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PAPER

Asymmetric synthesis of α,β-diamino acid derivatives with an aziridine-, azetidine- and γ-lactone-skeleton *via* Mannich-type additions across α-chloro-*N*-sulfinylimines†

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The efficient asymmetric synthesis of new chiral γ-chloro-α,β-diamino acid derivatives *via* highly diastereoselective Mannich-type reactions of *N*-(diphenylmethylene) glycine esters across a chiral α-chloro-*N*-*p*-toluenesulfinylimine was developed. The influence of the base, LDA or LiHMDS, used for the formation of the glycine enolates, was of great importance for the *anti*-/*syn*-diastereoselectivity of the Mannich-type reaction. The γ-chloro-α,β-diamino acid derivatives proved to be excellent building blocks for ring closure towards optically pure *anti*- and *syn*-β,γ-aziridino-α-amino esters, and subsequent ring transformation into *trans*-3-aminoazetidine-2-carboxylic acid derivatives and α,β-diamino-γ-butyrolactones.

Introduction

Nature uses α-amino acid derivatives with a leaving group at the γ-position as versatile building blocks in the biosynthesis of a broad range of biologically important natural products. For example, (*S*)-adenosylmethionine (SAM) is a biological sulfonium compound that is involved in many biological processes. SAM is the second most common co-enzyme in the human body, after ATP, and it is known as the major biological methyl donor in reactions catalyzed by methyltransferases.[1] Enzymological studies have demonstrated that SAM is not only used as a methyl donor in biological reactions, but that SAM is also a precursor for a variety of natural products such as 1-aminocyclopropane-1-carboxylic acid (α-ACC), precursor of the plant hormone ethylene, *N*-acylhomoserine lactones (AHLs), signal molecules involved in bacterial quorum sensing, and L-azetidine-2-carboxylic acid (L-Aze), a non-proteinogenic amino acid homologue of proline.[1c,2] Besides the biosynthesis of these carbocyclic and heterocyclic compounds starting from SAM, γ-chloro-α-amino acids also constitute excellent precursors for the preparation of these molecules.[3] Moreover, γ-chloro-α-amino acids are involved in the biosynthesis of a wide range of natural products such as cytotrienins (apoptosis-inducing *Streptomycete* metabolite),[3a] coronatine (phytotoxin),[3b,3c] and bactobolins (antibiotic activity).[4]

Some γ-chloro-α-amino acids are also biologically active as a free amino acid, such as armentomycin, a non-proteinogenic amino acid with antibiotic properties,[3a,5] and 4-chloro-L-threonine, which is biologically active as a serine hydroxymethyltransferase-inhibitor,[3d] and as a herbicidal antimetabolite.[6] 4-Chloro-L-threonine is also a constituent of naturally occurring syringomycins (antifungal compound),[7] and actinomycins (cytotoxic and antibacterial compound).[8]

Next to γ-chloro-α-amino acid derivatives, β-amino acids[9] and α,β-diamino acid derivatives have also gained a lot of attention as non-proteinogenic amino acids for different reasons. Several of these biologically important compounds, such as β-(*N*-oxalyl)-L-α,β-diaminopropionic acid (neurotoxin),[10] β-methylamino-L-alanine (neurotoxin),[11] L-quisqualic acid (vermicide),[12] L-mimosine (cell proliferation blocker),[13] and L-willardine (agonist of AMPA and kainate receptor)[14] are found in this group of atypical amino acids.

α,β-Diamino acids can also serve as building blocks for the synthesis of new heterocyclic compounds and peptides.[15] Previously published results disclosed the successful racemic synthesis and elaboration of γ-chloro-α,β-diamino acid derivatives *via* a Mannich-type addition of 'benzophenone imine glycinates' across *N*-(*p*-toluenesulfonyl) α-chloroaldimines.[16] Results

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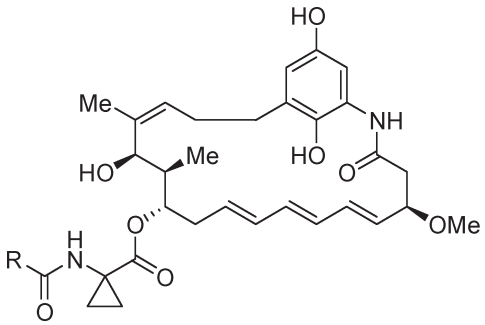
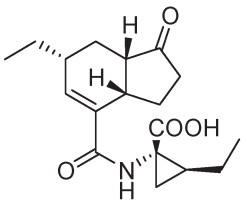
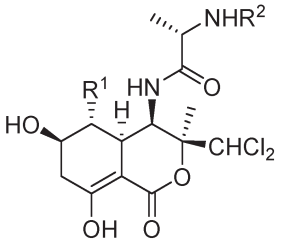


Cytotrienin A (R = 1-cyclohexenyl)
Cytotrienin B (R = cyclohexyl)

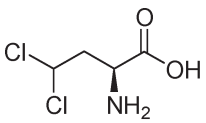


Coronatine

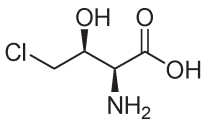


Bactobolin A (R^1 = OH, R^2 = H)
B (R^1 = OH, R^2 = *L*-Ala)
C (R^1 = H, R^2 = H)
D (R^1 = H, R^2 = *L*-Ala)

discussed within the present paper demonstrate the first asymmetric synthesis and elaboration of γ-chloro-α,β-diamino acid derivatives, as new building blocks for heterocyclic scaffolds, which incorporate the biologically interesting γ-chloro-α-amino acid moiety as well as the α,β-diamino acid moiety.



Armentomycin



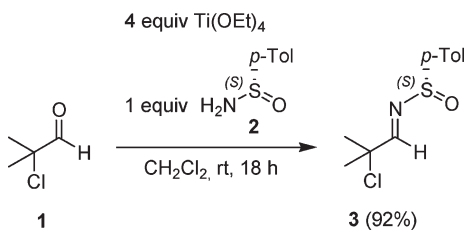
4-Chloro-L-threonine

Results and discussion

The new chiral α-chloro-*N*-sulfinylimine **3** was efficiently prepared by condensation of α-chloroisobutyraldehyde **1** with (*S*)-(+)-*p*-toluenesulfinamide **2** in dichloromethane in the presence of $Ti(OEt)_4$ (Scheme 1).[17]

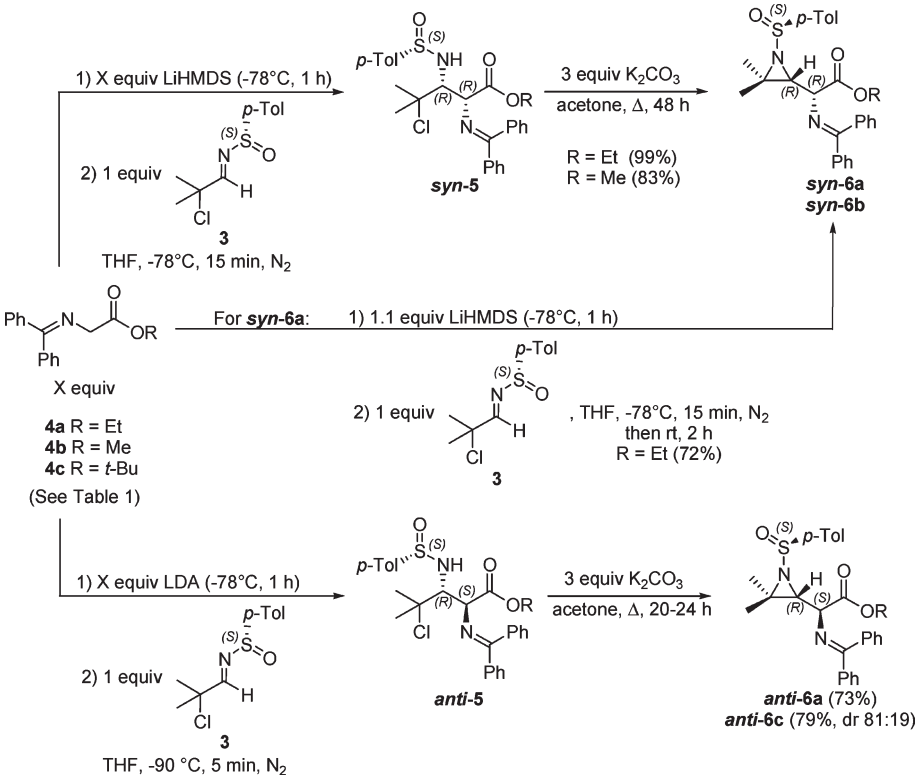
The stereoselective synthesis of chiral azaheterocyclic α,β-diamino acid derivatives was performed *via* a Mannich-type addition of *N*-protected glycine esters **4** across chiral α-chloro-*N*-sulfinylimine **3** and was optimized by systematically changing the reaction conditions (Scheme 2, Table 1) in the synthesis of γ-chloro-α,β-diamino esters **5a**. It was found that the base, LDA or LiHMDS, used for the deprotonation of the glycine ester **4a**, had a dramatic influence on the *syn*- or *anti*-selectivity of the reaction (Table 1).

In a first reaction (Table 1, entry 1), the Mannich-type addition of ethyl glycinate **4a** across chiral α-chloro-*N*-*p*-toluenesulfinyl isobutyraldimine **3** was performed at −78 °C using five equivalents of LiHMDS. ^{1}H NMR of the crude reaction mixture indicated that the resulting *syn*-γ-chloro-α,β-diamino ester ***syn*-5a** was obtained with good *syn*-selectivity (dr = 93 : 7). The *syn*-adduct ***syn*-5a** was isolated as a single diastereomer in a yield of 63% after purification by column chromatography and subsequent recrystallization. Repeating the reaction with 1.1 equivalents of LiHMDS (entry 2) led to the formation of *syn*-γ-chloro-α,β-diamino ester ***syn*-5a** in an excellent *syn*-selectivity (dr = 99 : 1) after recrystallization in 88% yield. When 1.1 equivalents of the enolate were used, column chromatography to purify the *syn*-adduct ***syn*-5a** could be avoided which resulted in an improved yield. The use of methyl glycinate **4b** using the same (entry 3) conditions resulted in a similar *syn*-selectivity (dr = 97 : 3) and yield (86%). In the following reaction (entry 4), the Mannich-type addition was performed with 1.1 equivalents of LDA, resulting in γ-chloro-α,β-diamino ester ***anti*-5a** with good *anti*-selectivity (dr = 87 : 13). The *anti*-γ-chloro-α,β-diamino ester ***anti*-5a** was obtained in 79% yield as a mixture of two diastereomers (dr 89 : 11) after purification by column chromatography. Unfortunately, the *anti*-adduct ***anti*-5a** was not crystalline and could not be obtained as a single diastereomer. In order to improve the diastereoselectivity, the reaction was conducted with 1.6 equivalents of LDA (entry 5), according to a procedure as reported for the synthesis of *anti*-ethyl diamino-3-phenylpropanoates from *N*-(benzylidene)-*p*-toluenesulfinamide and glycine enolates.[18a] These conditions led to a slightly better diastereoselectivity (dr 90 : 10), but unfortunately the *anti*-γ-chloro-α,β-diamino ester ***anti*-5a** was obtained in a lower yield of 55% as a mixture of two diastereomers (dr 90 : 10) after purification by tedious column chromatography. Next, *tert*-butyl glycinate **4c** was subjected to the Mannich-type reaction conditions with α-chloro-*N*-*p*-toluenesulfinyl isobutyraldimine **3** using 1.6 equivalents of LDA (entry 6). The resulting *anti*-γ-chloro-α,β-diamino ester ***anti*-5c** was obtained with moderate *anti*-selectivity (dr = 72 : 28) and was isolated in 52% yield as a mixture of two diastereomers (dr 81 : 19) after purification by column chromatography.



Scheme 1 Synthesis of chiral *N*-(2-chloro-2-methylpropylidene) *p*-toluenesulfinamide **3**.

Both the *syn*- and *anti*-addition products **5** were subsequently cyclized to the corresponding *N*-sulfinylaziridines **6** (Scheme 2) upon treatment with K_2CO_3 in acetone under reflux in good to excellent isolated yields (73–99%). The *syn*-*N*-sulfinylaziridine ***syn*-6a** could also be prepared directly in 72% yield *via* a



Scheme 2 Synthesis of *syn*-and *anti*-*N*-sulfinylaziridines **6**.

Table 1 Addition of *N*-(diphenylmethylene) glycine esters **4** across *N*-*p*-toluenesulfinylimine **3** producing *syn*-and *anti*-addition products **5**

Entry	Ester	Base	Equiv. Enolate	Time/Temp	*syn*/*anti* ratio[a]	Product	Yield (%)
1	**4a**	LiHMDS	5	15 min, −78 °C	93 : 7	***syn*-5a**	63[b]
2	**4a**	LiHMDS	1.1	15 min, −78 °C	99 : 1[c]	***syn*-5a**	88[b]
3	**4b**	LiHMDS	1.1	15 min, −78 °C	97 : 3[c]	***syn*-5b**	86[b]
4	**4a**	LDA	1.1	5 min, −90 °C	13 : 87	***anti*-5a**	79[d]
5	**4a**	LDA	1.6	5 min, −90 °C	10 : 90	***anti*-5a**	55[e]
6	**4c**	LDA	1.6	5 min, −90 °C	28 : 72	***anti*-5c**	52[f]
7	**4a**	LiHMDS	1.1	15 min, −78 °C; 2 h, rt	>99 : 0	***syn*-6a**	72[b]
8	**4a**	LDA	1.1	5 min, −90 °C; 2 h, rt	>99 : 0	***syn*-6a**	—

[a] Determinated *via* ^{1}H NMR of crude reaction mixtures with ***syn*-5** or ***syn*-6** as standard [b] Isolated yield of single diastereomer (dr >97 : 3) [c] Determinated *via* ^{1}H NMR after recrystallisation of crude reaction mixtures [d] Isolated yield of *anti*- and *syn*-diastereomers (dr 89 : 11) [e] Isolated yield of *anti*- and *syn*-diastereomers (dr 90 : 10) [f] Isolated yield of *anti*- and *syn*-diastereomers (dr 81 : 19)

single-step reaction starting from ethyl glycinate **4a**, if the reaction mixture from the Mannich-type addition across imine **3** after 15 min at −78 °C was subsequently stirred for two hours at room temperature (Table 1, entry 7). This procedure was not applicable for the synthesis of *anti*-*N*-sulfinylaziridines ***anti*-6** as the *anti*-adducts are the kinetically favored diastereomers which isomerize to the thermodynamically more stable *syn*-isomers (entry 8). The absolute stereochemistry of the *anti*-*N*-*p*-toluenesulfinylaziridine ***anti*-6a** and *syn*-adduct ***syn*-5a** were unambiguously determined by means of X-ray diffraction analysis (Fig. 1).

The dramatic influence of the base, LDA or LiHMDS (Scheme 2), on the stereochemical outcome of the Mannich-type reaction across α-chloro-*N*-sulfinylimine **3** under kinetic conditions (for example −90 °C, 5 min) is rationalized on the basis of the enolate geometry of the anions derived from the deprotonation of *N*-(diphenylmethylene) glycine esters **4**. As reported in the literature, the enolates obtained *via* deprotonation of *N*-(diphenylmethylene) glycine esters **4** with LDA are expected to have the *Z*-geometry (Scheme 3), which is favoured by intramolecular chelation.[18] As commonly performed in the assignment of enolate geometry, in contrast to conventional *E*/*Z*-nomenclature, the highest priority designation is allocated to the O-metal group of the enolate substituents. Alternatively, we suggest that upon deprotonation of *N*-(diphenylmethylene) glycine esters **4** with the less basic LiHMDS in THF, a shift towards the formation of the *E*-enolate occurs (Scheme 3). Unfortunately, the enolate geometry could not be determinated *via* trapping experiments with TMSCl.[19] Reaction of the *Z*- and *E*-enolates *via* **TS-7a** and **TS-7b** (Scheme 3) results in the formation of ***anti*-5** and ***syn*-5**, respectively.[18a]

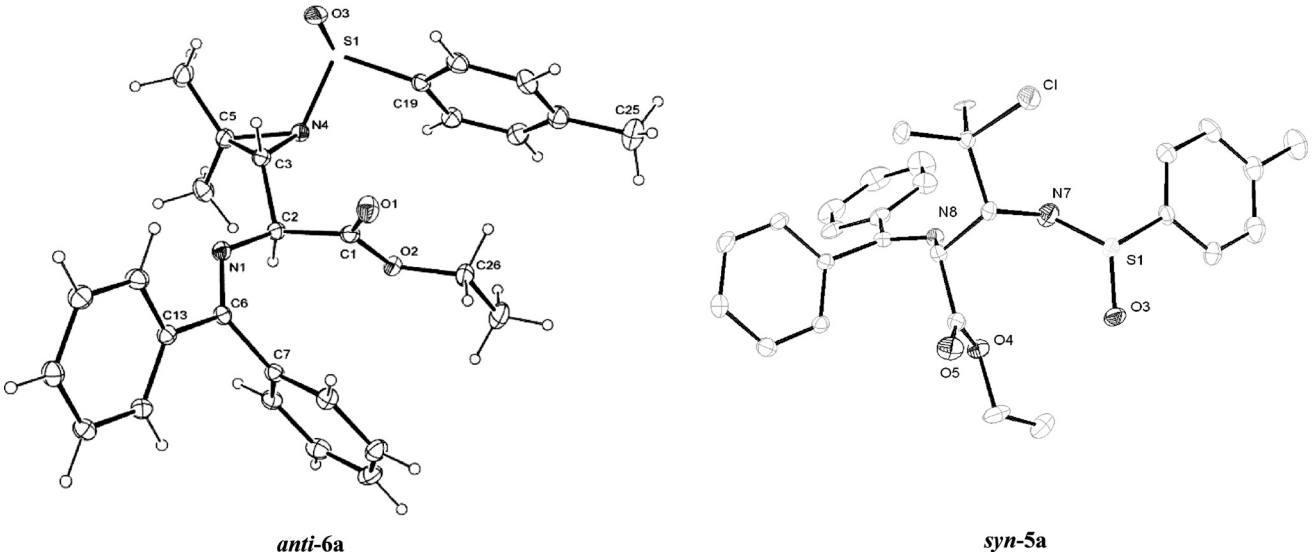
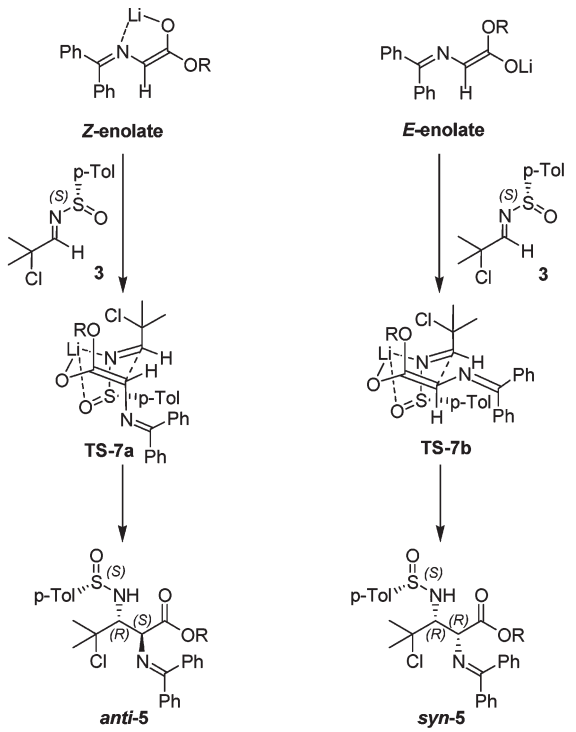


Fig. 1 X-ray diffraction analysis of *anti*-*N*-sulfinylaziridine ***anti*-6a** and *syn*-adduct ***syn*-5a**.

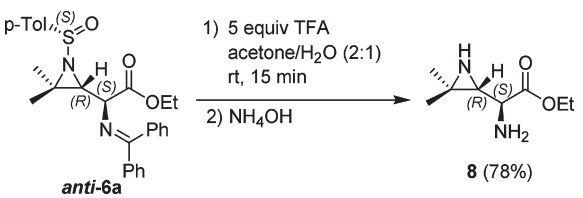


[a] For the assignment of the *E*/*Z*-geometry of the enolates, the highest priority designation is allocated to the O-metal group of the enolate substituents.

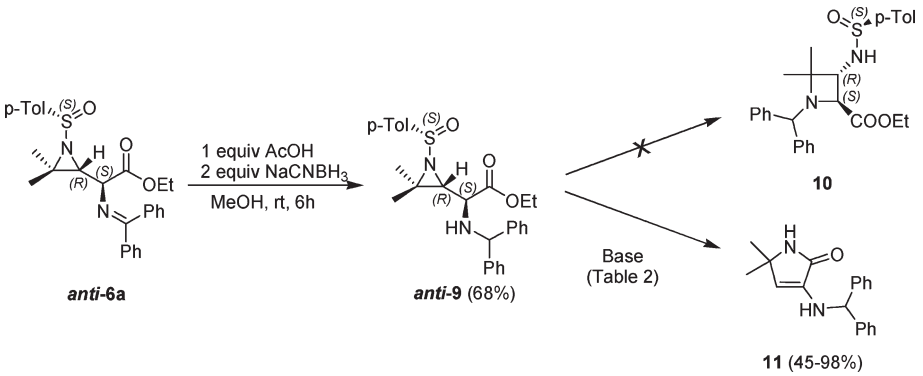
Scheme 3 Transition state model for the reaction of *Z*- and *E*-enolate of glycine esters **4** in the Mannich-type addition across chiral *N*-(2-chloro-2-methylpropylidene) *p*-toluenesulfinamide **3**.[a]

The *N*-protective groups of *anti*-aziridine **6a** (Scheme 4) were readily removed by treatment with five equivalents of trifluoroacetic acid in acetone/water (2 : 1) at room temperature for 15 min, resulting in the *N*-deprotected *anti*-β,γ-aziridino-α-amino ester **8** in 78% yield after a basic workup with NH_4OH.[20]

The *N*-sulfinyl β,γ-aziridino moiety of aziridine ***anti*-6a** could be functionally equivalent to the γ-chloro substituent of natural



Scheme 4 Deprotection of *anti*-aziridine ***anti*-6a** with TFA.

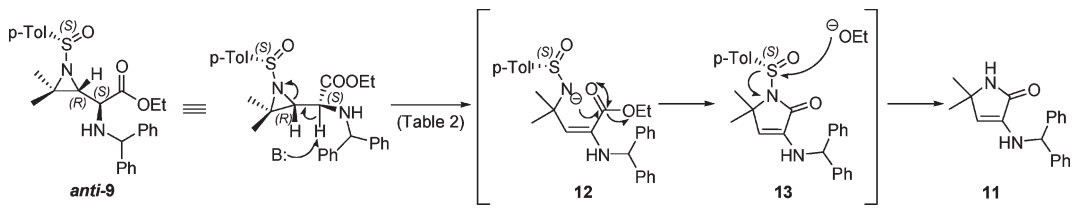


Scheme 5 Synthesis of aziridine ***anti*-9** and further transformation into 3-amino-1,5-dihydropyrrol-2-one **11**.

Table 2 Different reaction conditions for the ring transformation of aziridine ***anti*-9**

Entry	Solvent	Equiv. base	Base	Temp	Time	Result	Yield
1	THF	1	KOtBu	Δ	2.5 h	**11**	87%[a]
2	THF	1	NaH	Δ	1 h	**11**	45%[b]
3	EtOH	3	K_2CO_3	Δ	22 h	**11**	98%[a]
4	DMSO	3	K_2CO_3	Δ	22 h	Complex mixture	—
5	DMSO	2.5	NaH	80 °C	2 h	**11**	56%[b]

[a] Yield after precipitation of dihydropyrrol-2-one **11** in diethyl ether [b] Yield after recrystallization from diethyl ether



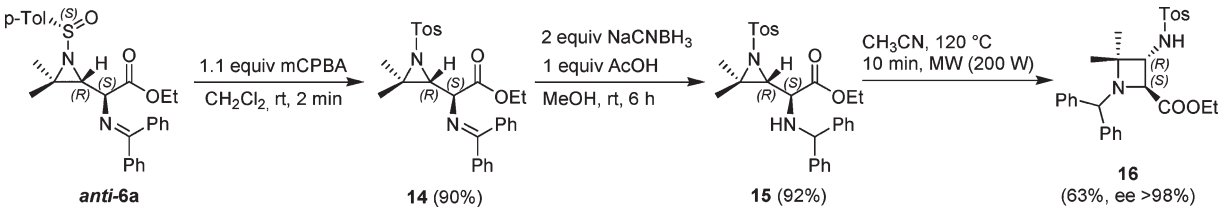
Scheme 6 Reaction mechanism for the synthesis of 3-amino-1,5-dihydropyrrol-2-one **11**.

γ-chloro-α-amino acids,[3] or the adenosyl-S^+-CH_3 cation of SAM,[1] in activating the γ-carbon as an electrophile. Eventually, this reactivity could be used in a ring transformation *via* intramolecular *N*-alkylation to the corresponding *trans*-β-aminoazetidine-2-carboxylate **10**. The *N*-diphenylmethylene group of *anti*-*N*-sulfinylaziridine ***anti*-6a** (Scheme 5) was reduced with $NaCNBH_3$ in the presence of acetic acid in MeOH, resulting in aziridine ***anti*-9** containing a nucleophilic α-amino function (68% yield). Several attempts were made to achieve the ring transformation of *N*-sulfinylaziridine ***anti*-9** into *trans*-β-aminoazetidine-2-carboxylate **10**, albeit without success (Scheme 5, Table 2). A possible explanation for this failure is the poorer electron-withdrawing character of the *p*-toluenesulfinyl group, relative to the *p*-toluenesulfonyl group. Previously, the latter sulfonyl group allowed to achieve an intramolecular ring opening towards the corresponding azetidines.[16b]

An initial attempt using similar reaction conditions as in our previously reported ring transformation into racemic *anti*-*N*-tosylazetidines, *via* heating in acetonitrile in the presence of one equivalent Et_3N,[16b] did not result in the formation of *trans*-β-aminoazetidine-2-carboxylate **10**. Also, use of more equivalents of triethylamine, other solvents (EtOH, DMSO), and/or increased reaction times and temperatures, did not lead to the desired conversion. Reaction with one equivalent of $BF_3{\cdot}Et_2O$ at room temperature for 20 h resulted in a complex reaction mixture, in which the *trans*-β-aminoazetidine-2-carboxylate **10** was not detected. Also the use of one equivalent LiHMDS led to a complex reaction mixture after heating at reflux for 2.5 h. When aziridine **9** was treated with one equivalent KOtBu in THF at reflux temperature for 2.5 h (Table 2, entry 1), the selective formation of 3-amino-1,5-dihydropyrrol-2-one **11** was observed and isolated in 87% yield.

The proposed reaction mechanism begins with deprotonation at the α-position of the ester, which leads to an antiperiplanar elimination resulting in ring opening of the aziridine ***anti*-9** (Scheme 6). The secondary amide group of alkenoate **12** then attacks the ester group leading to γ-lactam **13**. The *p*-toluenesulfinyl group of the ring-closed product **13** was subsequently cleaved by attack of the expelled ethoxide anion, resulting in dihydropyrrol-2-one **11**.

Repeating the reaction with one equivalent NaH for one hour (Table 2, entry 2), also afforded the 3-amino-1,5-dihydropyrrol-2-one **11** however in a lower yield (45%). Performing the reaction in EtOH for 22 h at reflux temperature in the presence of

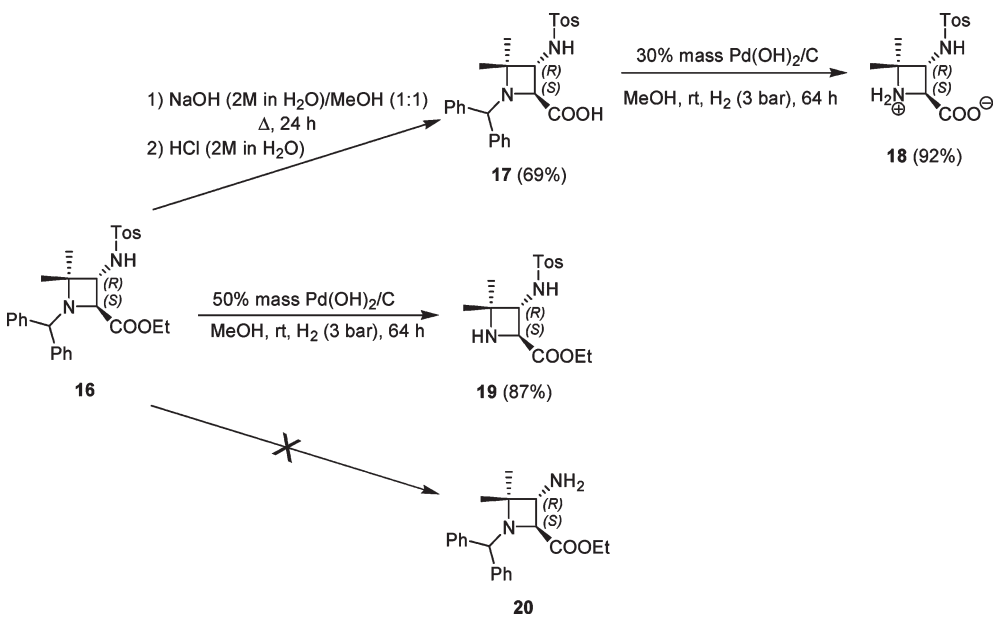


Scheme 7 Synthesis of aziridines **14** and **15** and further ring transformation to *trans*-*N*-tosylazetidine **16**.

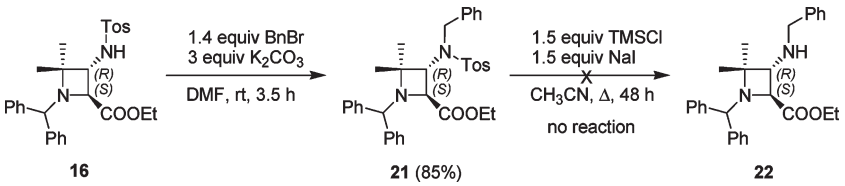
three equivalents of K_2CO_3 (entry 3), afforded the 3-amino-1,5-dihydropyrrol-2-one **11** in an excellent yield of 98%. Repeating the reaction in DMSO led to a complex reaction mixture (entry 4), while the use of 2.5 equivalents of NaH in DMSO at 80 °C for two hours (entry 5), resulted in the 3-amino-1,5-dihydropyrrol-2-one **11** in a yield of 56%. When aziridine ***anti*-9** was treated with one equivalent of DBU in toluene for 24 h at room temperature, no reaction was observed. Reaction of aziridine ***anti*-9** with two equivalents of $LiClO_4$ in acetonitrile at reflux temperature for 24 h, resulted only in a complex reaction mixture. In an additional series of attempts, a microwave (MW) reactor was used for the ring transformation of aziridine ***anti*-9** to *trans*-β-aminoazetidine-2-carboxylate **10**, albeit without success. An initial reaction, performed in acetonitrile at 120 °C for 10 min, led to degradation of the starting material ***anti*-9**. Lowering reaction times and temperatures resulted in degradation or no reaction, without formation of the desired azetidine **10**. In a final attempt, NaI was added to the reaction mixture, but no conversion of the starting material into the envisaged product was achieved.

Subsequently, the *p*-toluenesulfinyl group of *N*-sulfinylaziridine ***anti*-6a** (Scheme 7) was selectively oxidized with 3-chloroperbenzoic acid (mCPBA), resulting in enantiomerically pure *anti*-*N*-sulfonylaziridine **14** containing a strong electron-withdrawing activating group at the aziridine nitrogen. Based on our previously reported ring transformation of racemic *anti*-*N*-tosylaziridine **15** to racemic *anti*-*N*-tosylazetidine **16**, it was expected that the targeted ring transformation of aziridine **14** to optically pure azetidine **16** should be straightforward.[16b] The *N*-diphenylmethylene moiety of this *anti*-*N*-sulfonylaziridine **14** was subsequently reduced with $NaCNBH_3$, resulting in the formation of *anti*-*N*-sulfonylaziridine **15** in 92% yield. It was found that the *anti*-*N*-sulfonylaziridine **15** is an excellent precursor for an easy ring transformation towards *trans*-3-(*N*-tosylamino)azetidine-2-carboxylate **16** *via* simple heating in acetonitrile at 120 °C for 10 min under microwave (MW) conditions. Noteworthy, the latter transformation as reported for the racemic azetidine **16** required heating at 70 °C in acetonitrile for 20 h under conventional heating conditions.[16b] The enantiomeric excess of *trans*-3-(*N*-tosylamino)azetidine-2-carboxylate **16** (ee > 98%) was determined *via* chiral HPLC involving comparison to a racemic mixture of azetidine **16** (see Supporting Information).

In a series of follow up experiments, in order to extend the potential applicability of the synthesized 3-aminoazetidine-2-carboxylic acid derivative **16** as building block for the synthesis of peptides, azetidine **16** (Scheme 8) was subjected to several deprotection reactions. In an initial reaction, the ester group was hydrolyzed under basic conditions in 2 M NaOH in aq. methanol, resulting in *trans*-3-(*N*-tosylamino)azetidine-2-carboxylic acid **17** in 69% yield after acidic workup with aqueous HCl. Subsequently, the *N*-(diphenylmethyl)amino group of the azetidine **17** was *N*-deprotected by hydrogenolysis in the presence of



Scheme 8 Synthesis of the deprotected azetidines **17**, **18** and **19**.



Scheme 9 Benzylation and further attempted detosylation of azetidine **16**.

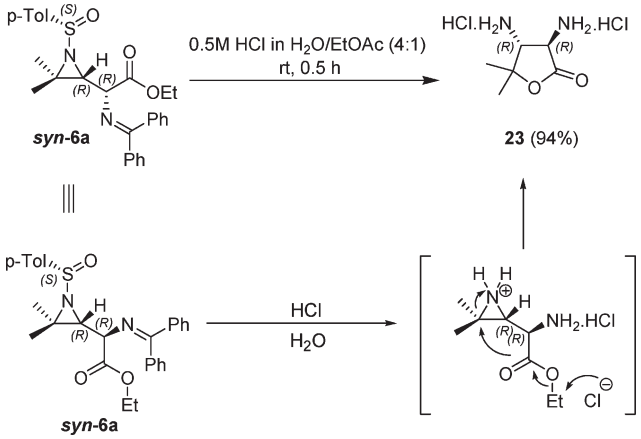
$Pd(OH)_2/C$.[21] After precipitation in diethyl ether, the *trans*-3-(*N*-tosylamino)azetidine-2-carboxylic acid **18** was obtained in 92% yield. The hydrogenolysis of the *N*-(diphenylmethyl)amino group could be directly applied on the ethyl ester **16**, affording ethyl 3-(*N*-tosylamino)azetidine-2-carboxylate **19** in 87% yield, also after precipitation from diethyl ether.

Furthermore, some efforts were made to cleave the *N*-tosyl group from *trans*-3-(*N*-tosylamino)azetidine-2-carboxylic ester **16** (Scheme 8), unfortunately without success. In an initial attempt, treatment of azetidine **16** with Mg turnings in MeOH,[22] gave no reaction. When azetidine **16** was treated with sodium or lithium naphthalenide in THF at −78 °C or at −20 °C,[23,24] no reaction occurred and the starting material was totally recovered. Performing the reaction with sodium naphthalenide at room temperature for 30 min led to a complex mixture of unidentified products. The use of phenol and 48% HBr in H_2O,[18,25] or the use of sodium amalgam and disodium hydrogen phosphate in dry methanol,[26] both under reflux conditions gave rise to complex reaction mixtures. Application of conditions reported for the deprotection of tertiary sulfonamides using trimethylsilyl chloride in the presence of sodium iodide,[27] failed also to deprotect azetidine **16**.

The procedure for the deprotection of tertiary sulfonamides using TMSCl in the presence of NaI is reported as straightforward.[27] Thus this strategy was used and azetidine **16** was *N*-benzylated with benzyl bromide in the presence of K_2CO_3 in DMF (Scheme 9).[28] Next, the *trans*-*N*-benzyl-*N*-tosylazetidine **21** was stirred under reflux for 48 h with 1.5 equivalents TMSCl in the presence of 1.5 equivalents NaI, but unfortunately without formation of the *trans*-(3-*N*-benzylamino)-azetidine **22**.

As the synthesis of the racemic *cis*-isomer of azetidine **16** starting from the *syn*-isomer of aziridine **14** was not possible, but racemic *syn*-aziridine could be transformed into a racemic α,β-diamino-γ-butyrolactone,[16b] a similar ring transformation of *syn*-*N*-sulfinylaziridine ***syn*-6a** to chiral α,β-diamino-γ-butyrolactones was evaluated (Scheme 10). (2*R*,3*R*)-2,3-diamino-4,4-dimethylbutyrolactone **23** was prepared *via* acid-mediated synthesis in quantitative yield. The reaction required careful optimization and final reaction conditions involved stirring aziridine ***syn*-6a** in 0.5 M HCl in H_2O/EtOAc for 30 min at room temperature (Scheme 10). The optically pure lactone **23** is of interest in further applications towards the synthesis of new β-amino-substituted analogues of *N*-acyl homoserine lactones acting as quorum sensing interfering molecules.[29]

Similarly, *syn*-γ-chloro-α,β-diamino ester ***syn*-5a** was treated with 5 equivalents of trifluoroacetic acid in acetone/water (2 : 1) for 15 min (Scheme 11). Following basic workup with NH_4OH, the *syn*-γ-chloro-α,β-diamino ester ***syn*-24** was isolated in 83% yield. The fact that the *N*-sulfinyl group is not removed under these conditions is remarkable, as the deprotection of *anti*-



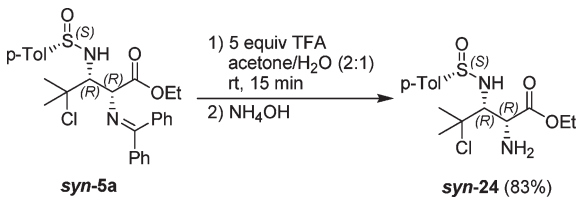
Scheme 10 Transformation of *syn*-*N*-sulfinylaziridine ***syn*-6a** into (2*R*,3*R*)-2,3-diamino-butyrolactone **23**.

aziridine ***anti*-6a** under the same reaction conditions led to unprotected aziridine **8** (Scheme 4).

In conclusion, it was demonstrated that new chiral *syn*- and *anti*-γ-chloro-α,β-diamino esters are formed in high yield and in excellent diastereomeric ratios *via* stereoselective Mannich-type reactions of *N*-(diphenylmethylene) glycine esters across a chiral α-chloro-*N*-*p*-toluenesulfinylimine. The base used for the deprotonation of the glycine ester had a dramatic and unexpected influence on the diastereoselectivity of the Mannich-type reaction, with LDA leading selectively to *anti*-diastereomers, whereas the use of LiHMDS leads to *syn*-diastereomers. The γ-chloro-α,β-diamino esters proved to be versatile building blocks in asymmetric synthesis as demonstrated by several selective transformations to new *syn*- and *anti*-β,γ-aziridino-α-amino esters, *trans*-3-aminoazetidine-2-carboxylates and an α,β-diamino-γ-butyrolactone.

General methods

Flame-dried glassware was used for all non-aqueous reactions. Commercially available solvents and reagents were purchased from common chemical suppliers and used without further



Scheme 11 Deprotection of *syn*-γ-chloro-α,β-diamino ester ***syn*-5a** with TFA.

purification, unless stated otherwise. Tetrahydrofuran (THF) and diethyl ether (Et_2O) were freshly distilled under a nitrogen atmosphere from sodium/benzophenone ketyl. Petroleum ether refers to the 40–60 °C boiling fraction. ^{1}H NMR (300 MHz), ^{13}C NMR (75 MHz) spectra were recorded in deuterated solvents with tetramethylsilane (TMS, δ = 0 ppm) as internal standard unless specified otherwise. Mass spectra were recorded using a direct inlet system (ESI, 4000 V). IR spectra were obtained from samples in neat form with an ATR (Attenuated Total Reflectance) accessory. Elementary analyses were performed using a CHNS/O elementary analyzer. HRMS analysis was performed using an Agilent 1100 series HPLC coupled to an Agilent 6220 TOF-Mass Spectrometer equipped with ESI/APCI-multimode source. Melting points of crystalline compounds were determined in open-end capillary tubes using a hot stage apparatus and were not corrected. The purification of the reaction mixtures was performed by column chromatography with silica gel (particle size 0.035–0.070 mm, pore diameter *ca.* 6 nm). Thin layer chromatography (TLC) was performed on glass plates coated with silica gel 60 F_{254}, using UV and $KMnO_4$ as a visualizing agent. (S_S)-*p*-Toluenesulfinamide is commercially available (>98% ee).

Experimental section

Synthesis of (S_S)-α-chloro-*N*-*p*-toluenesulfinyl isobutyraldimine 3

To a flame dried round-bottomed flask charged with α-chloroisobutyraldehyde **1** (3.43 g, 32.21 mmol) in dry CH_2Cl_2 (100 mL) was added $Ti(OEt)_4$ (4 equiv, 29.40 g, 128.85 mmol) and (S_S)-*p*-toluenesulfinamide **2** (5.00 g, 32.21 mmol) under nitrogen atmosphere. The reaction mixture was stirred for 18 h at room temperature. After completion, the reaction mixture was poured into water (100 mL) while rapidly stirring. The suspension was filtered over Celite® and the solids were washed with CH_2Cl_2 (2 × 20 mL). Subsequently, the filtrate was extracted with CH_2Cl_2 (3 × 30 mL) and the combined organic phases were dried ($MgSO_4$), filtered and evaporated *in vacuo*. The crude product was purified by column chromatography to yield 7.25 g (29.74 mmol) of pure (S_S)-α-chloro-*N*-*p*-toluenesulfinyl isobutyraldimine **3**.

(S_S)-α-chloro-*N*-*p*-toluenesulfinyl isobutyraldimine 3

R_f 0.25 (petroleum ether/EtOAc: 5/1). White crystals, yield 92%. Mp 54.6 ± 1.0 °C. IR (cm^{-1}): ν_{max} 816, 1086, 1071, 1621. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.70 (3H, s), 1.77 (3H, s), 2.41 (3H, s), 7.31 (2H, d, J = 8.0 Hz), 7.55 (2H, d, J = 8.0 Hz), 8.17 (1H, s). ^{13}C NMR (75 MHz, $CDCl_3$): δ 21.5, 29.0, 29.1, 66.6, 124.7 (2C), 129.9 (2C), 141.0, 142.0, 165.9. MS (ES, pos. mode) *m*/*z* (%): 288/290 (100), 244/246 (M + H$^+$, 80). HRMS (ES) calcd for $C_{11}H_{14}ClNOS$: 244.0557 MH$^+$; found: 244.0548 (<1%), 219.1737 (100%).

Synthesis of (S_S,2*S*,3*R*)-alkyl 2-(diphenylmethyleneamino)-4-chloro-4-methyl-3-(*p*-toluenesulfinylamino)pentanoates *anti*-5

The synthesis of (S_S,2*S*,3*R*)-alkyl 2-(diphenylmethyleneamino)-4-chloro-4-methyl-3-(*p*-toluenesulfinylamino)pentanoate ***anti*-5a** is representative. To a flame dried round-bottomed flask with freshly distilled diisopropylamine (1.1 equiv, 6.76 mmol, 0.67 g) in dry THF (15 mL) was added n-BuLi (1.21 equiv, 7.43 mmol, 2.5 M in hexane, 2.97 mL) under nitrogen atmosphere. The reaction mixture was stirred for 5 min at 0 °C and was subsequently cooled to −78 °C. After 5 min, a solution of *N*-(diphenylmethylene) glycine ethyl ester **4a** (1.1 equiv, 6.76 mmol, 1.81 g) in dry THF (5 mL) was slowly added and the resulting solution was stirred for 1 h at −78 °C. After deprotonation, the reaction mixture was cooled to −90 °C and a solution of (S_S)-α-chloro-*N*-*p*-toluenesulfinyl isobutyraldimine **3** (1.0 equiv, 6.14 mmol, 1.50 g), in dry THF (20 mL) was added dropwise and the reaction mixture was stirred at −90 °C for 5 min. To the reaction mixture was added a saturated solution of NH_4Cl (40 mL) while stirring was continued at −90 °C for 2 min. The reaction mixture was brought to room temperature, followed by an extraction with EtOAc (3 × 40 mL). The combined organic phases were dried ($MgSO_4$), filtered and evaporated *in vacuo*. The crude product was purified by column chromatography to yield 2.48 g (4.85 mmol) of (S_S,2*S*,3*R*)-ethyl 2-(diphenylmethyleneamino)-4-chloro-4-methyl-3-(*p*-toluenesulfinylamino)pentanoate ***anti*-5a** as a 89 : 11 mixture with *syn*-adduct ***syn*-5a**.

(S_S,2*S*,3*R*)-Ethyl 2-(diphenylmethyleneamino)-4-chloro-4-methyl-3-(*p*-toluenesulfinylamino)pentanoate *anti*-5a

R_f 0.23 (petroleum ether/EtOAc: 3/1). White crystals, yield 79%, dr 89 : 11. Mp 52.7 ± 0.3 °C. IR (cm^{-1}): ν_{max} 1624, 1731, 3280. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.19 (3H, t, J = 7.15 Hz), 1.62 (3H, s), 1.64 (3H, s), 2.37 (3H, s), 3.90 (1H, d × d, J = 8.81 Hz, 3.30 Hz), 3.99–4.16 (2H, m), 4.58 (1H, d, J = 3.30 Hz), 5.47 (1H, d, J = 8.81 Hz), 7.14–7.77 (14H, m). ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.0, 21.5, 30.6, 30.8, 61.5, 66.4, 67.2, 73.0, 125.6 (2C), 127.8 (2C), 128.2 (2C), 128.7 (2C), 128.9, 129.4 (2C), 129.6 (2C), 130.8, 136.0, 139.3, 141.3, 142.9, 170.7, 172.6. MS (ES, pos. mode) *m*/*z* (%): 511/513 (M + H$^+$, 100). HRMS (ES) calcd for $C_{28}H_{31}ClN_2O_3S$: 511.1817 MH$^+$; found: 511.1825.

(S_S,2*S*,3*R*)-*tert*-Butyl 2-(diphenylmethyleneamino)-4-chloro-4-methyl-3-(*p*-toluenesulfinylamino)pentanoate *anti*-5c

R_f 0.29 (petroleum ether/EtOAc: 3/1). White crystals, yield 52%, dr 81 : 19. Mp 57.2 ± 0.5 °C. IR (cm^{-1}): ν_{max} 1624, 1725, 3284. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.35 (9H, s), 1.64 (3H, s), 1.69 (3H, s), 2.37 (3H, s), 3.82 (1H, d × d, J = 8.53 Hz, 2.5 Hz), 4.44 (1H, d, J = 2.20 Hz), 5.62 (1H, d, J = 8.81 Hz), 7.15–7.78 (14H, m). ^{13}C NMR (75 MHz, $CDCl_3$): δ 21.3, 27.8, 30.4, 30.8, 66.6, 67,3, 73.0, 82.2, 125.7 (2C), 127.9 (2C), 128.0 (2C), 128.5 (2C), 128.7, 129.3 (2C), 129.4 (2C), 130.5, 136.0, 139.4, 141.0, 142.5, 169.5, 172.3. MS (ES, pos. mode) *m*/*z* (%): 539/541 (M + H$^+$, 100). HRMS (ES) calcd for $C_{30}H_{35}ClN_2O_3S$: 539.2130 MH$^+$; found: 539.2114.

Synthesis of (S_S,2*R*,3*R*)-alkyl 2-(diphenylmethyleneamino)-4-chloro-4-methyl-3-(*p*-toluenesulfinylamino)pentanoates *syn*-5

The synthesis of (S_S,2*R*,3*R*)-ethyl 2-(diphenylmethyleneamino)-4-chloro-4-methyl-3-(*p*-toluenesulfinylamino)pentanoate ***syn*-5a**

is representative. A solution of *N*-(diphenylmethylene) glycine ethyl ester **4a** (1.1 equiv, 6.76 mmol, 1.81 g) in THF (20 mL) was cooled to −78 °C under nitrogen atmosphere. A 1.0 M solution of LiHMDS (1.1 equiv, 6.76 mL, 6.76 mmol) in THF was slowly added and the resulting solution was stirred for 1 h at −78 °C. After deprotonation, a solution of (S_S)-α-chloro-*N*-*p*-toluenesulfinyl isobutyraldimine **3** (1.0 equiv, 6.14 mmol, 1.50 g) in THF (20 mL) was added dropwise and the reaction mixture was stirred at −78 °C for 15 min. To the reaction mixture was added a saturated solution of NH_4Cl (40 mL) while stirring at −78 °C for 2 min. The reaction mixture was brought to room temperature followed by an extraction with EtOAc (3 × 100 mL). The combined organic phases were dried ($MgSO_4$), filtered and evaporated *in vacuo*. The crude product was purified by recrystallization from diethyl ether to yield 2.76 g (5.40 mmol) of pure (S_S,2*R*,3*R*)-ethyl 2-(diphenylmethyleneamino)-4-chloro-4-methyl-3-(*p*-toluenesulfinylamino)pentanoate ***syn*-5a**.

(S_S,2*R*,3*R*)-Ethyl 2-(diphenylmethyleneamino)-4-chloro-4-methyl-3-(*p*-toluenesulfinylamino)pentanoate *syn*-5a

R_f 0.21 (petroleum ether/EtOAc: 3/1). White crystals, yield 88%. $[\alpha]_D$ +193.8 (*c* 0.6, $CHCl_3$). Mp 144.2 ± 1.0 °C. IR (cm^{-1}): ν_{max} 815, 1070, 1088, 1259, 1621, 1721, 3312. ^1H NMR (300 MHz, $CDCl_3$): δ 1.30 (3H, t, J = 7.15 Hz), 1.51 (3H, s), 1.63 (3H, s), 2.45 (3H, s), 4.21–4.38 (3H, m), 4.66 (1H, d, J = 1.10 Hz), 5.83 (1H, d, J = 8.26 Hz), 7.13–7.19 (2H, m), 7.26–7.46 (8H, m), 7.51–7.54 (2H, m), 7.74 (2H, d, J = 8.26 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.1, 21.4, 29.0, 30.6, 62.2, 65.6, 67,1, 72.6, 125.7 (2C), 127.1 (2C), 128.1 (2C), 128.6 (2C), 128.9 (2C), 129.0, 129.6 (2C), 130.7, 136.4, 138.8, 141.3, 143.6, 169.6, 171.7. MS (ES, pos. mode) *m*/*z* (%): 511/513 (M + H^+, 100). HRMS (ES) calcd for $C_{28}H_{31}ClN_2O_3S$: 511.1817 MH^+; found: 511.1838.

(S_S,2*R*,3*R*)-Methyl 2-(diphenylmethyleneamino)-4-chloro-4-methyl-3-(*p*-toluenesulfinylamino)pentanoate *syn*-5b

R_f 0.08 (petroleum ether/EtOAc: 4/1). White crystals, yield 86%. $[\alpha]_D$ +224.1 (*c* 1.6, $CHCl_3$). Mp 136.4 ± 0.5 °C. IR (cm^{-1}): ν_{max} 1071, 1092, 1261, 1727, 3319. ^1H NMR (300 MHz, $CDCl_3$): δ 1.51 (3H, s), 1.63 (3H, s), 2.45 (3H, s), 3.83 (3H, s), 4.30 (1H, d × d, J = 8.53 Hz, 1.38 Hz), 4.70 (1H, d, J = 1.10 Hz), 5.83 (1H, d, J = 8.81 Hz), 7.13–7.16 (2H, m), 7.28–7.45 (8H, m), 7.50–7.53 (2H, m), 7.74 (2H, d, J = 8.26 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 21.4, 29.0, 30.6, 53.1, 65.6, 67,2, 72.4, 125.7 (2C), 127.0 (2C), 128.1 (2C), 128.7 (2C), 128.9 (2C), 129.0, 129.6 (2C), 130.8, 136.4, 138.7, 141.3, 143.5, 170.2, 171.8. MS (ES, pos. mode) *m*/*z* (%): 497/499 (M + H^+, 100). HRMS (ES) calcd for $C_{27}H_{29}ClN_2O_3S$: 497.1660 MH^+; found: 497.1658.

Synthesis of (S_S,2′*R*)-alkyl 2-(diphenylmethyleneamino)-2-[3,3-dimethyl-1-(*p*-toluenesulfinyl)aziridin-2-yl]acetates 6

The synthesis of (S_S,2*S*,2′*R*)-ethyl 2-(diphenylmethyleneamino)-2-[3,3-dimethyl-1-(*p*-toluenesulfinyl)aziridin-2-yl]acetate ***anti*-6a** is representative. To a solution of (S_S,2*S*,3*R*)-ethyl 2-(diphenylmethyleneamino)-4-chloro-4-methyl-3-(*p*-toluenesulfinylamino)-pentanoate ***anti*-5a** (1.50 g, 2.93 mmol) in acetone (35 mL) was added K_2CO_3 (3.0 equiv, 8.80 mmol, 1.22 g) at room temperature. The reaction mixture was allowed to stir for 24 h at reflux temperature. After 24 h, the K_2CO_3 was filtered off and the solvent was evaporated *in vacuo*. The resulting oil was redissolved in EtOAc (40 mL) and washed with water (2 × 15 mL). The organic phase was dried ($MgSO_4$), filtered and evaporated *in vacuo*. The crude product was purified by column chromatography to yield 1.02 g (2.14 mmol) of (S_S,2*S*,2′*R*)-ethyl 2-(diphenylmethyleneamino)-2-[3,3-dimethyl-1-(*p*-toluenesulfinyl)-aziridin-2-yl]acetate ***anti*-6a**.

(S_S,2*S*,2′*R*)-Ethyl 2-(diphenylmethyleneamino)-2-[3,3-dimethyl-1-(*p*-toluenesulfinyl)aziridin-2-yl]acetate *anti*-6a

R_f 0.25 (petroleum ether/EtOAc: 3/1). White crystals, yield 73%. $[\alpha]_D$ −24.1 (*c* 0.4, $CHCl_3$). Mp 103.8 ± 0.2 °C. IR (cm^{-1}): ν_{max} 1613, 1732. ^1H NMR (300 MHz, $CDCl_3$): δ 1.01 (3H, t, J = 7.15 Hz), 1.06 (3H, s), 1.60 (3H, s), 2.36 (3H, s), 3.50 (1H, d, J = 8.26 Hz), 3.53–3.66 (2H, m), 3.84 (1H, d, J = 8.81 Hz), 7.02–7.05 (2H, m), 7.22 (2H, d, J = 8.26 Hz), 7.30–7.41 (6H, m), 7.55 (2H, d, J = 8.26 Hz), 7.59–7.63 (2H, m). ^{13}C NMR (75 MHz, $CDCl_3$): δ 13.8, 20.9, 21.3, 21.7, 42.0, 44.6, 60.8, 65.4, 125.6 (2C), 128.0 (2C), 128.3 (2C), 128.9, 129.0 (2C), 129.2 (2C), 130.6, 135.8, 139.4, 140.8, 143.1, 170.1, 170.9. MS (ES, pos. mode) *m*/*z* (%): 475 (M + H^+, 100). Anal. calcd for $C_{28}H_{30}N_2O_3S$: C 70.86; H 6.37; N 5.90; found: C 71.00; H 6.21; N 5.85.

(S_S,2*S*,2′*R*)-*tert*-Butyl 2-(diphenylmethyleneamino)-2-[3,3-dimethyl-1-(*p*-toluenesulfinyl)aziridin-2-yl]acetate *anti*-6c

R_f 0.38 (petroleum ether/EtOAc: 3/1). White crystals, yield 79%, dr 81 : 19. Mp 92.2 ± 0.1 °C. IR (cm^{-1}): ν_{max} 1149, 1619, 1741. ^1H NMR (300 MHz, $CDCl_3$): δ 1.23 (3H, s), 1.25 (9H, s), 1.60 (3H, s), 2.33 (3H, s), 3.41 (1H, d, J = 8.26 Hz), 3.86 (1H, d, J = 7.71 Hz), 6.91–7.61 (14H, m). ^{13}C NMR (75 MHz, $CDCl_3$): δ 21.25, 21.28, 21.8, 27.8 (3C), 42.2, 44.5, 65.5, 81.5, 125.9 (2C), 127.9 (2C), 128.1 (4C), 128.7, 128.9 (2C), 129.2 (2C), 130.3, 135.8, 139.7, 140.7, 143.3, 168.9, 170.1. MS (ES, pos. mode) *m*/*z* (%): 503 (M + H^+, 100). Anal. calcd for $C_{30}H_{34}N_2O_3S$: C 71.68; H 6.82; N 5.57; found: C 72.05; H 6.79; N 5.57.

(S_S,2*R*,2′*R*)-Ethyl 2-(diphenylmethyleneamino)-2-[3,3-dimethyl-1-(*p*-toluenesulfinyl)aziridin-2-yl]acetate *syn*-6a

R_f 0.23 (petroleum ether/EtOAc: 3/1). Colourless oil, yield 99%. $[\alpha]_D$ +117.8 (*c* 0.7, $CHCl_3$). IR (cm^{-1}): ν_{max} 695, 1072, 1092, 1624, 1735. ^1H NMR (300 MHz, $CDCl_3$): δ 1.07 (3H, s), 1.24 (3H, t, J = 6.9 Hz), 1.60 (3H, s), 1.95 (3H, s), 3.53 (1H, d, J = 9.36 Hz), 3.77 (1H, d, J = 9.36 Hz), 4.07–4.22 (2H, m), 6.54–6.72 (4H, m), 7.25–7.33 (5H, m), 7.39–7.50 (5H, m). ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.1, 20.4, 21.2, 22.6, 42.2, 45.4, 61.2, 64.4, 124.6 (2C), 127.7 (2C), 128.0 (4C), 128.3, 129.1 (2C), 129.2 (2C), 130.2, 135.6, 138.9, 141.0, 143.2, 169.8,

170.5. MS (ES, pos. mode) *m/z* (%): 475 (M + H^+, 100). HRMS (ES) calcd for $C_{28}H_{30}N_2O_3S$: 475.2050 MH^+; found: 475.2071.

(S_S,2*R*,2′*R*)-Methyl 2-(diphenylmethyleneamino)-2-[3,3-dimethyl-1-(*p*-toluenesulfinyl)aziridin-2-yl]acetate *syn*-6b

R_f 0.26 (petroleum ether/EtOAc: 3/1). White crystals, yield 83%. $[\alpha]_D$ +178.9 (*c* 1.6, $CHCl_3$). Mp 108.0 ± 0.3 °C. IR (cm^{-1}): ν_{max} 698, 1070, 1091, 1622, 1741. ^1H NMR (300 MHz, $CDCl_3$): δ 1.07 (3H, s), 1.60 (3H, s), 1.95 (3H, s), 3.53 (1H, d, *J* = 9.1 Hz), 3.70 (3H, s), 3.80 (1H, d, *J* = 9.8 Hz), 6.54–6.86 (4H, m), 7.25–7.35 (5H, m), 7.39–7.50 (5H, m). ^{13}C NMR (75 MHz, $CDCl_3$): δ 20.4, 21.2, 22.5, 42.2, 45.4, 52.4, 64.3, 124.5 (2C), 127.7 (2C), 128.0 (4C), 128.3, 129.1 (2C), 129.2 (2C), 130.3, 135.5, 138.8, 141.0, 143.2, 170.4, 170.6. MS (ES, pos. mode) *m/z* (%): 461 (M + H^+, 100). HRMS (ES) calcd for $C_{27}H_{28}N_2O_3S$: 461.1893 MH^+; found: 461.1894.

Synthesis of (2*S*,2′*R*)-Ethyl amino-(3,3-dimethylaziridin-2-yl)-acetate 8

To a solution of (S_S,2*S*,2′*R*)-ethyl 2-(diphenylmethyleneamino)-2-[3,3-dimethyl-1-(*p*-toluenesulfinyl)aziridin-2-yl]acetate ***anti*-6a** (0.50 g, 1.05 mmol) in acetone/H_2O: 2/1 (30 mL) was added dropwise trifluoroacetic acid (5 equiv, 5.27 mmol, 0.41 mL) at room temperature. The reaction mixture was stirred for 15 min at room temperature and subsequently quenched with NH_4OH in H_2O until pH = 10 and concentrated *in vacuo*. The residue was redissolved in water (10 mL) and NH_4OH was added until pH = 10. The aqueous phase was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic phases were dried ($MgSO_4$), filtered and evaporated *in vacuo*. The crude product was purified by rapid filtration over a short silica column with petroleum ether and the silica was subsequently extracted with CH_2Cl_2/MeOH: 4/1. The latter phase was filtered and evaporated *in vacuo* to yield 0.14 g (0.82 mmol) of (2*S*,2′*R*)-ethyl amino-(3,3-dimethylaziridin-2-yl)-acetate **8**.

(2*S*,2′*R*)-Ethyl amino-(3,3-dimethylaziridin-2-yl)acetate 8

Yellowish oil, yield 78%. $[\alpha]_D$ + 131.5 (*c* 0.9, $CHCl_3$). IR (cm^{-1}): ν_{max} 831, 1027, 1187, 1382, 1729, 2957. ^1H NMR (300 MHz, $CDCl_3$): δ 1.21 (3H, s), 1.23 (3H, t, *J* = 7.15 Hz), 1.25 (3H, s), 1.39 (3H, br s), 1.91 (1H, d, *J* = 8.81 Hz), 3.08 (1H, d, *J* = 8.81 Hz), 4.16 (2H, q, *J* = 7.15 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.3, 19.7, 27.2, 35.6, 45.8, 55.6, 61.2, 174.6. MS (ES, pos. mode) *m/z* (%): 173 (M + H^+, 100). HRMS (ES) calcd for $C_8H_{16}N_2O_2$: 173.1285 MH^+; found: 173.1282.

Synthesis of (S_S,2*S*,2′*R*)-ethyl 2-(diphenylmethylamino)-2-[3,3-dimethyl-1-(*p*-toluenesulfinyl)aziridin-2-yl]acetate 9

To a solution of (S_S,2*S*,2′*R*)-ethyl 2-(diphenylmethyleneamino)-2-[3,3-dimethyl-1-(*p*-toluenesulfinyl)aziridin-2-yl]acetate ***anti*-6a** (0.37 g, 0.78 mmol) in methanol (4 mL) was added dropwise acetic acid (1 equiv, 0.78 mmol, 0.05 g) at room temperature. Subsequently, $NaCNBH_3$ (2 equiv, 1.56 mmol, 0.10 g) was added in portions during 5 min. The reaction mixture was allowed to stir for 6 h at room temperature. After completion, the reaction was quenched with H_2O (100 equiv, 78 mmol, 1.4 mL) and concentrated *in vacuo*. The resulting precipitate was redissolved in EtOAc (4 mL) and washed with H_2O (3 × 2 mL). The organic phase was dried ($MgSO_4$), filtered and evaporated *in vacuo*. The crude product was purified by column chromatography to yield 0.25 g (0.53 mmol) of (S_S,2*S*,2′*R*)-ethyl 2-(diphenylmethylamino)-2-[3,3-dimethyl-1-(*p*-toluenesulfinyl)-aziridin-2-yl]acetate **9**.

(S_S,2*S*,2′*R*)-Ethyl 2-(diphenylmethylamino)-2-[3,3-dimethyl-1-(*p*-toluenesulfinyl)aziridin-2-yl]acetate 9

R_f 0.28 (hexane/Et_2O: 10/1). White crystals, yield 68%. $[\alpha]_D$ +80.6 (*c* 1.9, $CHCl_3$). Mp 99.8 ± 0.5 °C. IR (cm^{-1}): ν_{max} 1742, 3287. ^1H NMR (300 MHz, $CDCl_3$): δ 0.99 (3H, t, *J* = 7.15 Hz), 1.21 (3H, s), 1.61 (3H, s), 2.22 (1H, br s), 2.37 (3H, s), 2.88 (1H, d, *J* = 9.36 Hz), 2.91 (1H, d, *J* = 8.81 Hz), 3.26 (1H, d × q, *J* = 11.01 Hz, 7.15 Hz), 3.61 (1H, d × q, *J* = 10.46 Hz, 7.15 Hz), 4.63 (1H, s), 7.16–7.33 (12H, m), 7.50 (2H, d, *J* = 8.26 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.0, 20.7, 21.3, 21.8, 41.1, 45.3, 58.5, 60.4, 65.2, 125.3 (2C), 127.0 (2C), 127.3, 127.4, 127.7 (2C), 128.4 (2C), 128.5 (2C), 129.2 (2C), 140.9, 142.1, 142.8, 143.5, 172.7. MS (ES, pos. mode) *m/z* (%): 477 (M + H^+, 100). HRMS (ES) calcd for $C_{28}H_{32}N_2O_3S$: 477.2206 MH^+; found: 477.2210.

Synthesis of 3-(diphenylmethylamino)-5,5-dimethyl-1,5-dihydropyrrol-2-one 11

To a solution of (S_S,2*S*,2′*R*)-ethyl 2-(diphenylmethylamino)-2-[3,3-dimethyl-1-(*p*-toluenesulfinyl)aziridin-2-yl]acetate **9** (0.10 g, 0.21 mmol) in ethanol (2 mL) was added K_2CO_3 (3.0 equiv, 0.63 mmol, 0.09 g) at room temperature. The reaction mixture was stirred for 22 h at reflux. Subsequently, the K_2CO_3 was filtered off and the solvent was evaporated *in vacuo*. Precipitation in diethyl ether afforded 0.06 g (0.20 mmol) of 3-(diphenylmethylamino)-5,5-dimethyl-1,5-dihydropyrrol-2-one **11**.

3-(Diphenylmethylamino)-5,5-dimethyl-1,5-dihydropyrrol-2-one 11

White crystals, yield 98%. Mp 213.2 ± 1.0 °C. IR (cm^{-1}): ν_{max} 704, 1344, 1650, 1697, 3181, 3359. ^1H NMR (300 MHz, $CDCl_3$): δ 1.24 (6H, s), 4.52 (1H, br d, *J* = 3.6 Hz), 4.91 (1H, d, *J* = 1.65 Hz), 5.25 (1H, d, *J* = 3.6 Hz), 6.21 (1H, br s), 7.21–7.34 (10H, m). ^{13}C NMR (75 MHz, $CDCl_3$): δ 27.6, 57.5, 63.7, 115.2, 127.3 (4C), 127.4 (2C), 128.6 (4C), 136.6, 141.8 (2C), 169.0. MS (ES, pos. mode) *m/z* (%): 293 (M + H^+, 100). HRMS (ES) calcd for $C_{19}H_{20}N_2O$: 293.1648 MH^+; found: 293.1651.

Synthesis of (2*S*,2′*R*)-ethyl 2-(diphenylmethyleneamino)-2-[3,3-dimethyl-1-(*p*-toluenesulfonyl)aziridin-2-yl]acetate 14

To a solution of (S_S,2*S*,2′*R*)-ethyl 2-(diphenylmethyleneamino)-2-[3,3-dimethyl-1-(*p*-toluenesulfinyl)aziridin-2-yl]acetate ***anti*-6a** (1.10 g, 2.32 mmol) in dry CH_2Cl_2 (40 mL) was added mCPBA

(1.1 equiv, 2.55 mmol, 0.44 g) at room temperature. The reaction mixture was allowed to stir for 2 min at room temperature and was subsequently quenched with a saturated solution of $NaHCO_3$ (20 mL). The organic phase was dried ($MgSO_4$), filtered and evaporated *in vacuo*. The crude product was purified by recrystallization from EtOAc to yield 1.02 g (2.09 mmol) of (2*S*,2′*R*)-ethyl 2-(diphenylmethyleneamino)-2-[3,3-dimethyl-1-(*p*-toluenesulfonyl)aziridin-2-yl]acetate **14**. All spectroscopic data were in good agreement with reported data of the racemate of **14**.[16b] White crystals, yield 90%. $[\alpha]_D$ −137.1 (*c* 0.4, $CHCl_3$). Mp 128.4 ± 0.5 °C.

Synthesis of (2*S*,2′*R*)-ethyl 2-(diphenylmethylamino)-2-[3,3-dimethyl-1-(*p*-toluenesulfonyl)aziridin-2-yl]acetate 15

To a solution of (2*S*,2′*R*)-ethyl 2-(diphenylmethyleneamino)-2-[3,3-dimethyl-1-(*p*-toluenesulfonyl)aziridin-2-yl]acetate **14** (1.33 g, 2.71 mmol) in methanol (15 mL) was added dropwise acetic acid (1 equiv, 2.71 mmol, 0.16 g) at room temperature. Subsequently, $NaCNBH_3$ (2 equiv, 5.42 mmol, 0.34 g) was added in portions during 5 min. The reaction mixture was stirred for 6 h at room temperature. After completion, the reaction was quenched with H_2O (100 equiv, 271 mmol, 4.9 mL) and concentrated *in vacuo*. The resulting precipitate was redissolved in EtOAc (15 mL) and washed with water (3 × 10 mL). The organic phase was dried ($MgSO_4$), filtered and evaporated *in vacuo*. The crude product was purified by recrystallization from EtOAc/Et_2O: 1/1 to yield 1.23 g (2.50 mmol) of (2*S*,2′*R*)-ethyl 2-(diphenylmethylamino)-2-[3,3-dimethyl-1-(*p*-toluenesulfonyl)-aziridin-2-yl]acetate **15**. All spectroscopic data were in good agreement with reported data of the racemate of **15**.[16b] White crystals, yield 92%. $[\alpha]_D$ −45.3 (*c* 0.9, $CHCl_3$). Mp 95.8 ± 1.0 °C.

Synthesis of (2*S*,3*R*)-ethyl 1-diphenylmethyl-4,4-dimethyl-3-(*p*-toluenesulfonylamino)azetidine-2-carboxylate 16

In a 10 mL microwave vial containing (2*S*,2′*R*)-ethyl 2-(diphenylmethylamino)-2-[3,3-dimethyl-1-(*p*-toluenesulfonyl)aziridin-2-yl]acetate **15** (0.40 g, 0.81 mmol) was added acetonitrile (3 mL). The reaction mixture was stirred vigorously at 120 °C for 10 min. Subsequently, the reaction mixture was concentrated *in vacuo* and the residue was recrystallized from Et_2O to afford 0.25 g (0.51 mmol) of (2*S*,3*R*)-ethyl 1-diphenylmethyl-4,4-dimethyl-3-(*p*-toluenesulfonylamino)azetidine-2-carboxylate **16**. All spectroscopic data were in good agreement with reported data of the racemate of **16** (ee > 98%).[16b] White crystals, yield 63%. $[\alpha]_D$ +15.6 (*c* 0.2, $CHCl_3$). Mp 188.1 ± 0.5 °C.

Synthesis of (2*S*,3*R*)-1-diphenylmethyl-4,4-dimethyl-3-(*p*-toluenesulfonylamino)azetidine-2-carboxylic acid 17

(2*S*,3*R*)-Ethyl 1-diphenylmethyl-4,4-dimethyl-3-(*p*-toluenesulfonylamino)azetidine-2-carboxylate **16** (0.37 g, 0.80 mmol) was dissolved in 2 M NaOH/MeOH: 1/1 (40 mL). The reaction mixture was stirred for 24 h at reflux temperature and subsequently washed with EtOAc (1 × 20 mL). The aqueous phase was brought to pH = 4 with 2 M HCl and extracted with EtOAc (3 × 20 mL). The combined organic phases were dried ($MgSO_4$), filtered and evaporated *in vacuo*. Recrystallization from diethyl ether/hexane: 1/1 afforded 0.24 g (0.52 mmol) of (2*S*,3*R*)-1-diphenylmethyl-4,4-dimethyl-3-(*p*-toluenesulfonylamino)azetidine-2-carboxylic acid **17**.

(2*S*,3*R*)-1-Diphenylmethyl-4,4-dimethyl-3-(*p*-toluenesulfonylamino)azetidine-2-carboxylic acid 17

White crystals, yield 69%. $[\alpha]_D$ +61.0 (*c* 0.5, MeOH). Mp 121.0 ± 0.2 °C. IR (cm^{-1}): ν_{max} 705, 1092, 1153, 1321, 1454, 1643, 1714, 3062. ^1H NMR (300 MHz, $CDCl_3$): δ 1.19 (3H, s), 1.24 (3H, s), 2.36 (3H, s), 3.65–3.73 (2H, m), 4.88 (1H, s), 6.33 (2H, br s), 7.14–7.36 (10H, m), 7.53 (2H, d, J = 7.15 Hz), 7.70 (2H, d, J = 7.71 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 16.5, 21.6, 29.7, 56.0, 66.7, 69.3, 70.3, 127.0 (2C), 127.7 (2C), 128.0, 128.6 (3C), 128.8 (2C), 129.1 (2C), 129.9, 136.8, 137.4, 140.2, 143.9, 170.7. MS (ES, pos. mode) m/z (%): 465 ($M + H^+$, 100). HRMS (ES) calcd for $C_{26}H_{28}N_2O_4S$: 465.1843 MH^+; found: 465.1848.

Synthesis of (2*S*,3*R*)-4,4-dimethyl-3-(*p*-toluenesulfonylamino)-azetidine-2-carboxylic acid derivatives 18 & 19

The synthesis of (2*S*,3*R*)-4,4-dimethyl-3-(*p*-toluenesulfonylamino)azetidine-2-carboxylic acid **18** is representative. To a solution of (2*S*,3*R*)-1-diphenylmethyl-4,4-dimethyl-3-(*p*-toluenesulfonylamino)azetidine-2-carboxylic acid **17** (0.060 g, 0.13 mmol) in methanol (5 mL) was added $Pd(OH)_2/C$ (30% mass fraction, 0.018 g) at room temperature. The mixture was stirred for 64 h at room temperature under H_2-atmosphere (3 bar) and subsequently filtered through a short pad of Celite®. The Celite® pad was washed exhaustively with CH_2Cl_2 and the collected organic fractions were evaporated *in vacuo*. Precipitation in diethyl ether afforded 0.035 g (0.12 mmol) of (2*S*,3*R*)-4,4-dimethyl-3-(*p*-toluenesulfonylamino)azetidine-2-carboxylic acid **18**.

(2*S*,3*R*)-4,4-Dimethyl-3-(*p*-toluenesulfonylamino)azetidine-2-carboxylic acid 18

White crystals, yield 92%. $[\alpha]_D$ +66.9 (*c* 0.4, MeOH). Mp 171.0 ± 1.0 °C. IR (cm^{-1}): ν_{max} 665, 1094, 1159, 1326, 1620, 3063. ^1H NMR (300 MHz, CD_3OD): δ 1.47 (6H, s), 2.42 (3H, s), 3.87 (1H, d, J = 8.0 Hz), 4.27 (1H, d, J = 8.0 Hz), 7.38 (2H, d, J = 7.71 Hz), 7.76 (2H, d, J = 7.71 Hz). ^{13}C NMR (75 MHz, CD_3OD): δ 21.3, 21.5, 26.5, 59.4, 60.4, 69.8, 128.2 (2C), 130.9 (2C), 138.9, 145.2, 171.4 (tentative assignment). MS (ES, pos. mode) m/z (%): 299 ($M + H^+$, 100). HRMS (ES) calcd for $C_{13}H_{18}N_2O_4S$: 299.1060 MH^+; found: 299.1066.

(2*S*,3*R*)-Ethyl 4,4-dimethyl-3-(*p*-toluenesulfonylamino)azetidine-2-carboxylate 19

White crystals, yield 87%. $[\alpha]_D$ +54.2 (*c* 0.9, MeOH). Mp 183.6 ± 1.5 °C. IR (cm^{-1}): ν_{max} 664, 907, 1095, 1167, 1228, 1338, 1732, 2771. ^1H NMR (300 MHz, $CDCl_3$): δ 1.10 (3H, t, J = 6.9 Hz), 1.65 (3H, s), 1.68 (3H, s), 1.65–1.68 (1H, br s), 2.42 (3H, s), 3.99–4.13 (3H, m), 5.36 (1H, d, J = 7.71 Hz), 7.29 (2H, d,

J = 8.0 Hz), 7.80 (2H, d, J = 8.0 Hz), 8.16 (1H, d, J = 8.81 Hz). ^{13}C NMR (75 MHz, CD_3OD): δ 14.2, 20.8, 21.5, 26.0, 57.9, 59.1, 64.0, 72.0, 128.2 (2C), 131.0 (2C), 139.2, 145.4, 167.5. MS (ES, pos. mode) m/z (%): 327 (M + H$^+$, 100). HRMS (ES) calcd for $C_{15}H_{22}N_2O_4S$: 327.1373 MH$^+$; found: 327.1379.

Synthesis of (2*S*,3*R*)-ethyl 1-diphenylmethyl-4,4-dimethyl-3-[benzyl-(*p*-toluenesulfonyl)amino]azetidine-2-carboxylate 21

To a solution of (2*S*,3*R*)-ethyl 1-diphenylmethyl-4,4-dimethyl-3-(*p*-toluenesulfonylamino)azetidine-2-carboxylate **16** (0.22 g, 0.45 mmol) in DMF (4 mL) was added K_2CO_3 (3 equiv, 1.35 mmol, 0.19 g) at room temperature. Subsequently, benzyl bromide (1.4 equiv, 0.63 mmol, 0.11 g) was added dropwise and the reaction mixture was stirred for 3.5 h at room temperature. The reaction mixture was poured in diethyl ether (5 mL) and washed with NH_4Cl in H_2O (2 mL) and brine (3 × 2 mL). The organic phase was dried ($MgSO_4$), filtered and evaporated *in vacuo*. The crude product was purified by column chromatography to yield 0.22 g (0.38 mmol) of (2*S*,3*R*)-ethyl 1-diphenylmethyl-4,4-dimethyl-3-[benzyl-(*p*-toluenesulfonyl)amino]azetidine-2-carboxylate **21**.

(2*S*,3*R*)-Ethyl 1-diphenylmethyl-4,4-dimethyl-3-[benzyl-(*p*-toluenesulfonyl)amino]azetidine-2-carboxylate 21

R_f 0.18 (petroleum ether/EtOAc: 5/1). White crystals, yield 85%. $[\alpha]_D$ +54.0 (c 0.2, $CHCl_3$). Mp 165.5 ± 0.5 °C. IR (cm^{-1}): ν_{max} 671, 695, 706, 1157, 1216, 1332, 1720. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.81 (3H, t, J = 7.15 Hz), 0.93 (3H, s), 1.18 (3H, s), 2.39 (3H, s), 3.38–3.49 (1H, m), 3.54–3.65 (1H, m), 3.74 (1H, d, J = 7.71 Hz), 3.90 (1H, d, J = 16.2 Hz), 3.93 (1H, d, J = 7.71 Hz), 4.40 (1H, s), 4.64 (1H, d, J = 16.2 Hz), 7.06–7.37 (15H, m), 7.49 (2H, d, J = 7.15 Hz), 7.64 (2H, d, J = 8.26 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 13.6, 17.1, 21.5, 29.6, 51.4, 60.4, 62.0, 63.6, 68.6, 69.9, 127.2, 127.4, 127.5 (2C), 127.7, 128.0 (2C), 128.1 (4C), 128.3 (2C), 128.4 (2C), 128.9 (2C), 129.7 (2C), 135.5, 137.7, 140.7, 142.8, 143.6, 171.4. MS (ES, pos. mode) m/z (%): 583 (M + H$^+$, 100). HRMS (ES) calcd for $C_{35}H_{38}N_2O_4S$: 583.2625 MH$^+$; found: 583.2620.

Synthesis of (*R*,*R*)-2,3-diamino-4,4-dimethylbutyrolactone dihydrochloride 23

(S_S,2*R*,2′*R*)-ethyl 2-(diphenylmethyleneamino)-2-[3,3-dimethyl-1-(*p*-toluenesulfinyl)aziridin-2-yl]acetate ***syn*-6a** (0.14 g, 0.29 mmol) was dissolved in a mixture of 0.5 M HCl (aq.)/EtOAc: 4/1 (10 mL) and the mixture was stirred for 30 min at room temperature. Subsequently, the reaction mixture was concentrated *in vacuo*. Precipitation in diethyl ether afforded 0.06 g (0.28 mmol) of (2*R*,3*R*)-2,3-diamino-4,4-dimethylbutyrolactone dihydrochloride **23**.

(2*R*,3*R*)-2,3-Diamino-4,4-dimethylbutyrolactone dihydrochloride 23

White crystals, yield 94%. $[\alpha]_D$ +12.5 (c 0.3, MeOH). Mp 243.8 ± 1.5 °C. IR (cm^{-1}): ν_{max} 1042, 1070, 1136, 1273, 1500, 1763, 1787, 2857. ^{1}H NMR (300 MHz, CD_3OD, int. ref. H_2O): δ 1.48 (3H, s), 1.59 (3H, s), 3.97 (1H, d, J = 10.46 Hz), 4.61 (1H, d, J = 10.46 Hz). ^{13}C NMR (75 MHz, D_2O, int. ref. CH_3CN): δ 21.7, 26.5, 52.3, 57.2, 84.9, 168.1. MS (ES, pos. mode) m/z (%): 145 (M + H$^+$ − 2×HCl, 100). Anal. calcd for $C_6H_{14}Cl_2N_2O_2$: C 33.19; H 6.50; N 12.90; found: C 33.55; H 6.51; N 12.66.

Synthesis of (S_S,2*R*,3*R*)-ethyl 2-amino-4-chloro-4-methyl-3-(*p*-toluenesulfinylamino)pentanoate *syn*-24

To a solution of (S_S,2*R*,3*R*)-ethyl 2-(diphenylmethyleneamino)-4-chloro-4-methyl-3-(*p*-toluenesulfinylamino)pentanoate ***syn*-5a** (0.50 g, 0.98 mmol) in acetone/H_2O: 2/1 (30 mL) was added dropwise trifluoroacetic acid (5 equiv, 4.89 mmol, 0.38 mL) at room temperature. The reaction mixture was stirred for 15 min at room temperature and subsequently quenched with NH_4OH in H_2O until pH = 10 and concentrated *in vacuo*. The residue was redissolved in water (10 mL) and NH_4OH in H_2O was added until pH = 10. The aqueous phase was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic phases were dried ($MgSO_4$), filtered and evaporated *in vacuo*. The crude product was purified by rapid filtration over a short silica column with petroleum ether and the silica was subsequently extracted with CH_2Cl_2/MeOH: 4/1. The latter phase was filtered and evaporated *in vacuo* to yield 0.28 g (0.81 mmol) of (S_S,2*R*,3*R*)-ethyl 2-amino-4-chloro-4-methyl-3-(*p*-toluenesulfinylamino)pentanoate ***syn*-24**.

(S_S,2*R*,3*R*)-Ethyl 2-amino-4-chloro-4-methyl-3-(*p*-toluenesulfinylamino)pentanoate *syn*-24

Yellowish oil, yield 83%. $[\alpha]_D$ +155.2 (c 0.5, $CHCl_3$). IR (cm^{-1}): ν_{max} 811, 1064, 1090, 1224, 1734, 3208. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.36 (3H, t, J = 7.15 Hz), 1.63 (3H, s), 1.69 (2H, br s), 1.74 (3H, s), 2.41 (3H, s), 4.07 (1H, d × d, J = 9.1 Hz, 1.10 Hz), 4.17 (1H, d, J = 1.10 Hz), 4.24–4.37 (2H, m), 5.40 (1H, d, J = 9.1 Hz), 7.30 (2H, d, J = 8.0 Hz), 7.63 (2H, d, J = 8.0 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.2, 21.3, 29.2, 30.8, 53.3, 62.2, 65.3, 73.0, 125.4 (2C), 129.5 (2C), 141.4, 142.8, 173.0. MS (ES, pos. mode) m/z (%): 347 (M + H$^+$, 100). HRMS (ES) calcd for $C_{15}H_{23}ClN_2O_3S$: 347.1191 MH$^+$; found: 347.1205.

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