“The meeting of two personalities is like the contact of two chemical substances: if there is any reaction, both are transformed.”

C.G. Jung

Members of the jury

- **Prof. Dr. ir. Paul Van der Meeren (Chairman)**
  Department of Applied analytical and physical chemistry
  Faculty of Bioscience Engineering,Ghent University

- **Prof. Dr. Claudia Tomasini**
  Dipartimento di Chimica "G. Ciamician"
  Università di Bologna, Italy

- **Prof. Dr. Steven Ballet**
  Department of Chemistry
  Faculty of Sciences, Vrije Universiteit Brussel

- **Prof. Dr. ir. Matthias D'hooghe**
  Department of Sustainable Organic Chemistry and Technology
  Faculty of Bioscience Engineering, Ghent University

- **Prof. Dr. ir. Bruno De Meulenaer**
  Department of Food Safety and Food Quality
  Faculty of Bioscience Engineering, Ghent University

Promoters

- **Prof. Dr. ir. Norbert De Kimpe**
  Department of Sustainable Organic Chemistry and Technology
  Faculty of Bioscience Engineering, Ghent University

- **Prof. Dr. ir. Sven Mangelinckx**
  Department of Sustainable Organic Chemistry and Technology
  Faculty of Bioscience Engineering, Ghent University

Dean

Prof. Dr. ir. Guido Van Huylenbroeck

Rector

Prof. Dr. Paul Van Cauwenberge

Faculty of Bioscience Engineering

Academic year 2012 – 2013

Gert Callebaut

Synthesis and applications of chiral *N*-sulfinylimines and -aziridines as versatile building blocks in organic chemistry

Thesis submitted in fulfillment of the requirements for the degree of Doctor (PhD) in Applied Biological Sciences: Chemistry

Dutch translation of the title:

Synthese en toepassingen van chirale *N*-sulfinyliminen en -aziridinen als veelzijdige bouwsteen in de organische chemie

Cover illustration:

View on elemental sulfur of the Papandayan Volcano mountain in West Java, Indonesia.

ISBN 978-90-5989-668-0

Ghent, December 2013

The author, *The promoters,*

ir. Gert Callebaut Prof. Dr. ir. Norbert De Kimpe Prof. Dr. ir. Sven Mangelinckx

Woord vooraf

Toen ik intussen meer dan 9 jaar geleden voor het eerst het ‘Boerekot’ betrad, had ik nooit durven denken zoveel tijd op deze fantastische plek te zullen doorbrengen. Ik had al helemaal niet in gedachten ooit een doctoraat te zullen aanvatten en het feit dat ik nu het sluitstuk van deze periode aan het schrijven ben, brengt een zekere vorm van melancholie in mij naar boven. De jaren die ik aan onze faculteit verbleven heb, mag ik beschouwen als een zeer gelukkige en leuke periode, zowel professioneel als persoonlijk, en dit is te danken aan de prachtige (werk)sfeer die hier te vinden is. Graag had ik dan ook een aantal mensen willen bedanken die dit alles mogelijk hebben gemaakt voor mij.

Vooreerst wil ik mijn promotoren bedanken: Prof. De Kimpe wil ik danken voor de kans die hij me geboden heeft dit doctoraal onderzoek aan te vangen en me te laten werken in deze unieke omgeving, voorzien van een uitstekende begeleiding. Ik wil U ook danken voor het in mij gestelde vertrouwen dat ik steeds kon aanvoelen en enorm apprecieerde. Sven, ondertussen Prof. Mangelinckx, van bij de start van mijn thesisonderzoek heb je mij intensief begeleid en ik kan me niemand voorstellen die dit beter had kunnen doen dan jij. Geen moeite was jou te veel om weer eens tijd voor me vrij te maken om bepaalde problemen te bespreken en je enthousiasme werkte dan ook heel aanstekelijk op mij. Bedankt voor alles!

Furthermore, I would like to thank the members of the jury for all the efforts you have done by reading this PhD-thesis in a very detailed way. I believe that your corrections and constructive remarks have brought this work to a higher level.

Vervolgens kom ik toe aan de mensen die me dag in dag uit omringd hebben gedurende dit doctoraat. *I would like to thank all of my (former) colleague PhD-students and Postdocs,* de mensen van het ATP, alsook de thesisstudenten die ik doorheen de jaren ontmoet heb, voor de steeds opgewekte atmosfeer die in het labo te vinden was. Jullie allemaal bij naam opnoemen is onmogelijk zonder iemand te vergeten of oneer aan te doen. Toch zou ik graag een aantal

mensen persoonlijk willen bedanken voor de fantastische jaren in het labo. Stijn, je bent een echte kameraad geworden doorheen de jaren dat we samen in het labo werkten. We delen samen heel wat interesses zoals het kleurenwiezen en het quizzen, en het verleden heeft al uitgewezen dat het afscheid van het labo geen afscheid van de vriendschap hoeft te zijn. Pieter en Nils, jullie waren steeds de *partners-in-crime* bij het beoefenen van de eerder vernoemde hobby's en ik hoop dan ook dat hier nog een mooi vervolg op mag komen. Koen en Karel, mijn Corsica-maatjes, het is altijd fun als we samen op stap zijn en ik kon me geen twee betere '*sjarels*' voorstellen om alle verschillende extra-labo activiteiten mee te beleven. Ik heb ook hier het gevoel dat onze wegen zich op o.a. menig kaart- of quizevenement zullen kruisen. Tamara, alhoewel we al vijf jaar hetzelfde hadden studeerd, hebben we elkaar pas echt goed leren kennen gedurende ons verblijf op 't vierde. Je bent een echte vriendin geworden die steeds een luisterend oor was als het even wat minder ging en ik hoop dan ook dat we elkaar niet uit het oog zullen verliezen ondanks de drukke agenda's!

Gedurende mijn gehele academische loopbaan heb ik ook ontzettend veel steun gekregen en gevoeld van mijn familie en vrienden. Mama, papa, bedankt voor alles wat jullie voor mij gedaan hebben en nog steeds doen, voor alle opofferingen die jullie voor mij doen en om er steeds te zijn voor mij. Mijn vrienden van 't Karmelieten zou ik ook graag willen bedanken voor de aanmoedigingen die ik van jullie kreeg bij het uitvoeren van 'steeds gekkere' zaken. Hierbij wil ik ook graag mijn beste vriend Wouter bedanken voor alle steun en alle avonturen die we samen beleefden, wat het leven toch zo aangenaam maakt.

En ten slotte rest er me nog één iemand te bedanken. *Moja mala Sonja*, jij bent zonder enige twijfel het beste wat ik aan mijn tijd op het 'Boerekot' heb overgehouden. We hebben elkaar nog niet zo lang geleden pas echt goed leren kennen, maar ik kan me niet meer inbeelden hoe mijn leven zonder jou zijn. Bedankt om er altijd te zijn voor mij, door jou kijk ik vol vertrouwen de toekomst tegemoet…

TABLE OF CONTENTS

List of abbreviations

ACC: 1-aminocyclopropane-1-carboxylic acid

AHL: *N*-acyl homoserine lactone

AMPA: 2-amino-3-(3-hydroxy-5-methyl-isoxazol-4-yl) propanoic acid

ATP: adenosine triphosphate

Bn: benzyl

Boc: *tert*-butoxycarbonyl

CDI: 1,1'-carbonyldiimidazole

DCC: *N*,*N*'-dicyclohexylcarbodiimide

DEAD: diethyl azodicarboxylate

DIAD: diisopropyl azodicarboxylate

DIPEA: *N*,*N*-diisopropylethylamine

DMAP: 4-dimethylaminopyridine

DMF: dimethylformamide

DMSO: dimethyl sulfoxide

DPP: dipeptidyl peptidase

dr: diastereomeric ratio

ee: enantiomeric excess

equiv: equivalent(s)

FAP: fibroblast activation protein

HMDS: hexamethyldisilazane

HMPA: Hexamethylphosphoramide

L-Aze: *L*-azetidine-2-carboxylic acid

LDA: lithium diisopropylamide

*m*CPBA: 3-chloroperoxybenzoic acid

MW: microwave

Ns: nitrobenzenesulfonyl

Nu: nucleophile

p-Tol: *para*-tolyl

Ph: phenyl

PMP: *para*-methoxyphenyl

SAM: (*S*)-adenosylmethionine

t-Bu: *tert*-butyl

TFA: trifluoroacetic acid

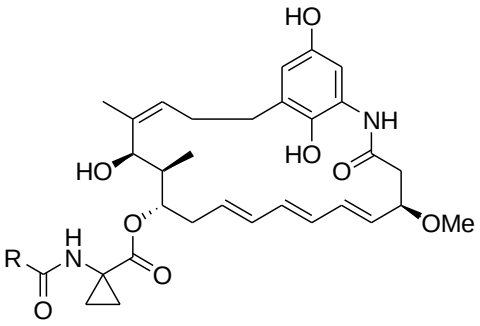
THF: tetrahydrofuran

Tos: *para*-toluenesulfonyl

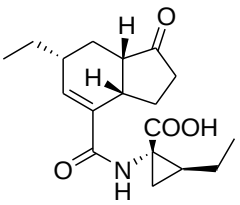
1. Introduction and Goals

The incorporation of conformationally constrained α- and β-amino acids into biologically active peptides has gained great interest in the preparation of peptide-based drug molecules. γ-Chloro-α-amino acid derivatives or the chlorinated β-amino acid analogues, have received far less attention. Nevertheless these halogenated amino acid derivatives are biologically relevant compounds, which can also serve as very promising building blocks in synthetic organic chemistry.

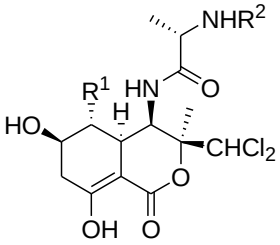
Nature uses α-amino acid derivatives with a leaving group at the γ-position as versatile building blocks in the biosynthesis of a broad range of biologically important natural products. For example, (*S*)-adenosylmethionine (SAM) is a biological sulfonium compound that is involved in many biological processes. SAM is the second most common cosubstrate for enzymes 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*-acyl homoserine 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 carbocylic 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 **1** (apoptosis-inducing *Streptomycete* metabolite),[3a] coronatine (phytotoxin) **2**,[3b-c] and bactobolins (antibiotic activity) **3** (Figure 1).[4]



1a (R = 1-cyclohexenyl), cytotrienin A
1b (R = cyclohexyl), cytotrienin B



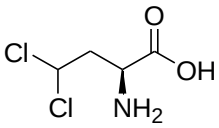
2
coronatine



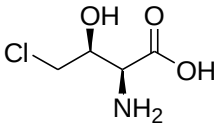
3a (R^1 = OH, R^2 = H), bactobolin A
3b (R^1 = OH, R^2 = *L*-Ala), bactobolin B
3c (R^1 = H, R^2 = H), bactobolin C
3d (R^1 = H, R^2 = *L*-Ala), bactobolin D

Figure 1

Some γ-chloro-α-amino acids are also biologically active as a free amino acid, such as armentomycin **4**, a non-proteinogenic amino acid with antibiotic properties,[3a,5] and 4-chloro-*L*-threonine **5**, which is biologically active as a serine hydroxymethyltransferase inhibitor,[3d] and as a herbicidal antimetabolite (Figure 2).[6] 4-Chloro-*L*-threonine is also a constituent of naturally occurring syringomycins (antifungal compounds),[7] and actinomycins (cytotoxic and antibacterial compounds).[8]



4
armentomycin

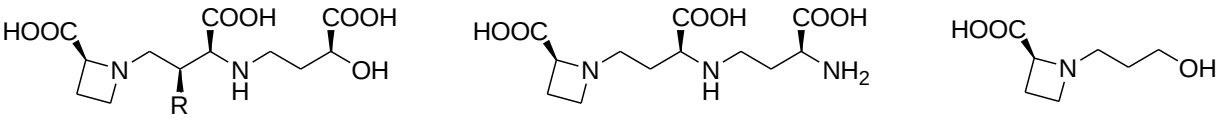


5
4-chloro-*L*-threonine

Figure 2

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 among organic chemists and biochemists.[10,11] This is due to the fact that these diamino carboxylic acids are present as key structural fragments in biologically active compounds such as β-(*N*-oxalyl)-*L*-α,β-diaminopropionic acid (neurotoxin),[12] β-methylamino-*L*-alanine (neurotoxin),[13] *L*-quisqualic acid (vermicide),[14] *L*-mimosine (cell proliferation blocker),[15] and *L*-willardine (agonist of AMPA and kainate receptor).[16]

These α,β-diamino acids can also serve as building blocks for the synthesis of new heterocyclic compounds and peptides.[10,17] For example, γ-chloro-α,β-diamino acid derivatives are precursors for the synthesis of 3-aminoazetidine-2-carboxylates, belonging to the class of 3-aminoazetidines which have received considerable attention,[18] especially because of their antibacterial activities.[19] The constrained *L*-azetidine-2-carboxylic acid skeleton of these 3-aminoazetidine-2-carboxylates has found many applications in the modification of peptide conformations,[2,20] and is present in several natural products such as mugineic acid **6**,[21] 2'-deoxymugineic acid **7**,[22] nicotianamine **8**,[23] and medicanine **9** (Figure 3).[24]



6 (R = OH), mugineic acid
7 (R = H), 2'-deoxymugineic acid

8
nicotianamine

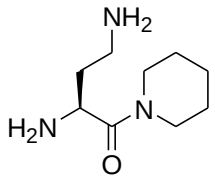
9
medicanine

Figure 3

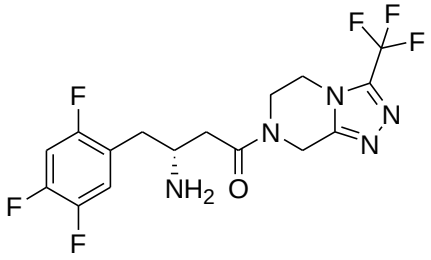
Moreover, some diamino acids are also bioactive as free diamino carboxylic acid derivatives.[7,10,11,25,26] For example, α,γ-diaminoacylamides are known for their high potency and selectivity as dipeptidyl peptidase (DPP) inhibitors.[27]

DPPIVs are proteases which specifically cleave off *N*-terminal dipeptides and are involved in the degradation of incretin hormones, including glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP). GLP-1 is involved in the regulation of glucose homeostasis *via* stimulation of insulin secretion, inhibition of glucagon release and delay of gastric emptying. It has been demonstrated that the presence of intravenous GLP-1 increases insulin secretion as response to elevated glucose levels and as such, GLP-1 can offer therapeutic benefits for patients with type 2 diabetes. Unfortunately, therapeutic application of GLP-1 is problematic by the lack of oral activity and the rapid degradation by plasma DPPIV. Therefore, DPPIV inhibitors could offer a solution to this problem, as they can extend the duration of action of GLP-1 and prolong the beneficial effects.[28]

Besides DPPIV, a few related enzymes are present in the family of DPPs: DPPII, DPP8, DPP9 and FAP being the most important regarding the therapeutic potential, when focusing on the inhibitory potency and selectivity.[28] In the research towards DPPII and DPPIV inhibitors, it has been found that the α,γ-diaminoacylpiperidine, (*S*)-2,4-diamino-1-(piperidine-1-yl)butan-1-one **10**, is a lead compound in the development of large series of highly potent and selective DPPII inhibitors (Figure 4).[27] Next to the α,γ-diaminoacylpyrrolidines and -piperidines which exhibit a DPP inhibitory effect, also some β-amino carboxylic amides, such as sitagliptin are known as DPP inhibitors.[29] Sitagliptin **11** is a commercialized oral antihyperglycemic drug of the DPPIV inhibitor class (Figure 4).[30]



10
(*S*)-2,4-diaminobutanoylpiperidine

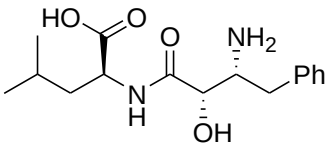


11
sitagliptin

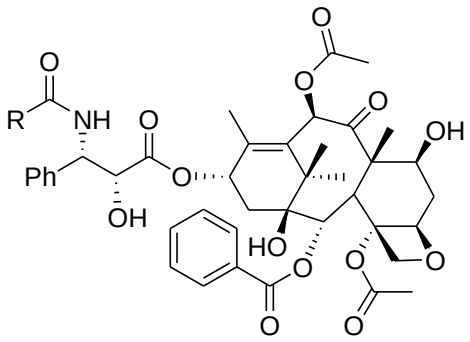
Figure 4

As α,γ-diamino carboxylic amides, as well as β-amino carboxylic amides, are known for their activity as DPP inhibitors, an increasing interest to study the DPP inhibitory potency of analogous α,β-diamino carboxylic amides and α,β,γ-triamino carboxylic amides exists.[31]

Next to the diamino carboxylic acid derivatives, α-hydroxy-β-amino carboxylic acids gained also a lot of interest among organic chemists.[32] This can be explained by the fact that the α-hydroxy-β-amino carboxylic acid unit is present in a wide range of biologically active molecules, such as (-)-bestatin **12**, which is an aminopeptidase inhibitor, paclitaxel **13a** and docetaxel **13b**, which are both known for their anti-mitotic activity (Figure 5).[33]



12
(-)-bestatin



13a (R = Ph), paclitaxel
13b (R = Ot-Bu), docetaxel

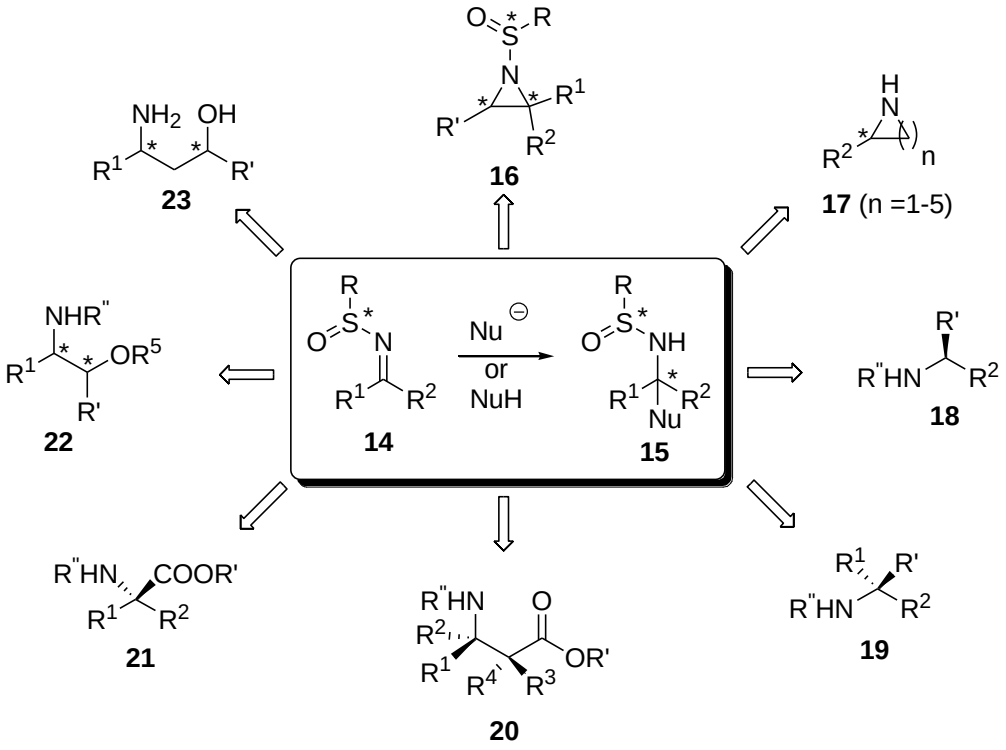
Figure 5

In light of the ubiquitous applications of α,β-diamino acid- and α-hydroxy-β-amino acid-containing compounds as building blocks in organic chemistry and as biologically active molecules, efforts will be done to synthesize new representatives of these interesting classes of non-proteinogenic amino acids and their further transformations in this doctoral study. The entries developed in this study towards novel densely functionalized chiral α- or β-amino acid derivatives will fill up important gaps within the chemistry of these non-proteinogenic amino acid derivatives.

In the literature, enantiopure *p*-toluenesulfinamide (Prof. Davis) as well as enantiopure *tert*-butanesulfinamide (Prof. Ellman, Prof Garcia Ruano) have already been utilized quite extensively in the asymmetric synthesis of a large number of biologically interesting molecules. Both types of sulfinamides are commercially available and can easily been used in condensation reactions with aldehydes, ketones or orthoesters in the presence of a Lewis acid (e.g. $Ti(OEt)_4$). The corresponding imines or imidates exhibited a high diastereofacial selectivity in nucleophilic addition reactions and are stable under mild conditions. In this way, the *p*-toluene- and *tert*-butanesulfinyl group serve both as powerful chiral directing groups and comprise one of the most efficient auxiliaries developed to date. Next to the difference in price, by which enantiopure *tert*-butanesulfinamides are significantly cheaper than

enantiopure *p*-toluenesulfinamide, both compounds differ also with respect to the electron withdrawing character of the sulfinyl group, which is more pronounced for the *p*-toluenesulfinamides. Furthermore, the *tert*-butanesulfinyl group can be selectively deprotected with (dry) HCl, whereas the deprotection of the *p*-toluenesulfinyl group can easily be performed with aqueous TFA.

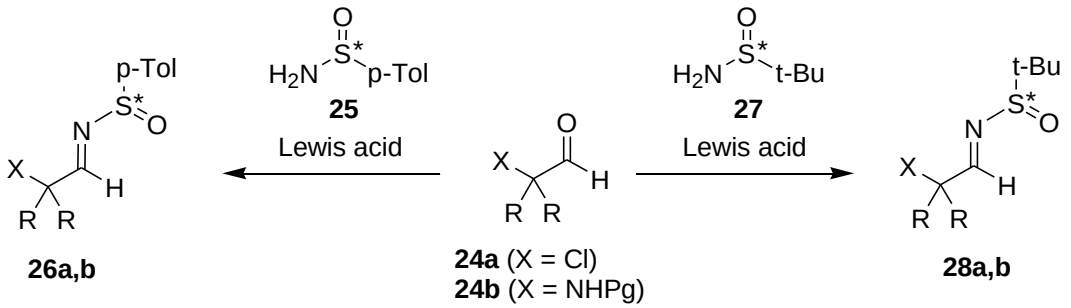
In this PhD thesis, the synthesis and reactivity of *N*-sulfinyl-α-chloroaldimines in stereoselective Mannich-type additions, will be investigated. In the past, chiral *N*-sulfinylimines **14** have already proven to be valuable synthons for the preparation of a wide range of enantiopure aliphatic and cyclic amines (Scheme 1), such as aziridines **16**[34,35] and **17** (n = 1),[36,37] azetidines **17** (n = 2),[37] pyrrolidines **17** (n = 3),[36,37] piperidines **17** (n = 4),[36,37] azepanes **17** (n = 5),[37] α-branched and α,α-dibranched amines **18** and **19**,[34,35,38,39] β-amino esters **20**,[34,35,38] α-amino esters **21**,[34,35,38] 1,2-amino alcohols **22**[34,35,38,39] and 1,3-amino alcohols **23**.[35,38,40] In addition, nucleophilic additions of α-chloroimines[41,42] with different carbon and heteroatom nucleophiles have extensively been used in the past for the synthesis of azaheterocyclic compounds.[43,44,45,46,47,48]



Scheme 1

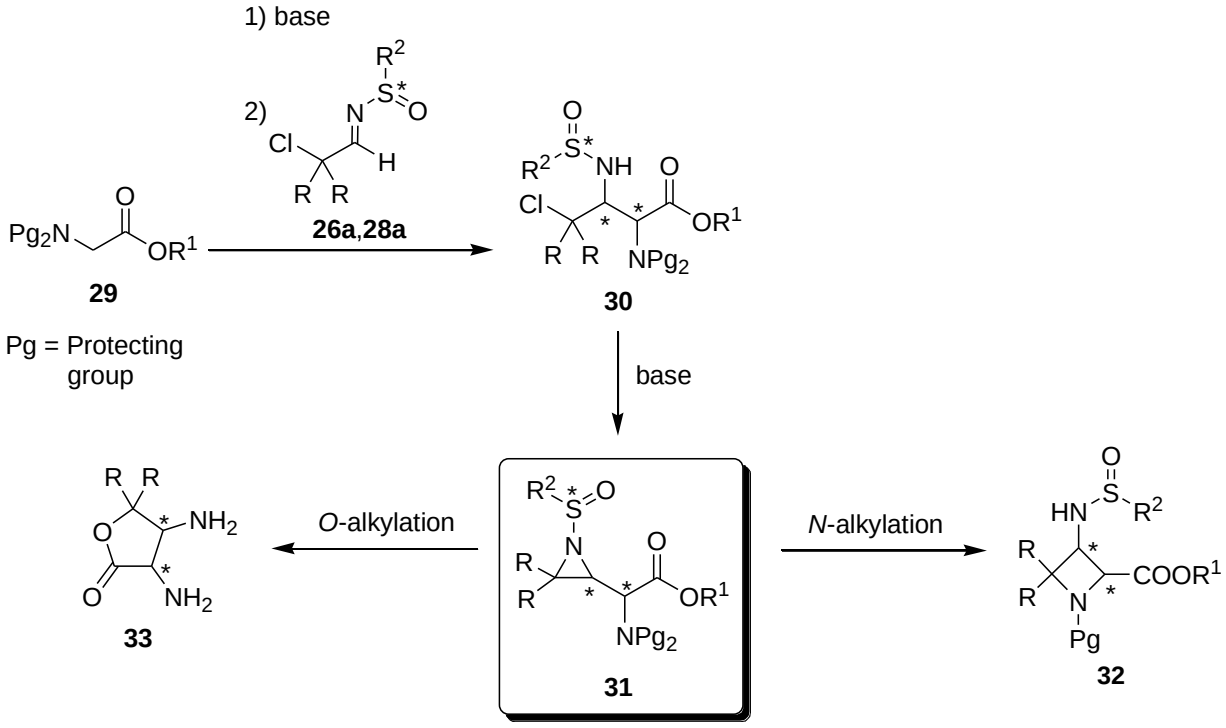
In comparison with the huge number of reports on the synthesis of chiral *N*-(*p*-toluenesulfinyl)-imines, the synthesis of *N*-(*p*-toluenesulfinyl)-α-chloroaldimines **26a** or aliphatic *N*-(*p*-toluenesulfinyl)-α-aminoaldimines **26b** has not been reported so far. Therefore, the synthesis of chiral *N*-(*p*-toluenesulfinyl)-α-functionalized aldimines **26**, starting from a condensation reaction of the corresponding α-functionalized aldehydes **24** with chiral *p*-toluenesulfinamide **25** in the presence of a Lewis acid, will be investigated in the first part of this PhD thesis (Scheme 2).

Moreover, *N*-(*tert*-butanesulfinyl)aldimines have also proven to be valuable synthons in organic synthesis in contrast to the *N*-(*tert*-butanesulfinyl)-α-functionalized aldimines **28**, which have received far less interest in the literature despite the synthetic potential of these compounds. The synthesis of these α-functionalized imines **28** will also be explored *via* condensation reaction of the corresponding α-functionalized aldehydes **24** with chiral *tert*-butanesulfinamide **27** in the presence of a Lewis acid (Scheme 2).



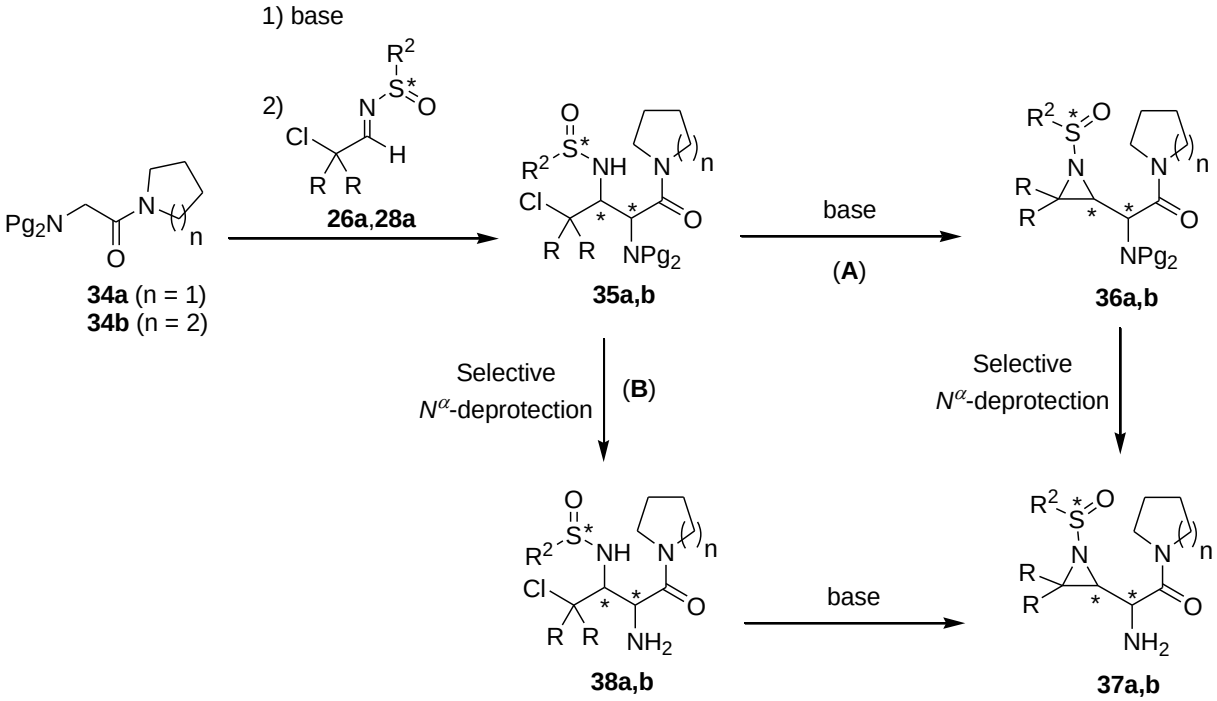
Scheme 2

In the next part, the asymmetric synthesis of protected γ-chloro-α,β-diamino esters **30** will be studied *via* stereoselective Mannich-type additions of *N*-protected glycine esters **29** across *N*-sulfinyl-α-chloroaldimines **26a** and **28a** (Scheme 3). Hereby, the influence of the reaction conditions on the stereochemical outcome of the reaction will be optimized with the aim to develop an efficient and stereoselective approach towards these compounds **30**. Bearing in mind that (chiral) β-haloamines are excellent precursors for the synthesis of aziridines, a base-induced cyclization reaction towards the protected β,γ-aziridino-α-amino esters **31** will be attempted on the γ-chloro-α,β-diamino esters **30**. Furthermore, several intramolecular ring transformations of β,γ-aziridino-α-amino esters **31** will be attempted in order to synthesize novel biologically interesting 3-aminoazetidine-2-carboxylates **32** and α,β-diamino-γ-butyrolactones **33**.



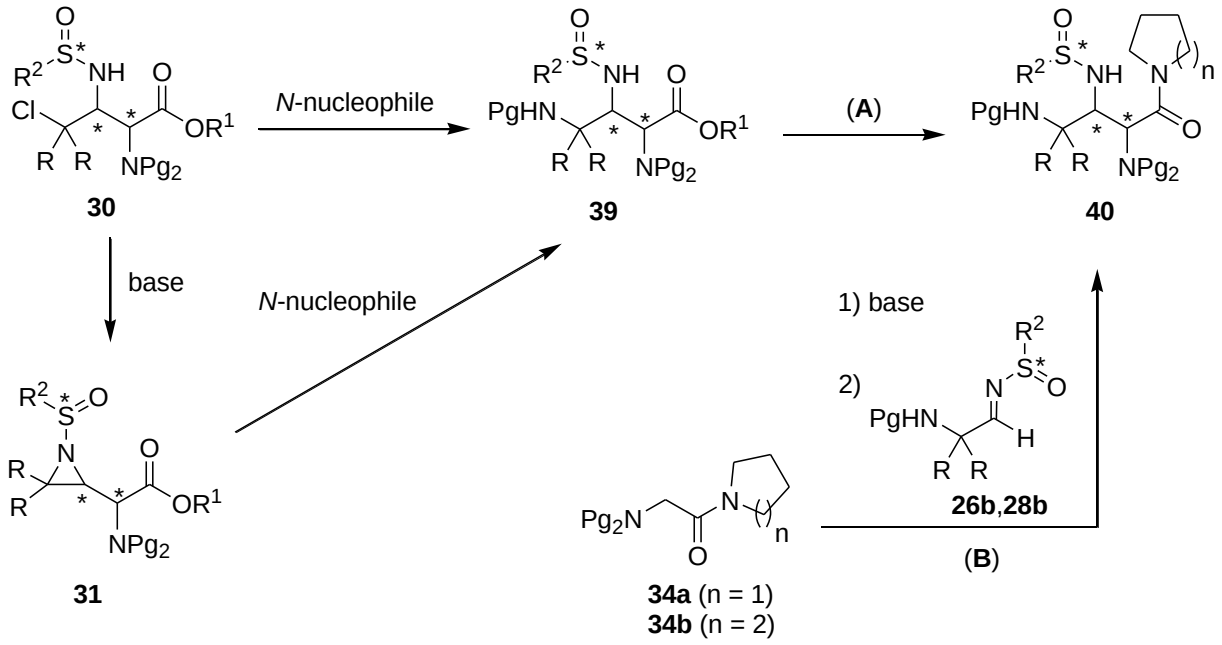
Scheme 3

The asymmetric synthesis of chiral γ-chloro-α,β-diaminoacylpyrrolidines and -piperidines **35** will also be investigated *via* stereoselective Mannich-type additions of *N*-protected glycinamides **34a,b** across *N*-sulfinyl-α-chloroaldimines **26a** and **28a** (Scheme 4). In order to develop potential DPP inhibitors, the ring closure and selective deprotection of the α-amino functionality of these chiral γ-chloro-α,β-diaminoacylpyrrolidines and -piperidines **35** will be explored as well. Hereby, two possible approaches towards the α-deprotected β,γ-aziridino-α-aminoacylpyrrolidines and β,γ-aziridino-α-aminoacylpiperidines **37** will be elaborated. In a first approach (**A**), ring closure of γ-chloro-α,β-diaminoacylpyrrolidines and -piperidines **35a,b** towards the corresponding β,γ-aziridino-α-aminoacylpyrrolidines and -piperidines **36** will be followed by a selective deprotection of the α-amino functionality, while in a second approach (**B**) N^{α}-deprotected γ-chloro-α,β-diaminoacylpyrrolidines and -piperidines **38** will be cyclized to the corresponding aziridines **37**.



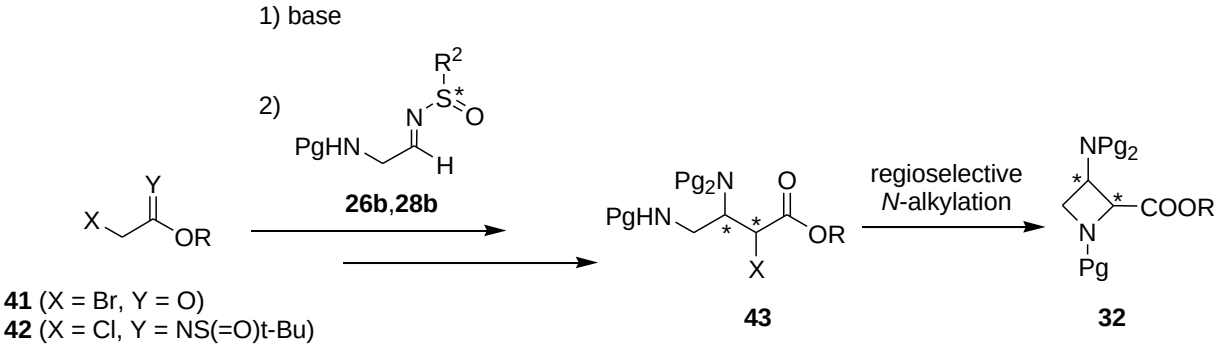
Scheme 4

In the following part, the synthesis of chiral α,β,γ-triaminoacylpyrrolidines and -piperidines **40** will be investigated *via* two reaction pathways, as these novel α,β,γ-triamino amides are also interesting in studies towards their potential activity as DPP and FAP inhibitors. In the first strategy (**A**), γ-chloro-α,β-diamino esters **30** and β,γ-aziridino-α-amino esters **31** will be reacted with different nitrogen nucleophiles *via* substitution or ring-opening reactions, respectively, in order to synthesize new α,β,γ-triamino esters **39** which could be converted in the corresponding α,β,γ-triaminoacylpyrrolidines and -piperidines **40** (Scheme 5). A second possible approach (**B**), would involve the synthesis of α,β,γ-triamino amides **40** *via* Mannich-type addition of *N*-protected glycine amides **34** across *N*-sulfinyl-α-aminoaldimines **26b** and **28b** (Scheme 5).



Scheme 5

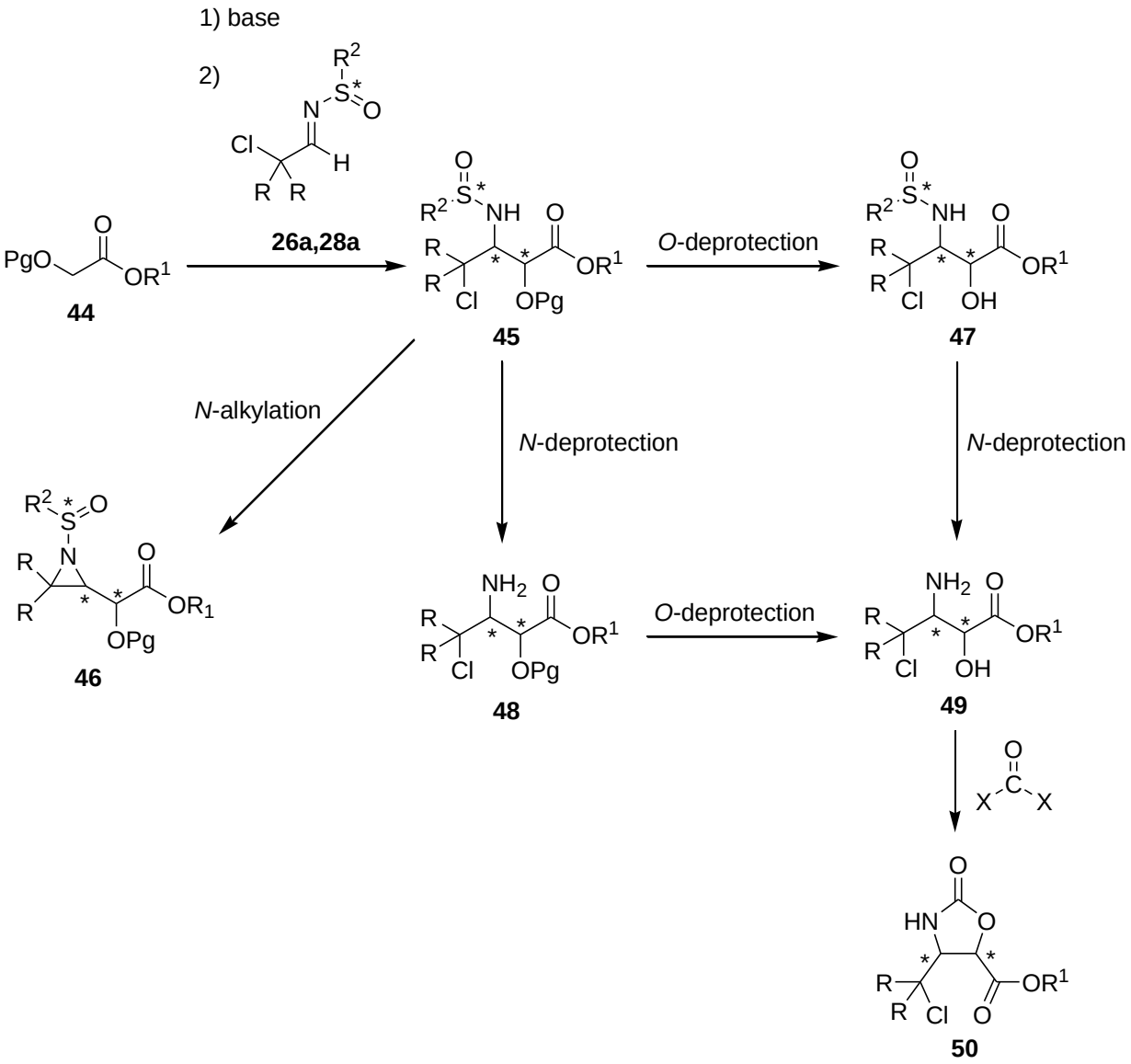
Furthermore, the asymmetric synthesis of α-halo-β,γ-diamino ester derivatives **43** will be studied, *via* stereoselective Mannich-type addition of α-haloacetates **41** or α-haloimidates **42** across chiral *N*-sulfinyl-α-aminoaldimines **26b** and **28b** (Scheme 6). These α-halo-β,γ-diamino ester derivatives **43** are potential precursors of 3-aminoazetidine-2-carboxylates **32**, belonging to a very interesting class of molecules, with potential application as building blocks for the synthesis of oligopeptides and as antibiotics.



Scheme 6

The last part of this PhD thesis will include the asymmetric synthesis of protected γ-chloro-β-amino-α-hydroxy esters **45**, *via* stereoselective Mannich-type additions of *O*-protected glycol esters **44** across *N*-sulfinyl-α-chloroaldimines **26a** and **28a** (Scheme 7). These γ-chloro-β-

amino-α-hydroxy esters **45** are considered as precursors for the synthesis of the corresponding β,γ-aziridino-α-hydroxy esters **46**. Furthermore, several selective deprotection conditions will be tested on the γ-chloro-β-amino-α-hydroxy esters **45**, in order to obtain *O*-deprotected and/or *N*-deprotected α-hydroxy esters **47-49**. Compounds **49** could be used as precursor for the synthesis of oxazolidinones **50**, which might serve as building blocks in biomedicinal chemistry.[49]



Scheme 7

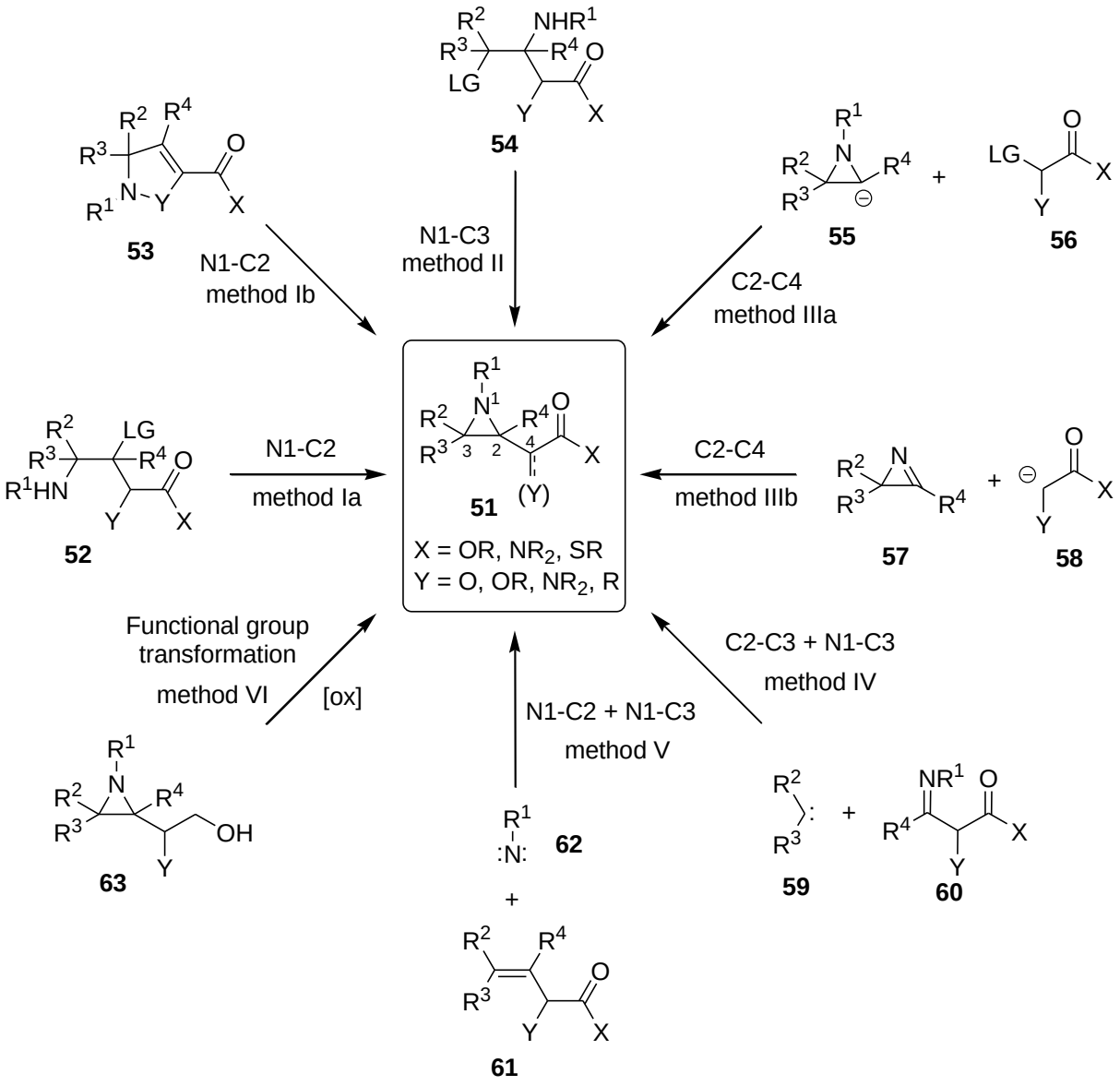
2. Literature Overview

In the following chapter, the synthesis of 2-(carboxymethyl)aziridines will be dealt with. 2-(Carboxymethyl)aziridines comprise key-intermediates in the synthesis of γ-functionalised-β-amino acid derivatives and β-functionalised-γ-amino acid derivatives and can be synthesized starting from γ-chloro-β-amino acid derivatives. Moreover, some 2-(carboxymethyl)aziridines are showing interesting biological activities and can find application in as lead-compounds in medicinal chemistry.

Several synthetic approaches towards 2-(carboxymethyl)aziridines **51** based on the different bond connections or transformations are schematically illustrated in Scheme 8. A distinction has been made between three types of intramolecular reactions (methods Ia, Ib and II), four types of intermolecular reactions (methods IIIa, IIIb, IV and V) and a final method based on functional group transformation (method VI). Hereby, all relevant references will be presented in the following sections.

Furthermore, the intramolecular reactions and addition reactions were subdivided with respect to the mechanism of these reactions. The intramolecular nucleophilic substitution reactions (methods Ia and II) involve an attack of a nucleophilic amino group on an adjacent carbon atom bearing a leaving group (LG), to afford 2-(carboxymethyl)aziridines. To allow aziridine synthesis in an asymmetric way, the use of starting products **54** derived from the chiral pool was also described (method II). Besides, an intramolecular (thermal) rearrangement of 4-isoxazoline-5-carboxylates **53** (Y = O) has been used as an approach towards the synthesis of this type of aziridines (method Ib).

2-(Carboxymethyl)aziridines are also accessible *via* addition reactions with carbanions **55** and **58** (methods IIIa and IIIb). Substitution reactions of stabilized aziridinyl anions **55** with acetates bearing a leaving group in α-position present an efficient synthetic pathway towards the corresponding 2-(carboxymethyl)aziridines (method IIIa).



Scheme 8

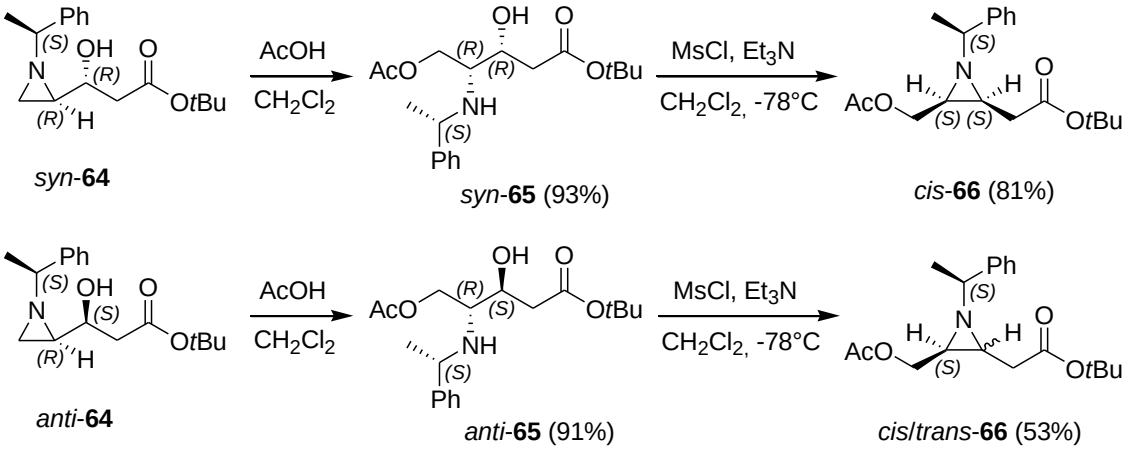
Furthermore, addition reactions of α-deprotonated acetate derivatives **58** across 2*H*-azirines have been performed as well *via* Reformatsky, and Ivanov reactions (method IIIb). Moreover, addition reactions *via* addition of electron-deficient carbenes **59** or nitrenes **62** to double bonds will be discussed (methods IV and V). This part also includes the additions of sulfur ylides to imines (method IV) and the addition of substituted azides across olefins (method V). Furthermore, the synthesis of 2-(carboxymethyl)aziridines is effectuated *via* functional group transformations of compounds **63** derived from the chiral pool (method VI).

2.1. Synthesis through N1-C2 bond formation

2.1.1. Synthesis *via* intramolecular nucleophilic substitution (method Ia)

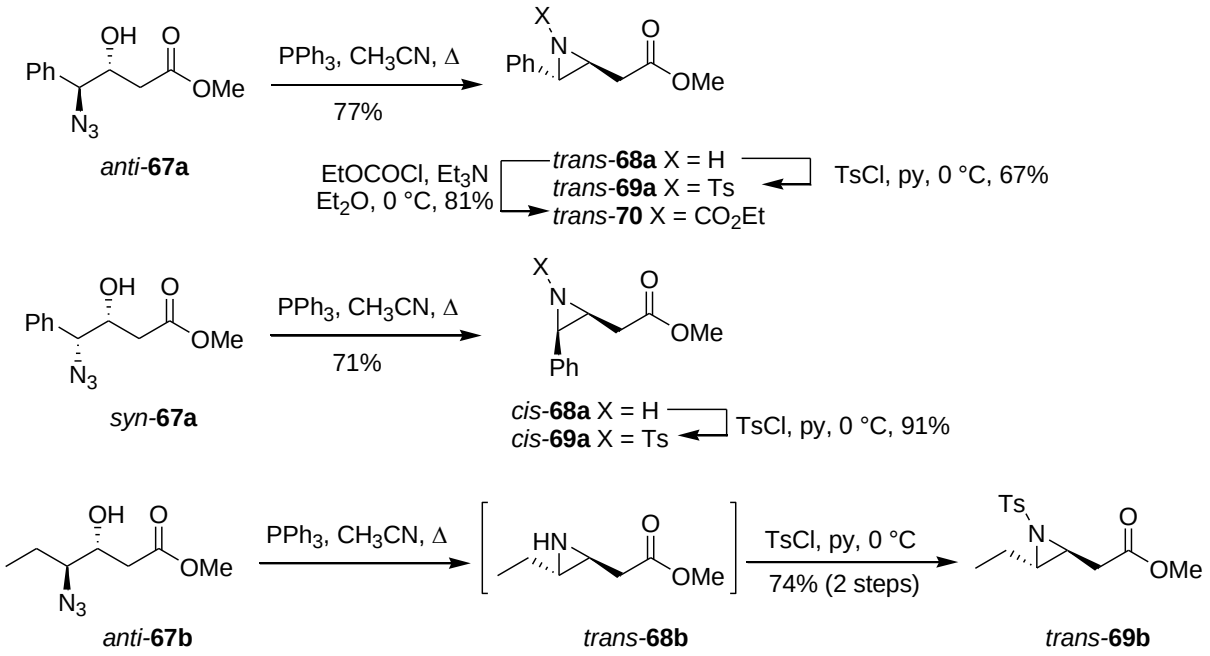
γ-Amino carboxylic acid derivatives which bear a leaving group in the β-position are suitable building blocks for the synthesis of monocyclic 2-(carboxymethyl)aziridines.[50,51,52]

For example, γ,δ-aziridino-β-hydroxy esters *syn*-**64** and *anti*-**64** were transformed into 2-(carboxymethyl)aziridines **66** (Scheme 9).[50] The enantiopure amino alcohols *syn*-**65** and *anti*-**65** were obtained in excellent yield by a regioselective ring opening of the chiral γ,δ-aziridino-β-hydroxy esters *syn*-**64** and *anti*-**64** at the less substituted carbon atom with AcOH in CH_2Cl_2. Intramolecular ring closure of amino alcohols *syn*-**65** and *anti*-**65** with MsCl and Et_3N provided the corresponding chiral non-activated 2-(carboxymethyl)aziridines **66**. It is well known that *cis*-2,3-disubstituted aziridines are thermodynamically more stable than *trans*-2,3-disubstituted aziridines.[53] The *syn*-γ,δ-aziridino-β-hydroxy ester *syn*-**64** was readily transformed into the corresponding chiral *cis*-2,3-disubstituted aziridine *cis*-**66**, but the *anti*-derivative *anti*-**64** provided the diastereomeric mixture of chiral *trans*- and *cis*-2,3-disubstituted aziridines **66**. The mesylation of the amino alcohols *anti*-**65** seemed to be followed by elimination in the presence of Et_3N to provide the corresponding α,β-unsaturated ester to which the amino group adds conjugatively to result in a mixture of *trans*- and *cis*-2,3-disubstituted aziridines **66**.



Scheme 9

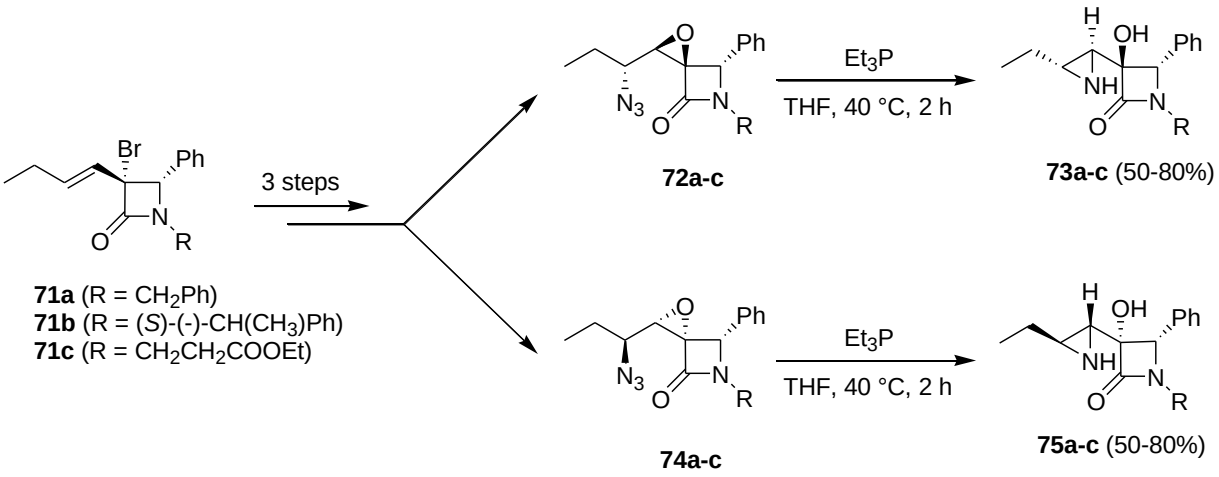
γ-Azido-β-hydroxy carboxylic acid derivatives **67** were also used as precursor for the stereoselective synthesis of 2-(carboxymethyl)aziridines **68** *via* a Staudinger reduction (Scheme 10).[51] The vicinal azido alcohols (±)-*anti*-**67a**, (±)-*syn*-**67a** and (±)-*anti*-**67b** were treated with PPh_3 in anhydrous CH_3CN under reflux to afford their corresponding *N*-H-aziridines (±)-*trans*-**68a**, (±)-*cis*-**68a** and (±)-*cis*-**68b**, respectively, as the sole products. Purification of *N*-H-aziridine (±)-*trans*-**68b** was problematic due to the low molecular weight of this compound. In order to isolate this aziridine, an *in situ N*-tosylation was performed with TsCl in pyridine, which resulted in the formation of *N*-tosyl-2-(carboxymethyl)aziridine (±)-*trans*-**69b** in a good overall yield. Tosylation of the diastereomerically pure aziridines (±)-*trans*-**68a** and (±)-*cis*-**68a** afforded *N*-tosyl-2-(carboxymethyl)aziridines (±)-*trans*-**69a** and (±)-*cis*-**69a** in moderate to good yields. Additionally, aziridine (±)-*trans*-**68a** was reacted with ethyl chloroformate in basic medium to provide carbamate (±)-*trans*-**70a** (X = COOEt).



Scheme 10

In accordance with these results, Staudinger reduction has also been employed in the synthesis of 3-hydroxy-β-lactams **73** and **75**, containing an aziridine moiety, starting from 3-bromo-3-alkenyl-azetidin-2-ones **71** (Scheme 11).[52] The diastereomeric spiro-β-lactams **73**

and **75** were efficiently synthesized *via* a three-step synthesis starting from the same 3-alkenyl-β-lactam precursor **71**. In the next step, both diastereomeric azides **72** and **74** were reduced with triethylphosphine in dry THF at 40 °C for two hours, to afford the corresponding β-lactams **73** and **75** in 50-80% yield *via* an aza-Payne-like ring opening[54] of the epoxides **72** and **74**.

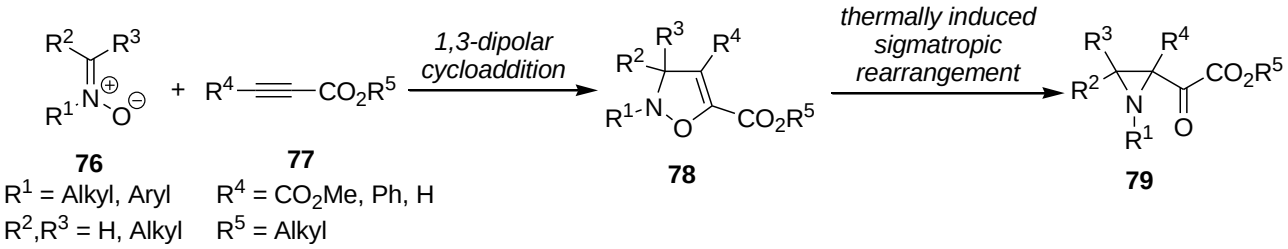


Scheme 11

2.1.2. Synthesis *via* rearrangement of 4-isoxazoline-5-carboxylate derivatives (method Ib)

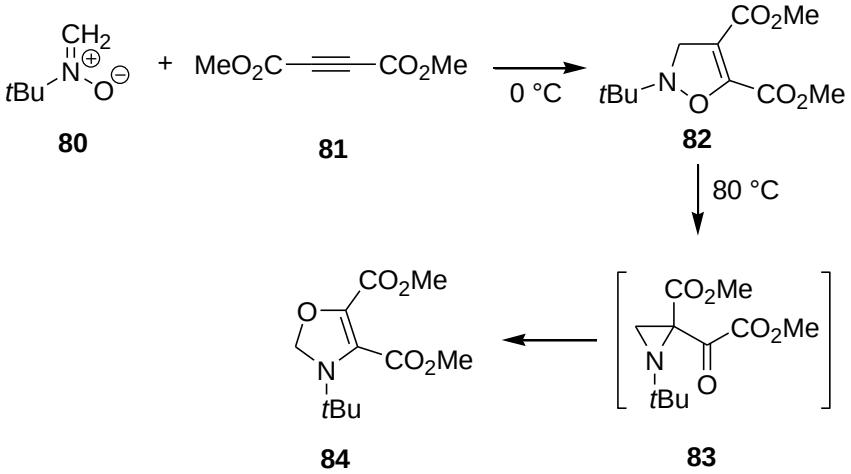
2.1.2.1. Synthesis of *N*-alkyl- and *N*-arylaziridines

The reaction of nitrones **76** with alkyl acetylenecarboxylates **77** *via* 1,3-dipolar cycloaddition resulted in the selective and efficient synthesis of 4-isoxazoline-5-carboxylates **78**, which proved to be excellent precursors for the synthesis of the corresponding *N*-alkyl- and *N*-aryl-2-oxalylaziridines **79** *via* a thermally induced sigmatropic rearrangement (Scheme 12). Some examples of this methodology will be described in the following part.



Scheme 12

A 1,3-dipolar cycloaddition of *tert*-butylmethylenenitrone **80** with dimethyl acetylenedicarboxylate **81** proceeded rapidly at 0 °C and resulted quantitatively in the formation of dimethyl 2-*tert*-butyl-4-isoxazoline-4,5-dicarboxylate **82** (Scheme 13).[55,56] It was shown that the latter compound **82** easily underwent thermal rearrangement upon heating at 80 °C in the dark under N_2-atmosphere to afford 4-oxazoline **84**. The isomerization occurred most probably *via* formation of aziridine intermediate **83**.

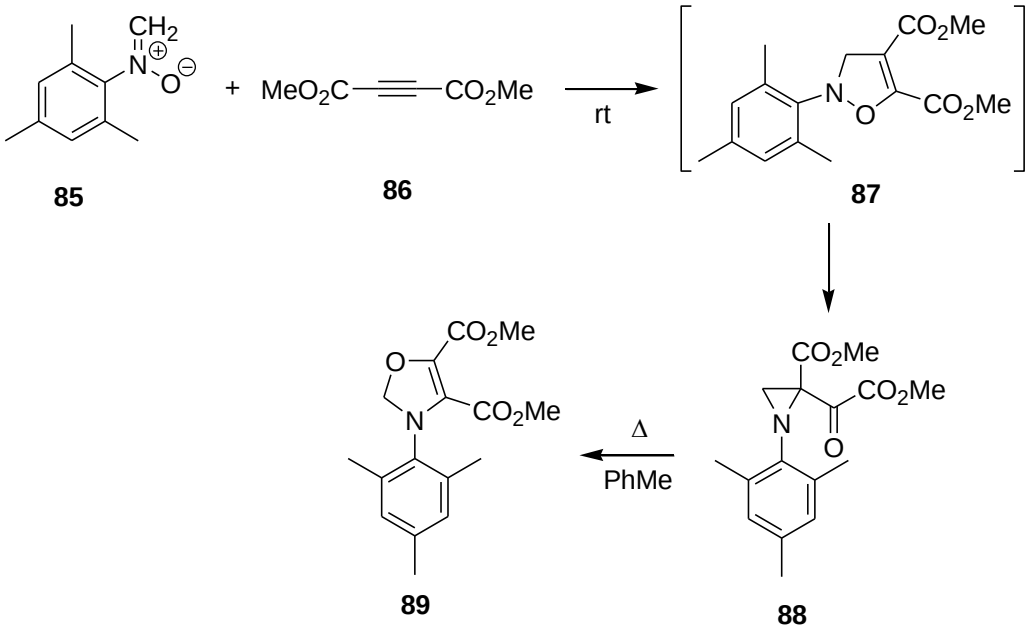


Scheme 13

Furthermore, it was shown that suitable choice of substituents could result in the formation of the corresponding 4-isoxazoline-4,5-dicarboxylate with a weakened N-O bond.[55] In this way, the isolation of aziridine **83** as potential precursor in this thermal rearrangement, would become possible.

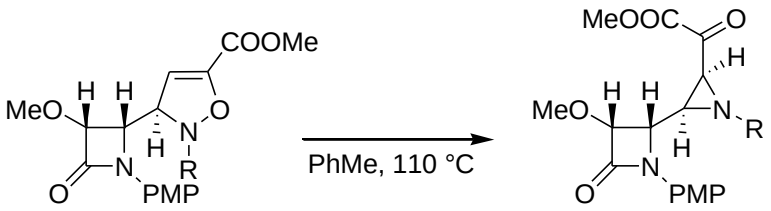
Thus, the reaction of *N*-(2,4,6-trimethylphenyl)methylenenitrone **85** with dimethyl acetylene-dicarboxylate **86** resulted in the synthesis of the even more thermally labile **87**, which immediately rearranged to the corresponding aziridine **88** at room temperature (Scheme 14).

Treatment of this aziridine **88** in toluene under reflux gave again the thermally more stable 4-oxazoline **89**.



Scheme 14

In another report, the reactivity of polyfunctionalized 4-isoxazoline-5-carboxylates **90** has been evaluated by thermal treatment (Scheme 15).[57] Interestingly, by heating of these compounds **90** in toluene at 110 °C, the 2-acylaziridinyl-containing β-lactams **91** were obtained as single isomers. This result was again rationalized by a thermally induced sigmatropic rearrangement, where the stereochemical outcome of the reaction was controlled by steric interactions.

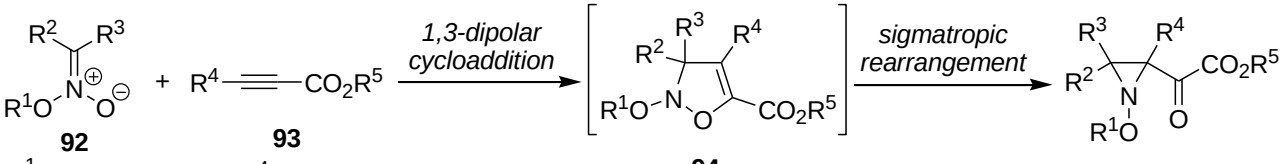


90 (R = Bn, Me) **91** (40-50%)

Scheme 15

2.1.2.2. Synthesis of *N*-alkoxyaziridines

The reaction of nitronium esters **92** with alkyl acetylenecarboxylates **93** resulted in the regioselective formation of *N*-alkoxyaziridines **95** (Scheme 16). This reaction proceeded *via* a 1,3-dipolar cycloaddition through intermediacy of 4-isoxazoline-5-carboxylates **94**. These 4-isoxazolines **94** isomerized easily and selectively to deliver the corresponding aziridines **95** *via* a sigmatropic rearrangement. Two examples of this synthetic approach are presented below.

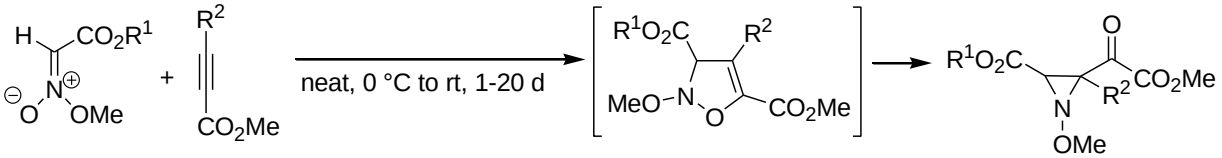


92 **93** **94** **95**

R^1 = Alkyl; R^2,R^3 = COOR, H, Alkyl, CN; R^4 = H, Me; R^5 = Me, *t*Bu

Scheme 16

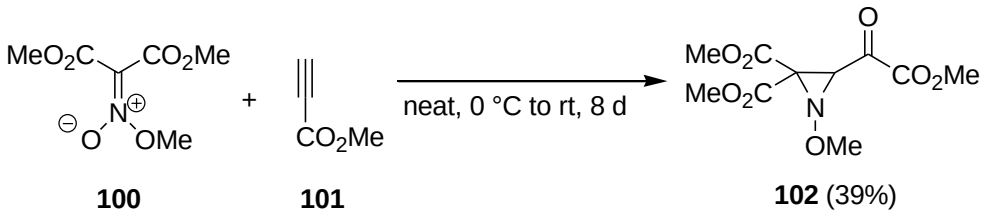
In contrast to the 1,3-dipolar cycloaddition of nitrones **76**, 1,3-dipolar cycloaddition of nitronium esters **92** across acetylenecarboxylates **93** afforded *N*-alkoxyaziridines **95** as end products, while intermediate 4-isoxazoline-5-carboxylates **94** were never isolated. The synthesis of the disubstituted *N*-methoxyaziridines **99** was accomplished in high yield (74-79%) by stirring nitronium esters **96** with methyl acetylenecarboxylate **97** neat at 0 °C to room temperature for one to five days (Scheme 17).[58,59] The cycloaddition reaction of nitronium ester **96b** across tetrolic acid methyl ester **97b** proceeded more slowly and afforded the trisubstituted *N*-methoxyaziridine **99** only in 15% yield after 20 days.[58,59]



96a (R^1 = Me) **97a** (R^1 = H) **98** **99** (15-79%)
96b (R^2 = Et) **97b** (R^2 = Me)

Scheme 17

Similarly to the cycloaddition of monosubstituted nitronium esters **96** across methyl acetylenecarboxylate **97**, also disubstituted nitronium ester **100** was used for the synthesis of *N*-methoxyaziridine **102** (Scheme 18). [59]



100 **101** **102** (39%)

Scheme 18

2.2. Synthesis through N1-C3 bond formation (method II)

2.2.1. Enantioselective synthesis starting from the chiral pool

The strategy of using the chiral pool for enantioselective synthesis has gained a lot of attention among (bio-)organic and medicinal chemists the past decades. Chiral pool synthesis is especially helpful if the desired compounds have a great resemblance to cheap and readily available enantiopure natural products. To date, the enantiopure synthesis of 2-(carboxymethyl)aziridines starting from the chiral pool has used a few natural products. Two examples will be discussed in the following part, L- and D-aspartic acid L-**103** and D-**103** (Figure 6).

L-**103** D-**103**

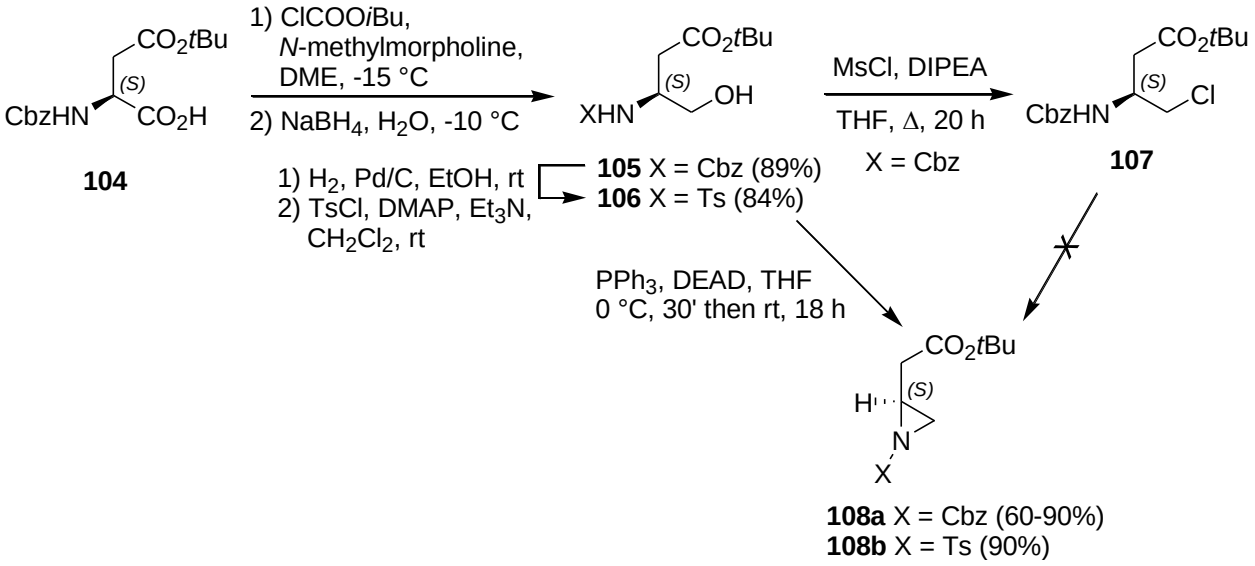
Figure 6

2.2.1.1. Synthesis through modifications of L-aspartic acid

N-Protected L-aspartic acid derivatives **104** have been used for the enantioselective synthesis of *N*-Cbz-, *N*-Ts- and *N*-Boc-protected 2-(carboxymethyl)aziridines **108**.[60,61,62,63,64] The first step in the synthesis of *N*-Cbz-2-(carboxymethyl)aziridine **108a** was an activation of *N*-Cbz-protected L-aspartic acid derivative **104** with isobutyl chloroformate (Scheme 19).[60,61,63,65]

This reaction was performed by dissolving compound **104** in 1,2-dimethoxyethane at -15 °C, followed by the addition of *N*-methylmorpholine and isobutyl chloroformate. The activated aspartic acid derivative was subsequently reduced with aqueous sodium borohydride to lead to the corresponding alcohol **105** in very good yield. In a next step, amino alcohol **105** was treated either under Mitsunobu conditions (PPh_3, DEAD, THF) or with methanesulfonyl chloride in the presence of diisopropylethylamine (Scheme 19).[60,61,63] However, only the Mitsunobu reaction yielded *N*-Cbz-2-(carboxymethyl)-aziridine **108a**. The mesylation of amino alcohol **105** followed by heating under reflux in THF with DIPEA gave the chloride **107** as the sole product.[61] This chloride resisted further treatment with various bases (K_2CO_3, $KHCO_3$, $NaHSO_3$, AgO, KF, NaH), which gave either no reaction or decomposition. Similar β-aminobutanoates have already been used as precursors in the synthesis of another class of β-amino acids with a three-membered ring as a core structure, more specifically 2-aminocyclopropanecarboxylic acids (not shown).[66]

Remarkably, the procedure for the synthesis of *N*-Cbz-protected 2-(carboxymethyl)aziridine **108a** starting from *N*-Cbz-protected L-aspartic acid derivative **104** did not work for the synthesis of analogous *N*-Ts-protected 2-(carboxymethyl)aziridine **108b** as the reduction step did not work at all, even when other reduction methods were applied.[63] For that reason, an alternative attempt to access amino alcohol **108b** was made by a de- and reprotection sequence starting from amino alcohol **105** (Scheme 19).[63] Catalytic hydrogenolysis over Pd/C and subsequent *N*-tosylation gave amino alcohol **106** in 84% overall yield. Treatment of this amino alcohol **106** under the previously mentioned Mitsunobu conditions delivered the *N*-Ts-protected 2-(carboxymethyl)aziridine **108b** in 90% yield.



104

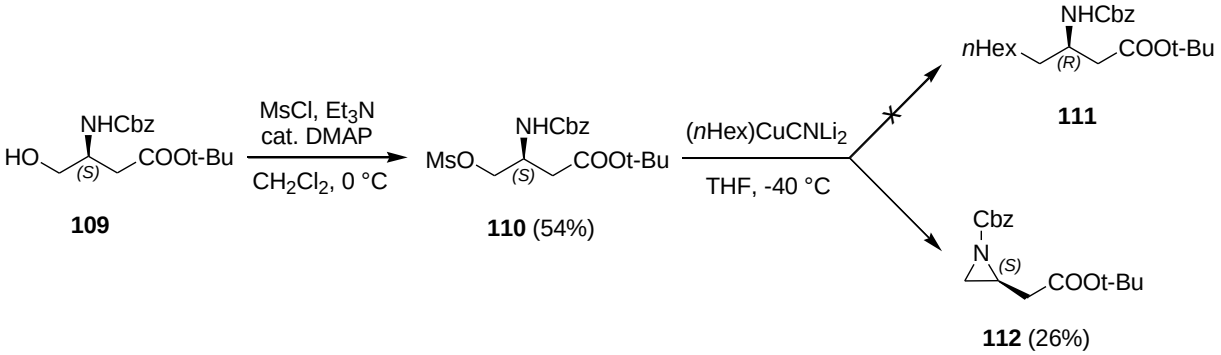
105 X = Cbz (89%)
106 X = Ts (84%)

107

108a X = Cbz (60-90%)
108b X = Ts (90%)

Scheme 19

In contrast with the mesylation procedure of amino alcohol **105** by heating under reflux in THF with DIPEA which afforded the chloride **107** as the sole product,[61] mesyloxy compound **110** was obtained when amino alcohol **109** was treated with mesyl chloride in the presence of triethylamine and a catalytic amount of DMAP in CH_2Cl_2 at 0 °C (**Scheme 20**).[62] In the next step, treatment of mesylate **110** with cyanocuprate in THF at -40 °C gave *N*-Cbz-protected 2-(carboxymethyl)aziridine **112** in 26% yield, instead of the expected β-amino ester **111**.



109

110 (54%)

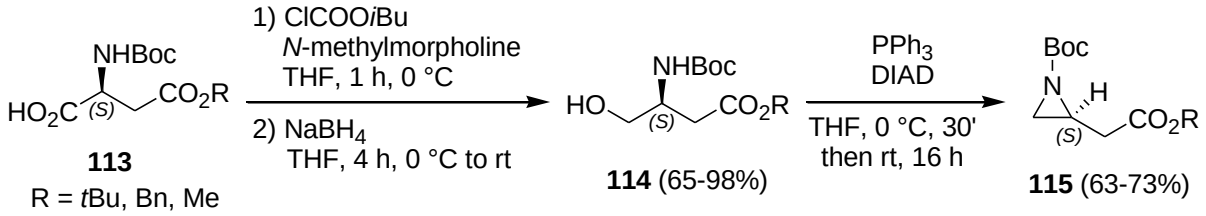
111

112 (26%)

Scheme 20

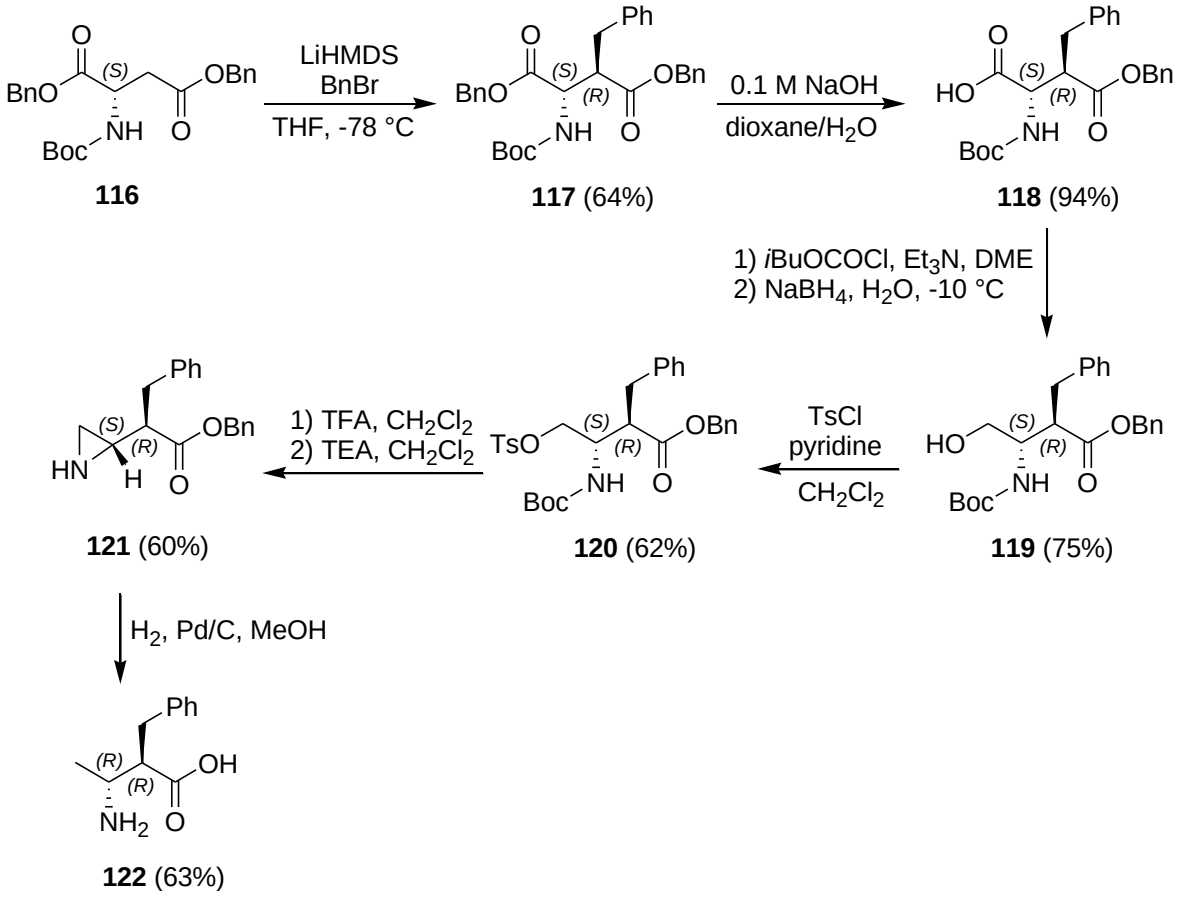
Furthermore, *N*-Boc-2-(carboxymethyl)aziridine **115** was synthesized *via* a similar reaction sequence as *N*-Cbz-2-(carboxymethyl)aziridine **112**. At first, the activation of *N*-Boc-protected L-aspartic acid derivative **113** with isobutyl chloroformate occurred in the presence of *N*-methylmorpholine in THF at 0 °C for one hour, followed by a reduction with sodium borohydride in THF which afforded *N*-Boc-amino alcohols **114** in high yields (Scheme 21).[64]

Subsequently, a Mitsunobu reaction with DIAD took place which delivered the corresponding *N*-Boc-2-(carboxymethyl)aziridine **115** in good yields (63-73%).



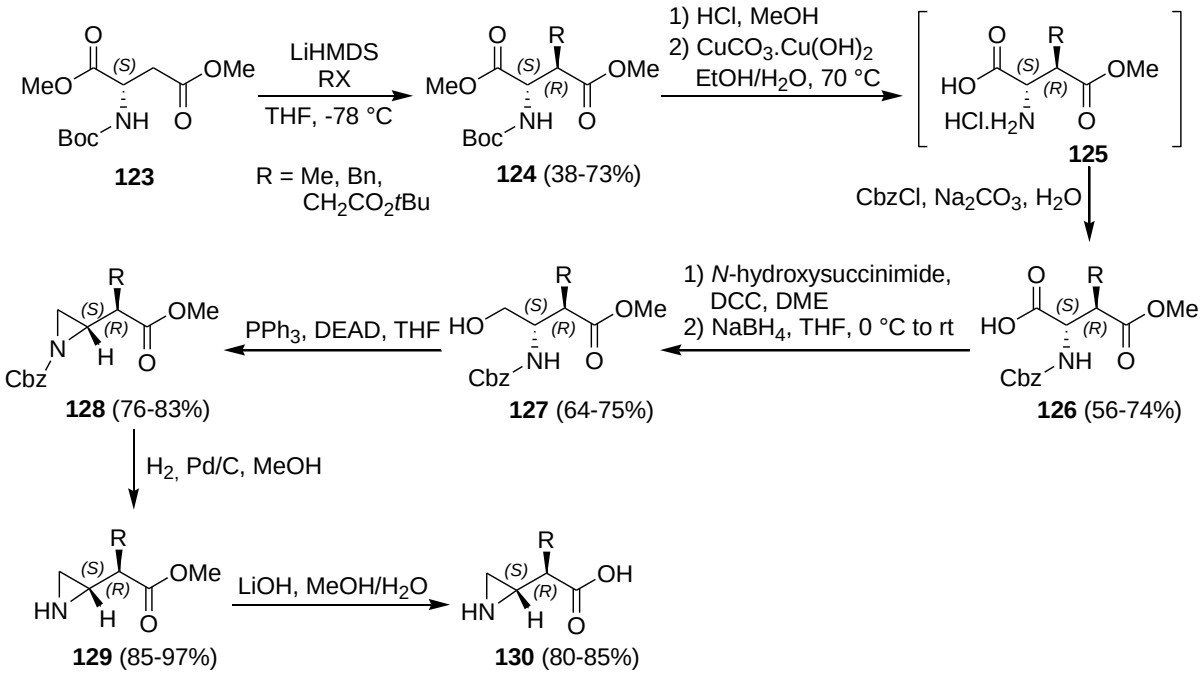
Scheme 21

In addition, besides the synthesis of enantiopure unsubstituted 2-(carboxymethyl)aziridines **115**, also the synthesis of branched 2-(carboxymethyl)aziridines was performed starting from *N*-protected L-aspartic acid derivatives.[67,68] A first attempt for the synthesis of the unprotected (2*R*,3*S*)-2-benzyl-substituted 2-(carboxymethyl)aziridine (2*R*,3*S*)-**121** was made starting from *N*-protected dibenzyl L-aspartate **116** (Scheme 22).[67]



Scheme 22

In order to obtain the unprotected branched (2*R*,3*S*)-2-(carboxymethyl)aziridines (2*R*,3*S*)-**130**, another synthetic route was developed starting from *N*-protected dimethyl L-aspartate **123** (Scheme 23).[67] As debenzylation of 2-(carboxymethyl)aziridine **121** *via* catalytic hydrogenolysis with Pd/C was not possible without ring opening of the aziridine ring, a final saponification of the methyl ester functionality has been performed to overcome this problem.



Scheme 23

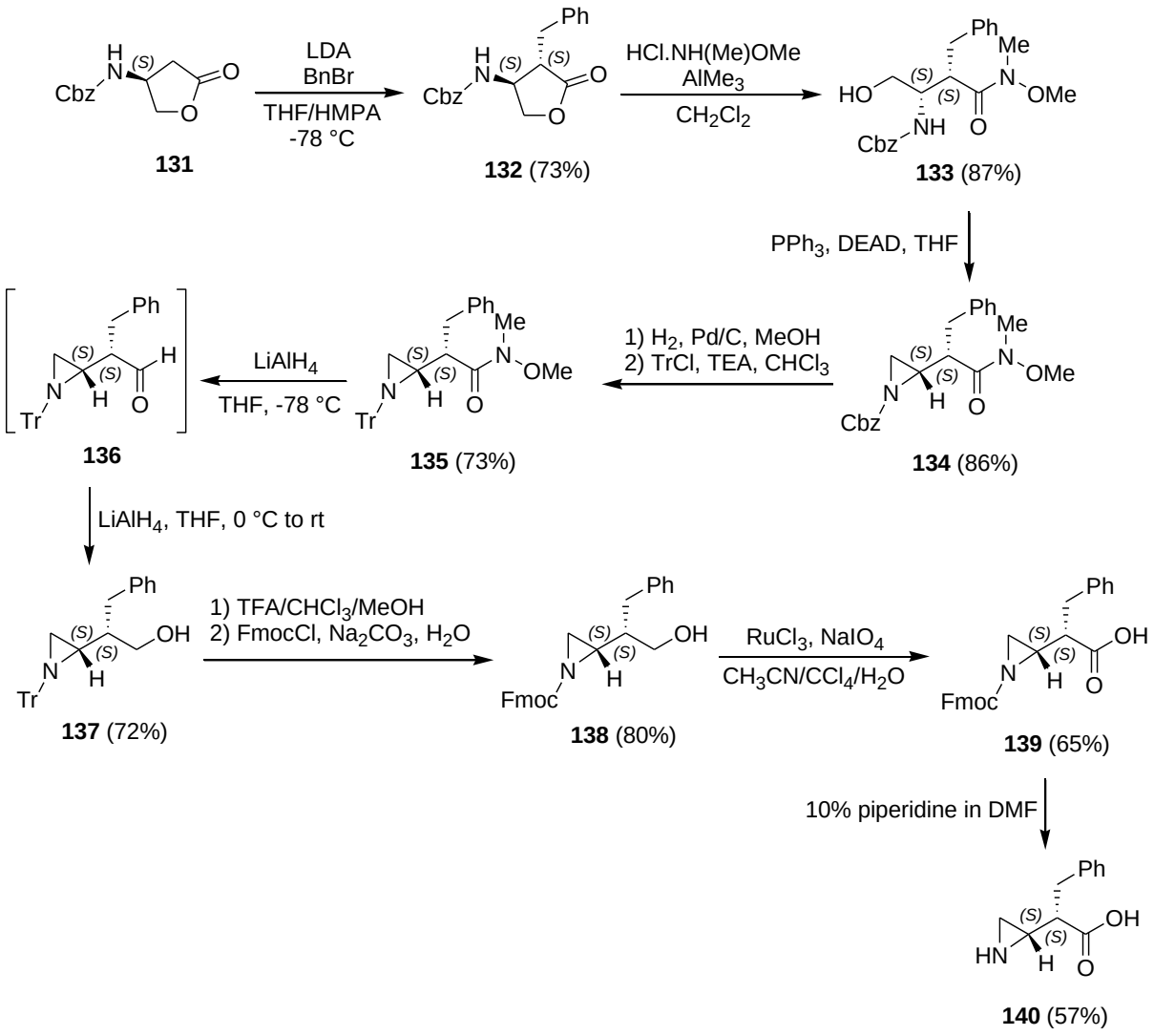
Treatment of *N*-protected dimethyl L-aspartate **123** with two equivalents of LiHMDS at -78 °C delivered the enolate dianion which reacted with an alkyl halide to give **124**. In the case of methylation, two products in a diastereomeric relationship in about equal ratio were formed and separation by means of column chromatography proceeded readily. Application of bulkier alkylating reagents such as benzyl bromide and *tert*-butyl bromoacetate provided diastereomeric ratios of 4:1 and 7:1, respectively, in favor of the *anti* alkylation with respect to the Boc-protected amino group. Treatment of compounds **124** with a methanolic hydrochloride solution provided the *N*-deprotected products, which were then regioselectively hydrolyzed by using $CuCO_3 \cdot Cu(OH)_2$ in an ethanol/water mixture,[71] to afford hydrochloride salts **125**. In the case of compounds **124** (R = CH_2CO_2tBu), the *tert*-butyl ester moiety was

converted into the corresponding methyl ester under the latter reaction conditions. Subsequently, the amino group of the L-aspartic esters **125** was protected with CbzCl. The conversion of the α-carboxylate group into a hydroxymethyl group was accomplished in good yield by sodium borohydride reduction of the activated ester that was formed by treating compound **126** with *N*-hydroxysuccinimide in the presence of DCC.[72] In the next step, the aziridine ring formation was effected under Mitsunobu conditions using triphenylphosphine in the presence of DEAD in 83% yield for **128** (R = Bn).[73] The remaining steps to the target compound (2*R*,3*S*)-**130** comprised removal of the Cbz group from the aziridine nitrogen and hydrolysis of the methyl ester moiety by catalytic hydrogenolysis in the presence of Pd/C and subsequent treatment with methanolic lithium hydroxide solution. The synthesis of the enantiomer of compound (2*R*,3*S*)-**130** with a (2*S*,3*R*)-configuration was also performed for R = Bn in an overall yield of 13%, starting from D-aspartic acid **103** by an analogous synthetic pathway used for the preparation of (2*R*,3*S*)-**130**.[67]

An alternative route had to be sought for the synthesis of the (2*S*,3*S*)- and (2*R*,3*R*)-enantiomers (2*S*,3*S*)-**130** and (2*R*,3*R*)-**130** because the precursor to the key intermediate, namely, the γ-hydroxy ester that corresponds to **127** in the synthesis of (2*S*,3*R*)-**130**, had a strong tendency to cyclize to the corresponding γ-lactone.[67,68] Thus, instead of a methyl ester, the corresponding Weinreb amide that resisted lactonization but still could be readily converted into the carboxylate *via* an aldehyde moiety was used (Scheme 24).[67,74]

Lactone **131**, that was prepared from L-aspartic acid,[75] was subjected to α-benzylation in THF and HMPA using two equivalents of LDA to give a diastereomeric mixture, from which (2*S*,3*S*)-**132** was isolated in 73% yield. Alkylation of γ-lactones such as **132** *via* a dianion intermediate is known to afford a mixture of diastereoisomers, in which the *trans*-alkylated product predominates, especially when the alkylating reagent bears a bulky group.[76] The lactone **132** was then readily converted into **133** by treatment with *N*,*O*-

dimethylhydroxylamine in the presence of trimethylaluminum.[77] The aziridine ring formation was then effected by the intramolecular Mitsunobu-type reaction to yield **134**.[73] While the attempts towards a selective reduction of the Weinreb amide moiety in **135** to the aldehyde were unsuccessful, conversion of the Cbz protecting group into a bulkier trityl group allowed the selective reduction of the Weinreb amide by lithium aluminum hydride to deliver aldehyde **136**.[74]



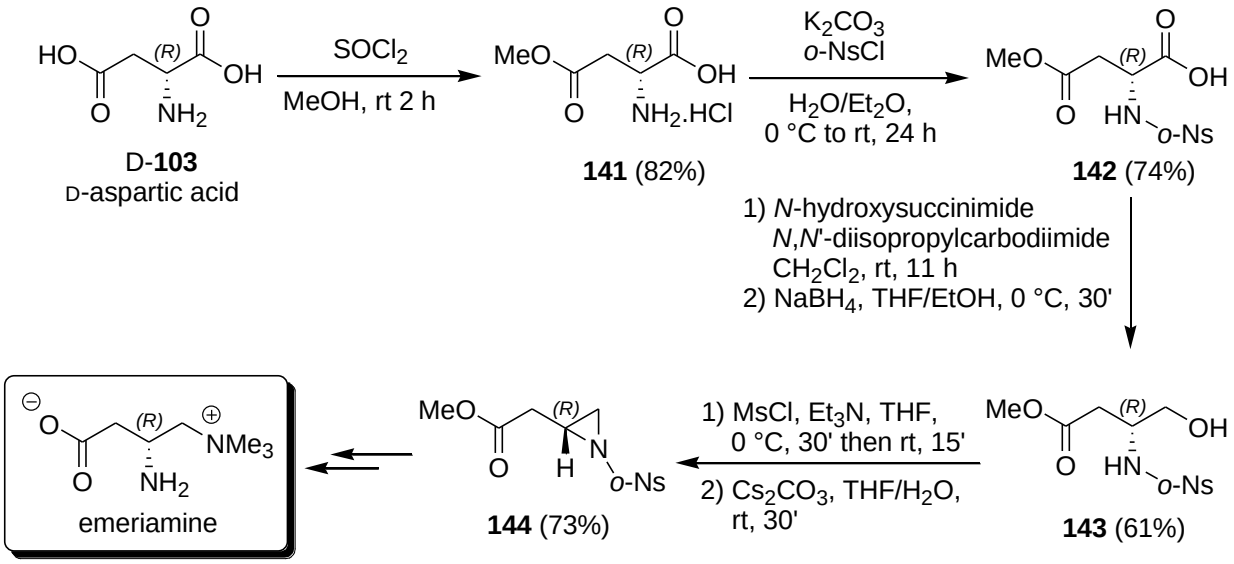
Scheme 24

Since this aldehyde **136** showed to be unstable upon exposure to air, it was not isolated and further reduction of the crude reaction mixture with lithium aluminum hydride gave the stable alcohol **137**. Moreover, there was a potential risk of the aldehyde **136** undergoing

racemization during the workup and purification. Nonetheless, direct conversion of the Weinreb amide into a hydroxymethyl group with lithium aluminum hydride failed, as the reduced amide carbonyl formed an intramolecular complex with the lithium ion, which resisted further reduction.[78] At this stage, the trityl moiety on the aziridine nitrogen atom was replaced with a 9-fluorenylmethyl carbamate (Fmoc) moiety, which showed excellent acid stability, demonstrated under the oxidation conditions for converting the primary alcohol group to a carboxylic acid.[79] Ruthenium(VIII) oxide catalyzed periodate oxidation[80] of compound **138** followed by deprotection of the Fmoc group with piperidine in DMF produced finally (2*S*,3*S*)-**140**. Compound (2*R*,3*R*)-**140** was similarly synthesized in an overall yield of 4% starting with D-aspartic acid.

2.2.1.2. Synthesis through modifications of D-aspartic acid

A last example of enantioselective synthesis starting from the chiral pool is the synthesis of 2-(carboxymethyl)aziridine **144** starting from D-aspartic acid D-**103** (Scheme 25).[81]



Scheme 25

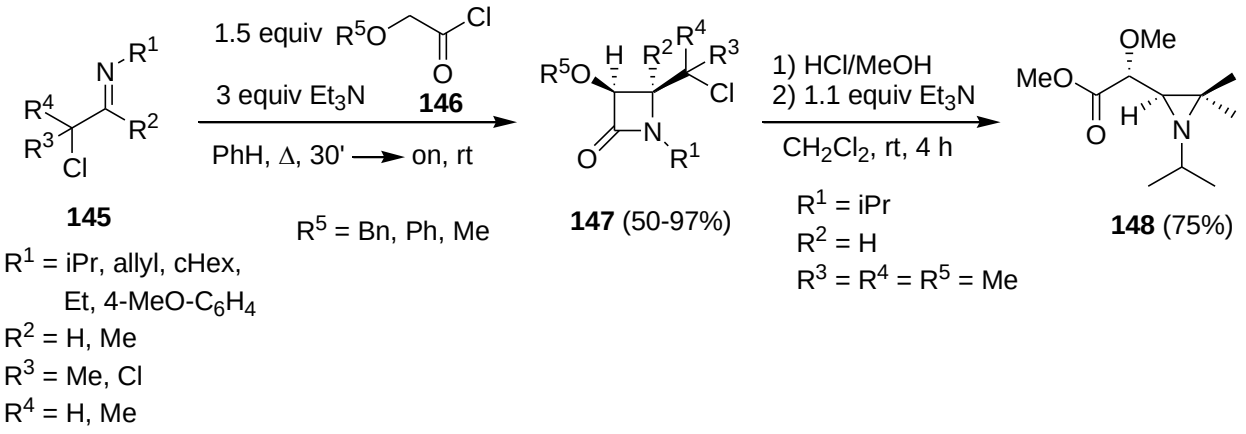
At first, a selective esterification of the β-carboxylic group occurred in high yield (82%) by reaction with thionyl chloride in methanol, followed by subsequent *o*-nosylation of the amine

which delivered monocarboxylic acid **142** in 74% yield. Chemoselective reduction of the carboxylic group by activation with *N*,*N*'-diisopropylcarbodiimide and *N*-hydroxysuccinimide and subsequent treatment with sodium borohydride in THF/EtOH successfully gave the alcohol **143** in 61% yield. Subsequent mesylation and cyclization using Cs_2CO_3 provided the chiral 2-(carboxymethyl)aziridine **144** in 73% yield. Furthermore, the chiral 2-(carboxymethyl)aziridine **144** is an intermediate in the synthesis of emeriamine, which was obtained after five additional steps, including ring opening of the aziridine moiety with *N*-chloro-*N*-sodiocarbamate (not shown) and deprotection of the *o*-nosyl group with thiophenol.

2.2.2. Stereoselective synthesis starting from addition reactions across imines

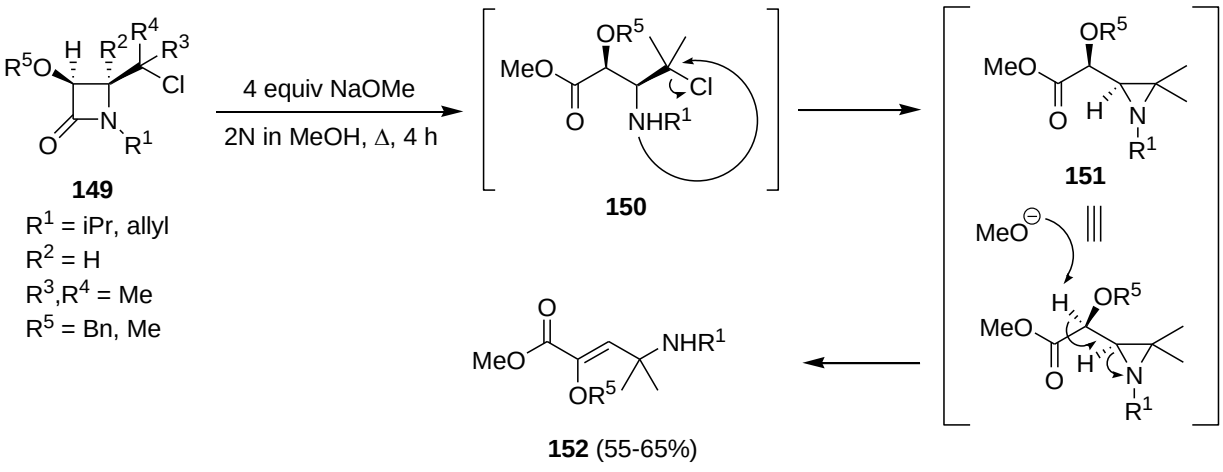
2.2.2.1. Synthesis *via* the Staudinger reaction

The utility of β-lactams as synthons for a wide range of heterocyclic compounds has already been known for a long time and was demonstrated in the following example where β-lactams **147**, synthesized *via* a Staudinger reaction, were transformed in the corresponding 2-(carboxymethyl)aziridine **148** (Scheme 26).[47,82] 4-(1-Chloroalkyl)-substituted 2-azetidinones **147** were prepared in a stereochemical way by condensation of α-chloroimines **145** with *in situ* generated ketenes in a Staudinger reaction. α-Chloroimines **145** were reacted with different types of acid chlorides **146** in benzene in the presence of triethylamine to generate *in situ* the intermediate ketenes, which underwent [2+2]-cyclocondensation to afford the corresponding β-lactams **147** in good yields. In the next step, 4-(1-chloroalkyl)-2-azetidinone **147** underwent ring opening *via* acidic methanolysis (Scheme 26).[47,82] The intermediate salt was not characterized, but was immediately reacted with triethylamine in dichloromethane for four hours at room temperature to afford the corresponding 2-(carboxymethyl)aziridine **148** in 75% yield.



Scheme 26

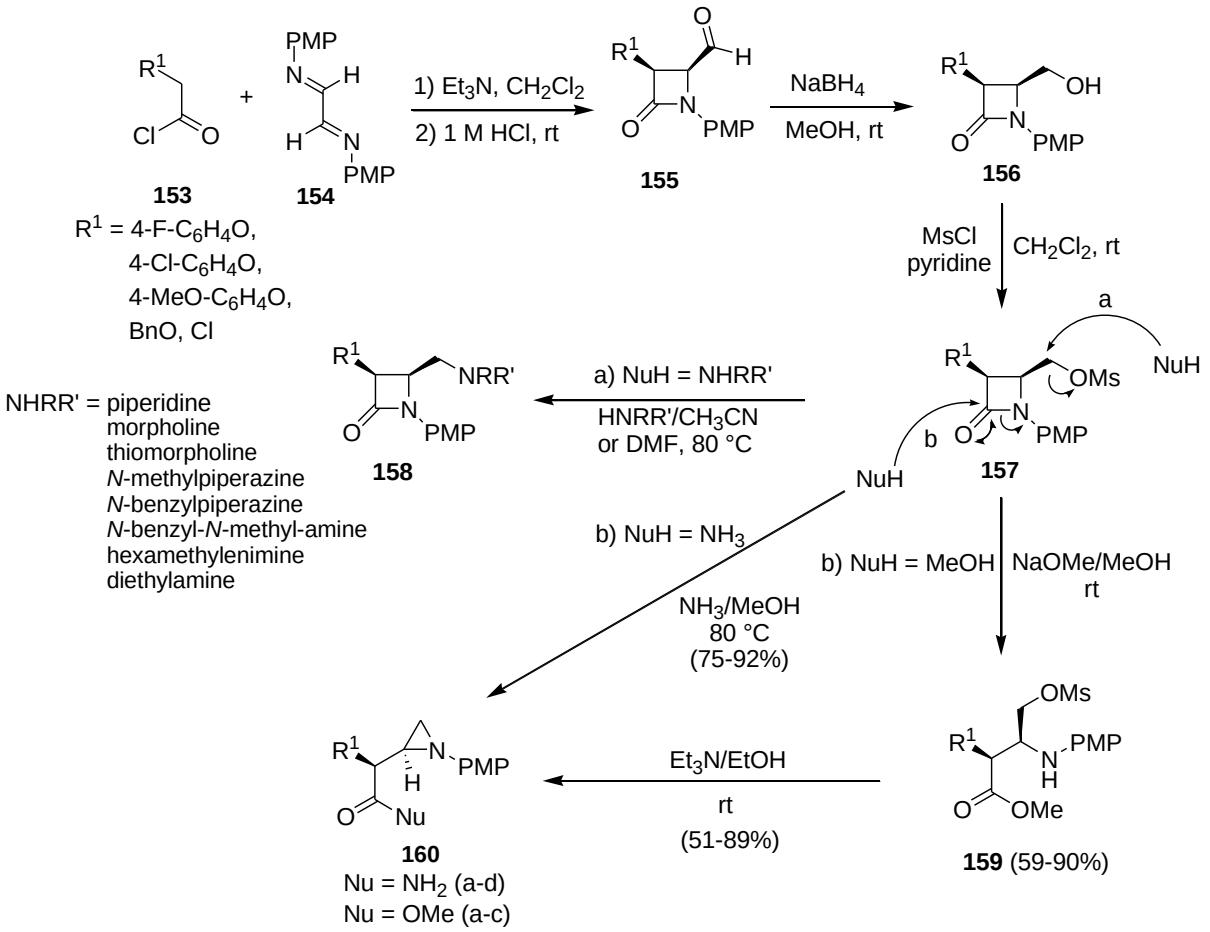
Noteworthy, base-promoted ring opening of β-lactams **149** by treatment with sodium methoxide in methanol at reflux temperature did not afford the corresponding 2-(carboxymethyl)aziridine **151**, but the ring-opened products (*Z*)-**152** (Scheme 27).[47,82] The proposed reaction mechanism concerns the nucleophilic attack of sodium methoxide across the amide functionality of β-lactam **149**, resulting in ring opening. The secondary amine **150** obtained in this way attacked the halogenated carbon, leading to ring closure by intramolecular nucleophilic substitution. The ring-closed products **151** were the originally expected aziridine derivatives. However, in the presence of excess sodium methoxide, deprotonation at the α-position of the ester **151** occurred and *anti* elimination led unexpectedly to the stereospecific formation of alkenoates (*Z*)-**152**.



Scheme 27

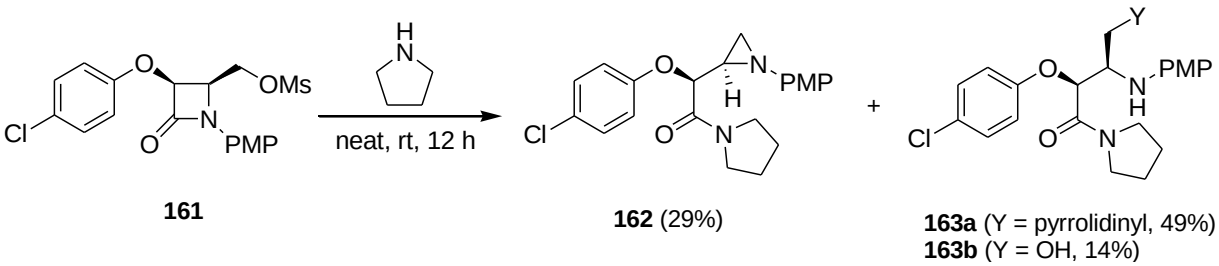
Another study towards the synthesis of 2-(carboxymethyl)aziridines **160** started from a Staudinger reaction between *N*,*N*-di-*p*-methoxyphenyl 1,2-diimine **154** and an *in situ* generated ketene from acid chlorides **153**, which resulted in the formation of imino-β-lactams which were directly hydrolysed to the corresponding aldehydes **155** (Scheme 28).[83,84,85,86,87] Next, 4-formyl-β-lactams **155** were reduced with sodium borohydride in methanol to alcohols **156**,[86,87,88] which were subsequently mesylated to give the corresponding mesyloxy-β-lactams **157**.[87,88,89] Previously, the reactivity of these compounds **157** was studied in order to obtain the corresponding *N*,*N*-disubstituted 4-(aminomethyl)azetidin-2-ones **158** by reaction with secondary amines.[90] In extension of this research, preparation of the unsubstituted aminomethyl-analogues was envisioned by changing the nucleophile from a secondary amine to ammonia, however, this resulted in the unexpected formation of 2-(carboxymethyl)aziridines **160**.[83,84]

Furthermore, the same type of aziridines **160** were obtained by reaction of these mesyloxy-β-lactams **157** with methanolic sodium methoxide at room temperature to afford the corresponding ring-opened products **159**.[83,84] Subsequent treatment of **159** with ethanolic triethylamine furnished 2-(carboxymethyl)aziridines **160** in good yields (51-89%).



Scheme 28

Surprisingly, application of pyrrolidine as nucleophile resulted also in an azetidinone-aziridine transformation in contrast with all other used secondary amines (Scheme 29).[83] Thus, reaction of mesyloxy-β-lactams **161** with neat pyrrolidine at room temperature afforded the 2-aziridinylacetamide **162** together with compounds **163a** and **163b**.



Scheme 29

A possible explanation of these results was found in the difference in nucleophilicity of these reagents, based on their basicity and steric requirements. Thus, the nucleophilic methoxide anion reacted in all cases selectively with the electrophilic lactam carbonyl function, while the

nucleophilicity of piperidine, a quite strong base, was overruled by the sterical hindrance allowing only attack at the less hindered side chain electrophilic center. Pyrrolidine is situated intermediate (strong base with lower sterical requirements) between piperidine and ammonia and could react with both electrophilic centers. Therefore, the regioselectivity was here determined by the activation energy requirements being lower in the reaction with the carbonyl in comparison with the side chain center. Bearing in mind the low sterical requirements of ammonia, it could react with both centers, as a result of its weak basicity. Since the reaction was carried out at room temperature, the reaction, however, took place exclusively at the carbonyl center, which comprises a lower energy barrier pathway.

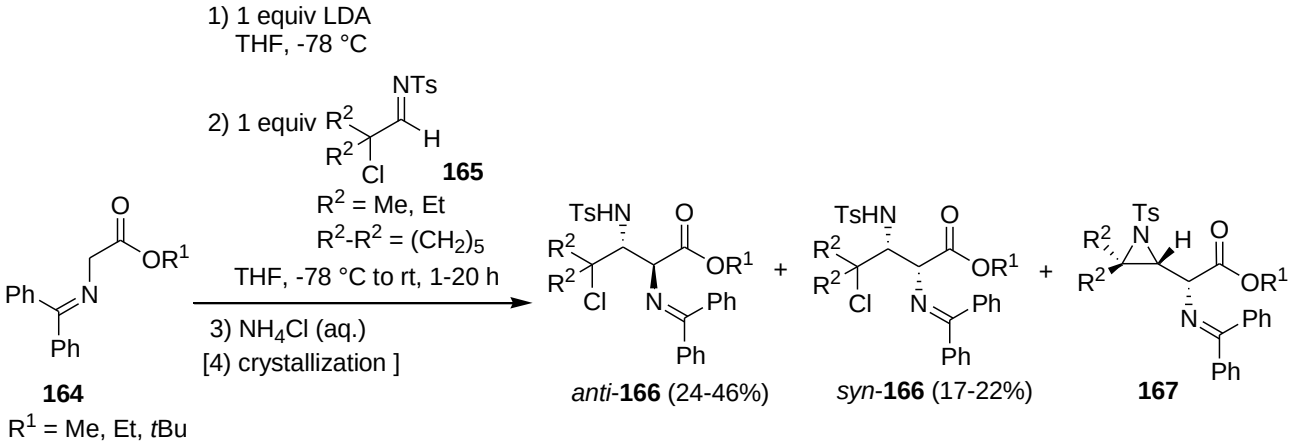
2.2.2.2. Synthesis *via* the Mannich-type reaction

In recent years, the diastereo- and enantioselective synthesis of 2-(carboxymethyl)aziridines *via* Mannich-type addition reactions has gained a lot of attention.[91,92] This Mannich-type reaction proceeded *via* addition of enolates across *N*-Ts-α-haloimines **165** and resulted in the formation of γ-chloro-β-amino acid derivatives **166**, which were further transformed into the corresponding 2-(carboxymethyl)aziridines **167** by a base-promoted ring-closure reaction (Scheme 30).

In the first reaction, benzophenone imine glycine esters **164** were deprotonated with lithium diisopropylamide (LDA) in THF, followed by the addition of *N*-Ts-α-haloimines **165** (Scheme 30).[91] After quenching with aqueous ammonium chloride, a mixture of *anti* and *syn* diastereomers *anti*-**166** and *syn*-**166** was formed in good yield with moderate diastereoselectivity (dr 3.5:1 to 1:1). For most of the synthesized derivatives, the *anti*- and *syn*-γ-chloro-β-amino esters *anti*-**166** and *syn*-**166** could be isolated as single diastereomers by crystallization.

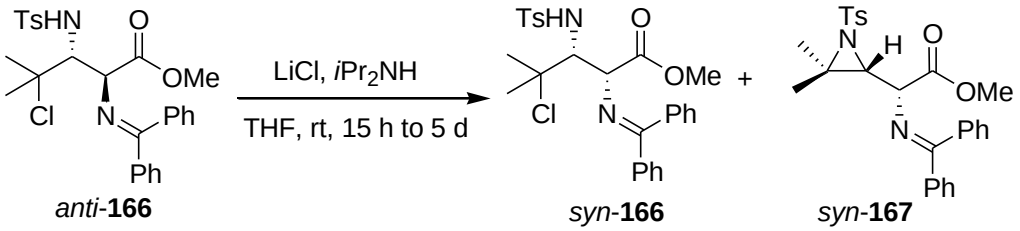
Performing this reaction under thermodynamic control, i.e. prolonged reaction times (20 h), afforded only *syn*-γ-chloro-β-amino esters *syn*-**166** and *syn*-2-(carboxymethyl)aziridines *syn*-

167 in a 1:1 ratio. When the reaction was performed under kinetic control (1 h), the *anti*/*syn* ratio was 9:1.[91]



Scheme 30

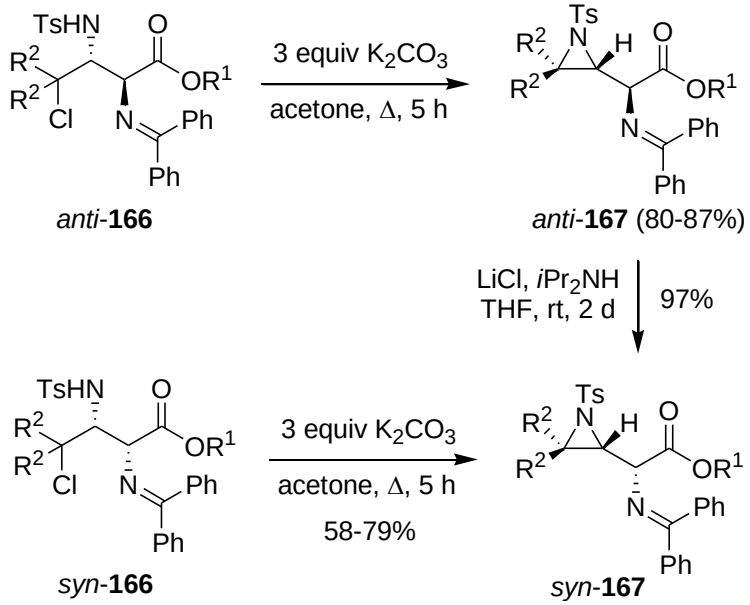
Furthermore, the isomerization of the isolated *anti*-isomer *anti*-**166** (R^1,R^2 = Me) into the thermodynamically more stable *syn*-isomer *syn*-**166** (R^1,R^2 = Me) and *syn*-aziridine *syn*-**167** (R^1,R^2 = Me) was observed upon stirring under mild basic conditions for an extended time (*i*Pr_2NH, LiCl, rt, 15 h to 5 d) (Scheme 31).[91]



Scheme 31

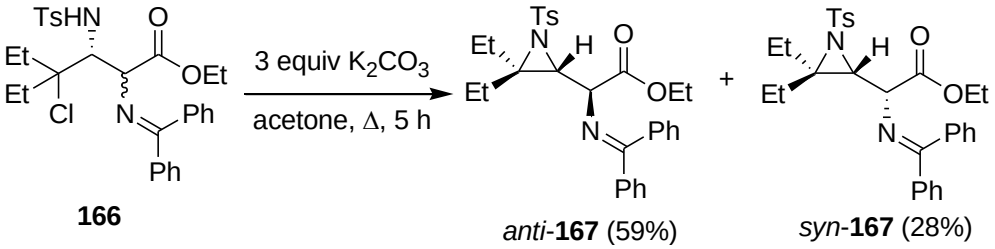
It was also possible to access diastereomerically pure β,γ-aziridino carboxylic acid esters *anti*-**167** and *syn*-**167** *via* 1,3-displacement of the chlorine atom under basic conditions.[91,92] The reaction of the pure diastereomers *anti*-**166** and *syn*-**166** was performed easily with K_2CO_3 in acetone for five hours at reflux temperature giving the β,γ-aziridino-α-(*N*-diphenylmethylidene)amino esters *anti*-**167** and *syn*-**167** in 80-87% yield (Scheme 32). Interestingly, when the cyclization reaction from the *anti*-adduct *anti*-**166** was continued for a longer time (16 h), the mixture of aziridines *anti*-**167** and *syn*-**167** was obtained in 5:1 ratio. In analogy with the isomerization of *anti*-**166** (R^1,R^2 = Me) to *syn*-**166** (R^1,R^2 = Me), the *anti*-

aziridine *anti*-**167** could be isomerized under mild basic conditions (*i*Pr_2NH, LiCl, THF, rt) to the *syn*-isomer *syn*-**167** in 97% yield (Scheme 32).[91]



Scheme 32

The complete separation of adducts *anti*-**166** and *syn*-**166** (R^1,R^2 = Et) proved impossible. Noteworthy, the aziridine formation from the mixture of these adducts gave a mixture of diethyl-substituted aziridines *anti*-**167** and *syn*-**167** (R^1,R^2 = Et), which could be separated by crystallization in good yields (Scheme 33).[91]



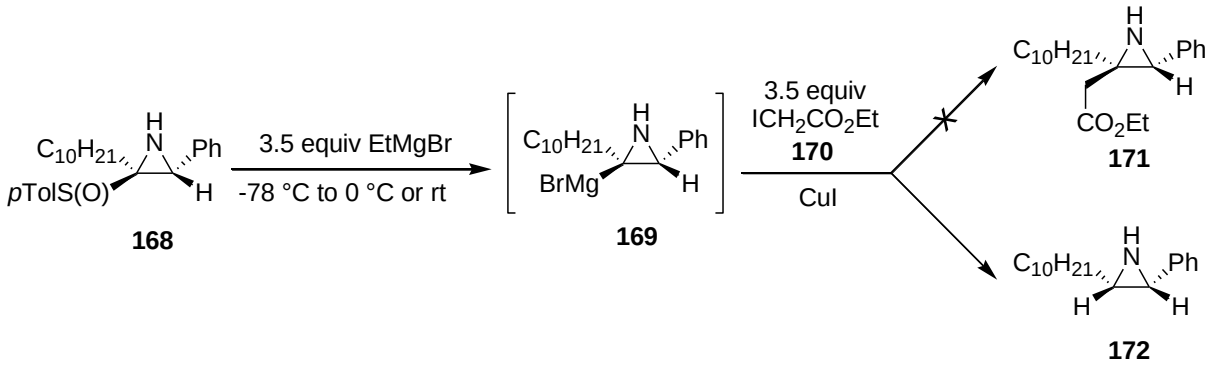
Scheme 33

2.3. Synthesis through C2-C4 bond formation

2.3.1. Synthesis through reaction of an aziridinyl anion (method IIIa)

Several studies have been performed in order to synthesize 2-(carboxymethyl)aziridines **171** *via* reactions of aziridinyl anions with α-haloacetates **170**.[93,94,95]

A first attempt to synthesize β,γ-aziridino carboxylic ester **171** was made by treatment of 2-sulfinylaziridine **168** with 3.5 equivalents of EtMgBr at -78 °C, followed by stirring at room temperature (Scheme 34).[93] This reaction resulted in the formation of the aziridinylmagnesium species **169**, which was found to be stable for several hours at room temperature, in quantitative yield. This compound **169** reacted easily with alkyl halides in the presence of catalytic CuI.[93] However, reaction with ethyl iodoacetate **170** failed to give 2-(carboxymethyl)aziridine **171** and resulted in desulfinated aziridine **172**.

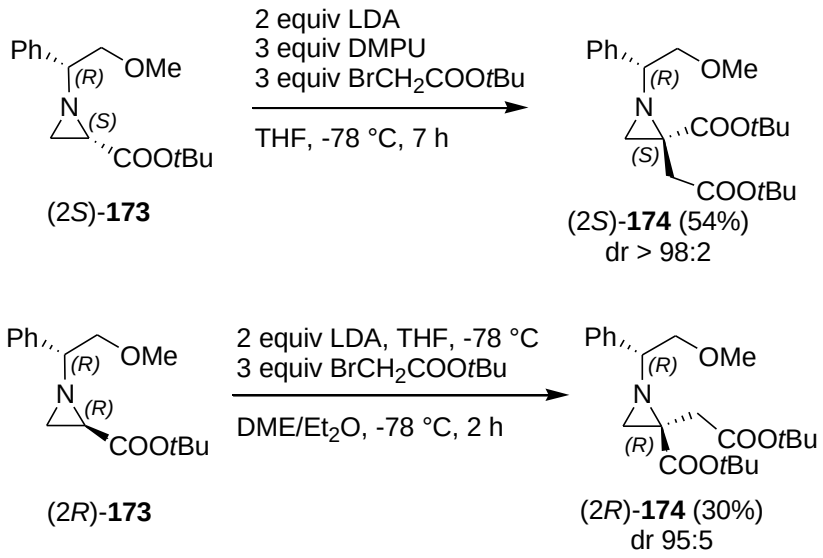


Scheme 34

In the next study, the functionalization of configurationally and chemically stable aziridine carboxylate anions has been performed by reaction with electrophiles with good to excellent retention of configuration.[94,95] Aziridine ester (2*S*)-**173**,[96] was deprotonated with LDA in THF at -78 °C and subsequently reacted with bromoacetate to afford 2-(carboxymethyl)aziridines (2*S*)-**174** as single diastereomers after column chromatography (Scheme 35). Hereby, it has been stated that application of the less hindered methyl and ethyl aziridine esters only led to self-condensation. The use of 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone (DMPU) as co-solvent resulted in improved chemical yields, but was not essential in contrast to previous observations on aziridine carbothioate anions.[97]

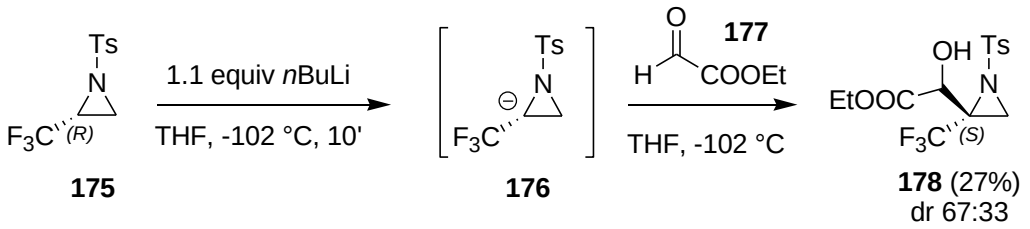
When aziridine ester (2*R*)-**173** was treated under analogous reaction conditions (LDA, THF, -78 °C), only self-condensation was observed.[94,95] Since intramolecular stabilization appeared to be negligible in this compound, the highly reactive lithiated intermediate was stabilized by

intermolecular chelation in a more adequate solvent system. When a 5:1 mixture of DME:Et_2O was used, a more stabilized aziridine carboxylate anion was formed, which reacted with bromoacetate towards aziridine (2*R*)-**174** in a moderate yield (30%) but with excellent retention of configuration (Scheme 35).[94,95]



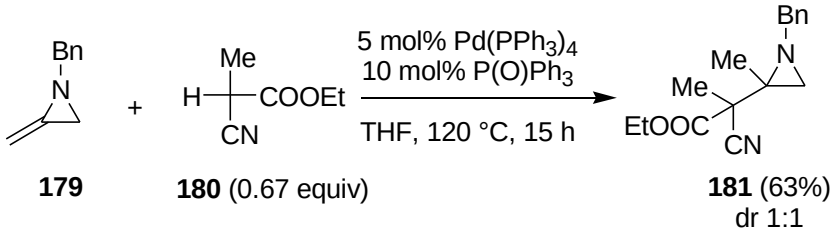
Scheme 35

Besides the synthesis of 2-(carboxymethyl)aziridines *via* reactions of aziridinyl anions with α-haloacetate electrophiles, also the application of glyoxylate **177** as electrophile has been evaluated.[98,99,100] In the first step, *N*-tosyl-2-(trifluoromethyl)aziridine **175** was regioselectively deprotonated with *n*-BuLi in THF at -102 °C (Scheme 36). Hereby, it has been stated that the generation of the anion **176** was markedly influenced by the nature of the *N*-substituent. The *N*-(*o*-anisyl)- and *N*-(*p*-anisyl)aziridinyl anions could only be partially generated upon deprotonation with the stronger base *sec*-BuLi, whereas generation of the *N*-benzylaziridinyl anion with *sec*-BuLi was unsuccessful. Subsequent reaction of the *N*-tosylaziridinyl anion **176** with ethyl glyoxylate **177** in THF at -102 °C afforded (2*S*)-2-(1-ethoxycarbonyl-1-hydroxymethyl)-2-(trifluoromethyl)-aziridine **178** in 27% yield as a mixture of two diastereomers (dr = 67:33).



Scheme 36

Even though the following example falls out of the scope of nucleophilic addition of aziridinyl anions, it is interesting to report here the synthesis of 2-(carboxymethyl)aziridines **181** *via* palladium-catalyzed hydrocarbonation of methyleneaziridine **179**.[101,102] The reaction of methyleneaziridines **179** with carbon pronucleophiles proceeded smoothly in the presence of a palladium catalyst to give the cyclic products in good yields. For example, optimization of different reaction conditions showed that in the presence of catalytic amounts of $Pd(PPh_3)_4$ (5 mol%) and triphenylphosphine oxide (10 mol%), the reaction of 1-benzyl-2-methyleneaziridine **179** with ethyl 2-cyanopropionate **180** as pronucleophile, in THF at 120 °C for 15 h gave **181** in 63% yield as a 1:1-mixture of both diastereomers (Scheme 37).

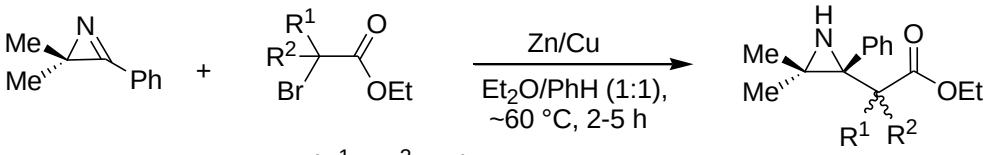


Scheme 37

2.3.2. Synthesis starting from 2*H*-azirines *via* the Reformatsky reaction (method IIIb)

The utility of the Reformatsky reaction for the synthesis of 2-(carboxymethyl)aziridines **184** starting from 2*H*-azirines **182** and α-bromoacetates **183** was demonstrated by several examples. [103,104,105,106,107]

In the first example, α-bromoacetates **183** were reacted with a zinc-copper couple[108] in a 1:1 solvent mixture of benzene and diethyl ether to afford the corresponding Reformatsky reagents (Scheme 38).[103] Addition of these Reformatsky reagents across 3,3-dimethyl-2-phenyl-2*H*-azirine **182a** resulted in the selective formation of β,γ-aziridino esters **184** in good yields (65-81%) upon reaction at 60 °C for 2-5 hours. Changing the solvent to toluene resulted in lower yields of the desired product **184** and the formation of 3-pyrrolidinones as side-products.[104] Use of α-bromoacetates **183c** (R^1 = R^2 = Me) under the given reaction conditions resulted as well in the formation of the corresponding 3-pyrrolidinone as side-product (10% in benzene/Et_2O; 26% in toluene).



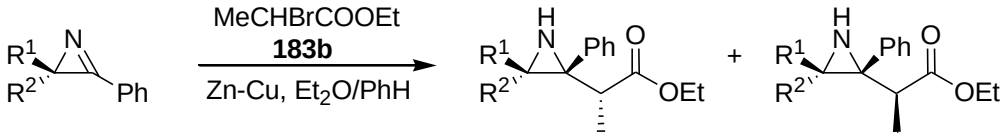
182a

183a (R^1 = R^2 = H)
183b (R^1 = H, R^2 = Me)
183c (R^1 = R^2 = Me)

184a (65%)
184b (81%)
184c (66%)

Scheme 38

In the following study, the diastereoselectivity of the Reformatsky reaction with ethyl 2-bromopropionate **183b** and 2*H*-azirines **182** has been studied (Scheme 39).[105] It has been proven that the formation of both diastereomers *syn*-**184** and *anti*-**184** was irreversible. As no isomerization of the formed compounds *syn*-**184** and *anti*-**184** was possible, the major isomer obtained by this reaction was the product of kinetic control.[105] The structures of *syn*-**184** and *anti*-**184** have been deduced from those of the corresponding 4-aminolactones, obtained by treatment of both diastereomers separately with Olah's reagent (pyridine-HF) or with aqueous hydrochloric acid.[105]



182a ($R^1 = R^2$ = Me)
182b (R^1-R^2 = -$(CH_2)_5$-)
182c (R^1 = Me, R^2 = H)

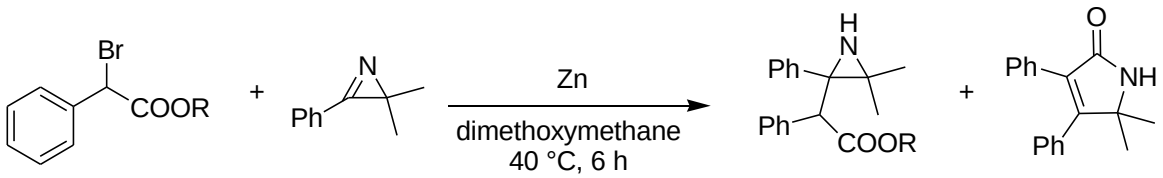
anti-**184a** (minor)
anti-**184b** (minor)
anti-**184c** (major)

syn-**184a** (major)
syn-**184b** (major)
syn-**184c** (minor)

anti-**184a**/*syn*-**184a** (80%, dr 10:90)
anti-**184b**/*syn*-**184b** (90%, dr 10:90)
anti-**184c**/*syn*-**184c** (60%, dr 70:30)

Scheme 39

In addition, the Reformatsky reaction of α-bromophenylacetates **185** and 3,3-dimethyl-2-phenyl-2*H*-azirine **182a** in the presence of zinc was studied.[106,107] Performing the reaction in dimethoxymethane at 40 °C for six hours afforded the 2-(carboxymethyl)aziridines **186** as a single diastereomer in 37-42% yield (Scheme 40). In this case, the formation of pyrrolinone **187** was less than 5%, whereas the same reaction in toluene or THF resulted in pyrrolinone **187**, exclusively.[106]

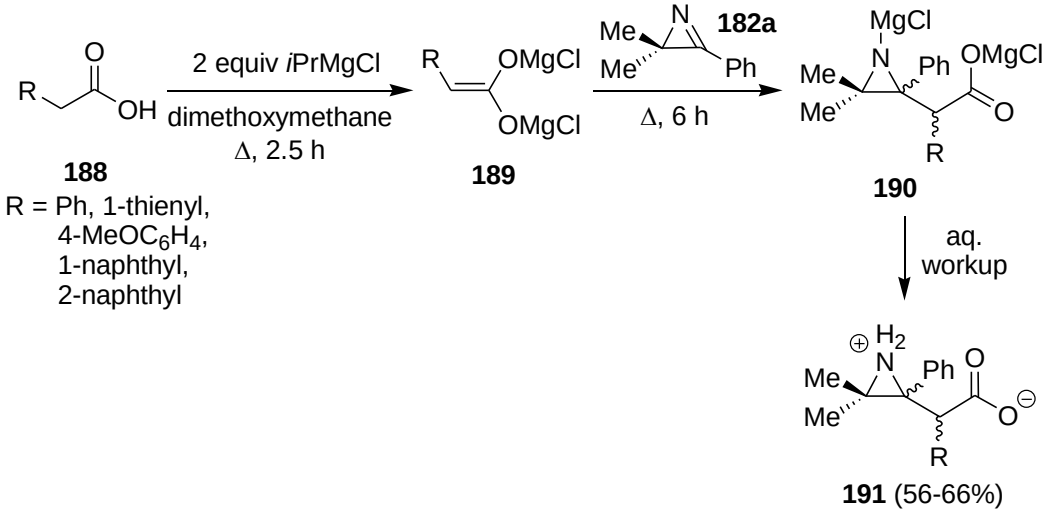


185 **182a** **186** (37-42%) R = Me, *t*Bu **187** (<5%)

Scheme 40

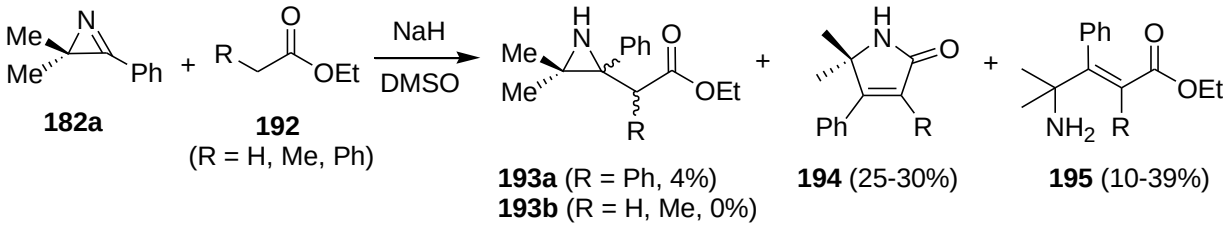
Similarly to the Reformatsky reaction, also the Ivanov reaction[109] was evaluated for the synthesis of 2-(carboxymethyl)aziridines **191** (Scheme 41).[107] In the first step, arylacetic acids **188** were treated with two equivalents of isopropylmagnesium chloride in dimethoxymethane, affording the corresponding organomagnesium compounds **189**. Subsequent addition of 2*H*-azirine **182a** and heating at reflux temperature for six hours furnished β,γ-aziridino carboxylic acid salts **190** which were isolated as the corresponding zwitterions **191** as single diastereomers in good yields after an aqueous workup. Noteworthy, all attempts to synthesize

2-(carboxymethyl)aziridines **191** starting from arylacetic acids **188** with sodium naphthalenide were shown to be unsuccessful.[107]



Scheme 41

Besides, the nucleophilic addition of enolates, derived from the corresponding ethyl esters **192** upon treatment with sodium hydride in DMSO, across 3,3-dimethyl-2-phenyl-2*H*-azirine **182a**, in order to synthesize the corresponding 2-(carboxymethyl)aziridines **193** has also been investigated (Scheme 42).[110] This reaction resulted in multi-component reaction mixtures, from which the desired 2-(carboxymethyl)aziridine **193a** was isolated in only 4% yield when ethyl phenylacetate **192** (R = Ph) was used.

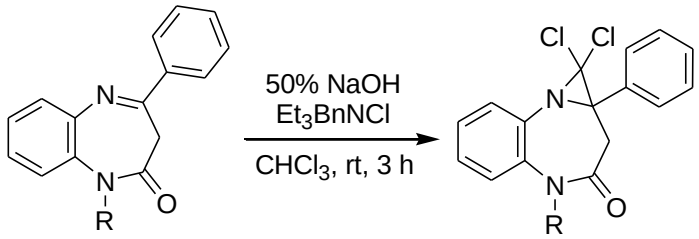


Scheme 42

2.4. Synthesis *via* addition of carbene equivalents across imines (method IV)

The synthesis of aziridines *via* addition reactions of carbenes across imines has been already well explored in the past.[111] In a first synthetic strategy, dichlorocarbene was used as a

carbenoid compound in addition reactions across imines **196** to afford 2-(carboxymethyl)aziridines **197**.[112] Treatment of benzodiazepine **196** with sodium hydroxide in chloroform, in the presence of Et_3BnNCl as a catalyst, resulted in the *in situ* formation of dichlorocarbene, which reacted with the imino moiety of benzodiazepines **196**. This reaction led to the selective formation of the corresponding tricyclic dichloroaziridines **197** in 80-85% yield (Scheme 43).

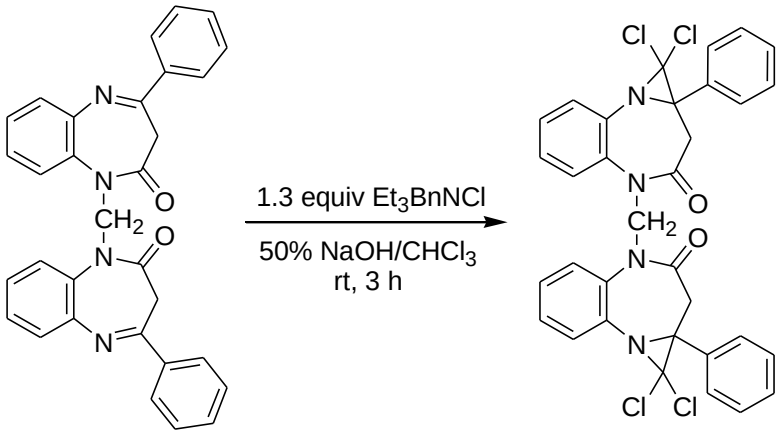


196
R = Me, Et

197 (80-85%)

Scheme 43

The addition reaction with dichlorocarbene was also performed with bis-1,1'-(1,5-benzodiazepin-1-yl)methane **198** under similar reaction conditions and afforded the corresponding polycyclic dichloroaziridine **199** in 45% yield (Scheme 44).[112]



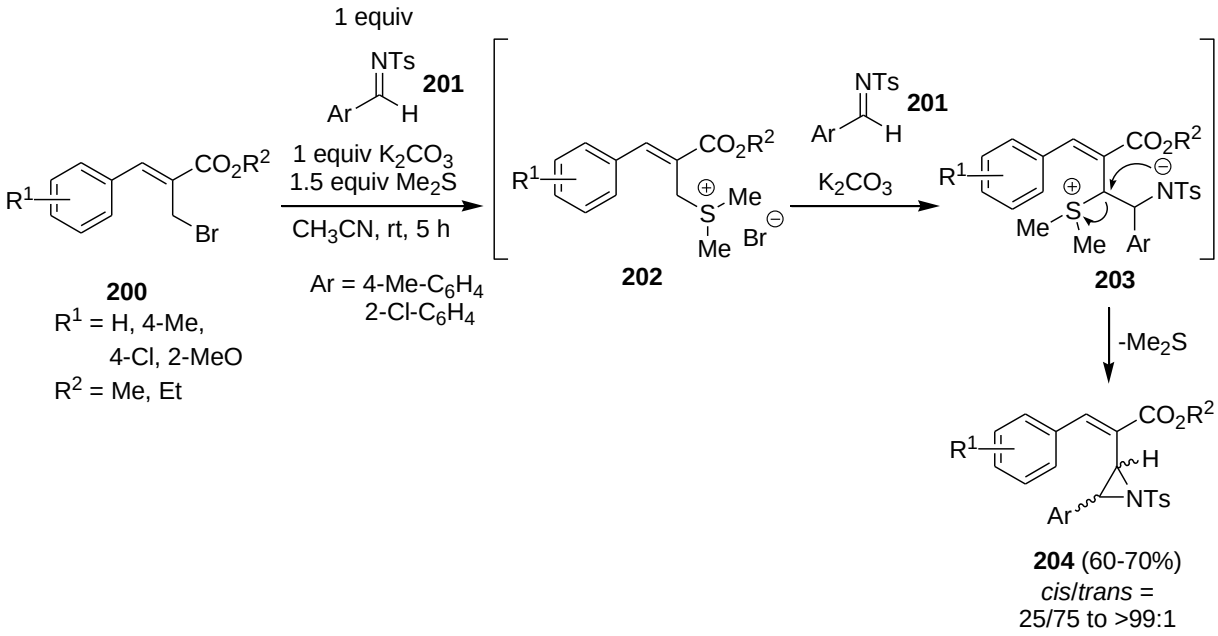
198

199 (45%)

Scheme 44

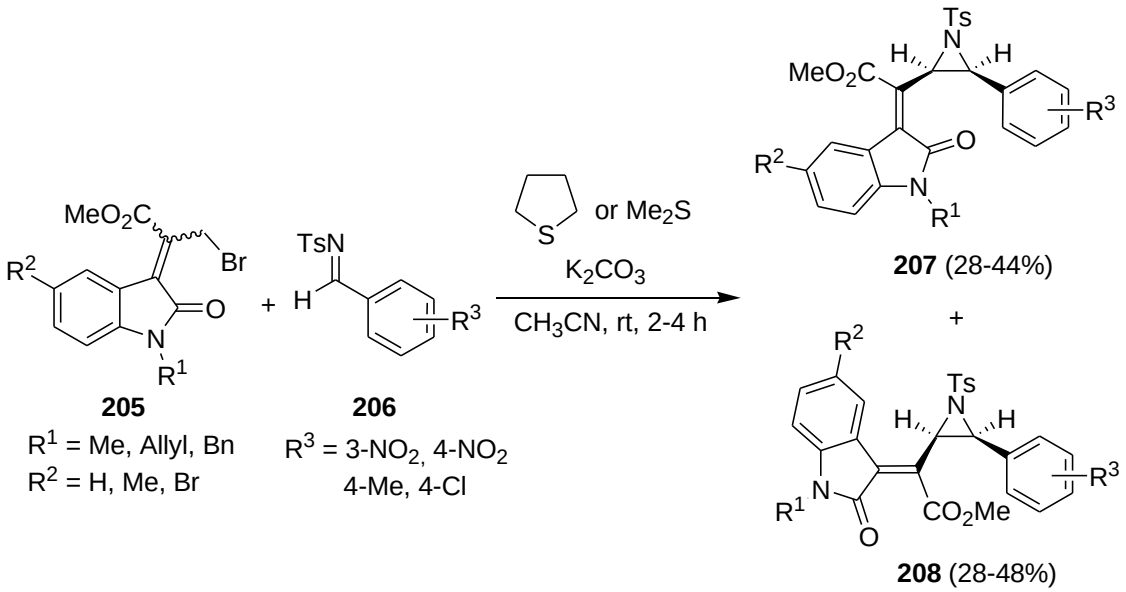
In the next part, the synthesis of 2-(carboxymethyl)aziridines **204** *via* addition of sulfur ylides across imines **201** is described.[113,114,115] Application of the well-known ylide chemistry in aziridination reactions[116] resulted in the synthesis of *N*-tosyl-2-(carboxymethyl)aziridines **204**

via reaction of *N*-tosylimines **201** and functionalized allyl bromides **200**.[113,114] Hereby, *N*-tosylimines **201** and functionalized allyl bromides **200** reacted in the presence of dimethylsulfide and K_2CO_3 for five hours in acetonitrile at room temperature to afford the corresponding *N*-tosyl-2-(carboxymethyl)aziridines **204** in 60-70% yield as an inseparable mixture of *cis*- and *trans*-diastereomers (Scheme 45).



Scheme 45

In the same manner, treatment of an *E*/*Z*-mixture of bromo compounds **205** with dimethylsulfide or tetrahydrothiophene as sulfur source, K_2CO_3 and *N*-tosylimines **206** for 2-4 hours in acetonitrile at room temperature, furnished a 1:1 mixture of *E*/*Z* isomers of *cis*-alkenylaziridines **207** and **208** in very good combined yields, which were separated by means of silica gel column chromatography (Scheme 46).[115]



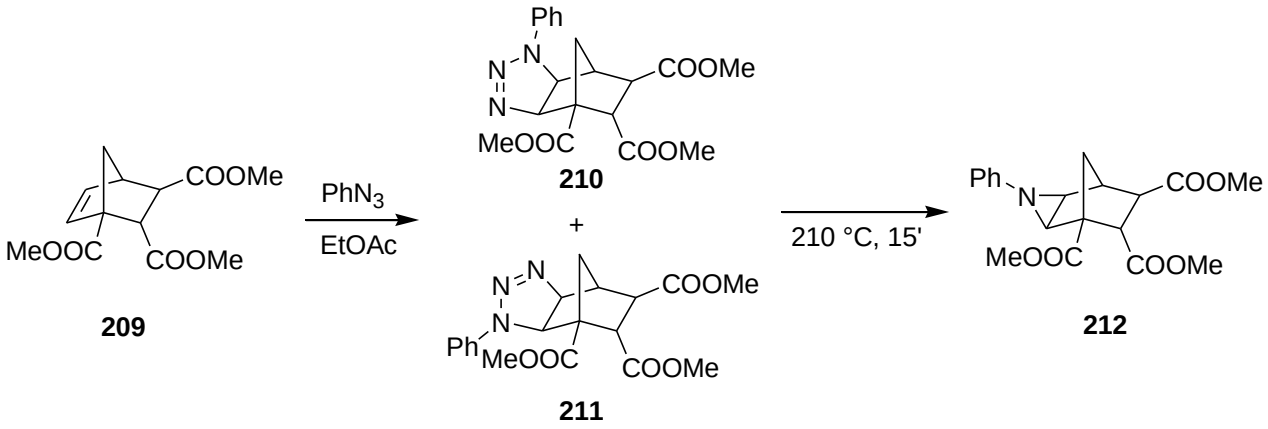
Scheme 46

2.5. Synthesis through reactions of nitrene equivalents with olefins (method V)

2.5.1. Synthesis through addition of azides across alkenes

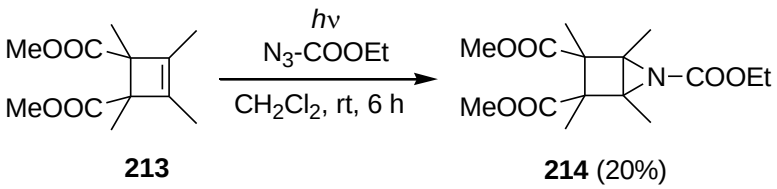
The synthesis of aziridines *via* addition reactions of azides to olefins has gained a lot of interest the past decades.[117,118] Several reports have described the synthesis of 2-(carboxymethyl)aziridines **212** *via* reactions of azides with α,β-unsaturated esters **209**.[119,120,121,122,123,124,125,126,127,128,129,130] Some examples are described in the following part.

A first attempt to synthesize β,γ-aziridino carboxylic esters **212** started with the addition of phenylazide across alkene **209**.[119] Reaction of trimethyl ester **209** with phenylazide in ethyl acetate resulted in a separable mixture of regioisomers **210** and **211** (Scheme 47). Heating of both dihydrotriazoles **210** and **211** at 210 °C for 15 minutes afforded the corresponding β,γ-aziridino carboxylic ester **212**.



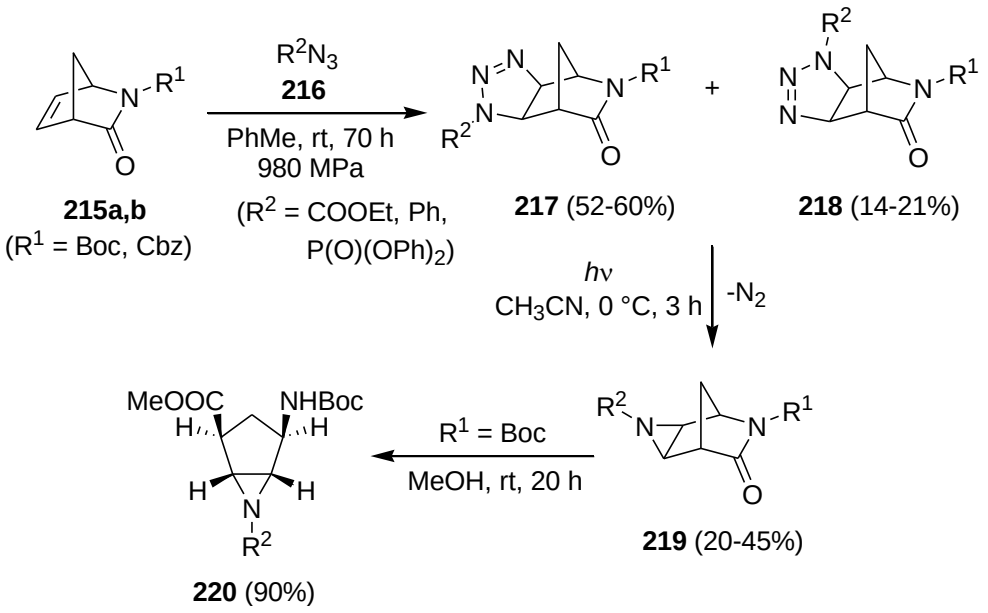
Scheme 47

Efforts have been made in order to synthesize the bicyclic aziridine carboxylate **214**.[124] The photochemical reaction between cyclobutenedicarboxylate **213** and ethyl azidocarboxylate in dichloromethane for six hours at room temperature afforded the corresponding bicyclic aziridine **214** in 20% yield (Scheme 48).



Scheme 48

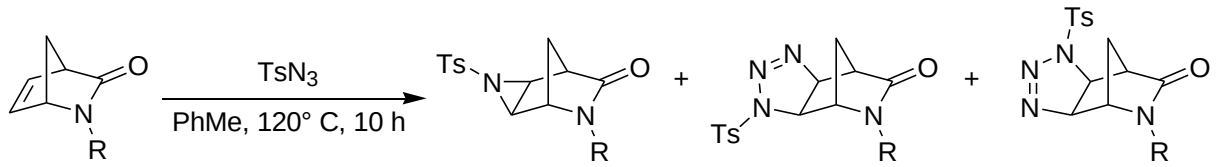
The synthesis of β,γ-aziridino carboxylic amides **219** *via* additions of azides **216** across *N*-protected 2-azabicyclo[2.2.1]hept-5-en-3-ones **215** has also been investigated.[126,127,128,129,130] First, bicyclic olefins **215** reacted with different azides **216** *via* an intermolecular [2+3] cycloaddition in toluene under high pressure (980 MPa) to afford a mixture of two regioisomeric triazolines **217** and **218**, which could be separated *via* column chromatography in good yields (Scheme 49).[126] However, irradiation of a mixture of both triazolines **217** and **218** in acetonitrile afforded polycyclic 2-(carbamoylmethyl)aziridines **219** after nitrogen loss. Subsequent ring opening of the lactam functionality of aziridines **219** with methanol furnished the corresponding β,γ-aziridino carboxylic esters **220** in excellent yield.



Scheme 49

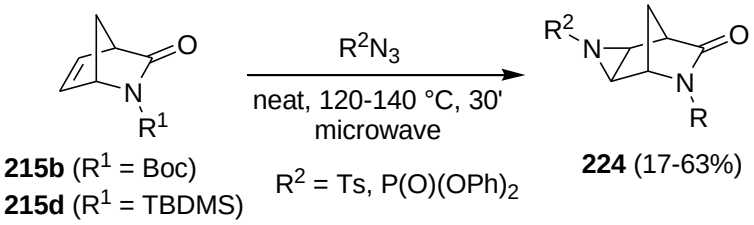
In addition, the synthesis of 2-(carbamoylmethyl)aziridines **221** was also performed with tosylazide, as a prominent nitrene precursor, and bicyclic olefins **215** under thermal conditions.[128,129] This thermal approach formed a good alternative to the previously described cycloaddition-photolysis reaction sequence.[126,127]

Reaction of *N*-protected lactams **215** with tosylazide in toluene at 120 °C resulted in the formation of aziridines **221** as single isomers *via* the *exo*-cyclic addition of nitrene across the double bound of **215** (Scheme 50). Noteworthy, the reaction of *N*-Cbz-lactam **215a** with tosylazide resulted also in the formation of triazolines **222** (6%) and **223** (2%) as minor products.[129]



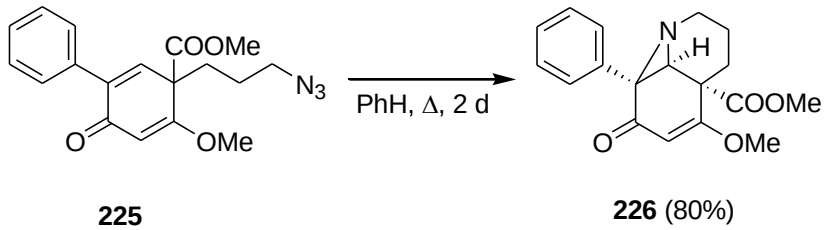
Scheme 50

The synthesis of β,γ-aziridino carboxylic amides **224** *via* reaction of bicyclic olefins **215** with different azides was also effected under microwave conditions, with significantly reduced reaction times.[130] After optimization of reaction conditions, microwave irradiation of a mixture of *N*-protected lactams **215** and electron-poor azides (R^2 = Ts, $P(O)(OPh)_2$) at 120-140 °C for 30 minutes without solvent afforded the corresponding tricyclic 2-(carbamoylmethyl)aziridines **224** through nitrene addition (Scheme 51).



Scheme 51

A final example of this synthetic approach comprised the aziridination reaction *via* an intramolecular 1,3-dipolar cycloaddition of azido dienone **225**.[125] Heating compound **225** in benzene at reflux temperature for two days resulted in a conversion towards tricyclic aziridine **226** in 80% yield with complete regio- and stereocontrol (Scheme 52). The isolation of the fully characterized aziridine **226** rather than a triazoline product was probably due to the thermal triazoline instability, which accelerated the extrusion of nitrogen in the corresponding triazoline intermediate.[131]

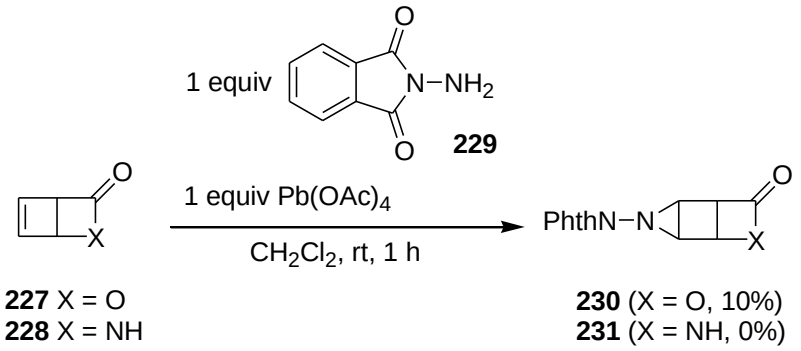


Scheme 52

2.5.2. Synthesis *via in situ* generated nitrenes

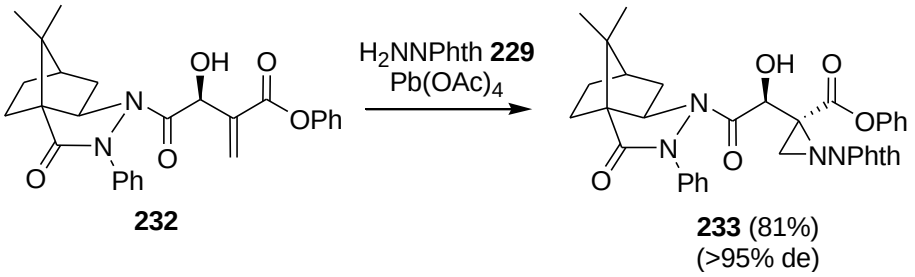
Since several decades, aziridine synthesis *via* nitrene additions across olefins represents a well explored field in organic synthesis.[117,132] In order to synthesize *N*-phthalimido-2-(carboxymethyl)aziridines, the generation of singlet aminonitrenes for the application in cycloaddition reactions with olefins, has been already frequently reported.[133,134,135,136,137,138,139,140]

A first approach of this methodology started with the generation of phthalimidonitrene *via* oxidation of *N*-aminophthalimide **229** with $Pb(OAc)_4$.[133,141] The addition of phthalimidonitrene across bicyclic lactone **227** (X = O) and lactam **228** (X = NH) proceeded by reacting bicyclic lactone **227** with *N*-aminophthalimide **229** and $Pb(OAc)_4$ for one hour in dichloromethane at room temperature and furnished the corresponding tricyclic compound **230** in 10% yield (Scheme 53).[134] However, performing the reaction with bicyclic lactam **228** under the same reaction conditions failed to deliver the desired tricyclic aziridino lactam **231** (X = NH). Furthermore, the reaction of the bicyclic compounds **227** and **228** with the less nucleophilic ethoxycarbonylnitrene also did not result in aziridine formation. Where phthalimidonitrene had a distinct nucleophilic character, the strong electron-withdrawing group in ethoxycarbonylnitrene rendered an electrophilic species whose reactivity was diminished to the point that it would only add to electron-rich double bonds.[134]



Scheme 53

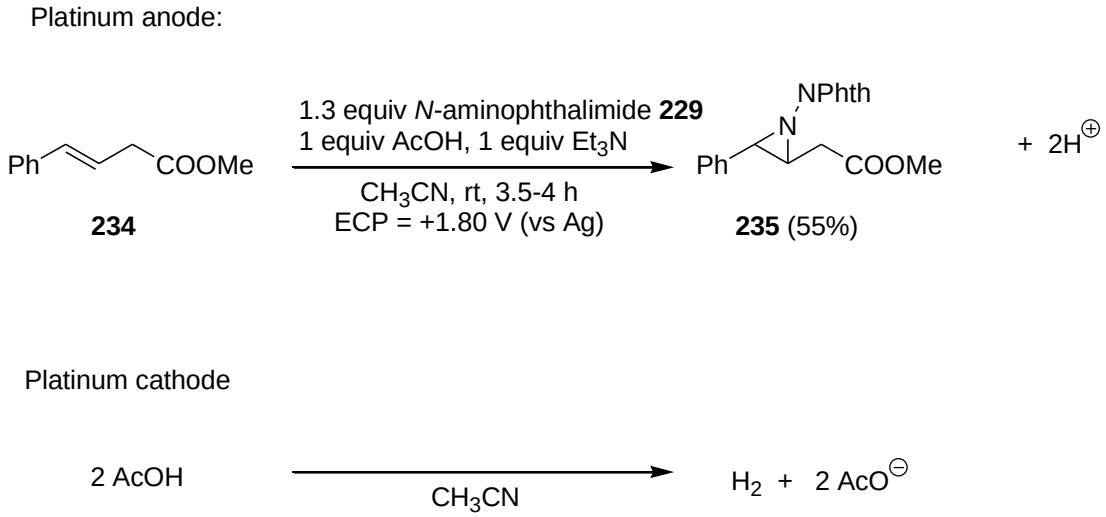
More recently, the diastereoselective synthesis of the 2,2-disubstituted *N*-phthalimidoaziridine **233** *via* addition of *in situ* generated phthalimidonitrene across α-substituted α,β-unsaturated ester **232** has also been reported.[135] The reaction of alkene **232** with *N*-aminophthalimide **229** in the presence of lead(IV) acetate, provided the corresponding 2,2-disubstituted *N*-phthalimidoaziridine **233** in 81% yield and excellent diastereoselectivity (Scheme 54).



232 **233** (81%) (>95% de)

Scheme 54

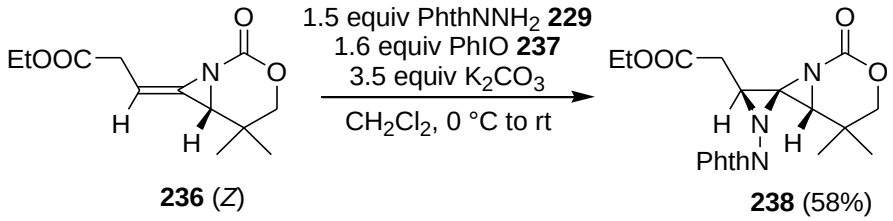
In addition, the electrochemical aziridination of β,γ-unsaturated ester **234** with phthalimidonitrene has been explored.[136,137] This study illustrated the possibility of a rational approach that bypasses the requirement for stoichiometric amounts of toxic oxidants and metal additives in organic redox reactions.[136] The reaction was performed in an electrochemical cell, where the anodic compartment was charged with olefin **234**, *N*-aminophthalimide **229**, acetic acid and triethylamine in acetonitrile (Scheme 55). Besides, the cathodic compartment contained a solution of acetic acid in acetonitrile. Implementation of the electrolysis at +1.80 V at ambient temperature delivered the *N*-phthalimido-2-(carboxymethyl)aziridine **235** in good yield (55%), after the reaction was stopped when the cell current dropped to less than 5% of its original value.[137]



Scheme 55

Furthermore, the *in situ* generation of nitrenes has been performed by using hypervalent iodine reagents such as iodosylbenzene and PIDA. [138,139,140,142,143]

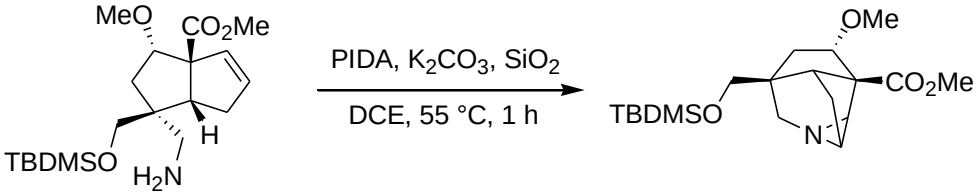
In the first study, the aziridination of *Z*-alkylideneaziridine (*Z*)-**236** *via* reaction with *N*-aminophthalimide **229** in the presence of iodosylbenzene **237** as oxidant has been examined.[138,139,140] Treatment of aziridine (*Z*)-**236** with 1.5 equivalents of *N*-aminophthalimide **229** in the presence of 1.6 equivalents of iodosylbenzene **237** and 3.5 equivalents of potassium carbonate resulted in the formation of bisaziridino carboxylic ester **238** in 58% yield as one single diastereomer when reacted in dichloromethane at 0 °C to room temperature (Scheme 56).[138]



Scheme 56

Furthermore, the synthesis of bridged aziridine **240** starting from primary amine **239** *via* a modified Nagata intramolecular aziridination reaction has been investigated.[142] After optimization of different reaction conditions, it has been shown that reaction of amine **239** in the presence of phenyliodine(III) diacetate (PIDA), potassium carbonate and silica gel in 1,2-

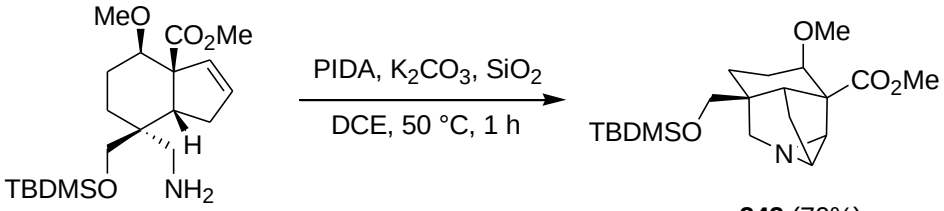
dichloroethane at 55 °C for one hour gave the bridged aziridine **240** selectively in 72% yield (Scheme 57). This efficient intramolecular aziridination reaction proceeded *via* an iminoiodinane intermediate generated from the cycloalkenyl primary amine in the absence of a metal catalyst.[142]



239 **240** (72%)

Scheme 57

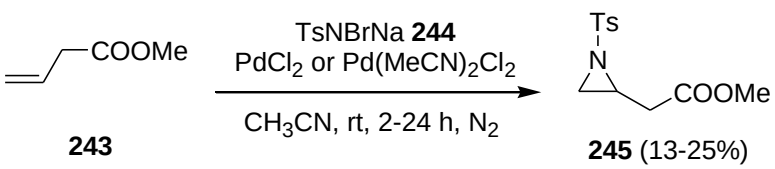
Similarly, the application of the modified Nagata intramolecular aziridination method,[142] resulted also in the formation of aziridine **242** in 70% yield (Scheme 58).[143]



241 **242** (70%)

Scheme 58

Along with aziridination reactions *via in situ* generated phthalimidonitrene and ethoxycarbonylnitrene across olefins, also the palladium(II)-mediated aziridination of olefins with bromamine-T **244** has been employed.[144] Different reaction conditions were tested in order to synthesize 2-(carboxymethyl)aziridine **245** *via* a palladium(II)-mediated aziridination. Hereby, reaction of olefin **243** with bromamine-T **244** in the presence of $PdCl_2$ or $Pd(MeCN)_2Cl_2$ afforded the corresponding *N*-tosyl-2-(carboxymethyl)aziridine **245** in low yield (13-25%) after reaction for 2-24 hours in acetonitrile at room temperature (Scheme 59).



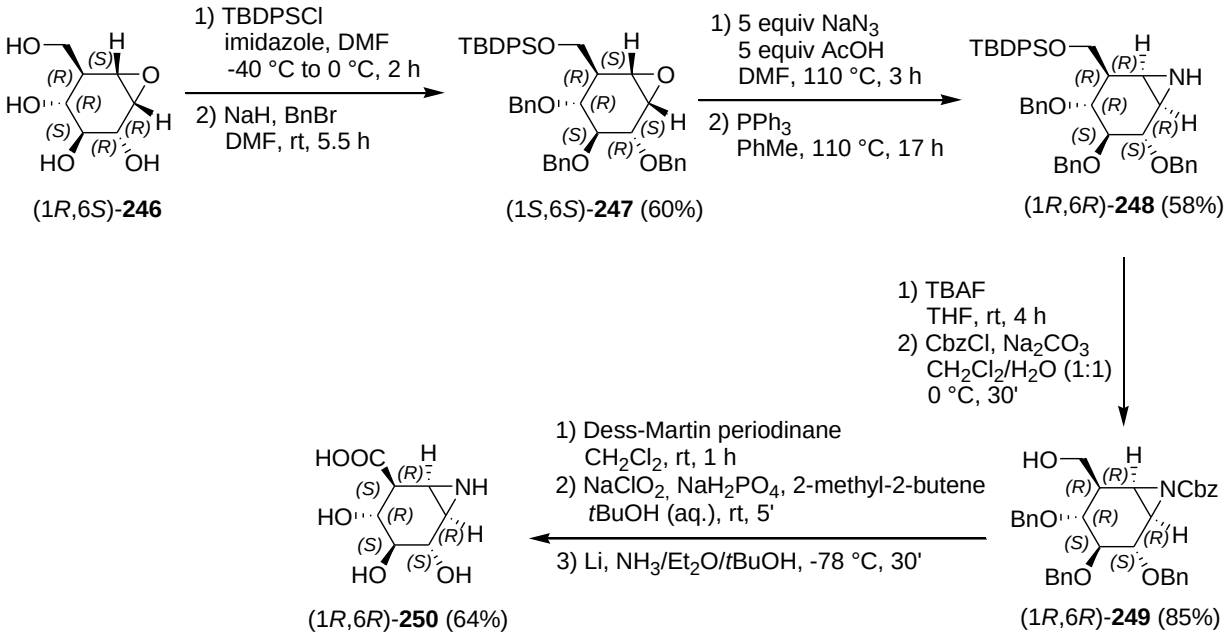
243 **245** (13-25%)

Scheme 59

2.6. Functional group transformation starting from the chiral pool (method VI)

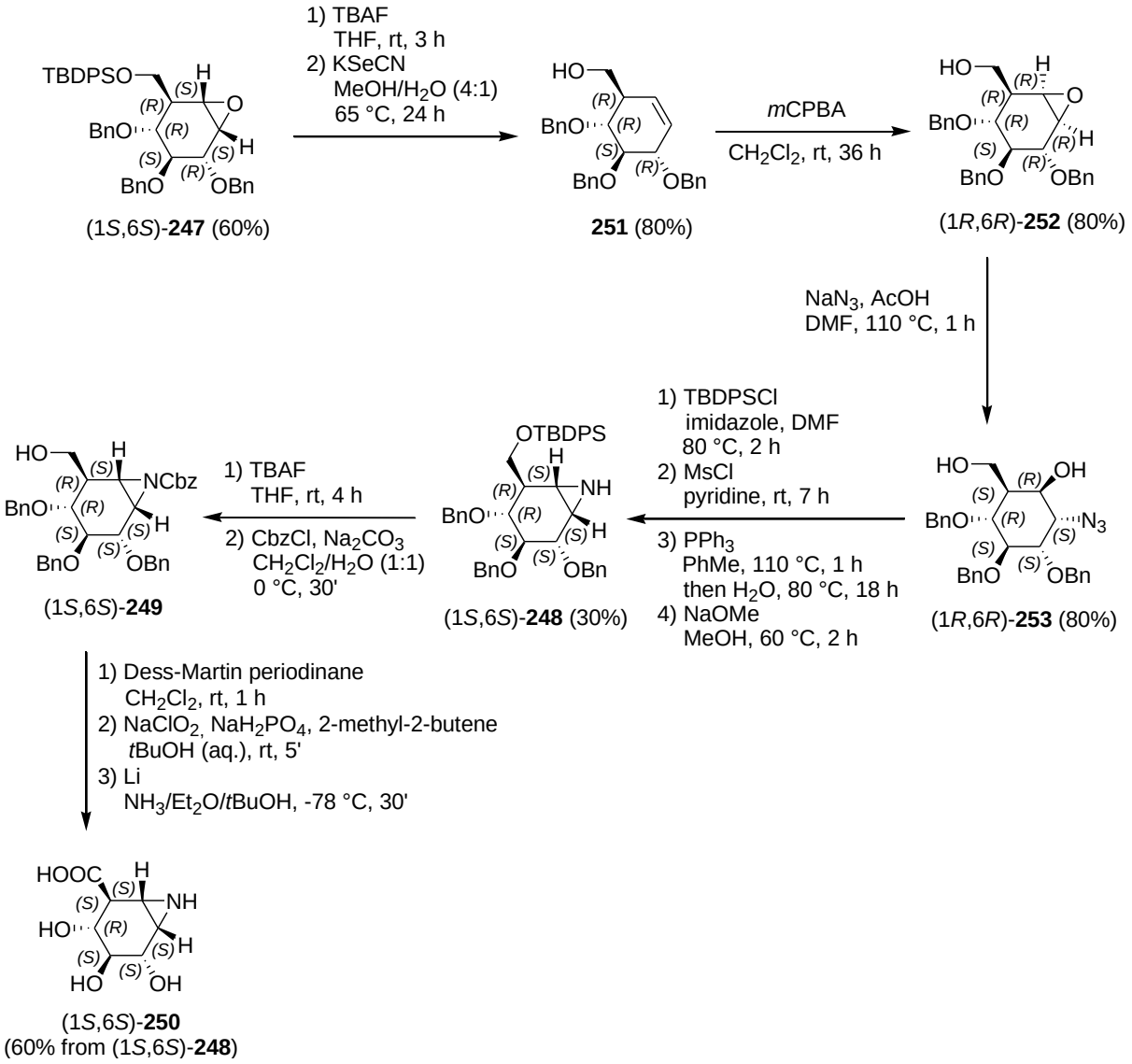
In this part, the synthesis of 2-(carboxymethyl)aziridines *via* functional group transformation starting from products from the chiral pool will be described.[145,146] Hereby, several transformations of the chiral skeletons were required to furnish the corresponding enantiopure bicyclic 2-(carboxymethyl)aziridines.

In a first study, the use of (1*R*,6*S*)-cyclophellitol **246** in the synthesis of two enantiopure aziridines (1*R*,6*R*)-**250** and (1*S*,6*S*)-**250** with a 3,4,5-trihydroxy-7-azabicyclo[4.1.0]heptane-2-carboxylic acid skeleton has been demonstrated.[145] The synthesis of cyclophellitol carboxylic acid aziridine analog (1*R*,6*R*)-**250** started with a two-step protection of the four hydroxyl groups of (1*R*,6*S*)-**246**, with TBDPSCl and benzylbromide, respectively (Scheme 60). The epoxide functionality of the resulting protected compound (1*S*,6*S*)-**247** underwent subsequent ring-opening reaction with sodium azide in the presence of acetic acid and gave the diaxially opened azide as a sole product, which was directly subjected to reductive aziridination with triphenylphosphine in toluene to afford a single aziridine (1*R*,6*R*)-**248** in good yield. Desilylation with TBAF, followed by Cbz-protection of the amino group resulted in compound (1*R*,6*R*)-**249** in 85% yield. As direct oxidation of this compound (1*R*,6*R*)-**249** with $RuCl_3$-$NaIO_4$ failed, a stepwise oxidation with Dess-Martin periodinane and $NaClO_2$ was necessary to obtain the corresponding carboxylate. Subsequently, the resulting carboxylic acid was *O*-debenzylated to afford bicyclic 2-(carboxymethyl)aziridine (1*R*,6*R*)-**250** in good yield.



Scheme 60

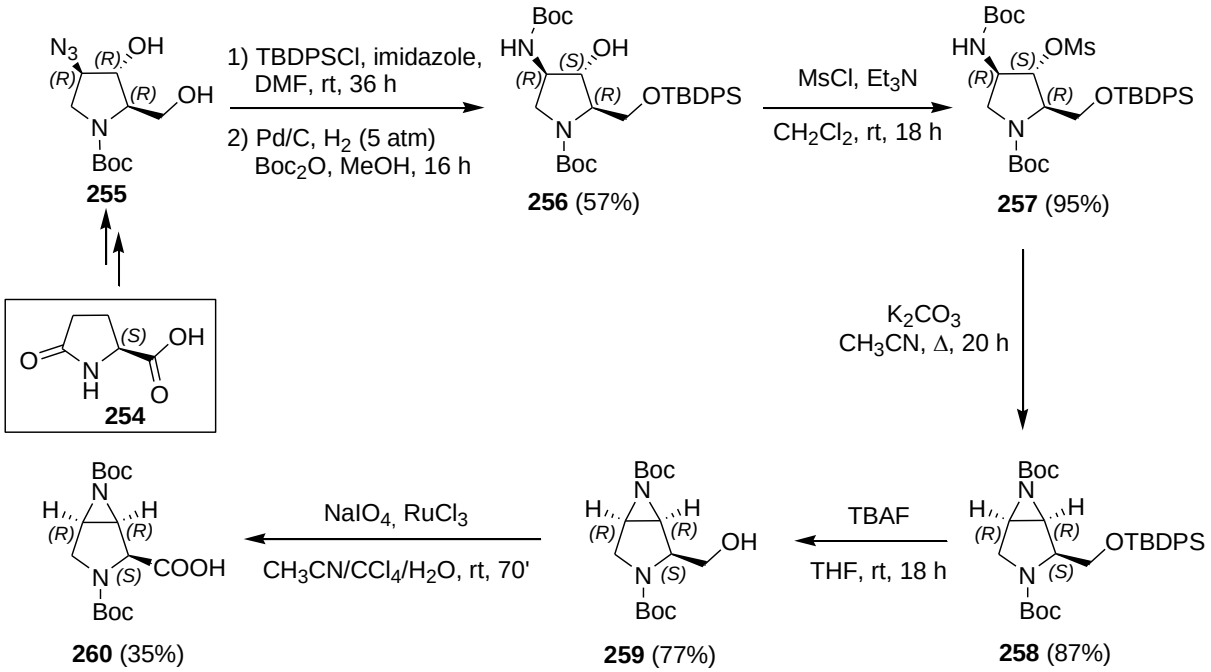
Next, cyclophellitol carboxylic acid aziridine analog (1*S*,6*S*)-**250** was prepared from the *O*-protected epoxide (1*S*,6*S*)-**247** (Scheme 61). Desilylation of compound (1*S*,6*S*)-**247** with TBAF, followed by deoxygenation with KSeCN provided olefin **251** in 80% overall yield. Stereoselective epoxidation of **251** with *m*CPBA gave epoxide (1*R*,6*R*)-**252** in 80% yield, after which ring opening with sodium azide and acetic acid afforded the diaxially opened azide (1*R*,6*R*)-**253** in 81% yield as a sole product. Since direct aziridine formation, after silylation of (1*R*,6*R*)-**253** with TBDPSCl was not successful, a stepwise procedure was required. Thus, mesylation with MsCl, reduction with triphenylphosphine and base-induced cyclization with sodium methoxide afforded the desired aziridine (1*S*,6*S*)-**248** in 30% overall yield. By the same procedure used in the transformation of (1*R*,6*R*)-**248** to (1*R*,6*R*)-**250**, (1*S*,6*S*)-**248** was converted to bicyclic 2-(carboxymethyl)aziridine (1*S*,6*S*)-**250** *via* (1*S*,6*S*)-**249** in 60% overall yield.



Scheme 61

cis-Aziridino-*L*-proline **260**, a bicyclic 2-(carboxymethyl)aziridine, has also been synthesized *via* functional group transformations starting from *S*-pyroglutamic acid **254**.[146] Azidoprolinol derivative **255**, derived from *S*-pyroglutamic acid **254**, has shown to be an ideal precursor in the synthesis of aziridinoproline **260** (Scheme 62). Hereto, the primary alcohol function was selectively protected as the TBDPS ether, which gave compound **256** upon hydrogenation in the presence of Boc_2O. Subsequent reaction of alcohol **256** with mesyl chloride resulted in the formation of the corresponding mesylated product **257** in excellent yield. The cyclization to the fully protected *cis*-aziridinoprolinol derivative **258** was achieved with potassium carbonate in acetonitrile under reflux in 87% yield. After *O*-desilylation of **258** and oxidation

of the primary alcohol function with $RuCl_3/NaIO_4$, aziridinoproline **260** was obtained in low yield (35%).



Scheme 62

In conclusion, it can be stated that the 2-(carboxymethyl)aziridines are a class of useful and attractive substrates in contemporary organic synthesis. Therefore, new synthetic approaches for the construction of 2-(carboxymethyl)aziridines are required, as the current available methodologies have often a limited scope or low yields or a limited chemoselectivity. Moreover, the application of more appropriate protecting groups at the nitrogen (and carbon) atom would be desirable to allow access to the corresponding unprotected amino acid derivatives. Further elaboration of asymmetric synthetic methods are also required, with special attention for the syntheses of all possible diastereo- and enantiomers. From this point of view, the further application of these 2-(carboxymethyl)aziridines as chemical probes, bioactive compounds and enzyme inhibitors is still largely uninvestigated.

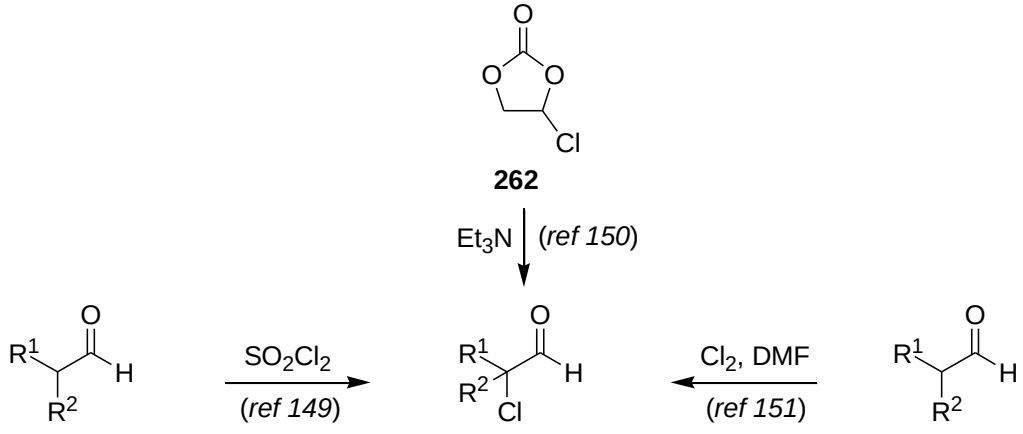
3. Results and Discussion

3.1. Synthesis of *N*-sulfinylimines

3.1.1. Synthesis of *N*-(*p*-toluenesulfinyl)-α-functionalized aldimines

As already mentioned in the introduction and goals, the synthesis of chiral *N*-(*p*-toluenesulfinyl)aldimines has extensively been reported in the literature.[36,147,148] Moreover, the synthesis of chiral *N*-sulfonyl-α-haloaldimines has also been reported as straightforward.[149] Nevertheless, the synthesis of chiral *N*-(*p*-toluenesulfinyl)-α-chloroaldimines or aliphatic *N*-(*p*-toluenesulfinyl)-α-aminoaldimines has not been reported so far.

The synthesis of this new class of chiral *N*-(*p*-toluenesulfinyl)-α-chloroaldimines 266 started from α-chloroaldehydes **264** (Scheme 63). The preparation of the used α-chloroaldehydes **264a-c,h** proceeded *via* chlorination of the corresponding aldehydes **261a-c** with SO_2Cl_2,[150] or *via* (*in situ* generated) Et_3NHCl-catalysed loss of CO_2 from 4-chloro-1,3-dioxolan-2-one **262**.[151]



261a (R^1,R^2 = Me)
261b (R^1,R^2 = Et)
261c (R^1,R^2 = -$(CH_2)_5$-)

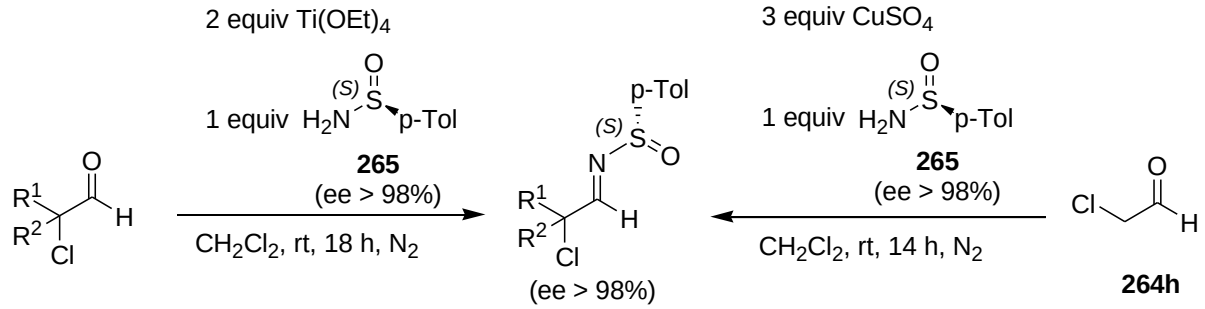
264a (R^1,R^2 = Me)
264b (R^1,R^2 = Et)
264c (R^1,R^2 = $(CH_2)_5$)
264d (R^1 = Me, R^2 = Cl)
264e (R^1 = Et, R^2 = Cl)
264f (R^1 = *n*Pr, R^2 = Cl)
264g (R^1 = *i*Pr, R^2 = Cl)
264h (R^1,R^2 = H)

263d (R^1 = Me, R^2 = H)
263e (R^1 = Et, R^2 = H)
263f (R^1 = *n*Pr, R^2 = H)
263g (R^1 = *i*Pr, R^2 = H)

Scheme 63

α,α-Dichloroaldehydes **264d-g** were available at the department and have been synthesized *via* direct chlorination of aldehydes **263d-g** with chlorine in DMF.[152]

Condensation of α-chlorinated aldehydes **264a-g** with (*S*)-(+)-*p*-toluenesulfinamide **265** in the presence of $Ti(OEt)_4$ in dichloromethane at room temperature,[147] provided *N*-(*p*-toluenesulfinyl)-α-chloroaldimines **266a-g** (Scheme 64) in moderate to high yields and with excellent enantiomeric excess, as determined by chiral HPLC analysis of the *N*-(*p*-toluenesulfinyl)-α-chloroaldimine derived (2*S*,3*R*)-*trans*-3-(*N*-tosylamino)azetidine-2-carboxylate (ee > 98%) (*vide infra*). These imines **266a-g** showed to be very stable during purification by column chromatography on silica gel to provide analytically pure samples. The synthesis of *N*-(*p*-toluenesulfinyl)-α-chloroaldimine **266h** was, however, unsuccessful under the above-mentioned conditions and only led to decomposition. Performing the synthesis under milder conditions using anhydrous $CuSO_4$ in dichloromethane,[153] generated the desired imine **266h** in high yield after 14 hours at room temperature. This highly unstable *N*-(*p*-toluenesulfinyl)imine **266h** was used as such without further purification.



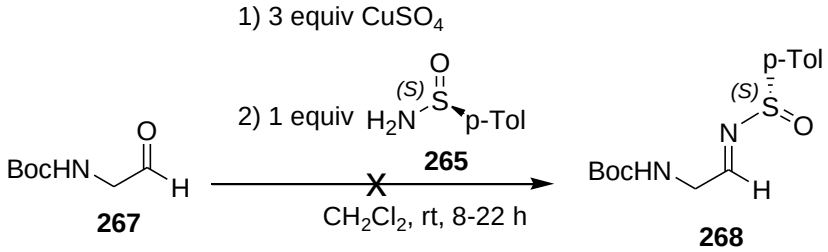
264a (R^1,R^2 = Me)
264b (R^1,R^2 = Et)
264c (R^1,R^2 = $(CH_2)_5$)
264d (R^1 = Me, R^2 = Cl)
264e (R^1 = Et, R^2 = Cl)
264f (R^1 = *n*Pr, R^2 = Cl)
264g (R^1 = *i*Pr, R^2 = Cl)

266a (92%)
266b (66%)
266c (30%)
266d (40%)
266e (59%)
266f (47%)
266g (56%)
266h (96%)

Scheme 64

In addition, the synthesis of aliphatic *N*-(*p*-toluenesulfinyl)-α-aminoimine **268** was also pursued in order to obtain this polyaminated building block. Condensation of the

commercially available *N*-Boc-α-aminoacetaldehyde **267** with (*S*)-(+)-*p*-toluenesulfinamide **265** in the presence of $CuSO_4$ in dichloromethane at room temperature for eight hours did not result in a complete consumption of the starting aldehyde **267** (Scheme 65). Prolonging the reaction time for 22 hours gave complex reaction mixtures due to decomposition of the desired compound **268**. No further efforts for the synthesis of the aliphatic *N*-(*p*-toluenesulfinyl)-α-aminoimine **268** were made, while the synthesis of the corresponding aliphatic *N*-(*tert*-butanesulfinyl)-α-aminoimine was evaluated instead (*vide infra*).



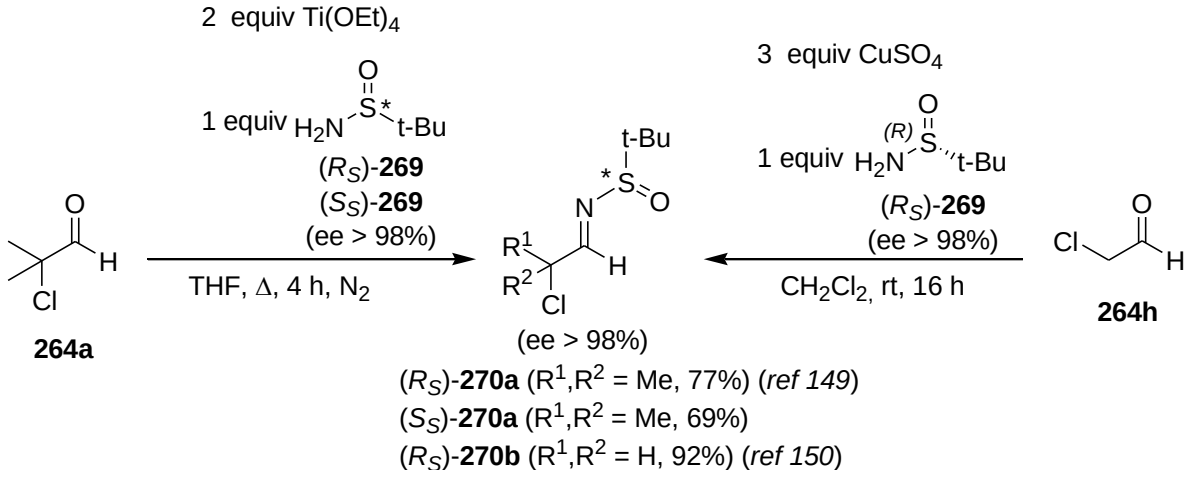
Scheme 65

3.1.2. Synthesis of *N*-(*tert*-butanesulfinyl)-α-functionalized aldimines

Chiral *N*-(*tert*-butanesulfinyl)aldimines have proven to be valuable synthons for a wide variety of azaheterocyclic compounds and aliphatic amines *via* nucleophilic addition reactions across these activated imines.[38,35,40,148]

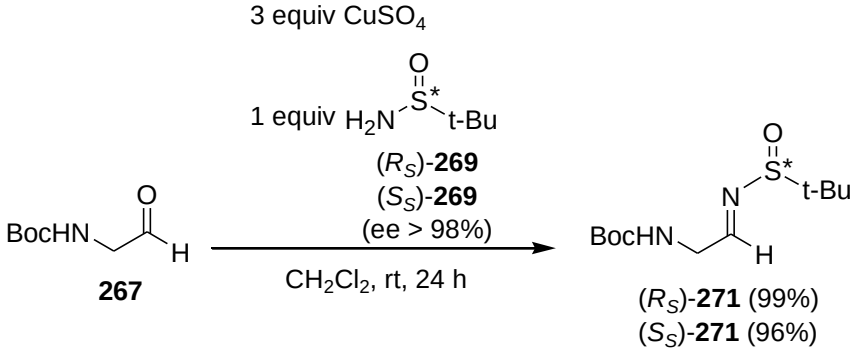
In order to evaluate the unexplored reactivity of chiral *N*-(*tert*-butanesulfinyl)-α-chloroaldimines **270** in Mannich-type additions, the chiral *N*-(*tert*-butanesulfinyl)-α-chloroaldimine (R_S)-**270a**,[150] and the new imine (S_S)-**270a** were efficiently prepared by condensation of α-chloroaldehyde **264a** with the enantiopure *tert*-butanesulfinamides (R_S)-**269** and (S_S)-**269**, respectively, in the presence of $Ti(OEt)_4$ in THF at reflux temperature (Scheme 66). The chiral *N*-(*tert*-butanesulfinyl)-α-chloroacetaldimine (R_S)-**270b** was prepared by condensation of α-chloroaldehyde **264h** with (R_S)-*tert*-butanesulfinamide (R_S)-**269** in the presence of anhydrous $CuSO_4$ in dichloromethane,[153] after 16 hours at room temperature in 92% yield (Scheme 66). This unstable *N*-(*tert*-butanesulfinyl)imine (R_S)-**270b** required no

further purification after filtration and solvent removal. Previously described results on the enantioselective synthesis of chiral *N*-(*tert*-butanesulfinyl)-α-chloroimines, starting from condensation reactions with the enantiopure *tert*-butanesulfinamides (R_S)-**269** (ee > 98%), have demonstrated that no racemization occurred at the sulphur atom, and it can be assumed that this is also valid for the synthesis of analogous *N*-(*tert*-butanesulfinyl)-α-chloroaldimines **270**, as the latter compounds **270a** were synthesized under the same reaction conditions.[150b]



Scheme 66

In addition, the synthesis of novel aliphatic *N*-(*tert*-butanesulfinyl)-α-aminoimines **271** was effectuated in order to obtain a valuable polyaminated building block suitable for addition reactions (Scheme 67).



Scheme 67

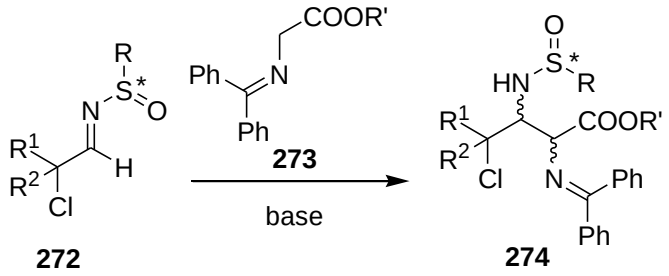
Condensation of *N*-Boc-α-aminoacetaldehyde **267** with the enantiopure *tert*-butanesulfinamides (R_S)-**269** and (S_S)-**269**, respectively, in the presence of $CuSO_4$ in dichloromethane for 24 hours at room temperature resulted in the formation of the

corresponding *N*-(*tert*-butanesulfinyl)-α-aminoimines (R_S)-**271** and (S_S)-**271**. Purification by filtration over silica gel afforded these stable imines (R_S)-**271** and (S_S)-**271** in excellent yields (96-99%).

3.2. Asymmetric synthesis of α,β-diamino carboxylic acid derivatives *via* stereoselective Mannich-type additions across *N*-sulfinyl-α-chloroimines

The utility of α,β-diamino acids and γ-chloro-α-amino acids as building blocks for the synthesis of new heterocyclic compounds and peptides, has already extensively been demonstrated in the past.[10,17] Preliminary results at the Department of Sustainable Organic Chemistry and Technology, Faculty of Bioscience-engineering, UGent, disclosed the successful racemic synthesis of γ-chloro-α,β-diamino acid derivatives *via* a Mannich-type addition of 'benzophenone imine glycinates' across *N*-(*p*-toluenesulfonyl)-α-chloroaldimines.[91,92] In this part, the first asymmetric synthesis of γ-chloro-α,β-diamino acid derivatives as new building blocks for heterocyclic scaffolds, incorporating the biologically interesting γ-chloro-α-amino acid moiety as well as the α,β-diamino acid moiety, will be discussed.

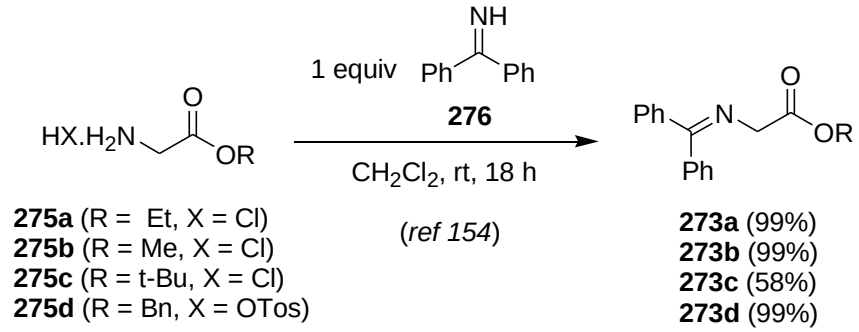
The synthesis of γ-chloro-α,β-diamino acid derivatives **274** *via* Mannich-type additions of enolates derived from benzophenone imine glycinates **273** across enantiopure *N*-sulfinyl-α-chloroaldimines **272** was investigated with special attention to the enantio- and diastereoselectivity of this reaction (Scheme 68). For this purpose, *N*-(*p*-toluenesulfinyl)-α-chloroaldimines **266a,h** and *N*-(*tert*-butanesulfinyl)-α-chloroaldimines (R_S)-**270a,b** were used, as these compounds were known for their good reactivity and stereoselectivity in the Mannich-type reactions.[154]



Scheme 68

3.2.1. Synthesis of alkyl *N*-(diphenylmethylene)glycinates

Alkyl *N*-(diphenylmethylene)glycinates **273** were prepared, according to an established literature procedure,[91,92,155] by reaction of glycinate hydrochloric acid salts **275a-c** or glycinate *p*-toluenesulfonic acid salt **275d** with one equivalent of benzophenone imine **276** for 18 hours in dry dichloromethane at room temperature (Scheme 69). This gave rise to alkyl *N*-(diphenylmethylene)glycinates **273a-b,d** in almost quantitative yields (99%), while the *tert*-butyl *N*-(diphenylmethylene)glycinate **273c** was synthesized in a significantly lower yield (58%).

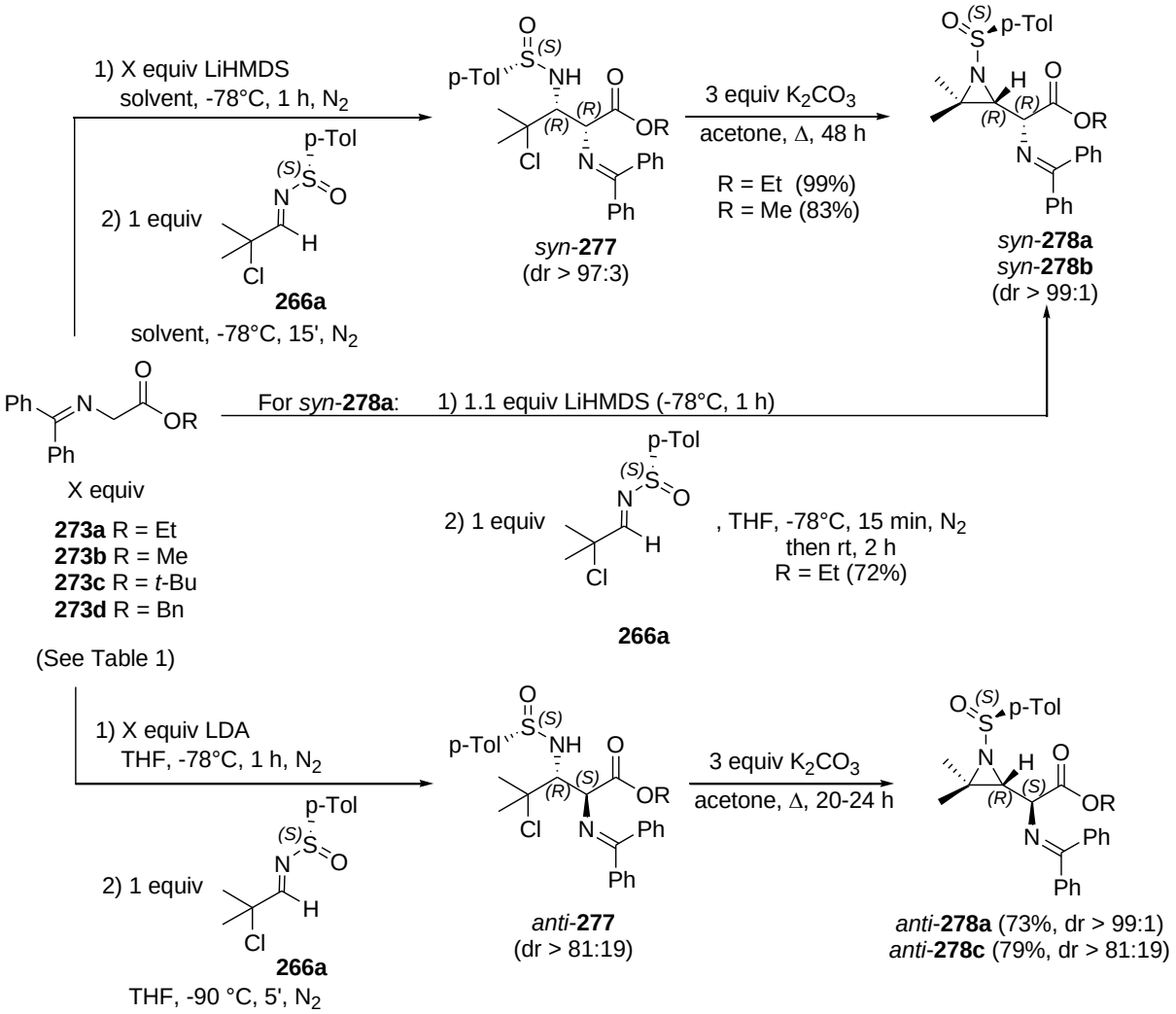


Scheme 69

3.2.2. Synthesis and elaboration of γ-chloro-α-diphenylmethyleneamino-β-*p*-toluenesulfinylamino carboxylic acid derivatives

The stereoselective synthesis of chiral α,β-diamino acid derivatives **277** was achieved by a Mannich-type addition of *N*-(diphenylmethylene)glycine esters **273** across chiral *N*-*p*-toluenesulfinyl-α-chloroaldimine **266a** *via* systematically changing the reaction conditions

(Scheme 70, Table 1). It was found that the choice of base, LDA or LiHMDS, used for the deprotonation of the glycine ester **273a**, had a dramatic influence on the *syn*- or *anti*-selectivity of the reaction (Table 1).



Scheme 70

In a first reaction (Table 1, entry 1), the Mannich-type addition of ethyl glycinate **273a** across chiral

N-*p*-toluenesulfinyl-α-chloroisobutyraldimine **266a** was performed at -78 °C using five equivalents of LiHMDS. ^{1}H NMR analysis of the crude reaction mixture indicated that the resulting *syn*-γ-chloro-α,β-diamino ester *syn*-**277a** was obtained with good *syn*-selectivity (dr = 93:7). The *syn*-adduct *syn*-**277a** was isolated in 63% yield (dr = 97:3) 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*-**277a** in an excellent *syn*-selectivity (dr = 99:1) after recrystallization. In this way, column chromatography to purify the *syn*-adduct *syn*-**277a** could be avoided, which resulted in an improved yield of 88%. Changing the solvent system to either methyl *tert*-butyl ether or 2-methyltetrahydrofuran resulted in lower diastereoselectivities (entries 3-4). The use of methyl glycinate **273b** using the optimal reaction conditions described in entry 2 resulted in a similar *syn*-selectivity (dr = 97:3) and yield (86%) (entry 5).

Table 1. Addition of *N*-(diphenylmethylene)glycine esters **273** across *N*-*p*-toluenesulfinylimine **266a** producing *syn*- and *anti*-addition products **277**

Entry	Ester	Solvent	Base	X	Time / Temp	*syn*/*anti* ratio [a]	Product	Yield (%)
1	**273a**	THF	LiHMDS	5	15', -78 °C	93:7	*syn*-**277a**	63 [b]
2	**273a**	THF	LiHMDS	1.1	15', -78 °C	99:1[c]	*syn*-**277a**	88 [b]
3	**273a**	MTBE	LiHMDS	1.1	15', -78 °C	77:23	*syn*-**277a**	-
4	**273a**	2-Me-THF	LiHMDS	1.1	15', -78 °C	84:16	*syn*-**277a**	-
5	**273b**	THF	LiHMDS	1.1	15', -78 °C	97:3[c]	*syn*-**277b**	86 [b]
6	**273a**	THF	LDA	1.1	5', -90 °C	13:87	*anti*-**277a**	79[d]
7	**273a**	THF	LDA	1.6	5', -90 °C	10:90	*anti*-**277a**	55[e]
8	**273c**	THF	LDA	1.6	5', -90 °C	28:72	*anti*-**277c**	52[f]
9	**273d**	THF	LDA	1.1	5', -90 °C	18:82	*anti*-**277d**	-
10	**273a**	THF	LiHMDS	1.1	15', -78 °C 2 h, rt	> 99:1	*syn*-**278a**	72[b]
11	**273a**	THF	LDA	1.1	5', -90 °C 2 h, rt	> 99:1	*syn*-**278a**	-

[a] Determined *via* ^{1}H NMR analysis of crude reaction mixtures with *syn*-**277** or *syn*-**278** as standard
[b] Isolated yield of single diastereomer (dr > 97:3)
[c] Determined *via* ^{1}H NMR after recrystallization 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)

Performing the reaction with 1.1 equivalents of LDA, resulted in γ-chloro-α,β-diamino ester *anti*-**277a** with good *anti*-selectivity (dr = 87:13) (entry 6). The *anti*-γ-chloro-α,β-diamino ester *anti*-**277a** was obtained in 79% yield as a mixture of two diastereomers (dr = 89:11)

after purification by column chromatography. Unfortunately, the *anti*-adduct *anti*-**277a** 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 the procedure for the synthesis of *anti*-ethyl 2,3-diamino-3-phenylpropanoates from *N*-(benzylidene)-*p*-toluenesulfinamide and glycine enolates.[156] These conditions led to a slightly better diastereoselectivity (dr = 90:10), but unfortunately the *anti*-γ-chloro-α,β-diamino ester *anti*-**277a** was obtained in a lower yield (55%) as a mixture of two diastereomers (dr = 90:10) after purification by tedious column chromatography. When *tert*-butyl glycinate **273c** was subjected to the Mannich-type reaction conditions with *N*-*p*-toluenesulfinyl-α-chloroisobutyraldimine **266a** using 1.6 equivalents of LDA (entry 8), the resulting *anti*-γ-chloro-α,β-diamino ester *anti*-**277c** 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. In addition, upon deprotonation of benzyl glycinate **273d** with 1.1 equivalents of LDA and subsequent addition across *N*-*p*-toluenesulfinyl-α-chloroisobutyraldimine **266a** (entry 9), ^{1}H NMR analysis of the crude reaction mixture showed that the expected *anti*-addition products were formed in good diastereoselectivity (dr = 82:18), yet purification by column chromatography failed to deliver pure compound *anti*-**277d**.

Both the *syn*- and *anti*-addition products **277** were subsequently cyclized to the corresponding *N*-sulfinylaziridines **278** (Scheme 70) upon treatment with K_2CO_3 in acetone under reflux for 20-48 hours, followed by column chromatography, which led to improved diastereomeric ratios in case of *syn*-**278** and *anti*-**278a** (dr > 99:1).

Hereby, the diastereomeric ratios were determined via ^{1}H NMR analysis of the isolated products in which no other diastereomers were observed. Moreover, all the reported diastereomeric ratios were determined in this way.

The *syn*-*N*-sulfinylaziridine *syn*-**278a** could also be prepared directly in 72% yield *via* a single-step reaction starting from ethyl glycinate **273a**, if the reaction mixture from the Mannich-type addition across imine **264a** after 15 minutes at -78 °C was subsequently stirred for two hours at room temperature (Table 1, entry 10). This procedure was not applicable for the synthesis of *anti*-*N*-sulfinylaziridines *anti*-**278** as the *anti*-adducts were the kinetically favored diastereomers which isomerize to the thermodynamically more stable *syn*-isomers (entry 11). The absolute stereochemistry of the *anti*-*N*-*p*-toluenesulfinylaziridine *anti*-**278a** and *syn*-adduct *syn*-**277a** were unambiguously determined by means of X-ray diffraction analysis (in collaboration with Prof. R. Sillanpää, Department of Chemistry, University of Jyväskylä, Finland) (Figure 7).

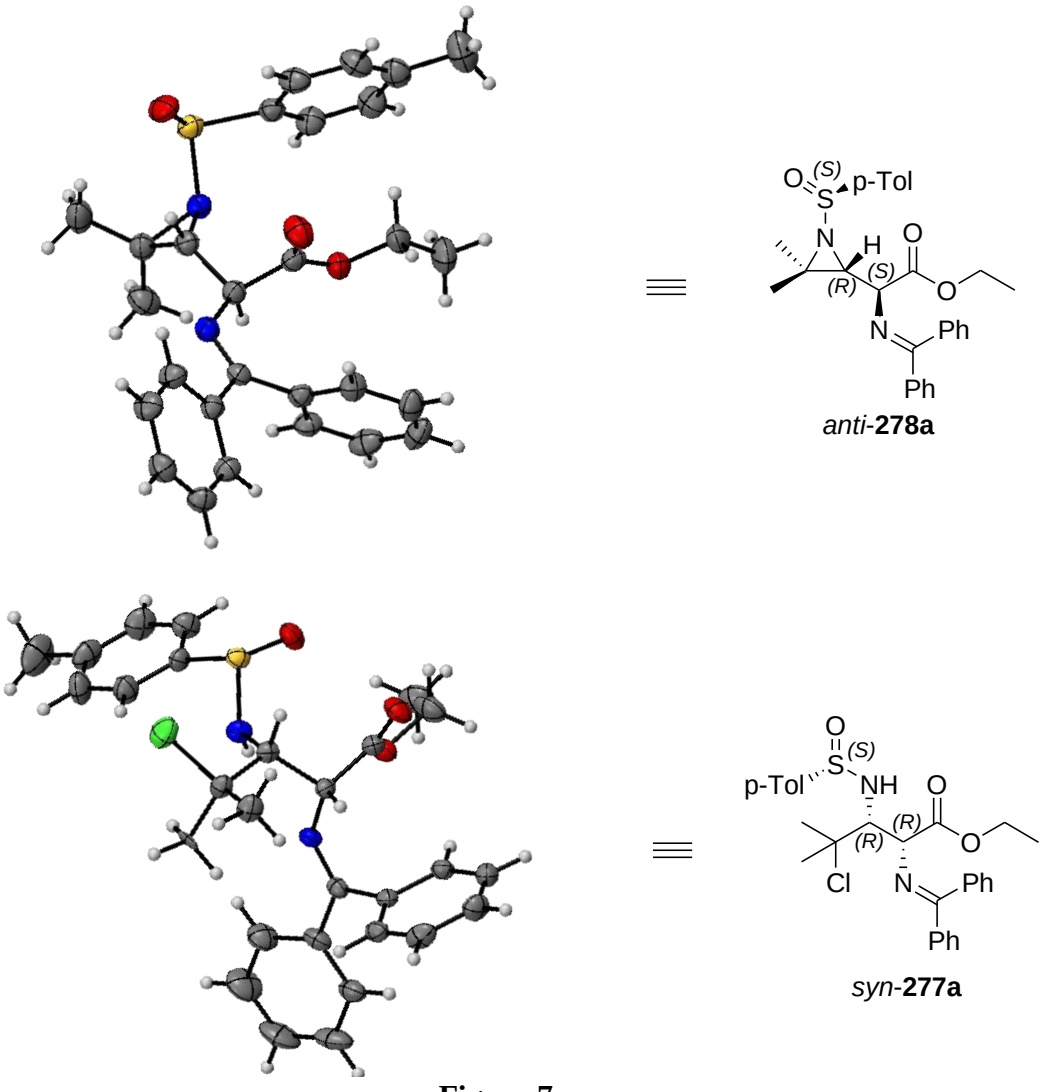
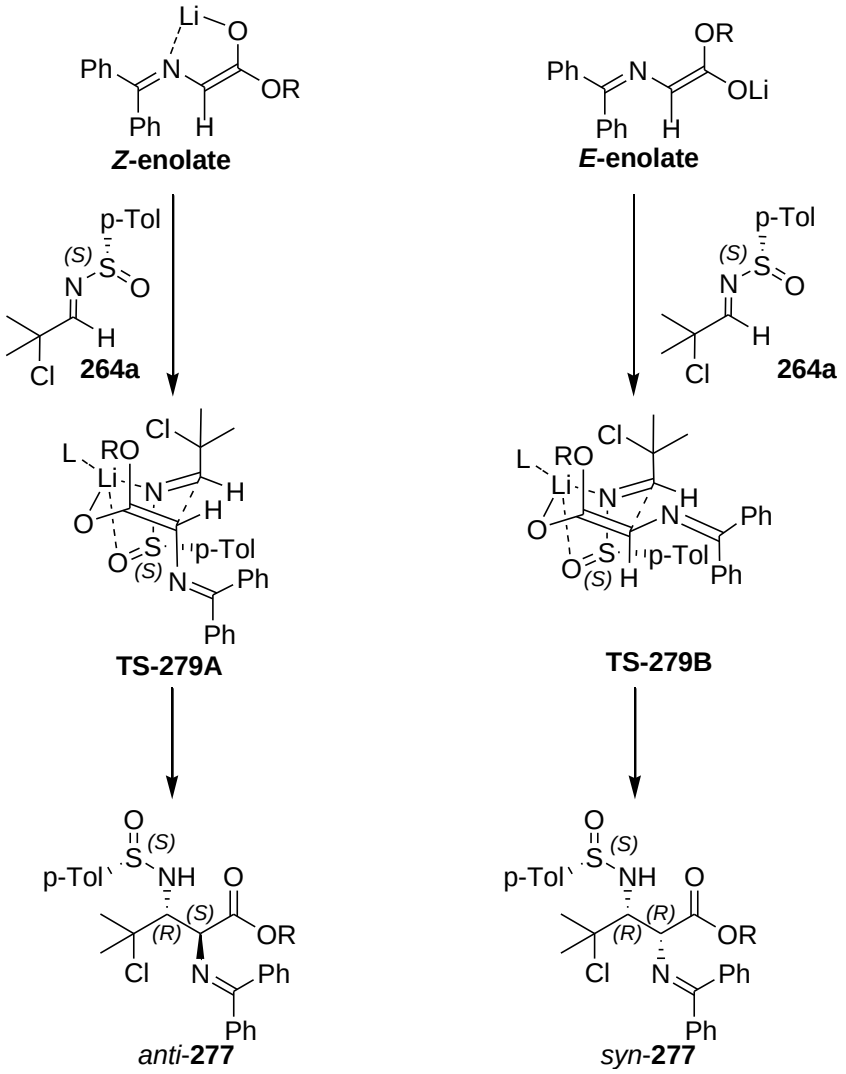


Figure 7.

X-ray diffraction analysis of *anti*-*N*-sulfinylaziridine *anti*-**278a** and *syn*-adduct *syn*-**277a**

The dramatic influence of the base, LDA or LiHMDS (Scheme 70), on the stereochemical outcome of the Mannich-type reaction across *N*-sulfinyl-α-chloroimine **266a** under kinetic conditions (for example -90 °C, 5 min) was rationalized on the basis of the enolate geometry of the anions derived from the deprotonation of *N*-(diphenylmethylene)glycine esters **273**.

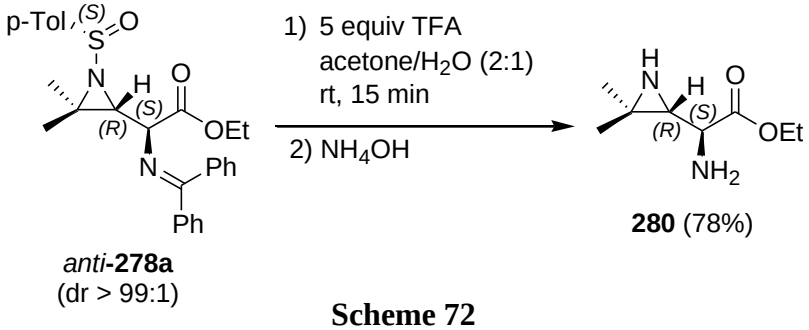


Scheme 71

As reported in the literature, the enolates obtained *via* deprotonation of *N*-(diphenylmethylene)glycine esters **273** with LDA were expected to have the *Z*-geometry (Scheme 71), which was favoured by intramolecular chelation.[156,157,158] As commonly performed in the assignment of enolate geometry, in contrast to conventional *E*/*Z*-nomenclature, the highest priority designation was allocated to the O-metal group of the enolate substituents. Alternatively, it was proposed that upon deprotonation of *N*-

(diphenylmethylene)glycine esters **273** with the less basic LiHMDS in THF, a shift towards the formation of the *E*-enolate occurs (Scheme 71). Unfortunately, the enolate geometry could not be determined *via* trapping experiments with TMSCl.[159] Reaction of the *Z*- and *E*-enolates *via* **TS-279A** and **TS-279B** results in the formation of *anti*-**277** and *syn*-**277**, respectively.[156]

The *p*-toluenesulfinyl group of *anti*-aziridine **278a** (Scheme 72) was readily removed by treatment with five equivalents of trifluoroacetic acid in acetone/water (2:1) at room temperature for 15 minutes, resulting in the *N*-deprotected *anti*-β,γ-aziridino-α-amino ester **280** in 78% yield after a basic workup with NH_4OH.[160]

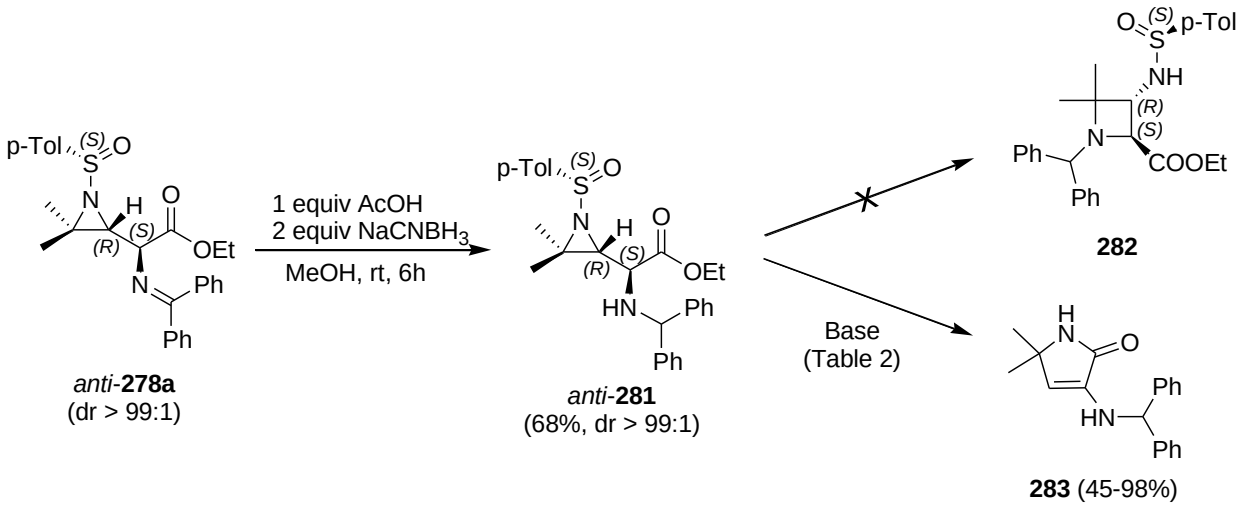


anti-**278a**
(dr > 99:1)

280 (78%)

Scheme 72

The *N*-sulfinyl β,γ-aziridino moiety of aziridine *anti*-**278a** could be seen as functional equivalent to the γ-chloro substituent of natural γ-chloro-α-amino acids,[3] or the adenosyl-S^+-CH_3 cation of *S*-adenosylmethionine,[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 **282**. The *N*-diphenylmethylene group of *anti*-*N*-sulfinylaziridine *anti*-**278a** (Scheme 73) was reduced by means of $NaCNBH_3$ in the presence of acetic acid in MeOH, resulting in aziridine *anti*-**281** with a nucleophilic α-amino function (68% yield). Several attempts were made to achieve the ring transformation of *N*-sulfinylaziridine *anti*-**281** into *trans*-β-aminoazetidine-2-carboxylate **282**, albeit without success (Scheme 73, Table 2). A possible explanation for this failure was the weaker electron-withdrawing character of the *p*-toluenesulfinyl group, with respect to the *p*-toluenesulfonyl group. Previously, the presence of the sulfonyl group has shown to promote an intramolecular ring opening towards the corresponding azetidines.[92]



Scheme 73

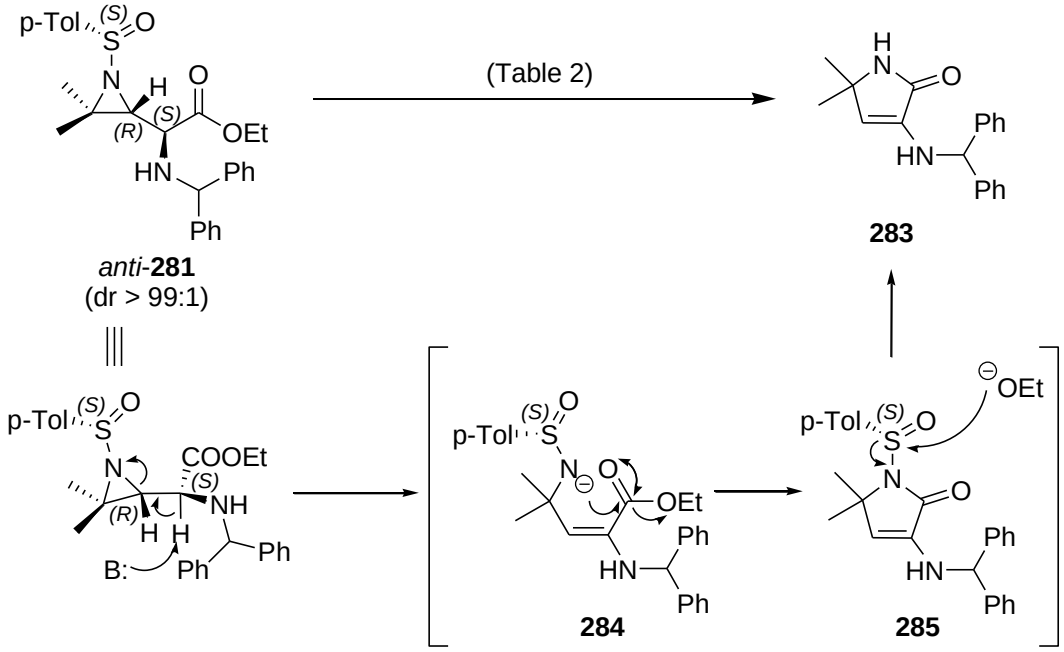
Table 2. Different reaction conditions for the ring transformation of aziridine *anti*-**281**

Entry	Solvent	Base/Acid	Temperature	Time	Result	Yield
1	CH_3CN	1 equiv Et_3N	Δ	20 h	no reaction	-
2	CH_3CN	5 equiv Et_3N	100 °C[a]	22 h	no reaction	-
3	EtOH	1 equiv Et_3N	Δ	96 h	decomposition	-
4	DMSO	1 equiv Et_3N	70 °C	28 h	no reaction	-
5	DMSO	1 equiv Et_3N	Δ	20 h	decomposition	-
6	CH_2Cl_2	1 equiv $BF_3.Et_2O$	rt	20 h	complex mixture	-
7	THF	1 equiv LiHMDS	Δ	2.5 h	complex mixture	-
8	THF	1 equiv KOtBu	Δ	2.5 h	**283**	87%[b]
9	THF	1 equiv NaH	Δ	1 h	**283**	45%[c]
10	EtOH	3 equiv K_2CO_3	Δ	22 h	**283**	98%[b]
11	DMSO	3 equiv K_2CO_3	Δ	22 h	complex mixture	-
12	DMSO	2.5 equiv NaH	80 °C	2 h	**283**	56%[c]
13	Toluene	1 equiv DBU	rt	24 h	no reaction	-
14	CH_3CN	2 equiv $LiClO_4$	Δ	24 h	complex mixture	-
15	CH_3CN	-	120 °C (MW)	10 min	decomposition	-
16	CH_3CN	-	90 °C (MW)	5 min	decomposition	-
17	CH_3CN	-	70 °C (MW)	5 min	no reaction	-
18	CH_3CN	-	50 °C (MW)	30 min	no reaction	-
19	CH_3CN	1 equiv NaI	rt	30 min	no reaction	-
20	CH_3CN	1 equiv NaI	50 °C (MW)	30 min	no reaction	-

[a] The reaction was performed in a pressure vial
[b] Yield after precipitation of dihydropyrrole-2-one **283** in diethyl ether
[c] Yield after recrystallization from diethyl ether

An initial attempt using similar reaction conditions as in a previously reported ring transformation towards racemic *anti*-*N*-tosylazetidines, *via* heating in acetonitrile in the presence of one equivalent Et_3N,[92] did not result in the formation of *trans*-β-aminoazetidine-2-carboxylate **282** (Table 2, entry 1). 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 (entries 2-5). Reaction with one equivalent of $BF_3.Et_2O$ at room temperature for 20 hours resulted in a complex reaction mixture, in which no trace of *trans*-β-aminoazetidine-2-carboxylate **282** was detected (entry 6). Also the use of one equivalent LiHMDS led to a complex reaction mixture after heating at reflux for 2.5 hours (entry 7). When aziridine **281** was treated with one equivalent KOtBu in THF at reflux for 2.5 hours (entry 8), the selective formation of 3-amino-1,5-dihydropyrrole-2-one **283** was observed (87% yield).

The proposed reaction mechanism, leading to this γ-lactam **283**, begins with deprotonation at the α-position of the ester, which leads to an *anti*-periplanar elimination resulting in ring opening of the aziridine *anti*-**281** (Scheme 74).



Scheme 74

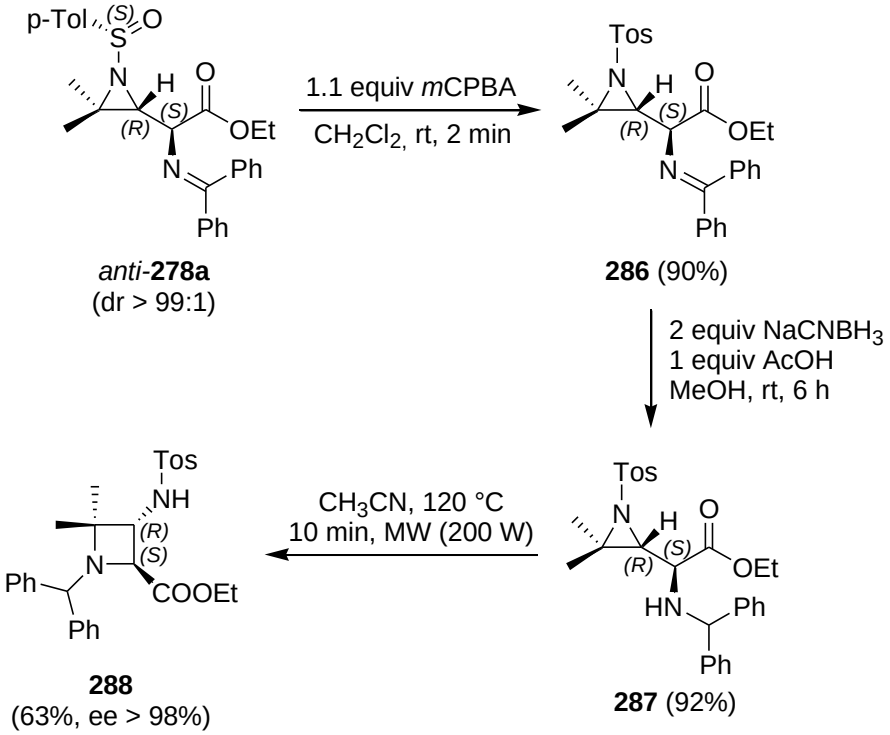
The secondary amide group of alkenoate **284** then attacked the ester group leading to γ-lactam **285**. The *p*-toluenesulfinyl group of the ring-closed product **285** was subsequently cleaved by attack of the expelled ethoxide anion, resulting in dihydropyrrole-2-one **283**.

Using one equivalent of NaH for one hour instead (Table 2, entry 9), also afforded the 3-amino-1,5-dihydropyrrole-2-one **283** however in a lower yield (45%). Performing the reaction in EtOH for 22 hours at reflux temperature in the presence of three equivalents of K_2CO_3 (entry 10), afforded the 3-amino-1,5-dihydropyrrole-2-one **283** in an excellent yield of 98%.

The same reaction in DMSO led to a complex reaction mixture (entry 11), whereas the use of 2.5 equivalents of NaH in DMSO at 80 °C for two hours (entry 12), resulted in the 3-amino-1,5-dihydropyrrole-2-one **283** in a yield of 56%. When aziridine *anti*-**281** was treated with one equivalent of DBU in toluene for 24 hours at room temperature, no reaction was observed (entry 13). Reaction of aziridine *anti*-**281** with two equivalents of $LiClO_4$ in acetonitrile at reflux for 24 hours, resulted only in a complex reaction mixture (entry 14). In an additional series of attempts, a microwave reactor (200 W) was employed to promote ring transformation of aziridine *anti*-**281** to *trans*-β-aminoazetidine-2-carboxylate **282**, albeit without success. An initial reaction, performed in acetonitrile at 120 °C for 10 minutes, led to degradation of the starting material *anti*-**281** (entry 15). Lowering reaction times and temperatures resulted in degradation or no reaction, without formation of the desired azetidine **282** (entry 16-18). In a final attempt, NaI was added to the reaction mixture, but no conversion of the starting material into the envisaged product was achieved (entry 19-20).

Since none of these attempts resulted in the intramolecular ring transformation to azetidine **282**, the *p*-toluenesulfinyl group of *N*-sulfinylaziridine *anti*-**278a** (Scheme 75) was selectively oxidized with 3-chloroperbenzoic acid (*m*CPBA), resulting in enantiomerically pure *anti*-*N*-sulfonylaziridine **286** containing a strong electron-withdrawing activating group at the aziridine nitrogen. Based on the previously reported ring transformation of racemic *anti*-*N*-

tosylaziridine **287** to racemic *anti*-*N*-tosylazetidine **288**, the targeted ring transformation of aziridine **286** to optically pure azetidine **287** was expected to be straightforward.[92] The *N*-diphenylmethylene moiety of this *anti*-*N*-sulfonylaziridine **286** was subsequently reduced with $NaCNBH_3$ in methanol in the presence of acetic acid, resulting in the formation of *anti*-*N*-sulfonylaziridine **287** in 92% yield. It was shown that the *anti*-*N*-sulfonylaziridine **287** was an excellent precursor for an easy ring transformation towards *trans*-3-(*N*-tosylamino)azetidine-2-carboxylate **288** *via* simple heating in acetonitrile at 120 °C for 10 minutes under microwave (MW) conditions. Noteworthy, it has been reported that the latter transformation to prepare the racemic azetidine **288** has required heating at 70 °C in acetonitrile for 20 hours under conventional heating conditions.[92]



Scheme 75

The enantiomeric excess of *trans*-3-(*N*-tosylamino)azetidine-2-carboxylate **288** (ee > 98%) was deduced from the analysis on chiral HPLC involving comparison to a racemic mixture of azetidine **288** (Figure 8).

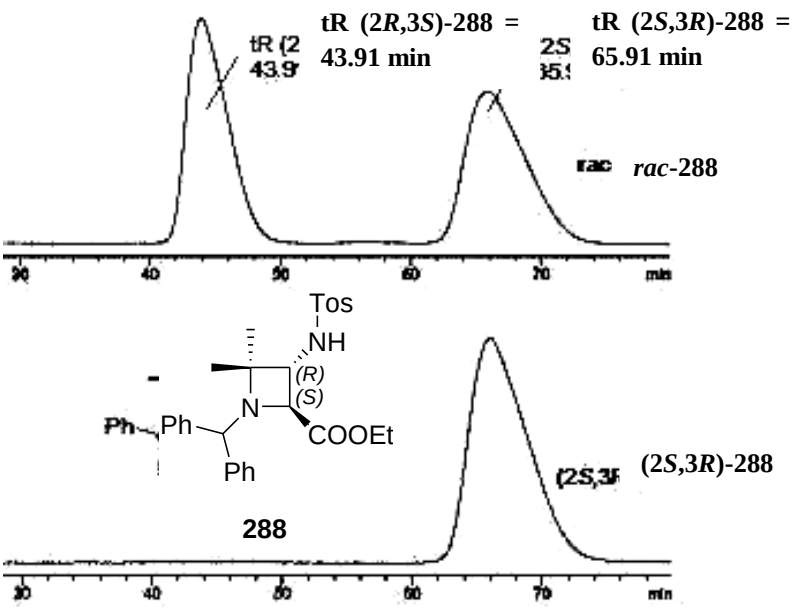
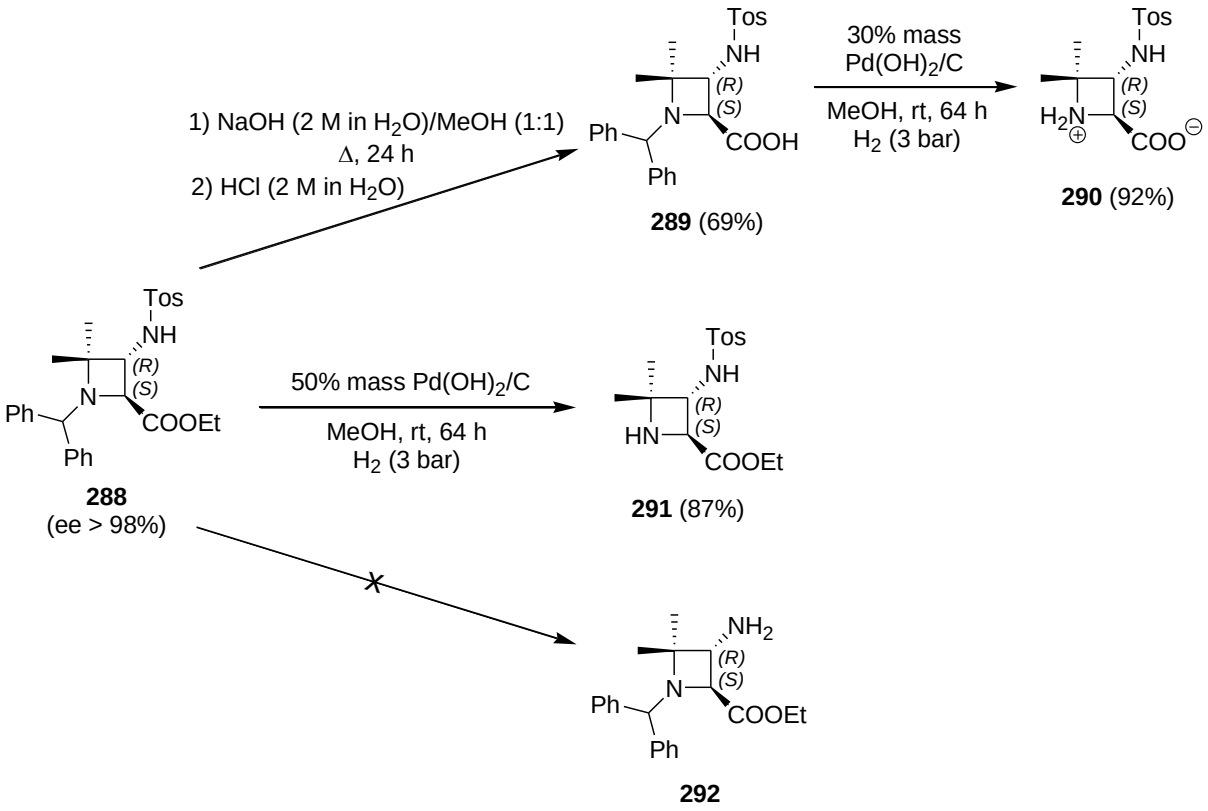


Figure 8. Chiral HPLC chromatogram of racemic and (2*S*,3*R*)-*trans*-3-(*N*-tosylamino)-azetidine-2-carboxylate **288**

acid derivative **288** as building block for the synthesis of peptides, azetidine **288** (Scheme 76) was subjected to several deprotection reactions. In an initial reaction, the ester group was hydrolyzed under basic conditions in 2 M NaOH in aqueous methanol, resulting in *trans*-3-(*N*-tosylamino)azetidine-2-carboxylic acid **289** in 69% yield after acidic workup with aqueous HCl. Subsequently, the *N*-(diphenylmethyl)amino group of the azetidine **289** was *N*-deprotected by hydrogenolysis in the presence of $Pd(OH)_2/C$.[161] After precipitation in diethyl ether, the *trans*-3-(*N*-tosylamino)azetidine-2-carboxylic acid **290** was obtained in 92% yield. The hydrogenolysis of the *N*-(diphenylmethyl)amino group could be directly applied on the ethyl ester **288**, affording ethyl 3-(*N*-tosylamino)azetidine-2-carboxylate **291** in 87% yield, also after precipitation from diethyl ether.



Scheme 76

Furthermore, some efforts were made to cleave the *N*-tosyl group from *trans*-3-(*N*-tosylamino)azetidine-2-carboxylic ester **288** (Scheme 76, Table 3), unfortunately without success. In an initial attempt, treatment of azetidine **288** with Mg turnings in MeOH,[162,163] gave no reaction (Table 3, entry 1). When azetidine **288** was treated with sodium naphthalenide in THF at -78 °C (entry 2) or at -20 °C (entry 3),[164] no reaction occurred and the starting material was completely recovered. Performing this reaction at room temperature for 30 minutes led to a complex mixture of unidentified products (entry 4). Also treatment of azetidine **288** with lithium naphthalenide instead of sodium naphthalenide did not afford the detosylated azetidine **292** (entry 5).[165] The use of phenol and 48% HBr in H_2O (entry 6),[156,157,158,166] or the use of sodium amalgam and disodium hydrogen phosphate in dry methanol (entry 7),[167] 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 (entry 8),[168] failed also to deprotect azetidine **288**.

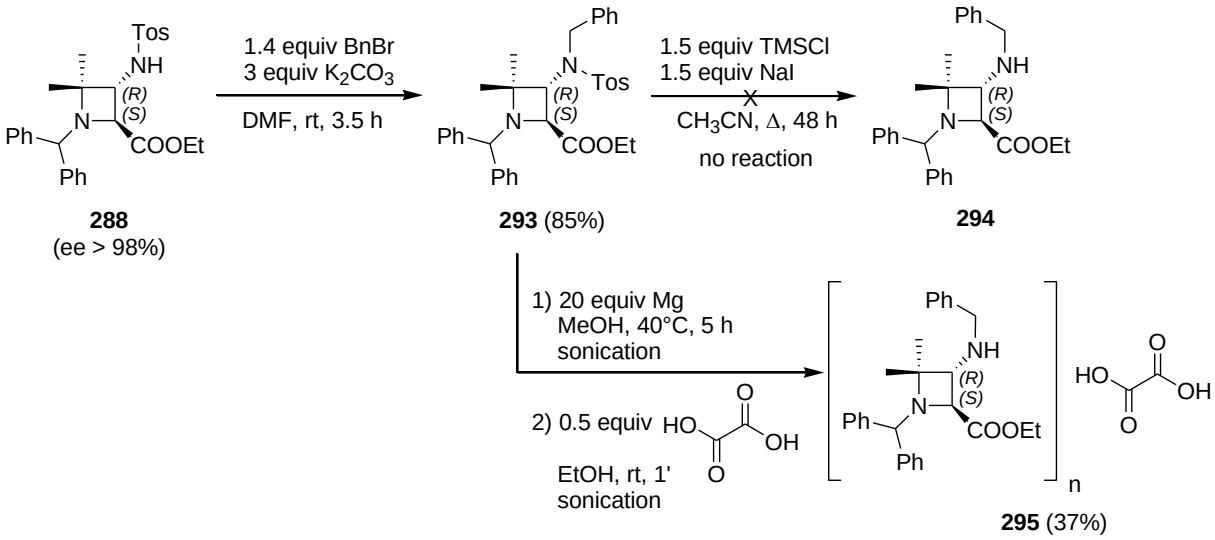
Table 3. Different attempts towards the synthesis of detosylated azetidine **292** from azetidine **288**

Entry	Solvent	Reagent	Temperature	Time	Result
1	MeOH	10 equiv Mg	rt	3 h	no reaction
2	THF	4 equiv Na 4.5 equiv naphthalene	-78 °C	1 h	no reaction
3	THF	4 equiv Na 4.5 equiv naphthalene	-78 °C -> -20 °C	1 h	no reaction
4	THF	4 equiv Na 4.5 equiv naphthalene	rt	0.5 h	decomposition
5	THF	14 equiv Li 0.04 equiv naphthalene	-78 °C	1 h	no reaction
6	HBr (48 % in H_2O)	10 equiv phenol	Δ	24 h	decomposition
7	MeOH	110% mass Na/Hg 5 equiv Na_2HPO_4	Δ	1 h	decomposition
8	CH_3CN	1.5 equiv NaI 1.5 equiv TMSCl	Δ	3 h	no reaction

The procedure for the deprotection of tertiary sulfonamides using TMSCl in the presence of NaI was reported as straightforward.[168] Following this strategy, azetidine **288** was *N*-benzylated with benzyl bromide in the presence of K_2CO_3 in DMF to afford azetidine **293** in 85% yield (Scheme 77).[169] Next, the *trans*-*N*-benzyl-*N*-tosylazetidine **293** was stirred under reflux for 48 hours with 1.5 equivalents TMSCl in the presence of 1.5 equivalents NaI, yet without formation of the *trans*-(3-*N*-benzylamino)azetidine **294**.

In accordance with literature procedures,[162,163] a final attempt was made by treatment of *trans*-*N*-benzyl-*N*-tosylazetidine **293** with Mg turnings in MeOH *via* sonication for five hours at 40 °C. This procedure afforded the detosylated *trans*-*N*-benzylazetidine **295** as the corresponding oxalate salt in diethyl ether (Scheme 77). Noteworthy, application of similar reaction conditions on the *trans*-*N*-tosylazetidine **288** failed to give any reaction. The fact that the

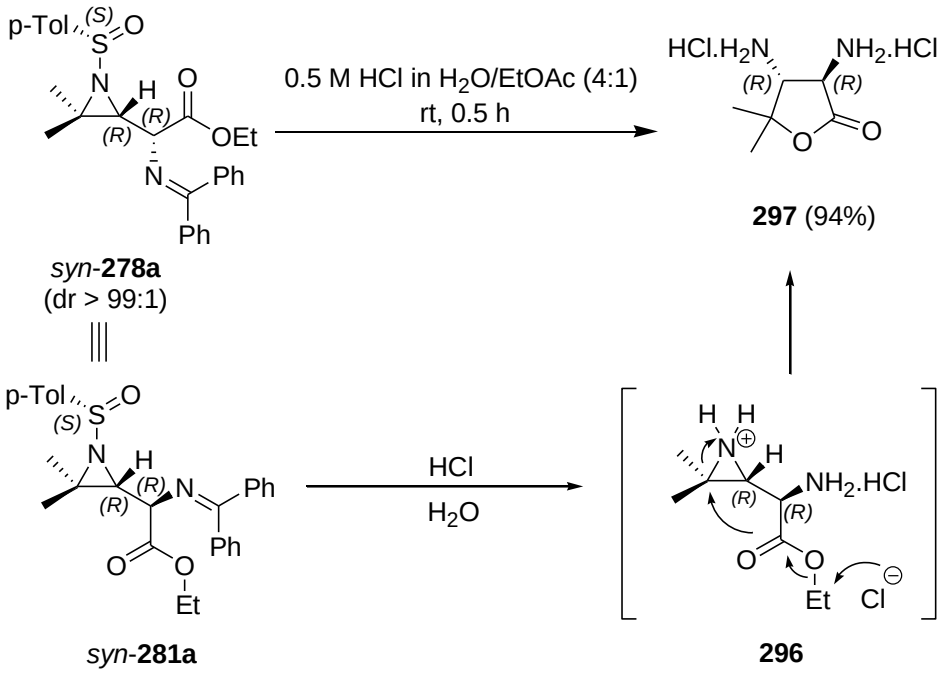
detosylation procedure with Mg turnings in MeOH was only suitable for tertiary sulfonamides and not for secondary sulfonamides could be explained by the presence of a moderately acidic proton in secondary sulfonamides that could be deprotonated by the produced methoxide anions, giving rise to the formation of the corresponding magnesium salts with a different reactivity.



288 (ee > 98%) **293** (85%) **294** **295** (37%)

Scheme 77

As the synthesis of the racemic *cis*-isomer of azetidine **288** starting from the *syn*-isomer of aziridine **286** was not possible, but racemic *syn*-aziridine could be transformed into a racemic α,β-diamino-γ-butyrolactone,[92] a similar ring transformation of *syn*-*N*-sulfinylaziridine *syn*-**278a** to chiral α,β-diamino-γ-butyrolactones was evaluated (Scheme 78).

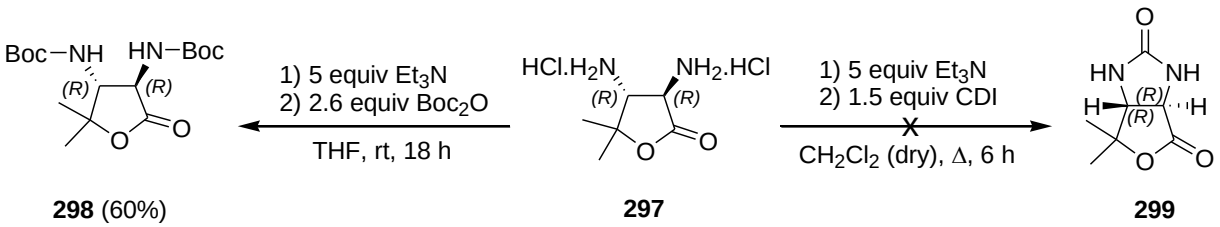


Scheme 78

By careful optimization of reaction conditions, (2*R*,3*R*)-2,3-diamino-4,4-dimethyl-butyrolactone **297** was prepared by treatment of aziridine *syn*-**278a** in 0.5 M HCl in H_2O/EtOAc for 30 minutes at room temperature in quantitative yield (Scheme 78). The optically pure lactone **297** could further be applied in the synthesis of new β-amino-substituted analogues of *N*-acyl homoserine lactones acting as quorum sensing interfering compounds.[170,171,172]

(2*R*,3*R*)-2,3-Diamino-4,4-dimethylbutyrolactone **297** was subsequently treated with different electrophiles. In a first reaction, the amino groups of the chiral α,β-diamino-γ-butyrolactone **297** were protected by reaction with 2.6 equivalents of Boc_2O in the presence of five equivalents of Et_3N in THF for 18 hours at room temperature (Scheme 79). The resulting double Boc-protected α,β-diamino-γ-butyrolactone **298** was obtained in 60% yield after flash chromatography on silica gel. In order to synthesize a bicyclic α,β-diamino-γ-butyrolactone **299**, the (2*R*,3*R*)-2,3-diamino-4,4-dimethylbutyrolactone **297** was treated with 1.5 equivalents of 1,1'-carbonyldiimidazole (CDI) in the presence of five equivalents of Et_3N for six hours in dry dichloromethane at reflux (Scheme 79). Unfortunately, application of these reaction

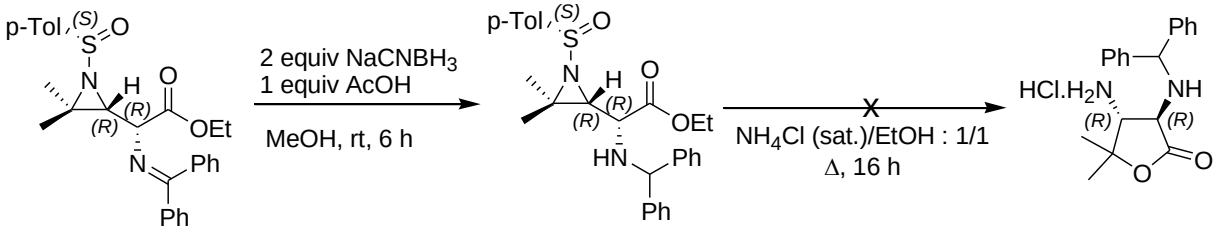
conditions failed to afford the desired bicyclic α,β-diamino-γ-butyrolactone **299** and only a complex reaction mixture was obtained according to ^{1}H NMR analysis.



298 (60%) **297** **299**

Scheme 79

In order to prepare an α,β-diamino-γ-butyrolactone which can be selectively protected/deprotected, the synthesis of *N*-(diphenylmethylamino)aziridine *syn*-**281** was performed as this was a potential precursor of the N^{α}-protected α,β-diamino-γ-butyrolactone **300**. Therefore, the diphenylmethylene group of *syn*-*N*-sulfinylaziridine *syn*-**278a** was first reduced with $NaCNBH_3$ in the presence of acetic acid in MeOH, which afforded the *N*-(diphenylmethylamino)aziridine *syn*-**281** in 71% yield after column chromatography on silica gel (Scheme 80). Unfortunately, the transformation of *N*-(diphenylmethylamino)aziridine *syn*-**281** towards N^{α}-protected α,β-diamino-γ-butyrolactone **300** by treatment in a 1:1 solvent mixture of NH_4Cl (sat.)/ethanol for 16 hours at reflux was not successful.

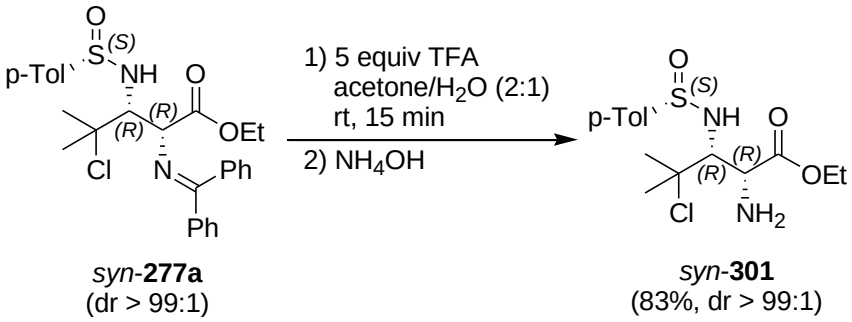


syn-**278a** (dr > 99:1) *syn*-**281** (71%, dr > 99:1) **300**

Scheme 80

Additionally, *syn*-γ-chloro-α,β-diamino ester *syn*-**277a** was subjected to a deprotection reaction by treatment with TFA as previously described for the deprotection of the *anti*-*N*-sulfinylaziridines *anti*-**278a**. Thus, *syn*-γ-chloro-α,β-diamino ester *syn*-**277a** was treated with five equivalents of trifluoroacetic acid in acetone/water (2:1) for 15 minutes (Scheme 81). Following basic workup with NH_4OH, the *syn*-γ-chloro-α,β-diamino ester *syn*-**301** was

isolated in 83% yield. The fact that the *N*-sulfinyl group was not removed under these conditions was remarkable, as the deprotection of *anti*-aziridine *anti*-**278a** under the same reaction conditions led to unprotected aziridine **280** (*vide supra*).



syn-**277a**
(dr > 99:1)

syn-**301**
(83%, dr > 99:1)

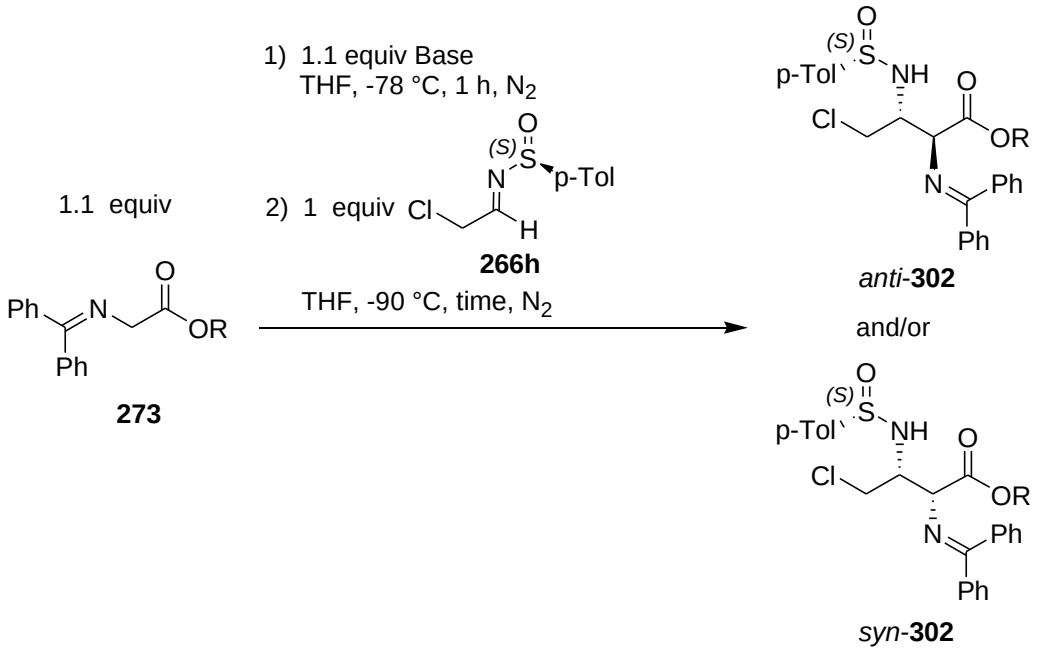
Scheme 81

Next to the Mannich-type addition of *N*-(diphenylmethylene)glycine esters **273** across chiral *N*-sulfinyl-α-chloroisobutyraldimine **266a**, the addition across *N*-sulfinyl-α-chloroacetaldimine **266h** was also investigated (Scheme 82).

In a first reaction (Table 4, entry 1), the Mannich-type addition was performed by deprotonation of ethyl glycinate **273a** for one hour at -78 °C using 1.1 equivalents of LDA followed by addition across chiral *N*-*p*-toluenesulfinyl-α-chloroacetaldimine **266h** for five minutes at -90 °C. ^{1}H NMR analysis of the crude reaction mixture indicated that the resulting γ-chloro-α,β-diamino ester *major*-**302a** was obtained with a moderate selectivity (dr = 74:26). After purification by tedious column chromatography, the Mannich-type adduct *major*-**302a** was isolated as one single diastereomer in 54% yield.

In the following reaction (entry 2), the Mannich-type addition was performed by deprotonation of ethyl glycinate **273a** for one hour at -78 °C using 1.1 equivalents of LiHMDS and subsequent reaction across chiral *N*-*p*-toluenesulfinyl-α-chloroacetaldimine **266h** for an additional hour at -90 °C. Based on the ^{1}H NMR spectrum of the crude reaction mixture, the resulting γ-chloro-α,β-diamino ester *major*-**302a** had the same stereochemistry as this obtained by reaction with LDA (entry 1). γ-Chloro-α,β-diamino ester *major*-**302a** was

obtained in a similar selectivity (dr = 77:23), and was again isolated as one single diastereomer in 59% yield by tedious column chromatography.



Scheme 82

Table 4. Addition of *N*-(diphenylmethylene)glycine esters **273** across *N*-*p*-toluenesulfinylimine **266h** producing *syn*- or *anti*-addition products **302**

Base	Time	R	*major*/*minor* ratio [a]	Yield (%)
LDA	5 min	Et	74:26	54 [b]
LiHMDS	1 h	Et	77:23	59 [b]
LiHMDS	5 min	Me	85:15	- [c]

[a] Determined *via* ^{1}H NMR of crude reaction mixtures
[b] Isolated yield of the single *major*-diastereomer **302a**
[c] Reaction mixture could not be purified

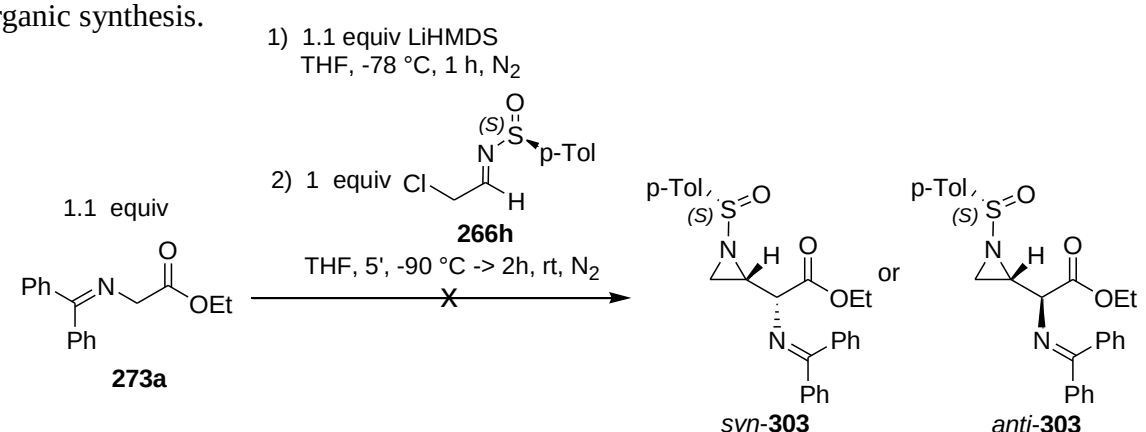
Repeating the reaction by deprotonation of methyl glycinate **273b** with 1.1 equivalents of LiHMDS for one hour at -78 °C (Table 4, entry 3) and subsequent reaction across chiral *N*-*p*-toluenesulfinyl-α-chloroacetaldimine **266h** for five minutes at -90 °C led to the formation of γ-chloro-α,β-diamino ester *major*-**302b** in a slightly improved diastereoselectivity (dr = 85:15), but efforts to purify the crude reaction mixture by column chromatography on silica gel failed to give the pure γ-chloro-α,β-diamino ester *major*-**302b**. Moreover, there was no influence of the used base, LiHMDS or LDA, on the diastereoselectivity of the Mannich-type

additions across chiral *N*-sulfinyl-α-chloroacetaldimine **266h**, in contrast to the great importance of the base in the synthesis of the γ-chloro-α,β-diamino pentanoates *syn*-**277** and *anti*-**277** (*vide supra*).

Unfortunately, neither the absolute nor the relative stereochemistry could unambiguously be determined by comparison of the ^{1}H NMR chemical shifts or the characteristic vicinal coupling constants of these γ-chloro-α,β-diamino esters *major*-**302** with the previously synthesized γ-chloro-α,β-diamino esters *syn*-**277** (*vide supra*). Furthermore, it was also impossible to determine the absolute stereochemistry of the *major*-adduct *major*-**302a** by means of an X-ray diffraction analysis as this compound was not crystalline.

In order to determine the absolute stereochemistry of the γ-chloro-α,β-diamino esters *major*-**302**, the direct preparation of the corresponding *N*-sulfinylaziridine **303** *via* a single-step reaction was investigated. The Mannich-type addition of the Li-enolate derived from ethyl glycinate **273a**, across imine **266h** was, after five minutes at -90 °C, stirred for an additional two hours at room temperature (Scheme 83). Unfortunately, this procedure, which was previously shown to afford *syn*-*N*-sulfinylaziridine *syn*-**278a**, gave only a complex reaction mixture.

Therefore, further investigation will be necessary to assign the absolute stereochemistry of these compounds *major*-**302** in order to use them as potential building blocks in asymmetric organic synthesis.



Scheme 83

In conclusion, it was demonstrated that new chiral *syn*- and *anti*-γ-chloro-α,β-diaminopentanoates were formed in high yield and excellent diastereomeric ratios *via* stereoselective Mannich-type reactions of *N*-(diphenylmethylene)glycine esters across a chiral *N*-*p*-toluenesulfinyl-α-chloroimine. The base used for the deprotonation of the glycine ester had a crucial influence on the diastereoselectivity of the Mannich-type reaction, with LDA leading selectively to *anti*-diastereomers, whereas the use of LiHMDS gave exclusively *syn*-diastereomers. The γ-chloro-α,β-diaminopentanoates 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 α,β-diamino-γ-butyrolactones. Unfortunately, the preparation of the corresponding γ-chloro-α,β-diaminobutanoates occurred only in moderate diastereoselectivities and the absolute stereochemistry of these derivatives remained unknown.

3.2.3. Synthesis and elaboration of γ-chloro-α-diphenylmethyleneamino-β-*tert*-butanesulfinylamino carboxylic acid derivatives

In addition to the stereoselective Mannich-type additions across (S_S)-*N*-*p*-toluenesulfinyl-α-chloroaldimine (S_S)-**266a** (*vide supra*), the synthesis of chiral α,β-diamino acid derivatives with the enantiotopic stereochemistry has also been explored *via* addition of *N*-(diphenylmethylene)glycine ester **273a** across (R_S)-*N*-*tert*-butanesulfinyl-α-chloroaldimines (R_S)-**270**. The choice for the (R_S)-*N*-*tert*-butanesulfinyl-α-chloroaldimines (R_S)-**270** was based on the high price of the (R_S)-*p*-toluenesulfinamide (456 £/5 g) in comparison with the price of the (R_S)-*tert*-butanesulfinamide (26 £/5 g),[173] and also on the fact that the *tert*-butanesulfinyl group can be readily deprotected.

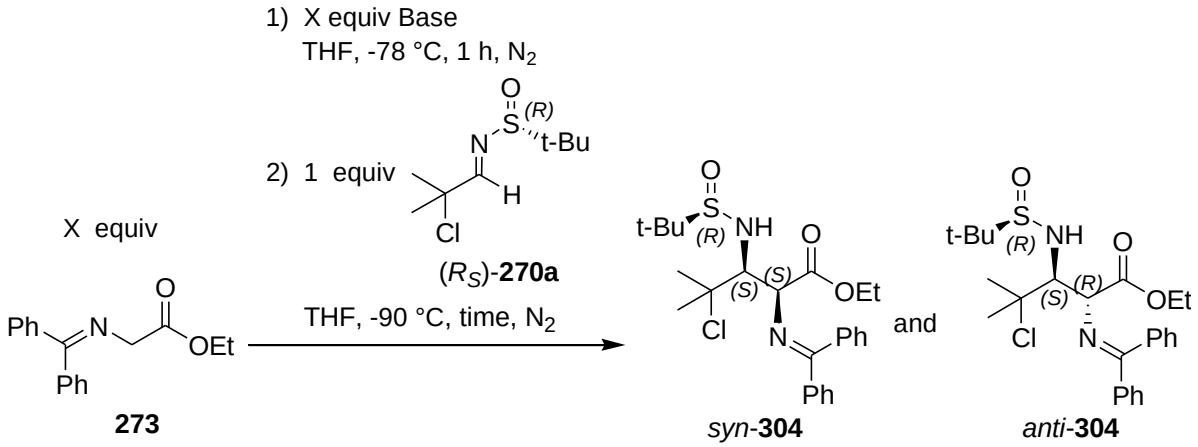
The Mannich-type addition was performed by systematically changing the reaction conditions for the synthesis of γ-chloro-α,β-diamino esters **304** (Scheme 84, Table 5). It was found that

the base, LDA or LiHMDS, used for the deprotonation of the glycine ester **273a**, had again a great influence on the *syn*- or *anti*-selectivity of this reaction (Table 5). In a first reaction (Table 5, entry 1), the Mannich-type addition of ethyl glycinate **273a** across chiral *N*-*tert*-butanesulfinyl-α-chloroisobutyraldimine (R_S)-**270a** was performed for five minutes at -90 °C using 1.1 equivalents of LiHMDS. ^{1}H NMR analysis of the crude reaction mixture indicated that the resulting *syn*-γ-chloro-α,β-diamino ester *syn*-**304** was formed with a good *syn*-selectivity, but no full conversion of the starting imine (R_S)-**270a** was obtained (ratio (R_S)-**270a**/*syn*-**304**/*anti*-**304** = 19:73:8). The *syn*-adduct *syn*-**304** was isolated as a single diastereomer in a yield of 54% after purification by column chromatography and subsequent recrystallization in diethyl ether. Repeating the reaction with LiHMDS for prolonged reaction times (15 to 90 minutes) led again to the formation of *syn*-γ-chloro-α,β-diamino ester *syn*-**304**, but surprisingly more starting product was recovered at longer reaction times (entries 2 and 4). Unfortunately, also performing the reaction with 1.6 equivalents of the Li-enolate for 15 minutes at -90 °C (entry 3) did not result in higher conversions of the starting material. These remarkable results whereby prolonged reaction times were leading to lower conversions of the starting *N*-*tert*-butanesulfinyl-α-chloroisobutyraldimine (R_S)-**270a** could be explained by the fact that Mannich-type addition across this *N*-*tert*-butanesulfinylimine (R_S)-**270a** was probably more susceptible for a retro-Mannich-type reaction. Noteworthy, the diastereoselectivity of the reaction decreased also at prolonged reaction times (Table 5), which could be an indication that the *syn*-γ-chloro-α-diphenylmethyleneamino-β-*tert*-butanesulfinylamino ester *syn*-**304** was not the thermodynamically favoured reaction product, which was the case for the *syn*-γ-chloro-α-diphenylmethyleneamino-β-*p*-toluenesulfinylamino esters *syn*-**277** (*vide supra*).

In the following reaction (entry 5), the Mannich-type addition was performed for five minutes at -90 °C with 1.1 equivalents of LDA, resulting in a low conversion towards *anti*-γ-chloro-

α,β-diamino ester *anti*-**304** accompanied by a large recovery of the starting imine (R_S)-**270a** (ratio (R_S)-**270a**/*syn*-**304**/*anti*-**304** = 64:7:29). In order to improve the conversion towards *anti*-**304**, the reaction was performed for 15 minutes at -90 °C using 1.1 equivalents of LDA (entry 6). These conditions led to a slightly better conversion (ratio (R_S)-**270a**/*syn*-**304**/*anti*-**304** = 41:13:46), and *anti*-γ-chloro-α,β-diamino ester *anti*-**304** was obtained in 22% yield as a single diastereomer (as partially characterized by ^{1}H NMR analysis) after purification by column chromatography. Unfortunately, the prolongation of the reaction time to 90 minutes at -90 °C using 1.1 equivalents of LDA (entry 7), failed again to give a higher conversion towards the *anti*-adduct *anti*-**304**.

Hereby, the assignment for the *syn*- and *anti*-stereochemistry of the Mannich-type addition products **304** was based on a comparison of analytical data with a combination of analogous ^{1}H NMR chemical shifts ($H_{\beta,syn}$: δ = 4.12 ppm, $H_{\beta,anti}$: δ = 3.69 ppm) and the characteristic vicinal coupling constants ($^3J_{H\alpha\text{-}H\beta,syn}$ = 0 Hz, $^3J_{H\alpha\text{-}H\beta,anti}$ = 3.3 Hz) of the previously described *syn*- and *anti*-γ-chloro-α-diphenylmethyleneamino-β-*p*-toluenesulfinylamino esters **277** (*vide supra*).



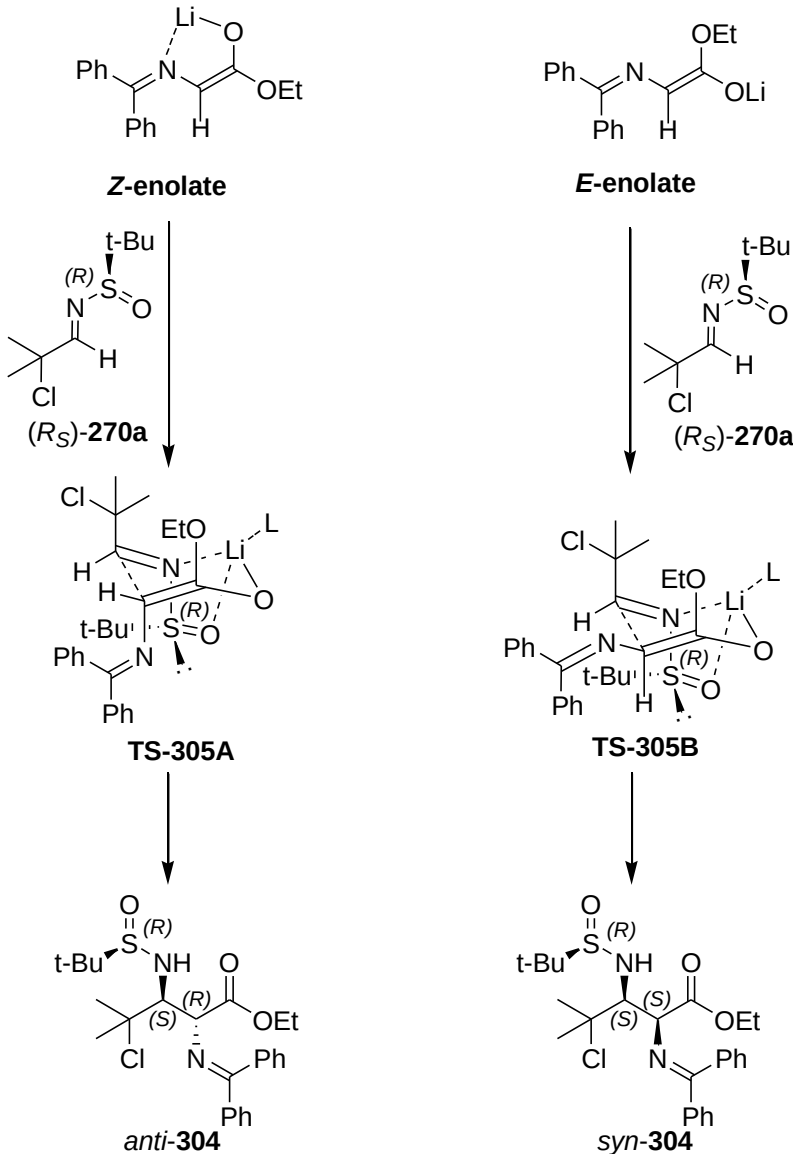
Scheme 84

Table 5. Addition of *N*-(diphenylmethylene)glycine ester **273a** across *N*-*tert*-butanesulfinylimine (R_S)-**270a** producing *syn*- and *anti*-addition products **304**

Entry	X	Base	Time (min)	(R_S)-**270a**/*syn*-**304**/*anti*-**304**[a]	Yield (Product)
1	1.1	LiHMDS	5	19:73:8	54% (*syn*-**304**)[b]
2	1.1	LiHMDS	15	24:57:19	-[c]
3	1.6	LiHMDS	15	23:54:23	-[c]
4	1.1	LiHMDS	90	34:29:37	-[c]
5	1.1	LDA	5	64:7:29	-[c]
6	1.1	LDA	15	41:13:46	22% (*anti*-**304**)[b]
7	1.1	LDA	90	52:13:35	-[c]

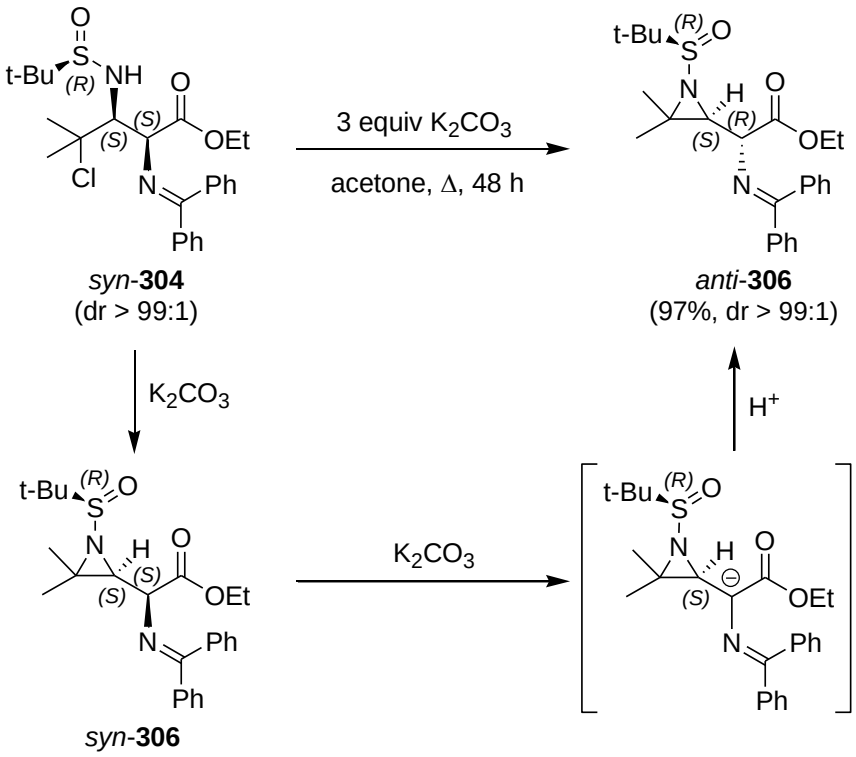
[a] Ratio determined *via* ^{1}H NMR of crude reaction mixtures
[b] Isolated yield of the single diastereomer (dr > 99:1)
[c] Reaction mixture was not purified

The great influence of the used base, LDA or LiHMDS (Scheme 84), on the stereochemical outcome of the Mannich-type reaction across *N*-*tert*-butanesulfinyl-α-chloroimine (R_S)-**270a** was again rationalized on the basis of the enolate geometry of the anions derived from the deprotonation of *N*-(diphenylmethylene)glycine ester **273a**. As previously described, the enolates obtained *via* deprotonation of *N*-(diphenylmethylene)glycine ester **273a** with LDA were expected to have the *Z*-geometry, whereas deprotonation with the less basic LiHMDS in THF would afford the *E*-enolate (*vide supra*). Reaction of the *Z*- and *E*-enolates *via* **TS-305A** and **TS-305B** (Scheme 85) resulted in the formation of *anti*-**304** and *syn*-**304**, respectively.



Scheme 85

The *syn*-addition product *syn*-**304** was subsequently cyclized to the corresponding *N*-sulfinylaziridine *anti*-**306** in excellent yield (97%) upon treatment with K_2CO_3 for 48 hours in acetone under reflux (Scheme 86). The fact that treatment of *syn*-addition product *syn*-**304** under the latter conditions did not afford the corresponding *syn*-*N*-sulfinylaziridine *syn*-**306** showed that a base-induced isomerization in α-position occurred, which resulted in the thermodynamically controlled formation of the *anti*-*N*-sulfinylaziridine *anti*-**306**.



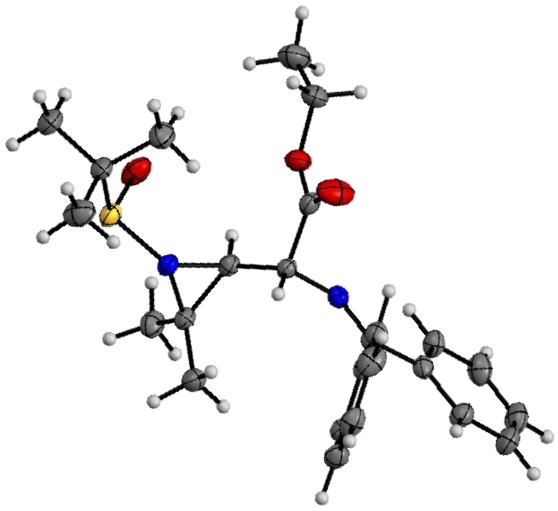
syn-**304**
(dr > 99:1)

anti-**306**
(97%, dr > 99:1)

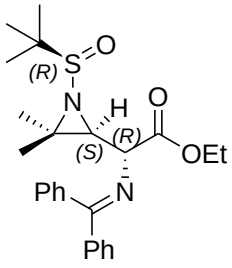
syn-**306**

Scheme 86

The absolute stereochemistry of this *N*-*tert*-butanesulfinylaziridine *anti*-**306** was elucidated by means of an X-ray diffraction analysis (in collaboration with Prof. R. Sillanpää, Department of Chemistry, University of Jyväskylä, Finland) (Figure 9),[171] and showed that the aziridine *anti*-**306** had an (R_S,2*R*,2'*S*)-stereochemistry.



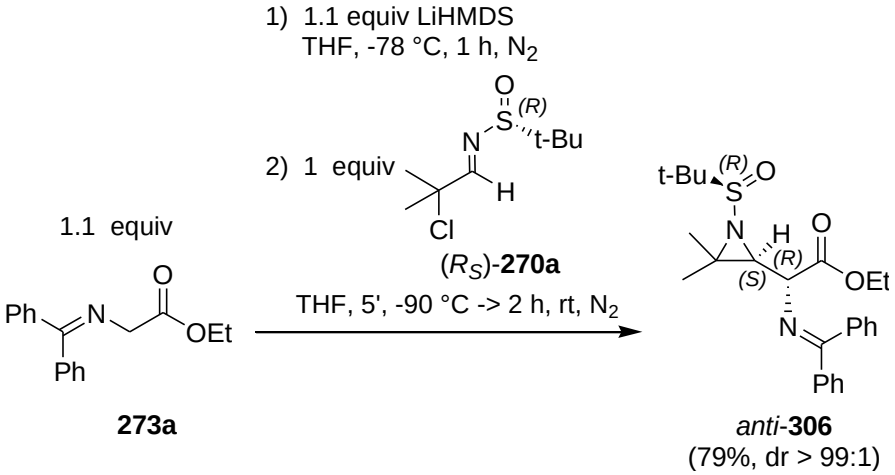
(*ref 170*)



anti-**306**

Figure 9. X-ray diffraction analysis of *anti*-*N*-sulfinylaziridine *anti*-**306**

In addition, this *anti*-*N*-sulfinylaziridine *anti*-**306** could also be prepared directly in 79% yield *via* a single-step reaction starting from ethyl glycinate **273a**, if the reaction mixture from the Mannich-type addition across imine (R_S)-**270a** after five minutes at -90 °C was subsequently stirred for two hours at room temperature (Scheme 87). As this procedure resulted as well in the synthesis of *anti*-aziridine *anti*-**306**, it could be concluded that *anti*-**306** was the thermodynamically controlled diastereomer. The fact that the *N*-*p*-toluenesulfinylaziridine **278** did not gave the *anti*-isomers, but the *syn*-isomers as the thermodynamically favored diastereomers, could be explained by the stabilizing effect of the π-π-stacking between the *N*-*p*-toluenesulfinyl group and a phenyl group of the benzophenone imine functionality. The characteristic ^{1}H NMR chemical shift of the *para*-methyl group of the *N*-*p*-toluenesulfinyl functionality ($C_{arom}CH_{3,syn}$: δ = 1.95 ppm, $C_{arom}CH_{3,anti}$: δ = 2.33-2.36 ppm) suggested this as well, as the π-π-stacking induced a shielding effect at the *para*-methyl group, which was accompanied by a upfield shift of this group.



Scheme 87

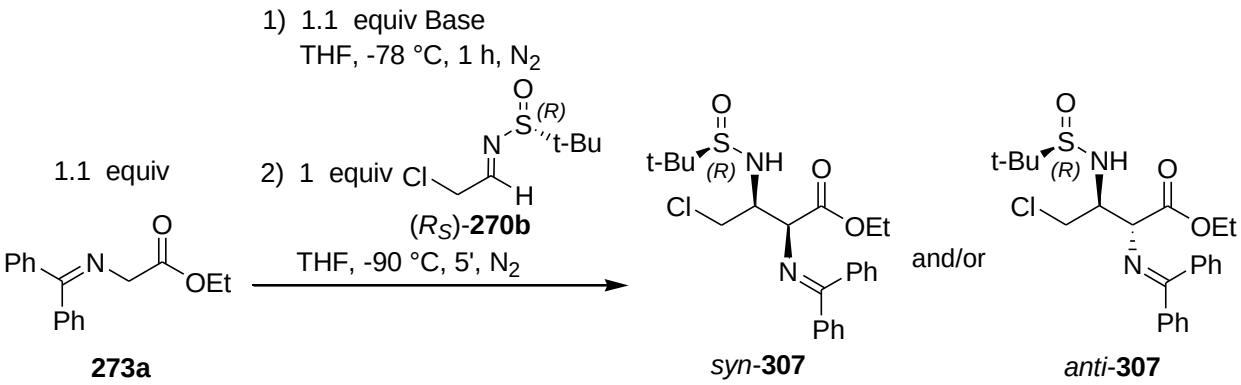
Next to the Mannich-type addition of *N*-(diphenylmethylene)glycine esters **273** across chiral *N*-*tert*-butanesulfinyl-α-chloroisobutyraldimine (R_S)-**270a**, the addition across chiral *N*-*tert*-butanesulfinyl-α-chloroacetaldimine (R_S)-**270b** was also investigated (Scheme 88).

In a first reaction (Table 6, entry 1), the Mannich-type addition was performed by deprotonation of ethyl glycinate **273a** for one hour at -78 °C using 1.1 equivalents of LiHMDS and subsequent reaction across *N*-*tert*-butanesulfinyl-α-chloroacetaldimine (R_S)-**270b** for five minutes at -90 °C. ^{1}H NMR analysis of the crude reaction mixture indicated that the resulting γ-chloro-α,β-diamino ester *major*-**307** was obtained with good selectivity (dr = 84:16). After purification by column chromatography, the Mannich-type adduct *major*-**307** was isolated in 79% yield.

In the following reaction (entry 2), the Mannich-type addition was performed by deprotonation of ethyl glycinate **273a** for one hour at -78 °C using 1.1 equivalents of LDA and subsequent reaction across *N*-*tert*-butanesulfinylimine (R_S)-**270b** for five minutes at -90 °C. According to the ^{1}H NMR spectrum of the crude reaction mixture, the resulting γ-chloro-α,β-diamino ester *major*-**307** was the same product as that obtained by reaction with LiHMDS (entry 1), similar to the results obtained for the previously described γ-chloro-α-diphenylmethyleneamino-β-*p*-toluenesulfinylamino esters **302** (*vide supra*). The γ-chloro-α,β-diamino ester *major*-**307** was obtained with a slightly lower diastereoselectivity (dr = 72:28), and was isolated in 56% yield after column chromatography.

In accordance with the synthesis of γ-chloro-α-diphenylmethyleneamino-β-*p*-toluenesulfinylamino esters **302** (*vide supra*), there was no influence of the used base, LiHMDS or LDA, on the diastereoselectivity of the Mannich-type additions across chiral *N*-*tert*-butanesulfinylimine (R_S)-**270b**.

Furthermore, the absolute or the relative stereochemistry of *major*-**307** could not be determined by analysis of the ^{1}H NMR chemical shifts or the characteristic vicinal coupling constants and X-ray diffraction analysis was not possible, since this compound *major*-**307** was not crystalline.



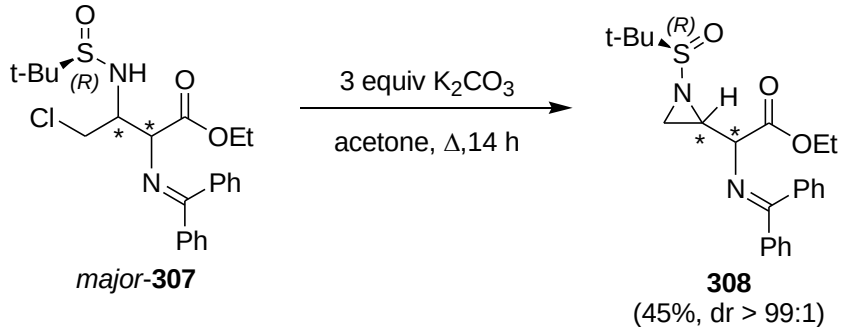
Scheme 88

Table 6. Addition of *N*-(diphenylmethylene)glycine ester **273a** across *N*-*tert*-butanesulfinylimine (R_S)-**270b** producing *syn*- or *anti*-addition products **307**

Base	*major*/*anti* ratio [a]	Yield (%) [b]
LiHMDS	84:16	79
LDA	72:28	56

[a] Determined *via* ^{1}H NMR of crude reaction mixtures
[b] Isolated yield of single diastereomer (dr > 99:1)

The *major*-addition product *major*-**307** was subsequently cyclized to the corresponding *N*-sulfinylaziridine **308** in 45% yield upon treatment with K_2CO_3 for 14 hours in acetone under reflux (Scheme 89). Unfortunately, the synthesis of this aziridine **308** did not offer the possibility to assign the absolute or relative stereochemistry.



Scheme 89

In conclusion, it was demonstrated that new enantiopure *syn*- and *anti*-γ-chloro-α,β-diamino-pentanoates were formed in moderate yields *via* stereoselective Mannich-type reactions of the ethyl *N*-(diphenylmethylene)glycine ester across a chiral *N*-*tert*-butanesulfinyl-α-chloroimine. These lower yields were caused by the low conversions of the chiral *N*-*tert*-butanesulfinyl-α-

chloroimine to the corresponding *syn*- and *anti*-γ-chloro-α,β-diaminopentanoates, probably due to retro-Mannich-type addition. The base used for the deprotonation of the glycine ester had again a great 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. Furthermore, the *syn*-γ-chloro-α,β-diaminopentanoate was selectively transformed into a new *anti*-β,γ-aziridino-α-amino ester, whose structure was unambiguously determined by means of X-ray diffraction analysis. The preparation of the corresponding γ-chloro-α,β-diaminobutanoate occurred in better yield and good diastereoselectivity and this compound was also transformed into the corresponding β,γ-aziridino-α-amino ester. Unfortunately, the stereochemistry of these derivatives could not be revealed.

3.3. Asymmetric synthesis of α,β-diaminoacylpyrrolidines and -piperidines *via* stereoselective Mannich-type additions across *N*-sulfinyl-α-chloroimines

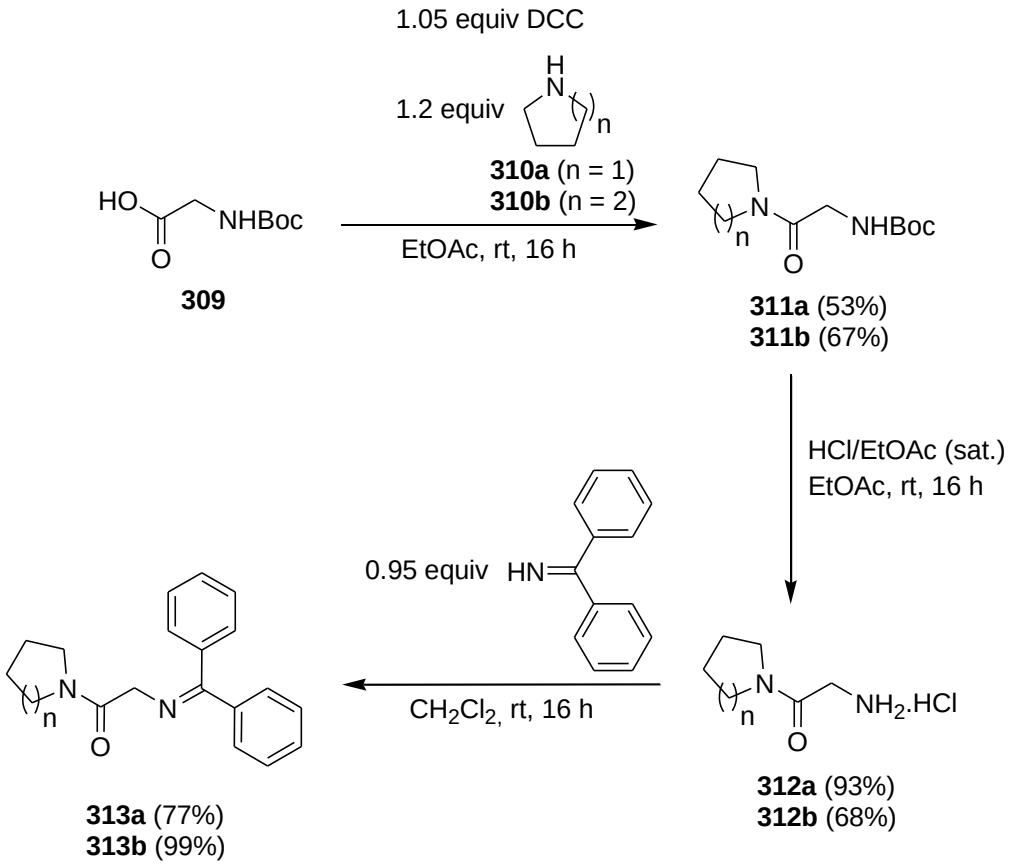
Given the fact that α,γ-diamino carboxylic amides, as well as β-amino carboxylic amides, are known for their activity as dipeptidyl peptidase (DPP) inhibitors, there is an increasing interest to study the DPP inhibitory potency of analogous α,β-diamino carboxylic amides.[31] The synthesis of chiral α,β-diamino carboxylic acid derivatives *via* asymmetric Mannich-type addition of enolates across activated imines, *e.g*. *N*-sulfinylimines,[156,157,174,175] is one of the most common and versatile methods in organic chemistry and has continuously been under development.[10,11] The asymmetric synthesis of new chiral γ-chloro-α,β-diamino carboxylic esters *via* highly diastereoselective Mannich-type reactions across the chiral *N*-*p*-toluenesulfinyl-α-chloroimine has previously been described (*vide supra*), however, transformation of these γ-chloro-α,β-diamino carboxylic esters into the corresponding carboxylic acids, en route to further coupling to carboxylic amides, has not been investigated

because these diamino acid derivatives are prone towards ring transformation to α,β-diamino-γ-butyrolactones.

In the following part, the synthesis and elaboration of chiral *syn*-γ-chlorinated-α,β-diamino carboxylic amide derivatives with excellent diastereoselectivity will be demonstrated. In order to develop potential DPP inhibitors, the ring closure and deprotection of the α-amino functionality of the synthesized γ-chloro-α,β-diamino carboxylic amides were explored as well.

3.3.1. Synthesis of *N*-(diphenylmethylene)glycine amides

The synthesis of *N*-(diphenylmethylene)glycine amides **313** was performed starting from *N*-Boc-glycine **309**, in accordance with literature procedures.[176] Activation of *N*-Boc-glycine by *N*,*N*'-dicyclohexylcarbodiimide (DCC) and subsequent addition of a cyclic amine **310** resulted in the formation of the corresponding *N*-Boc-glycine amides **311** (Scheme 90).



Scheme 90

Subsequent *N*-Boc-deprotection of the amides **311** by treatment with a saturated HCl/EtOAc solution afforded the glycine amide hydrochloric acid salts **312** (68-93% yield). Reaction of these glycine amide salts **312** with 0.95 equivalents of benzophenone imine for 16 hours in dichloromethane at room temperature resulted in the desired *N*-(diphenylmethylene)glycine amides **313** in high yields (77-99%).

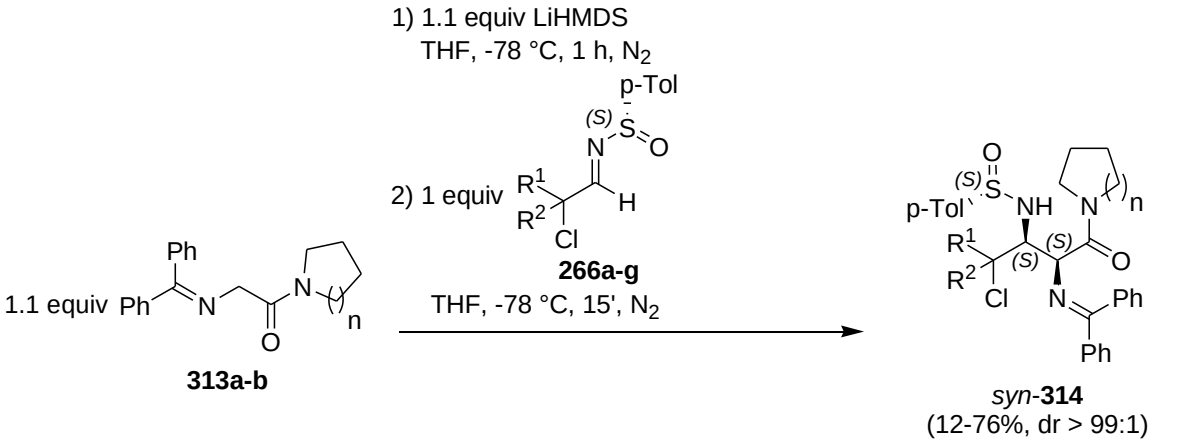
3.3.2. Synthesis and elaboration of γ-chloro-α,β-diamino carboxylic amide derivatives

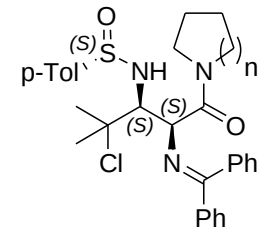
The stereoselective synthesis of chiral γ-chloro-α,β-diamino carboxylic amides was performed using a Mannich-type addition of glycine amides **313** across chiral *N*-sulfinyl-α-chloroimines **266**.

Based on the previously reported Mannich-type addition of glycine esters across chiral *N*-*p*-toluenesulfinyl-α-chloroaldimine **266a** (*vide supra*), the influence of the base (LiHMDS or LDA) used for the deprotonation of glycine amides **313a-b** on the *syn*- or *anti*-selectivity of the Mannich-type addition was investigated (Scheme 91).

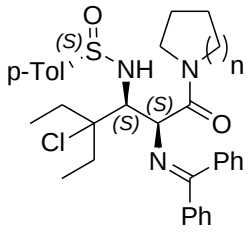
Initially, the Mannich-type addition of glycine amide **313b** across chiral *N*-*p*-toluenesulfinyl-α-chloroisobutyraldimine **266a** was performed at -78 °C using 1.1 equivalents of LDA. According to the ^{1}H NMR analysis of the crude reaction mixture, the resulting *syn*-γ-chloro-α,β-diamino carboxylic amide *syn*-**314b** was formed with an excellent stereoselectivity (dr > 99:1), yet in rather low conversion. After crystallization, the *syn*-adduct *syn*-**314b** was isolated in a low yield of 16%. Repeating the Mannich-type addition of glycine amides **313** across chiral *N*-*p*-toluenesulfinyl-α-chloroaldimines **266** with 1.1 equivalents of LiHMDS resulted also in the formation of *syn*-γ-chlorinated-α,β-diamino carboxylic amides *syn*-**314** with an excellent stereoselectivity (dr > 99:1). The conversion of the substrates was complete under these reaction conditions (-78 °C, 15 minutes), and the *syn*-adducts *syn*-**314** were isolated in 12-76% yield after recrystallization. The diastereomeric ratio of these *syn*-γ-chlorinated-α,β-

diamino carboxylic amides *syn*-**314** (dr > 99:1) was determined by means of ^{1}H NMR, ^{13}C NMR and HPLC analysis where no signals from other diastereomers could be detected.

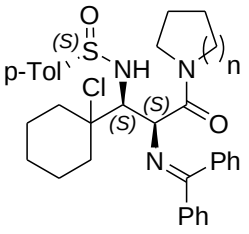




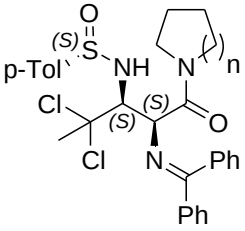
syn-**314a** (n = 1), 57%
syn-**314b** (n = 2), 71% (16%)[a]



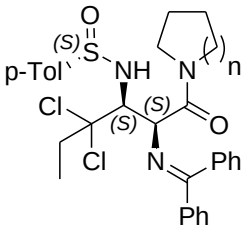
syn-**314c** (n = 1), 41%
syn-**314d** (n = 2), 65%



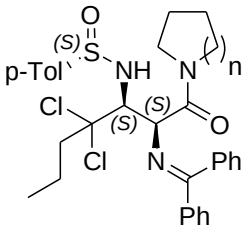
syn-**314e** (n = 1), 59%
syn-**314f** (n = 2), 73%



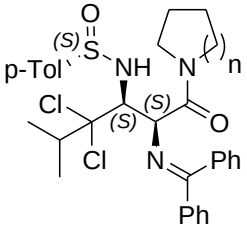
syn-**314g** (n = 1), 12%
syn-**314h** (n = 2), 55%



syn-**314i** (n = 1), 44%
syn-**314j** (n = 2), 70%



syn-**314k** (n = 1), 23%
syn-**314l** (n = 2), 39%



syn-**314m** (n = 1), 43%
syn-**314n** (n = 2), 76%

[a] Yield in parentheses result from the use of LDA instead of LiHMDS

Scheme 91

In contrast to the Mannich-type addition of glycine esters **273** across chiral *N*-*p*-toluenesulfinyl-α-chloroimine **266a** (*vide supra*), the diastereoselectivity of the Mannich-type addition of glycine amides **313** across chiral *N*-*p*-toluenesulfinyl-α-chloroaldimines **266a-g** was independent of the choice of the base used. The absolute stereochemistry of γ-chloro-α,β-diamino carboxylic amides *syn*-**314a-f** and γ,γ-dichloro-α,β-diamino carboxylic amides *syn*-**314g-n** was unambiguously determined by means of X-ray diffraction analysis of compounds

syn-**314b** and *syn*-**314h** (in collaboration with Prof. K. W. Törnroos, Department of Chemistry, University of Bergen, Norway), respectively (Figure 10). Additionally, analogous ^{1}H NMR chemical shifts (H_{α}: $\delta = 4.91\text{-}5.25$ ppm, H_{β}: $\delta = 3.74\text{-}4.25$ ppm) and the characteristic vicinal coupling constants ($^{3}J_{H\alpha\text{-}H\beta}$ = 0-1.1 Hz) of all derivatives *syn*-**314a-n** pointed out the (S_S,2*S*,3*S*)-stereochemistry.

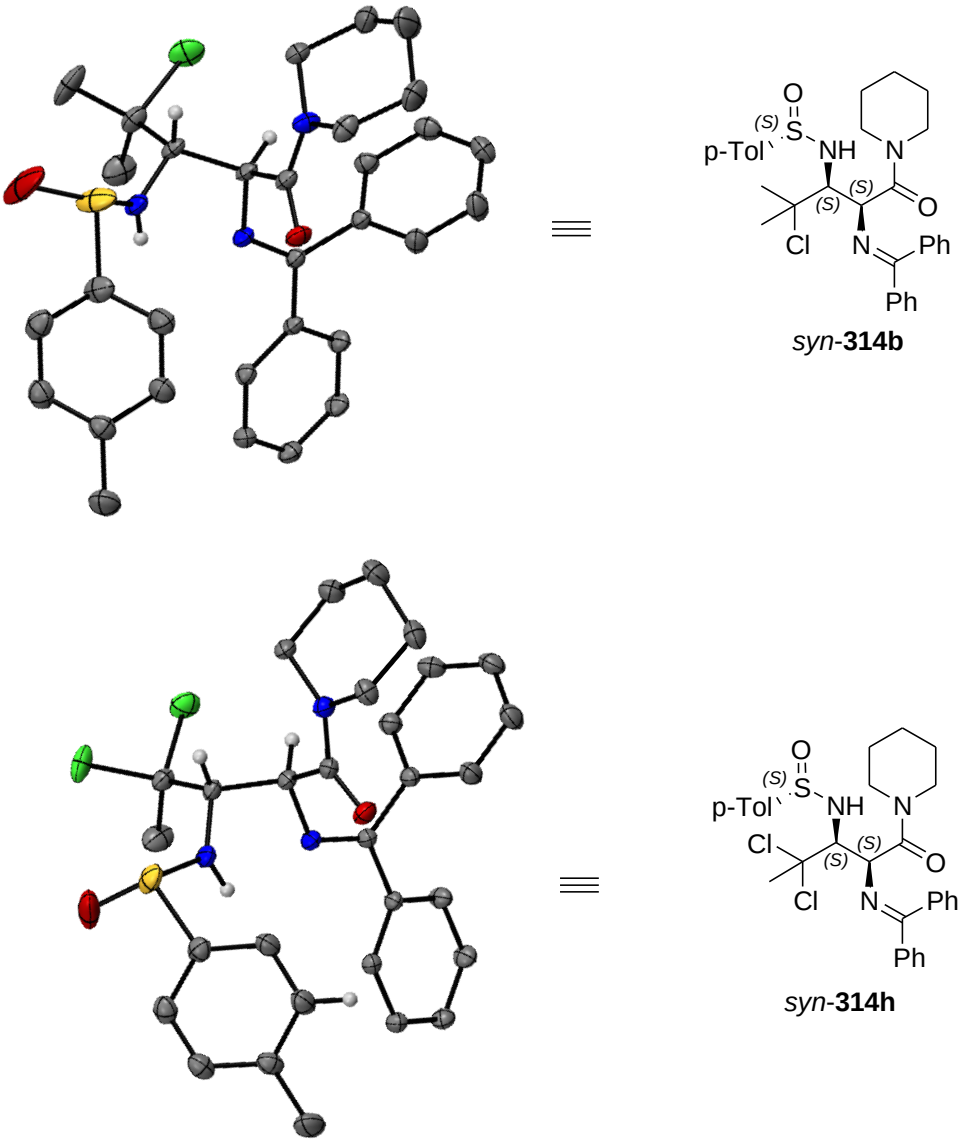
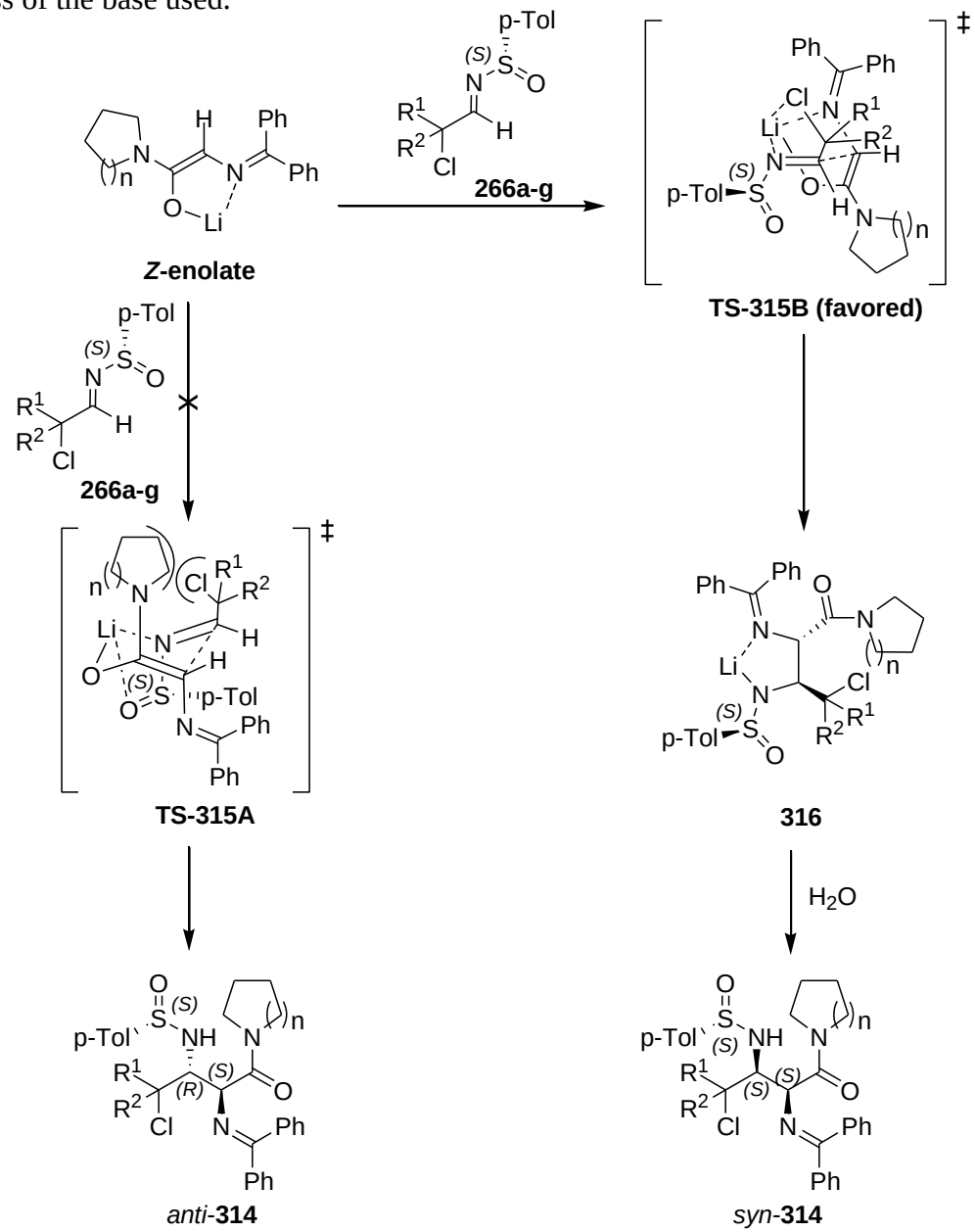


Figure 10. Crystal structures of (S_S,2*S*,3*S*)-γ-chlorinated-α,β-diamino carboxylic amides *syn*-**314b** and *syn*-**314h**

The vicinal coupling constant $^{3}J_{H\alpha\text{-}H\beta}$ = 0-1.1 Hz for the *syn*-amides **314** had a comparable small value as the observed vicinal coupling constant $^{3}J_{H\alpha\text{-}H\beta}$ of the closely related *syn*-γ-

chloro-α,β-diamino carboxylic esters ($^3J_{H\alpha\text{-}H\beta}$ = 1.1 Hz). Notably, the (*S*$_S$,2*S*,3*S*)-γ-chlorinated-α,β-diamino carboxylic amides *syn*-**314** were obtained with the opposite enantioselectivity as compared to the (*S*$_S$,2*R*,3*R*)-γ-chloro-α,β-diamino carboxylic esters *syn*-**277** obtained *via* Mannich-type addition of *E*-enolates derived from glycine esters **273** across imine **266a** (*vide supra*). The monosubstituted tertiary amide enolates obtained via deprotonation of *N*-(diphenylmethylene)glycine amides **313** were expected to have the *Z*-geometry in which A(1,3) interactions were minimized and Li-chelation stabilizes the conformation (Scheme 92), regardless of the base used.[177]



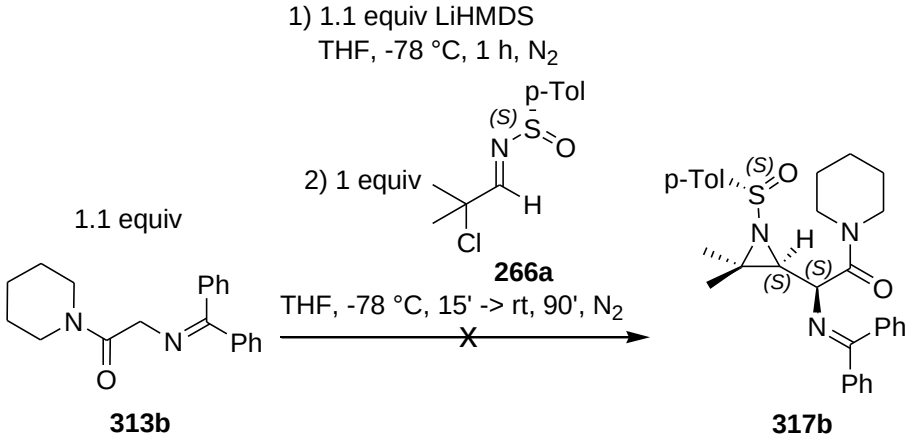
Scheme 92

Reaction of the *Z*-enolates *via* a cyclic chelated six-membered chairlike transition state model **TS-315A**, would have resulted in *anti*-addition products *anti*-**314** in analogy with the previously obtained results on the synthesis of (S_S,2*S*,3*R*)-γ-chloro-α,β-diamino carboxylic esters (*vide supra*). However, starting from glycine amides **313**, due to the important 1,3-diaxial interaction between the haloalkyl group (-CClR^{1}R^2) and the cyclic amine moiety [-N(CH$_2$)$_n$(CH$_2$)$_3$] in this transition state, **TS-315A** was highly disfavoured. The formation of the (S_S,2*S*,3*S*)-γ-chlorinated-α,β-diamino carboxylic amides *syn*-**314** could be explained by a boatlike transition state model **TS-315B** involving the (*E*)-*N*-*p*-toluenesulfinylaldimines **266a-g**.[91,178] This less sterically hindered transition state **TS-315B** in which the haloalkyl group (-CClR^{1}R^2) occupied the less hindered pseudoequatorial position and the corresponding Li-adduct **316**, were stabilized by the interaction between the Li-cation, the diphenylmethyleneamino group and the sulfinylimine nitrogen.

The reversal of the enantiotopic face selectivity in the reaction of the *N*-sulfinyl imines **266a-g** with the glycine amides **313**, as compared to the reaction with glycine esters **273**, was attributed to the α-coordinating ability of the chlorine atom with the lithium of the incoming enolate as depicted in transition state **TS-315B**. The coordinating α-chloro atom in **TS-315B** overrode the chelation of the sulfinyl oxygen (e.g. **TS-315A**) and allowed the sulfinylimine to react in the conformation wherein the S=O bond and the lone pair of electrons on the nitrogen atom were anti-periplanar.[179] This reversal of stereoselectivity was analogous to results obtained with other *N*-*p*-toluenesulfinyl imines containing an oxygen atom as α-coordinating group.[34,180]

In a next attempt, the direct preparation of the corresponding *N*-sulfinyl-β,γ-aziridino-α-amino carboxylic amide **317b** was evaluated *via* a single-step reaction. Thus, the reaction mixture from the Mannich-type addition of the Li-enolate derived from amide **313b**, across imine **266a** was after 15 minutes at -78 °C additionally stirred for 90 minutes at room temperature

(Scheme 93). Unfortunately, this procedure proved to be unsuccessful for the preparation of *syn*-*N*-sulfinylaziridine **317b** and afforded only a complex reaction mixture.



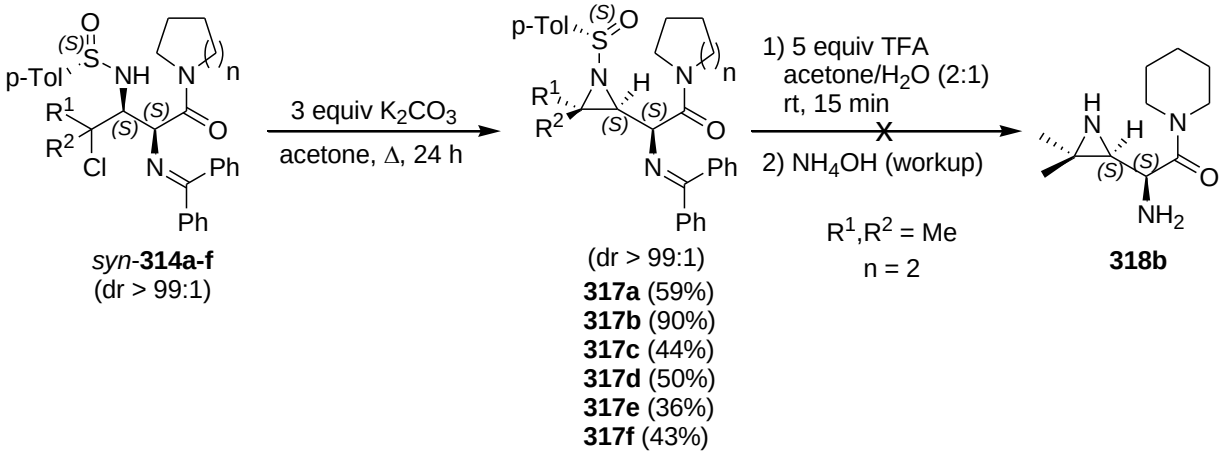
Scheme 93

Next, the *syn*-addition products *syn*-**314** were cyclized to the corresponding *N*-sulfinyl-β,γ-aziridino-α-amino carboxylic amides **317** upon treatment with K_2CO_3 in acetone under reflux in a moderate to very good yield (36-90%) (Scheme 94).

The conversion of the ring-closure reaction was always complete as determined by TLC analysis, but purification of these *N*-sulfinyl-β,γ-aziridino-α-amino carboxylic amides **317** by flash chromatography resulted in a considerable loss of product.

In order to extend the potential applicability of the synthesized *N*-sulfinyl-β,γ-aziridino-α-amino carboxylic amides **317** as building blocks in biomedicinal chemistry, some attempts were made to remove the *N*-protective groups of diamino carboxylic amides **317** under mild acidic conditions (Scheme 94). In analogy with the previously described results on the corresponding aziridino esters **280** (*vide supra*), amide **317b** was treated with five equivalents of trifluoroacetic acid in acetone/water (2:1) at room temperature for 15 minutes. After a basic workup with NH_4OH, it was concluded that the conversion towards the *N*-deprotected *syn*-β,γ-aziridino-α-amino carboxylic amide **318b** was complete, based on ^{1}H NMR and LC-MS analysis of the crude reaction mixture. Unfortunately, all attempted purification techniques (column chromatography, preparative TLC, acid-base extraction) in order to remove

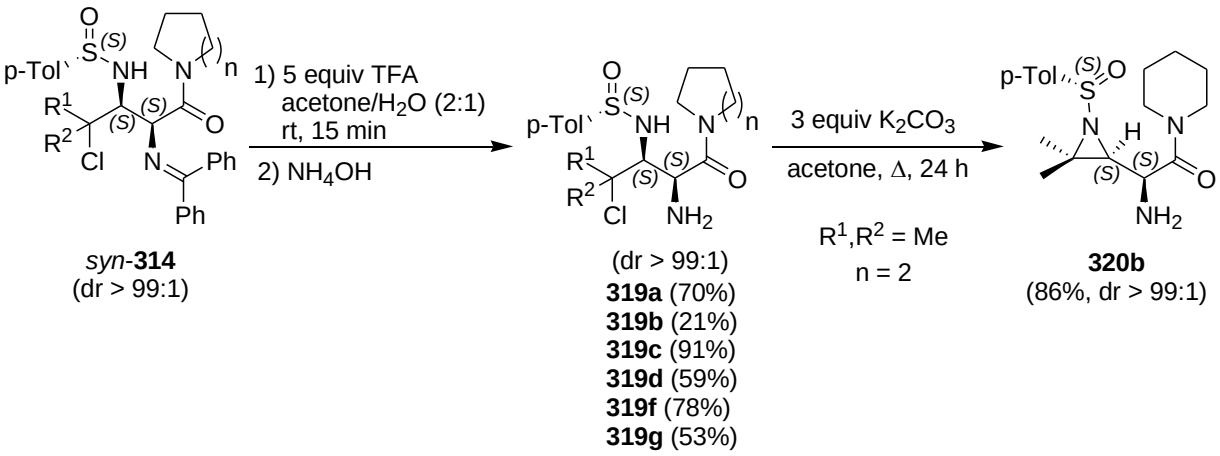
benzophenone and some other minor impurities from the crude reaction mixture, failed to provide the pure *N*-deprotected *syn*-β,γ-aziridino-α-amino carboxylic amide **318b**.



Scheme 94

Alternatively, the deprotection of the α-amino functionality of the synthesized *syn*-γ-chlorinated-α,β-diamino carboxylic amides *syn*-**314** was investigated en route towards the development of potential DPP inhibitors.[27] For this purpose, *syn*-γ-chlorinated-α,β-diamino carboxylic amides *syn*-**314a-d,f-g** were treated with five equivalents of trifluoroacetic acid in acetone/water (2:1) for 15 minutes (Scheme 95). After a basic workup with NH_4OH, the α-deprotected *syn*-γ-chloro-α,β-diamino carboxylic amides **319** could be purified by crystallization or preparative TLC (21-91% yield). The obtained result was in accordance with the earlier reported selective deprotection of a benzophenone imine functionality of diamino esters, containing a *N*-*p*-toluenesulfinyl moiety, with H_3PO_4/H_2O/THF.[175,181]

In a next step, *syn*-γ-chloro-α,β-diamino carboxylic amide **319b** was chemoselectively cyclized to the corresponding *N*-sulfinyl-β,γ-aziridino-α-amino carboxylic amide **320b** upon treatment with K_2CO_3 in acetone under reflux in 86% yield.



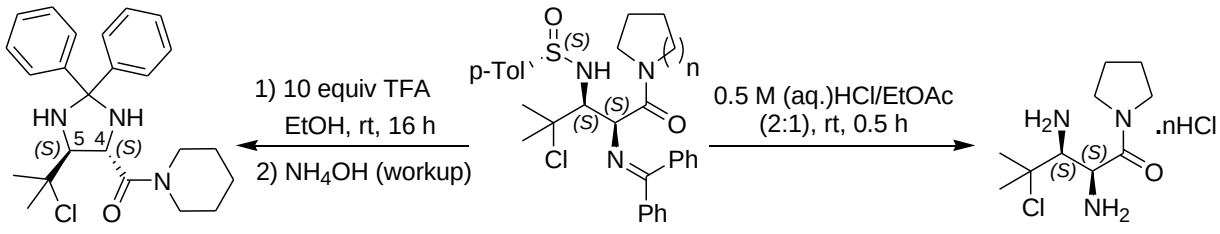
syn-**314**
(dr > 99:1)

(dr > 99:1)
319a (70%)
319b (21%)
319c (91%)
319d (59%)
319f (78%)
319g (53%)

320b
(86%, dr > 99:1)

Scheme 95

In order to provide access to the N^{α},N^{β}-deprotected *syn*-γ-chloro-α,β-diamino carboxylic amides, *syn*-γ-chloro-α,β-diamino carboxylic amides *syn*-**314** were subjected to some alternative acidic deprotection reactions (Scheme 96).



321b (55%)

(dr > 99:1)
syn-**314a** (n = 1)
syn-**314b** (n = 2)

322a (83%)

Scheme 96

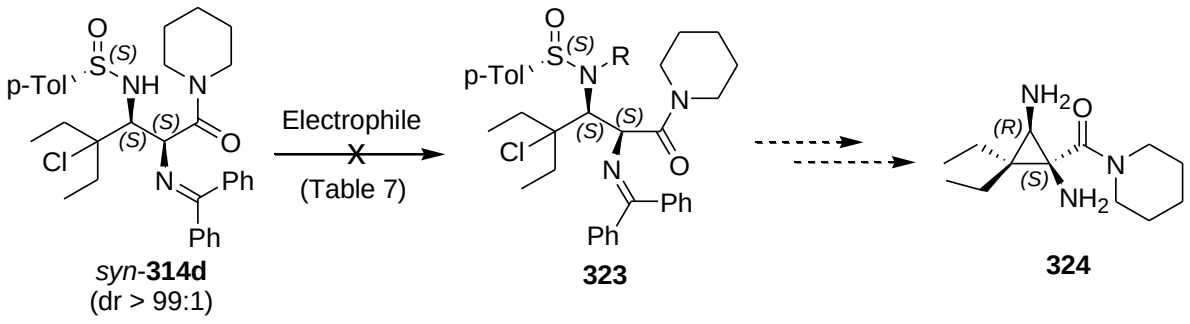
In a first reaction, *syn*-γ-chloro-α,β-diamino carboxylic amide *syn*-**314b** was treated with ten equivalents of trifluoroacetic acid in ethanol at room temperature.[156] This resulted in *trans*-imidazolidine **321b** after basic workup with NH_4OH. It was remarkable that the *N*-(diphenylmethylene) group was not removed under these reaction conditions, but was trapped by the deprotected β-amino group, as the deprotection of analogous *anti*-substrates under the same reaction conditions led to unprotected *anti*-α,β-diamino carboxylic esters.[156] This was possibly due to the fact that solvolysis of the imine functionality with ethanol was not favorable and an acid-catalyzed deprotection of the sulfinyl moiety would occur first.[182] The resulting β-amino deprotected *syn*-γ-chloro-α,β-diamino carboxylic amide could subsequently

ring close further to *trans*-imidazolidine **321b**, which was less sterically congested than an analogous *cis*-imidazolidine. In the literature, comparable non-halogenated *trans*-imidazolidines have already been synthesized *via* 1,3-dipolar cycloaddition of *N*-(diphenylmethylene)glycine ester enolates across *N*-sulfinyl aldimines in the presence of a Lewis acid.[183] The *trans*-stereochemistry of imidazolidine **321b** was confirmed by the vicinal coupling constant $^{3}J_{H4\text{-}H5}$ = 7.2 Hz and the ^{1}H NMR chemical shift of H4 (3.85 ppm) which were in the same range as for closely related *trans*-imidazolidines and *trans*-oxazolidines.[183,184] The *trans*-imidazolidine **321b** could be a potential building block for foldamers, as the corresponding *trans*-oxazolidin-2-ones have already been applied for this purpose.[49] *Trans*-imidazolidine **321b** could also be used as precursor for the corresponding N^{α},N^{β}-deprotected α,β-diamino carboxylic amide, obtained *via* hydrolysis under acidic conditions, as described for the deprotection of imidazolidines, imidazolines and oxazolines in the literature.[174,185] However, in a second reaction, *syn*-γ-chloro-α,β-diamino carboxylic amide *syn*-**314a** was directly converted into the hydrochloride of the N^{α},N^{β}-deprotected *syn*-γ-chloro-α,β-diamino carboxylic amide **322a**, by stirring in 0.5 M (aq.) HCl/EtOAc (2:1) for 30 minutes at room temperature, in a yield of 83%. In this reaction, the acid-catalyzed hydrolysis of the benzophenone imine functionality proceeds readily and prevents the formation of the corresponding *trans*-imidazolidine.

Furthermore, it was endeavored to use the synthesized *syn*-γ-chloro-α,β-diamino carboxylic amides *syn*-**314** as building blocks for the synthesis of 1,2-diaminocyclopropanecarboxylic acid derivatives **324**, which are structural analogues of 1-aminocyclopropane-1-carboxylic acid (α-ACC), the precursor of the plant hormone ethylene. Nature uses an imination/α-deprotonation/ring closure strategy in the biosynthesis of α-ACC (not shown), and broadening of this approach delivered already new amino- and alkoxy-substituted cyclopropanes.[186] For

this purpose, the synthesis of precursor **323** with a fully protected β-amino group *via* reaction with different electrophiles was envisioned (Scheme 97, Table 7).

In accordance with the previously described *N*-benzylation of azetidine **288** (*vide supra*), γ-chloro-α,β-diamino carboxylic amide *syn*-**314d** was treated with benzyl bromide in the presence of K_2CO_3 for three hours in DMF, which resulted in a complete recovery of the starting material *syn*-**314d** (Table 7, entry 1). A next attempt was made by reaction of *syn*-**314d** with two equivalents of Boc_2O in the presence of DMAP in dry CH_2Cl_2 at room temperature for 10 days, which gave again no conversion (entry 2). The reaction of *syn*-**314d** with three equivalents of methyl iodide in the presence of K_2CO_3 in a DMF/CH_3CN-solvent mixture at room temperature for 16 hours afforded, next to unreacted starting material *syn*-**314d**, 18% of aziridine **317d** according to ^1H NMR analysis of the crude reaction mixture (entry 3). Performing the reaction with 2.5 equivalents of trimethyloxonium tetrafluoroborate ($Me_3O^+.BF_4^-$) in the presence of 3.5 equivalents of DIPEA for 16 hours in dry CH_2Cl_2 at room temperature, did not result in the desired compound **323** (R = Me) (entry 4). In a final attempt, the reaction was conducted with five equivalents of diazomethane in dry CH_2Cl_2 for three hours at room temperature, but again no reaction occurred under these conditions (entry 5). No further attempts towards the synthesis of the fully protected *syn*-γ-chloro-α,β-diamino carboxylic amide **323** were made, as it was assumed that too many sterical interactions were present to obtain the desired compound **323**.



syn-**314d** (dr > 99:1) **323** **324**

Scheme 97

Table 7. Different reaction conditions for the conversion of *syn*-**314d** towards compound **323**

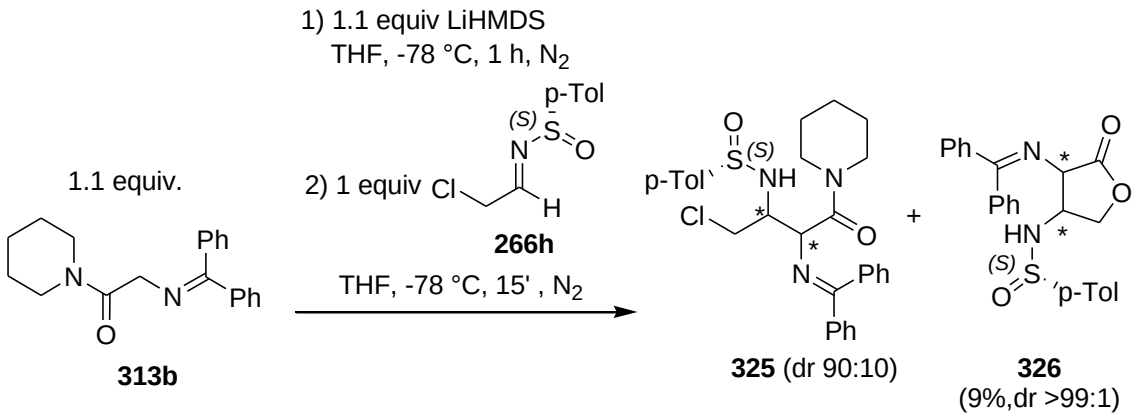
Reagent (Equiv)	Additive (Equiv)	Solvent	Time	Temp. (°C)	Result
BnBr (1.1)	K_2CO_3 (1.2)	DMF	3 h	rt	No reaction
Boc_2O (2)	DMAP (1.1)	CH_2Cl_2 (dry)	10 d	rt	No reaction
MeI (3)	K_2CO_3 (3)	DMF/CH_3CN (2:1)	16 h	rt	**317d** (18%) [a]
$Me_3O^+.BF_4^-$ (2.5)	DIPEA (3.5)	CH_2Cl_2 (dry)	16 h	rt	No reaction
CH_2N_2 (5)	-	CH_2Cl_2 (dry)	3 h	rt	No reaction

[a] Determined *via* ^{1}H NMR of crude reaction mixture

In order to extend the scope of this synthetic strategy, the Mannich-type addition of *N*-(diphenylmethylene)glycine amides **313** across *N*-sulfinyl-α-chloroacetaldimine **266h** was also investigated (Scheme 98).

Therefore, the Mannich-type addition was performed by deprotonation of glycine amide **313b** for one hour at -78 °C using 1.1 equivalents of LiHMDS and subsequent reaction across chiral *N*-*p*-toluenesulfinyl-α-chloroacetaldimine **266h** for 15 minutes at -78 °C. ^{1}H NMR analysis of the crude reaction mixture indicated that the resulting γ-chloro-α,β-diamino amide **325** was obtained in high selectivity (dr = 90:10). However, upon purification by tedious column chromatography, the Mannich-type adducts **325** could not be isolated and only side product **326** was obtained as one single diastereomer in 9% yield. The formation of side product **326** could be explained by hydrolysis of the amide group of Mannich-type adduct **325**, resulting in the corresponding carboxylic acid, which subsequently underwent ring closure to the corresponding γ-lacton.

Unfortunately, the stereochemistry of compound **325** could not be assigned by comparison of the ^{1}H NMR chemical shifts or the characteristic vicinal coupling constants of this γ-chloro-α,β-diamino carboxylic amide **325** with the previously synthesized γ-chloro-α,β-diamino carboxylic amides *syn*-**314** (*vide supra*). Furthermore, it was also impossible to determine the stereochemistry of compound **326** by means of an X-ray diffraction analysis as this compound was not crystalline.



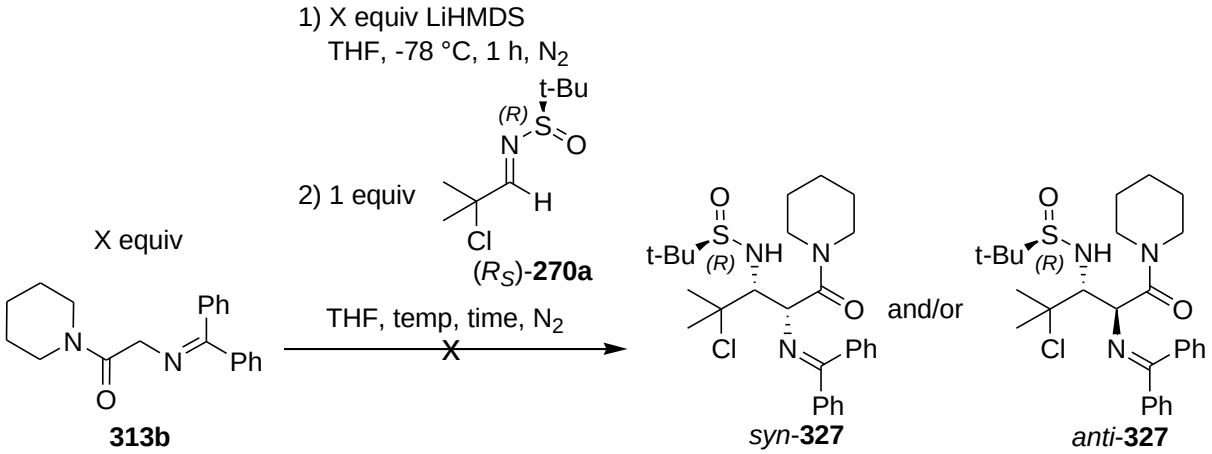
Scheme 98

In addition, some attempts were made to synthesize the *syn*-γ-chloro-α,β-diamino carboxylic amides **327** with the enantiotopic stereochemistry by means of stereoselective Mannich-type addition of *N*-(diphenylmethylene)glycine amide **313b** across (R_S)-*N*-*tert*-butanesulfinyl-α-chloroimine (R_S)-**270a**.

The Mannich-type addition was performed by systematically changing the reaction conditions (Scheme 99, Table 8). In a first attempt (entry 1), the Mannich-type addition of glycine amide **313b** across chiral *N*-*tert*-butanesulfinyl-α-chloroisobutyraldimine (R_S)-**270a** was performed for 15 minutes at -78 °C using 1.1 equivalents of LiHMDS. ^{1}H NMR analysis of the crude reaction mixture indicated that the resulting γ-chloro-α,β-diamino carboxylic amide **327** was formed as one single diastereomer but only with 30% conversion of the starting imine (R_S)-**270a**. Performing the reaction with LiHMDS for a prolonged reaction time (180 minutes) led to 70% conversion of the starting imine (R_S)-**270a**, yet the resulting γ-chloro-α,β-diamino carboxylic amide **327** was obtained as a mixture of three diastereomers (entry 2). In a following attempt, the reaction was performed with five equivalents of the Li-enolate for 15 minutes at -78 °C (entry 3), which resulted in 50% conversion of the starting material and the formation of one single diastereomer of compound **327**. In a final attempt, the Mannich-type addition of the Li-enolate derived from glycine amide **313b**, across imine (R_S)-**270a** was after 15 minutes at -78 °C, additionally stirred for 90 minutes at room temperature (entry 4).

Unfortunately, this procedure afforded a complex mixture of different diastereomeric aziridines.

As none of these adducts **327** could be isolated, it was impossible to assign the stereochemistry of these γ-chloro-α,β-diamino carboxylic amides **327**. Therefore, further investigation is required to reveal the relative and absolute stereochemistry of compounds **327** in order to use them as potential building blocks in asymmetric organic synthesis.



Scheme 99

Table 8. Addition of *N*-(diphenylmethylene)glycine amide **313b** across *N*-*tert*-butanesulfinylimine (R_S)-**270a** producing adducts **327**

Entry	X	Time (min)	Temp. (°C)	Result
1	1.1	15	-78	30% conversion, 1 diastereomer **327**
2	1.1	180	-78	70% conversion, 3 diastereomers **327**
3	5	15	-78	50% conversion, 1 diastereomer **327**
4	1.1	15 + (90)	-78 + (rt)	complex mixture of aziridines

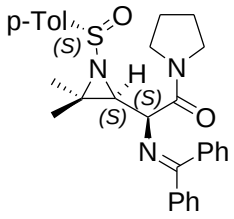
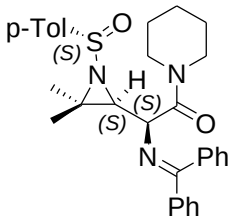
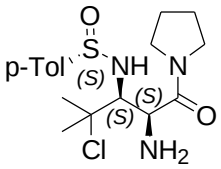
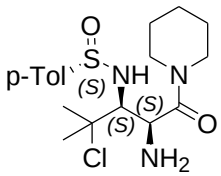
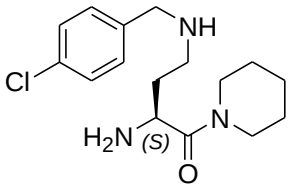
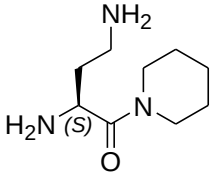
In conclusion, it was demonstrated that new chiral *syn*-γ-chlorinated-α,β-diamino carboxylic amides were formed in acceptable to good yields with excellent diastereomeric ratios *via* stereoselective Mannich-type reactions of *N*-(diphenylmethylene)glycine amides across chiral *N*-*p*-toluenesulfinyl-α-chloroaldimines. Notably, a very high *syn*-diastereoselectivity was obtained in the synthesis of these (S_S,2*S*,3*S*)-γ-chlorinated-α,β-diamino carboxylic amides with the opposite enantiotopic face selectivity as compared to the Mannich-type additions of *N*-(diphenylmethylene)glycine esters across chiral *N*-*p*-toluenesulfinyl-α-chloroaldimines.

The synthesized γ-chloro-α,β-diamino carboxylic amides were ring closed to the corresponding aziridines or selectively deprotected under acidic conditions, and the resulting α,β-diaminoacylpyrrolidines and -piperidines could have a potential applicability as dipeptidyl peptidase inhibitors which is currently under investigation.

3.3.3. Biotesting results of α,β-diamino carboxylic amide derivatives

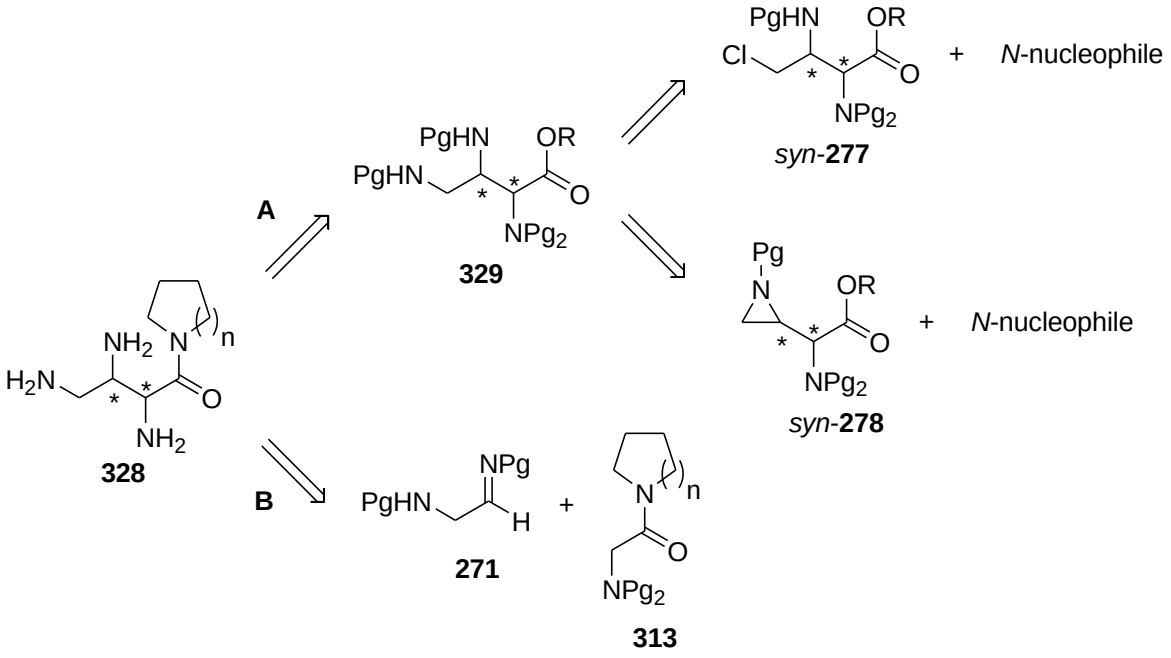
A first small library of diamino amide derivatives **317** and **319** was screened by the research group of Prof. K. Augustyns and Prof. P. Van der Veken, Department of Medicinal Chemistry, University of Antwerp, Belgium for their FAP and DPP inhibitory activity (Table 9). These biotesting results showed that only the deprotected α-amino pyrrolidine amide **319a** had some selective inhibitor activity for DPP2 and that the presence of the benzophenone imine lowers the affinity for the enzymes. Therefore, the biotesting of a new library of N^{α}-unprotected γ-chloro-α,β-diamino amides **319**, an α-deprotected β,γ-aziridino-α-amino amide **320b**, a fully deprotected γ-chloro-α,β-diamino amide **322a** and some selectively or completely deprotected α,β,γ-triamino amides (*vide infra*) is currently under investigation for their activity as FAP- and DPP-inhibitors by the group of Prof. K. Augustyns and Prof. P. Van der Veken.

Table 9. IC_{50}-values of diamino amide derivatives **317a-b** and **319a-b** tested for *in vitro* FAP and DPP inhibitory activity and literature values[28b] of reference compounds UAMC 0039 (DPPIV) and (*S*)-2,4-diaminobutanoylpiperidine **10** (DPPII)

Compound	FAP IC_{50} (µM)	DPPIV IC_{50} (µM)	DPP9 IC_{50} (µM)	DPPII IC_{50} (µM)	PO IC_{50} (µM)
 **317a**	>12.5	>100	>100	>100	>100
 **317b**	>12.5	>100	>100	>100	>100
 **319a**	>100	>100	>100	37±5	>50
 **319b**	>100	>100	>100	>50	>100
 **UAMC 0039**	-	165	-	0.00048	-
 **10**	-	>1000	-	0.130	-

3.4. Asymmetric synthesis of triamino carboxylic acid derivatives *via* stereoselective Mannich-type additions across *N*-sulfinylimines

As mentioned in section 3.3, α,γ-diamino carboxylic amides and β-amino carboxylic amides have gained a lot of interest in studies on their activity as DPP inhibitors.[31,187] In addition to the synthesis of γ-chloro-α,β-diamino carboxylic amides (*vide supra*), the library of diamino amides has been further expanded towards novel enantiopure α,β,γ-triamino amides **328**. For this purpose, the synthesis of chiral α,β,γ-triamino carboxylic amides **328** was pursued *via* two possible synthetic approaches (Scheme 100). In a first synthetic strategy (**A**), the previously described *syn*-γ-chloro-α,β-diamino esters *syn*-**277** and *syn*-β,γ-aziridino-α-amino esters *syn*-**278**, synthesized *via* diastereoselective Mannich-type reactions (*vide supra*), were reacted with different nitrogen-nucleophiles to access the corresponding α,β,γ-triamino esters **329** which could subsequently be converted in the desired α,β,γ-triamino carboxylic amides **328**. A second approach (**B**) involved the synthesis of α,β,γ-triamino carboxylic amides **328** *via* Mannich-type addition of glycine amides **313** across α-aminoimines **271**.



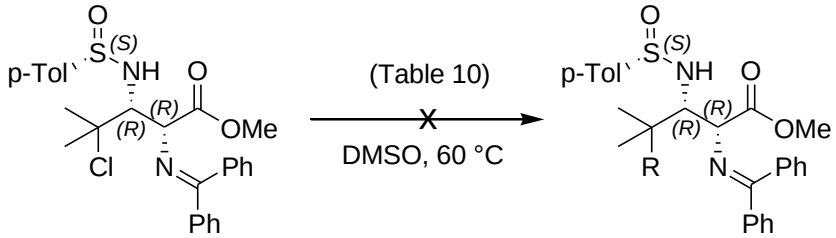
Scheme 100

3.4.1. Attempted synthesis of α,β,γ-triamino carboxylic acid derivatives *via* nucleophilic attack on α,β-diamino esters with a leaving group in γ-position

In the following part, the synthesis of chiral *syn*-α,β,γ-triamino carboxylic acid derivatives *via* substitution reactions of *syn*-γ-chloro-α,β-diamino esters *syn*-**277** with different nucleophiles has been explored (Scheme 101, Table 10).

syn-γ-Chloro-α,β-diamino ester *syn*-**277b** was heated in the presence of two equivalents of NaN_3 in DMSO at 60 °C for two hours,[188] without providing *syn*-α,β,γ-triamino ester **330** (Table 10, entry 1). Repeating the reaction for a prolonged reaction time (five days), resulted in the formation of degradation products, next to the recovery of the starting material *syn*-**277b** (entry 2).

In analogy, an attempt was made to provide access to the corresponding potential *syn*-α,β,δ-triamino carboxylic ester precursor **331** by reaction of *syn*-γ-chloro-α,β-diamino ester *syn*-**277b** with one equivalent of KCN in DMSO at 60 °C for two hours, but no conversion was observed (entry 3). Prolongation of the reaction time to five days, also did not afford the desired compound **331** (entry 4).



syn-**277b**
(dr > 99:1)

330 (R = N_3)
331 (R = CN)

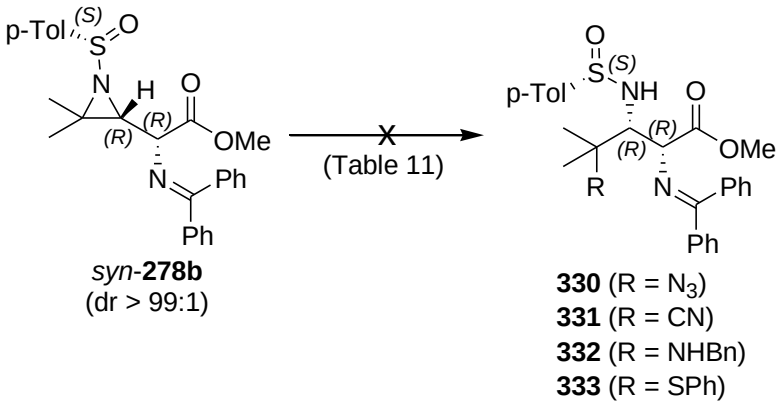
Scheme 101

Table 10. Different reaction conditions for the substitution reactions of *syn*-γ-chloro-α,β-diamino ester *syn*-**277b**

Entry	Nucleophile (Equiv)	Time	Result
1	NaN_3 (2 equiv)	2 h	no reaction
2	NaN_3 (2 equiv)	5 d	decomposition
3	KCN (1 equiv)	2 h	no reaction
4	KCN (1 equiv)	5 d	decomposition

As substitution of chloride in *syn*-γ-chloro-α,β-diamino esters *syn*-**277** failed to afford the desired esters **330** and **331**, the synthesis of the same compounds **330** and **331** was investigated through selective aziridine ring opening of *syn*-β,γ-aziridino-α-amino esters *syn*-**278** with different nucleophiles (Scheme 102, Table 11).

In a first attempt, treatment of aziridine *syn*-**278** with two equivalents of NaN_3 in DMSO at 70 °C for two hours, gave no reaction (Table 11, entry 1). When aziridine *syn*-**278** was treated under the same reaction conditions for a prolonged reaction time (five days), a degradation of the starting material was observed (entry 2). Performing the reaction in DMSO at 120 °C for 10 minutes under microwave (MW) conditions, led to degradation of the starting material *syn*-**278** (entry 3). Lowering reaction time and temperature did not result in the formation of the desired α,β,γ-triamino ester **330** (entry 4). Furthermore, treatment of aziridine *syn*-**278** with two equivalents of benzylamine in acetonitrile at reflux did not afford the desired compound **332** and led only to a complex reaction mixture (entry 5). Performing the ring-opening reaction with one equivalent of KCN in DMSO at 70 °C for two hours, led to a complete recovery of *syn*-**278** (entry 6). Repeating the reaction with prolonged reaction times (three days) gave rise to a complex reaction mixture (entry 7). In a final attempt, thiophenol was used as nucleophile to effect a ring-opening reaction, as this reagent is known for its good nucleophilicity. Treatment of aziridine *syn*-**278** with two equivalents PhSH in acetonitrile at reflux for one hour, gave no reaction (entry 8). Performing this reaction for three days, unfortunately gave rise to a complex reaction mixture.



Scheme 102

Table 11. Different reaction conditions for the ring opening of *syn*-β,γ-aziridino-α-amino ester *syn*-**278b**

Entry	Nucleophile (Equiv)	Solvent	Time	Temp. (°C)	Result
1	NaN_3 (2 equiv)	DMSO	2 h	70	no reaction
2	NaN_3 (2 equiv)	DMSO	5 d	70	decomposition
3	NaN_3 (2 equiv)	DMSO	10'	120 (MW)	decomposition
4	NaN_3 (2 equiv)	DMSO	10'	70 (MW)	no reaction
5	$BnNH_2$ (2 equiv)	CH_3CN	1 d	Δ	decomposition
6	KCN (1 equiv)	DMSO	2 h	70	no reaction
7	KCN (1 equiv)	DMSO	3 d	70	decomposition
8	PhSH (2 equiv)	CH_3CN	1 h	Δ	no reaction
9	PhSH (2 equiv)	CH_3CN	3 d	Δ	decomposition

Given the fact that all efforts to perform the ring-opening reaction of aziridine *syn*-**278** with different nucleophiles (NaN_3, KCN, PhSH, $BnNH_2$) failed, no further attempts were made to synthesize chiral functionalized diamino carboxylic acid derivatives *via* this synthetic route.

3.4.2. Asymmetric synthesis of α,β,γ-triamino carboxylic acid derivatives *via* stereoselective Mannich-type additions across *N*-sulfinyl-α-aminoimines

Since the synthesis of enantiopure α,β,γ-triamino carboxylic amides **328** could not be realized *via* nucleophilic attack on α,β-diamino esters with a leaving group in γ-position, the second

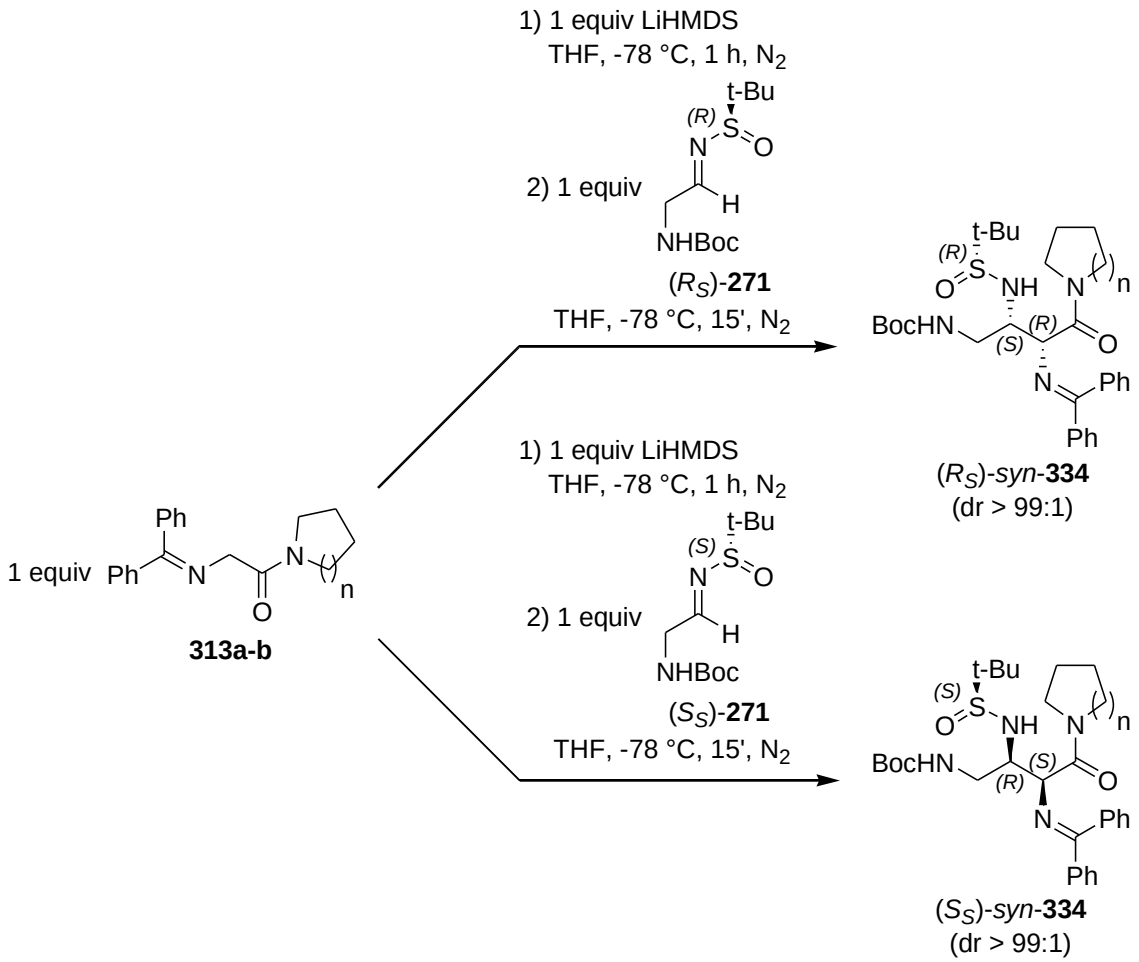
approach comprising Mannich-type addition of glycine amides **313** across *N*-sulfinyl-α-aminoimines (R_S)-**271** and (S_S)-**271** was envisioned (Scheme 103, Table 12).

Initially, the Mannich-type addition was performed by deprotonation of glycine amide **313a** for one hour at -78 °C using 1.1 equivalents of LiHMDS and subsequent reaction across (R_S)-*N*-*tert*-butanesulfinyl-α-*N*-Boc-aminoacetaldimine (R_S)-**271** for 15 minutes at -78 °C (Table 12, entry 1). ^{1}H NMR analysis of the crude reaction mixture indicated that the resulting *syn*-α,β,γ-triamino carboxylic amide (R_S)-*syn*-**334a** was obtained with excellent *syn*-selectivity (dr > 99:1). After purification by tedious column chromatography, the Mannich-type adduct (R_S)-*syn*-**334a** was isolated in 22% yield.

When glycine amide **313b** was used in the Mannich-type addition under the same reaction conditions (entry 2), this resulted in the formation of *syn*-α,β,γ-triamino carboxylic amide (R_S)-*syn*-**334b** as one single diastereomer (dr > 99:1) in 60% yield after column chromatography.

In the following reaction (entry 3), the Mannich-type addition was performed by deprotonation of glycine amide **313a** for one hour at -78 °C using 1.1 equivalents of LiHMDS and subsequent reaction across (S_S)-*N*-*tert*-butanesulfinyl-α-*N*-Boc-aminoacetaldimine (S_S)-**271** for 15 minutes at -78 °C. The resulting *syn*-α,β,γ-triamino carboxylic amide (S_S)-*syn*-**334a** was obtained in 69% yield and again with excellent *syn*-selectivity (dr > 99:1).

In addition, the Mannich-type reaction was also performed with glycine amide **313b** under the same reaction conditions (entry 4), which afforded the *syn*-α,β,γ-triamino carboxylic amide (S_S)-*syn*-**334b** in 74% yield with excellent diastereoselectivity (dr > 99:1) after column chromatography.



Scheme 103

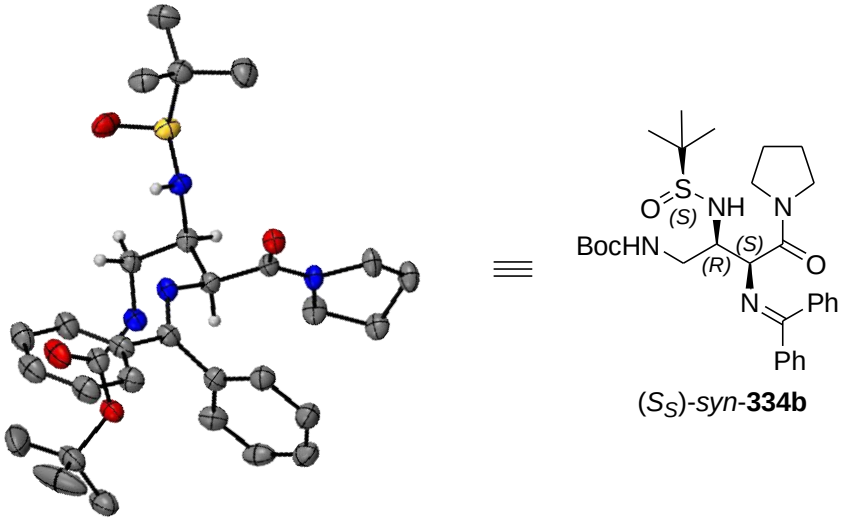
Table 12. Addition of *N*-(diphenylmethylene)glycine amides **313** across *N*-sulfinyl-α-aminoimines (R_S)-**271** and (S_S)-**271** producing *syn*-addition products (R_S)-*syn*-**334** and (S_S)-*syn*-**334**

Entry	imine	n	*anti/syn* ratio [a]	Yield (%) [b]	Product
1	(R_S)-**271**	1	> 99:1	22	(R_S)-*syn*-**334a**
2	(R_S)-**271**	2	> 99:1	60	(R_S)-*syn*-**334b**
3	(S_S)-**271**	1	> 99:1	69	(S_S)-*syn*-**334a**
4	(S_S)-**271**	2	> 99:1	74	(S_S)-*syn*-**334b**

[a] Determined *via* ^{1}H NMR of crude reaction mixtures
[b] Isolated yield of single diastereomer dr > 99:1

The absolute stereochemistry of *syn*-α,β,γ-triamino carboxylic amides *syn*-**334** was unambiguously determined by means of an X-ray diffraction analysis of compound (S_S)-*syn*-**334b** (in collaboration with Prof. K. Van Hecke, Inorganic and Physical Chemistry, Ghent

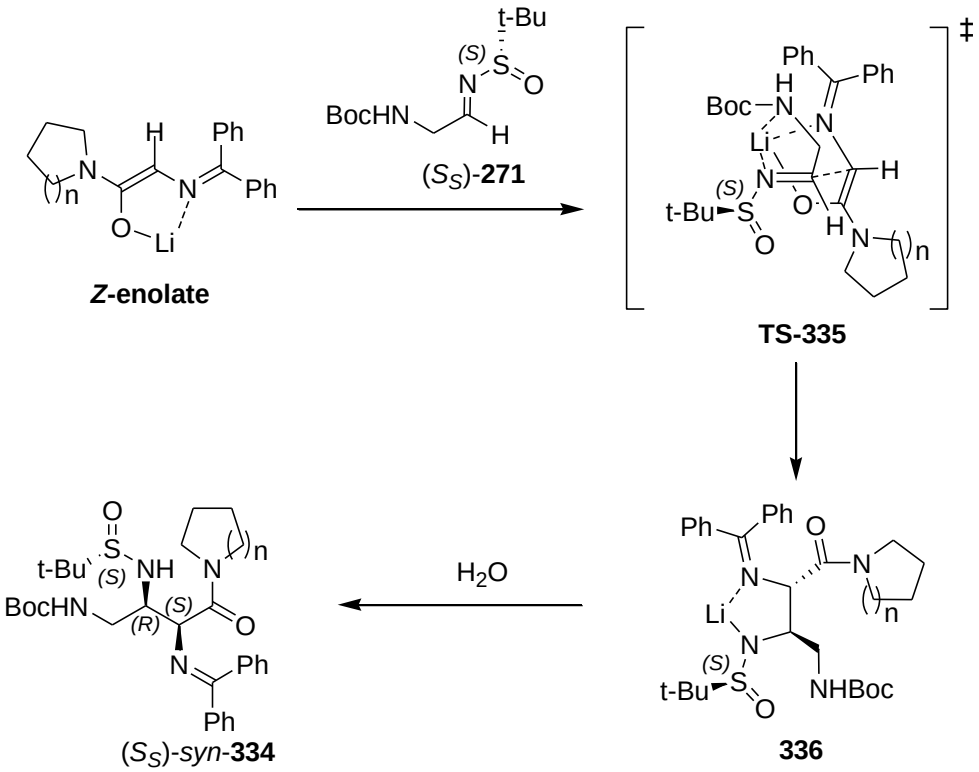
University, Belgium) (Figure 11), in combination with the comparable ^{1}H NMR chemical shifts (H_{α}: $\delta = 4.21\text{-}4.33$ ppm, H_{β}: $\delta = 3.56\text{-}3.71$ ppm) and the characteristic vicinal coupling constants ($^{3}J_{H\alpha\text{-}H\beta} = 2.8$ Hz) of all derivatives *syn*-**334**.



(S_S)-*syn*-**334b**

Figure 11. X-ray diffraction analysis of (S_S)-*syn*-α,β,γ-triamino carboxylic amide (S_S)-*syn*-**334b**

The formation of *syn*-α,β,γ-triamino carboxylic amides *syn*-**334** could be explained *via* transition state model **TS-335** (Scheme 104), which was analogous to **TS-315B** for the formation of (*S*$_S$,2*S*,3*S*)-γ-chlorinated-α,β-diamino carboxylic amides *syn*-**314** (*vide supra*). In accordance with the literature,[34-180,189,190,35] the α-heteroatom effect in this type of reactions can be considered as generally applicable as the nature of the heteroatom (chloro or *N*-Boc-amino) did not have an influence on the observed diastereoselectivity.



Scheme 104

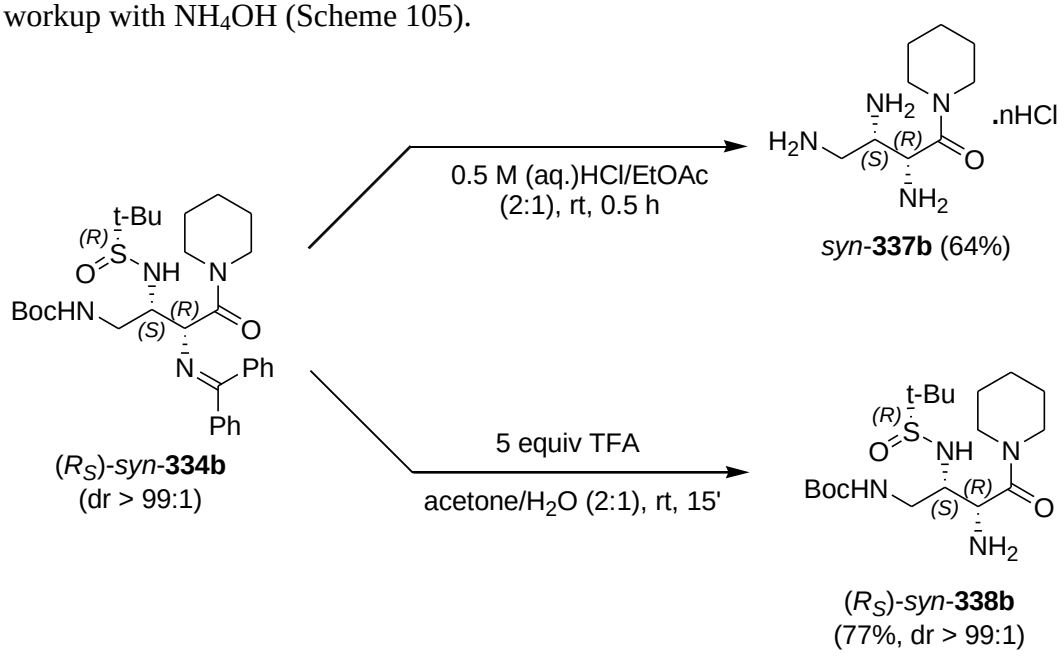
Bearing this in mind, the monosubstituted tertiary amide enolates obtained *via* deprotonation of *N*-(diphenylmethylene)glycine amides **313** were expected to have again a *Z*-geometry (Scheme 104). The formation of the (S_S,2*S*,3*R*)-α,β,γ-triamino carboxylic amides (S_S)-*syn*-**334** could be explained by a boat-like transition state model **TS-335** in which the (*E*)-*N*-*tert*-butanesulfinylaldimine (S_S)-**271** participated in the reaction (*vide supra*). This less sterically hindered transition state **TS-335**, in which the aminoalkyl group (-CH_2NHBoc) occupied the less hindered pseudoequatorial position, and the corresponding Li-adduct **336**, were stabilized by the interaction between the Li-cation, the diphenylmethyleneamino group and the sulfinylimine nitrogen.

In addition, the use of the enantiomeric (R_S)-*N*-*tert*-butanesulfinyl-α-*N*-Boc-aminoacetaldimine (R_S)-**271** induced a reversal of the enantiotopic face selectivity in this reaction as compared to the reaction with (S_S)-imine (S_S)-**271**.

In order to extend the potential applicability of the synthesized enantiopure α,β,γ-triamino carboxylic amides *syn*-**334** as building blocks in biomedicinal chemistry, some attempts were made to remove the *N*-protective groups under mild acidic conditions (Scheme 105).

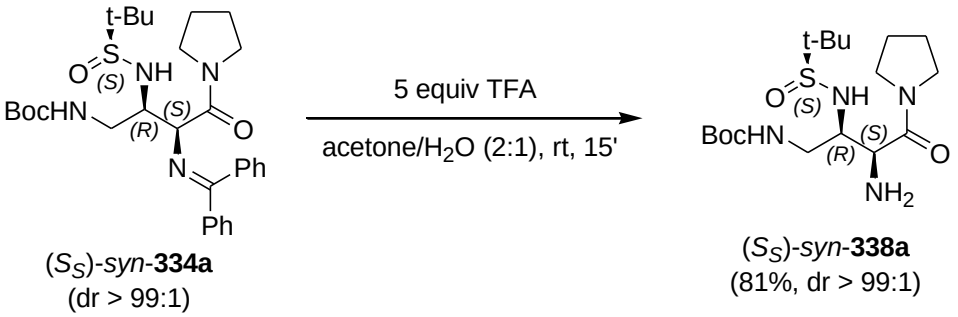
In analogy with the previously described results on the *syn*-γ-chloro-α,β-diamino carboxylic amide *syn*-**314a** (*vide supra*), (*R*$_S$,2*R*,3*S*)-α,β,γ-triamino carboxylic amide (*R*$_S$)-*syn*-**334b** was directly converted into the corresponding hydrochloride salt of the N^{α},N^{β},N^{γ}-deprotected (2*R*,3*S*)-α,β,γ-triamino carboxylic amide *syn*-**337b**, by stirring in 0.5 M (aq.) HCl/EtOAc (2:1) for 30 minutes at room temperature, providing the product in 64% yield.

Alternatively, the deprotection of the α-amino functionality of the (*R*$_S$,2*R*,3*S*)-α,β,γ-triamino carboxylic amide (*R*$_S$)-*syn*-**334b** was investigated en route towards the development of potential DPP and FAP inhibitors.[27] According to the previously described selective deprotection of the α-amino functionality of the *syn*-γ-chloro-α,β-diamino ester *syn*-**277a** (*vide supra*), the (*R*$_S$,2*R*,3*S*)-α,β,γ-triamino carboxylic amide (*R*$_S$)-*syn*-**334b** was treated with five equivalents of trifluoroacetic acid in acetone/water (2:1) for 15 minutes, resulting in the N^{α}-deprotected (*R*$_S$,2*R*,3*S*)-α,β,γ-triamino carboxylic amide (*R*$_S$)-*syn*-**338b** in 77% yield after a basic workup with NH_4OH (Scheme 105).



Scheme 105

Similarly, the selective N^{α}-deprotection of the (S_S,2*S*,3*R*)-α,β,γ-triamino carboxylic amide (S_S)-*syn*-**334a** was also performed and afforded the corresponding (S_S,2*S*,3*R*)-α,β,γ-triamino carboxylic amide (S_S)-*syn*-**338a** in 81% yield (Scheme 106).



(S_S)-*syn*-**334a**
(dr > 99:1)

(S_S)-*syn*-**338a**
(81%, dr > 99:1)

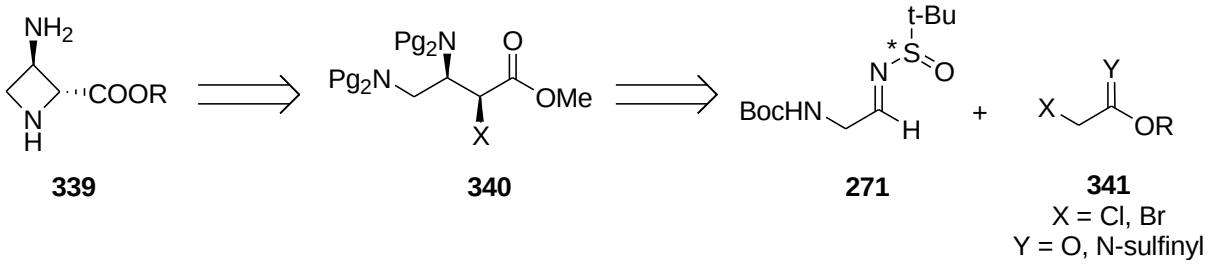
Scheme 106

In conclusion, it was demonstrated that new chiral α,β,γ-triamino carboxylic amides were formed in moderate to good yields and excellent diastereomeric ratios *via* stereoselective Mannich-type reactions of *N*-(diphenylmethylene)glycine amides across chiral *N*-*tert*-butanesulfinyl-α-*N*-Boc-aminoacetaldimines. Notably, a very high *syn*-diastereoselectivity was obtained in the synthesis of these compounds, which were formed *via* the same transition state model as the previously described (S_S,2*S*,3*S*)-γ-chlorinated-α,β-diamino carboxylic amides. The synthesized α,β,γ-triamino carboxylic amides were selectively deprotected under acidic conditions, and the resulting α,β,γ-triaminoacylpyrrolidines and -piperidines could have again a potential applicability as dipeptidyl peptidase inhibitors or as fibroblast activation protein inhibitors. This applied topic is currently under investigation.

3.5. Asymmetric synthesis of α-halo-β,γ-diamino carboxylic acid derivatives *via* stereoselective Mannich-type additions across *N*-sulfinyl-α-aminoimines

In extention to this methodology, the synthesis of the unsubstituted *trans*-3-amino-azetidine-2-carboxylate **339** was envisioned. The chiral azetidine **339** belongs to a very interesting class of molecules (*vide supra*) and could be used as a building block for the synthesis of

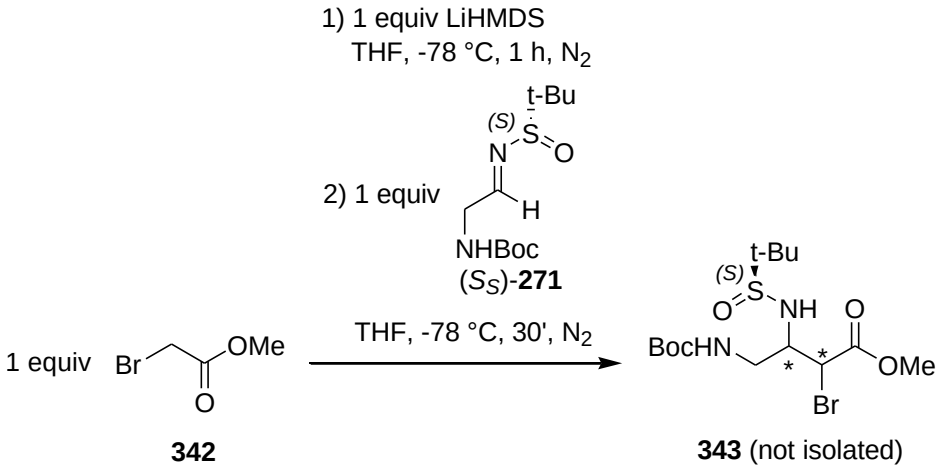
oligopeptides. The suggested synthetic approach comprised a Mannich-type addition of the enolate derived from an α-haloacetic acid derivative **341** across the chiral *N*-*tert*-butanesulfinyl-α-*N*-Boc-aminoacetaldimine **271** (Scheme 107). Regioselective cyclization of the resulting Mannich-type addition product **340** could subsequently afford the desired chiral *trans*-3-aminoazetidine-2-carboxylate **339.**



339 **340** **271** **341**
X = Cl, Br
Y = O, N-sulfinyl

Scheme 107

In a first reaction, the Mannich-type addition was performed by deprotonation of one equivalent of methyl bromoacetate **342** with LiHMDS for one hour at -78 °C and subsequent reaction with (S_S)-*N*-*tert*-butanesulfinyl-α-*N*-Boc-aminoacetaldimine (S_S)-**271** for 30 minutes at -78 °C (Scheme 108). ^{1}H NMR analysis of the crude reaction mixture indicated the formation of a complex reaction mixture, containing all four different diastereomers of the desired α-bromo-β,γ-diamino ester **343**. As purification of this reaction mixture by column chromatography on silica gel failed, another pathway towards the desired Mannich-type addition product **340** was investigated.

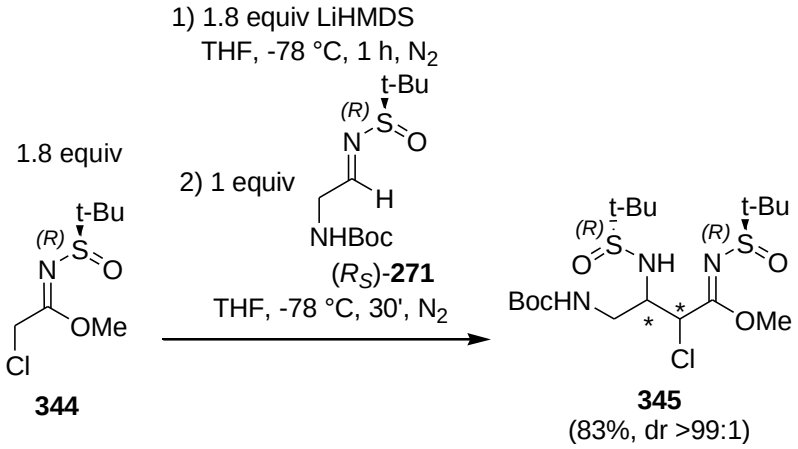


342 **343** (not isolated)

Scheme 108

In order to synthesize the enantiopure α-halo-β,γ-diamino carboxylic acid derivative **340**, the Mannich-type addition across the chiral *N*-*tert*-butanesulfinyl-α-*N*-Boc-aminoacetaldimine **271** was performed using the Li-enolate of the α-chloro-*N*-*tert*-butanesulfinyl imidate (R_S)-**344** (Scheme 109). This chiral *N*-sulfinyl imidate **344**, which was available at the Department of Sustainable Organic Chemistry and Technology, Faculty of Bioscience Engineering, UGent, has already been successfully used for the chiral synthesis of many heterocyclic compounds.[191]

In this case, the Mannich-type addition was performed by deprotonation of 1.8 equivalents of α-chloro-*N*-*tert*-butanesulfinyl imidate (R_S)-**344** with LiHMDS for one hour at -78 °C and subsequent reaction with (R_S)-*N*-*tert*-butanesulfinyl-α-*N*-Boc-aminoacetaldimine (R_S)-**271** for 30 minutes at -78 °C (Scheme 109). ^{1}H NMR analysis of the crude reaction mixture indicated that the α-chloro-β,γ-diamino imidate **345** was formed as one single diastereomer (dr > 99:1). Subsequent purification by column chromatography on silica gel afforded the desired compound **345** in 83% yield.



Scheme 109

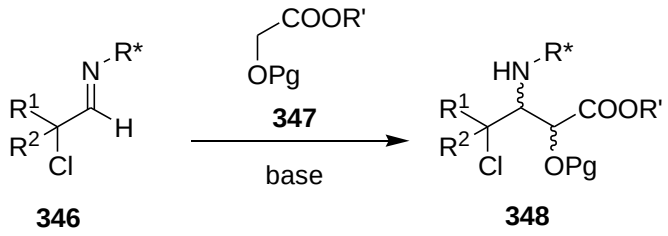
Unfortunately, neither the absolute nor the relative stereochemistry could be determined by comparison of the ^{1}H NMR chemical shifts or the vicinal coupling constants of this α-chloro-β,γ-diamino imidate **345** with previously synthesized analogous compounds (*vide supra*). It

was also impossible to determine the absolute stereochemistry of α-chloro-β,γ-diamino imidate **345** by means of an X-ray diffraction analysis as this compound was not crystalline.

In conclusion, it was demonstrated that a new chiral α-chloro-β,γ-diamino imidate was formed in high yield and excellent diastereoselectivity *via* a stereoselective Mannich-type reaction of an α-chloro-*N*-*tert*-butanesulfinyl imidate across the chiral *N*-*tert*-butanesulfinyl-α-*N*-Boc-aminoacetaldimine. Further efforts are required to determine the absolute stereochemistry of this representative of this new class of compounds and to use this compound as potential building block in heterocyclic chemistry.

3.6. Asymmetric synthesis of γ-chloro-α-hydroxy-β-amino acid derivatives *via* stereoselective Mannich-type additions across *N*-sulfinyl-α-chloroimines

In this part, the synthesis of γ-chloro-α-hydroxy-β-amino acid derivatives **348** *via* Mannich-type additions across enantiopure *N*-sulfinyl-α-chloroaldimines **266a** and **270a** was investigated. This Mannich-type addition concerned an enantio- and diastereoselective reaction of enolates derived from *O*-protected alkyl α-hydroxyacetates **347** across chiral α-chloroaldimines **346** (Scheme 110).



Scheme 110

In this study, *N*-sulfinylaldimines **266a** and **270a** were used as starting products as these imines were known for their good reactivity and stereoselectivity by incorporation of chiral directing groups.[154] In this context, analogous reactions across non-halogenated *N*-

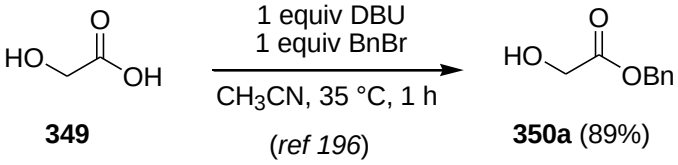
sulfinylimines were already performed for the asymmetric synthesis of β-amino acid derivatives.[156,192,193,194,195]

It has already been reported that the addition of enolates, derived from *O*-protected alkyl α-hydroxyacetates **347**, across non-functionalized (S_S)-*N*-(*tert*-butanesulfinyl)imines led to the diastereoselective synthesis of α-hydroxy-β-amino acid derivatives, when the reactions were performed at -78 °C in THF by using five equivalents of *O*-protected alkyl α-hydroxyacetates and LiHMDS as a base.[193] According to these good results, the addition of *O*-protected alkyl α-hydroxyacetates **347** across *N*-sulfinyl-α-chloroimines **346** was investigated under similar reaction conditions.

3.6.1. Synthesis of *O*-protected alkyl α-hydroxyacetates

At first, the used *O*-protected alkyl α-hydroxyacetates **347** were synthesized according to literature procedures.[154,196]

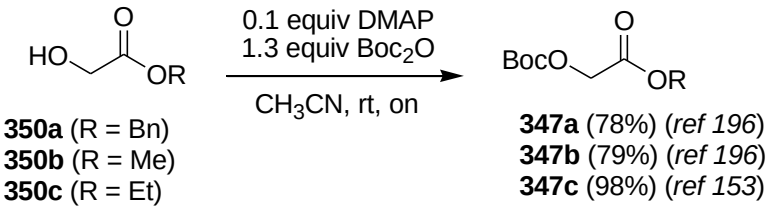
Benzyl α-hydroxyacetate **350a** was efficiently prepared (89% yield) by reaction of glycolic acid **349** with one equivalent benzyl bromide in the presence of an equimolar amount of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) for one hour in acetonitrile at 35 °C (Scheme 111).[196]



349 (*ref 196*) **350a** (89%)

Scheme 111

In a next step, the hydroxy group of benzyl α-hydroxyacetate **350a** and the commercially available methyl and ethyl ester derivatives **350b-c** was protected by reaction with 1.3 equivalents of di-*tert*-butyl dicarbonate in the presence of a catalytic amount of DMAP to afford the corresponding *O*-Boc alkyl α-hydroxyacetates **347a-c** in high yields (Scheme 112).[154,196]



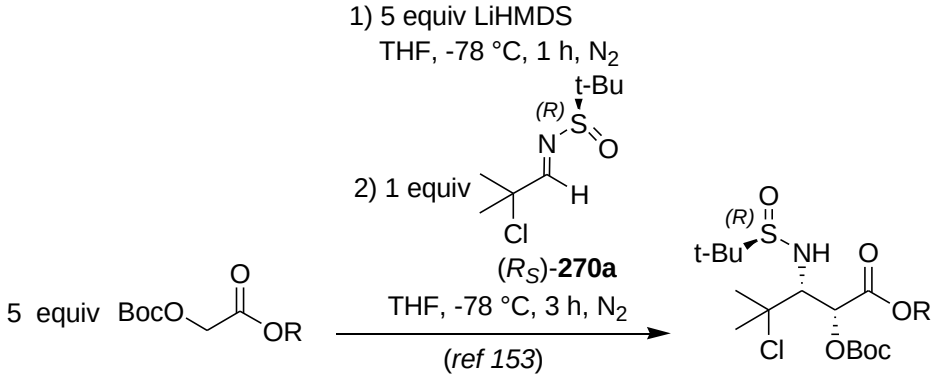
350a (R = Bn)
350b (R = Me)
350c (R = Et)

347a (78%) (*ref 196*)
347b (79%) (*ref 196*)
347c (98%) (*ref 153*)

Scheme 112

3.6.2. Synthesis and elaboration of *syn*-alkyl 2-(*tert*-butoxycarbonyloxy)-4-chloro-4-methyl-3-(*tert*-butanesulfinylamino)pentanoates

(R_S)-*N*-(*tert*-Butanesulfinyl)-α-chloroaldimine (R_S)-**270a** was subjected to a Mannich-type addition by reaction with the Li-enolates derived from the *O*-Boc alkyl α-hydroxyacetates **347a-c**. The reaction started with deprotonation of five equivalents of *O*-Boc alkyl α-hydroxyacetate **347a-c** with five equivalents of LiHMDS for one hour in THF at -78 °C and subsequent addition of (R_S)-*N*-(*tert*-butanesulfinyl)-α-chloroaldimine (R_S)-**270a** (Scheme 113). The reaction mixture was stirred for three hours at -78 °C and quenched with a saturated NH_4Cl-solution (aq.). ^1H NMR analysis of the crude reaction mixtures showed that the corresponding Mannich-type addition products (R_S)-**351a-c** were formed in good to excellent diastereomeric ratios high yields after purification *via* column chromatography on silica gel (Table 13).[154]



347a (R = Bn)
347b (R = Me)
347c (R = Et)

(R_S)-**351a-c**

Scheme 113

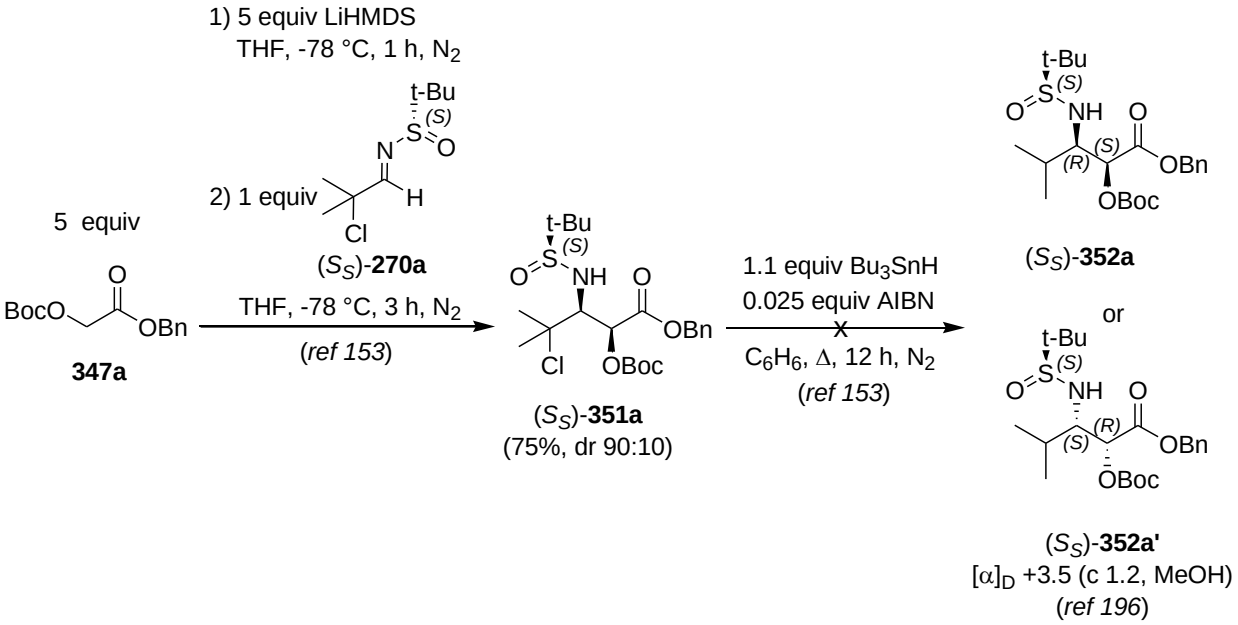
Table 13. Overview of the Mannich-type reaction of (R_S)-*N*-(*tert*-butanesulfinyl)-α-chloroaldimine (R_S)-**270a** with α-hydroxy esters **347** at -78 ° C.

R	dr [a]	Yield (%) [b]
Bn	80:20:0:0	75
Me	98:2:0:0	86
Et	89:11:0:0	88

[a] Determined *via* ^{1}H NMR of crude reaction mixtures
[b] Isolated yield of single diastereomer (dr > 99:1)

Based on the ^{1}H NMR analysis, it was determined that the isolated major diastereomers were *syn*-adducts, as the typical doublet times doublet signals ascribed to H-3 were readily observed, whereas the corresponding *anti*-adducts have a typical triplet signal.[193] Unfortunately, it was impossible to determine the absolute stereochemistry of these *syn*-adducts (R_S)-**351a-c** by means of an X-ray diffraction analysis as none of these compounds were crystalline. Therefore, the corresponding (S_S)-γ-chloro-α-hydroxy-β-amino ester (S_S)-**351a** was synthesized by Mannich-type addition of the Li-enolate derived from the *O*-Boc benzyl α-hydroxyacetate **347a** across (S_S)-*N*-(*tert*-butanesulfinyl)-α-chloroaldimine (S_S)-**270a** under the same reaction conditions (Scheme 114).

As the optical rotation of the corresponding dehalogenated (S_S,2*R*,3*S*)-α-hydroxy-β-amino ester (S_S,2*R*,3*S*)-**352a'** was known in the literature,[196] the reaction of compound (S_S)-**351a** with Bu_3SnH and AIBN was performed. Unfortunately, this reaction failed to provide the desired dechlorinated compound **352a** or **352a'**, which would have allowed the determination of the absolute stereochemistry of **351a** by comparison of the optical rotation.



Scheme 114

The absolute stereochemistry of (R_S)-γ-chloro-α-hydroxy-β-amino acid derivative (R_S)-**351c** was determined by means of an X-ray diffraction analysis (in collaboration with Prof. K. W. Törnroos, Department of Chemistry, University of Bergen, Norway) (Figure 12) of the crystalline (R_S,2*R*,3*R*)-Boc-deprotected derivative (R_S,2*R*,3*R*)-**356c** (*vide infra*). The (R_S,2*R*,3*R*)-stereochemistry of the other synthesized (R_S)-γ-chloro-α-hydroxy-β-amino esters (R_S)-**351a-b** was deduced from the vicinal coupling constant $^3J_{H2\text{-}H3}$ = 1.10 Hz and the ^{1}H NMR chemical shift of H3 (4.01 ppm),[154] which were in the same range as for the (R_S)-γ-chloro-α-hydroxy-β-amino ester (R_S)-**351c**.

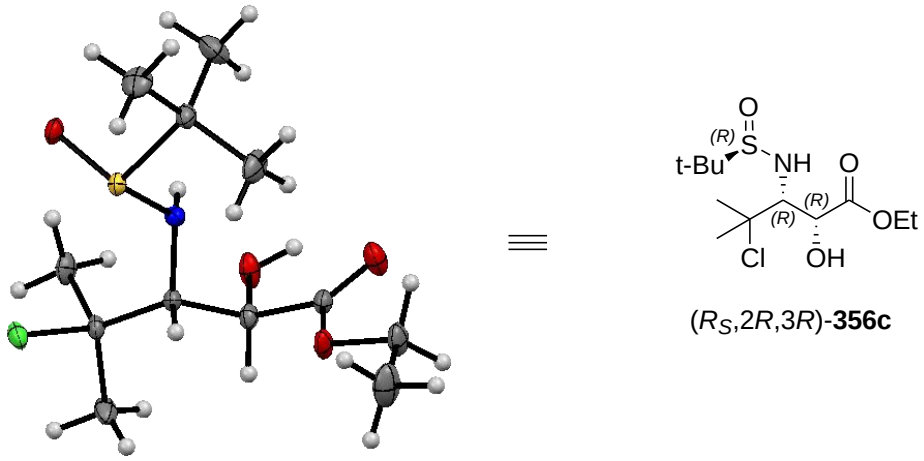
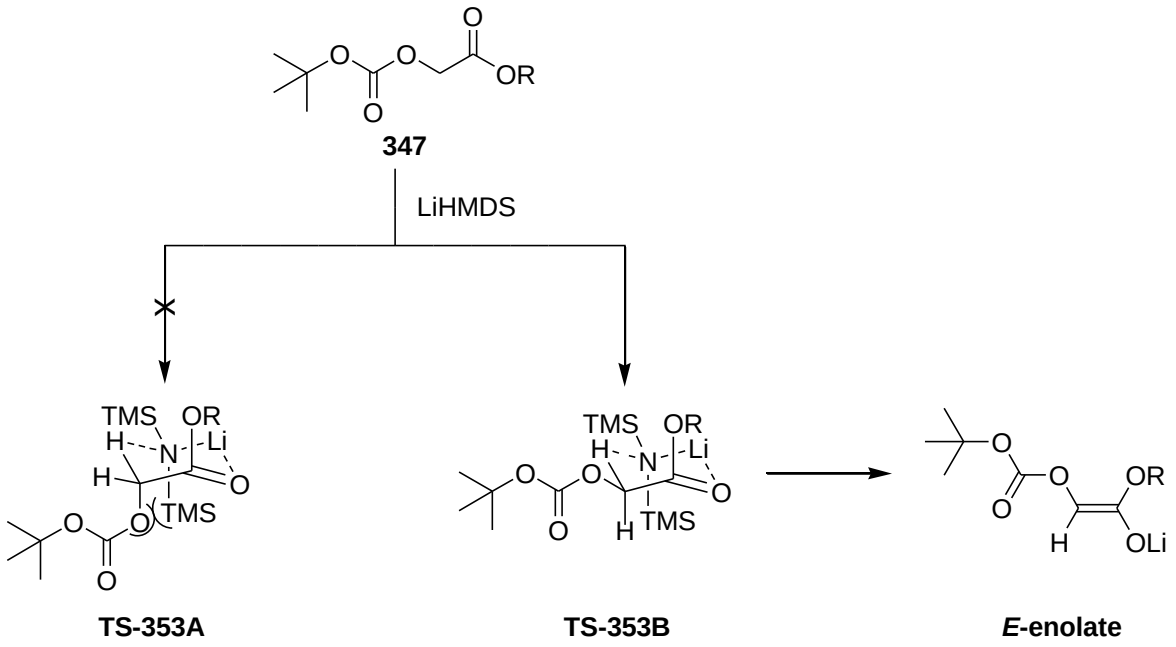


Figure 12. X-ray diffraction analysis of (R_S,2*R*,3*R*)-γ-chloro-α-hydroxy-β-amino ester (R_S,2*R*,3*R*)-**356c**

The stereochemical outcome of the Mannich-type reaction across (R_S)-*N*-(*tert*-butanesulfinyl)-α-chloroaldimine (R_S)-**270a** was rationalized on the basis of the enolate geometry of the anions derived from the deprotonation of *O*-Boc alkyl α-hydroxyacetates **347**. As reported in the literature,[193,197] the enolates obtained *via* deprotonation of *O*-Boc alkyl α-hydroxyacetates **347** with LiHMDS in THF were expected to have the *E*-geometry (Scheme 115). As commonly performed in the assignment of enolate geometry, in contrast to conventional *E*/*Z*-nomenclature, the highest priority designation was allocated to the *O*-metal group of the enolate substituents. The stereoselective formation of the *E*-enolates has been rationalized with the Ireland model,[197] which showed that deprotonation of *O*-Boc alkyl α-hydroxyacetates **347** with LiHMDS *via* transition state **TS-353A**, induced adverse sterical interactions of the axial TMS group and the O-Boc group. For this reason, the deprotonation proceeds *via* transition state **TS-353B** and afforded the corresponding *E*-enolate.

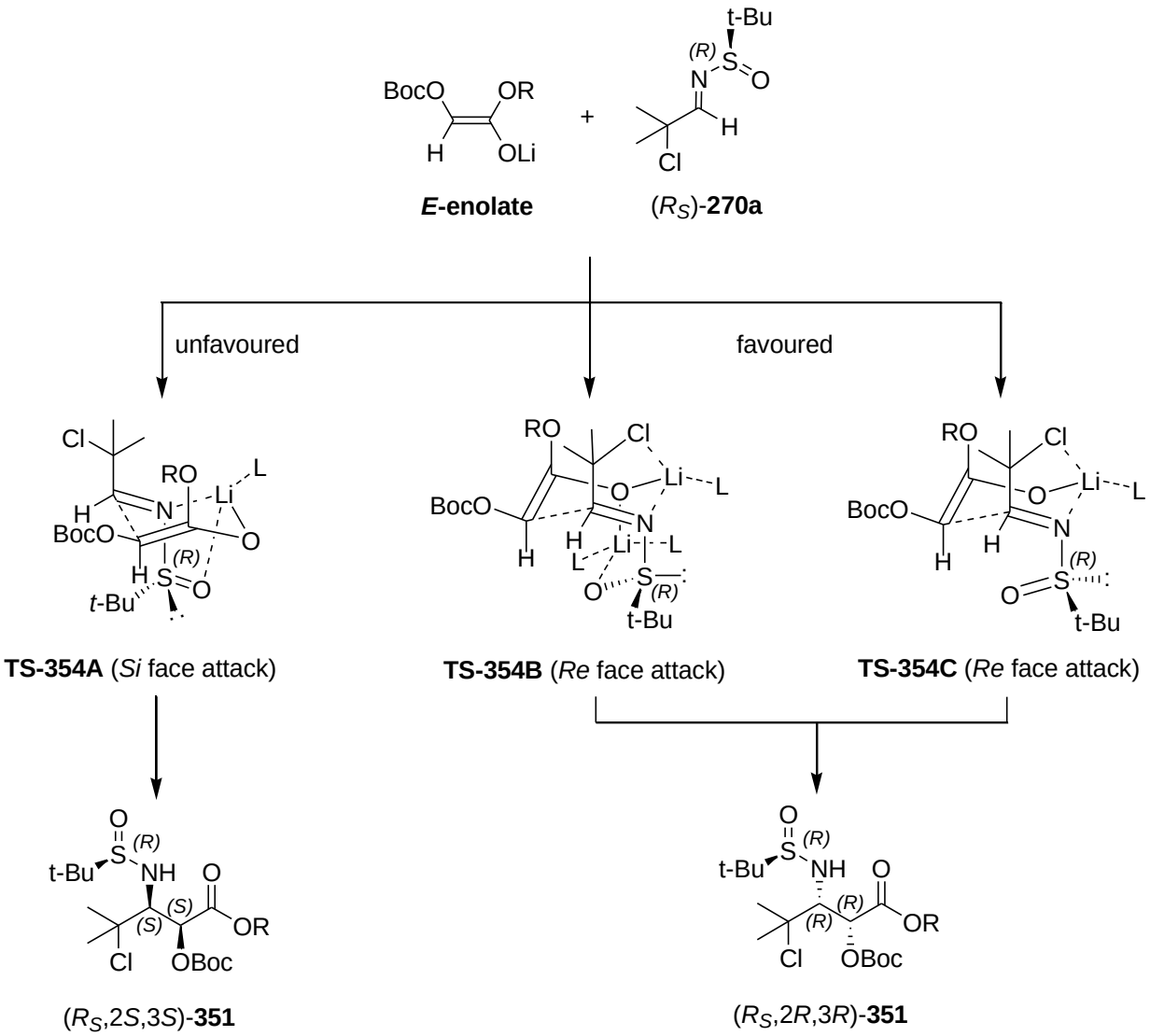


Scheme 115

Reaction of the *E*-enolates *via* a six/four-membered Li-chelated bicyclic chairlike transition state model **TS-354A**, which was valid for Mannich-type additions across non-functionalized *N*-sulfinyl imines,[193] would have resulted in the formation of (R_S,2*S*,3*S*)-γ-chloro-α-hydroxy-β-amino esters (R_S,2*S*,3*S*)-**351** (Scheme 116). However, this transition state model **TS-354A**, which proceeded *via* a Si-face attack, lacked the important chelation between the α-coordinating chlorine atom and the lithium atom.

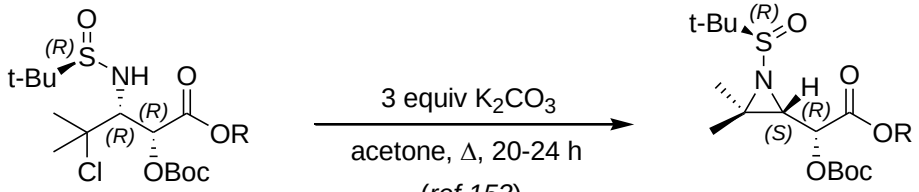
The formation of the (R_S,2*R*,3*R*)-γ-chloro-α-hydroxy-β-amino esters (R_S,2*R*,3*R*)-**351** could be explained by a six/six-membered di-metal-chelated bicyclic chairlike transition state model **TS-354B**,[198,199] or by a six-membered Li-chelated cyclic chairlike transition state model **TS-354C** which proceeded both *via* a Re-face attack of the *E*-enolate (Scheme 116). In a first possible transition state model **TS-354B**, the α-coordinating ability of the chlorine atom overrode the chelation of the sulfinyl oxygen with the lithium ion of the incoming *E*-enolate and induced chelation of the sulfinyl oxygen with an extra Li-cation to form a six/six-membered di-Li-chelated bicyclic chairlike transition state model. In an alternative transition state model **TS-354C**, the coordinating ability of the chlorine atom overruled the chelation of

the sulfinyl oxygen as well and an extra stabilizing effect was attained by the fact that the *N*-sulfinyl imine (R_S)-**270a** in this transition state was present in the energetically favoured s-*cis* configuration.[35]



Scheme 116

The resulting (R_S,2*R*,3*R*)-γ-chloro-α-hydroxy-β-amino esters (R_S,2*R*,3*R*)-**351** were subsequently cyclized to the corresponding *N*-sulfinyl-β,γ-aziridino-α-hydroxy esters **355** upon treatment with K_2CO_3 in acetone under reflux in good yields (67-88%) (Scheme 117).[154]



(dr > 99:1)
351a (R = Bn)
351b (R = Me)
351c (R = Et)

(dr > 99:1)
355a (68%)
355b (88%)
355c (67%)

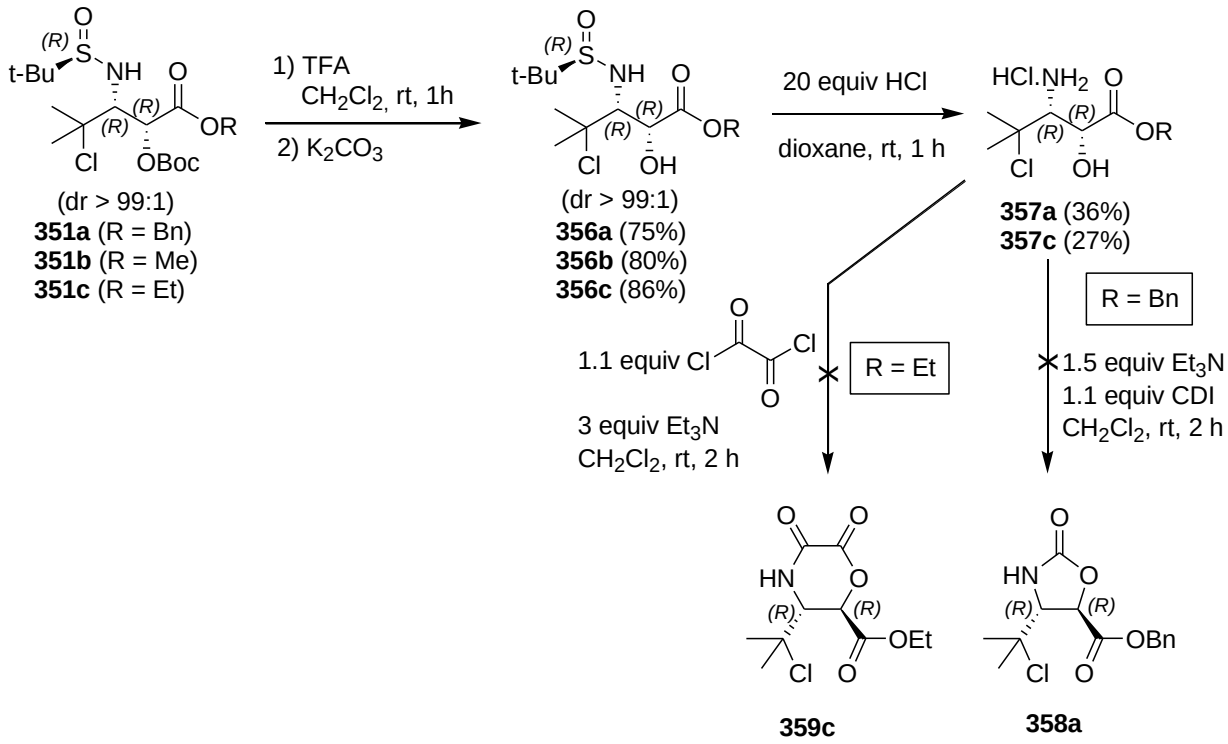
Scheme 117

In order to extend the potential applicability of the synthesized (R_S,2*R*,3*R*)-γ-chloro-α-hydroxy-β-amino esters (R_S,2*R*,3*R*)-**351** as building blocks in biomedicinal chemistry, a number of attempts was made to remove the protective groups of (R_S,2*R*,3*R*)-**351** under acidic conditions (Scheme 118). In a first reaction, (R_S,2*R*,3*R*)-γ-chloro-α-hydroxy-β-amino ester (R_S,2*R*,3*R*)-**351** was dissolved in dichloromethane and treated with trifluoroacetic acid (30% v/v) at room temperature for one hour. After a basic workup with K_2CO_3, the α-deprotected *syn*-γ-chloro-α-hydroxy-β-amino esters **356** could be purified by crystallization in Et_2O or by column chromatography on silica gel (75-86% yield). The obtained result was in accordance with the previously reported selective deprotection of a *O*-Boc-protected group, in the presence of an *N*-*tert*-butanesulfinyl moiety, of α-hydroxy-β-amino esters with TFA.[196] Moreover, the *O*-deprotected (R_S,2*R*,3*R*)-γ-chloro-α-hydroxy-β-amino ester (R_S,2*R*,3*R*)-**356c** was isolated as a crystalline product which allowed the implementation of an X-ray diffraction analysis (*vide infra*).

In a next step, the *N*-(*tert*-butanesulfinyl) group of the *O*-deprotected (R_S,2*R*,3*R*)-γ-chloro-α-hydroxy-β-amino esters (R_S,2*R*,3*R*)-**356a-b** was deprotected by reaction in a saturated HCl-solution in dioxane for one hour at room temperature (Scheme 118). After evaporation of the solvent, it was concluded that the conversion towards the *N*,*O*-deprotected (R_S,2*R*,3*R*)-γ-chloro-α-hydroxy-β-amino esters (R_S,2*R*,3*R*)-**357a-b** was complete based on ^{1}H NMR analysis of the crude reaction mixture. Unfortunately, attempting different purification techniques (crystallization, preparative TLC, acid-base extraction) in order to improve the

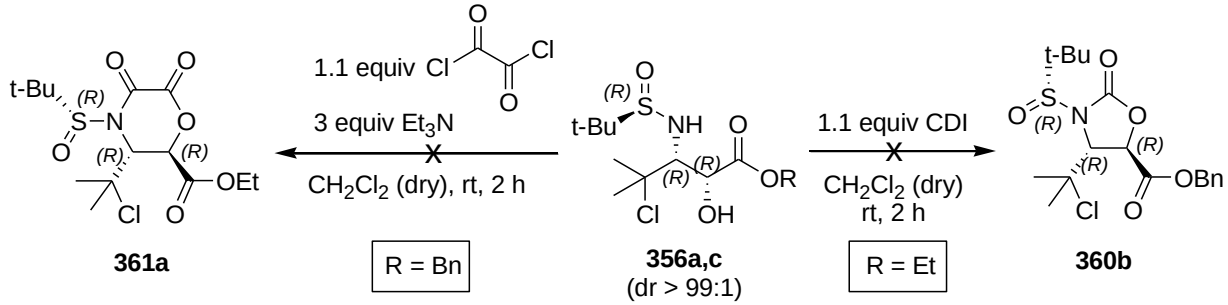
yield of the pure *N*,*O*-deprotected (*R*$_S$,2*R*,3*R*)-γ-chloro-α-hydroxy-β-amino esters (*R*$_S$,2*R*,3*R*)-**357a-b**, was shown to be only partially successful, giving 27-36% yield of (*R*$_S$,2*R*,3*R*)-**357a-b** after crystallization in dichloromethane. Therefore, another route towards the *N*,*O*-deprotected (*R*$_S$,2*R*,3*R*)-γ-chloro-α-hydroxy-β-amino esters (*R*$_S$,2*R*,3*R*)-**364** was envisioned (*vide infra*).

In order to synthesize new heterocyclic derivatives **358a** and **359c**, the *N*,*O*-deprotected (*R*$_S$,2*R*,3*R*)-γ-chloro-α-hydroxy-β-amino esters (*R*$_S$,2*R*,3*R*)-**357a,c** were treated with different cyclizing agents in accordance to literature procedures (Scheme 118).[200,201] In a first attempt, the amino alcohol (*R*$_S$,2*R*,3*R*)-**357a** was treated with 1.1 equivalents of 1,1'-carbonyldiimidazole (CDI) in the presence of 1.5 equivalents of Et_3N for two hours in dichloromethane at room temperature. Unfortunately, application of these reaction conditions failed to afford the desired oxazolidinone **358a** as only a complex reaction mixture was obtained according to ^1H NMR analysis. In addition, reaction of amino alcohol (*R*$_S$,2*R*,3*R*)-**357c** with 1.1 equivalents of oxalyl chloride in the presence of three equivalents of Et_3N for two hours in dichloromethane at room temperature gave again a complex reaction mixture with no traces of the corresponding morpholine-2,3-dione **359c**.



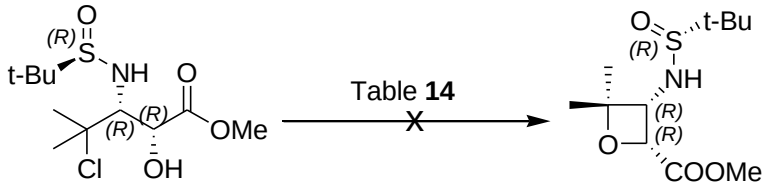
Scheme 118

Next to the attempts to synthesize oxazolidinone **358a** and morpholine-2,3-dione **359c** *via* reaction of the unprotected amino alcohols **357a,c** with the cyclizing agents CDI and oxalyl chloride, these reactions were also performed with the *N*-(*tert*-butanesulfinyl)-protected (R_S,2*R*,3*R*)-γ-chloro-α-hydroxy-β-amino esters (R_S,2*R*,3*R*)-**356a** and (R_S,2*R*,3*R*)-**356c** (Scheme 119). However, reaction of the *N*-protected compound (R_S,2*R*,3*R*)-**356c** with CDI also resulted in the formation of a complex reaction mixture. Furthermore, a complex reaction mixture was observed when *N*-protected compound (R_S,2*R*,3*R*)-**356a** was treated with oxalyl chloride.



Scheme 119

In addition, some attempts were made to synthesize new 3-aminooxetane-2-carboxylic acid derivatives **362** *via* intramolecular nucleophilic substitution reactions (Scheme 120). In accordance with a literature procedure,[202] the reaction of the *O*-deprotected amino alcohol (R_S,2*R*,3*R*)-**356b** with one equivalent of $AgBF_4$ in the presence of one equivalent of pyridine in toluene at reflux temperature for two hours (Table 14, entry 1) resulted in a complex reaction mixture, which could not be purified. In a next attempt, a similar reaction without pyridine gave also a complex reaction mixture (entry 2). Alternatively, performing the reaction for two hours in toluene at reflux temperature without additives, did not afford the desired oxetane derivative **362** (entry 3). In a final attempt, the reaction was conducted in pyridine for two hours at room temperature. However, no reaction occurred under these conditions (entry 4). No further attempts towards the synthesis of *cis*-3-aminooxetane-2-carboxylic acid derivatives *cis*-**362** were made, as it was assumed that the *cis*-configuration of the 3-amino- and the 2-alkoxycarbonyl group caused too much sterical interactions to allow the synthesis of oxetane **362**.



356b
(dr > 99:1)

362b

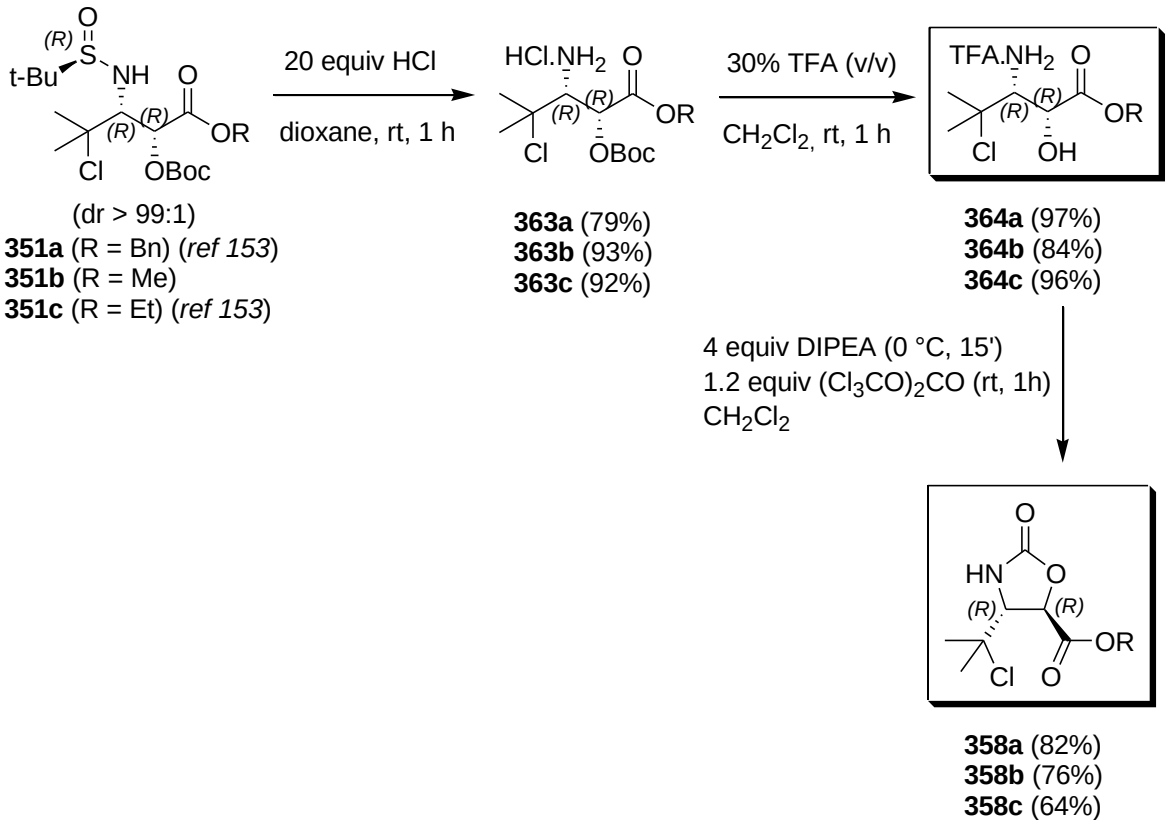
Scheme 120

Table 14. Different reaction conditions for the ring transformation towards oxetane **362b**

Entry	Additive	Solvent	Time (h)	Temperature	Result
1	1 equiv $AgBF_4$ 1 equiv pyridine	toluene	2	Δ	complex reaction mixture
2	1 equiv $AgBF_4$	toluene	2	Δ	complex reaction mixture
3	-	toluene	2	Δ	no reaction
4	-	pyridine	2	rt	no reaction

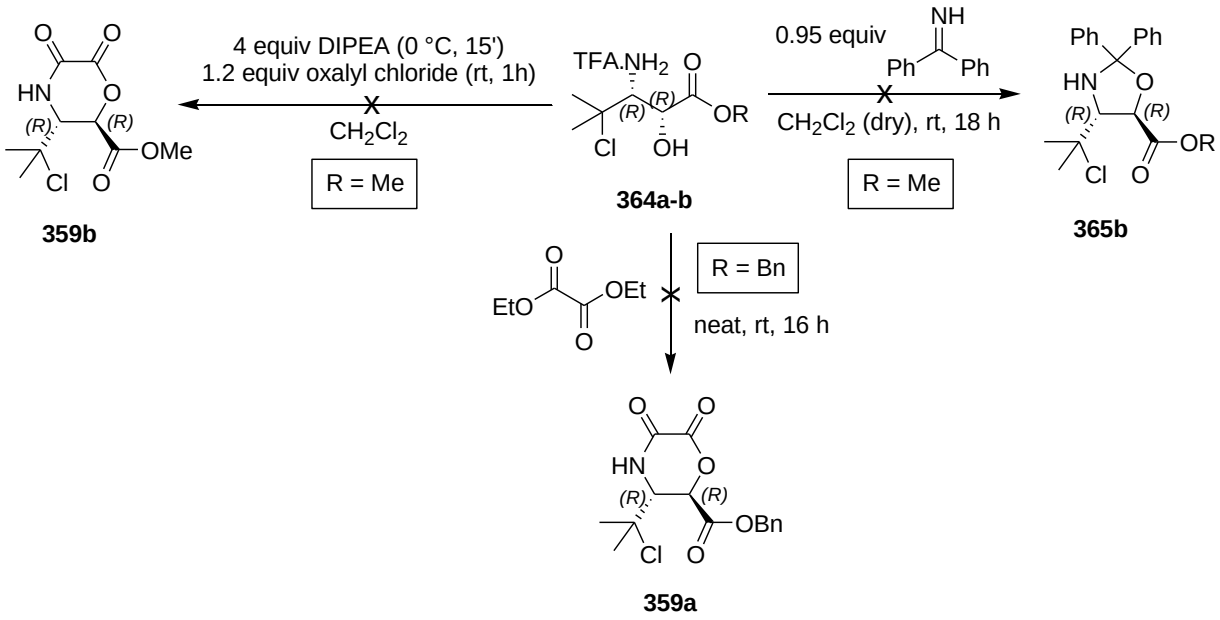
Alternatively, the deprotection of the (R_S,2*R*,3*R*)-γ-chloro-α-hydroxy-β-amino esters (R_S,2*R*,3*R*)-**351** could also be effected starting with the initial synthesis of the *N*-deprotected (2*R*,3*R*)-γ-chloro-α-hydroxy-β-amino esters (2*R*,3*R*)-**363** (Scheme 121).[154] The *N*-(*tert*-butanesulfinyl) group of Mannich-type adducts (R_S,2*R*,3*R*)-**351** was easily deprotected under mild conditions *via* acidic hydrolysis.[154,182a] Treatment of compounds (R_S,2*R*,3*R*)-**351** with a saturated HCl-solution in dioxane for one hour at room temperature afforded the *N*-deprotected esters (2*R*,3*R*)-**363** in high yields (79-93%) upon evaporation of the solvent and subsequent precipitation in Et_2O. The subsequent deprotection of the *O*-Boc protective group of (2*R*,3*R*)-**363** was realized by stirring in dichloromethane/trifluoroacetic acid (30% v/v) at room temperature for one hour. After evaporation of the solvent *in vacuo*, the O^{α},N^{β}-deprotected (2*R*,3*R*)-γ-chloro-α-hydroxy-β-amino ester salts (2*R*,3*R*)-**364** were obtained as pure products in excellent yields (84-97% yield). In this way, the synthesis of the O^{α},N^{β}-deprotected esters (2*R*,3*R*)-**364** starting from the (R_S,2*R*,3*R*)-γ-chloro-α-hydroxy-β-amino esters (R_S,2*R*,3*R*)-**351** proceeded in higher overall yields, than *via* the synthetic route that first involved the deprotection of *O*-Boc protective group (*vide supra*).

Furthermore, some additional reactions were performed in order to synthesize oxazolidinones **358**. In accordance with a literature procedure,[203] the *N*,*O*-deprotected (2*R*,3*R*)-γ-chloro-α-hydroxy-β-amino ester salts (2*R*,3*R*)-**364** were treated with four equivalents of *N*,*N*-diisopropylethylamine (DIPEA) in dichloromethane for 15 minutes at 0 °C to neutralize the trifluoroacetic acid salt (Scheme 121). Dropwise addition of 1.2 equivalents of triphosgene dissolved in dichloromethane, resulted in the formation of the corresponding oxazolidinones **358** in high yields (64-82%) after one hour at room temperature followed by aqueous workup.



Scheme 121

Finally, some efforts were made to synthesize new morpholine-2,3-diones **359** and oxazolidines **365** *via* reaction with different cyclizing reagents (Scheme 122). In analogy with the previously described successful synthesis of oxazolidinones **358** (*vide supra*), the *N*,*O*-deprotected (2*R*,3*R*)-γ-chloro-α-hydroxy-β-amino ester salt (2*R*,3*R*)-**364** was treated with four equivalents of *N*,*N*-diisopropylethylamine (DIPEA) and 1.2 equivalents of oxalyl chloride. Unfortunately, after aqueous workup, the desired morpholine-2,3-dione **359b** was not detected based on ^{1}H NMR and LC-MS analysis of the crude reaction mixture. In addition, neat reaction of *N*,*O*-deprotected (2*R*,3*R*)-γ-chloro-α-hydroxy-β-amino ester salt (2*R*,3*R*)-**364a** with diethyl oxalate,[204] for 16 hours at room temperature did not result in the corresponding morpholine-2,3-dione **359a**. Reaction of TFA-salt (2*R*,3*R*)-**364b** with 0.95 equivalents of benzophenone imine for 18 hours in dry dichloromethane at room temperature was also attempted to synthesize the corresponding oxazolidine **365b**. However, this reaction did not give any transformation.



Scheme 122

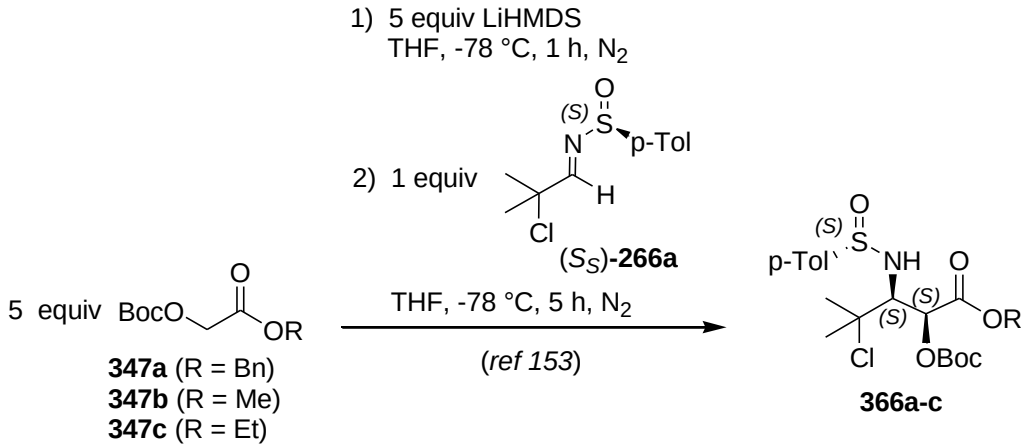
3.6.3. Synthesis and elaboration of *syn*-alkyl 2-(*tert*-butoxycarbonyloxy)-4-chloro-4-methyl-3-(*p*-toluenesulfinylamino)pentanoates

The high reactivity and diastereoselectivity observed in the Mannich-type addition reaction of Li-enolates derived from *O*-Boc alkyl α-hydroxyacetates **347a-c** across *N*-(*tert*-butanesulfinyl)-α-chloroaldimines **270a** prompted the further investigation of the Mannich-type additions across *N*-(*p*-toluenesulfinyl)-α-chloroaldimine **266a**.[154]

The *N*-(*p*-toluenesulfinyl)-α-chloroaldimine **266a** was subjected to a Mannich-type addition under similar reaction conditions. The reaction started with deprotonation of five equivalents of the *O*-Boc alkyl α-hydroxyacetates **347a-c** with five equivalents of LiHMDS for one hour in THF at -78 °C and subsequent addition of the (S_S)-*N*-(*p*-toluenesulfinyl)-α-chloroaldimines (S_S)-**266a** (Scheme 123). After stirring the reaction mixture for five hours at -78 °C and quenching with a saturated NH_4Cl-solution (aq.), ^1H NMR analysis of the crude reaction mixtures showed that the corresponding Mannich-type addition products (S_S)-**366a-c** were formed in good to excellent diastereomeric ratios. Purification of (S_S)-**366a-c** *via* column

chromatography on silica gel afforded the pure esters (S_S)-**366a-c** in moderate to high yields (Table 15).[154]

The diastereoselectivity and the efficiency of these Mannich-type additions was similar to the addition across *N*-(*tert*-butanesulfinyl)-α-chloroaldimines **270a**, leading to the conclusion that these addition products (S_S)-**366a-c** also have potential for the synthesis of chiral aziridines. The reaction of benzyl ester **347a** with aldimine (S_S)-**266a** afforded the *syn*-adduct (S_S)-**366a** in the lowest yield, although the addition proceeded with a high stereoselectivity. The ethyl ester (S_S)-**366c** was in the most efficient way synthesized *via* this approach.[154]



Scheme 123

Table 15. Overview of the Mannich-type reaction of (S_S)-*N*-(*tert*-butanesulfinyl)-α-chloroaldimine (S_S)-**266a** with α-hydroxy esters **347** at -78 ° C.

R	dr [a]	Yield (%) [b]
Bn	95:5:0:0	51
Me	87:13:0:0	83
Et	82:18:0:0	75

[a] Determined *via* ^{1}H NMR of crude reaction mixtures
[b] Isolated yield of single diastereomer (dr > 99:1)

Based on ^{1}H NMR analysis, it was determined that the isolated major diastereomers were again the *syn*-adducts (*vide supra*). In analogy with the transition state models **TS-354B** and **TS-354C** (*vide supra*), which were proposed for the synthesis of (R_S,2*R*,3*R*)-γ-chloro-α-hydroxy-β-amino esters (R_S,2*R*,3*R*)-**351**, it was assumed that the Mannich-type addition

products (S_S)-**366a-c** would have an (S_S,2*S*,3*S*)-stereochemistry. Indeed, determination of the absolute stereochemistry of the crystalline (S_S)-γ-chloro-α-hydroxy-β-amino acid derivative (S_S)-**366b** by means of an X-ray diffraction analysis (in collaboration with Prof. K. W. Törnroos, Department of Chemistry, University of Bergen, Norway) proved this assumption (Figure 13). The (S_S,2*S*,3*S*)-stereochemistry of the other (S_S)-γ-chloro-α-hydroxy-β-amino esters (S_S)-**366a,c** was again confirmed by comparison of the vicinal coupling constant $^3J_{H2\text{-}H3}$ = 1.10 Hz and the ^{1}H NMR chemical shift of H3 (4.00 ppm),[154] which were in the same range as for the (S_S)-γ-chloro-α-hydroxy-β-amino ester (S_S)-**366b**.

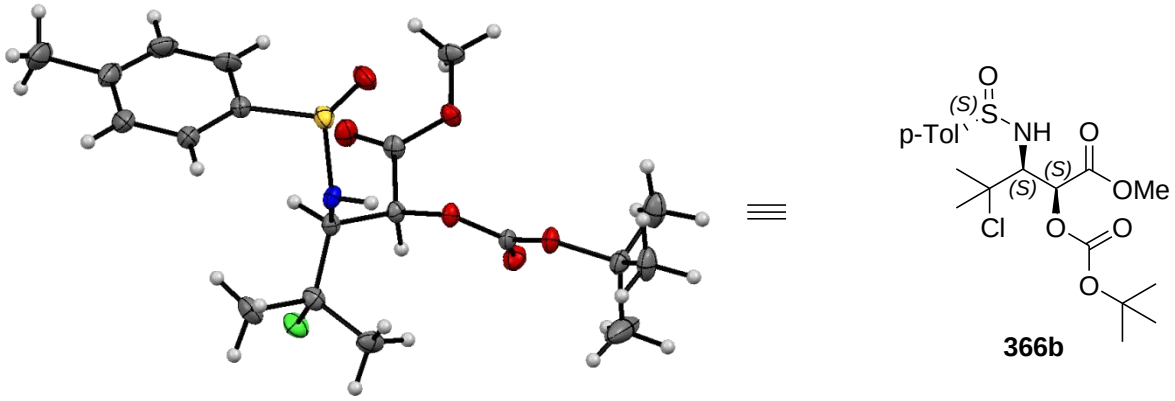
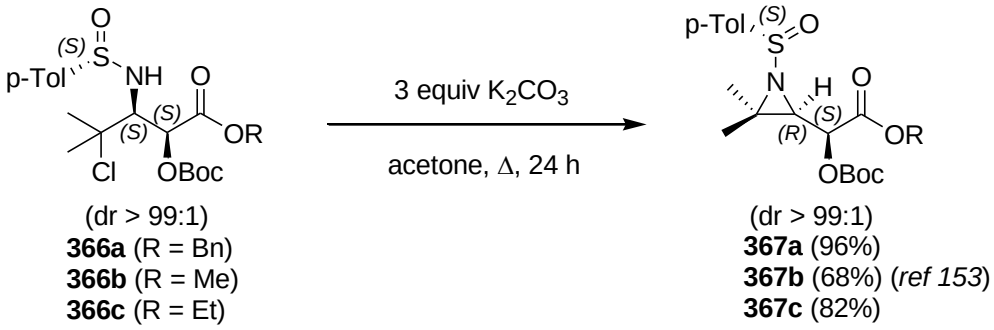


Figure 13. X-ray diffraction analysis of (S_S,2*S*,3*S*)-γ-chloro-α-hydroxy-β-amino ester (S_S,2*S*,3*S*)-**366b**

The (S_S,2*S*,3*S*)-γ-chloro-α-hydroxy-β-amino esters (S_S,2*S*,3*S*)-**366** were cyclized to the corresponding *N*-sulfinyl-β,γ-aziridino-α-hydroxy esters **367** upon treatment with K_2CO_3 in acetone under reflux in good yields (68-96%) (Scheme 124).



(dr > 99:1)
366a (R = Bn)
366b (R = Me)
366c (R = Et)

(dr > 99:1)
367a (96%)
367b (68%) (*ref 153*)
367c (82%)

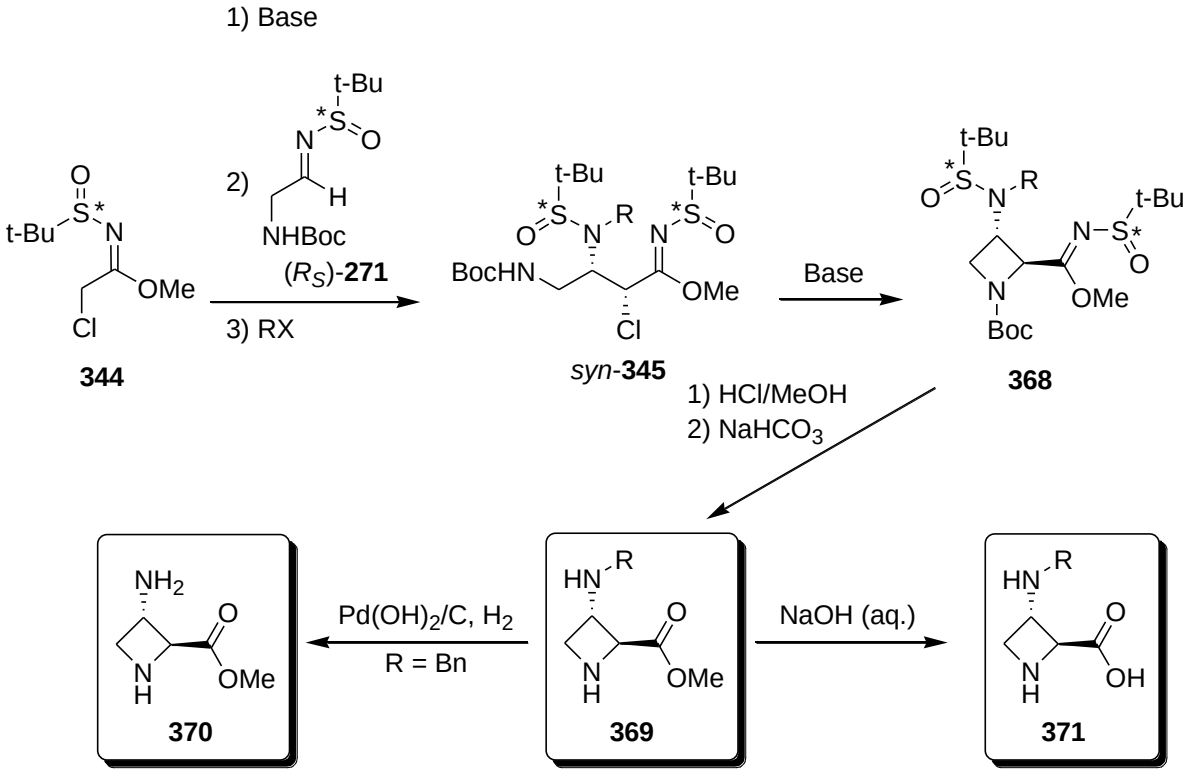
Scheme 124

In conclusion, it was demonstrated that new (*R*$_S$,2*R*,3*R*)- and (*S*$_S$,2*S*,3*S*)-*N*-sulfinyl-γ-chloro-α-hydroxy-β-amino esters could be synthesized in high yields and excellent diastereomeric ratios *via* stereoselective Mannich-type reactions of *O*-Boc glycolic esters across chiral *N*-sulfinyl-α-chloroimines. In these reactions, the influence of the used imine in the Mannich-type addition, i.e. *N*-(*tert*-butanesulfinyl)-α-chloroaldimines or *N*-(*p*-toluenesulfinyl)-α-chloroaldimines, did not cause significant differences in the obtained yields and diastereoselectivities. Furthermore, the γ-chloro-α-hydroxy-β-amino esters proved to be versatile building blocks in asymmetric synthesis of novel *syn*-β,γ-aziridino-α-hydroxy esters and *trans*-alkyl oxazolidinonecarboxylates.

4. Perspectives

In this PhD thesis, the efficient and enantioselective synthesis of the α-chloro-β,γ-diamino imidate **345** (Scheme 109) has been reported. In light of the synthetic potential of this compound **345**, belonging to the class of α-chloro-β,γ-diamino carboxylic acid derivatives, some straightforward transformations can be foreseen which could provide the desired 4,4-unsubstituted 3-aminoazetidine-2-carboxylic derivatives **339** (Scheme 107), constituting interesting building blocks for the synthesis of oligopeptides.

In analogy with the preparation of α-chloro-β,γ-diamino imidate **345**, the synthesis of β-alkylamino imidates **368** could be performed *via* Mannich-type addition of the enolate obtained by deprotonation of a chiral α-chloro-*N*-*tert*-butanesulfinyl imidate **344** (Scheme 109) with an appropriate base (LiHMDS, LDA,...), across chiral *N*-*tert*-butanesulfinyl-α-*N*-Boc-aminoacetaldimine **271** (Scheme 67) and subsequent quenching with an alkyl halide (Scheme 125). Using different combinations of enantiomeric α-chloro-*N*-*tert*-butanesulfinyl imidates **344** and chiral *N*-*tert*-butanesulfinyl-α-*N*-Boc-aminoacetaldimines **271**, it should be possible to obtain an α-chloro-β,γ-diamino imidate *syn*-**345** with a *syn*-stereochemistry. Base-induced cyclization of compounds *syn*-**345** could provide access to the protected methyl 3-aminoazetidine-2-imidates **368**, which can be transformed into the corresponding 3-aminoazetidine-2-carboxylates **369** by deprotection of the Boc- and sulfinyl groups with methanolic HCl.[191] Selective transformations of these 3-aminoazetidine-2-carboxylates **369**, by hydrolysis of the ester moiety or debenzylation of the 3-benzylamino group could give access to 3-aminoazetidine-2-carboxylic acids **371** and totally *N*-deprotected methyl 3-amino-azetidine-2-carboxylate **370**, respectively. These target compounds could be used as valuable building blocks in the synthesis of oligopeptides.

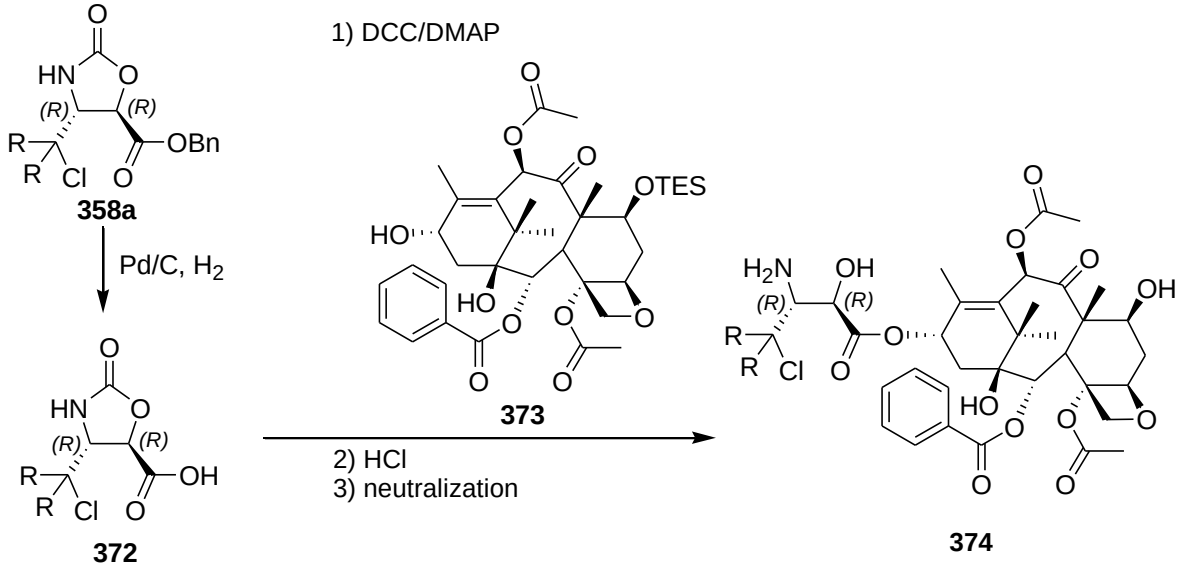


Scheme 125

As mentioned before, the α-hydroxy-β-amino carboxylic acid unit is present in a wide range of biologically active molecules, such as paclitaxel **13a** and docetaxel **13b**, which are both known for their anti-mitotic activity (Figure 5). For this reason, α-hydroxy-β-amino carboxylic acid derivatives represent versatile building blocks for the synthesis of novel taxoids with potential antitumor activity,[205,206,207] *via* a well-studied coupling reaction with the trimethylsilyl ether of baccatine III (**373**).[208]

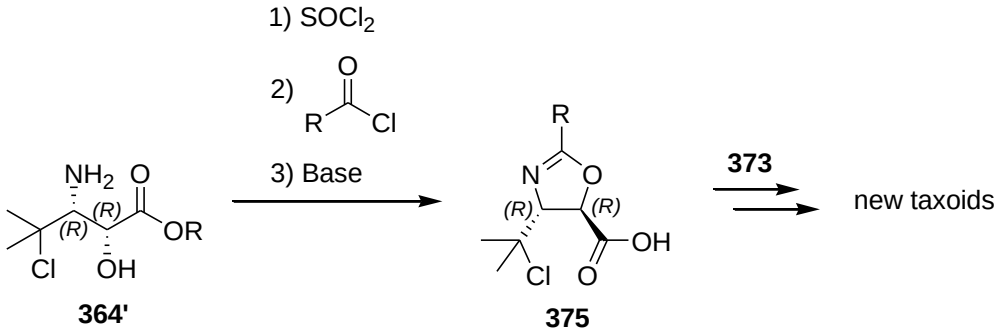
As hydrolysis of *syn*-γ-chloro-α-functionalized-β-amino esters resulted consistently in the synthesis of the corresponding *trans*-α,β-disubstituted γ-lactones, a new strategy could be developed (Scheme 126), starting from the *trans*-4-alkyl oxazolidin-2-one-5-carboxylic esters **358**, derived from the corresponding *syn*-γ-chloro-α-hydroxy-β-amino esters **364** (Scheme 121). *O*-Debenzylation of benzyl *trans*-4-alkyl oxazolidin-2-one-5-carboxylic ester **358a** *via* Pd/C-catalyzed hydrogenolysis, could provide the corresponding carboxylic acid **372**, which will not rearrange to the corresponding γ-lactone due to configurational constraints.

Subsequent (Steglich-)coupling with the trimethylsilyl ether of baccatine III (**373**) and acid-mediated cleavage of the protective groups would afford taxoid compounds **374**.



Scheme 126

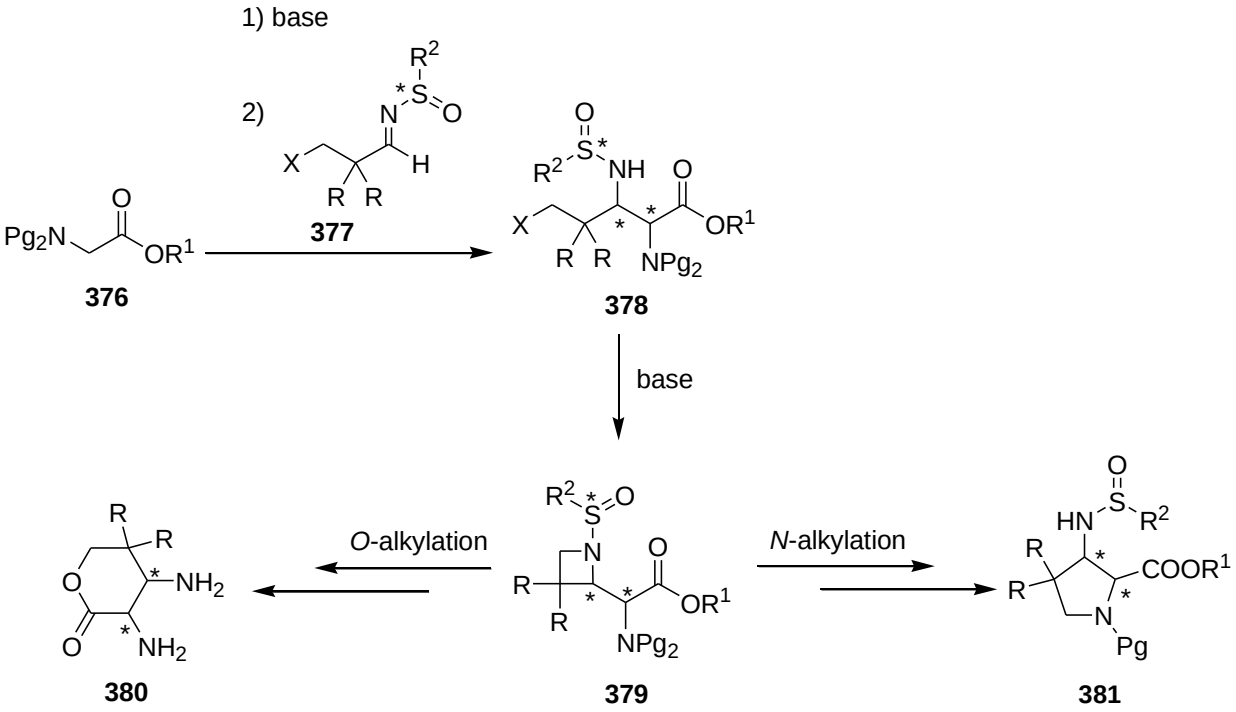
In an extent of this methodology, also some new *trans*-substituted oxazolines **375** could be synthesized starting from *syn*-γ-chloro-α-hydroxy-β-amino esters **364'** (Scheme 127). Treatment of amino alcohols **364'** with thionyl chloride, an acyl chloride and a base could provide the desired oxazolines **375**,[209,210] which can afford new taxoid compounds *via* the previously described coupling reaction with the trimethylsilyl ether of baccatine III (**373**).



Scheme 127

In order to provide an efficient access to a novel class of enantiopure δ-chloro-α,β-diamino esters **378**, a stereoselective Mannich-type addition of the enolates derived from deprotonation of *N*-protected glycine esters **376** with an appropriate base (LiHMDS, LDA,...), across chiral *N*-sulfinyl-β-haloaldimines **377** could be developed (Scheme 128). In this way,

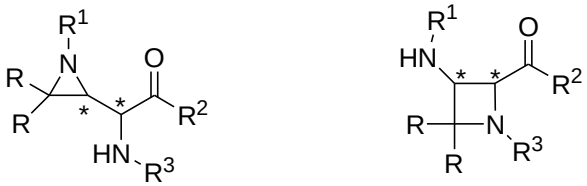
2-azetidinylglycinates **379** could be synthesized as analogs of 2-(aminomethyl)azetidines, from which Pt-complexes have been derived, known for their anti-cancer activity.[211] In addition, 2-azetidinylglycinates **379** have also potential as building blocks for the synthesis of α,β-diamino-δ-valerolactones **380** and 3-aminopyrrolidine-2-carboxylic acid derivatives **381**.



Scheme 128

Furthermore, the synthesized β,γ-aziridino-α-amino carboxylic acid derivatives and 3-aminoazetidine-2-carboxylates can be used as α- or β-amino acid building blocks for the synthesis of short synthetic peptides **382** and **383** (Figure 14) or foldamers, by coupling reactions with other (non-)natural amino acid residues.[212,213] These conformationally constrained α- and β-amino acids have become very interesting in biologically active peptides due to their ability as synthons in the preparation of peptide-based drug molecules. Moreover, these (non-)natural amino acid residues can influence the principal secondary structural motifs adopted by the assembled peptides, such as the occurrence of 14-, 12-, 10-, 12/10-, and 8-helices, as well as the hairpin turn, extended structures, stacks, and sheets.[214] In recent years,

the chemistry of foldamers gained also a lot of attention, since these compounds are useful tools for studying different chemical, physico-chemical and biological problems.[49,215,216,217,218]



382 **383**

R^1 and/or R^2 and/or R^3 = peptide chain

Figure 14

5. Experimental part

5.1. 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 purification, unless stated otherwise. The enantiopure reagents (S_S)-*p*-toluenesulfinamide and (R_S)- and (S_S)-*tert*-butanesulfinamide were commercially available (ee > 98%).

Tetrahydrofuran (THF), diethyl ether (Et_2O) and toluene (PhMe) were freshly distilled under a nitrogen atmosphere from sodium and sodium/benzophenone ketyl prior to use, whereas dichloromethane (CH_2Cl_2) was distilled from calcium hydride. Methanol (MeOH) and ethanol (EtOH) were reacted in the presence of magnesium metal and iodine, distilled and kept over molecular sieves. Petroleum ether refers to the 40-60 °C boiling fraction.

The purification of the reaction mixtures was performed by column chromatography with silica gel (Acros, 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 (Merck, Kieselgel 60 F_{254}, precoated 0.25 mm) using standard visualization techniques or agents: UV fluorescence (254 nm and 366 nm), coloring with iodine vapors or with potassium permanganate solution.

High resolution ^{1}H NMR (300 MHz), ^{13}C NMR (75 MHz) spectra were recorded on a Jeol Eclipse FT 300 NMR spectrometer at room temperature. Peak assignments were obtained with the aid of DEPT, COSY and/or HSQC spectra. The compounds were diluted in deuterated solvents, quoted in parts per million (ppm) with tetramethylsilane (TMS, $\delta = 0$ ppm) as internal standard unless specified otherwise.

IR spectra were recorded on a Perkin Elmer Spectrum BX FT-IR Spectrometer. All compounds were analyzed in neat form with an ATR (Attenuated Total Reflectance) accessory. Only selected absorbances (ν_{max}/cm^{-1}) were reported.

LC-MS analysis was performed with Agilent 1100 series SL (ES, 4000 V) equipment, preceded by a reverse phase LC-column (Eclipse plus C18 column). The LC column has dimensions of 50x4.6 mm and has a particle size of 3.5 μm. Gradient elution was used (30% acetonitrile in water to 100% acetonitrile over 6 minutes) and the MS analysis was performed *via* electron-spray ionization at 4 kV (positive mode) or 3.5 kV (negative mode) and fragmentation at 70 eV, with only molecular ions ($M + H^+$) and major peaks being reported with intensities quoted as percentage of the base peak, using either an LC-MS coupling or a direct inlet system.

Chiral HPLC analysis was performed using a Daicel Chiralcel OD-(R)H column [cellulose tris (3,5-dimethylphenylcarbamate) coated on 5 μm silica gel] or OJ-RH column [cellulose tris (4-methylbenzoate) coated on 5 μm silica gel] and with a solvent mixture of hexane/ethanol 99:1 as the mobile phase.

HRMS analysis was performed using an Agilent 1100 series HPLC coupled to an Agilent 6210 TOF-Mass Spectrometer, equipped with ESI/APCI-multimode source.

Elementary analyses were obtained by means of a Perkin Elmer series II CHNS/O elementary analyzer 2400.

Melting points of crystalline compounds were determined using a Büchi B-540 apparatus or a Kofler bench, type WME Heizbank of Wagner & Munz.

Optical rotations were determined using a JASCO P-2000 Series Polarimeter at a wavelength of 589 nm.

All microwave reactions were performed in a CEM Discover Benchmate with a continuous power output from 0 to 300 watt and a self-adjusting, single mode MW cavity. The reactions

were performed in 10 mL thick-walled Pyrex reaction vessels, closed with a 'snap-on' septa cap and equipped with a small stirring bar. A ramp time of maximum five minutes was used whereby the temperature was increased from room temperature to the desired one. This temperature was maintained during the course of the reaction for the indicated time. The temperature control system used a non-contact infrared sensor to measure the temperature on the bottom of the vessel and was used in a feedback loop with the on-board computer to regulate the temperature from 25 to 250 °C by adjusting the power output (1 Watt increments). The pressure control, IntelliVent™ Pressure Control system, used an indirect measurement of the pressure by sensing changes in the external deflection of the septa on the top of the sealed pressure vessel. Stirring was performed by a rotating magnetic plate, located below the floor of the microwave cavity. When the reaction was done, cooling of the vial was performed by a stream of clean air onto the vial, which decreased the temperature of a 2 mL solution from approximately 150 °C to 40 °C in less than 120 seconds.

5.2. Synthesis of (S_S)-*N*-*p*-toluenesulfinyl-α-chloroaldimines 266a-c and (S_S)-*N*-*p*-toluenesulfinyl-α,α-dichloroaldimines 266d-g

The synthesis of (S_S)-*N*-(2-chloro-2-methylpropylidene)-*p*-toluenesulfinamide **266a** is representative. To a flame dried round-bottomed flask, charged with α-chloroisobutyraldehyde **264a** (3.43 g, 32.21 mmol) in dry CH_2Cl_2 (100 mL), was added $Ti(OEt)_4$ (2 equiv, 14.70 g, 64.42 mmol) and (S_S)-*p*-toluenesulfinamide **265** (5.00 g, 32.21 mmol) under nitrogen atmosphere. The reaction mixture was stirred for 18 hours at room temperature. The reaction mixture was then poured into H_2O/CH_2Cl_2 (1:1) (200 mL) while rapidly stirring. The suspension was filtered over Celite® and the solids were washed with CH_2Cl_2 (2 x 50 mL). Subsequently, 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)-*N*-(2-chloro-2-methylpropylidene)-*p*-toluene-sulfinamide **266a**.

(S_S)-*N*-(2-Chloro-2-methylpropylidene)-*p*-toluenesulfinamide 266a. R_f = 0.25 (petroleum ether/EtOAc : 5/1). White crystals, yield 92%. $[\alpha]_D$ +326.2 (*c* 0.3, MeOH). 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, $CC\underline{H}_3(CH_3)$), 1.77 (3H, s, $CCH_3(C\underline{H}_3)$), 2.41 (3H, s, CH_3C_{arom}), 7.31 (2H, d, *J* = 8.0 Hz, CH_{arom}), 7.55 (2H, d, *J* = 8.0 Hz, CH_{arom}), 8.17 (1H, s, CH=N). ^{13}C NMR (75 MHz, $CDCl_3$): δ 21.5 ($\underline{C}H_3C_{arom}$), 29.0 ($C\underline{C}H_3(CH_3)$), 29.1 ($CCH_3(\underline{C}H_3)$), 66.6 ($\underline{C}(CH_3)_2$), 124.7 (2 x CH_{arom}), 129.9 (2 x CH_{arom}), 141.0 (C_{arom}), 142.0 (C_{arom}), 165.9 (CH=N). 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.

(S_S)-*N*-(2-Chloro-2-ethylbutylidene)-*p*-toluenesulfinamide 266b. R_f = 0.35 (petroleum ether/EtOAc : 9/1). Yellow oil, yield 66% (5.27 g). $[\alpha]_D$ +264.4 (*c* 1.1, $CHCl_3$). IR (cm^{-1}): ν_{max} 808, 1075, 1099, 1144, 1617. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.87 (3H, t, *J* = 7.2 Hz, $CCH_2C\underline{H}_3$), 0.97 (3H, t, *J* = 7.2 Hz, $CCH_2C\underline{H}_3$), 1.89-2.13 (4H, m, $C(C\underline{H}_2CH_3)_2$), 2.40 (3H, s, CH_3C_{arom}), 7.30 (2H, d, *J* = 8.3 Hz, CH_{arom}), 7.55 (2H, d, *J* = 8.3 Hz, CH_{arom}), 8.11 (1H, s, CH=N). ^{13}C NMR (75 MHz, $CDCl_3$): δ 8.7 ($CCH_2\underline{C}H_3$), 8.8 ($CCH_2\underline{C}H_3$), 21.5 ($\underline{C}H_3C_{arom}$), 32.0 ($C\underline{C}H_2CH_3$), 32.1 ($C\underline{C}H_2CH_3$), 76.1 (CCl), 124.7 (2 x CH_{arom}), 130.0 (2 x CH_{arom}), 141.3 (C_{arom}), 142.1 (C_{arom}), 166.2 (C=N). MS (ES, pos. mode) *m/z* (%): 263 (100), 272/274 (M + H^+, 60). HRMS (ES) calcd for $C_{13}H_{18}ClNOS$: 272.0870 MH^+; found: 272.0864.

(S_S)-*N*-(1-Chlorocyclohexylmethylidene)-*p*-toluenesulfinamide 266c. R_f = 0.31 (petroleum ether/EtOAc : 9/1). Colorless oil, yield 30% (0.80 g). $[\alpha]_D$ +251.0 (*c* 1.2, $CHCl_3$). IR (cm^{-1}): ν_{max} 809, 1075, 1098, 1144, 1618. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.18-1.35 (1H, m) and 1.49-2.13 (9H, m) ($(CH_2)_5$), 2.41 (3H, s, CH_3C_{arom}), 7.31 (2H, d, *J* = 8.3 Hz, CH_{arom}), 7.55 (2H, d, *J* = 8.3 Hz, CH_{arom}), 8.15 (1H, s, CH=N). ^{13}C NMR (75 MHz, $CDCl_3$): δ 21.5 ($\underline{C}H_3C_{arom}$), 22.0 (2 x CH_2), 25.0 (CH_2), 36.6 (2 x CH_2), 71.6 (CCl), 124.8 (2 x CH_{arom}), 130.0 (2 x CH_{arom}), 141.3 (C_{arom}),

142.0 (C_{arom}), 166.0 (C=N). MS (ES, pos. mode) *m/z* (%): 177 (100), 284/286 ($M + H^+$, 40). HRMS (ES) calcd for $C_{14}H_{18}ClNOS$: 284.0870 MH^+; found: 284.0861.

(S_S)-*N*-(2,2-Dichloropropylidene)-*p*-toluenesulfinamide 266d. R_f = 0.38 (petroleum ether/EtOAc : 9/1). Colorless oil, yield 40% (1.67 g). $[\alpha]_D$ +500.7 (*c* 1.0, $CHCl_3$). IR (cm^{-1}): ν_{max} 808, 1072, 1102, 1619. ^1H NMR (300 MHz, $CDCl_3$): δ 2.27 (3H, s, CH_3CCl_2), 2.40 (3H, s, CH_3C_{arom}), 7.32 (2H, d, *J* = 8.1 Hz, CH_{arom}), 7.55 (2H, d, *J* = 8.1 Hz, CH_{arom}), 8.22 (1H, s, CH=N). ^{13}C NMR (75 MHz, $CDCl_3$): δ 21.5 ($\underline{C}H_3C_{arom}$), 32.5 ($\underline{C}H_3CCl_2$), 82.9 ($\underline{C}Cl_2$), 124.7 (2 x CH_{arom}), 130.1 (2 x CH_{arom}), 140.1 (C_{arom}), 142.4 (C_{arom}), 160.5 (C=N). MS (ES, pos. mode) *m/z* (%): 139 (100), 264/266/268 ($M + H^+$, 20).

(S_S)-*N*-(2,2-Dichlorobutylidene)-*p*-toluenesulfinamide 266e. R_f = 0.43 (petroleum ether/EtOAc : 9/1). Colorless oil, yield 59% (2.30 g). $[\alpha]_D$ +405.0 (*c* 1.3, $CHCl_3$). IR (cm^{-1}): ν_{max} 808, 1074, 1101, 1619. ^1H NMR (300 MHz, $CDCl_3$): δ 1.15 (3H, t, *J* = 7.2 Hz, $C\underline{H}_3CH_2$), 2.39 (3H, s, CH_3C_{arom}), 2.40 (1H, dxq, *J* = 14.5 Hz, 7.2 Hz, $C\underline{H}(H)CH_3$), 2.43 (1H, dxq, *J* = 14.5 Hz, 7.2 Hz, $CH(\underline{H})CH_3$), 7.30 (2H, d, *J* = 8.1 Hz, CH_{arom}), 7.55 (2H, d, *J* = 8.1 Hz, CH_{arom}), 8.20 (1H, s, CH=N). ^{13}C NMR (75 MHz, $CDCl_3$): δ 9.3 ($\underline{C}H_3CH_2$), 21.5 ($\underline{C}H_3C_{arom}$), 37.2 ($CH_3\underline{C}H_2$), 88.5 ($\underline{C}Cl_2$), 124.7 (2 x CH_{arom}), 130.0 (2 x CH_{arom}), 140.3 (C_{arom}), 142.3 (C_{arom}), 160.5 (C=N). MS (ES, pos. mode) *m/z* (%): 139 (100), 278/280/282 ($M + H^+$, 10).

(S_S)-*N*-(2,2-Dichloropentylidene)-*p*-toluenesulfinamide 266f. R_f = 0.44 (petroleum ether/EtOAc : 9/1). Colorless oil, yield 47% (1.77 g). $[\alpha]_D$ +352.5 (*c* 1.1, $CHCl_3$). IR (cm^{-1}): ν_{max} 808, 1076, 1102, 1619. ^1H NMR (300 MHz, $CDCl_3$): δ 0.96 (3H, t, *J* = 7.4 Hz, $C\underline{H}_3CH_2$), 1.53-1.73 (2H, m, $CH_3C\underline{H}_2$), 2.29-2.43 (2H, m, CH_2CCl_2), 2.40 (3H, s, CH_3C_{arom}), 7.31 (2H, d, *J* = 7.7 Hz, CH_{arom}), 7.55 (2H, d, *J* = 7.7 Hz, CH_{arom}), 8.18 (1H, s, CH=N). ^{13}C NMR (75 MHz, $CDCl_3$): δ 13.5 ($\underline{C}H_3CH_2$), 18.3 ($CH_3\underline{C}H_2$), 21.5 ($\underline{C}H_3C_{arom}$), 45.7 ($\underline{C}H_2CCl_2$), 87.5 ($\underline{C}Cl_2$), 124.7 (2 x CH_{arom}), 130.0 (2 x CH_{arom}), 140.2 (C_{arom}), 142.4 (C_{arom}), 160.6 (C=N). MS (ES, pos. mode) *m/z* (%): 139 (100), 292/294/296 ($M + H^+$, 10).

(S_S)-*N*-(2,2-Dichloro-3-methylbutylidene)-*p*-toluenesulfinamide 266g. R_f = 0.57 (petroleum ether/EtOAc : 9/1). Colorless oil, yield 56% (2.10 g). $[\alpha]_D$ +314.8 (*c* 1.1, $CHCl_3$). IR (cm^{-1}): ν_{max} 808, 1075, 1103, 1622. ^1H NMR (300 MHz, $CDCl_3$): δ 1.10 (3H, d, *J* = 6.6 Hz, ($C\underline{H}_3(CH_3)CH$), 1.12 (3H, d, *J* = 6.6 Hz, ($CH_3(C\underline{H}_3)CH$), 2.39 (3H, s, CH_3C_{arom}), 2.61 (1H, sept, *J* = 6.6 Hz, $(CH_3)_2C\underline{H}$), 7.31 (2H, d, *J* = 7.8 Hz, CH_{arom}), 7.56 (2H, d, *J* = 7.8 Hz, CH_{arom}), 8.15 (1H, s, CH=N). ^{13}C NMR (75 MHz, $CDCl_3$): δ 17.9 ($\underline{C}H_3(CH_3)CH$), 18.0 ($CH_3(\underline{C}H_3)CH$), 21.5 ($\underline{C}H_3C_{arom}$), 40.6 $(CH_3)_2\underline{C}H$), 93.3 ($\underline{C}Cl_2$), 124.7 (2 x CH_{arom}), 130.0 (2 x CH_{arom}), 140.3 (C_{arom}), 142.3 (C_{arom}), 161.0 (C=N). MS (ES, pos. mode) *m/z* (%): 139 (100), 292/294/296 (M + H^+, 5).

5.3. Synthesis of (S_S)-*N*-*p*-toluenesulfinyl-α-chloroaldimine 266h

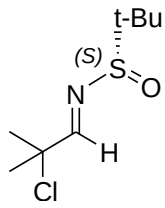
To a flame dried round-bottomed flask, charged with α-chloroacetaldehyde **264h** (1.63 g, 20.76 mmol) in dry CH_2Cl_2 (30 mL), was added $CuSO_4$ (3 equiv, 9.94 g, 62.30 mmol) and (S_S)-*p*-toluenesulfinamide **265** (3.22 g, 20.76 mmol) under nitrogen atmosphere. The reaction mixture was stirred for 14 hours at room temperature. The reaction mixture was then filtered over Celite® and the filter cake was washed with CH_2Cl_2 (2 x 15 mL). Evaporation of the solvent *in vacuo* afforded 4.15 g (19.93 mmol) of the (S_S)-*N*-(2-chloroethylidene)-*p*-toluenesulfinamide **266h** as a pale yellow oil. The crude product thus obtained, 90% pure by ^1H-NMR analysis, was used without further purification or characterization, due to the instability of compound **266h**.

(S_S)-*N*-(2-Chloroethylidene)-*p*-toluenesulfinamide 266h. Pale yellow oil, yield 96%. ^1H NMR (300 MHz, $CDCl_3$): δ 2.41 (3H, s, CH_3C_{arom}), 4.25 (1H, dxd, *J* = 13.8 Hz, 4.4 Hz, $C\underline{H}(H)Cl$), 4.30 (1H, dxd, *J* = 13.8 Hz, 4.4 Hz, $CH(\underline{H})Cl$), 7.33 (2H, d, *J* = 8.3 Hz, CH_{arom}), 7.56 (2H, d, *J* = 8.3 Hz, CH_{arom}), 8.18 (1H, t, *J* = 4.4 Hz, CH=N).

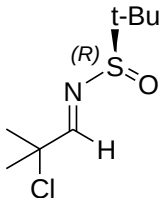
5.4. Synthesis of (R_S)- and (S_S)-*N*-*tert*-butanesulfinyl-α-chloroaldimines 270a

The synthesis of (S_S)-*N*-(2-chloro-2-methylpropylidene)-*tert*-butanesulfinamide (S_S)-**270a** is representative. To a flame dried round-bottomed flask, charged with α-chloroisobutyraldehyde **264a** (2.13 g, 20.00 mmol) in dry THF (75 mL), was added $Ti(OEt)_4$ (2 equiv, 9.13 g, 40.00 mmol) and (S_S)-*tert*-butanesulfinamide (S_S)-**269** (2.42 g, 20.00 mmol) under nitrogen atmosphere. The reaction mixture was stirred for four hours at reflux temperature. The reaction mixture was then poured into brine/EtOAc (1:1) (150 mL) while rapidly stirring. The suspension was filtered over Celite® and the solids were washed with EtOAc (2 x 30 mL). Subsequently, the combined organic phases were dried ($MgSO_4$), filtered and evaporated *in vacuo*. The crude product was purified by column chromatography to yield 2.90 g (13.80 mmol) of pure (S_S)-*N*-(2-chloro-2-methylpropylidene)-*tert*-butanesulfinamide (S_S)-**270a**.

(S_S)-*N*-(2-Chloro-2-methylpropylidene)-*tert*-butanesulfinamide (S_S)-270a. R_f = 0.25 (petroleum ether/EtOAc : 5/1). Colorless oil, yield 69%. $[\alpha]_D$ +365.2 (*c* 1.2, $CHCl_3$). IR (cm^{-1}): ν_{max} 1089, 1365, 1622. ^1H NMR (300 MHz, $CDCl_3$): δ 1.22 (9H, s, *t*Bu), 1.77 (3H, s, $CC\underline{H}_3(CH_3)$), 1.78 (3H, s, $CCH_3(C\underline{H}_3)$), 8.02 (1H, s, CH=N). ^{13}C NMR (75 MHz, $CDCl_3$): δ 22.4 ($C(\underline{C}H_3)_3$), 29.1 ($C\underline{C}H_3(CH_3)$), 29.3 ($CCH_3(\underline{C}H_3)$), 57.6 ($\underline{C}(CH_3)_3$), 66.7 ($\underline{C}(CH_3)_2$), 168.2 (CH=N). MS (ES, pos. mode) *m/z* (%): 210/212 ($M + H^+$, 100).



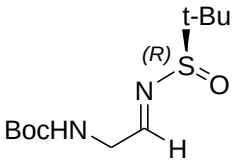
(R_S)-*N*-(2-Chloro-2-methylpropylidene)-*tert*-butanesulfinamide (R_S)-270a. Viscous white oil, yield 77%. All spectroscopic data were in good agreement with reported data of **(R_S)-270a**.[150]



5.5. Synthesis of (R_S)- and (S_S)-*N*-*tert*-butanesulfinyl-α-functionalized aldimines 270b and 271

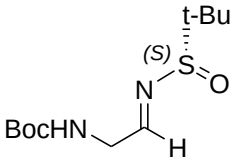
The synthesis of (R_S)-*N*-(2-*tert*-butoxycarbonylaminoethylidene)-*tert*-butanesulfinamide (R_S)-**271** is representative. To a flame dried round-bottomed flask, charged with *N*-Boc-α-aminoacetaldehyde **267** (0.10 g, 0.63 mmol) in dry CH_2Cl_2 (5 mL), was added $CuSO_4$ (3 equiv, 0.30 g, 1.89 mmol) and (R_S)-*tert*-butanesulfinamide (R_S)-**269** (0.08 g, 0.63 mmol) under nitrogen atmosphere. The reaction mixture was stirred for 24 hours at room temperature. The reaction mixture was then filtered over Celite® and the filter cake was washed with CH_2Cl_2 (2 x 2 mL). Evaporation of the solvent *in vacuo* and subsequent filtration over silica gel afforded 0.16 g (0.62 mmol) of the pure (R_S)-*N*-(2-*tert*-butoxycarbonylaminoethylidene)-*tert*-butanesulfinamide (R_S)-**271**.

(R_S)-*N*-(2-*tert*-Butoxycarbonylaminoethylidene)-*tert*-butanesulfinamide (R_S)-271. Yellow



oil, yield 99%. IR (cm^{-1}): ν_{max} 752, 1064, 1164, 1365, 1634, 1699, 3322. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.21 (9H, s, S*t*Bu), 1.46 (9H, s, O*t*Bu), 4.15 (1H, dxdxd, J = 19.8 Hz, 4.7 Hz, 2.2 Hz, C<u>H</u>(H)NH), 4.26 (1H, dxdxd, J = 19.8 Hz, 6.1 Hz, 2.2 Hz, CH(<u>H</u>)NH), 5.18 (1H, br s, NH), 8.07 (1H, t, J = 2.2 Hz, CH=N). ^{13}C NMR (75 MHz, $CDCl_3$): δ 22.3 (SC(<u>C</u>H_3)$_3$), 28.3 (OC(<u>C</u>H_3)$_3$), 45.4 (<u>C</u>H_2NH), 57.1 (S<u>C</u>(CH_3)$_3$), 79.8 (O<u>C</u>(CH_3)$_3$), 155.7 (N(C=O)O), 165.3 (CH=N). MS (ES, pos. mode) *m/z* (%): 207 (M + H^+ - isobutene, 100). HRMS (ES) calcd for $C_7H_{14}N_2O_3S$: 207.0798 MH^+ - isobutene; found: 207.0802.

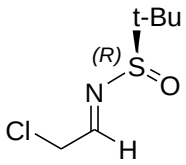
(S_S)-*N*-(2-*tert*-Butoxycarbonylaminoethylidene)-*tert*-butanesulfinamide (S_S)-271. Yellow



oil, yield 96%. $[\alpha]_D$ +86.1 (*c* 2.5, $CHCl_3$). IR (cm^{-1}): ν_{max} 754, 1064, 1163, 1365, 1633, 1696, 3331. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.21 (9H, s, S*t*Bu), 1.46 (9H, s, O*t*Bu), 4.10-4.20 (1H, m, C<u>H</u>(H)NH), 4.26 (1H, dxd, J

= 19.8 Hz, 5.0 Hz, CH(H)NH), 5.20 (1H, br s, NH), 8.05-8.08 (1H, m CH=N). ^{13}C NMR (75 MHz, $CDCl_3$): δ 22.4 ($SC(\underline{C}H_3)_3$), 28.4 ($OC(\underline{C}H_3)_3$), 45.5 ($\underline{C}H_2NH$), 57.2 ($S\underline{C}(CH_3)_3$), 80.0 ($O\underline{C}(CH_3)_3$), 155.7 (N(C=O)O), 165.1 (CH=N). MS (ES, pos. mode) *m/z* (%): 261 ($M - H^+$).

(R_S)-*N*-(2-Chloroethylidene)-*tert*-butanesulfinamide (R_S)-270b. Pale yellow oil, yield 92%.

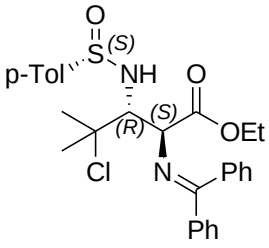


All spectroscopic data were in good agreement with reported data of (R_S)-**270b**.[151]

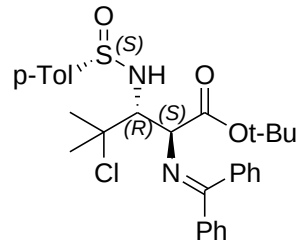
5.6. Synthesis of (S_S,2*S*,3*R*)-alkyl 2-diphenylmethyleneamino-4-chloro-4-methyl-3-(*p*-toluenesulfinylamino)pentanoates *anti*-277

The synthesis of (S_S,2*S*,3*R*)-alkyl 2-diphenylmethyleneamino-4-chloro-4-methyl-3-(*p*-toluenesulfinylamino)pentanoate *anti*-**277a** 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, 2.5M in hexane, 2.97 mL) under nitrogen atmosphere. The reaction mixture was stirred for five minutes at 0 °C and was subsequently cooled to -78 °C. After five minutes, a solution of *N*-(diphenylmethylene)glycine ethyl ester **273a** (1.1 equiv, 6.76 mmol, 1.81 g) in dry THF (5 mL) was slowly added and the resulting solution was stirred for one hour at -78 °C. After deprotonation, the reaction mixture was cooled to -90 °C and a solution of (S_S)-*N*-*p*-toluenesulfinyl-α-chloroisobutyraldimine **266a** (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 five minutes. To the reaction mixture was added a saturated solution of NH_4Cl (40 mL) while stirring was continued at -90 °C for two minutes. The reaction mixture was brought to room temperature, followed by an extraction with EtOAc (3 x 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*-**277a** as a 89:11 mixture with *syn*-adduct *syn*-**277a**.



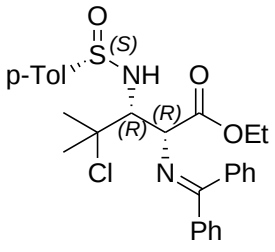
(S_S,2*S*,3*R*)-Ethyl 2-diphenylmethyleneamino-4-chloro-4-methyl-3-(*p*-toluenesulfinylamino)pentanoate *anti*-277a. R_f = 0.23 (petroleum ether/EtOAc : 3/1). White crystals, yield 79%, dr 89:11. Mp 52.7 ± 0.3 °C. IR (cm^{-1}): ν_{max} 1624, 1731, 3280. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.19 (3H, t, *J* = 7.2 Hz, $CH_2C\underline{H}_3$), 1.62 (3H, s, $CC\underline{H}_3(CH_3)$), 1.64 (3H, s, $CCH_3(C\underline{H}_3)$), 2.37 (3H, s, $C_{arom}CH_3$), 3.90 (1H, dxd, *J* = 8.8 Hz, 3.3 Hz, NHC<u>H</u>), 3.99-4.16 (2H, m, $OC\underline{H}_2CH_3$), 4.58 (1H, d, *J* = 3.3 Hz, CHN), 5.47 (1H, d, *J* = 8.8 Hz, N<u>H</u>CH), 7.14-7.77 (14H, m, CH_{arom}). ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.0 ($CH_2\underline{C}H_3$), 21.5 ($C_{arom}\underline{C}H_3$) 30.6 ($C\underline{C}H_3(CH_3)$), 30.8 ($CCH_3(\underline{C}H_3)$), 61.5 ($O\underline{C}H_2CH_3$), 66.4 and 67.2 (NHCH and CHN), 73.0 ($\underline{C}(CH_3)_2$), 125.6, 127.8, 128.2, 128.7, 128.9, 129.4, 129.6, 130.8 ($14xCH_{arom}$), 136.0, 139.3, 141.3, 142.9 ($4xC_{arom}$), 170.7 and 172.6 (C=N and C=O). 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*-277c. 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, $C(CH_3)_3$), 1.64 (3H, s, $CC\underline{H}_3(CH_3)$), 1.69 (3H, s, $CCH_3(C\underline{H}_3)$), 2.37 (3H, s, $C_{arom}CH_3$), 3.82 (1H, dxd, *J* = 8.8 Hz, 2.2 Hz, NHC<u>H</u>), 4.44 (1H, d, *J* = 2.2 Hz, CHN), 5.62 (1H, d, *J* = 8.8 Hz, NH), 7.15-7.78 (14H, m, CH_{arom}). ^{13}C NMR (75 MHz, $CDCl_3$): δ 21.3 ($C_{arom}\underline{C}H_3$), 27.8 ($C(\underline{C}H_3)_3$), 30.4 ($C\underline{C}H_3(CH_3)$), 30.8 ($CCH_3(\underline{C}H_3)$), 66.6 and 67.3 (NHCH and CHN), 73.0 ($\underline{C}(CH_3)_2$), 82.2 ($O\underline{C}(CH_3)_3$), 125.7, 127.9, 128.0, 128.5, 128.7, 129.3, 129.4, 130.5 ($14xCH_{arom}$), 136.0, 139.4, 141.0, 142.5 ($4xC_{arom}$), 169.5 and 172.3 (C=N and C=O). 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.

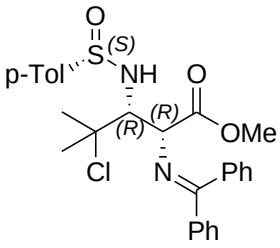
5.7. Synthesis of (S_S,2*R*,3*R*)-alkyl 2-diphenylmethyleneamino-4-chloro-4-methyl-3-(*p*-toluenesulfinylamino)pentanoates *syn*-277

The synthesis of (S_S,2*R*,3*R*)-ethyl 2-diphenylmethyleneamino-4-chloro-4-methyl-3-(*p*-toluenesulfinylamino)pentanoate *syn*-**277a** is representative. A solution of *N*-(diphenylmethylene)glycine ethyl ester **273a** (1.1 equiv, 6.76 mmol, 1.81 g) in THF (20 mL) was cooled to -78 °C under nitrogen atmosphere. A 1.0M solution of LiHMDS (1.1 equiv, 6.76 mL, 6.76 mmol) in THF was slowly added and the resulting solution was stirred for one hour at -78 °C. After deprotonation, a solution of (S_S)-*N*-*p*-toluenesulfinyl-α-chloroisobutyraldimine **266a** (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 minutes. To the reaction mixture was added a saturated solution of NH_4Cl (40 mL) while stirring at -78 °C for two minutes. The reaction mixture was brought to room temperature followed by an extraction with EtOAc (3 x 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*-**277a**.



(S_S,2*R*,3*R*)-Ethyl 2-diphenylmethyleneamino-4-chloro-4-methyl-3-(*p*-toluenesulfinyl-amino)pentanoate *syn*-277a. 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. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.30 (3H, t, *J* = 7.2 Hz, $CH_2C\underline{H}_3$), 1.51 (3H, s, $CC\underline{H}_3(CH_3)$), 1.63 (3H, s, $CCH_3(C\underline{H}_3)$), 2.45 (3H, s, $C_{arom}CH_3$), 4.21-4.38 (3H, m, NHC<u>H</u> and $OC\underline{H}_2CH_3$), 4.66 (1H, d, *J* = 1.1 Hz, CHN), 5.83 (1H, d, *J* = 8.3 Hz, N<u>H</u>CH), 7.13-7.19 (2H, m, CH_{arom}), 7.26-7.46 (8H, m, CH_{arom}), 7.51-7.54 (2H, m, CH_{arom}), 7.74 (2H, d, *J* = 8.3 Hz, CH_{arom}). ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.1 ($CH_2\underline{C}H_3$), 21.4 ($C_{arom}\underline{C}H_3$), 29.0 ($C\underline{C}H_3(CH_3)$), 30.6 ($CCH_3(\underline{C}H_3)$), 62.2 ($O\underline{C}H_2CH_3$), 65.6 and 67.1 (NHCH

and CHN), 72.6 ($\underline{C}(CH_3)_2$), 125.7, 127.1, 128.1, 128.6, 128.9, 129.0, 129.6, 130.7 ($14xCH_{arom}$), 136.4, 138.8, 141.3, 143.6 ($4xC_{arom}$), 169.6 and 171.7 (C=N and C=O). 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.

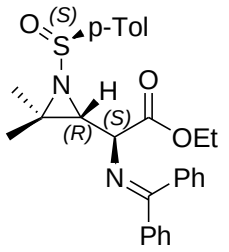
(*S*$_S$,2*R*,3*R*)-Methyl 2-diphenylmethyleneamino-4-chloro-4-methyl-3-(*p*-toluenesulfinyl-amino)pentanoate *syn*-277b. 

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. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.51 (3H, s, $CC\underline{H}_3(CH_3)$), 1.63 (3H, s, $CCH_3(C\underline{H}_3)$), 2.45 (3H, s, $C_{arom}CH_3$), 3.83 (3H, s, OCH_3), 4.30 (1H, dxd, *J* = 8.3 Hz, 1.7 Hz, NHC$\underline{H}$), 4.70 (1H, d, *J* = 1.7 Hz, CHN), 5.83 (1H, d, *J* = 8.3 Hz, N$\underline{H}$CH), 7.13-7.16 (2H, m, CH_{arom}), 7.28-7.45 (8H, m, CH_{arom}), 7.50-7.53 (2H, m, CH_{arom}), 7.74 (2H, d, *J* = 8.3 Hz, CH_{arom}). ^{13}C NMR (75 MHz, $CDCl_3$): δ 21.4 ($C_{arom}\underline{C}H_3$), 29.0 ($C\underline{C}H_3(CH_3)$), 30.6 ($CCH_3(\underline{C}H_3)$), 53.1 (OCH_3), 65.6 and 67.2 (NHCH and CHN), 72.4 ($\underline{C}(CH_3)_2$), 125.7, 127.0, 128.1, 128.7, 128.9, 129.0, 129.6, 130.8 ($14xCH_{arom}$), 136.4, 138.7, 141.3, 143.5 ($4xC_{arom}$), 170.2 and 171.8 (C=N and C=O). 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.

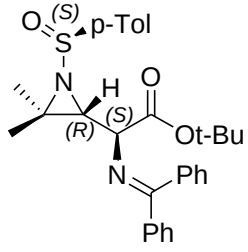
5.8. Synthesis of (*S*$_S$,2'*R*)-alkyl 2-diphenylmethyleneamino-2-[3,3-dimethyl-1-(*p*-toluenesulfinyl)aziridin-2-yl]acetates 278

The synthesis of (*S*$_S$,2*S*,2'*R*)-ethyl 2-diphenylmethyleneamino-2-[3,3-dimethyl-1-(*p*-toluenesulfinyl)aziridin-2-yl]acetate *anti*-**278a** is representative. To a solution of (*S*$_S$,2*S*,3*R*)-ethyl 2-diphenylmethyleneamino-4-chloro-4-methyl-3-(*p*-toluenesulfinylamino)pentanoate *anti*-**277a** (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 hours at reflux temperature. After 24 hours, 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 x 15

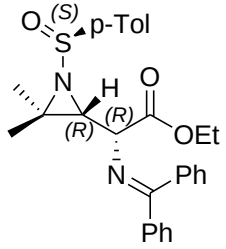
mL). The organic phase was dried ($MgSO_4$), filtered and evaporated *in vacuo*. The crude product was purified by column chromatography to yield 1.02 g (2.14 mmol) of (*S*$_S$,2*S*,2'*R*)-ethyl 2-diphenylmethyleneamino-2-[3,3-dimethyl-1-(*p*-toluenesulfinyl)aziridin-2-yl]acetate *anti*-**278a**.



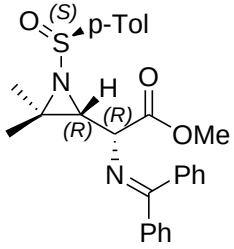
(*S*$_S$,2*S*,2'*R*)-Ethyl 2-diphenylmethyleneamino-2-[3,3-dimethyl-1-(*p*-toluenesulfinyl)-aziridin-2-yl]acetate *anti*-278a. R_f = 0.25 (petroleum ether/EtOAc : 3/1). White crystals, yield 73%. $[\alpha]_D$ - 24.1 (*c* 0.4, $CHCl_3$). Mp 103.8 ± 0.2 °C. IR (cm^{-1}): ν_{max} 1613, 1732. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.01 (3H, t, *J* = 7.2 Hz, $CH_2C\underline{H}_3$), 1.06 (3H, s, $CC\underline{H}_3(CH_3)$), 1.60 (3H, s, $CCH_3(C\underline{H}_3)$), 2.36 (3H, s, $C_{arom}CH_3$), 3.50 (1H, d, *J* = 8.3 Hz, $NC\underline{H}_{azir}CHN$), 3.53-3.66 (2H, m, $C\underline{H}_2CH_3$), 3.84 (1H, d, *J* = 8.3 Hz, $NCH_{azir}C\underline{H}N$), 7.02-7.05 (2H, m, CH_{arom}), 7.22 (2H, d, *J* = 8.26 Hz, CH_{arom}), 7.30-7.41 (6H, m, CH_{arom}), 7.55 (2H, d, *J* = 8.26 Hz, CH_{arom}), 7.59-7.63 (2H, m, CH_{arom}). ^{13}C NMR (75 MHz, $CDCl_3$): δ 13.8 ($CH_2\underline{C}H_3$), 20.9 ($CCH_3(\underline{C}H_3)$), 21.3 ($C_{arom}\underline{C}H_3$), 21.7 ($C\underline{C}H_3(CH_3)$), 42.0 ($N\underline{C}H_{azir}CHN$), 44.6 ($\underline{C}(CH_3)_2$), 60.8 ($\underline{C}H_2CH_3$), 65.4 ($NCH_{azir}\underline{C}HN$), 125.6, 128.0, 128.3, 128.9, 129.0, 129.2, 130.6 ($14xCH_{arom}$), 135.8, 139.4, 140.8, 143.1 ($4xC_{arom}$), 170.1 and 170.9 (C=N and C=O). 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*-278c. 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. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.23 (3H, s, $CC\underline{H}_3(CH_3)$), 1.25 (9H, s, $C(CH_3)_3$), 1.60 (3H, s, $CCH_3(C\underline{H}_3)$), 2.33 (3H, s, $C_{arom}CH_3$), 3.41 (1H, d, *J* = 8.3 Hz, $NC\underline{H}_{azir}CHN$), 3.86 (1H, d, *J* = 8.3 Hz, $NCH_{azir}C\underline{H}N$), 6.91-7.61 (14H, m, CH_{arom}). ^{13}C NMR (75 MHz, $CDCl_3$): δ 21.25 ($CCH_3(\underline{C}H_3)$), 21.28 ($C_{arom}\underline{C}H_3$), 21.8 ($C\underline{C}H_3(CH_3)$), 27.8 ($C(\underline{C}H_3)_3$), 42.2 ($N\underline{C}H_{azir}CHN$), 44.5 ($\underline{C}(CH_3)_2$), 65.5 ($NCH_{azir}\underline{C}HN$), 81.5 ($O\underline{C}(CH_3)_3$), 125.9, 127.9, 128.1, 128.7, 128.9, 129.2, 130.3 ($14xCH_{arom}$), 135.8, 139.7, 140.7, 143.3 ($4xC_{arom}$), 168.9 and 170.1 (C=N and C=O). 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*-278a. 

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. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.07 (3H, s, CC$\underline{H}_3$(CH$_3$)), 1.24 (3H, t, *J* = 6.9 Hz, CH$_2$C$\underline{H}_3$), 1.60 (3H, s, CCH$_3$(C$\underline{H}_3$)), 1.95 (3H, s, C$_{arom}$CH$_3$), 3.53 (1H, d, *J* = 9.4 Hz, NC$\underline{H}_{azir}$CHN), 3.77 (1H, d, *J* = 9.4 Hz, NCH$_{azir}$C$\underline{H}$N), 4.07-4.22 (2H, m, C$\underline{H}_2$CH$_3$), 6.54-6.72 (4H, m, CH$_{arom}$), 7.25-7.33 (5H, m, CH$_{arom}$), 7.39-7.50 (5H, m, CH$_{arom}$). ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.1 (CH$_2$$\underline{C}H_3$), 20.4 (CCH$_3$($\underline{C}H_3$)), 21.2 (C$_{arom}$$\underline{C}H_3$), 22.6 (C$\underline{C}H_3$(CH$_3$)), 42.2 (N$\underline{C}H_{azir}$CHN), 45.4 ($\underline{C}$(CH$_3$)$_2$), 61.2 ($\underline{C}H_2CH_3$), 64.4 (NCH$_{azir}$$\underline{C}$HN), 124.6, 127.7, 128.0, 128.3, 129.1, 129.2, 130.2 (14xCH$_{arom}$), 135.6, 138.9, 141.0, 143.2 (4xC$_{arom}$), 169.8 and 170.5 (C=N and C=O). MS (ES, pos. mode) *m/z* (%): 475 (M + H$^+$, 100). HRMS (ES) calcd for $C_{28}H_{30}N_2O_3S$: 475.2050 MH$^+$; found: 475.2071.

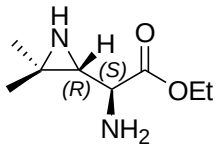
(*S*$_S$,2*R*,2'*R*)-Methyl 2-diphenylmethyleneamino-2-[3,3-dimethyl-1-(*p*-toluenesulfinyl)-aziridin-2-yl]acetate *syn*-278b. 

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. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.07 (3H, s, CC$\underline{H}_3$(CH$_3$)), 1.60 (3H, s, CCH$_3$(C$\underline{H}_3$)), 1.95 (3H, s, C$_{arom}$CH$_3$), 3.53 (1H, d, *J* = 8.8 Hz, NC$\underline{H}_{azir}$CHN), 3.70 (3H, s, OCH$_3$), 3.80 (1H, d, *J* = 8.8 Hz, NCH$_{azir}$C$\underline{H}$N), 6.54-6.86 (4H, m, CH$_{arom}$), 7.25-7.35 (5H, m, CH$_{arom}$), 7.39-7.50 (5H, m, CH$_{arom}$). ^{13}C NMR (75 MHz, $CDCl_3$): δ 20.4 (CCH$_3$($\underline{C}$H$_3$)), 21.2 (C$_{arom}$$\underline{C}H_3$), 22.5 (C$\underline{C}H_3$(CH$_3$)), 42.2 (N$\underline{C}H_{azir}$CHN), 45.4 ($\underline{C}$(CH$_3$)$_2$), 52.4 (OCH$_3$), 64.3 (NCH$_{azir}$$\underline{C}$HN), 124.5, 127.7, 128.0, 128.3, 129.1, 129.2, 130.3 (14xCH$_{arom}$), 135.5, 138.8, 141.0, 143.2 (4xC$_{arom}$), 170.4 and 170.6 (C=N and C=O). MS (ES, pos. mode) *m/z* (%): 461 (M + H$^+$, 100). HRMS (ES) calcd for $C_{27}H_{28}N_2O_3S$: 461.1893 MH$^+$; found: 461.1894.

5.9. Synthesis of (2*S*,2'*R*)-ethyl amino-(3,3-dimethylaziridin-2-yl)acetate 280

To a solution of (*S*$_S$,2*S*,2'*R*)-ethyl 2-diphenylmethyleneamino-2-[3,3-dimethyl-1-(*p*-toluene-sulfinyl)aziridin-2-yl]acetate *anti*-**278a** (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 minutes 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 x 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 **280**.

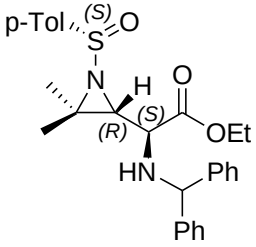
(2*S*,2'*R*)-Ethyl amino-(3,3-dimethylaziridin-2-yl)acetate 280. Yellowish oil, yield 78%. 

$[\alpha]_D$ + 131.5 (*c* 0.9, $CHCl_3$). IR (cm^{-1}): ν_{max} 831, 1027, 1187, 1382, 1729, 2957. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.21 (3H, s, CC$\underline{H}_3$(CH_3)), 1.23 (3H, t, *J* = 7.2 Hz, $CH_2C\underline{H}_3$), 1.25 (3H, s, $CCH_3(C\underline{H}_3)$), 1.39 (3H, br s, NH and NH_2), 1.91 (1H, d, *J* = 8.8 Hz, $NC\underline{H}_{azir}CHN$), 3.08 (1H, d, *J* = 8.8 Hz, $NCH_{azir}C\underline{H}N$), 4.16 (2H, q, *J* = 7.2 Hz, $C\underline{H}_2CH_3$). ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.3 ($CH_2\underline{C}H_3$), 19.7 ($C\underline{C}H_3(CH_3)$), 27.2 ($CCH_3(\underline{C}H_3)$), 35.6 ($\underline{C}(CH_3)_2$), 45.8 ($N\underline{C}H_{azir}CHN$), 55.6 ($\underline{C}H_2CH_3$), 61.2 ($CHNH_2$), 174.6 (C=O). 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.

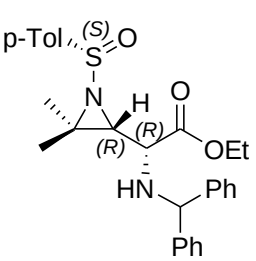
5.10. Synthesis of (S_S)-ethyl 2-diphenylmethylamino-2-[3,3-dimethyl-1-(*p*-toluenesulfinyl)aziridin-2-yl]acetate 281

The synthesis of (S_S,2*S*,2'*R*)-ethyl 2-diphenylmethylamino-2-[3,3-dimethyl-1-(*p*-toluenesulfinyl)aziridin-2-yl]acetate *anti*-**281** is representative. 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*-**278a** (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 five minutes. The reaction mixture was allowed to stir for six hours at room temperature. The reaction was then 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 x 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 *anti*-**281**.



(*S*$_S$,2*S*,2'*R*)-Ethyl 2-diphenylmethylamino-2-[3,3-dimethyl-1-(*p*-toluenesulfinyl)aziridin-2-yl]acetate *anti*-281. 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. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.99 (3H, t, *J* = 7.2 Hz, $CH_2C\underline{H}_3$), 1.21 (3H, s, $CC\underline{H}_3(CH_3)$), 1.61 (3H, s, $CCH_3(C\underline{H}_3)$), 2.22 (1H, br s, NH), 2.37 (3H, s, $C_{arom}CH_3$), 2.88 (1H, d, *J* = 9.4 Hz,) and 2.91 (1H, d, *J* = 9.4 Hz) ($NC\underline{H}_{azir}CHN$ and $NCH_{azir}C\underline{H}N$), 3.26 (1H, dxq, *J* = 11.0 Hz, 7.2 Hz, $C\underline{H}(H)CH_3$), 3.61 (1H, dxq, *J* = 11.0 Hz, 7.2 Hz, $CH(\underline{H})CH_3$), 4.63 (1H, s, $CHPh_2$), 7.16-7.33 (12H, m, CH_{arom}), 7.50 (2H, d , *J* = 8.3 Hz, CH_{arom}). ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.0 ($CH_2\underline{C}H_3$), 20.7 ($CCH_3(\underline{C}H_3)$), 21.3 ($C_{arom}\underline{C}H_3$), 21.8 ($C\underline{C}H_3(CH_3)$), 41.1 and 58.5 ($N\underline{C}H_{azir}CHN$ and $NCH_{azir}\underline{C}HN$), 45.3 ($\underline{C}(CH_3)_2$), 60.4 ($O\underline{C}H_2CH_3$), 65.2 ($\underline{C}HPh_2$), 125.3, 127.0, 127.3, 127.4, 127.7, 128.4, 128.5, 129.2 ($14xCH_{arom}$), 140.9, 142.1, 142.8, 143.5 ($4xC_{arom}$), 172.7 ($CH\underline{C}OO$). 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.



(*S*$_S$,2*R*,2'*R*)-Ethyl 2-diphenylmethylamino-2-[3,3-dimethyl-1-(*p*-toluenesulfinyl)aziridin-2-yl]acetate *syn*-281. White crystals, yield 71%. $[\alpha]_D$ +112.0 (*c* 0.8, $CHCl_3$). Mp 144.0 ± 0.5 °C. IR (cm^{-1}): ν_{max} 1725, 2970. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.22 (3H, s, $CC\underline{H}_3(CH_3)$), 1.25 (3H, t, *J* = 7.2 Hz, $CH_2C\underline{H}_3$), 1.53 (3H, s, $CCH_3(C\underline{H}_3)$), 1.78 (1H, br s, NH), 2.35 (3H, s, $C_{arom}CH_3$), 2.82 (1H, d, *J* = 8.8 Hz,) and 2.89 (1H, d , *J* = 8.8 Hz) ($NC\underline{H}_{azir}CHN$ and $NCH_{azir}C\underline{H}N$), 4.11 (1H, dxq, *J* = 10.6 Hz, 7.2 Hz, $C\underline{H}(H)CH_3$), 4.21 (1H, dxq, *J* = 10.6 Hz, 7.2 Hz, $CH(\underline{H})CH_3$), 4.61 (1H, s, $CHPh_2$), 6.84-6.90 (2H, m, CH_{arom}), 6.92-

6.98 (2H, m, CH_{arom}), 7.11-7.23 (4H, m, CH_{arom}), 7.25-7.32 (2H, m, CH_{arom}), 7.71 (2H, d, J = 8.3 Hz, CH_{arom}). ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.3 ($CH_2\underline{C}H_3$), 20.5 ($CCH_3(\underline{C}H_3)$), 21.5 ($C_{arom}\underline{C}H_3$), 22.6 ($C\underline{C}H_3(CH_3)$), 41.7 and 57.8 ($N\underline{C}H_{azir}CHN$ and $NCH_{azir}\underline{C}HN$), 45.8 ($\underline{C}(CH_3)_2$), 60.9 ($O\underline{C}H_2CH_3$), 64.5 ($\underline{C}HPh_2$), 125.3, 126.8, 127.0, 127.3, 127.4, 128.1, 128.2, 129.4 ($14xCH_{arom}$), 141.3, 142.1, 143.1, 143.9 ($4xC_{arom}$), 172.6 ($CH\underline{C}OO$). 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: 477.2217.

5.11. Synthesis of 3-(diphenylmethylamino)-5,5-dimethyl-1,5-dihydropyrrole-2-one 283

To a solution of (*S*$_S$,2*S*,2'*R*)-ethyl 2-diphenylmethylamino-2-[3,3-dimethyl-1-(*p*-toluene-sulfinyl)aziridin-2-yl]acetate *anti*-**281** (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 hours 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-dihydropyrrole-2-one **283**.

3-(Diphenylmethylamino)-5,5-dimethyl-1,5-dihydropyrrole-2-one 283. 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, $C(CH_3)_2$), 4.52 (1H, br d, J = 3.6 Hz, $N\underline{H}CH$), 4.91 (1H, d, J = 1.65 Hz, CH=C), 5.25 (1H, d, J = 3.6 Hz, $CHPh_2$), 6.21 (1H, br s, NHCO), 7.21-7.34 (10H, m, CH_{arom}). ^{13}C NMR (75 MHz, $CDCl_3$): δ 27.6 ($C(\underline{C}H_3)_2$), 57.5 ($\underline{C}(CH_3)_2$), 63.7 ($CHPh_2$), 115.2 ($\underline{C}H$=C), 127.3, 127.4, 128.6 ($10xCH_{arom}$), 136.6 (CH=$\underline{C}$), 141.8 ($2xC_{arom}$), 169.0 (C=O). 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.

5.12. Synthesis of (2*S*,2'*R*)-ethyl 2-diphenylmethyleneamino-2-[3,3-dimethyl-1-(*p*-toluenesulfonyl)aziridin-2-yl]acetate 286

To a solution of (S_S,2*S*,2'*R*)-ethyl 2-diphenylmethyleneamino-2-[3,3-dimethyl-1-(*p*-toluene-sulfinyl)aziridin-2-yl]acetate *anti*-**278a** (1.10 g, 2.32 mmol) in dry CH_2Cl_2 (40 mL) was added *m*CPBA (1.1 equiv, 2.55 mmol, 0.44 g) at room temperature. The reaction mixture was allowed to stir for two minutes 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*-toluene-sulfonyl)aziridin-2-yl]-acetate **286**. All spectroscopic data were in good agreement with reported data of the racemate of **286**.[92] White crystals, yield 90%. $[\alpha]_D$ -137.1 (*c* 0.4, $CHCl_3$). Mp 128.4 ± 0.5 °C.

5.13. Synthesis of (2*S*,2'*R*)-ethyl 2-diphenylmethylamino-2-[3,3-dimethyl-1-(*p*-toluenesulfonyl)aziridin-2-yl]acetate 287

To a solution of (2*S*,2'*R*)-ethyl 2-diphenylmethyleneamino-2-[3,3-dimethyl-1-(*p*-toluene-sulfonyl)aziridin-2-yl]acetate **286** (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 five minutes. The reaction mixture was stirred for six hours at room temperature. The reaction was then 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 x 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 **287**.

All spectroscopic data were in good agreement with reported data of the racemate of **287**.[92] White crystals, yield 92%. $[\alpha]_D$ -45.3 (*c* 0.9, $CHCl_3$). Mp 95.8 ± 1.0 °C.

5.14. Synthesis of (2*S*,3*R*)-ethyl 1-diphenylmethyl-4,4-dimethyl-3-(*p*-toluenesulfonylamino)azetidine-2-carboxylate 288

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 **287** (0.40 g, 0.81 mmol) was added acetonitrile (3 mL). The reaction mixture was stirred vigorously at 120 °C for 10 minutes. 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 **288**. All spectroscopic data were in good agreement with reported data of the racemate of **288** (ee > 98%). White crystals, yield 63%. $[\alpha]_D$ +15.6 (*c* 0.2, $CHCl_3$). Mp 188.1 ± 0.5 °C.

5.15. Synthesis of (2*S*,3*R*)-1-diphenylmethyl-4,4-dimethyl-3-(*p*-toluene-sulfonylamino)azetidine-2-carboxylic acid 289

(2*S*,3*R*)-Ethyl 1-diphenylmethyl-4,4-dimethyl-3-(*p*-toluenesulfonylamino)azetidine-2-carboxylate **288** (0.37 g, 0.80 mmol) was dissolved in 2 M NaOH/MeOH (1:1) (40 mL). The reaction mixture was stirred for 24 hours at reflux temperature and subsequently washed with EtOAc (1 x 20 mL). The aqueous phase was brought to pH = 4 with 2 M HCl and extracted with EtOAc (3 x 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 **289**.

(2*S*,3*R*)-1-Diphenylmethyl-4,4-dimethyl-3-(*p*-toluenesulfonylamino)azetidine-2-carboxylic acid 289. 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. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.19 (3H, s, $CC\underline{H}_3(CH_3)$), 1.24 (3H, s, $CCH_3(C\underline{H}_3)$), 2.36 (3H, s, $C_{arom}CH_3$), 3.65-3.73 (2H, m, C<u>H</u>NH and C<u>H</u>COOH), 4.88 (1H, s, $CHPh_2$), 6.33 (2H, br s, NH), 7.14-7.36 (10H, m, CH_{arom}), 7.53 (2H, d, *J* = 7.7 Hz, CH_{arom}), 7.70 (2H, d, *J* = 7.7 Hz, CH_{arom}). ^{13}C NMR (75 MHz, $CDCl_3$): δ 16.5 ($CCH_3(\underline{C}H_3)$), 21.6 ($C_{arom}\underline{C}H_3$), 29.7 ($C\underline{C}H_3(CH_3)$), 56.0 (CHNH), 66.7 (<u>C</u>HCOOH), 69.3 ($CHPh_2$), 70.3 ($\underline{C}(CH_3)_2$), 127.0, 127.7, 128.0, 128.6, 128.8, 129.1, 129.9 ($14xCH_{arom}$), 136.8, 137.4, 140.2, 143.9 ($4xC_{arom}$), 170.7 (COOH). 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.

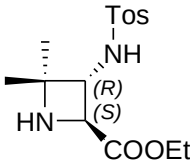
5.16. Synthesis of (2*S*,3*R*)-4,4-dimethyl-3-(*p*-toluenesulfonylamino)-azetidine-2-carboxylic acid derivatives 290 and 291

The synthesis of (2*S*,3*R*)-4,4-dimethyl-3-(*p*-toluenesulfonylamino)azetidine-2-carboxylic acid **290** is representative. To a solution of (2*S*,3*R*)-1-diphenylmethyl-4,4-dimethyl-3-(*p*-toluenesulfonyl-amino)azetidine-2-carboxylic acid **289** (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 hours 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 **290**.

(2*S*,3*R*)-4,4-Dimethyl-3-(*p*-toluenesulfonylamino)azetidine-2-carboxylic acid 290. 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. ^{1}H NMR (300 MHz, CD_3OD): δ 1.47 (6H, s, $C(C\underline{H}_3)_2$), 2.42 (3H, s, $C_{arom}CH_3$), 3.87 (1H, d, *J* = 8.0 Hz,

CHNH), 4.27 (1H, d, *J* = 8.0 Hz, CHCOO), 7.38 (2H, d, *J* = 7.7 Hz, CH_{arom}), 7.76 (2H, d, *J* = 7.7 Hz, CH_{arom}). ^{13}C NMR (75 MHz, CD_3OD): δ 21.3 ($C\underline{C}H_3(CH_3)$), 21.5 ($C_{arom}\underline{C}H_3$), 26.5 ($CCH_3(\underline{C}H_3)$), 59.4 (CHNH), 60.4 (CHCOO), 69.8 ($\underline{C}(CH_3)_2$), 128.2, 130.9 ($4xCH_{arom}$), 138.9, 145.2 ($2xC_{arom}$), 171.4 (C=O, 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.

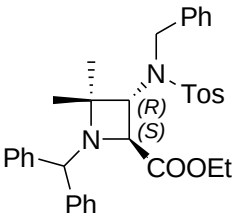
(2*S*,3*R*)-Ethyl 4,4-dimethyl-3-(*p*-toluenesulfonylamino)azetidine-2-carboxylate 291.



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, $CH_2C\underline{H}_3$), 1.65 (3H, s, $CC\underline{H}_3(CH_3)$), 1.68 (3H, s, $CCH_3(C\underline{H}_3)$), 1.65-1.68 (1H, br s, NH), 2.42 (3H, s, $C_{arom}CH_3$), 3.99-4.13 (3H, m, $C\underline{H}_2CH_3$ and CHNH), 5.36 (1H, d, *J* = 7.7 Hz, CHCOO), 7.29 (2H, d, *J* = 8.0 Hz, CH_{arom}), 7.80 (2H, d, *J* = 8.0 Hz, CH_{arom}), 8.16 (1H, d, *J* = 8.81 Hz, NH). ^{13}C NMR (75 MHz, CD_3OD): δ 14.2 ($CH_2\underline{C}H_3$), 20.8 ($C\underline{C}H_3(CH_3)$), 21.5 ($C_{arom}\underline{C}H_3$), 26.0 ($CCH_3(\underline{C}H_3)$), 57.9 (CHNH), 59.1 (CHCOO), 64.0 ($\underline{C}H_2CH_3$), 72.0 ($\underline{C}(CH_3)_2$), 128.2, 131.0 ($4xCH_{arom}$), 139.2, 145.4 ($2xC_{arom}$), 167.5 (C=O). 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.

5.17. Synthesis of (2*S*,3*R*)-ethyl 1-diphenylmethyl-4,4-dimethyl-3-[benzyl-(*p*-toluenesulfonyl)amino]azetidine-2-carboxylate 293

To a solution of (2*S*,3*R*)-ethyl 1-diphenylmethyl-4,4-dimethyl-3-(*p*-toluenesulfonylamino)-azetidine-2-carboxylate **288** (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 hours 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 x 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*-toluene-sulfonyl)amino]azetidine-2-carboxylate **293**.



(2*S*,3*R*)-Ethyl 1-diphenylmethyl-4,4-dimethyl-3-[benzyl-(*p*-toluenesulfonyl)amino]-azetidine-2-carboxylate 293. 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* = 7.2 Hz, $CH_2C\underline{H}_3$), 0.93 (3H, s, $CC\underline{H}_3(CH_3)$), 1.18 (3H, s, $CCH_3(C\underline{H}_3)$), 2.39 (3H, s, $C_{arom}CH_3$), 3.38-3.49 (1H, m, $C\underline{H}(H)CH_3$), 3.54-3.65 (1H, m, $CH(\underline{H})CH_3$), 3.74 (1H, d, *J* = 7.7 Hz, $C\underline{H}$NBn), 3.90 (1H, d, *J* = 16.2 Hz, $NC\underline{H}(H)$Ph), 3.93 (1H, d, *J* = 7.7 Hz, CHCOO), 4.40 (1H, s, $CHPh_2$), 4.64 (1H, d, *J* = 16.2 Hz, $CH(\underline{H})$Ph), 7.06-7.37 (15H, m, CH_{arom}), 7.49 (2H, d, *J* = 7.2 Hz, CH_{arom}), 7.64 (2H, d, *J* = 8.3 Hz, CH_{arom}). ^{13}C NMR (75 MHz, $CDCl_3$): δ 13.6 ($CH_2\underline{C}H_3$), 17.1 ($C\underline{C}H_3(CH_3)$), 21.5 ($C_{arom}\underline{C}H_3$), 29.6 ($CCH_3(\underline{C}H_3)$), 51.4 ($\underline{C}H_2$Ph), 60.4 ($\underline{C}H_2CH_3$), 62.0 ($\underline{C}$HCOO), 63.6 (CHNH), 68.6 ($\underline{C}(CH_3)_2$), 69.9 ($\underline{C}HPh_2$), 127.2, 127.4, 127.5, 127.7, 128.0, 128.1, 128.3, 128.4, 128.9, 129.7 (19xCH_{arom}), 135.5, 137.7, 140.7, 142.8, 143.6 (5xC_{arom}), 171.4 (C=O). 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.

5.18. Synthesis of bis-[(2*S*,3*R*)-ethyl 1-diphenylmethyl-4,4-dimethyl-3-(benzylamino)azetidine-2-carboxylate] oxalic acid salt 295

A mixture of magnesium powder (83 mg, 3.4 mmol) in dry MeOH (1 mL) was sonicated at 40 °C for one minute. Subsequently, a solution of (2*S*,3*R*)-ethyl 1-diphenylmethyl-4,4-dimethyl-3-[benzyl-(*p*-toluenesulfonyl)amino]azetidine-2-carboxylate **293** (100 mg, 0.2 mmol) in MeOH (0.4 mL) was added dropwise and the resulting suspension was sonicated for five hours at 40 °C. Next, the reaction mixture was concentrated under reduced pressure to afford a white powder which was redissolved in an aqueous solution of NH_4Cl (sat.), which was immediatly extracted with $CHCl_3$ (3 x 5 mL). Drying of the combined organic phases with $MgSO_4$, filtration of the drying agent and evaporation of the solvent *in vacuo* afforded a crude mixture containing the detosylated compound. This crude mixture was redissoved in Et_2O (1.0 ml), and addition, under sonication, of a solution of anhydrous oxalic acid (8 mg,

0.1 mol) in EtOH (0.2 ml) resulted immediately in the formation of a precipitate. The solid was filtered and dried under reduced pressure to give the pure title compound **295**.

Bis-[(2*S*,3*R*)-ethyl 1-diphenylmethyl-4,4-dimethyl-3-(benzylamino)azetidine-2-carboxylate] oxalic acid salt 295. White powder, yield 37%. $[\alpha]_D$ +32.7 (*c* 0.5, $CHCl_3$). Mp 168.0 ± 1.0 °C. IR (cm^{-1}): ν_{max} 695, 706, 1192, 1271, 1599, 1740. ^1H NMR (300 MHz, $CDCl_3$): δ 0.94 (3H, t, *J* = 7.2 Hz, $CH_2C\underline{H}_3$), 1.13 (3H, s, $CC\underline{H}_3(CH_3)$), 1.22 (3H, s, $CCH_3(C\underline{H}_3)$), 1.26 (2H, br s, NH_2) 3.44-3.91 (6H, m, $C\underline{H}_2CH_3$ and $C\underline{H}$NBn and $NC\underline{H}_2$Ph and CHCOO), 4.74 (1H, s, $CHPh_2$), 7.06-7.31 (11H, m, 11xCH_{arom}), 7.36 (2H, d, *J* = 6.1 Hz, 2xCH_{arom}), 7.57 (2H, d, *J* = 7.2 Hz, 2xCH_{arom}). ^{13}C NMR (75 MHz, $CDCl_3$): δ 13.9 ($CH_2\underline{C}H_3$), 16.0 ($CCH_3(\underline{C}H_3)$), 30.5 ($C\underline{C}H_3(CH_3)$), 50.6 ($\underline{C}H_2$Ph), 59.6 ($CHNH_2$), 60.8 ($\underline{C}H_2CH_3$), 65.7 ($\underline{C}$HCOO), 65.9 ($\underline{C}(CH_3)_2$), 70.1 ($\underline{C}HPh_2$), 127.4, 127.6, 128.0, 128.3, 128.8, 129.1, 129.5 (15xCH_{arom}), 140.8, 142.8 (3xC_{arom}), 163.3 ($O(C{=}O)_2O$), 171.5 (CH$\underline{C}$=O). MS (ES, pos. mode) *m/z* (%): 429 ($M + H^+$ - oxalic acid, 100). HRMS (ES) calcd for $C_{28}H_{32}N_2O_2$: 429.2537 (MH^+- oxalic acid); found: 429.2540.

5.19. Synthesis of (*R*,*R*)-2,3-diamino-4,4-dimethylbutyrolactone dihydrochloride 297

(S_S,2*R*,2'*R*)-Ethyl 2-diphenylmethyleneamino-2-[3,3-dimethyl-1-(*p*-toluenesulfinyl)aziridin-2-yl]-acetate *syn*-**278a** (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 minutes at room temperature. Subsequently, the reaction mixture was concentrated *in vacuo*. Precipitation from diethyl ether afforded 0.06 g (0.28 mmol) of (2*R*,3*R*)-2,3-diamino-4,4-dimethylbutyrolactone dihydrochloride **297**.

(2*R*,3*R*)-2,3-Diamino-4,4-dimethylbutyrolactone dihydrochloride 297. 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, $CC\underline{H}_3(CH_3)$), 1.59 (3H, s, $CCH_3(C\underline{H}_3)$), 3.97 (1H, d, *J* = 10.46 Hz) and 4.61 (1H, d, *J* = 10.46 Hz) ($C(CH_3)_2C\underline{H}$ and CHCO). ^{13}C NMR (75 MHz, D_2O, int. ref. CH_3CN): δ 21.7 ($C\underline{C}H_3(CH_3)$), 26.5 ($CCH_3(\underline{C}H_3)$), 52.3 and 57.2 ($\underline{C}$HCO and $C(CH_3)_2\underline{C}$H), 84.9 ($\underline{C}(CH_3)_2$), 168.1 (C=O). MS (ES, pos. mode) *m/z* (%): 145 (M + H^+ - 2xHCl, 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.

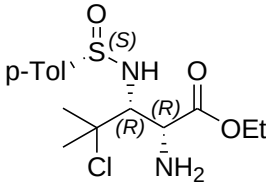
5.20. Synthesis of (*R*,*R*)-2,3-(di-*tert*-butoxycarbonylamino)-4,4-dimethyl-butyrolactone 298

A mixture of (2*R*,3*R*)-2,3-diamino-4,4-dimethylbutyrolactone hydrochloride **297** (0.10 g, 0.46 mmol), Et_3N (0.23 g, 2.30 mmol) and Boc_2O (0.26 g, 1.20 mmol) was dissolved in THF (10 mL) and the mixture was stirred for 18 hours at room temperature. Subsequently, the precipitate was filtered over Celite® and the filtrate was concentrated *in vacuo*. Precipitation in diethyl ether afforded 0.09 g (0.28 mmol) of (*R*,*R*)-2,3-(di-*tert*-butoxycarbonylamino)-4,4-dimethylbutyrolactone **298**.

(*R*,*R*)-2,3-(Di-*tert*-butoxycarbonylamino)-4,4-dimethylbutyrolactone 298. White powder, yield 60%. $[\alpha]_D$ -18.2 (*c* 3.8, $CHCl_3$). Mp 156.8 ± 1.0 °C. IR (cm^{-1}): ν_{max} 1160, 1252, 1517, 1689, 1776, 3366. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.36 (3H, s, $CC\underline{H}_3(CH_3)$), 1.44 (9H, s, $OC(C\underline{H}_3)_3$), 1.45 (9H, s, $OCC\underline{H}_3)_3$), 1.55 (3H, s, $CCH_3(C\underline{H}_3)$), 3.97-4.08 (1H, m) and 4.48-4.60 (1H, m) ($C(CH_3)_2C\underline{H}$ and CHCO), 5.02-5.17 (1H, m) and 5.28-5.41 (1H, m) (2xNH). ^{13}C NMR (75 MHz, $CDCl_3$): δ 21.6 ($C\underline{C}H_3(CH_3)$), 27.2 ($CCH_3(\underline{C}H_3)$), 27.7 ($2xOC(\underline{C}H_3)_3$), 54.0 and 59.6 ($\underline{C}$HCO and $C(CH_3)_2\underline{C}$H), 78.7 and 79.1 ($2xO\underline{C}(CH_3)_3$), 82.7 ($\underline{C}(CH_3)_2$), 155.7 and 155.9 (2xNC=O), 171.0 (OC=O). MS (ES, pos. mode) *m/z* (%): 233 (M + H^+ - 2 x isobutene, 100). HRMS (ES) calcd for $C_7H_{12}N_2O_4$: 189.0870 (MH^+ - CO_2 - 2 x isobutene); found: 189.0878.

5.21. Synthesis of (S_S,2*R*,3*R*)-ethyl 2-amino-4-chloro-4-methyl-3-(*p*-toluenesulfinylamino)pentanoate *syn*-301

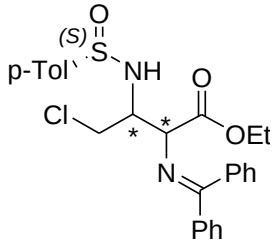
To a solution of (S_S,2*R*,3*R*)-ethyl 2-diphenylmethyleneamino-4-chloro-4-methyl-3-(*p*-toluenesulfinylamino)pentanoate *syn*-**277a** (0.50 g, 0.98 mmol) in acetone/H_2O (2:1) (30 mL) was added dropwise trifluoroacetic acid (5 equiv, 4.89 mmol, 0.38 mL) at room temperature. The reaction mixture was stirred for 15 minutes 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 x 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*-**301**.



(S_S,2*R*,3*R*)-Ethyl 2-amino-4-chloro-4-methyl-3-(*p*-toluenesulfinylamino)pentanoate *syn*-301. 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, $CH_2C\underline{H}_3$), 1.63 (3H, s, $CC\underline{H}_3(CH_3)$), 1.69 (2H, br s, NH_2), 1.74 (3H, s, $CCH_3(C\underline{H}_3)$), 2.41 (3H, s, $C_{arom}CH_3$), 4.07 (1H, dxd, *J* = 9.1 Hz, 1.10 Hz, C<u>H</u>NH), 4.17 (1H, d, *J* = 1.10 Hz, C<u>H</u>NH_2), 4.24-4.37 (2H, m, $C\underline{H}_2CH_3$), 5.40 (1H, d, *J* = 9.1 Hz, NH), 7.30 (2H, d, *J* = 8.0 Hz, CH_{arom}), 7.63 (2H, d, *J* = 8.0 Hz, CH_{arom}). ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.2 ($CH_2\underline{C}H_3$), 21.3 ($C_{arom}CH_3$), 29.2 ($C\underline{C}H_3(CH_3)$), 30.8 ($CCH_3(\underline{C}H_3)$), 53.3 ($CHNH_2$), 62.2 ($\underline{C}H_2CH_3$), 65.3 (CHNH), 73.0 ($\underline{C}(CH_3)_2$), 125.4, 129.5 ($4xCH_{arom}$), 141.4, 142.8 ($2xC_{arom}$), 173.0 (C=O). MS (ES, pos. mode) *m/z* (%): 347/349 (M + H^+, 100). HRMS (ES) calcd for $C_{15}H_{23}ClN_2O_3S$: 347.1191 MH^+; found: 347.1205.

5.22. Synthesis of (S_S)-ethyl 2-diphenylmethyleneamino-4-chloro-3-(*p*-toluenesulfinylamino)butanoate *major*-302a

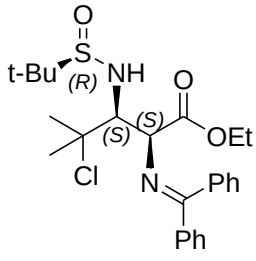
A solution of *N*-(diphenylmethylene)glycine ethyl ester **273a** (1.1 equiv, 8.40 mmol, 2.25 g) in THF (20 mL) was cooled to -78 °C under nitrogen atmosphere. A 1.0M solution of LiHMDS (1.1 equiv, 8.40 mL, 8.40 mmol) in THF was slowly added and the resulting solution was stirred for 1 hour at -78 °C. After deprotonation, a solution of (S_S)-*N*-*p*-toluenesulfinyl-α-chloroacetaldimine **266h** (1.0 equiv, 7.60 mmol, 1.65 g) in THF (20 mL) was added dropwise and the reaction mixture was stirred at -90 °C for one hour. To the reaction mixture was added a saturated solution of NH_4Cl (40 mL) while stirring at -78 °C for two minutes. The reaction mixture was brought to room temperature followed by an extraction with EtOAc (3 x 100 mL). The combined organic phases were dried ($MgSO_4$), filtered and evaporated *in vacuo*. The crude product was purified by column chromatography to yield 2.30 g (4.48 mmol) of pure (S_S)-ethyl 2-diphenylmethyleneamino-4-chloro-3-(*p*-toluenesulfinylamino)butanoate *major*-**302a**.

(S_S)-Ethyl 2-diphenylmethyleneamino-4-chloro-3-(*p*-toluenesulfinylamino)butanoate *major*-302a. 

R_f = 0.04 (petroleum ether/EtOAc : 4/1). Yellowish oil, yield 59%. $[\alpha]_D$ +2.0 (*c* 1.2, $CHCl_3$). IR (cm^{-1}): ν_{max} 697, 1064, 1090, 1242, 1626, 1736, 3293. ^1H NMR (300 MHz, $CDCl_3$): δ 1.28 (3H, t, *J* = 7.2 Hz, $CH_2C\underline{H}_3$), 2.41 (3H, s, $C_{arom}CH_3$), 3.44 (1H, t, *J* = 11.0 Hz, C<u>H</u>(H)Cl), 3.72 (1H, dxd, *J* = 11.0 Hz, 4.4 Hz, CH(<u>H</u>)Cl), 4.13-4.34 (3H, m, $C\underline{H}_2CH_3$ and C<u>H</u>NH), 4.54 (1H, d, *J* = 2.2 Hz, CHCOO), 5.36 (1H, d, *J* = 10.5 Hz, NH), 7.13-7.20 (2H, m, CH_{arom}), 7.27-7.35 (4H, m, CH_{arom}), 7.37-7.46 (4H, m, CH_{arom}), 7.54-7.62 (4H, m, CH_{arom}). ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.3 ($CH_2\underline{C}H_3$), 21.4 ($C_{arom}CH_3$), 44.2 (CH_2Cl), 58.8 (CHNH), 61.5 ($\underline{C}H_2CH_3$), 64.5 (<u>C</u>HCOO), 125.7, 127.5, 128.1, 128.5, 128.8, 128.9, 129.7, 131.0 ($14xCH_{arom}$), 135.9, 138.6, 141.6, 142.0 ($4xC_{arom}$), 170.2 and 174.3 (C=N and C=O). MS (ES, pos. mode) *m/z* (%): 483/485 ($M + H^+$, 100). HRMS (ES) calcd for $C_{26}H_{27}ClN_2O_3S$: 483.1504 MH^+; found: 483.1500.

5.23. Synthesis of (R_S,2*S*,3*S*)-ethyl 2-diphenylmethyleneamino-4-chloro-4-methyl-3-(*tert*-butanesulfinylamino)pentanoate *syn*-304

A solution of *N*-(diphenylmethylene)glycine ethyl ester **273a** (1.1 equiv, 2.75 mmol, 0.74 g) in THF (15 mL) was cooled to -78 °C under nitrogen atmosphere. A 1.0M solution of LiHMDS (1.1 equiv, 2.75 mL, 2.75 mmol) in THF was slowly added and the resulting solution was stirred for one hour at -78 °C. After deprotonation, the reaction mixture was cooled to -90 °C and a solution of (R_S)-*N*-*tert*-butanesulfinyl-α-chloroisobutyraldimine (R_S)-**270a** (1.0 equiv, 2.5 mmol, 0.52 g) in THF (5 mL) was added dropwise and the reaction mixture was stirred at -90 °C for five minutes. To the reaction mixture was added a saturated solution of NH_4Cl (10 mL) while stirring at -78 °C for two minutes. The reaction mixture was brought to room temperature followed by an extraction with EtOAc (3 x 30 mL). The combined organic phases were dried ($MgSO_4$), filtered and evaporated *in vacuo*. The crude product was purified by column chromatography to yield 0.64 g (1.35 mmol) of (R_S,2*S*,3*S*)-ethyl 2-diphenylmethyleneamino-4-chloro-4-methyl-3-(*tert*-butanesulfinylamino)-pentanoate ***syn*-304**.

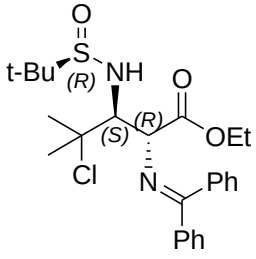


(R_S,2*S*,3*S*)-Ethyl 2-diphenylmethyleneamino-4-chloro-4-methyl-3-(*tert*-butanesulfinyl-amino)pentanoate *syn*-304. R_f = 0.05 (petroleum ether/EtOAc : 4/1). White crystals, yield 54%. Mp 97.3 ± 1.5 °C. IR (cm^{-1}): ν_{max} 691, 1076, 1255, 1624, 1726, 3278. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.27 (3H, t, *J* = 7.2 Hz, $CH_2C\underline{H}_3$), 1.35 (9H, s, *t*Bu), 1.45 (3H, s, $CC\underline{H}_3(CH_3)$), 1.54 (3H, s, $CCH_3(C\underline{H}_3)$), 4.12 (1H, d , *J* = 7.7 Hz, NHC$\underline{H}$), 4.15-4.32 (2H, m, $OC\underline{H}_2CH_3$), 4.69 (1H, s, CHCOO), 5.77 (1H, d , *J* = 7.7 Hz, N$\underline{H}$CH), 7.16-7.22 (2H, m, CH_{arom}), 7.32-7.39 (2H, m, CH_{arom}), 7.40-7.47 (4H, m, CH_{arom}), 7.59-7.63 (2H, m, CH_{arom}). ^{13}C NMR (75 MHz, $CDCl_3$): δ 13.8 ($CH_2\underline{C}H_3$), 22.8 ($C(\underline{C}H_3)_3$), 28.2 ($C\underline{C}H_3(CH_3)$), 30.5 ($CCH_3(\underline{C}H_3)$), 56.3 ($\underline{C}(CH_3)_3$), 61.7 ($O\underline{C}H_2CH_3$), 64.9 ($\underline{C}$HCOO), 66.0 (NHCH), 72.0 ($\underline{C}(CH_3)_2$), 126.8, 127.8, 128.2, 128.4, 128.6, 130.4 (10xCH_{arom}), 136.1, 138.7 (2xC_{arom}),

169.1 and 170.8 (C=N and C=O). MS (ES, pos. mode) *m/z* (%): 477/479 ($M + H^+$, 100). HRMS (ES) calcd for $C_{25}H_{33}ClN_2O_3S$: 477.1973 MH^+; found: 477.1977.

5.24. Synthesis of (R_S,2*R*,3*S*)-ethyl 2-diphenylmethyleneamino-4-chloro-4-methyl-3-(*tert*-butanesulfinylamino)pentanoate *anti*-304

To a flame dried round-bottomed flask with freshly distilled diisopropylamine (1.1 equiv, 2.75 mmol, 0.27 g) in dry THF (15 mL) was added n-BuLi (1.21 equiv, 3.03 mmol, 2.5M in hexane, 1.21 mL) under nitrogen atmosphere. The reaction mixture was stirred for five minutes at 0 °C and was subsequently cooled to -78 °C. After five minutes, a solution of *N*-(diphenylmethylene)glycine ethyl ester **273a** (1.1 equiv, 2.75 mmol, 0.74 g) in dry THF (5 mL) was slowly added and the resulting solution was stirred for one hour at -78 °C. After deprotonation, the reaction mixture was cooled to -90 °C and a solution of (R_S)-*N*-*tert*-butanesulfinyl-α-chloroisobutyraldimine (R_S)-**270a** (1.0 equiv, 2.50 mmol, 0.52 g), in dry THF (5 mL) was added dropwise and the reaction mixture was stirred at -90 °C for 15 minutes. To the reaction mixture was added a saturated solution of NH_4Cl (8 mL) while stirring was continued at -90 °C for two minutes. The reaction mixture was brought to room temperature, followed by an extraction with EtOAc (3 x 15 mL). The combined organic phases were dried ($MgSO_4$), filtered and evaporated *in vacuo*. The crude product was purified by column chromatography to yield 0.26 g (0.55 mmol) of (R_S,2*R*,3*S*)-ethyl 2-diphenylmethyleneamino-4-chloro-4-methyl-3-(*tert*-butanesulfinylamino)pentanoate *anti*-**304**.

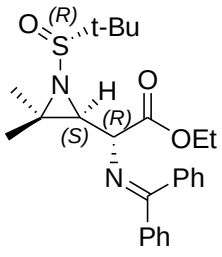


(R_S,2*R*,3*S*)-Ethyl 2-diphenylmethyleneamino-4-chloro-4-methyl-3-(*tert*-butanesulfinyl-amino)-pentanoate *anti*-304. R_f = 0.10 (petroleum ether/EtOAc : 4/1). Yellow oil, yield 22%. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.22 (3H, t, J = 7.2 Hz, $CH_2C\underline{H}_3$), 1.31 (9H, s, *t*Bu), 1.54 (6H, s, $C(C\underline{H}_3)_2$), 3.69 (1H, dxd, J = 7.7 Hz, 3.3 Hz, NHC<u>H</u>), 4.01-4.21 (2H, m, $OC\underline{H}_2CH_3$), 4.72

(1H, d, *J* = 3.3 Hz, CHN), 5.23 (1H, d, *J* = 7.7 Hz, NHCH), 7.19-7.24 (2H, m, CH_{arom}), 7.31-7.53 (6H, m, CH_{arom}), 7.74-7.79 (2H, m, CH_{arom}).

5.25. Synthesis of (*R*$_S$,2*R*,2'*S*)-ethyl 2-diphenylmethyleneamino-2-[3,3-dimethyl-1-(*tert*-butanesulfinyl)aziridin-2-yl]acetate *anti*-306

A solution of *N*-(diphenylmethylene)glycine ethyl ester **273a** (1.1 equiv, 2.75 mmol, 0.74 g) in THF (15 mL) was cooled to -78 °C under nitrogen atmosphere. A 1.0M solution of LiHMDS (1.1 equiv, 2.75 mL, 2.75 mmol) in THF was slowly added and the resulting solution was stirred for one hour at -78 °C. After deprotonation, the reaction mixture was cooled to -90 °C and a solution of (*R*$_S$)-*N*-*tert*-butanesulfinyl-α-chloroisobutyraldimine (*R*$_S$)-**270a** (1.0 equiv, 2.5 mmol, 0.52 g) in THF (5 mL) was added dropwise and the reaction mixture was stirred at -90 °C for five minutes. Subsequently, the reaction mixture was allowed to warm up to room temperature and the reaction continued for two hours at room temperature. To the reaction mixture was added a saturated solution of NH_4Cl (10 mL) while stirring at room temperature for two minutes. Extraction with EtOAc (3 x 30 mL) was followed by drying ($MgSO_4$), filtration and evaporation *in vacuo* of the combined organic phases. The crude product was purified by column chromatography to yield 0.87 g (1.98 mmol) of (*R*$_S$,2*R*,2'*S*)-ethyl 2-diphenylmethyleneamino-2-[3,3-dimethyl-1-(*tert*-butanesulfinyl)aziridin-2-yl]acetate *anti*-**306**.

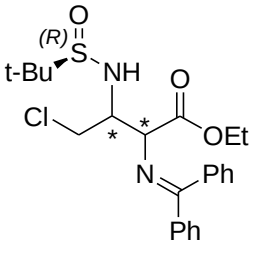


(*R*$_S$,2*R*,2'*S*)-Ethyl 2-diphenylmethyleneamino-2-[3,3-dimethyl-1-(*tert*-butanesulfinyl)-aziridin-2-yl]acetate *anti*-306. R_f = 0.10 (petroleum ether/EtOAc : 5/1). White crystals, yield 79%. $[\alpha]_D$ +42.7 (*c* 1.0, $CHCl_3$). Mp 137.1 ± 1.0 °C. IR (cm^{-1}): ν_{max} 1619, 1735. ^1H NMR (300 MHz, $CDCl_3$): δ 1.05 (3H, s, $CCH_3(CH_3)$), 1.14 (9H, s, *t*Bu), 1.27 (3H, t, *J* = 7.2 Hz, CH_2CH_3), 1.49 (3H, s, $CCH_3(CH_3)$), 3.29 (1H, d, *J* = 8.8 Hz, $NCH_{azir}CHN$), 4.08 (1H, d, *J* = 8.8 Hz, $NCH_{azir}CHN$), 4.19 (2H, q, *J* = 7.2 Hz, CH_2CH_3), 7.23-7.49 (8H, m, CH_{arom}), 7.64-

7.70 (2H, m, CH_{arom}). ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.1 ($CH_2\underline{C}H_3$), 20.7 ($CCH_3(\underline{C}H_3)$), 22.2 ($C\underline{C}H_3(CH_3)$), 22.5 ($C(\underline{C}H_3)_3$), 43.3 ($\underline{C}(CH_3)_2$), 44.4 ($N\underline{C}H_{azir}CHN$), 55.8 ($\underline{C}(CH_3)_3$), 61.3 ($\underline{C}H_2CH_3$), 65.3 ($NCH_{azir}\underline{C}HN$), 127.9, 128.0, 128.3, 128.8, 129.1, 130.4 ($10xCH_{arom}$), 135.8, 139.1 ($2xC_{arom}$), 169.7 and 171.3 (C=N and C=O). MS (ES, pos. mode) *m/z* (%): 441 ($M + H^+$, 100). HRMS (ES) calcd for $C_{25}H_{32}N_2O_3S$: 441.2206 MH^+; found: 441.2216.

5.26. Synthesis of (R_S)-ethyl 2-diphenylmethyleneamino-4-chloro-3-(*tert*-butanesulfinylamino)butanoate *major*-307

A solution of *N*-(diphenylmethylene)glycine ethyl ester **273a** (1.1 equiv, 2.75 mmol, 0.74 g) in THF (10 mL) was cooled to -78 °C under nitrogen atmosphere. A 1.0M solution of LiHMDS (1.1 equiv, 2.75 mL, 2.75 mmol) in THF was slowly added and the resulting solution was stirred for one hour at -78 °C. After deprotonation, a solution of (R_S)-*N*-*tert*-butanesulfinyl-α-chloroacetaldimine (R_S)-**270b** (1.0 equiv, 2.50 mmol, 0.45 g) in THF (5 mL) was added dropwise and the reaction mixture was stirred at -90 °C for five minutes. To the reaction mixture was added a saturated solution of NH_4Cl (8 mL) while stirring at -90 °C for two minutes. The reaction mixture was brought to room temperature followed by an extraction with EtOAc (3 x 20 mL). The combined organic phases were dried ($MgSO_4$), filtered and evaporated *in vacuo*. The crude product was purified by column chromatography to yield 0.89 g (1.98 mmol) of pure (R_S)-ethyl 2-diphenylmethyleneamino-4-chloro-3-(*tert*-butanesulfinylamino)butanoate *major*-**307**.

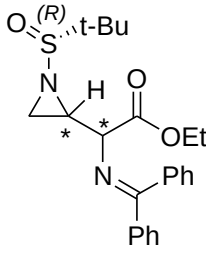


(R_S)-Ethyl 2-diphenylmethyleneamino-4-chloro-3-(*tert*-butanesulfinylamino)butanoate *major*-307. R_f = 0.10 (petroleum ether/EtOAc : 3/1). Yellowish viscous oil, yield 79%. $[\alpha]_D$ +28.3 (*c* 1.3, $CHCl_3$). IR (cm^{-1}): ν_{max} 696, 1073, 1191, 1627, 1741, 3305. ^1H NMR (300 MHz, $CDCl_3$): δ 1.22 (3H, t, *J* = 7.2 Hz, $CH_2C\underline{H}_3$), 1.24 (9H, s, $C(CH_3)_3$), 3.48 (1H, t, *J* = 11.0 Hz, C<u>H</u>Cl(H)), 3.97 (1H, dxd, *J* = 11.0 Hz, 3.9 Hz, CHCl(<u>H</u>)), 4.07-4.15 (3H, m, $OC\underline{H}_2CH_3$ and C<u>H</u>NH), 4.51 (1H, d, *J* = 2.2 Hz, CHN), 4.58 (1H, d, *J* = 11.0 Hz,

NHCH), 7.17-7.20 (2H, m, CH_{arom}), 7.35-7.38 (2H, m, CH_{arom}), 7.42-7.44 (4H, m, CH_{arom}), 7.61-7.64 (2H, m, CH_{arom}). ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.2 (CH_2CH_3), 22.6 ($C(CH_3)_3$), 44.1 (CH_2Cl), 56.6 ($C(CH_3)_3$), 60.9 and 61.3 (CHNH and OCH_2CH_3), 64.1 (CHCOO), 127.5, 128.2, 128.5, 128.8, 128.9, 131.0 ($10xCH_{arom}$), 135.8, 138.7 ($2xC_{arom}$), 170.0 and 174.5 (C=N and C=O). MS (ES, pos. mode) *m/z* (%): 449/451 ($M + H^+$, 100). HRMS (ES) calcd for $C_{23}H_{29}ClN_2O_3S$: 449.1660 MH^+; found: 449.1659.

5.27. Synthesis of (R_S)-ethyl 2-diphenylmethyleneamino-2-[1-(*tert*-butanesulfinyl)aziridin-2-yl]acetate *major*-308

To a solution of (R_S)-ethyl 2-diphenylmethyleneamino-4-chloro-3-(*tert*-butanesulfinylamino)-butanoate *major*-**307** (1.37 g, 3.05 mmol) in acetone (30 mL) was added K_2CO_3 (3.0 equiv, 9.15 mmol, 1.26 g) at room temperature. The reaction mixture was allowed to stir for 14 hours at reflux temperature. After 14 hours, 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 x 15 mL). The organic phase was dried ($MgSO_4$), filtered and evaporated *in vacuo*. The crude product was purified by column chromatography to yield 0.57 g (1.38 mmol) of (R_S)-ethyl 2-diphenylmethyleneamino-2-[1-(*tert*-butanesulfinyl)aziridin-2-yl]acetate *major*-**308**.



(R_S)-Ethyl 2-diphenylmethyleneamino-2-[1-(*tert*-butanesulfinyl)aziridin-2-yl]acetate *major*-308. R_f = 0.18 (petroleum ether/EtOAc : 3/1). Yellowish viscous oil, yield 45%. $[\alpha]_D$ -29.7 (*c* 1.4, $CHCl_3$). IR (cm^{-1}): ν_{max} 1660, 1736. ^1H NMR (300 MHz, $CDCl_3$): δ 1.20 (9H, s, $C(CH_3)_3$), 1.27 (3H, t, J = 7.2 Hz, CH_2CH_3), 1.91 (1H, d, J = 3.9 Hz, CH(H)N), 2.73 (1H, d, J = 7.7 Hz, CH(H)N), 2.83 (1H, txd, J = 7.7 Hz, 3.9 Hz, $NCH_{azir}CHN$), 3.87 (1H, d, J = 7.7 Hz, $NCH_{azir}CHN$), 4.11-4.28 (2H, m, CH_2CH_3), 7.17-7.25 (2H, m, CH_{arom}), 7.30-7.47 (6H, m, CH_{arom}), 7.63-7.69 (2H, m, CH_{arom}). ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.2 (CH_2CH_3), 22.7 ($C(CH_3)_3$), 23.4 (CH_2N), 35.5 ($NCH_{azir}CHN$), 57.1 ($C(CH_3)_3$), 61.3 (CH_2CH_3), 67.7

($NCH_{azir}\underline{C}HN$), 128.1, 128.2, 128.8, 129.0, 130.6 ($10xCH_{arom}$), 135.9, 139.4 ($2xC_{arom}$), 169.6 and 171.8 (C=N and C=O). MS (ES, pos. mode) *m/z* (%): 413 (M + H^+, 100). HRMS (ES) calcd for $C_{23}H_{28}N_2O_3S$: 413.1893 MH^+; found: 413.1783.

5.28. Synthesis of (*S*$_S$,2*S*,3*S*) *N*-[4-chloro-2-diphenylmethyleneamino-3-(*p*-toluenesulfinylamino)alkanoyl]amines *syn*-314

The synthesis of (*S*$_S$,2*S*,3*S*) *N*-[4-chloro-2-diphenylmethyleneamino-4-methyl-3-(*p*-toluenesulfinylamino)pentanoyl]piperidine *syn*-**314b** is representative. A solution of *N*-[2-diphenylmethyleneaminoacetyl]piperidine **313b** (1.1 equiv, 0.91 mmol, 0.28 g) in THF (10 mL) was cooled to -78 °C under nitrogen atmosphere. A 1.0M solution of LiHMDS (1.1 equiv, 0.91 mL, 0.91 mmol) in THF was slowly added and the resulting solution was stirred for one hour at -78 °C. After deprotonation, a solution of (*S*$_S$)-*N*-*p*-toluenesulfinyl-α-chloroisobutyraldimine **266a** (1.0 equiv, 0.82 mmol, 0.20 g) in THF (5 mL) was added dropwise and the reaction mixture was stirred at -78 °C for 15 minutes. To the reaction mixture was added a saturated solution of NH_4Cl (5 mL) while stirring at -78 °C for two minutes. The reaction mixture was brought to room temperature followed by an extraction with EtOAc (3 x 20 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 0.32 g (0.58 mmol, 71%) of pure (*S*$_S$,2*S*,3*S*) *N*-[4-chloro-2-diphenylmethyleneamino-4-methyl-3-(*p*-toluenesulfinylamino)pentanoyl]piperidine *syn*-**314b**.

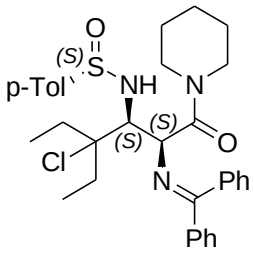
(*S*$_S$,2*S*,3*S*) *N*-[4-Chloro-2-diphenylmethyleneamino-4-methyl-3-(*p*-toluenesulfinylamino)-pentanoyl]pyrrolidine *syn*-314a. White crystals, yield 57% (0.30 g). $[\alpha]_D$ +64.7 (*c* 1.3, $CHCl_3$). Mp 132.3 ± 2.0 °C. IR (cm^{-1}): ν_{max} 697, 703, 1069, 1096, 1277, 1424, 1444, 1635, 3291 (weak). ^1H NMR (300 MHz, $CDCl_3$): δ 1.45 (3H, s, $CC\underline{H}_3(CH_3)$), 1.53-1.86 (4H, m, $2xC\underline{H}_2(CH_2)_2$), 1.77 (3H, s, $CCH_3(C\underline{H}_3)$), 2.25-2.35 (1H, m, $C\underline{H}(H)N$), 2.41 (3H, s,

$C_{arom}CH_3$), 3.26-3.40 (3H, m, CH(H)N and CH_2N), 3.77 (1H, d, *J* = 9.4 Hz, CHNH), 4.93 (1H, s, CHCO), 6.16 (1H, d, *J* = 9.4 Hz, NH), 7.12-7.19 (2H, m, CH_{arom}), 7.23-7.35 (4H, m, CH_{arom}), 7.35-7.50 (4H, m, CH_{arom}), 7.50-7.57 (2H, m, CH_{arom}), 8.07 (2H, d, *J* = 8.3 Hz, CH_{arom}). ^{13}C NMR (75 MHz, $CDCl_3$): δ 21.4 ($C_{arom}CH_3$), 24.0, 26.0 (2x$CH_2(CH_2)_2$), 27.3 ($CCH_3(CH_3)$), 32.4 ($CCH_3(CH_3)$), 46.1, 46.2 (2xCH_2N), 62.5 (CHCO), 66.6 (CHNH), 73.6 ($C(CH_3)_2$), 126.1 (2xCH_{arom}), 126.8 (2xCH_{arom}), 128.1 (2xCH_{arom}), 128.5 (2xCH_{arom}), 128.6 (CH_{arom}), 128.7 (2xCH_{arom}), 129.6 (2xCH_{arom}), 130.7 (CH_{arom}), 137.8, 138.5, 141.2, 143.8 (4xC_{arom}), 169.5 and 170.1 (C=N and C=O). MS (ES, pos. mode) *m/z* (%): 536/538 ($M + H^+$, 100). HRMS (ES) calcd for $C_{30}H_{34}ClN_3O_2S$: 536.2133 MH^+; found: 536.2146.

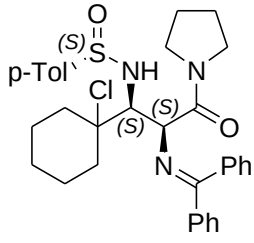
(*S*$_S$,2*S*,3*S*) *N*-[4-Chloro-2-diphenylmethyleneamino-4-methyl-3-(*p*-toluenesulfinylamino)-pentanoyl]piperidine *syn*-314b. White crystals, yield 71% (0.32 g). $[\alpha]_D$ +78.1 (*c* 0.9, $CHCl_3$). Mp 125.4 ± 2.0 °C. IR (cm^{-1}): ν_{max} 700, 1070, 1098, 1222, 1442, 1640, 3355 (weak). ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.83-0.97 (1H, m, CH(H)$(CH_2)_2$), 1.30-1.59 (5H, m, CH(H)$(CH_2)_2$ and 2x$CH_2(CH_2)_2$), 1.47 (3H, s, $CCH_3(CH_3)$), 1.76 (3H, s, $CCH_3(CH_3)$), 2.41 (3H, s, $C_{arom}CH_3$), 3.08-3.36 (3H, m, CH(H)N and CH_2N), 3.52-3.64 (1H, m, CH(H)N), 3.78 (1H, d, *J* = 9.4 Hz, CHNH), 5.12 (1H, s, CHCO), 6.04 (1H, d, *J* = 9.4 Hz, NH), 7.12-7.18 (2H, m, CH_{arom}), 7.23-7.50 (8H, m, CH_{arom}), 7.53 (2H, d, *J* = 8.3 Hz, CH_{arom}), 7.95 (2H, d, *J* = 8.3 Hz, CH_{arom}). ^{13}C NMR (75 MHz, $CDCl_3$): δ 21.4 ($C_{arom}CH_3$), 24.4, 25.4, 25.8 (3x$CH_2(CH_2)_2$), 27.5 ($CCH_3(CH_3)$), 32.6 ($CCH_3(CH_3)$), 43.3, 46.1 (2xCH_2N), 61.3 (CHCO), 66.5 (CHNH), 73.7 ($C(CH_3)_2$), 126.0 (2xCH_{arom}), 127.1 (2xCH_{arom}), 128.0 (2xCH_{arom}), 128.57 (3xCH_{arom}), 128.63 (2xCH_{arom}), 129.6 (2xCH_{arom}), 130.6 (CH_{arom}), 137.4, 138.7, 141.3, 143.6 (4xC_{arom}), 169.2 and 170.0 (C=N and C=O). MS (ES, pos. mode) *m/z* (%): 550/552 ($M + H^+$, 100). HRMS (ES) calcd for $C_{31}H_{36}ClN_3O_2S$: 550.2290 MH^+; found: 550.2306.

(*S*$_S$,2*S*,3*S*) *N*-[4-Chloro-2-diphenylmethyleneamino-4-ethyl-3-(*p*-toluenesulfinylamino)-hexanoyl]pyrrolidine *syn*-314c. White crystals, yield 41% (0.71 g). $[\alpha]_D$ +60.4 (*c* 2.7, $CHCl_3$). Mp 143.3 ± 1.0 °C. IR (cm^{-1}): ν_{max} 699, 1073, 1103, 1294, 1422, 1442, 1636, 3348 (weak). ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.93 (3H, t, *J* = 7.2 Hz) and 1.12 (3H, t, *J* = 7.2 Hz) ($C(CH_2CH_3)_2$), 1.51-2.20 (8H, m, 2xCH_2CH_3 and 2x$CH_2(CH_2)_2$), 2.24-2.35 (1H, m, CH(H)N), 2.41 (3H, s, $C_{arom}CH_3$), 3.24-3.38 (3H, m, CH(H)N and CH_2N), 4.00

(1H, d, *J* = 9.4 Hz, C<u>H</u>NH), 4.91 (1H, s, CHCO), 6.12 (1H, d, *J* = 9.4 Hz, NH), 7.13-7.22 (2H, m, CH_{arom}), 7.23-7.35 (4H, m, CH_{arom}), 7.36-7.58 (6H, m, CH_{arom}), 8.12 (2H, d, *J* = 8.3 Hz, CH_{arom}). ^{13}C NMR (75 MHz, $CDCl_3$): δ 8.7 ($CH_2\underline{C}H_3$), 8.9 ($CH_2\underline{C}H_3$), 21.5 ($C_{arom}\underline{C}H_3$), 24.0, 26.1 (2x$\underline{C}H_2(CH_2)_2$), 29.4 and 30.2 ($C(\underline{C}H_2CH_3)_2$), 46.2, 46.3 (2x$CH_2N$), 62.2 (<u>C</u>HCO), 63.5 (CHNH), 83.0 ($\underline{C}(CH_2CH_3)_2$), 126.4 (2x$CH_{arom}$), 126.9 (2x$CH_{arom}$), 128.2 (2x$CH_{arom}$), 128.7 (3x$CH_{arom}$), 128.8 (2x$CH_{arom}$), 129.7 (2x$CH_{arom}$), 130.8 ($CH_{arom}$), 137.9, 138.7, 141.2, 144.1 (4xC_{arom}), 169.7 and 170.0 (C=N and C=O). MS (ES, pos. mode) *m/z* (%): 564/566 (M + H^+, 100). HRMS (ES) calcd for $C_{32}H_{38}ClN_3O_2S$: 564.2446 MH^+; found: 564.2454.

(*S*$_S$,2*S*,3*S*) *N*-[4-Chloro-2-diphenylmethyleneamino-4-ethyl-3-(*p*-toluenesulfinylamino)-hexanoyl]piperidine *syn*-314d. 

White crystals, yield 65% (0.33 g). $[\alpha]_D$ +61.1 (*c* 0.9, $CHCl_3$). Mp 138.5 ± 2.0 °C. IR (cm^{-1}): ν_{max} 701, 1074, 1111, 1252, 1439, 1634, 3332 (weak). ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.83-1.04 (1H, m, C<u>H</u>(H)$(CH_2)_2$), 0.93 (3H, t, *J* = 7.15 Hz) and 1.12 (3H, t, *J* = 7.15 Hz) ($C(CH_2C\underline{H}_3)_2$), 1.30-1.65 (5H, m, CH(<u>H</u>)$(CH_2)_2$ and 2x$C\underline{H}_2(CH_2)_2$), 1.72-2.16 (4H, m, 2x$C\underline{H}_2CH_3$), 2.40 (3H, s, $C_{arom}CH_3$), 2.98-3.09 (1H, m, C<u>H</u>(H)N), 3.20-3.31 (1H, m, CH(<u>H</u>)N), 3.39-3.47 (2H, m, CH_2N), 4.05 (1H, d, *J* = 9.4 Hz, C<u>H</u>NH), 5.09 (1H, s, CHCO), 5.95 (1H, d, *J* = 9.4 Hz, NH), 7.12-7.17 (2H, m, CH_{arom}), 7.24-7.31 (4H, m, CH_{arom}), 7.35-7.49 (4H, m, CH_{arom}), 7.54 (2H, d, *J* = 8.3 Hz, CH_{arom}), 8.00 (2H, d, *J* = 8.3 Hz, CH_{arom}). ^{13}C NMR (75 MHz, $CDCl_3$): δ 8.6 ($CH_2\underline{C}H_3$), 8.9 ($CH_2\underline{C}H_3$), 21.5 ($C_{arom}\underline{C}H_3$), 24.5, 25.6, 26.1 (3x$\underline{C}H_2(CH_2)_2$), 29.4 and 30.3 ($C(\underline{C}H_2CH_3)_2$), 43.4, 46.1 (2x$CH_2N$), 61.2 (<u>C</u>HCO), 63.1 (CHNH), 83.3 ($\underline{C}(CH_2CH_3)_2$), 126.2 (2x$CH_{arom}$), 127.2 (2x$CH_{arom}$), 128.1 (2x$CH_{arom}$), 128.7 (5x$CH_{arom}$), 129.7 (2x$CH_{arom}$), 130.7 ($CH_{arom}$), 137.5, 138.9, 141.3, 143.9 (4xC_{arom}), 169.7 (C=N and C=O). MS (ES, pos. mode) *m/z* (%): 578/580 (M + H^+, 100). HRMS (ES) calcd for $C_{33}H_{40}ClN_3O_2S$: 578.2603 MH^+; found: 578.2609.

(*S*$_S$,2*S*,3*S*) *N*-[3-(1-Chlorocyclohexyl)-2-diphenylmethyleneamino-3-(*p*-toluenesulfinyl-amino)propanoyl]pyrrolidine *syn*-314e. 

White crystals, yield 59% (1.14 g). $[\alpha]_D$ +83.5 (*c* 2.5, $CHCl_3$). Mp 138.8 ± 2.0 °C. IR (cm^{-1}): ν_{max} 696, 704, 1068, 1092, 1294, 1430, 1634, 3309 (weak). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.05-1.21 (1H, m, C<u>H</u>(H)CH_2), 1.48-1.94 (12H, m, 2xCH(<u>H</u>)CH_2 and 5x$C\underline{H}_2CH_2$), 2.24-2.47 (2H, m, C<u>H</u>(H)CH_2 and C<u>H</u>(H)N), 2.41 (3H, s, $C_{arom}CH_3$), 3.27-3.40 (3H, m, CH(<u>H</u>)N and CH_2N), 3.74 (1H, d, *J* =

9.4 Hz, CHNH), 5.01 (1H, s, CHCO), 6.16 (1H, d , *J* = 9.4 Hz, NH), 7.12-7.18 (2H, m, CH_{arom}), 7.24-7.35 (4H, m, CH_{arom}), 7.36-7.56 (6H, m, CH_{arom}), 8.10 (2H, d, *J* = 8.3 Hz, CH_{arom}). ^{13}C NMR (75 MHz, $CDCl_3$): δ 21.5 ($C_{arom}CH_3$), 21.7, 22.1, 24.0, 24.8, 26.1, 33.7, 37.2 (7xCH_2CH_2), 46.2, 46.3 (2xCH_2N), 62.3 (CHCO), 67.7 (CHNH), 80.1 (CCl), 126.2 (2xCH_{arom}), 126.9 (2xCH_{arom}), 128.2 (2xCH_{arom}), 128.6 (3xCH_{arom}), 128.8 (2xCH_{arom}), 129.7 (2xCH_{arom}), 130.8 (CH_{arom}), 137.9, 138.7, 141.3, 143.9 (4xC_{arom}), 169.7 and 169.8 (C=N and C=O). MS (ES, pos. mode) *m/z* (%): 576/578 (M + H^+, 100). HRMS (ES) calcd for $C_{33}H_{38}ClN_3O_2S$: 576.2446 MH^+; found: 576.2436.

(*S*$_S$,2*S*,3*S*) *N*-[3-(1-Chlorocyclohexyl)-2-diphenylmethyleneamino-3-(*p*-toluenesulfinyl-amino)propanoyl]piperidine *syn*-314f. White crystals, yield 73% (1.20 g). $[\alpha]_D$ +86.9 (*c* 2.9, $CHCl_3$). Mp 132.2 ± 1.0 °C. IR (cm^{-1}): ν_{max} 701, 1073, 1104, 1221, 1441, 1638, 3320 (weak). ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.82-0.98 (1H, m, CH(H)CH_2), 1.05-1.21 (1H, m, CH(H)CH_2), 1.31-1.81 (13H, m, 3xCH(H)CH_2 and 5xCH_2CH_2), 2.30-2.45 (1H, m, CH(H)CH_2), 2.41 (3H, s, $C_{arom}CH_3$), 3.06-3.16 (1H, m, CH(H)N), 3.18-3.38 (2H, m, CH(H)N and CH(H)N), 3.48-3.59 (1H, m, CH(H)N), 3.76 (1H, dxd, *J* = 9.4 Hz, 1.1 Hz, CHNH), 5.20 (1H, d , *J* = 1.1 Hz, CHCO), 6.03 (1H, d , *J* = 9.4 Hz, NH), 7.12-7.17 (2H, m, CH_{arom}), 7.24-7.56 (10H, m, CH_{arom}), 7.99 (2H, d, *J* = 8.3 Hz, CH_{arom}). ^{13}C NMR (75 MHz, $CDCl_3$): δ 21.5 ($C_{arom}CH_3$), 21.7, 22.1, 24.5, 24.8, 25.5, 25.9, 33.8, 37.4 (8xCH_2CH_2), 43.4, 46.2 (2xCH_2N), 61.1 (CHCO), 67.8 (CHNH), 80.4 (CCl), 126.1 (2xCH_{arom}), 127.2 (2xCH_{arom}), 128.1 (2xCH_{arom}), 128.7 (5xCH_{arom}), 129.7 (2xCH_{arom}), 130.6 (CH_{arom}), 137.5, 138.9, 141.4, 143.7 (4xC_{arom}), 169.5 and 169.6 (C=N and C=O). MS (ES, pos. mode) *m/z* (%): 590/592 (M + H^+, 100). HRMS (ES) calcd for $C_{34}H_{40}ClN_3O_2S$: 590.2603 MH^+; found: 590.2609.

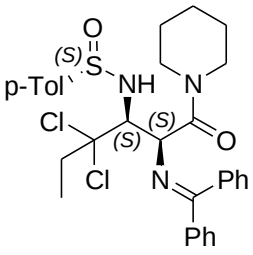
(*S*$_S$,2*S*,3*S*) *N*-[4,4-Dichloro-2-diphenylmethyleneamino-3-(*p*-toluenesulfinylamino)-pentanoyl]pyrrolidine *syn*-314g. White crystals, yield 12% (0.44 g). $[\alpha]_D$ +28.4 (*c* 1.2, $CHCl_3$). Mp 181.8 ± 1.0 °C. IR (cm^{-1}): ν_{max} 696, 1066, 1100, 1427, 1444, 1638, 3320 (weak). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.56-1.86 (4H, m, 2x$CH_2(CH_2)_2$), 2.19-2.29 (1H, m, CH(H)N), 2.25 (3H, s, CCH_3Cl_2), 2.43 (3H, s, $C_{arom}CH_3$), 3.21-3.31 (1H, m, CH(H)N), 3.34-3.44 (2H, m, CH_2N), 4.04 (1H, d, *J* = 9.4 Hz, CHNH), 5.03 (1H, s,

CHCO), 6.48 (1H, d, *J* = 9.4 Hz, NH), 7.15-7.65 (12H, m, CH_{arom}), 8.11 (2H, d, *J* = 8.3 Hz, CH_{arom}). ^{13}C NMR (75 MHz, $CDCl_3$): δ 21.5 ($C_{arom}\underline{C}H_3$), 24.0, 26.1 (2x$\underline{C}H_2(CH_2)_2$), 35.6 ($\underline{C}H_3CCl_2$), 46.2, 46.3 (2xCH_2N), 62.5 ($\underline{C}HCO$), 68.5 ($\underline{C}HNH$), 92.5 ($CH_3\underline{C}Cl_2$), 126.3 (2xCH_{arom}), 126.9 (2xCH_{arom}), 128.1 (2xCH_{arom}), 128.8 (3xCH_{arom}), 128.9 (2xCH_{arom}), 129.7 (2xCH_{arom}), 130.8 (CH_{arom}), 137.8, 138.6, 141.5, 143.6 (4xC_{arom}), 168.8 and 170.0 (C=N and C=O). MS (ES, pos. mode) *m/z* (%): 556/558/560 (M + H^+, 100). HRMS (ES) calcd for $C_{29}H_{31}Cl_2N_3O_2S$: 556.1587 MH^+; found: 556.1591.

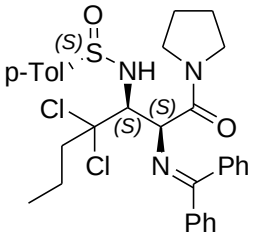
(*S*$_S$,2*S*,3*S*) *N*-[4,4-Dichloro-2-diphenylmethyleneamino-3-(*p*-toluenesulfinylamino)-pentanoyl]piperidine *syn*-314h. White crystals, yield 55% (0.43 g). $[\alpha]_D$ +55.6 (*c* 0.9, $CHCl_3$). Mp 186.2 ± 1.0 °C. IR (cm^{-1}): ν_{max} 700, 1067, 1101, 1443, 1642, 3310 (weak). ^1H NMR (300 MHz, $CDCl_3$): δ 0.92-1.06 (1H, m, C$\underline{H}$(H)$(CH_2)_2$), 1.30-1.66 (5H, m, CH($\underline{H}$)$(CH_2)_2$ and 2x$C\underline{H}_2(CH_2)_2$), 2.23 (3H, s, CCH_3Cl_2), 2.42 (3H, s, $C_{arom}CH_3$), 2.97-3.09 (1H, m, C$\underline{H}$(H)N), 3.16-3.29 (1H, m, CH($\underline{H}$)N), 3.37-3.60 (2H, m, CH_2N), 4.04 (1H, d, *J* = 9.4 Hz, CHNH), 5.20 (1H, s, CHCO), 6.36 (1H, d , *J* = 9.4 Hz, NH), 7.14-7.63 (12H, m, CH_{arom}), 7.99 (2H, d, *J* = 8.3 Hz, CH_{arom}). ^{13}C NMR (75 MHz, $CDCl_3$): δ 21.5 ($C_{arom}\underline{C}H_3$), 24.5, 25.5, 26.0 (3x$\underline{C}H_2(CH_2)_2$), 35.4 ($\underline{C}H_3CCl_2$), 43.5, 46.3 (2xCH_2N), 61.0 ($\underline{C}HCO$), 68.4 (CHNH), 92.4 ($CH_3\underline{C}Cl_2$), 126.2 (2xCH_{arom}), 127.2 (2xCH_{arom}), 128.1 (2xCH_{arom}), 128.80 (3xCH_{arom}), 128.83 (2xCH_{arom}), 129.7 (2xCH_{arom}), 130.8 (CH_{arom}), 137.5, 138.8, 141.6, 143.4 (4xC_{arom}), 168.6 and 170.1 (C=N and C=O). MS (ES, pos. mode) *m/z* (%): 570/572/574 (M + H^+, 100). HRMS (ES) calcd for $C_{30}H_{33}Cl_2N_3O_2S$: 570.1743 MH^+; found: 570.1747.

(*S*$_S$,2*S*,3*S*) *N*-[4,4-Dichloro-2-diphenylmethyleneamino-3-(*p*-toluenesulfinylamino)-hexanoyl]pyrrolidine *syn*-314i. White crystals, yield 44% (0.77 g). $[\alpha]_D$ +43.2 (*c* 1.0, $CHCl_3$). Mp 187.8 ± 1.0 °C. IR (cm^{-1}): ν_{max} 696, 1070, 1098, 1278, 1433, 1633, 3342 (weak). ^1H NMR (300 MHz, $CDCl_3$): δ 1.23 (3H, t, *J* = 7.2 Hz, $CH_2C\underline{H}_3$), 1.53-1.86 (4H, m, 2x$C\underline{H}_2(CH_2)_2$), 2.16-2.26 (1H, m, C$\underline{H}$(H)N), 2.27-2.39 (1H, m, C$\underline{H}$(H)CH_3), 2.43 (3H, s, $C_{arom}CH_3$), 2.53-2.67 (1H, m, CH($\underline{H}$)CH_3), 3.20-3.30 (1H, m, CH($\underline{H}$)N), 3.33-3.44 (2H, m, CH_2N), 4.07 (1H, d, *J* = 9.4 Hz, C$\underline{H}$NH), 5.08 (1H, s, CHCO), 6.47 (1H, d, *J* = 9.4 Hz, NH), 7.16-7.55 (12H, m, CH_{arom}), 8.16 (2H, d, *J* = 8.3 Hz, CH_{arom}). ^{13}C NMR (75 MHz, $CDCl_3$): δ9.4 ($CH_2\underline{C}H_3$), 21.6 ($C_{arom}\underline{C}H_3$), 24.0, 26.2 (2x$\underline{C}H_2(CH_2)_2$),

38.3 ($\underline{C}H_2CCl_2$), 46.2, 46.3 (2xCH_2N), 62.3 ($\underline{C}HCO$), 68.0 ($\underline{C}HNH$), 98.8 ($CH_2\underline{C}Cl_2$), 126.4 (2xCH_{arom}), 127.0 (2xCH_{arom}), 128.1 (2xCH_{arom}), 128.8 (3xCH_{arom}), 128.9 (2xCH_{arom}), 129.7 (2xCH_{arom}), 130.8 (CH_{arom}), 137.9, 138.7, 141.5, 143.6 (4xC_{arom}), 169.0 and 169.6 (C=N and C=O). MS (ES, pos. mode) *m/z* (%): 570/572/574 ($M + H^+$, 100). HRMS (ES) calcd for $C_{30}H_{33}Cl_2N_3O_2S$: 570.1743 MH^+; found: 570.1746.

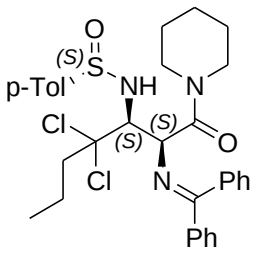
(*S*$_S$,2*S*,3*S*) *N*-[4,4-Dichloro-2-diphenylmethyleneamino-3-(*p*-toluenesulfinylamino)-hexanoyl]piperidine *syn*-314j. 

White crystals, yield 70% (1.18 g). $[\alpha]_D$ +54.5 (*c* 1.0, $CHCl_3$). Mp 158.3 ± 1.0 °C. IR (cm^{-1}): ν_{max} 702, 1071, 1102, 1217, 1433, 1643, 3322 (weak). ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.95-1.08 (1H, m, C$\underline{H}$(H)$(CH_2)_2$), 1.22 (1H, t, *J* = 7.2 Hz, $CH_2C\underline{H}_3$), 1.29-1.65 (5H, m, CH($\underline{H}$)$(CH_2)_2$ and 2x$C\underline{H}_2(CH_2)_2$), 2.20-2.39 (1H, m, C$\underline{H}$(H)CH_3), 2.42 (3H, s, $C_{arom}CH_3$), 2.48-2.64 (1H, m, CH($\underline{H}$)CH_3), 2.92-3.04 (1H, m, C$\underline{H}$(H)N), 3.16-3.28 (1H, m, CH($\underline{H}$)N), 3.39-3.56 (2H, m, CH_2N), 4.08 (1H, d, *J* = 9.4 Hz, CHNH), 5.25 (1H, s, CHCO), 6.34 (1H, d, *J* = 9.4 Hz, NH), 7.15-7.56 (12H, m, CH_{arom}), 8.05 (2H, d, *J* = 8.3 Hz, CH_{arom}). ^{13}C NMR (75 MHz, $CDCl_3$): δ 9.3 ($CH_2\underline{C}H_3$), 21.5 ($C_{arom}\underline{C}H_3$), 24.5, 25.6, 26.1 (3x$\underline{C}H_2(CH_2)_2$), 38.3 ($\underline{C}H_2CCl_2$), 43.5, 46.2 (2xCH_2N), 60.9 ($\underline{C}HCO$), 67.8 (CHNH), 98.6 ($CH_2\underline{C}Cl_2$), 126.3 (2xCH_{arom}), 127.3 (2xCH_{arom}), 128.1 (2xCH_{arom}), 128.8 (3xCH_{arom}), 128.9 (2xCH_{arom}), 129.7 (2xCH_{arom}), 130.7 (CH_{arom}), 137.5, 138.9, 141.6, 143.4 (4xC_{arom}), 168.8 and 169.7 (C=N and C=O). MS (ES, pos. mode) *m/z* (%): 584/586/588 ($M + H^+$, 100). HRMS (ES) calcd for $C_{31}H_{35}Cl_2N_3O_2S$: 584.1900 MH^+; found: 584.1903.

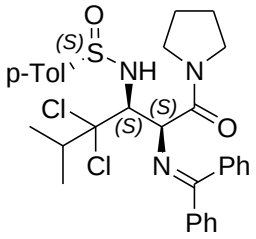
(*S*$_S$,2*S*,3*S*) *N*-[4,4-Dichloro-2-diphenylmethyleneamino-3-(*p*-toluenesulfinylamino)-heptanoyl]pyrrolidine *syn*-314k. 

White crystals, yield 23% (0.41 g). $[\alpha]_D$ +57.7 (*c* 1.0, $CHCl_3$). Mp 165.3 ± 1.0 °C. IR (cm^{-1}): ν_{max} 696, 1070, 1096, 1252, 1430, 1637, 3285. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.98 (3H, t, *J* = 7.2 Hz, $CH_2C\underline{H}_3$), 1.53-1.86 (7H, m, 2x$C\underline{H}_2(CH_2)_2$ and $C\underline{H}_2CH_3$), 2.19-2.48 (3H, m, C$\underline{H}$(H)N and $C\underline{H}_2CCl_2$), 2.42 (3H, s, $C_{arom}CH_3$), 3.19-3.29 (1H, m, CH($\underline{H}$)N), 3.34-3.44 (2H, m, CH_2N), 4.08 (1H, d, *J* = 9.4 Hz, C$\underline{H}$NH), 5.06 (1H, s, CHCO), 6.47 (1H, d, *J* = 9.4 Hz, NH), 7.16-7.56 (12H, m, CH_{arom}), 8.14 (2H, d, *J* = 8.3 Hz, CH_{arom}). ^{13}C NMR (75 MHz, $CDCl_3$): δ 13.5 ($CH_2\underline{C}H_3$), 18.4 ($\underline{C}H_2CH_3$), 21.5 ($C_{arom}\underline{C}H_3$), 24.0, 26.2 (2x$\underline{C}H_2(CH_2)_2$), 46.2, 46.4 (2xCH_2N), 46.9 ($\underline{C}H_2CCl_2$), 62.5 ($\underline{C}HCO$), 67.4 ($\underline{C}HNH$), 97.7 ($CH_2\underline{C}Cl_2$), 126.5 (2xCH_{arom}), 127.0 (2xCH_{arom}), 128.1

(2xCH$_{arom}$), 128.8 (3xCH$_{arom}$), 128.9 (2xCH$_{arom}$), 129.7 (2xCH$_{arom}$), 130.8 (CH$_{arom}$), 137.9, 138.7, 141.4, 143.8 (4xC$_{arom}$), 169.0 and 169.6 (C=N and C=O). MS (ES, pos. mode) *m/z* (%): 584/586/588 (M + H$^+$, 100). HRMS (ES) calcd for $C_{31}H_{35}Cl_2N_3O_2S$: 584.1900 MH$^+$; found: 584.1904.

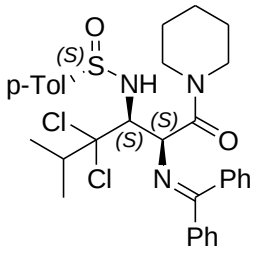
(*S*$_S$,2*S*,3*S*) *N*-[4,4-Dichloro-2-diphenylmethyleneamino-3-(*p*-toluenesulfinylamino)-heptanoyl]piperidine *syn*-314l. 

White crystals, yield 39% (0.68 g). $[\alpha]_D$ +52.6 (*c* 1.1, $CHCl_3$). Mp 161.8 ± 1.0 °C. IR (cm^{-1}): ν_{max} 702, 1072, 1102, 1431, 1645, 3362 (weak). ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.96 (3H, t, *J* = 7.2 Hz, $CH_2C\underline{H}_3$), 1.00-1.10 (1H, m, C<u>H</u>(H)$(CH_2)_2$), 1.28-1.82 (7H, m, CH(<u>H</u>)$(CH_2)_2$ and 2xC<u>H</u>$_2(CH_2)_2$ and C<u>H</u>$_2$CH$_3$), 2.16-2.40 (2H, m, C<u>H</u>$_2$CCl$_2$), 2.42 (3H, s, C$_{arom}$CH$_3$), 2.93-3.04 (1H, m, C<u>H</u>(H)N), 3.17-3.29 (1H, m, CH(<u>H</u>)N), 3.40-3.57 (2H, m, CH$_2$N), 4.08 (1H, d, *J* = 9.4 Hz, CHNH), 5.23 (1H, s, CHCO), 6.37 (1H, d, *J* = 9.4 Hz, NH), 7.15-7.59 (12H, m, CH$_{arom}$), 8.03 (2H, d, *J* = 8.3 Hz, CH$_{arom}$). ^{13}C NMR (75 MHz, $CDCl_3$): δ 13.5 ($CH_2\underline{C}H_3$), 18.3 ($\underline{C}H_2CH_3$), 21.5 (C$_{arom}$<u>C</u>H$_3$), 24.5, 25.6, 26.1 (3x<u>C</u>H$_2$(CH$_2$)$_2$), 43.5, 46.2 (2xCH$_2$N), 46.9 ($\underline{C}H_2CCl_2$), 61.1 (<u>C</u>HCO), 67.1 (CHNH), 97.5 ($CH_2\underline{C}Cl_2$), 126.3 (2xCH$_{arom}$), 127.3 (2xCH$_{arom}$), 128.0 (2xCH$_{arom}$), 128.7 (3xCH$_{arom}$), 128.9 (2xCH$_{arom}$), 129.7 (2xCH$_{arom}$), 130.7 (CH$_{arom}$), 137.6, 138.9, 141.5, 143.6 (4xC$_{arom}$), 168.8 and 169.6 (C=N and C=O). MS (ES, pos. mode) *m/z* (%): 598/600/602 (M + H$^+$, 100). HRMS (ES) calcd for $C_{32}H_{37}Cl_2N_3O_2S$: 598.2056 MH$^+$; found: 598.2060.

(*S*$_S$,2*S*,3*S*) *N*-[4,4-Dichloro-2-diphenylmethyleneamino-5-methyl-3-(*p*-toluenesulfinyl-amino)hexanoyl]pyrrolidine *syn*-314m. 

White crystals, yield 43% (0.24 g). $[\alpha]_D$ +41.9 (*c* 0.9, $CHCl_3$). Mp 152.1 ± 1.0 °C. IR (cm^{-1}): ν_{max} 698, 1072, 1102, 1427, 1641, 3288 (weak). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.22 (3H, d, *J* = 6.6 Hz, CHC<u>H</u>$_3$(CH$_3$)), 1.24 (3H, d, *J* = 6.6 Hz, CHCH$_3$(C<u>H</u>$_3$)), 1.52-1.84 (4H, m, 2xC<u>H</u>$_2$(CH$_2$)$_2$), 2.10-2.19 (1H, m, C<u>H</u>(H)N), 2.43 (3H, s, C$_{arom}$CH$_3$), 3.05 (1H, sept, *J* = 6.6 Hz, C<u>H</u>(CH$_3$)$_2$), 3.16-3.26 (1H, m, CH(<u>H</u>)N), 3.34-3.44 (2H, m, CH$_2$N), 4.23 (1H, d, *J* = 9.4 Hz, C<u>H</u>NH), 5.05 (1H, s, CHCO), 6.46 (1H, d, *J* = 9.4 Hz, NH), 7.17-7.55 (12H, m, CH$_{arom}$), 8.22 (2H, d, *J* = 8.3 Hz, CH$_{arom}$). ^{13}C NMR (75 MHz, $CDCl_3$): δ 18.3 (CH($\underline{C}H_3$)$_2$), 21.5 (C$_{arom}$<u>C</u>H$_3$), 24.0, 26.1 (2x<u>C</u>H$_2$(CH$_2$)$_2$), 38.8 ($\underline{C}HCCl_2$), 46.2, 46.3 (2xCH$_2$N), 62.3 (<u>C</u>HCO), 65.9 (<u>C</u>HNH), 103.8 (CH<u>C</u>Cl$_2$), 126.5 (2xCH$_{arom}$), 127.0 (2xCH$_{arom}$), 128.0 (2xCH$_{arom}$), 128.7 (3xCH$_{arom}$), 128.9 (2xCH$_{arom}$), 129.7

(2xCH$_{arom}$), 130.7 (CH$_{arom}$), 138.0, 138.8, 141.4, 143.8 (4xC$_{arom}$), 169.0 and 169.2 (C=N and C=O). MS (ES, pos. mode) *m/z* (%): 584/586/588 (M + H$^+$, 100). HRMS (ES) calcd for $C_{31}H_{35}Cl_2N_3O_2S$: 584.1900 MH$^+$; found: 584.1909.

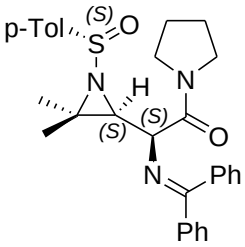
(*S*$_S$,2*S*,3*S*) *N*-[4,4-Dichloro-2-diphenylmethyleneamino-5-methyl-3-(*p*-toluenesulfinyl-amino)hexanoyl]piperidine *syn*-314n. 

White crystals, yield 76% (1.28 g). $[\alpha]_D$ +44.9 (*c* 1.1, $CHCl_3$). Mp 171.2 ± 1.0 °C. IR (cm^{-1}): ν_{max} 698, 1070, 1103, 1441, 1641, 1288 (weak). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.21 (3H, d, *J* = 6.6 Hz, CHC<u>H</u>$_3$(CH$_3$)), 1.23 (3H, d, *J* = 6.6 Hz, CHCH$_3$(C<u>H</u>$_3$)), 1.00-1.16 (1H, m, C<u>H</u>(H)(CH$_2$)$_2$), 1.27-1.64 (5H, m, CH(<u>H</u>)(CH$_2$)$_2$ and 2xC<u>H</u>$_2$(CH$_2$)$_2$), 2.43 (3H, s, C$_{arom}$CH$_3$), 2.82-2.94 (1H, m, C<u>H</u>(H)N), 3.03 (1H, sept, *J* = 6.6 Hz, C<u>H</u>(CH$_3$)$_2$), 3.18-3.38 (1H, m, CH(<u>H</u>)N and C<u>H</u>(H)N), 3.57-3.68 (1H, m, CH(<u>H</u>)N), 4.25 (1H, d, *J* = 9.4 Hz, CHNH), 5.23 (1H, s, CHCO), 6.30 (1H, d, *J* = 9.4 Hz, NH), 7.16-7.55 (12H, m, CH$_{arom}$), 8.14 (2H, d, *J* = 8.3 Hz, CH$_{arom}$). ^{13}C NMR (75 MHz, $CDCl_3$): δ 18.3 (CH(<u>C</u>H$_3$)$_2$), 21.5 (C$_{arom}$<u>C</u>H$_3$), 24.5, 25.6, 26.2 (3x<u>C</u>H$_2$(CH$_2$)$_2$), 38.9 (<u>C</u>HCCl$_2$), 43.5, 46.1 (2xCH$_2$N), 60.9 (<u>C</u>HCO), 65.4 (CHNH), 103.4 (CH$_2$<u>C</u>Cl$_2$), 126.4 (2xCH$_{arom}$), 127.3 (2xCH$_{arom}$), 128.0 (2xCH$_{arom}$), 128.77 (3xCH$_{arom}$), 128.84 (2xCH$_{arom}$), 129.7 (2xCH$_{arom}$), 130.6 (CH$_{arom}$), 137.7, 139.0, 141.5, 143.6 (4xC$_{arom}$), 169.1 (C=N and C=O). MS (ES, pos. mode) *m/z* (%): 598/600/602 (M + H$^+$, 100). HRMS (ES) calcd for $C_{32}H_{37}Cl_2N_3O_2S$: 598.2056 MH$^+$; found: 598.2066.

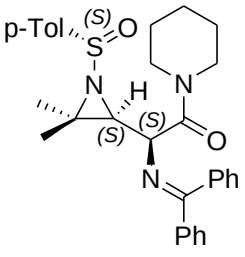
5.29. Synthesis of (*S*$_S$,2*S*,2'*S*) *N*-{2-amino-2-[1-(*p*-toluenesulfinyl)aziridin-2-yl]acetyl}amines 317 and 320b

The synthesis of (*S*$_S$,2*S*,2'*S*) *N*-{2-diphenylmethyleneamino-2-[3,3-dimethyl-1-(*p*-toluenesulfinyl)aziridin-2-yl]acetyl}piperidine **317b** is representative. To a solution of (*S*$_S$,2*S*,3*S*) *N*-[4-chloro-2-diphenylmethyleneamino-4-methyl-3-(*p*-toluenesulfinylamino)pentanoyl]-piperidine *syn*-**314b** (2.10 g, 3.82 mmol) in acetone (40 mL) was added K_2CO_3 (3.0 equiv, 11.45 mmol, 1.58 g) at room temperature. The reaction mixture was allowed to stir for 24 hours at reflux temperature. After 24 hours, 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 x 15 mL). The organic phase was dried ($MgSO_4$), filtered and evaporated *in vacuo*. The crude product was purified by column chromatography to yield 1.75 g (3.41 mmol, 90%) of (*S*$_S$,2*S*,2'*S*) *N*-[2-diphenylmethyleneamino-2-[3,3-dimethyl-1-(*p*-toluenesulfinyl)aziridin-2-yl]acetyl]piperidine **317b**.

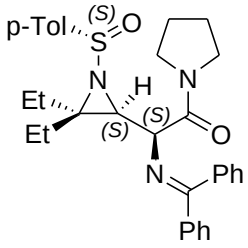
(*S*$_S$,2*S*,2'*S*) *N*-{2-diphenylmethyleneamino-2-[3,3-dimethyl-1-(*p*-toluenesulfinyl)aziridin-2-yl]acetyl}pyrrolidine 317a. 

R_f = 0.09 (petroleum ether/EtOAc : 1/1). Yellow oil, yield 59% (0.33 g). $[\alpha]_D$ +37.4 (*c* 4.1, $CHCl_3$). IR (cm^{-1}): ν_{max} 697, 1072, 1093, 1278, 1444, 1638. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.15 (3H, s, CC$\underline{H}_3$(CH_3)), 1.60-1.78 (4H, m, 2xC$\underline{H}_2$(CH_2)$_2$), 1.69 (3H, s, CCH_3(C$\underline{H}_3$)), 1.98 (3H, s, $C_{arom}CH_3$), 2.80 (2H, t, *J* = 6.6 Hz, NCH_2), 3.34-3.51 (2H, m, NCH_2), 3.40 (1H, d, *J* = 8.3 Hz, NC$\underline{H}_{azir}$CHN), 4.05 (1H, d, *J* = 8.3 Hz, NCH_{azir}C$\underline{H}$N), 6.74 (2H, d, *J* = 8.3 Hz, CH_{arom}), 7.07-7.15 (2H, m, CH_{arom}), 7.28-7.49 (8H, m, CH_{arom}), 7.57 (2H, d, *J* = 8.3 Hz, CH_{arom}). ^{13}C NMR (75 MHz, $CDCl_3$): δ 20.8 (CCH_3(C$\underline{H}_3$)), 21.5 ($C_{arom}\underline{C}H_3$), 22.7 (C$\underline{C}H_3$(CH_3)), 23.8, 26.1 (2xC$\underline{H}_2$(CH_2)$_2$), 46.0, 46.4 (2xNCH_2), 48.0 ($\underline{C}(CH_3)_2$), 50.7 (N$\underline{C}H_{azir}$CHN), 64.7 ($NCH_{azir}\underline{C}$HN), 124.9 (2xCH_{arom}), 127.9 (2xCH_{arom}), 128.1 (2xCH_{arom}), 129.05 (CH_{arom}), 129.14 (2xCH_{arom}), 129.4 (2xCH_{arom}), 130.4 (CH_{arom}), 135.1, 139.4 (2xC_{arom}), 141.8 (2xC_{arom}), 168.2 and 169.6 (C=N and C=O). MS (ES, pos. mode) *m/z* (%): 500 (M + H^+, 100). HRMS (ES) calcd for $C_{30}H_{33}N_3O_2S$: 500.2366 MH^+; found: 500.2375.

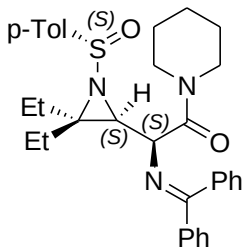
(*S*$_S$,2*S*,2'*S*) *N*-{2-diphenylmethyleneamino-2-[3,3-dimethyl-1-(*p*-toluenesulfinyl)aziridin-2-yl]-acetyl}piperidine 317b. 

R_f = 0.10 (petroleum ether/EtOAc : 1/1). Yellow oil, yield 90% (1.75 g). $[\alpha]_D$ +43.8 (*c* 2.7, $CHCl_3$). IR (cm^{-1}): ν_{max} 696, 726, 1076, 1102, 1216, 1443, 1639. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.15 (3H, s, CC$\underline{H}_3$(CH_3)), 1.17-1.31 (2H, m, C$\underline{H}_2$(CH_2)$_2$), 1.34-1.63 (4H, m, 2x C$\underline{H}_2$(CH_2)$_2$), 1.70 (3H, s, CCH_3(C$\underline{H}_3$)), 1.99 (3H, s, $C_{arom}CH_3$), 2.83 (2H, br s, NCH_2), 3.19-3.31 (1H, m, NC$\underline{H}$(H)), 3.43 (1H, d, *J* = 8.3 Hz, NC$\underline{H}_{azir}$CHN), 3.66-3.78 (1H, m, NCH(H)), 4.15 (1H, d, *J* = 8.3 Hz, NCH_{azir}C$\underline{H}$N), 6.74 (2H, d, *J* = 7.7 Hz, CH_{arom}), 7.11 (2H, d, *J* = 7.7 Hz, CH_{arom}), 7.25-7.49 (8H, m, CH_{arom}), 7.57 (2H, d, *J* = 7.7 Hz, CH_{arom}). ^{13}C NMR (75 MHz, $CDCl_3$): δ 20.7 (CCH_3(C$\underline{H}_3$)), 21.4 ($C_{arom}\underline{C}H_3$), 22.4 (C$\underline{C}H_3$(CH_3)), 24.4, 25.6, 26.5 (3x$\underline{C}H_2$(CH_2)$_2$), 43.4, 46.0 (2xNCH_2), 47.7 ($\underline{C}(CH_3)_2$), 50.6

(N<u>C</u>H$_{azir}$CHN), 63.0 (NCH$_{azir}$<u>C</u>HN), 124.8 (2xCH$_{arom}$), 127.7 (2xCH$_{arom}$), 127.9 (2xCH$_{arom}$), 129.0 (2xCH$_{arom}$), 129.15 (CH$_{arom}$), 129.21 (2xCH$_{arom}$), 129.3 (2xCH$_{arom}$), 130.3 (CH$_{arom}$), 134.5, 139.4, 141.60, 141.64 (4xC$_{arom}$), 167.8 and 169.3 (C=N and C=O). MS (ES, pos. mode) *m/z* (%): 514 (M + H$^+$, 100). Anal. calcd for $C_{31}H_{35}N_3O_2S$: 514.2523 MH$^+$; found: 514.2513.

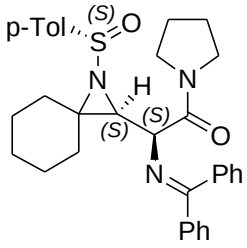
(*S*$_S$,2*S*,2'*S*) *N*-{2-diphenylmethyleneamino-2-[3,3-diethyl-1-(*p*-toluenesulfinyl)aziridin-2-yl]-acetyl}pyrrolidine 317c. 

R_f = 0.07 (petroleum ether/EtOAc : 1/1). Yellow oil, yield 44% (0.12 g). $[\alpha]_D$ +71.6 (*c* 1.9, $CHCl_3$). IR (cm^{-1}): ν_{max} 696, 1076, 1102, 1277, 1427, 1444, 1644. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.79 (3H, t, *J* = 7.2 Hz, CH$_2$C<u>H</u>$_3$), 1.04 (3H, t, *J* = 7.2 Hz, CH$_2$C<u>H</u>$_3$), 1.08-1.22 (1H, m, C(<u>H</u>)HCH$_3$), 1.32-1.45 (1H, m, C(H)<u>H</u>CH$_3$), 1.53-1.70 (4H, m, 2xC<u>H</u>$_2$(CH$_2$)$_2$), 1.88 (3H, s, C$_{arom}$CH$_3$), 1.90-2.10 (2H, m, C<u>H</u>$_2$CH$_3$), 2.60-2.75 (2H, m, CH$_2$N), 3.24-3.42 (2H, m, CH$_2$N), 3.39 (1H, d, *J* = 8.3 Hz, NC<u>H</u>$_{azir}$CHN), 4.03 (1H, d, *J* = 8.3 Hz, NCH$_{azir}$C<u>H</u>N), 6.65 (2H, d, *J* = 8.3 Hz, CH$_{arom}$), 7.00-7.07 (2H, m, CH$_{arom}$), 7.19-7.45 (8H, m, CH$_{arom}$), 7.49 (2H, d, *J* = 8.3 Hz, CH$_{arom}$). ^{13}C NMR (75 MHz, $CDCl_3$): δ 9.3 (CH$_2$<u>C</u>H$_3$), 10.6 (CH$_2$<u>C</u>H$_3$), 21.4 (C$_{arom}$<u>C</u>H$_3$), 23.8 (<u>C</u>H$_2$(CH$_2$)$_2$), 24.0, 24.4 (2x<u>C</u>H$_2$CH$_3$), 26.0 (<u>C</u>H$_2$(CH$_2$)$_2$), 45.8, 46.2 (2xNCH$_2$), 51.1 (N<u>C</u>H$_{azir}$CHN), 56.1 (<u>C</u>(CH$_2$CH$_3$)$_2$), 64.0 (NCH$_{azir}$<u>C</u>HN), 124.9 (2xCH$_{arom}$), 127.7 (2xCH$_{arom}$), 127.9 (2xCH$_{arom}$), 129.0 (CH$_{arom}$), 129.1 (2xCH$_{arom}$), 129.2 (2xCH$_{arom}$), 129.3 (2xCH$_{arom}$), 130.3 (CH$_{arom}$), 135.2, 139.3, 141.6, 141.8 (4xC$_{arom}$), 168.2 and 169.4 (C=N and C=O). MS (ES, pos. mode) *m/z* (%): 528 (M + H$^+$, 100). Anal. calcd for $C_{32}H_{37}N_3O_2S$: 528.2679 MH$^+$; found: 528.2691.

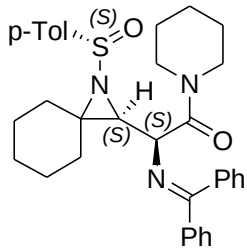
(*S*$_S$,2*S*,2'*S*) *N*-{2-diphenylmethyleneamino-2-[3,3-diethyl-1-(*p*-toluenesulfinyl)aziridin-2-yl]-acetyl}piperidine 317d. 

R_f = 0.08 (petroleum ether/EtOAc : 1/1). Yellow oil, yield 50% (0.07 g). $[\alpha]_D$ +79.9 (*c* 2.8, $CHCl_3$). IR (cm^{-1}): ν_{max} 696, 1077, 1101, 1214, 1442, 1641. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.85 (3H, t, *J* = 7.2 Hz, CH$_2$C<u>H</u>$_3$), 1.11 (3H, t, *J* = 7.2 Hz, CH$_2$C<u>H</u>$_3$), 1.15-1.30 (3H, m, C(<u>H</u>)HCH$_3$ and C<u>H</u>$_2$(CH$_2$)$_2$), 1.37-1.60 (5H, m, C(H)<u>H</u>CH$_3$ and 2xC<u>H</u>$_2$(CH$_2$)$_2$), 1.89-2.17 (2H, m, C<u>H</u>$_2$CH$_3$), 1.96 (3H, s, C$_{arom}$CH$_3$), 2.78-2.89 (2H, m, CH$_2$N), 3.18-3.31 (1H, m, C<u>H</u>(H)N), 3.46 (1H, d, *J* = 8.3 Hz, NC<u>H</u>$_{azir}$CHN), 3.63-3.74 (1H, m, CH(<u>H</u>)N), 4.19 (1H, d, *J* = 8.3 Hz, NCH$_{azir}$C<u>H</u>N), 6.73 (2H, d, *J* = 7.7 Hz, CH$_{arom}$), 7.12 (2H, d, *J* = 7.2 Hz, CH$_{arom}$), 7.27-7.45 (8H, m, CH$_{arom}$), 7.56 (2H, d, *J* = 7.2 Hz, CH$_{arom}$). ^{13}C

NMR (75 MHz, $CDCl_3$): δ 9.4 ($CH_2\underline{C}H_3$), 10.7 ($CH_2\underline{C}H_3$), 21.5 ($C_{arom}\underline{C}H_3$), 24.1, 24.3 (2x$\underline{C}H_2CH_3$), 24.5, 25.7, 26.7 (3x$\underline{C}H_2(CH_2)_2$), 43.5, 46.1 (2xNCH_2), 51.1 ($N\underline{C}H_{azir}CHN$), 56.2 ($\underline{C}(CH_2CH_3)_2$), 62.6 ($NCH_{azir}\underline{C}HN$), 124.9 (2x$CH_{arom}$), 127.8 (2x$CH_{arom}$), 128.0 (2x$CH_{arom}$), 129.1 (2x$CH_{arom}$), 129.2 ($CH_{arom}$), 129.3 (4x$CH_{arom}$), 130.3 ($CH_{arom}$), 134.8, 139.5, 141.7, 141.8 (4xC_{arom}), 167.9 and 169.3 (C=N and C=O). MS (ES, pos. mode) *m/z* (%): 542 (M + H^+, 100). HRMS (ES) calcd for $C_{33}H_{39}N_3O_2S$: 542.2836 MH^+; found: 542.2846.

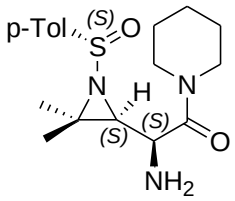
(*S*$_S$,2*S*,2'*S*) *N*-{2-diphenylmethyleneamino-2-[1-(*p*-toluenesulfinyl)-1-azaspiro[2.5]oct-2-yl]-acetyl}pyrrolidine 317e. 

R_f = 0.21 (petroleum ether/EtOAc : 2/1). Yellow oil, yield 36% (0.09 g). $[\alpha]_D$ +53.9 (*c* 2.5, $CHCl_3$). IR (cm^{-1}): ν_{max} 696, 751, 1075, 1096, 1260, 1431, 1444, 1638. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.14-1.77 (11H, m, C$\underline{H}$(H)$(CH_2)_2$ and 4xC$\underline{H}_2(CH_2)_2$ and CC$\underline{H}_2CH_2$), 1.80-1.92 (1H, m, C$\underline{H}$(H)CH_2), 1.94 (3H, s, $C_{arom}CH_3$), 2.05-2.12 (2H, m, CC$\underline{H}_2CH_2$), 2.60-2.76 (2H, m, CH_2N), 3.32-3.50 (2H, m, CH_2N), 3.46 (1H, d, *J* = 8.8 Hz, NC$\underline{H}_{azir}$CHN), 4.10 (1H, d, *J* = 8.8 Hz, $NCH_{azir}C\underline{H}N$), 6.70 (2H, d, *J* = 8.3 Hz, CH_{arom}), 7.07-7.14 (2H, m, CH_{arom}), 7.28-7.50 (8H, m, CH_{arom}), 7.57 (2H, d, *J* = 8.3 Hz, CH_{arom}). ^{13}C NMR (75 MHz, $CDCl_3$): δ 21.5 ($C_{arom}\underline{C}H_3$), 23.9, 24.8, 25.3, 25.7, 26.1 (5x$\underline{C}H_2(CH_2)_2$), 32.0, 33.0 (2xC$\underline{C}H_2CH_2$), 45.8, 46.3 (2xCH_2N), 51.0 ($N\underline{C}H_{azir}CHN$), 53.1 ($\underline{C}(CH_2)_5$), 63.9 ($NCH_{azir}\underline{C}HN$), 124.9 (2x$CH_{arom}$), 127.8 (2x$CH_{arom}$), 128.0 (2x$CH_{arom}$), 129.0 ($CH_{arom}$), 129.2 (2x$CH_{arom}$), 129.3 (2x$CH_{arom}$), 129.4 (2x$CH_{arom}$), 130.3 ($CH_{arom}$), 135.1, 139.4, 141.7, 141.8 (4xC_{arom}), 168.3 and 169.4 (C=N and C=O). MS (ES, pos. mode) *m/z* (%): 540 (M + H^+, 100). HRMS (ES) calcd for $C_{33}H_{37}N_3O_2S$: 540.2679 MH^+; found: 540.2681.

(*S*$_S$,2*S*,2'*S*) *N*-{2-diphenylmethyleneamino-2-[1-(*p*-toluenesulfinyl)-1-azaspiro[2.5]oct-2-yl]-acetyl}piperidine 317f. 

R_f = 0.13 (petroleum ether/EtOAc : 2/1). Yellow oil, yield 43% (0.10 g). $[\alpha]_D$ +49.1 (*c* 2.3, $CHCl_3$). IR (cm^{-1}): ν_{max} 696, 751, 1075, 1099, 1218, 1443, 1639. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.10-1.75 (13H, m, C$\underline{H}$(H)$(CH_2)_2$ and 5xC$\underline{H}_2(CH_2)_2$ and CC$\underline{H}_2CH_2$), 1.80-1.92 (1H, m, CH($\underline{H}$)$(CH_2)_2$), 1.95 (3H, s, $C_{arom}CH_3$), 2.04-2.14 (2H, m, CC$\underline{H}_2CH_2$), 2.70-2.86 (2H, m, CH_2N), 3.20-3.31 (1H, m, C$\underline{H}$(H)N), 3.45 (1H, d, *J* = 8.3 Hz, NC$\underline{H}_{azir}$CHN), 3.67-3.77 (1H, m, CH($\underline{H}$)N), 4.18 (1H, d, *J* = 8.3 Hz, $NCH_{azir}C\underline{H}N$), 6.70 (2H, d, *J* = 8.3 Hz, CH_{arom}), 7.08-7.16 (2H, m, CH_{arom}), 7.28-7.47 (8H, m, CH_{arom}), 7.56 (2H, d, *J* = 8.3 Hz, CH_{arom}). ^{13}C NMR (75 MHz, $CDCl_3$): δ 21.4 ($C_{arom}\underline{C}H_3$),

24.4, 24.8, 25.2, 25.6, 26.6 (6x$\underline{C}H_2(CH_2)_2$), 31.9, 32.7 (2xC$\underline{C}H_2CH_2$), 43.3, 46.0 (2xCH_2N), 50.8 (N$\underline{C}H_{azir}$CHN), 53.1 ($\underline{C}(CH_2)_5$), 62.2 (NCH$_{azir}\underline{C}$HN), 124.8 (2xCH_{arom}), 127.7 (2xCH_{arom}), 127.9 (2xCH_{arom}), 129.08 (2xCH_{arom}), 129.14 (CH_{arom}), 129.2 (2xCH_{arom}), 130.2 (CH_{arom}), 134.6, 139.4, 141.6, 141.7 (4xC_{arom}), 167.9 and 169.1 (C=N and C=O). MS (ES, pos. mode) *m/z* (%): 554 (M + H^+, 100). HRMS (ES) calcd for $C_{34}H_{39}N_3O_2S$: 554.2836 MH^+; found: 554.2836.

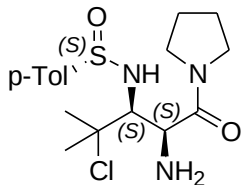
(S_S,2*S*,2'*S*) *N*-{2-Amino-2-[3,3-dimethyl-1-(*p*-toluenesulfinyl)aziridin-2-yl]acetyl}-piperidine 320b. 

R_f = 0.10 (petroleum ether/EtOAc : 1/1). Yellow oil, yield 86% (0.18 g). $[\alpha]_D$ +52.0 (*c* 2.1, $CHCl_3$). IR (cm^{-1}): ν_{max} 751, 813, 1065, 1088, 1221, 1444, 1631, 3272. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.07-1.36 (2H, m, C$\underline{H}_2(CH_2)_2$), 1.28 (3H, s, CC$\underline{H}_3(CH_3)$), 1.40-1.71 (6H, m, NH_2 and 2xC$\underline{H}_2(CH_2)_2$), 1.57 (3H, s, $CCH_3(C\underline{H}_3)$), 2.42 (3H, s, $C_{arom}CH_3$), 2.63 (1H, d, *J* = 8.3 Hz, N$\underline{C}H_{azir}$CHN), 3.32 (1H, d, *J* = 8.3 Hz, NCH$_{azir}$C$\underline{H}$N), 3.35-3.62 (4H, m, 2xCH_2N), 7.34 (2H, d, *J* = 8.3 Hz, CH_{arom}), 7.72 (2H, d, *J* = 8.3 Hz, CH_{arom}). ^{13}C NMR (75 MHz, $CDCl_3$): δ 20.9 ($CCH_3(\underline{C}H_3)$), 21.5 ($C_{arom}\underline{C}H_3$), 22.0 ($C\underline{C}H_3(CH_3)$), 24.4, 25.5, 26.6 (3x$\underline{C}H_2(CH_2)_2$), 43.1, 46.5 (CH_2N), 49.9 ($\underline{C}(CH_3)_2$), 51.0 (NCH$_{azir}\underline{C}$HN), 51.3 (N$\underline{C}H_{azir}$CHN), 125.3 (2xCH_{arom}), 129.7 (2xCH_{arom}), 142.7, 142.8 (2xC_{arom}), 169.9 (C=O). MS (ES, pos. mode) *m/z* (%): 350 (M + H^+, 100). HRMS (ES) calcd for $C_{18}H_{27}N_3O_2S$: 350.1897 MH^+; found: 350.1892.

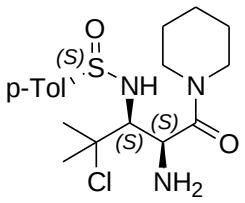
5.30. Synthesis of (S_S,2*S*,3*S*) *N*-[2-amino-4-chloro-3-(*p*-toluenesulfinyl-amino)alkanoyl]amines 319

The synthesis of (S_S,2*S*,3*S*) *N*-[2-amino-4-chloro-4-methyl-3-(*p*-toluenesulfinylamino)-pentanoyl]piperidine **319b** is representative. To a solution of (S_S,2*S*,3*S*) *N*-[4-chloro-2-diphenylmethyleneamino-4-methyl-3-(*p*-toluenesulfinylamino)pentanoyl]piperidine *syn*-**314b** (0.82 g, 1.49 mmol) in acetone/H_2O (2:1) (30 mL) was added dropwise trifluoroacetic acid (5 equiv, 7.45 mmol, 0.57 mL) at room temperature. The reaction mixture was stirred for 15 minutes 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 x 10 mL). The combined organic phases were dried ($MgSO_4$), filtered and evaporated *in vacuo*. The crude product was purified by crystallization in diethyl ether to yield 0.12 g (0.31 mmol, 21%) of pure (*S*$_S$,2*S*,3*S*) *N*-[2-amino-4-chloro-4-methyl-3-(*p*-toluenesulfinylamino)pentanoyl]-piperidine **319b**.



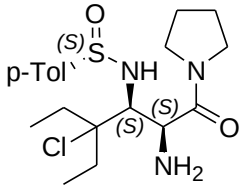
(*S*$_S$,2*S*,3*S*) *N*-[2-Amino-4-chloro-4-methyl-3-(*p*-toluenesulfinylamino)pentanoyl]-pyrrolidine 319a. White crystals, yield 70% (0.26 g). $[\alpha]_D$ +51.0 (*c* 2.9, $CHCl_3$). Mp 125.4 ± 2.0 °C. IR (cm^{-1}): ν_{max} 892, 1062, 1083, 1343, 1451, 1599, 1629, 3230. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.55 (3H, s, CC$\underline{H}_3$(CH$_3$)), 1.68 (3H, s, CCH$_3$(C$\underline{H}_3$)), 1.77 (2H, br s, NH$_2$), 1.84-2.13 (4H, m, 2xC$\underline{H}_2$(CH$_2$)$_2$), 2.41 (3H, s, C$_{arom}$CH$_3$), 3.44-3.66 (4H, m, 2xCH$_2$N), 3.66 (1H, dxd, *J* = 9.4 Hz, 2.2 Hz, C$\underline{H}$NH), 4.24 (1H, d, *J* = 2.2 Hz, CHCO), 4.89 (1H, d, *J* = 9.4 Hz, NH), 7.32 (2H, d, *J* = 8.3 Hz, CH$_{arom}$), 7.83 (2H, d, *J* = 8.3 Hz, CH$_{arom}$). ^{13}C NMR (75 MHz, $CDCl_3$): δ 21.4 (C$_{arom}$C$\underline{H}_3$), 24.0, 26.3 (2xC$\underline{H}_2$(CH$_2$)$_2$), 29.2 (CC$\underline{H}_3$(CH$_3$)), 31.9 (CCH$_3$(C$\underline{H}_3$)), 46.6, 46.8 (2xCH$_2$N), 52.4 (C$\underline{H}$CO), 65.0 (CHNH), 73.7 (CCl), 125.7 (2xCH$_{arom}$), 129.6 (2xCH$_{arom}$), 141.6, 142.7 (2xC$_{arom}$), 171.7 (C=O). MS (ES, pos. mode) *m/z* (%): 372/374 (M + H$^+$, 100). HRMS (ES) calcd for $C_{17}H_{26}ClN_3O_2S$: 372.1507 MH$^+$; found: 372.1513.



(*S*$_S$,2*S*,3*S*) *N*-[2-Amino-4-chloro-4-methyl-3-(*p*-toluenesulfinylamino)pentanoyl]-piperidine 319b. White crystals, yield 21% (0.12 g). $[\alpha]_D$ +67.5 (*c* 2.4, $CHCl_3$). Mp 119.8 ± 2.0 °C. IR (cm^{-1}): ν_{max} 821, 854, 1066, 1092, 1244, 1446, 1460, 1613, 3181. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.50-1.77 (6H, m, 3xC$\underline{H}_2$(CH$_2$)$_2$), 1.56 (3H, s, CC$\underline{H}_3$(CH$_3$)), 1.69 (3H, s, CCH$_3$(C$\underline{H}_3$)), 1.81 (2H, br s, NH$_2$), 2.41 (3H, s, C$_{arom}$CH$_3$), 3.46-3.58 (2H, m, CH$_2$N), 3.61 (1H, dxd, *J* = 9.9 Hz, 1.7 Hz, C$\underline{H}$NH), 3.67-3.81 (2H, m, CH$_2$N), 4.49 (1H, d, *J* = 1.7 Hz, CHCO), 4.93 (1H, d, *J* = 9.9 Hz, NH), 7.32 (2H, d, *J* = 8.3 Hz, CH$_{arom}$), 7.79 (2H, d, *J* = 8.3 Hz, CH$_{arom}$). ^{13}C NMR (75 MHz, $CDCl_3$): δ 21.4 (C$_{arom}$C$\underline{H}_3$), 24.6, 25.6, 26.3 (3xC$\underline{H}_2$(CH$_2$)$_2$), 28.7 (CC$\underline{H}_3$(CH$_3$)), 32.3 (CCH$_3$(C$\underline{H}_3$)), 44.0, 46.4 (2xCH$_2$N), 50.4 (C$\underline{H}$CO), 65.6 (CHNH), 73.8 (CCl), 125.8 (2xCH$_{arom}$), 129.6 (2xCH$_{arom}$), 141.5, 142.7 (2xC$_{arom}$), 171.5 (C=O). MS (ES, pos. mode) *m/z*

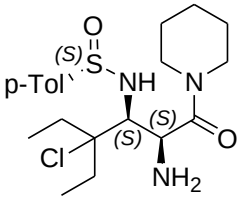
(%): 386/388 (M + H^+, 100). HRMS (ES) calcd for $C_{18}H_{28}ClN_3O_2S$: 386.1664 MH^+; found: 386.1676.

(S_S,2*S*,3*S*) *N*-[2-Amino-4-chloro-4-ethyl-3-(*p*-toluenesulfinylamino)hexanoyl]pyrrolidine



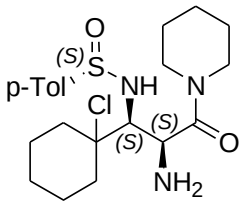
319c. White crystals, yield 91% (0.16 g). $[\alpha]_D$ +49.4 (*c* 2.6, $CHCl_3$). Mp 127.3 ± 2.0 °C. IR (cm^{-1}): ν_{max} 637, 811, 1056, 1086, 1324, 1440, 1612, 1630, 3282. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.90 (3H, t, *J* = 7.2 Hz, $CH_2C\underline{H}_3$), 1.06 (3H, t, *J* = 7.15 Hz, $CH_2C\underline{H}_3$), 1.76 (2H, br s, NH_2), 1.82-2.10 (8H, m, 2x$C\underline{H}_2(CH_2)_2$ and 2x$C\underline{H}_2CH_3$), 2.41 (3H, s, $C_{arom}CH_3$), 3.42-3.70 (4H, m, 2xCH_2N), 3.90 (1H, dxd, *J* = 9.4 Hz, 2.2 Hz, C<u>H</u>NH), 4.17 (1H, d, *J* = 2.2 Hz, CHCO), 4.78 (1H, d, *J* = 9.4 Hz, NH), 7.32 (2H, d, *J* = 8.3 Hz, CH_{arom}), 7.86 (2H, d, *J* = 8.3 Hz, CH_{arom}). ^{13}C NMR (75 MHz, $CDCl_3$): δ 8.7, 8.8 ($C(CH_2\underline{C}H_3)_2$), 21.5 ($C_{arom}\underline{C}H_3$), 24.1, 26.4 (2x$\underline{C}H_2(CH_2)_2$), 29.7, 30.5 ($C(\underline{C}H_2CH_3)_2$), 46.7, 46.8 (2x$CH_2$N), 52.7 (<u>C</u>HCO), 61.3 (CHNH), 83.0 (CCl), 125.8 (2xCH_{arom}), 129.7 (2xCH_{arom}), 141.6, 143.0 (2xC_{arom}), 171.8 (C=O). MS (ES, pos. mode) *m/z* (%): 400/402 (M + H^+, 100). HRMS (ES) calcd for $C_{19}H_{30}ClN_3O_2S$: 400.1820 MH^+; found: 400.1827.

(S_S,2*S*,3*S*) *N*-[2-Amino-4-chloro-4-ethyl-3-(*p*-toluenesulfinylamino)hexanoyl]piperidine

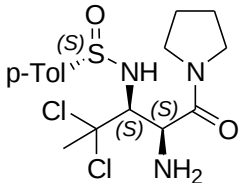


319d. Yellow oil, yield 59% (0.07 g). $[\alpha]_D$ +41.8 (*c* 2.3, $CHCl_3$). IR (cm^{-1}): ν_{max} 751, 812, 1056, 1087, 1254, 1444, 1598, 1638, 3188. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.92 (3H, t, *J* = 7.2 Hz, $CH_2C\underline{H}_3$), 1.10 (3H, t, *J* = 7.2 Hz, $CH_2C\underline{H}_3$), 1.48-1.72 (6H, m, 3x$C\underline{H}_2(CH_2)_2$), 1.76 (2H, br s, NH_2), 1.85-2.12 (4H, m, $C(C\underline{H}_2CH_3)_2$), 2.41 (3H, s, $C_{arom}CH_3$), 3.36-3.53 (2H, m, 2xC<u>H</u>(H)N), 3.70-3.90 (2H, m, 2xCH(<u>H</u>)N), 3.85 (1H, dxd, *J* = 9.9 Hz, 1.7 Hz, C<u>H</u>NH), 4.43 (1H, d, *J* = 1.7 Hz, CHCO), 4.80 (1H, d, *J* = 9.9 Hz, NH), 7.32 (2H, d, *J* = 8.3 Hz, CH_{arom}), 7.82 (2H, d, *J* = 8.3 Hz, CH_{arom}). ^{13}C NMR (75 MHz, $CDCl_3$): δ 8.7, 8.9 ($C(CH_2\underline{C}H_3)_2$), 21.5 ($C_{arom}\underline{C}H_3$), 24.7, 25.7, 26.6 (3x$\underline{C}H_2(CH_2)_2$), 29.6, 30.5 ($C(\underline{C}H_2CH_3)_2$), 44.0, 46.4 (2x$CH_2$N), 50.6 (<u>C</u>HCO), 61.7 (CHNH), 83.0 (CCl), 125.9 (2xCH_{arom}), 129.7 (2xCH_{arom}), 141.6, 142.9 (2xC_{arom}), 171.7 (C=O). MS (ES, pos. mode) *m/z* (%): 414/416 (M + H^+, 100). HRMS (ES) calcd for $C_{20}H_{32}ClN_3O_2S$: 414.1977 MH^+; found: 414.1980.

(S_S,2*S*,3*S*) *N*-[2-Amino-3-(1-chlorocyclohexyl)-3-(*p*-toluenesulfinylamino)propanoyl]-piperidine 319f. Yellow crystals, yield 78% (0.28 g). $[\alpha]_D$ +73.2 (*c* 2.3, $CHCl_3$). Mp 95.7 ±



2.0 °C. IR (cm^{-1}): ν_{max} 813, 853, 889, 1068, 1092, 1243, 1444, 1634, 3165. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.05-2.20 (18H, m, 6x$C\underline{H}_2(CH_2)_2$ and 2x$CC\underline{H}_2CH_2$ and NH_2), 2.41 (3H, s, $C_{arom}CH_3$), 3.44-3.59 (2H, m, CH_2N), 3.62 (1H, dxd, *J* = 9.9 Hz, 1.7 Hz, C<u>H</u>NH), 3.67-3.80 (2H, m, CH_2N), 4.50 (1H, d, *J* = 1.7 Hz, CHCO), 4.91 (1H, d, *J* = 9.9 Hz, NH), 7.32 (2H, d, *J* = 8.3 Hz, CH_{arom}), 7.82 (2H, d, *J* = 8.3 Hz, CH_{arom}). ^{13}C NMR (75 MHz, $CDCl_3$): δ 21.5 ($C_{arom}\underline{C}H_3$), 21.6, 22.1, 24.7, 24.8, 25.6, 26.4 (6x$\underline{C}H_2(CH_2)_2$), 35.8, 37.4 (2x$C\underline{C}H_2CH_2$), 44.0, 46.4 (2xCH_2N), 50.3 (<u>C</u>HCO), 66.5 (CHNH), 80.0 (CCl), 125.9 (2xCH_{arom}), 129.7 (2xCH_{arom}), 141.6, 142.8 (2xC_{arom}), 171.6 (C=O). MS (ES, pos. mode) *m/z* (%): 426/428 ($M + H^+$, 100). HRMS (ES) calcd for $C_{21}H_{32}ClN_3O_2S$: 426.1977 MH^+; found: 426.1972.

(*S*$_S$,2*S*,3*S*) *N*-[2-Amino-4,4-dichloro-3-(*p*-toluenesulfinylamino)pentanoyl]pyrrolidine 319g. 

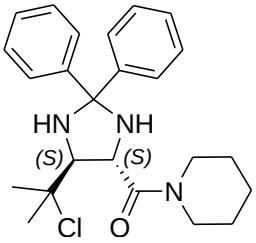
White crystals, yield 53% (0.09 g). $[\alpha]_D$ +52.9 (*c* 1.2, $CHCl_3$). Mp 133.8 ± 1.0 °C. IR (cm^{-1}): ν_{max} 814, 850, 893, 1054, 1086, 1446, 1596, 1630, 3203. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.83-2.07 (6H, m, 2x$C\underline{H}_2(CH_2)_2$ and NH_2), 2.08 (3H, s, CH_3CCl_2), 2.41 (3H, s, $C_{arom}CH_3$), 3.45-3.69 (4H, m, 2xCH_2N), 4.03 (1H, dxd, *J* = 9.4 Hz, 2.2 Hz, C<u>H</u>NH), 4.39 (1H, d, *J* = 2.2 Hz, CHCO), 5.34 (1H, d, *J* = 9.4 Hz, NH), 7.33 (2H, d, *J* = 8.3 Hz, CH_{arom}), 7.82 (2H, d, *J* = 8.3 Hz, CH_{arom}). ^{13}C NMR (75 MHz, $CDCl_3$): δ 21.5 ($C_{arom}\underline{C}H_3$), 24.2, 26.3 (2x$\underline{C}H_2(CH_2)_2$), 35.9 ($\underline{C}H_3CCl_2$)), 46.7, 46.9 (2xCH_2N), 52.7 (<u>C</u>HCO), 65.8 (CHNH), 92.8 (CCl_2), 125.8 (2xCH_{arom}), 129.7 (2xCH_{arom}), 141.9, 142.0 (2xC_{arom}), 171.1 (C=O). MS (ES, pos. mode) *m/z* (%): 392/394 ($M + H^+$, 100). HRMS (ES) calcd for $C_{16}H_{23}Cl_2N_3O_2S$: 392.0961 MH^+; found: 392.068.

5.31. Synthesis of (4'*S*,5'*S*) *N*-[5-(2-chloro-2-propyl)-2,2-diphenyl-imidazolidin-4-yl]carbonylpiperidine 321b

To a solution of (*S*$_S$,2*S*,3*S*) *N*-[4-chloro-2-diphenylmethyleneamino-4-methyl-3-(*p*-toluene-sulfinylamino)pentanoyl]piperidine *syn*-**314b** (0.40 g, 0.73 mmol) in EtOH (20 mL) was added dropwise trifluoroacetic acid (10 equiv, 7.26 mmol, 0.56 mL) at room temperature. The reaction mixture was stirred for 16 hours 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 x 10 mL). The combined organic phases were dried ($MgSO_4$), filtered and evaporated *in vacuo*. The crude product was purified by crystallization in diethyl ether to yield 0.16 g (0.40 mmol, 55%) of pure (4'*S*,5'*S*) *N*-[5-(2-chloro-2-propyl)-2,2-diphenylimidazolidin-4-yl]carbonylpiperidine **321b**.

(4'*S*,5'*S*) *N*-[5-(2-Chloro-2-propyl)-2,2-diphenylimidazolidin-4-yl]carbonylpiperidine



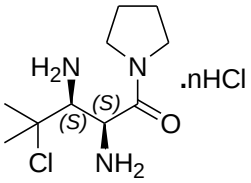
321b. White crystals, yield 55% (0.16 g). $[\alpha]_D$ -33.4 (*c* 0.8, $CHCl_3$). Mp 132.7 ± 2.0 °C. IR (cm^{-1}): ν_{max} 707, 752, 1025, 1216, 1260, 1452, 1642, 3315 (weak). ^1H NMR (300 MHz, $CDCl_3$): δ 1.49-1.89 (6H, m, 3x$C\underline{H}_2(CH_2)_2$), 1.52 (3H, s, $CC\underline{H}_3(CH_3)$), 1.73 (3H, s, $CCH_3(C\underline{H}_3)$), 2.59-2.74 (2H, m, 2xNH), 3.32-3.43 (1H, m, C<u>H</u>(H)N), 3.52-3.69 (2H, m, CH(<u>H</u>)N and C<u>H</u>(H)N), 3.76-3.98 (1H, m, CH(<u>H</u>)N), 3.85 (1H, d, *J* = 7.2 Hz, CHCCl), 3.92 (1H, d, *J* = 7.2 Hz, CHCO), 7.13-7.35 (6H, m, CH_{arom}), 7.57-7.65 (4H, m, CH_{arom}). ^{13}C NMR (75 MHz, $CDCl_3$): δ 24.7, 25.5, 26.4 (3x$\underline{C}H_2(CH_2)_2$), 31.3 ($C\underline{C}H_3(CH_3)$), 31.7 ($CCH_3(\underline{C}H_3)$), 43.5, 47.1 (2xCH_2N), 60.4 (<u>C</u>HCO), 71.3 (<u>C</u>HCCl), 73.3 (CCl), 85.6 (CPh_2), 125.7 (2xCH_{arom}), 126.0 (2xCH_{arom}), 127.1 (2xCH_{arom}), 128.2 (2xCH_{arom}), 128.4 (2xCH_{arom}), 146.2, 146.7 (2xC_{arom}), 169.6 (C=O). MS (ES, pos. mode) *m/z* (%): 412/414 ($M + H^+$, 100). HRMS (ES) calcd for $C_{24}H_{30}ClN_3O$: 412.2150 MH^+; found: 376.2376 (100%), 412.2144 (70%).

5.32. Synthesis of (2*S*,3*S*) *N*-[2,3-diamino-4-chloro-4-methylpentanoyl]-pyrrolidine hydrochloride 322a

(*S*$_S$,2*S*,3*S*) *N*-[4-Chloro-2-diphenylmethyleneamino-4-methyl-3-(*p*-toluenesulfinylamino)-pentanoyl]pyrrolidine *syn*-**314a** (0.19 g, 0.35 mmol) was dissolved in a mixture of 0.5 M (aq.) HCl/EtOAc (2:1) (12 mL) and the mixture was stirred for 30 minutes at room temperature. The organic phase was removed and the aqueous phase was washed with EtOAc (3 x 5 mL).

Subsequently, the aqueous phase was lyophilized to yield 0.09 g (0.29 mmol, 83%) of pure (2*S*,3*S*) *N*-[2,3-diamino-4-chloro-4-methylpentanoyl]pyrrolidine hydrochloride **322a**.

(2*S*,3*S*) *N*-[2,3-diamino-4-chloro-4-methylpentanoyl]pyrrolidine hydrochloride 322a.



White crystals, yield 83% (0.09 g). $[\alpha]_D$ -3.1 (*c* 2.4, MeOH). Mp 227.3 ± 2.0 °C. IR (cm^{-1}): ν_{max} 1123, 1166, 1404, 1453, 1514, 1543, 1636, 2973, 3399. ^{1}H NMR (300 MHz, D_2O): δ 1.79 (3H, s, CC<u>H</u>$_3$(CH_3)), 1.82-2.04 (4H, m, 2xC<u>H</u>$_2$(CH_2)$_2$), 1.86 (3H, s, CCH_3(C<u>H</u>$_3$)), 3.35-3.60 (3H, m, C<u>H</u>(H)N and CH_2N), 3.62-3.77 (1H, m, CH(<u>H</u>)N), 4.07 (1H, d, *J* = 2.2 Hz, CHCCl), 4.90 (1H, d, *J* = 2.2 Hz, CHCO). ^{13}C NMR (75 MHz, D_2O): δ 23.8, 25.5 (2xC<u>H</u>$_2$(CH_2)$_2$), 29.0 (CCH_3(C<u>H</u>$_3$)), 30.9 (C<u>C</u>H$_3$(CH_3)), 47.3, 47.6 (2xCH_2N), 49.8 (<u>C</u>HCO), 57.6 (CHCCl), 67.8 (CCl), 164.1 (C=O). MS (ES, pos. mode) *m/z* (%): 234/236 (M + H^+ - nxHCl, 100). HRMS (ES) calcd for $C_{10}H_{20}ClN_3O$: 198.1601 (MH^+ - nxHCl); found: 198.1596.

5.33. Synthesis of (S_S)-2-diphenylmethyleneamino-3-(*p*-toluenesulfinyl-amino)butyrolactone 326

A solution of *N*-[2-diphenylmethyleneaminoacetyl]piperidine **313b** (1.1 equiv, 8.19 mmol, 2.50 g) in THF (100 mL) was cooled to -78 °C under nitrogen atmosphere. A 1.0M solution of LiHMDS (1.1 equiv, 8.19 mL, 8.19 mmol) in THF was slowly added and the resulting solution was stirred for one hour at -78 °C. After deprotonation, a solution of (S_S)-*N*-*p*-toluenesulfinyl-α-chloroacetaldimine **266h** (1.0 equiv, 7.45 mmol, 1.60 g) in THF (20 mL) was added dropwise and the reaction mixture was stirred at -78 °C for 15 minutes. To the reaction mixture was added a saturated solution of NH_4Cl (20 mL) while stirring at -78 °C for two minutes. The reaction mixture was brought to room temperature followed by an extraction with EtOAc (3 x 20 mL). The combined organic phases were dried ($MgSO_4$), filtered and evaporated *in vacuo*. The crude product was purified by column chromatography

to yield 0.28 g (0.67 mmol) of pure (S_S)-2-diphenylmethyleneamino-3-(*p*-toluenesulfinylamino)butyrolactone **326**.

(S_S)-2-Diphenylmethyleneamino-3-(*p*-toluenesulfinylamino)butyrolactone 326. R_f = 0.17 (petroleum ether/EtOAc : 4/3). Yellow oil, yield 9% (0.28 g). $[\alpha]_D$ +1.4 (*c* 1.0, $CHCl_3$). IR (cm^{-1}): ν_{max} 696, 1017, 1088, 1158, 1624, 1780, 3179 (weak). ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.42 (3H, s, $C_{arom}CH_3$), 3.84 (1H, dxd, *J* = 8.8 Hz, 7.2 Hz, C<u>H</u>(H)O), 3.98 (1H, d, *J* = 7.7 Hz, NH), 4.25 (1H, d, *J* = 7.2 Hz, CHC=O), 4.48-4.63 (2H, m, CH(<u>H</u>)O and C<u>H</u>NH), 7.27-7.54 (12H, m, CH_{arom}), 7.65-7.71 (2H, m, CH_{arom}). ^{13}C NMR (75 MHz, $CDCl_3$): δ 21.5 ($C_{arom}\underline{C}H_3$), 57.9 (CHNH), 67.1 (<u>C</u>HC=O), 70.9 (<u>C</u>H_2O), 125.5 (2xCH_{arom}), 128.3 (2xCH_{arom}), 128.4 (2xCH_{arom}), 128.7 (2xCH_{arom}), 129.3 (2xCH_{arom}), 129.4 (CH_{arom}), 129.8 (2xCH_{arom}), 131.1 (CH_{arom}), 135.5, 138.9, 141.1, 142.2 (4xC_{arom}), 172.4 and 174.7 (C=N and C=O). MS (ES, pos. mode) *m/z* (%): 419 (M + H^+, 100). HRMS (ES) calcd for $C_{24}H_{22}N_2O_3S$: 419.1424 MH^+; found: 419.1434.

5.34. Synthesis of *syn N*-[4-(*tert*-butoxycarbonylamino)-2-(diphenylmethyleneamino)-3-(*tert*-butanesulfinylamino)butanoyl]amines *syn*-334

The synthesis of (R_S,2*R*,3*S*) *N*-[4-(*tert*-butoxycarbonylamino)-2-diphenylmethyleneamino-3-(*tert*-butanesulfinylamino)butanoyl]pyrrolidine (R_S)-*syn*-**334a** is representative. A solution of *N*-[2-diphenylmethyleneaminoacetyl]piperidine **313a** (1 equiv, 0.50 mmol, 0.15 g) in THF (10 mL) was cooled to -78 °C under nitrogen atmosphere. A 1.0M solution of LiHMDS (1 equiv, 0.50 mL, 0.50 mmol) in THF was slowly added and the resulting solution was stirred for one hour at -78 °C. After deprotonation, a solution of (R_S)-*N*-*tert*-butanesulfinyl-α-(*tert*-butoxycarbonylamino)acetaldimine (R_S)-**271** (1.0 equiv, 0.50 mmol, 0.13 g) in THF (3 mL) was added dropwise and the reaction mixture was stirred at -78 °C for 15 minutes. To the reaction mixture was added a saturated solution of NH_4Cl (5 mL) while stirring at -78 °C for two minutes. The reaction mixture was brought to room temperature followed by an

extraction with EtOAc (3 x 20 mL). The combined organic phases were dried ($MgSO_4$), filtered and evaporated *in vacuo*. The crude product was purified by column chromatography to yield 0.06 g (0.11 mmol, 22%) of pure (R_S,2*R*,3*S*) *N*-[4-(*tert*-butoxycarbonylamino)-2-diphenylmethyleneamino-3-(*tert*-butanesulfinylamino)butanoyl]-pyrrolidine (R_S)-*syn*-**334a**.

(R_S,2*R*,3*S*) *N*-[4-(*tert*-Butoxycarbonylamino)-2-diphenylmethyleneamino-3-(*tert*-butanesulfinylamino)butanoyl]pyrrolidine (R_S)-*syn*-334a. White crystals, yield 22% (0.06 g). $[\alpha]_D$ -42.4 (*c* 0.7, $CHCl_3$). Mp 191.8 ± 2.0 °C. IR (cm^{-1}): ν_{max} 696, 1066, 1161, 1249, 1446, 1529, 1621, 1714, 3266. ^1H NMR (300 MHz, $CDCl_3$): δ1.24 (9H, s, $SC(CH_3)_3$), 1.40 (9H, s, $OC(CH_3)_3$), 1.61-1.82 (4H, m, $2xC\underline{H}_2(CH_2)_2$), 2.67-2.74 (1H, m, $NC\underline{H}(H)CH_2$), 3.11-3.30 (3H, m, $NCH(\underline{H})CH_2$ and $NC\underline{H}(H)CH_2$ and $NHC\underline{H}(H)$), 3.35-3.47 (2H, m, $NCH(\underline{H})CH_2$ and $NHCH(\underline{H})$), 3.62-3.70 (1H, m, $C\underline{H}NH$), 4.21 (1H, d, *J* = 2.8 Hz, CHCO), 4.74 (1H, d, *J* = 9.9 Hz, SNH), 5.84-5.88 (1H, m, CONH), 7.11-7.14 (2H, m, CH_{arom}), 7.30-7.43 (6H, m, CH_{arom}), 7.61-7.64 (2H, m, CH_{arom}). ^{13}C NMR (75 MHz, $CDCl_3$): δ22.8 ($SC(\underline{C}H_3)_3$), 23.9, 26.3 ($2xC\underline{H}_2(CH_2)_2$), 28.5 ($OC(CH_3)_3$), 45.1 ($NHCH_2$), 46.26, 46.28 ($2xCH_2N$), 56.6 ($S\underline{C}(CH_3)_3$), 59.7 (CHNH), 66.5 ($\underline{C}HCO$), 79.3 ($O\underline{C}(CH_3)_3$), 127.4 ($2xCH_{arom}$), 128.2 ($2xCH_{arom}$), 128.75 ($2xCH_{arom}$), 128.83 ($CH_{arom}$), 128.9 ($2xCH_{arom}$), 130.9 ($CH_{arom}$), 137.0, 138.7 ($2xC_{arom}$), 156.7 (OCONH), 168.8, 171.8 (C=N and C=O). MS (ES, pos. mode) *m/z* (%): 555 ($M + H^+$, 100). HRMS (ES) calcd for $C_{30}H_{42}N_4O_4S$: 555.3000 MH^+; found: 555.3005.

(S_S,2*S*,3*R*) *N*-[4-(*tert*-Butoxycarbonylamino)-2-diphenylmethyleneamino-3-(*tert*-butanesulfinylamino)butanoyl]pyrrolidine (S_S)-*syn*-334a. White crystals, yield 69% (1.40 g). $[\alpha]_D$ +40.5 (*c* 0.9, $CHCl_3$). Mp 190.4 ± 2.0 °C. IR (cm^{-1}): ν_{max} 696, 704, 1066, 1162, 1249, 1620, 1715, 3266. ^1H NMR (300 MHz, $CDCl_3$): δ1.24 (9H, s, $SC(CH_3)_3$), 1.40 (9H, s, $OC(CH_3)_3$), 1.61-1.82 (4H, m, $2xC\underline{H}_2(CH_2)_2$), 2.66-2.74 (1H, m, $NC\underline{H}(H)CH_2$), 3.11-3.30 (3H, m, $NCH(\underline{H})CH_2$ and $NC\underline{H}(H)CH_2$ and $NHC\underline{H}(H)$), 3.35-3.49 (2H, m, $NCH(\underline{H})CH_2$ and $NHCH(\underline{H})$), 3.63-3.71 (1H, m, $C\underline{H}NH$), 4.21 (1H, d, *J* = 2.8 Hz, CHCO), 4.75 (1H, d, *J* = 9.9 Hz, SNH), 5.87-5.91 (1H, m, CONH), 7.11-7.14 (2H, m, CH_{arom}), 7.30-7.46 (6H, m, CH_{arom}), 7.61-7.65 (2H, m, CH_{arom}). ^{13}C NMR (75 MHz, $CDCl_3$): δ22.7

($SC(\underline{C}H_3)_3$), 23.8, 26.2 ($2x\underline{C}H_2(CH_2)_2$), 28.4 ($OC(\underline{C}H_3)_3$), 45.0 ($NHCH_2$), 46.1, 46.2 ($2xCH_2N$), 56.5 ($S\underline{C}(CH_3)_3$), 59.5 (CHNH), 66.4 ($\underline{C}HCO$), 79.2 ($O\underline{C}(CH_3)_3$), 127.3 ($2xCH_{arom}$), 128.1 ($2xCH_{arom}$), 128.6 ($2xCH_{arom}$), 128.7 ($CH_{arom}$), 128.8 ($2xCH_{arom}$), 130.7 ($CH_{arom}$), 136.9, 138.6 ($2xC_{arom}$), 156.6 (OCONH), 168.6, 171.6 (C=N and C=O). MS (ES, pos. mode) *m/z* (%): 555 ($M + H^+$, 100). HRMS (ES) calcd for $C_{30}H_{42}N_4O_4S$: 555.3000 MH^+; found: 555.3003.

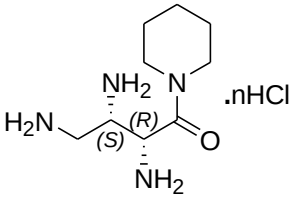
(R_S,2*R*,3*S*) *N*-[4-(*tert*-Butoxycarbonylamino)-2-diphenylmethyleneamino-3-(*tert*-butanesulfinylamino)butanoyl]piperidine (R_S)-*syn*-334b. Yellow oil, yield 60% (1.19 g). $[\alpha]_D$ -53.7 (*c* 0.6, $CHCl_3$). IR (cm^{-1}): ν_{max} 696, 1051, 1169, 1248, 1638, 1703, 3308 (weak). ^1H NMR (300 MHz, $CDCl_3$): δ 0.90-1.02 (1H, m, $C\underline{H}(H)(CH_2)_2$), 1.23 (9H, s, $SC(CH_3)_3$), 1.41 (9H, s, $OC(CH_3)_3$), 1.35-1.65 (5H, m, $2xC\underline{H}_2(CH_2)_2$ and $CH(\underline{H})(CH_2)_2$), 3.03-3.24 (4H, m, $NHC\underline{H}(H)$ and $NC\underline{H}(H)CH_2$ and $NC\underline{H}_2CH_2$), 3.35-3.43 (1H, m, $NHCH(\underline{H})$), 3.56-3.70 (2H, m, $NHC\underline{H}$ and $NCH(\underline{H})CH_2$), 4.33 (1H, d, *J* = 2.8 Hz, CHCO), 4.72 (1H, d, *J* = 9.9 Hz, SNH), 5.91-5.96 (1H, m, CONH), 7.10-7.15 (2H, m, CH_{arom}), 7.29-7.46 (6H, m, CH_{arom}), 7.60-7.66 (2H, m, CH_{arom}). ^{13}C NMR (75 MHz, $CDCl_3$): δ 22.8 ($SC(CH_3)_3$), 24.6, 25.6, 26.2 ($3xCH_2(CH_2)_2$), 28.5 ($OC(CH_3)_3$), 43.3 (CH_2N), 45.4 ($NHCH_2$), 46.5 (CH_2N), 56.7 ($S\underline{C}(CH_3)_3$), 60.1 (CHNH), 64.9 ($\underline{C}HCO$), 79.4 ($O\underline{C}(CH_3)_3$), 127.7 ($2xCH_{arom}$), 128.1 ($2xCH_{arom}$), 128.7 ($2xCH_{arom}$), 128.8 (CH_{arom}), 128.9 ($2xCH_{arom}$), 130.2 (CH_{arom}), 136.9, 138.8 ($2xC_{arom}$), 156.7 (OCONH), 168.3, 171.8 (C=N and C=O). MS (ES, pos. mode) *m/z* (%): 569 ($M + H^+$, 100). HRMS (ES) calcd for $C_{31}H_{44}N_4O_4S$: 569.3156 MH^+; found: 569.3162.

(S_S,2*S*,3*R*) *N*-[4-(*tert*-Butoxycarbonylamino)-2-diphenylmethyleneamino-3-(*tert*-butanesulfinylamino)butanoyl]piperidine (S_S)-*syn*-334b. Yellow oil, yield 74% (1.34 g). $[\alpha]_D$ +55.9 (*c* 1.0, $CHCl_3$). IR (cm^{-1}): ν_{max} 697, 1047, 1169, 1247, 1637, 1705, 3305 (weak). ^1H NMR (300 MHz, $CDCl_3$): δ 0.88-1.02 (1H, m, $C\underline{H}(H)(CH_2)_2$), 1.23 (9H, s, $SC(CH_3)_3$), 1.41 (9H, s, $OC(CH_3)_3$), 1.35-1.65 (5H, m, $2xC\underline{H}_2(CH_2)_2$ and $CH(\underline{H})(CH_2)_2$), 3.05-3.24 (4H, m, $NHC\underline{H}(H)$ and $NC\underline{H}(H)CH_2$ and $NC\underline{H}_2CH_2$), 3.35-3.43 (1H, m, $NHCH(\underline{H})$), 3.56-3.69 (2H, m, $NHC\underline{H}$ and $NCH(\underline{H})CH_2$), 4.33 (1H, d, *J* = 2.8 Hz, CHCO), 4.70 (1H, d, *J* = 9.9 Hz, SNH), 5.88-5.96 (1H, m, CONH), 7.09-7.15 (2H, m, CH_{arom}), 7.29-7.45 (6H, m, CH_{arom}), 7.59-7.64 (2H, m, CH_{arom}).^{13}C NMR (75 MHz, $CDCl_3$): δ

22.8 (SC($\underline{C}H_3)_3$), 24.5, 25.6, 26.2 (3x$\underline{C}H_2(CH_2)_2$), 28.4 (OC($\underline{C}H_3)_3$), 43.2 (CH_2N), 45.3 ($NHCH_2$), 46.5 (CH_2N), 56.6 (S$\underline{C}(CH_3)_3$), 60.1 (CHNH), 64.8 ($\underline{C}HCO$), 79.3 (O$\underline{C}(CH_3)_3$), 127.6 (2xCH_{arom}), 128.1 (2xCH_{arom}), 128.6 (2xCH_{arom}), 128.7 (CH_{arom}), 128.8 (2xCH_{arom}), 130.7 (CH_{arom}), 136.8, 138.8 (2xC_{arom}), 156.7 (OCONH), 168.3, 171.7 (C=N and C=O). MS (ES, pos. mode) *m/z* (%): 569 ($M + H^+$, 100). HRMS (ES) calcd for $C_{31}H_{44}N_4O_4S$: 569.3156 MH^+; found: 569.3168.

5.35. Synthesis of (2*R*,3*S*) *N*-(2,3,4-triaminobutanoyl)piperidine hydrochloride *syn*-337b

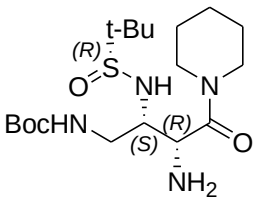
(R_S,2*R*,3*S*) *N*-[4-(*tert*-butoxycarbonylamino)-2-diphenylmethyleneamino-3-(*tert*-butanesulfinylamino)butanoyl]piperidine (R_S)-*syn*-**334b** (0.20 g, 0.35 mmol) was dissolved in a mixture of 0.5 M (aq.) HCl/EtOAc (2:1) (12 mL) and the mixture was stirred for 30 minutes at room temperature. The organic phase was removed and the aqueous phase was washed with EtOAc (3 x 5 mL). Subsequently, the aqueous phase was lyophilized to yield 0.07 g (0.22 mmol, 64%) of pure (2*R*,3*S*) *N*-(2,3,4-triaminobutanoyl)piperidine hydrochloride *syn*-**337b**.



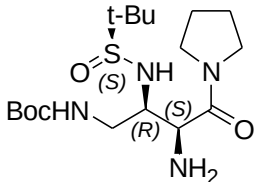
(2*R*,3*S*) *N*-(2,3,4-Triaminobutanoyl)piperidine hydrochloride *syn*-337b. White powder, yield 64% (0.07 g). $[\alpha]_D$ +18.8 (*c* 1.0, H_2O). Mp 173.1 ± 2.0 °C. IR (cm^{-1}): ν_{max} 1052, 1164, 1710, 2845, 2862, 2949, 3190, 3358. ^{1}H NMR (300 MHz, D_2O): δ 1.56-1.67 (2H, m, C$\underline{H}_2(CH_2)_2$), 1.68-1.78 (4H, m, 2xC$\underline{H}_2(CH_2)_2$), 3.08-3.15 (4H, m, 2xNC$\underline{H}_2CH_2$), 3.51 (1H, dxd, *J* = 11.0 Hz, *J* = 7.2 Hz, $NH_2C\underline{H}$(H)), 3.93 (1H, dxd, *J* = 11.0 Hz, *J* = 8.3 Hz, $NH_2CH(\underline{H})$), 4.34 (1H, q, *J* = 8.3 Hz, $CH_2C\underline{H}N$), 4.44 (1H, d, *J* = 8.3 Hz, CHCO). ^{13}C NMR (75 MHz, D_2O): δ 21.7 ($\underline{C}H_2(CH_2)_2$), 22.4 (2x$\underline{C}H_2(CH_2)_2$), 43.0 (NH_2CH_2), 44.8 (2xCH_2N), 49.4 ($CH_2\underline{C}HN$), 53.3 ($\underline{C}HCO$), 168.9 (C=O).

5.36. Synthesis of (R_S)-*syn* *N*-[2-amino-4-(*tert*-butoxycarbonylamino)-3-(*tert*-butanesulfinylamino)butanoyl]amines *syn*-338

The synthesis of (R_S,2*R*,3*S*) *N*-[2-amino-4-(*tert*-butoxycarbonylamino)-3-(*tert*-butanesulfinyl-amino)butanoyl]piperidine (R_S)-*syn*-**338b** is representative. To a solution of (R_S,2*R*,3*S*) *N*-[4-(*tert*-butoxycarbonylamino)-2-diphenylmethyleneamino-3-(*tert*-butanesulfinylamino)-butanoyl]piperidine (R_S)-*syn*-**334b** (0.25 g, 0.44 mmol) in acetone/H_2O (2:1) (9 mL) was added dropwise trifluoroacetic acid (5 equiv, 2.20 mmol, 0.17 mL) at room temperature. The reaction mixture was stirred for 15 minutes 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 x 10 mL). The combined organic phases were dried ($MgSO_4$), filtered and evaporated *in vacuo*. The crude product was purified by column chromatography to yield 0.14 g (0.34 mmol, 77%) of pure (R_S,2*R*,3*S*) *N*-[2-amino-4-(*tert*-butoxycarbonylamino)-3-(*tert*-butanesulfinylamino)butanoyl]piperidine (R_S)-*syn*-**338b**.



(R_S,2*R*,3*S*) *N*-[2-Amino-4-(*tert*-butoxycarbonylamino)-3-(*tert*-butanesulfinylamino)-butanoyl]piperidine (R_S)-*syn*-338b. Yellow oil, yield 77% (0.14 g). $[\alpha]_D$ -69.6 (*c* 0.9, $CHCl_3$). IR (cm^{-1}): ν_{max} 730, 1045, 1169, 1249, 1638, 1698, 3298. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.19 (9H, s, $SC(CH_3)_3$), 1.45 (9H, s, $OC(CH_3)_3$), 1.53-1.72 (6H, m, 3x$C\underline{H}_2(CH_2)_2$), 2.40 (2H, br s, NH_2), 3.19-3.38 (2H, m, NHC$\underline{H}$(H) and NC$\underline{H}$(H)CH_2), 3.38-3.55 (4H, m, C$\underline{H}$NH and NHCH($\underline{H}$) and NCH($\underline{H}$)CH_2 and CH_2NC$\underline{H}$(H)), 3.55-3.68 (1H, m, CH_2NCH($\underline{H}$)), 3.88 (1H, br s, CHCO), 4.01-4.09 (1H, m, SNH), 5.67-5.75 (1H, m, CONH). ^{13}C NMR (75 MHz, $CDCl_3$): δ 22.8 (SC($\underline{C}H_3)_3$), 24.6, 25.7, 26.6 (3x$\underline{C}H_2(CH_2)_2$), 28.5 (OC($\underline{C}H_3)_3$), 43.7 (CH_2N), 44.7 (CH_2NH), 46.6 (CH_2N), 52.2 ($CHNH_2$), 56.7 (S$\underline{C}(CH_3)_3$), 60.1 (CHNH), 79.7 (O$\underline{C}(CH_3)_3$), 156.8 (OCONH), 170.4 (C=O). MS (ES, pos. mode) *m/z* (%): 405 ($M + H^+$, 100). HRMS (ES) calcd for $C_{18}H_{36}N_4O_4S$: 405.2530 MH^+; found: 405.2530.

(*S*$_S$,2*S*,3*R*) *N*-[2-Amino-4-(*tert*-butoxycarbonylamino)-3-(*tert*-butanesulfinylamino)-butanoyl]pyrrolidine (*S*$_S$)-*syn*-338a. 

Yellow oil, yield 81% (0.17 g). $[\alpha]_D$ +45.4 (*c* 0.8, $CHCl_3$). IR (cm^{-1}): ν_{max} 730, 1042, 1166, 1253, 1365, 1453, 1519, 1633, 1693, 3286. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.04 (9H, s, $SC(CH_3)_3$), 1.27 (9H, s, $OC(CH_3)_3$), 1.63-1.88 (4H, m, $2xCH_2(CH_2)_2$), 2.22 (2H, br s, NH_2), 3.11-3.56 (8H, m, $2xNCH_2$ and $NHCH_2$ and CHNH and CHCO), 4.06-4.23 (1H, m, SNH), 5.84-5.96 (1H, m, CONH). ^{13}C NMR (75 MHz, $CDCl_3$): δ 23.5 ($SC(CH_3)_3$), 24.8, 27.0 ($2xCH_2(CH_2)_2$), 29.2 ($OC(CH_3)_3$), 44.5 (CH_2NH), 47.0, 47.1 ($2xCH_2N$), 54.8 ($CHNH_2$ or CHNH), 57.2 ($SC(CH_3)_3$), 59.9 (CHNH or $CHNH_2$), 80.0 ($OC(CH_3)_3$), 157.5 (OCONH), 171.9 (C=O). MS (ES, pos. mode) *m/z* (%): 391 ($M + H^+$, 100). HRMS (ES) calcd for $C_{17}H_{34}N_4O_4S$: 391.2374 MH^+; found: 391.2390.

5.37. Synthesis of (*R*$_S$,*R*$_S$)-Methyl 4-(*tert*-butoxycarbonylamino)-3-(*tert*-butanesulfinylamino)-2-chloro-*N*-*tert*-butanesulfinylbutanimidate 345

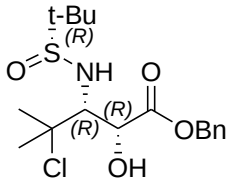
A solution of (*R*$_S$)-α-chloro-*N*-*tert*-butanesulfinyl imidate (*R*$_S$)-**344** (1.8 equiv, 0.69 mmol, 0.15 g) in THF (10 mL) was cooled to -78 °C under nitrogen atmosphere. A 1.0M solution of LiHMDS (1.8 equiv, 0.69 mL, 0.69 mmol) in THF was slowly added and the resulting solution was stirred for 45 minutes at -78 °C. After deprotonation, a solution of (*R*$_S$)-*N*-*tert*-butanesulfinyl-α-(*tert*-butoxycarbonylamino)acetaldimine (*R*$_S$)-**271** (1.0 equiv, 0.38 mmol, 0.10 g) in THF (3 mL) was added dropwise and the reaction mixture was stirred at -78 °C for 30 minutes. To the reaction mixture was added a saturated solution of NH_4Cl (5 mL) while stirring at -78 °C for two minutes. The reaction mixture was brought to room temperature followed by an extraction with EtOAc (3 x 10 mL). The combined organic phases were dried ($MgSO_4$), filtered and evaporated *in vacuo*. The crude product was purified by column chromatography to yield 0.15 g (0.31 mmol, 83%) of pure (*R*$_S$,*R*$_S$)-methyl 4-(*tert*-butoxycarbonylamino)-3-(*tert*-butanesulfinylamino)-2-chloro-*N*-*tert*-butane-sulfinylbutanimidate **345**.

(R_S,R_S)-Methyl 4-(*tert*-butoxycarbonylamino)-3-(*tert*-butanesulfinylamino)-2-chloro-*N*-*tert*-butanesulfinylbutanimidate 345. Yellow oil, yield 83% (0.15 g). $[\alpha]_D$ -48.8 (*c* 1.1, $CHCl_3$). IR (cm^{-1}): ν_{max} 730, 915, 1045, 1167, 1242, 1367, 1736, 3310. ^1H NMR (300 MHz, $CDCl_3$): δ1.23 (9H, s, $SC(CH_3)_3$), 1.28 (9H, s, $SC(CH_3)_3$), 1.44 (9H, s, $OC(CH_3)_3$), 3.11-3.16 (1H, m, C<u>H</u>NH), 3.31-3.41 (1H, m, C<u>H</u>(H)NH), 3.75 (3H, s, OCH_3), 3.96 (1H, d, *J* = 3.3 Hz, CHCl), 4.00-4.07 (1H, m, CH(<u>H</u>)NH), 5.66-5.74 (1H, m, CONH), SNH (not visible). ^{13}C NMR (75 MHz, $CDCl_3$): δ22.0, 22.3 (2xSC(<u>C</u>$H_3)_3$), 28.5 ($OC(CH_3)_3$), 38.1 (CHCl), 39.3 (CH_2NH), 46.2 (CHNH), 54.7 (OCH_3) 57.1, 57.9 (2xS<u>C</u>$(CH_3)_3$), 79.6 (O<u>C</u>$(CH_3)_3$), 155.9 (C=O), 167.2 (C=N). MS (ES^+): *m*/*z* (%): 474/476 ($M+H^+$, 100). HRMS (ES) calcd for $C_{18}H_{36}ClN_3O_5S_2$: 474.1858 MH^+; found: 474.1861.

5.38. Synthesis of (R_S,2*R*,3*R*)-alkyl 4-chloro-2-hydroxy-4-methyl-3-(*tert*-butanesulfinylamino)pentanoates 356

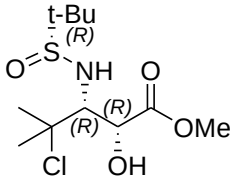
The synthesis of (R_S,2*R*,3*R*)-benzyl 4-chloro-2-hydroxy-4-methyl-3-(*tert*-butanesulfinylamino)-pentanoate **356a** is representative. To a solution of (R_S,2*R*,3*R*)-benzyl 2-(*tert*-butoxycarbonyloxy)-4-chloro-4-methyl-3-(*tert*-butanesulfinylamino)pentanoate **351a** (synthesized according to *ref 153*) 0.61 g, 1.28 mmol) in CH_2Cl_2 (7 mL) was added dropwise trifluoroacetic acid (3 mL) at room temperature. The reaction mixture was stirred for one hour at room temperature and subsequently poured out in water (7 mL) and quenched with K_2CO_3 until pH = 7. The aqueous phase was extracted with CH_2Cl_2 (3 x 10 mL) and the combined organic phases were dried ($MgSO_4$), filtered and evaporated *in vacuo*. The crude product was purified by crystallization in diethyl ether to yield 0.36 g (0.96 mmol, 75%) of pure (R_S,2*R*,3*R*)-benzyl 4-chloro-2-hydroxy-4-methyl-3-(*tert*-butanesulfinylamino)pentanoate **356a**.

(R_S,2*R*,3*R*)-Benzyl 4-chloro-2-hydroxy-4-methyl-3-(*tert*-butanesulfinylamino)pentanoate 356a. R_f = 0.27 (petroleum ether/EtOAc: 1/1). Yellow oil, yield 75% (0.36 g). $[\alpha]_D$ +6.3 (*c*



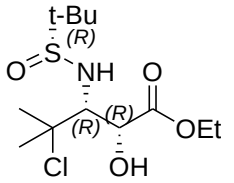
2.0, $CHCl_3$). IR (cm^{-1}): 1739, 3266. ^1H NMR (300 MHz, $CDCl_3$): δ 1.09 (9H, s, $SC(CH_3)_3$), 1.68 (3H, s, $CC\underline{H}_3(CH_3)$), 1.82 (3H, s, $CCH_3(C\underline{H}_3)$), 3.48 (1H, br s, OH), 3.88 (1H, dxd, *J* = 9.9 Hz, 1.1 Hz, NHC<u>H</u>CH), 4.04 (1H, d, *J* = 9.9 Hz, NH), 4.86 (1H, d, *J* = 1.1 Hz, OCH), 5.16 (1H, d, *J* = 12.1 Hz, C<u>H</u>(H)Ph), 5.24 (1H, d, *J* = 12.1 Hz, CH(<u>H</u>)Ph), 7.35-7.40 (5H, m, CH_{arom}). ^{13}C NMR (75 MHz, $CDCl_3$): δ 22.6 ($SC(\underline{C}H_3)_3$), 28.8 ($C\underline{C}H_3(CH_3)$), 31.5 ($CCH_3(\underline{C}H_3)$), 57.1 ($S\underline{C}(CH_3)_3$), 66.7 (NH<u>C</u>H), 68.1 (COO<u>C</u>H_2), 70.8 (CHOH), 71.8 ($\underline{C}Cl(CH_3)_2$), 128.69 (2xCH_{arom}), 128.74 (2xCH_{arom}), 128.8 (CH_{arom}), 134.5 (C_{arom}), 173.5 (<u>C</u>OO). MS (ES^+): *m*/*z* (%): 376/378 ($M+H^+$, 100). HRMS (ES) calcd for $C_{17}H_{26}ClNO_4S$: 376.1344 MH^+; found: 376.1345.

(R_S,2*R*,3*R*)-Methyl 4-chloro-2-hydroxy-4-methyl-3-(*tert*-butanesulfinylamino)pentanoate



356b. R_f = 0.29 (petroleum ether/EtOAc: 1/2). White crystals, yield 80% (0.27 g). $[\alpha]_D$ -27.1 (*c* 2.0, $CHCl_3$). Mp 114.1 ± 1.0 °C. IR (cm^{-1}): 1742, 3293. ^1H NMR (300 MHz, $CDCl_3$): δ 1.17 (9H, s, $SC(CH_3)_3$), 1.70 (3H, s, $CC\underline{H}_3(CH_3)$), 1.85 (3H, s, $CCH_3(C\underline{H}_3)$), 3.23 (1H, br s, OH), 3.82 (3H, s, OCH_3), 3.86 (1H, d, *J* = 9.9 Hz, NHC<u>H</u>), 3.97 (1H, d, *J* = 9.9 Hz, NH), 4.86 (1H, s, C<u>H</u>O). ^{13}C NMR (75 MHz, $CDCl_3$): δ 22.6 ($SC(\underline{C}H_3)_3$), 28.8 ($C\underline{C}H_3(CH_3)$), 31.5 ($CCH_3(\underline{C}H_3)$), 53.1 (O<u>C</u>H_3), 57.1 ($S\underline{C}(CH_3)_3$), 66.6 (NH<u>C</u>H), 70.7 (CHOH), 71.8 ($\underline{C}(CH_3)_2$), 174.1 (COO). MS (ES^+): *m*/*z* (%): 300/302 ($M+H^+$, 100). HRMS (ES) calcd for $C_{11}H_{22}ClNO_4S$: 300.1031 MH^+; found: 300.1024.

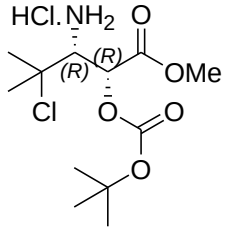
(R_S,2*R*,3*R*)-Ethyl 4-chloro-2-hydroxy-4-methyl-3-(*tert*-butanesulfinylamino)pentanoate



356c. White crystals, yield 86% (0.24 g). $[\alpha]_D$ -9.3 (*c* 2.1, $CHCl_3$). Mp 98.3 ± 2.0 °C. IR (cm^{-1}): 1738, 3288. ^1H NMR (300 MHz, $CDCl_3$): δ 1.18 (9H, s, $SC(CH_3)_3$), 1.34 (3H, t, *J* = 7.2 Hz, $CH_2C\underline{H}_3$), 1.70 (3H, s, $CC\underline{H}_3(CH_3)$), 1.85 (3H, s, $CCH_3(C\underline{H}_3)$), 3.29 (1H, *J* = 3.9 Hz, OH), 3.85 (1H, dxd, *J* = 9.9 Hz, 1.1 Hz, NHC<u>H</u>), 3.99 (1H, d, *J* = 9.9 Hz, NH), 4.16-4.35 (2H, m, O<u>C</u>H_2CH_3), 4.82 (1H, dxd, *J* = 3.9 Hz, 1.1 Hz, C<u>H</u>O). ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.2 ($CH_2\underline{C}H_3$), 22.6 ($SC(\underline{C}H_3)_3$), 28.8 ($C\underline{C}H_3(CH_3)$), 31.6 ($CCH_3(\underline{C}H_3)$), 57.0 ($S\underline{C}(CH_3)_3$), 62.6 ($\underline{C}H_2CH_3$), 66.6 (NH<u>C</u>HCH), 70.7 (CH<u>C</u>HO), 71.8 ($\underline{C}Cl(CH_3)_2$), 173.7 (C=O). MS (ES^+): *m*/*z* (%): 314/316 ($M+H^+$, 100). HRMS (ES) calcd for $C_{12}H_{24}ClNO_4S$: 314.1187 MH^+; found: 314.1176.

5.39. Synthesis of (2*R*,3*R*)-methyl 3-amino-2-(*tert*-butoxycarbonyloxy)-4-chloro-4-methylpentanoate hydrochloride 363b

To a solution of (R_S,2*R*,3*R*)-methyl 2-(*tert*-butoxycarbonyloxy)-4-chloor-4-methyl-3-(*tert*-butane-sulfinylamino)pentanoate **351b** (0.19 g, 0.48 mmol) in dioxane (20 mL) was added a saturated solution of HCl in dioxane (5 mL) at room temperature. The reaction mixture was stirred for one hour at room temperature and subsequently the solvent was evaporated *in vacuo*. The crude product was purified by washing with diethyl ether to yield 0.14 g (0.45 mmol, 93%) of pure (2*R*,3*R*)-methyl 3-amino-2-(*tert*-butoxycarbonyloxy)-4-chloro-4-methylpentanoate hydrochloride **363b**.



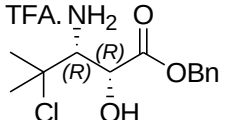
(2*R*,3*R*)-Methyl 3-amino-2-(*tert*-butoxycarbonyloxy)-4-chloro-4-methylpentanoate hydrochloride 363b. White powder, yield 93% (0.14 g). $[\alpha]_D$ -13.0 (*c* 2.2, $CHCl_3$). Mp 149.2 ± 2.0 °C. IR (cm^{-1}): 1727, 1752, 2509 (broad). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.50 (9H, s, $OC(CH_3)_3$), 1.87 (6H, br s, $C(CH_3)_2$), 3.89 (3H, s, OCH_3), 4.26 (1H, br s, $NH_2C\underline{H}$), 5.73 (1H, br s, CHO), 9.01 (3H, br s, NH_3Cl). ^{13}C NMR (75 MHz, ref = $CDCl_3$): δ 27.8 ($OC(\underline{C}H_3)_3$), 30.4 ($C\underline{C}H_3(CH_3)$), 31.3 ($CCH_3(\underline{C}H_3)$), 54.2 (NH_2CH), 59.8 (OCH_3), 67.8 ($\underline{C}(CH_3)_2$), 70.8 (CHO), 84.3 ($O\underline{C}(CH_3)_3$), 151.8 (O(C=O)O), 167.7 ($CH\underline{C}OO$). MS (ES^+): *m*/*z* (%): 296/298 ($M+H^+$ - HCl, 100). HRMS (ES) calcd for $C_{12}H_{22}ClNO_5$: 296.1259 MH^+ - HCl; found: 296.1259.

5.40. Synthesis of (2*R*,3*R*)-alkyl 3-amino-4-chloro-2-hydroxy-4-methyl-pentanoate trifluoroacetic acid salts 364

The synthesis of (2*R*,3*R*)-benzyl 3-amino-4-chloro-2-hydroxy-4-methylpentanoate **364a** is representative. To a solution of (2*R*,3*R*)-benzyl 3-amino-2-(*tert*-butoxycarbonyloxy)-4-chloro-4-methylpentanoate **363a** (synthesized according to *ref 153*) (0.78 g, 1.91 mmol) in CH_2Cl_2 (14 mL) was added trifluoroacetic acid (6 mL) at room temperature. The reaction

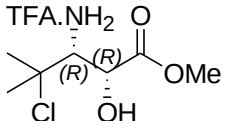
mixture was stirred for one hour at room temperature and subsequently evaporated *in vacuo*, affording the pure (2*R*,3*R*)-benzyl 3-amino-4-chloro-2-hydroxy-4-methylpentanoate **364a**.

(2*R*,3*R*)-Benzyl 3-amino-4-chloro-2-hydroxy-4-methylpentanoate 364a. Yellow oil, yield



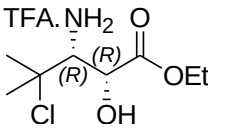
97% (0.72 g). $[\alpha]_D$ -4.5 (*c* 1.3, $CHCl_3$). IR (cm^{-1}): 1142, 1665, 1739, 3038. ^1H NMR (300 MHz, $CDCl_3$): δ 1.70 (3H, s, $C(C\underline{H}_3)CH_3$), 1.76 (3H, s, $C(CH_3)C\underline{H}_3$), 3.95 (1H, s, $NH_2C\underline{H}CH$), 4.65 (1H, s, $CHC\underline{H}O$), 5.12 (1H, d, *J* = 12.1 Hz, $COOC\underline{H}(H)$), 5.29 (1H, d, *J* = 12.1 Hz, $COOCH(\underline{H})$), 7.26-7.35 (5H, m, $C\underline{H}_{arom}$), 8.21 (4H, br s, NH_2.TFA and OH). ^{13}C NMR (75 MHz, ref = $CDCl_3$): δ 28.1 ($C\underline{C}H_3(CH_3)$), 29.9 ($CCH_3(\underline{C}H_3)$), 61.9 ($NH_2\underline{C}HCH$), 67.1 ($CH\underline{C}HO$), 68.9 ($COO\underline{C}H_2$), 69.2 ($\underline{C}Cl(CH_3)_2$), 128.7 ($2xCH_{arom}$), 128.9 ($2xCH_{arom}$), 129.1 (CH_{arom}), 134.1 (C_{arom}), 171.6 ($CH\underline{C}OO$). MS (ES^+): *m*/*z* (%): 272/274 ($M+H^+$ - TFA, 100). HRMS (ES) calcd for $C_{13}H_{18}ClNO_3$: 272.1048 MH^+ - TFA; found: 272.1058.

(2*R*,3*R*)-Methyl 3-amino-4-chloro-2-hydroxy-4-methylpentanoate 364b. Yellow oil, yield



84% (0.98 g). $[\alpha]_D$ -18.4 (*c* 2.0, $CHCl_3$). IR (cm^{-1}): 1135, 1183, 1669, 1742, 2961. ^1H NMR (300 MHz, $CDCl_3$): δ 1.72 (3H, s, $C(C\underline{H}_3)CH_3$), 1.78 (3H, s, $C(CH_3)C\underline{H}_3$), 3.79 (3H, s, OCH_3), 3.91 (1H, s, $NH_2C\underline{H}CH$), 4.66 (1H, s, $CHC\underline{H}O$), 7.60 (4H, br s, NH_2.TFA and OH). ^{13}C NMR (75 MHz, ref = $CDCl_3$): δ 28.2 ($C\underline{C}H_3(CH_3)$), 29.7 ($CCH_3(\underline{C}H_3)$), 53.6 (OCH_3), 61.8 ($NH_2\underline{C}HCH$), 67.0 ($CH\underline{C}HO$), 69.0 ($\underline{C}Cl(CH_3)_2$), 172.4 ($CH\underline{C}OO$). MS (ES^+): *m*/*z* (%): 196/198 ($M+H^+$ - TFA, 100). HRMS (ES) calcd for $C_7H_{14}ClNO_3$: 196.0735 MH^+ - TFA; found: 196.0740.

(2*R*,3*R*)-Ethyl 3-amino-4-chloro-2-hydroxy-4-methylpentanoate 364c. Yellow oil, yield

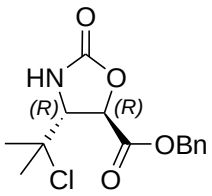


96% (0.27 g). $[\alpha]_D$ -14.7 (*c* 1.0, $CHCl_3$). IR (cm^{-1}): 1135, 1184, 1668, 1734, 2987. ^1H NMR (300 MHz, $CDCl_3$): δ 1.30 (3H, t, *J* = 7.2 Hz, $CH_2C\underline{H}_3$), 1.73 (3H, s, $CC\underline{H}_3(CH_3)$), 1.80 (3H, s, $CCH_3(C\underline{H}_3)$), 3.90 (1H, br s, $NH_2C\underline{H}$), 4.16-4.36 (2H, m, $OC\underline{H}_2CH_3$), 4.62 (1H, br s, CHO), 6.96 (4H, br s, NH_2.TFA and OH). ^{13}C NMR (75 MHz, ref = $CDCl_3$): δ 13.8 ($CH_2\underline{C}H_3$), 28.1 ($C\underline{C}H_3(CH_3)$), 29.9 ($CCH_3(\underline{C}H_3)$), 61.9 (NH_2CH), 63.5 ($COO\underline{C}H_2$), 67.0 ($\underline{C}(CH_3)_2$), 69.2 (CHO), 171.9 ($CH\underline{C}OO$). MS (ES^+): *m*/*z* (%): 210/212 ($M+H^+$ - TFA, 100). HRMS (ES) calcd for $C_8H_{16}ClNO_3$: 210.0891 MH^+ - TFA; found: 210.0896.

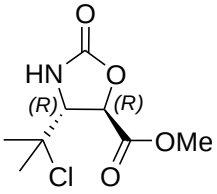
5.41. Synthesis of (4*R*,5*R*)-alkyl 4-(2-chloro-2-propyl)oxazolidin-2-one-5-carboxylates 358

The synthesis of (4*R*,5*R*)-ethyl 4-(2-chloro-2-propyl)oxazolidin-2-one-5-carboxylate **358c** is representative. To a solution of (2*R*,3*R*)-ethyl 3-amino-4-chloro-2-hydroxy-4-methylpentanoate **364c** (0.09 g, 0.28 mmol) in dry CH_2Cl_2 (5 mL) was added dropwise DIPEA (4 equiv, 0.14 g, 1.11 mmol) at 0 °C. The reaction mixture was stirred for 15 minutes at 0 °C, and subsequently triphosgene (1.2 equiv, 0.10 g, 0.33 mmol) dissolved in dry CH_2Cl_2 was added dropwise. The reaction was allowed to warm up to room temperature and after one hour, the reaction mixture was poured out in brine (5 mL). The aqueous phase was extracted with CH_2Cl_2 (3 x 5 mL) and the combined organic phases were dried ($MgSO_4$), filtered and evaporated *in vacuo*. The crude product was purified by crystallization in diethyl ether to yield 0.05 g (0.21 mmol, 76%) of pure (4*R*,5*R*)-ethyl 4-(2-chloro-2-propyloxazolidin-2-one-5-carboxylate **358c**.

(4*R*,5*R*)-Benzyl 4-(2-chloro-2-propyl)oxazolidin-2-one-5-carboxylate 358a. White powder, yield 82% (0.09 g). $[\alpha]_D$ -16.1 (*c* 0.8, $CHCl_3$). Mp 68.0 ± 2.0 °C. IR (cm^{-1}): 1096, 1209, 1761, 3262. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.57 (6H, s, $C(CH_3)_2$), 3.93 (1H, d, *J* = 3.3 Hz, NHC<u>H</u>), 4.91 (1H, d, *J* = 3.3 Hz, CHO), 5.26 (1H, d, *J* = 12.1 Hz, OC<u>H</u>(H)), 5.28 (1H, d, *J* = 12.1 Hz, OCH(<u>H</u>)), 7.02 (1H, br s, NH), 7.28-7.47 (5H, m, CH_{arom}). ^{13}C NMR (75 MHz, $CDCl_3$): δ 27.6 ($C\underline{C}H_3(CH_3)$), 27.8 ($CCH_3(\underline{C}H_3)$), 65.1 (NHCH), 68.1 (OCH_2), 69.2 ($\underline{C}(CH_3)_2$), 75.0 (CHO), 128.5 ($2xCH_{arom}$), 128.9 ($3xCH_{arom}$), 134.6 (C_{arom}), 158.3 (N(C=O)O), 168.4 (CH<u>C</u>OO). MS (ES^+): *m*/*z* (%): 315/317 ($M+NH_4^+$, 100). HRMS (ES) calcd for $C_{14}H_{16}ClNO_4$: 298.0841 MH^+; found: 298.0844.

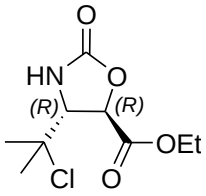


(4*R*,5*R*)-Methyl 4-(2-chloro-2-propyl)oxazolidin-2-one-5-carboxylate 358b. White powder, yield 76% (0.08 g). $[\alpha]_D$ -23.1 (*c* 0.9, $CHCl_3$). Mp 127.4 ± 2.0 °C. IR (cm^{-1}): 1116, 1240, 1720, 1746, 3297. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.60 (6H, s, $C(CH_3)_2$), 3.86 (3H, s, OCH_3), 3.97 (1H, dxd, *J* = 3.3 Hz, 1.1 Hz, NHC<u>H</u>), 4.89 (1H, d, *J* = 3.3 Hz, CHO), 6.89 (1H,



br s, NH). ^{13}C NMR (75 MHz, $CDCl_3$): δ 27.6 ($C\underline{C}H_3(CH_3)$), 27.7 ($CCH_3(\underline{C}H_3)$), 53.4 (OCH_3), 65.1 (NHCH), 69.2 ($\underline{C}(CH_3)_2$), 74.9 (CHO), 158.1 (N(C=O)O), 169.1 (CH$\underline{C}$OO). MS (ES^+): *m*/*z* (%): 239/241 ($M+NH_4^+$, 100). HRMS (ES) calcd for $C_8H_{12}ClNO_4$: 222.0528 MH^+; found: 222.0530.

(4*R*,5*R*)-Ethyl 4-(2-chloro-2-propyl)oxazolidin-2-one-5-carboxylate 358c. White powder,



yield 64% (0.06 g). $[\alpha]_D$ -23.0 (*c* 0.5, $CHCl_3$). Mp 142.1 ± 2.0 °C. IR (cm^{-1}): 1110, 1238, 1728, 1754, 3251. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.34 (3H, t, *J* = 7.2 Hz, $CH_2C\underline{H}_3$), 1.60 (6H, s, $C(CH_3)_2$), 3.96 (1H, d, *J* = 3.3 Hz, NHC$\underline{H}$), 4.31 (2H, q, *J* = 7.2 Hz, OCH_2), 4.86 (1H, d, *J* = 3.3 Hz, CHO), 6.95 (1H, br s, NH). ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.1 ($CH_2\underline{C}H_3$), 27.6 ($C\underline{C}H_3(CH_3)$), 27.7 ($CCH_3(\underline{C}H_3)$), 62.7 (OCH_2), 65.2 (NHCH), 69.3 ($\underline{C}(CH_3)_2$), 75.0 (CHO), 158.2 (N(C=O)O), 168.6 (CH$\underline{C}$OO). MS (ES^+): *m*/*z* (%): 253/255 ($M+NH_4^+$, 100). HRMS (ES) calcd for $C_9H_{14}ClNO_4$: 236.0684 MH^+; found: 236.0685.

5.42. Synthesis of (*S*$_S$,2*S*,2'*R*)-alkyl 2-(*tert*-butoxycarbonyloxy)-2-(3,3-dimethyl-1-*p*-toluenesulfinylaziridin-2-yl)acetates 367

The synthesis of (*S*$_S$,2*S*,2'*R*)-benzyl 2-(*tert*-butoxycarbonyloxy)-2-(3,3-dimethyl-1-*p*-toluenesulfinylaziridin-2-yl)acetate **367a** is representative. To a solution of (*S*$_S$,2*S*,3*S*)-benzyl 2-(*tert*-butoxycarbonyloxy)-4-chloro-4-methyl-3-(*tert*-butanesulfinylamino)pentanoate **366a** (0.18 g, 0.35 mmol) in acetone (10 mL) was added K_2CO_3 (3.0 equiv, 1.06 mmol, 0.15 g) at room temperature. The reaction mixture was allowed to stir for 24 hours at reflux temperature. After 24 hours, the K_2CO_3 was filtered off and the solvent was evaporated *in vacuo*. The resulting oil was redissolved in EtOAc (10 mL) and washed with water (2 x 5 mL). The organic phase was dried ($MgSO_4$), filtered and evaporated *in vacuo*. The crude product was purified by column chromatography to yield 0.16 g (0.34 mmol, 96%) of (*S*$_S$,2*S*,2'*R*)-benzyl 2-(*tert*-butoxycarbonyloxy)-2-(3,3-dimethyl-1-*p*-toluenesulfinylaziridin-2-yl)acetate **367a**.

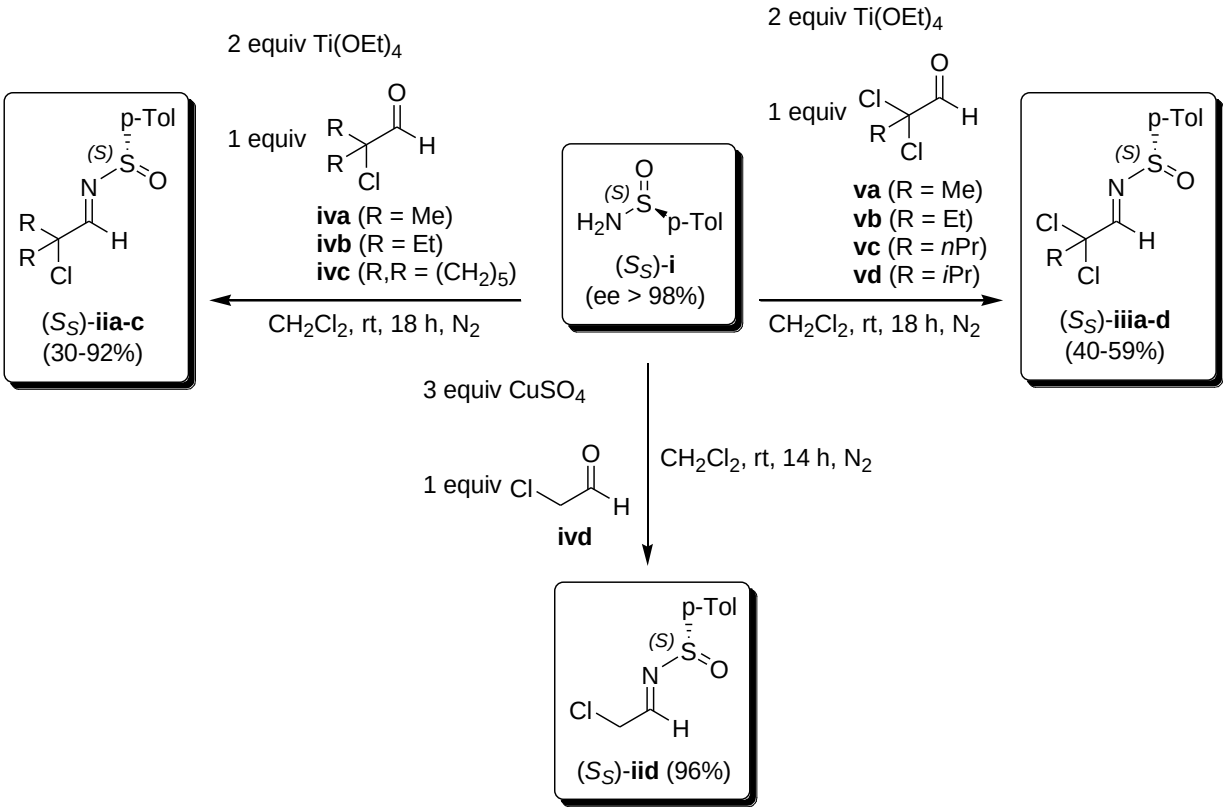
(S_S,2*S*,2'*R*)-Benzyl 2-(*tert*-butoxycarbonyloxy)-2-(3,3-dimethyl-1-*p*-toluenesulfinyl-aziridin-2-yl)acetate 367a. R_f = 0.31 (petroleum ether/EtOAc: 3/1). Yellow oil, yield 96% (0.16 g). $[\alpha]_D$ -50.5 (*c* 2.1, $CHCl_3$). IR (cm^{-1}): 1099, 1252, 1743. ^1H NMR (300 MHz, $CDCl_3$): δ 1.24 (3H, s, $CC\underline{H}_3(CH_3)$), 1.34 (3H, s, $CCH_3(C\underline{H}_3)$), 1.44 (9H, s, $OC(CH_3)_3$), 2.42 (3H, s, $C_{arom}CH_3$), 2.77 (1H, d, *J* = 9.4 Hz, NCH), 4.72 (1H, d, *J* = 9.4 Hz, CHO), 5.08 (1H, d, *J* = 12.1 Hz, $OC\underline{H}$(H)), 5.33 (1H, d, *J* = 12.1 Hz, $OC\underline{H}$(H)), 7.26-7.37 (7H, m, CH_{arom}), 7.65 (2H, d, *J* = 8.3 Hz, 2xCH_{arom}). ^{13}C NMR (75 MHz, $CDCl_3$): δ 20.5 ($CC\underline{H}_3(CH_3)$), 21.5 ($C_{arom}\underline{C}H_3$), 23.1 ($CCH_3(\underline{C}H_3)$), 27.6 ($OC(\underline{C}H_3)_3$), 44.4 (NCH), 49.1 ($\underline{C}(CH_3)_2$), 67.5 ($O\underline{C}H_2Ph$), 74.0 (CHO), 83.2 ($O\underline{C}(CH_3)_3$), 125.4 (2xCH_{arom}), 128.47 (2xCH_{arom}), 128.53 (CH_{arom}), 128.6 (2xCH_{arom}), 129.5 (2xCH_{arom}), 134.9 (C_{arom}), 141.6 (C_{arom}), 142.0 (C_{arom}), 152.5 (O(C=O)O), 167.7 ($CH\underline{C}OO$). MS (ES^+): *m*/*z* (%): 474 ($M+H^+$, 100). HRMS (ES) calcd for $C_{25}H_{31}NO_6S$: 474.1945 MH^+; found: 474.1934.

(S_S,2*S*,2'*R*)-Ethyl 2-(*tert*-butoxycarbonyloxy)-2-(3,3-dimethyl-1-*p*-toluenesulfinyl-aziridin-2-yl)acetate 367c. R_f = 0.33 (petroleum ether/EtOAc: 3/1). Yellow oil, yield 82% (0.50 g). $[\alpha]_D$ +18.0 (*c* 2.8, $CHCl_3$). IR (cm^{-1}): 1045, 1241, 1737. ^1H NMR (300 MHz, $CDCl_3$): δ 1.28 (3H, t, *J* = 7.2 Hz, $OCH_2C\underline{H}_3$), 1.34 (3H, s, $CC\underline{H}_3(CH_3)$), 1.46 (3H, s, $CCH_3(C\underline{H}_3)$), 1.48 (9H, s, $OC(CH_3)_3$), 2.43 (3H, s, $C_{arom}CH_3$), 2.81 (1H, d, *J* = 9.4 Hz, NCH), 4.11-4.35 (2H, m, $OC\underline{H}_2CH_3$), 4.70 (1H, d, *J* = 9.4 Hz, CHO), 7.31 (2H, d, *J* = 8.3 Hz, 2xCH_{arom}), 7.67 (2H, d, *J* = 8.3 Hz, 2xCH_{arom}). ^{13}C NMR (75 MHz, ref = $CDCl_3$): δ 14.1 ($OCH_2\underline{C}H_3$), 20.7 ($CC\underline{H}_3(CH_3)$), 21.6 ($C_{arom}\underline{C}H_3$), 23.2 ($CCH_3(\underline{C}H_3)$), 27.7 ($OC(\underline{C}H_3)_3$), 44.4 (NCH), 49.2 ($\underline{C}(CH_3)_2$), 61.9 ($O\underline{C}H_2CH_3$), 74.1 (CHO), 83.2 ($O\underline{C}(CH_3)_3$), 125.5 (2xCH_{arom}), 129.6 (2xCH_{arom}), 141.6 (C_{arom}), 142.2 (C_{arom}), 152.6 (O(C=O)O), 167.8 ($CH\underline{C}OO$). MS (ES^+): *m*/*z* (%): 412 ($M+H^+$, 100). HRMS (ES) calcd for $C_{20}H_{29}NO_6S$: 412.1788 MH^+; found: 412.1781.

6. Summary

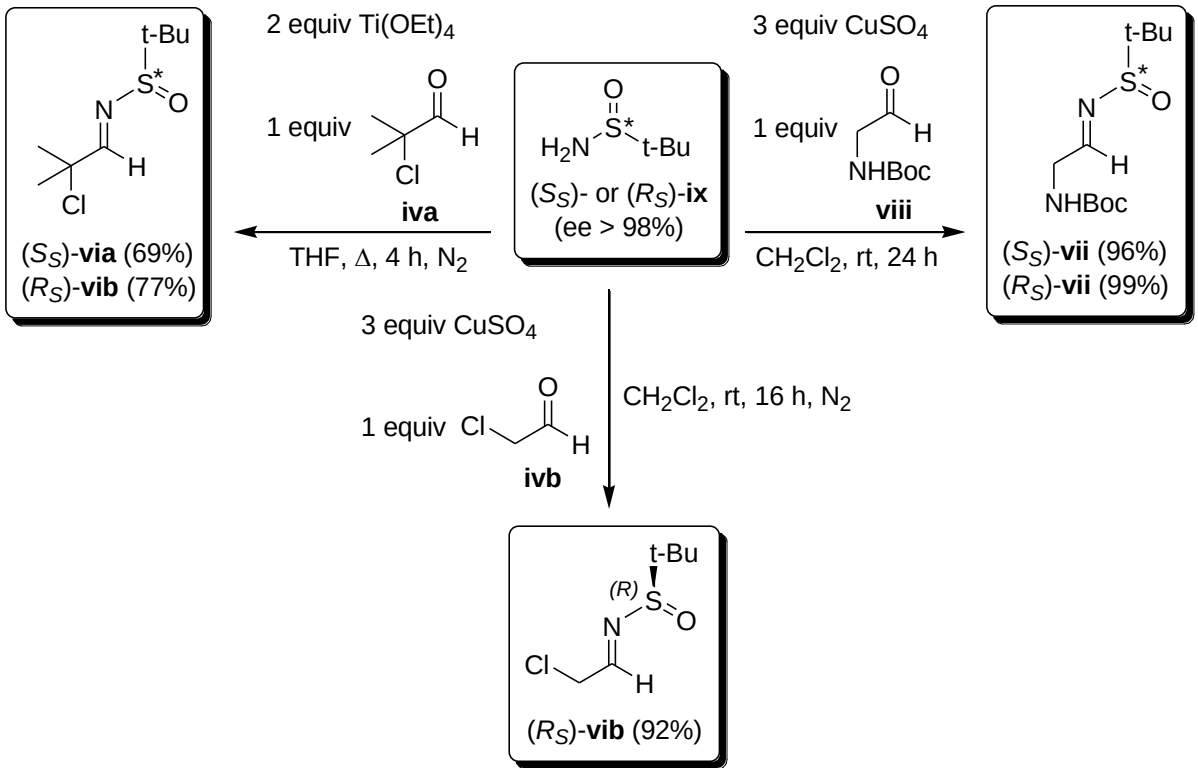
Nucleophilic ring opening of *N*-protected aziridines is one of the few known methods for providing access to a protected chiral aminoethyl unit in organic chemistry. The interest in *N*-sulfinylaziridines as new chiral building blocks for introducing a chiral aminoethyl-unit in a regio- and stereoselective manner increased significantly in recent years and this is mainly due to the ubiquity of the aminoethyl function in a wide range of natural products and *N*-containing drugs. Therefore, new *N*-sulfinylaziridines were synthesized starting from Mannich-type additions of various enolates across chiral *N*-sulfinyl-α-chloroimines. The application of this methodology with various substrates also provided access to new α,β-diamino carboxylic acid derivatives, α,β-diaminoacylpyrrolidines and -piperidines, α,β,γ-triamino carboxylic amides, an α-chloro-β,γ-diamino imidate and γ-chloro-α-hydroxy-β-amino esters. Next to synthetic applications as building blocks in organic chemistry, these compounds had also a potential as bioactive molecules.

In this PhD thesis, the synthesis and reactivity of *N*-sulfinyl-α-functionalized aldimines in stereoselective Mannich-type additions has been investigated. These *N*-sulfinyl-α-functionalized aldimines showed great potential in the asymmetric synthesis of a variety of new chiral chemically and biologically important compounds such as *N*-sulfinylaziridines. First, new chiral *N*-(*p*-toluenesulfinyl)-α-chloroaldimines (S_S)-**iia-d** and *N*-(*p*-toluenesulfinyl)-α,α-dichloroaldimines (S_S)-**iiia-d** were synthesized in good to excellent yield *via* condensation of the corresponding α-chloro-aldehydes **iva-d** or α,α-dichloroaldehydes **va-d**, respectively, with (S_S)-*p*-toluenesulfinamide **i** in the presence of a Lewis acid (Scheme 129).



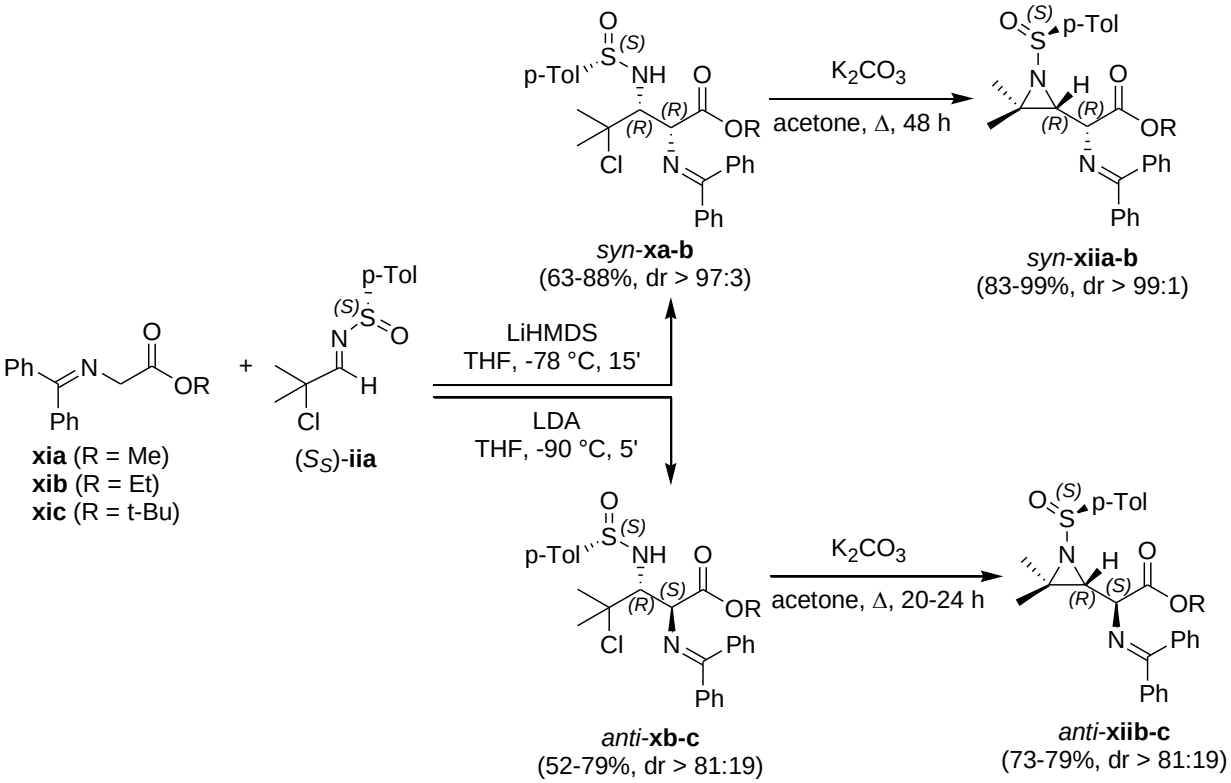
Scheme 129

In addition, chiral *N*-(*tert*-butanesulfinyl)-α-chloroaldimines (S_S)-**via** and (R_S)-**via-b**, and *N*-(*tert*-butanesulfinyl)-α-*N*-Boc-aminoaldimines (S_S)-**vii** and (R_S)-**vii** were also synthesized starting from the corresponding α-chloroaldehydes **iva-b** and α-*N*-Boc-aminoaldehyde **viii** and (R_S)- or (S_S)-*tert*-butanesulfinamide (S_S)-**ix** and (R_S)-**ix**, again in the presence of a Lewis acid (Scheme 130).



Scheme 130

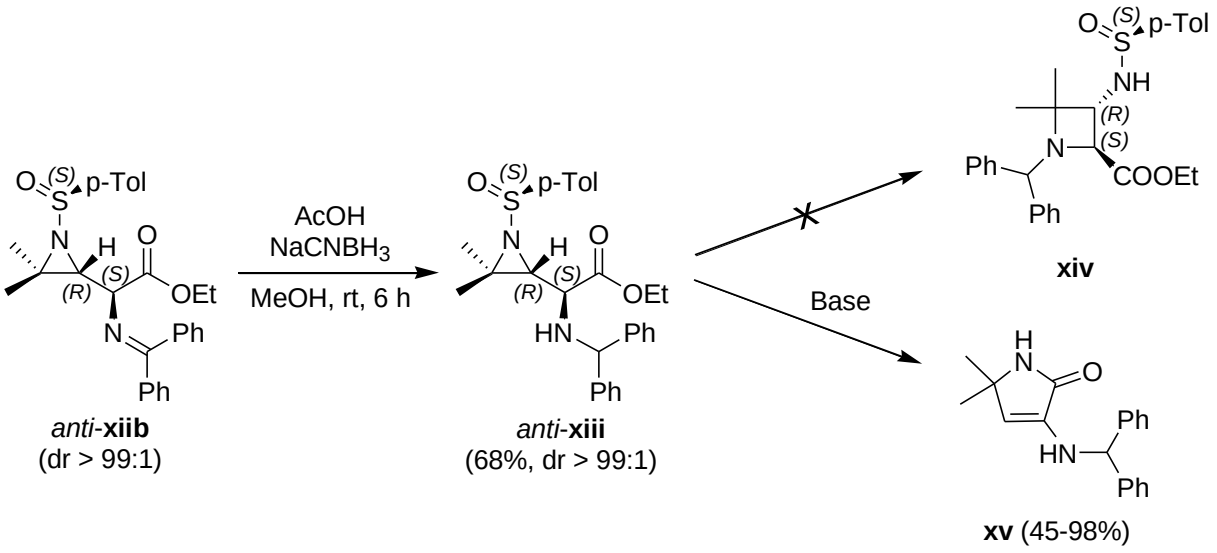
In a second part of this work, the asymmetric synthesis of new protected *syn*- and *anti*-γ-chloro-α,β-diamino esters **x** was elaborated *via* stereoselective Mannich-type additions of *N*-(diphenylmethylene)glycine esters **xia-c** across *N*-*p*-toluenesulfinyl-α-chloroimine (S_S)-**iia** (Scheme 131). The influence of the base used for deprotonation of the glycine esters **xi** was crucial for the diastereoselectivity of the Mannich-type reaction, with LDA leading selectively to *anti*-diastereomers *anti*-**x**, whereas LiHMDS gave exclusively *syn*-diastereomers *syn*-**x**. Both the *syn*- and *anti*-addition products *syn*-**x** and *anti*-**x**, were in a next step cyclized to the corresponding *N*-sulfinylaziridines **xii** upon treatment with K_2CO_3 (73-99% yield).



Scheme 131

The chiral γ-chloro-α,β-diamino esters **x** have shown to be useful building blocks in asymmetric synthesis as demonstrated by several selective transformations.

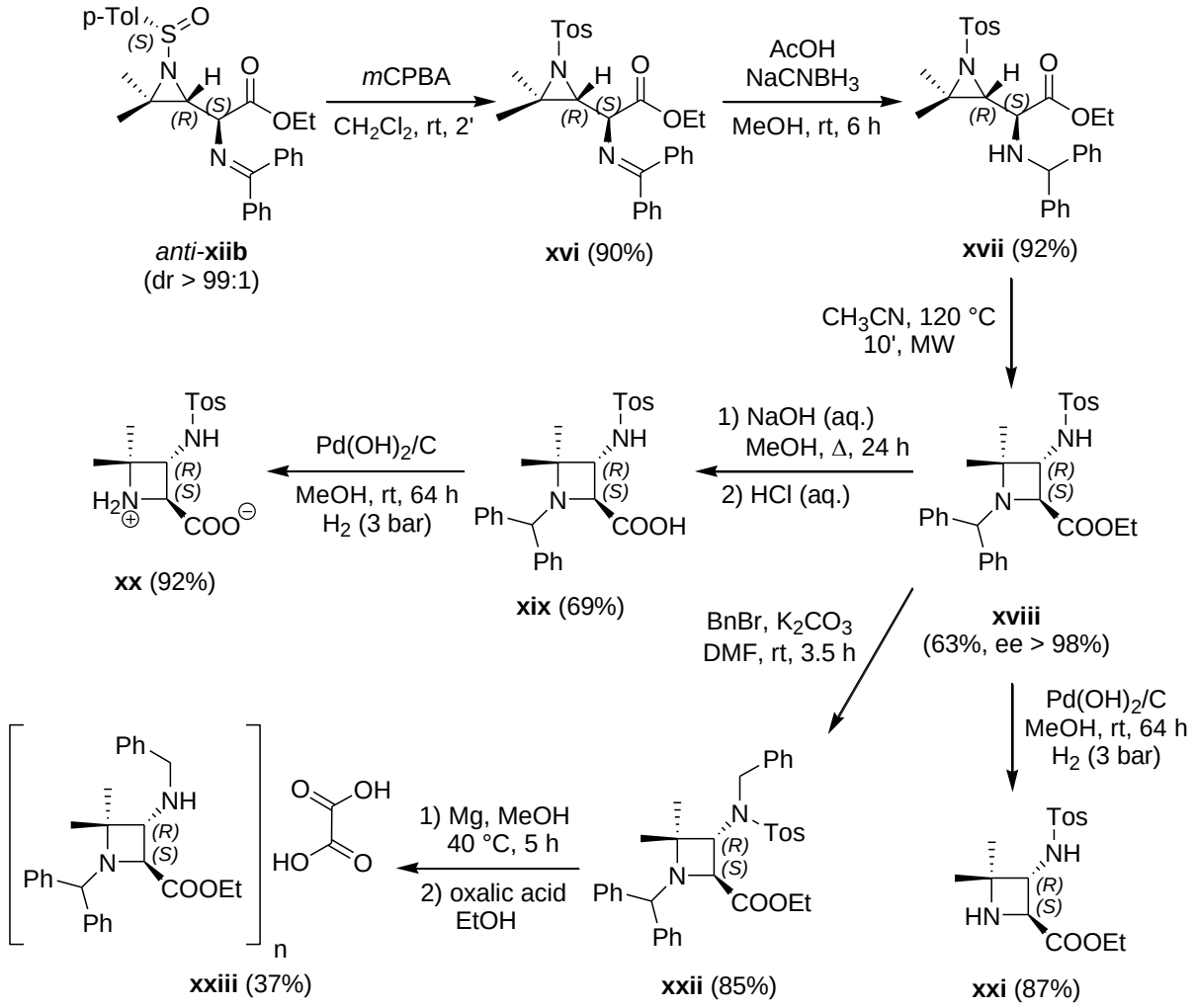
Reduction of the *N*-diphenylmethylene group of *anti*-*N*-sulfinylaziridine *anti*-**xiib** by means of $NaCNBH_3$ resulted in the formation of aziridine *anti*-**xiii** with a nucleophilic α-amino function (68% yield) (Scheme 132). Several attempts were made to achieve ring transformation of *N*-sulfinylaziridine *anti*-**xiii** into *trans*-3-aminoazetidine-2-carboxylate **xiv**, but only formation of the 3-amino-1,5-dihydropyrrol-2-one **xv** was observed upon treatment with various bases (45-98% yield).



Scheme 132

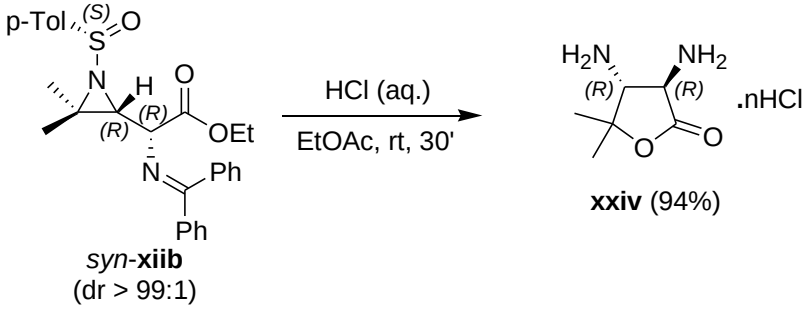
In order to synthesize the *trans*-3-aminoazetidine-2-carboxylate derivatives, the *p*-toluenesulfinyl group of aziridine *anti*-**xiib** was oxidized with *m*CPBA to the corresponding tosyl group, which has a stronger electron-withdrawing character (Scheme 133). The resulting *N*-tosylaziridine *anti*-**xvi** was reduced by treatment with $NaCNBH_3$, and the reduced product **xvii** underwent a microwave-induced ring transformation into the desired *trans*-3-aminoazetidine-2-carboxylate **xviii**, which was subjected to several deprotection steps. In a first reaction, azetidine-2-carboxylate **xviii** was treated with NaOH (aq.) resulting in the formation of the corresponding carboxylic acid **xix** (69% yield). Hydrogenolysis of the *N*-(diphenylmethyl)amino group in the presence of $Pd(OH)_2/C$ afforded azetidine **xx** in 92% yield. This hydrogenolysis procedure was also directly applied on the ethyl ester **xviii**, leading to ethyl 3-(*N*-tosylamino)azetidine-2-carboxylate **xxi** in 87% yield.

As direct deprotection of the *N*-tosyl group of azetidine **xviii** was not successful, *N*-benzylation of azetidine **xviii** with benzyl bromide, prior to the *N*-tosyl deprotection, was performed. Treatment of the resulting *N*-benzylazetidine **xxii** with magnesium metal resulted in the formation of the detosylated azetidine **xxiii**, *via* precipitation as the corresponding oxalate salt.



Scheme 133

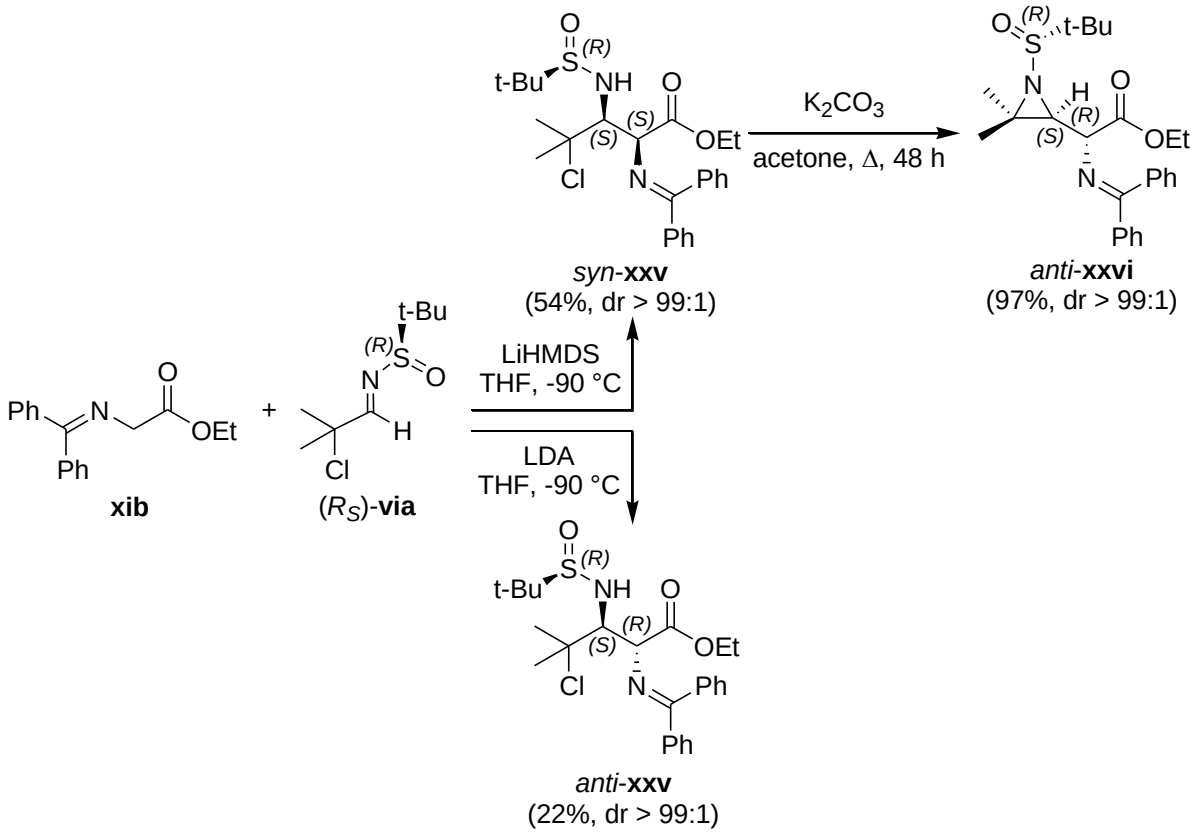
In addition, the *syn*-*N*-sulfinylaziridine *syn*-**xiib** was transformed into *trans*-α,β-diamino-γ-butyrolactone **xxiv** in almost quantitative yield, *via* an acid-promoted ring transformation involving intramolecular *O*-alkylation (Scheme 134).



Scheme 134

The synthesis of the analogous enantiopure *syn*- and *anti*-γ-chloro-β-*N*-*tert*-butanesulfinylamino-α-amino esters **xxv** was also demonstrated *via* stereoselective Mannich-

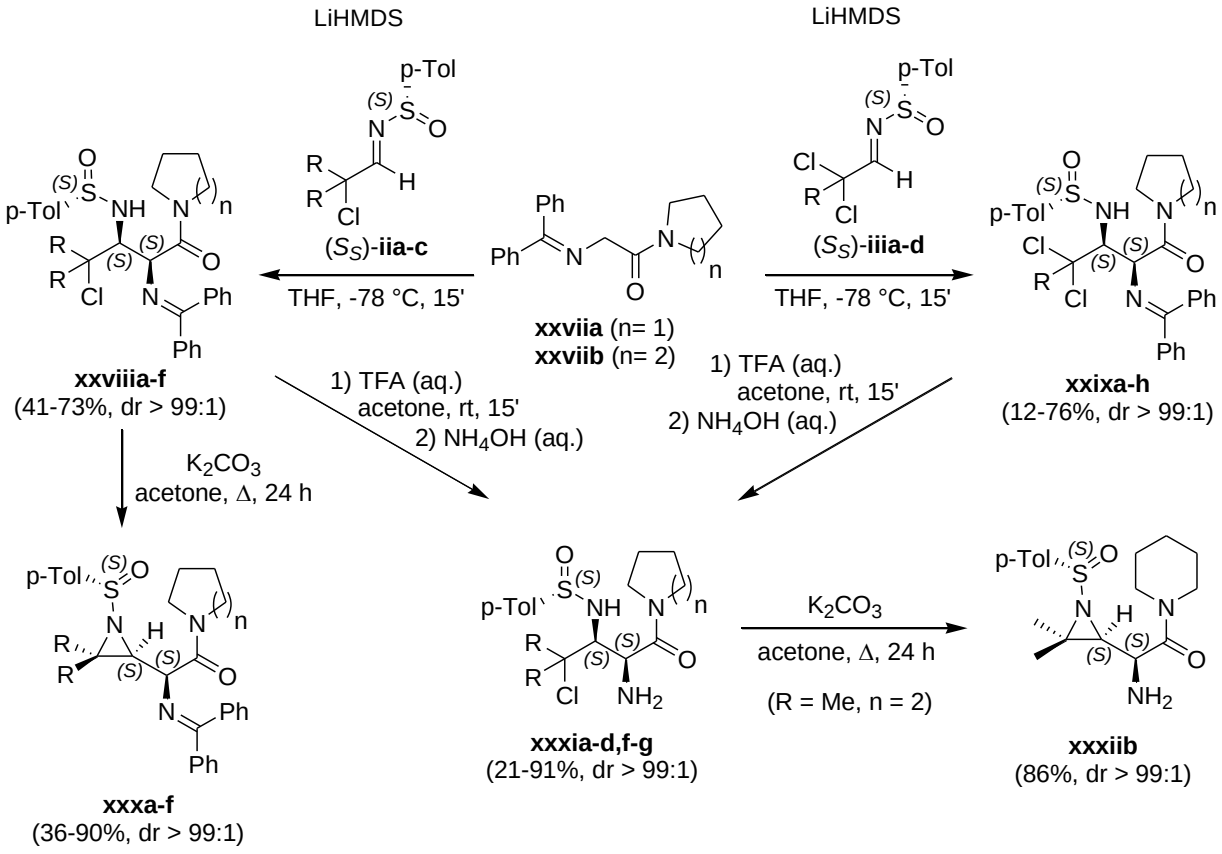
type reactions of the ethyl *N*-(diphenylmethylene)glycine ester **xib** across chiral *N*-*tert*-butanesulfinyl-α-chloroimine (R_S)-**via** (Scheme 135). The base used for the deprotonation of the glycine ester **xib** had again a great influence on the diastereoselectivity of the Mannich-type reaction, with LDA leading selectively to *anti*-diastereomers *anti*-**xxv**, whereas the use of LiHMDS led to *syn*-diastereomers *syn*-**xxv**. This addition reaction proceeded in lower yields, caused by the low conversions of the chiral *N*-*tert*-butanesulfinyl-α-chloroimine (R_S)-**via**, which was probably due to retro-Mannich-type addition. Noteworthy, the *syn*-γ-chloro-α,β-diamino ester **xxv** was selectively transformed into a new *anti*-β,γ-aziridino-α-amino ester **xxvi** upon base-induced cyclization with K_2CO_3.



Scheme 135

Given the fact that α,γ-diamino carboxylic amides, as well as β-amino carboxylic amides, are known for their activity as dipeptidyl peptidase inhibitors, novel α,β-diamino carboxylic amides have been synthesized. Asymmetric Mannich-type addition of *N*-(diphenylmethylene)glycine amides **xxviia-b** across chiral *N*-*p*-toluenesulfinyl-α-

chloroaldimines (S_S)-**iia-c** and *N*-*p*-toluenesulfinyl-α,α-dichloroaldimines (S_S)-**iiia-d** resulted in the formation of chiral *syn*-γ-chloro-α,β-diamino carboxylic amides **xxviiia-f** and *syn*-γ,γ-dichloro-α,β-diamino carboxylic amides **xxixa-h** in acceptable to good yields and with excellent diastereomeric ratios (Scheme 136). Notably, a very high *syn*-diastereoselectivity was obtained in the synthesis of these (S_S,2*S*,3*S*)-γ-chlorinated-α,β-diamino carboxylic amides **xxviiia-f** and **xxixa-h**, with the opposite enantiotopic face selectivity as compared to the Mannich-type additions of *N*-(diphenylmethylene)glycine esters **xia-b** across chiral *N*-*p*-toluenesulfinyl-α-chloroaldimine (S_S)-**iia**. The synthesized γ-chloro-α,β-diamino carboxylic amides **xxviiia-f** underwent again a base-promoted ring-closure reaction to the corresponding aziridines **xxxa-f**. In addition, γ-chloro-α,β-diamino carboxylic amides **xxviiia-d,f** and γ,γ-dichloro-α,β-diamino carboxylic amide **xxixa** were selectively N^{α}-deprotected under acidic conditions and the resulting α,β-diaminoacylpiperidine **xxxib** could be ring closed to the corresponding N^{α}-deprotected aziridine **xxxiib**.

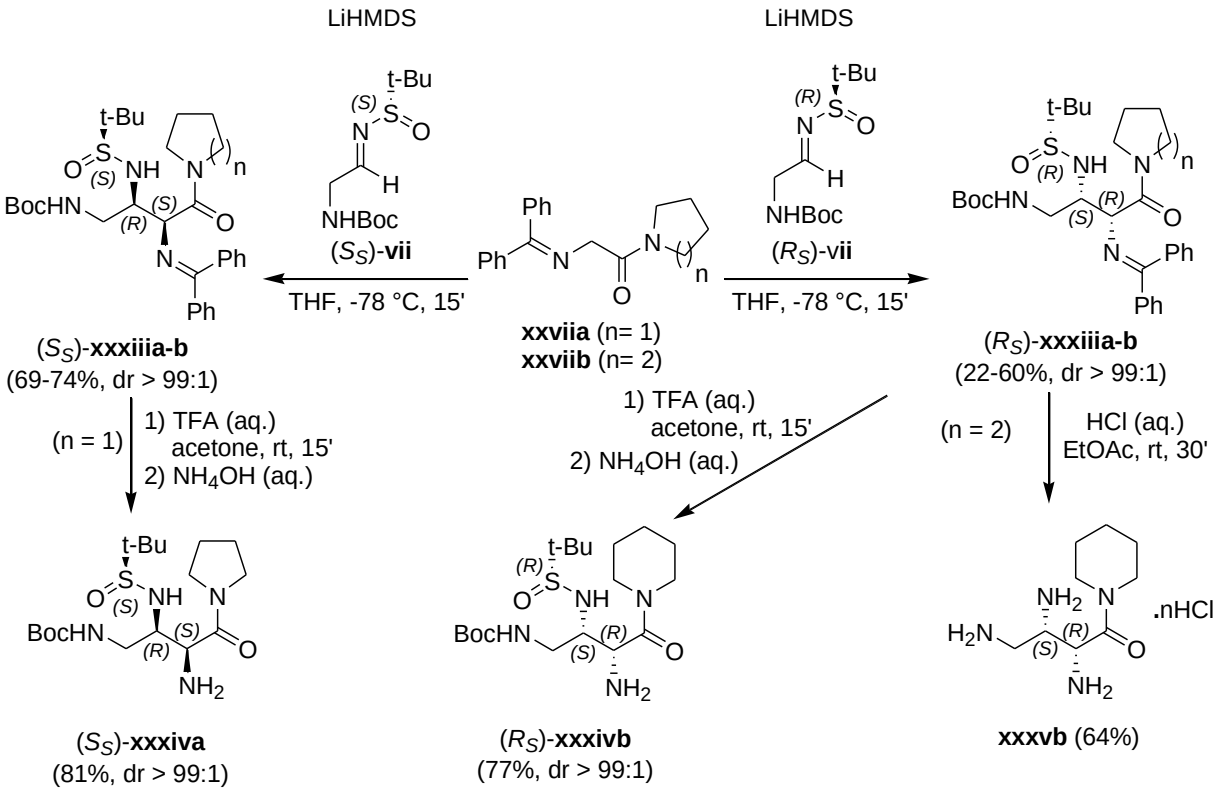


Scheme 136

Furthermore, a first small library of diamino amide derivatives **xxxa-b** and **xxxia-b** was screened for their FAP and DPP inhibitory activity. These biotesting results showed that only the deprotected α-amino pyrrolidine amide **45a** had some selectivity for DPP2 and that presence of the diphenylmethyleneamino moiety lowers the affinity for the enzymes.

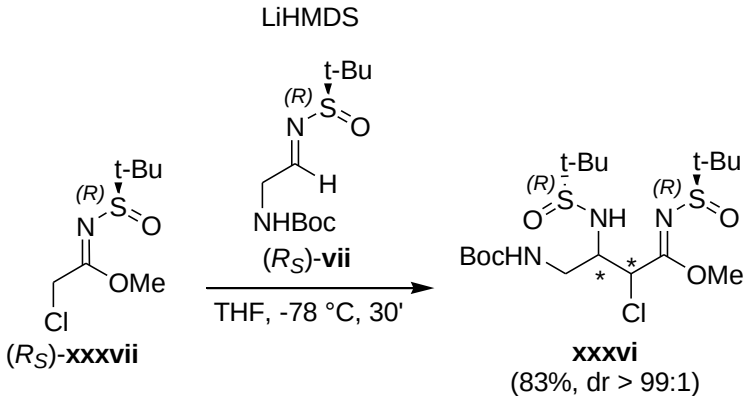
In analogy, it was demonstrated that new chiral α,β,γ-triamino carboxylic amides (S_S)-**xxxiiia-b** and (R_S)-**xxxiiia-b** could be synthesized in moderate to good yields and excellent diastereomeric ratios *via* stereoselective Mannich-type reactions of *N*-(diphenylmethylene)glycine amides **xxviia-b** across chiral *N*-*tert*-butanesulfinyl-α-*N*-Boc-aminoacetaldimines (S_S)-**vii** and (R_S)-**vii** (Scheme 137). Notably, a very high *syn*-diastereoselectivity was again obtained in the synthesis of these compounds **xxxiii**, which were formed *via* the same transition state model as the previously described (S_S,2*S*,3*S*)-γ-chlorinated-α,β-diamino carboxylic amides **xviiia-f** and **xxixa-h**. The synthesized α,β,γ-

triamino carboxylic amides (S_S)-**xxxiiia** and (R_S)-**xxxiiib** were selectively N^{α}-deprotected under acidic conditions (aq. TFA), and the resulting α,β,γ-triaminoacylpyrrolidines and -piperidines (S_S)-**xxxiva** and (R_S)-**xxxivb** could have a potential applicability as dipeptidyl peptidase inhibitors or as fibroblast activation protein inhibitors. In addition, also the fully deprotected α,β,γ-triaminoacylpiperidine **xxxvb** was obtained by treatment of compound (R_S)-**xxxiiib** with an aqueous HCl-solution.



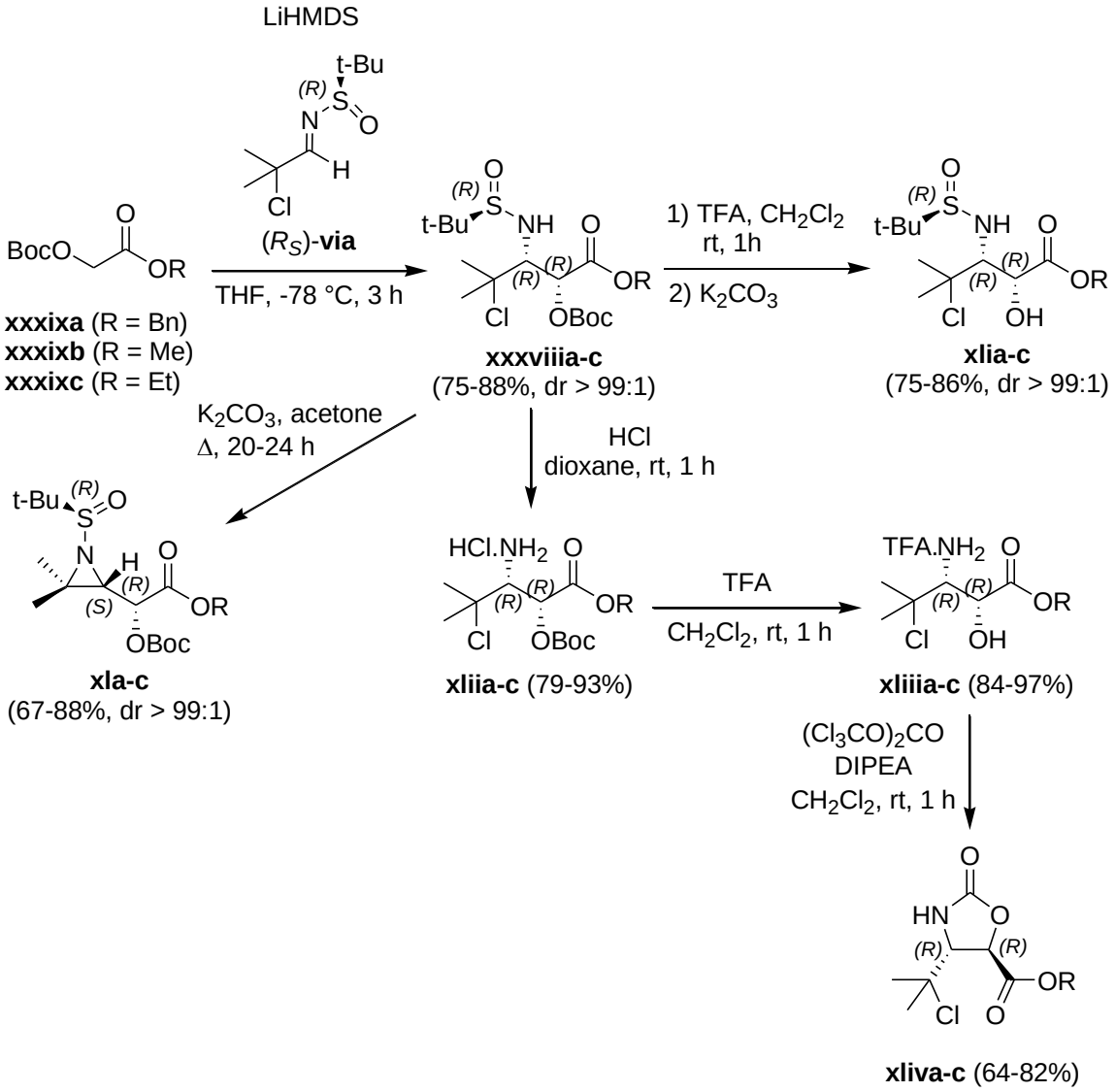
Scheme 137

The synthesis of the chiral α-chloro-β,γ-diamino imidate **xxxvi** has also been performed in high yield and excellent diastereoselectivity *via* a stereoselective Mannich-type reaction of an α-chloro-*N*-*tert*-butanesulfinyl imidate (R_S)-**xxxvii** across the chiral *N*-*tert*-butanesulfinyl-α-*N*-Boc-aminoacetaldimine (R_S)-**vii** (Scheme 138). Unfortunately, the absolute stereochemistry of this compound **xxxvi** could not be determined and further efforts are required to use this compound **xxxvi** as a potential building block in heterocyclic chemistry.



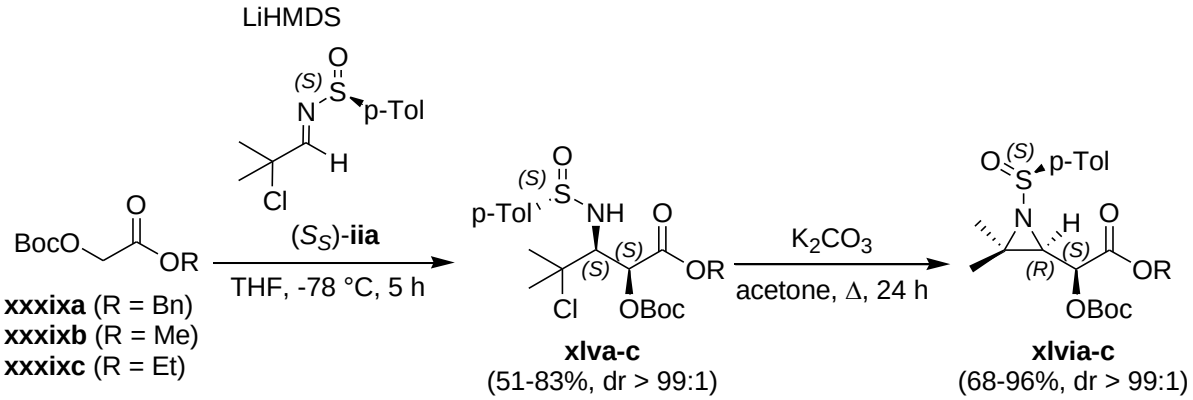
Scheme 138

The synthesis of non-proteinogenic α-hydroxy-β-amino acids has attracted much attention, as these compounds provide access to new drug candidates and act as valuable biological probes. Therefore, the efficient and stereoselective synthesis of new (R_S,2*R*,3*R*)-γ-chloro-α-hydroxy-β-amino esters **xxxviiia-c**, *via* stereoselective Mannich-type reactions of *O*-Boc glycolic esters **xxxixa-c** across chiral *N*-(*tert*-butanesulfinyl)-α-chloroaldimine (R_S)-**via** was elaborated (Scheme 139). Furthermore, the γ-chloro-α-hydroxy-β-amino esters **xxxviiia-c** proved to be useful building blocks in asymmetric synthesis of novel *syn*-β,γ-aziridino-α-hydroxy esters **xla-c** *via* a base-induced cyclization. Next, the synthesized γ-chloro-α-hydroxy-β-amino esters **xxxviiia-c** were selectively O^{α}-deprotected by treatment with TFA, affording α-hydroxy esters **xlia-c** in high yields. The selective cleavage of the N^{β}-*tert*-butanesulfinyl group was performed as well by treatment with HCl, resulting in the formation of hydrochloric acid salts **xliia-c**. In addition, also the fully deprotected γ-chloro-α-hydroxy-β-amino esters **xliiia-c** were obtained by treatment of compounds **xliia-c** with TFA. Treatment of the fully deprotected γ-chloro-α-hydroxy-β-amino esters **xliiia-c** with triphosgene afforded finally the corresponding *trans*-oxazolidinone carboxylic esters **xliva-c**.



Scheme 139

The synthesis of the enantiopure (S_S,2*S*,3*S*)-γ-chloro-α-hydroxy-β-amino esters **xlva-c** has also been performed by Mannich-type reactions of *O*-Boc glycolic esters **xxxixa-c** across chiral *N*-*p*-toluenesulfinyl-α-chloroaldimine (S_S)-**iia** (Scheme 140). Treatment of these compounds **xlva-c** with K_2CO_3 afforded the corresponding *N*-*p*-toluenesulfinylaziridines **xlvia-c**.



Scheme 140

In conclusion, this research showed that the use of *N*-*p*-toluenesulfinyl- and *N*-*tert*-butanesulfinyl-α-functionalized aldimines has great potential in the development of very straightforward and enantioselective syntheses of a large variety of biologically important molecules *via* Mannich-type additions.

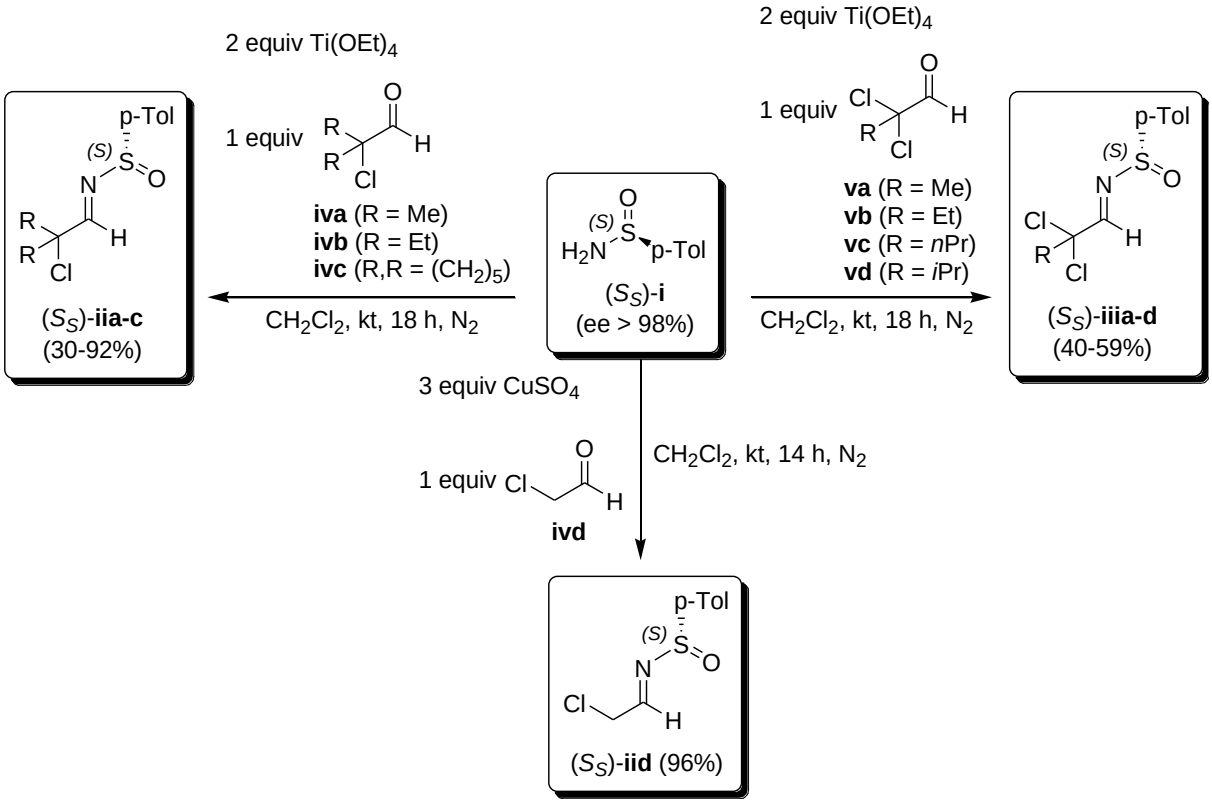
The significance of the developed methodologies was acknowledged by the (novel) asymmetric synthesis of *syn*- and *anti*-γ-chloro-α,β-diamino esters, *syn*- and *anti*-β,γ-aziridino-α-amino esters, *trans*-3-aminoazetidine-2-carboxylates, a *trans*-α,β-diamino-γ-butyrolactone, *syn*-γ-chloro-α,β-diamino carboxylic amides, *syn*-γ,γ-dichloro-α,β-diamino carboxylic amides, *syn*-β,γ-aziridino-α-amino carboxylic amides, *syn*-α,β,γ-triamino carboxylic amides, a α-chloro-β,γ-diamino imidate, *syn*-γ-chloro-α-hydroxy-β-amino esters, *syn*-β,γ-aziridino-α-hydroxy esters and *trans*-oxazolidinone carboxylic esters.

The newly established synthetic approaches in this PhD thesis provide further great potential in the straightforward syntheses of various (biologically) interesting compounds.

7. Samenvatting

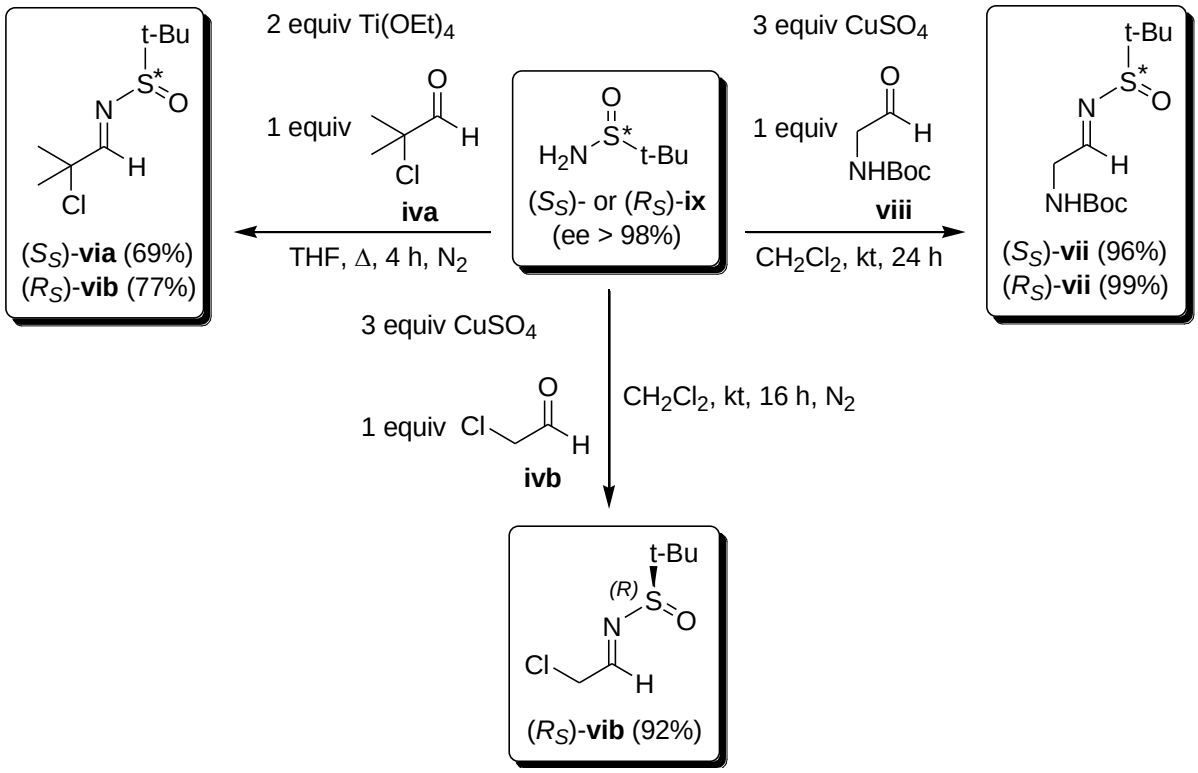
De nucleofiele ringopening van *N*-beschermde aziridinen staat bekend als één van de weinige methoden voor het leveren van een beschermde chirale aminoëthyl-eenheid in de organische chemie. De interesse in *N*-sulfinylaziridinen als nieuwe chirale bouwstenen voor het produceren van een chirale aminoëthyl-eenheid op een regio- en stereoselectieve manier, is de voorbije jaren significant toegenomen, hetgeen hoofdzakelijk te wijten is aan de alomtegenwoordigheid van de aminoëthyl-eenheid in een grote waaier aan natuurproducten en *N*-bevattende geneesmiddelen. Om aan deze vraag te kunnen beantwoorden, zullen nieuwe *N*-sulfinylaziridinen worden gesynthetiseerd startende van een Mannich-type additie van verscheidene enolaten aan chirale *N*-sulfinyl-α-gechloreerde iminen. Het toepassen van deze methodologie met verschillende substraten biedt ook de mogelijkheid voor de synthese van nieuwe α,β-diaminocarbonzuurderivaten, α,β-diaminoacylpyrrolidinen en -piperidinen, α,β,γ-triaminoamiden, een α-chloor-β,γ-diamino-imidaat en γ-chloor-α-hydroxy-β-amino-esters. Deze verbindingen hebben naast hun synthetische toepassingen als bouwsteen in de organische chemie, ook potentieel als bioactieve verbindingen.

In deze doctoraatsthesis zal de synthese en reactiviteit van *N*-sulfinyl-α-gefunctionaliseerde aldiminen in stereoselectieve Mannich-type addities worden onderzocht. Deze *N*-sulfinyl-α-gefunctionaliseerde aldiminen vertoonden een groot potentieel in de asymmetrische synthese van een grote waaier van nieuwe chirale, chemisch en biologisch belangrijke verbindingen zoals *N*-sulfinylaziridinen. Eerst werden nieuwe chirale *N*-(*p*-tolylsulfinyl)-α-chlooraldiminen (S_S)-**iia-d** en *N*-(*p*-tolylsulfinyl)-α,α-dichlooraldiminen (S_S)-**iiia-d** gesynthetiseerd in goede tot uitstekende rendementen via condensatie van respectievelijk de overeenkomstige α-chlooraldehyden **iva-d** of α,α-dichlooraldehyden **va-d** met (S_S)-*p*-tolylsulfinamide **i** in de aanwezigheid van een Lewiszuur (Schema 129).



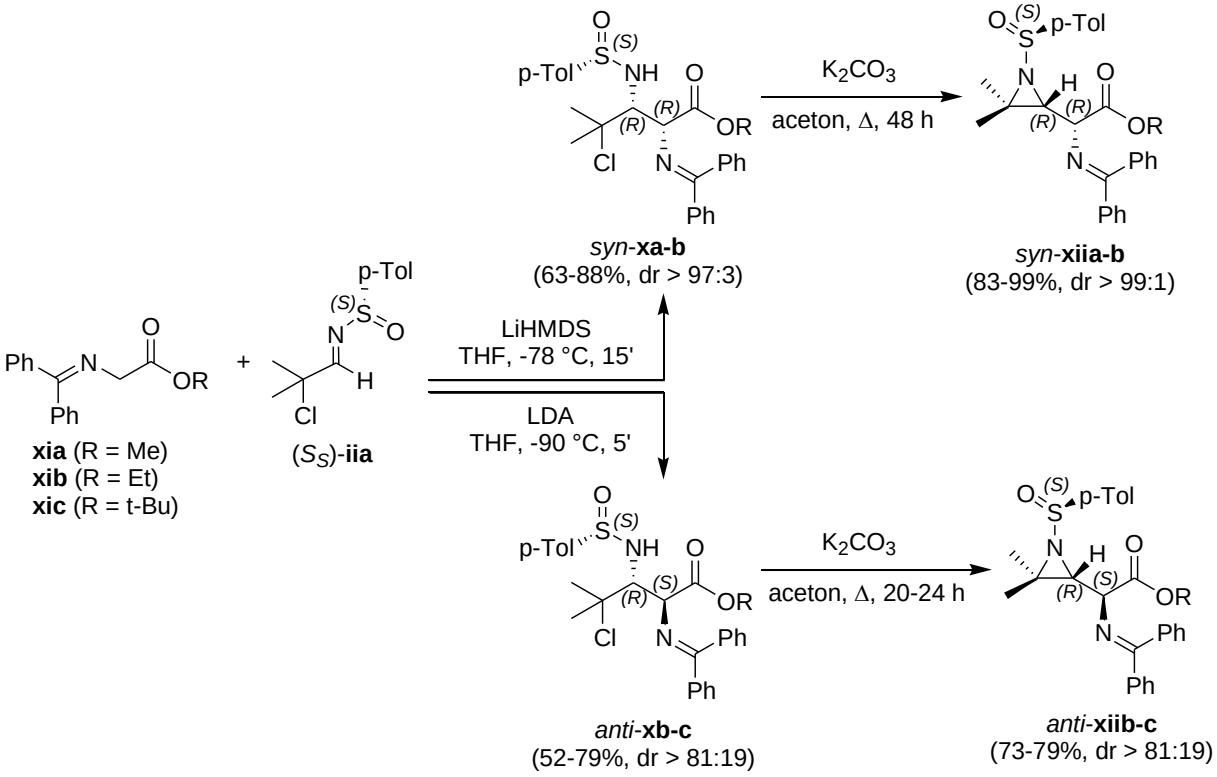
Schema 129

Vervolgens werden de chirale *N*-(*tert*-butylsulfinyl)-α-chlooraldiminen (S_S)-**via** en (R_S)-**via-b**, en *N*-(*tert*-butylsulfinyl)-α-*N*-Boc-aminoaldiminen (S_S)-**vii** en (R_S)-**vii** gesynthetiseerd uitgaande van de overeenkomstige α-chlooraldehyden **iva-b** en α-*N*-Boc-aminoaldehyde **viii** en (R_S)- of (S_S)-*tert*-butylsulfinamide (S_S)-**ix** en (R_S)-**ix**, opnieuw in de aanwezigheid van een Lewiszuur (Schema 130).



Schema 130

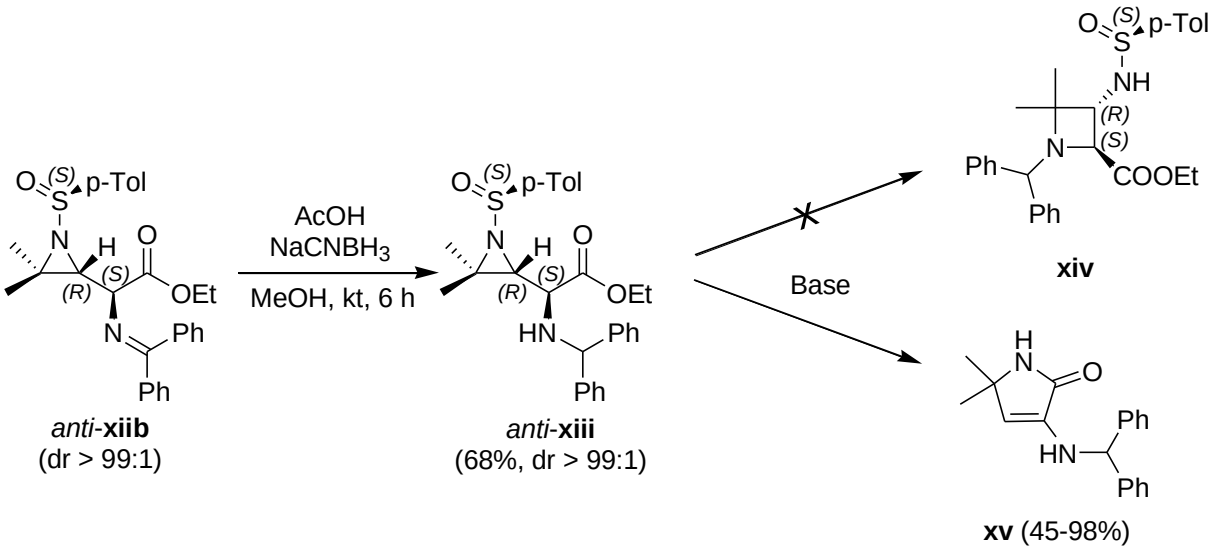
In het tweede deel van dit werk werd de asymmetrische synthese van nieuwe beschermde *syn*- en *anti*-γ-chloor-α,β-diamino-esters **x** beschreven, via stereoselectieve Mannich-type addities van *N*-(difenylmethyleen)glycine-esters **xia-c** aan *N*-*p*-tolylsulfinyl-α-chloorimine (S_S)-**iia** (Schema 131). De invloed van de gebruikte base bij deprotonering van de glycine-esters **xi** was van cruciaal belang voor de diastereoselectiviteit van de Mannich-type reactie, waarbij LDA selectief aanleiding gaf tot *anti*-diastereomeren *anti*-**x**, en LiHMDS exclusief leidde tot *syn*-diastereomeren *syn*-**x**. Zowel de *syn*- als *anti*-additieproducten *syn*-**x** en *anti*-**x** werden in een volgende stap gecycliseerd tot de overeenkomstige *N*-sulfinylaziridinen **xii** door behandeling met K_2CO_3 (73-99% rendement).



Schema 131

De chirale γ-chloor-α,β-diamino-esters **x** bleken tevens in asymmetrische synthese nuttige bouwstenen te zijn, zoals gedemonstreerd werd via enkele selectieve transformaties.

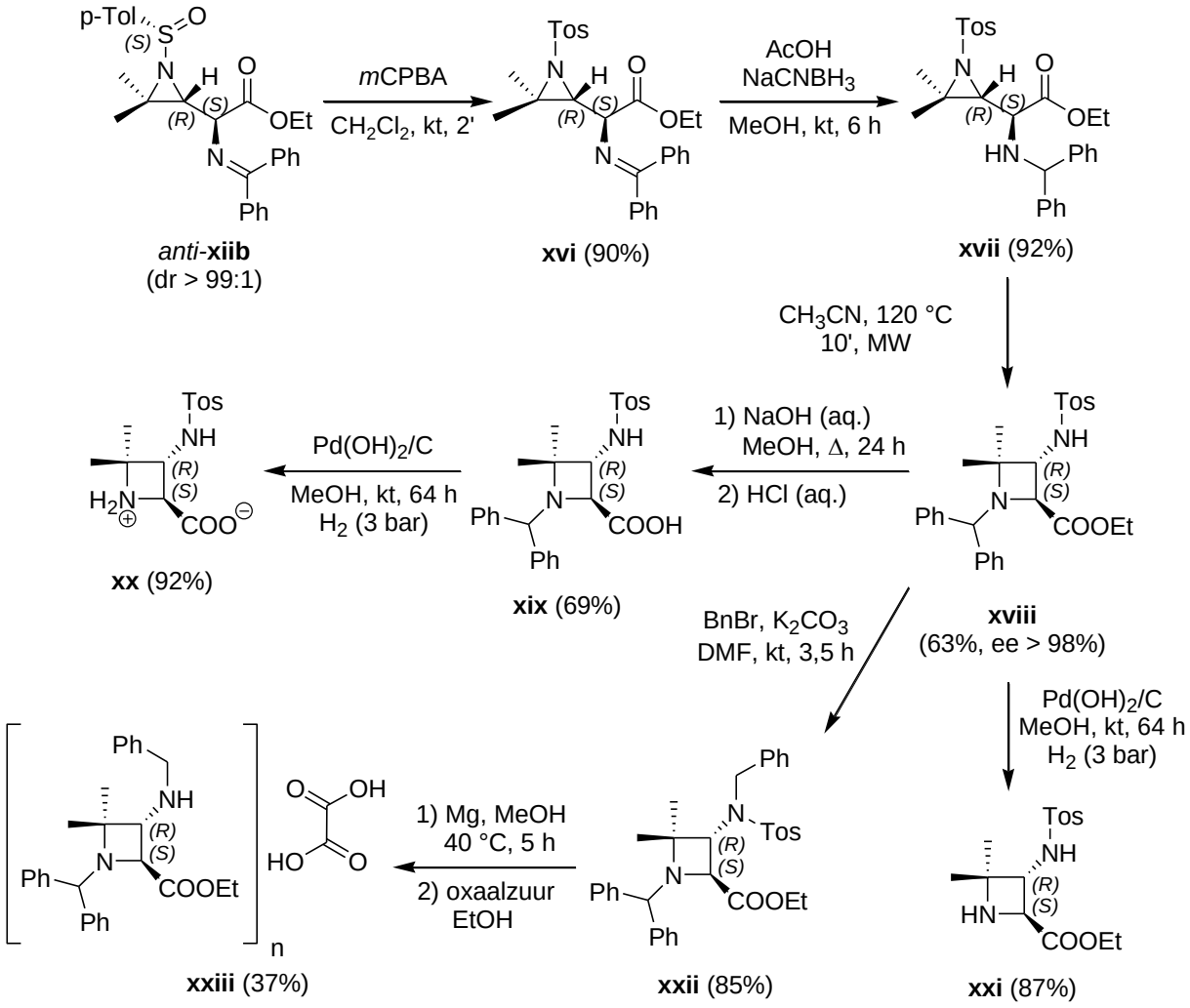
Reductie van de *N*-difenylmethyleengroep van *anti*-*N*-sulfinylaziridine *anti*-**xiib** door middel van $NaCNBH_3$, resulteerde in de vorming van aziridine *anti*-**xiii** met een nucleofiele α-aminogroep (68% rendement) (Schema 132). Verschillende pogingen werden ondernomen om het *N*-sulfinylaziridine *anti*-**xiii** een ringtransformatie te laten ondergaan tot het overeenkomstige *trans*-3-aminoazetidine-2-carboxylaat **xiv**, maar deze pogingen leidden slechts tot de vorming van het 3-amino-1,5-dihydropyrrool-2-on **xv** via behandeling met verschillende basen (45-98% rendement).



Schema 132

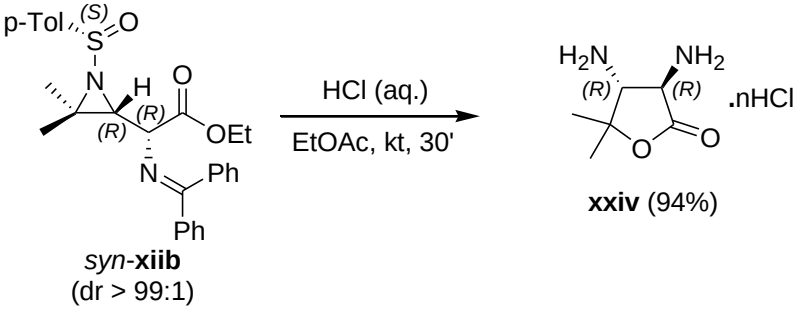
Om de beoogde *trans*-3-aminoazetidine-2-carbonzuurderivaten te synthetiseren, werd de *p*-tolylsulfinylgroep van aziridine *anti*-**xiib** geoxideerd met *m*CPBA tot de overeenkomstige tosylgroep, dewelke een sterker elektronenzuigend karakter heeft (Schema 133). Vervolgens werd het resulterende *N*-tosylaziridine *anti*-**xvi** gereduceerd door behandeling met $NaCNBH_3$, en dit gereduceerde product **xvii** onderging een microgolf-geïnduceerde ringtransformatie tot het gewenste *trans*-3-aminoazetidine-2-carbonzuurderivaat **xviii**, dat onderworpen werd aan verscheidene ontschermingsreacties. In een eerste reactie werd het azetidine-2-carboxylaat **xviii** met NaOH (aq.) omgezet tot het overeenkomstige carbonzuur **xix** (69% rendement). Hydrogenolyse van de *N*-(difenylmethyl)aminogroep van dit carbonzuur **xix** in de aanwezigheid van $Pd(OH)_2/C$ leverde het azetidine **xx** op in 92% rendement. Deze hydrogenolyseprocedure kon tevens direct toegepast worden op ethylester **xviii**, wat ethyl-3-(*N*-tosylamino)azetidine-2-carboxylaat **xxi** opleverde in 87% rendement.

Omdat directe ontscherming van de *N*-tosylgroep van azetidine **xviii** niet succesvol was, werd een *N*-benzylering van azetidine **xviii** met benzylbromide uitgevoerd, voorafgaand aan de *N*-tosyl ontscherming. Behandeling van het resulterende *N*-benzylazetidine **xxii** met magnesium metaal gaf aanleiding tot het gedetosyleerde azetidine **xxiii**, via precipitatie van het overeenkomstige oxalaat.



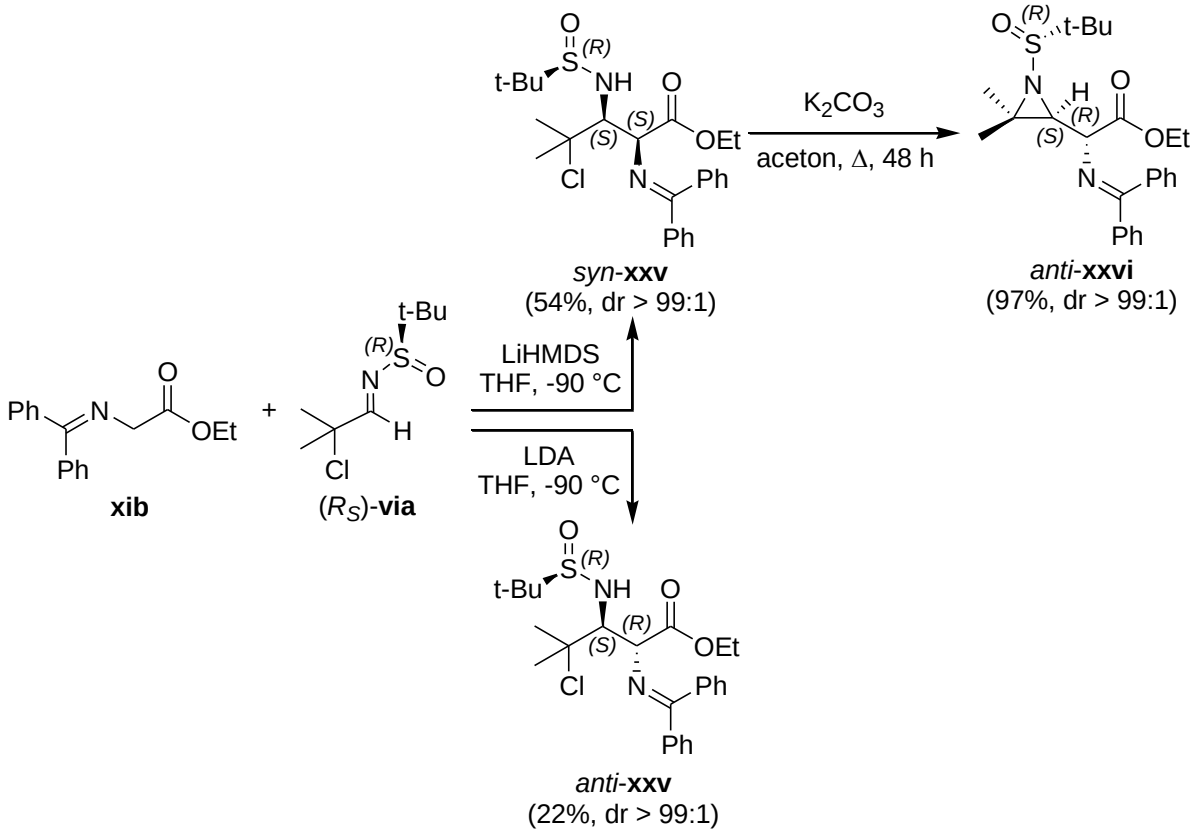
Schema 133

Het *syn*-*N*-sulfinylaziridine *syn*-**xiib** kon door middel van een zuurgekatalyseerde ringtransformatie via een intramoleculaire *O*-alkylering tevens omgezet worden tot het *trans*-α,β-diamino-γ-butyrolacton **xxiv** in een bijna kwantitatief rendement (Schema 134).



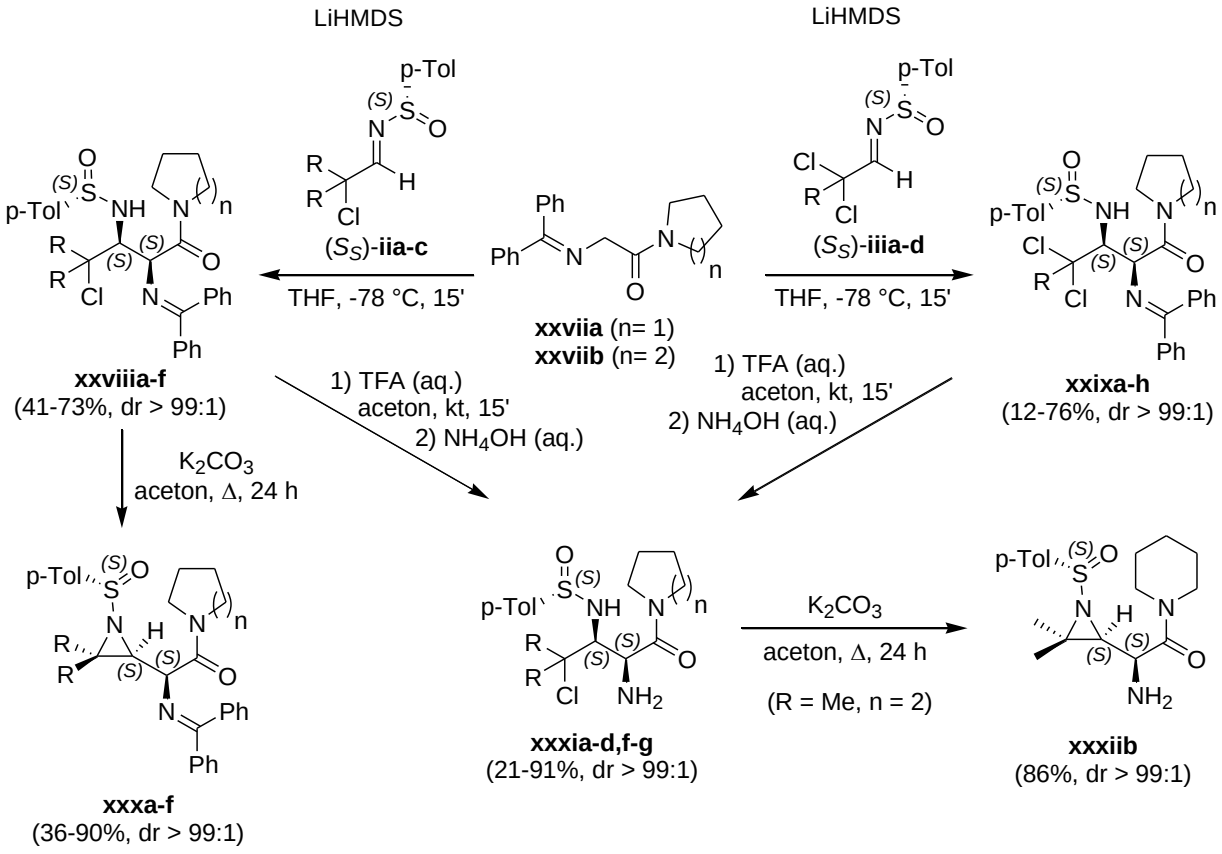
Schema 134

De synthese van de analoge enantiomeer zuivere *syn*- en *anti*-γ-chloor-β-*N*-*tert*-butylsulfinylamino-α-amino-esters **xxv** was eveneens mogelijk via een stereoselectieve Mannich-type additie van ethyl-*N*-(difenylmethyleen)glycine-ester **xib** aan chiraal *N*-*tert*-butylsulfinyl-α-chloorimine (R_S)-**via** (Schema 135). De gebruikte base bij deprotonering van het glycine-ester **xib** had opnieuw een grote invloed op de diastereoselectiviteit van de Mannich-type reactie, waarbij LDA selectief leidde tot *anti*-diastereomeren *anti*-**xxv**, en LiHMDS aanleiding gaf tot *syn*-diastereomeren *syn*-**xxv**. Deze additie reactie verliep in lagere rendementen, wat veroorzaakt werd door de lage conversie van het chiraal *N*-*tert*-butylsulfinyl-α-chloorimine (R_S)-**via**, omdat er waarschijnlijk een retro-Mannich-type additie optrad. Het *syn*-γ-chloor-α,β-diamino-ester **xxv** kon opmerkelijk genoeg, selectief in een nieuw *anti*-β,γ-aziridino-α-amino-ester **xxvi** getransformeerd worden via een base-geïnduceerde cyclizatie met K_2CO_3.



Schema 135

Gezien het feit dat zowel α,γ-diaminoamiden als β-aminoamiden gekend zijn om hun activiteit als dipeptidyl peptidase inhibitoren, werden tevens nieuwe α,β-diaminoamiden gesynthetiseerd. Asymmetrische Mannich-type additie van *N*-(difenylmethyleen)glycinamiden **xxviia-b** aan chirale *N*-*p*-tolylsulfinyl-α-chlooraldiminen (S_S)-**iia-c** en *N*-*p*-tolylsulfinyl-α,α-dichlooraldiminen (S_S)-**iiia-d** resulteerde in de vorming van chirale *syn*-γ-chloor-α,β-diaminoamiden **xxviiia-f** en *syn*-γ,γ-dichloor-α,β-diaminoamiden **xxixa-h** in matige tot goede rendementen en in uitstekende diastereomere verhoudingen (Schema 136). Er werd tevens een hoge *syn*-diastereoselectiviteit verkregen bij de synthese van deze (S_S,2*S*,3*S*)-γ-gechloreerde-α,β-diaminoamiden **xxviiia-f** en **xxixa-h**, dewelke een tegenovergestelde enantioselectiviteit bekomen werden in vergelijking met de Mannich-type addities van *N*-(difenylmethyleen)glycine-esters **xia-b** aan het chiraal *N*-*p*-tolylsulfinyl-α-chlooraldimine (S_S)-**iia**. De gesynthetiseerde γ-chloor-α,β-diaminoamiden **xxviiia-f** ondergingen vervolgens een base-geïnduceerde ringsluitingsreactie tot de overeenkomstige aziridinen **xxxa-f**. Bovendien konden de γ-chloor-α,β-diaminoamiden **xxviiia-d,f** en het γ,γ-dichloor-α,β-diaminoamide **xxixa** selectief N^{α}-ontschermd worden door een zure behandeling en het resulterende α,β-diaminoacylpiperidine **xxxib** kon vervolgens gecycliseerd worden tot het overeenkomstige N^{α}-ontschermde aziridine **xxxiib**.

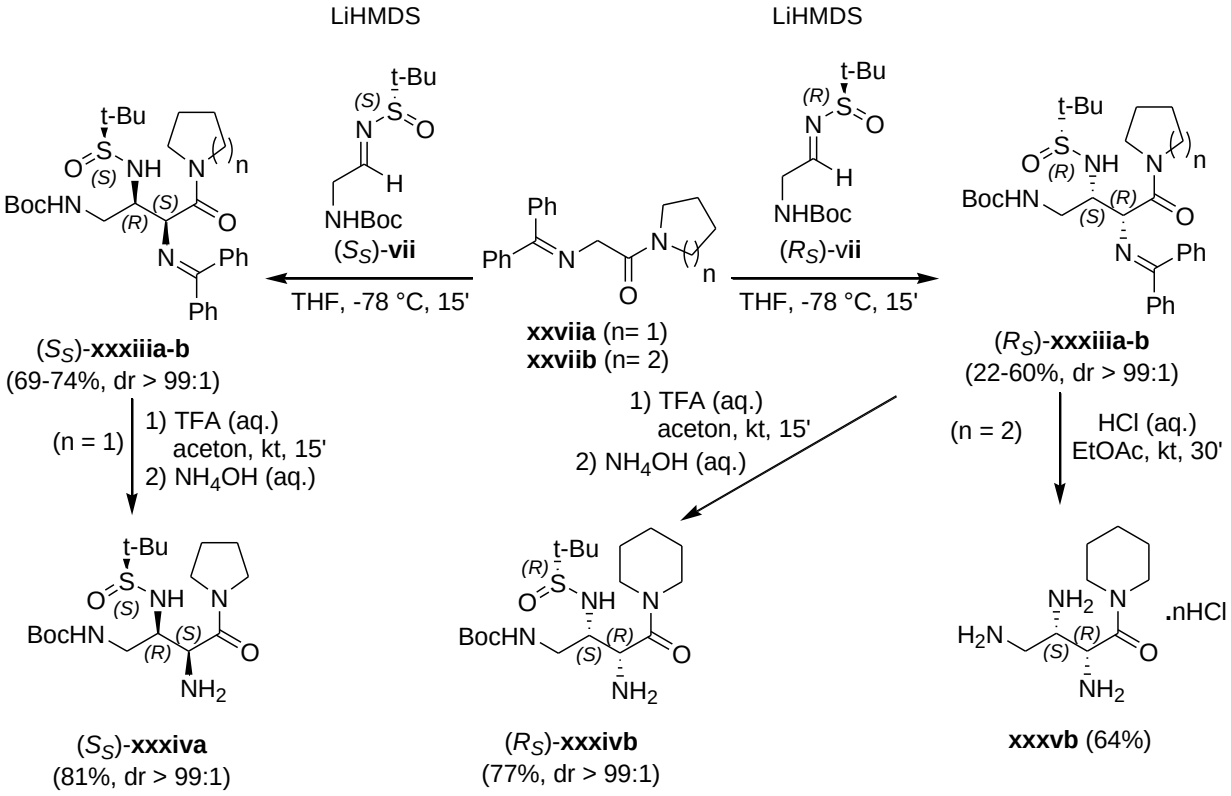


Schema 136

Er werd tevens een kleine bibliotheek aan diaminoamidederivaten **xxxa-b** en **xxxia-b** getest op hun potentiële FAP en DPP inhibitoractiviteit. Dese biotesting resultaten toonden aan dat enkel het ontschermde α-aminopyrrolidine **45a** enige selectiviteit had voor de DPP2-receptor en dat de aanwezigheid van de difenylmethyleenaminogroep de affiniteit voor de enzymen sterk verlaagde.

In analogie werd er aangetoond dat nieuwe chirale α,β,γ-triaminoamiden (S_S)-**xxxiiia-b** en (R_S)-**xxxiiia-b** gesynthetiseerd konden worden in matige tot goede rendementen en uitstekende diastereomere verhoudingen via stereoselectieve Mannich-type reacties van *N*-(difenylmethyleen)-glycinamiden **xxviia-b** aan chirale *N*-*tert*-butylsulfinyl-α-*N*-Boc-aminoacetaldiminen (S_S)-**vii** en (R_S)-**vii** (Schema 137). Er werd opnieuw een zeer hoge *syn*-diastereoselectiviteit bekomen bij de synthese van deze verbindingen **xxxiii**, dewelke werden gevormd via eenzelfde transitietoestandsmodel als de eerder beschreven (S_S,2*S*,3*S*)-γ-

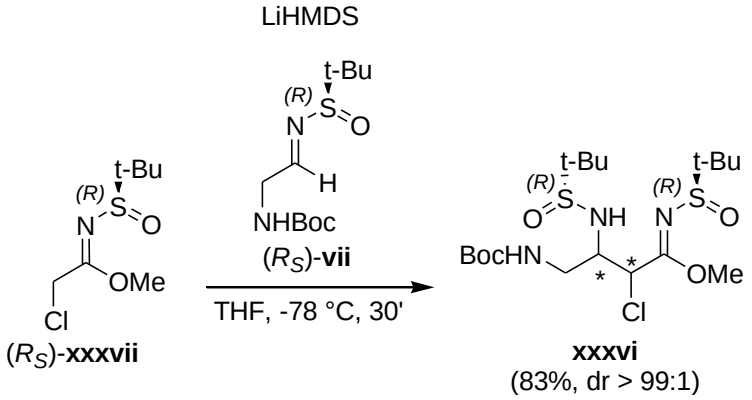
gechloreerde-α,β-diaminoamiden **xviiia-f** en **xxixa-h**. De gesynthetiseerde α,β,γ-triaminoamiden (S_S)-**xxxiiia** en (R_S)-**xxxiiib** werden selectief N^{α}-ontschermd onder zure reactie condities (aq. TFA), en de resulterende α,β,γ-triaminoacylpyrrolidinen en -piperidinen (S_S)-**xxxiva** en (R_S)-**xxxivb** konden een potentiële toepassing vinden als dipeptidyl-peptidase-inhibitoren of als fibroblast activerende proteïne inhibitoren. Bovendien kon ook het volledig ontschermde α,β,γ-triaminoacylpiperidine **xxxvb** bekomen worden door behandeling van verbinding (R_S)-**xxxiiib** met een waterige HCl-oplossing.



Schema 137

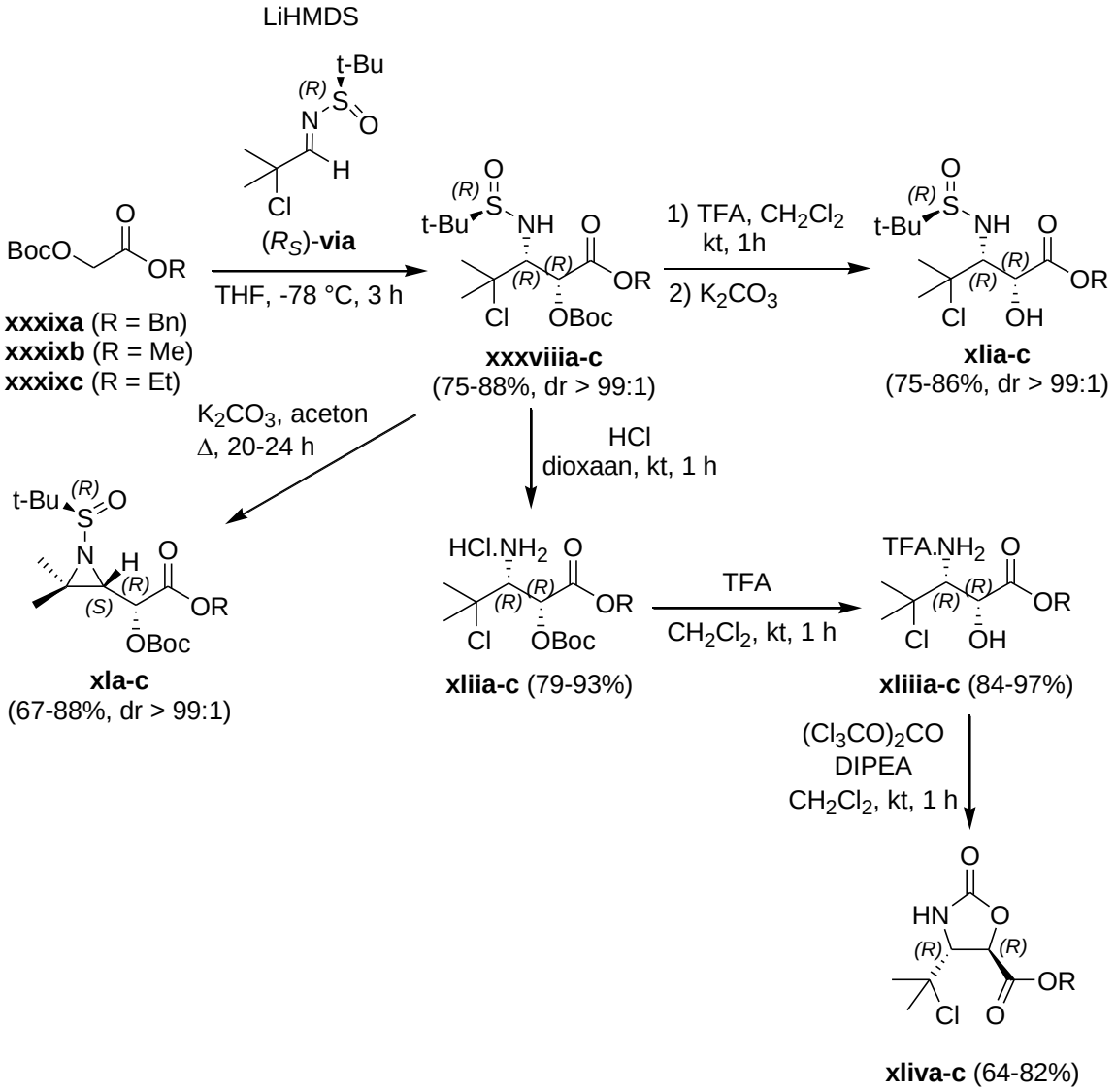
De synthese van het chirale α-chloor-β,γ-diamino-imidaat **xxxvi** werd tevens uitgevoerd in hoog rendement en met een uitstekende diastereoselectiviteit via een stereoselectieve Mannich-type reactie van het α-chloor-*N*-*tert*-butylsulfinyl imidaat (R_S)-**xxxvii** aan het chirale *N*-*tert*-butylsulfinyl-α-*N*-Boc-aminoacetaldimine (R_S)-**vii** (Schema 138). Helaas kon de absolute stereochemie van deze verbinding **xxxvi** niet bepaald worden en is er verder

onderzoek nodig om deze verbinding **xxxvi** als een potentiële bouwsteen in de heterocyclische chemie te gebruiken.



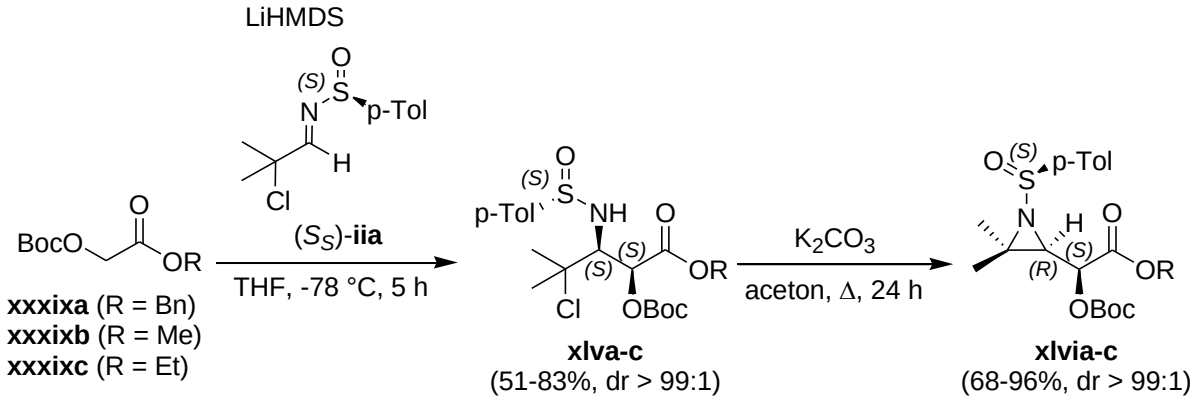
Schema 138

De voorbije jaren heeft de synthese van niet-proteïnogene α-hydroxy-β-aminozuren veel aandacht gekregen omdat deze verbindingen gebruikt kunnen worden bij de ontwikkeling van nieuwe geneesmiddelen en omdat het waardevolle biologische verbindingen zijn. Daarom werd de efficiënte en stereoselectieve synthese van nieuwe (R_S,2*R*,3*R*)-γ-chloor-α-hydroxy-β-amino-esters **xxxviiia-c**, via een stereoselectieve Mannich-type reactie van *O*-Boc glycol-esters **xxxixa-c** aan het chirale *N*-(*tert*-butylsulfinyl)-α-chlooraldimine (R_S)-**via** uitgewerkt (Schema 139). Bovendien kunnen deze γ-chloor-α-hydroxy-β-amino-esters **xxxviiia-c** gebruikt worden als bouwstenen in de asymmetrische synthese van nieuwe *syn*-β,γ-aziridino-α-hydroxy-esters **xla-c** via een base-geïnduceerde cyclizatie. De gesynthetiseerde γ-chloor-α-hydroxy-β-amino-esters **xxxviiia-c** werden tevens selectief O^{α}-ontschermd door behandeling met TFA, hetgeen α-hydroxy-esters **xlia-c** in hoge rendementen opleverde. De selectieve ontscherming van de N^{β}-*tert*-butylsulfinylgroep werd uitgevoerd door behandeling met HCl, en resulteerde in de vorming van HCl-zouten **xliia-c**. Tevens werden de volledig ontschermde γ-chloor-α-hydroxy-β-amino-esters **xliiia-c** bekomen door behandeling van verbindingen **xliia-c** met TFA. Behandeling van deze volledig ontschermde γ-chloor-α-hydroxy-β-amino-esters **xliiia-c** met trifosgeen leverde uiteindelijk de overeenkomstige *trans*-oxazolidinon-esters **xliva-c** op.



Schema 139

De synthese van de enantiomeer zuivere (*S*$_S$,2*S*,3*S*)-γ-chloor-α-hydroxy-β-amino-esters **xlva-c** werd tevens uitgevoerd via Mannich-type reacties van *O*-Boc glycolesters **xxxixa-c** aan chiraal *N*-*p*-tolylsulfinyl-α-chlooraldimine (*S*$_S$)-**iia** (Schema 140). Behandeling van deze verbindingen **xlva-c** met K_2CO_3 resulteerde in de vorming van de overeenkomstige *N*-*p*-tolylsulfinylaziridinen **xlvia-c**.



Schema 140

Samenvattend kan gesteld worden dat in de loop van dit onderzoek is aangetoond dat het gebruik van *N*-*p*-tolylsulfinyl- en *N*-*tert*-butylsulfinyl-α-gefunctionaliseerde aldiminen, een groot potentieel heeft in de ontwikkeling van efficiënte en enantioselectieve synthesen van een hele waaier aan verbindingen van biologisch belang via Mannich-type addities.

De mogelijkheden van de ontwikkelde methoden werd aangetoond door de (nieuwe) asymmetrische synthese van *syn*- en *anti*-γ-chloor-α,β-diamino esters, *syn*- en *anti*-β,γ-aziridino-α-amino esters, *trans*-3-aminoazetidine-2-carboxylaten, een *trans*-α,β-diamino-γ-butyrolacton, *syn*-γ-chloor-α,β-diamino amiden, *syn*-γ,γ-dichloor-α,β-diamino amiden, *syn*-β,γ-aziridino-α-amino amiden, *syn*-α,β,γ-triamino amiden, een α-chloor-β,γ-diamino imidaat, *syn*-γ-chloor-α-hydroxy-β-amino esters, *syn*-β,γ-aziridino-α-hydroxy esters en *trans*-oxazolidinon carbonzuur derivaten.

Naast de ontwikkelde methoden hebben andere reacties in dit domein eveneens een groot potentieel en is er nog een groot scala aan verdere toepassingen mogelijk.

8. References

1. (a) Cantoni, G. L. *Annu. Rev. Biochem.* **1975**, *44*, 435-451; (b) Townsend, A. P.; Roth, S.; Williams, H. E. L.; Stylianou, E.; Thomas, N. R. *Org. Lett.* **2009**, *11*, 2976-2979; (c) Fontecave, M.; Atta, M.; Mulliez, E. *Trends Biochem. Sci.* **2004**, *29*, 243-249.
2. Couty, F.; Evano, G. *Org. Prep. Proced. Int.* **2006**, *38*, 427-465.
3. (a) Ueki, M.; Galonić, D. P.; Vaillancourt, F. H.; Garneau-Tsodikova, S.; Yeh, E.; Vosburg, D. A.; Schroeder, F. C.; Osada, H.; Walsh, C. T. *Chem. Biol.* **2006**, *13*, 1183-1191; (b) Vaillancourt, F. H.; Yeh, E.; Vosburg, D. A.; O'Connor, S. E.; Walsh, C. T. *Nature* **2005**, *436*, 1191-1194; (c) Kelly, W. L.; Boyne, M. T., II; Yeh, E.; Vosburg, D. A.; Galonić, D. P.; Kelleher, N. L.; Walsh, C. T. *Biochemistry* **2007**, *46*, 359-368; (d) Webb, H. K.; Matthews, R. G. *J. Biol. Chem.* **1995**, *270*, 17204-17209; (e) Chen, T.-Y.; Sanjiki, T.; Kato, H.; Ohta, M. *Bull. Chem. Soc. Jpn.* **1967**, *40*, 2398-2401.
4. Seyedsayamdost, M. R.; Chandler, J. R.; Blodgett, J. A. V.; Lima, P. S.; Duerkop, B. A.; Oinuma, K.-I.; Greenberg, E. P.; Clardy, J. *Org. Lett.* **2010**, *12*, 716-719.
5. Liu, K.; White, R. L.; He, J.-Y.; Vining, L. C. *J. Antibiot.* **1995**, *48*, 347-348.
6. Yoshida, H.; Arai, N.; Sugoh, M.; Shiomi, K.; Shinose, M.; Tanaka, Y.; Omura, S. *J. Antibiot.* **1994**, *47*, 1165-1166.
7. Blasiak, L. C.; Vaillancourt, F. H.; Walsh, C. T.; Drennan, C. L. *Nature* **2006**, *440*, 368-371.
8. Bitzer, J.; Streibel, M.; Langer, H.-J.; Grond, S. *Org. Biomol. Chem.* **2009**, *7*, 444-450.
9. (a) Fülöp, F. *Chem. Rev.* **2001**, *101*, 2181-2204; (b) Fülöp, F.; Martinek, T. A.; Tóth, G. K. *Chem. Soc. Rev.* **2006**, *35*, 323-334; (c) Gelman, M. A.; Gellman, S. H., Using constrained β-amino acid residues to control β-peptide shape and function. In *Enantioselective Synthesis of β-Amino Acids (2nd Edition)*, Juaristi, E.; Soloshonok, V. A., Eds.; John Wiley & Sons, Inc.: **2005**, pp 527-591; (d) Gnad, F.; Reiser, O. *Chem.*

Rev. **2003**, *103*, 1603-1623; (e) Kuhl, A.; Hahn, M. G.; Dumic, M.; Mittendorf, J. *Amino Acids* **2005**, *29*, 89-100; (f) Miller, J. A.; Nguyen, S. T. *Mini-Rev. Org. Chem.* **2005**, *2*, 39-45; (g) North, M. *J. Pept. Sci.* **2000**, *6*, 301-313; (h) Ortuño, R. M., Enantioselective Synthesis of Conformationally Constrained β-Amino Acids. In *Enantioselective Synthesis of β-Amino Acids (2nd Edition)*, Juaristi, E.; Soloshonok, V. A., Eds.; John Wiley & Sons, Inc.: **2005**, pp 117-138; (i) Lelais, G.; Seebach, D. *Biopolymers* **2004**, *76*, 206-243; (j) Seebach, D.; Beck, A. K.; Capone, S.; Deniau, G.; Groselj, U.; Zass, E. *Synthesis* **2009**, 1-32; (k) Seebach, D.; Gardiner, J. *Acc. Chem. Res.* **2008**, *41*, 1366-1375.

10. (a) Viso, A.; Fernández de la Pradilla, R.; García, A.; Flores, A. *Chem. Rev.* **2005**, *105*, 3167-3196; (b) Viso, A.; Fernández de la Pradilla, R., Mariola; García, A.; Flores, A. *Chem. Rev.* **2011**, *111*, PR1-42.
11. Gómez Arrayás, R.; Carretero, J. C. *Chem. Soc. Rev.* **2009**, *38*, 1940-1948.
12. (a) Ross, S. M.; Roy, D. N.; Spencer, P. S. *J. Neurochem.* **1989**, *53*, 710-715; (b) Sabri, M. I.; Lystrup, B.; Roy, D. N.; Spencer, P. S. *J. Neurochem.* **1995**, *65*, 1842-1848; (c) Abraham, M.; Abay, S. M. *PharmacologyOnline* **2009**, 381-388; (d) Yan, Z.-Y.; Spencer, P. S.; Li, Z.-X.; Liang, Y.-M.; Wang, Y.-F.; Wang, C.-Y.; Li, F.-M. *Phytochemistry* **2006**, *67*, 107-121; (e) Chase, L. A.; Peterson, N. L.; Koerner, J. F. *Toxicol. Appl. Pharmacol.* **2007**, *219*, 1-9; (f) Lambein, F.; Kuo, Y.-H.; Kusama-Eguchi, K.; Ikegami, F. *ARKIVOC* **2007**, *(ix)*, 45-52; (g) Van Moorhem, M.; Lambein, F.; Leybaert, L. *Food Chem. Toxicol.* **2011**, *49*, 550-555.
13. (a) Copani, A.; Canonico, P. L.; Catania, M. V.; Aronica, E.; Bruno, V.; Ratti, E.; Van Amsterdam, F. T. M.; Gaviraghi, G.; Nicoletti, F. *Brain Res.* **1991**, *558*, 79-86; (b) Vega, A.; Bell, E. A. *Phytochemistry* **1967**, *6*, 759-762; (c) Davis, A. J.; Hawkes, G. E.; O'Brien, P.; Wang, G.; Nunn, P. B. *J. Chem. Res., Synop.* **1991**, 84-85.

14. (a) Subasinghe, N.; Schulte, M.; Roon, R. J.; Koerner, J. F.; Johnson, R. L. *J. Med. Chem.* **1992**, *35*, 4602-4607; (b) Hermit, M. B.; Greenwood, J. R.; Brauner-Osborne, H. *J. Biol. Chem.* **2004**, *279*, 34811-34817.

15. (a) Chang, H. C.; Lee, T. H.; Chuang, L. Y.; Yen, M. H.; Hung, W. C. *Cancer Lett.* **1999**, *145*, 1-8; (b) Dobbin, P. S.; Hider, R. C.; Hall, A. D.; Taylor, P. D.; Sarpong, P.; Porter, J. B.; Xiao, G.; van der Helm, D. *J. Med. Chem.* **1993**, *36*, 2448-2458.

16. (a) Martinez, A. P.; Lee, W. W. *J. Org. Chem.* **1965**, *30*, 317-318; (b) Jane, D. E.; Hoo, K.; Kamboj, R.; Deverill, M.; Bleakman, D.; Mandelzys, A. *J. Med. Chem.* **1997**, *40*, 3645-3650; (c) Nollet, A. J. H.; Pandit, U. K. *Tetrahedron* **1969**, *25*, 5983-5987.

17. Palomo, C.; Aizpurua, J. M.; Ganboa, I.; Oiarbide, M. *Amino Acids* **1999**, *16*, 321-343.

18. (a) Karikomi, M.; De Kimpe, N. *Tetrahedron Lett.* **2000**, *41*, 10295-10298; (b) Ikee, Y.; Hashimoto, K.; Nakashima, M.; Hayashi, K.; Sano, S.; Shiro, M.; Nagao, Y. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 942-945; (c) Kuramoto, Y.; Ohshita, Y.; Yoshida, J.; Yazaki, A.; Shiro, M.; Koike, T. *J. Med. Chem.* **2003**, *46*, 1905-1917.

19. (a) Bacque, E.; Paris, J.-M.; Le Bitoux, S. *Synth. Commun.* **1995**, *25*, 803-812; (b) Frigola, J.; Pares, J.; Corbera, J.; Vano, D.; Merce, R.; Torrens, A.; Mas, J.; Valenti, E. *J. Med. Chem.* **1993**, *36*, 801-810; (c) Jones, R. N. *Eur. J. Clin. Microbiol. Infect. Dis.* **1992**, *11*, 188-194; (d) Guinea, J.; Robert, M.; Gargallo-Viola, D.; Xicota, M. A.; Garcia, J.; Tudela, E.; Esteve, M.; Coll, R.; Pares, M.; Roser, R. *Antimicrob. Agents Chemother.* **1993**, *37*, 868-874; (e) Gargallo-Viola, D.; Esteve, M.; Llovera, S.; Roca, X.; Guinea, J. *Antimicrob. Agents Chemother.* **1991**, *35*, 442-447.

20. (a) Zagari, A.; Nemethy, G.; Scheraga, H. A. *Biopolymers* **1990**, *30*, 951-959; (b) Deming, T. J.; Fournier, M. J.; Mason, T. L.; Tirrell, D. A. *Macromolecules* **1996**, *29*, 1442-1444; (c) Schlechtingen, G.; DeHaven, R. N.; Daubert, J. D.; Cassel, J.; Goodman,

M. *Biopolymers* **2003**, *71*, 71-76; (d) Boni, R.; Verdini, A. S.; Deber, C. M.; Blout, E. R. *Biopolymers* **1978**, *17*, 2385-2399.

21. (a) Takemoto, T.; Nomoto, K.; Fushiya, S.; Ouchi, R.; Kusano, G.; Hikino, H.; Takagi, S.; Matsuura, Y.; Kakudo, M. *Proc. Jpn. Acad., Ser. B* **1978**, *54*, 469-473; (b) Matsuura, F.; Hamada, Y.; Shiori, T. *Tetrahedron* **1994**, *50*, 265-274.
22. (a) Shioiri, T.; Hamada, Y.; Matsuura, F. *Tetrahedron* **1995**, *51*, 3939-3958; (b) Singh, S.; Crossley, G.; Ghosal, S.; Lefievre, Y.; Pennington, M. W. *Tetrahedron Lett.* **2005**, *46*, 1419-1421.
23. Kinoshita, E.; Yamakoshi, J.; Kikuchi, M. *Biosci. Biotechnol. Biochem.* **1993**, *57*, 1107-1110.
24. Fushiya, S.; Tamura, T.; Tashiro, T.; Nozoe, S. *Heterocycles* **1984**, *22*, 1039-1040.
25. Vértesy, L.; Ehlers, E.; Kogler, H.; Kurz, M.; Meiwes, J.; Seibert, G.; Vogel, M.; Hammann, P. *J. Antibiot.* **2000**, *53*, 816-827.
26. Harrison, L.; Teplow, D. B.; Rinaldi, M.; Strobel, G. *J. Gen. Microbiol.* **1991**, *137*, 2857-2865.
27. (a) Senten, K.; Van der Veken, P.; Bal, G.; De Meester, I.; Lambeir, A.-M.; Scharpé, S.; Bauvois, B.; Haemers, A.; Augustyns, K. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 2825-2828; (b) Senten, K.; Van der Veken, P.; De Meester, I.; Lambeir, A.-M.; Scharpé, S.; Haemers, A.; Augustyns, K. *J. Med. Chem.* **2003**, *46*, 5005-5014; (c) Senten, K.; Van der Veken, P.; De Meester, I.; Lambeir, A.-M.; Scharpé, S.; Haemers, A.; Augustyns, K. *J. Med. Chem.* **2004**, *47*, 2906-2916.
28. (a) Chen, S.-J.; Jiaang, W.-T. *Curr. Top. Med. Chem.* **2011**, *11*, 1447-1463; (b) Van der Veken, P.; Haemers, A.; Augustyns, K. *Curr. Top. Med. Chem.* **2007**, *7*, 621-635; (c) Augustyns, K.; Van der Veken, P.; Senten, K.; Haemers, A. *Curr. Med. Chem.* **2005**, *12*, 971-998.

29. Scheen, A. J. *Expert Opin. Pharmacother.* **2012**, *13*, 81-99.

30. Baetta, R.; Corsini, A. *Drugs* **2011**, *71*, 1441-1467.

31. Scharpé, S.; Augustyns, K.; Haemers, A.; Lambeir, A.-M.; De Meester, I.; Senten, K.; Van Der Veken, P. *PCT Int. Appl.*, WO 2004076433 (A1), **2004**.

32. Cardillo, G.; Tolomelli, A.; Tomasini, C. *Eur. J. Org. Chem.* **1999**, 155-161.

33. Kudyba, I.; Raczko, J.; Jurczak, J. *Tetrahedron Lett.* **2003**, *44*, 8685-8687.

34. Morton, D.; Stockman, R. A. *Tetrahedron* **2006**, *62*, 8869-8905.

35. Ferreira, F.; Botuha, C.; Chemla, F.; Pérez-Luna, A. *Chem. Soc. Rev.* **2009**, *38*, 1162-1186.

36. Davis, F. A. *J. Org. Chem.* **2006**, *71*, 8993-9003.

37. Pablo, O.; Guijarro, D.; Yus, M. *J. Org. Chem.* **2013**, *78*, 9181-9189.

38. Ellman, J. A.; Owens, T. D.; Tang, T. P. *Acc. Chem. Res.* **2002**, *35*, 984-995.

39. Lin, G.-Q.; Xu, M.-H.; Zhong, Y.-W.; Sun, X.-W. *Acc. Chem. Res.* **2008**, *41*, 831-840.

40. Robak, M. T.; Herbage, M. A.; Ellman, J. A. *Chem. Rev.* **2010**, *110*, 3600-3740.

41. De Kimpe, N.; Verhé, R.; De Buyck, L.; Moens, L.; Schamp, N. *Synthesis* **1982**, 43-46.

42. De Kimpe, N.; Verhé, R. *The Chemistry of α-Halo ketones, α-Halo aldehydes, and α-Halo imines*, John Wiley and Sons: **1988**, 496 pp.

43. De Kimpe, N.; Verhé, R.; De Buyck, L.; Schamp, N. *Recl. Trav. Chim. Pays-Bas (J. Royal Neth. Chem. Soc.)* **1977**, *96*, 242-246.

44. De Kimpe, N.; Sulmon, P.; Verhé, R.; De Buyck, L.; Schamp, N. *J. Org. Chem.* **1983**, *48*, 4320-4326.

45. De Kimpe, N.; Moens, L. *Tetrahedron* **1990**, *46*, 2965-2974.

46. Van Nguyen, T.; De Kimpe, N. *Tetrahedron* **2000**, *56*, 7299-7304.

47. Dejaegher, Y.; De Kimpe, N. *J. Org. Chem.* **2004**, *69*, 5974-5985.

48. D'hooghe, M.; Aelterman, W.; De Kimpe, N. *Org. Biomol. Chem.* **2009**, *7*, 135-141.

49. Tomasini, C.; Angelici, G.; Castellucci, N. *Eur. J. Org. Chem.* **2011**, *2011*, 3648-3669.

50. Park, C. S.; Choi, H. G.; Lee, H.; Lee, W. K.; Ha, H. J. *Tetrahedron-Asymmetry* **2000**, *11*, 3283-3292.

51. Bisol, T. B.; Bortoluzzi, A. J.; Sá, M. M. *J. Org. Chem.* **2011**, *76*, 948-962.

52. Benfatti, F.; Cardillo, G.; Gentilucci, L.; Perciaccante, R.; Tolomelli, A.; Catapano, A. *J. Org. Chem.* **2006**, *71*, 9229-9232.

53. (a) Ibuka, T.; Mimura, N.; Ohno, H.; Nakai, K.; Akaji, M.; Habashita, H.; Tamamura, H.; Miwa, Y.; Taga, T.; Fujii, N.; Yamamoto, Y. *J. Org. Chem.* **1997**, *62*, 2982-2991; (b) Ibuka, T.; Mimura, N.; Aoyama, H.; Akaji, M.; Ohno, H.; Miwa, Y.; Taga, T.; Nakai, K.; Tamamura, H.; Fujii, N.; Yamamoto, Y. *J. Org. Chem.* **1997**, *62*, 999-1015; (c) Davis, F. A.; Reddy, G. V. *Tetrahedron Lett.* **1996**, *37*, 4349-4352; (d) Davis, F. A.; Liu, H.; Reddy, G. V. *Tetrahedron Lett.* **1996**, *37*, 5473-5476; (e) Atkinson, R. S.; Coogan, P. M.; Cornell, C. L. *J. Chem. Soc., Chem. Commun.* **1993**, 1215-1216.

54. Ibuka, T. *Chem. Soc. Rev.* **1998**, *27*, 145-154.

55. Baldwin, J. E.; Pudussery, R. G.; Qureshi, A. K.; Sklarz, B. *J. Am. Chem. Soc.* **1968**, *90*, 5325-5326.

56. Confalone, P. N.; Huie, E. M. *Org. React.* **1988**, *36*, 1-173.

57. Alcaide, B.; Almendros, P.; Alonso, J. M.; Aly, M. F.; Pardo, C.; Sáez, E.; Torres, M. R. *J. Org. Chem.* **2002**, *67*, 7004-7013.

58. Tartakovskii, V. A.; Luk'yanov, O. A.; Novikov, S. S. *Izv. Akad. Nauk SSSR, Ser. Khim.* **1966**, 2246-2247.

59. Tartakovskii, V. A.; Luk'yanov, O. A.; Novikov, S. S. *Dokl. Akad. Nauk SSSR* **1968**, *178*, 123-126.

60. Thierry, J.; Servajean, V. *Tetrahedron Lett.* **2004**, *45*, 821-823.

61. Song, L.; Servajean, V.; Thierry, J. *Tetrahedron* **2006**, *62*, 3509-3516.

62. Buron, F.; Turck, A.; Plé, N.; Bischoff, L.; Marsais, F. *Tetrahedron Lett.* **2007**, *48*, 4327-4330.

63. Aaseng, J. E.; Gautun, O. R. *Tetrahedron* **2010**, *66*, 8982-8991.

64. Kwak, W. Y.; Kim, H. J.; Min, J. P.; Yoon, T. H.; Shim, H. J.; Yoo, M. *PCT Int. Appl.*, WO 2010114292 (A2), **2010**.

65. Rodriguez, M.; Linares, M.; Doulut, S.; Heitz, A.; Martinez, J. *Tetrahedron Lett.* **1991**, *32*, 923-926.

66. Meiresonne, T.; Mangelinckx, S.; De Kimpe, N. *Tetrahedron* **2012**, *68*, 9566-9571.

67. Park, J.-i.; Tian, G. R.; Kim, D. H. *J. Org. Chem.* **2001**, *66*, 3696-3703.

68. Park, J.-i.; Kim, D. H. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 2967-2970.

69. (a) Baldwin, J. E.; Moloney, M. G.; North, M. *Tetrahedron* **1989**, *45*, 6309-6318; (b) Baldwin, J. E.; Moloney, M. G.; North, M. *J. Chem. Soc., Perkin Trans. 1* **1989**, 833-834.

70. Berger, A.; Katchalski, E. *J. Am. Chem. Soc.* **1951**, *73*, 4084-4088.

71. Gmeiner, P.; Feldman, P. L.; Chu-Moyer, M. Y.; Rapoport, H. *J. Org. Chem.* **1990**, *55*, 3068-3074.

72. Humphrey, J. M.; Aggen, J. B.; Chamberlin, A. R. *J. Am. Chem. Soc.* **1996**, *118*, 11759-11770.

73. Wipf, P.; Miller, C. P. *Tetrahedron Lett.* **1992**, *33*, 6267-6270.

74. Nahm, S.; Weinreb, S. M. *Tetrahedron Lett.* **1981**, *22*, 3815-3818.

75. Jefford, C. W.; Wang, J. *Tetrahedron Lett.* **1993**, *34*, 1111-1114.

76. (a) Namikoshi, M.; Rinehart, K. L.; Dahlem, A. M.; Beasley, V. R.; Carmichael, W. W. *Tetrahedron Lett.* **1989**, *30*, 4349-4352; (b) Takahashi, Y.; Hasegawa, S.; Izawa, T.; Kobayashi, S.; Ohno, M. *Chem. Pharm. Bull.* **1986**, *34*, 3020-3024.

77. Basha, A.; Lipton, M.; Weinreb, S. M. *Tetrahedron Lett.* **1977**, 4171-4174.

78. Fehrentz, J. A.; Castro, B. *Synthesis* **1983**, 676-678.

79. Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis (2nd Edition)*, John Wiley and Sons, Inc.: **1991**, 473 pp.

80. Carlsen, P. H. J.; Katsuki, T.; Martin, V. S.; Sharpless, K. B. *J. Org. Chem.* **1981**, *46*, 3936-3938.

81. Takeda, Y.; Murakami, Y.; Ikeda, Y.; Minakata, S. *Asian J. Org. Chem.* **2012**, *1*, 226-230.

82. Van Brabandt, W.; Dejaegher, Y.; De Kimpe, N. *Pure Appl. Chem.* **2005**, *77*, 2061-2071.

83. Boros, E.; Bertha, F.; Czira, G.; Feller, A.; Fetter, J.; Kajtár-Peredy, M.; Simig, G. *J. Heterocycl. Chem.* **2006**, *43*, 87-94.

84. Boros, E.; Bertha, F.; Feller, A.; Fetter, J.; Simig, G. In *Periodica Polytechnica Ser. Chem. Eng*, 2nd Conference of PhD students at Faculty of Chemical Engineering, **2005**, *49*, 33-34.

85. (a) Bertha, F.; Fetter, J.; Kajtár-Peredy, M.; Lempert, K.; Czira, G. *Tetrahedron* **1998**, *54*, 15227-15242; (b) Sápi, A.; Bertha, F.; Fetter, J.; Kajtár-Peredy, M.; Keserű, G. M.; Lempert, K. *Tetrahedron* **1996**, *52*, 771-782; (c) Bertha, F.; Fetter, J.; Kajtár-Peredy, M.; Lempert, K. *Tetrahedron* **1999**, *55*, 5567-5580.

86. Alcaide, B.; Martin-Cantalejo, Y.; Pérez-Castells, J.; Rodriguez-López, J.; Sierra, M. A.; Monge, A.; Pérez-Garcia, V. *J. Org. Chem.* **1992**, *57*, 5921-5931.

87. Tombor, Z.; Greff, Z.; Nyitrai, J.; Kajtár-Peredy, M. *Liebigs Ann.* **1995**, 825-835.

88. Lee, H. K.; Chun, J. S.; Pak, C. S. *Tetrahedron Lett.* **2001**, *42*, 3483-3486.

89. Fetter, J.; Keskeny, E.; Czuppon, T.; Lempert, K.; Kajtár-Peredy, M.; Tamás, J. *J. Chem. Soc., Perkin Trans. 1* **1992**, 3061-3067.

90. Boros, E.; Bertha, F.; Czira, G.; Feller, A.; Fetter, J.; Kajtár-Peredy, M.; Simig, G. *J. Heterocycl. Chem.* **2006**, *43*, 371-388.

91. Kiss, L.; Mangelinckx, S.; Sillanpää, R.; Fülöp, F.; De Kimpe, N. *J. Org. Chem.* **2007**, *72*, 7199-7206.

92. Kiss, L.; Mangelinckx, S.; Fülöp, F.; De Kimpe, N. *Org. Lett.* **2007**, *9*, 4399-4402.

93. Satoh, T.; Matsue, R.; Fujii, T.; Morikawa, S. *Tetrahedron Lett.* **2000**, *41*, 6495-6499.

94. Alezra, V.; Bonin, M.; Micouin, L.; Husson, H.-P. *Tetrahedron Lett.* **2000**, *41*, 651-654.

95. Alezra, V.; Bonin, M.; Micouin, L.; Policar, C.; Husson, H.-P. *Eur. J. Org. Chem.* **2001**, 2589-2594.

96. Harada, K.; Nakamura, I. *J. Chem. Soc., Chem. Commun.* **1978**, 522-523.

97. (a) Seebach, D.; Häner, R. *Chem. Lett.* **1987**, 49-52; (b) Häner, R.; Olano, B.; Seebach, D. *Helv. Chim. Acta* **1987**, *70*, 1676-1693.

98. Yamauchi, Y.; Kawate, T.; Katagiri, T.; Uneyama, K. *Tetrahedron* **2003**, *59*, 9839-9847.

99. Yamauchi, Y.; Kawate, T.; Itahashi, H.; Katagiri, T.; Uneyama, K. *Tetrahedron Lett.* **2003**, *44*, 6319-6322.

100. Sweeney, J. B. *Sci. Synth.* **2009**, *40a*, 643-772.

101. Oh, B. H.; Nakamura, I.; Yamamoto, Y. *Tetrahedron Lett.* **2002**, *43*, 9625-9628.

102. Oh, B. H.; Nakamura, I.; Yamamoto, Y. *ARKIVOC* **2003**, *(viii)*, 67-78.

103. Kryczka, B.; Laurent, A.; Marquet, B. *Tetrahedron* **1978**, *34*, 3291-3298.

104. Kryczka, B.; Laurent, A. *Tetrahedron Lett.* **1977**, 31-32.

105. Alvernhe, G.; Lacombe, S.; Laurent, A.; Marquet, B. *J. Chem. Res., Synop.* **1980**, 54-55.

106. Blagoev, B.; Novkova, S. *C. R. Hebd. Seances Acad. Sci., Ser. C* **1979**, *288*, 281-282.

107. Blagoev, B.; Novkova, S. *Tetrahedron* **1982**, *38*, 1609-1613.

108. Santaniello, E.; Manzocchi, A. *Synthesis* **1977**, 698-699.

109. Blagoev, B.; Ivanov, D. *Synthesis* **1970**, 615-627.

110. Cebulska, Z.; Laurent, A. *Tetrahedron Lett.* **1977**, 3939-3942.

111. Sweeney, J. B., Synthesis of aziridines. In *Aziridines and Epoxides in Organic Synthesis*, Yudin, A. K., Ed. Wiley-VCH: **2006**, pp 117-144.

112. Achour, R.; Essassi, E. M.; Salem, M.; Zniber, R. *Bull. Soc. Chim. Belg.* **1989**, *98*, 405-412.

113. Lee, K. Y.; Kim, S. C.; Kim, J. N. *Tetrahedron Lett.* **2006**, *47*, 977-980.

114. Lee, K. Y.; Lee, H. S.; Kim, J. N. *Tetrahedron Lett.* **2007**, *48*, 2007-2011.

115. Lingam, K. A. P.; Shanmugam, P.; Mandal, A. B. *Synlett* **2012**, *23*, 2903-2908.

116. (a) Matano, Y.; Yoshimune, M.; Suzuki, H. *J. Org. Chem.* **1995**, *60*, 4663-4665; (b) Li, A.-H.; Dai, L.-X.; Hou, X.-L.; Chen, M.-B. *J. Org. Chem.* **1996**, *61*, 4641-4648; (c) Li, A.-H.; Dai, L.-X.; Hou, X.-L. *J. Chem. Soc., Perkin Trans. 1* **1996**, 2725-2729; (d) Li, A.-H.; Dai, L.-X.; Hou, X.-L. *J. Chem. Soc., Perkin Trans. 1* **1996**, 867-869; (e) Zhou, Y.-G.; Li, A.-H.; Hou, X.-L.; Dai, L.-X. *Tetrahedron Lett.* **1997**, *38*, 7225-7228.

117. Lwowski, W. *Angew. Chem., Int. Ed. Engl.* **1967**, *6*, 897-906.

118. (a) Gilchrist, T. L.; Alves, M. J., Small rings by azide chemistry. In *Organic Azides: Syntheses and Applications*, Bräse, S.; Banert, K., Eds.; John Wiley & Sons Ltd.: **2010**, pp 167-190; (b) Jung, N.; Brase, S. *Angew. Chem., Int. Ed.* **2012**, *51*, 5538-5540.

119. Alder, K.; Flock, F. H.; Hausweiler, A.; Reeber, R. *Chem. Ber.* **1954**, *87*, 1752-1759.

120. Wiesner, K.; Philipp, A. *Tetrahedron Lett.* **1966**, 1467-1470.

121. Wiesner, K.; Ho, P.-T.; Chang, D.; Blount, J. F. *Experientia* **1972**, *28*, 766-767.

122. Ho, P.-T.; Oida, S.; Wiesner, K. *J. Chem. Soc., Chem. Commun.* **1972**, 883-884.

123. Wiesner, K.; Ho, P.-T.; Jain, R. C.; Lee, S. F.; Oida, S.; Philipp, A. *Can. J. Chem.* **1973**, *51*, 1448-1457.

124. Maier, G.; Schmidt, C.; Reisenauer, H. P.; Endlein, E.; Becker, D.; Eckwert, J.; Hess, B. A., Jr.; Schaad, L. J. *Chem. Ber.* **1993**, *126*, 2337-2352.

125. Guo, Z.; Schultz, A. G. *Tetrahedron Lett.* **2004**, *45*, 919-921.

126. Ishikura, M.; Kudo, S.; Hino, A.; Ohnuki, N.; Katagiri, N. *Heterocycles* **2000**, *53*, 1499-1504.

127. Malpass, J. R.; Belkacemi, D.; Griffith, G. A.; Robertson, M. D. *ARKIVOC* **2002**, *(vi)*, 164-174.

128. Ishikura, M.; Matsumoto, K.; Hasunuma, M.; Katagiri, N. *Heterocycles* **2003**, *60*, 2737-2742.

129. Ishikura, M.; Murakami, A.; Katagiri, N. *Org. Biomol. Chem.* **2003**, *1*, 452-453.

130. Ishikura, M.; Hasunuma, M.; Yamada, K.; Yanada, R. *Heterocycles* **2006**, *68*, 2253-2257.

131. (a) Schultz, A. G.; Dittami, J. P.; Myong, S. O.; Sha, C. K. *J. Am. Chem. Soc.* **1983**, *105*, 3273-3279; (b) Schultz, A. G. *Adv. Cycloaddit.* **1988**, *1*, 53-85.

132. (a) Nagata, W. *Lect. Heterocycl. Chem.* **1972**, *1*, 29-37; (b) Watson, I. D. G.; Yu, L.; Yudin, A. K. *Acc. Chem. Res.* **2006**, *39*, 194-206; (c) Karila, D.; Dodd, R. H. *Curr. Org. Chem.* **2011**, *15*, 1507-1538.

133. Atkinson, R. S.; Malpass, J. R. *Tetrahedron Lett.* **1975**, 4305-4306.

134. Aitken, R. A.; Gosney, I.; Farries, H.; Palmer, M. H.; Simpson, I.; Cadogan, J. I. G.; Tinley, E. J. *Tetrahedron* **1985**, *41*, 1329-1346.

135. Pan, J.-F.; Chen, K. *Tetrahedron Lett.* **2004**, *45*, 2541-2543.

136. Siu, T.; Yudin, A. K. *J. Am. Chem. Soc.* **2002**, *124*, 530-531.

137. Yudin, A. K.; Siu, T. *PCT Int. Appl.*, WO 2003010361 (A2), **2003**.

138. Rigoli, J. W.; Boralsky, L. A.; Hershberger, J. C.; Marston, D.; Meis, A. R.; Guzei, I. A.; Schomaker, J. M. *J. Org. Chem.* **2012**, *77*, 2446-2455.

139. Weatherly, C. D.; Rigoli, J. W.; Schomaker, J. M. *Org. Lett.* **2012**, *14*, 1704-1707.

140. Schomaker, J.; Boralsky, L.; Hershberger, J.; Rigoli, J.; Adams, C. S. *PCT Int. Appl.*, WO 2013033245 (A1), **2013**.

141. Anderson, D. J.; Gilchrist, T. L.; Horwell, D. C.; Rees, C. W. *J. Chem. Soc. C* **1970**, 576-582.

142. Mei, R.-H.; Liu, Z.-G.; Cheng, H.; Xu, L.; Wang, F.-P. *Org. Lett.* **2013**, *15*, 2206-2209.

143. Liu, Z.-G.; Cheng, H.; Ge, M.-J.; Xu, L.; Wang, F.-P. *Tetrahedron* **2013**, *69*, 5431-5437.

144. Antunes, A. M. M.; Bonifácio, V. D. B.; Nascimento, S. C. C.; Lobo, A. M.; Branco, P. S.; Prabhakar, S. *Tetrahedron* **2007**, *63*, 7009-7017.

145. Ohba, K.; Matsuda, M.; Nakata, M. *Carbohydr. Lett.* **1996**, *1*, 449-456.

146. Herdeis, C.; Aschenbrenner, A.; Kirfel, A.; Schwabenländer, F. *Tetrahedron-Asymmetry* **1997**, *8*, 2421-2432.

147. Davis, F. A.; Zhang, Y.; Andemichael, Y.; Fang, T.; Fanelli, D. L.; Zhang, H. *J. Org. Chem.* **1999**, *64*, 1403-1406.

148. Senanayake, C. H.; Krishnamurthy, D.; Lu, Z.-H.; Han, Z.; Gallou, I. *Aldrichimica Acta* **2005**, *38*, 93-104.

149. Stanton, G. R.; Goellue, M.; Platoff, R. M.; Rich, C. E.; Carroll, P. J.; Walsh, P. J. *Adv. Synth. Catal.* **2013**, *355*, 757-764.

150. (a) Denolf, B.; Mangelinckx, S.; Törnroos, K. W.; De Kimpe, N. *Org. Lett.* **2006**, *8*, 3129-3132; (b) PhD-thesis of Denolf, B., Faculty of Bioscience Engineering, Department of Sustainable Organic Chemistry and Technology, 2007.

151. Hodgson, D. M.; Kloesges, J.; Evans, B. *Synthesis* **2009**, 1923-1932.

152. De Buyck, L.; Verhé, R.; De Kimpe, N.; Courtheyn, D.; Schamp, N. *Bull. Soc. Chim. Belg.* **1980**, *89*, 441-458.

153. Liu, G.; Cogan, D. A.; Owens, T. D.; Tang, T. P.; Ellman, J. A. *J. Org. Chem.* **1999**, *64*, 1278-1284.

154. Master thesis of Callebaut, G., Faculty of Bioscience Engineering, Department of Sustainable Organic Chemistry and Technology, UGent, 2009.

155. Hernández-Toribio, J.; Gómez Arrayás, R.; Carretero, J. C. *Chem. - Eur. J.* **2010**, *16*, 1153-1157.

156. Davis, F. A.; Deng, J. *Org. Lett.* **2004**, *6*, 2789-2792.

157. Davis, F. A.; Zhang, Y.; Qiu, H. *Org. Lett.* **2007**, *9*, 833-836.

158. Ezquerra, J.; Pedregal, C.; Merino, I.; Florez, J.; Barluenga, J.; Garcia-Granda, S.; Llorca, M.-A. *J. Org. Chem.* **1999**, *64*, 6554-6565.

159. Gillies, M. B.; Tønder, J. E.; Tanner, D.; Norrby, P.-O. *J. Org. Chem.* **2002**, *67*, 7378-7388.

160. (a) Davis, F. A.; Zhou, P.; Reddy, G. V. *J. Org. Chem.* **1994**, *59*, 3243-3245; (b) Davis, F. A.; Liu, H.; Zhou, P.; Fang, T.; Reddy, G. V.; Zhang, Y. *J. Org. Chem.* **1999**, *64*, 7559-7567.

161. Allwein, S. P.; Secord, E. A.; Martins, A.; Mitten, J. V.; Nelson, T. D.; Kress, M. H.; Dolling, H. *Synlett* **2004**, 2489-2492.

162. Burkhard, J. A.; Guérot, C.; Knust, H.; Rogers-Evans, M.; Carreira, E. M. *Org. Lett.* **2010**, *12*, 1944-1947.

163. Žukauskaitė, A.; Mangelinckx, S.; Callebaut, G.; Wybon, C.; Šačkus, A.; De Kimpe, N. *Tetrahedron* **2013**, *69*, 3437-3443.

164. Bergmeier, S. C.; Seth, P. P. *Tetrahedron Lett.* **1999**, *40*, 6181-6184.

165. (a) Alonso, E.; Ramón, D. J.; Yus, M. *Tetrahedron* **1997**, *53*, 14355-14368; (b) Concellón, J. M.; Rodriguez-Solla, H.; Simal, C. *Org. Lett.* **2008**, *10*, 4457-4460.

166. Pei, Y.; Brade, K.; Brulé, E.; Hagberg, L.; Lake, F.; Moberg, C. *Eur. J. Org. Chem.* **2005**, 2835-2840.

167. Ajayi, K.; Thakur, V. V.; Lapo, R. C.; Knapp, S. *Org. Lett.* **2010**, *12*, 2630-2633.

168. Sabitha, G.; Reddy, B. V. S.; Abraham, S.; Yadav, J. S. *Tetrahedron Lett.* **1999**, *40*, 1569-1570.

169. Arndt, H.-D.; Welz, R.; Müller, S.; Ziemer, B.; Koert, U. *Chem. - Eur. J.* **2004**, *10*, 3945-3962.

170. (a) Teplitski, M.; Mathesius, U.; Rumbaugh, K. P. *Chem. Rev.* **2011**, *111*, 100-116; (b) Mattmann, M. E.; Blackwell, H. E. *J. Org. Chem.* **2010**, *75*, 6737-6746.

171. Master thesis of Balcaen, M., Faculty of Bioscience Engineering, Department of Sustainable Organic Chemistry and Technology, UGent, 2012.

172. Master thesis of Rugwiro, A., Faculty of Bioscience Engineering, Department of Sustainable Organic Chemistry and Technology, UGent, 2013.

173. http://www.fluorochem.co.uk.

174. Viso, A.; Fernández de la Pradilla, R.; Lopez-Rodriguez, M. L.; García, A.; Flores, A.; Alonso, M. *J. Org. Chem.* **2004**, *69*, 1542-1547.

175. Viso, A.; Fernández de la Pradilla, R.; Flores, A.; García, A.; Tortosa, M.; Lopez-Rodriguez, M. L. *J. Org. Chem.* **2006**, *71*, 1442-1448.

176. (a) Venuti, M. C.; Alvarez, R.; Bruno, J. J.; Strosberg, A. M.; Gu, L.; Chiang, H. S.; Massey, I. J.; Chu, N.; Fried, J. H. *J. Med. Chem.* **1988**, *31*, 2145-2152; (b) O'Donnell, M. J.; Polt, R. L. *J. Org. Chem.* **1982**, *47*, 2663-2666.

177. (a) Manthorpe, J. M.; Gleason, J. L. *J. Am. Chem. Soc.* **2001**, *123*, 2091-2092; (b) Evans, D. A.; Takacs, J. M. *Tetrahedron Lett.* **1980**, *21*, 4233-4236.

178. (a) Bernardi, A.; Gennari, C.; Raimondi, L.; Villa, M. B. *Tetrahedron* **1997**, *53*, 7705-7714; (b) Silveira, C. C.; Vieira, A. S.; Braga, A. L.; Russowsky, D. *Tetrahedron* **2005**,

61, 9312-9318; (c) Mangelinckx, S.; De Sterck, B.; Colpaert, F.; Catak, S.; Jacobs, J.; Rooryck, S.; Waroquier, M.; Van Speybroeck, V.; De Kimpe, N. *J. Org. Chem.* **2012**, *77*, 3415-3425.

179. Turcaud, S.; Berhal, F.; Royer, J. *J. Org. Chem.* **2007**, *72*, 7893-7897.
180. (a) Fujisawa, T.; Kooriyama, Y.; Shimizu, M. *Tetrahedron Lett.* **1996**, *37*, 3881-3884; (b) Koriyama, Y.; Nozawa, A.; Hayakawa, R.; Shimizu, M. *Tetrahedron* **2002**, *58*, 9621-9628.
181. Davis, F. A.; Zhang, Y. *Tetrahedron Lett.* **2009**, *50*, 5205-5207.
182. (a) Mikolajczyk, M.; Drabowicz, J.; Bujnicki, B. *J. Chem. Soc., Chem. Commun.* **1976**, 568-569; (b) Mikotajczyk, M.; Drabowicz, J.; Bujnicki, B. *Tetrahedron Lett.* **1985**, *26*, 5699-5702.
183. Viso, A.; Fernández de la Pradilla, R.; García, A.; Guerrero-Strachan, C.; Alonso, M.; Tortosa, M.; Flores, A.; Martínez-Ripoll, M.; Fonseca, I.; André, I.; Rodríguez, A. *Chem. - Eur. J.* **2003**, *9*, 2867-2876.
184. (a) Szöllősy, Á.; Tischer, T.; Kádas, I.; Tőke, L.; Tóth, G. *Tetrahedron* **1999**, *55*, 7279-7288; (b) Ooi, T.; Kameda, M.; Taniguchi, M.; Maruoka, K. *J. Am. Chem. Soc.* **2004**, *126*, 9685-9694.
185. (a) Hiyama, T.; Koide, H.; Fujita, S.; Nozaki, H. *Tetrahedron* **1973**, *29*, 3137-3139; (b) Papa, C.; Tomasini, C. *Eur. J. Org. Chem.* **2000**, 1569-1576.
186. Mangelinckx, S.; Kadam, S. T.; Semina, E.; Callebaut, G.; Colpaert, F.; De Smaele, D.; De Kimpe, N. *Tetrahedron* **2013**, *69*, 3728-3735.
187. (a) Senten, K.; Van der Veken, P.; Bal, G.; Haemers, A.; Augustyns, K. *Tetrahedron Lett.* **2001**, *42*, 9135-9138; (b) Van Goethem, S.; Matheeussen, V.; Joossens, J.; Lambeir, A.-M.; Chen, X.; De Meester, I.; Haemers, A.; Augustyns, K.; Van der Veken, P. *J. Med. Chem.* **2011**, *54*, 5737-5746; (c) Jansen, K.; De Meester, I.; Heirbaut, L.;

Cheng, J. D.; Joossens, J.; Augustyns, K.; Van der Veken, P. *PCT Int. Appl.*, WO 2013107820 (A1), **2013**.

188. Žukauskaitė, A.; Mangelinckx, S.; Buinauskaité, V.; Šačkus, A.; De Kimpe, N. *Amino Acids* **2011**, *41*, 541-558.
189. Davis, F. A.; McCoull, W. *J. Org. Chem.* **1999**, *64*, 3396-3397.
190. Kuduk, S. D.; DiPardo, R. M.; Chang, R. K.; Ng, C.; Bock, M. G. *Tetrahedron Lett.* **2004**, *45*, 6641-6643.
191. Colpaert, F.; Mangelinckx, S.; De Brabandere, S.; De Kimpe, N. *J. Org. Chem.* **2011**, *76*, 2204-2213.
192. Davis, F. A.; Prasad, K. R.; Nolt, M. B.; Wu, Y. *Org. Lett.* **2003**, *5*, 925-927.
193. Wang, Y.; He, Q.-F.; Wang, H.-W.; Zhou, X.; Huang, Z.-Y.; Qin, Y. *J. Org. Chem.* **2006**, *71*, 1588-1591.
194. Tang, T. P.; Ellman, J. A. *J. Org. Chem.* **2002**, *67*, 7819-7832.
195. Evans, J. W.; Ellman, J. A. *J. Org. Chem.* **2003**, *68*, 9948-9957.
196. Qin, Y.; Wang, Y.; Guo, P.; Gao, J.; Feng, X.; Luo, X.; Zhang, X. *Faming Zhuanli Shenqing Gongkai Shuomingshu*, CN 1709864 (A), **2005**.
197. (a) Ireland, R. E.; Willard, A. K. *Tetrahedron Lett.* **1975**, 3975-3978; (b) Ireland, R. E.; Wipf, P. *Tetrahedron Lett.* **1989**, *30*, 919-922; (c) Narula, A. S. *Tetrahedron Lett.* **1981**, *22*, 4119-4122; (d) Xie, L.; Isenberger, K. M.; Held, G.; Dahl, L. M. *J. Org. Chem.* **1997**, *62*, 7516-7519.
198. Hjelmgaard, T.; Faure, S.; Lemoine, P.; Viossat, B.; Aitken, D. J. *Org. Lett.* **2008**, *10*, 841-844.
199. Stanton, G. R.; Norrby, P.-O.; Carroll, P. J.; Walsh, P. J. *J. Am. Chem. Soc.* **2012**, *134*, 17599-17604.

200. (a) Skwarczynski, M.; Sohma, Y.; Noguchi, M.; Kimura, T.; Hayashi, Y.; Kiso, Y. *J. Org. Chem.* **2006**, *71*, 2542-2545; (b) Iizuka, K.; Kamijo, T.; Harada, H.; Akahane, K.; Kubota, T.; Umeyama, H.; Ishida, T.; Kiso, Y. *J. Med. Chem.* **1990**, *33*, 2707-2714.

201. (a) Alcaide, B.; Lopez-Mardomingo, C.; Lopez-Saez, B.; Perez-Ossorio, R.; Plumet, J. *J. Heterocycl. Chem.* **1985**, *22*, 289-291; (b) Pansare, S. V.; Bhattacharyya, A. *Tetrahedron Lett.* **2001**, *42*, 9265-9267; (c) Pansare, S. V.; Shinkre, B. A.; Bhattacharyya, A. *Tetrahedron* **2002**, *58*, 8985-8991; (d) Pansare, S. V.; Adsool, V. A. *Org. Lett.* **2006**, *8*, 2035-2037.

202. Dekeukeleire, S.; D'hooghe, M.; De Kimpe, N. *J. Org. Chem.* **2009**, *74*, 1644-1649.

203. Alcaide, B.; Almendros, P.; Cabrero, G.; Ruiz, M. P. *Tetrahedron* **2012**, *68*, 10761-10768.

204. Nelson, T. D.; Rosen, J. D.; Brands, K. M. J.; Craig, B.; Huffman, M. A.; McNamara, J. M. *Tetrahedron Lett.* **2004**, *45*, 8917-8920.

205. Fang, W. S.; Liang, X. T. *Mini-Rev. Med. Chem.* **2005**, *5*, 1-12.

206. Comezoglu, S. N. *PCT Int. Appl.*, WO 2004037211 (A2), **2004**.

207. Ly, V. T.; Caceres-Cortes, J.; Zhang, D.; Humphreys, W. G.; Ekhato, I. V.; Everett, D.; Comezoglu, S. N. *Drug Metab. Dispos.* **2009**, *37*, 1115-1128.

208. Kingston, D. G. I.; Chaudhary, A. G.; Gunatilaka, A. A. L.; Middleton, M. L. *Tetrahedron Lett.* **1994**, *35*, 4483-4484.

209. Bando, K.; Taguchi, K. *Jpn. Kokai Tokkyo Koho*, JP 2009007348 (A), **2009**.

210. Ano, Y.; Tobisu, M.; Chatani, N. *Synlett* **2012**, *23*, 2763-2767.

211. Goto, M.; Tsutsui, H.; Matsuda, S.; Tanaka, Y.; Tsuruda, N.; Kurosaki, H. *Chem. Pharm. Bull.* **2004**, *52*, 47-50.

212. Hecht, S.; Huc, I. *Foldamers: Structure, Properties and Applications*, Wiley-VCH: **2007**, 431 pp.

213. Gellman, S. H. *Acc. Chem. Res.* **1998**, *31*, 173-180.

214. Seebach, D.; Hook, D. F.; Glattli, A. *Biopolymers* **2006**, *84*, 23-37.

215. Angelici, G.; Falini, G.; Hofmann, H.-J.; Huster, D.; Monari, M.; Tomasini, C. *Chem. - Eur. J.* **2009**, *15*, 8037-8048.

216. Tomasini, C.; Trigari, V.; Lucarini, S.; Bernardi, F.; Garavelli, M.; Peggion, C.; Formaggio, F.; Toniolo, C. *Eur. J. Org. Chem.* **2003**, 259-267.

217. Gentilucci, L.; Tolomelli, A.; De, M. R.; Tomasini, C.; Feddersen, S. *Eur. J. Org. Chem.* **2011**, *2011*, 4925-4930.

218. Lucarini, S.; Tomasini, C. *J. Org. Chem.* **2001**, *66*, 727-732.

Curriculum Vitae

Personalia

Gert Callebaut 19.12.1986, Zottegem, Belgium
Groteweg 349
9500 Geraardsbergen, Belgium
0472/40.12.35
Gert.Callebaut@hotmail.be

Education

2004-2009: Ghent University, Belgium
Faculty of Bioscience Engineering
M.Sc. in Bioscience Engineering: Chemistry and Bioprocess Technology
Thesis: "Application of *N*-sulfinyl-α-chloroimines in the synthesis of new analogues of the β-amino acid side chain of taxol"
Promoter: Prof. Dr. ir. Norbert De Kimpe
Co-promoter: Prof. Dr. ir. Sven Mangelinckx

1998-2004: Sint-Jozefsinstituut, Geraardsbergen
Mathematics & Science

Career

2009-2013: Grant holder of the Agency for Innovation by Science and Technology (IWT)
Department of Sustainable Organic Chemistry and Technology
Faculty of Bioscience Engineering
PhD thesis: "Synthesis and applications of chiral *N*-sulfinylimines and -aziridines as versatile building blocks in organic chemistry"
Promoters: Prof. Dr. ir. Norbert De Kimpe
Prof. Dr. ir. Sven Mangelinckx

Publications in International Journals with Peer-Review

1. Mangelinckx, S.; Kadam, S. T.; Semina, E.; **Callebaut, G.**; Colpaert, F.; De Smaele, D.; De Kimpe, N. "Synthesis of *cis*-2-alkoxycyclopropylamines *via* intramolecular cyclization of 2-azaallylic anions derived from alkoxybrominated *N*-(arylidene)-2-methyl-2-propenylamines", Tetrahedron (2013), 69(18), 3728-3735.

2. Zukauskaite, A.; Mangelinckx, S.; **Callebaut, G.**; Wybon, C.; Sackus, A.; De Kimpe, N. "Synthesis of 1,5-diazaspiro[2.3]hexanes, a novel diazaspirocyclic system", Tetrahedron (2013), 69(16), 3437-3443.

3. **Callebaut, G.**; Mangelinckx, S.; Van der Veken, P.; Törnroos, K. W.; Augustyns, K.; De Kimpe, N. "Asymmetric synthesis of γ-chloro-α,β-diamino- and β,γ-aziridine-α-aminoacylpyrrolidines and -piperidines *via* stereoselective Mannich-type additions of *N*-(diphenylmethylene)glycinamides across α-chloro-*N*-sulfinylimines", Beilstein Journal of Organic Chemistry (2012), 8, 2124-2131.

4. **Callebaut, G.**; Mangelinckx, S.; Kiss, L.; Sillanpää, R.; Fülöp, F.; De Kimpe, N. "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", Organic & Biomolecular Chemistry (2012), 10(11), 2326-2338.

5. Aper, J.; Mechant, E.; Rubin, B.; Heyerick, A.; **Callebaut, G.**; Mangelinckx, S.; Deforce, D.; De Kimpe, N.; Bulcke, R.; Reheul, D. "Absorption, translocation and metabolism of metamitron in *Chenopodium album*", Pest Management Science (2012), 68(2), 209-216.

Conferences and Seminars **(the presenting author is underlined)**

1. 16th Sigma Aldrich Organic Synthesis Meeting, December 6-7, 2012, Sol Cress, Spa, Belgium. Poster: **Callebaut, G.**; Mangelinckx, S.; Nonn, M.; Kiss, L.; Törnroos, K. W.; Fülöp,F.; De Kimpe, N. "Asymmetric stereoselective synthesis of γ-chloro-α-hydroxy-β-amino acid derivatives *via* Mannich-type additions of Boc-protected glycolate esters across α-chloro-*N*-sulfinylimines".

2. 13th Belgian Organic Synthesis Symposium (BOSS XIII), July 15-20, 2012, Leuven, Belgium. Poster: **Callebaut, G.**; Mangelinckx, S.; Van der Veken, P.; Törnroos, K. W.; Augustyns, K.; De Kimpe, N. "Asymmetric stereoselective synthesis of γ-chloro-α,β-diamino- and β,γ-aziridino-α-aminoacylpyrrolidines and -piperidines *via* Mannich-type additions of *N*-(diphenylmethylene)glycine amides across α-chloro-*N*-sulfinylimines".

3. COST Action CM0803, Bordeaux 2012 Symposium on Foldamers, January 30-February 2, 2012, Bordeaux-Pessac, France. Lecture: **Callebaut, G.**; Mangelinckx, S.; Kiss, L.; Sillanpää, R.; Fülöp, F.; De Kimpe, N. "Asymmetric synthesis and selective deprotection of γ-chloro-α,β-diamino acid derivatives".

4. 15th Sigma Aldrich Organic Synthesis Meeting, December 1-2, 2011, Sol Cress, Spa, Belgium. Poster: **Callebaut, G.**; Mangelinckx, S.; Kiss, L.; Sillanpää, R.; Fülöp, F.; De Kimpe, N. "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".

5. COST Action CM0803, FOLDAMERS: Synthesis and structure of functional materials, April 7-9, 2011, Barcelona, Spain. Lecture: Mangelinckx, S.; Colpaert, F.; **Callebaut, G.**; De Brabandere, S.; Kiss, L.; Augustyns, K.; Fülöp, F.; De Kimpe, N. "Synthesis of α-, β-, γ-amino acid derivatives with an aziridine skeleton".

6. COST Action CM0803, FOLDAMERS: Synthesis and structure of functional materials, April 7-9, 2011, Barcelona, Spain. Lecture: Nonn, M.; **Callebaut, G.**; Mangelinckx, S.; Kiss, L.; Sillanpää, R.; Fülöp, F.; De Kimpe, N. "Stereoselective Mannich-type reaction

of *O*-protected glycolate esters across *N*-sulfinyl α-chloro aldimines. Synthesis of α-hydroxy-β,γ-aziridino ester derivatives".

7. 14th Sigma Aldrich Organic Synthesis Meeting, December 2-3, 2010, Sol Cress, Spa, Belgium. Poster: **Callebaut, G.**; Mangelinckx, S.; Nonn, M.; Kiss, L.; Fülöp,F.; De Kimpe, N. "Synthesis of α-hydroxy-β,γ-aziridino esters *via* stereoselective Mannich-type addition of Boc-protected glycolate esters across chiral *N*-sulfinyl α-chloroaldimines".

8. COST Action CM0803, FOLDAMERS: Design, Synthesis and Applications, October 6-8, 2010, Bologna, Italy. Lecture: Mangelinckx, S.; **Callebaut, G.**; Colpaert, F.; Kiss, L.; Fülöp, F.; De Kimpe, N. "Application of *N*-sulfinyl imines and imidates in the asymmetric synthesis of β-amino acid derivatives".

9. COST Action CM0803, Foldamers: from design to protein recognition, January 25-28, 2010, Bordeaux-Pessac, France. Lecture: Mangelinckx, S.; Žukauskaite, A.; Buinauskaite, V.; Šačkus, A.; **Callebaut, G.**; Kiss, L.; Fülöp, F.; De Kimpe, N. "Application of allylamines and halogenated imines in the synthesis of conformationally constrained β-amino acid derivatives".

10. 12th Belgian Organic Synthesis Symposium (BOSS XII), July 11-16, 2010, Namen, Belgium. Poster: **Callebaut, G.**; Mangelinckx, S.; Kiss, L.; Fülöp,F.; De Kimpe, N. "Stereoselective synthesis of γ-chloro- α,β-diamino esters and β,γ-aziridino α-amino esters *via* Mannich-type reaction across chiral *N*-sulfinyl α-chloroaldimines".