A Facile Synthesis of Enantiopure 2-Aziridinesulfinimines and Their Highly Diastereoselective Reactions with Phosphite Anions

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Two novel enantiopure 1-benzyl-2-aziridinesulfinimines bearing a chiral group on both sides of the carbon−nitrogen double bond were synthesized from the condensation of racemic 1-benzyl-2-aziridinecarboxaldehyde and enantiopure *p*-toluenesulfinamide. The addition reaction with phosphite anion followed by the ring-opening reaction with thiophenol provided chiral α,*β*-diamino-phosphonic acid derivatives. The addition reactions showed the operation of a double-stereodifferentiation effect. The possible transition states of the reaction were proposed, and high diastereoselectivities of the addition reactions of phosphite anions to both aziridinesulfinimines were realized in the presence or absence of zinc bromide.

Introduction

Both imines[1] and aziridines[2] are compounds of undoubted synthetic interest in organic chemistry, and their transformations have been well documented. Although the chemistry of 2-aziridinealdehydes[3] and 2-aziridineketones[4] has been studied, considerably less attention has been paid to the corresponding 2-aziridineimine despite the fact that two transformable functional groups are contained in these molecules. To the best of our knowledge, the only report concerning 2-aziridineimine is the synthesis and reduction of 1-*tert*-butyl-aziridinyl phenyl ketimine.[4c] Perhaps this is due to the stability as well as the synthetic difficulty, especially the stereospecific synthesis of enantiopure 2-aziridineimines. The racemic 1-benzyl-2-aziridinecarboxaldehyde **1**[3a] can be easily prepared in three steps in 65% overall yield from methyl acrylate on a large scale, while the synthesis of enantiopure 1-benzyl-2-aziridinecarboxaldehydes is not so convenient. (*S*)-1-Benzyl-2-aziridinecarboxaldehyde **4**[3b] is provided in only 14% overall yield from L-serine in six steps. In addition, the manipulations are very harsh, especially the ring-closing step, which needs 26.2 g of Ph_3P, 33.2 g of CBr_4, 32 mL of Et_3N, 150 mL of CH_2Cl_2, and 50 mL of $CHCl_3$ to afford 2.66 g of methyl (−)-(*S*)-1-benzylaziridine-2-carboxylate. Thus, obtaining stable, optically active 2-aziridineimines is a great challenge.

In the course of studies on the transformations of imines and aziridines,[5] we were interested in the 2-aziridineimines. Now we would like to disclose our results on the synthesis of enantiopure 2-aziridinesulfinimines and their highly diastereoselective reactions with phosphite anions to provide (2-aziridinyl)-α-aminophosphonic acid derivatives, from which chiral α,*β*-diamino-phosphonic acid derivatives are also prepared by ring-opening reaction of the aziridine ring.

Results and Discussions

Treatment of the racemic 1-benzyl-2-aziridinecarboxaldehyde **1**[3a] with commercially available (*S*)-(+)-*p*-toluenesulfinamide **2** in the presence of 5 equiv of $Ti(OEt)_4$ in CH_2Cl_2 for 10 h gave rise to the corresponding 1-benzyl-2-aziridinesulfinimine, which is easily separated by flash chromatography to afford the two diastereoisomeres **3a** and **3b** in 38 and 40% yields, respectively (Scheme 1). The sulfinyl group was chosen as the chiral auxiliary because sulfinimines, including enolizable ones, are very stable. The N-sulfinyl group in sulfinimines is an excellent auxiliary that activates the C=N bond for nucleophilic addition, exerts a powerful stereodirecting effect, and is easily deprotected in the product.[6,7]

To determine the absolute configurations of these two 2-aziridinesulfinimines, optically pure (*S*)-1-benzyl-2-

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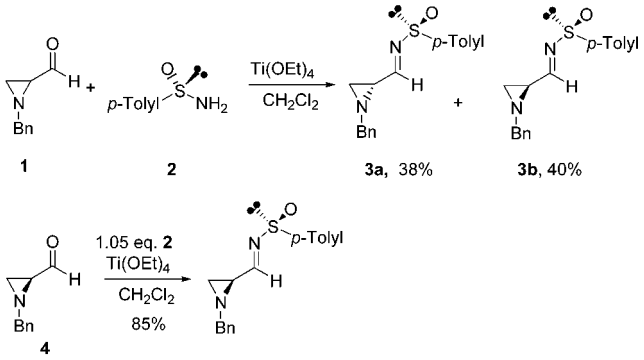
Scheme 1



aziridine carboxaldehyde **4** was synthesized from L-serine.[3b] After the same condensing manipulation of (*S*)-1-benzyl-2-aziridine carboxaldehyde **4** and (*S*)-(+)-*p*-toluenesulfinamide **2**, (2*S*,s*S*)-1-benzyl-2-aziridinesulfinimine was obtained in 85% yield. By comparison of the optical rotations and ^{1}H NMR spectra, we confirmed that the absolute configuration of **3a** is (2*R*,s*S*) and that of **3b** is (2*S*,s*S*). The structure of two 1-benzyl-2-aziridinesulfinimines shows that two chiral centers are present on both sides of the carbon−nitrogen double bond.

Fiaud and Kagan[8] reported the first asymmetric addition of organometallic reagents to enantiomerically pure α-imino ester bearing two chiral auxiliaries, *N*-α-methylbenzyl on one side of the C=N bond and menthyl on the other side, and showed that the menthyl ester moiety was the major stereochemical determinant, as replacement of the *N*-(*S*)-α-methylbenzyl substituent with the corresponding (*R*)-isomer had little effect on reaction diastereoselectivity (40 vs 41% de by using ^{n}Pr$_2$Cd). During the course of our research, Davis reported the asymmetric Strecker reaction of the *β*-hydroxyl sulfinimines,[9] the results of which suggest the operation of a double-stereodifferentiation effect where the chirality of the resident hydroxyl moiety influences the asymmetric induction. To evaluate the uses of aziridinesulfinimines **3a** and **3b**[5] and the stereochemistry course of their reaction, addition reactions of phosphine anion with **3a** and **3b** were chosen.[10]

The additions of phosphite anions to the 2-aziridinesulfinimines **3a** and **3b** were performed at −78 °C in THF. Quenching with a saturated solution of ammonium chloride at −78 °C afforded almost quantitative yields of the oily products, which were pure enough by TLC, ^{1}H NMR, ^{31}P NMR and elemental analysis (Scheme 2). The results are listed in Table 1. From the ^{31}P NMR of the crude products, the diastereoselectivity for the addition of lithium phosphite to the (2*S*,s*S*)-aziridinesulfinimine **3b** was much better than that to the (2*R*,s*S*)-aziridinesulfinimine **3a (**entries 1 vs 3 and entries 5 vs 6, Table 1). According to the report of Evans,[10a] the diastereoselectivities for the addition of sodium phosphites to the phenylsulfinimines were better than those of lithium phosphites. But this is not the case for 2-aziridinesulfinimines: when the lithium bis(*N*,*N*-diethylamino) phosphite was changed to sodium bis(*N*,*N*-diethylamino) phosphite, the diastereoselectivities were far worse. For **3b**, the de was 56% (entry 4, Table 1), while >98% de was given for lithium phosphite (entry 3); for **3a**, the de was only 24% (entry 2, Table 1), but 68% de was provided for lithium phosphite (entry 1, Table 1).

Scheme 2

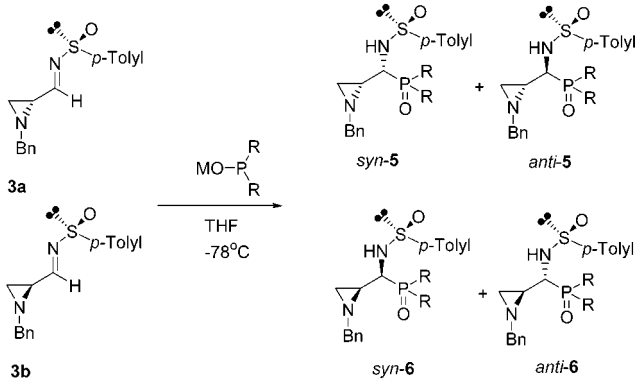


Table 1. Diastereoselective Addition of Phosphite Anions to Enantiopure 2-Aziridinesulfinimines

entry	imine	R	M	yield (%)[a]	syn:anti[b]
1	**3a**	NEt_2	Li	96	84:16
2	**3a**	NEt_2	Na	92	62:38
3	**3b**	NEt_2	Li	94	<1:99
4	**3b**	NEt_2	Na	93	22:78
5	**3a**	OMe	Li	95	85:15
6	**3b**	OMe	Li	94	<1:99

[a] Isolated yield. [b] Diastereoselectivity was determined by ^{31}P NMR.

The stereochemistry of products was determined by ^{1}H NMR. According to the literature,[11] the vicinal coupling constants between the methine proton at the amino-bearing carbon and the proton attached to the carbon of the aziridine ring were always larger for the syn isomers than that for the anti isomer. The reaction of **3a** gives the syn isomer as the major product, while in the reaction of **3b**, the anti isomer is predominant; however, the configuration of the newly formed chiral carbon center of major products for both reactions is (*R*). These results also suggested the operation of a double-stereodifferentiation effect, but the chirality of the sulfinyl group dominated the asymmetric induction.[9]

According to the different results of the addition of lithium phosphite and sodium phosphite, the transition states were proposed (Scheme 3).

Because the lithium cation has a strong ability to coordinate with nitrogen, when 2-aziridinesulfinimine **3a** or **3b** was added to the solution of the lithium phosphite, a five-membered ring complex might be formed as the intermediate. For the (2*S*,s*S*)-2-aziridinesulfinimine **3b**, the phosphite group in such an intermediate would be at the suitable position for the attack to the imino group through a "monomolecular model" and the anti product is provided (model 1), while the formation of the syn product occurs through the attack of phosphite in an unfavorable "bimolecular model" (model 2). For (2*R*,s*S*)-2-aziridinesulfinimine **3a**, the addition of the phosphite of the complex had a potentially steric hindrance between the bulky R group and the oxygen atom of the sulfinyl

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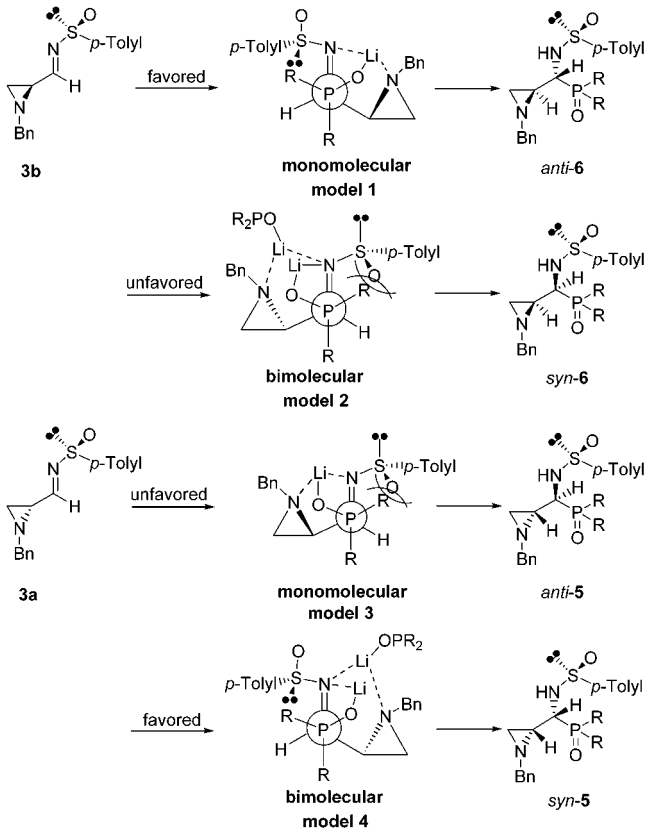
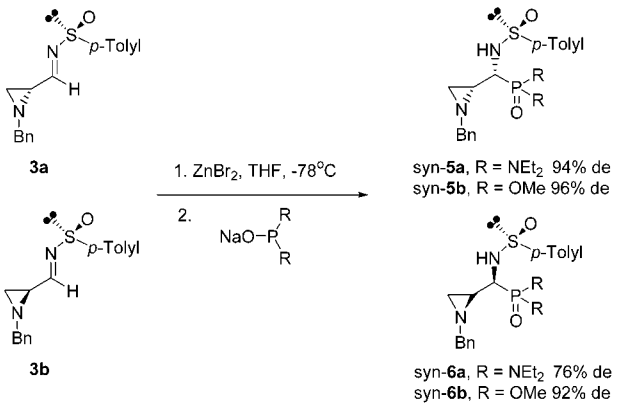
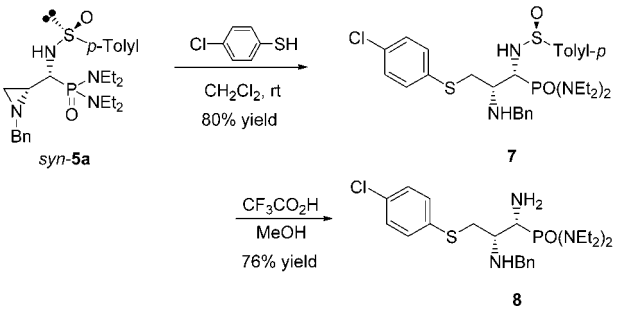
Scheme 3



Scheme 4



Scheme 5



group (model 3). So another phosphite would attack the imino group to form the syn product through a so-called bimolecular model (model 4).

The ability of a sodium cation to coordinate nitrogen is much weaker than that of a lithium cation, so the diastereoselectivity of the addition of sodium phosphite was much worse than that of lithium phosphite.

If the proposed transition states were reasonable, then when a Lewis acid with a stronger ability to coordinate nitrogen is added to the solution of 2-aziridinesulfinimine in advance, a five-membered ring complex would be formed; then, the addition of phosphite anion would follow model 2 or 4 and the syn product would be obtained.

When $ZnBr_2$ was used as the additive, the addition of sodium phosphite to (2*R*,s*S*)-2-aziridinesulfinimine **3a** afforded the syn product with better diastereoselectivity than that of the addition without $ZnBr_2$ (Scheme 4). The addition to the (2*S*,s*S*)-2-aziridinesulfinimine **3b** also afforded the syn product, contrary to the anti product from the addition without $ZnBr_2$. If $CuBr_2$ was used instead of $ZnBr_2$, then reaction of **3a** with $NaOP(OMe)_2$ gave syn-**5b** as the major product in 96% de also. These results confirmed our proposal.

α-Amino phosphonic acids, the phosphorus analogues of α-amino carboxylic acids, exhibit a large spectrum of biological activities: enzyme inhibition, plant growth regulation, and herbicidal, antibacterial, neurological, and anticancer activities.[12] As a consequence, a number of asymmetric syntheses have been devised during the past two decades. There have been very few reports about the synthesis and biological studies of α,*β*-diamino phosphonic acid, though the α,*β*-diamino acids[13] have been investigated widely in both their biologic activities and their preparation.

The addition of phosphite anions to the enantiopure 2-aziridinesulfinimines gave α-amino-2-aziridinemethanphosphonates, which are a kind of α,*β*-diamino phosphonates and also the intermediates for the preparation of a variety of α,*β*-diamino phosphonates by ring opening of the aziridine with various nucleophiles. To show this, the ring-opening reaction of *syn*-**5a** with 4-chlorothiophenol was carried out and the corresponding product, α-(*N*-sulfinylamino)-*β*-benzylamino phosphate **7** was obtained in 80% yield (Scheme 5). The N-sulfinyl group was removed according to the literature procedure to afford α,*β*-diamino phosphonate **8** in 76% yield.[14] ^{1}H NMR showed that two amino groups of which were at the syn position, which was confirmed by single-crystal X-ray analysis of **7**.

In conclusion, we have developed a convenient and efficient procedure to enantiopure 2-aziridinesulfinimines and showed their usefulness in organic synthesis. With the understanding of the transition state of the reaction, high diastereoselectivities of the addition reactions of phosphite anions to both aziridinesulfinimines were achieved by using different reaction conditions. Investigations on the biological activities of α,*β*-diamino phosphonate derivatives and further applications of 2-aziridinesulfinimines are under way.

Experimental Section

General Procedures. ^{1}H NMR spectra were recorded at 400 MHz, and the chemical shifts were referenced to $CHCl_3$ (δ 7.27) in $CDCl_3$. ^{31}P NMR spectra were recorded at 162 MHz,

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and the chemical shifts were referenced to external 85% H_3PO_4. Optical rotations were measured using a polarimeter with a thermally jacketed 10 cm cell at 25 °C (concentrations (*c*) are given in g/100 mL). IR spectra were recorded neat, and measured in cm^{-1}

All reactions were performed under a dry argon atmosphere. The commercially available reagents were used without further purification. CH_2Cl_2 was distilled from calcium hydride; THF was freshly distilled under nitrogen from a purple solution of sodium and benzophenone. Compounds **1**, **2**, and **4** were synthesized according to literature procedures.[3a,b,6a]

1-Benzyl-2-aziridinesulfinimines (3a and 3b). To a solution of 1-benzyl-2-aziridinecarboxaldehyde **1** (483 mg, 3 mmol) and (*S*)-(+)-*p*-toluenesulfinamide (488 mg, 3.2 mmol) in CH_2Cl_2 (30 mL) was added $Ti(OEt)_4$ (3.2 mL, 3.4222 mg, 15 mmol), and the mixture was refluxed for 10 h and monitored by TLC. After the completion of the refluxing, the reaction was quenched at 0 °C by addition of H_2O (30 mL). The solution was filtered through Celite, and the filter cake was washed with CH_2Cl_2 (3 × 20 mL). The aqueous phase was washed with 30 mL of CH_2Cl_2, and the combined organic portions were dried over Na_2SO_4, concentrated, and purified by column chromatography over silica gel (4% ^{i}PrOH in petroleum ether) to give 340.1 mg (38% yield) of (2*R*,s*S*)-1-benzyl-2-aziridinesulfinimine **3a** and 356.8 mg (40% yield) of (2*S*,s*S*)-1-benzyl-2-aziridinesulfinimine **3b**.

(2*R*,s*S*)-1-Benzyl-2-aziridinesulfinimine 3a: $[\alpha]_D^{20}$ +473.3 (*c* 1.09, $CHCl_3$); IR (neat) 1615, 1090 cm^{-1}; EI-MS *m*/*z* (%) 299 (M + 1, 0.31), 91 (100); ^{1}H NMR ($CDCl_3$/TMS, 300MH_Z) δ 1.88 (d, J = 6.5 Hz, 1 H), 2.17 (d, J = 3.0 Hz, 1 H), 2.40 (S, 3 H), 2.45−2.51 (m, 1 H), 3.56 (S, 2 H), 7.26−7.37 (m, 7 H), 7.55 (d, J = 8.2 Hz, 2 H), 7.70 (d, J = 7.5 Hz, 1 H). Anal. Calcd for $C_{17}H_{18}N_2OS$: C, 68.43; H, 6.08; N, 9.39. Found: C, 68.09; H, 5.97; N, 9.32.

(2*S*,s*S*)-1-Benzyl-2-aziridinesulfinimine 3b: $[\alpha]_D^{20}$ +316.2 (*c* 1.73, $CHCl_3$); IR (neat) 1620, 1096 cm^{-1}; EI-MS *m*/*z* (%) 299 (M + 1, 2.9), 91 (100); ^{1}H NMR ($CDCl_3$/TMS, 300MH_Z) δ 1.92 (d, J = 6.5 Hz, 1 H), 2.25 (d, J = 3.0 Hz, 1 H), 2.41 (S, 3 H), 2.45−2.49 (m, 1 H), 3.45, 3.63 (AB, d = 13.5 Hz, each 1 H), 7.25−7.33 (m, 7 H), 7.54 (d, J = 8.2 Hz, 2H), 7.77 (d, J = 7.4 Hz, 1 H). Anal. Calcd for $C_{17}H_{18}N_2OS$: C, 68.43; H, 6.08; N, 9.39. Found: C, 68.29; H, 6.15; N, 9.11.

Typical Procedure for the Addition of Phosphite Anions to 1-Benzyl-2-aziridinesulfinimines. To a solution of phosphite (0.2 mmol) in THF (3 mL) at −78 °C was added a solution of LiHMDS (0.2 mL, 1.0 M in THF, 0.2 mmol) dropwise via syringe, and the reaction mixture was stirred for 15 min at −78 °C. At this stage, a solution 2-aziridinesulfinimine (58.6 mg, 0.2 mmol) dissolved in 1 mL of anhydrous THF was added dropwise. After the reaction was completed (monitored by TLC), the reaction was quenched with a saturated solution of NH_4Cl (1 mL) and extracted with ether (20 mL × 2). The organic phase was dried over Na_2SO_4 and concentrated in a vacuum to afford an oily material, which was pure by TLC, ^{1}H NMR, ^{31}P NMR, and elemental analysis. ^{31}P NMR was used to determine the diastereoselectivity.

(a) Addition of lithium bis(*N*,*N*-diethylamino) phosphite to (2*R*,s*S*)-1-benzyl-2-aziridinesulfinimine **3a** afforded **5a** (94.1 mg, 96% yield). ^{31}P NMR indicated that **5a** was a mixture of diastereoisomers *syn*-**5a** and *anti*-**5a** in a ratio of 84:16.

(b) Addition of sodium bis(*N*,*N*-diethylamino) phosphite to (2*R*,s*S*)-1-benzyl-2-aziridinesulfinimine **3a** afforded **5a** (90.2 mg, 92% yield). ^{31}P NMR indicated that **5a** was a mixture of diastereoisomers *syn*-**5a** and *anti*-**5a** in a ratio of 62:38.

(c) Addition of sodium bis(*N*,*N*-diethylamino) phosphite to (2*R*,s*S*)-1-benzyl-2-aziridinesulfinimine **3a** in the presence of $ZnBr_2$ (45 mg, 0.2 mmol) afforded **5a** (92.1 mg, 94% yield). ^{31}P NMR indicated that **5a** was a mixture of diastereoisomers *syn*-**5a** and *anti*-**5a** in a ratio of 97:3.

(d) Addition of lithium bis(*N*,*N*-diethylamino) phosphite to (2*S*,s*S*)-1-benzyl-2-aziridinesulfinimine **3b** afforded **6a** (92.1 mg, 94% yield). ^{31}P NMR indicated that **6a** was a mixture of diastereoisomers *syn*-**6a** and *anti*-**6a** in a ratio of <1:99.

(e) Addition of sodium bis(*N*,*N*-diethylamino) phosphite to (2*R*,s*S*)-1-benzyl-2-aziridinesulfinimine **3b** afforded **6a** (91.1 mg, 93% yield). ^{31}P NMR indicated that **6a** was a mixture of diastereoisomers *syn*-**6a** and *anti*-**6a** in a ratio of 22:78.

(f) Addition of sodium bis(*N*,*N*-diethylamino) phosphite to (2*R*,s*S*)-1-benzyl-2-aziridinesulfinimine **3b** in the presence of $ZnBr_2$ (45 mg, 0.2 mmol) afforded **6a** (88.2 mg, 90% yield). ^{31}P NMR indicated that **6a** was a mixture of diastereoisomers *syn*-**6a** and *anti*-**6a** in a ratio of 88:12.

(g) Addition of lithium dimethyl phosphite to (2*R*,s*S*)-1-benzyl-2-aziridinesulfinimine **3a** afforded **5b** (77.5 mg, 95% yield). ^{31}P NMR indicated that **5b** was a mixture of diastereoisomers *syn*-**5b** and *anti*-**5b** in a ratio of 85:15.

(h) Addition of sodium dimethyl phosphite to (2*R*,s*S*)-1-benzyl-2-aziridinesulfinimine **3a** in the presence of $ZnBr_2$ (45 mg, 0.2 mmol) afforded **5b** (67.7 mg, 83% yield). ^{31}P NMR indicated that **5b** was a mixture of diastereoisomers *syn*-**5b** and *anti*-**5b** in a ratio of 98:2.

(i) Addition of sodium dimethyl phosphite to (2*R*,s*S*)-1-benzyl-2-aziridinesulfinimine **3a** in the presence of $CuBr_2$ (44 mg, 0.2 mmol) afforded **5b** (66.1 mg, 81% yield). ^{31}P NMR indicated that **5b** was a mixture of t wo diastereoisomers *syn*-**5b** and *anti*-**5b** in a ratio of 98:2.

(j) Addition of lithium dimethyl phosphite to (2*S*,s*S*)-1-benzyl-2-aziridinesulfinimine **3b** afforded **6b** (76.7 mg, 94% yield). ^{31}P NMR indicated that **6b** was a mixture of diastereoisomers *syn*-**6b** and *anti*-**6b** in a ratio of <1:99.

(k) Addition of sodium dimethyl phosphite to (2*R*,s*S*)-1-benzyl-2-aziridinesulfinimine **3b** in the presence of $ZnBr_2$ (45 mg, 0.2 mmol) afforded **6b** (66.9 mg, 82% yield). ^{31}P NMR indicated that **6b** was a mixture of diastereoisomers *syn*-**6b** and *anti*-**6b** in a ratio of 96:4.

(1*R*,2*R*,s*S*)-1,2-Diamino Phosphoramide (*syn*-5a): $[\alpha]_D^{20}$ +182.4 (*c* 1.10, $CHCl_3$);^{31}P NMR (161.9 Hz) δ 32.206 ppm; IR (neat) 3031, 1214, 1020 cm^{-1}; EI-MS *m*/*z* (%) 491 (M + 1, 16), 91 (100); ^{1}H NMR ($CDCl_3$−D_2O, 300 MHz) δ 1.12 (t, J = 7.1 Hz, 6 H), 1.17 (t, J = 7.2 Hz, 6 H), 1.31 (d, J = 5.4 Hz, 1 H), 1.81 (d, J = 3.1 Hz, 1 H), 1.91−1.96 (m, 1 H), 2.38 (s, 3 H), 2.76 (d, J = 13.4 Hz, 1 H), 3.05−3.23 (m, 8 H), 3.52 (dd, J_{PH^a} = 11.1 Hz, $J_{H^aH^b}$ = 8.1 Hz, 1 H, H^a), 4.14 (d, J = 13.4 Hz, 1 H), 7.21−7.33 (m, 7 H), 7.60 (d, J = 8.2 Hz, 2 H). Anal. Calcd for $C_{25}H_{39}N_4O_2PS$: C, 61.20; H, 8.01; N, 11.42. Found: C, 60.99; H, 7.78; N, 11.56.

(1*S*,2*R*,s*S*)-1,2-Diamino Phosphoramide (*anti*-5a): $[\alpha]_D^{20}$ +51.7 (*c* 0.96, $CHCl_3$); ^{31}P NMR (161.9 Hz) δ 31.712 ppm; IR (neat) 2974, 1216, 1023, 1020 cm^{-1}. EI-MS *m*/*z* (%) 491 (M + 1, 13), 91 (100); ^{1}H NMR ($CDCl_3$−D_2O, 300 MHz) δ 1.07−1.12 (m, 12 H), 1.56 (d, J = 6.3 Hz, 1 H), 1.98−2.10 (m, 2 H), 2.40 (s, 3 H), 2.93−3.19 (m, 9 H), 3.60 (dd, J_{PH^a} = 12.8 Hz, $J_{H^aH^b}$ = 7.7 Hz, 1 H, H^a), 3.96 (d, J = 13.0 Hz, 1 H), 7.32−7.50 (m, 9 H). Anal. Calcd for $C_{25}H_{39}N_4O_2PS$: C, 61.20; H, 8.01; N, 11.42. Found: C, 60.83; H, 7.80; N, 11.17.

(1*S*,2*S*,s*S*)-1,2-Diamino Phosphoramide (*syn*-6a): $[\alpha]_D^{20}$ +24.9 (*c* 0.86, $CHCl_3$); ^{31}P NMR (161.9 Hz) δ 32.055 ppm; IR (neat) 2972, 1215, 1020 cm^{-1}; EI-MS *m*/*z* (%) 491 (M + 1, 6), 91 (100); ^{1}H NMR ($CDCl_3$−D_2O, 300 MHz) δ 1.06−1.16 (m, 12 H), 1.53 (d, J = 5.4 Hz, 1 H), 1.96−2.00 (m, 2 H), 2.40 (s, 3 H), 2.99−3.18 (m, 9 H), 3.76 (dd, J_{PH^a} = 12.2 Hz, $J_{H^aH^b}$ = 5.7 Hz, 1 H, H^a), 3.98 (d, J = 13.3 Hz, 1 H), 7.26−7.36 (m, 7 H), 7.66 (d, J = 8.2 Hz, 2 H). Anal. Calcd for $C_{25}H_{39}N_4O_2PS$: C, 61.20; H, 8.01; N, 11.42. Found: C, 60.89; H, 8.16; N, 11.11.

(1*R*,2*S*,s*S*)-1,2-Diamino Phosphoramide (*anti*-6a): $[\alpha]_D^{20}$ +72.8 (*c* 0.91, $CHCl_3$); ^{31}P NMR (161.9 Hz) δ 32.099 ppm; IR (neat) 3437, 2974, 1211, 1019 cm^{-1}; EI-MS *m*/*z* (%) 491 (M + 1, 9), 91 (100); ^{1}H NMR ($CDCl_3$−D_2O, 300 MHz) δ 1.08 (t, J = 7.0 Hz, 6 H), 1.18 (t, J = 7.1 Hz, 6 H), 1.48 (d, J = 6.2 Hz, 1 H), 2.18−2.26 (m, 2 H), 2.40 (s, 3 H), 2.84 (d, J = 13.3 Hz, 1 H), 3.00−3.26 (m, 8 H), 3.86 (dd, J_{PH^a} = 11.7 Hz, $J_{H^aH^b}$ = 3.5 Hz, 1 H, H^a), 4.29 (d, J = 13.3 Hz, 1 H), 7.20−7.30 (m, 7 H), 7.59 (d, J = 8.2 Hz, 2 H). Anal. Calcd for $C_{25}H_{39}N_4O_2PS$: C, 61.20; H, 8.01; N, 11.42. Found: C, 60.82; H, 7.92; N, 11.16.

(2*R*,s*S*)-1,2-Diamino Phosphonate 5b: ^{31}P NMR (161.9 Hz) δ 25.613 (0.85), 25.421 (0.15); IR (neat) 3479, 1251, 1033 cm^{-1}; EI-MS *m*/*z* (%) 408 (M$^+$, 0.51), 316 (89), 139 (33), 91 (100); ^{1}H NMR ($CDCl_3$, 400 MHz) δ of the major product 1.51 (d, J = 6.4 Hz, 1 H), 2.05−2.08 (m, 1 H), 2.20−2.21 (m, 1 H), 2.40 (s, 3 H), 3.21 (d, J = 13.3 Hz, 1 H), 3.44 (d, J = 10.7 Hz, 3 H),

3.58 (d, $J = 10.7$ Hz, 3 H), 3.73−3.88 (m, 2 H), 4.93 (d, $J = 7.6$ Hz, 1 H, NH), 7.27−7.35 (m, 7 H), 7.55 (d, $J = 8.2$ Hz, 2 H). Anal. Calcd for $C_{19}H_{25}N_2O_4PS$: C, 55.87; H, 6.17; N, 6.86. Found: C, 55.62; H, 6.42; N, 7.07.

(1*R*,2*S*,s*S*)-1,2-Diamino Phosphonate (*anti*-6b): $[\alpha]_D^{20}$ +54.3 (*c* 1.05, $CHCl_3$); ^{31}P NMR (161.9 Hz) δ 25.039 ppm; IR (neat) 3477, 1247, 1037 cm^{-1}. EI-MS *m*/*z* (%) 408 (M^+, 0.66), 316 (83), 139(31), 91(100); ^1H NMR ($CDCl_3$, 400 MHz) δ 1.59 (dd, $J_1 = 6.2$ Hz, $J_2 = 1.4$ Hz, 1 H), 1.96−2.00 (m, 1 H), 2.05 (d, $J = 3.2$ Hz, 1 H), 2.40 (s, 3 H), 3.28−3.53 (m,2 H), 3.60 (d, $J = 10.8$ Hz, 3 H), 3.68−3.74 (m, 4 H), 4.56−4.59 (m, 1 H, NH), 7.28−7.35 (m, 7 H), 7.59 (d, $J = 8.2$ Hz, 2 H). Anal. Calcd for $C_{19}H_{25}N_2O_4PS$: C, 55.87; H, 6.17; N, 6.86. Found: C, 55.62; H, 6.40; N, 7.15.

Ring-Opening Reaction of *syn*-5a with 4-Chlorothiophenol. To a solution of ***syn*-5a** (98 mg, 0.2 mmol) in CH_2Cl_2 (5 mL) was added 4-chlorothiophenol (87 mg, 0.6 mmol). After the mixture was stirred overnight at room temperature, the solvent was removed by evaporation under vacuum and purified by column chromatography over silica gel (PE:Ac = 1:1) to give thioether **7** (101.2 mg, 80% yield): $[\alpha]_D^{20}$ +152.5 (C 1.22, $CHCl_3$). mp. 142−143 °C. IR(KBr) 3278, 1215, 1093 cm^{-1}. EI-MS *m*/*z* (%) 635 (M + 1, 3), 497 (3), 91 (100); ^1H NMR ($CDCl_3-D_2O$, 300 MHz) δ 0.84 (t, $J = 6.8$ Hz, 6 H), 1.10 (t, $J = 7.0$ Hz, 6 H), 2.40 (s, 3 H), 2.85−3.30 (m, 11 H), 3.70, 3.94 (AB, $J_{AB} = 14.7$ Hz, 2 H), 4.40 (d, $J = 8.4$ Hz, 1 H), 6.95 (d, $J = 8.4$ Hz, 2 H), 7.06 (d, $J = 8.4$ Hz, 2 H), 7.25−7.29 (m, 7 H), 7.66 (d, $J = 8.0$ Hz, 2 H). Anal. Cald for $C_{31}H_{44}N_4ClO_2PS_2$: C, 58.61; H, 6.98; N, 8.82. Found: C, 58.81; H, 6.74; N, 8.99.

α,*β*-Diamino Phosphoramide 8. To a solution of thioether **7** (63.4 mg, 0.1 mmol) in anhydrous methanol (3 mL) at 0 °C was added trifluoroacetic acid (0.023 mL, 34 mg, 0.3 mmol) dropwise. After the mixture was stirred for 1 h at ambient temperature, the solvent was removed by evaporation under vacuum. The reaction mixture was diluted with Et_2O (15 mL) and extracted twice with a 15% HCl (5 mL) solution. The aqueous layer was cooled to 0 °C after addition of CH_2Cl_2 (7 mL). It was then neutralized to pH 8 with $NaHCO_3$ and extracted with CH_2Cl_2 (4 mL). The organic extract was washed with brine (3 mL) and dried over Na_2SO_4, and purification by flash chromatography afforded α,*β*-diamino phosphoramide **8** (38.1 mg, 76% yield): $[\alpha]_D^{20}$ +146.4 (*c* 1.13, $CHCl_3$); IR (neat) 3286, 1211 cm^{-1}; EI-MS *m*/*z* (%) 496 (M, 3), 221 (100); ^1H NMR ($CDCl_3-D_2O$, 300 MHz) δ 0.89 (t, $J = 7.1$ Hz, 6 H), 1.09 (t, $J = 7.0$ Hz, 6 H), 2.83−3.08 (m, 9 H), 3.27 (d, $J = 7.6$ Hz, 2 H), 3.47 (dd, $J_1 = 6.5$ Hz, $J_2 = 1.5$ Hz, 1 H), 3.75, 3.97 (AB, $J_{AB} = 14.0$ Hz, 2 H), 7.13−7.32 (m, 9 H). Anal. Cald for $C_{24}H_{28}N_4ClOPS$: C, 57.99; H, 7.71; N, 11.27. Found: C, 58.32; H, 7.88; N, 10.96.

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Supporting Information Available: ORTEP drawing of ring-opening product **7**. This material is available free of charge via the Internet at http://pubs.acs.org.

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