A stereocontrolled access to functionalized cispentacins and acyclic $\beta^{2,3}$-amino acids through oxidative ring cleavage

PhD Thesis

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2014

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Papers related to the thesis

I. Loránd Kiss, **Maria Cherepanova**, Enikő Forró, Ferenc Fülöp
A novel access to functionalized cispentacins from norbornene β-amino acids
Chem. Eur. J. **2013**, *19*, 2102-2107. **IF: 5.83***

II. **Maria Cherepanova**, Loránd Kiss, Reijo Sillanpää, Ferenc Fülöp
Synthesis of novel functionalized cispentacins through C-C oxidative cleavage of *diendo*-norbornene β-amino acid
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*2012 impact factors

Conference lectures

I. **Maria Cherepanova**
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XXXIV. Kémiai Előadói Napok
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II. **Maria Cherepanova**
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A Szegedi Ifjú Szerves Kémikusok Támogatásáért Alapítvány Tudományos Előadóülése
Szeged, 8 May 2012.

III. **Maria Cherepanova**, Loránd Kiss, Ferenc Fülöp
Synthesis of novel highly functionalized cispentacins
MTA Heterociklusos és Elemorganikus Kémiai Munkabizottság ülése
Balatonszemes, 6-8 June,2012.

IV. **Maria Cherepanova**, Loránd Kiss, Ferenc Fülöp
Synthesis of novel highly functionalized cyclic β-amino acids
BOSS XII – 13th Belgian Organic Synthesis Symposium,
Leuven, Belgium, 15-20 July 2012.

V. **Maria Cherepanova**, Loránd Kiss, Enikő Forró, Ferenc Fülöp
A *de novo* stereocontrolled approach to *syn* and *anti* disubstituted acyclic $\beta^{2,3}$-amino acids
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List of abbreviations

BINAP	2,2'-bis(diphenylphosphino)-1,1'-binaphthyl
CAL-B	*Candida antarctica* lipase B
CSA	camphorsulfonic acid
CSI	*N*-chlorosulfonyl isocyanate
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
d.e.	diasteremeric excess
DMAP	4-dimethylaminopyridine
DPPA	diphenylphosphoryl azide
d.r.	diastereomeric ratio
e.e.	enantiomeric excess
e.r.	enantiomeric ratio
HMPA	hexamethylphosphoramide
KHMDS	potassium bis(trimethylsilyl)amide
LDA	lithium diisopropylamide
LiHMDS	lithium bis(trimethylsilyl)amide
m-CPBA	*meta*-chloroperoxybenzoic acid
MeO-BIPHEP	[2-[2-di(phenyl)phosphanyl-6-methoxy-phenyl]-3-methoxy-phenyl]-di(phenyl)phosphane
NMM	*N*-methylmorpholine
NMO	*N*-methylmorpholine *N*-oxide
(*R*)-BINOL	(R)-(+)-1,1'-bi-2-naphthol
(*R*,*R*)-Me-BPE-Rh(I)	(+)-1,2-bis((2*R*,5*R*)-2,5-dimethylphospholano)ethane(1,5-cyclooctadiene)
(*S*)-TunaPhos	(*S*)-bis(diphenylphosphino)-7,8-dihydro-6*H*-dibenzo[f,h][1,5]dioxonin
(*S*,*S*)-*i*-Pr-pybox	(*S*,*S*)-2,2-(2,6-pyridinediyl)bis(4-isopropyl-2-oxazoline

1. INTRODUCTION AND AIMS

β-Amino acids are in the limelight of current interest due to their valuable pharmacological properties. They serve as essential structural units of a number of biologically active compounds, found in natural products. Naturally occurring cyclopentane-based β-amino acids, such as cispentacin[1-10] and icofungipen[1-10], are strong antifungal agents, while the cyclohexane amino acid Tamiflu[11] and the *O*-heterocyclic amino acid Zanamivir[12] exert notable antiviral activities. These compounds serve as building blocks of β-lactams, antibiotics and peptides. Open-chain β-amino acids, and particularly $\beta^{2,3}$-amino acids, a subclass of β-amino acids, are also structural elements of natural products with activity against leukemia, e.g. Dolastatin 11, 12, 16 and D[13], Majusculamide C[14] and Onchidin[15], natural antitumoural agents such as Guineamide C and D[16], Ulongapeptin[17] and Malevamide C[17-39].

The Institute of Pharmaceutical Chemistry at the University of Szeged has extensive experience in the field of the synthesis and transformation of β-amino acids. The research is focused on the development of stereoselective approaches towards highly functionalized alicyclic and open-chain β-amino acid derivatives. The regio- and stereoselective syntheses of mono- and dihydroxylated, mono- and difluorinated, protected amino, epoxy, azido, isoxazoline alicyclic β-amino acid derivatives, starting from the appropriate alicyclic unsaturated β-lactams have been successfully accomplished by C-C ring double bond functionalization[40-54] (Figure 1).

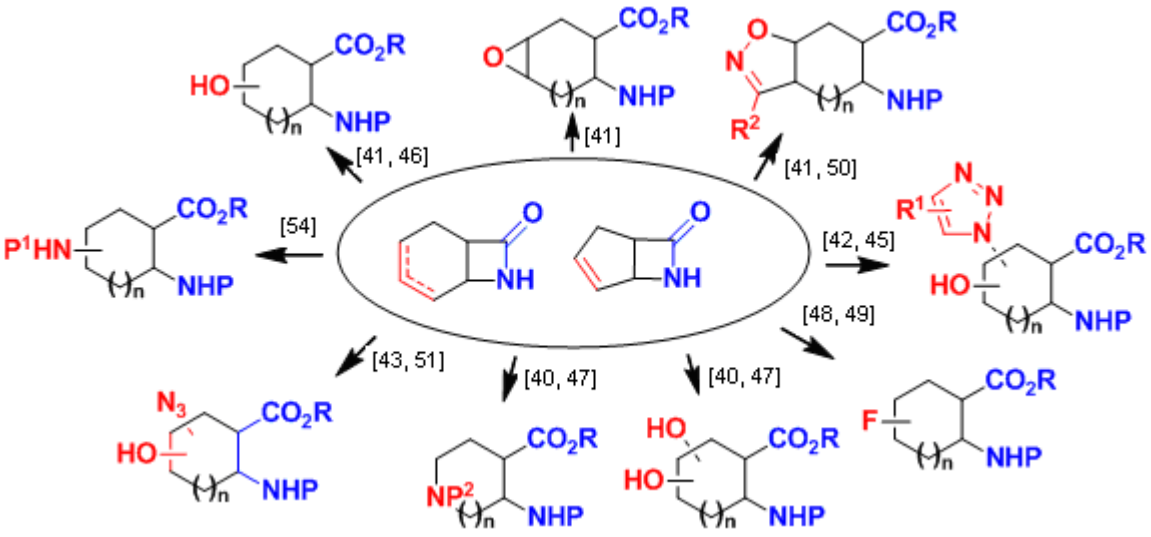


Figure 1. Selected examples of the functionalization of cyclic β-amino acid derivatives

Although numerous methods have been reported for the synthesis of β-amino acid derivatives, the development of new regio-, stereocontrolled, efficient approaches towards highly functionalized enantiomerically pure species still remains an important goal.

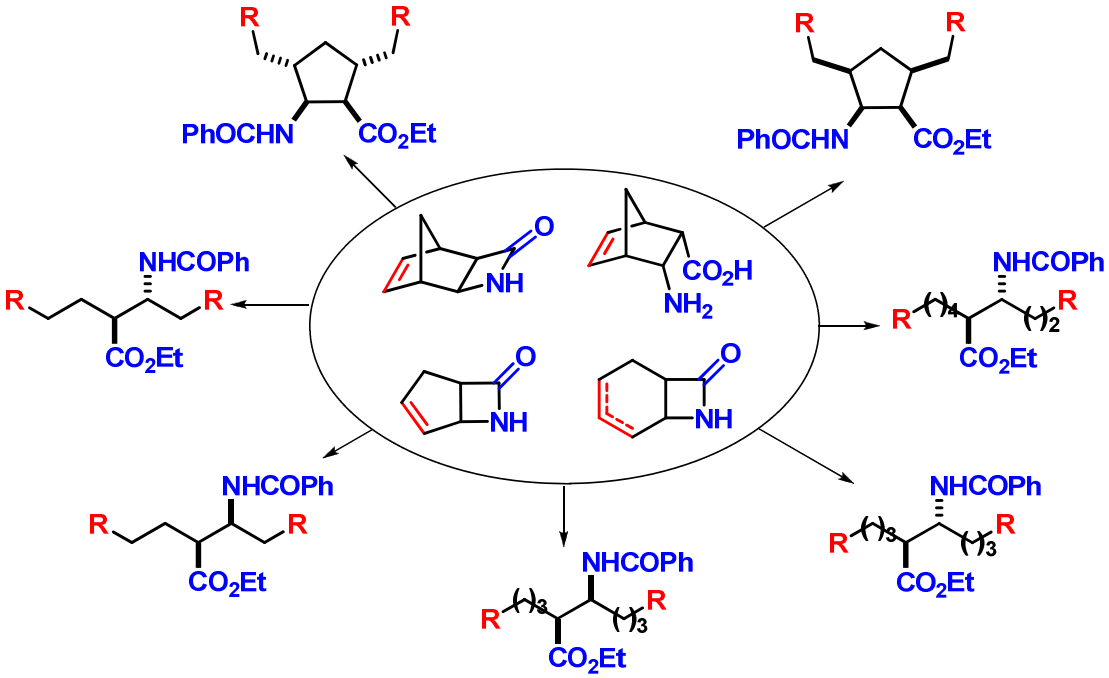


Figure 2. Reactions investigated in the present PhD work

The present PhD work was focused on the development of stereocontrolled synthetic strategies to novel enantiomerically pure disubstituted alicyclic β-amino esters derived from norbornene-based *diendo*- and *diexo*-β-amino carboxylates and acyclic $\beta^{2,3}$-substituted amino acid derivatives from *cis* or *trans* cyclopentene and cyclohexene β-amino acids. The method is based on functionalization of the ring C-C double bond of the β-lactam through dihydroxylation, and oxidative C-C bond cleavage of the vicinal diol, followed by Wittig transformation with different phosphoranylides and reduction of the olefinic bond. All products were obtained in both racemic and optically pure forms (Figure 2).

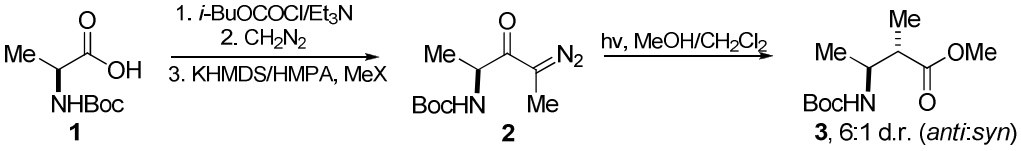
2. LITERATURE BACKGROUND

Synthetic routes towards $\beta^{2,3}$-amino acids

Since the Institute of Pharmaceutical Chemistry has gained considerable experience in the synthetic elaboration of functionalized cyclic β-amino acid derivatives, and a significant number of papers have been published on this field[55], the current literature survey is focused on the synthesis of open-chain β-amino acids, and particularly $\beta^{2,3}$-amino acid derivatives. The most relevant synthetic procedures will be highlighted below.

2.1. Homologation of α-amino acids via Wolff rearrangement of α-alkylated-α-diazoketones

The Wolff rearrangement is one of the most practical reactions for elongation of the carbon chain of carboxylic acids by one carbon atom. Yang et al. reported a synthesis of $\beta^{2,3}$-dialkylated β-amino acids through the photo-induced Wolff rearrangement[56]. The α-alkyl-α-diazoketone **2** required as precursor for the reaction was synthetized from the corresponding α-amino acid **1** through diazomethane coupling, followed by an anionic alkylation reaction. The subsequent Wolff rearrangement was triggered by UV light at -78 °C to give a ketene intermediate, which was further trapped by alcohol to furnish the desired $\beta^{2,3}$-amino acid derivatives (Scheme 1).

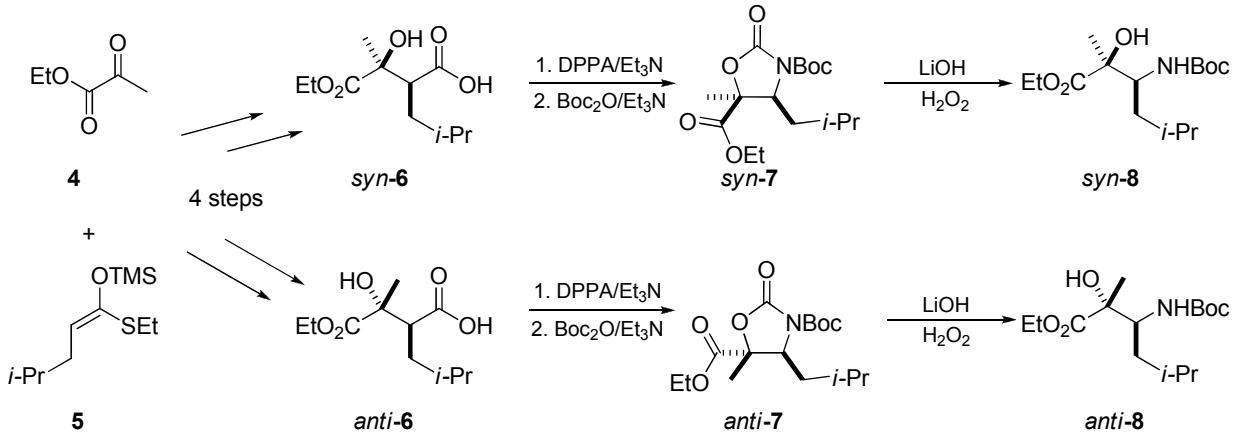


Scheme 1. Homologation of α-amino acids via the Wolff rearrangement

The stereochemistry of the major diastereomer was determined to be *anti*. The steric size of the substituents plays a crucial role in the stereoselectivity of this reaction.

2.2. Curtius rearrangement of 2,3-disubstituted 1,4-dicarboxylic acids

The Curtius rearrangement provides access to di- or trisubstituted β-amino acid derivatives through a carboxyl → amine conversion.



Scheme 2. Synthesis of α-hydroxy $\beta^{2,3}$-amino acids via the Curtius rearrangement

Roers and co-workers reported the synthesis of *syn* and *anti* α-hydroxy $\beta^{2,3}$-amino acids (*syn*-**8** and *anti*-**8)** via a modified Curtius rearrangement, utilizing DPPA (diphenyl phosphoryl azide) as an azide source (Scheme 2). The synthetic sequence includes a stereoselective aldol reaction catalysed by chiral Sn(II) and Cu(II) complexes, which allows the preparation of *syn*-**6** and *anti*-**6** precursors in an optically pure form with e.e. up to 91%. The modified Curtius rearrangement leads to oxazolidinones *syn*-**7** and *anti*-**7** through an isocyanate intermediate, which undergoes further intramolecular cyclization. After Boc protection, the cyclic oxazolidinones were submitted to basic hydrolysis in order to obtain the target $\beta^{2,3}$-amino acids *syn*-**8** and *anti*-**8** in good yields[57].

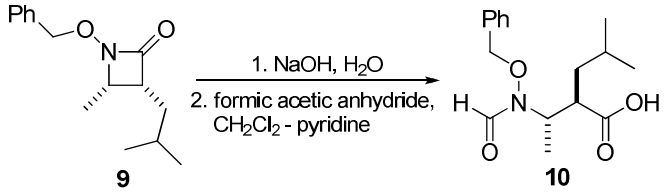
A further example of the Curtius rearrangement-based approach is the synthesis of iturinic acid and 2-methyl-3-aminopropanoic acid as reported by Sibi and Deshpande. They described a stereo- and chemoselective carboxyl group conversion into an amino group in alkyl-substituted succinates, while the other carboxyl group was protected by a chiral auxiliary[58]. Similar methodology was applied by the Evans group in order to obtain both β-alkyl and β-aryl amino acid species with high enantiomeric excess[59]. Balamurugan et al. described the preparation of *trans*-$\beta^{2,3}$-amino acids via an *anti*-selective aldol reaction, azidation and controlled hydrolysis of the chiral auxiliary[60].

2.3. Ring opening of disubstituted β-lactams

The single-step conversion of 2,3-disubstituted β-lactams provided a direct access route to $\beta^{2,3}$-amino acids, although the synthesis of the precursor β-lactams in stereo- and chemoselective fashion still remains a synthetic challenge. It should be noted that the use of

N-acyl β-lactams is preferable, since the acyl group enhances the β-lactam carbonyl reactivity towards nucleophilic attack and serves as a protecting group of the newly formed amino function[29].

Musso et al. described a synthesis of formamido acid derivative **10** via hydrolysis of β-lactam **9** in basic aqueous media, followed by an *N*-formylation reaction[61] (Scheme 3).

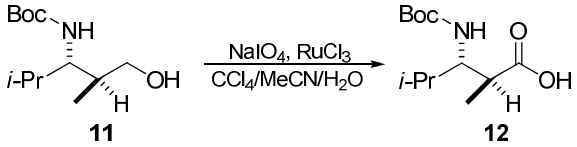


Scheme 3. Ring opening of a β-lactam via basic hydrolysis

Ojima and co-workers reported a hydrolysis of β-lactam under acidic conditions to afford enantiomerically pure α-alkylisoserine hydrochlorides[62]. For substrates showing high instability in strong basic media, mild alcoholysis in the presence of NaN_3 or KCN can be an alternative, demonstrated by Palomo et al[63].

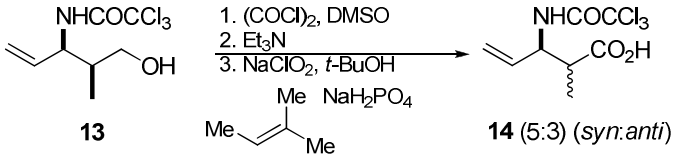
2.4. Oxidation of 2,3-disubstituted 1,3-amino alcohols

Sabala et al. recently reported the oxidation of dialkylated amino alcohol **11** into an *N*-protected amino acid **12** by means of $NaIO_4$, with a catalytic amount of $RuCl_3$ and enantiomerically pure starting materials (Scheme 4)[64]. The same strategy was earlier applied by the Davis group for the synthetic generation of dialkylated *N*-Ts-protected amino acids in asymmetric fashion with good yields[65].



Scheme 4. Oxidation of 1,3-amino alcohols by $NaIO_4$ and $RuCl_3$

The Swern–Pinnick oxidation of 1,3-amino alcohol **13,** demonstrated by Meiries et al., resulted in α-methyl-β-vinyl β-amino acid derivative **14.** The first step involved Swern oxidation of the primary alcohol to the aldehyde, using dimethyl sulfoxide activated by oxalyl chloride. Further Pinnick oxidation of the aldehyde group into the carboxylic acid was performed by treatment with $NaClO_2$ and NaH_2PO_4 (Scheme 5)[66].

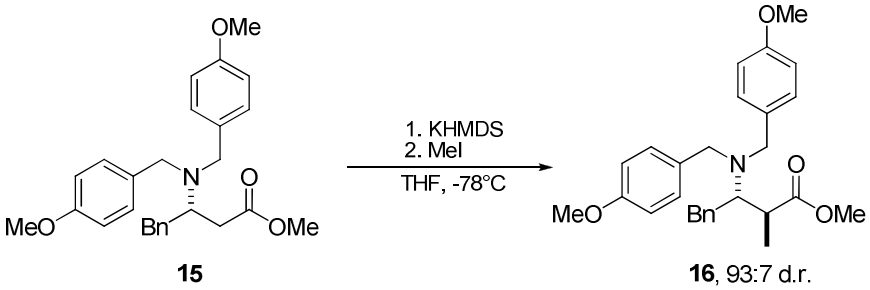


Scheme 5. Swern–Pinnick oxidation of amino alcohol **13**

The disadvantage of the procedure was the significant level of epimerization that occurred in the course of the Swern oxidation, resulting in an inseparable 5:3 mixture of *syn/anti* diastereomers.

2.5. Alkylation of β^3-amino acid derivatives

A highly diastereoselective synthesis of $\beta^{2,3}$-dialkylated amino acid derivatives can be achieved through the direct alkylation of β^3-amino acids. Capone et al., for instance, described a versatile synthesis of *anti*-α,β-dialkyl β-amino acid **16** by exploiting the α-acidity of the β^3-amino acid derivative **15**[67]. Deprotonation of the active methylene first took place, leading to enolate formation, which is followed by treatment with methyl iodide (Scheme 6).



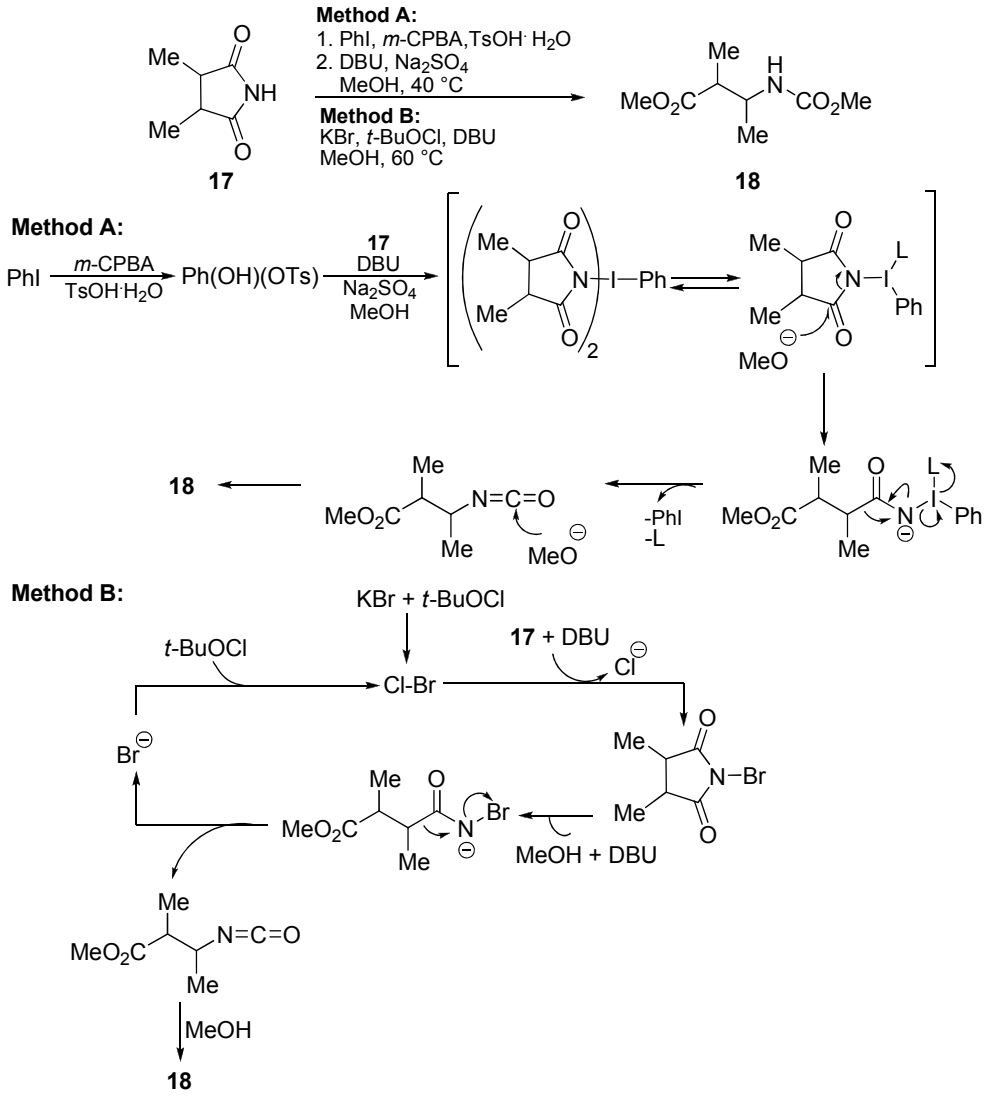
Scheme 6. Alkylation of β^3-amino acid derivatives

The high *anti* diastereoselectivity obtained can be explained by the presence of two *N*-protective groups, which help to avoid side-reactions in the basic reaction medium. The formation of a *Z*-enolate, providing the more stable conformation, can account for the excellent diastereoselectivity through the alkylation from the less hindered face.

This methodology was successfully applied in a number of additional papers, including the preparation of the disubstituted 3-aminobutanoic acids as starting materials for enzymatic resolution by Cardillo et al.[68], the synthesis of dialkylated amino esters of methionine, allylglycine and serine by Gardiner and co-workers[69], and dialkylated 3-aminobutanoic acid synthesis by Heinrich and Seebach[70].

2.6. Rearrangement of imides with hypervalent iodine reagents

Aliphatic amides can be transformed into aliphatic amino acid derivatives via the Hoffmann rearrangement. Two recent synthetic variations of this reaction are known and presented herein. The first method describes the synthesis of dialkylated β-amino acid derivatives by means of hypervalent iodine(III) generated *in situ* from an iodoarene and an oxidant (Scheme 7)[71]. The rearrangement involves the formation of an imide-hypervalent iodine(III) complex, followed by ring opening of the imide. The proposed mechanism includes the oxidation of iodobenzene by *m*-CPBA in the presence of $TsOH \cdot H_2O$, followed by formation of the imide-λ^3-iodane intermediate through the reaction with imide under basic conditions. The ring opening leads to formation of an isocyanate, and subsequent alcohol addition yields the $\beta^{2,3}$-amino acid species **18**.



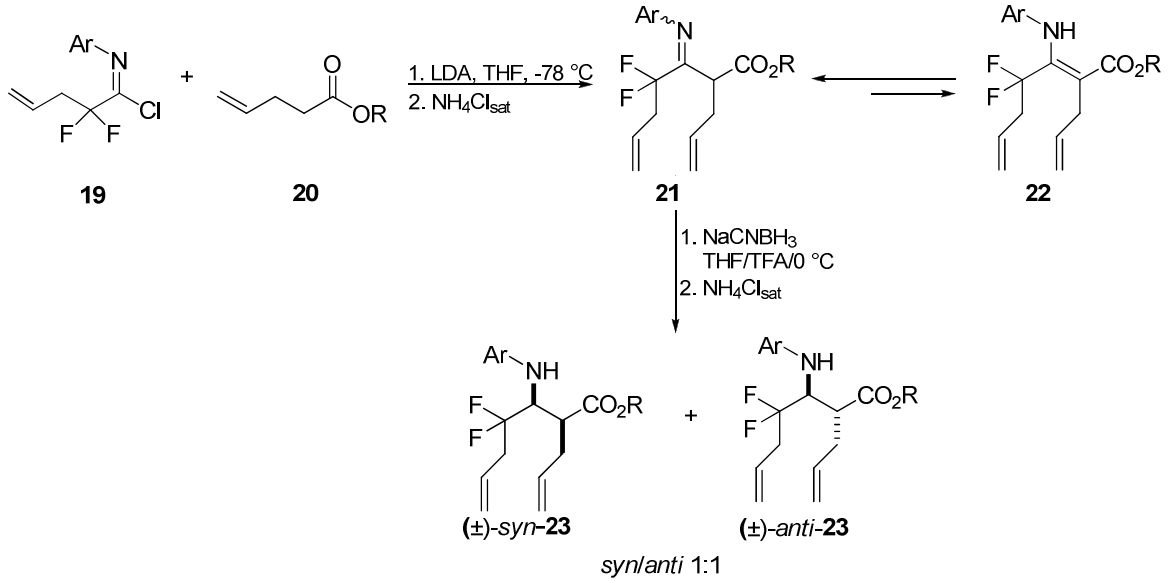
Scheme 7. Hoffmann rearrangement of imides with hypervalent iodine reagents

The second method introduces a Hoffmann rearrangement of imides via the oxidation of alkali metal halides[72]. KBr was used as a bromine source, which was oxidized by *t*-BuOCl in order to generate bromine chloride *in situ*. *N*-Bromo imide formation then takes place, followed by ring opening, and the Hoffmann rearrangement affords the isocyanate. The corresponding carbamate **18** is next formed via bromide elimination and addition of alcohol. The eliminated bromide is oxidized to bromine chloride by *t*-BuOCl, and participates in a new catalytic cycle. This method allows the synthesis of desired products without halogen-containing organic waste.

Saavedra et al. reported another methodology for the preparation of dialkylated β-amino acid derivatives from α-amino acids via a one-pot scission-oxidation-Mannich reaction[73].

2.7. Reaction of carboxylic acid esters with imidoyl chlorides

One specific application towards disubstituted β-amino acid derivatives is based on the reactions between carboxylic acid esters with imidoyl chlorides described by Fustero's group[74]. The synthetic protocol used for the preparation of the imidoyl chlorides was previously described by Uneyama et al.[75]. The first step in the Fustero synthesis, depicted in Scheme 8, includes enolate formation by the treatment of pentenoic esters with LDA, followed by a direct Mannich-like reaction that gives β-amino ester **21** after work-up. The final product **21** was isolated as a mixture of imino-enamino tautomers **21** and **22**.

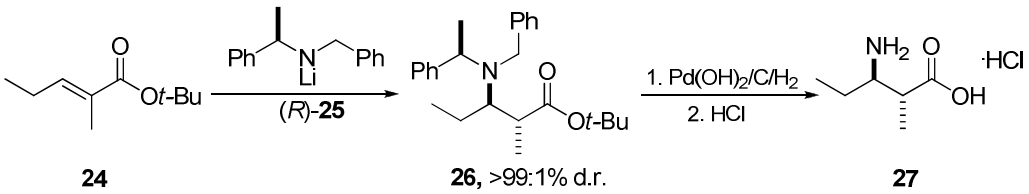


Scheme 8. Reactions of carboxylic acid esters with imidoyl chlorides

Subsequent reduction with sodium cyanoborohydride as reducing agent proved to be best in terms of the isolated yield, but the reaction did not display any stereoselectivity, since both diastereomers were obtained, in 1:1 ratio.

2.8. Michael addition of chiral amines to α, β-unsaturated esters

The Michael addition of chiral lithium amides to α,β-unsaturated esters serves as a powerful synthetic tool for the preparation of β-amino acid derivatives. Davies and co-workers were the first to demonstrate the stereoselective 1,4-conjugate addition of optically pure lithium amide (*R*)-**25** to disubstituted ester **24** with a d.e. >95%, followed by protection group cleavage with H_2 and $Pd(OH)_2/C$, and ester hydrolysis furnished enantiomerically pure dimethyl-β-amino acid **27** (Scheme 9)[76].



Scheme 9. Michael addition of lithium amide **25** to α,β-unsaturated ester **24**

The high diastereoselectivity can be envisioned in terms of a proposed model (Figure 3), wherein the lowest energy transition state belongs to the α,β-unsaturated ester with an *s-cis* conformation. The lithium is chelated to both the carbonyl oxygen and the nitrogen lone pair, and the two phenyl groups are situated almost parallel to each other. In this case the *si*-face addition is the favourable process, resulting in pronounced stereoselectivity.

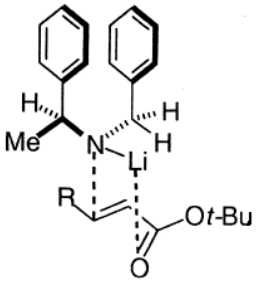
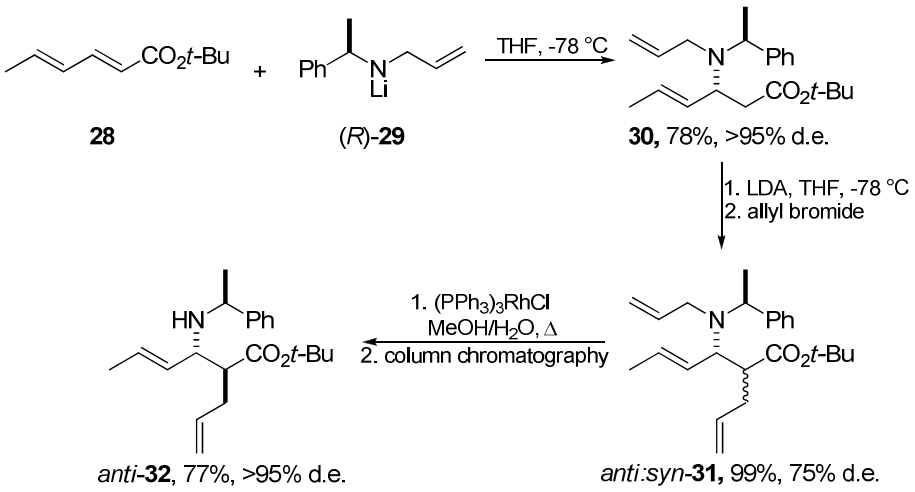


Figure 3. Proposed transition model of the lithium amide-α,β-unsaturated ester complex

The hydrogenolysis applied in the final step often cannot be used in the cases of substances containing certain functionalities, such as a π-bond, in consequence of likely undesired reductions. In order to avoid these side-reactions, the utilization of milder

protecting group chemistry is required. One such example of the synthesis of $\beta^{2,3}$-amino acid derivatives, introducing *N*-allyl protecting group chemistry, is that reported by Chippindale et al[77]. First, conjugate addition of chiral allylated lithium amide (*R*)-**29** to (*E*,*E*)-*tert*-butylhexa-2,4-dieneoate **28** gave access to **30** in a yield of 78% and >95% d.e. (Scheme 10).



Scheme 10. Michael addition of chiral amide **29** to ester **28**

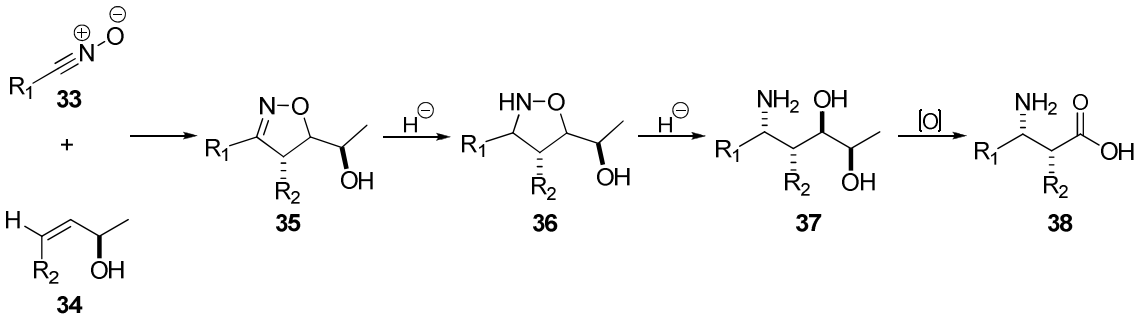
The next step involved a deprotonation of *N*-allyl β-amino ester **30** by LDA, and subsequent allylation with allyl bromide led to an inseparable mixture of *anti* and *syn* diastereomers in 75% d.e. Subsequent deallylation by Wilkinson's catalyst produced a mixture of secondary amines, which could be separated by means of column chromatography, furnishing the major *anti* diastereomer **32** in >95% d.e.

This approach was further successfully applied by Bentley et al. in order to obtain $\beta^{2,2,3}$-trisubstituted amino acids via conjugate addition of a "hydroxylamine equivalent" lithium amide to β-alkyl and β-aryl α,β-unsubstituted esters[78,79]. Ozeki et al. reported a synthesis of β-amino-β'-hydroxy esters through the Michael addition of *N*-benzyl-2(*R*)-methoxy-(+)-10-bornylamide to α,β-unsaturated esters[80].

2.9. Dipolar cycloaddition of nitrile oxides to olefins

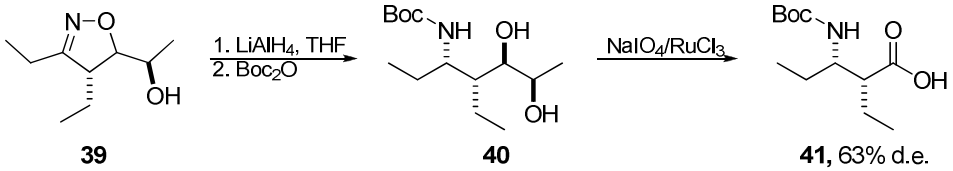
Chiral isoxazolinones serve as key intermediates for the synthesis of various highly substituted β-amino acid derivatives. Their stereoselective synthesis can be achieved through 1,3-dipolar cycloaddition of a nitrile oxide and a chiral allylic alcohol, originally described by Kanemasa et al.[81]. A general strategy for the synthesis of β-amino acids from isoxazolines is depicted in Scheme 11. Cycloaddition of nitrile oxide **33** and allyl alcohol **34** followed by

reduction gave isoxazolidine **36**. Subsequent reductive cleavage of the N-O bond, followed by oxidative C-C bond cleavage of the diol **37,** furnished the final product amino acid **38.**



Scheme 11. General scheme of the isoxazoline strategy towards the synthesis of β-amino acids

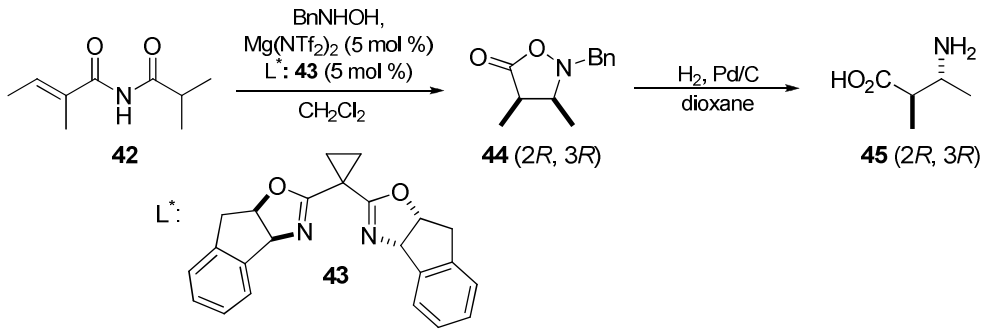
On the basis of the above-mentioned procedure, Minter and co-workers reported a similar route to dialkylated $\beta^{2,3}$-amino acids (Scheme 12)[82]. First, isoxazoline **39** was gained via 1,3-dipolar cycloaddition of a nitrile oxide, generated *in situ* from the corresponding oxime, to a magnesium allyl alcoholate. Compound **39** was then reduced with $LiAlH_4$ in THF, and subsequent one-pot *N*-protection afforded amino diol **40** as a mixture of diastereomers. Oxidative C-C bond cleavage with $NaIO_4$ and $RuCl_3$ gave diethyl-*N*-Boc-protected β-amino acid **41** in 67% d.e. The method was supported by theoretical considerations and further extended to the synthetic generation of various substrates by the same group[83, 84].



Scheme 12. Reduction of isoxazoline **39** and further oxidation to β-amino acid **41**

One more intriguing example of asymmetric disubstituted β-amino acid synthesis via dipolar cycloaddition was presented by Sibi and co-workers[85]. The first step in the synthesis involved a Lewis acid-catalysed aza-Michael addition of *N*-benzylhydroxylamine to α,β-disubstituted imide **42,** and intramolecular S_N acyl lactonization then resulted in the formation of isoxazolidinone **44** (Scheme 13). The active Lewis acid catalyst formed *in situ* was derived from the chiral *bis*-dihydro-oxazole framework **43** as ligand and a magnesium salt. The high stereocontrol of the aza-Michael addition is proven by the chiral ligand, which provides

sufficient steric hindrance, and the subsequent addition of nitrogen occurs on the *Re* face of the β-carbon.



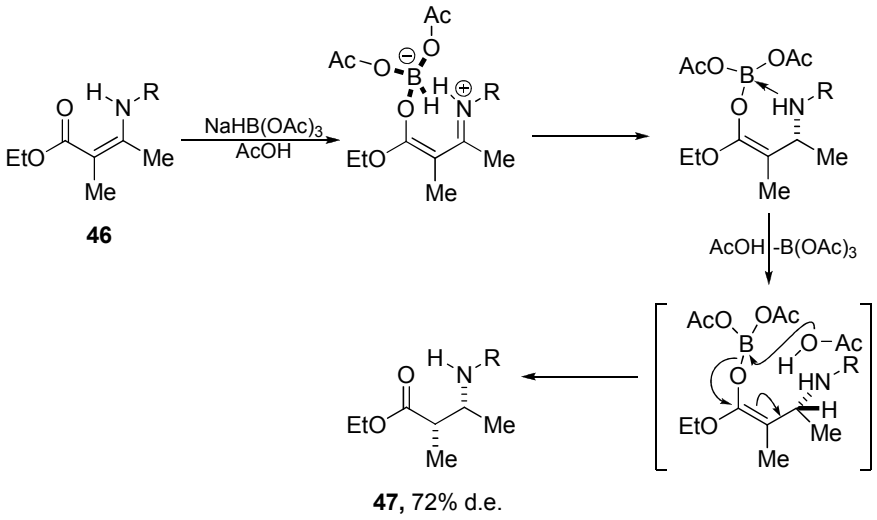
Scheme 13. Enantioselective synthesis of β-amino acid **45** through cycloaddition

The reductive ring cleavage of isoxazolidinone **44** through Pd/C-catalysed hydrogenolysis furnished dimethyl-β-amino acid **45** in optically pure form.

2.10. Asymmetric hydrogenation of β-enamino esters

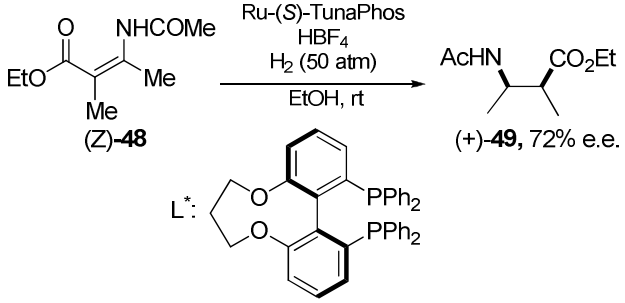
Catalytic asymmetric hydrogenation or reduction of β-enamino esters is a practical method for the preparation of optically pure β-amino carboxylates in the presence of chiral ruthenium(II) or rhodium(I) complexes[86]. A large number of catalytic systems have been developed in order to improve the yields and stereoselectivities[87], including rhodium-based catalysts with mono- and bidentate ligands[88-93], and chiral phosphine-based ruthenium catalysts[94,95].

To the best of our knowledge, the first approach towards dialkylated $\beta^{2,3}$-amino acid derivatives was developed by Cimarelli et al.[96] in 1996. In that paper, the diastereoselective reduction of prochiral β-enamino ester **46** was performed in the presence of $NaHB(OAc)_3$ in acetic acid, affording the *syn* β-amino ester **47** in 72% d.e. (Scheme 14).



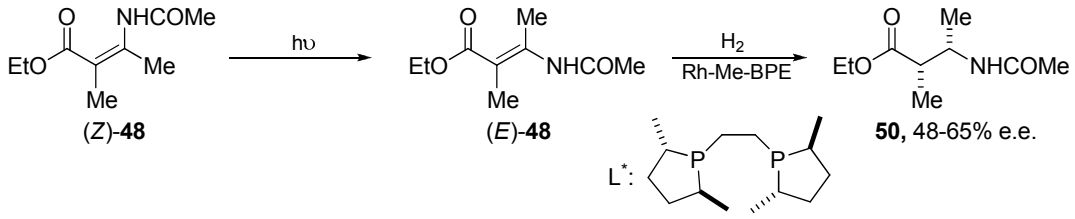
Scheme 14. Reduction of β-enamino ester **46** to β-amino ester **47** with $NaHB(OAc)_3$/AcOH

A ruthenium-catalysed hydrogenation methodology towards dialkylated β-amino esters was reported by Tang and co-workers[97]. They described the hydrogenation of enamide (*Z*)-**48** by means of a ruthenium(II) catalyst generated *in situ* by ligand exchange of Ru(COD)-$(methallyl)_2$ and a (*S*)-C_3-TunaPhos chiral ligand. The reaction, performed under 50 atm hydrogen pressure in EtOH, resulted in the (2*S*,3*R*)-*threo* isomer in 72% e.e. (Scheme 15). The application of other chiral ligands, such as BINAP, MeO-BIPHEP, C_2-, C_4-, or C_5-TunaPhos, provided similar results in terms of enantioselectivity.



Scheme 15. Hydrogenation of $\beta^{2,3}$-enamide **48** with Ru-(*S*)-TunaPhos as catalyst

The above work was extended by Elaridi and co-workers in order to obtain the *erythro* derivative[98]. Asymmetric hydrogenation of enamide (*E*)-**48** in the presence of the chiral rhodium catalyst (*R*,*R*)-Me-BPE-Rh(I) in methanol at 60 psi hydrogen pressure gave the (2*R*,3*R*)-*erythro* derivative **50** in 48% e.e. (Scheme 16).

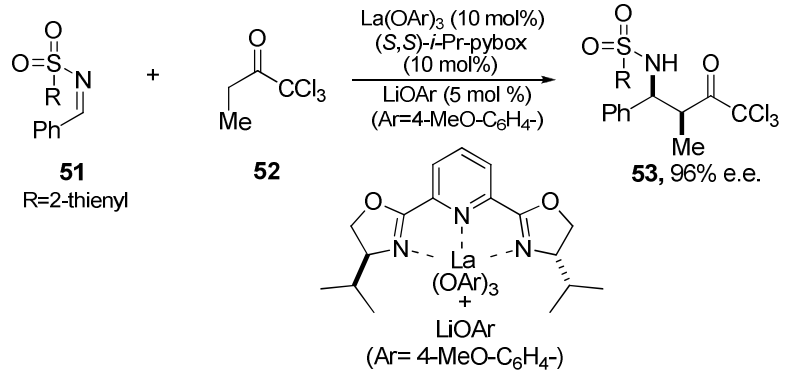


Scheme 16. Hydrogenation of $\beta^{2,3}$-enamide **48** catalysed by Rh-Me-BPE

The reaction was then further optimized, and the highest e.e. of 65% was obtained with benzene as solvent at 90 psi hydrogen pressure.

2.11. Addition of carboxylic acid derivatives or aldehydes to aldimines

The asymmetric Mannich reaction is a powerful tool for the preparation of optically active β-amino acid derivatives. Lewis acids are often employed to activate the aldehyde or the imine and to control the stereoselectivity. Morimoto and co-workers reported the improved rare metal-based enantio- and diastereoselective Mannich reaction depicted in Scheme 17[99].

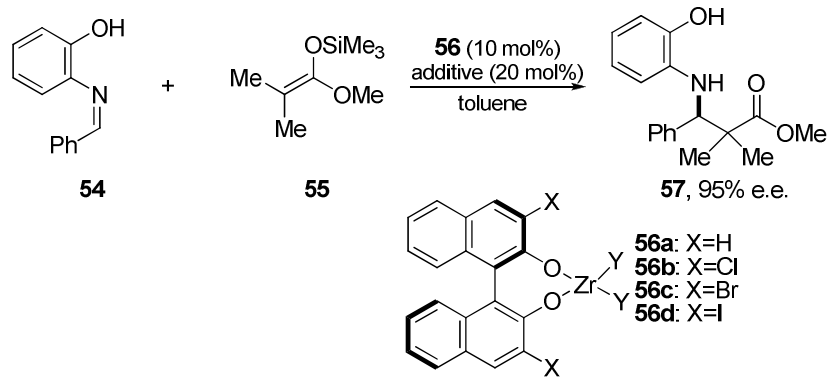


Scheme 17. Lanthanum aryloxide/pybox ligand–catalysed Mannich reaction

In this work, 1,1,1-trichlorobutan-2-one **52** was used as a Mannich donor in the reaction. A new lanthanum aryloxide-*i*-Pr-pybox + lithium aryloxide catalyst was introduced, giving *syn*-adduct **53** in 96% e.e. and *syn*:*anti* = 21:1 d.r.

While several successful examples of the chiral Lewis acid activation of aldehydes have been reported, few examples are known for imine activation by Lewis acids, probably due to the different coordination manner. Lewis acid coordinates the aldehyde from the *syn* face of the hydrogen atom of the aldehyde, but in the case of the imine the Lewis acid can coordinate either from the *syn* or from the *anti* direction of the imine hydrogen atom. Kobayashi et al.

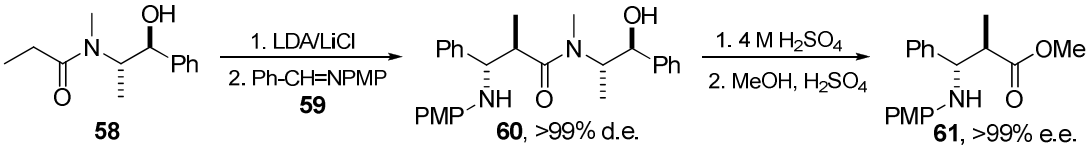
reported an example of effective imine activation in a Mannich reaction by means of a chiral zirconium catalyst (Scheme 18)[100].



Scheme 18. Chiral zirconium–catalysed Mannich reaction

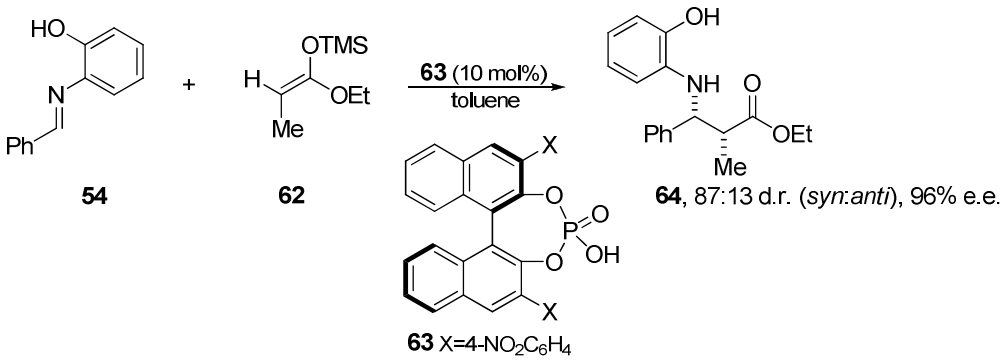
The Mannich reaction between imine **54** and silyl enolate **55**, catalysed by zirconium complex **56**, derived from $Zr(O^tBu)_4$, (*R*)-3,3'-BrBINOL, afforded the Mannich adduct **57** in 99% yield and 69% e.e. It should be mentioned that the use of water as an additive dramatically increased the enantiomeric excess up to 95%. The high enantioselectivity can be explained by the bidentate coordination of imines to the chiral zirconium catalyst, then silyl enolate interaction with the zirconium, and further attack on the stereo-activated imine furnishes product **57,** along with regeneration of the catalyst.

A further interesting example of highly diastereo- and enantioselective Mannich reactions, depicted in Scheme 19, was described by Vicario and co-workers[101]. Propionamide derivative **58** was deprotonated with LDA, and further reacted with imine **59,** yielding *anti* diastereomer β-aminoamide **60** with a d.r. of >99:1. It should be mentioned that the presence of LiCl plays a crucial role in the stability and reactivity control of the enolate; in its absence no reaction occurred. Amide **60** was transformed into optically pure disubstituted β-amino ester **61** through a hydrolysis-esterification sequence. Importantly, no racemization was observed during the transformations.



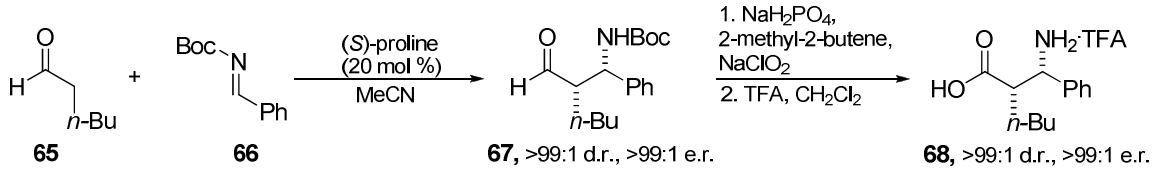
Scheme 19. Mannich reaction between the (*S*,*S*)-(+)-pseudoephedrine propionamide-derived compound **58** and imine **59**

Besides Lewis acid-catalysed Mannich reactions, a number of organocatalysts with such advantages as stability towards water and oxygen have been developed. Chiral Bronsted acids act as stronger electrophilic activators as compared with hydrogen-bond activation-based organocatalysts. A versatile Bronsted acid-catalysed Mannich reaction was recently reported by Yamanaka et al.[102] (Scheme 20). Catalyst **63** was prepared from (*R*)-BINOL. Aldimine **54** was reacted with ketene silyl acetal **62** in the presence of a catalytic amount of Bronsted acid **63,** giving the corresponding Mannich adduct **64** in 96% e.e.



Scheme 20. Chiral Bronsted acid-catalysed Mannich reaction

Several examples of highly efficient proline-catalysed Mannich reactions have also been reported, including the synthesis of α-hydroxy-β-amino acids by Dziedzic and co-workers[103] and 2,3-dialkylated β-amino acids synthesis by Yang et al.[104]. The latter approach is illustrated by the Mannich reaction between benzaldehyde-derived *N*-Boc-imine **66** and hexanal **65** in the presence of (*S*)-proline, affording the dialkylated product **67** in >99:1 d.r. and >99:1 e.r. Compound **67** was then readily converted into the corresponding β-amino acid **68** by Pinnick oxidation and acid-mediated deprotection procedures (Scheme 21).

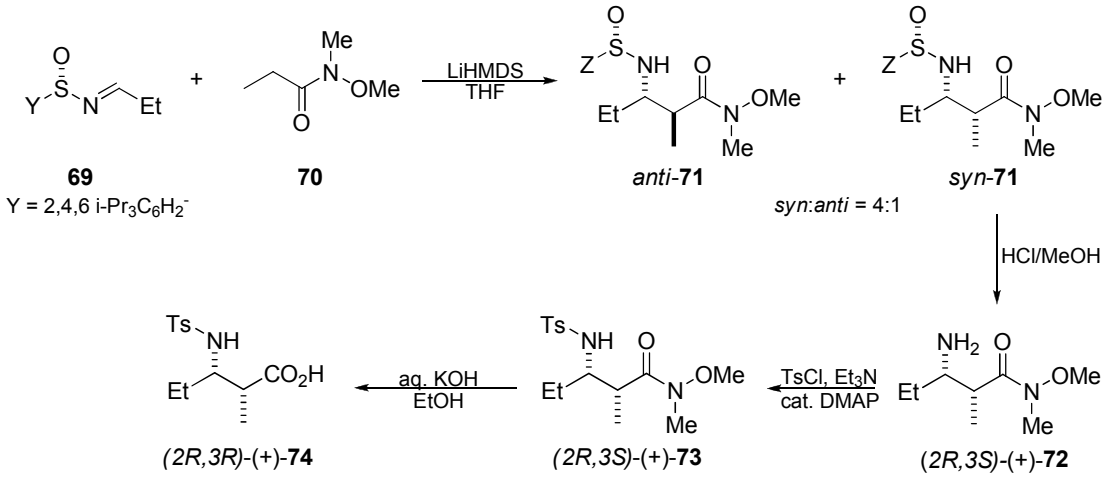


Scheme 21. Proline-catalysed Mannich reaction

The reaction catalysed by proline proved to be highly stereoselective and practical, as it does not require chromatographic purification. The current limitation of the process is that aliphatic imines cannot be used as reactants.

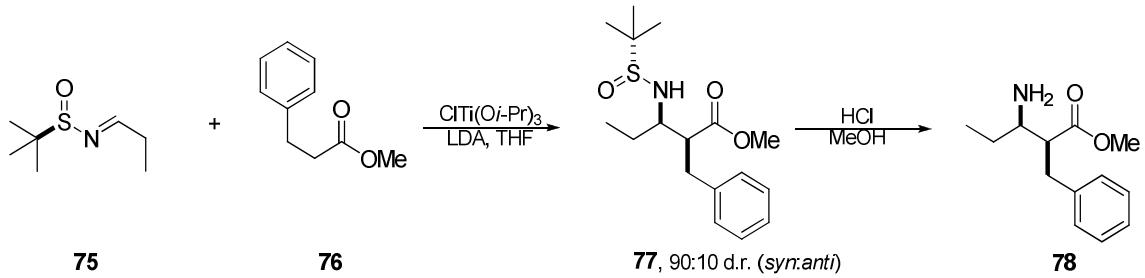
2.12. Addition of ester enolates to chiral sulfinylimines

One promising method for the preparation of disubstituted β-amino carboxylates is the addition of ester enolates to sulfinylimines, which proceeds with high yields and diastereoselectivities; moreover, the sulfinyl group can be removed with ease by treatment with HCl in protic solvents. Several studies in this field have been published by Davis et al.[105-107]. In order to obtain α,β-dialkylated β-amino Weinreb amide **71,** addition of prochiral Weinreb amide enolate **70** to chiral sulfinylimine **69** was performed, resulting in a 4:1 mixture of *syn-anti* diastereomers **71**. The diastereomeric mixture could then be separated, affording the major *syn* diastereomer in 76% yield. Selective removal of the *N*-sulfinyl group was next performed by HCl in MeOH, yielding amide **72,** which was further *N*-tosylated and hydrolysed to give the desired β-amino acid **74** (Scheme 22).



Scheme 22. Addition of Weinreb amide **70** to sulfinimine **69**

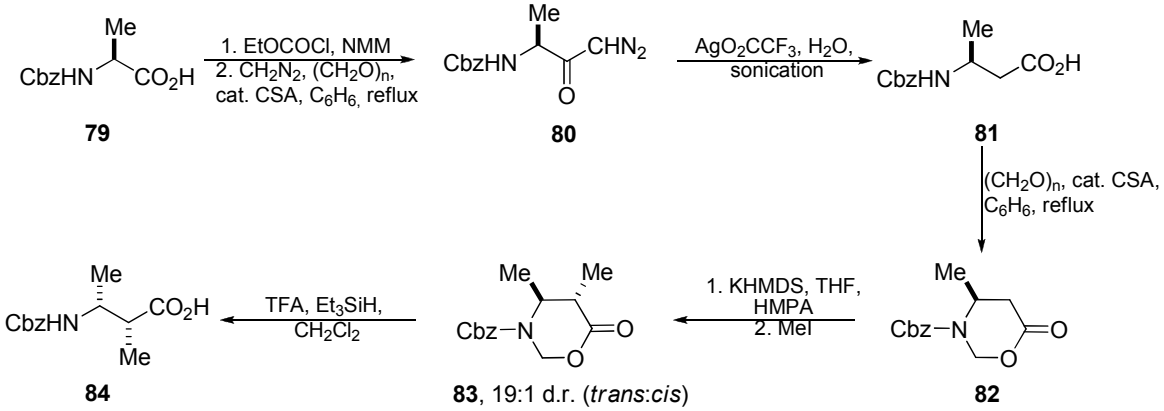
The addition of titanium enolates of carboxylic esters to sulfinylimines, described in the work of Tang et al.[108], afforded *N*-sulfinyl β-amino esters with high diastereoselectivities up to 99:1. The *N*-sulfinyl β-amino ester **77,** formed as a single diastereomer in 90:10 d.r., underwent an *N*-deprotection procedure to give access to amino acid ester **78** (Scheme 23).



Scheme 23. Addition of ester **76** to sulfinylimine **75**

2.13. Ring opening of 4,5-dialkyl-1,3-oxazinan-6-ones

The ring opening of 4,5-dialkyl-1,3-oxazinan-6-ones provides access to a diverse range of $\beta^{2,3}$-disubstituted amino acid derivatives[109,110]. The synthesis of 1,3-oxazinan-6-one **82** is depicted in Scheme 24. First, β-amino acid **81** was prepared through Arndt-Eistert homologation of α-amino acid **79**. Acid-catalysed cyclization of *N*-protected β-amino acid **81** then resulted in the desired intermediate **82**. Further alkylation of **82** in the presence of KHMDS and MeI furnished 5-alkyl-1,3-oxazinan-6-one **83** in a 19:1 *trans*:*cis* d.r. The diastereomers formed were separated by crystallization. The reductive cleavage of **83** proceeded smoothly, affording the *N*-protected $\beta^{2,3}$-disubstituted amino acid **84**.



Scheme 24. Synthesis of $\beta^{2,3}$-disubstituted amino acid derivative **84** via 1,3-oxazinan-6-one **82**

Different approaches towards the ring opening of 1,3-oxazinan-6-ones can give access to numerous disubstituted β-amino acid derivatives (Figure 4). The manipulations presented highlight the versatility of oxazinanones.

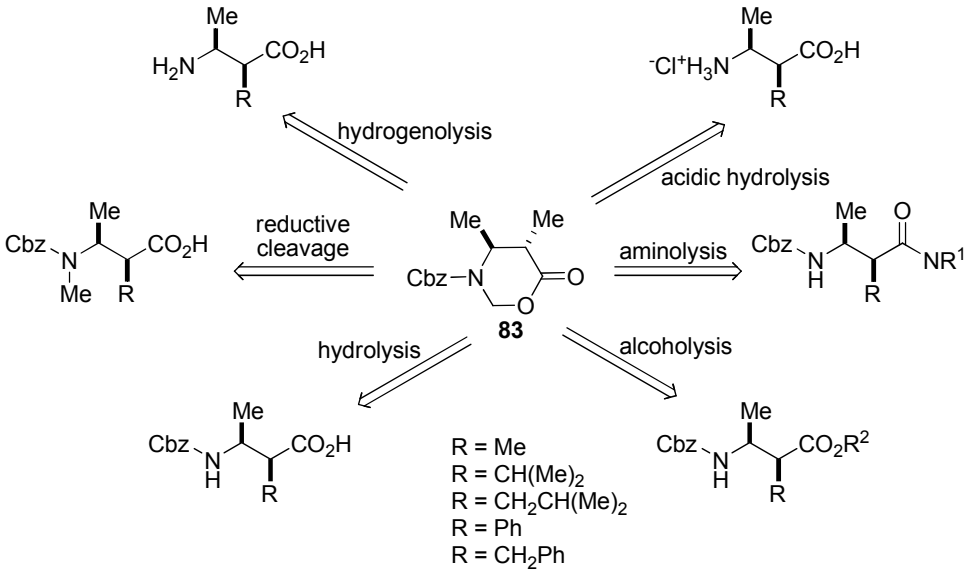


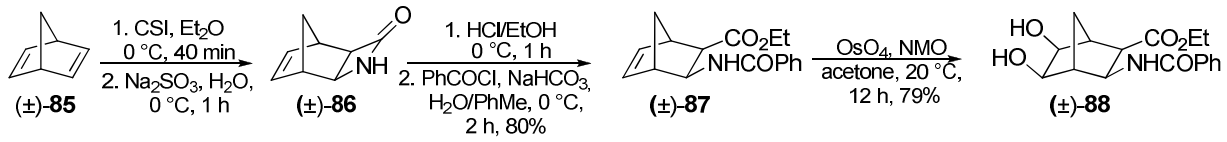
Figure 4. Oxazinanone ring openings

A wide range of synthetic strategies towards $\beta^{2,3}$-disubstituted amino acid derivatives were described above; most of them are efficient and versatile. However, a number of limitations should still be emphasized, including in some cases an insufficient level of reaction stereocontrol, the availability of properly substituted reactants, the possibility of large-scale synthesis, the difficulty of the experimental procedures, and the cost of the materials used.

3. RESULTS AND DISCUSSION

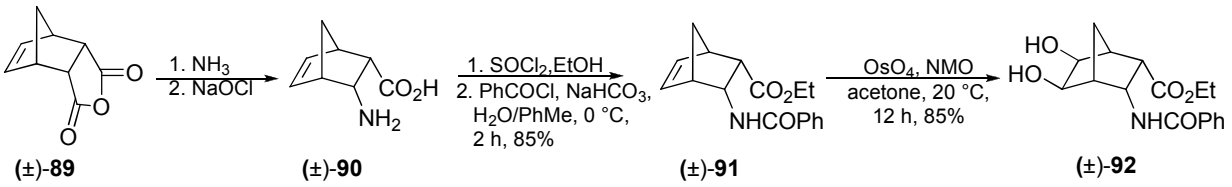
3.1. Synthesis of racemic and enantiomerically pure starting materials

The synthetic preparation of racemic dihydroxylated *diexo*-β-amino ester **(±)-88** as required starting material is depicted in Scheme 25. First, bicyclic β-lactam **(±)-86** was synthetized by *N*-chlorosulfonyl isocyanate (CSI) addition to norbornadiene, followed by chlorosulfonamide hydrolysis with Na_2SO_3[111]. The lactam ring was then opened at 0 °C with ethanolic HCl solution, and subsequent *N*-benzoyl protection resulted in *diexo*-β-amino ester **(±)-87**[112]. Further *cis*-selective dihydroxylation of **(±)-87** in the presence of a catalytic amount of OsO_4 and *N*-methylmorpholine *N*-oxide (NMO) as co-oxidant yielded dihydroxylated *diexo*-β-amino ester **(±)-88** (for the analogous transformation of Boc-protected β-amino esters, see reference 40).



Scheme 25. Synthesis of dihydroxylated *diexo*-norbonane β-amino ester **(±)-88**

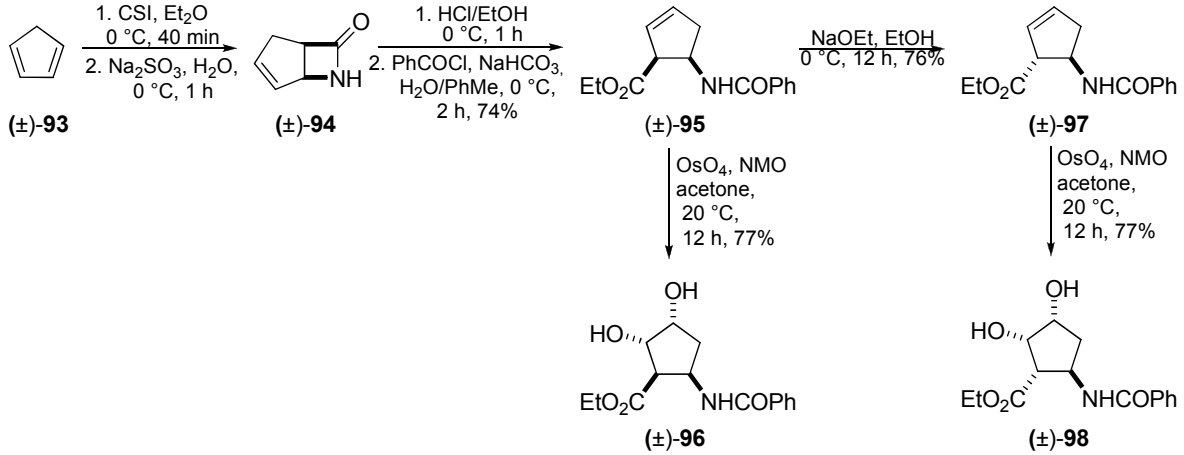
Bicyclic *diendo*-β-amino acid **(±)-90** was obtained from bicyclic *diendo*-anhydride **(±)-89** via a ring opening reaction with NH_3, followed by Hoffmann degradation[113]. The subsequent esterification procedure with EtOH and $SOCl_2$ and *N*-benzoyl protection gave *diendo*-β-amino ester **(±)-91**[112]. Stereoselective dihydroxylation of **(±)-91** by means of NMO and a catalytic amount of OsO_4 furnished the dihydroxylated *diendo*-β-amino ester **(±)-92** (Scheme 26)[40].



Scheme 26. Preparation of dihydroxylated *diendo*-norbornane β-amino ester **(±)-92**

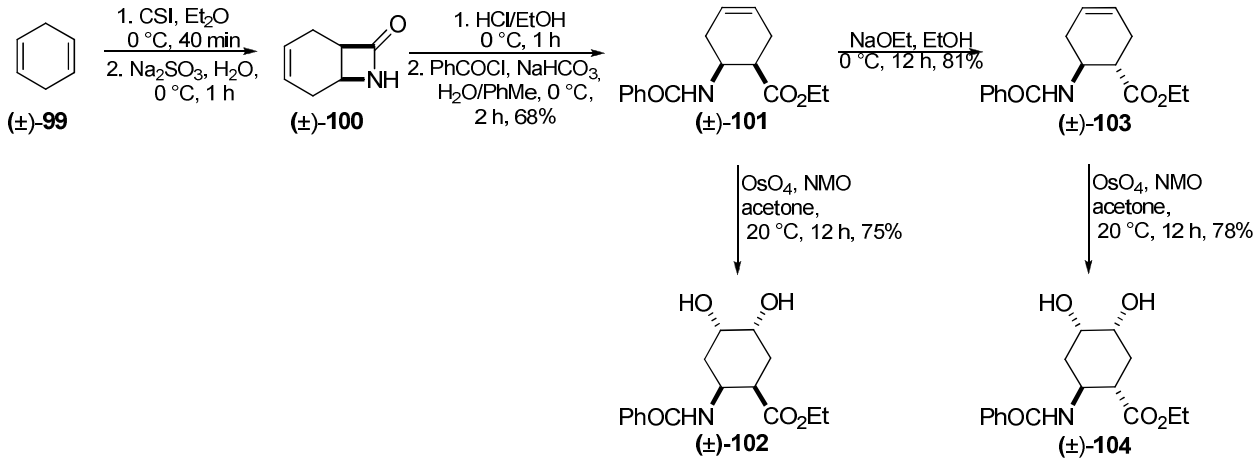
Cyclopentene-fused β-lactam **(±)-94** was prepared from cyclopentadiene **(±)-93** through CSI addition, followed by $NaSO_3$-mediated hydrolysis[114]. The β-lactam **(±)-94** was further transformed into a β-amino carboxylate **(±)-95** through ring opening with ethanolic HCl solution and benzoylation[115]. Base-induced inversion of *cis* derivative **(±)-95** with NaOEt resulted in the

trans form **(±)-97**. Further dihydroxylation of both *cis*- and *trans*-β-amino esters yielded the corresponding vicinal diols **(±)-96** and **(±)-98** (Scheme 27)[115].



Scheme 27. Synthesis of dihydroxylated *cis* and *trans* cyclopentane-based β-amino esters

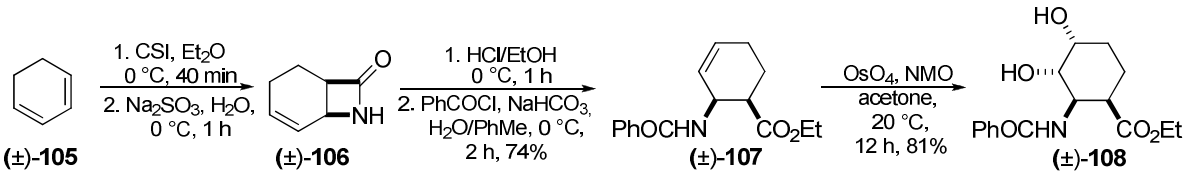
The synthesis of 1,4-unsaturated cyclohexadiene-derived β-lactam **(±)-100** was achieved from the corresponding 1,4-cyclohexadiene **(±)-99** by CSI addition[116]. Ring opening followed by *N*-benzoylation afforded β-amino ester **(±)-101**[117]. When **(±)-101** was subjected to NaOEt-mediated inversion, it gave *trans* derivative **(±)-103**. Stereoselective double bond dihydroxylation gave access to the corresponding diols **(±)-102** and **(±)-104** (Scheme 28).



Scheme 28. Synthesis of dihydroxylated *cis* and *trans* cyclohexane-based β-amino esters

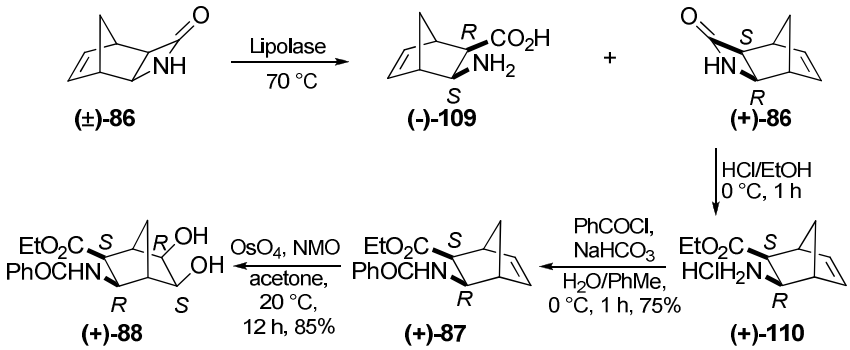
The 1,3-unsaturated cyclohexadiene-derived β-lactam **(±)-106** was prepared from the 1,3-cyclohexadiene **(±)-105**[116]. Ring opening followed by group protection afforded β-amino ester

(±)-107[117]. Stereoselective double bond dihydroxylation gave access to the corresponding diol **(±)-108** (Scheme 29).



Scheme 29. Synthesis of dihydroxylated *cis* cyclohexane-based β-amino esters

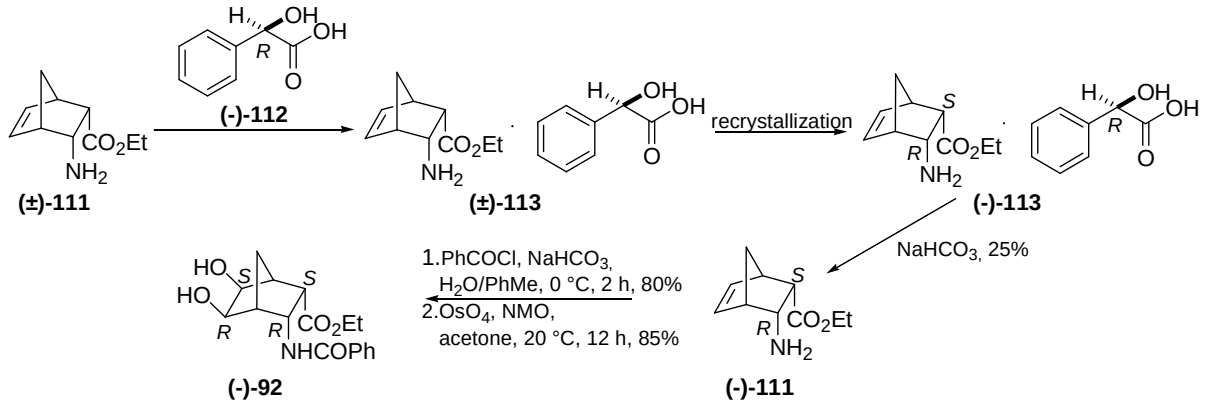
The well-established protocol for the synthesis of dihydroxylated β-amino esters allowed the preparation of starting materials in enantiomerically pure form. Racemic β-lactam was subjected to enzyme-catalysed enantioselective ring opening, which was scaled up successfully[118]. Lactam **(±)-86** was mixed with Lipolase, water was then added, and the mixture was shaken in an incubator shaker at 70 °C. Enantiomerically pure amino acid **(-)-109** (e.e. > 98%) and unreacted β-lactam **(+)-86** (e.e. = 99%) were obtained and easily separated. Enantiomer **(+)-86** was then transformed to optically pure β-amino carboxylate **(+)-87** through ring opening with HCl/EtOH solution and *N*-Bz protection. Subsequent C-C double bond dihydroxylation with OsO_4 resulted in vicinal diol **(+)-88** (Scheme 30).



Scheme 30. Enzymatic resolution of β-lactam **(±)-86** and synthesis of *diexo*-β-amino esters

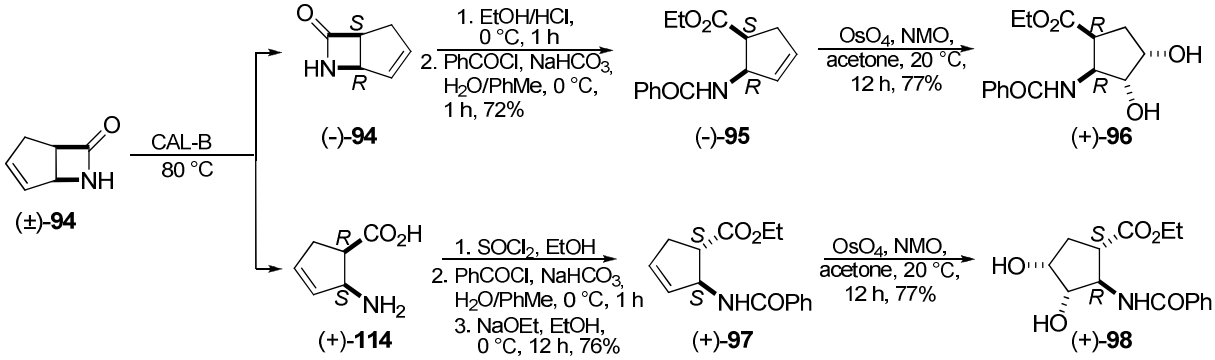
The preparation of enantiomerically pure β-amino ester **(-)-111** was attained through diastereomeric salt recrystallization. The reaction between racemic *diendo*-β-amino ester **(±)-111** and 1 equivalent of enantiomerically pure *D*-(-)-mandelic acid **(-)-112** in EtOAc for 10 min yielded the corresponding diastereomeric salt mixture **(±)-113.** The salt mixture was then twice recrystallized from EtOAc-EtOH 10:1; the diastereomeric ratio was monitored by ^{1}H NMR. The pure diastereomer was filtered off and treated with a saturated $NaHCO_3$ solution, giving optically pure *diendo*-β-amino ester **(-)-111** with e.e. = 99.9% (determined on a chiral HPLC Chiralpack IA

column, eluent: *n*-hexane–IPA (80:20), flow rate: 0.5 mL/min^{-1}, detection at 210 nm). Benzoylation and stereoselective dihydroxylation resulted in enantiomer **(-)-92** (Scheme 31).



Scheme 31. Synthesis of enantiomerically pure *diendo*-β-amino ester **(-)-92**

Cyclopentane *cis* and *trans* β-amino esters were gained through the enzyme-catalyzed kinetic resolution of β-lactam by a slightly modified literature procedure[118]. The β-lactam **(±)-94** was mixed with CAL-B (*Candida antarctica* lipase B) in *t*-BuOMe and then shaken in an incubator shaker at 80 °C. The reaction was stopped by filtering off the enzyme at 50% conversion. The solvent was evaporated off and the unreacted β-lactam **(-)-94** (e.e. = 99%) was crystallized out from diisopropyl ether. The filtered-off enzyme was washed with distilled water, and the water was evaporated off, yielding enantiomerically pure amino acid **(+)-114** (e.e. > 99%). Next, **(-)-94** was treated with HCl/EtOH solution, and the following benzoylation and dihydroxylation led to optically pure diol (1*R*,2*R*)-**(+)-96.** The amino acid **(+)-114** was transformed to *trans* β-amino carboxylate (1*S*,2*S*)-**(+)-97** via esterification, group protection and base-induced epimerization procedures. The following dihydroxylation of (+)-**97** led to formation of the enantiomer (1*S*,2*R*)-**(+)-98** (Scheme 32).

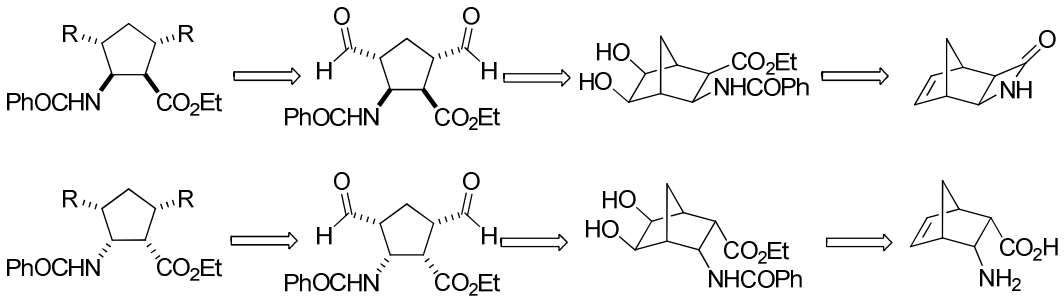


Scheme 32. Enzymatic resolution of β-lactam **(±)-94** and synthesis of dihydroxylated *cis* and *trans* β-amino esters

Preliminary experiments were first conducted by utilizing the racemic substances, and the well-established strategy was then extended to the preparation of enantiomerically pure compounds.

3.2. Functionalization of cispentacins through C-C oxidative cleavage of *diexo*-and *diendo*-norbornene β-amino acids

The syntheses of *trans*- and *all-cis*-disubstituted cispentacin derivatives were based on similar strategies, i.e. the transformation of the C-C double bond of carbocycles. The concept of the synthetic route, presented in Scheme 33, included functionalization of the ring C-C double bonds of *diexo*-norbornene β-lactam and *diendo*-β-amino acid through stereoselective dihydroxylation, and conversion of the vicinal diol by oxidative ring cleavage in order to generate the corresponding dialdehyde key intermediate, followed by Wittig transformation with different phosphoranylides and hydrogenation of the double bond formed.

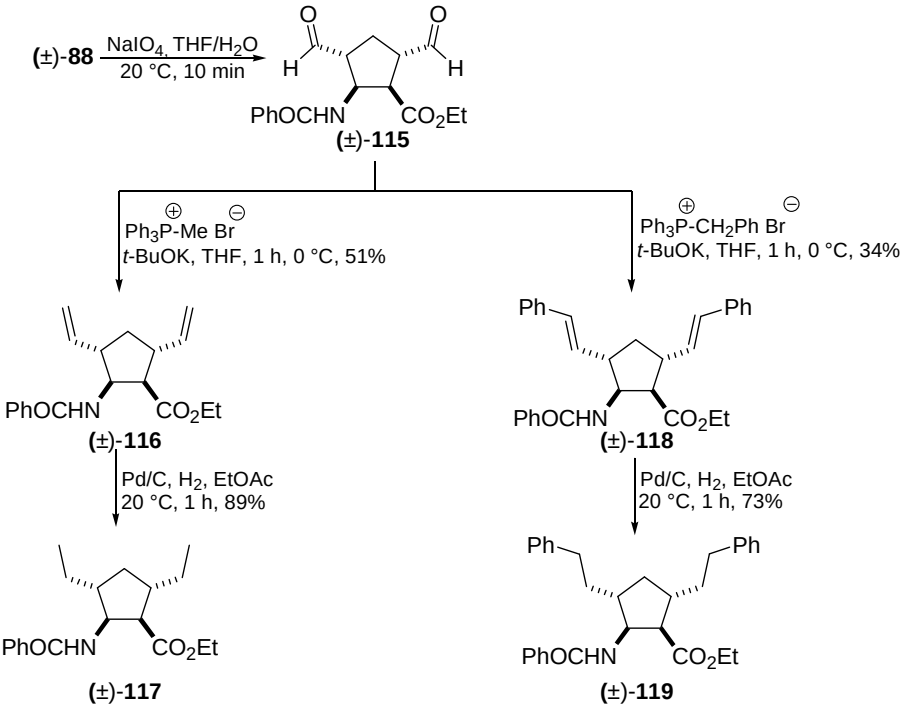


Scheme 33. Retrosynthetic scheme for the preparation of difunctionalized cispentacins from *diexo*- and *diendo*-norbornene derivatives

The first step in the *trans*-disubstituted cispentacin derivatives synthesis involved the $NaIO_4$-mediated oxidative ring cleavage[40] of vicinal diol **(±)-88** (preparation of which was described in the previous section). This resulted in dialdehyde key intermediate **(±)-115,** which proved to be a stable, isolable compound. The two formyl moieties of **(±)-115** are in *trans* relationship relative to the carboxylate and amide groups, which is predetermined by the rigid structure of the starting dihydroxylated β-amino ester.

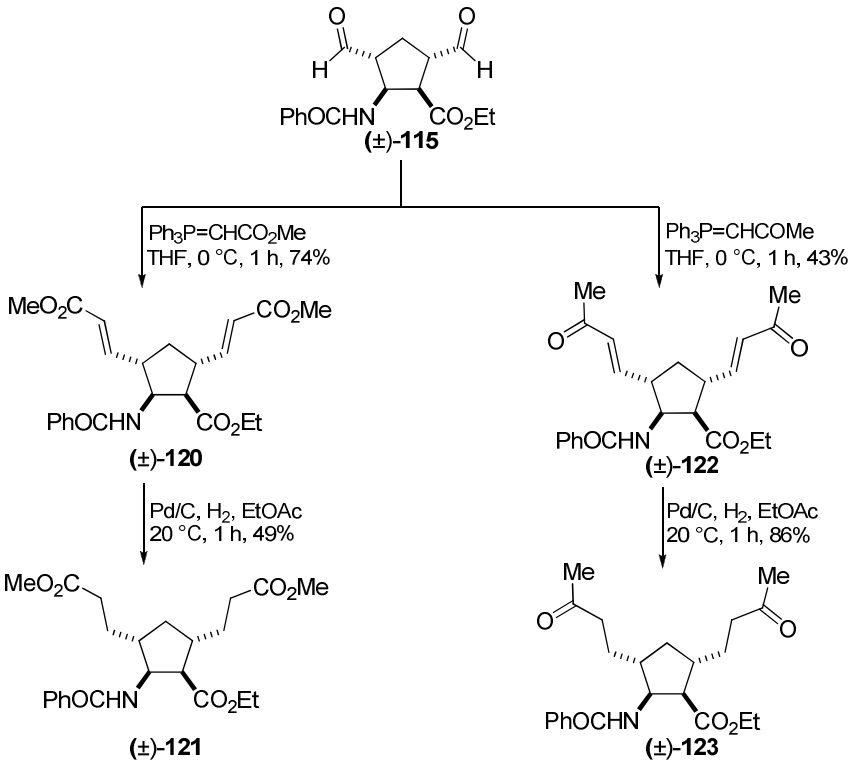
The diformyl derivative **(±)-115** was an excellent precursor for further transformations, e.g. the synthesis of dialkenylated cispentacins. In order to obtain these derivatives, dialdehyde **(±)-**

115 was subjected to an *in situ* Wittig reaction[119]. First, methyltriphenylphosphonium bromide was treated with potassium *tert*-butoxide in dry THF for 15 min in order to generate the corresponding phosphoranylide, which was reacted with dialdehyde **(±)-115** to furnish dialkenylated product **(±)-116** in moderate yield. Similarly, the reaction of another phosphorane, generated from benzyltriphenylphosphonium bromide and potassium *tert*-butoxide, with diformyl derivative **(±)-117,** led to the corresponding dialkenylated Wittig product **(±)-118**. Subsequent catalytic hydrogenation of **(±)-116** and **(±)-118** resulted in dialkylated cispentacin derivatives **(±)-117** and **(±)-119** in good yields (Scheme 34).



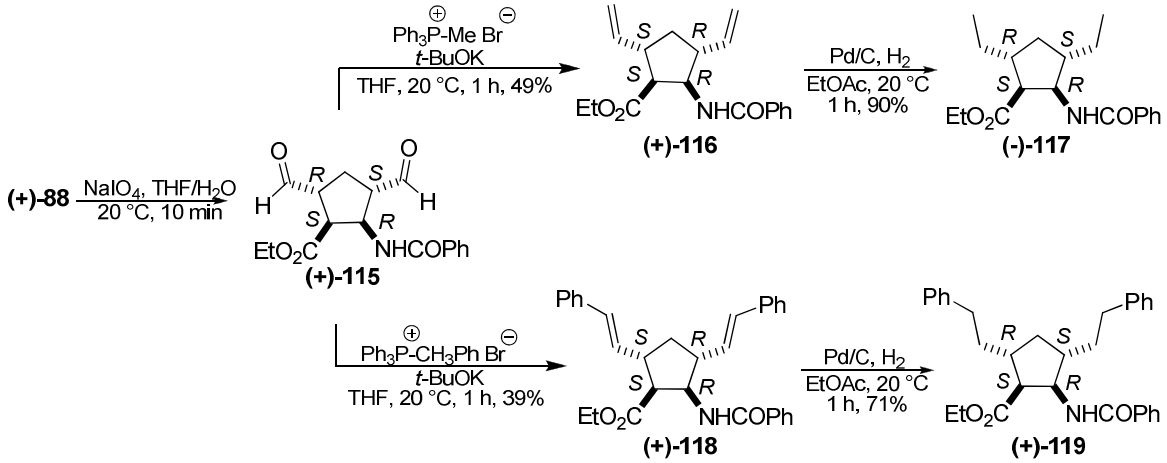
Scheme 34. Preparation of difunctionalized cispentacin derivatives **(±)-117** and **(±)-119** from dialdehyde **(±)-115**

Further disubstituted cispentacins were obtained via analogous synthetic sequences by utilizing various commercially available phosphoranes. The Wittig reaction of dialdehyde **(±)-115** with methyl (triphenylphosphoranylidene)acetate in THF afforded compound **(±)-120** in good yield. In a similar reaction with (triphenylphosphoranylidene)-2-propanone, olefinic product **(±)-122** was formed. Hydrogenolysis with a catalytic amount of Pd/C gave saturated final products **(±)-121** and **(±)-123** (Scheme 35).



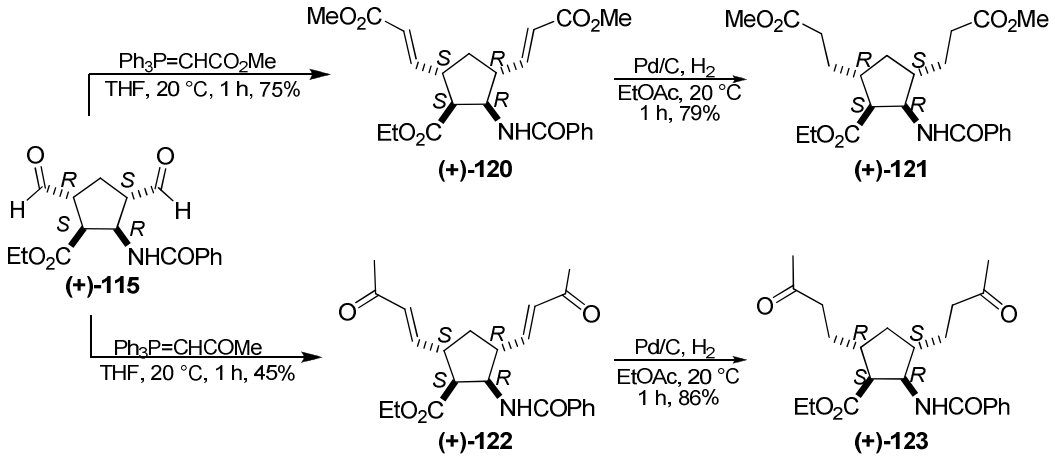
Scheme 35. Preparation of difunctionalized cispentacin derivatives **(±)-121** and **(±)-123** from dialdehyde **(±)-115**

The newly developed synthetic strategy allowed the preparation of novel cispentacin derivatives in enantiomerically pure form. The C-C bond cleavage of optically active dihydroxylated β-amino carboxylate **(+)-88** with $NaIO_4$ gave access to dialdehyde **(+)-115.** The *in situ* Wittig reaction allowed the preparation of dialkenylated compounds **(+)-116** and **(+)-118**, and further the saturation of the olefinic bonds led to optically pure substituted cispentacins **(-)-117** and **(+)-119** in good yields (Scheme 36).



Scheme 36. Preparation of optically pure difunctionalized cispentacin derivatives **(-)-117** and **(+)-119**

The diformyl β-amino ester was further transformed into the corresponding enantiomers **(+)-120** and **(+)-122** in reactions with methyl (triphenylphosphoranylidene)acetate and (triphenylphosphoranylidene)-2-propanone, and catalytic reduction of the double bonds furnished saturated cispentacin derivatives **(+)-121** and **(+)-123** (Scheme 37).



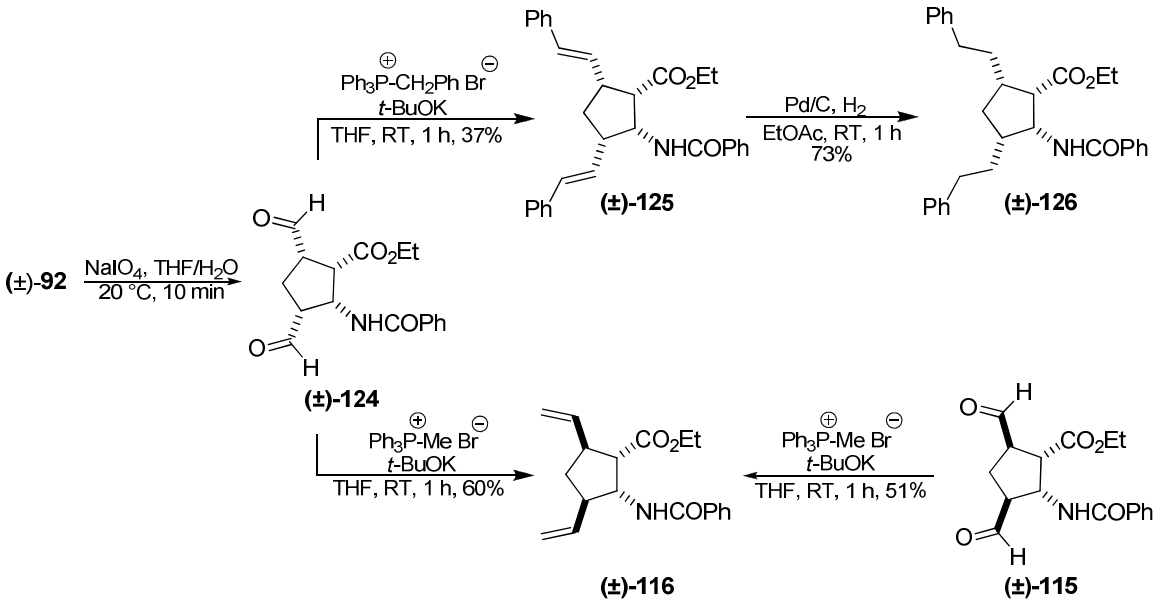
Scheme 37. Preparation of optically pure difunctionalized cispentacin derivatives **(+)-121** and **(+)-123**

All the enantiomers were obtained with high optical purity (e.e. up to 97%). No epimerization was observed during the reactions, as proven by the absence of additional peaks in the ^{1}H NMR spectra.

The synthesis of *all-cis*-disubstituted cispentacin derivatives was based on a similar strategy as for the previously described *trans*-disubstituted analogues, i.e. the transformation of the C-C double bond of the carbocycle by dihydroxylation, oxidative ring cleavage and Wittig transformation of the dialdehyde formed.

Preliminary experiments were performed with the racemic substances. The *all-cis*-dialdehyde **(±)-124** was obtained from *diendo*-dihydroxylated β-amino ester **(±)-92** by oxidative ring cleavage with $NaIO_4$[40]. Next, the *in situ* Wittig reaction[119] between diformyl derivative **(±)-124** and the phosphorane generated from benzyltriphenylphosphonium bromide and *t*-BuOK in THF, furnished the *all-cis* distyryl cyclopentane derivative **(±)-125**. Surprisingly, the reaction of dialdehyde **(±)-124** with the Wittig reagent generated from methyltriphenylphosphonium bromide yielded not the expected *all-cis* dialkenylated product after 1 h, but *trans* disubstituted compound **(±)-116**, which was earlier prepared from diformyl derivative **(±)-115** (Scheme 38). In order to avoid the isomerization during the reaction with

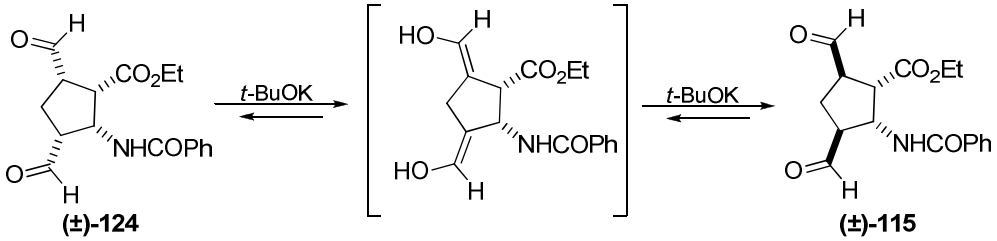
methyltriphenylphosphonium bromide and *t*-BuOK, the experimental procedure was modified by inverse addition of the reagents: the *in situ* generated Wittig reagent was added to the dialdehyde to reduce the strong basic medium. However, after completion of the reaction, no traces of the *all-cis* product were detected: the reaction yielded exclusively the isomerized product **(±)-116**.



Scheme 38. Preparation of disubstituted cispentacin derivatives **(±)-126** and **(±)-116**

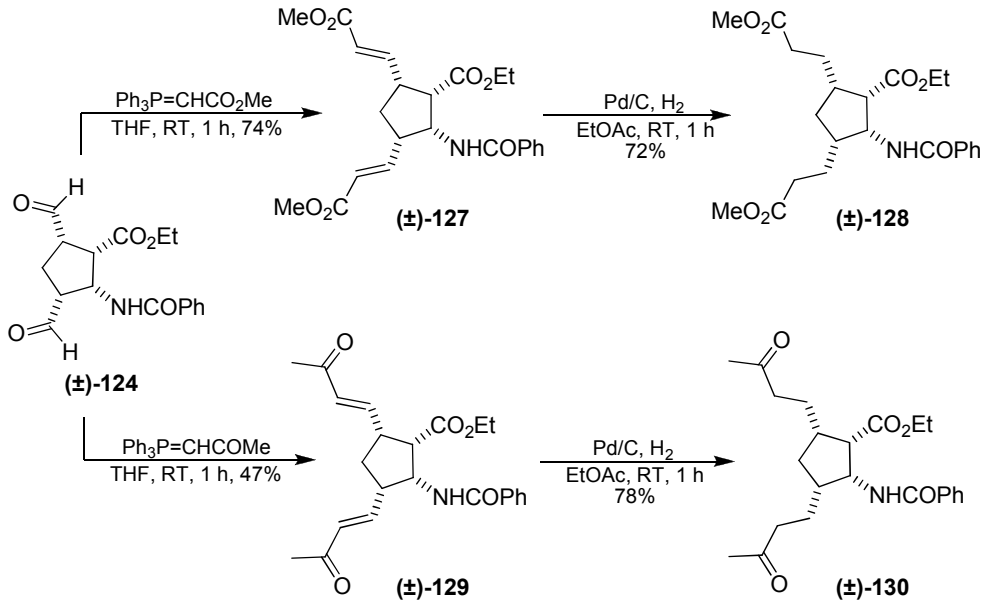
The formation of isomerized product **(±)-116** from dialdehyde **(±)-124** can be explained by the isomerization of **(±)-124,** which was induced by *t*-BuOK, in a keto-enol equilibrium to the thermodynamically more stable **(±)-115,** followed by a Wittig reaction (Scheme 39). This led us to suppose that formation of the phosphorane from methyltriphenylphosphonium bromide required a longer time. Hence, the phosphonium salt was stirred with *t*-BuOK not for 15 min, but for 2 h. When the resulting phosphorane was reacted with **(±)-124** for either 30 min or 1 h, product **(±)-116** was again obtained.

Hydrogenation of **(±)-125** under catalytic conditions resulted in disubstituted derivative **(±)-126** in good yield (Scheme 38).



Scheme 39. Interconversion of **(±)-115** and **(±)-124**

The dialdehyde **(±)-124** was further subjected to the Wittig reaction with methyl (triphenylphosphoranylidene)acetate, giving dialkenylated cispentacin **(±)-127** in 74% yield. The Ortep diagram of compound **(±)-127** is presented in Figure 4. In the reaction with (triphenylphosphoranylidene)-2-propanone, **(±)-124** gave the *all-cis* derivative **(±)-129.** Subsequent catalytic reduction of the olefinic bonds led to functionalized cispentacins **(±)-128** and **(±)-130** (Scheme 40)**.**



Scheme 40. Preparation of disubstituted cispentacin derivatives **(±)-128** and **(±)-130**

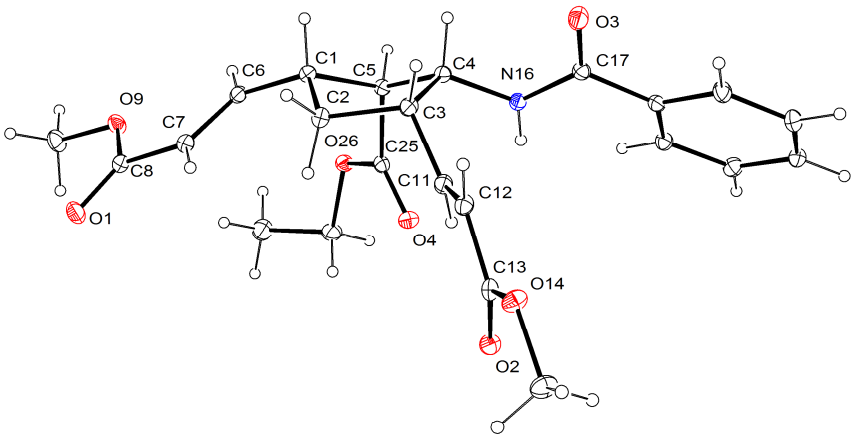
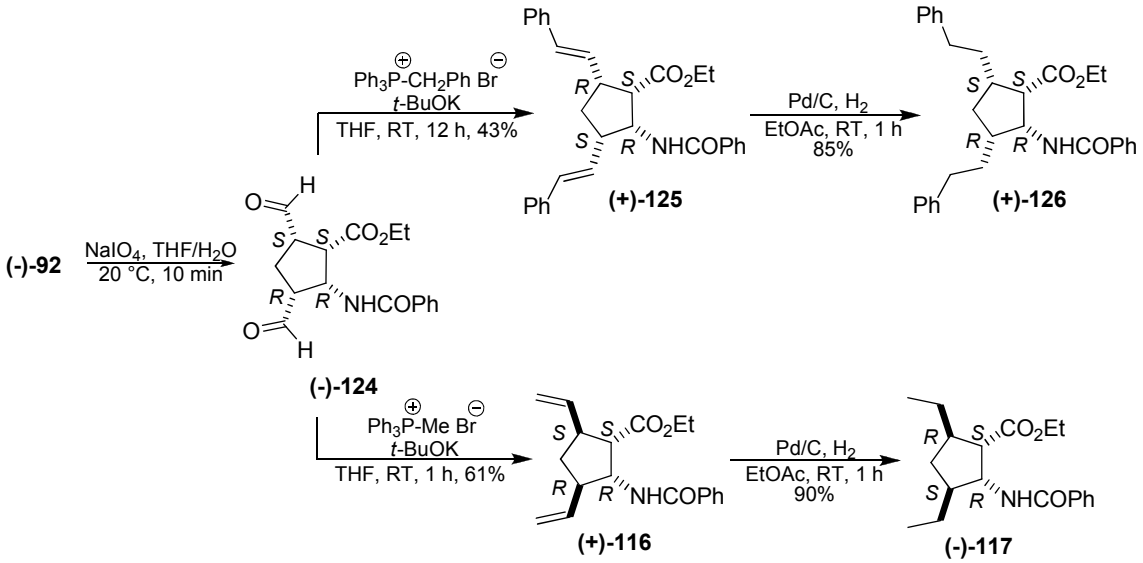


Figure 4. Ortep diagram of compound **(±)-127**

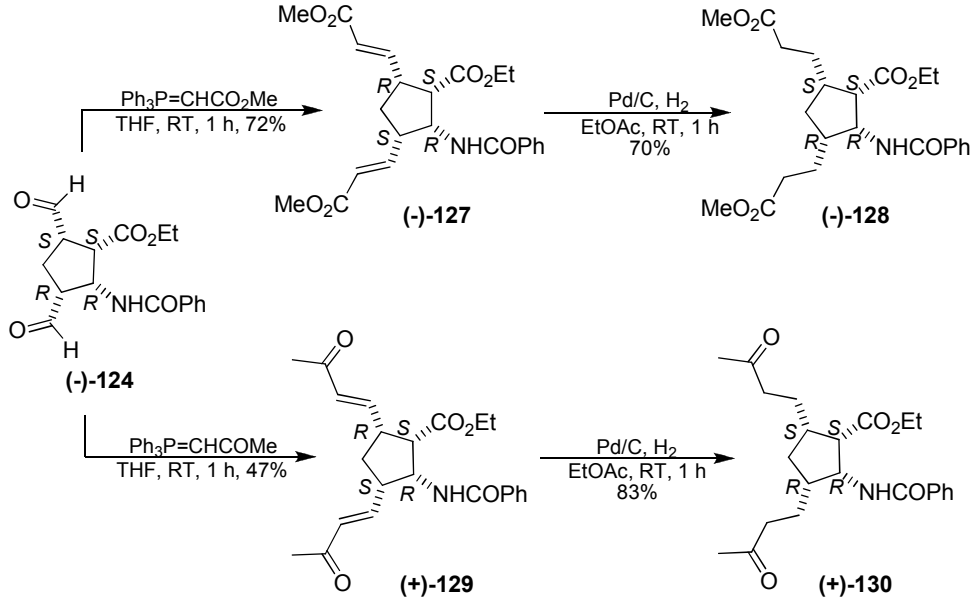
The synthetic protocol described above was further extended to the preparation of optically pure substances. Enantiomerically pure dihydroxylated β-amino ester **(-)-92** was obtained according to the methodology presented earlier (Scheme 26). *all-cis*-Dialdehyde **(-)-124** was synthetized in optically pure form from **(-)-92** by oxidative ring cleavage. The absolute configurations of the stereocenters in **(-)-124** were determined by chemical correlation. When **(-)-124** was treated with the Wittig reagent generated from methyltriphenylphosphonium bromide and *t*-BuOK, *trans* disubstituted derivative **(+)-116** was gained. Catalytic reduction of **(+)-116** afforded **(-)-117;** the NMR data, HPLC ChiralPak IA, *n*-hexane/IPA, 0.5 ml/min, 210 nm, the same retention time: 10.05 min, opposite enantiomer 9.09) and comparison of the optical rotations revealed that this compound was identical to that prepared earlier from optically pure **(+)-115**: ethyl (1*S*,2*R*,3*S*,4*R*)-2-benzoylamino-3,5-diformylcyclopentanecarboxylate, with known absolute configurations. Since the stereocentres were not affected during the transformations, it can be assumed from these results that **(-)-124** is ethyl (1*S*,2*R*,3*R*,4*S*)-2-benzoylamino-3,5-diformylcyclopentanecarboxylate, and hence **(-)-92** has the 1*R*,2*S*,3*R*,4*S* absolute configuration.

Optically active dialdehyde **(-)-124** was transformed into dialkenylated Wittig product **(+)-125** in the reaction with the benzyltriphenylphosphonium bromide-generated phosphorane. After C-C bond reduction, saturated compound **(+)-126** was attained (Scheme 41).



Scheme 41. Synthesis of optically pure disubstituted cispentacin derivatives **(+)-126** and **(-)-117**

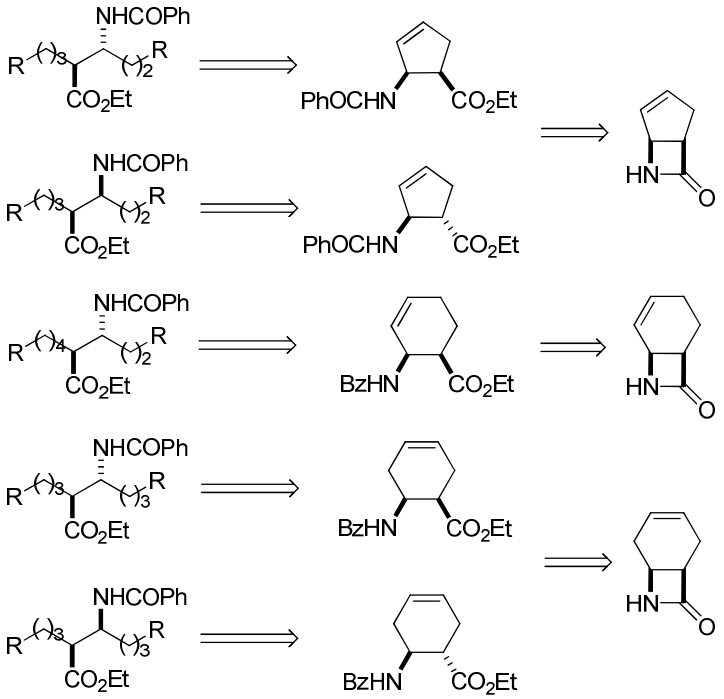
The reaction of diformyl derivative **(-)-124** with commercially available phosphoranes methyl (triphenylphosphoranylidene)acetate and triphenylphosphoranylidene-2-propanone gave access to optically pure **(-)-127** and **(+)-129**, reduction of these products leading to **(-)-128** and **(+)-130** in enantiomerically pure form (Scheme 42).



Scheme 42. Synthesis of enantiomerically pure disubstituted cispentacin derivatives **(-)-128** and **(+)-130**

3.3. Synthesis of disubstituted acyclic β^{2,3}-amino acids from 2-amino-3-cyclopentene carboxylic acid and 2-amino-3-cyclohexene carboxylic acid

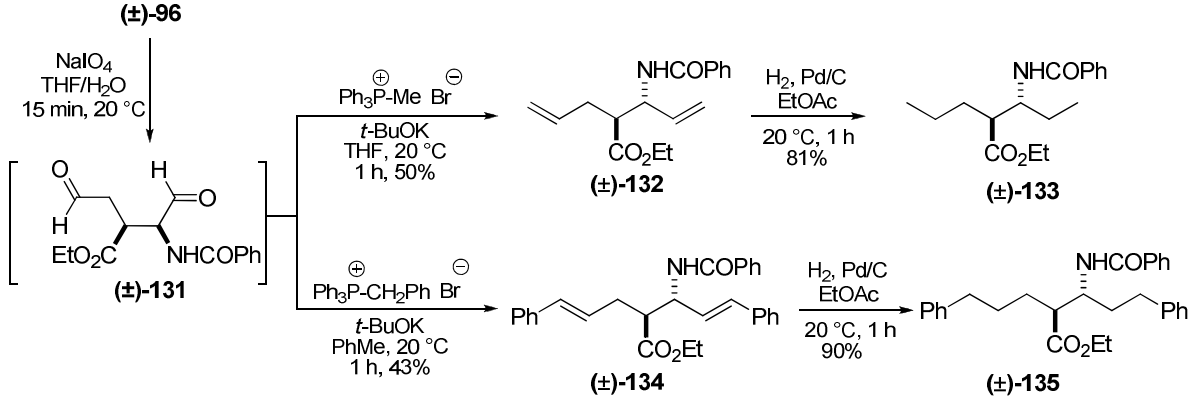
The synthesis of β^{2,3}-disubstituted open-chain amino acid derivatives was approached by the transformation of *cis* and *trans* cyclopentene β-amino acids and cyclohexene β-amino carboxylates through the above-described strategy, i.e. dihydroxylation, and oxidative ring opening, followed by the Wittig reaction. The stereochemistry of the acyclic products is predetermined by the configuration of the cyclic starting materials. The syntheses based on the *cis* and *trans* unsaturated 5-membered β-amino acid species from the racemic 1,3-cyclopentadiene-derived β-lactam are expected to give acyclic *anti* and *syn* β^{2,3}-amino acid derivatives, respectively, while *syn* or *anti* acyclic β-amino acids with a chain one carbon atom longer can be prepared by starting from 1,3- or 1,4-cyclohexadiene-derived β-lactams (Scheme 43).



Scheme 43. Retrosynthetic route to β^{2,3}-disubstituted acyclic amino esters

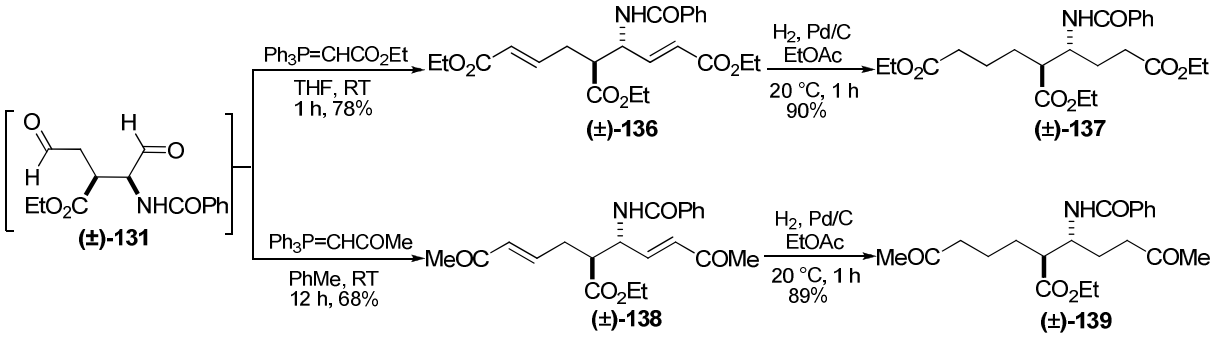
Preliminary experiments were carried out with the racemic substances, and the protocol was further extended in order to obtain enantiomerically pure products. Open-chain dialdehyde intermediate **(±)-131**, prepared from diol **(±)-96** via oxidative ring cleavage[40], did not prove to be as stable as the previously presented diformyl cispentacin derivatives **(±)-115**

and **(±)-124.** Hence further experiments were conducted by using the dialdehyde prepared *in situ*. The reactions of **(±)-131** with phosphoranes generated from methyltriphenylphosphonium bromide or benzyltriphenylphosphonium bromide and *t*-BuOK furnished the corresponding diolefinated *anti* products **(±)-132** and **(±)-134** in moderate yields. Catalytic hydrogenation of these compounds led to saturated β-amino esters **(±)-133** and **(±)-135** (Scheme 44).



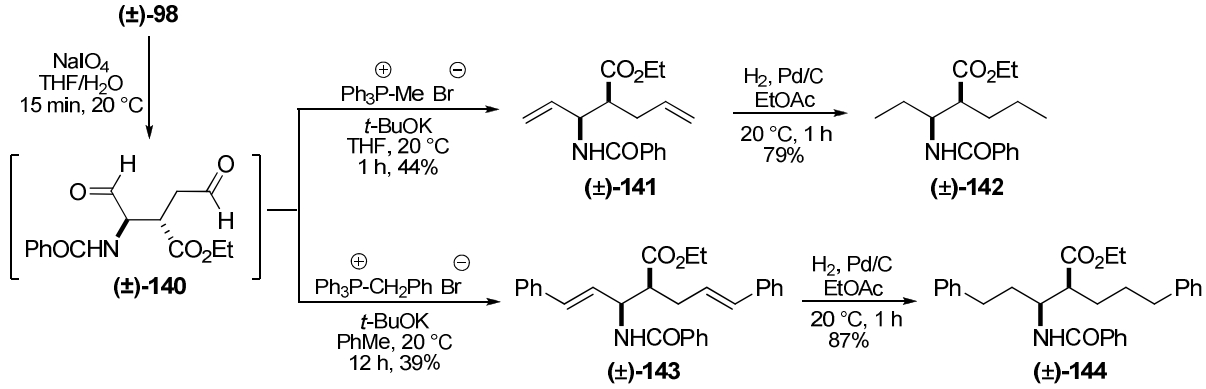
Scheme 44. Synthesis of disubstituted *anti* acyclic β-amino acid derivatives **(±)-133** and **(±)-135**

Further *anti* Wittig products **(±)-136** and **(±)-138** were synthetized from dialdehyde **(±)-131** in reactions with commercially available phosphoranes, ethyl (triphenylphosphoranylidene)acetate or 1-(triphenylphosphoranylidene)-2-propanone. Subsequent olefinic bond saturation resulted in dialkylated β-amino esters **(±)-137** and **(±)-139** in good yields (Scheme 45).



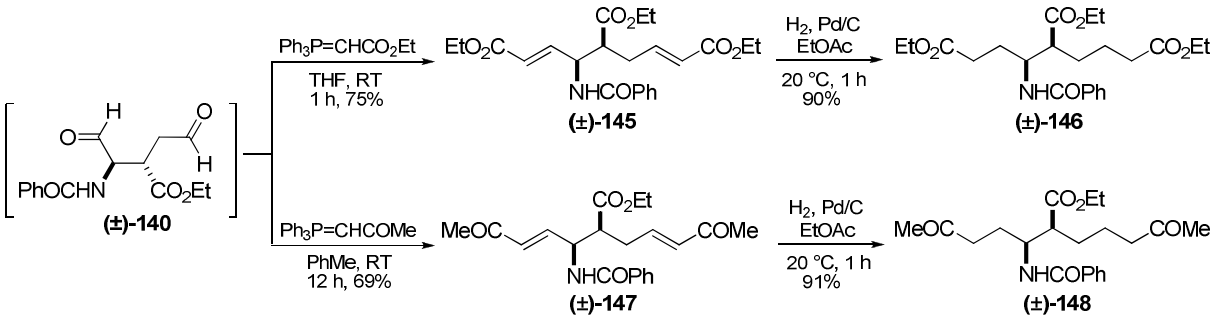
Scheme 45. Preparation of disubstituted *anti* acyclic β-amino acid derivatives **(±)-137** and **(±)-139**

The synthetic methodology was further successfully extended to the preparation of *syn* β-amino acid derivatives. Dialdehyde **(±)-141,** obtained from dihydroxylated β-amino carboxylate **(±)-98** via $NaIO_4$-mediated ring cleavage, exhibited similar instability to that of its earlier-described analogue **(±)-131.** The *in situ* Wittig reaction furnished the corresponding dialkenylated *syn* products **(±)-141** and **(±)-143,** which were further transformed into the saturated β-amino esters **(±)-142** and **(±)-144** through a catalytic hydrogenation procedure (Scheme 46).



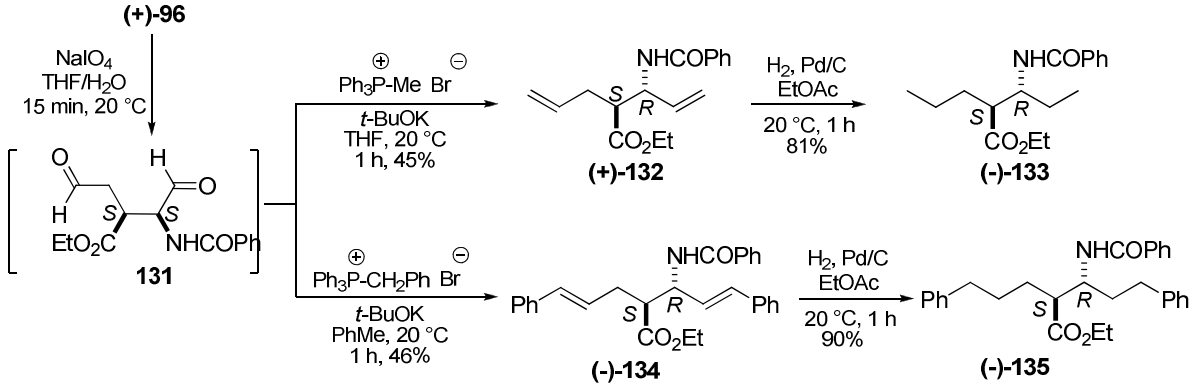
Scheme 46. Synthesis of disubstituted *syn* acyclic β-amino acid derivatives **(±)-142** and **(±)-144**

The reaction of diformyl derivative **(±)-140** with ethyl (triphenylphosphoranylidene)acetate or 1-(triphenylphosphoranylidene)-2-propanone gave the *syn* Wittig products **(±)-145** and **(±)-147.** Subsequent Pd/C-catalysed hydrogenation led to compounds **(±)-146** and **(±)-148** in good yields (Scheme 47)**.**



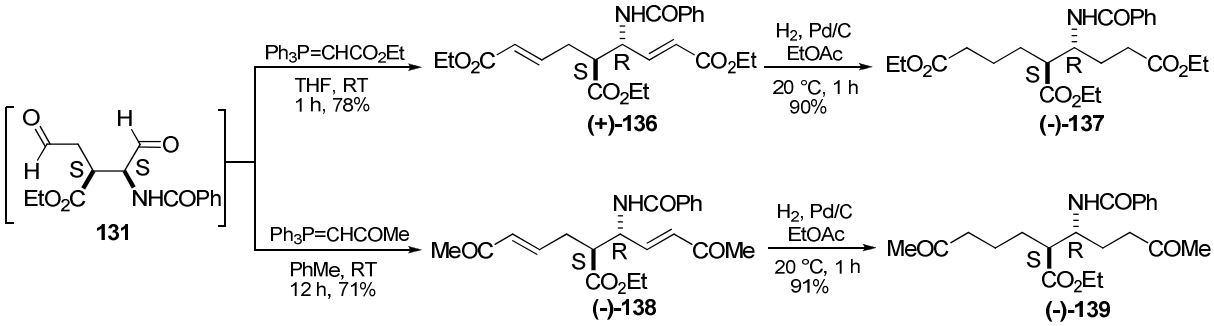
Scheme 47. Preparation of disubstituted *syn* acyclic β-amino acid derivatives **(±)-146** and **(±)-148**

The synthetic methodology was further extended for the preparation of all the open-chain dialkylated products in enantiomerically pure form. Optically pure dialkenylated products **(+)-132** and **(-)-134** were prepared from dialdehyde **131** via the Wittig reaction. The saturation of these products furnished *anti* β-amino carboxylates **(-)-133** and **(-)-135** (Scheme 48).



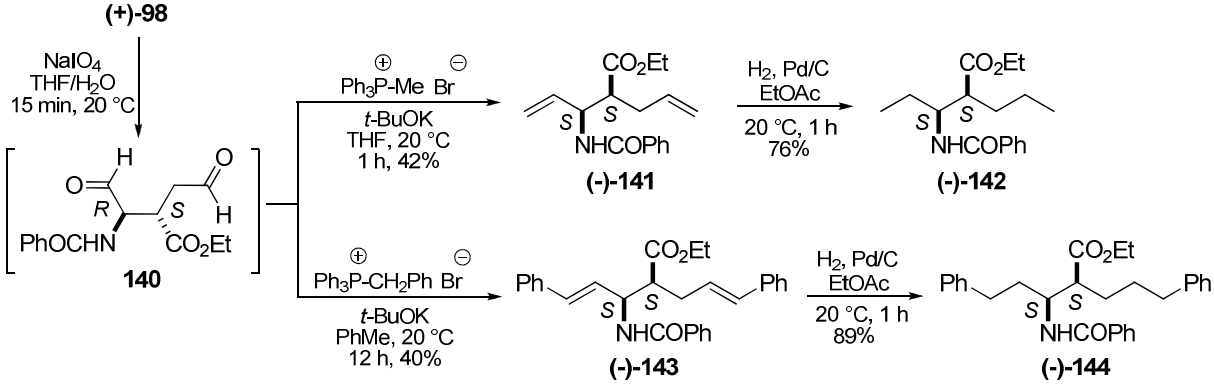
Scheme 48. Synthesis of optically pure disubstituted *anti* acyclic β-amino acid derivatives **(-)-133** and **(-)-135**

Further optically active *anti* β-amino acid derivatives **(+)-136** and **(-)-138** were synthetized by treating diformyl compound **131** with commercially available phosphoranes. Subsequent catalytic hydrogenation led to enantiomers **(-)-137** and **(-)-139** (Scheme 49).



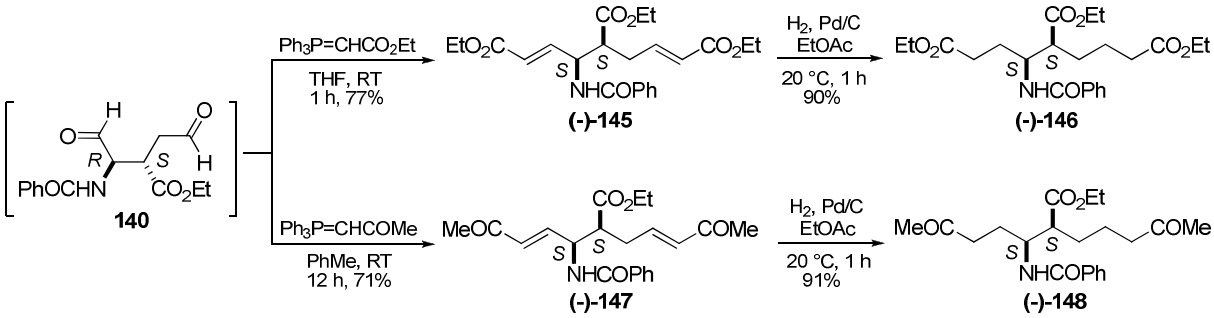
Scheme 49. Preparation of disubstituted enantiomerically pure *anti* acyclic β-amino acid derivatives **(-)-137** and **(-)-139**

Next, enantiomerically pure dialdehyde **140** was transformed into acyclic *syn* Wittig products **(-)-141** and **(-)-143**. Reduction of the olefinic bond afforded final products **(-)-142** and **(-)-144** in 99% enantiomeric purity (Scheme 50).



Scheme 50. Synthesis of disubstituted optically active *syn* acyclic β-amino acid derivatives **(-)-142** and **(-)-144**

Finally, similar synthetic procedures afforded the dialkenylated β-amino acid derivatives **(-)-145** and **(-)-147** in enantiomerically pure form. Catalytic hydrogenation of these products in the presence of Pd/C gave access to *syn* saturated final products **(-)-146** and **(-)-148** (Scheme 51).

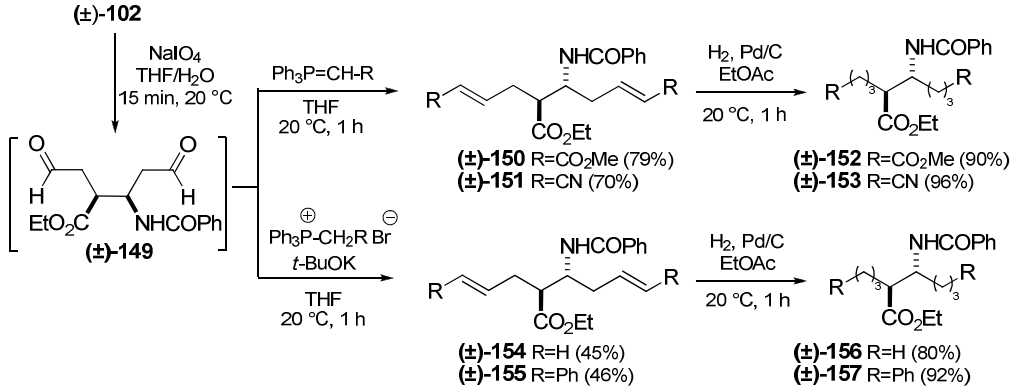


Scheme 51. Preparation of disubstituted *syn* acyclic β-amino acid derivatives **(-)-146** and **(-)-148** in optically pure form

Following the extension of our study with novel Wittig reagents on the synthesis of open-chain β-amino acid derivatives, the synthetic approach towards dialkylated $\beta^{2,3}$-amino acid species based on cyclohexene β-amino carboxylates was demonstrated.

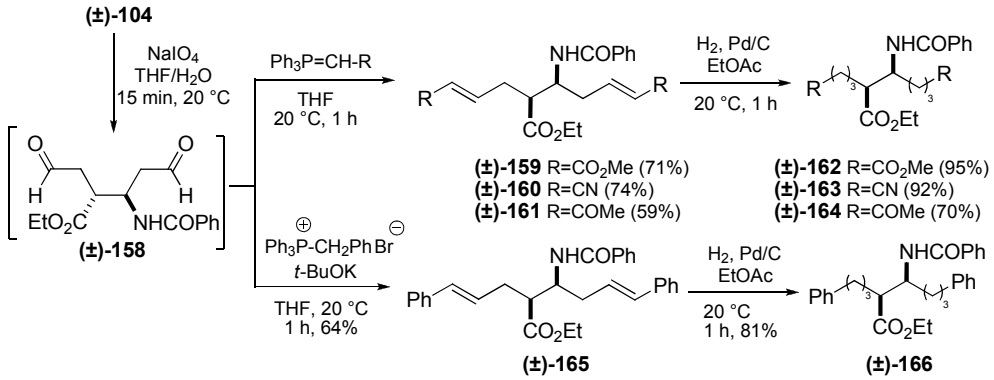
Diformyl derivative **(±)-149** was synthetized from dihydroxylated β-amino ester **(±)-102** through an oxidative ring cleavage protocol, which was previously successfully applied for the preparation of cispentacin-based diformyl derivatives **(±)-115** and **(±)-124** or open-

chain dialdehydes **(±)-131** and **(±)-140**. It should be noted that dialdehyde **(±)-149** displayed similar instability to that of the previously described acyclic dialdehydes **(±)-131** and **(±)-140.** As it could not be isolated, further experiments were conducted with dialdehyde generated *in situ*. The Wittig reaction between **(±)-149** and methyl (triphenylphosphoranylidene)acetate or (triphenylphosphoranylidene) acetonitrile resulted in *anti* open-chain dialkenylated products **(±)-150** and **(±)-151**. The following hydrogenation under catalytic conditions furnished saturated β-amino esters **(±)-152** and **(±)-153** in good yields. Further *anti* disubstituted compounds **(±)-154** and **(±)-155** were obtained via the reactions of dialdehyde **(±)-149** and *in situ* generated ylides from methyltriphenylphosphonium bromide or benzyltriphenylphosphonium bromide. Subsequent double bond reduction yielded β-amino acid derivatives **(±)-156** and **(±)-157** (Scheme 52).



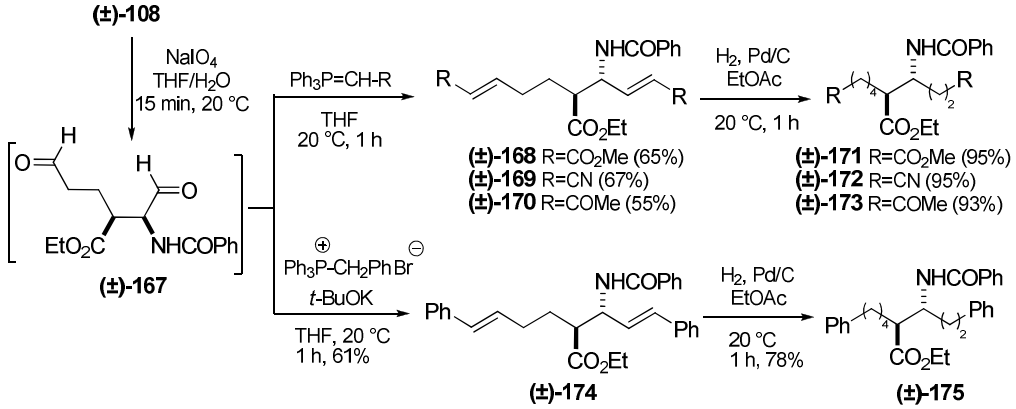
Scheme 52. Preparation of disubstituted *anti* open-chain derivatives **(±)-152, (±)-153, (±)-156** and **(±)-157**

The above synthetic protocol was subsequently extended to the preparation of open-chain *syn* β-amino esters. The diformyl derivative **(±)-158** synthetized from diol **(±)-104** demonstrated similar instability to that of the previously described acyclic analogues. Difunctionalized Wittig products **(±)-159**, **(±)-160** and **(±)-161** were formed by treating dialdehyde **(±)-158** with commercially available phosphoranes. Subsequent catalytic hydrogenation resulted in saturated acyclic compounds **(±)-162**, **(±)-163** and **(±)-164** in good yields. The reaction of dialdehyde **(±)-158** with the ylide generated from benzyltriphenylphosphonium bromide then afforded the disubstituted Wittig product **(±)-165**, which was further reduced to derivative **(±)-166** (Scheme 53). For unknown reasons, in the reaction of dialdehyde **(±)-158** with the ylide generated from methyltriphenylphosphonium bromide, no product formation was observed.



Scheme 53. Synthesis of disubstituted *syn* open-chain derivatives **(±)-162, (±)-163, (±)-164** and **(±)-166**

Dialdehyde **(±)-167** was obtained from the dihydroxylated β-amino carboxylate **(±)-108** via oxidative ring cleavage. The dialkenylated species **(±)-168**, **(±)-169**, **(±)-170** and **(±)-174**, isomers of earlier prepared derivatives (Schemes 52 and 53), were gained via the Wittig reaction. Subsequent olefinic bond reduction furnished novel *anti* β-amino acid derivatives **(±)-171**, **(±)-172**, **(±)-173** and **(±)-174** (Scheme 54). As in the previous case, the *in situ* Wittig reaction between dialdehyde **(±)-167** and the ylide generated from methyltriphenylphosphonium bromide failed.



Scheme 54. Preparation of disubstituted *anti* open-chain derivatives **(±)-171, (±)-172, (±)-173** and **(±)-175**

4. SUMMARY

A novel stereocontrolled synthetic access route has been developed to difunctionalized cispentacin derivatives from *diexo*- and *diendo*-norbornene β-amino acids and acyclic $\beta^{2,3}$-amino acid species derived from *cis*- or *trans*- β-aminocyclopentene and cyclohexenecarboxylates. The syntheses were based on transformation of the C-C double bond in the cyclic starting materials by stereoselective dihydroxylation with OsO_4, followed by $NaIO_4$-mediated oxidative ring cleavage of the corresponding diols, with subsequent Wittig transformations of the dialdehyde intermediates and Pd/C-catalysed hydrogenations of the dialkenylated β-amino esters formed.

Preliminary experiments were performed with the racemic substances, and the protocol was then extended to enantiomerically pure substances. Racemic β-amino esters **87**, **91**, **95**, **97**, **101**, **103** and **107** were synthetized as required starting materials by β-lactams ring opening, followed by *N*-protection. Bicyclic *diendo*-β-amino ester **91** was obtained from bicyclic *diendo*-anhydride via ring opening, followed by Hoffmann degradation, esterification and *N*-Bz protection. Stereoselective dihydroxylation of these compounds by means of NMO and a catalytic amount of OsO_4 furnished dihydroxylated β-amino esters **88, 92, 96, 98, 102, 104** and **108** (Schemes 25, 26, 27, 28 and 29).

The well-established protocol for the synthesis of dihydroxylated β-amino esters allowed the preparation of starting materials in enantiomerically pure form. Racemic β-lactam **86** was subjected to enzyme-catalyzed enantioselective ring opening, resulting in enantiomerically pure amino acid **(-)-109** and unreacted β-lactam **(+)-86**. Enantiomer **(+)-86** was then transformed to optically pure diol **(+)-88** through ring opening, *N*-Bz protection and dihydroxylation (Scheme 30).

The preparation of enantiomerically pure β-amino ester **(-)-92** was attained through diastereomeric salt recrystallization. The reaction between racemic *diendo*-β-amino ester **(±)-111** and enantiomerically pure *D*-(-)-mandelic acid **(-)-113** yielded the corresponding diastereomeric salt mixture **(±)-113.** This mixture was then recrystallized, and the diastereomeric ratio was monitored by ^{1}H NMR. The pure diastereomer was treated with saturated $NaHCO_3$ solution to give optically pure *diendo*-β-amino ester **(-)-111** with ee = 99.9%. Subsequent benzoylation and stereoselective dihydroxylation resulted in enantiomer **(-)-92** (Scheme 31).

Cyclopentane *cis* and *trans* β-amino esters were gained through the enzyme-catalysed kinetic resolution of β-lactam. Enantiomerically pure amino acid **(+)-114** and unreacted β-lactam

(-)-94 were obtained and separated. Next, **(-)-94** was treated with HCl/EtOH solution, and the following benzoylation and dihydroxylation led to optically pure diol (1*R*,2*R*)-**(+)-96.** Amino acid **(+)-114** was transformed to dihydroxylated *trans* β-amino carboxylate (1*S*,2*R*)-**(+)-98** via esterification, group protection, base-induced epimerization and dihydroxylation procedures (Scheme 32).

The C-C bond cleavage of optically active dihydroxylated β-amino carboxylate **(+)-88** with $NaIO_4$ gave access to ethyl 2-benzamido-3,5-diformylcyclopentanecarboxylate **(+)-115.** The *in situ* Wittig reaction allowed the preparation of dialkenylated compounds **(+)-116** and **(+)-118**, and the saturation of the olefinic bonds led to the optically pure substituted cispentacins ethyl 2-benzamido-3,5-diethylcyclopentanecarboxylate **(-)-117** and ethyl 2-benzamido-3,5-diphenethylcyclopentanecarboxylate **(+)-119** (Scheme 34).

The diformyl β-amino ester was further transformed into the corresponding enantiomers **(+)-120** and **(+)-122** by reaction with methyl (triphenylphosphoranylidene)acetate and (triphenylphosphoranylidene)-2-propanone, and catalytic reduction of the double bonds furnished saturated cispentacin derivatives 3,3'-dimethyl 4-benzamido-5-(ethoxycarbonyl)cyclopentane-1,3-diyl)dipropanoate **(+)-121** and ethyl 2-benzamido-3,5-bis(3-oxobutyl)cyclopentanecarboxylate **(+)-123** (Scheme 35).

The syntheses of *all-cis*-disubstituted cispentacin derivatives were based on a similar strategy. *all-cis*-Ethyl 2-benzoylamino-3,5-diformylcyclopentanecarboxylate **(-)-124** was synthetized in optically pure form from **(-)-92** by oxidative ring cleavage. Dialdehyde **(-)-124** was transformed into dialkenylated Wittig product **(+)-125** through reaction with the benzyltriphenylphosphonium bromide-generated phosphorane. After C-C bond reduction, saturated ethyl 2-benzoylamino-3,5-diphenethylcyclopentanecarboxylate **(+)-126** was attained (Scheme 38).

The reaction of ethyl 2-benzoylamino-3,5-diformylcyclopentanecarboxylate **(-)-124** with commercially available phosphoranes gave access to optically pure **(-)-127** and **(+)-129**, reduction of these products leading to ethyl (1*S*,2*R*,3*R*,4*S*)-2-benzoylamino-3,5-*bis*-(2-methoxycarbonylethyl)cyclopentanecarboxylate **(-)-128** and ethyl 2-benzoylamino-3,5-*bis*-(3-oxobutyl)cyclopentanecarboxylate **(+)-130** (Scheme 40).

The synthesis of $\beta^{2,3}$-disubstituted open-chain amino acid derivatives was approached by the transformation of *cis* and *trans* cyclopentene and cyclohexene β-amino acids through the above-described strategy. Optically pure dialkenylated products **(+)-132** and **(-)-134** were prepared from dialdehyde **131** via the Wittig reaction. The saturation of these products

furnished *anti* β-amino carboxylates ethyl 3-benzamido-2-propylpentanoate **(-)-133** and ethyl 3-benzamido-5-phenyl-2-(3-phenylpropyl)pentanoate **(-)-135** (Scheme 44).

Further optically active *anti* β-amino acid derivatives triethyl 3-benzamidoheptane-1,4,7-tricarboxylate **(+)-137** and ethyl 3-benzamido-6-oxo-2-(4-oxopentyl)heptanoate **(-)-139** were synthetized by treating diformyl compound **131** with commercially available phosphoranes and subsequent catalytic hydrogenation (Scheme 45).

Next, enantiomerically pure dialdehyde **140** was transformed into the acyclic *syn* Wittig products ethyl 3-benzamido-2-propylpentanoate **(-)-142** and ethyl 3-benzamido-5-phenyl-2-(3-phenylpropyl)pentanoate **(-)-144**. (Scheme 46).

Finally, similar synthetic procedures afforded the dialkenylated β-amino acid derivatives **(-)-146** and **(-)-148** in enantiomerically pure form (Scheme 47).

Following the extension of our study with novel Wittig reagents to the synthesis of open-chain β-amino acid derivatives, a synthetic approach towards dialkylated $\beta^{2,3}$-amino acid species based on cyclohexene β-amino carboxylates was developed. Diformyl derivative **149** was synthetized from dihydroxylated β-amino ester **102** through an oxidative ring cleavage protocol. The Wittig reaction between **149** and methyl (triphenylphosphoranylidene)acetate or (triphenylphosphoranylidene)acetonitrile resulted in *anti* open-chain dialkenylated products **150** and **151**. The following hydrogenation under catalytic conditions furnished saturated β-amino esters 4-ethyl 1,8-dimethyl 5-benzamidooctane-1,4,8-tricarboxylate **152** and ethyl 3-benzamido-6-cyano-2-(3-cyanopropyl)hexanoate **153**. Further *anti* disubstituted compounds ethyl 3-benzamido-2-propylhexanoate **156** and ethyl 3-benzamido-6-phenyl-2-(3-phenylpropyl)hexanoate **157** were obtained via *in situ* Wittig reactions and subsequent double bond reduction (Scheme 52).

The above synthetic protocol was subsequently extended to the preparation of open-chain *syn* β-amino esters. Difunctionalized Wittig products **159**, **160** and **161** were formed by treating dialdehyde **158** with commercially available phosphoranes. The following catalytic hydrogenation resulted in saturated acyclic compounds 4-ethyl 1,8-dimethyl-5-benzamidooctane-1,4,8-tricarboxylate **162**, ethyl 3-benzamido-6-cyano-2-(3-cyanopropyl)hexanoate **163** and ethyl 3-benzamido-7-oxo-2-(4-oxopentyl)octanoate **164**. The reaction of dialdehyde **158** with the ylide generated from benzyltriphenylphosphonium bromide then afforded the disubstituted Wittig product **165**, which was further reduced to derivative **166** (Scheme 53).

Dialdehyde **167** was obtained from the dihydroxylated β-amino carboxylate **108** via oxidative ring cleavage. The dialkenylated species 4-ethyl 1,8-dimethyl 3-benzamidooctane-1,4,8-tricarboxylate **171**, 2-ethyl 1-benzamido-3-cyanopropyl)-6-cyanohexanoate **172**, 2-ethyl 1-benzamido-4-oxopentyl)-7-oxooctanoate **173** and 2-ethyl-1-benzamido-3-phenylpropyl)-6-phenylhexanoate **175** were gained via Wittig reactions and subsequent olefinic bond reduction (Scheme 54).

It should be emphasized that the stereochemistry of the target difunctionalized β-amino esters was predetermined by the configurations of the cyclic starting materials. Since the stereogenic centres of the starting materials were not affected during the transformations, their stereochemistry determined the configurations of the asymmetric centres in the final products.

The presented synthetic methodology proved to be simple, efficient and completely stereocontrolled. Through use of this synthetic approach, 54 novel cyclic and open-chain β-amino acid derivatives have been obtained. It may be generalized and applied for the synthesis of a variety of substituted cyclic and open-chain β-amino acid derivatives.

5. ACKNOWLEDGEMENTS

The presented work was carried out in the Institute of Pharmaceutical Chemistry, University of Szeged between 2010 and 2013.

I would like to express my gratitude to my supervisors **Professor Ferenc Fülöp** and **Dr. Loránd Kiss** for their scientific guidance of my project, their help and their valuable advice.

I am grateful to **Dr. Enikő Forró** for the preparation of enantiomerically pure β-lactams as starting materials and for the GC and HPLC measurements.

I would like to thank all my colleagues for their help, friendship and pleasant working atmosphere, and especially my colleagues from the 2nd laboratory, **Dr. Melinda Nonn** and **Aranka Polyák.**

And finally, I would like to express my sincere appreciation to my family and friends for their love and unceasing support.

6. REFERENCES

1. Fülöp, F. *Chem. Rev.* **2001**, *101*, 2181.
2. "Synthesis of Carbocyclic β-Amino Acids": Kiss. L.; Forró. E.; Fülöp. F. in *Amino Acids, Peptides and Proteins in Organic Chemistry*, Vol. 1 (Ed.: Hughes, A. B.) Wiley, Weiheim **2009**, p. 367.
3. Kuhl, A.; Hahn, M. G.; Dumic, M.; Mittendorf, J. *Amino Acids* **2005**, *29*, 89.
4. Park, K. H.; Kurth, M. J. *Tetrahedron* **2002**, *58*, 8629.
5. Pandey, S. K.; Jogdand, G. F.; Oliveira, J. C. A. Mata, R. A.; Rajamohanan, P. R.; Ramana, C. V. *Chem. Eur. J.* **2011**, *17*, 12946.
6. Coursindel, T.; Martinez, J.; Parrot, I. *Eur. J. Org. Chem.* **2011**, 4519.
7. Chandrasekhar, S.; Sudhakar, A.; Kiran, M. U.; Babu, B. N.; Jagadeesh, B. *Tetrahedron Lett*. **2008**, *49*, 7368.
8. Mittendorf, J.; Kunisch, F.; Matzke, M.; Militzer, H-C.; Schmidt, A.; Schönfeld, W. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 433.
9. Hamersak, Z.; Roje, M.; Avdagic, A.; Sunjic, V. *Tetrahedron: Asymmetry* **2007**, *18*, 635.
10. Rathore, N.; Gellman, S. H.; Pablo, J. J. *Biophys. J.* **2006**, *91*, 3425.
11. McClellan, K.; Perry, C. M. *Drugs* **2001**, *61*, 775.
12. Dunn, C. J.; Goa, K. L. *Drugs* **1999**, *58*, 761.
13. Poncet, J. *Cur. Pharm. Des.* **1999**, *5*, 139.
14. Moore, R. E. *J. Ind. Microbiol.* **1996**, *16*, 134.
15. Rodríguez, J.; Fernández, R.; Quiñoá, E.; Riguera, R.; Debitus, C.; Bouchet, P. *Tetrahedron Lett*. **1994**, *35*, 9239.
16. Han, B.; Gross, H.; McPhail, K. L.; Goeger, D.; Maier, C. S.; Gerwick, W. H. *J. Microbiol. Biotechnol.* **2011**, *21*, 930.
17. Williams, P. G.; Yoshida, W. Y.; Quon, M. K., Moore, R. E.; Paul, V. J. *J. Nat. Prod.* **2003**, *66*, 651.
18. Horgen, F.D.; Kazmierski, E. B.; Westenburg, H. E.; Yoshida, W. Y.; Scheuer, P. J. *J. Nat. Prod.* **2002**, *65*, 487.
19. Fernandes, C.; Gauzy, C.; Yang, Y.; Roy, O.; Pereira, E.; Faure, S.; Aitken, D. J. *Synthesis* **2007**, 2222.
20. Miller, J. A.; Nguyen, S. T. *Mini Rev. Org. Chem.* **2005**, *2*, 39.
21. Porter, E. A.; Weisblum, B.; Gellman, S. H. *J. Am. Chem. Soc*. **2005**, *127*, 11516.

22. Rua, F.; Boussert, F. S.; Parella, T.; Diez-Perez, I.; Branchadell, E. G.; Ortuno, R. M. *Org. Lett*. **2007**, *9*, 3643.
23. Torres, E.; Acosta-Silva, C.; Rua, F.; Alvaraez-Larena, A.; Parella, T.; Branchadell, E. G.; Ortuno, R. M. *Tetrahedron* **2009**, *65*, 5669.
24. Fernandes, D.; Torres, E.; Aviles, F. X.; Ortuno, R. M. Vendrell, J. *Bioorg. Med. Chem*. **2009**, *17*, 3824.
25. Fernandes, C.; Pereira, E.; Faure, S.; Aitken, D. J.*; J. Org. Chem*. **2009**, *74*, 3217.
26. Fernandes, C.; Faure, S.; Pereira, E.; Declerck, V. V. Guillot, R.; Aitken, D. *J. Org. Lett*. **2010**, *12*, 3606.
27. Fülöp, F.; Martinek, T. A.; Tóth, G. K. *Chem. Soc. Rev.* **2006**, *35*, 323.
28. Martinek, T. A.; Tóth, G. K.; Vass, E.; Hollósi, M.; Fülöp, F. *Angew. Chem. Int. Ed*. **2002**, *41*, 1718.
29. Juaristi, E.; Soloshonok, V. A. (Editors) Enantioselective Synthesis of β-Amino Acids (2nd edition) Wiley-VCH, New York, **2005**.
30. Liu, M.; Sibi, M. P. *Tetrahedron* **2002**, *58*, 7991.
31. Cheng, R. P.; Gellman, S. H. deGrado, W. F. *Chem. Rev.* **2001**, *101*, 3219.
32. Seebach, D.; Gardiner, J. *Acc. Chem. Res.* **2008**, *41*, 1366.
33. Seebach, D.; Beck, A. K.; Capone, S.; Deniau, G.; Grošelj, U.; Zass, E. *Synthesis* **2009**, 1.
34. Liljeblad, A.; Kanerva, L. T. *Tetrahedron* **2006**, *62*, 5831.
35. March, T. L.; Johnston, M. R.; Duggan, P. J.; Gardiner, J. *Chem. Biodiv.* **2012**, *9*, 2410.
36. Sleebs, B. E.; Van Nguyen, T. T.; Hughes, A. B. *Org. Prep. Proc. Int.* **2009**, *41*, 429.
37. Weiner, B.; Szymanski, W.; Janssen, D. B.; Minnaard, A. J.; Feringa, B. L. *Chem. Soc. Rev*., **2010**, *39*, 1656.
38. Juaristi, E.; Escalante, J.; Lamatsch, B.; Seebach, D. *J. Org. Chem.* **1992**, *57*, 2396.
39. Kiss, L.; Forró, E.; Sillanpää, R.; Fülöp, F. *J. Org. Chem.* **2007**, *72*, 8786.
40. Kazi, B.; Kiss, L.; Forró, E.; Mándity, I.; Fülöp, F. *Arkivoc* **2010**, *ix*, 31.
41. Kiss, L.; Fülöp, F. *Synlett*, **2010**, 1302.
42. Kiss, L.; Forró, E.; Sillanpää, R.; Fülöp, F. *Tetrahedron* **2010**, *66*, 3599.
43. Kiss, L.; Forró, E.; Sillanpää, R.; Fülöp, F. *Synthesis* **2010**, 153.
44. Kiss, L.; Forró, E.; Sillanpää, R.; Fülöp, F. *Nucleic Acids Symposium Series* **2008**, *52*, 551.
45. Kiss, L.; Forró, E.; Sillanpää, R.; Fülöp, F. *Tetrahedron: Asymmetry* **2008**, *19*, 2856.

46. Kiss, L.; Forró, E.; Martinek, T. A.; Bernáth, G.; De Kimpe, N.; Fülöp, F. *Tetrahedron* **2008**, *64*, 5036.
47. Kiss, L.; Kazi, B.; Forró, E.; Fülöp, F. *Tetrahedron Lett.* **2008**, *49*, 339.
48. Kiss, L.; Forró, E.; Fustero, S.; Fülöp, F. *Org. Biomol. Chem*. **2011**, *9*, 6528.
49. Kiss, L.; Forró, E.; Fustero, S.; Fülöp, F. *Eur. J. Org. Chem.* **2011**, 4993.
50. Nonn, M.; Kiss, L.; Forró, E.; Sillanpää, R.; Fülöp, F. *Beilstein J. Org. Chem*. **2012**, *8*, 100.
51. Kiss, L.; Forró, E.; Fülöp, F. *Tetrahedron* **2012**, *68*, 4438.
52. Nonn, M.; Kiss, L.; Haenninen, M. M.; Sillanpää, R.; Fülöp, F. *Chem. Biodiv.* **2012**, *9*, 2571.
53. Nonn, M.; Kiss, L.; Sillanpää, R.; Fustero, S.; Fülöp, F. *Beilstein J. Org. Chem*. **2013**, *9*, 1164.
54. Kiss, L.; Szatmári, I.; Fülöp, F. *Lett. Org. Chem.* **2006**, *3*, 463.
55. Kiss, L.; Fülöp, F. *Chem. Rev.* **2014**, *114*, 1116.
56. Yang, H.; Foster, K.; Stephenson, C. R. J.; Brown, W.; Roberts, E. *Org. Lett.* **2000**, *2*, 2177.
57. Roers, R.; Verdine, G. L. *Tetrahedron Lett.* **2001**, *42*, 3563.
58. Sibi, M. P.; Deshpande, P. K. *J. Chem. Soc*., *Perkin Trans. 1* **2000**, 1461.
59. Evans, D. A.; Wu, L. D.; Wiener, J. J. M.; Johnson, J. S.; Ripin, D. H. B.; Tedrow, J. S. *J. Org. Chem.* **1999**, *64*, 6411.
60. Balamurugan, D.; Muraleedharan, K. M. *Tetrahedron* **2009**, *65*, 10074.
61. Musso, D. L.; Andersen, M. W.; Andrews, R. C.; Austin, R.; Beaudet, E. J.; Becherer, J. D. et al. *Bioorg.Med. Chem. Lett.* **2001**, *11*, 2147.
62. Ojima, I.; Wang, T.; Delaloge, F. *Tetrahedron Lett.* **1998**, *39*, 3663.
63. Palomo, C.; Aizpurua, J. M.; Cuevas, C.; Mielgo, A.; Galarza, R. *Tetrahedron Lett*., **1995**, *36*, 9027.
64. Sabala, R.; Hernandez, J.; Carranza, V.; Meza-Leon, R.L.; Bernes, S.; Sansinenea, E., Ortiz, A. *Tetrahedron* **2010**, *66*, 111.
65. Davis, F. A.; Reddy, G. V.; Liang, C.- H. *Tetrahedron Lett*., **1997**, *38*, 5139.
66. Meiries, S.; Parkin, A.; Marquez, R. *Tetrahedron*, **2009**, *65*, 2951.
67. Capone, S.; Pedatella, S.; Guaragna, A.; De Nisco, M.; Palumbo, G. *Tetrahedron* **2007**, *63*, 12202.
68. Cardillo, G.; Tolomelli, A.; Tomasini, C. *J. Org. Chem.* **1996**, *61*, 8651.

69. Gardiner, J.; Anderson, K. H.; Downard, A.; Abell, A. D. *J. Org. Chem*. **2004**, *69*, 3375.
70. Heinrich, E.; Seebach, D. *Helv. Chim. Acta*, **1988,** *71*, 1824
71. Moriyama, K.; Ishida, K.; Togo, H. *Org. Lett.* **2012**, *14*, 946.
72. Moriyama, K.; Ishida, K.; Togo, H. *Chem. Commun*., **2012**, *48*, 8574.
73. Saavedra, C.; Hernández, R.; Boto, A.; Álvarez, E. *J. Org. Chem.* **2009**, *74*, 4655.
74. Fustero, S.; Sanz-Cervera, J.-F.; Piera, J.; Sanchez-Rosello, M. Chiva, G.; Simon-Fuentes, A. *J. Fluorine Chem*. **2004**, *125*, 621.
75. Tamura, K.; Mizukami, H.; Maeda, K.; Watanabe, H.; Uneyama, K. *J. Org. Chem*. **1993**, *58*, 32.
76. Davies, S. G.; Ichihara, O.; Walters, I. A. *J. Chem. Soc., Perkin 1,* **1994**, 1141.
77. Chippindale, A. M.; Davies, S. G.; Iwamoto, K.; Parkin, R. M.; Smethurst, C. A. P.; Smith, A. D.; Rodriguez-Solla, H. *Tetrahedron* **2003**, *59*, 3253.
78. Bentley, S. A.; Davies, S. G.; Lee, J. A.; Roberts, P. M.; Russell, A. J.; Thomson, J. E.; Toms, S. M. *Tetrahedron* **2010**, *66*, 4604.
79. Davies, S. G.; Fletcher, A. M.; Roberts, P. M.; Thomson, J. E. *Tetrahedron: Asymmetry* **2012**, *23*, 1111.
80. Ozeki, M.; Ochi, S.; Hayama, N.; Hosoi, S.; Kajimoto, T.; Node, M. *J. Org. Chem.* **2010**, *75*, 4201.
81. Kanemasa, S.; Nishiuchi, M.; Kamimura, A.; Hori, K. *J. Am. Chem. Soc*. **1994**, *116*, 2324.
82. Minter, A. R.; Fuller, A. A.; Mapp, A. K. *J. Am. Chem. Soc*. **2003**, *125*, 6846.
83. Fuller, A. A.; Chen, B.; Minter, A. R.; Mapp, A. K. *J. Am. Chem. Soc*. **2005**, *127*, 5376.
84. Sewald, N. *Angew. Chem. Int. Ed*. **2003**, *42*, 5794.
85. Sibi, M. P.; Prabagaran, N.; Ghorpade, S. G.; Jasperse, C. P. *J. Am. Chem. Soc*. **2003**, *125*, 11796.
86. Bruneau, C.; Renaud, J.-C.; Jerphagnon, T. *Coord. Chem. Rev.* **2007**, *252*, 532.
87. Xie, J-H.; Zhu, S-F.; Zhou, Q-L. *Chem. Soc. Rev*. **2012**, *41*, 4126.
88. Zhu, G.; Chen, Z.; Zhang, X. *J. Org. Chem*. **1999**, *64*, 6907.
89. Heller, D., Holz, J.; Drexler, H.-J.; Lang, J.; Drauz, K.; Krimmer, H.-P.; Borner, A. *J. Org. Chem*. **2001**, *66*, 6816.
90. Jerphagnon, T.; Renaud, J.-L.; Demonchaux, P.; Ferreira, A.; Bruneau, C. *Tetrahedron: Asymmetry* **2003**, *14*, 1973.

91. Holz, J.; Sturmer, R.; Schmidt, U.; Drexler, H.-J.; Heller, D.; Krimmer, H.-P.; Borner, A. *Eur. J. Org. Chem*. **2001**, *2001*, 4615.
92. Pena, D.; Minnaard, A. J.; de Vries, J. G.; Feringa, B.L. *J. Am. Chem. Soc*. **2002**, *124*, 14552.
93. Pena, D.; Minnaard, A. J.; de Vries, A. H. M.; de Vries, J.G.; Feringa, B.L. *Org. Lett*. **2003**, *5*, 475.
94. Zhou , Y.-G.; Tang, W.; Wang, W.-B.; Li, W.; Zhang, X. *J. Am. Chem. Soc*. **2002**, *124*, 4952.
95. Qiu, L., Kwong, F. Y.; Wu, J.; Lam, W. H., Chan, S., Yu, W.-Y.; Li, Y.-M.; Guo, R.; Zhou, Z.; Chan, A. S. C. *J. Am. Chem. Soc*. **2006**, *128*, 5955.
96. Cimarelli, C.; Palmieri, G. *J. Org. Chem*. **1996**, *61*, 5557.
97. Tang, W.; Wu, S.; Zhang, X. *J. Am. Chem. Soc*. **2003**, *125*, 9570.
98. Elaridi, J.; Thaqi, A.; Prosser, A.; Jackson, W. R.; Robinson, A. J. *Tetrahedron: Asymmetry* **2005**, *16*, 1309.
99. Morimoto, H.; Lu, G.; Aoyama, N.; Matsunaga, S.; Shibasaki, M. *J. Am. Chem. Soc*. **2007**, *129*, 9588.
100. Kobayashi, S.; Ishitani, H.; Yamashita, Y.; Ueno, M.; Shimizu, H. *Tetrahedron* **2001**, *57*, 861.
101. Vicario, J. L.; Badía, D., Carrillo, L. *Org. Lett.* **2001**, *3*, 773.
102. Yamanaka, M.; Itoh, J.; Fuchibe, K.; Akiyama, T. *J. Am. Chem. Soc.* **2007**, *129*, 6756.
103. Dziedzic, P.; Vesely, J.; Cordova, A. *Tetrahedron Lett*. **2008**, *49*, 6631.
104. Yang, J. W.; Stadler, M.; List, B. *Angew. Chem. Int. Ed.* **2007**, *46*, 609.
105. Davis, F. A.; Szewczyk, J. M.; Reddy, R. E. *J. Org. Chem.* **1996**, *61*, 2222.
106. Davis, F. A.; Song, M. *Org. Lett.* **2007**, *9*, 2413.
107. Davis, F. A., Theddu, N. *J. Org. Chem*. **2010**, *75*, 3814.
108. Tang, T. P.; Ellman, J. A. *J. Org. Chem.* **2002**, *67*, 7819.
109. Sleebs, B. D.; Van Nguyen, T. T.; Hughes, A. B. *Org. Prep. Proc. Int.* **2009**, *41*, 429.
110. Sleebs, B. D.; Hughes, A. B. *J. Org. Chem.* **2007**, *72*, 3340.
111. Moriconi, E. J.; Crawford, W. C. *J. Org. Chem*. **1967**, *32*,370.
112. Fülöp, F. Stájer, G.; Bernáth, G.; Sohár, P. *Tetrahedron* **1985**, 41, 5159.
113. Stájer, G.; Szabó, E. A.; Fülöp, F.; Bernáth, G.; Sohár, P. *J. Heterocyclic Chem.* **1983**, *20*, 1181.
114. Besada, P.; González-Moa, M. J.; Terán, C.; Santana, L.; Uriarte, E. *Synthesis* **2002**, *16*, 2445.

115. Coldham, I.; Price, K. N.; Rathmell, R. E. *Org. Biomol. Chem*. **2003**, 1, 2111.
116. Forró, E.; Fülöp, F. *Tetrahedron: Asymmetry* **2004**, *15*, 2875.
117. Fülöp, F.; Palkó, M.; Forró, E.; Dervarics, M.; Martinek, T. A.; Sillanpää, R. *Eur. J. Org. Chem*. **2005**, 3214.
118. Forró, E.; Fülöp, F. *Tetrahedron: Asymmetry* **2008**, *19*, 1005.
119. Maercker, A. *Org. React.* **1965**, *14*, 270.

ANNEX