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Aziridine mediated asymmetric synthesis of α-benzylserine and α-*n*-butylserine

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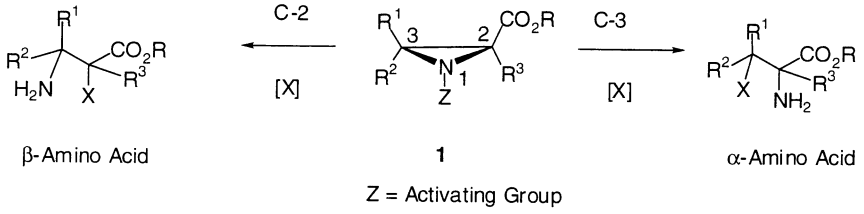
Abstract—Regioselective hydrogenolysis of enantiopure 2-benzyloxyaziridine 2-carboxylates represents a general method for the asymmetric synthesis of α-substituted serines. The aziridines are readily prepared via an aza-Darzens reaction of the enolate of methyl 3-benzyloxy-2-bromopropanoate with an enantiopure sulfinimine (*N*-sulfinyl imine). © 2001 Elsevier Science Ltd. All rights reserved.

The current interest in quaternary, α-alkyl α-amino acids relates to the important effects they have on biological activity.[1] While a number of these compounds are naturally occurring and found as substructures of natural products, most of the recent focus has been on synthetic examples.[2] These type of amino acids are useful in studies of enzyme mechanisms,[3] as enzyme inhibitors[4] and in the preparation of peptidomimetics. On incorporation into peptides they introduce conformational constraints that have been used to obtain important information on receptor-site structure and to optimize therapeutic activity.[4,5] Furthermore, these amino acids have been found to increase the metabolic stability of peptides.[6]

The asymmetric synthesis of quaternary α-amino acids has been reviewed.[7] More recent methods include a catalytic[8] and a diastereoselective[9] asymmetric Strecker synthesis and others.[10] The regio- and stereoselective ring-opening reactions of aziridine 2-carboxylates **1** are valuable sources of structurally diverse amino acids including α-alkyl examples (Scheme 1).[11] Activation of the aziridine nitrogen by an electron-withdrawing group (acyl, sulfonyl), by protonation, or by Lewis acids promotes either C-2 attack to give β-amino acids or C-3 attack to give α-amino acids. The stereo- and regioselectivity is determined by the ring substituents and the reaction conditions, with the majority of nucleophiles reacting at C-3.

We recently described a general methodology for the asymmetric synthesis of α-alkyl α-amino acid derivatives using *N*-sulfinyl aziridines carboxylates.[12] For example, *E*-(S_S,2*R*,3*S*)-(+)-*N*-(*p*-toluenesulfinyl)-2-carbomethoxy-3-phenylaziridine (**2**), prepared via an aza-Darzens reaction of the lithium enolate of methyl α-bromopropionate with an enantiopure sulfinimine (*N*-sulfinyl imine),[13,14] gave, on treatment with TFA, (2*R*,3*R*)-(+)-α-methyl β-phenylserine (**3**) in 75% yields and >96% de (Scheme 2).[15] The *N*-tosyl derivative **4**, on hydrogenation gave (*R*)-(−)-**5**, and removal of the *N*-tosyl group with HBr/PhOH, gave (*R*)-(+)-α-methylphenylalanine (**6**) in 73% overall yield. In a related study the first asymmetric synthesis of (*R*)-(+)-α-methylphosphophenylalanine (**9**) was accomplished in 92% yield by transfer hydrogenation of 2-methylaziridine-2-phosphonate (2*R*,3*R*)-(+)-**8**, despite the lack of activation on nitrogen (Scheme 2).[16] Selective removal of the sulfinyl group in aziridine (+)-**7** using TFA in acetone–water afforded (+)-**8** in 76% yield without ring-opening.

Our aziridine methodology can also be applied to the asymmetric synthesis of β-substituted α-alkyl amino acids. The



Scheme 1.

Keywords: asymmetric synthesis; aziridines; α-amino acids; *N*-sulfinyl imines.
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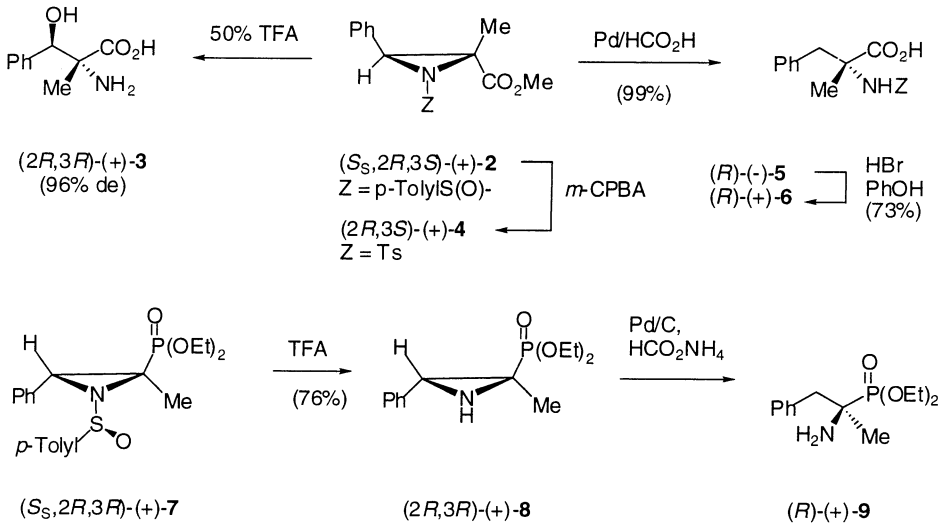
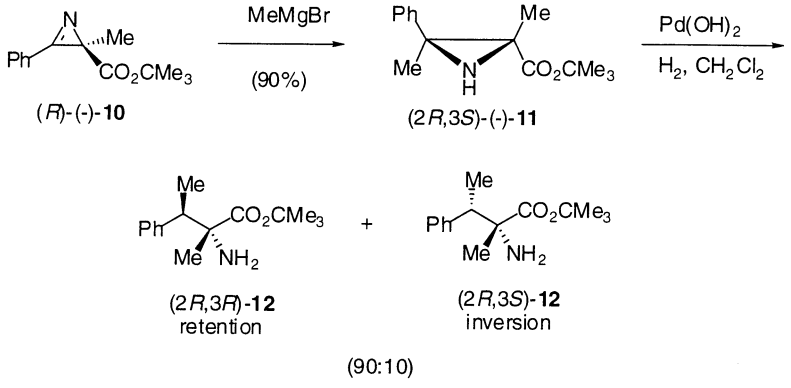


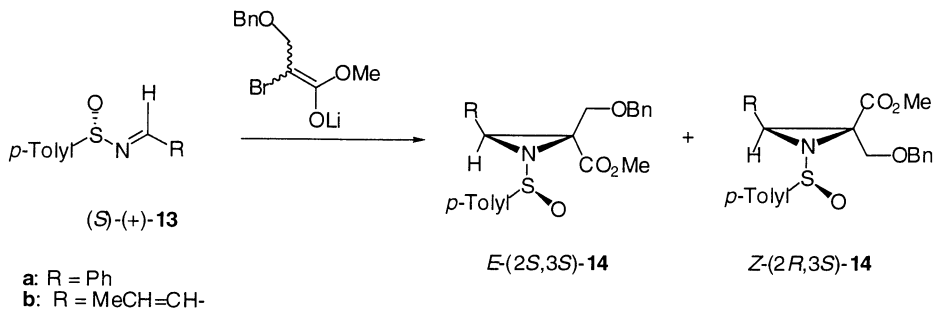
Scheme 2.

requisite 3-substituted aziridine (2*R*,3*S*)-(−)-**11** was prepared by *cis* addition of methylmagnesium bromide to 2*H*-azirine (*R*)-(−)-**10** (Scheme 3).[17,18] Hydrogenolysis of **11** over $Pd(OH)_2$ occurred primarily with retention of configuration in methylene chloride (90:10 retention: inversion), but with inversion in hexane (40:60). The major isomer (2*R*,3*R*)-**12** was isolated in 80% yield.

Serine, a β-hydroxy α-amino acid,[19] is found in a number of biologically active molecules[20] and is a useful chiral building block for asymmetric synthesis.[21] Methods for the asymmetric synthesis of α-alkyl analogs include alkylation of chiral nonracemic enolates derived from oxazolidines,[22,23] oxazinones,[24] and bislactam ethers.[25] Enzyme kinetic resolution of α-alkyl-α-aminomalonates[26] from azlactones[27] and via an asymmetric Strecker synthesis[28] have also been utilized to prepare these compounds. Despite the acknowledged versatility of aziridine carboxylates for the asymmetric synthesis of amino acids,[11] there is only a single report employing an aziridine generated from a chiral epoxide, for the preparation of α-methylserine.[29] As an extension of our aziridine methodology we describe here a general protocol for the aziridine mediated asymmetric synthesis of α-alkyl serines.



Scheme 3.

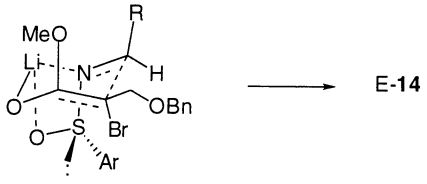


Scheme 4.

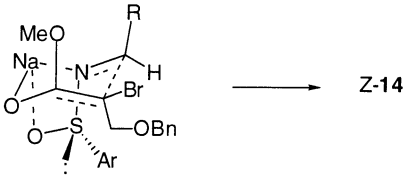
1. Results and discussion

To prepare α-alkyl serines via our aziridine methodology a 2-benzyloxymethylaziridine 2-carboxylate is required that on C-3 ring-opening would give the desired product. The requisite *N*-sulfinylaziridines carboxylates **14** were prepared by treating sulfinimines (*N*-sulfinyl imines **13**)[13] with the enolate generated from methyl 3-benzyloxy-2-bromopropanoate[30] in the aza-Darzens reaction outlined in Scheme 4. The lithium enolate of 3-benzyloxy-2-bromopropanoate was generated by treatment with LiHMDS and (*S*)-(+)-*N*-(benzylidene)-*p*-toluenesulfinamide (**13a**) was added at −78°C. However, work-up resulted in recovery of starting material in ca. 60% yield. Under these conditions (*S*)-(+)-*N*-(crotonylidene)-*p*-toluenesulfinamide (**13b**) gave similar results (Table 1). In an earlier study with other bromo enolates we encountered modest yields in the sulfinimine-mediated aza-Darzens synthesis, which we attributed to their instability and propensity to self-condense.[31] To improve the yields we developed an in situ trapping method that involves treating a mixture of the α-haloester and the sulfinimine with base. The idea was to trap the reactive enolate with the sulfinimine before it could self-condense. Yields improved, but the selectivity suffered.[12] In a similar fashion 1.0 equiv. of (+)-**13a** and 3.0 equiv. methyl 3-benzyloxy-2-bromopropanoate at −78°C followed by addition of 2.5 equiv. of LiHMDS gave an overall 90% yield of the *E*- and *Z*-aziridines **14a** in a 95:5 ratio (Table 1, entry 2). With the sodium enolate the ratio dropped to 80:20 (Table 1, entry 3). The major aziridine diastereoisomer *E*-(2*S*,3*S*)-(+)-**14a** was isolated in 70% yield by chromatography. There was no selectivity observed under these conditions with the crotonaldehyde-derived sulfinimine (*S*)-(+)-**13b** and the lithium enolate afforded *E*,*Z* **14b** in an 1:1 ratio in 42% yield (Table 1, entries 4–7). However, the sodium enolate improved the selectivity to 70% de, but unexpectedly gave the *Z* aziridine (2*R*,3*S*)-(+)-**14b** as the major diastereoisomer in 79% isolated yield (Table 1, entry 8). Attempts to further improve the selectivity by varying the solvent and base equivalents resulted in reduced yields and selectivity (Table 1).

The stereochemical assignments for aziridines **14** are based on NOE experiments and conversion to known compounds (see below). In (2*S*,3*S*)-**14b** no NOE was observed between the C-3 proton and the C-2 methylene group whereas in (2*R*,3*S*)-**14b** the value was 20%. As was noted earlier the possibility exists for the formation of four stereoisomeric aziridines, but only the *Z* and *E*-aziridines are formed.[12] It was found in these studies that substituted bromo enolates gave aziridines having predominantly the *E*-geometry and this finding is consistent with chair-like transition state **TS-1** containing a four-membered metallocycle. A reasonable assumption is that in solution the sulfinimine adopts the thermodynamically favored *E*-geometry[32,33] and that the bromo enolate has the *Z*-geometry. The reason that the crotonaldehyde-derived sulfinimine (*S*)-(+)-**13b** affords the *Z*-aziridine (2*R*,3*S*)-**14b** is not readily apparent. A change in the geometry of the sulfinimine from *E* to *Z* is one possibility, but seems unlikely due to the strong thermodynamic preference for the former. A more probable explanation is that the geometry of the sodium enolate is *E*; i.e. **TS-2**. It is worth recalling that the lithium and sodium enolates give a 1:1 and 85:15 ratios of the *Z*/*E* aziridines **14b**, respectively (Table 1: compare entries 4 with 7). The fact that *E*-**14a** was obtained regardless of the counterion could reflect the larger size of phenyl verses propenyl. Open transitions states can also not be excluded for the sodium enolates.



TS-1

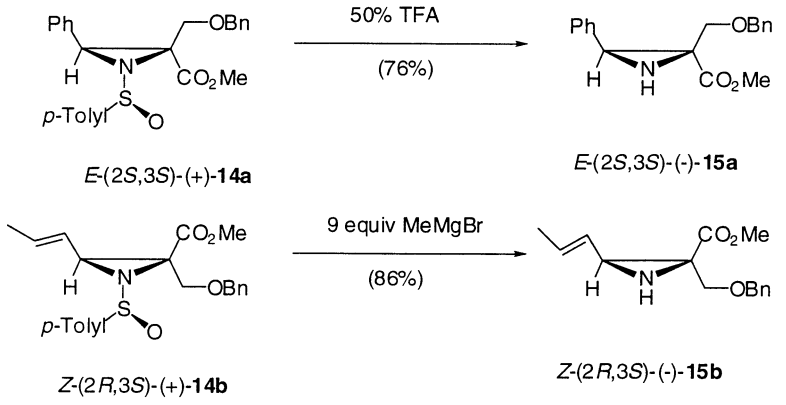


TS-2

Table 1. Aza-Darzens synthesis of 2-benzyloxymethyl aziridines **14** at −78°C in THF

Entry	Sulfinimine **13** R=	Reaction conditions[a] **13**:base:bromopropionate	Configuration of major diastereomer	Dr (% de)[b]	% Isolated yield of major diastereomer
1	(*S*)-(+)-**13a**, Ph	1:2 LiHMDS:2[c]			No reaction[d]
2		1:2.5 LiHMDS:3 (in situ)[e]	*E*-(2*S*,3*R*)-(+)-**14a**	95:5 (90)	70
3		1:2.5 NaHMDS	*E*-(2*S*,3*R*)-(+)-**14a**	80:20 (60)	70
4	(*S*)-(+)-**13b**, *E*-MeCH=CH$_2$–	1:2 LiHMDS:2[c]			No reaction[d]
5		1.3 LiHMDS:2 (in situ)[e]	*Z*-(2*R*,3*S*)-(+)-**14b**	1:1 (0)	42
6		2.0 LiHMDS:2	*Z*-(2*R*,3*S*)-(+)-**14b**	1:1 (0)	44
7		6.0 LiHMDS:2 (Et_2O)	*Z*-(2*R*,3*S*)-(+)-**14b**	1:1 (0)	40
8		1.3 NaHMDS:2	*Z*-(2*R*,3*S*)-(+)-**14b**	15:85 (70)	79
9		6.0 NaHMDS:2	*Z*-(2*R*,3*S*)-(+)-**14b**	15:85 (70)	40
10		2.0 NaHMDS:2 (PhMe)	*Z*-(2*R*,3*S*)-(+)-**14b**	33:67 (34)	44
11		2.0 NaHMDS:2 (Et_2O)	*Z*-(2*R*,3*S*)-(+)-**14b**	33:67 (34)	48
12		1.3 KHMDS:2	*Z*-(2*R*,3*S*)-(+)-**14b**	40:60 (20)	20

[a] Equivalents of **13**/base/bromoproponate used.
[b] Drs determined on the crude reaction mixture by ^{1}H NMR.
[c] Sulfinimine added to the enolate at −78°C.
[d] Starting material recovered.
[e] Base added to a mixture of the bromopropionate and sulfinimine.



Scheme 5.

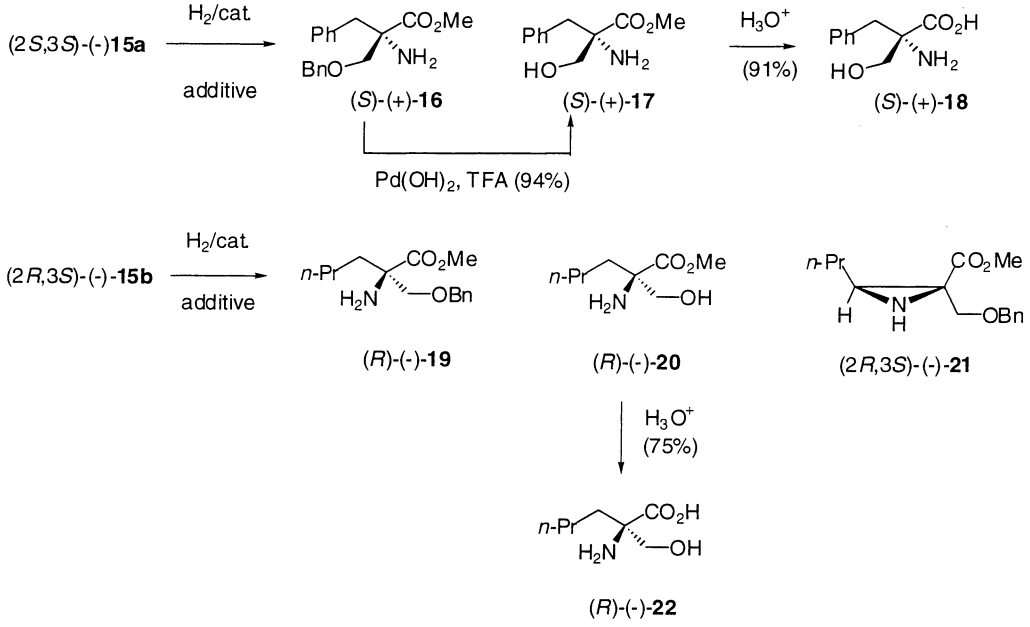
Table 2. Hydrogenolysis of aziridine **15** to α-alkyl serines **16** and **17**

Entry	Aziridine	Catalyst	Solvent	Products (% isolated yield)
1	(−)-**15a**	$Pd(OH)_2$	THF	(*S*)-(+)-**16** (100)
2	(−)-**15a**	$Pd(OH)_2$/TFA	3:1 EtOH:THF	(*S*)-(−)-**17** (99)
3	(−)-**15a**	$Pd(OH)_2$	MeOH	(S)-(−)-**17** (90)
5	(−)-**15b**	$Pd(OH)_2$	THF	(2*R*,3*S*)-(−)-**21** (30)
6	(−)-**15b**	$Pd(OH)_2$/TFA	3:1 EtOH:THF	(*R*)-(−)-**19** (25)
7	(−)-**15b**	Pd/C	THF	(*R*)-(−)-**19** (65)
8	(−)-**15b**	$Pd(OH)_2$	MeOH	(*R*)-(−)-**20** (60)

Reaction time: 18 h.

The *N*-sulfinyl group in (2*S*,3*S*)-**14a** was selectively removed, without ring-opening, by treatment with 50% aqueous TFA in acetone to give (2*S*,3*S*)-**15a** in 76% yield (Scheme 5). Similarly **14b** gave a ca. 40% yield of **15b**, but was difficult to purify because of numerous side products. These products may result from generation of carbocations following protonation of the alkene by the acid. Fortunately, the NH aziridine (−)-**15b** was obtained in 86% yield on reaction of **14b** with 9.0 equiv. of methylmagnesium bromide.

The results for the low-pressure (balloon) hydrogenolysis of aziridines **15** using various catalyst/solvent systems are summarized in Table 2. With Pearlman's catalyst, $Pd(OH)_2$, in THF, aziridine *E*-**15a** gave a quantitative yield of (*S*)-(+)-benzyloxy α-benzylserine methyl ester (**16**) (Scheme 6). The inhibition of *O*-debenzylation by amines has been reported and appears to be related to the preferential affinity of the palladium surface for the more basic nitrogen atom.[34] Both ring-opening and debenzylation can be readily accomplished by hydrogenolysis of *E*-**15a** in



Scheme 6.

the presence of 4 equiv. of TFA or in MeOH affording a nearly quantitative yields of (*S*)-(−)-α-benzylserine methyl ester (**17**) (Table 2, entries 2 and 3).

The situation is more complex for the hydrogenolysis of the crotonaldehyde-derived aziridine *Z*-(−)-**15b**. On hydrogenolysis with $Pd(OH)_2$ the aziridine failed to open and a low, ca. 30%, yield of aziridine **21** was obtained (Scheme 6). With $Pd(OH)_2$/TFA ring-opening occurred to give (*R*)-(−)-**19**, but the yield was only 25% along with many uncharacterizable products. Here again protonation of the alkene by the acid may be responsible for these undesirable products. Hydrogenolysis over Pd/C in THF, however, gave (*R*)-(−)-**19** in 65% isolated yield (Table 2, entry 7). Both ring-opening, and debenzylation was accomplished using $Pd(OH)_2$ in MeOH affording (*R*)-(−)-α-*n*-butylserine methyl ester (**20**) in 60% isolated yield (Table 2, entry 8). We speculate that the different reactivities of the two aziridines are associated with the affinities of the alkene and aromatic π-systems for the catalysts, with the former having the greater affinity.

Treatment of (*S*)-(−)-**17** and (*R*)-(−)-**20** with LiOH in THF, neutralization with 1N HCl, and isolation by Dowex 50WX8-100 ion exchange column gave (*S*)-(+)-α-benzylserine (**18**)[28b] and (*R*)-(−)-α-*n*-butylserine (**22**)[35] in 91 and 75% yields, respectively (Scheme 6). Their properties were in agreement with literature values, which indicates the % ee, as expected, was >95 because at no time in the reaction sequence are any bonds to the stereogenic carbon broken.

In summary, general methodology for the asymmetric synthesis of α-substituted serines via the regioselective hydrogenolysis of 2-benzyloxyaziridine-2-carboxylates is described. Either the *O*-benzyloxy serine, which can be used for further elaboration of the amino acid, or the deprotected serine can be readily obtained by varying the reaction conditions.

2. Experimental

2.1. General procedure

Column chromatography was performed on silica gel, Merck grade 60 (230–400 mesh). Analytical and preparative thin-layer chromatography was performed on precoated silica gel plates (250 and 400 μm) purchased from Analtech Inc. TLC plates were visualized by quenching of UV fluorescence (λ_{max} 254 nm), staining with iodine or with 0.5% ninhydin in ethanol. IR spectra were obtained using NaCl plates or KBr discs and recorded on a Mattson 4020 FTIR spectrometer. ^{1}H- and ^{13}C NMR were recorded on a General Electric Omega 500, operating at 500 and 125 MHz, respectively. The spectra were referenced to solvent residues as internal standards. HRMS analyses were performed in the Department of Chemistry, Drexel University, Philadelphia, PA using a Fissions ZAB HF double-focusing mass spectrometer. Melting points were recorded on a MEL-TEMP apparatus and are uncorrected. Optical rotations were measured on a Perkin–Elmer 341 polarimeter and elemental analyses were performed in the Department of Chemistry, University of Pennsylvania, Philadelphia, PA.

THF and Et_2O were freshly distilled under an inert atmosphere from a purple solution of sodium/benzophenone ketyl. Anhydrous CH_2Cl_2 was obtained by refluxing over calcium hydride followed by distillation under an inert atmosphere. Sulfinimines (*S*)-(+)-**13a** and (*S*)-(+)-**13b**[13] and 3-benzyloxy-2-bromopropanoate[30] were prepared according to literature procedures. All other reagents were obtained from commercial sources and used without further purification. Reactions were performed under an inert atmosphere of argon unless otherwise stated and all glassware was vacuum or oven dried prior to use.

2.1.1. Preparation of *E*-(S_S,2*S*,3*S*)-(+)-*N*-*p*-toluenesulfinyl-2-benzyloxymethyl-2-carbomethoxy-3-phenylaziridine (14a). In a 250 mL oven-dried two-necked round-bottomed flask fitted with a magnetic stirring bar, a rubber septum and an argon balloon was placed 1.0 g (4.09 mmol) of (S_S)-(+)-*N*-(benzylidene)-*p*-toluenesulfinamide (**13a**) in THF (60 mL). The solution was cooled to −78°C and 2.24 mL (12.3 mmol) of methyl 2-bromo-3-(phenylmethoxy)-propionate was added. After 3 min, 11.1 mL (10.3 mmol, 1.0 M in THF) of LiHMDS was added slowly via syringe. The reaction was stirred at −78°C for 2 h, quenched with water (4 mL) at −78°C, and diluted with EtOAc (2×20 mL). The combined extracts were washed with brine (20 mL), dried ($NaSO_4$), and concentrated to give the crude product (90% de). Purification by flash chromatography (EtOAc/pentane, 20:80) afforded 1.13 g (70%) of *E*-(2*S*,3*S*)-**14a**; colorless oil; $[\alpha]^{20}_D$=+70.8 (*c* 3.9, $CHCl_3$); IR (neat) 1738, 1453, 1102, 553 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.72 (d, 2H, *J*=8.5 Hz), 7.2 (m, 12H), 4.48 (s, 1H), 4.16 (d, 2H, *J*=3.5 Hz), 3.85 (s, 3H), 3.82 (d, 1H, *J*=10 Hz), 3.08 (d, 1H, *J*=10 Hz), 2.42 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 168.4, 143.0, 142.1, 138.2, 133.6, 130.3, 126.0, 73.6, 68.0, 53.7, 52.4, 46.2, 22.2. HRMS: calcd for $C_{25}H_{25}NO_4S$ (M+H) 436.1583; found: 436.1564.

2.1.2. Methyl *E*-(S_S,2*S*,3*S*)-(−)-2-benzyloxymethyl-3-phenyl-1*H*-aziridine-2-carboxylate (15a). In a 25 mL round-bottom flask equipped with a magnetic stirring bar were placed 0.44 g (1.0 mmol) of (+)-**14a** and 0.40 mL (5 mmol) of TFA in acetone (5 mL) and water (5 mL). The solution was stirred vigorously for 15 min at rt, conc. NH4OH was added to adjust the pH to 10, and concentrated. The residue was washed with CH_2Cl_2 (3×15 mL), dried (Na_2SO_4), and concentrated to give a residue that was purified by flash chromatography (EtOAc/*n*-hexane, 3:7) affording 0.264 g (89%) of an oil; $[\alpha]^{20}_D$=−96.2 (*c* 4.8, $CHCl_3$); IR (neat) 3282, 1726, 1437, 1219, 1097 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.231 (m, 10H), 4.54 (d, 1H, *J*=12 Hz), 4.38 (d, 1H, *J*=12 Hz), 3.86 (s, 3H), 3.82 (d, 1H, *J*=10.5 Hz), 3.55 (s, 1H), 3.15 (d, 1H, *J*=10.5 Hz), 2.35 (bs, 1H); ^{13}C NMR ($CDCl_3$) δ 173.8, 138.8, 135.9, 128.9, 128.7, 128.5, 128.4, 128.2, 73.9, 68.4, 53.8, 45.2, 45.0. Anal. Calcd for $C_{18}H_{19}NO_3$: C, 72.71; H, 6.44; N, 4.71. Found: C, 72.33; H, 6.68; N, 4.63.

2.1.3. (*S*)-(+)-2-Amino-2-benzyloxymethyl-3-phenylpropionic acid methyl ester (16). In a 25 mL round-bottomed flask equipped with magnetic stirring bar and hydrogen balloon was placed with 0.050 g (0.17 mmol) of (−)-**15a**, 0.05 g of $Pd(OH)_2$ in THF (8 mL). The solution was stirred at rt for 8 h, filtered, and concentrated to give 0.049 g (98%)

of a white solid, mp 66–67°C; $[\alpha]^{20}_D$=+5.37 (*c* 2.14, $CHCl_3$); IR (KBr) 3362, 1741 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.25 (m, 10H), 4.57 (d, 1H, *J*=12.5 Hz), 4.52 (d, 1H, *J*=12.5 Hz), 3.85 (d, 1H, *J*=9 Hz), 3.69 (s, 3H), 3.49 (d, 1H, *J*=9 Hz), 3.06 (d, 1H, *J*=13 Hz), 2.75 (d, 1H, *J*=13 Hz), 1.92 (s, 2H); ^{13}C NMR ($CDCl_3$) δ 176.2, 138.5, 136.0, 130.5, 129.1, 129.0, 128.4, 128.3, 127.8. Anal. Calcd for $C_{18}H_{21}NO_3$: C, 72.22; H, 7.07; N, 4.68. Found: C, 71.96; H, 7.27; N, 4.59.

2.1.4. (*S*)-(+)-2-Amino-2-hydroxymethyl-3-phenylpropionic acid methyl ester (17). In a 25 mL round-bottomed flask fitted with magnetic stirring bar and hydrogen balloon were placed 0.05 g (0.17 mmol) of (+)-**16** and 0.05 g of $Pd(OH)_2$ in EtOH (6 mL), THF (2mL), and 0.05 mL (0.68 mmol, 4 equiv.) of TFA. The solution was stirred at rt for 8 h, filtered, and concentrated to give 0.034 g (97%) of (−)-**17** as a white solid, mp 110–111°C; $[\alpha]^{20}_D$=+1.57 (*c* 1.27, $CHCl_3$); IR (KBr) 3254, 1743, 1601, 1422 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.21 (m, 10H), 3.87 (d, 1H, *J*=10.5 Hz), 3.74 (s, 3H), 3.59 (d, 1H, *J*=10.5 Hz), 3.09 (d, 1H, *J*=13.5 Hz), 2.79 (d, 1H, *J*=13.5 Hz), 2.23 (bs, 3H); ^{13}C NMR ($CDCl_3$) δ 176.2, 135.9, 130.5, 129.3, 127.9, 68.6, 64.3, 53.0, 42.6. Anal. Calcd for $C_{11}H_{15}NO_3$: C, 63.14; H, 7.23; N, 6.69. Found: C, 62.79; H, 7.49; N, 6.51.

2.1.5. (*S*)-(+)-α-Benzylserine (18). In a 25 mL round-bottom flask equipped with a magnetic stirring bar was place 0.035 g (0.167 mmol) (−)-**17** in THF (5 mL). The solution was treated with 0.006 g (0.25 mmol, 1.5 equiv.) of LiOH in H_2O (5 mL). The reaction mixture was refluxed for 10 h, concentrated, and the pH adjusted to 1–2 with 1N HCl. The solution was evaporated to dryness and the residue was purified through a DOWEX 50WX8-100 column eluting with 15% NH_4OH (200 mL) to give 0.03 g (91%) of a white solid, mp 157–158°C (dec); $[\alpha]^{20}_D$=+16.6 (*c* 0.9, H_2O) [lit.[28b] $[\alpha]^{20}_D$=+16.4 (*c* 0.81, H_2O)]. Spectral properties of (−)-**18** were consistent with literature values.[28b]

2.1.6. *Z*-(+)-*N*-*p*-Toluenesulfinyl-2-benzyloxymethyl-2-carbomethoxy-3-propenylaziridine (14b). In a 50 mL round-bottomed flask equipped with a magnetic stirring bar, a rubber septum, and an argon balloon was placed 0.1 g (0.48 mmol) of (*S*)-(+)-**13b** in THF (15 mL). The solution was cooled to −78°C and 0.16 mL (0.96 mmol, 2.0 equiv.) of methyl 2-bromo-3-(phenylmethoxy)propionate was added. After 5 min, 0.63 mL (1.0 M solution in THF, 0.63 mmol, 1.3 equiv.) of NaHMDS was introduced dropwise via a syringe. The reaction mixture was stirred at −78°C for 3 h and quenched with saturated NH_4Cl (10 mL). Ethyl acetate (10 mL) was added, the organic phase was separated, and the aqueous phase was washed with ethyl acetate (2×10 mL). The organic phases were combined, washed with brine (10 mL), dried (Na_2SO_4), and concentrated to give an 85:15 mixture of diastereomers. Purification by flash chromatography (15% EtOAc/hexanes) afforded 0.150 g (79%) of (2*R*,3*S*)-(+)-**14b**; mp 66–70°C; $[\alpha]^{20}_D$=+65.5 (*c* 4.3, $CHCl_3$); IR (KBr pellet) 1745, 1444, 1220, 1096 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.67 (d, 3H, *J*=6.6 Hz), 2.42 (s, 3H), 3.37 (d, 1H, *J*=10.2 Hz), 3.69 (d, 1H, *J*=6.9 Hz), 3.78 (s, 3H), 3.94 (d, 1H, *J*=10.5 Hz), 4.45 (dd, 2H, *J*=12.3 Hz, *J*=33.9 Hz), 5.26 (m, 1H), 5.82 (m, 1H), 7.37 (m, 7H), 7.64 (d, 2H, *J*=8.1 Hz); ^{13}C NMR ($CDCl_3$) δ 18.6, 22.2, 46.0, 51.3, 53.5, 68.5, 73.7, 123.5, 126.0, 128.4, 128.5, 128.9, 130.1, 133.8, 138.4, 142.4, 142.7, 168.7. Anal. Calcd for $C_{22}H_{25}NO_4S$: C, 66.14; H, 6.31; N, 3.51. Found: C, 65.97; H, 6.30; N, 3.32.

2.1.7. (2*R*,3*S*)-(−)-2-Benzyloxymethyl-2-carbomethoxy-3-propenylaziridine (15b). In a 50 mL round-bottomed flask equipped with a magnetic stirring bar, a rubber septum, and an argon balloon was placed 0.068 g (0.17 mmol) of *cis*-(S_S,2*R*,3*S*)-(+)-**14b** in THF (15 mL). The solution was cooled to −78°C and 0.17 mL (3.0 M in ethyl ether, 1.53 mmol, 9.0 equiv.) of methyl magnesium bromide was added dropwise via a syringe. The reaction mixture was stirred for 4 h, quenched with saturated NH_4Cl (10 mL), and diluted with ethyl acetate (10 mL). The organic phase was separated and the aqueous phase was washed with EtOAc (2×15 mL). The organic phases were combined, dried (Na_2SO_4), and concentrated to give an oil. Purification by preparative TLC (50% EtOAc/hexanes) afforded 0.038 g (86%) of (2*R*,3*S*)-(−)-**15b**: $[\alpha]^{20}_D$=−64.1 (*c* 1.5, $CHCl_3$); IR (neat) 3683, 1737, 1521 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.69 (d, 3H, *J*=6.6 Hz), 2.07 (s, broad, 1H), 2.83 (d, 1H, *J*=5.0 Hz), 3.49 (d, 1H, *J*=10.0 Hz), 3.77 (s, 3H), 3.93 (d, 1H, *J*=10.0 Hz), 4.59 (dd, 2H, *J*=12.0, 71 Hz), 5.2 (m, 1H), 5.84 (m, 1H), 7.28 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 18.6, 44.2, 53.5, 68.9, 74.0, 126.6, 128.2, 128.5, 128.6, 128.9, 173.8. HRMS calcd for $C_{15}H_{19}NO_3$ (M+Na) 284.1263. Found: 284.1252.

2.1.8. (*R*)-(−)-2-Amino-2-benzyloxymethylhexanoic acid methyl ester (19). In a 25 mL two-necked round-bottomed flask equipped with a magnetic stirring bar and a rubber septum was placed 0.030 g (0.11 mmol) of (−)-**15b** and 0.030 g of Pd black in THF (5 mL). After two vacuum/H_2 cycles to remove air from the reaction vessel, the stirred mixture was hydrogenated at ordinary pressure (balloon) at rt for 18 h. The solution was filtered, concentrated, and purified by preparative TLC (50% EtOAc/hexanes) to give 0.020 g (65%) of an oil: $[\alpha]^{20}_D$=−29.6 (*c* 0.55, $CHCl_3$); IR (neat) 3385, 2954, 1733, 1208, 1104 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.86 (t, 3H, *J*=7.3 Hz), 1.07 (m, 1H), 1.27 (m, 4H), 1.49 (m, 1H), 1.62 (m, 1H), 1.93 (s, broad, 2H), 3.42 (d, 1H, *J*=9.5 Hz), 3.71 (s, 3H), 3.74 (d, 1H, *J*=9.5 Hz), 4.52 (dd, 2H, *J*=12.5, 29.0 Hz), 7.31 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 14.5, 23.5, 26.2, 36.8, 52.8, 62.7, 73.9, 76.7, 128.2, 128.3, 128.4, 129.0, 138.7, 177.1. HRMS calcd for $C_{15}H_{23}NO_3$ (M+H) 266.1748. Found: 266.1756.

2.1.9. (*R*)-(−)-2-Amino-2-hydroxymethylhexanoic acid methyl ester (20). In a 25 mL two-necked round-bottomed flask equipped with a magnetic stirring bar and a rubber septum was placed 0.030 g (0.11 mmol) of (−)-**15b** and 0.1 g of $Pd(OH)_2$ in MeOH (5 mL). The reaction mixture was hydrogenated at rt for 18 h and the product was purified as described above to give a 0.012 g (60%) of (−)-**20** as an oil; $[\alpha]^{20}_D$=−13.3 (*c* 0.33, $CHCl_3$); IR (neat) 3745, 3683, 1699, 1521 cm^{-1}; ^1H NMR (CDCl3) δ 0.95 (t, 3H, *J*=7.2 Hz), 1.35 (m, 4H), 1.5 5 (m, 1H), 1.7 2 (m, 1H), 3.53 (d, 1H, *J*=10.8 Hz), 3.81 (s, 3H), 3.87 (d, 1H, *J*=10.5 Hz); ^{13}C NMR ($CDCl_3$) δ 14.5, 23.5, 26.3, 36.7, 53.2, 63.3, 68.6, 175.4. HRMS calcd for $C_8H_{17}NO_3$ (M+H) 176.1284. Found 176.1287.

2.1.10. (2*R*,2*S*)-(−)-2-Benzyloxymethyl-2-carbomethoxy-3-propylaziridine (21). In a 10 mL two-necked round-bottomed flask equipped with a magnetic stirring bar and a rubber septum was placed 0.014 g (0.05 mmol) of (−)-**15b** and 0.014 g of $Pd(OH)_2$ in THF (5 mL) and hydrogenated at room temperature for 18 h. The reaction mixture was filtered and the filtrate was concentrated and purified by preparative TLC (50% EtOAc/hexanes) to give 0.0042 g (30%) of (−)-**21** as a yellow oil, $[\alpha]^{20}_D=-60.0$ (*c* 0.2, $CHCl_3$); IR (neat) 3677, 2955, 1728, 1516 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.92 (t, 3H, *J*=3.4 Hz), 1.45 (m, 4H), 1.9 (s, broad, 1H), 2.3 (m, 1H), 3.5 (d, 1H, *J*=10.26 Hz), 3.8 (s, 3H), 3.9 (d, 1H, *J*=10.27 Hz), 4.5 (d, 1H, *J*=12.47 Hz), 4.7 (d, 1H, *J*=12.1 Hz), 7.3 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 13.8, 20.9, 31.3, 42.6, 43.2, 52.8, 68.5, 73.4, 127.6, 127.8, 128.2, 138.1, 174.3. HRMS calcd for $C_{15}H_{21}NO_3$ (M+H) 264.1600. Found: 264.1605.

2.1.11. (*R*)-(−)-2-*n*-Butylserine (22). In a 10 mL round bottom flask equipped with a magnetic stirring bar was placed 0.007 g (0.039 mmol) in THF (1 mL). The solution was treated with 0.0024 g (0.057 mmol, 1.5 equiv.) of LiOH in H_2O (1 mL). The reaction mixture was stirred at room temperature for 12 h, concentrated and the pH adjusted to 1–2 with 1N HCl. The solution was evaporated to dryness and the residue was purified through a DOWEX 50WX8-100 column eluting with 10% NH_4OH (20 mL) to give 0.0048 g (75%) as a white solid, mp 226–232°C (dec) [lit.[35] mp 225–232°C (dec)]; $[\alpha]^{20}_D=-11.6$ (*c* 0.23, H_2O) [lit.[35] $[\alpha]^{20}_D=-11.8$ (*c* 0.3, H_2O)]. Spectral properties of (−)-**22** were consistent with literature values.[35]

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