**PhD Thesis**

# Syntheses of functionalised β-amino acids through ring-opening/cross metathesis


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**Doctoral School of Pharmaceutical Sciences**

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# Márton Kardos

## Syntheses of functionalised β-amino acids through ring-opening/cross metathesis

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## 1. Introduction and aims

As a consequence of their high biological relevance, β-amino acids have gained an important role in medicinal and organic chemistry in the last twenty years. These structures are present in many natural compounds either in free form or as part of more complex molecules. Certain representatives such as the 5-membered carbocyclic cispentacin (isolated from the culture broth of *Bacillus cereus*) or icofungipen possess strong antifungal activities. Moreover, new generation peptides built from β-amino acids show well-ordered secondary structures and exhibit stability against proteases or peptidases; therefore, they are important molecules for medicinal chemistry. Since the early 1990s thanks to the effective development and commercial availability of well-defined Ru-based catalysts, olefin metathesis reactions have revolutionised the synthetic thinking. Metathesis, consequently, has become a powerful tool for the creation of one or more C–C double bonds. With this new method in hand, many natural and biologically active compounds have been prepared, which were previously challenging or impossible to synthesize.

In the Institute of Pharmaceutical Chemistry at the University of Szeged, a number of synthetic methods were developed to access highly-functionalised cyclic β-amino acids. Although the synthetic approaches presented in these studies cover a broad spectrum of chemical transformations including selective techniques, olefin metathesis reactions were not utilised.

The present PhD work focuses on the development of stereocontrolled synthetic methods for the preparation of novel alkenyl-functionalised β-amino acids and β-lactams through ring-opening metathesis reaction and on their subsequent functionalisation via cross metathesis taking place in highly selective manner in some cases. The ring-opening protocol is based on the high ring strain of the starting bi- or tricyclic compounds, which works as a driving force during stereocontrolled transformations. The products sometimes were prepared in optically pure form through enzymatic kinetic resolution of racemic compounds with azetidinone framework.

## 2. Applied methods

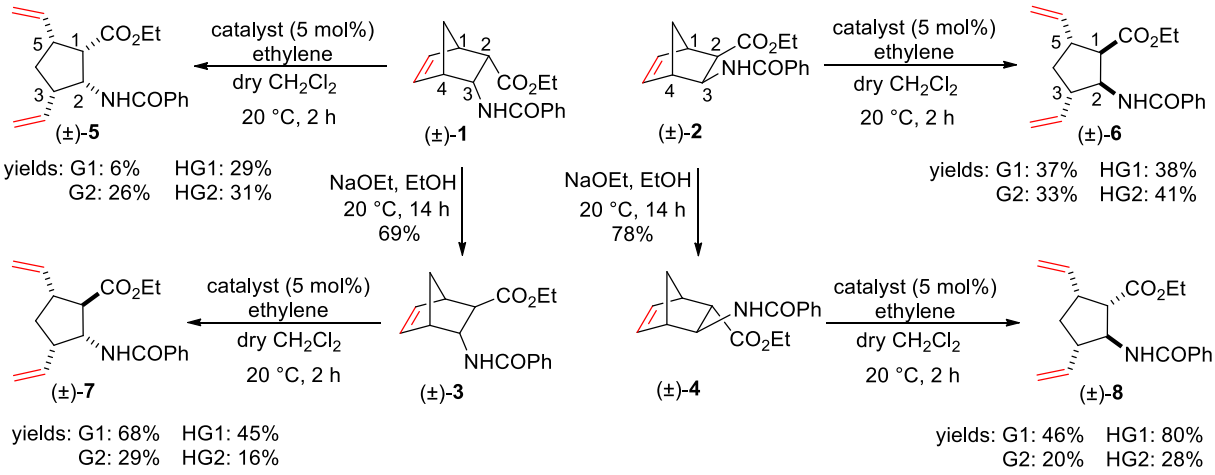
The synthesised compounds were separated and purified by column chromatography on silica gel and by crystallization. The newly prepared products were characterized by melting point measurements, NMR, mass spectroscopy and elemental analysis.

The *e.e.* values of the optically active compounds were determined by gas chromatography and HPLC. For determination of the stereochemistry of the compounds, 2D NMR spectroscopy (COSY) and X-ray diffraction were also used.

## 3. Results and discussion

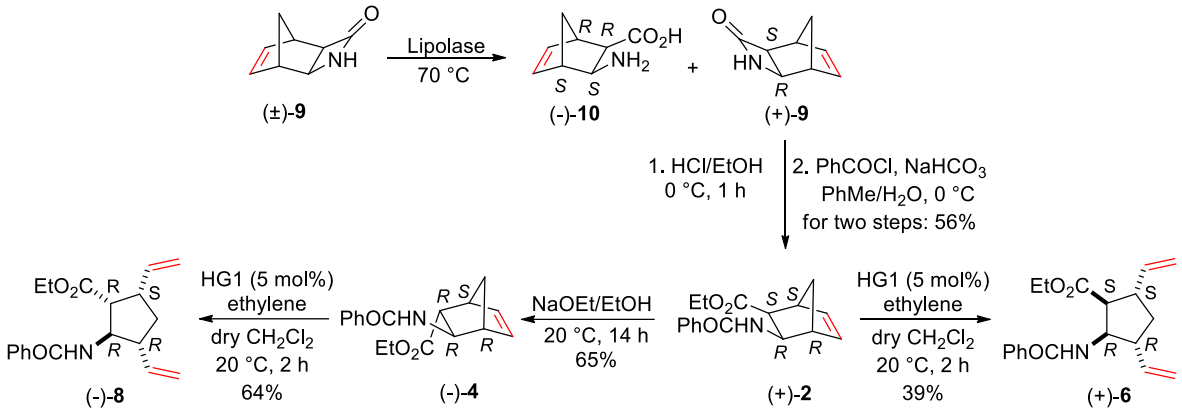
### 3.1. Stereocontrolled one-step synthesis of difunctionalised cispentacin and transpentacin derivatives through ring-opening metathesis (ROM) of norbornene β-amino acids

Our synthetic strategy towards difunctionalised cispentacin and transpentacin started with the preparation of *diendo*- and *diexo*-norbornene β-amino ester (±)-**1** and (±)-**2**. In order to increase the number of achievable cispentacin stereoisomers, epimerised derivatives of (±)-**1** and (±)-**2** were prepared by their treatment with NaOEt in EtOH (Scheme 1). With the four bicyclic metathesis substrates in hand [(±)-**1**, (±)-**2**, (±)-**3**, and (±)-**4**] ring-opening metathesis (ROM) reaction was performed which gave divinylated cispentacin derivatives (±)-**5**, (±)-**6**, (±)-**7**, and (±)-**8** in variable yield. The ring-opening reactions were executed in the presence of a metathesis catalysts [Grubbs 1 (G1), Grubbs 2 (G2), Hoveyda-Grubbs 1 (HG1) or Hoveyda-Grubbs 2 (HG2)] with ethylene under argon atmosphere.



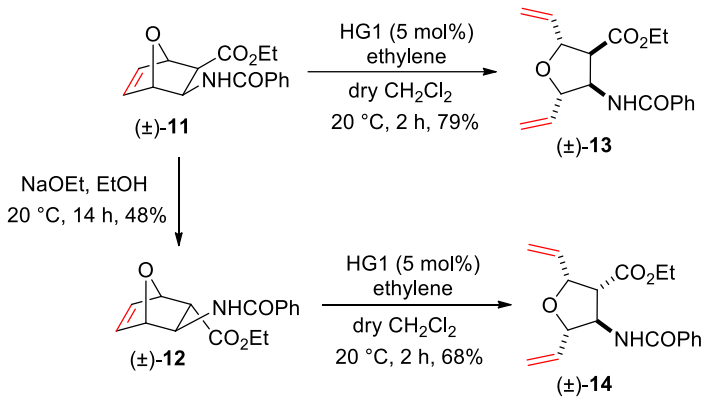

**Scheme 1.**

3,5-Divinylated β-amino ester stereoisomers (±)-**6** and (±)-**8** were prepared in enantiomerically pure form (Scheme 2). For this purpose, optically active β-lactam (+)-**9** was prepared by lipolase-catalysed enantioselective enzymatic ring opening of compound (±)-**9**. The resulting tricylic β-lactam was transformed similarly to the racemates (ethanolysis, benzoylation followed by ROM, or ethanolysis, benzoylation, isomerisation and subsequent ROM) to afford the desired final products (+)-**6**, and (–)-**8** in optically pure form.




**Scheme 2.**

In view of the relevance of oxygen-containing cyclic β-amino acids, the stereocontrolled one-step method applied earlier was extended toward divinylated tetrahydrofuran β-amino esters (±)-**13** and (±)-**14** as depicted in Scheme 3. First, *endo-exo* derivative (±)-**12** was prepared by epimerisation of compound (±)-**11**, then ROM reaction of the corresponding starting materials with ethylene, in the presence of HG1 catalyst gave the desired β-amino esters (±)-**13** and (±)-**14** with vinyl side chains in good yields.

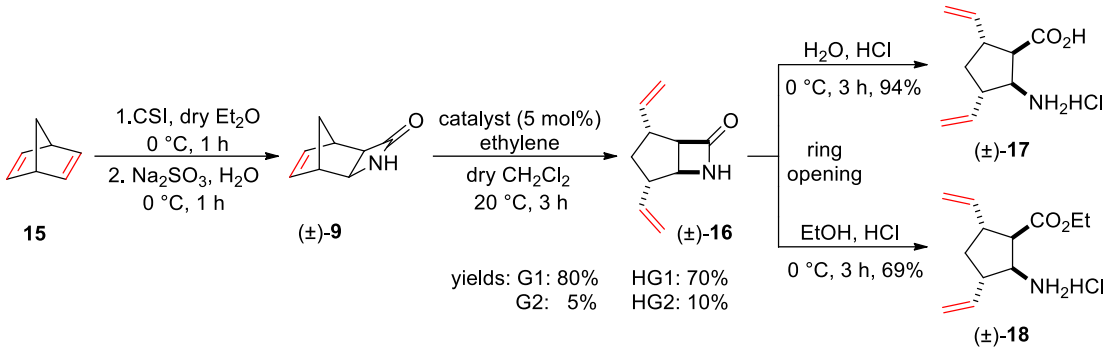



**Scheme 3.**

### 3.2. Stereocontrolled one-step synthesis of difunctionalised azetidinones and β-amino acid derivatives from condensed ring β-lactams by ring-opening metathesis (ROM)

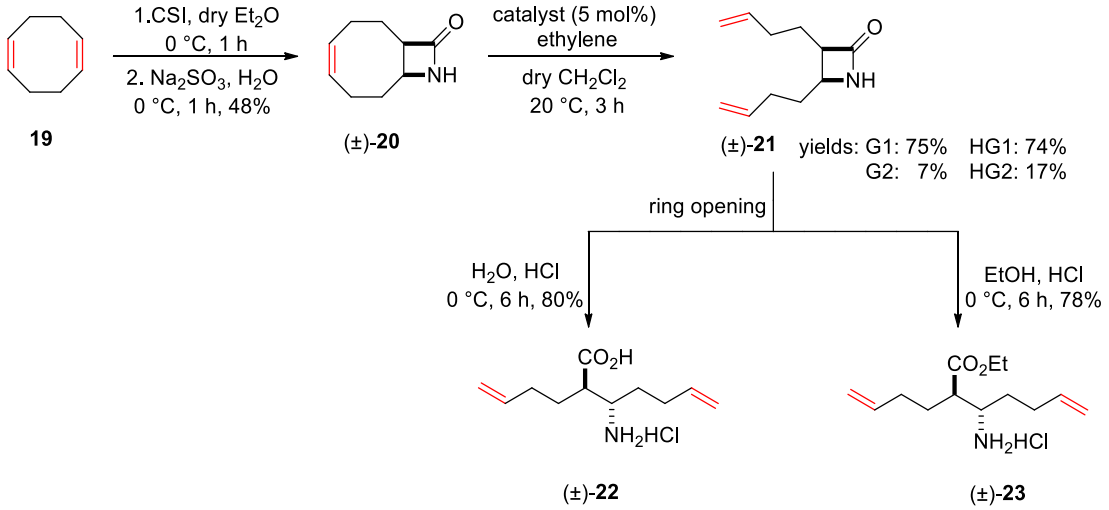
The stereocontrolled ring-opening method detailed above was applied to the preparation of difunctionalised bicyclic β-lactam (±)-**16**. In the first step metathesis substrate (±)-**9** was prepared with the addition of chlorosulfonyl isocyanate (CSI) to norbornadiene **15** followed by chlorosulfonamide hydrolysis with $Na_2SO_3$ (Scheme 4). Next, ROM reaction was performed with ethylene in the presence of a metathesis catalysts (G1, G2, HG1 or HG2) to give divinylated β-lactam (±)-**16** in yields ranging from 5% to 80%.

In the final step, racemic cispentacin derivatives (±)-**17** and (±)-**18** containing valuable olefinic bonds were accessed through opening of the 4-membered heterocycle.

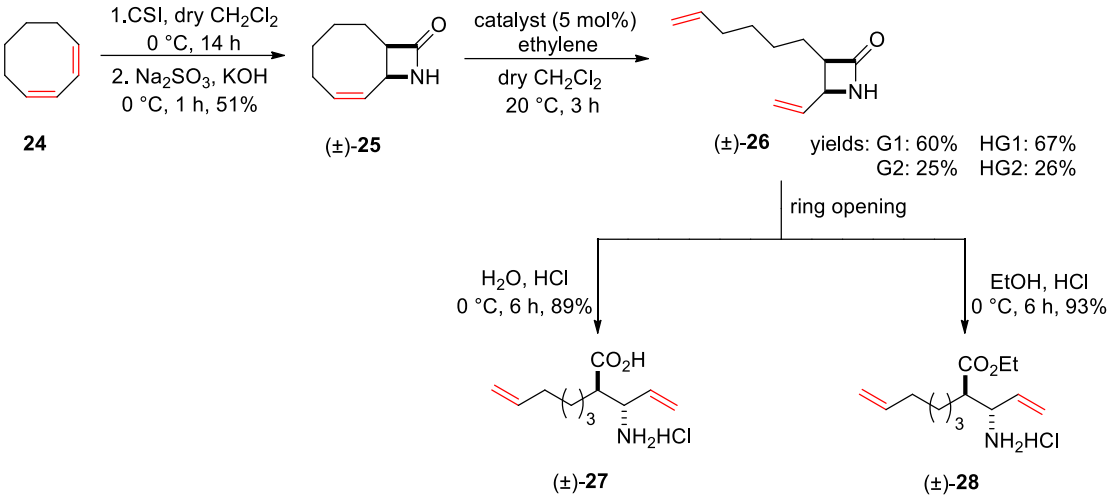



**Scheme 4.**

Following our strategy, bicyclic β-lactams (±)-**20** and (±)-**25** were prepared by the well-known pathway from readily available starting materials (Schemes 5 and 6). Subsequently, ROM reactions of these metathesis substrates (±)-**20** and (±)-**25** with ethylene in the presence of a metathesis catalysts (G1, G2, HG1 or HG2) smoothly afforded monocyclic β-lactams (±)-**21** and (±)-**26** containing olefinic bonds in variable yields. Finally, the 4-membered heterocycles (±)-**21** and (±)-**26** were opened by $H_2O$ or EtOH under protic conditions giving the expected products (±)-**22**, (±)-**23**, (±)-**27**, and (±)-**28** in all cases with the carboxyl and amino hydrochloride groups in *anti* arrangement.



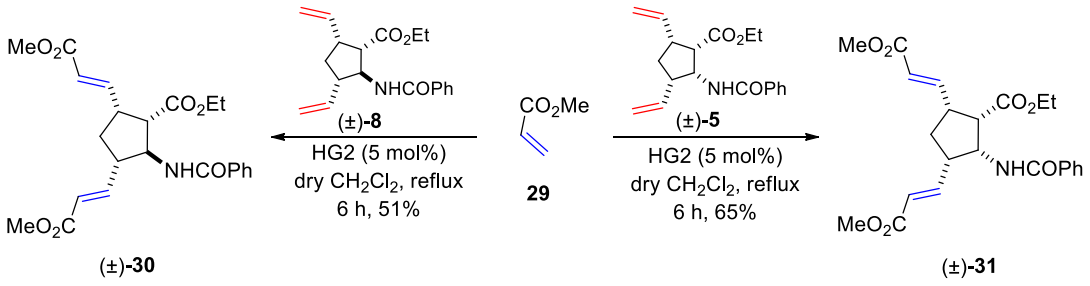

**Scheme 5.**




**Scheme 6.**

### 3.3. Carbon–carbon double bond functionalisation of β-amino acid derivatives and β-lactams with α,β-unsaturated carbonyl compounds through cross metathesis (CM)

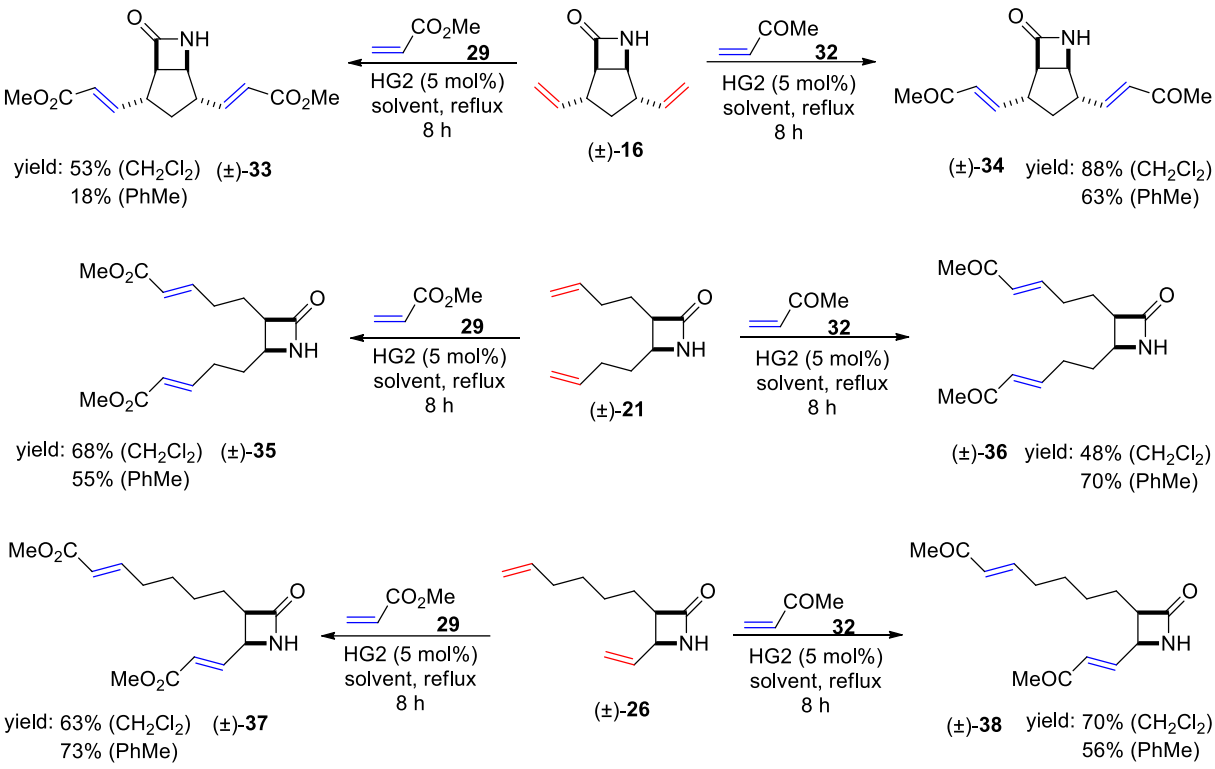
Novel dicoupled cispentacin derivatives (±)-**30** and (±)-**31** were synthesised in moderate yields by CM reaction in the presence of HG2 catalyst between divinylated β-amino esters (±)-**5** or (±)-**8** prepared earlier and acrylate **29** (Scheme 7). It is important to note that compound (±)-**31** was identical to the material prepared earlier on an alternative synthetic pathway. It may be concluded that the CM reaction proceeded under stereocontroll with *E* selectivity, that is the configuration of the newly created C–C double bonds in (±)-**30** and (±)-**31** also have *E* geometry.




**Scheme 7.**

The well-established cross metathesis protocol for the syntheses of highly-functionalised cispentacin derivatives was expanded to bi- and monocyclic unsaturated β-lactams (±)-**16**, (±)-**21**, and (±)-**26** (Scheme 8). The terminal alkene moieties, in these cases, were transformed with both methyl acrylate **29** and methyl vinyl ketone **32**.

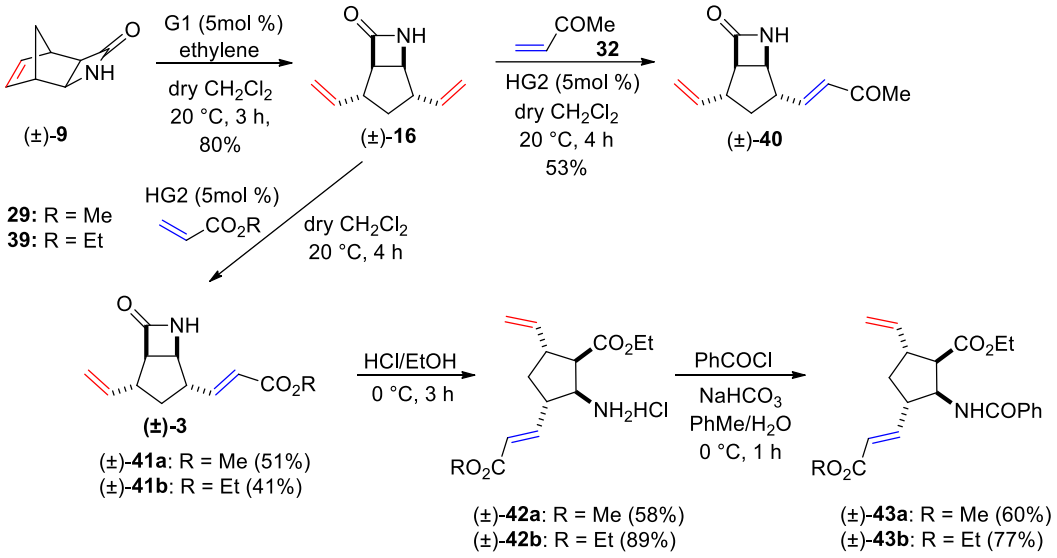
The coupling reactions were carried out in dry toluene or dry $CH_2Cl_2$ at reflux temperature, in the presence of HG2 catalyst. It is important to note that in all cases, the cross metathesis products (±)-**33**, (±)-**34**, (±)-**35**, (±)-**36**, (±)-**37**, and (±)-**38** with *E* geometry (high *J* values, in accordance with earlier literature data) were isolated in moderate to good yields.




**Scheme 8.**

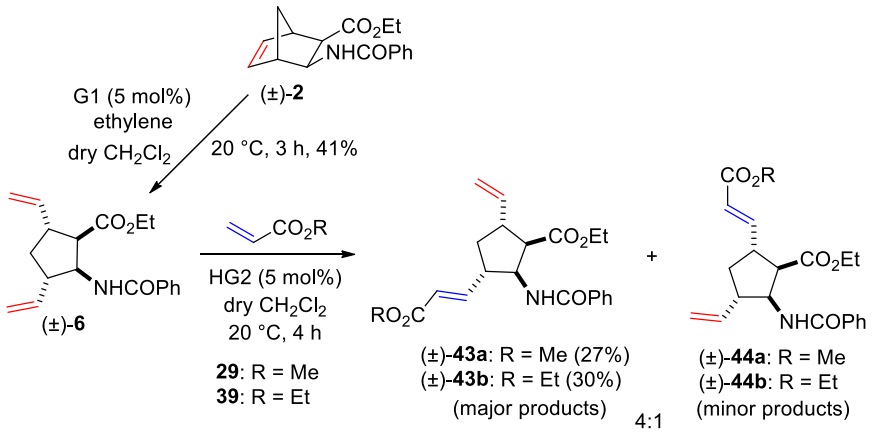
### 3.4. Syntheses of functionalised β-amino acid derivatives and β-lactams through chemoselective cross metathesis (CM)

During our experimental investigation we realised that under appropriately selected reaction conditions, chemodiscrimination of the olefinic bonds in cross metathesis reactions is achievable. First, divinyl-substituted azetidinone (±)-**16** was subjected to coupling reactions with methyl vinyl ketone **32** or acrylic esters **29** and **39** in the presence of HG2 catalyst (Scheme 9). After chromatography purification, monocoupled products, (±)-**40** and (±)-**41a**,**b** involving the α,β-unsaturated carbonyl part located near to the amide *N*-atom were isolated in moderate yields. In the final step novel functionalised cispentacin derivatives (±)-**43a**,**b** were synthesised from the corresponding β-lactams (±)-**41a**,**b** by ethanolysis followed by benzoylation. The selectivity in the coupling reaction originates from the hydrogen bond between the catalyst chloride atom and the N–H moiety.



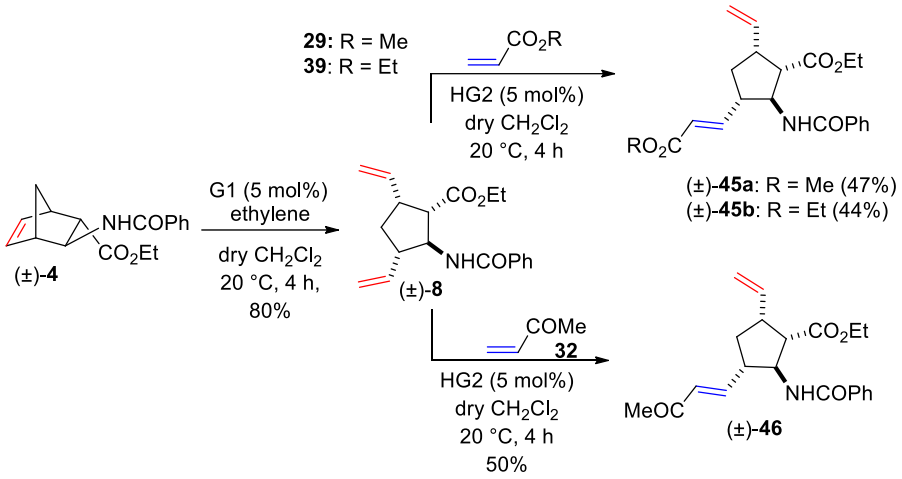

**Scheme 9.**

Next, divinyl-substitued cispentacin (±)-**6** (prepared by our ROM method) was submitted to CM reactions with acrylic esters **29** and **39** as depicted in Scheme 10. However, contrary to our previous experimental results, these cross metathesis reactions of compound (±)-**6** in view of monocoupled products [(±)-**43a**,**b** and (±)-**44a**,**b**] were not completely selective.



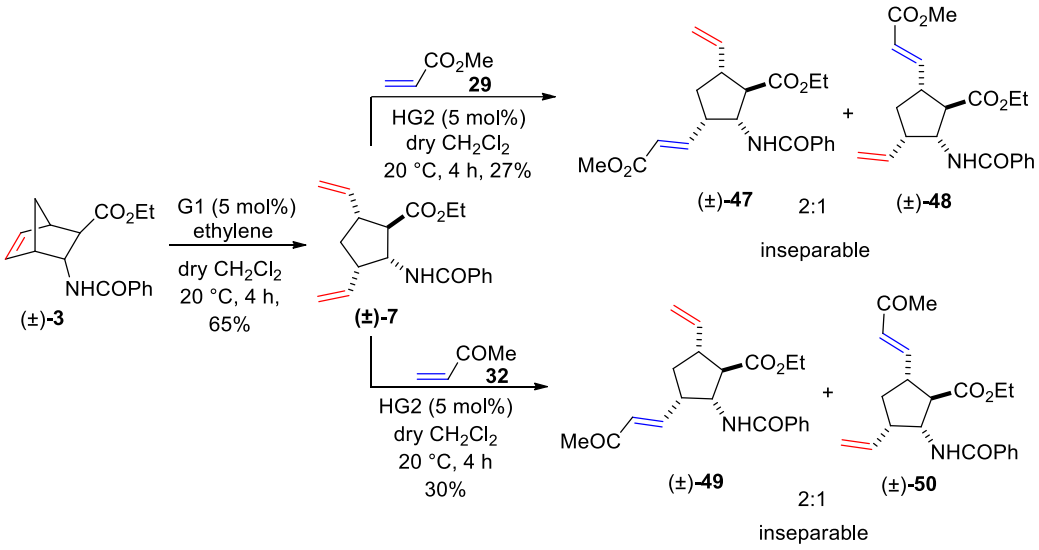

**Scheme 10.**

After the unexpected experimental results, compound (±)-**8** was submitted to cross-coupling with acrylic esters **29** and **39** or methyl vinyl ketone **32** (Scheme 11). In contrast with divinylated cispentacin (±)-**6** [and at the same time similarly to divinylated β-lactam (±)-**16**] CM reactions, in these cases, resulted in single monocoupled isomers (±)-**45a**,**b** and (±)-**46**.



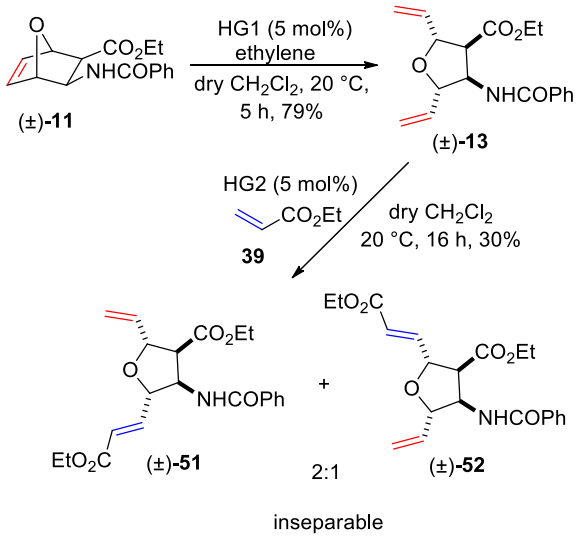

**Scheme 11.**

However, when another diolefinated transpentacin stereoisomer, namely (±)-**7** was submitted to CM reaction with α,β-unsaturated carbonyl compounds **29** and **32**, inseparable mixtures of regioisomers (±)-**47**/(±)-**48** and (±)-**49**/(±)-**50** were formed, respectively (Scheme 12). These results clearly suggested that in addition to the hydrogen bonding effect, other factors (such as steric effects) also influence the outcome of the coupling reactions in the case of compounds (±)-**6**, (±)-**7**, and (±)-**8**.



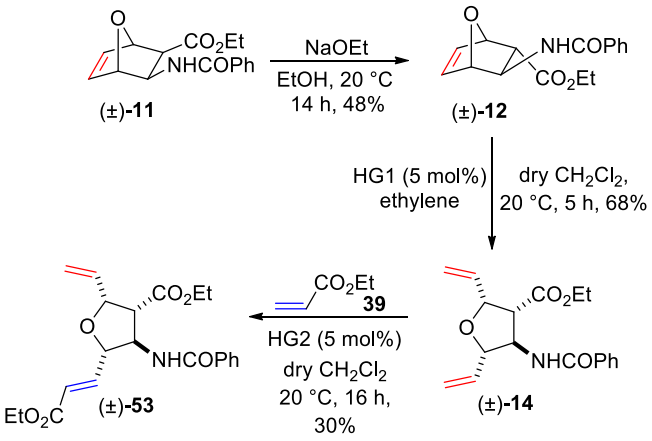

**Scheme 12.**

Finally, we extended the scope of the chemoselective transformations with CM reactions to the synthesis of monocoupled *O*-heterocyclic counterparts (Scheme 13). β-Amino ester (±)-**13** in which the ester and the protected amino group are in a *cis* arrangement was submitted to CM reaction with ethyl acrylate **39** and, analogously to its carbocyclic counterpart (±)-**6**, it afforded an inseparable mixture of regioisomers (±)-**51**/(±)-**52**.




**Scheme 13.**

According to our expectations, CM reaction between ethyl acrylate **39** and oxatranspentacin (±)-**14** in the presence of HG2 catalyst led to single monocoupled product (±)-**53** analogously to *trans* amino ester (±)-**8** (Scheme 14).




**Scheme 14.**

## 4. List of publications and lectures

### Full papers related to the thesis

I. Loránd Kiss, **Márton Kardos**, Enikő Forró, Ferenc Fülöp
Stereocontrolled one-step synthesis of difunctionalised cispentacin derivatives through ring-opening metathesis of norbornene β-amino acids
*Eur. J. Org. Chem.* **2015**, 1283. **IF: 3.068***

II. **Márton Kardos**, Loránd Kiss, Ferenc Fülöp
Stereocontrolled synthesis of difunctionalized azetidinones and $\beta^{2,3}$-amino acid derivatives from cyclodienes by ring-opening and cross-metathesis reactions
*Asian. J. Org. Chem.* **2015**, *4*, 1155. **IF: 3.275***

III. **Márton Kardos,** Loránd Kiss, Matti Haukka, Santos Fustero, Ferenc Fülöp
Olefin-bond chemodifferentiation through cross-metathesis reactions: a stereocontrolled approach to functionalized $\beta^{2,3}$-amino acid derivatives
*Eur. J. Org. Chem.* **2017**, 1894. **IF: 3.068***

*2015 impact factors

### Scientific lectures related to the thesis

I. **Kardos Márton**, Kiss Loránd, Fülöp Ferenc
Telítetlen ciklusos β-aminosavak átalakításai metatézis reakcióval
*MTA Heterociklusos és Elemorganikus Kémiai Munkabizottság ülése*
Balatonszemes, Hungary, 21-23, May, 2014, oral presentation

II. **Kardos Márton**
Funkcionalizált ciszpentacin származékok sztereokontrollált szintézise biciklusos β-aminosavakból gyűrűnyitó metatézissel
*XXXVII. Kémiai Előadói Napok*
Szeged, Hungary, 3-5, November, 2014, oral presentation

III. Kiss Loránd, **Kardos Márton**, Forró Enikő, Fülöp Ferenc
Funkcionalizált ciszpentacin származékok sztereokontrollált szintézise biciklusos β-aminosavakból gyűrűnyitó metatézissel
*XX. Nemzetközi Vegyészkonferencia*
Cluj Napoca, Romania, 6-9, November, 2014, poster presentation

IV. **Kardos Márton**

Funkcionalizált $\beta^{2,3}$-aminosav származékok sztereokontrollált szintézisei gyűrűnyitó/keresztmetatézissel

*A Szegedi Ifjú Szerves Kémikusok Támogatásáért Alapítvány 14. Tudományos Előadóülése*

Szeged, Hungary, 29, April, 2015, oral presentation

V. **Kardos Márton**, Kiss Loránd, Fülöp Ferenc

Funkcionalizált $\beta^{2,3}$-aminosav származékok sztereokontrollált szintézisei biciklusos β-laktámok gyűrűnyitó/keresztmetatézisével

*MTA Heterociklusos és Elemorganikus Kémiai Munkabizottság ülése*

Balatonszemes, Hungary, 27-29, May, 2015, oral presentation

VI. **Kardos Márton**, Kiss Loránd, Fülöp Ferenc

Kemoszelektív keresztmetatézis β-aminosavszármazékokon

*MTA Heterociklusos és Elemorganikus Kémiai Munkabizottság ülése*

Balatonszemes, Hungary, 18-20, May, 2016, oral presentation