Regioselective and Stereoselective Nucleophilic Ring Opening Reactions of A Phenyl-Substituted Aziridine: Enantioselective Synthesis of β-Substituted Tryptophan, Cysteine, and Serine Derivatives

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Abstract: The asymmetric synthesis of β-phenyl-substituted cysteine, tryptophan, and serine derivatives was successfully developed. In this approach, the key intermediate, enantiomerically pure 3-phenylaziridine-2-carboxylic ester **7**, was prepared from α,β-unsaturated ester **1** by employing the Sharpless asymmetric dihydroxylation. The aziridine **7** was treated with 4-methoxybenzylthiol, indole, and acetic acid to give β-phenyl-substituted cysteine, tryptophan, and serine, respectively, in a clean S_N2 type ring opening at the C_3 position. This general approach can be used to synthesize a variety of β-substituted novel amino acids.

Restricting flexible peptides can enhance their biological activities and selectivities. One successful approach to the design of conformationally restricted peptides is the incorporation of side chain restricted amino acids in χ space. The side chain conformation can be controlled by introducing an alkyl or aryl group at the β-position of amino acid residues. As researchers in this field, our group has designed and synthesized many β-substituted novel amino acids.

Furthermore, we have demonstrated the incorporation of these side chain constrained amino acids into biologically active peptides to improve their bioactivity and selectivity.[1] As part of our continuing effort in this field to obtain either backbone and/or side chain conformationally constrained, novel amino acids, we have designed a new asymmetric synthesis of β-functionalized amino acids, namely, β-substituted cysteines, serines, and tryptophans. Cysteine plays a unique function in the conformation and the formation of secondary structures of peptides through disulfide bond formation. β-Substituted cysteines, when introduced into the peptide chain, not only can constrain the backbone conformation through the formation of a disulfide bridge but also can preserve the respective side chain, which is important for molecular recognition.[2] β-Substituted cysteines and serines also can be used as building blocks for dipeptide β-turn mimetics (Figure 1).[3] β-Phenyl-substituted tryptophans are chimeric amino acids containing two bulky side chain groups, an indole and a phenyl group. The interaction between these two bulky side chain groups can produce strong constraints simultaneously for both χ^1 and χ^2 side chain torsional angles.[4] However, convenient syntheses of these amino acids have not been reported, particularly for β-substituted cysteines. Herein, we report a general and efficient approach for synthesizing the β-substituted cysteines, serines, and tryptophans through the ring openings of aziridines. Since many biologically active peptides possess critical aromatic residues, we have focused much of our attention on unnatural β-functionalized aromatic amino acids.[5]

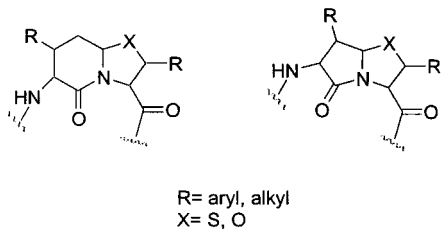

Figure 1. Dipeptide β-turn mimetics.

Aziridines as important synthetic intermediates can be subjected to ring openings with various nucleophiles in excellent stereo- and regioselectivities.[6] In our initial efforts, we targeted β-phenyl-substituted cysteine, serine, and tryptophan. Therefore, chiral 3-phenylaziridine-2-carboxylic ester **7** was chosen as a substrate. Several approaches to the synthesis of 3-phenylaziridine-2-carboxylates **7** have been reported. However, in most of these cases, the aziridine group was protected as a sulfonamide, requiring harsh conditions for cleavage, or the synthetic approaches are nonstereospecific.[7] Little attention has been paid to the synthesis of unprotected 3-phenylaziridine-2-carboxylates due to the lack of convenient routes to synthesize such compounds. We have developed a novel synthetic method for the preparation of optically pure *N*-unsubstituted 3-phenylaziridine-2-carboxylates **7** (Scheme 1), which subsequently underwent regiospecific ring opening with a thiol, indole, and acetic acid to provide β-phenyl-substituted cysteine, tryptophan, and serine derivatives, respectively.

The synthesis of benzyl 3-phenylaziridine-2-carboxylate **7** is illustrated in Scheme 1. In the synthesis, we used the well-documented Sharpless asymmetric dihy-

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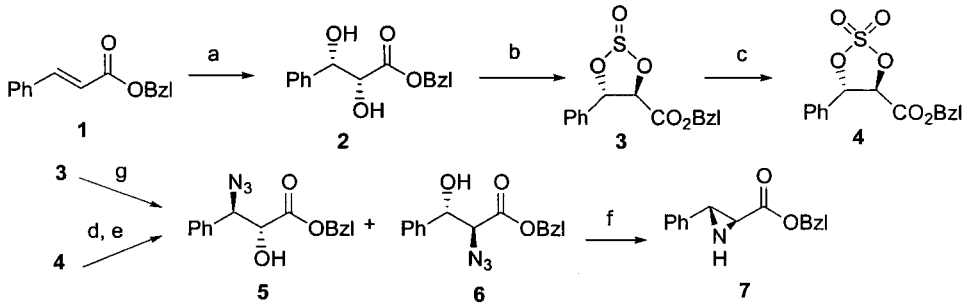
Scheme 1. Synthesis of Benzyl 3-Phenylaziridine-2-carboxylate[a]



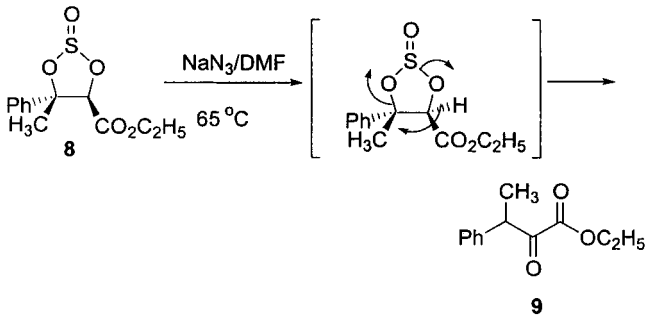
[a] Key: (a) Sharpless AD, AD-mix-α, 90%; (b) $SOCl_2$, DCM, 85%; (c) $NaIO_4$, $RuCl_3$, 87%; (d) NaN_3, acetone, H_2O; (e) 20% H_2SO_4, ether, two steps: 84%; (f) PPh_3, MeCN, 91%; (g) NaN_3, DMF, 60 °C, 85%.

droxylation as a key step to prepare **7**. Commercially available *trans*-benzyl cinnamate **1** was the starting point of our synthesis (Scheme 1). The cinnamate **1** was subjected to Sharpless asymmetric dihydroxylation in the presence of $(DHQ)_2PHAL$ (AD-mix-α) and methanesulfonamide to yield (2*R*,3*S*)-diol **2** in high yield and excellent optical purity (>95% ee).[8,9] The resulting vicinal diol **2** was first converted to the cyclic sulfite **3** as a mixture of diastereomers in a 1:1 ratio using $SOCl_2$, and then the cyclic sulfite **3** was further oxidized to the cyclic sulfate **4** with RuO_4 (generated in situ from $NaIO_4$/catalytic $RuCl_3$) in acetonitrile and water. Ring opening of cyclic sulfate **4** in an S_N2 fashion with N_3^- was generally carried out for 2 h at room temperature and provided the azido alcohols **5** and **6** in a 6:1 ratio (β/α = 6:1),[10] as determined by ^1H NMR spectroscopy.

Since the cyclic sulfate **4** of the cinnamate derivatives was extremely unstable, isolation gave some decomposition byproducts. We solved this problem by ring opening the cyclic sulfite **3** in DMF at higher temperature (60 °C) with sodium azide;[11,14] the mixture of regioisomers **5** and **6** was formed in a 5:1 ratio in high yield. From this point, we can see that the behavior of 3-aryl-substituted cyclic sulfate or sulfite-2-carboxylic esters is different from that of the 3-aryl-substituted oxirane-2-carboxylic esters, in the ring opening reaction by sodium azide. In the case of the 3-aryl-substituted oxirane-2-carboxylic esters, only one regioisomer of the azido alcohol was obtained upon treatment with sodium azide by attack at the benzylic C-3 position.[12] We did not make any effort to improve the regioselectivity, since the hydroxy group serves as a leaving group in the subsequent aziridine formation and both regioisomers **5** and **6** lead to the same chiral product **7**.

In the following so-called Staudinger reaction,[13] reduction of the azide function formed first an imino phosphorane and then an oxazaphospholine intermediate which was thermally induced to yield an aziridine. The ring closure took place with inversion of configuration at the carbon bearing the leaving group. Therefore, from the cyclic sulfate **4** to aziridine **7**, the stereochemical configurations at both atoms have been inverted.[10]

Scheme 2. Rearrangement Reaction



We also wanted to extend this methodology to the synthesis of 3,3-aryl,alkyl-disubstituted aziridines which would lead to β,β-disubstituted amino acids. We started from the ethyl *trans* β-methyl cinnamate through the Sharpless AD reaction to provide the diol in a good yield and high selectivity. The same procedure as described above can smoothly convert the diol to cyclic sulfite **8**, but further oxidation using ruthenium trichloride with sodium periodate gave decomposed products. At this point, we tried the ring opening reaction of cyclic sulfite **8** with sodium azide in DMF at 65 °C. Interestingly, instead of forming the azido alcohol, an unprecedented rearrangement reaction occurred as shown in Scheme 2 to provide the α-keto ester **9**.[14] Theoretically, the substitution at the 3-position would favor initial formation of a stabilized, tertiary benzylic carbonium ion. Abstraction of the acidic proton α to the ester group to generate the alkene, followed by loss of SO_2, would lead to the enol form of the observed α-keto ester product.[15]

3-Phenylaziridine-2-carboxylic ester **7** underwent ring openings with nucleophiles including 4-methoxybenzylthiol, indole, and acetic acid to give β-phenyl-substituted cysteine, tryptophan, and serine derivatives, respectively (Scheme 3). 4-Methoxybenzylthiol was chosen as a sulfur nucleophile since the 4-methoxybenzyl group can serve as a S-protecting group, which is compatible with *N*-α-

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(9) Enantiomeric excess was determined by chiral HPLC to be of >95% ee ((R,R)Whelk-01 column, 20% 2-propanol in hexane as elute).

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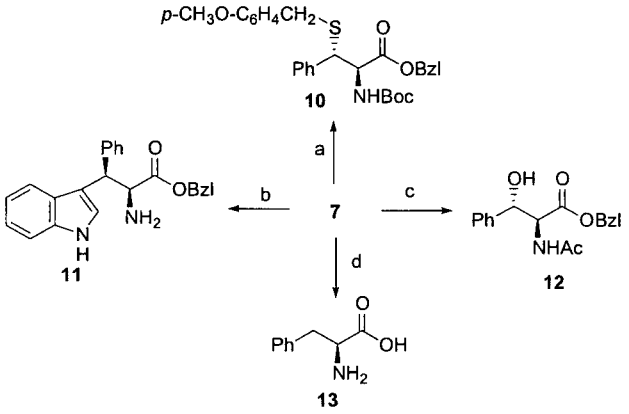
(15) The ^1H NMR, ^{13}C NMR, and HRMS data for compound **9** were similar to those of authentic samples [Mayers, D. A.; Kagan, J. *J. Org. Chem.* **1974**, *39*, 3147] and were further determined by HMBC NMR studies in which the methyl proton had strong coupling with the aromatic carbon.

Scheme 3. The Regiospecific Ring Opening Reaction of Benzyl 3-Phenylaziridine-2-carboxylate[a]



[a] Key: (a) (i) DCM, $BF_3{\cdot}Et_2O$, *p*-$MeOC_6H_5CH_2SH$, 67%; (ii) $(Boc)_2O$, TEA/THF, 90%; (b) DCM, $BF_3{\cdot}Et_2O$, indole, 48%; (c) acetic acid, 70 °C, 88%; (d) H_2, MeOH, 10% Pd−C, 90%.

Boc solid phase peptide synthesis. HF treatment should remove the peptide from the resin and deprotect the sulfur simultaneously without affecting the integrity of the peptides.[16] Treatment of aziridine **7** with 3 equiv of 4-methoxybenzylthiol in dichloromethane in the presence of 1.5 equiv of $BF_3{\cdot}Et_2O$ followed by amino group protection resulted in (2*R*,3*S*)-Boc protected *β*-phenylcysteine derivative **10** in 67% yield. The reaction was a stereospecific S_N2 reaction at the benzylic C_3 position. The regiochemistry of the ring opening was specific too, supported by the mass spectrum exhibiting the fragment $[C_6H_5CHSCH_2C_6H_4OCH_3]^+$ (*m*/*z*: 243). In the case of indole as a nucleophile, the exclusive, stereospecific attack of the carbon at the benzylic C_3 position also was observed. The regiochemistry of the reaction was deduced from the mass spectrum and ^1H NMR characteristics of the (2*S*,3*R*)-product **11**. The optical purity of **10** and **11** was determined by Mosher's agents.[17] The *β*-phenylserine was obtained when substrate **7** was stirred at 70 °C with acetic acid for 2 h. The ring opening proceeded with complete inversion of configuration at C_3 position, probably via initial ring opening by attack of acetate anion at C_3 and subsequent acyl migration from oxygen to nitrogen to give the (2*S*,3*S*)-product **12** in 88% yield.[12,18] Substrate **7** also underwent reductive opening reaction via hydrogenolysis at the aziridine benzylic position to stereospecifically provide (*S*)-phenylalanine **13**. ($[\alpha]^{23}_D = -33.3$ (*c* 1.6, H_2O), lit. $[\alpha]^{25}_D = -32.7$ to -34.7 (*c* 2.0, H_2O) Merck Index 12, 7425).

In conclusion, an efficient procedure was developed for making the enantiomerically enriched phenyl-substituted aziridine **7** through Sharpless asymmetric dihydroxylation. The stereospecific and regioselective ring opening reaction of aziridine intermediate **7** with 4-methoxybenzylthiol, indole, and acetic acid gave *β*-phenyl-substituted cysteine, tryptophan, and serine derivatives, respectively. This method could be used for the preparation of other novel amino acids with various nucleophiles, providing a general and efficient approach for the synthesis of *β*-substituted amino acids. The synthesis of *β*-alkyl-substituted amino acids using a similar strategy is under investigation.

Experimental Section

General. ^1H and ^{13}CNMR spectra were recorded on a Varian 300 MHz and DRX 500 spectrometers. The chemical shifts were expressed in ppm (*δ*) downfield from tetramethylsilane as an internal standard. Mass spectrometric analyses were conducted by the Department of Chemistry, University of Arizona Mass Spectrometry Laboratory. Optical rotations were measured on a JACSO P1020 polarimeter. Column chromatography was performed with 200−400 mesh size silica gel which was purchased from Aldrich Chemical Co. Thin-layer chromatography (TLC) was performed with Kodak F-254 silica gel plates. Dichoromethane was distilled from CaH_2, and THF from Na and benzophenone under a N_2 atmosphere. All other chemicals were purchased from Aldrich Chemical Co. and used as received. All new compounds were characterized by ^1H and ^{13}C NMR and high-resolution mass spectrometry (HRMS).

(2*R*,3*S*)-Benzyl 2,3-Dihydroxy-3-phenylpropionate (2). To a stirred solution of AD-mix-α (42 g) and methanesulfonamide (0.3 g, 30 mmol) in *tert*-butyl alcohol (150 mL) and water (150 mL) at room temperature was added *trans*-benzyl cinnamate **1** (8.16 g, 30 mmol). The reaction was stirred at room temperature for 24 h. Sodium sulfite (45 g) was added as a solid, and the mixture was stirred for 30 min. Ethyl acetate was added, the mixture was washed with water, and the organic phase was dried ($MgSO_4$) and concentrated under reduced pressure. The pure product (7.34 g, 90%) was obtained as a colorless oil by silica gel chromatography with hexanes−ethyl acetate (70:30, v/v). The enantiomeric excess was determined by HPLC to be >95% ee using an (R,R)Whalk-01 column, 20% 2-propanol in hexane as the elute: $[\alpha]^{20}_D = +4.94$ (*c* 2.30, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) *δ* 2.77 (d, *J* = 6.6 Hz, 1H), 3.12 (d, *J* = 6.0 Hz, 1H),4.42 (dd, *J* = 5.7 Hz, *J* = 3.0 Hz, 1H), 5.03 (dd, *J* = 6.9 Hz, *J* = 3.3 Hz, 1H), 5.23 (m, 2H), 7.28−7.39 (m, 10H); ^{13}C NMR 67.8, 74.5, 74.7, 126.2, 128 (m, 4C), 134.7, 139.7, 172.6; HRMS MH^+ calcd for $C_{16}H_{17}O_4$ 273.1049, found 273.1127.

Cyclic Sulfite 3. To an ice-cooled stirred solution of **2** (4.08 g, 15 mmol) and triethylamine (6.25 g, 60 mmol) in methylene chloride (60 mL) was added thionyl choride (1.64 mL, 22.5 mmol) dropwise over a period of 10 min; stirring was continued for another 5 min at 0 °C. The reaction mixture was diluted with cold ether and washed with cold water. The aqueous phase was extracted with ether. The combined organic phases were washed with cold brine and concentrated under reduced pressure to remove solvent. The crude cyclic sulfite was purified by chromatography with hexanes−ethyl acetate (60:40 v/v) to give products (4.05 g, 85%) as diastereomers in a 1:1 ratio: $[\alpha]^{20}_D = -78$ (*c* 0.85, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) *δ* 4.82 (d, *J* = 7.5 Hz, 0.5H), 5.18−5.32 (m, 2.5H), 5.52 (d, *J* = 8.5 Hz, 0.5H), 6.11 (d, *J* = 7.5 Hz, 0.5H), 7.30−7.41 (m, 10H); ^{13}C NMR 68.1, 68.2, 81.2, 83.2, 83.3, 87.9, 126.8−129.7 (m, 11C), 133.5, 133.7, 134.3, 134.5, 165.8, 166.8; HRMS MH^+ calcd for $C_{16}H_{15}O_5S$ 319.0562, found 319.0638.

Cyclic Sulfate 4. The cyclic sulfite **3** (1.48 g, 4.65 mmol) was dissolved in a mixture of water (29 mL), CH_3CN (13 mL), and CCl_4 (13 mL). $NaIO_4$ (1.49 g, 6.98 mmol) and $RuCl_3$ hydrate (catalytical amount) were added, and the solution was vigorously stirred for 1 h at room temperature. The reaction mixture was diluted with ether (100 mL), and the organic layer was filtered through a pad of Celite. The filtered organic layer was washed

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(17) The deprotection of the N^{α}-Boc in **10** and its enantionmer gave free amine, which were coupled with (*S*)-(−)-α-methoxyl-α-trifluoromethylphenylacetyl chloride (Mosher's agent) to afford amides. Measurement of the diastereomeric methyl singlets at 3.35 and 3.28 ppm in proton NMR spectra in $CDCl_3$ demonstrated the amides to be of >96% diastereomeric excess (only one peak observed in each case). Hence, amino acid **10** and its enantiomer are determined to be of >96% enantiomeric excess. Amino acid derivative **11** was coupled with (*R*)- and (*S*)-Mosher's agents respectively to give amides, which were directly examined in proton NMR spectroscopy in $CDCl_3$. Measurement of the diastereomeric methyl singlets at 3.26 and 3.06 ppm demonstrated the amides to be of >96% diastereomeric excess (only one peak observed in each case). Hence, amino acid **11** is determined to be of >96% enantiomeric excess.

(18) Compound **12** was transformed to its methyl ester, a known compound ($[\alpha]^{23}_D$ +142.8 (*c* 1.06, $CHCl_3$), lit.[12] ($[\alpha]^{25}_D$ +140.2 (*c* 0.9, $CHCl_3$), indicating that compound **12** has high optical purity.

with water and saturated sodium bicarbonate solution followed by brine and dried over $MgSO_4$ and concentrated under reduced pressure. The pure cyclic sulfate (1.28 g, 87%) was isolated as a colorless oil by silica gel chromatography with hexanes−ethyl acetate (60:40 v/v): ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.08 (d, J = 9.3 Hz, 1H), 5.18 (m, 2H), 5.78 (d, J = 9.0 Hz, 1H), 7.20−7.36 (m, 10H); ^{13}C NMR 68.7, 81.4, 84.4, 127.1, 128.5, 128.7, 128.9, 129.3, 130.7, 131.7, 133.8, 163.9.

Benzyl (2*R*,3*R*)-3-Azido-2-hydroxy-3-phenylpropionate (5) and Benzyl (2*S*,3*S*)-2-Azido-3-hydroxy-3-phenylpropionate (6). Method A. To a stirred solution of cyclic sulfate **4** (0.54 g, 1.62 mmol) in acetone (10 mL) and water (1 mL) was added sodium azide (130 mg, 2 mmol) as a solid. The mixture was stirred at 0 °C for 5 min and room temperature for 2 h. The mixture was concentrated under reduced pressure. Ethyl ether (7 mL) was added, and solution was chilled to 0 °C followed by dropwise addition of a 20% H_2SO_4 aqueous solution. The solution was stirred vigorously at 0 °C for 24 h. The organic layer was collected and washed with sodium bicarbonate and water. After removal of solvent, the pure products (0.41 g, 85%) were isolated by silica gel chromatography with hexanes−ethyl acetate (80:20 v/v). **Method B.** To a stirred solution of cyclic sulfite **3** (320 mg, 1 mmol) in DMF (2.5 mL) was added sodium azide (130 mg, 2 mmol). The temperature was raised to 60 °C for 6 h. The mixture was concentrated under reduced pressure, and the pure product (250 mg, 85%) was obtained by silica gel chromatography with hexanes−ethyl acetate (70:30 v/v). The products were a mixture of the regioisomers. The minor product **6** was not detected. ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.99 (d, J = 6.5 Hz, 1H), 4.56 (dd, J = 4.0 Hz, J = 6.5 Hz, 1H), 4.86 (d, J = 4.0 Hz, 1H), 5.12 (m, 2H), 7.20−7.27 (m, 10H); HRMS MH$^+$ calcd for $C_{16}H_{16}O_3N_3$ 298.1113, found 298.1196.

Benzyl (2*S*,3*R*)-3-Phenylaziridine-2-carboxylate (7). To a stirred solution of azido alcohol **5** and **6** (1 g, 3.36 mmol) in acetonitrile (15 mL) was added PPh_3 (0.91 g, 3.48 mmol) as a solid. The mixture was stirred at 20 °C for 1 h and then refluxed for 6 h. After removal of solvent, the pure product (0.8 g, 91%) was isolated by silica gel chromatography with hexanes−ethyl acetate (80:20 v/v): $[\alpha]^{20}_D$ = +186 (*c* 0.9, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.93 (b, 1H), 2.64 (b, 1H), 3.29 (b, 1H), 5.23 (m, 2H), 7.25−7.35 (m, 10H); ^{13}C NMR 39.4, 40.5, 67.5, 126.1, 127.7, 128.3, 128.4, 128.5, 128.6, 135.1, 137.6, 171.6; HRMS MH$^+$ calcd for $C_{16}H_{16}O_2N$ 254.1103, found 254.1178.

Benzyl N^{α}-(*tert*-Butyloxycarbonyl)-(2*R*,3*S*)-3-phenyl-3-(4-methoxybenzylthio)propanoate (10). To a stirred solution of **7** (1.57 g, 6.2 mmol) and 4-methoxybenzylthiol (2.58 mL, 18.6 mmol) in dry methylene chloride (60 mL) at 0 °C was added anhydrous boron trifluoride diethyl etherate (1.17 mL, 9.3 mmol) dropwise. The mixture was stirred at 0 °C for 24 h, and then the reaction was quenched by addition of saturated sodium bicarbonate. The organic layer was washed with brine and water and dried over $MgSO_4$. After removal of solvent, the pure product (1.69 g, 67%) was obtained as colorless oil by silica gel chromatography with hexanes−ethyl acetate (60:40 v/v). The product was dissolved in 30 mL of THF. The solution was treated with TEA (420 mg, 4.12 mmol) and di-*tert*-butyl dicarbonate (0.89 g, 4.12 mmol). The solution was stirred at room temperature overnight, and then the solvent was evaporated off. The residue was dissolved in 50 mL of EtOAc, washed with saturated sodium bicarbonate and brine, and dried over $MgSO_4$. After removal of the solvent, the pure product (2.11 g, 67%) was obtained: $[\alpha]^{20}_D$ = +127 (*c* 2.25, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.40 (s, 9H), 3.48 (d, J = 13 Hz, 1H), 3.62 (d, J = 13 Hz,1H), 3.76 (s, 3H), 4.14 (d, J = 5.0 Hz, 1H), 4.85 (dd, J = 5 Hz, J = 9.5 Hz, 1H), 4.98 (d, J = 9.5 Hz, 1H), 5.02 (d, J = 12.5 Hz, 1H), 5.11 (d, J = 12 Hz, 1H), 6.77−7.34 (m); ^{13}C NMR 28.2, 35.1, 50.7, 55.2, 56.9, 67.1, 80.1, 113.8, 127.9, 128.4, 128.5, 128.6, 129.1, 130.1, 135, 136.8, 155.2, 158.6, 170.1; HRMS MH$^+$ calcd for $C_{29}H_{34}O_5NS$ 508.2079, found 508.2141.

Benzyl (2*S*,3*R*)-2-Amino-3-phenyl-3-(indol-3-yl)propanoate (11). Boron trifluoride etherate (0.1 g, 0.72 mmol) was added dropwise to a solution of **7** (0.12 g, 0.47 mmol) and indole (0.11 g, 0.94 mmol) in dichloromethane (5 mL) at 0 °C under argon. After 2 h, a saturated sodium bicarbonate solution (5 mL) was then added and the aqueous layer was extracted with dichloromethane. The combined organic layer was washed with brine and dried over $MgSO_4$. After removal of solvent, the pure product (83 mg, 48%) was isolated as a colorless oil by silica gel chromatography with hexanes−ethyl acetate (60:40 v/v): $[\alpha]^{20}_D$ = −33.2 (*c* 0.65, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.58 (b, 2H), 4.27 (d, J = 7.5 Hz, 1H), 4.67 (d, J = 7 Hz, 1H), 5.00 (s, 2H), 6.99−7.26 (m, 15H), 8.02 (s, 1H); ^{13}C NMR 47.1, 59.0, 66.7, 110.9, 116.3, 119.2, 119.4,122 (m, 2C), 126.9−128 (m, 5C), 135.4, 136.0, 140.1, 174.4; HRMS MH$^+$ calcd for $C_{24}H_{23}O_2N_2$ 371.1758, found 371.1760.

Benzyl (2*S*,3*S*)-2-Acetylamino-3-phenyl-3-hydroxylpropanoate (12). A mixture of aziridine **7** (0.14 g, 0.56 mmol) and acetic acid (5 mL) was stirred at 70 °C for 2 h. Excess acetic acid was removed under reduced pressure; the pure product (154 mg, 88%) was obtained as a colorless oil by silica gel chromatography with hexanes−ethyl acetate (80:20 v/v): $[\alpha]^{20}_D$ = +47.9 (*c* 1.2, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.98 (s, 3H), 4.58 (b, 1H), 5.03 (dd, J = 7.5 Hz, J = 3.5 Hz, 1H), 5.10 (m, 2H), 5.21 (d, J = 3.5 Hz, 1H), 6.40 (d, J = 7 Hz, 1H), 7.09−7.29 (m, 10H); ^{13}C NMR 22.8, 59.1, 67.5, 74.8, 125.8, 128 (m), 134.5, 138.9, 169.2, 171.5; HRMS MH$^+$ calcd for $C_{18}H_{20}O_4N$ 314.1314, found 314.1404.

(*S*)-Phenylalanine (13). Aziridine **7** (0.25 g, 1 mmol) was hydrogenated over a catalytic amount of Pd−C in methanol (2 mL) for 12 h at room temperature under an H_2 atmosphere (36 psi). The catalyst was filtered off, and the filtrate was concentrated in vacuo to give a residue, which was purified by recrystallization from hexane and ethyl acetate: $[\alpha]^{23}_D$ = −33.3 (*c* 1.6, H_2O); ^{1}H NMR (300 MHz, D_2O) δ 3.05−3.29 (m, 2H), 3.94−3.98 (m, 2H), 7.28−7.42 (m, 5H); ^{13}C NMR 31.9, 51.6, 123.3, 124.5, 130.7, 143.4, 169.6; HRMS MH$^+$ calcd for $C_{19}H_{12}O_2N$ 166.0810, found 166.0790.

Benzenepropanoic Acid, β-Methyl-α-oxo, Ethyl Ester (9). To a stirred solution of β-methyl cyclic sulfite **8** (270 mg, 1 mmol) in DMF (2.5 mL) was added sodium azide (130 mg, 2 mmol). The temperature was raised to 65 °C for 6 h. The mixture was concentrated under reduced pressure, the pure product (100 mg, 48%) was obtained, and 80 mg of starting material was recovered by silica gel chromatography with hexanes−ethyl acetate (80:20 v/v): $[\alpha]^{20}_D$ = +7.14 (*c* 0.35, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.19 (t, J = 7.2 Hz, 3H), 1.46 (d, J = 7.2 Hz, 3H), 4.17 (m, 2H), 4.48 (q, J = 7.2 Hz, 1H), 7.20−7.36 (m, 5H); ^{13}C NMR 13.8, 16.7, 48.4, 62.2, 127.6, 128.5, 128.9, 137.7, 161.3, 194; HRMS MH$^+$ calcd for $C_{12}H_{15}O_3$ 207.1021, found 207.1022.

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Supporting Information Available: ^{1}H and ^{13}C NMR spectra for compound **2**, **7**, and **9**−**12**. This material is available free of charge via the Internet at http://pubs.acs.org.

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