd for $C_{19}H_{27}N_3O_4$: C, 63.14; H, 7.53; N, 11.63. Found: C, 63.27; H, 7.60; N, 11.67. (*S,S*)-**7a**: mp 84−85 °C (AcOEt/hexane); $[\alpha]^{26}_D$ −78.9 (*c* 1, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.37 (3H, d, *J* = 6.8 Hz), 1.46 (9H, s), 2.12 (1H, s), 2.88 (3H, s), 3.31 (1H, dd, *J* = 4.0, 9.7 Hz), 3.61, 3.73 (2H, ABq, *J* = 13.0 Hz), 3.66 (1H, t, *J* = 9.7 Hz), 4.61 (1H, dd, *J* = 4.0, 9.7 Hz), 4.71 (1H, q, *J* = 6.8 Hz), 7.13−7.37 (5H, m); IR (KBr) 1743, 1682 cm^{-1}; SIMS *m*/*z* 362 (M^+ + 1), 306, 134, 91 (base). Anal. Calcd for $C_{19}H_{27}N_3O_4$: C, 63.14; H, 7.53; N, 11.63. Found: C, 63.40; H, 7.63; N, 11.59.

Physical properties of the new compounds are as follows:

Methyl (4*S*)-3-[(2*R*)-2-(*N*-Benzylamino)propionyl]-1-methyl-2-oxoimidazolidine-4-carboxylate [(*S,R*)-7b]: colorless oil; $[\alpha]^{21}_D$ −20.4 (*c* 1, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.32 (3H, d, *J* = 6.9 Hz), 2.00 (1H, br), 2.89 (3H, s), 3.40 (1H, dd, *J* = 3.9, 9.8 Hz), 3.61, 3.77 (2H, ABq, *J* = 12.4 Hz), 3.72 (1H, t, *J* = 9.8 Hz), 3.82 (3H, s), 4.73 (1H, q, *J* = 6.9 Hz), 4.81 (1H, dd, *J* = 3.9, 9.8 Hz), 7.15−7.40 (5H, m); IR (film) 1740, 1680 cm^{-1}; SIMS *m*/*z* 320 (M^+ + 1, base), 159, 134, 91. Anal. Calcd for $C_{16}H_{21}N_3O_4$: C, 60.18; H, 6.63; N, 13.16. Found: C, 60.11; H, 6.70; N, 13.12.

Methyl (4*S*)-3-[(2*S*)-2-(*N*-Benzylamino)propionyl]-1-methyl-2-oxoimidazolidine-4-carboxylate [(*S,S*)-7b]: colorless oil; $[\alpha]^{25}_D$ −67.6 (*c* 1, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.38 (3H, d, *J* = 6.8 Hz), 2.04 (1H, s), 2.88 (3H, s), 3.37 (1H, dd, *J* = 3.9, 9.8 Hz), 3.57−3.83 (3H, m), 3.78 (3H, s), 4.65−4.82 (2H, m), 7.15−7.40 (5H, m); IR (film) 1739, 1680 cm^{-1}; SIMS *m*/*z* 320 (M^+ + 1, base), 269, 159, 134, 91. Anal. Calcd for $C_{16}H_{21}N_3O_4$: C, 60.18; H, 6.63; N, 13.16. Found: C, 60.39; H, 6.77; N, 13.05.

***tert*-Butyl (4*S*)-1-Benzyl-3-[(2*R*)-2-(*N*-benzylamino)propionyl]-2-oxoimidazolidine-4-carboxylate [(*S,R*)-7c]**: colorless oil; $[\alpha]^{25}_D$ −18.2 (*c* 1, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.35 (3H, d, *J* = 6.9 Hz), 1.44 (9H, s), 2.13 (1H, br), 3.20 (1H, dd, *J* = 3.6, 9.8 Hz), 3.56 (1H, t, *J* = 9.8 Hz), 3.65, 3.80 (2H, ABq, *J* = 12.2 Hz), 4.31, 4.61 (2H, ABq, *J* = 14.3 Hz), 4.62 (1H, dd, *J* = 3.6, 9.8 Hz), 4.80 (1H, q, *J* = 6.9 Hz), 7.15−7.42 (10H, m); IR (film) 1732, 1684 cm^{-1}; SIMS *m*/*z* 438 (M^+ + 1), 382, 134, 91 (base). Anal. Calcd for $C_{25}H_{31}N_3O_4$: C, 68.63; H, 7.14; N, 9.60. Found: C, 68.43; H, 7.29; N, 9.41.

***tert*-Butyl (4*S*)-1-Benzyl-3-[(2*S*)-2-(*N*-benzylamino)propionyl]-2-oxoimidazolidine-4-carboxylate [(*S,S*)-7c]**: colorless oil; $[\alpha]^{25}_D$ −55.8 (*c* 1, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.40 (9H, s), 1.42 (3H, d, *J* = 6.8 Hz), 2.11 (1H, br), 3.18 (1H, dd, *J* = 3.5, 9.8 Hz), 3.54 (1H, t, *J* = 9.8 Hz), 3.66, 3.75 (2H, ABq, *J* = 12.5 Hz), 4.27−4.63 (3H, m), 4.73 (1H, q, *J* = 6.8 Hz), 7.15−7.42 (10H, m); IR (film) 1736, 1684 cm^{-1}; SIMS *m*/*z* 438 (M^+ + 1), 382, 134, 91 (base). Anal. Calcd for $C_{25}H_{31}N_3O_4$: C, 68.63; H, 7.14; N, 9.60. Found: C, 68.34; H, 7.35; N, 9.60.

***tert*-Butyl (4*S*)-3-[(2*R*)-2-(*N*-Benzylamino)butyryl]-1-methyl-2-oxoimidazolidine-4-carboxylate [(*S,R*)-7d]**: colorless needles, mp 82−83 °C (hexane); $[\alpha]^{25}_D$ −28.6 (*c* 1, MeOH); ^{1}H NMR ($CDCl_3$) δ 0.99 (3H, t, *J* = 7.3 Hz), 1.46−1.87 (2H, m), 1.51 (9H, s), 1.98 (1H, br), 2.89 (3H, s), 3.32 (1H, dd, *J* = 4.1, 9.7 Hz), 3.60, 3.79 (2H, ABq, *J* = 12.4 Hz), 3.68 (1H, t, *J* = 9.7 Hz), 4.57−4.67 (2H, m), 7.18−7.39 (5H, m); IR (KBr) 1745, 1731, 1679, 1660 cm^{-1}; SIMS *m*/*z* 376 (M^+ + 1), 320, 148, 91 (base). Anal. Calcd for $C_{20}H_{29}N_3O_4$: C, 63.98; H, 7.78; N, 11.19. Found: C, 64.05; H, 7.75; N, 11.20.

***tert*-Butyl (4*S*)-3-[(2*S*)-2-(*N*-Benzylamino)butyryl]-1-methyl-2-oxoimidazolidine-4-carboxylate [(*S,S*)-7d]**: colorless needles, mp 118−119 °C (hexane); $[\alpha]^{25}_D$ −68.4 (*c* 0.53, MeOH); ^{1}H NMR ($CDCl_3$) δ 1.04 (3H, t, *J* = 7.4 Hz), 1.46 (9H,

s), 1.48–1.92 (3H, m), 2.87 (3H, s), 3.29 (1H, dd, J = 4.2, 9.6 Hz), 3.61, 3.73 (2H, ABq, J = 12.9 Hz), 3.63 (1H, t, J = 9.6 Hz), 4.53–4.60 (2H, m), 7.18–7.34 (5H, m); IR (KBr) 1735, 1729, 1676 cm^{-1}; SIMS m/z 376 (M^+ + 1), 320, 148, 91 (base). Anal. Calcd for $C_{20}H_{29}N_3O_4$: C, 63.98; H, 7.78; N, 11.19. Found: C, 64.20; H, 7.80; N, 11.18.

***tert*-Butyl (4*S*)-3-[(2*R*)-2-(*N*-Benzylamino)-4-methylvaleryl]-1-methyl-2-oxoimidazolidine-4-carboxylate [(*S,R*)-7e]**: colorless oil; $[\alpha]^{25}_D$ −24.0 (c 0.6, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 0.90 (6H, d, J = 6.7 Hz), 1.51 (9H, s), 1.20–2.08 (4H, m), 2.89 (3H, s), 3.31 (1H, dd, J = 4.1, 9.6 Hz), 3.53–3.88 (3H, m), 4.62 (1H, dd, J = 4.1, 10.2 Hz), 4.71 (1H, dd, J = 5.0, 8.9 Hz), 7.13–7.40 (5H, m); IR (film) 1747, 1678 cm^{-1}; SIMS m/z 404 (M^+ + 1), 348, 176, 91 (base). Anal. Calcd for $C_{22}H_{33}N_3O_4$: C, 65.48; H, 8.24; N, 10.41. Found: C, 65.40; H, 8.29; N, 10.33.

***tert*-Butyl (4*S*)-3-[(2*S*)-2-(*N*-Benzylamino)-4-methylvaleryl]-1-methyl-2-oxoimidazolidine-4-carboxylate [(*S,S*)-7e]**: colorless oil; $[\alpha]^{25}_D$ −56.0 (c 0.8, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 0.94 (3H, d, J = 6.7 Hz), 0.95 (3H, d, J = 6.6 Hz), 1.46 (9H, s), 1.22–2.17 (4H, m), 2.87 (3H, s), 3.29 (1H, dd, J = 4.3, 9.6 Hz), 3.54–3.80 (3H, m), 4.56 (1H, dd, J = 4.3, 9.6 Hz), 4.68 (1H, dd, J = 3.9, 10.0 Hz), 7.12–7.40 (5H, m); IR (film) 1741, 1675 cm^{-1}; SIMS m/z 404 (M^+ + 1), 348, 176, 91 (base). Anal. Calcd for $C_{22}H_{33}N_3O_4$: C, 65.48; H, 8.24; N, 10.41. Found: C, 65.20; H, 8.40; N, 10.31.

***tert*-Butyl (4*S*)-3-[(2*R*)-2-(*N*-Benzylamino)-4-phenylbutyryl]-1-methyl-2-oxoimidazolidine-4-carboxylate [(*S,R*)-7f]**: colorless needles, mp 95–97 °C (i-Pr_2O); $[\alpha]^{25}_D$ −39.6 (c 1, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.50 (9H, s), 1.57–2.20 (3H, m), 2.57–3.05 (2H, m), 2.88 (3H, s), 3.29 (1H, dd, J = 4.0, 9.6 Hz), 3.62 (1H, t, J = 9.6 Hz), 3.63, 3.82 (2H, ABq, J = 12.5 Hz), 4.53 (1H, dd, J = 4.0, 9.6 Hz), 4.71 (1H, dd, J = 4.8, 7.9 Hz), 7.05–7.40 (10H, m); IR (KBr) 1754, 1713, 1685 cm^{-1}; SIMS m/z 452 (M^+ + 1), 396, 224, 91 (base). Anal. Calcd for $C_{26}H_{33}N_3O_4$: C, 69.16; H, 7.37; N, 9.31. Found: C, 69.21; H, 7.40; N, 9.43.

***tert*-Butyl (4*S*)-3-[(2*S*)-2-(*N*-Benzylamino)-4-phenylbutyryl]-1-methyl-2-oxoimidazolidine-4-carboxylate [(*S,S*)-7f]**: colorless oil; $[\alpha]^{21}_D$ −52.4 (c 0.5, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.44 (9H, s), 1.66–2.23 (3H, m), 2.63–3.05 (2H, m), 2.87 (3H, s), 3.29 (1H, dd, J = 4.2, 9.6 Hz), 3.64 (1H, t, J = 9.6 Hz), 3.63, 3.76 (2H, ABq, J = 12.9 Hz), 4.58 (1H, dd, J = 4.2, 9.6 Hz), 4.68 (1H, dd, J = 4.3, 8.0 Hz), 7.07–7.43 (10H, m); IR (film) 1742, 1673 cm^{-1}; SIMS m/z 452 (M^+ + 1), 396, 224, 91 (base). Anal. Calcd for $C_{26}H_{33}N_3O_4$: C, 69.16; H, 7.37; N, 9.31. Found: C, 69.05; H, 7.40; N, 9.29.

***tert*-Butyl (4*S*)-3-[(2*R*)-2-[*N*-(Diphenylmethyl)amino]propionyl]-1-methyl-2-oxoimidazolidine-4-carboxylate [(*S,R*)-7g]**: colorless oil; $[\alpha]^{25}_D$ −14.6 (c 1, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.30 (3H, d, J = 6.9 Hz), 1.56 (9H, s), 2.51 (1H, br), 2.80 (3H, s), 3.30 (1H, dd, J = 4.3, 9.6 Hz), 3.63 (1H, t, J = 9.6 Hz), 4.49–4.68 (2H, m), 4.77 (1H, s), 7.06–7.60 (10H, m); IR (KBr) 1746, 1678 cm^{-1}; SIMS m/z 438 (M^+ + 1), 304, 270, 214, 167 (base). Anal. Calcd for $C_{25}H_{31}N_3O_4$: C, 68.63; H, 7.14; N, 9.60. Found: C, 68.60; H, 7.20; N, 9.51.

***tert*-Butyl (4*S*)-3-[(2*S*)-2-[*N*-(Diphenylmethyl)amino]propionyl]-1-methyl-2-oxoimidazolidine-4-carboxylate [(*S,S*)-7g]**: colorless needles, mp 158–160 °C (i-Pr_2O); $[\alpha]^{25}_D$ −80.4 (c 0.5, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.39 (3H, d, J = 6.9 Hz), 1.45 (9H, s), 2.50 (1H, br-s), 2.80 (3H, s), 3.26 (1H, dd, J = 3.9, 9.6 Hz), 3.60 (1H, t, J = 9.6 Hz), 4.53–4.69 (2H, m), 4.76 (1H, s), 7.10–7.45 (10H, m); IR (KBr) 1736, 1677 cm^{-1}; SIMS m/z 438 (M^+ + 1), 380, 304, 270, 214, 167 (base). Anal. Calcd for $C_{25}H_{31}N_3O_4$: C, 68.63; H, 7.14; N, 9.60. Found: C, 68.83; H, 7.19; N, 9.50.

***tert*-Butyl (4*S*)-3-[(2*R*)-2-(*N*-Benzyl-*N*-methylamino)propionyl]-1-methyl-2-oxoimidazolidine-4-carboxylate [(*S,R*)-7h]**: colorless oil; $[\alpha]^{25}_D$ −30.4 (c 1, MeOH); ^{1}H NMR ($CDCl_3$) δ 1.37 (3H, d, J = 7.0 Hz), 1.49 (9H, s), 2.30 (3H, s), 2.89 (3H, s), 3.31 (1H, dd, J = 4.7, 9.6 Hz), 3.63, 3.91 (2H, ABq, J = 13.6 Hz), 3.66 (1H, t, J = 9.6 Hz), 4.64 (1H, dd, J = 4.7, 9.6 Hz), 5.02 (1H, q, J = 7.0 Hz), 7.15–7.40 (5H, m); IR (film) 1740, 1680 cm^{-1}; SIMS m/z 376 (M^+ + 1), 320, 148 (base). Anal. Calcd for $C_{20}H_{29}N_3O_4$: C, 63.98; H, 7.78; N, 11.19. Found: C, 63.80; H, 7.81; N, 11.15.

***tert*-Butyl (4*S*)-3-[(2*S*)-2-(*N*-Benzyl-*N*-methylamino)propionyl]-1-methyl-2-oxoimidazolidine-4-carboxylate [(*S,S*)-7h]**: colorless oil; $[\alpha]^{25}_D$ −88.8 (c 0.32, MeOH); ^{1}H NMR ($CDCl_3$) δ 1.41 (3H, d, J = 7.0 Hz), 1.47 (9H, s), 2.27 (3H, s), 2.89 (3H, s), 3.30 (1H, dd, J = 3.9, 9.6 Hz), 3.66, 3.82 (2H, ABq, J = 13.5 Hz), 3.67 (1H, t, J = 9.6 Hz), 4.64 (1H, dd, J = 3.9, 9.6 Hz), 4.97 (1H, q, J = 7.0 Hz), 7.13–7.40 (5H, m); IR (film) 1739, 1680 cm^{-1}; SIMS m/z 376 (M^+ + 1), 320, 148 (base).

Methyl (2*S*)-2-Aminobutanoate Hydrochloride [(*S*)-14]. Thionyl chloride (5.7 mL, 788 mmol) was added dropwise to MeOH (100 mL) at −20 °C, and stirred for 30 min at the same temperature. (2*S*)-2-Aminobutanoic acid[10] (4.00 g, 39 mmol) was added to the solution and stirred at rt overnight. The solution was concentrated to dryness in *vacuo*. The crystalline residue was triturated with Et_2O and recrystallized from AcOEt–EtOH to afford (*S*)-**14** (5.50 g, 92%) as colorless needles: mp 111–113 °C; $[\alpha]^{26}_D$ +17.0 (c 1, MeOH); ^{1}H NMR ($CDCl_3$) δ 1.12 (3H, t, J = 7.4 Hz), 2.00–2.25 (2H, m), 3.82 (3H, s), 4.14 (1H, t, J = 6.1 Hz), 8.79 (3H, br-s); IR (KBr) 3400, 1746 cm^{-1}; SIMS m/z 118 (M^+ + 1, base). Anal. Calcd for $C_5H_{11}NO_2$·HCl: C, 39.10; H, 7.87; N, 9.12. Found: C, 38.91; H, 7.80; N, 9.00.

Methyl (2*S*)-2-(Benzylamino)butanoate [(*S*)-12]. A solution of (*S*)-**14** (1.50 g, 9.8 mmol) in H_2O was basified with K_2CO_3 and extracted with AcOEt. The extracts were dried over $MgSO_4$ and concentrated under reduced pressure. Sodium triacetoxyborohydride (2.64 g, 12.5 mmol) was added to the solution of the residue, benzaldehyde (0.94 g, 8.9 mmol), and glacial acetic acid (0.53 g, 8.9 mmol) in 1,2-dichloroethane (50 mL), and the reaction mixture was stirred for 1 h at rt. The reaction was quenched with saturated aqueous $NaHCO_3$, and the oily product was extracted with AcOEt. The extracts were washed with brine, dried over $MgSO_4$, and concentrated in *vacuo*. The residue was chromatographed on silica gel eluting with $CHCl_3$–AcOEt (4:1) to give (*S*)-**12** (1.44 g, 78%) as a colorless oil: $[\alpha]^{25}_D$ −42.1 (c 1, MeOH); ^{1}H NMR ($CDCl_3$) δ 0.93 (3H, t, J = 7.4 Hz), 1.55–1.77 (2H, m), 1.78 (1H, br-s), 3.23 (1H, t, J = 6.5 Hz), 3.63, 3.81 (2H, ABq, J = 13.0 Hz), 3.72 (3H, s), 7.15–7.39 (5H, m); IR (KBr) 3320, 1736 cm^{-1}; SIMS m/z 208 (M^+ + 1), 148, 91 (base). Anal. Calcd for $C_{12}H_{17}NO_2$: C, 69.54; H, 8.27; N, 6.76. Found: C, 69.59; H, 8.30; N, 6.70.

Reaction of (*S,R*)-7d with Sodium Methoxide. To a solution of (*S,R*)-**7d** (300 mg, 0.8 mmol) in MeOH (3 mL) was added MeONa (43 mg, 0.8 mmol) under stirring. After stirring was continued for 15 h at rt, the reaction mixture was diluted with AcOEt and water. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated in *vacuo*. The residue was chromatographed on silica gel eluting with $CHCl_3$–AcOEt (4:1) to give (*R*)-**12** (141 mg, 85%) as a colorless oil: $[\alpha]^{25}_D$ +42.4 (c 1, MeOH). The physical data of the product are identical with those of (*S*)-**12**.

Methyl *N*-Benzyl-*N*-methyl-D-alaninate [(*R*)-15]. To a solution of (*S,R*)-**7h** (360 mg, 0.96 mmol) in MeOH (5 mL) was added MeONa (78 mg, 1.44 mmol) under stirring. After stirring was continued for 15 h at rt, the reaction mixture was diluted with AcOEt and water. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated in *vacuo*. The residue was chromatographed on silica gel eluting with hexane–AcOEt (4:1) to give (*R*)-**15** (144 mg, 72%) as a colorless oil: $[\alpha]^{24}_D$ +68.9 (c 1, MeOH); ^{1}H NMR ($CDCl_3$) δ 1.34 (3H, d, J = 7.1 Hz), 2.28 (3H, s), 3.48 (1H, q, J = 7.1 Hz), 3.60, 3.73 (2H, ABq, J = 14.5 Hz), 3.73 (3H, s), 7.18–7.38 (5H, m); IR (KBr) 1736 cm^{-1}; SIMS m/z 208 (M^+ + 1), 148, 91 (base). Anal. Calcd for $C_{12}H_{17}NO_2$: C, 69.54; H, 8.27; N, 6.76. Found: C, 69.59; H, 8.30; N, 6.69.

Methylation of Methyl *N*-Benzyl-D-alaninate [(*R*)-16a]. A mixture of (*R*)-**16a**[9] (270 mg, 1.4 mmol), K_2CO_3 (290 mg), and methyl iodide (595 mg, 4.2 mmol) in DMSO (1 mL) was stirred at rt for 1 h. The reaction mixture was diluted with AcOEt and water. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated in *vacuo*. The residue was chromatographed on silica gel eluting with hexane–AcOEt (4:1) to give (*R*)-**15** (177 mg, 61%): $[\alpha]^{24}_D$ +70.3 (c 1.2, MeOH).

The physical data of the product are identical with those of (*R*)-**15** described above.

(4*S*)-3-[(Benzyloxy)carbonyl]-1-methyl-2-oxoimidazolidine-4-carboxylic Acid [(*S*)-18]. Compound (*S*)-**17**[1] (10.0 g, 30 mmol) was dissolved in 4 N HCl–dioxane solution (50 mL). After being stirred at rt for 6 h, the mixture was evaporated to dryness in *vacuo*. The residue was dissolved in AcOEt and the solution was washed with brine, dried over $MgSO_4$, and concentrated in *vacuo*. The resulting residue was crystallized from AcOEt to give (*S*)-**18** (6.1 g, 73%) as colorless needles: mp 153–155 °C dec.; $[\alpha]^{25}_D$ −55.8 (*c* 1, MeOH); ^{1}H NMR (DMSO-d_6) δ 2.71 (3H, s), 3.35 (1H, dd, J = 3.3, 9.6 Hz), 3.67 (1H, dd, J = 9.6, 10.2 Hz), 4.65 (1H, dd, J = 3.3, 10.2 Hz), 5.19 (2H, s), 7.26–7.43 (5H, m), 13.33 (1H, br); IR (KBr) 3075 (br), 1758 cm^{-1}; SIMS m/z 279 (M^+ + 1), 235, 91 (base). Anal. Calcd for $C_{13}H_{14}N_2O_5$: C, 56.11; H, 5.07; N, 10.07. Found: C, 56.16; H, 4.95; N, 9.81.

(4*S*)-3-[(Benzyloxy)carbonyl]-4-(*tert*-butoxymethyl)-1-methyl-2-oxoimidazolidine [(*S*)-19]. To a solution of (*S*)-**18** (5.0 g, 18 mmol) in THF (50 mL) was added a BH_3–SMe_2 complex (10 M solution) (2.7 mL). The resulting solution was stirred for 2 h at rt and for 2 h under reflux. The solvent was removed on a rotary evaporator, and the resulting white slurry was diluted with water and extracted with AcOEt. The organic layer was dried over $MgSO_4$, concentrated in *vacuo*, and chromatographed on silica gel eluting with $CHCl_3$–MeOH (9:1). The resulting material was dissolved in CH_2Cl_2 (50 mL) and to it were added a drop of H_2SO_4 and isobutene (15 mL) at −30 °C. The resulting solution in the pressure bottle was allowed to stand at rt overnight. After the excess isobutene was volatilized at rt, the solution was washed with saturated aqueous $NaHCO_3$ and brine, dried over $MgSO_4$, and concentrated in *vacuo*. The residue was purified by column chromatography on silica gel with $CHCl_3$–AcOEt (2:1) as an eluent to afford (*S*)-**19** (3.7 g, 64%) as a colorless oil: $[\alpha]^{26}_D$ −59.6 (*c* 1, $CHCl_3$); ^{1}H NMR ($CHCl_3$) δ 1.12 (9H, s), 2.84 (3H, s), 3.25–3.63 (4H, m), 4.12–4.28 (1H, m), 5.23, 5.32 (2H, ABq, J = 12.5 Hz), 7.21–7.49 (5H, m); IR (film) 1775, 1747, 1700 cm^{-1}; SIMS m/z 321 (M^+ + 1), 91 (base).

(4*S*)-4-(*tert*-Butoxymethyl)-1-methyl-2-oxoimidazolidine [(*S*)-20]. A mixture of (*S*)-**19** (3.5 g, 11 mmol) in MeOH (50 mL) was hydrogenolyzed in the presence of 10% palladium on carbon (0.5 g) under atmospheric pressure at rt for 3 h. After the catalyst was filtered off, the filtrate was concentrated to dryness in *vacuo*. The resulting residue was chromatographed on silica gel with AcOEt as an eluent to give (*S*)-**20** (1.9 g, 93%) as a colorless oil: $[\alpha]^{25}_D$ +54.2 (*c* 1, $CHCl_3$); ^{1}H NMR ($CHCl_3$) δ 1.18 (9H, s), 2.77 (3H, s), 3.09 (1H, dd, J = 5.1, 8.9 Hz), 3.32 (2H, d, J = 6.6 Hz), 3.49 (1H, t, J = 8.9 Hz), 3.63–3.85 (1H, m), 5.00 (1H, br-s); IR (film) 3249, 1704 cm^{-1}; SIMS m/z 187 (M^+ + 1), 99 (base). Anal. Calcd for $C_9H_{18}N_2O_2$: C, 58.04; H, 9.74; N, 15.04. Found: C, 57.75; H, 10.00; N, 15.24.

(4*S*)-3-(2-Bromopropionyl)-4-(*tert*-butoxymethyl)-1-methyl-2-oxoimidazolidine [(*S,S*)-21 + (*S,R*)-21]. Potassium *tert*-butoxide (1.45 g, 13 mmol) was added portionwise to a solution of (*S*)-**20** (2.40 g, 13 mmol) in THF (40 mL) at −50 °C. After being stirred at the same temperature for 20 min, 2-bromopropionyl bromide (2.78 g, 13 mmol) was added dropwise to the above mixture. The mixture was stirred at −30 °C for 30 min and then poured into a mixture of AcOEt (50 mL), AcOH (0.77 g), and brine (50 mL) in one portion. The organic layer was separated and washed successively with brine, 5% aqueous K_2CO_3, and brine, dried over $MgSO_4$, and concentrated in *vacuo*. The residue was purified by column chromatography on silica gel with $CHCl_3$–AcOEt (9:1) as an eluent to afford a mixture of diastereomers of **21** (2.90 g, 70%) as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 1.14 (s) and 1.17 (s) (total 9H), 1.80 (d, J = 6.8 Hz) and 1.82 (d, J = 6.8 Hz) (total 3H), 2.89 (s) and 2.90 (s) (total 3H), 3.28–3.64 (4H, m), 4.30-4.51 (1H, m), 5.87–6.03 (1H, m); IR (film) 1736, 1680 cm^{-1}; SIMS m/z 323/321 (M^+ + 1), 267/265, 131, 99, 57 (base).

Reaction of 21 with Benzylamine. A mixture of **21** (1.00 g, 3.1 mmol), benzylamine (0.33 g, 3.1 mmol), and K_2CO_3 (0.43 g) in HMPA (3 mL) was stirred at 25 °C for 14 h. The reaction mixture was diluted with AcOEt and water. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated in *vacuo*. The residue was chromatographed on silica gel eluting with $CHCl_3$–AcOEt (2:1) to give a mixture of (4*S*)-3-[(2*R*)-2-(*N*-benzylamino)propionyl]-4-(*tert*-butoxymethyl)-1-methyl-2-oxoimidazolidine [(*S,R*)-**22**] and (4*S*)-3-[(2*S*)-2-(*N*-benzylamino)propionyl]-4-(*tert*-butoxymethyl)-1-methyl-2-oxoimidazolidine [(*S,S*)-**22**] (1.01 g, 93%). The diastereomers were separated by preparative TLC (AcOEt). (*S,R*)-**22**: colorless oil; $[\alpha]^{26}_D$ −54.6 (*c* 1, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.17 (9H, s), 1.29 (3H, d, J = 6.8 Hz), 1.93 (1H, br-s), 2.87 (3H, s), 3.30–3.79 (6H, m), 4.32–4.48 (1H, m), 4.75 (1H, q, J = 6.8 Hz), 7.16–7.38 (5H, m); IR (film) 3320, 1734, 1675 cm^{-1}; SIMS m/z 348 (M^+ + 1), 134, 91 (base). Anal. Calcd for $C_{19}H_{29}N_3O_3$: C, 65.68; H, 8.41; N, 12.09. Found: C, 65.40; H, 8.55; N, 11.98. (*S,S*)-**22**: colorless oil; $[\alpha]^{26}_D$ −79.4 (*c* 1, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.14 (9H, s), 1.33 (3H, d, J = 6.8 Hz), 2.12 (1H, br-s), 2.86 (3H, s), 3.27–3.80 (6H, m), 4.27–4.41 (1H, m), 4.69 (1H, q, J = 6.8 Hz), 7.16–7.35 (5H, m); IR (film) 3310, 1732, 1665 cm^{-1}; SIMS m/z 348 (M^+ + 1), 134, 91 (base).

Reaction of (*S,R*)-22 with Sodium Methoxide. To a solution of (*S,R*)-**20** (230 mg, 0.66 mmol) in MeOH (5 mL) was added MeONa (36 mg, 0.66 mmol) under stirring. After stirring was continued for 4 h at rt, the reaction mixture was diluted with AcOEt and water. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated in *vacuo*. The residue was chromatographed on silica gel eluting with hexane–AcOEt (2:1) to give (*R*)-**16a** (96 mg, 75%) as a colorless oil: $[\alpha]^{25}_D$ +43.5 (*c* 1.0, MeOH); ^{1}H NMR ($CDCl_3$) δ 1.32 (3H, d, J = 7.0 Hz), 1.73 (1H, s), 3.40 (1H, q, J = 7.0 Hz), 3.66, 3.81 (2H, ABq, J = 13.0 Hz), 3.73 (3H, s), 7.18–7.37 (5H, m); IR (film) 3340, 1737 cm^{-1}; SIMS m/z 194 (M^+ + 1), 171, 157 (base). Anal. Calcd for $C_{11}H_{15}NO_2$: C, 68.37; H, 7.82; N, 7.25. Found: C, 68.11; H, 7.76; N, 7.50.

Reaction of (*S,R*)-7a with Sodium Methoxide. To a solution of (*S,R*)-**7a** (500 mg, 1.4 mmol) in MeOH (5 mL) was added MeONa (75 mg, 1.4 mmol) under stirring. After stirring was continued for 2 h at rt, AcOH (83 mg) was added to the mixture. The solvent was removed in *vacuo*, and the residue was chromatographed on silica gel eluting with $CHCl_3$–MeOH (19:1) to give (*R*)-**16a** (241 mg, 90%, $[\alpha]^{29}_D$ +45.0 (*c* 1.0, MeOH)) and **1a** (157 mg, 72%, $[\alpha]^{24}_D$ 0.0 (*c* 1.0, MeOH)). Their physical data are identical with those of (*R*)-**16a** and (*S*)-**1a** described above.

Reaction of (*S,R*)-7a with Lithium Benzyl Oxide. To a solution of benzyl alcohol (0.60 g, 5.5 mmol) in Et_2O (14 mL) was added *n*-BuLi (1.6 M in hexane) (1.73 mL, 2.8 mmol) at 0 °C under stirring. After stirring was continued for 10 min at the same temperature, (*S,R*)-**7a** (1.00 g, 2.8 mmol) was added to the solution. The resulting solution was stirred at 0 °C for 30 min, and then saturated aqueous NH_4Cl (14 mL) was added to the solution. The organic phase was separated, and the aqueous phase was extracted three times with $CHCl_3$. The combined organic layer was dried over $MgSO_4$ and concentrated in *vacuo*. The residue was chromatographed on silica gel eluting with $CHCl_3$–MeOH (19:1) to give benzyl *N*-benzyl-D-alaninate (*R*)-**16b** (0.65 g, 87%) as a colorless oil and (*S*)-**1b** (0.42 g, 76%, $[\alpha]^{21}_D$ +24.9 (*c* 1.0, MeOH) (lit.[1] $[\alpha]^{23}_D$ +24.9)). (*R*)-**16b**: $[\alpha]^{25}_D$ +40.4 (*c* 1.0, MeOH); ^{1}H NMR ($CDCl_3$) δ 1.33 (3H, d, J = 7.0 Hz), 1.83 (1H, s), 3.44 (1H, q, J = 7.0 Hz), 3.65, 3.80 (2H, ABq, J = 12.8 Hz), 5.17 (2H, s), 7.15–7.43 (10H, m); IR (film) 3330, 1732 cm^{-1}; SIMS m/z 270 (M^+ + 1), 134, 91 (base). Anal. Calcd for $C_{17}H_{19}NO_2$: C, 75.81; H, 7.11; N, 5.20. Found: C, 75.59; H, 7.32; N, 5.43.

***N*-Benzyl-D-alanine [(*R*)-16c].** A mixture of (*R*)-**16b** (0.55 g, 2.0 mmol) in MeOH (10 mL) was hydrogenolyzed in the presence of 10% palladium on carbon (0.05 g) under atmospheric pressure at rt for 20 min. After the catalyst was filtered off, the filtrate was concentrated to dryness in *vacuo*. The crystalline residue was recrystallized from MeOH to afford (*R*)-**16c** (0.31 g, 85%) as colorless needles: mp > 240 °C; $[\alpha]^{25}_D$ −4.0 (*c* 0.9, 6 N HCl) (lit.[15] $[\alpha]^{24}_D$ +3.9 for L-amino acid); ^{1}H

NMR (D_2O) δ 1.51 (3H, d, J = 7.2 Hz), 3.71 (1H, q, J = 7.2 Hz), 4.20, 4.28 (2H, ABq, J = 12.3 Hz), 7.50 (5H, s); IR (KBr) 1577 cm^{-1}; SIMS m/z 180 ($M^+ + 1$), 91 (base). Anal. Calcd for $C_{10}H_{13}NO_2$: C, 67.02; H, 7.31; N, 7.82. Found: C, 67.20; H, 7.44; N, 7.86.

Acknowledgment. We thank Dr. T. Yamazaki, Chief of Protein NMR Section, Department of Applied Physiology, National Institute of Agrobiological Resources, for his valuable suggestion.

Supporting Information Available: Copies of ^1H NMR spectra of compounds lacking analyses, crystal data and structure of (*S,S*)-**4a**, (*S,R*)-**4a**, (*S,R*)-**7f**, and HPLC conditions for **7a-h**, **22** (15 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

JO9511152