Stereoselective Synthesis of *Erythro* β-Substituted Aspartates

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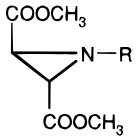
The nucleophilic ring opening of *trans*-aziridine-2,3-dicarboxylate **1** and substituted *N*-acyl-, *N*-(methoxycarbonyl)-, and *N*-(methanesulfonyl)aziridine-2,3-dicarboxylates **2**−**4** allows an easy synthetic approach to β-hydroxy, β-amino, β-(alkylthio), and β-halogenoaspartates **5**−**8**; in this respect, compounds **2**−**4** display higher reactivities. The *erythro* stereochemistry of the synthesized aspartates and the S_N2-like mechanism of the nucleophilic attack were unambiguously identified by the (2*R*,3*S*) X-ray absolute configuration determination of enantiomerically pure β-amino derivative **9**, obtained from (2*R*,3*R*)-**4**, and by its chemical correlation with *meso* α,β-bis[*N*-(methanesulfonyl)amino]succinate (**10**).

Highly stereoselective syntheses of β-substituted aspartates, such as β-hydroxy, β-amino, or β-alkyl derivatives, have long generated considerable interest owing to the occurrence of these compounds as unusual amino acids in microorganisms, as constituents of peptides, and as useful synthetic intermediates of biologically active molecules.[1] Many procedures for synthesis have been proposed in the literature;[1] in particular, it is well-known that aziridinecarboxylates may be useful intermediates for obtaining functionalized amino acids.[2]

In previous papers, we demonstrated that the nucleophilic ring-opening reactions at aziridine-2-carboxylates afforded α- and β-amino acids via an S_N2-like mechanism and nucleophile-dependent regioselectivity.[3] Now we report a stereoselective synthetic approach to β-hydroxy, β-amino, β-(alkylthio), and β-halogenoaspartates through the nucleophilic ring opening of the racemic *trans*-aziridine-2,3-dicarboxylates **1**−**4**. These compounds can be easily resolved in optical antipodes by enzymatic hydrolysis of the ester groups;[4] moreover, their C_2-symmetry obviates nucleophilic attack regiochemistry. In this respect, they represent a convenient synthetic equivalent for the β-cation of either (*R*)- or (*S*)-aspartic acid.[2] The ring-opening reactions were performed both on aziridine **1** and on the corresponding activated compounds **2**−**4**. The latter were expected to be more reactive toward nucleophiles than the corresponding *N*-unsubstituted aziridine **1**, since these derivatives contain a strong electron-withdrawing group on the ring-nitrogen atom, namely acetyl (**2**), methoxycarbonyl (**3**), or methanesulfonyl (**4**).[2]

The *erythro* stereochemistry of the synthesized aspartates **5**−**8** and the S_N2-like mechanism of the nucleophilic attack were unambiguously identified by chemical correlation of an enantiomerically pure sample of *N*-(methanesulfonyl)-β-aminoaspartate **9**, obtained from the nucleophilic ring opening of (2*R*,3*R*)-**4**, with the *meso* α,β-bis[*N*-(methanesulfonyl)amino]succinate and by the (2*R*,3*S*) absolute configuration determination of the same sample **9** by X-ray diffraction analysis.



1-4

	R
1	H
2	$COCH_3$
3	$COOCH_3$
4	SO_2CH_3

Results and Discussion

Synthesis of Racemic Aziridines 1−4. Racemic *trans*-aziridines **1**−**4** were synthesized in high overall yields (80%) as described elsewhere.[4] Aziridine **1** was synthesized by reaction with ammonia from the dimethyl α,β-dibromosuccinate, obtained by bromination of the commercially available dimethyl fumarate. The reaction of **1** in pyridine, with acetic anhydride at 60 °C or with methyl chloroformate at room temperature, afforded **2** and **3**, respectively. Sulfonylation of **1** into **4** was carried out with methanesulfonyl chloride and triethylamine. Analytical and spectroscopic data of compounds **1**−**4** were in close agreement with the structures and indicated the presence of the single *trans* diastereoisomeric form.

Synthesis of β-Substituted Aspartates by Nucleophilic Ring Opening. Racemic aziridines **1**−**4** were subjected to nucleophilic ring opening with Bronsted acids, such as hydrogen chloride, acetic acid, or trifluoroacetic acid, or with nucleophiles such as methanol, α-toluenethiol, sodium azide, or sodium iodide, in the presence of a Lewis acid catalyst. Protonation or Lewis acid coordination to the ring-nitrogen atom were expected further to increase the reactivity of the ring toward nucleophiles.[5] Most of the ring-opening reactions proceeded with high stereoselection to afford only one stereoisomer of the β-substituted aspartates **5**−**8** (Scheme 1).

Products **5**−**8** were identified by their mass spectra, microanalyses, and ^1H NMR data. The results are summarized in Table 1. In particular, aziridines **1**−**4**, upon treatment with dry HCl in CH_2Cl_2 or diethyl ether (Table 1, entries 1, 8, 15, and 22), yielded the correspond-

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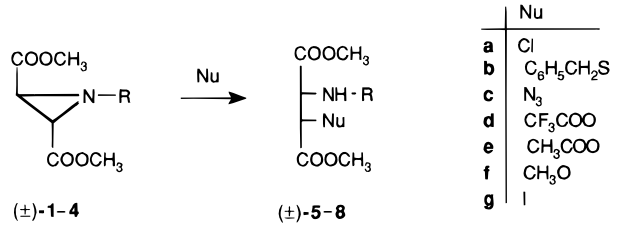
Table 1. β-Substituted Aspartates 5−8 from Nucleophilic Ring-Opening Reactions of Aziridines 1−4

		reaction condns				
entry	aziridine	reagents	time	*T* (°C)	product	yield[a] (%)
1	**1**	HCl/CH_2Cl_2	1 h	20	**5a**	87
2	**1**	$C_6H_5CH_2SH/BF_3/CHCl_3$	5 d	45	**5b**	25
3	**1**	NaN_3/BF_3/DMF	7 d	25		
4	**1**	CF_3COOH	24 h	60	**5d**[b]	64
5	**1**	CH_3COOH	24 h	70		
6	**1**	CH_3OH/BF_3	48 h	60	**5f**	50[c]
7	**1**	$NaI/BF_3/CH_3COCH_3$	2 h	20	*d*	
8	**2**	$HCl/(C_2H_5)_2O$	1 h	20	**6a**	94
9	**2**	$C_6H_5CH_2SH/BF_3/CHCl_3$	3 h	37	**6b**	75
10	**2**	$NaN_3/AlCl_3$/DMF	11 d	20	**6c**[e]	46
11	**2**	CF_3COOH	8 d	20	**1**	70
12	**2**	CH_3COOH	5 d	70	**2**[f]	
13	**2**	CH_3OH/H^+	3 h	20	**1**	90
14	**2**	$NaI/BF_3/CH_3COCH_3$	30 min	20	*d*	
15	**3**	$HCl/(C_2H_5)_2O$	30 min	20	**7a**	80
16	**3**	$C_6H_5CH_2SH/BF_3/CHCl_3$	18 h	20	**7b**	52
17	**3**	NaN_3/BF_3/DMF	24 d	20	**7c**[e]	41
18	**3**	CF_3COOH	5 d	20	**7d**[g]	84
19	**3**	CH_3COOH	6 d	20		
20	**3**	CH_3OH/CH_3O^-	1 h	20	**1**	
21	**3**	$NaI/BF_3/CH_3COCH_3$	2 d	20	*d*	
22	**4**	$HCl/(C_2H_5)_2O$	3 h	20	**8a**	62
23	**4**	HCl/H_2O/DMF	30 min	20	**8a**	82
24	**4**	$C_6H_5CH_2SH/BF_3/CHCl_3$	28 h	20	**8b**	86
25	**4**	NaN_3/BF_3/DMF	30 min	20	**8c**	20
26	**4**	$NaN_3/NR_4HSO_4/H_2O/CHCl_3$	16 h	20	**8c**	60
27	**4**	CF_3COOH	2 d	20		
28	**4**	CH_3COOH	3 d	20		
29	**4**	CH_3OH/CH_3O^-	90 min	20	**4**[f]	
30	**4**	$NaI/CH_3COOH/CH_3COCH_3$	30 min	20	**8g**	75

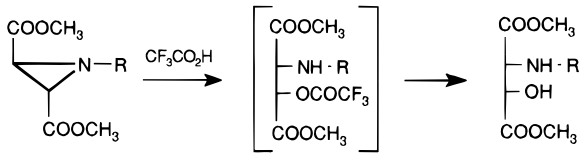
[a] Referred to the products purified by chromatography and/or crystallization. [b] Recovered as *N*-(trifluoroacetyl)-β-hydroxy derivative **11** by trifluoroacyl migration. [c] Gas chromatographic yield. [d] Unsolvable mixture of unknown compounds. [e] *Erythro/threo* mixture. [f] *Cis/trans* mixture. [g] Recovered after purification by chromatography as β-hydroxy derivative **12**.

Scheme 1



1,5 R=H; **2,6** R=$COCH_3$; **3,7** R=$COOCH_3$; **4,8** R=SO_2CH_3

Scheme 2

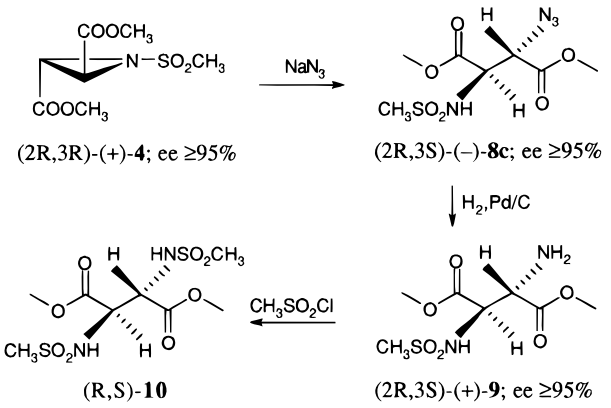


1,5d R=H; **3,7d,12** R=$COOCH_3$; **11** R=$COCF_3$

ing β-chloro aspartates **5a**, **6a**, **7a**, and **8a** in good chemical yields. Aziridine **4** also reacted rapidly and in nearly quantitative yield in DMF with aqueous (37%) HCl (Table 1, entry 23). The reaction of aziridines **1**−**4** with α-toluenethiol in CH_2Cl_2 and in the presence of boron trifluoride ethyl etherate afforded the corresponding β-benzylthioaspartates **5b**, **6b**, **7b**, and **8b**; as expected, activated aziridines **2**−**4** displayed a higher reactivity (Table 1, entries 9, 16, and 24) than unactivated compound **1** (Table 1, entry 2), giving the ring-opening products **6b**, **7b**, and **8b** in higher chemical yields and in shorter reaction times. Aziridine **1** in DMF was essentially inert toward sodium azide in the presence of boron trifluoride ethyl etherate (Table 1, entry 3); aziridines **2** and **3** provided the corresponding β-azidoaspartates **6c** and **7c** in low chemical yield and as a diastereoisomeric mixture (Table 1, entries 10 and 17). Aziridine **4** afforded easier ring opening to produce the β-azido derivative **8c** with sodium azide in a $CHCl_3/H_2O$ solution and in the presence of a phase-transfer catalyst (Table 1, entry 26) with respect to the reaction carried out in DMF and in the presence of boron trifluoride ethyl etherate as the catalyst (Table 1, entry 25).

A further contrast in reactivity between aziridine **4** and aziridines **1**−**3** was provided by the reaction with sodium iodide: only aziridine **4** reacted quickly in acetone and in the presence of acetic acid (Table 1, entry 30) to produce the corresponding dimethyl *N*-(methanesulfonyl)-β-iodoaspartate (**8g**) in good yield. None of the aziridines **1**−**4** underwent methanolysis (Table 1, entries 6, 13, 20, and 29) or acetolysis (Table 1, entries 5, 12, 19, and 28). Attempts to obtain ring opening under strong basic conditions (CH_3O^- in CH_3OH) were unsuccessful: the conversion of *N*-substituted aziridines **2** and **3** into *N*-unsubstituted compound **1** and the *cis/trans* isomerization of aziridine **4** were observed. On the other hand, the reaction with trifluoroacetic acid showed an interesting unexpected reactivity of aziridines **1** and **3**, Scheme 2: by treating aziridine **1** with trifluoroacetic acid at 60 °C for 24 h (Table 1, entry 4), a product was isolated, namely dimethyl *N*-(trifluoroacetyl)-β-hydroxyaspartate (**11**), which was obtained by an initial attack of the trifluoroacetate anion at the C-3 ring-carbon atom, affording **5d**, followed by the trifluoroacyl migration from the oxygen to the nitrogen, probably via a cyclic intermediate.[6] After 5 days at room temperature, trifluoroacetolysis of aziridine **3** (Table 1, entry 18) afforded the

Scheme 3



ring-opening product, dimethyl *N*-(methoxycarbonyl)-*β*-[(trifluoroacetyl)oxy]aspartate (**7d**), as identified by GC/MS spectroscopy. After purification on column chromatography, only the dimethyl *N*-(methoxycarbonyl)-*β*-hydroxyaspartate (**12**) was isolated in high chemical yield.

Aziridine **2**, under the same reaction conditions (Table 1, entry 11), deacylated to afford chiefly aziridine **1**; no reaction was observed for aziridine **4** (Table 1, entry 27).

The results illustrated in Table 1 demonstrate that the nucleophilic ring-opening reactions at the aziridine-2,3-dicarboxylates **1**−**4** provide a useful pathway for a highly diastereoestereoselective synthesis of *β*-substituted aspartates. On the basis of the ^{1}H NMR spectral analysis ($^3J_{\mathrm{H-H}\ erythro} > {}^3J_{\mathrm{H-H}\ threo}$),[7] and bearing in mind that the nucleophilic attack on the aziridine ring was expected to occur with clean inversion,[8] *erythro* stereochemistry was assigned to derivatives **5**−**8**. To verify the mechanism of the ring nucleophilic attack and to assign unequivocally the reaction-product stereochemistry, the derivative **8c**, obtained through the reaction of the optically active aziridine **4** with sodium azide, was correlated with the *meso* compound, dimethyl α,*β*-bis[*N*-(methanesulfonyl)amino]succinate (**10**), Scheme 3.

Chemical Correlations. The chemical correlation, reported in Scheme 3, was carried out using the enantiomerically pure aziridine **4**, whose optical resolution was achieved through enzymatic hydrolysis catalyzed by *Candida antarctica* Lipase (CAL), following the general procedure reported elsewhere.[4] Previous results showed that the enzymatic resolution, catalyzed by *Candida cylindracea* Lipase (CCL), afforded aziridine **4** in low enantiomeric excess (ee).[4] The higher enantioselectivity of CAL allowed optically pure **4** to be obtained simply by crystallizing the enantiomerically enriched sample.

CAL-catalyzed hydrolysis of aziridine **4** was carried out in phosphate buffer (0.1 mol dm^{-3} and NaCl 0.1 mol dm^{-3}; pH 7.5) at 37 °C, with an enzyme/aziridine ratio (w/w) of 1:100. The reaction was stopped after 75 min when conversion reached 60%: under these conditions, enzymatic hydrolysis yielded the unhydrolyzed aziridine **4** and the corresponding *N*-(methanesulfonyl)-2-(methoxycarbonyl)aziridine-3-carboxylic acid as hydrolysis product, both in optically active forms. The dextrorotatory unchanged aziridine **4** was isolated in 50% ee from the reaction mixture by extraction with CH_2Cl_2. The hydrolysis product, recovered from the aqueous phase by acidification with 5% HCl, was treated with diazomethane and yielded the levorotatory aziridine **4** in ee 36%.

Crystallization of crude (+)-**4** from CH_2Cl_2/*n*-pentane afforded the nearly racemic form as the crystalline product and the enantiomerically enriched compound as residue. The ^{1}H NMR spectrum of the residue, recorded in the presence of the chiral shift reagent *d*-Eu(hfc)$_3$, tris[3-(heptafluoropropylhydroxymethylene)-(+)-camphorato]europium(III), indicated that its enantiomeric purity was not less than 95%. Alternatively, optically pure aziridine **4** (ee ≥95%) was obtained from the enzymatic (CCL) resolution of aziridine **2**, followed by deacylation (Table 1, entry 13) to 2,3-bis(methoxycarbonyl)aziridine (**1**) and sulfonylation of the latter. The absolute configuration (2*R*,3*R*) of (+)-**4** was known from the literature.[4]

By treating (2*R*,3*R*)-(+)-**4**, ee ≥95%, with sodium azide in $CHCl_3/H_2O$ and in the presence of the phase-transfer catalyst tetrabutylammonium hydrogen sulfate, the optically active ring-opening product (−)-**8c** was isolated with ee ≥95%, as determined by analysis of the ^{1}H NMR spectrum recorded in the presence of *d*-Eu(hfc)$_3$. Catalytic hydrogenation of *β*-azido derivative (−)-**8c**, in CH_3OH with Pd 10% on carbon as catalyst, afforded dimethyl (+)-*N*-(methanesulfonyl)-*β*-aminoaspartate (**9**) with ee ≥95% evaluated from analysis of the ^{1}H NMR spectrum recorded in the presence of the chiral solvating agent (*R*)-(−)-2,2,2-trifluoro-1-(9-anthryl)ethanol. Treatment of crude *β*-aminoaspartate (+)-**9** with methanesulfonyl chloride and triethylamine yielded symmetrical α,*β*-bis[*N*-(methanesulfonyl)amino]succinate (**10**) as an optically inactive compound ($[\alpha]_D = 0$), indicative of a *meso* form. Chemical correlation of **8c** and **9** with *meso* derivative **10** assigns the *erythro* relative configuration to **8c** and **9**, since reduction and sulfonylation do not involve the chiral centers. Moreover, since the C_2-symmetry of aziridine **4** obviates regiochemistry, compounds **8c**, **9**, and **10** must have the same *R* configuration as aziridine **4** at the chiral carbon atom that bears both the methoxycarbonyl and the methanesulfonyl groups as substituents and the opposite *S* configuration at the chiral carbon atom that meets the nucleophilic attack: we can infer that compounds **8c** and **9** must have the (2*R*,3*S*) configuration at the chiral carbon atoms.

This configurational assignment was unequivocally confirmed by single-crystal X-ray diffraction analysis (Figure 1) of diastereoisomerically and enantiomerically pure (+)-**9**, obtained by crystallization from EtOAc.[9]

Crystal Structure of (+)-9. The molecular structure of **9** is shown in Figure 1, along with the atom numbering scheme and thermal motion ellipsoids. The main result of the structural determination corroborates the experimental evidence of the *erythro* nature of the compound. Furthermore, X-ray analysis allowed unambiguous *R* and *S* absolute configurations to be assigned, respectively, to the C(2) and C(3) chiral centers present in the molecule. The molecule exhibits staggered conformation around the C(2)−C(3) bond with the H atoms in a gauche orientation. The molecular conformation is also staggered around the C(2)−N(1) and C(3)−N(2) bonds. All bond distances and

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(9) The authors have 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, CB2 1EZ, UK.

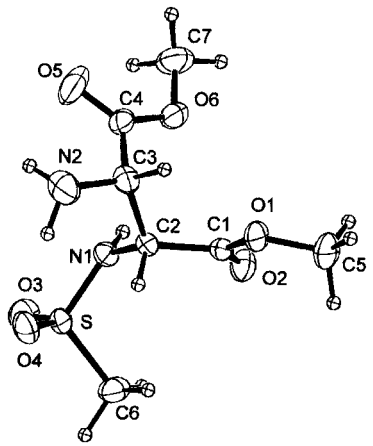

Figure 1. Molecular structure of compound **9** with atom numbering scheme. Thermal ellipsoids for non-H atoms enclose 40% probability.

angles are typical.[10] The molecular packing shows some rather unexpected features. There is only one unique hydrogen bond that ties the molecules into helicoidal chains along the *b* cell axis. Such an interaction involves the NH group as proton donor and the NH_2 function as hydrogen bond acceptor. This is somewhat surprising since the molecule contains four negatively charged carboxylic or sulfonylic oxygen atoms, very often acting as proton acceptors in hydrogen bonding. Nevertheless, these oxygens are involved in a large number (16 less than 3.60 Å) of even extremely short O···O, O···N and O···C van der Waals contacts. The shortest one is an O(1)···O(4) separation of 3.121(5) Å. It is likely that these interactions could play an important role not only in determining the molecular packing but also in determining the conformation of the molecule.

Conclusion. The results reported in Table 1 show that nucleophilic ring opening of aziridines **1**−**4** allows an easy synthetic approach to β-substituted aspartates, and that *N*-substituted aziridines **2**−**4** generally display higher reactivity.

Chemical correlation of optically active nucleophilic ring-opening product **8c** with *meso* α,β-bis[*N*-(methane sulfonyl)amino]succinate (**10**) indicates the *erythro* stereochemistry of the β-substituted aspartate. X-ray diffraction analysis of an enantiomerically pure sample of dimethyl (+)-*N*-(methanesulfonyl)-β-aminoaspartate (**9**), obtained by reduction of optically pure **8c**, shows an overall configuration inversion at the chiral carbon atom that meets the nucleophilic attack, proving that a clean S_N2 ring-opening mechanism takes place, as observed for the parent aziridinemonocarboxylates.[3a]

These results and the ^{1}H NMR spectral analysis of compounds **5**−**8** indicate that the *erythro* relative configuration can legitimately be extended to all of them.

Experimental Section

General Methods. The instrumentations have already been described.[3,4] Optical rotations were measured at 20 °C. ^{1}H NMR spectra were recorded in $CDCl_3$ solution if not otherwise stated. Coupling constants (*J*) are reported in Hz. Enantiomeric purities (ee's) were evaluated from the ^{1}H NMR spectra recorded in $CDCl_3$ and in the presence of the chiral lanthanide shift reagent *d*-Eu(hfc)$_3$, tris[3-(heptafluoropropylhydroxymethylene)-(+)-camphorato]europium(III) or of the chiral solvating agent (*R*)-(−)-2,2,2-trifluoro-1-(9-anthryl)-ethanol: accuracy was within ±2% (±5% for ee values ≥90%).[11] Chromatographic purification of the compounds was performed on silica gel (Φ 0.05−0.20). Eu(hfc)$_3$ and (*R*)-(−)-2,2,2-trifluoro-1-(9-anthryl)ethanol were purchased from Ega-Chemie and used without purification. The enzymes *Candida cylindracea* Lipase and *Candida antarctica* Lipase were purchased from Fluka and used without purification. Racemic aziridines **1**, **2**, and **4** were synthesized as described in the literature.[4] Aziridine **3** was synthesized as follows:

Dimethyl *N*-(Methoxycarbonyl)aziridine-2,3-dicarboxylate (3). A solution of methyl chloroformate (0.35 g, 3.7 mmol) in $CHCl_3$ (1 mL) was added dropwise to a pyridine solution (5 mL) of **1** (0.30 g, 1.9 mmol) cooled at −10 °C. The mixture was stirred at −10 °C for 1 h and then evaporated to give a residue that was taken up in CH_2Cl_2. The CH_2Cl_2 solution (20 mL) was washed with HCl (5 mL, 5%) and water, dried (Na_2SO_4), filtered, and evaporated to give a residue that was purified by column chromatography (ethyl ether/light petroleum 1:1) to give 327 mg (80%) of aziridine **3**. Crystallization from ethyl ether/*n*-pentane 2:1 yielded pure **3**: mp 65−66 °C; ^{1}H NMR δ 3.4 (s, 2H), 3.76 (s, 3H), 3.80 (s, 6H); EI-MS *m*/*z* 217 (M^+), 186, 173, 158, 114, 103, 99, 59 (base peak). Anal. Calcd for $C_8H_{11}NO_6$: C, 44.24; H, 5.10; N, 6.45. Found: C, 44.17; H, 5.08; N, 6.42.

Reaction of Aziridines 1−4 with HCl. General Procedure. Anhydrous HCl was gently bubbled for 10 min at −5 °C into a solution of the aziridine (1 mmol) in ethyl ether or CH_2Cl_2 (20 mL). The cooling bath was removed and the reaction mixture stirred vigorously at rt until TLC analysis showed that the aziridine had disappeared. After the removal of the solvent *in vacuo*, the residue was purified by column chromatography and crystallization.

Dimethyl β-Chloroaspartate (5a). After 1 h at rt, evaporation of the solvent from the reaction mixture of aziridine **1** afforded **5a** (87%) as a hygroscopic hydrochloride salt: mp 88−89 °C; ^{1}H NMR (DMSO-d_6) δ 3.84 (s, 3H), 3.89 (s, 3H), 5.03 (d, *J* = 2.7, 1H), 5.72 (d, *J* = 2.7, 1H), 9.31 (br, 3H); EI-MS *m*/*z* 196 ($[M + 1]^+$), 164, 159, 138, 136 (base peak), 104, 88, 77, 59, 42. Anal. Calcd for $C_6H_{10}ClNO_4 \cdot HCl \cdot H_2O$: C, 28.81; H, 5.65; N, 5.6. Found: C, 28.91; H, 5.64; N, 5.58.

Dimethyl *N*-Acetyl-β-chloroaspartate (6a). After 1 h at rt, treatment of aziridine **2** in ethyl ether with anhydrous HCl yielded an oily residue that was purified by column chromatography (CH_2Cl_2/ethyl ether 8:2); **6a** was obtained (94%) as a solid: mp 75−77 °C (from CH_2Cl_2/*n*-pentane); ^{1}H NMR δ 2.11 (s, 3H), 3.77 (s, 3H), 3.85 (s, 3H), 4.9 (d, *J* = 3.5, 1H), 5.41 (dd, *J* = 3.5, 8.3, 1H), 6.5 (d, *J* = 8.3, 1H); EI-MS *m*/*z* 239 (M^+), 237, 202, 180, 178, 136 (base peak), 130, 88, 59, 57. Anal. Calcd for $C_8H_{12}ClNO_5$: C, 40.43; H, 5.09; N, 5.89. Found: C, 40.55; H, 5.11; N, 5.91.

Dimethyl *N*-(Methoxycarbonyl)-β-chloroaspartate (7a). After 30 min at rt, removal of the solvent from the reaction mixture of aziridine **3** in ethyl ether afforded **7a** as a solid residue (98%) that was crystallized from CH_2Cl_2/*n*-pentane: mp 94−96 °C (80%); ^{1}H NMR δ 3.74 (s, 3H), 3.77 (s, 3H), 3.84 (s, 3H), 4.88 (d, *J* = 2.8, 1H), 5.12 (dd, *J* = 2.8, 8.4, 1H), 5.71 (d, *J* = 8.4, 1H); EI-MS *m*/*z* 255 (M^+), 253, 218, 196, 194 (base peak), 146, 59, 42. Anal. Calcd for $C_8H_{12}ClNO_6$: C, 37.88; H, 4.77; N, 5.52. Found: C, 37.77; H, 4.75; N, 5.5.

Dimethyl *N*-(Methanesulfonyl)-β-chloroaspartate (8a). After 3 h at rt, the reaction mixture of aziridine **4** in ethyl ether was evaporated to yield **8a** (62%) as a solid: mp 77−78 °C (from CH_2Cl_2/*n*-pentane); ^{1}H NMR δ 3.10 (s, 3H), 3.83 (s, 3H), 3.84 (s, 3H), 4.78 (dd, *J* = 3.6, 9.6, 1H), 4.92 (d, *J* = 3.6, 1H), 5.61 (d, *J* = 9.6, 1H); EI-MS *m*/*z* 273 (M^+), 237, 214 (base peak), 182, 166, 136, 108, 95, 88, 79, 59. Anal. Calcd for $C_7H_{12}ClNO_6S$: C, 30.72; H, 4.42; N, 5.12; S, 11.71. Found: C, 30.74; H, 4.40; N, 5.10; S, 11.68.

Compound **8a** was also prepared by reaction of aziridine **4** (0.5 mmol) in DMF (3.5 mL) with 36% aqueous HCl (0.35 mL). The reaction mixture was stirred vigorously for 30 min at rt.

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Removal of the solvent *in vacuo* and purification by chromatography (EtOAc/*n*-hexane 8:2) of the residue gave **8a** (82%).

Reaction of Aziridines 1−4 with α-Toluenethiol. General Procedure. Boron trifluoride ethyl etherate (1.4 mmol) was gradually added to a solution of the aziridine (1.4 mmol) and α-toluenethiol (2.8 mmol) in anhydrous $CHCl_3$ (12 mL) at rt. The reaction was stopped when TLC analysis showed that no aziridine was present. The organic solution was washed with saturated aqueous $NaHCO_3$ and evaporated to give a residue that was purified by chromatography and crystallization.

Dimethyl *β*-Benzylthioaspartate (5b). The reaction mixture of aziridine **1** was stirred at 45 °C for 5 days. Evaporation of the washed organic solution afforded a crude reaction product that was purified by chromatography (EtOAc/*n*-hexane 6:4) to yield **5b** (25%) as a solid: mp 55−58 °C (from anhydrous ethyl ether); ^{1}H NMR δ 1.65 (br, 2H), 3.56 (d, J = 7.2, 1H), 3.7 (s, 3H), 3.73 (s, 3H), 3.73 (d, J = 7.2, 1H), 3.87 (s, 2H), 7.2−7.4 (m, 5H); EI-MS m/z 284 ([M + 1]$^+$), 283, 224, 196, 161, 123, 102, 91 (base peak), 88, 70, 65. Anal. Calcd for $C_{13}H_{17}NO_4S$: C, 55.11; H, 6.05; N, 4.94; S, 11.31. Found: C, 54.90; H, 6.07; N, 4.92; S, 11.28.

Dimethyl *N*-Acetyl-*β*-benzylthioaspartate (6b). After 3 h at 37 °C, the reaction with aziridine **2** was stopped and the organic solution washed and evaporated to give a residue that was purified by chromatography (CH_2Cl_2/ethyl ether 8:2). Pure **6b** (75%) was obtained as a solid: mp 119−121 °C; ^{1}H NMR δ 2.05 (s, 3H), 3.69 (s, 3H), 3.74 (s, 3H), 3.82 (d, J = 4.4, 1H), 3.89 (d, J = 12, 1H), 3.91 (d, J = 12, 1H), 5.09 (dd, J = 4.4, 9.6, 1H), 6.54 (d, J = 9.6, 1H), 7.2−7.4 (m, 5H); EI-MS m/z 325 (M$^+$), 266, 234, 203, 160, 143, 102, 91 (base peak), 88. Anal. Calcd for $C_{15}H_{19}NO_5S$: C, 55.38; H, 5.89; N, 4.31; S, 9.85. Found: C, 55.43; H, 5.91; N, 4.33; S, 9.87.

Dimethyl *N*-(Methoxycarbonyl)-*β*-benzylthioaspartate (7b). After 18 h at rt, evaporation of the washed organic solution of aziridine **3** reaction afforded a residue that was purified by chromatography (ethyl ether/light petroleum 1:1), yielding **7b** (52%) as a solid: mp 91−93 °C; ^{1}H NMR δ 3.69 (s, 3H), 3.71 (s, 3H), 3.73 (s, 3H), 3.82 (d, J = 4.3, 1H), 3.89 (d, J = 13.4, 1H), 3.92 (d, J = 13.4, 1H), 4.73 (dd, J = 4.3, 10, 1H), 5.79 (d, J = 10, 1H), 7.2−7.4 (m, 5H); EI-MS m/z 341 (M$^+$), 310, 281, 266, 250, 234, 219, 187, 159, 146, 128, 91 (base peak), 59. Anal. Calcd for $C_{15}H_{19}NO_6S$: C, 52.78; H, 5.61; N, 4.10; S, 9.39. Found: C, 52.92; H, 5.63; N, 4.08; S, 9.36.

Dimethyl *N*-(Methanesulfonyl)-*β*-benzylthioaspartate (8b). After 28 h at rt, the reaction mixture of aziridine **4** was diluted with $CHCl_3$ and the organic solution washed and evaporated. The residue was purified by chromatography twice (first with EtOAc/*n*-hexane 1:1 and then with toluene/EtOAc/acetone 8:2:1) to obtain **8b** (86%) as a solid: mp 118−119 °C (from CH_2Cl_2/*n*-pentane); ^{1}H NMR δ 3.08 (s, 3H), 3.76 (s, 6H), 3.80 (d, J = 4.6, 1H), 3.95 (d, J = 13.2, 1H), 3.97 (d, J = 13.2, 1H), 4.39 (dd, J = 4.6, 10.1, 1H), 5.56 (d, J = 10.1, 1H), 7.2−7.4 (m, 5H); EI-MS m/z 361 (M$^+$), 266, 239, 207, 196, 160, 123, 91 (base peak), 88, 65. Anal. Calcd for $C_{14}H_{19}NO_6S_2$: C, 46.52; H, 5.30; N, 3.88; S, 17.74. Found: C, 46.65; H, 5.32; N, 3.90; S, 17.69.

Reaction of Aziridines 1−4 with NaN_3. General Procedure. Boron trifluoride ethyl etherate (1.2 mmol) or $AlCl_3$ (1.2 mmol, for aziridine **2**) was gradually added to a solution of aziridine (1.0 mmol) and NaN_3 (3.0 mmol) in anhydrous DMF (8 mL) at rt. The reaction mixture was stirred for the time and the temperature shown in Table 1. After removal of the solvent, the residue was taken up in $CHCl_3$; the organic solution was washed with water and evaporated. The crude reaction product was purified by column chromatography and crystallization. No reaction was observed for aziridine **1**.

Dimethyl *N*-Acetyl-*β*-azidoaspartate (6c). Purification of the reaction residue of aziridine **2** by chromatography (CH_2Cl_2/ethyl ether 8:2) afforded a mixture of the two diastereoisomers *erythro*/*threo* in an overall ratio 7:3 of **6c** (46%). All attempts at isomer chromatographic separation failed. From analysis of the ^{1}H NMR and mass spectroscopies of the mixture, *erythro* **6c** (predominant isomer) showed: ^{1}H NMR δ 2.1 (s, 3H), 3.78 (s, 3H), 3.87 (s, 3H), 4.6 (d, J = 3.2, 1H), 5.24 (dd, J = 3.2, 7.6, 1H), 6.35 (d, J = 7.6, 1H). Minor *threo* isomer: ^{1}H NMR δ 2.05 (s, 3H), 3.83 (s, 3H), 3.84 (s, 3H), 4.66 (d, J = 2.4, 1H), 5.22 (dd, J = 2.4, 8.6, 1H), 6.1 (d, J = 8.6, 1H). Both isomers showed identical mass fragmentation, as follows: EI-MS m/z 216 ([M − N_2]$^+$), 201, 185, 174, 130, 114, 88 (base peak), 59, 43.

Dimethyl *N*-(Methoxycarbonyl)-*β*-azidoaspartate (7c). Both the *erythro* and *threo* stereoisomers **7c** were recovered in a ratio of 1.5:1 and in 41% chemical yield by chromatographic purification (ethyl ether/light petroleum 1:1) of the reaction residue of aziridine **3**. *erythro*-**7c**: ^{1}H NMR δ 3.74 (s, 3H), 3.77 (s, 3H), 3.86 (s, 3H), 4.55 (d, J = 2.9, 1H), 4.98 (dd, J = 2.9, 7.6, 1H), 5.56 (d, J = 7.6, 1H). *threo*-**7c**: ^{1}H NMR δ 3.69 (s, 3H), 3.82 (s, 3H), 3.84 (s, 3H), 4.65 (d, J = 2.7, 1H), 4.94 (dd, J = 2.7, 8.1, 1H), 5.37 (d, J = 8.1, 1H). For both isomers GC/MS spectroscopy showed the following fragmentation: EI-MS m/z ([M − N_2]$^+$), 201, 200, 173, 146 (base peak), 115, 59, 42.

Dimethyl *N*-(Methanesulfonyl)-*β*-azidoaspartate (8c). Purification by chromatography (EtOAc/*n*-hexane 7:3) of the reaction residue of aziridine **4** yielded **8c** (20%): mp 85−87 °C (from ethyl ether/*n*-pentane); ^{1}H NMR δ 3.07 (s, 3H), 3.81 (s, 3H), 3.86 (s, 3H), 4.6 (d, J = 3.2, 1H), 4.66 (dd, J = 3.2, 8.9, 1H), 5.42 (d, J = 8.9, 1H); EI-MS m/z ([M + 1]$^+$), 237, 221, 166, 134, 106, 88 (base peak), 79, 59. Anal. Calcd for $C_7H_{12}N_4O_6S$: C, 30.00; H, 4.32; N, 19.99; S, 11.44. Found: C, 30.10; H, 4.33; N, 20.00; S, 11.47.

Compound **8c** was also prepared by reaction of aziridine **4** (0.4 mmol) with NaN_3 (1.6 mmol) in $CHCl_3$ (5 mL) and water (5 mL) and in the presence of phase-transfer catalyst tetrabutylammonium bisulfate (0.07 mmol). The reaction mixture was stirred at rt for 16 h, the organic solution separated, and the aqueous phase extracted with CH_2Cl_2. Evaporation of the combined organic extracts afforded an oily residue as a mixture of the *erythro* and *threo* diastereomers, together with the elimination product in the ratio 8:1:1, respectively, that was purified by chromatography to give pure *erythro* **8c** in 60% chemical yield.

Reaction of Aziridines 1−4 with Trifluoroacetic Acid. General Procedure. A solution of the aziridine (0.4 mmol) in CF_3COOH (2 mL) was stirred for the time and at the temperature indicated in Table 1. The reaction mixture, concentrated *in vacuo*, yielded a residue that was analyzed by ^{1}H NMR and mass spectroscopies. The crude reaction product from aziridine **2** consisted largely of aziridine **1** (70%) together with a trace of the ring-opening product **6d**. Aziridine **4** was recovered as unchanged product. The reaction residues from aziridines **1** and **3** were purified by column chromatography to obtain the corresponding ring-opening derivatives **11** and **12**.

Dimethyl *N*-(Trifluoroacetyl)-*β*-hydroxyaspartate (11). Purification by chromatography (CH_2Cl_2/ethyl ether/CH_3OH 16:4:1) of aziridine **1** reaction residue afforded the derivative **11** (64%): mp 54−57 °C; ^{1}H NMR δ 3.25 (d, J = 4.6, 1H), 3.78 (s, 3H), 3.89 (s, 3H), 4.49 (dd, J = 2.5, 4.6, 1H), 5.12 (dd, J = 2.5, 8.3, 1H), 7.19 (br, 1H); EI-MS m/z 274 ([M + 1]$^+$), 214, 185, 182, 154, 153, 126, 125, 101, 90 (base peak), 86, 69, 59. Anal. Calcd for $C_8H_{10}NO_6F_3$: C, 35.17; H, 3.69; N, 5.13. Found: C, 35.28; H, 3.71; N, 5.11.

Dimethyl *N*-(Methoxycarbonyl)-*β*-hydroxyaspartate (12). Purification by chromatography of aziridine **3** reaction residue (CH_2Cl_2/ethyl ether/CH_3OH 16:4:1) afforded the derivative **12** (84%): ^{1}H NMR δ 3.35 (br, 1H), 3.65 (s, 3H), 3.67 (s, 3H), 3.78 (s, 3H), 4.45 (d, J = 2.2, 1H), 4.81 (dd, J = 2.2, 7.0, 1H), 5.62 (d, J = 7.0, 1H); EI-MS m/z 236 ([M + 1]$^+$), 204, 176, 147, 146 (base peak), 144, 115, 103, 88, 59. Before chromatography the residue showed EI-MS m/z 300 ([M − CH_3O]$^+$), 272, 240 (base peak), 217, 208, 196, 186, 158, 146, 100, 69, 59, 42, consistent with the structure of the derivative dimethyl *N*-(methoxycarbonyl)-*β*-[(trifluoroacetyl)oxy]aspartate (**7d**).

Acetolysis of Aziridines 1−4 with CH_3COOH. General Procedure. A solution of aziridine (0.5 mmol) in CH_3COOH (5 mL) was stirred for the time and at the temperature reported in Table 1. After concentration of the reaction mixture *in vacuo*, the residue was taken up in CH_2Cl_2; the organic solution was then washed with saturated aqueous

$NaHCO_3$ and water and evaporated to give a residue that was analyzed by ^1H NMR and mass spectroscopies. Aziridines **1**, **3**, and **4** were recovered unchanged, whereas *cis*/*trans* isomerization of aziridine **2** was observed.

Methanolysis of Aziridines 1−4 with CH_3OH. General Procedure. A solution of aziridine (0.4 mmol) in CH_3OH (2 mL) was treated with boron trifluoride ethyl etherate (0.8 mmol) or H_2SO_4 96% (0.9 mmol) and stirred for the time and at the temperature indicated in Table 1. After concentration of the reaction mixture, the residue was dissolved in CH_2Cl_2; evaporation of the washed (saturated $NaHCO_3$ and water) organic solution yielded the corresponding *N*-unsubstituted aziridine **1** from aziridine **2** and **3** reactions. Aziridine **1** afforded impure dimethyl β-methoxyaspartate (**5f**) identified by GC/MS spectroscopy: EI-MS *m*/*z* 191 (M^+), 132, 104 (base peak), 88, 72, 44, 32. Analogous treatment of aziridines **2** and **3** with 1.5 M CH_3ONa in anhydrous CH_3OH resulted in the yield of aziridine **1**; aziridine **4** was recovered unchanged from the reaction in the presence of acids, while *cis*/*trans* isomerization was observed with CH_3ONa in CH_3OH.

Reaction of Aziridines 1−4 with NaI in Acetone. General Procedure. NaI (1.00 mmol) and boron trifluoride ethyl etherate (0.65 mmol) were stirred into a solution of aziridine (0.50 mmol) in acetone (5 mL) at −10 °C. The reaction was allowed to warm to rt, stirring for the time indicated in Table 1. The solvent was removed *in vacuo* and the residue taken up in CH_2Cl_2; evaporation of the washed (water) organic phase afforded a crude reaction product that was analyzed by ^1H NMR and GC/MS spectroscopies. From the reaction of aziridines **1**−**3** the crude product appeared as an unsolvable mixture of unknown compounds. The crude reaction product from aziridine **4** was purified by chromatography (CH_2Cl_2/ethyl ether 4:1) to yield pure **8g** (75%).

Dimethyl *N*-(Methanesulfonyl)-β-iodoaspartate (8g): mp 113−115 °C (from ethyl ether/*n*-pentane); ^1H NMR δ 3.12 (s, 3H), 3.77 (s, 3H), 3.81 (s, 3H), 4.42 (dd, *J* = 4.6, 10.5, 1H), 5.09 (d, *J* = 4.6, 1H), 5.74 (d, *J* = 10.5, 1H); EI-MS *m*/*z* 365 (M^+), 306 (base peak), 274, 179, 148, 101, 79, 59. Anal. Calcd for $C_7H_{12}NIO_6S$: C, 23.03; H, 3.31; N, 3.84; S, 8.78. Found: C, 23.10; H, 3.30; N, 3.85; S, 8.80.

Resolution of Aziridine 4 through Enzyme-Catalyzed Hydrolysis. The procedure is typical:[4] the enzyme *C. antarctica* Lipase (5 mg) was added under vigorous stirring at 37 °C to a solution of racemic aziridine **4** (500 mg) in 0.1 M potassium phosphate buffer (30 mL; pH 7.5 and containing NaCl 0.1 M). Hydrolysis was followed by GC and stopped after 75 min at 60% conversion. The reaction mixture was extracted with CH_2Cl_2, and the organic extracts were washed with water and evaporated. The residue, unchanged aziridine **4** (220 mg), $[\alpha]_D$ +23.9 (*c* 1.15, $CHCl_3$), ee 50%, afforded the nearly racemic derivative, as the main product, by crystallization from CH_2Cl_2/*n*-pentane. Column chromatography (CH_2Cl_2/ethyl ether 9:1) of the crystallization residue afforded (+)-**4** (22%, referred to racemic **4**) with $[\alpha]_D$ +43.2 (*c* 0.96, $CHCl_3$), ee ≥95%, mp 57−60 °C whose absolute configuration (2*R*,3*R*) was known from the literature.[4] The enzymatic hydrolysis product, *N*-(methanesulfonyl)aziridine-2,3-dicarboxylic acid monomethyl ester, was recovered from the aqueous reaction mixture phase by acidification with 5% HCl followed by evaporation *in vacuo*. The residue, taken up with CH_2Cl_2, was treated with diazomethane. After evaporation of the solvent, purification by chromatography of the crude product gave (−)-**4** (250 mg), $[\alpha]_D$ −17.1 (*c* 1, $CHCl_3$), ee 36%. Enantiomeric excesses were calculated from the ^1H NMR spectra recorded in $CDCl_3$ in the presence of the chiral lanthanide shift reagent *d*-Eu(hfc)$_3$. Alternatively, optically pure aziridine **4** was obtained from the enzymatic resolution of aziridine **2**, *N*-acetyl-2,3-bis(methoxycarbonyl)aziridine, followed by deacylation to 2,3-bis(methoxycarbonyl)aziridine (**1**) and sulfonylation of the latter. Aziridine **2** was resolved by enzymatic hydrolysis catalyzed by *C. cylindracea* Lipase:[4] the unchanged aziridine (2*R*,3*R*)-(−)-**2** (30%), $[\alpha]_D$ −56.4 (*c* 1.4, $CHCl_3$), ee ≥95%, and the enantiomer, hydrolysis product, (2*S*,3*S*)-(+)-**2** (45%), $[\alpha]_D$ +33.4 (*c* 0.6, $CHCl_3$), ee 60%, were obtained. Aziridine (2*R*,3*R*)-(−)-**2**, ee ≥95% (1 mmol), in CH_3OH solution (10 mL) was treated with 96% H_2SO_4 (2 mmol) at 0 °C under stirring. After 3 h at rt the reaction mixture was poured into saturated aqueous Na_2CO_3 (50 mL). Extractions with ethyl ether and evaporation of the combined organic phases afforded an oily residue that was purified by column chromatography (CH_2Cl_2/ethyl ether 8:2) to obtain pure (2*R*,3*R*)-(−)-2,3-bis(methoxycarbonyl)aziridine (**1**) (90%), $[\alpha]_D$ −167.0 (*c* 0.66, $CHCl_3$), ee ≥95% evaluated from the ^1H NMR spectrum recorded in the presence of (*R*)-(−)-2,2,2-trifluoro-1-(9-anthryl)ethanol. Sulfonylation[4] of **1** with methanesulfonyl chloride in CH_2Cl_2 at −10 °C, in the presence of triethylamine and a few crystals of DMAP, afforded (2*R*,3*R*)-(+)-**4** (77%), $[\alpha]_D$ +44.0 (*c* 1.4, $CHCl_3$), ee ≥95%, mp 50−53 °C.

(2*R*,3*S*)-(−)-Dimethyl *N*-(Methanesulfonyl)-β-azidoaspartate (8c). Following the procedure described for the corresponding racemic derivative, pure (−)-**8c** was obtained by the treatment of a solution of (2*R*,3*R*)-(+)-**4**, ee ≥95%, in $CHCl_3$ and water with NaN_3 in the presence of phase-transfer catalyst tetrabutylammonium bisulfate. The crude reaction product (60%), (2*R*,3*S*)-(−)-**8c**, showed $[\alpha]_D$ −87.1 (*c* 1.01, $CHCl_3$), ee ≥95% (from the ^1H NMR spectrum in the presence of the *d*-Eu(hfc)$_3$), mp 60−64 °C (from ethyl ether/*n*-pentane).

(2*R*,3*S*)-(+)-Dimethyl *N*-(Methanesulfonyl)-β-aminoaspartate (9). A solution of (2*R*,3*S*)-(−)-**8c**, ee ≥95% (0.6 mmol), in CH_3OH (6 mL) was stirred at rt with Pd 10% on carbon, as a catalyst, under 1 atm of H_2 until TLC analysis (EtOAc/*n*-hexane 1:1) showed that no azide remained. After 2 h, the catalyst was removed by filtration and the solution concentrated *in vacuo*. The identity of the reaction product (50%) was confirmed by ^1H NMR and mass spectroscopies. Crystallization from EtOAc afforded pure crystals of **9**: $[\alpha]_D$ +24.6 (*c* 1.14, CH_3OH), ee ≥95% (from the ^1H NMR spectrum in the presence of (*R*)-(−)-2,2,2-trifluoro-1-(9-anthryl)ethanol); mp 105−107 °C; ^1H NMR δ 1.75 (br, 2H), 3.08 (s, 3H), 3.80 (s, 3H), 3.81 (s, 3H), 4.00 (d, *J* = 3.6, 1H), 4.57 (d, *J* = 3.6, 1H), 5.55 (br, 1H); EI-MS *m*/*z* 255 ($[M + 1]^+$), 195, 175, 163, 116, 89, 88 (base peak), 57. Anal. Calcd for $C_7H_{14}N_2O_6S$: C, 33.07; H, 5.51; N, 11.02; S, 12.59. Found: C, 32.95; H, 5.53; N, 11.06; S, 12.53. Racemic **9**, obtained by analogous treatment, gave mp 81−84 °C (from ethyl ether).

(*R*,*S*)-Dimethyl α,β-Bis[*N*-(Methanesulfonyl)amino]-succinate (10). Anhydrous triethylamine (0.4 mmol), a few crystals of DMAP, and methanesulfonyl chloride (0.3 mmol) were added dropwise to a solution of (2*R*,3*S*)-(+)-**9**, ee ≥95% (0.2 mmol), in anhydrous THF (30 mL) cooled at 0 °C. After 2 h at rt, the mixture was evaporated and the residue taken up in water (2 mL). Filtration afforded pure **10**, as insoluble precipitate, optically inactive: mp 174−176 °C; ^1H NMR (DMSO-d_6) δ 2.99 (s, 6H), 3.70 (s, 6H), 4.49 (m, *J* = 9.2, 2H), 7.87 (m, *J* = 9.2, 2H); EI-MS *m*/*z* 333 ($[M + 1]^+$), 273, 241, 194, 167, 166, 134, 115, 88 (base peak), 79, 55. Anal. Calcd for $C_8H_{16}N_2O_8S_2$: C, 28.92; H, 4.80; N, 8.40; S, 19.28. Found: C, 29.02; H, 4.82; N, 8.37; S, 19.32.

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Supporting Information Available: Tables of crystal data and structure refinements, final fractional coordinates and equivalent isotropic thermal parameters, bond distances and angles, anisotropic displacement parameters, torsion angles, hydrogen bonding, shortest intermolecular contacts, and a stereoview of the molecular packing (6 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.

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