Organic & Biomolecular Chemistry

PAPER

View Article Online
View Journal | View Issue

Cite this: *Org. Biomol. Chem.*, 2014, **12**, 3393

Asymmetric synthesis of chloroisothreonine derivatives *via syn*-stereoselective Mannich-type additions across *N*-sulfinyl-α-chloroimines†

Gert Callebaut,‡[a] Filip Colpaert,§[a] Melinda Nonn,[b] Loránd Kiss,[b] Reijo Sillanpää,[c] Karl W. Törnroos,[d] Ferenc Fülöp,[b] Norbert De Kimpe[a] and Sven Mangelinckx*[a]

Received 31st January 2014,
Accepted 17th March 2014

DOI: 10.1039/c4ob00243a

www.rsc.org/obc

Mannich-type reactions of *O*-Boc glycolic esters across chiral *N*-sulfinyl-α-chloroaldimines resulted in the efficient and *syn*-stereoselective synthesis of new γ-chloro-α-hydroxy-β-amino esters (dr > 99 : 1). The α-coordinating ability of the chlorine atom was of great importance for the diastereoselectivity of the Mannich-type reaction and overruled the chelation of the sulfinyl oxygen with the lithium ion of the incoming *E*-enolate in the transition state model. These novel chloroisothreonine derivatives proved to be excellent building blocks in asymmetric synthesis of novel *syn*-β,γ-aziridino-α-hydroxy esters and biologically relevant *trans*-oxazolidinone carboxylic esters.

Introduction

The enantioselective synthesis of β-amino acid derivatives, as biologically active compounds, constituents of biologically active natural products, chiral building blocks and monomers for the preparation of β-peptides, received a lot of attention from organic chemists and biochemists.[1] The incorporation of conformationally constrained α- and β-amino acids into biologically active peptides gained great interest in the preparation of peptide-based drug molecules. In particular, much effort has been focused on synthetic methods towards α-hydroxy-β-amino carboxylic acid derivatives.[2] 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 **1**, which is an aminopeptidase inhibitor,[3] paclitaxel **2a** and docetaxel **2b**, both of which are known for their anti-mitotic activity (Fig. 1).[4] The α-hydroxy-β-amino carboxylic acid moiety is also present in the natural product leuhistin, an inhibitor of aminopeptidase M.[5]

The synthesis of non-proteinogenic α-hydroxy-β-amino acids, including norstatine, isoserine and isothreonine derivatives, has attracted much attention, as these compounds give access to new drug candidates and act as valuable biological

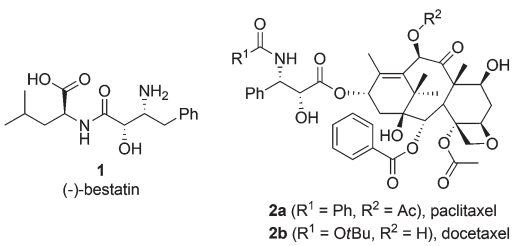


Fig. 1 Biologically active compounds containing an α-hydroxy-β-amino carboxylic acid unit.

[a]*Department of Sustainable Organic Chemistry and Technology, Faculty of Bioscience Engineering, Ghent University, Coupure Links 653, B-9000 Ghent, Belgium. E-mail: Sven.Mangelinckx@UGent.be; Fax: +32 (0)9 264 62 21; Tel: +32 (0)9 264 59 51*

[b]*Institute of Pharmaceutical Chemistry and Stereochemistry Research Group of the Hungarian Academy of Sciences, H-6720, Szeged, Eötvös u. 6, Hungary*

[c]*Department of Chemistry, University of Jyväskylä, Fin-40351 Jyväskylä, Finland*

[d]*Department of Chemistry, University of Bergen, Allégt. 41, N-5007 Bergen, Norway*

†Electronic supplementary information (ESI) available: General experimental conditions and copies of ^{1}H NMR and ^{13}C NMR spectra for ethyl (*tert*-butoxycarbonyloxy)acetate **3c**, γ-chloro-α-hydroxy-β-amino esters (*R*$_S$,2*R*,3*R*)-**5** and (*S*$_S$,2*S*,3*S*)-**5**, *N*-*tert*-butanesulfinyl-β,γ-aziridino-α-hydroxy esters (*R*$_S$,2*R*,2′*S*)-**6**, *N*-*p*-toluenesulfinyl-β,γ-aziridino-α-hydroxy esters (*S*$_S$,2*S*,2′*R*)-**6**, *O*-deprotected (*R*$_S$,2*R*,3*R*)-γ-chloro-α-hydroxy-β-amino ester (*R*$_S$,2*R*,3*R*)-**7**, *N*-deprotected esters (2*R*,3*R*)-**9**, *O*,*N*-deprotected esters (2*R*,3*R*)-**10** and oxazolidinones (4*R*,5*R*)-**11**. Crystallographic data were collected at 123 K with a Nonius-Kappa CCD area detector diffractometer, using graphite-monochromatized Mo-K$_\alpha$ radiation (λ = 0.71073 Å). The structures were solved by direct methods by the use of the SHELXS-97 program and the full-matrix, least-squares refinements on F^2 were also performed using the SHELXL-97 program.[26] The hydrogen atoms were included at fixed distances with the fixed displacement parameters from their host atoms. More details are presented in the Crystallographic Information Format (CIF) files for the X-ray crystal structure of compounds (*S*$_S$,2*S*,3*S*)-**5db**, (*R*$_S$,2*R*,2′*S*)-**6cc** and (*R*$_S$,2*R*,3*R*)-**7ac**. CCDC 977960–977962. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c4ob00243a

‡Grant holder of the Agency for Innovation by Science and Technology in Flanders (IWT).

§Postdoctoral Fellow of the Research Foundation – Vlaanderen (FWO).

probes. Norstatine and its analogues have been used in the synthesis of peptide-based inhibitors of aspartyl proteases such as renin and HIV-1 protease.[6] Halogenated analogues of these non-proteinogenic α-hydroxy-β-amino carboxylic acids are of great interest for the design of new protease inhibitors. Fluoroalkyl isoserine derivatives were synthesized *via* ring opening of the corresponding *cis*-4-(fluoroalkyl)-3-hydroxyazetidin-2-ones.[7] The synthesis of γ-iodo-α-hydroxy-β-amino acid derivatives was also reported starting from aspartic acid *via* a lactone intermediate.[8] Nevertheless, γ-chloro-α-hydroxy-β-amino acid derivatives are virtually unknown in the literature, with the exception of one racemic example of a γ-chloro-γ,γ-difluoro-α-hydroxy-β-amino acid derivative.[7] More recently, in analogy with the synthesis of (3-fluoroalkyl)isoserinates,[7] our research group explored the use of 4-(chloroalkyl)-3-hydroxyazetidin-2-ones in the synthesis of chlorinated α-hydroxy-β-amino acid derivatives.[9] Unfortunately, the chlorinated α-hydroxy-β-amino acid derivatives were only observed as intermediates towards the corresponding ω-alkylaminopentenoates. Therefore, in an effort to synthesize regioisomeric derivatives of the natural product 4-chloro-L-threonine, the present paper deals with the asymmetric synthesis of γ-chloro-α-hydroxy-β-amino acid derivatives, *i.e.* chloroisothreonine derivatives, *via* Mannich-type additions of *O*-Boc glycolic esters across enantiopure *N*-sulfinyl-α-chloroaldimines. 4-Chloro-L-threonine is biologically active as a serine hydroxymethyltransferase inhibitor,[10] and as a herbicidal antimetabolite,[11] and is also a constituent of naturally occurring syringomycins (antifungal compounds),[12] and actinomycins (cytotoxic and antibacterial compounds).[13]

Generally, halogenated amino acid derivatives are biologically relevant compounds, which can also serve as very promising building blocks in synthetic organic chemistry due to the presence of leaving groups. Recently, our research group reported the stereoselective synthesis of γ-chloro α,β-diamino acid derivatives *via* Mannich-type additions of *N*-(diphenylmethylene)glycine esters across α-chloro-*N*-sulfinylimines,[14] and α-chloro β-amino acid derivatives *via* Mannich-type reactions of *N*-sulfinyl imidates with aromatic aldimines.[15] Also γ-chloro-α,β-diamino- and β,γ-aziridino-α-aminoacylpyrrolidines and -piperidines, as potential dipeptidyl peptidase (DPP) inhibitors,[16] were synthesized *via* stereoselective Mannich-type additions of *N*-(diphenylmethylene)glycinamides across α-chloro-*N*-sulfinylimines.[17]

Chiral *N*-sulfinylimines have already proven to be valuable synthons for the preparation of a wide range of enantiopure aliphatic and cyclic amines.[18] In this study, α-chloro *N*-sulfinylaldimines were used as starting products as these imines are known for their good reactivity and stereoselectivity by incorporation of chiral directing groups.[19] In this context, addition reactions across non-halogenated *N*-sulfinylimines were already performed for the asymmetric synthesis of β-amino acid derivatives.[20] In addition, nucleophilic additions across α-chloroimines with different carbon and heteroatom nucleophiles have extensively been used in the past for the synthesis of azaheterocyclic compounds.[9,21]

Results and discussion

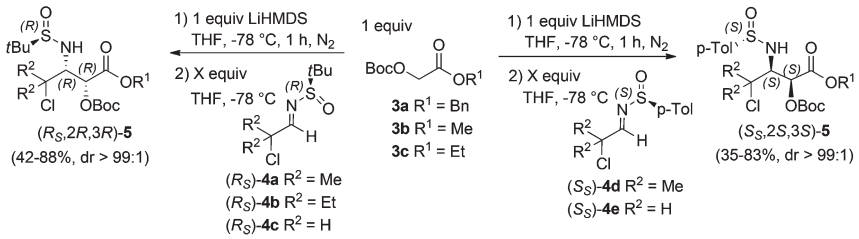
According to the good results obtained in the diastereoselective synthesis of non-functionalized α-hydroxy-β-amino acid derivatives,[20c] the addition of *O*-protected alkyl α-hydroxyacetates **3** across *N*-sulfinyl-α-chloroimines **4** was investigated (Scheme 1, Table 1) in view of providing access to γ-functionalized-α-hydroxy-β-amino acid building blocks, suitable for the synthesis of chloroisothreonine derivatives and functionalized heterocyclic compounds. Therefore, the *O*-protected alkyl α-hydroxyacetates **3**,[20c] α-chloro *N*-*tert*-butanesulfinylaldimines **4a–c**,[19f,g] and α-chloro *N*-*p*-toluenesulfinylaldimines **4d–e**[14,17] were synthesized *via* (modified) literature procedures.

In the first step, *O*-Boc alkyl α-hydroxyacetates **3a–c** were deprotonated using LiHMDS and subsequent addition of 0.20 equivalents of (R_S)-*N*-(*tert*-butanesulfinyl)-2-chloro-2,2-dimethylacetaldimine (R_S)-**4a** at −78 °C for 3 hours resulted in the formation of Mannich-type addition products (R_S)-**5aa–ac** in good to excellent diastereomeric ratios (Scheme 1, Table 1, entries 1–3). γ-Chloro-α-hydroxy-β-amino esters (R_S,2*R*,3*R*)-**5aa–ac** were isolated as single *syn*-diastereomers in high yields (75–88%) after purification *via* flash chromatography.

Furthermore, to expand the scope, the use of *N*-(*tert*-butanesulfinyl)-α-chloroaldimines (R_S)-**4b–c** was explored. Performing the Mannich-type addition with *N*-(*tert*-butanesulfinyl)-2-chloro-2,2-diethylacetaldimine (R_S)-**4b**, the desired adducts (R_S)-**5ba–bc** were formed with excellent *syn*-diastereoselectivity (Table 1, entries 4–6). After purification *via* flash chromatography, single *syn*-diastereomers of γ-chloro-α-hydroxy-β-amino esters (R_S)-**5ba–bc** were isolated, although in moderate yields (44–65%). These lower yields were obtained due to the concomitant formation of the corresponding aziridines (R_S)-**6ba–bc**, resulting in a more tedious separation *via* flash chromatography. In the case of the Mannich-type adduct (R_S)-**5bb**, which was isolated in 44% yield, the corresponding aziridine (R_S)-**6bb** was also isolated in 13% yield (Table 1, entry 5).

Surprisingly, when *N*-(*tert*-butanesulfinyl)-α-chloroaldimine (R_S)-**4c** was used in the Mannich-type addition with benzyl ester **3a**, formation of the desired Mannich-type adduct could not be observed (Table 1, entry 7). The Mannich-type addition of aldimine (R_S)-**4c** with methyl and ethyl esters **3b–c** occurred with excellent *syn*-diastereoselectivity (Table 1, entries 8–9). Nevertheless, the reaction time was limited to 1 hour, as longer reaction times resulted in lower yields, due to the instability of aldimine (R_S)-**4c**. Single *syn*-diastereomers of chloroisothreonine derivatives (R_S)-**5cb–cc** were isolated in moderate yield (42%) after purification *via* flash chromatography (Table 1, entries 8–9).

The high reactivity and *syn*-diastereoselectivity observed in the Mannich-type additions of Li-enolates derived from *O*-Boc alkyl α-hydroxyacetates **3a–c** across *N*-(*tert*-butanesulfinyl)-α-chloroaldimines (R_S)-**4** prompted the further investigation of the Mannich-type additions across *N*-(*p*-toluenesulfinyl)-α-chloroaldimines (S_S)-**4d** and (S_S)-**4e**, which were reacted under similar conditions. Using (S_S)-*N*-(*p*-toluenesulfinyl)-α-chloroaldimine (S_S)-**4d**, the desired γ-chloro-α-hydroxy-



Scheme 1 Synthesis of chloroisothreonine derivatives **5**.

Table 1 Mannich-type addition reactions of α-hydroxyacetates **3** across (*R*$_S$)-*N*-(*tert*-butanesulfinyl)-α-chloroaldimines **4a–c** and (*S*$_S$)-*N*-(*p*-toluenesulfinyl)-α-chloroaldimines **4d–e**

Entry	R^1	R^2	X	**4**	Time (h)	*syn*/*anti*[a]	Yield **5**[b] (%)
1	Bn	Me	0.20	(*R*$_S$)-**4a**	3	80/20	(*R*$_S$,2*R*,3*R*)-**5aa** (75)
2	Me	Me	0.20	(*R*$_S$)-**4a**	3	98/2	(*R*$_S$,2*R*,3*R*)-**5ab** (86)
3	Et	Me	0.20	(*R*$_S$)-**4a**	3	89/11	(*R*$_S$,2*R*,3*R*)-**5ac** (88)
4	Bn	Et	0.33	(*R*$_S$)-**4b**	4	>99/1	(*R*$_S$,2*R*,3*R*)-**5ba** (62)
5	Me	Et	0.33	(*R*$_S$)-**4b**	4	>99/1	(*R*$_S$,2*R*,3*R*)-**5bb** (44)[c]
6	Et	Et	0.33	(*R*$_S$)-**4b**	4	>99/1	(*R*$_S$,2*R*,3*R*)-**5bc** (65)
7	Bn	H	0.25	(*R*$_S$)-**4c**	1–4	—	(*R*$_S$,2*R*,3*R*)-**5ca** (–)
8	Me	H	0.25	(*R*$_S$)-**4c**	1	>99/1	(*R*$_S$,2*R*,3*R*)-**5cb** (42)
9	Et	H	0.25	(*R*$_S$)-**4c**	1	>99/1	(*R*$_S$,2*R*,3*R*)-**5cc** (42)
10	Bn	Me	0.20	(*S*$_S$)-**4d**	5	95/5	(*S*$_S$,2*S*,3*S*)-**5da** (51)
11	Me	Me	0.20	(*S*$_S$)-**4d**	5	87/13	(*S*$_S$,2*S*,3*S*)-**5db** (83)
12	Et	Me	0.20	(*S*$_S$)-**4d**	5	82/18	(*S*$_S$,2*S*,3*S*)-**5dc** (75)
13	Bn	H	0.33	(*S*$_S$)-**4e**	4	—	(*S*$_S$,2*S*,3*S*)-**5ea** (–)
14	Et	H	0.33	(*S*$_S$)-**4e**	4	>99/1	(*S*$_S$,2*S*,3*S*)-**5ec** (35)

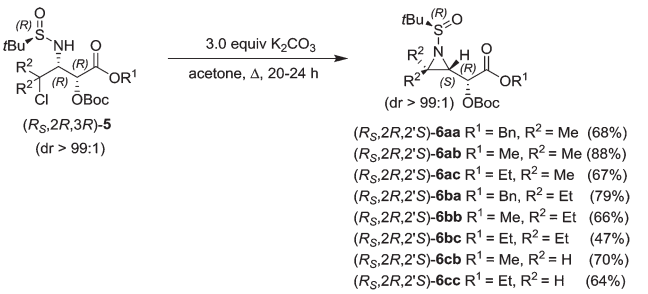
[a] Determined *via* ^{1}H NMR analysis of the crude reaction mixture. [b] Isolated yield of a single diastereomer (dr > 99 : 1) after purification *via* flash chromatography. [c] The corresponding aziridine **6bb** was also formed and isolated in 13% yield.

β-amino esters (*S*$_S$)-**5da–dc** were formed in good to excellent diastereomeric ratios (Table 1, entries 10–12). Purification *via* flash chromatography afforded the pure chloroisothreonine derivatives (*S*$_S$)-**5da–dc** as single *syn*-diastereomers in moderate to high yields (51–83%).

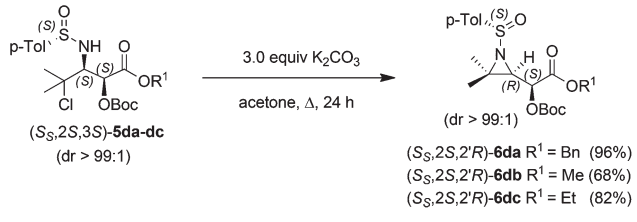
When *N*-(*p*-toluenesulfinyl)-α-chloroaldimine (*S*$_S$)-**4e** was applied, again no formation of the desired adduct (*S*$_S$)-**5ea** was observed (Table 1, entry 13). Due to the high instability of aldimine (*S*$_S$)-**4e**, the Mannich-type addition with ethyl ester **3c** afforded the desired γ-chloro-α-hydroxy-β-amino esters (*S*$_S$)-**5ec** in moderate yield, although with an excellent *syn*-diastereoselectivity (Table 1, entry 14).

The γ-chloro-α-hydroxy-β-sulfinylamino esters (*R*$_S$,2*R*,3*R*)-**5** and (*S*$_S$,2*S*,3*S*)-**5da–dc** were subsequently cyclized to the corresponding *N*-*tert*-butanesulfinyl-β,γ-aziridino-α-hydroxy esters (*R*$_S$,2*R*,2′*S*)-**6** and *N*-*p*-toluenesulfinyl-β,γ-aziridino-α-hydroxy esters (*S*$_S$,2*S*,2′*R*)-**6**, respectively, upon treatment with K_2CO_3 in acetone under reflux in good to excellent yields (47–96%) and all with an excellent diastereoselectivity (dr > 99 : 1) (Schemes 2 and 3).

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*)-**5** as building blocks in biomedicinal chemistry, a number of attempts were made to remove the protective groups of (*R*$_S$,2*R*,3*R*)-**5** under acidic conditions (Scheme 4). In the first step, α-hydroxy-β-amino esters (*R*$_S$,2*R*,3*R*)-**5aa–ac** and

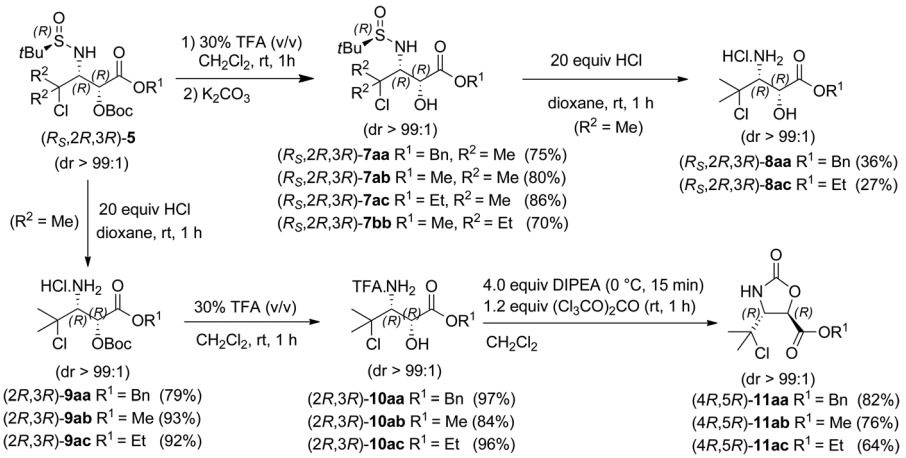


Scheme 2 Synthesis of *N*-*tert*-butanesulfinyl-β,γ-aziridino-α-hydroxy esters (*R*$_S$,2*R*,2′*S*)-**6**.



Scheme 3 Synthesis of *N*-*p*-toluenesulfinyl-β,γ-aziridino-α-hydroxy esters (*S*$_S$,2*S*,2′*R*)-**6**.

(*R*$_S$,2*R*,3*R*)-**5bb** were treated with trifluoroacetic acid (30% v/v) in dichloromethane. After a basic workup with K_2CO_3, the desired α-deprotected *syn*-γ-chloro-α-hydroxy-β-amino esters



Scheme 4 Further transformations of chloroisothreonine derivatives (*R*$_S$,2*R*,3*R*)-**5** and synthesis of oxazolidinones (4*R*,5*R*)-**11**.

(*R*$_S$,2*R*,3*R*)-**7** were purified by crystallization in Et_2O or by flash chromatography on silica gel (70–86% yield) (Scheme 4). Hereby, a selective deprotection of the *O*-Boc-protecting group with TFA occurred in the presence of an *N*-*tert*-butanesulfinyl moiety. Moreover, the *O*-deprotected (*R*$_S$,2*R*,3*R*)-γ-chloro-α-hydroxy-β-amino ester (*R*$_S$,2*R*,3*R*)-**7ac** was isolated as a crystalline product which allowed the implementation of X-ray diffraction analysis (*vide infra*).

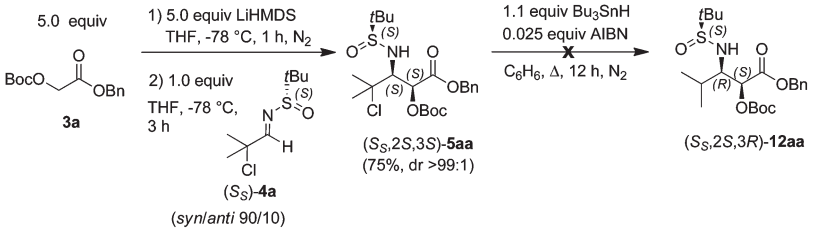
In the next step, the *N*-*tert*-butanesulfinyl group of the *O*-deprotected chloroisothreonine derivatives (*R*$_S$,2*R*,3*R*)-**7aa** and **7ac** was deprotected by reaction with a saturated HCl-solution in dioxane towards the *N*,*O*-deprotected γ-chloro-α-hydroxy-β-amino esters (*R*$_S$,2*R*,3*R*)-**8aa** and **8ac** (Scheme 4). Unfortunately, intensive screening of different purification techniques (crystallization, preparative TLC, acid–base extraction) in order to obtain the pure *N*,*O*-deprotected esters (*R*$_S$,2*R*,3*R*)-**8aa** and **8ac** in good yield was only partially successful, affording 27–36% yield of (*R*$_S$,2*R*,3*R*)-**8aa** and **8ac** after crystallization in dichloromethane.

Alternatively, a selective deprotection of the *N*-*tert*-butanesulfinyl group of (*R*$_S$,2*R*,3*R*)-γ-chloro-α-hydroxy-β-amino esters (*R*$_S$,2*R*,3*R*)-**5aa–ac** was performed under mild acidic treatment with HCl in dioxane, leading to *N*-deprotected (2*R*,3*R*)-γ-chloro-α-hydroxy-β-amino esters (2*R*,3*R*)-**9aa–ac** in high yields (79–93%) (Scheme 4). In the next step, deprotection of the *O*-Boc protective group of esters (2*R*,3*R*)-**9aa–ac** was realized by stirring in dichloromethane/trifluoroacetic acid (30% v/v), resulting in the isolation of *O*,*N*-deprotected (2*R*,3*R*)-γ-chloro-α-hydroxy-β-amino ester salts (2*R*,3*R*)-**10aa–ac** as pure products in excellent yields (84–97% yield). In this way, a straightforward route towards the enantioselective synthesis of the *O*,*N*-deprotected chloroisothreonine derivatives (2*R*,3*R*)-**10aa–ac** starting from the esters (*R*$_S$,2*R*,3*R*)-**5** was developed (Scheme 4).

Furthermore, additional reactions were performed in order to synthesize oxazolidinones (4*R*,5*R*)-**11**. The *N*,*O*-deprotected ester salts (2*R*,3*R*)-**10aa–ac** were treated with *N*,*N*-diisopropylethylamine (DIPEA) in dichloromethane for 15 minutes at 0 °C to neutralize the trifluoroacetic acid salt (Scheme 4). Dropwise addition of triphosgene[22] resulted in the formation of the corresponding oxazolidinones (4*R*,5*R*)-**11aa–ac** in good isolated yields (64–82%) (Scheme 4).

Upon determination of the relative configuration of the synthesized γ-chloro-α-hydroxy-β-*N*-*tert*-butanesulfinylamino esters (*R*$_S$)-**5**, based on ^{1}H NMR analysis, it was observed that the isolated major diastereomers were *syn*-adducts, by comparison of the characteristic vicinal coupling constants ($^3J_{H2-H3,syn}$ = 0–1.4 Hz), whereas the corresponding *anti*-adducts have larger coupling constants ($^3J_{H2-H3,anti}$ > 2.5 Hz).[20c] Unfortunately, it was impossible to determine the absolute stereochemistry of these *syn*-adducts (*R*$_S$)-**5** 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*$_S$)-**5aa** was synthesized by Mannich-type addition of the Li-enolate derived from the *O*-Boc benzyl α-hydroxyacetate **3a** across (*S*$_S$)-*N*-(*tert*-butanesulfinyl)-α-chloroaldimine (*S*$_S$)-**4a** under the same reaction conditions as described in Table 1 (Scheme 2). 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*)-**12aa** is known from the literature,[23] the reaction of compound (*S*$_S$)-**5aa** with Bu_3SnH and AIBN was attempted (Scheme 5). Unfortunately, this reaction failed to provide the desired dechlorinated compound (*S*$_S$,2*S*,3*R*)-**12aa**, which would have allowed the determination of the absolute stereochemistry of (*S*$_S$)-**5aa** by comparison of the optical rotation. Additionally, having both enantiomers (*R*$_S$,2*S*,3*R*)-**5aa** and (*S*$_S$,2*R*,3*S*)-**5aa** in hand, an enantiomeric excess of >98% for both enantiomers could be determined by chiral HPLC. In analogy with an enantiomeric excess of >98% for the commercially available starting materials *tert*-butanesulfinamide and *p*-toluenesulfinamide, an enantiomeric excess of >98% can be concluded for all synthesized γ-chloro-α-hydroxy-β-amino acid derivatives **5**.

However, the absolute stereochemistry of the chloroisothreonine derivative (*R*$_S$)-**5ac** was determined by means of



Scheme 5 Synthesis of (S_S)-γ-chloro-α-hydroxy-β-amino ester (S_S,2*S*,3*S*)-**5aa** and an attempt for further dechlorination towards (S_S,2*S*,3*R*)-**12aa**.

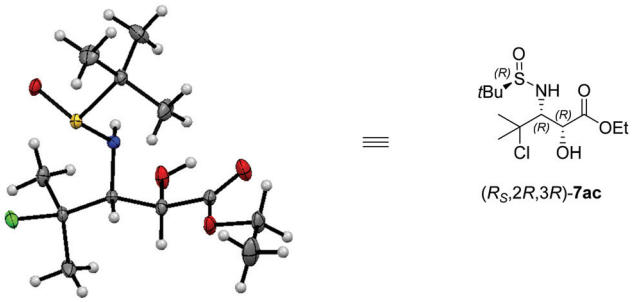


Fig. 2 X-ray crystal structure of (R_S,2*R*,3*R*)-γ-chloro-α-hydroxy-β-amino ester (R_S,2*R*,3*R*)-**7ac**.

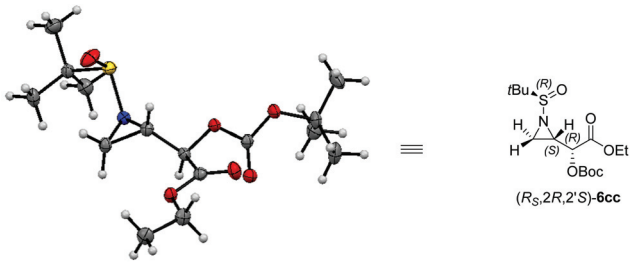
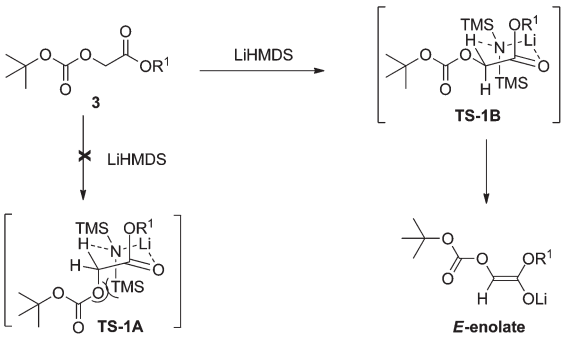


Fig. 3 X-ray crystal structure of *N*-*tert*-butanesulfinyl-β,γ-aziridino-α-hydroxy ester (R_S,2*R*,2′*S*)-**6cc**.

X-ray diffraction analysis (Fig. 2) of the corresponding crystalline (R_S,2*R*,3*R*)-*O*-deprotected derivative (R_S,2*R*,3*R*)-**7ac** (*vide supra*). The (R_S,2*R*,3*R*)-stereochemistry of the synthesized (R_S)-γ-chloro-α-hydroxy-β-amino esters (R_S)-**5aa–ab** was deduced from the vicinal coupling constant $^3J_{H2-H3,syn}$ = 1.0–1.3 Hz and the ^{1}H NMR chemical shift of H3 (4.01 ppm; $CDCl_3$), which were in the same range as for the (R_S)-γ-chloro-α-hydroxy-β-amino ester (R_S)-**5ac**. Also a (R_S,2*R*,3*R*)-stereochemistry could be ascribed to 4,4-diethyl-substituted (R_S)-γ-chloro-α-hydroxy-β-amino esters (R_S)-**5ba–bc** in analogy with their 4,4-dimethyl substituted derivatives (R_S)-**5aa–ac**.

The same absolute (R_S,2*R*,3*R*)-stereochemistry was confirmed for chloroisothreonine derivatives (R_S)-**5cb–cc** (R^2 = H) by means of an X-ray diffraction analysis of the corresponding crystalline *N*-*tert*-butanesulfinyl-β,γ-aziridino-α-hydroxy ester (R_S,2*R*,2′*S*)-**6cc** (Fig. 3).

The stereochemical outcome of the Mannich-type reaction across (R_S)-*N*-(*tert*-butanesulfinyl)-α-chloroaldimine (R_S)-**4a** was

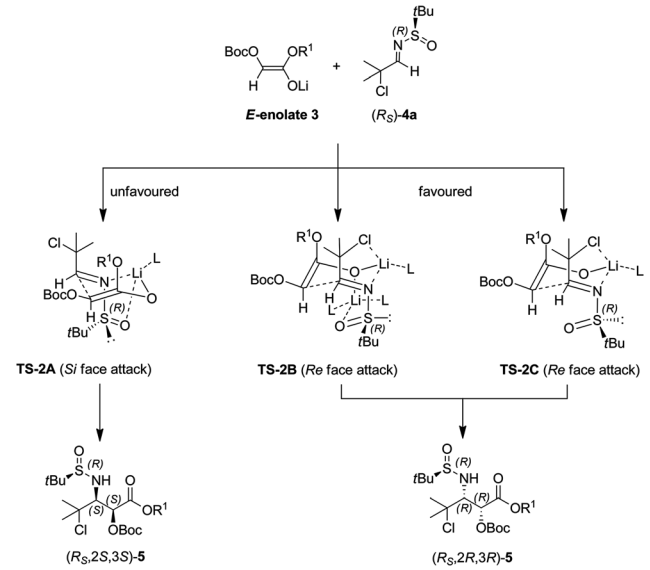


Scheme 6 Proposed transition state model for rationalization of the enolate geometry of *O*-Boc alkyl α-hydroxyacetates **3**.

rationalized on the basis of the enolate geometry of the anions derived from the deprotonation of *O*-Boc alkyl α-hydroxyacetates **3**. Enolates obtained *via* deprotonation of *O*-Boc alkyl α-hydroxyacetates **3** with LiHMDS in THF were expected to have the *E*-geometry (Scheme 6).[20c,24] As commonly performed in the assignment of enolate geometry, in contrast to the 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,[24] which showed that deprotonation of *O*-Boc alkyl α-hydroxyacetates **3** with LiHMDS *via* the transition state **TS-1A** induced adverse steric interactions of the axial TMS group and the O-Boc group. For this reason, the deprotonation proceeded *via* the transition state **TS-1B** and afforded the corresponding *E*-enolate (Scheme 6).

Reaction of the *E*-enolates of **3** *via* a six/four-membered Li-chelated bicyclic chairlike transition state model **TS-2A**, which was valid for Mannich-type additions across non-functionalized *N*-sulfinyl imines,[20c] 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*)-**5** (Scheme 7). However, this transition state model **TS-2A**, 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*)-**5** can be explained by a six/six-membered di-metal-chelated bicyclic chairlike transition state model **TS-2B**,[25] or by a six-membered Li-chelated cyclic chairlike



Scheme 7 Proposed transition state model for the Mannich-type addition reactions of *O*-Boc alkyl α-hydroxyacetates **3** across (*R*$_S$)-*N*-(*tert*-butanesulfinyl)-α-chloroaldimine (*R*$_S$)-**4a**.

transition state model **TS-2C** both of which proceeded *via* a *Re*-face attack of the *E*-enolate (Scheme 7).

In the transition state model **TS-2B**, the α-coordinating ability of the chlorine atom overrides 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-2C**, the coordinating ability of the chlorine atom overrules the chelation of the sulfinyl oxygen as well and an extra stabilizing effect is attained by the fact that the *N*-sulfinyl imine (*R*$_S$)-**4a** in this transition state is present in the energetically favoured s-*cis* configuration.[18b]

Concerning the γ-chloro-α-hydroxy-β-*N*-*tert*-butanesulfinylamino esters (*R*$_S$)-**5**, the major diastereomers of γ-chloro-α-hydroxy-β-*N*-*p*-toluenesulfinylamino esters (*S*$_S$)-**5** were assigned as *syn*-adducts based on ^{1}H NMR analysis. According to these transition state models **TS-2B** and **TS-2C** (Scheme 7), it was assumed that the Mannich-type addition products (*S*$_S$)-**5** would have an (*S*$_S$,2*S*,3*S*)-stereochemistry. Indeed, determination of the absolute stereochemistry of the crystalline chloroisothreonine derivative (*S*$_S$)-**5db** by means of X-ray diffraction analysis proved this assumption (Fig. 4). The (*S*$_S$,2*S*,3*S*)-stereochemistry of the other (*S*$_S$)-γ-chloro-α-hydroxy-β-amino esters (*S*$_S$)-**5da** and (*S*$_S$)-**5dc** was again confirmed by comparison of the vicinal coupling constant $^3J_{H2-H3}$ = 1.10 Hz and the ^{1}H NMR chemical shift of H3 (4.00 ppm), which were in the same range as for the (*S*$_S$)-γ-chloro-α-hydroxy-β-amino ester (*S*$_S$)-**5db**.

The absolute (*S*$_S$,2*S*,3*S*)-stereochemistry could be also ascribed for (*S*$_S$)-γ-chloro-α-hydroxy-β-amino esters (*S*$_S$)-**5eb–ec** (R^2 = H) in analogy with the assigned stereochemistry of (*R*$_S$)-γ-chloro-α-hydroxy-β-amino esters (*R*$_S$)-**5cb–cc** (R^2 = H).

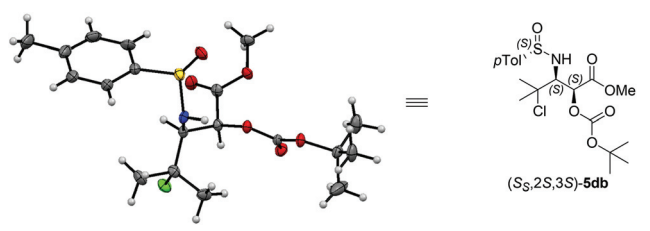


Fig. 4 X-ray crystal structure of (*S*$_S$,2*S*,3*S*)-γ-chloro-α-hydroxy-β-amino ester (*S*$_S$,2*S*,3*S*)-**5db**.

Conclusions

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 were synthesized in high yields and excellent diastereomeric ratios (dr > 99 : 1) *via* stereoselective Mannich-type reactions of *O*-Boc glycolic esters across chiral *N*-sulfinyl-α-chloroimines. In these reactions, the influence of the imine on 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, as novel chloroisothreonine derivatives, proved to be versatile building blocks in asymmetric synthesis of novel *syn*-β,γ-aziridino-α-hydroxy esters and *trans*-alkyl oxazolidinone-5-carboxylates.

Experimental section

Synthesis of alkyl (*tert*-butoxycarbonyloxy)acetates 3

Benzyl and methyl (*tert*-butoxycarbonyloxy)acetates **3a–b** were synthesized according to the literature starting from the corresponding benzyl and methyl α-hydroxyacetates.[20c] In a flame dried round-bottomed 250 mL flask, ethyl α-hydroxyacetate (1.0 equiv., 4.00 g, 38.42 mmol) was dissolved in acetonitrile (150 mL). Subsequently, DMAP (0.1 equiv., 0.43 g, 3.84 mmol) and Boc_2O (3.0 equiv., 10.90 g, 49.95 mmol) were added and the mixture was stirred for 18 hours at room temperature. The reaction mixture was poured into brine (300 mL) and the aqueous phase was extracted with diethyl ether (3 × 200 mL). The combined organic phases were dried ($MgSO_4$), filtered and evaporated *in vacuo* to yield 7.68 g (37.65 mmol, 98%) of ethyl (*tert*-butoxycarbonyloxy)acetate **3c**. Ethyl (*tert*-butoxycarbonyloxy)acetate **3c** was stored with molecular sieves for further use.

Ethyl (*tert*-butoxycarbonyloxy)acetate 3c. Brown oil, 98% (7.68 g). IR (cm^{-1}): 1745, ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.29 (3H, t, *J* = 7.15 Hz), 1.51 (9H, s), 4.25 (2H, q, *J* = 7.15 Hz), 4.56 (2H, s). ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.1, 27.7 (3C), 61.5, 62.8, 83.2, 153.0, 167.9, MS (ES$^+$): *m*/*z* (%): 527 (100), 427 (77), 222 (M + NH_4^+, 50). HRMS (ES) calcd for $C_9H_{16}O_5$: 205.1071 MH$^+$; found: 205.1082.

Synthesis of γ-chloro-α-hydroxy-β-amino esters 5

The synthesis of (*R*$_S$,2*R*,3*R*)-benzyl 2-(*tert*-butoxycarbonyloxy)-4-chloro-4-methyl-3-(*tert*-butanesulfinylamino)pentanoate **5aa** is a representative. A similar procedure was used for the synthesis of γ-chloro-α-hydroxy-β-amino esters **5**, using the amounts of reagents and the exact reaction time as depicted in Table 1. In a flame dried round-bottomed 250 mL flask, benzyl (*tert*-butoxycarbonyloxy)acetate **3a** (1.0 equiv., 3.00 g, 11.13 mmol) was dissolved in anhydrous THF (40 mL) under a N_2 atmosphere. Subsequently, the reaction mixture was cooled to −78 °C and a 1 M solution of LiHMDS in THF (1.0 equiv., 11.13 mL, 11.13 mmol) was added dropwise and the mixture was stirred for 1 hour at −78 °C. After deprotonation, *N*-(*tert*-butanesulfinyl)-α-chloroaldimine (*R*$_S$)-**4a** (0.20 equiv., 0.34 g, 2.26 mmol) in THF (10 mL) was added dropwise. The reaction mixture was stirred for 3 hours at −78 °C and quenched at −78 °C with a saturated aqueous solution of NH_4Cl (50 mL). After 2 minutes, the cooling bath was removed and the temperature was slowly increased to room temperature. The aqueous phase of the mixture was extracted with EtOAc (3 × 100 mL). The combined organic phases were dried ($MgSO_4$), filtered and evaporated *in vacuo*. The crude product was purified *via* flash chromatography to yield 0.80 g (1.70 mmol, 75%) of pure (*R*$_S$,2*R*,3*R*)-benzyl 2-(*tert*-butoxycarbonyloxy)-4-chloro-4-methyl-3-(*tert*-butanesulfinylamino)-pentanoate **5aa**.

(*R*$_S$,2*R*,3*R*)-Benzyl 2-(*tert*-butoxycarbonyloxy)-4-chloro-4-methyl-3-(*tert*-butanesulfinylamino)pentanoate 5aa. R_f = 0.20 (petroleum ether–EtOAc: 5/4). Brown oil, 75% (0.80 g). $[\alpha]_D$ −8.5 (*c* 0.4, $CHCl_3$). ee > 98%, HPLC Daicel Chiralcel OD-H column: hexane (99%)–EtOH (1%), 1.0 mL min^{-1}, 35 °C, t_R (*R*$_S$,2*R*,3*R*)-**5aa** = 21.77 min, (*S*$_S$,2*S*,3*S*)-**5aa** = 29.27 min. IR (cm^{-1}): 3333, 1745, ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.13 (9H, s), 1.47 (9H, s), 1.67 (3H, s), 1.81 (3H, s), 3.96 (1H, d, *J* = 10.5 Hz), 4.01 (1H, d × d, *J* = 10.5, 1.3 Hz), 5.12 (1H, d, *J* = 12.1 Hz), 5.19 (1H, d, *J* = 12.1 Hz), 5.65 (1H, d, *J* = 1.3 Hz), 7.33–7.39 (5H, m). ^{13}C NMR (75 MHz, $CDCl_3$): δ 22.6 (3C), 27.7 (3C), 29.8, 31.5, 57.2, 66.0, 67.7, 70.6, 74.3, 83.6, 128.5 (2C), 128.7 (3C), 134.7, 152.3, 168.3. MS (ES$^+$): *m*/*z* (%): 476/478 (M + H$^+$, 100). HRMS (ES) calcd for $C_{22}H_{34}ClNO_6S$: 476.1862 MH$^+$; found: 476.1876/478.1847.

(*S*$_S$,2*S*,3*S*)-Benzyl 2-(*tert*-butoxycarbonyloxy)-4-chloro-4-methyl-3-(*tert*-butanesulfinylamino)pentanoate 5aa. R_f = 0.20 (petroleum ether–EtOAc: 5/4). Brown oil, 75% (0.47 g). $[\alpha]_D$ +7.2 (*c* 0.3, $CHCl_3$). ee > 98%, HPLC Daicel Chiralcel OD-H column: hexane (99%)–EtOH (1%), 1.0 mL min^{-1}, 35 °C, t_R (*R*$_S$,2*R*,3*R*)-**5aa** = 21.77 min, (*S*$_S$,2*S*,3*S*)-**5aa** = 29.27 min. IR (cm^{-1}): 1745. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.13 (9H, s), 1.47 (9H, s), 1.67 (3H, s), 1.81 (3H, s), 3.96 (1H, d, *J* = 10.5 Hz), 4.02 (1H, d × d, *J* = 10.5, 1.4 Hz), 5.12 (1H, d, *J* = 12.1 Hz), 5.20 (1H, d, *J* = 12.1 Hz), 5.65 (1H, d, *J* = 1.4 Hz), 7.33–7.39 (5H, m). ^{13}C NMR (75 MHz, $CDCl_3$): δ 22.6 (3C), 27.7 (3C), 29.8, 31.5, 57.2, 66.0, 67.7, 70.6, 74.3, 83.6, 128.5 (2C), 128.7 (3C), 134.7, 152.2, 168.3. MS (ES$^+$): *m*/*z* (%): 476/478 (M + H$^+$, 100). HRMS (ES) calcd for $C_{22}H_{34}ClNO_6S$: 476.1862 MH$^+$; found: 476.1883/478.1854.

(*R*$_S$,2*R*,3*R*)-Methyl 2-(*tert*-butoxycarbonyloxy)-4-chloro-4-methyl-3-(*tert*-butanesulfinylamino)pentanoate 5ab. R_f = 0.28 (petroleum ether–EtOAc: 5/4). Yellow solid, 86% (0.89 g). $[\alpha]_D$ −6.5 (*c* 0.3, $CHCl_3$). Mp. 118.5–118.9 °C. IR (cm^{-1}): 1733. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.20 (9H, s), 1.51 (9H, s), 1.68 (3H, s), 1.82 (3H, s), 3.76 (3H, s), 3.94 (1H, d, *J* = 10.5 Hz), 4.01 (1H, d × d, *J* = 10.5, 1.0 Hz), 5.64 (1H, d, *J* = 1.0 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 22.6 (3C), 27.7 (3C), 29.7, 31.5, 52.7, 57.2, 66.1, 70.5, 74.2, 83.6, 152.3, 168.9. MS (ES$^+$): *m*/*z* (%): 400/402 (M + H$^+$, 100). Anal. Calcd for $C_{16}H_{30}ClNO_6S$: C 48.05; H 7.56; N 3.50, Found: C 48.27; H 7.83; N 3.59.

(*R*$_S$,2*R*,3*R*)-Ethyl 2-(*tert*-butoxycarbonyloxy)-4-chloro-4-methyl-3-(*tert*-butanesulfinylamino)pentanoate 5ac. R_f = 0.34 (petroleum ether–EtOAc: 5/4). Yellow solid, 88% (0.77 g). $[\alpha]_D$ −2.3 (*c* 0.4, $CHCl_3$). Mp. 73.6–74.4 °C. IR (cm^{-1}): 3325, 1743, 1726. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.20 (9H, s), 1.30 (3H, t, *J* = 7.2 Hz), 1.50 (9H, s), 1.68 (3H, s), 1.82 (3H, s), 3.96 (1H, d, *J* = 10.5 Hz), 4.00 (1H, d × d, *J* = 10.5, 1.1 Hz), 4.19 (1H, d × q, *J* = 10.9, 7.2 Hz), 4.21 (1H, d × q, *J* = 10.9, 7.2 Hz), 5.59 (1H, d, *J* = 1.1 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.1, 22.6 (3C), 27.7 (3C), 29.7, 31.5, 57.2, 62.0, 66.0, 70.6, 74.2, 83.4, 152.3, 168.4. MS (ES$^+$): *m*/*z* (%): 414/416 (M + H$^+$, 100). Anal. Calcd for $C_{17}H_{32}ClNO_6S$: C 49.32; H 7.79; N 3.38. Found: C 49.66; H 7.87; N 3.51.

(*R*$_S$,2*R*,3*R*)-Benzyl 2-(*tert*-butoxycarbonyloxy)-4-chloro-4-ethyl-3-(*tert*-butanesulfinylamino)hexanoate 5ba. R_f = 0.27 (petroleum ether–EtOAc: 5/1). Yellow oil, 62% (0.85 g). $[\alpha]_D$ −17.8 (*c* 0.3, $CHCl_3$). IR (cm^{-1}): 1737, 1280, 1241, 1046. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.98 (3H, t, *J* = 7.2 Hz), 1.03 (3H, t, *J* = 7.2 Hz), 1.13 (9H, s), 1.47 (9H, s), 1.87–2.11 (4H, m), 4.09 (1H, d, *J* = 10.2 Hz), 4.17 (1H, d, *J* = 10.2 Hz), 5.10 (1H, d, *J* = 12.1 Hz), 5.22 (1H, d, *J* = 12.1 Hz), 5.54 (1H, s (br)), 7.31–7.39 (5H, m). ^{13}C NMR (75 MHz, $CDCl_3$): δ 8.6 (2C), 22.6 (3C), 29.7 (3C), 30.0, 30.3, 57.1, 62.2, 67.7, 73.6, 79.1, 83.4, 128.5 (2C), 128.6 (3C), 134.8, 152.5, 168.5, MS (ES$^+$): *m*/*z* (%): 504/506 (M + H$^+$, 100). HRMS (ES) calcd for $C_{24}H_{38}ClNO_6S$: 504.2175 MH$^+$; found: 504.2177/506.2148.

(*R*$_S$,2*R*,3*R*)-Methyl 2-(*tert*-butoxycarbonyloxy)-4-chloro-4-ethyl-3-(*tert*-butanesulfinylamino)hexanoate 5bb. R_f = 0.22 (petroleum ether–EtOAc: 5/1). Yellow solid, 44% (0.70 g). $[\alpha]_D$ −39.4 (*c* 0.6, $CHCl_3$). Mp. 78.5–81.5 °C. IR (cm^{-1}): 1736, 1247, 1077. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.99 (3H, t, *J* = 7.2 Hz), 1.04 (3H, t, *J* = 7.2 Hz), 1.21 (9H, s), 1.50 (9H, s), 1.86–2.14 (4H, m), 3.76 (3H, s), 4.09 (1H, d, *J* = 9.9 Hz), 4.16 (1H, d, *J* = 9.9 Hz), 5.54 (1H, s (br)). ^{13}C NMR (75 MHz, $CDCl_3$): δ 8.6 (2C), 22.7 (3C), 27.7 (3C), 30.0, 30.3, 53.0, 57.1, 62.2, 73.5, 79.0, 83.4, 152.6, 169.2, MS (ES$^+$): *m*/*z* (%): 428/430 (M + H$^+$, 100). HRMS (ES) calcd for $C_{18}H_{34}ClNO_6S$: 428.1862 MH$^+$; found: 428.1849/430.1820.

(*R*$_S$,2*R*,3*R*)-Ethyl 2-(*tert*-butoxycarbonyloxy)-4-chloro-4-ethyl-3-(*tert*-butanesulfinylamino)hexanoate 5bc. R_f = 0.19 (petroleum ether–EtOAc: 3/1). Yellow oil, 65% (1.20 g). $[\alpha]_D$ −36.7 (*c* 0.8, $CHCl_3$). IR (cm^{-1}): 1737, 1240, 1046. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.99 (3H, t, *J* = 7.2 Hz), 1.04 (3H, t, *J* = 7.2 Hz), 1.22 (9H, s), 1.30 (3H, t, *J* = 7.2 Hz), 1.50 (9H, s), 1.86–2.13 (4H, m), 4.09–4.29 (4H, m), 5.49 (1H, s (br)). ^{13}C NMR (75 MHz, $CDCl_3$):

δ 8.6 (2C), 14.1, 22.8 (3C), 27.7 (3C), 30.0, 30.3, 53.0, 57.2, 62.0, 62.2, 73.5, 79.1, 83.3, 152.6, 168.6, MS (ES^+): *m*/*z* (%): 442/444 (M + H^+, 100). HRMS (ES) calcd for $C_{19}H_{36}ClNO_6S$: 442.2019 MH^+; found: 442.2027/444.1998.

(R_S,2*R*,3*R*)-Methyl 2-(*tert*-butoxycarbonyloxy)-4-chloro-3-(*tert*-butanesulfinylamino)butanoate 5cb. R_f = 0.25 (petroleum ether–EtOAc: 5/1). Yellow oil, 42% (0.60 g). $[\alpha]_D$ −37.4 (*c* 0.6, $CHCl_3$). IR (cm^{-1}): 1738, 1241, 1046. ^1H NMR (300 MHz, $CDCl_3$): δ 1.17 (9H, s), 1.52 (9H, s), 3.62 (2H, t, *J* = 11.0 Hz), 3.76 (3H, s), 3.92–4.19 (2H, m), 5.43 (1H, d, *J* = 1.7 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 22.4 (3C), 27.6 (3C), 42.6, 52.6, 56.8, 59.7, 72.9, 84.0, 152.1, 168.3, MS (ES^+): *m*/*z* (%): 394/396 (M + Na^+, 100). HRMS (ES) calcd for $C_{14}H_{26}ClNO_6S$: 372.1236 MH^+; found: 372.1254/374.1225.

(R_S,2*R*,3*R*)-Ethyl 2-(*tert*-butoxycarbonyloxy)-4-chloro-3-(*tert*-butanesulfinylamino)butanoate 5cc. R_f = 0.31 (petroleum ether–EtOAc: 5/1). Yellow oil, 35% (0.60 g). $[\alpha]_D$ −21.3 (*c* 0.9, $CHCl_3$). IR (cm^{-1}): 1739, 1248, 1046. ^1H NMR (300 MHz, $CDCl_3$): δ 1.18 (9H, s), 1.29 (3H, t, *J* = 7.2 Hz), 1.52 (9H, s), 3.62 (2H, t, *J* = 11.0 Hz), 3.96 (1H, d × d, *J* = 11.0, 4.4 Hz), 4.00–4.10 (1H, m), 4.21 (2H, q, *J* = 7.2 Hz), 5.39 (1H, d, *J* = 2.8 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.1, 22.4 (3C), 27.6 (3C), 42.7, 56.8, 59.7, 61.9, 72.9, 83.9, 152.1, 168.3. MS (ES^+): *m*/*z* (%): 386/388 (M + H^+, 100). HRMS (ES) calcd for $C_{15}H_{28}ClNO_6S$: 386.1392 MH^+; found: 386.1409/388.1380.

(S_S,2*S*,3*S*)-Benzyl 2-(*tert*-butoxycarbonyloxy)-4-chloro-4-methyl-3-(*p*-toluenesulfinylamino)pentanoate 5da. R_f = 0.63 (petroleum ether–EtOAc: 5/4). White solid, 51% (0.68 g). $[\alpha]_D$ +85.2 (*c* 0.4, $CHCl_3$). Mp. 127.2–127.6 °C. IR (cm^{-1}): 3301, 1747, 1722. ^1H NMR (300 MHz, $CDCl_3$): δ 1.46 (9H, s), 1.47 (3H, s), 1.53 (3H, s), 2.40 (3H, s), 4.00 (1H, d × d, *J* = 10.5, 1.1 Hz), 4.84 (1H, d, *J* = 10.5 Hz), 5.24 (1H, d, *J* = 12.1 Hz), 5.35 (1H, d, *J* = 12.1 Hz), 5.69 (1H, d, *J* = 1.1 Hz), 7.23 (2H, d, *J* = 8.3 Hz), 7.31–7.42 (5H, m), 7.49 (2H, d, *J* = 8.3 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 21.4, 27.6 (3C), 29.3, 31.3, 62.9, 67.9, 70.2, 73.8, 83.6, 125.8 (2C), 128.5, 128.6 (4C), 129.5 (2C), 135.0, 141.4, 141.7, 152.1, 168.3. MS (ES^+): *m*/*z* (%): 510/512 (M + H^+, 100). Anal. Calcd for $C_{25}H_{32}ClNO_6S$: C 58.87; H 6.32; N 2.75. Found: C 58.92; H 6.60; N 2.64.

(S_S,2*S*,3*S*)-Methyl 2-(*tert*-butoxycarbonyloxy)-4-chloro-4-methyl-3-(*p*-toluenesulfinylamino)pentanoate 5db. R_f = 0.20 (petroleum ether–EtOAc: 3/1). White solid, 51% (0.91 g). $[\alpha]_D$ +95.8 (*c* 0.4, $CHCl_3$). Mp. 149.4–149.8 °C. IR (cm^{-1}): 3283, 1748, 1720, ^1H NMR (300 MHz, $CDCl_3$): δ 1.47 (3H, s), 1.50 (9H, s), 1.54 (3H, s), 2.42 (3H, s), 3.88 (3H, s), 3.98 (1H, d × d, *J* = 10.5, 1.4 Hz), 4.86 (1H, d, *J* = 10.5 Hz), 5.66 (1H, d, *J* = 1.4 Hz), 7.32 (2H, d, *J* = 8.0 Hz), 7.57 (2H, d, *J* = 8.0 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 21.5, 27.8 (3C), 29.5, 31.3, 53.0, 62.8, 70.4, 73.7, 83.7, 125.9 (2C), 129.7 (2C), 141.4, 142.0, 152.2, 169.0, MS (ES^+): *m*/*z* (%): 434/436 (M + H^+, 100). Anal. Calcd for $C_{19}H_{28}ClNO_6S$: C 52.29; H 6.50; N 3.23. Found: C 52.59; H 6.59; N 3.41.

(S_S,2*S*,3*S*)-Ethyl 2-(*tert*-butoxycarbonyloxy)-4-chloro-4-methyl-3-(*p*-toluenesulfinylamino)pentanoate 5dc. R_f = 0.24 (petroleum ether–EtOAc: 3/1). White solid, 75% (1.03 g). $[\alpha]_D$ +85.1 (*c* 0.4, $CHCl_3$). Mp. 98.2–98.8 °C. IR (cm^{-1}): 3280, 1745, 1714. ^1H NMR (300 MHz, $CDCl_3$): δ 1.34 (3H, t, *J* = 7.2 Hz), 1.50 (9H, s), 1.51 (3H, s), 1.60 (3H, s), 2.42 (3H, s), 4.02 (1H, d × d, *J* = 10.7, 1.1 Hz), 4.30 (1H, d × q, *J* = 10.7, 7.2 Hz), 4.36 (1H, d × q, *J* = 10.7, 7.2 Hz), 4.82 (1H, d, *J* = 10.5 Hz), 5.63 (1H, d, *J* = 1.1 Hz), 7.31 (2H, d, *J* = 8.3 Hz), 7.59 (2H, d, *J* = 8.3 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.2, 21.4, 27.7 (3C), 29.4, 31.3, 62.2, 63.4, 70.2, 73.7, 83.5, 125.9 (2C), 129.6 (2C), 141.6, 141.8, 152.1, 168.5. MS (ES^+): *m*/*z* (%): 448/450 (M + H^+, 100). Anal. Calcd for $C_{20}H_{30}ClNO_6S$: C 53.62; H 6.75; N 3.13. Found: C 53.25; H 6.40; N 2.79.

(S_S,2*S*,3*S*)-Ethyl 2-(*tert*-butoxycarbonyloxy)-4-chloro-3-(*p*-toluenesulfinylamino)butanoate 5ec. R_f = 0.18 (petroleum ether–EtOAc: 2/1). Yellow oil, 35% (0.70 g). $[\alpha]_D$ +5.6 (*c* 0.2, $CHCl_3$). IR (cm^{-1}): 1744, 1251, 1093. ^1H NMR (300 MHz, $CDCl_3$): δ 1.35 (3H, t, *J* = 7.2 Hz), 1.49 (9H, s), 2.42 (3H, s), 3.52 (1H, t, *J* = 11.0 Hz), 3.66 (1H, d × d, *J* = 11.0, 4.4 Hz), 4.03–4.19 (1H, m), 4.23–4.41 (2H, m), 4.59 (1H, d, *J* = 11.0 Hz), 5.38 (1H, d, *J* = 2.2 Hz), 7.30 (2H, d, *J* = 8.0 Hz), 7.50 (2H, d, *J* = 8.0 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.2, 21.4, 27.6 (3C), 42.9, 56.6, 62.2, 73.1, 83.9, 125.5 (2C), 129.7 (2C), 141.1, 142.0, 152.0, 167.9, MS (ES^+): *m*/*z* (%): 420/422 (M + H^+, 100). HRMS (ES) calcd for $C_{18}H_{26}ClNO_6S$: 420.1236 MH^+; found: 420.1246/422.1217.

Synthesis of β,γ-aziridino-α-hydroxy esters 6

The synthesis of (R_S,2*R*,2′*S*)-benzyl 2-(*tert*-butoxycarbonyloxy)-2-(3,3-dimethyl-1-*tert*-butanesulfinylaziridin-2-yl)acetate **6aa** is a representative. To a solution of (R_S,2*R*,3*R*)-benzyl 2-(*tert*-butoxycarbonyloxy)-4-chloro-4-methyl-3-(*tert*-butanesulfinylamino)-pentanoate **5aa** (0.18 g, 0.38 mmol) in acetone (10 mL) was added K_2CO_3 (3.0 equiv., 1.13 mmol, 0.16 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 × 5 mL). The organic phase was dried ($MgSO_4$), filtered and evaporated *in vacuo*. The crude product was purified by flash chromatography to yield 0.13 g (0.26 mmol, 68%) of (R_S,2*R*,2′*S*)-benzyl 2-(*tert*-butoxycarbonyloxy)-2-(3,3-dimethyl-1-*tert*-butanesulfinylaziridin-2-yl)acetate **6aa**.

(R_S,2*R*,2′*S*)-Benzyl 2-(*tert*-butoxycarbonyloxy)-2-(3,3-dimethyl-1-*tert*-butanesulfinylaziridin-2-yl)acetate 6aa. R_f = 0.43 (petroleum ether–EtOAc: 5/4). Brown oil, 68% (0.13 g). $[\alpha]_D$ −54.8 (*c* 0.4, $CHCl_3$). IR (cm^{-1}): 1744. ^1H NMR (300 MHz, $CDCl_3$): δ 1.25 (9H, s), 1.33 (3H, s), 1.47 (9H, s), 1.50 (3H, s), 2.72 (1H, d, *J* = 9.6 Hz), 4.76 (1H, d, *J* = 9.6 Hz), 5.13 (1H, d, *J* = 12.1 Hz), 5.33 (1H, d, *J* = 12.1 Hz), 7.30–7.41 (5H, m). ^{13}C NMR (75 MHz, $CDCl_3$): δ 22.1, 22.8 (3C), 23.3, 27.8 (3C), 46.6, 48.6, 56.9, 67.7, 74.5, 83.5, 128.6 (2C), 128.8 (3C), 134.9, 152.7, 167.8. MS (ES^+): *m*/*z* (%): 440 (M + H^+, 50), 384 (100). HRMS (ES) calcd for $C_{22}H_{33}NO_6S$: 440.2095 MH^+; found: 440.2119.

(R_S,2*R*,2′*S*)-Methyl 2-(*tert*-butoxycarbonyloxy)-2-(3,3-dimethyl-1-*tert*-butanesulfinylaziridin-2-yl)acetate 6ab. R_f = 0.46 (petroleum ether–EtOAc: 5/4). Brown oil, 88% (0.15 g). $[\alpha]_D$ −11.5 (*c* 0.4, $CHCl_3$). IR (cm^{-1}): 1745. ^1H NMR (300 MHz, $CDCl_3$): δ 1.27 (9H, s), 1.42 (3H, s), 1.50 (9H, s), 1.63 (3H, s), 2.76 (1H, d, *J* = 9.4 Hz), 3.81 (3H, s), 4.78 (1H, d, *J* = 9.4 Hz). ^{13}C NMR

(75 MHz, $CDCl_3$): δ 22.2, 22.7 (3C), 23.2, 27.7 (3C), 46.4, 48.7, 52.8, 56.8, 74.2, 83.5, 152.6, 168.4. MS (ES^+): *m*/*z* (%): 364 (M + H^+, 99), 308 (100). HRMS (ES) calcd for $C_{16}H_{29}NO_6S$: 364.1782 MH^+; found: 364.1771.

(R_S,2*R*,2′*S*)-Ethyl 2-(*tert*-butoxycarbonyloxy)-2-(3,3-dimethyl-1-*tert*-butanesulfinylaziridin-2-yl)acetate 6ac. R_f = 0.41 (petroleum ether–EtOAc: 5/4). Brown oil, 67% (0.12 g). $[\alpha]_D$ −83.4 (*c* 0.4, $CHCl_3$). IR (cm^{-1}): 1744. ^1H NMR (300 MHz, $CDCl_3$): δ 1.26 (9H, s), 1.29 (3H, t, *J* = 7.2 Hz), 1.41 (3H, s), 1.48 (9H, s), 1.61 (3H, s), 2.73 (1H, d, *J* = 9.4 Hz), 4.21 (1H, d × q, *J* = 11.0, 7.2 Hz), 4.29 (1H, d × q, *J* = 11.0, 7.2 Hz), 4.72 (1H, d, *J* = 9.4 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.2, 22.3, 22.8 (3C), 23.4, 27.8 (3C), 46.6, 48.6, 56.9, 62.0, 74.5, 83.4, 152.7, 167.9. MS (ES^+): *m*/*z* (%): 378 (M + H^+, 100), 322 (76). HRMS (ES) calcd for $C_{17}H_{31}NO_6S$: 378.1939 MH^+; found: 378.1958.

(R_S,2*R*,2′*S*)-Benzyl 2-(*tert*-butoxycarbonyloxy)-2-(3,3-diethyl-1-*tert*-butanesulfinylaziridin-2-yl)acetate 6ba. R_f = 0.37 (petroleum ether–EtOAc: 3/1). Yellow oil, yield 79% (0.35 g). $[\alpha]_D$ −75.6 (*c* 1.0, $CHCl_3$). IR (cm^{-1}): 1756, 1734, 1298, 1112, 861. ^1H NMR (300 MHz, $CDCl_3$): δ 0.79 (3H, t, *J* = 7.2 Hz), 1.01 (3H, t, *J* = 7.2 Hz), 1.24 (9H, s), 1.46 (9H, s), 1.45–1.50 (1H, m), 1.60–1.75 (1H, m), 1.79–1.91 (1H, m), 2.10–2.23 (1H, m), 2.70 (1H, d, *J* = 9.4 Hz), 4.80 (1H, d, *J* = 9.4 Hz), 5.18 (1H, d, *J* = 11.7 Hz), 5.26 (1H, d, *J* = 11.7 Hz), 7.29–7.38 (5H, m). ^{13}C NMR (75 MHz, $CDCl_3$): δ 9.0, 11.1, 22.1 (3C), 24.5, 25.6, 27.6 (3C), 49.8, 54.8, 57.2, 67.7, 74.1, 83.4, 128.6 (2C), 128.7, 128.8 (2C), 134.7, 152.5, 167.8. MS (ES^+): *m*/*z* (%): 468 (M + H^+, 100). HRMS (ES) calcd for $C_{24}H_{37}NO_6S$: 468.2414 MH^+; found: 468.2425.

(R_S,2*R*,2′*S*)-Methyl 2-(*tert*-butoxycarbonyloxy)-2-(3,3-diethyl-1-*tert*-butanesulfinylaziridin-2-yl)acetate 6bb. R_f = 0.41 (petroleum ether–EtOAc: 3/1). White solid, 66% (0.15 g). $[\alpha]_D$ −118.9 (*c* 0.2, $CHCl_3$). Mp. 99.0–101.0 °C. IR (cm^{-1}): 1736, 1252, 1089. ^1H NMR (300 MHz, $CDCl_3$): δ 0.99 (3H, t, *J* = 7.2 Hz), 1.06 (3H, t, *J* = 7.2 Hz), 1.25 (9H, s), 1.49 (9H, s), 1.55–1.59 (2H, m), 1.90–2.05 (1H, m), 2.17–2.32 (1H, m), 2.71 (1H, d, *J* = 9.4 Hz), 3.80 (3H, s), 4.80 (1H, d, *J* = 9.4 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 9.0, 11.3, 22.1 (3C), 24.4, 25.6, 27.7 (3C), 49.8, 52.6, 54.7, 57.2, 73.9, 83.4, 152.5, 168.4, MS (ES^+): *m*/*z* (%): 392 (M + H^+, 100). HRMS (ES) calcd for $C_{18}H_{33}NO_6S$: 392.2095 MH^+; found: 392.2112.

(R_S,2*R*,2′*S*)-Ethyl 2-(*tert*-butoxycarbonyloxy)-2-(3,3-diethyl-1-*tert*-butanesulfinylaziridin-2-yl)acetate 6bc. R_f = 0.35 (petroleum ether–EtOAc: 3/1). Yellow oil, 47% (0.28 g). $[\alpha]_D$ −80.2 (*c* 1.2, $CHCl_3$). IR (cm^{-1}): 1744, 1252, 1089. ^1H NMR (300 MHz, $CDCl_3$): δ 1.00 (3H, t, *J* = 7.2 Hz), 1.08 (3H, t, *J* = 7.2 Hz), 1.26 (9H, s), 1.33 (3H, t, *J* = 7.2 Hz), 1.49 (9H, s), 1.52–1.60 (2H, m), 1.90–2.04 (1H, m), 2.20–2.32 (1H, m), 2.71 (1H, d, *J* = 9.4 Hz), 4.26 (2H, q, *J* = 7.2 Hz), 4.76 (1H, d, *J* = 9.4 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 9.0, 11.4, 14.1, 22.1 (3C), 24.5, 25.7, 27.7 (3C), 49.9, 54.7, 57.2, 62.0, 74.0, 83.3, 152.5, 167.9. MS (ES^+): *m*/*z* (%): 406 (M + H^+, 100). HRMS (ES) calcd for $C_{19}H_{35}NO_6S$: 406.2252 MH^+; found: 406.2271.

(R_S,2*R*,2′*S*)-Methyl 2-(*tert*-butoxycarbonyloxy)-2-(1-*tert*-butanesulfinylaziridin-2-yl)acetate 6cb. R_f = 0.35 (petroleum ether–EtOAc: 3/1). Yellow solid, 70% (0.70 g). $[\alpha]_D$ −179.4 (*c* 0.5, $CHCl_3$). Mp. 88.0–90.0 °C. IR (cm^{-1}): 1740, 1250, 1079. ^1H NMR (300 MHz, $CDCl_3$): δ 1.22 (9H, s), 1.51 (9H, s), 2.10 (1H, d, *J* = 3.9 Hz), 2.54–2.60 (1H, m), 2.72 (1H, d, *J* = 7.2 Hz), 3.79 (3H, s), 4.82 (1H, d, *J* = 6.6 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 22.1, 22.6 (3C), 27.6 (3C), 32.4, 53.0, 57.4, 74.5, 83.7, 152.5, 168.0, MS (ES^+): *m*/*z* (%): 358 (M + Na^+, 100). HRMS (ES) calcd for $C_{14}H_{25}NO_6S$: 336.1469 MH^+; found: 336.1459.

(R_S,2*R*,2′*S*)-Ethyl 2-(*tert*-butoxycarbonyloxy)-2-(1-*tert*-butanesulfinylaziridin-2-yl)acetate 6cc. R_f = 0.24 (petroleum ether–EtOAc: 3/1). Yellow solid, 64% (0.50 g). $[\alpha]_D$ −212.8 (*c* 1.1, $CHCl_3$). Mp. 119.0–121.0 °C. IR (cm^{-1}): 1739, 1244, 1117. ^1H NMR (300 MHz, $CDCl_3$): δ 1.22 (9H, s), 1.29 (3H, t, *J* = 7.2 Hz), 1.51 (9H, s), 2.10 (1H, d, *J* = 3.9 Hz), 2.58 (1H, d × d × d, *J* = 7.2, 6.9, 3.9 Hz), 2.72 (1H, d, *J* = 7.2 Hz), 4.16–4.32 (2H, m), 4.79 (1H, d, *J* = 6.9 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.2, 22.0, 22.6 (3C), 27.7 (3C), 32.4, 57.4, 61.8, 74.4, 83.5, 152.5, 167.4, MS (ES^+): *m*/*z* (%): 372 (M + Na^+, 100). HRMS (ES) calcd for $C_{15}H_{27}NO_6S$: 350.1626 MH^+; found: 350.1640.

(S_S,2*S*,2′*R*)-Benzyl 2-(*tert*-butoxycarbonyloxy)-2-(3,3-dimethyl-1-*p*-toluenesulfinylaziridin-2-yl)acetate 6da. R_f = 0.31 (petroleum ether–EtOAc: 3/1). Yellow oil, 96% (0.16 g). $[\alpha]_D$ −50.5 (*c* 2.1, $CHCl_3$). IR (cm^{-1}): 1743, 1252, 1099. ^1H NMR (300 MHz, $CDCl_3$): δ 1.24 (3H, s), 1.34 (3H, s), 1.44 (9H, s), 2.42 (3H, s), 2.77 (1H, d, *J* = 9.4 Hz), 4.72 (1H, d, *J* = 9.4 Hz), 5.08 (1H, d, *J* = 12.1 Hz), 5.33 (1H, d, *J* = 12.1 Hz), 7.26–7.37 (7H, m), 7.65 (2H, d, *J* = 8.3 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 20.5, 21.5, 23.1, 27.6 (3C), 44.4, 49.1, 67.5, 74.0, 83.2, 125.4 (2C), 128.5 (2C), 128.5, 128.6 (2C), 129.5 (2C), 134.9, 141.6, 142.0, 152.5, 167.7. 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*)-Methyl 2-(*tert*-butoxycarbonyloxy)-2-(3,3-dimethyl-1-*p*-toluenesulfinylaziridin-2-yl)acetate 6db. R_f = 0.41 (petroleum ether–EtOAc: 5/4). Brown oil, 68% (0.14 g). $[\alpha]_D$ +149.4 (*c* 0.4, $CHCl_3$). IR (cm^{-1}): 1744. ^1H NMR (300 MHz, $CDCl_3$): δ 1.33 (3H, s), 1.47 (3H, s), 1.48 (9H, s), 2.43 (3H, s), 2.81 (1H, d, *J* = 9.4 Hz), 3.79 (3H, s), 4.73 (1H, d, *J* = 9.4 Hz), 7.31 (2H, d, *J* = 8.3 Hz), 7.67 (2H, d, *J* = 8.3 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 20.6, 21.5, 23.1, 27.6 (3C), 44.3, 49.2, 52.8, 73.9, 83.2, 125.4 (2C), 129.5 (2C), 141.6, 142.1, 152.5, 168.3. MS (ES^+): *m*/*z* (%): 398 (M + H^+, 65), 342 (95), 288 (100). HRMS (ES) calcd for $C_{19}H_{27}NO_6S$: 398.1626 MH^+; found: 398.1644.

(S_S,2*S*,2′*R*)-Ethyl 2-(*tert*-butoxycarbonyloxy)-2-(3,3-dimethyl-1-*p*-toluenesulfinylaziridin-2-yl)acetate 6dc. R_f = 0.33 (petroleum ether–EtOAc: 3/1). Yellow oil, 82% (0.50 g). $[\alpha]_D$ +18.0 (*c* 2.8, $CHCl_3$). IR (cm^{-1}): 1737, 1241, 1045, ^1H NMR (300 MHz, $CDCl_3$): δ 1.28 (3H, t, *J* = 7.2 Hz), 1.34 (3H, s), 1.46 (3H, s), 1.48 (9H, s), 2.43 (3H, s), 2.81 (1H, d, *J* = 9.4 Hz), 4.11–4.35 (2H, m), 4.70 (1H, d, *J* = 9.4 Hz), 7.31 (2H, d, *J* = 8.3 Hz), 7.67 (2H, d, *J* = 8.3 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.1, 20.7, 21.6, 23.2, 27.7 (3C), 44.4, 49.2, 61.9, 74.1, 83.2, 125.5 (2C), 129.6 (2C), 141.6, 142.2, 152.6, 167.8. MS (ES^+): *m*/*z* (%): 412 (M + H^+, 100). HRMS (ES) calcd for $C_{20}H_{29}NO_6S$: 412.1788 MH^+; found: 412.1781.

Synthesis of *O*-deprotected (R_S,2*R*,3*R*)-γ-chloro-α-hydroxy-β-amino esters (R_S,2*R*,3*R*)-7

The synthesis of (R_S,2*R*,3*R*)-benzyl 4-chloro-2-hydroxy-4-methyl-3-(*tert*-butanesulfinylamino)pentanoate **7aa** is a representative. To a solution of (R_S,2*R*,3*R*)-benzyl 2-(*tert*-butoxycarbonyloxy)-4-chloro-4-methyl-3-(*tert*-butanesulfinylamino)pentanoate **5aa** (1.0 equiv., 0.61 g, 1.29 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 in water (7 mL) and quenched with K_2CO_3 until pH = 7. The aqueous phase was extracted with CH_2Cl_2 (3 × 10 mL) and the combined organic phases were dried ($MgSO_4$), filtered and evaporated *in vacuo*. The crude product was purified *via* flash chromatography 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 **7aa**. Compound **7ac** was purified by crystallization in diethyl ether.

(R_S,2*R*,3*R*)-Benzyl 4-chloro-2-hydroxy-4-methyl-3-(*tert*-butanesulfinylamino)pentanoate 7aa. R_f = 0.27 (petroleum ether–EtOAc: 1/1). Yellow oil, 75% (0.36 g). $[\alpha]_D$ +6.3 (*c* 2.0, $CHCl_3$). IR (cm^{-1}): 3266, 1739. ^1H NMR (300 MHz, $CDCl_3$): δ 1.09 (9H, s), 1.68 (3H, s), 1.82 (3H, s), 3.48 (1H, s (br)), 3.88 (1H, d × d, *J* = 9.9, 1.1 Hz), 4.04 (1H, d, *J* = 9.9 Hz), 4.86 (1H, d, *J* = 1.1 Hz), 5.16 (1H, d, *J* = 12.1 Hz), 5.24 (1H, d, *J* = 12.1 Hz), 7.35–7.40 (5H, m). ^{13}C NMR (75 MHz, $CDCl_3$): δ 22.6 (3C), 28.8, 31.5, 57.1, 66.7, 68.1, 70.8, 71.8, 128.7 (4C), 128.8, 134.5, 173.5. MS (ES^+): *m*/*z* (%): 376/378 (M + H^+, 100). HRMS (ES) calcd for $C_{17}H_{26}ClNO_4S$: 376.1344 MH^+; found: 376.1345/378.1311.

(R_S,2*R*,3*R*)-Methyl 4-chloro-2-hydroxy-4-methyl-3-(*tert*-butanesulfinylamino)pentanoate 7ab. R_f = 0.29 (petroleum ether–EtOAc: 1/2). White crystals, 80% (0.27 g). $[\alpha]_D$ −27.1 (*c* 2.0, $CHCl_3$). Mp. 113.1–115.1 °C. IR (cm^{-1}): 3293, 1742, ^1H NMR (300 MHz, $CDCl_3$): δ 1.17 (9H, s), 1.70 (3H, s), 1.85 (3H, s), 3.23 (1H, s (br)), 3.82 (3H, s), 3.86 (1H, d, *J* = 9.9 Hz), 3.97 (1H, d, *J* = 9.9 Hz), 4.86 (1H, s). ^{13}C NMR (75 MHz, $CDCl_3$): δ 22.6 (3C), 28.8, 31.5, 53.1, 57.1, 66.6, 70.7, 71.8, 174.1. MS (ES^+): *m*/*z* (%): 300/302 (M + H^+, 100). HRMS (ES) calcd for $C_{11}H_{22}ClNO_4S$: 300.1031 MH^+; found: 300.1024/302.0995.

(R_S,2*R*,3*R*)-Ethyl 4-chloro-2-hydroxy-4-methyl-3-(*tert*-butanesulfinylamino)pentanoate 7ac. White crystals, 86% (0.24 g). $[\alpha]_D$ −9.3 (*c* 2.1, $CHCl_3$). Mp 96.3–100.3 °C. IR (cm^{-1}): 3288, 1738. ^1H NMR (300 MHz, $CDCl_3$): δ 1.18 (9H, s), 1.34 (3H, t, *J* = 7.2 Hz), 1.70 (3H, s), 1.85 (3H, s), 3.29 (1H, d, *J* = 3.9 Hz), 3.85 (1H, d × d, *J* = 9.9, 1.1 Hz), 3.99 (1H, d, *J* = 9.9 Hz), 4.16–4.35 (2H, m), 4.82 (1H, d × d, *J* = 3.9, 1.1 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.2, 22.6 (3C), 28.8, 31.6, 57.0, 62.6, 66.6, 70.7, 71.8, 173.7. MS (ES^+): *m*/*z* (%): 314/316 (M + H^+, 100). HRMS (ES) calcd for $C_{12}H_{24}ClNO_4S$: 314.1187 MH^+; found: 314.1176/316.1147.

(R_S,2*R*,3*R*)-Methyl 4-chloro-4-ethyl-2-hydroxy-3-(*tert*-butanesulfinylamino)hexanoate 7bb. R_f = 0.58 (petroleum ether–EtOAc: 1/2). Yellow oil, 70% (0.19 g). $[\alpha]_D$ −12.5 (*c* 0.2, $CHCl_3$). IR (cm^{-1}): 3341, 2976, 1737, 1212, 1044. ^1H NMR (300 MHz, $CDCl_3$): δ 1.02 (3H, t, *J* = 7.2 Hz), 1.08 (3H, t, *J* = 7.2 Hz), 1.20 (9H, s), 1.94–2.18 (5H, m), 3.82 (3H, s), 4.00 (1H, d, *J* = 9.7 Hz), 4.14 (1H, d, *J* = 9.7 Hz), 4.71 (1H, s (br)). ^{13}C NMR (75 MHz, $CDCl_3$): δ 8.7 (2C), 22.7 (3C), 29.9, 30.4, 53.1, 57.2, 62.7, 70.5, 80.4, 174.0, MS (ES^+): *m*/*z* (%): 328/330 (M + H^+, 100). HRMS (ES) calcd for $C_{13}H_{26}ClNO_4S$: 328.1338 MH^+; found: 328.1348/330.1319.

Synthesis of *N*-deprotected (2*R*,3*R*)-γ-chloro-α-hydroxy-β-amino esters (2*R*,3*R*)-9

The synthesis of (2*R*,3*R*)-benzyl 3-amino-2-(*tert*-butoxycarbonyloxy)-4-chloro-4-methylpentanoate hydrochloride **9aa** is a representative. To a solution of (R_S,2*R*,3*R*)-benzyl 2-(*tert*-butoxycarbonyloxy)-4-chloro-4-methyl-3-(*tert*-butanesulfinylamino)-pentanoate **5aa** (1.0 equiv., 0.69 g, 1.45 mmol) in dioxane (60 mL) was added a saturated solution of HCl in dioxane (15 mL) at room temperature. The reaction mixture was stirred for one hour at room temperature and subsequently the solvent was evaporated *in vacuo*. Precipitation in dry Et_2O afforded 0.47 g (1.15 mmol, 79%) of pure (2*R*,3*R*)-benzyl 3-amino-2-(*tert*-butoxycarbonyloxy)-4-chloro-4-methylpentanoate hydrochloride **9aa**.

(2*R*,3*R*)-Benzyl 3-amino-2-(*tert*-butoxycarbonyloxy)-4-chloro-4-methylpentanoate hydrochloride 9aa. Yellow solid, 79% (0.47 g). $[\alpha]_D$ +5.3 (*c* 0.4, $CHCl_3$). Mp 150.9–151.7 °C. IR (cm^{-1}): 3232, 1752, 1728. ^1H NMR (300 MHz, $CDCl_3$): δ 1.34 (9H, s), 1.86 (6H, s), 4.48 (1H, s (br)), 5.25 (1H, d, *J* = 12.1 Hz), 5.33 (1H, d, *J* = 12.1 Hz), 5.76 (1H, s (br)), 7.20–7.37 (5H, m), 8.92 (3H, s (br)). ^{13}C NMR (75 MHz, $CDCl_3$): δ 27.6 (3C), 29.9, 31.1, 59.4, 68.1, 68.9, 70.7, 84.3, 128.4, 128.5 (2C), 128.6 (2C), 135.0, 151.8, 167.5. MS (ES^+): *m*/*z* (%): 372/374 (M + H^+ − HCl, 100). Anal. Calcd for $C_{18}H_{27}Cl_2NO_5$: C 52.95; H 6.67; N 3.43. Found: C 53.12; H 6.93; N 3.52.

(2*R*,3*R*)-Methyl 3-amino-2-(*tert*-butoxycarbonyloxy)-4-chloro-4-methylpentanoate hydrochloride 9ab. White solid, 93% (0.44 g). $[\alpha]_D$ −13.0 (*c* 2.2, $CHCl_3$). Mp 147.2–151.2 °C. IR (cm^{-1}): 2980, 1752, 1727. ^1H NMR (300 MHz, $CDCl_3$): δ 1.50 (9H, s), 1.87 (6H, s (br)), 3.89 (3H, s), 4.26 (1H, s (br)), 5.73 (1H, s (br)), 9.01 (3H, s (br)). ^{13}C NMR (75 MHz, $CDCl_3$): δ 27.8 (3C), 30.4, 31.3, 54.2, 59.8, 67.8, 70.8, 84.3, 151.8, 167.7. 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: 296.1259/298.1229.

(2*R*,3*R*)-Ethyl 3-amino-2-(*tert*-butoxycarbonyloxy)-4-chloro-4-methylpentanoate hydrochloride 9ac. White solid, 92% (0.43 g). $[\alpha]_D$ +14.0 (*c* 0.3, $CHCl_3$). Mp 140.0–142.0 °C. IR (cm^{-1}): 3198, 1751, 1729. ^1H NMR (300 MHz, $CDCl_3$): δ 1.32 (3H, t, *J* = 6.9 Hz), 1.50 (9H, s), 1.83 (3H, s), 1.89 (3H, s), 4.25 (1H, s (br)), 4.34 (2H, q, *J* = 6.9 Hz), 5.67 (1H, s (br)), 8.94 (3H, s (br)). ^{13}C NMR (75 MHz, $CDCl_3$): δ 13.9, 27.7 (3C), 29.8, 31.2, 59.4, 63.2, 67.9, 70.7, 84.1, 151.7, 167.1. MS (ES^+): *m*/*z* (%): 310/312 (M + H^+ − HCl, 100). Anal. Calcd for $C_{13}H_{25}Cl_2NO_5$: C 45.10; H 7.28; N 4.05. Found: C 45.12; H 7.19; N 3.99.

Synthesis of *N*,*O*-deprotected (2*R*,3*R*)-γ-chloro-α-hydroxy-β-amino ester trifluoroacetic acid salts (2*R*,3*R*)-10

The synthesis of (2*R*,3*R*)-benzyl 3-amino-4-chloro-2-hydroxy-4-methylpentanoate trifluoroacetate **10aa** is a representative.

To a solution of (2*R*,3*R*)-benzyl 3-amino-2-(*tert*-butoxycarbonyloxy)-4-chloro-4-methylpentanoate hydrochloride **9aa** (0.35 g, 0.86 mmol) in CH_2Cl_2 (6 mL) was added trifluoroacetic acid (2.7 mL) at room temperature. The reaction mixture was stirred for one hour at room temperature and subsequently evaporated *in vacuo*, affording 0.32 g of pure (2*R*,3*R*)-benzyl 3-amino-4-chloro-2-hydroxy-4-methylpentanoate trifluoroacetate **10aa** (0.83 mmol, 97%).

(2*R*,3*R*)-Benzyl 3-amino-4-chloro-2-hydroxy-4-methylpentanoate trifluoroacetate 10aa. Yellow oil, 97% (0.32 g). $[\alpha]_D$ −4.5 (*c* 1.3, $CHCl_3$). IR (cm^{-1}): 3038, 1739, 1665, 1142. ^1H NMR (300 MHz, $CDCl_3$): δ 1.70 (3H, s), 1.76 (3H, s), 3.95 (1H, s), 4.65 (1H, s), 5.12 (1H, d, J = 12.1 Hz), 5.29 (1H, d, J = 12.1 Hz), 7.26–7.35 (5H, m), 8.21 (4H, s (br)). ^{13}C NMR (75 MHz, $CDCl_3$): δ 28.1, 29.9, 61.9, 67.1, 68.9, 69.2, 128.7 (2C), 128.9 (2C), 129.1, 134.1, 171.6. 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: 272.1058/274.1029.

(2*R*,3*R*)-Methyl 3-amino-4-chloro-2-hydroxy-4-methylpentanoate trifluoroacetate 10ab. Yellow oil, 84% (0.37 g). $[\alpha]_D$ −18.4 (*c* 2.0, $CHCl_3$). IR (cm^{-1}): 2961, 1669, 1183, 1135, ^1H NMR (300 MHz, $CDCl_3$): δ 1.72 (3H, s), 1.78 (3H, s), 3.79 (3H, s), 3.91 (1H, s), 4.66 (1H, s), 7.60 (4H, s (br)). ^{13}C NMR (75 MHz, $CDCl_3$): δ 28.2, 29.7, 53.6, 61.8, 67.0, 69.0, 172.4. MS (ES^+): *m*/*z* (%): 196/198 (M + H^+ − TFA, 100). HRMS (ES) calcd for $C_7H_{14}ClNO_3$: 196.0735 MH^+ − TFA; found: 196.0740/198.0707.

(2*R*,3*R*)-Ethyl 3-amino-4-chloro-2-hydroxy-4-methylpentanoate trifluoroacetate 10ac. Yellow oil, 96% (0.27 g). $[\alpha]_D$ −14.7 (*c* 1.0, $CHCl_3$). IR (cm^{-1}): 2987, 1734, 1668, 1184, 1135, ^1H NMR (300 MHz, $CDCl_3$): δ 1.30 (3H, t, J = 7.2 Hz), 1.73 (3H, s), 1.80 (3H, s), 3.90 (1H, s (br)), 4.16–4.36 (2H, m), 4.62 (1H, s (br)), 6.96 (4H, s (br)). ^{13}C NMR (75 MHz, $CDCl_3$): δ 13.8, 28.1, 29.9, 61.9, 63.5, 67.0, 69.2, 171.9. MS (ES^+): *m*/*z* (%): 210/212 (M + H^+ − TFA, 100). HRMS (ES) calcd for $C_8H_{16}ClNO_3$: 210.0891 MH^+ − TFA; found: 210.0896/212.0866.

Synthesis of (4*R*,5*R*)-alkyl 4-(2-chloro-2-propyl)oxazolidin-2-one-5-carboxylates (4*R*,5*R*)-11

The synthesis of (4*R*,5*R*)-benzyl 4-(2-chloro-2-propyl)oxazolidin-2-one-5-carboxylate (4*R*,5*R*)-**11aa** is a representative. To a solution of (2*R*,3*R*)-benzyl 3-amino-4-chloro-2-hydroxy-4-methylpentanoate trifluoroacetate **10aa** (0.09 g, 0.23 mmol) in dry CH_2Cl_2 (5 mL) was added dropwise DIPEA (4.0 equiv., 0.12 g, 0.92 mmol) at 0 °C. The reaction mixture was stirred for 15 minutes at 0 °C, and subsequently triphosgene (1.2 equiv., 0.08 g, 0.28 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 in brine (5 mL). The aqueous phase was extracted with CH_2Cl_2 (3 × 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 0.06 g (0.19 mmol, 82%) of pure (4*R*,5*R*)-benzyl 4-(2-chloro-2-propyl)-oxazolidin-2-one-5-carboxylate (4*R*,5*R*)-**11aa**.

(4*R*,5*R*)-Benzyl 4-(2-chloro-2-propyl)oxazolidin-2-one-5-carboxylate 11aa. White solid, 82% (0.06 g). $[\alpha]_D$ −16.1 (*c* 0.8, $CHCl_3$). Mp. 66.0–70.0 °C. IR (cm^{-1}): 3262, 1761, 1209, 1096. ^1H NMR (300 MHz, $CDCl_3$): δ 1.57 (6H, s), 3.93 (1H, d, J = 3.3 Hz), 4.91 (1H, d, J = 3.3 Hz), 5.26 (1H, d, J = 12.1 Hz), 5.28 (1H, d, J = 12.1 Hz), 7.02 (1H, s (br)), 7.28–7.47 (5H, m). ^{13}C NMR (75 MHz, $CDCl_3$): δ 27.6, 27.8, 65.1, 68.1, 69.2, 75.0, 128.5 (2C), 128.9 (3C), 134.6, 158.3, 168.4. MS (ES^+): *m*/*z* (%): 315/317 (M + NH_4^+, 100). HRMS (ES) calcd for $C_{14}H_{16}ClNO_4$: 298.0841 MH^+; found: 298.0844/300.0815.

(4*R*,5*R*)-Methyl 4-(2-chloro-2-propyl)oxazolidin-2-one-5-carboxylate 11ab. White solid, 76% (0.08 g). $[\alpha]_D$ −23.1 (*c* 0.9, $CHCl_3$). Mp. 125.4–129.4 °C. IR (cm^{-1}): 3297, 1746, 1720, 1240, 1116. ^1H NMR (300 MHz, $CDCl_3$): δ 1.60 (6H, s), 3.86 (3H, s), 3.97 (1H, d × d, J = 3.3, 1.1 Hz), 4.89 (1H, d, J = 3.3 Hz), 6.89 (1H, s (br)). ^{13}C NMR (75 MHz, $CDCl_3$): δ 27.6, 27.7, 53.4, 65.1, 69.2, 74.9, 158.1, 169.1. MS (ES^+): *m*/*z* (%): 239/241 (M + NH_4^+, 100). HRMS (ES) calcd for $C_8H_{12}ClNO_4$: 222.0528 MH^+; found: 222.0530/224.0502.

(4*R*,5*R*)-Ethyl 4-(2-chloro-2-propyl)oxazolidin-2-one-5-carboxylate 11ac. White solid, 64% (0.06 g). $[\alpha]_D$ −23.0 (*c* 0.5, $CHCl_3$). Mp 140.1–144.1 °C. IR (cm^{-1}): 3251, 1754, 1728, 1238, 1110. ^1H NMR (300 MHz, $CDCl_3$): δ 1.34 (3H, t, J = 7.2 Hz), 1.60 (6H, s), 3.96 (1H, d, J = 3.3 Hz), 4.31 (2H, q, J = 7.2 Hz), 4.86 (1H, d, J = 3.3 Hz), 6.95 (1H, s (br)). ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.1, 27.6, 27.7, 62.7, 65.2, 69.3, 75.0, 158.2, 168.6. MS (ES^+): *m*/*z* (%): 253/255 (M + NH_4^+, 100). HRMS (ES) calcd for $C_9H_{14}ClNO_4$: 236.0684 MH^+; found: 236.0685/238.0658.

Acknowledgements

The authors are indebted to the Research Foundation – Flanders (FWO – Vlaanderen), the Agency for Innovation by Science and Technology in Flanders (IWT), Ghent University (BOF) and COST action CM0803 (STSM to M. N.) for financial support.

References

1 (*a*) F. Fülöp, *Chem. Rev.*, 2001, **101**, 2181–2204; (*b*) F. Fülöp, T. A. Martinek and G. K. Tóth, *Chem. Soc. Rev.*, 2006, **35**, 323–334; (*c*) M. A. Gelman and S. H. Gellman, Using constrained β-amino acid residues to control β-peptide shape and function, in *Enantioselective Synthesis of β-Amino Acids*, ed. E. Juaristi and V. A. Soloshonok, John Wiley & Sons, Inc., 2nd edn, 2005, pp. 527–591; (*d*) F. Gnad and O. Reiser, *Chem. Rev.*, 2003, **103**, 1603–1623; (*e*) A. Kuhl, M. G. Hahn, M. Dumic and J. Mittendorf, *Amino Acids*, 2005, **29**, 89–100; (*f*) J. A. Miller and S. T. Nguyen, *Mini-Rev. Org. Chem.*, 2005, **2**, 39–45; (*g*) M. North, *J. Pept. Sci.*, 2000, **6**, 301–313; (*h*) R. M. Ortuño, Enantioselective Synthesis of Conformationally Constrained β-Amino Acids, in *Enantioselective Synthesis of β-Amino Acids*, ed. E. Juaristi and V. A. Soloshonok, John Wiley & Sons, Inc., 2nd edn, 2005,

pp. 117–138; (*i*) G. Lelais and D. Seebach, *Biopolymers*, 2004, **76**, 206–243; (*j*) D. Seebach, A. K. Beck, S. Capone, G. Deniau, U. Groselj and E. Zass, *Synthesis*, 2009, 1–32; (*k*) D. Seebach and J. Gardiner, *Acc. Chem. Res.*, 2008, **41**, 1366–1375; (*l*) G. Cardillo and C. Tomasini, *Chem. Soc. Rev.*, 1996, **25**, 117.

2 (*a*) G. Cardillo, A. Tolomelli and C. Tomasini, *Eur. J. Org. Chem.*, 1999, 155–161; (*b*) I. Ibrahem and A. Córdova, *Tetrahedron Lett.*, 2005, **46**, 2839–2843; (*c*) P. Dziedzic, J. Vesely and A. Córdova, *Tetrahedron Lett.*, 2008, **49**, 6631–6634; (*d*) S. Harada, S. Handa, S. Matsunaga and M. Shibasaki, *Angew. Chem., Int. Ed.*, 2005, **44**, 4365–4368; (*e*) B. M. Trost and L. R. Terrell, *J. Am. Chem. Soc.*, 2003, **125**, 338–339.

3 O. N. Zefirova, E. V. Nurieva, A. N. Ryzhov, N. V. Zyk and N. S. Zefirov, *Russ. J. Org. Chem.*, 2005, **41**, 315–351.

4 (*a*) Y. Fu, S. Li, Y. Zu, G. Yang, Z. Yang, M. Luo, S. Jiang, M. Wink and T. Efferth, *Curr. Med. Chem.*, 2009, **16**, 3966–3985; (*b*) Y.-F. Wang, Q.-W. Shi, M. Dong, H. Kiyota, Y.-C. Gu and B. Cong, *Chem. Rev.*, 2011, **111**, 7652–7709; (*c*) Z.-Y. Ni, Y. Li, Y.-F. Wang, S.-M. Wang, M. Dong and Q.-W. Shi, *Curr. Org. Chem.*, 2012, **16**, 2038–2052; (*d*) J. Ojima, S. Lin and T. Wang, *Curr. Org. Chem.*, 1999, **6**, 927–954.

5 (*a*) S. J. Hecker and K. M. Werner, *J. Org. Chem.*, 1993, **58**, 1762–1765; (*b*) B. Bauvois and D. Dauzonne, *Med. Res. Rev.*, 2006, **26**, 88–130; (*c*) T. Aoyagi, S. Yoshida, N. Matsuda, T. Ikeda, M. Hamada and T. Takeuchi, *J. Antibiot.*, 1991, **44**, 573–578.

6 (*a*) D. H. Rich, *J. Med. Chem.*, 1985, **28**, 263–273; (*b*) M. L. Moore and G. B. Dreyer, *Perspect. Drug Discovery Des.*, 1993, **1**, 85–108; (*c*) I. Ojima, Y. H. Park, C. M. Sun, T. Brigaud and M. Zhao, *Tetrahedron Lett.*, 1992, **33**, 5737–5740.

7 (*a*) A. Abouabdellah, J.-P. Begué and D. Bonnet-Delpon, *Synlett*, 1996, 399–400; (*b*) A. Abouabdellah, J.-P. Begué, D. Bonnet-Delpon and T. T. T. Nga, *J. Org. Chem.*, 1997, **62**, 8826–8833.

8 (*a*) C. W. Jefford, J. McNulty, Z.-H. Lu and J. B. Wang, *Helv. Chim. Acta*, 1996, **79**, 1203–1216; (*b*) C. W. Jefford, J. McNulty and Z.-H. Lu, *J. Chem. Soc., Chem. Commun.*, 1995, 123–124; (*c*) C. W. Jefford, J. B. Wang and Z.-H. Lu, *Tetrahedron Lett.*, 1993, **34**, 7557–7560.

9 Y. Dejaegher and N. De Kimpe, *J. Org. Chem.*, 2004, **69**, 5974–5985.

10 H. K. Webb and R. G. Matthews, *J. Biol. Chem.*, 1995, **270**, 17204–17209.

11 H. Yoshida, N. Arai, M. Sugoh, K. Shiomi, M. Shinose, Y. Tanaka and S. Omura, *J. Antibiot.*, 1994, **47**, 1165–1166.

12 L. C. Blasiak, F. H. Vaillancourt, C. T. Walsh and C. L. Drennan, *Nature*, 2006, **440**, 368–371.

13 J. Bitzer, M. Streibel, H.-J. Langer and S. Grond, *Org. Biomol. Chem.*, 2009, **7**, 444–450.

14 G. Callebaut, S. Mangelinckx, L. Kiss, R. Sillanpää, F. Fülöp and N. De Kimpe, *Org. Biomol. Chem.*, 2012, **10**, 2326–2338.

15 (*a*) F. Colpaert, S. Mangelinckx and N. De Kimpe, *Org. Lett.*, 2010, **12**, 1904–1907; (*b*) F. Colpaert, S. Mangelinckx, S. De Brabandere and N. De Kimpe, *J. Org. Chem.*, 2011, **76**, 2204–2213.

16 (*a*) K. Senten, P. Van der Veken, G. Bal, I. De Meester, A.-M. Lambeir, S. Scharpé, B. Bauvois, A. Haemers and K. Augustyns, *Bioorg. Med. Chem. Lett.*, 2002, **12**, 2825–2828; (*b*) K. Senten, P. Van der Veken, I. De Meester, A.-M. Lambeir, S. Scharpé, A. Haemers and K. Augustyns, *J. Med. Chem.*, 2003, **46**, 5005–5014; (*c*) K. Senten, P. Van der Veken, I. De Meester, A.-M. Lambeir, S. Scharpé, A. Haemers and K. Augustyns, *J. Med. Chem.*, 2004, **47**, 2906–2916.

17 G. Callebaut, S. Mangelinckx, P. Van der Veken, K. W. Törnroos, K. Augustyns and N. De Kimpe, *Beilstein J. Org. Chem.*, 2012, **8**, 2124–2131.

18 (*a*) D. Morton and R. A. Stockman, *Tetrahedron*, 2006, **62**, 8869–8905; (*b*) F. Ferreira, C. Botuha, F. Chemla and A. Pérez-Luna, *Chem. Soc. Rev.*, 2009, **38**, 1162–1186; (*c*) F. A. Davis, *J. Org. Chem.*, 2006, **71**, 8993–9003; (*d*) O. Pablo, D. Guijarro and M. Yus, *J. Org. Chem.*, 2013, **78**, 9181–9189; (*e*) J. A. Ellman, T. D. Owens and T. P. Tang, *Acc. Chem. Res.*, 2002, **35**, 984–995; (*f*) G.-Q. Lin, M.-H. Xu, Y.-W. Zhong and X.-W. Sun, *Acc. Chem. Res.*, 2008, **41**, 831–840; (*g*) M. T. Robak, M. A. Herbage and J. A. Ellman, *Chem. Rev.*, 2010, **110**, 3600–3740.

19 (*a*) Q. Chen, J. Li and C. Yuan, *Synthesis*, 2008, 2986; (*b*) B. Denolf, S. Mangelinckx, K. W. Törnroos and N. De Kimpe, *Org. Lett.*, 2007, **9**, 187; (*c*) B. Denolf, E. Leemans and N. De Kimpe, *J. Org. Chem.*, 2007, **72**, 3211; (*d*) B. Denolf, E. Leemans and N. De Kimpe, *J. Org. Chem.*, 2008, **73**, 5662; (*e*) E. Leemans, S. Mangelinckx and N. De Kimpe, *Synlett*, 2009, 1265; (*f*) B. Denolf, S. Mangelinckx, K. W. Törnroos and N. De Kimpe, *Org. Lett.*, 2006, **8**, 3129; (*g*) D. M. Hodgson, J. Kloesges and B. Evans, *Synthesis*, 2009, 1923; (*h*) D. M. Hodgson, J. Kloesges and B. Evans, *Org. Lett.*, 2008, **10**, 2781.

20 (*a*) F. A. Davis and J. Deng, *Org. Lett.*, 2004, **6**, 2789–2792; (*b*) F. A. Davis, K. R. Prasad, M. B. Nolt and Y. Wu, *Org. Lett.*, 2003, **5**, 925–927; (*c*) Y. Wang, Q.-F. He, H.-W. Wang, X. Zhou, Z.-Y. Huang and Y. Qin, *J. Org. Chem.*, 2006, **71**, 1588–1591; (*d*) T. P. Tang and J. A. Ellman, *J. Org. Chem.*, 2002, **67**, 7819–7832; (*e*) J. W. Evans and J. A. Ellman, *J. Org. Chem.*, 2003, **68**, 9948–9957.

21 (*a*) N. De Kimpe, R. Verhé, L. De Buyck, L. Moens and N. Schamp, *Synthesis*, 1982, 43–46; (*b*) N. De Kimpe and R. Verhé, *The Chemistry of α-Halo ketones, α-Halo aldehydes, and α-Halo imines*, John Wiley and Sons, 1988, p. 496; (*c*) N. De Kimpe, P. Sulmon, R. Verhé, L. De Buyck and N. Schamp, *J. Org. Chem.*, 1983, **48**, 4320–4326; (*d*) N. De Kimpe and L. Moens, *Tetrahedron*, 1990, **46**, 2965–2974; (*e*) M. D'hooghe, W. Aelterman and N. De Kimpe, *Org. Biomol. Chem.*, 2009, **7**, 135–141.

22 B. Alcaide, P. Almendros, G. Cabrero and M. P. Ruiz, *Tetrahedron*, 2012, **68**, 10761–10768.

23 Y. Qin, Y. Wang, P. Guo, J. Gao, X. Feng, X. Luo and X. Zhang, Faming Zhuanli Shenqing Gongkai Shuomingshu, *CN* 1709864 (A), 2005.

24 (*a*) R. E. Ireland and A. K. Willard, *Tetrahedron Lett.*, 1975, 3975–3978; (*b*) R. E. Ireland and P. Wipf, *Tetrahedron Lett.*, 1989, **30**, 919–922; (*c*) A. S. Narula, *Tetrahedron Lett.*, 1981, **22**, 4119–4122; (*d*) L. Xie, K. M. Isenberger, G. Held and L. M. Dahl, *J. Org. Chem.*, 1997, **62**, 7516–7519.

25 (*a*) T. Hjelmgaard, S. Faure, P. Lemoine, B. Viossat and D. J. Aitken, *Org. Lett.*, 2008, **10**, 841–844; (*b*) G. R. Stanton, P.-O. Norrby, P. J. Carroll and P. J. Walsh, *J. Am. Chem. Soc.*, 2012, **134**, 17599–17604.

26 G. M. Sheldrick, *Acta Crystallogr., Sect. A: Fundam. Crystallogr.*, 2008, **64**, 112–122.