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Aziridine-mediated asymmetric synthesis of quaternary β-amino acids using 2*H*-azirine 2-carboxylate esters

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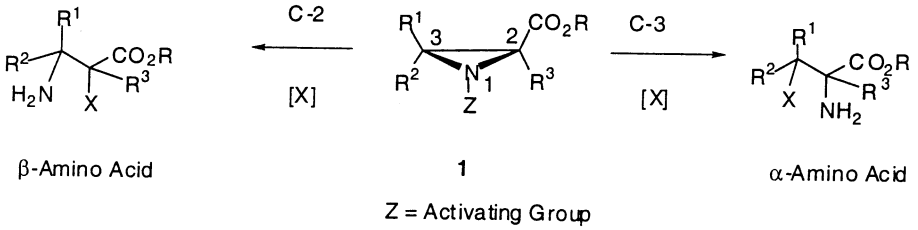
Abstract—Regioselective hydrogenation of enantiopure 3-substituted and 3,3-disubstituted aziridine 2-carboxylate esters affords β-amino acids and quaternary β-amino acids, respectively, in good yield. The aziridines are prepared via an aza-Darzens reaction of α-bromoenolates with enantiopure sulfinimines (*N*-sulfinyl imines) and by addition of Grignard reagents to 2*H*-azirine 2-carboxylate esters.

β-Amino acids, while not as common as α-amino acids, are present in natural products, such as peptides, and exhibit important biological properties.[1] β-Amino acids also serve as valuable building blocks for the asymmetric construction of β-lactam antibiotics,[2,3] and are increasingly employed as chiral building blocks.[4] Moreover, novel amino acids are frequently incorporated into biologically active molecules, both to enhance bioactivity and to probe mechanisms of action.[5] Indeed substitution of β-amino acids for α-amino acids can afford peptide analogs (peptidomimetics) with increased activity and enzymatic stability.[6] β-Peptides, oligomers of β-amino acids,[7] have been shown by the groups of DeGrado, Gillman, and Seebach to adopt to the same kinds of defined folded structures as proteins.[8] However, while a number of methods have been devised to prepare β-substituted β-amino acids as single enantiomers there very few methods to prepare quaternary examples (β,β-disubstituted β-amino acids).[9,10] Of these methods the addition of enolates to ketosulfinimines (*N*-sulfinyl imines) is particularly useful, but limited due to the facile *syn* and *anti* isomerization of some ketosulfinimines.[11,12] The catalytic hydrogenation of 3-substituted and 3,3-disubstituted aziridine 2-carboxylate esters described here offers another opportunity for the asymmetric synthesis of both secondary and quaternary β-amino acids.

The regio- and stereoselective ring-opening reactions of aziridine 2-carboxylate esters **1** serve as valuable sources of structurally diverse α and β-amino acids (Scheme 1). 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.[13] Since ring-opening does not effect the stereochemistry at C-2 or C-3 the aziridine stereochemistry is maintained in the amino acid product. The ring substituents and the reaction conditions determine stereo- and regioselectivity of the ring-opening.

With C-3 aryl or vinyl substituted aziridines, catalytic hydrogenation regiospecifically cleaves the benzylic/vinyl C–N bond in unactivated and sulfonyl-activated aziridine carboxylates.[14–22] The retention product always predominates for trisubstituted aziridine esters with CH_2Cl_2 solvent



Scheme 1.

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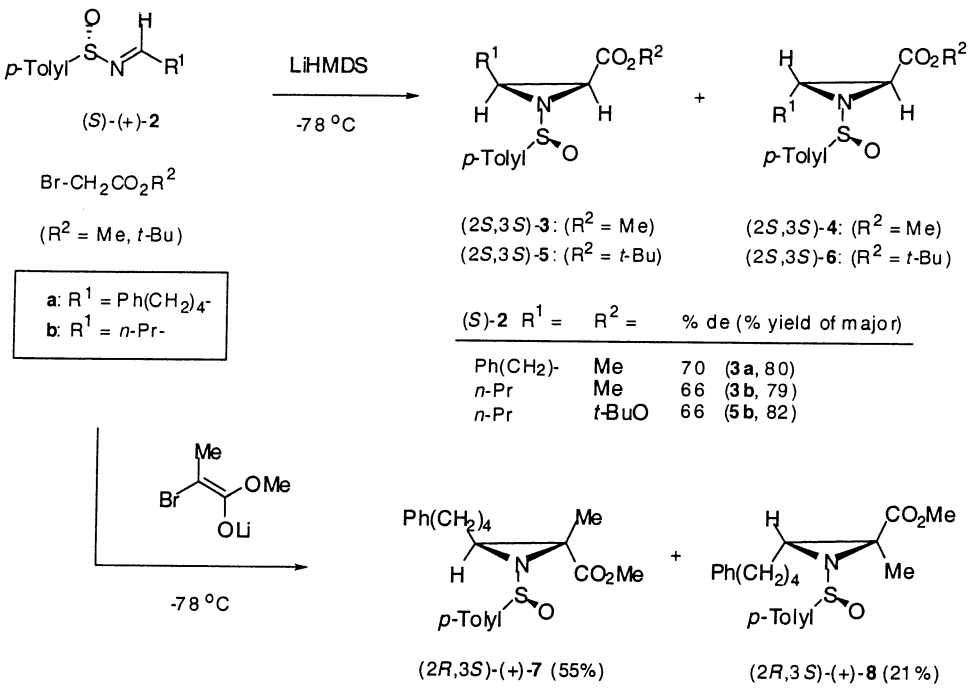


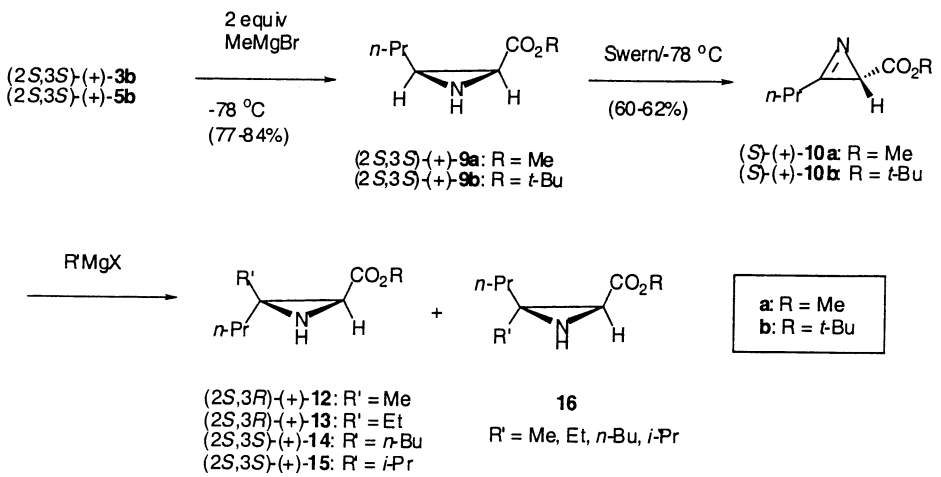
Scheme 2.

affording the best selectivity.[17] In the absence of a C-3 benzylic or vinyl aziridine substituent, hydrogenation occurs at C-2 for mono- and disubstituted aziridine-2-carboxylates to give β-amino esters.[20,21] Molander has shown, using samarium(II) iodide as the reductant, and *N*,*N*-dimethylethanolamine (DMEA) as the proton source, that C-3 alkyl and C-3 aryl aziridines are cleaved α to the carboxyl group to give β-amino acids in excellent yields.[22] In this study it was found that it was not necessary to activate nitrogen with an electron-withdrawing group and the trityl group could be used. Although the stereochemistry was preserved at the β-position, it was not maintained at the α-position. Similarly, magnesium in methanol affords β-amino acids from both aryl and alkyl *N*-sulfonyl activated aziridines.[23] As part of our continuing interest in aziridines and their application to the asymmetric synthesis of amino acids,[15–19] we report details of the catalytic hydrogenation of di- and trisubstituted aziridine 2-carboxylates to β-amino acids.

1. Results and discussion

1.1. Synthesis of aziridines

The *N*-sulfinylaziridine carboxylate esters were prepared using the aza-Darzens reaction developed earlier in our laboratory (Scheme 2).[18] This procedure entails treatment, in one pot, of the appropriate sulfinimine (*S*)-**2** and α-bromoacetate or *tert*-butyl α-bromoacetate with LiHMDS at −78°C. Diastereoselectivities were 66–70% and the isolated yield of the major aziridine diastereoisomers **3** and **5** was 79–82%. The stereochemistry of the major aziridine isomers were established as (2*S*,3*S*) in analogy



Scheme 3.

Table 1. Addition of Grignard reagents to 2*H*-azirine 2-carboxylates (+)-**10** at −78°C

Entry	(+)-**10** R=	R′MgX[a] (equiv.)	Solvent	Time (h)	Products % yield[b] (% de)[c]
1	**10a** Me	MeMgBr (3.5)	Et_2O	3	65 (**12a**+**16a**) (67)
2		MeMgBr (10)	THF	3	30 (**12a**+**16a**) (>92)
3		EtMgBr (10)	THF	0.5	53 (**13a**+**16a**) (60)
4	**10b** *t*-Bu	MeMgBr (3.5)	Et_2O	0.5	73 (**12b**+**16b**) (60)
5		MeMgBr (10)	THF	0.5[c]	73 (**12b**+**16b**) (>94)
6		EtMgBr (3.5)	Et_2O	0.1	81 (**13b**+**16b**) (25)
7		EtMgBr (10)	THF[d]	0.5	93 (**13b**+**16b**) (67)
8		*n*-BuMgCl (3.5)	Et_2O	0.3	88 (**14b**) (>94)
9		*n*-BuMgCl (10)	THF	0.3	92 (**14b**) (>94)
10		*i*-PrMgCl (3.5)	Et_2O	0.3	79 (**15b**) (>94)
11		*i*-PrMgCl (10)	THF	0.3	90 (**15b**) (>94)

[a] 3.4 equiv. of R′MgX added at −78°C.
[b] Isolated yield of both aziridines.
[c] Determined by ^{1}H NMR of the crude reaction mixture.
[d] After 0.5 h at −78°C the reaction mixture was warmed to −15°C for 10 min.

with our previous results as well as the 7 Hz $J_{2,3}$ coupling constant, which is indicative of a *cis* arrangement of the protons.[18] Attempts to use the one pot procedure for preparation of the 2-methyl aziridine carboxylate esters **7/8** failed. More successful was the addition of sulfinimine (*S*)-(+)-**2a** to the preformed lithium enolate of methyl α-bromo acetate. However the de was low (33%) and the yield of the major diastereoisomer (2*R*,3*S*)-**7** was 55% (Scheme 2).

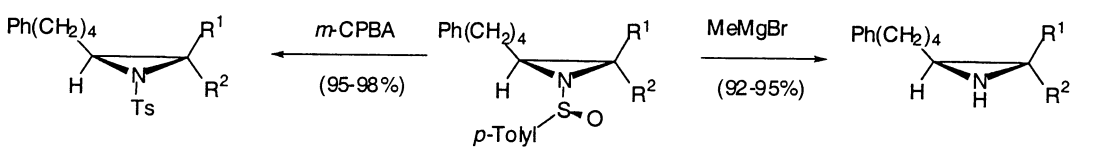
To prepare quaternary β-amino acids via aziridine hydrogenation it is necessary to have 3,3-disubstituted aziridines. While it is possible to prepare such aziridines by addition of α-haloenolates to ketosulfinimines, it is only practical when there is a large difference in size between the two keto groups.[18] When the groups are similar in size sulfinimines exist as inseparable mixtures of *E*/*Z* isomers and addition of organometallic reagents leads to poor diastereoselectivities.[24] An alternative method for preparing 3,3-disubstituted aziridines 2-carboxylates is the addition of Grignard reagents to 2*H*-azirine 2-carboxylate esters.[17] Indeed we found that Grignard reagents add *syn* to the ester group or from the more hindered face of the C−N double bond. We attributed this to pre-chelation of the organometallic reagent with the carboxyl group.

Treatment of aziridines **3b** and **5b** with 2 equiv. of MeMgBr readily removed the *N*-sulfinyl group, which afforded the NH aziridines in 70−84% yield after chromatography (Scheme 3). Swern oxidation[25] of **9** at −78°C gave the 2*H*-azirines (*S*)-(+)-**10** in 60−62% yield. Results of the addition of 3.4 equiv. of Grignard reagents to (+)-**10** are summarized in Table 1.

As can be seen from the results summarized in Table 1, addition of Grignard reagents to 2*H*-azirine (*S*)-(+)-**10a** (R=Me) gave mixtures of 3,3-disubstitued aziridines **12a** and **16a** that could not be separated (Table 1 entries 1 and 2). The best selectivity, >90% de, was observed in THF solvent (Table 1 entry 2). The *tert*-butyl ester, (*S*)-(+)-**10b** gave selectivities in excess of >94% de for addition of the methyl, *n*-butyl, and isopropyl Grignard reagents in THF (Table 1, entries 5, 9, and 11). By ^{1}H NMR only a single diastereoisomer was detected in these examples, but the ^{13}C NMR suggest that there may be a trace of the other isomer present. Addition of EtMgBr in THF to (*S*)-(+)-**10b** afforded an inseparable mixture of **13b/16b** in 67% de and a combined yield of 93% (Table 1, entry 7). The reasonable assumption is made that *syn* addition of RMgX to (*S*)-(+)-**10b** affords aziridines **12b**, **13b**, and **14b** as the major products (Scheme 3). Earlier studies had shown that Grignard reagents add exclusively *syn* to the methyl and *tert*-butyl ester moieties in 2*H*-azirine 2-carboxylates.[17] However, attempts to confirm this assumption by NOESY experiments proved inconclusive.

1.2. Synthesis of β-substituted β-amino acids

Because of the generally held perception that N-activation is necessary for aziridine ring-opening, hydrogenation studies were first conducted on the *N*-tosyl aziridines (−)-**17a** and (+)-**18a**. These aziridines were prepared in >90% yield by *m*-chloroperbenzoic acid (*m*-CPBA) oxidation of (2*S*,3*S*)-(+)-**3** and (2*R*,3*S*)-(+)-**7** (Scheme 4). However, we soon discovered N-activation was not necessary and that the NH aziridines, (+)-**17b** and (−)-**18b**, prepared from **3a** and **7** using the MeMgBr protocol, readily open to give the

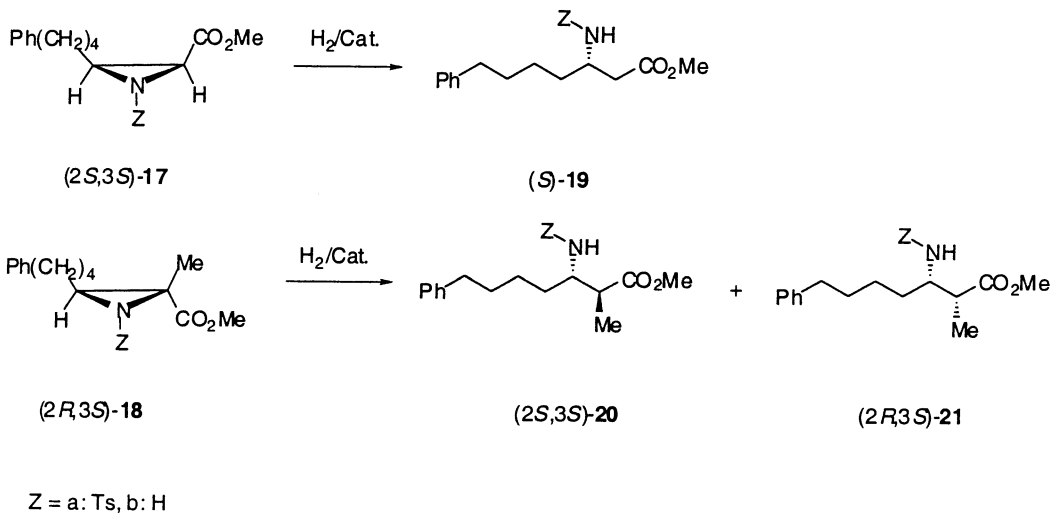


17a: $R^1 = CO_2Me$, $R^2 = H$
18a $R^1 = Me$, $R^2 = CO_2Me$

(+)-**3a**: $R^1 = CO_2Me$, $R^2 = H$
(+)-**7** $R^1 = Me$, $R^2 = CO_2Me$

17b: $R^1 = CO_2Me$, $R^2 = H$
18b $R^1 = Me$, $R^2 = CO_2Me$

Scheme 4.



Scheme 5.

parent β-amino acids (Scheme 4). Importantly, this means that the sometimes harsh conditions (HBr/PhOH) necessary to remove *N*-tosyl groups may not always be required.[26] Hydrogenations were conducted by treating the aziridines with the appropriate catalysis for 8 h under 1 atm of H_2 (balloon). In the absence of H_2 aziridine ring-opening was not observed (Scheme 5). The β-amino acids were isolated by flash chromatography and these results are summarized in Table 2.

As noted in Table 2 Raney-nickel proved to the best catalysts for NH or N–Ts aziridine ring-opening. Aziridine (−)-**17a** (Z=Ts) gave the corresponding β-amino acids (*S*)-(+)-**19** in near quantitative yield (Table 2, entries 2 and 3). 2-Methylaziridine (2*R*,3*S*)-(+)-**18a** gave two separable diastereoisomers (2*S*,3*S*)-(+)-**20a** and (2*R*,3*S*)-(−)-**21a**. The absolute configuration of the major diastereoisomer was determined by X-ray crystallography to have the (2*S*,3*S*) stereochemistry which indicates ring-opening occurs with retention of configuration (Fig. 1). The retention/inversion diastereoselectivity for (+)-**18a** was dependent on the alcohol solvent (Table 2). As the alcohol became more sterically demanding the de increased to a maximum of 70% for *tert*-butyl alcohol (Table 2 entries 6–8 and 11). While use of chiral alcohols failed to improve the de's, a double diastereodifferentiation effect was noted for (*R*) and (*S*)-2-butanol (e.g. 56 vs 32% de, respectively, Table 2 entries 9 and 10). It is clear from these results that the alcohol solvent is, in some manner, altering the catalysts surface, with the more hindered alcohols providing the best selectivity.

Table 2. Hydrogenation of aziridines **17** and **18** for 8 h at rt and with 1 atm H_2

Entry	Aziridine (Z=)	Catalyst/solvent	β-Amino acid (% yield)[a] (de)[b]
1	**17a** (Z=Ts)	Pd/C (H_2)/THF	No reaction
2		Pd/C (HCO_2H)/THF	(*S*)-**19a** (88)
3		Raney-Ni/EtOH	(*S*)-**19a** (100)
4	**17b** (Z=H)	Raney-Ni/EtOH	(*S*)-**19b** (84)
5	**18a** (Z=Ts)	Raney-Ni/THF	No reaction
6		Raney-Ni/MeOH	(2*S*,3*S*)-**20a** (60) (20)
7		Raney-Ni/EtOH	(2*S*,3*S*)-**20a** (62) (34)
8		Raney-Ni/*i*-PrOH	(2*S*,3*S*)-**20a** (80) (64)
9		Raney-Ni/(*R*)-2-BuOH	(2*S*,3*S*)-**20a** (72) (56)
10		Raney-Ni/(*S*)-2-BuOH	(2*S*,3*S*)-**20a** (60) (32)
11		Raney-Ni/*t*-BuOH	(2*S*,3*S*)-**20a** (77) (70)
12	**18b** (Z=H)	Raney-Ni/*t*-BuOH	(2*S*,3*S*)-**20b** (89)[c] (71)

Raney-Ni 2800.
[a] Isolated yield of major product.
[b] Determined by ^1H NMR on the crude product.
[c] Combined yield of inseparable (2*S*,3*S*)-**20** and (2*R*,3*S*)-**21**.

1.3. Quaternary β-amino acids

Hydrogenation of aziridines **12**, **14**, and **15** with Raney-Ni in ethanol under an atmosphere of H_2 gave quaternary, β,β-disubstituted β-amino acids (*S*)-**22** in good to excellent yields and >92% ee (Scheme 6). As noted earlier the diastereoselection for the addition of Grignard reagents to 2*H*-azirines (*S*)-(+)-**10b** (Scheme 3) was estimated to be >94%. In support of this value is the fact that the de's of the Mosher amides of **22** were >92% de.

In summary, methodology is presented for the synthesis of quaternary, β,β-disubstituted β-amino acids via hydrogenation of 3,3-disubstituted aziridine 2-carboxylates. The aziridines were prepared by addition of Grignard reagents to 2*H*-azirine 2-carboxylates.

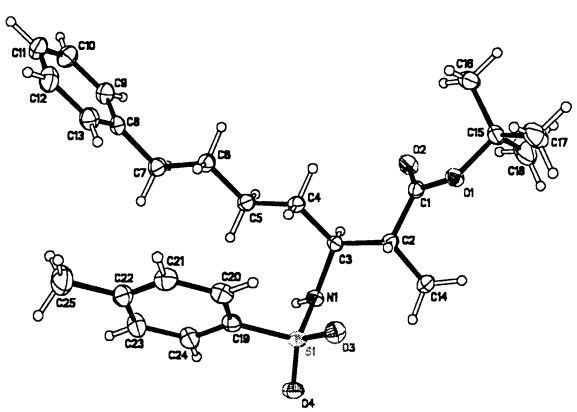
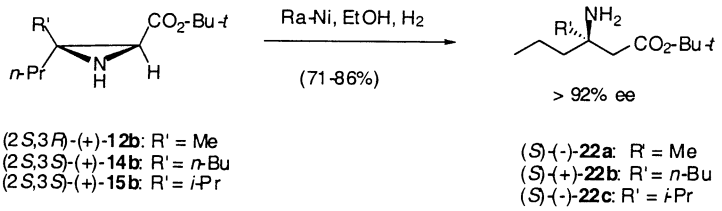


Figure 1. ORTEP view of (2*S*,3*S*)-(+)-**20**.



Scheme 6.

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 1000 μm) purchased from Analtech Inc. TLC plates were visualized with UV and in an iodine chamber. THF and diethyl ether were freshly distilled under argon from a purple solution of sodium and benzophenone. Elemental and HRMS analyses were performed in the Department of Chemistry, University of Pennsylvania, Philadelphia, and Department of Chemistry, Drexel University, Philadelphia, PA, respectively. Unless stated otherwise, all reagents were purchased from commercial sources and used without additional purification.

Sulfinimines (*S*)-(+)-*N*-(5-phenylpentylidene)-*p*-toluenesulfinamide (**2a**) and (*S*)-(+)-*N*-(*n*-butylidene)-*p*-toluenesulfinamide (**2b**) were prepared as previously described.[27]

2.1.1. (*S*)-(+)-*N*-(5-Phenylpentylidene)-*p*-toluenesulfinamide (2a). Purification by flash chromatography (*n*-hexane/EtOAc, 9:1): (92%) of a yellow oil: $[\alpha]_D^{20}=+230.8$ (*c* 1.19, $CHCl_3$); IR (neat) 1621, 1506, 1094 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.65 (m, 4H), 2.40 (s, 3H), 2.51 (m, 2H), 2.60 (t, 2H), 7.19 (m, 5H), 7.27 (d, 2H, *J*=7.4 Hz), 7.54 (d, 2H, *J*=2.0 Hz), 8.21 (t, 1H, *J*=5.0 Hz); ^{13}C NMR ($CDCl_3$) δ 147.6, 142.6, 142.3, 130.4, 129.0, 128.9, 126.4, 125.2, 36.3, 36.2, 31.4, 25.6, 22.1. Anal. calcd for $C_{18}H_{21}NOS$: C, 72.24; H, 7.02; N, 4.68. Found: C, 72.33; H, 7.14; N, 4.95.

2.1.2. *tert*-Butyl *Z*-(S_S,2*S*,3*S*)-(+)-*N*-*p*-toluenesulfinyl-3-*n*-propylaziridine 2-carboxylate (5b). Typical procedure. In a 100 mL, one-necked, round-bottomed flask equipped with a stirring bar, rubber septum, and argon filled balloon was placed 0.42 g (2.02 mmol) of sulfinimine (+)-**2b** in THF (40 mL). The reaction mixture was cooled to −78°C, 0.60 mL (4.04 mmol) of *tert*-butyl bromoacetate (Aldrich) was added followed after 10 min by 2.5 mL (2.5 mmol) of LiHMDS. The reaction mixture was stirred at −78°C for 30 min, quenched with H_2O (10 mL), and diluted with EtOAc (20 mL). The organic phase was separated, and the aqueous layer was extracted with EtOAc (2×10 mL). The combined organic phases were washed with brine (20 mL), dried (Na_2SO_4), and concentrated. Purification by silica gel flash chromatography (*n*-hexane/EtOAc, 10:1) gave 0.46 g (82%) of a clear oil: $[\alpha]_D^{20}=+87.7$ (*c* 0.7, $CHCl_3$); IR (neat) 2965, 2874, 1742, 1154 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.94 (t, 3H, *J*=7.0 Hz), 1.30 (s, 3H), 1.42–1.58 (m, 2H), 1.61–1.69 (m, 1H), 1.72–1.78 (m, 1H), 2.40 (s, 3H), 2.70 (dd, 1H, *J*=7.0, 13.7 Hz), 3.03 (d, 1H, *J*=7.0 Hz), 7.28 (d, 2H, *J*=8.0 Hz), 7.61 (d, 2H, *J*=8.0 Hz); ^{13}C NMR ($CDCl_3$) δ 166.9, 142.2, 142.1, 129.9, 125.5, 82.1, 41.7, 32.6, 29.3, 28.2, 21.8, 20.9, 14.2. Anal. calcd for $C_{17}H_{25}NO_3S$: C, 63.13; H, 7.79; N, 4.33. Found: C, 63.55; H, 7.53; N, 4.09.

2.1.3. *tert*-Butyl *E*-(S_S,2*S*,3*R*)-(−)-*N*-*p*-toluenesulfinyl-3-*n*-propylaziridine 2-carboxylate (6b). Purification by silica gel column chromatography (*n*-hexane/EtOAc, 10:1) gave 0.09 g (16%) of a clear oil: $[\alpha]_D^{20}=-116.7$ (*c* 1.2, $CHCl_3$); IR (neat) 2963, 2932, 2874, 1746, 1457 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.99 (t, 3H, *J*=7.5 Hz), 1.31 (s, 3H), 1.46–1.58 (m, 2H), 1.62–1.88 (m, 2H), 2.40 (s, 3H), 2.97 (m, 1H), 3.07 (d, 1H, *J*=4.0 Hz), 7.27 (d, 2H, *J*=8.0 Hz), 7.62 (d, 2H, *J*=8.0 Hz); ^{13}C NMR ($CDCl_3$) δ 168.2, 143.6, 142.0, 129.8, 125.4, 82.3, 46.0, 35.0, 30.3, 28.2, 21.8, 21.7, 14.1. HRMS calcd for $C_{17}H_{26}NO_3S$ (M+H): 324.1623. Found: 324.1633.

2.1.4. Methyl *Z*-(S_S,2*S*,3*S*)-(+)-*N*-*p*-toluenesulfinyl-3-*n*-propylaziridine 2-carboxylate (3b). Purification by silica gel column chromatography (*n*-hexane/EtOAc, 10:1) gave 0.35 g (79%) of a yellow oil: $[\alpha]_D^{20}=+100.5$ (*c* 1.2, $CHCl_3$); IR (neat) 2960, 2874, 1749, 1439, 1098 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.97 (t, 3H, *J*=7.5 Hz), 1.42–1.78 (m, 4H), 2.40 (s, 3H), 2.76 (m, 1H), 3.18 (d, 1H, *J*=7.0 Hz), 3.60 (s, 3H), 7.28 (d, 2H, *J*=8.0 Hz), 7.60 (d, 2H, *J*=8.0 Hz); ^{13}C NMR ($CDCl_3$) δ 168.1, 142.3, 141.5, 129.8, 125.5, 52.5, 41.6, 31.6, 30.0, 21.7, 20.7, 14.0. HRMS calcd For $C_{14}H_{20}NO_3S$ (M+H): 282.1164. Found 282.1169.

2.1.5. Methyl *E*-(S_S,2*S*,3*R*)-(−)-*N*-*p*-toluenesulfinyl-3-*n*-propylaziridine 2-carboxylate (4b). Purification by silica gel column chromatography (*n*-hexane/EtOAc, 10:1) gave 0.08 g (17%) of a yellow oil: $[\alpha]_D^{20}=-116.8$ (*c* 1.4, $CHCl_3$); IR (neat) 2960, 2931, 2874, 1747, 1441, 1227, 1099 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.92 (t, 3H, *J*=7.5 Hz), 1.42–1.55 (m, 2H), 1.65–1.74 (m, 1H), 1.76–1.88 (m, 1H), 2.33 (s, 3H), 2.92 (m, 1H), 3.11 (d, 1H, *J*=3.6 Hz), 3.56 (s, 3H), 7.22 (d, 2H, *J*=8.0 Hz), 7.54 (d, 2H, *J*=8.0 Hz); ^{13}C NMR ($CDCl_3$) δ 169.6, 143.0, 142.2, 130.0, 125.3, 52.8, 46.4, 30.3, 21.8, 21.6, 14.0.

2.1.6. Methyl *Z*-(S_S,2*S*,3*S*)-(+)-*N*-*p*-toluenesulfinyl-3-(5-phenylpentyl)aziridine 2-carboxylate (3a). Purification by flash chromatography (*n*-hexane/EtOAc, 8:2) afforded 0.40 g (72%) of a yellow oil: $[\alpha]_D^{20}=+73.5$ (*c* 1.08, $CHCl_3$); IR (neat) 3026, 1733, 1374, 1246 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.45 (m, 1H), 1.55 (m, 1H), 1.66 (m, 2H), 1.74 (m, 2H), 2.38 (s, 3H), 2.61 (t, 2H, *J*=5.0 Hz), 2.73 (m, 1H), 3.16 (d, 1H, *J*=7.0 Hz), 3.58 (s, 3H), 7.24 (m, 5H), 7.27 (d, 2H, *J*=7.5 Hz), 7.58 (d, 2H, *J*=7.5 Hz); ^{13}C NMR ($CDCl_3$) δ 168.5, 142.8, 141.8, 130.4, 129.1, 129.0, 126.4, 125.6, 52.9, 42.1, 36.3, 32.0, 31.6, 27.4, 27.3, 22.1. Anal. calcd for

$C_{21}H_{25}NO_3S$: C, 67.92; H, 6.74; N, 3.78. Found: C, 67.53; H, 6.90; N, 3.70.

2.1.7. Methyl *E*-(S_S,2*S*,3*R*)-(+)-*N*-*p*-toluenesulfinyl-3-(5-phenylpentyl)aziridine 2-carboxylate (4a). Purification by flash chromatography (*n*-hexane/EtOAc, 8:2) afforded 0.03 g (6%) of a yellow oil: $[\alpha]_D^{20}$=+114.4 (*c* 1.2, $CHCl_3$); IR (neat) 3026, 2857, 2933, 1734, 1442, 1216 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.10 (m, 2H), 1.43 (m, 3H), 1.65 (m, 1H), 2.36 (s, 3H), 2.40 (t, 2H, *J*=7.6 Hz), 2.69 (m, 1H), 3.00 (d, 1H, *J*=3.6 Hz), 3.71 (s, 3H), 7.03 (m, 2H), 7.10 (m, 1H), 7.18 (m, 2H), 7.25 (d, 2H, *J*=7.5 Hz), 7.64 (d, 2H, *J*=7.5 Hz); ^{13}C NMR ($CDCl_3$) δ 169.5, 142.8, 142.5, 142.3, 130.1, 128.7, 128.7, 126.1, 125.8, 53.1, 47.4, 40.4, 36.0, 31.1, 29.1, 27.4, 22.0.

2.1.8. Methyl *E*-(S_S,2*R*,3*S*)-(+)-*N*-*p*-toluenesulfinyl-2-methyl-3-(4-phenylbutyl) aziridine 2-carboxylate (7). In a 250 mL, two-necked, round-bottomed flask fitted with a magnetic stirring bar, a rubber septum, and an argon filled balloon was placed 13.5 mL (13.5 mmol, 1.0 M in THF) of LiHMDS in THF (80 mL). The solution was cooled to −78°C, 1.54 mL (13.5 mmol) of methyl α-bromopropionate was added, and after 0.5 h at −78°C a solution of 1.5 g (5.0 mmol) of (*S*)-(+)-**2a** in THF (20 mL) was added to the enolate via a cotton-wrapped, double-ended needle over 0.5 h. The reaction mixture was stirred for 0.5 h, quenched with H_2O (10 mL) at −78°C, and diluted with EtOAc (2×20 mL). The organic phase was washed with brine (20 mL), dried ($MgSO_4$), and concentrated. Purification by flash chromatography (*n*-hexane/EtOAc, 8:2) afforded 1.07 g (55%) of an oil: $[\alpha]_D^{20}$=+43.5 (*c* 1.7, $CHCl_3$); IR (neat) 2926, 1731, 1453, 1263, 1103, 846 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.10 (m, 2H), 1.32 (m, 1H), 1.47 (s, 3H), 1.51 (m, 3H), 2.41 (s, 3H), 2.49 (t, 2H, *J*=8.0 Hz), 2.91 (dd, 1H, *J*=6.5, 1.5 Hz), 3.77 (s, 3H), 7.11 (d, 2H, *J*=7.0 Hz), 7.28 (t, 2H, *J*=7.5 Hz), 7.30 (d, 2H, *J*=7.5 Hz), 7.68 (d, 2H, *J*=8.0 Hz); ^{13}C NMR ($CDCl_3$) δ 170.2, 160.5, 144.6, 142.8, 137.4, 130.3, 129.0, 127.9, 126.5, 73.8, 58.3, 53.6, 36.2, 31.5, 31.3, 25.2, 22.2. Anal. calcd for $C_{22}H_{27}NO_3S$: C, 68.54; H, 7.06; N, 3.63. Found: C, 68.39; H, 7.32; N, 3.63.

2.1.9. Methyl *Z*-(S_S,2*S*,3*S*)-(+)-*N*-*p*-toluenesulfinyl-2-methyl-3-(4-phenylbutyl) aziridine 2-carboxylate (8). Purification by flash chromatography (*n*-hexane/EtOAc, 8:2) afforded 0.59 g (21%) of an oil: $[\alpha]_D^{20}$=+32.5 (*c* 0.097, $CHCl_3$); IR (neat) 3026, 2933, 2858, 1746, 1730, 1453, 1148 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.32–1.58 (m, 6H), 1.47 (s, 1H), 2.35 (s, 3H), 2.51 (t, 2H, *J*=7.2 Hz), 2.66 (dd, 1H, *J*=5.6 Hz, *J*=6.8 Hz), 3.59 (s, 3H), 7.09 (m, 3H), 7.20 (m, 4H), 7.64 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 168.9, 141.3, 141.0, 140.7, 128.7, 127.5, 127.4, 124.9, 124.8, 51.5, 50.4, 44.9, 34.8, 30.1, 27.2, 25.7, 20.6, 14.8.

2.1.10. *tert*-Butyl *Z*-(2*S*,3*S*)-(+)-3-*n*-propyl 1*H*-aziridine 2-carboxylate (9b). Typical procedure. In a 50 mL, one-necked, round-bottomed flask equipped with a stirring bar, rubber septum, and argon filled balloon was placed 0.20 g (0.61 mmol) of (+)-**5b** in THF (10 mL). The reaction was cooled to −78°C, 0.40 mL (1.22 mmol) of MeMgBr (Aldrich) was added and the reaction mixture was stirred for 20 min. At this time the reaction was quenched with sat. NH_4Cl (3 mL), diluted with EtOAc (10 mL), and the organic phase was separated. The aqueous phase was extracted with EtOAc (2×5 mL), the combined organic phases were washed with brine (8 mL), dried (Na_2SO_4), and concentrated. Purification by silica gel column chromatography (*n*-hexane/EtOAc, 5:1) gave 0.09 g (77%) of a white solid; mp: 40–41°C; $[\alpha]_D^{20}$=+49.2 (*c* 1.0, $CHCl_3$); IR (neat) 3269, 2963, 2932, 2874, 1719, 1157 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.81 (b, 1H), 0.92 (t, 3H, *J*=7.0 Hz), 1.45 (s, 3H), 1.35–1.50 (m, 3H), 1.55–1.6 (m, 1H), 2.13 (m, 1H), 2.52 (d, 1H, *J*=6.5 Hz); ^{13}C NMR ($CDCl_3$) δ 170.5, 82.1, 38.9, 35.8, 30.2, 28.5, 21.5, 14.2. HRMS calcd for $C_{10}H_{20}NO_2$ (M+H): 186.1494. Found: 186.1496.

2.1.11. Methyl *cis*-(2*S*,3*S*)-(+)-3-*n*-propyl 1*H*-aziridine-2-carboxylate (9a). Purification by silica gel column chromatography (*n*-hexane/EtOAc, 5:1) gave 0.09 g (84%) of a colorless oil: $[\alpha]_D^{20}$=+64.0 (*c* 1.06, $CHCl_3$); IR (neat) 3270, 2969, 2873, 1734, 1202 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.91 (t, 3H, *J*=7.0 Hz), 1.36–1.62 (m, 4H), 2.22 (m, 1H), 2.64 (d, 1H, *J*=6.0 Hz), 3.75 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 171.9, 52.7, 39.1, 34.8, 30.3, 21.4, 14.1. HRMS calcd for $C_7H_{14}NO_2$ (M+H): 144.1024. Found: 144.1020.

2.1.12. Methyl *Z*-(2*S*,3*S*)-(+)-3-(5-phenylpentyl) 1*H*-aziridine-2-carboxylate (17b). Purification by flash chromatography (*n*-hexane/EtOAc, 10:1) afforded 0.11 g (95%) of a white solid; mp 40–41°C; $[\alpha]_D^{20}$=+47.7 (*c* 1.09, $CHCl_3$); IR (KBr) 3262, 3026, 2926, 2856, 1730, 1441, 1206 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.41 (m, 1H), 1.51 (m, 2H), 1.66 (m, 4H), 2.62 (m, 3H), 3.73 (s, 3H), 7.25 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 172.2, 142.9, 129.0, 128.9, 126.4, 53.0, 36.4, 35.1, 31.6, 30.3, 28.5, 28.0; Anal. calcd for $C_{14}H_{19}NO_2$: C, 72.10; H, 8.10; N, 6.00. Found: C, 71.83; H, 7.80; N, 5.94.

2.1.13. Methyl *E*-(2*R*,3*S*)-(−)-2-methyl-3-(5-phenylpentyl) 1*H*-aziridine-2-carboxylate (18b). Purification by flash chromatography (*n*-hexane/EtOAc 7:3) 0.12 g (92%) of an oil: $[\alpha]_D^{20}$=−61.6 (*c* 1.4, $CHCl_3$); IR (neat) 3290, 2933, 1724, 1456, 1287, 1207, 1106 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.36 (s, 3H), 1.59–1.43 (m, 4H), 1.68 (m, 2H), 2.20 (m, 2H), 2.63 (m, 2H), 3.74 (s, 3H), 7.18 (m, 3H), 7.27 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 176.1, 143.0, 129.0, 128.9, 126.4, 53.3, 44.5, 38.8, 36.4, 31.8, 29.5, 27.8, 14.4. HRMS calcd for $C_{15}H_{21}NO_2$ (m+Na): 270.1470. Found: 270.1463.

2.1.14. *tert*-Butyl (*S*)-(+)-3-*n*-propyl 2*H*-azirine-2-carboxylate (10b). Typical procedure. In a 50 mL, one-necked, round-bottomed flask equipped with a stirring bar, rubber septum, and argon filled balloon was placed 1.85 g (10.0 mmol) of **9b** in DCM (20 mL), and the solution was cooled to −78°C. In a second 250 mL, one-necked, round-bottomed flask equipped with a stirring bar, rubber septum and argon filled balloon was added 11.0 mL (21.9 mmol) of oxalyl chloride in DCM (80 mL) and the solution was cooled to −78°C. At this time 3.40 mL (47.8 mmol) of DMSO was added and after 10 min the solution of **9b** was transferred via a double ended needle to the DMSO solution. After stirring for 10 min at −78°C, 6.7 mL (49.9 mmol) of Et_3N was added and the reaction mixture was warmed to rt and stirred for 4 h. The reaction mixture was concentrated, Et_2O (80 mL) was added, and the precipitated salts were

removed by filtration. The organic phase was washed with H_2O (2×30 mL), the aqueous phase was extracted with Et_2O (2×10 mL), the combined organic phases were washed with brine (30 mL), dried (Na_2SO_4), and concentrated. Purification by silica gel column chromatography (*n*-hexane/EtOAc, 20:1) gave 1.10 g (60%) of a yellow liquid: $[\alpha]_D^{20}$=+67.8 (*c* 0.5, $CHCl_3$); IR (neat) 2976, 2937, 1725, 1344, 1168 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.07 (t, 3H, *J*=7.5 Hz), 1.45 (s, 3H), 1.61 (s, 1H), 1.80 (m, 2H), 2.33 (s, 1H), 2.79 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 172.0, 162.8, 82.0, 30.2, 29.2, 28.7, 18.5, 14.3. HRMS calcd for $C_{10}H_{18}NO_2$ (M+H): 184.1338. Found: 184.1343.

2.1.15. Methyl (*S*)-(+)-3-*n*-propyl 2*H*-azirine-2-carboxylate (10a). Purification by silica gel column chromatography (*n*-hexane/EtOAc, 20:1) gave 0.14 g (62 %) of a yellow oil: $[\alpha]_D^{20}$=+104.7 (*c* 0.74, $CHCl_3$); IR (neat) 2965, 2879, 1733, 1340, 1186 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.07 (t, 3H, *J*=7.5 Hz), 1.45 (s, 3H), 1.61 (s, 1H), 1.80 (m, 2H), 2.33 (s, 1H), 2.79 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 173.0, 162.3, 52.5, 29.0, 28.9, 18.3, 14.1. HRMS calcd for $C_7H_{12}NO_2$ (M+H): 142.0868. Found: 142.0867.

2.1.16. Methyl *E*-(2*S*,3*R*)-(+)-3-methyl-3-*n*-propyl 1*H*-aziridine-2-carboxylate (12a). Typical procedure. In a 10 mL, one-necked, round-bottomed flask equipped with a stirring bar, rubber septum, and argon filled balloon was placed 0.04 g (0.22 mmol) of **10a** in THF (5 mL). The reaction was cooled to −78°C and 0.025 mL (0.74 mmol) of MeMgBr was added. The reaction mixture was stirred at −78°C for 20 min, quenched with sat. NH_4Cl (2 mL), and diluted with EtOAc (5 mL). The organic phase was separated, and the aqueous layer was washed with EtOAc (2×5 mL). The combined organic phases were washed with brine (4 mL), dried (Na_2SO_4), and concentrated. Purification by silica gel column chromatography (*n*-hexane/EtOAc, 10:1) gave 0.01 g (30%) of a yellow oil: $[\alpha]_D^{20}$=+90.3 (*c* 0.058, $CHCl_3$); IR (neat) 3272, 2962, 2875, 1731, 1440, 1210, 1105 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.92 (t, 3H, *J*=7.0 Hz), 1.30–1.55 (m, 4H), 1.27 (s, 3H), 2.43 (b, 1H), 3.76 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 171.8, 52.7, 43.4, 42.2, 41.8, 19.4, 16.9, 14.4. HRMS calcd for $C_8H_{16}NO_2$ (M+H): 158.1181. Found: 158.1175.

2.1.17. Methyl (2*S*,3*R*/*S*)-3-ethyl-3-*n*-propyl 1*H*-aziridine-2-carboxylate (13a/16a). 0.03 g (53%) of a yellow oil. Major isomer (2*S*,3*R*)-**13a**: ^1H NMR ($CDCl_3$) δ 0.92 (m, 3H), 1.38–1.53 (m, 4H), 2.43 (b, 1H), 3.74 (s, 3H); ^{13}C NMR ($CDCl_3$) 171.9, 52.7, 41.7, 38.1, 31.9, 23.4, 19.7, 14.5, 10.7. Minor isomer (2*S*,3*S*)-**15a**: ^1H NMR ($CDCl_3$) δ 0.90 (m, 3H), 1.38–1.53 (m, 4H), 2.41 (b, 1H), 3.74 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 171.9, 47.6, 41.4, 38.1, 29.2, 23.4, 19.7, 14.5, 9.8.

2.1.18. *tert*-Butyl *E*-(2*S*,3*R*)-(+)-3-methyl-3-*n*-propyl 1*H*-aziridine-2-carboxylate (12b). Chromatographic purification (*n*-hexane/EtOAc, 9:1) gave 0.04 g (73%) of a yellow oil: $[\alpha]_D^{20}$=+54.0 (*c* 0.74, $CHCl_3$); IR (neat) 3276, 2967, 1721, 1158 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.92 (t, 3H, *J*=7.0 Hz), 1.25 (s, 3H), 1.30–1.35 (m, 1H), 1.47 (s, 9H), 1.41–1.51 (m, 3H), 2.32 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 170.6, 42.9, 42.5, 42.2, 28.6, 19.3, 16.7, 14.4. HRMS calcd for $C_{11}H_{22}NO_2$ (M+H): 200.1650. Found: 200.1642.

2.1.19. *tert*-Butyl (2*S*,3*R*/*S*)-3-ethyl-3-*n*-propyl 1*H*-aziridine-2-carboxylate (13b/16b). Chromatographic purification (*n*-hexane/EtOAc, 9:1) gave 0.05 g (93%) of **13b/16b** as a yellow oil: major isomer (2*S*,3*R*)-**13b**: ^1H NMR ($CDCl_3$) δ 0.87 (m, 6H), 1.30–1.48 (m, 4H), 1.53–1.63 (m, 2H), 1.41 (s, 9H), 2.26 (b, 1H); ^{13}C NMR ($CDCl_3$) 170.6, 82.0, 47.0, 42.7, 38.0, 28.5, 23.3, 18.8, 14.5, 10.9. Minor isomer (2*S*,3*S*)-**16b**: ^1H NMR ($CDCl_3$) 0.80–0.90 (m, 6H), 1.30–1.48 (m, 4H), 1.53–1.63 (m, 2H), 1.41 (s, 9H), 2.25 (b, 1H); ^{13}C NMR ($CDCl_3$) 170.6, 82.0, 47.0, 42.4, 32.0, 29.2, 23.4, 20.0, 14.4, 9.7.

2.1.20. *tert*-Butyl *Z*-(2*S*,3*S*)-(+)-3-*n*-butyl-3-*n*-propyl 1*H*-aziridine-2-carboxylate (14b). Chromatographic purification (*n*-hexane/EtOAc, 10:1) gave 0.06 g (88%) of a yellow oil: $[\alpha]_D^{20}$=+55.5 (*c* 0.82, $CHCl_3$); IR (neat) 3271, 2970, 2933, 2973, 1368, 1229, 1157 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.84 (m, 6H), 1.15–1.25 (m, 4H), 1.30–1.45 (m, 6H), 1.41 (s, 9H), 1.50–1.60 (m, 2H), 2.27 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 170.5, 82.0, 46.3, 42.7, 38.6, 30.1, 29.0, 28.5, 23.3, 18.9, 14.5, 14.4. HRMS calcd for $C_{14}H_{27}NO_2$ (M+H): 242.2120. Found: 241.3697.

2.1.21. *tert*-Butyl *Z*-(2*S*,3*S*)-(+)-3-*iso*-propyl-3-*n*-propyl 1*H*-aziridine-2-carboxylate (15b). Chromatographic purification (*n*-hexane/EtOAc, 9:1) gave 0.05 g (79%) of a yellow oil: $[\alpha]_D^{20}$=+54.8 (*c* 0.68, $CHCl_3$); IR (neat) 3266, 2963, 2933, 2874, 1719, 1368, 1225, 1155 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.89 (t, 3H, *J*=7.5 Hz), 0.93 (d, 3H, *J*=7.0 Hz), 1.02 (d, 3H, *J*=7.0 Hz), 1.18–1.26 (m, 2H), 1.44–1.50 (m, 1H), 1.46 (s, 3H), 1.58–1.67 (m, 2H), 2.47 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 170.8, 81.9, 49.6, 41.6, 31.9, 28.5, 20.2, 19.0, 18.3, 14.8. HRMS calcd for $C_{13}H_{26}NO_2$ (M+H): 250.1783. Found: 250.1774.

2.1.22. Methyl *E*-(2*S*,3*S*)-(−)-*N*-*p*-toluenesulfonyl-3-(5-phenylpentyl)aziridine 2-carboxylate (17a). Typical procedure. In a 25 mL, one-necked, round-bottomed flask equipped with a magnetic stirring bar was placed 0.25 g (0.67 mmol) of **3a** in $CHCl_3$ (10 mL). *m*-Chloroperbenzoic acid, 0.39 g (1.35 mmol, 60%, Aldrich) was added to the solution in small portions and the reaction mixture was stirred at rt for 30 min. The solution was diluted with DCM (10 mL), sat. $NaHCO_3$ (10 mL) was added, and the organic phase was dried ($MgSO_4$) and concentrated. Purification by flash chromatography (*n*-hexane/EtOAc, 9:1) afforded 0.26 g (98%) of a colorless oil: $[\alpha]_D^{20}$=−35.1 (*c* 3.75, $CHCl_3$); IR (neat) 2926, 1751, 1161 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.30 (m, 2H), 1.59 (m, 4H), 2.45 (s, 3H), 2.53 (t, 2H, *J*=7.5 Hz), 2.98 (m, 1H), 3.43 (d, 1H, *J*=8.0 Hz), 7.12–7.35 (m, 7H), 7.85 (d, 2H, *J*=8.5 Hz); ^{13}C NMR ($CDCl_3$) δ 166.3, 145.0, 142.0, 134.1, 129.7, 129.6, 128.3, 128.2, 128.1, 125.7, 52.6, 44.6, 40.9, 35.5, 30.6, 26.5, 26.4, 21.6; Anal. calcd for $C_{21}H_{25}NO_4S$: C, 65.09; H, 6.50; N, 3.61. Found: C, 65.51; H, 6.45; N, 3.11.

2.1.23. Methyl *E*-(2*R*,3*S*)-(+)-*N*-*p*-toluenesulfonyl-2-methyl-3-(4-phenylbutyl)-aziridine-2-carboxylate (18a). Chromatographic purification (*n*-hexane/EtOAc, 9:1) gave 0.28 g (95%) of a yellow oil: $[\alpha]_D^{20}$=+1.0 (*c* 1.5, $CHCl_3$); IR (neat) 2929, 1767, 1436, 1331, 1161, 1091, 956, 668 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.37–1.43 (m, 1H), 1.45 (s, 3H), 1.56–1.62 (m, 3H), 2.44 (s, 3H), 2.56 (t, 2H, *J*=8.5 Hz), 3.55 (dd,

1H, J=5.0, 2.0 Hz), 3.82 (s, 3H), 7.13–7.30 (m, 7H), 7.79 (d, 2H, J=8.0 Hz); ^{13}C NMR ($CDCl_3$) δ 189.4, 144.8, 142.8, 137.9, 130.2, 129.0, 128.2, 126.5, 53.8, 53.2, 49.6, 36.3, 31.5, 27.9, 27.3, 16.4. HRMS calcd for $C_{22}H_{27}NO_4S$ (M+1): 402.1739. Found: 402.1736.

2.1.24. Methyl (*S*)-(+)-3-amino-7-phenylheptanote (19b). In a 25 mL, two-neck, round-bottomed flask, equipped with a rubber septum, stirring bar, and hydrogen filled balloon was placed 0.05 g (0.21 mmol) of **17b** in EtOH (8 mL), and 0.04 g of Raney-Ni (W 2800). The reaction mixture was stirred for 8 h, the Raney-Ni was removed by filtration through Celite, and the solution was concentrated. The residue was extracted with DCM (3×4 mL), the combined organic phases were washed with brine (3 mL), dried (Na_2SO_4), and concentrated. Purification by silica gel column chromatography (*n*-hexane/EtOAc/MeOH, 12:7:1) gave 0.04 g (84%) of a yellow oil: $[\alpha]_D^{20}$=+8.77 (*c* 0.94, $CHCl_3$); IR (neat) 3380, 3307, 2930, 2856, 1736, 1602, 1436, 838 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.32–1.48 (m, 4H), 1.58–1.67 (m, 2H), 1.98 (b, 2H), 2.28 (dd, 1H, J=9.0, 16.0 Hz), 2.48 (dd, 1H, J=4.0, 16.0 Hz), 2.62 (t, 2H, J=7.5 Hz), 3.19 (b, 1H), 7.17 (m, 3H), 7.27 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 173.4, 142.8, 128.8, 128.7, 126.1, 52.0, 48.7, 42.6, 37.7, 36.2, 31.7, 26.1. HRMS calcd for $C_{14}H_{22}NO_2$ (M+H): 236.1650. Found: 236.1654.

2.1.25. Methyl (*S*)-(−)-3-*N*-(*p*-tolylsulfonyl)amino-7-phenyl heptanoate (19a). Chromatographic purification (*n*-hexane/EtOAc, 1:1) gave 0.09 g (88%) of an oil: $[\alpha]_D^{20}$=−10.3 (*c* 0.8, $CHCl_3$); IR (neat) 3318, 1733, 1100, 904 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.25 (m, 2H), 1.26 (m, 2H), 1.44–1.51 (m, 2H), 2.40 (m, 2H), 2.42 (s, 3H), 2.50 (t, 2H, J=9.0 Hz), 3.50 (m, 1H), 3.60 (s, 3H), 5.12 (d, 1H, J=9.0 Hz), 7.10 (d, 2H, J=8.0 Hz), 7.10–7.29 (m, 5H), 7.73 (d, 2H, J=8.0 Hz); ^{13}C NMR ($CDCl_3$) δ 172.5, 144.0, 142.9, 138.7, 130.3, 129.0, 127.7, 126.4, 52.4, 51.2, 39.2, 36.2, 35.2, 31.4, 26.0, 22.2. Anal. calcd for $C_{21}H_{27}NO_4S$: C, 64.75; H, 6.99; N, 3.60. Found: C, 64.38; H, 7.15; N, 3.43.

2.1.26. Methyl (2*S*,3*S*)-(+)-2-methyl-3-*N*-(*p*-tolylsulfonyl)amino-7-phenylheptanoate (20a). Chromatographic purification (*n*-hexane/EtOAc, 9:1) gave 0.22 g (80%) of a yellow oil: $[\alpha]_D^{20}$=+4.00 (*c* 2.0, $CHCl_3$); IR (neat) 3289, 2936, 1736, 1453, 1328, 1159, 1091 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.06 (d, 3H, J=7.5 Hz); 1.15 (m, 2H), 1.36–1.46 (m, 4H), 2.41 (s, 3H), 2.45 (t, 2H, J=7.5 Hz), 2.66 (m, 1H), 3.41 (m, 1H), 3.64 (s, 3H), 5.20 (d, 1H, J=9.5 Hz), 7.09 (d, 2H, J=7.0 Hz), 7.10–7.29 (m, 5H), 7.75 (d, 2H, J=7.0 Hz), ^{13}C NMR ($CDCl_3$) δ 175.9, 143.8, 139.3, 130.2, 129.0, 128.9, 127.6, 126.4, 56.6, 52.5, 42.9, 36.2, 34.3, 31.5, 26.1, 22.2, 14.8. Anal. calcd for $C_{22}H_{29}NO_4S$: C, 65.48; H, 7.24; N, 3.47. Found: C, 65.01; H, 7.60; N, 3.27.

2.1.27. Minor isomer: methyl (2*R*,3*S*)-(−)-2-methyl-3-*N*-(*p*-tolylsulfonyl)amino-7-phenylheptanoate acid (21a). Chromatographic purification (*n*-hexane/EtOAc, 9:1) gave 0.04 g (15%) of an oil: $[\alpha]_D^{20}$=−16.6 (*c* 3.65, $CHCl_3$); IR (neat) 3263, 2937, 1767, 1471, 1329, 1158, 1091 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.06 (d, 3H, J=7.5 Hz), 1.06–1.48 (m, 6H), 2.42 (s, 3H), 2.47 (m, 2H), 2.52 (m, 1H), 3.38 (m, 1H), 3.61 (s, 3H), 4.92 (d, 1H, J=9.7 Hz), 7.10 (d, 2H, J=8.5 Hz), 7.11–7.73 (m, 5H), 7.76 (d, 2H, J=8.5 Hz); ^{13}C NMR ($CDCl_3$) δ 175.0, 144.0, 143.0, 138.9, 130.3, 129.0, 128.9, 127.7, 126.4, 56.8, 52.5, 44.0, 36.3, 32.0, 31.6, 26.1, 22.1, 13.9; Anal. calcd for $C_{22}H_{29}NO_4S$: C, 65.48; H, 7.24; N, 3.47. Found: C, 65.09; H, 7.35; N, 3.33.

2.1.28. *tert*-Butyl (*R*)-(−)-3-amino-3-methyl hexanoate (22a). Chromatographic purification (*n*-hexane/EtOAc, 1:1) gave 0.04 g (71 %) of a yellow oil: $[\alpha]_D^{20}$=−2.67 (*c* 0.52, $CHCl_3$); IR (neat) 3366, 2965, 1730, 1374, 1150 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.92 (t, 3H, J=7.0 Hz), 1.25 (s, 3H), 1.35 (m, 2H), 1.45 (s, 9H), 1.59 (m, 2H), 2.39 (s, 2H), 4.14 (b, 2H); ^{13}C NMR δ ($CDCl_3$) 172.0, 81.8, 53.6, 46.4, 44.5, 28.7, 27.0, 17.9, 15.1. HRMS calcd for $C_{11}H_{24}NO_2$ (M+H): 202.1807. Found: 202.1873.

2.1.29. *tert*-Butyl (*S*)-(+)-3-amino-3-*n*-propyl heptanoate (22b). Chromatographic purification (*n*-hexane/EtOAc, 1:1) gave 0.04 g (78 %) of a yellow oil: $[\alpha]_D^{20}$=+1.38 (*c* 0.94, $CHCl_3$); IR (neat) 3379, 3312, 2959, 2933, 1724, 1367 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.90 (m, 6H), 1.20–1.30 (m, 6H), 1.30–1.40 (m, 4H), 1.44 (s, 9H), 1.68 (b, 2H), 2.25 (s, 2H); ^{13}C NMR ($CDCl_3$) δ 172.3, 81.2, 54.2, 46.4, 43.1, 40.4, 28.5, 26.3, 23.7, 17.3, 15.1, 14.5. HRMS calcd for $C_{14}H_{30}NO_2$ (M+H): 244.2276. Found: 244.2274.

2.1.30. *tert*-Butyl (*R*)-(−)-3-amino-3-*iso*-propyl-hexanoate (21c). Chromatographic purification (*n*-hexane/EtOAc 1:1) gave 0.04 g (86%) of a yellow oil: $[\alpha]_D^{20}$=−2.46 (*c* 0.73, $CHCl_3$); IR (neat) 3389, 3318, 2961, 2934, 1722, 1457, 1367 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.89 (m, 9H), 1.28–1.35 (m, 2H), 1.37–1.43 (m, 2H), 1.45 (s, 9H), 1.57 (b, 2H), 1.72 (m, 1H), 2.30 (dd, 2H, J=13.9, 38.1 Hz); ^{13}C NMR ($CDCl_3$) δ 172.6, 80.8, 56.1, 43.9, 40.6, 35.3, 28.5, 17.3, 17.2, 15.2. HRMS calcd for $C_{13}H_{28}NO_2$ (M+H): 230.2120. Found: 230.2118.

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