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Highly functionalized piperidines via ring-closing metathesis of dehydroamino acids

Proefschrift

ter verkrijging van de graad doctor
aan de Radboud Universiteit Nijmegen
op gezag van de rector magnificus prof. mr. S.C.J.J. Kortmann,
volgens besluit van het college van decanen
in het openbaar te verdedigen op vrijdag 31 januari 2014
om 10:30 uur precies

door

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Table of contents

List of abbreviations

1  Ring Closing Metathesis in synthesis of natural products  2
   1.1  Introduction  3
   1.2  Five-membered nitrogen heterocycles  5
       1.2.1  Dihydropyrroles  5
       1.2.2  Pyrrolidine alkaloids  6
           1.2.2.1  Pyrrolidines  6
           1.2.2.2  Dipyrrolidines  7
           1.2.2.3  Polyhydroxypyrrolidines  7
       1.2.3  Indolizidine alkaloids  9
           1.2.3.1  Polycyclic indolizidines  9
           1.2.3.2  Polyhydroxyindolizidines  15
       1.2.4  Pyrrolizidine alkaloids  18
   1.3  Six-membered nitrogen heterocycles  21
       1.3.1  Piperidine alkaloids  21
           1.3.1.1  Piperidines  21
           1.3.1.2  Piperidine carboxylic acids  28
           1.3.1.3  Piperidones  30
           1.3.1.4  Polyhydroxypiperidines  31
       1.3.2  Indolizidine alkaloids  32
       1.3.3  Quinolizidine alkaloids  37
   1.4  Seven-membered nitrogen heterocycles  41
   1.5  Eight-membered nitrogen heterocycles  43
   1.6  Purpose and outline of this investigation  44
   1.7  Acknowledgements  45
   1.8  References  46

2  Ring closing metathesis of α,β-unsaturated didehydroamino esters  50
   2.1  Introduction  51
   2.2  α,β-unsaturated didehydroamino ester precursors for RCM  53
   2.3  Ring closing metathesis of α,β-unsaturated didehydroamino esters  55
   2.4  Introduction of substituents  58
   2.5  Synthesis of 1-oxoisoquinoline carboxylic esters  59
   2.6  Conclusion  61
   2.7  Experimental section  62
   2.8  References  70

3  Diastereoselective synthesis of substituted morpholines  74
<table>
<thead>
<tr>
<th>Section</th>
<th>Title</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>6.1</td>
<td>Introduction</td>
<td>151</td>
</tr>
<tr>
<td>6.2</td>
<td>Asymmetric hydrogenation of tetrasubstituted dehydroamino esters</td>
<td>153</td>
</tr>
<tr>
<td>6.3</td>
<td>Asymmetric hydrogenation of didehydroamino acids: screening</td>
<td>156</td>
</tr>
<tr>
<td>6.4</td>
<td>Asymmetric hydrogenation of didehydroamino acids</td>
<td>158</td>
</tr>
<tr>
<td>6.5</td>
<td>Conclusions</td>
<td>161</td>
</tr>
<tr>
<td>6.6</td>
<td>Acknowledgements</td>
<td>162</td>
</tr>
<tr>
<td>6.7</td>
<td>Experimental section</td>
<td>163</td>
</tr>
<tr>
<td>6.8</td>
<td>References</td>
<td>166</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>7</th>
<th>A stereoselective total synthesis of tangutorine</th>
<th>170</th>
</tr>
</thead>
<tbody>
<tr>
<td>7.1</td>
<td>Introduction</td>
<td>171</td>
</tr>
<tr>
<td>7.2</td>
<td>Synthesis of the quinolizidine precursor of tangutorine</td>
<td>175</td>
</tr>
<tr>
<td>7.3</td>
<td>Bischler-Napieralski cyclizations</td>
<td>177</td>
</tr>
<tr>
<td>7.4</td>
<td>Completion of tangutorine</td>
<td>179</td>
</tr>
<tr>
<td>7.5</td>
<td>Conclusions</td>
<td>180</td>
</tr>
<tr>
<td>7.6</td>
<td>Acknowledgements</td>
<td>180</td>
</tr>
<tr>
<td>7.7</td>
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<td>181</td>
</tr>
<tr>
<td>7.8</td>
<td>References</td>
<td>186</td>
</tr>
</tbody>
</table>

Summary

Samenvatting

Dankwoord

List of publications
List of abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
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</tr>
</thead>
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<tr>
<td>ee</td>
<td>enantiomeric excess</td>
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<tr>
<td>et al.</td>
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Ring closing metathesis in synthesis of natural products

Abstract

Only twenty years have elapsed since Grubbs and Fu reported that Schrock’s molybdenum catalyst could be used to induce efficient cyclization of functionalized \( \alpha,\omega \)-diene-amines. Since then, a wide range of ring-closing metathesis reactions to form nitrogen heterocyclic products have been reported, including applications in the synthesis of natural products. These applications have been greatly facilitated by the advent of new and more reactive RCM catalysts, thereby continuously widening the range of substrates and increasing the scope of the metathesis processes. This Chapter shows that especially five- and six-membered heterocyclic rings are ideal targets for RCM and that applications in larger rings are lacking behind. On the one hand this is due to the lower occurrence of the larger rings in natural products, on the other hand especially eight-membered rings are significantly more difficult to form using the metathesis reaction.


1.1 Introduction

The formation of carbon-carbon bonds is a crucial issue in organic synthesis. Out of all methodologies available, the metathesis reaction has over the past decade evolved as one of the most useful tools in this field to rapidly construct the skeleton of carba- and heterocyclic molecules.\(^1\) The key step of the metathesis reaction entails the metal-catalyzed redistribution of two carbon-carbon double bonds by a scission-recombination process.\(^2\) Among various applications of the metathesis reaction, ring-closing metathesis (RCM) has emerged as one of the most powerful tools for the construction of natural and unnatural cyclic compounds (Scheme 1.1).\(^3\) Other types of metathesis reactions developed so far include cross-metathesis (CM), ring-opening metathesis (ROM), ring rearrangement metathesis (RRM, combining ROM with RCM in a tandem sequence), ring opening metathesis polymerisation (ROMP) and ene-yne methathesis.\(^3\)

\[ \text{RCM} \]

Scheme 1.1. Schematic illustration of the ring-closing metathesis reaction.

The metathesis reaction has already been used for several decades in polymer chemistry for ring-opening metathesis polymerization (ROMP).\(^4\) Only since the development of well-defined molybdenum and ruthenium carbene complexes by Schrock\(^5\) and Grubbs\(^6\) in 1990 and 1992, respectively, an explosion of their application in organic synthesis has been witnessed. Initially, it was demonstrated that the Schrock catalyst \( S1 \) could serve as a homogeneous catalyst for olefin ring-closing metathesis (Figure 1.1).\(^7\) Unfortunately, metal carbene complex \( S1 \) suffers from extreme sensitivity to air and moisture, which precluded widespread use among organic chemists. Not long thereafter, the more stable yet less reactive benzylidene ruthenium complex \( G4 \) was developed.\(^8\) Additional research in this field led in 1995 to the ruthenium carbene catalyst \( G1 \),\(^9\) which is currently commercially available as the Grubbs-I or \( 1^{\text{st}} \) generation Grubbs catalyst. This catalyst still appeared to be somewhat less reactive than catalyst \( S1 \) in olefin metathesis but yet retained the remarkable air and water stability characteristics of ruthenium complex \( G4 \). In 1999, the effectiveness of the ruthenium-based metathesis catalysts was even further enhanced by replacing one of the phosphine ligands with a heterocyclic carbene, the \( 1,3\text{-bis}(2,4,6\text{-trimethylphenyl})\text{-2-imidazolidinylidene} (\text{IMesH}_2) \) ligand to give catalyst \( G2 \).\(^10\) This carbene complex exhibits high olefin metathesis activity in RCM reactions due to amongst others a higher thermal stability and wider functional group tolerance, and is nowadays commercially available as the Grubbs-II or \( 2^{\text{nd}} \) generation Grubbs catalyst. Many (commercially available) modifications of these catalysts exist,\(^11\) in particular ones in which the tricyclohexylphosphine and benzylidene groups have been replaced by an ortho-isopropoxy-substituted benzylidene, the so-called Grubbs-Hoveyda catalysts \( G3 \) and \( G5 \).\(^12\)
Figure 1.1. Metal-alkylidene complexes as metathesis catalysts: Schrock’s catalyst S1, the first benzylidene ruthenium complex G4, Grubbs-I catalyst G1, Grubbs-II catalyst G2, Grubbs-Hoveyda-I catalyst G5, Grubbs-Hoveyda-II catalyst G3, Ru-catalyst G6-G10.

Formation of heterocycles by ring-closing metathesis was first reported by Grubbs and Fu, who found that a di-N-allylated trifluoroacetamide underwent cyclization in the presence of Schrock’s catalyst S1 to give the corresponding 3-pyrroline.\textsuperscript{13} At that time it was shown that the ruthenium-alkylidene complex G4 gave also excellent yields for similar heterocyclic RCM reactions, even when performed in undistilled solvents and in the presence of air. Although it was well established that free amines are generally incompatible with the metathesis reaction,\textsuperscript{14} later work demonstrated that this problem could be overcome by protection of the basic nitrogen atom as an amide or carbamate. In addition, protonation of the amine to give the corresponding ammonium salts and thus avoiding protecting groups is tolerated by catalysts G1 and G2.
Chapter 1

As a result of the compatibility of the Ru-catalysts with nitrogen-based functional groups, RCM became a widely applied synthetic tool in the total synthesis of nitrogen-containing natural products. In particular the formation of medium-sized (five- to eight-membered) heterocyclic systems, which frequently occur in naturally occurring alkaloids, became a key target for metathesis-mediated synthesis. Hence, the aim of this account is to provide an overview of the majority of syntheses of alkaloid natural products in which a medium-sized nitrogen-containing ring was constructed using RCM.

1.2 Five-membered nitrogen heterocycles

1.2.1 Dihydropyrroles

Interesting candidates for the application of RCM are the linear marine peptides (aeruginosins) that share a common 7-aza[4.3.0] bicyclic core unit. Hanessian et al. recently described the total syntheses of dysinosin A (1),\textsuperscript{15} isolated from a new genus of sponge of the family Dysideida and oscillarin (2)\textsuperscript{16} that was found in the algal cultures of Oscillatoria agardhii (Scheme 2). Both alkaloids were constructed via two peptide couplings between three common subunits: an indolizidine carboxylic acid (4 or 6) derived from L-glutamic acid, an acyclic peptide chain (5 or 7) and 3 (Scheme 1.2).

![Scheme 1.2. Retrosynthesis of the natural products dysinosin A (1) and oscillarin (2) sharing the RCM product 3.](image)

The synthesis of the Δ-3 pyrrole unit 3 is shown in Scheme 1.3 and started with readily available γ-butyrolactone. Six steps involving ring opening to the hydroxy ester and...
substitution of the reduced ester with allylamine were required to form metathesis precursor 8. Cyclization of N-Boc protected 8 into pyrrole 9 employing G1 (10 mol %) went smoothly in a high yield of 90%. The six-membered carbocycle of dysinonin A fragment dihydroxyindolizidine 4 was prepared via RCM as well (99% yield) using the same catalyst (1 mol %) as for 8.

\[ \text{Scheme 1.3. Synthesis of the } \Delta^-3 \text{ pyrrole unit.} \]

### 1.2.2 Pyrrolidine alkaloids

#### 1.2.2.1 Pyrrolidines

(−)-(S)-Nicotine (12) is one of the many piperidine and pyrrolidine alkaloids isolated from the leaves of *Nicotaiana tabacum*. Welter and coworkers developed a synthesis route where 12 was obtained in only six steps from pyridinylallyl carbonate 10 involving RCM (Scheme 1.4).\(^\text{17}\) The synthesis commenced with an Ir-catalyzed asymmetric allylic amination of 10 to produce diene 11 in excellent enantiomeric purity when using phosphoramidate ligand L1. Subsequently, secondary amine 11 was N-protected prior to RCM in order to prevent catalyst deactivation. Best RCM results were achieved with G2 yielding the corresponding dihydropyrrole derivative in >90% yield. The synthesis of (S)-nicotine was completed through a deprotection step and finally reduction of the double bond.

\[ \text{Scheme 1.4. Synthesis of (S)-nicotine.} \]

Over the past few decades, the biosyntheses of tropane alkaloids such as (−)-hyoscyamine, (−)-scopolamine and (−)-coca have been studied extensively.\(^\text{18}\) The skeletons of all these alkaloids feature the tropinone moiety, produced by oxidation and subsequent cyclization of (+)-hygrine (17).\(^\text{19}\) It was envisioned that RCM could be invoked in order to develop an enantioselective synthesis of 17.\(^\text{20}\) As depicted in Scheme 1.5, a phase-transfer catalytic
allylation reaction with methallyl bromide converted t-butyl ester 13 into product 14 in 97% ee. Metathesis precursor 15 was then prepared in six more steps, including transformation of the t-butyl ester of 14 into a terminal olefin. Dihydropyrrole 16 was formed in quantitative yield by RCM employing G2 (8 mol %). Subsequent hydrogenation and deprotection of 16 led to (+)-hygrine 17 in overall yield of 29% and an ee of 97%.

![Scheme 1.5. Synthesis of (+)-hygrine and tropinone.](image)

### 1.2.2.2 Dipyrrolidines

A total synthesis of the dipyrrolidine alkaloid (–)-trans-dendrochrysine (22), isolated from the orchid endemic *Dendrobium chrysanthum* was achieved by Blechert and coworkers utilizing ring rearrangement metathesis (RRM). The asymmetric synthesis commenced with preparation of diolefin 20 from commercially available tropone (19, Scheme 1.6) in 11 steps involving a solid-phase supported *Candida antarctica* lipase B (Cal-B)-mediated desymmetrization.

![Scheme 1.6. Synthesis of (–)-trans-dendrochrysine.](image)

Different ruthenium catalysts were evaluated for the RRM process and it appeared that G3 (5 mol %) in refluxing toluene under an ethylene atmosphere gave the best results providing bicycle 21 in 91% yield. Thus, (–)-trans-dendrochrysine (22) was synthesized in a yield of 5.9% over 18 linear steps.
1.2.2.3 Polyhydroxypyrrolidines

Naturally occurring iminosugars (azasugars) have been prominent target molecules for the utilization of RCM, involving formation of a cyclic olefin, followed by dihydroxylation. The mulberry tree (*Morus alba*) alkaloid 1,4-dideoxy-1,4-imino-D-ribitol [(+)-DRB, 27] is a potent inhibitor of glucosidases and of eukaryotic DNA polymerases. The Riera synthesis of polyhydroxypyrrolidine 27 featured a five-membered ring formation *via* RCM as illustrated in Scheme 1.7.

![Scheme 1.7. Synthesis of DBR.](image)

Divinylmethanol 23 was converted in a number of steps into the enantiomerically pure RCM precursor 25 (ee = 99%) via a Sharpless epoxidation and subsequent Payne rearrangement as the key steps. RCM under influence of the G2 catalyst (8 mol %) proceeded uneventfully despite the two unprotected alcohols to give intermediate 26 in a surprisingly high yield of 90%. Synthesis of (+)-DBR (27) was completed in several steps including a side chain-directed syn-dihydroxylation with OsO4 of the ring olefin.

A similar metathesis strategy was utilized by Trost *et al.* for total syntheses of the azasugars 2,5-dideoxy-2,5-imino-D-mannitol [(+)-DMDP, 28], (−)-bulgecinine (29) and the somewhat more complex (+)-broussonetine G (30).24,25 (+)-DMDP (28) can be isolated from several sources, but was initially discovered in the leaves of *Derris eliptica*. (−)-Bulgecinine was

![Scheme 1.8. Natural products (+)-DMDP (28), (−)-bulgecinine (29) and (+)-broussonetine G (30) sharing the same RCM-made building block 31.](image)
found in bacterial cultures of *Pseudomonas acidophila* and *Pseudomonas mesoacidophila*, and the broussonetine family including broussonetine G in branches of the deciduous tree *Broussonnia kazinoki*. All three natural products were obtained from the same metathesis product 31 (Scheme 1.8), from which broussonetine G was derived via a Grignard addition of 33 onto 32. Key steps in the synthesis of the central intermediate 31 were a palladium-catalyzed dynamic kinetic asymmetric transformation (DYKAT) and RCM.

The synthesis of 31 started with a double dynamic asymmetric allylic amination for the enantioselective construction of diallylamine 36 from allylic epoxide (34, Scheme 1.9) involving ligand \((R,R)\)-L3. While RCM with a free hydroxyl (36) appeared troublesome, the ring-closure proceeded smoothly in high yield using G2 (1.2 mol %) after benzyl protection (37), which presumably prevents undesired coordination to ruthenium. Finally, seven steps including a Grignard reaction between alkyl bromide 33 and the corresponding Weinreb-amide of 32 were required to afford (+)-broussonetine G (30) in 8.2% overall yield.

### 1.2.3 Indolizidine alkaloids

#### 1.2.3.1 Polycyclic indolizidines

Alkaloids with polycyclic skeletal frameworks are, when it comes to their synthesis, excellent candidates for RCM. Illustrative are the indolizidines rhynchophylline (43) and its C(7)-epimer iso-rhynchophylline (44), both isolated from the plant *Uncaria rhynchophylla* (Rubiaceae). Deiterss’ total synthesis of 43 started with the efficient construction of diallylamine 39 via amide formation between indole-3-acetic acid (38) and diallylamine (Scheme 1.10). One-pot RCM-carbomagnesation of 39 was smoothly achieved with only 1
mol % of G1 catalyst and 4 equiv of EtMgCl to afford the 2-ethyl-3-buten-1-amine derivative in 71% yield. It appeared that the electron-withdrawing carbonyl moiety was critical to the success of the RCM-carbomagnesation steps. Amide reduction and subsequent treatment with acryloyl chloride delivered the second metathesis precursor 40. Cyclization with G1 (5 mol %) then furnished the α,β-unsaturated lactam 41 in a high yield of 91%. Continuation of the total synthesis of alkaloid 43 included a Bischler-Napieralski cyclization (42) and subsequent rearrangement into the oxindole framework.

Scheme 1.10. Synthesis of rhynchophylline.

The erythrina alkaloids form a widely distributed family that lately has received considerable attention as a result of their unique tetracyclic skeleton and biological activities. Erythrocarine (46)27,28, erythravine (50)29 and (+)-β-erythroidine (56)30 are three members of this family that have been synthesized with metathesis as a key step. The molecular structures of erythrocarine, found in the seeds of Erythrina caribaea, and erythravine, isolated from Erythrina cochleata, are related. As a result, total syntheses independently proposed by respectively Mori et al. and Hatakeyama et al. proceeded via the comparable intermediates 45 and 48, respectively, as shown in Scheme 1.11. Enyne 49a was synthesized in a number of steps. This substrate was subjected to HCl, followed by the G1 catalyst (10 mol %) to induce a tandem enyne-ring-closing metathesis process to yield the acetylated natural product in a quantitative conversion as a 1:1 mixture of diastereoisomers. After separation of the two isomers, acetyl cleavage provided erythrocarine (46) in pure form.
Scheme 1.11. Synthesis of erythrocarine and erythravine.

Intermediate 49 was prepared from 48 in eight steps. The crucial tandem ene-yne-RCM process was also performed with the G1 catalyst (10 mol %) and afforded the tetracyclic product in 78% in a diastereomeric ratio of $\alpha$-OAc-50:$\beta$-OAc-50 is 63:37. Once more, separation of the products, followed by deacetylation of $\alpha$-OAc-50 afforded erythravine (50) in an overall yield of 7.0%.

Scheme 1.12. Synthesis of (+)-$\beta$-erythroidine.

The efficient approach to erythravine paved the way for a second erythrina alkaloid synthesis by Hatakeyama et al., (+)-$\beta$-erythroidine (56). This alkaloid was found in several species of the Erythrina genus and synthesized in 26 linear steps as depicted in Scheme 1.12.
Starting from 54, tandem enyne RCM of the isomeric mixture 55 underwent cyclization with the G1 catalyst (10 mol %) to furnish (+)-β-erythroidine (56) in a moderate yield together with a small amount of a mono-ring-closed byproduct.

(−)-Antofine 61 is a member of the small group of phenanthroindolizidine alkaloids and was initially found in Vincetoxicum nigrum, belonging to the Asclepiadaceae family. Recently, Kim et al. described two routes to enantiopure (−)-antofine.31,32 Both routes began with the coupling of homoveratric acid (57) and p-anisaldehyde in order to form phenanthryl alcohol, the precursor of bromide 58 (Scheme 1.13). In the first article, the synthesis was continued via enantioselective catalytic phase transfer alkylation of a protected glycine derivative with 58. The glycine fragment was further transformed into the diallylamine of 59 in three steps. In the more recent article, enantiopure 60 was obtained via a Stille coupling with an enantiopure fragment and subsequent Overman rearrangement. Both routes converged to 61 after an RCM step that was high yielding in both cases, followed by hydrogenation and Pictet-Spengler cyclization. Interestingly, RCM with diolefin 60 went ten times faster and was somewhat higher yielding in comparison with 59, probably as a result of different catalyst loading. Overall it can be concluded that the second approach to (−)-antofine was, though one step longer, more efficient and higher yielding.


The tricyclic tetraponenerines form an unusual class of alkaloids representing the major constituents of contact poison of the New Guinean ant Tetraponera sp. A flexible synthesis of tetraponerines T1-T8 is challenging as they differ in side chain, stereochemistry at C-9 and size of one of the rings. Stragies et al. proposed a combined ROM-RCM strategy that led to four of these alkaloids.33 One of them was tetraponerine T6 (65), synthesized in only six steps. The synthesis commenced with a palladium-catalyzed domino allylic alkylation on dicarbonate 62 to deliver the disulfonamide 63. A G1-induced (5 mol %) ROM-RCM yielded an equilibrium between precursor 63 and product 64 in a 1:10 ratio. Subsequent elaboration of the side chain, followed by cyclization finally provided tetraponerine T6 (65) in a good 30% overall yield.
One of the simple representatives of the indolizidine series isolated as a trace compound from the skin of the neotropical frog *Dendrobates speciosus* is indolizidine 167B (70). Although neither the relative nor the absolute configuration of 70 was known, Blechert and coworkers synthesized the alkaloid in accordance with literature data via RRM (Scheme 1.15).34 The two olefinic side chains of product 67 required for RRM process were introduced in four steps from cycloheptenediol-monoacetate (66). A RRM under the influence of G1 (5 mol%) was *in situ* followed by TBAF-mediated silyl ether cleavage into alcohol 69 in an outstanding 92% yield. Final ring closure via reductive amination and hydrogenation delivered natural product 70 in a stereocontrolled way in an overall yield of 35%.

Another member of the indolizidine family derived from the frog genera *Dendrobatid* is (–)-indolizidine 223A (73). Davis et al. discovered that an intramolecular Mannich reaction combined with metathesis provided a high yielding and enantioselective solution for its synthesis (Scheme 1.16).35 Reaction of 4-heptanone with enantiopure sulfinyl imine 71, followed by treatment with crotonaldehyde gave *via* an intramolecular Mannich reaction the
tetrasubstituted piperidinone 72. Subsequent RCM with G1 (5 mol %), followed by hydrogenation as the key steps afforded (−)-indolizidine 223A 73 in an overall yield of 9.3%.

Scheme 1.16. Synthesis of (−)-indolizidine 223A.

The first enantiomeric synthesis of the pentacyclic boehmeriasin A was reported by Couture et al. in 2010 (Scheme 1.17). Its synthesis started with benzyl-protected 3-hydroxypropionaldehyde 74, that was converted to the desired diene hydrazide 76 in two sequential steps introducing chirality with the SAMP-hydrazone S- (75). Next, ring-closing metathesis using the G1 catalyst provided the chiral piperidine 77 in an acceptable yield of 75%. From there, four additional steps were required to provide the intermediate amino alcohol 78. Finally, acylation of 78 with bromobenzoyl chloride and sequential cyclization to the phenanthrene framework provided boehmeriasin A after reduction of the lactam.

Scheme 1.17. Synthesis of boehmeriasin A.

In 2010 the first enantioselective natural product application of RCM was described in literature for the synthesis of (+)-isolysergol featuring a diastereoselective microwave-mediated ring-closing metathesis reaction using a chiral molybdenum catalyst (Scheme 1.18). The RCM precursor was constructed in five sequential steps from the known...
dehydroamino acid 80. While initial attempts failed with commercially available catalysts, the molybdenum catalyst S1 successfully converted precursor 81 into 82 upon microwave irradiation in a varying yield of 55%. With the core structure completed, another three steps were required to afford (+)-isolysergol 83.

![Scheme 1.18. Synthesis of (+)-isolysergol.](image)

**1.2.3.2 Polyhydroxyindolizidines**

Despite the availability of various existing synthetic procedures, application of RCM in the synthesis of polyhydroxyindolizidines recently became increasingly popular. The skeletons of all alkaloids described below were produced according to the same strategy involving N-alkenylation and RCM for the formation of five- and six-membered nitrogen heterocycles (Scheme 1.19).

![Scheme 1.19. Retrosyntheses of (+)-lentiginosine (84) and the putative structure of uniflorine A (85) proceed via similar RCM precursors (86 for 84, 87 for 85).](image)
The total synthesis of lentinosine, isolated from *Australahus lentiginosus*, was performed in the group of Spino. Uniflorine A, recently discovered in the tree *Eugenia uniflora* L., and initially proposed as structure 85, was independently synthesized by various groups including those of White, Pyne and Dhavale. However, NMR data of 85 did not correspond with the data of natural uniflorine A.

Synthesis of (+)-lentinosine’s metathesis precursor 90 commenced with the stereoselective transformation of commercially available L-menthone into compound 89 (Scheme 1.20). An RCM precursor 90 was efficiently cyclized with G1 (5 mol %) to dihydropyrrolidine 86, while the L-menthone auxiliary was recovered. From there, lentinosine (84) was eventually synthesized in five steps.

Scheme 1.20. Synthesis of (+)-lentinosine.

In 2004, White et al. were the first to report a synthesis of putative uniflorine 85 in which RCM was used as the key step (Scheme 1.19). A three-component boronic acid-Mannich reaction (Petasis reaction) of L-xylose, allylamine and (E)-styrene boronic acid provided the amino tetrol 91 as a single diastereoisomer in good yield. Application of G1 (10 mol %) on N-Boc and O-trityl protected 91 afforded metathesis product 87 in 86% yield. The route to tetrahydroxyindolizidine 85 was completed by catalytic syn-dihydroxylation of 86 and six-membered ring formation. Further investigations involving five-membered RCM in the quest to find the correct structure of uniflorine A provided 2-epi-85 and 1,2-diepi-8538 and 8a-epi-85 and 2,8a-diepi-85. Yet, all these putative structures delivered mismatching NMR data as well. In 2008, White et al. suggested therefore that uniflorine A is 1,2,6,7-tetrahydroxy-3-hydroxymethylpyrrolizidine.38

Next, Pyne et al. successfully utilized the synthetic methodology created for putative uniflorine 85 to construct the analogous castanospermine (94, Scheme 1.21).40 In this case, amino tetrol 91 had to be protected with three different protecting groups resulting in compound 92. Treatment of 92 with G2 (10 mol %) yielded pyrrolo-oxazolone 93 in 88% yield. Diastereoselective syn-dihydroxylation of the olefin, followed by several steps led then to castanospermine (94).
Another asymmetric synthesis of castanospermine was published in 2010 (Scheme 1.22). The addition of allenylzinc reagent \( \text{97} \) to sulfinyl imine \( \text{96} \), to obtain enantiopure sulfinyl imine \( \text{98} \), was used to access the enantiopure acetylenic amino alcohol bearing the \textit{anti}-1,2-amino alcohol moiety of castanospermine.\(^{41} \) Another three steps were then required to obtain the pyrrolidine ring \( \text{99} \). Next, RCM using the \textbf{G2} catalyst, followed by dihydroxylation and deprotection of the alcohols provided (+)-6-\textit{epi}-castanospermine \( \text{101} \) in 18 steps in an overall yield of 8.5%.

\[
\begin{align*}
\text{HO}_2\text{C} & \quad \text{CO}_2\text{H} \quad \text{(9 steps)} \quad \begin{array}{c}
\begin{array}{c}
\text{Cl} \\
\text{OPMB}
\end{array}
\end{array} \\
\text{95} & \quad \begin{array}{c}
\begin{array}{c}
\text{Cl} \\
\text{OPMB}
\end{array}
\end{array} \\
\text{96} & \quad \begin{array}{c}
\begin{array}{c}
\text{Cl} \\
\text{OPMB}
\end{array}
\end{array} \\
\text{97} & \quad \begin{array}{c}
\begin{array}{c}
\text{Cl} \\
\text{OPMB}
\end{array}
\end{array} \quad \text{SOMO}
\end{align*}
\]

\( \text{(3 steps)} \quad \begin{array}{c}
\begin{array}{c}
\text{PMBO} \\
\text{99}
\end{array}
\end{array} \\
\text{98} \quad \begin{array}{c}
\begin{array}{c}
\text{PMBO} \\
\text{OMOM}
\end{array}
\end{array} \\
\text{99} \quad \begin{array}{c}
\begin{array}{c}
\text{PMBO} \\
\text{OMOM}
\end{array}
\end{array} \quad \text{G2} (2 x 10 \text{ mol }\%)
\end{align*}
\]

\( \text{(3 steps)} \quad \begin{array}{c}
\begin{array}{c}
\text{PMBO} \\
\text{OMOM}
\end{array}
\end{array} \\
\text{98} \quad \begin{array}{c}
\begin{array}{c}
\text{PMBO} \\
\text{OMOM}
\end{array}
\end{array} \quad \text{G2} (2 x 10 \text{ mol }\%)
\end{align*}
\]

\( \text{(3 steps)} \quad \begin{array}{c}
\begin{array}{c}
\text{PMBO} \\
\text{OMOM}
\end{array}
\end{array} \\
\text{98} \quad \begin{array}{c}
\begin{array}{c}
\text{PMBO} \\
\text{OMOM}
\end{array}
\end{array} \quad \text{G2} (2 x 10 \text{ mol }\%)
\end{align*}
\]

\( \text{(4 steps)} \quad \begin{array}{c}
\begin{array}{c}
\text{PMBO} \\
\text{OMOM}
\end{array}
\end{array} \\
\text{98} \quad \begin{array}{c}
\begin{array}{c}
\text{PMBO} \\
\text{OMOM}
\end{array}
\end{array} \quad \text{G2} (2 x 10 \text{ mol }\%)
\end{align*}
\]

\[
\text{HO}_2\text{C} \quad \text{CO}_2\text{H} \quad \text{(9 steps)} \quad \begin{array}{c}
\begin{array}{c}
\text{Cl} \\
\text{OPMB}
\end{array}
\end{array} \\
\text{95} & \quad \begin{array}{c}
\begin{array}{c}
\text{Cl} \\
\text{OPMB}
\end{array}
\end{array} \\
\text{96} & \quad \begin{array}{c}
\begin{array}{c}
\text{Cl} \\
\text{OPMB}
\end{array}
\end{array} \\
\text{97} & \quad \begin{array}{c}
\begin{array}{c}
\text{Cl} \\
\text{OPMB}
\end{array}
\end{array} \quad \text{SOMO}
\end{align*}
\]

\( \text{(3 steps)} \quad \begin{array}{c}
\begin{array}{c}
\text{PMBO} \\
\text{OMOM}
\end{array}
\end{array} \\
\text{98} \quad \begin{array}{c}
\begin{array}{c}
\text{PMBO} \\
\text{OMOM}
\end{array}
\end{array} \quad \text{G2} (2 x 10 \text{ mol }\%)
\end{align*}
\]
Ring closing metathesis in synthesis of natural products

104 into the desired 3-pyrroline 105 in yields up to 89%, while the stereochemical integrity of the two chiral centers was completely preserved during the reaction. Next, elaboration of the side chain, ring-closure and olefin dihydroxylation using commercially available AD-mix-α afforded swainsonine 106 in an overall yield of 40%.

Scheme 1.23. Synthesis of (−)-swainsonine.

Pyne and coworkers reported a completely different synthetic approach to (−)-swainsonine (110) starting from readily available 4-pentynol (Scheme 1.24). This was elaborated via cis-diol 107 into the enantiopure metathesis precursor 108 in a number of steps. Next, RCM with G2 (6.5 mol %) converted 108 into the cyclic product 109 in 95% yield. Intramolecular N-alkylation and stereoselective cis-dihydroxylation via the same methodology as applied by Blechert et al. completed the synthesis of swainsonine (110).


1.2.4 Pyrrolizidine alkaloids

The family of polyhydroxyindizolidine alkaloids is not the only target of interest in the field of natural product synthesis when it comes to application of RCM. Several approaches for the formation of the hindered 5,5-fused bicyclic (poly)hydroxypyrrolidines have been reported as well. The RCM methodology is in some of these cases applied to construct the second pyrrole, while on the other hand a larger number of cases exist of both natural and non-natural products where the first cycle is created this way.

(+) -Australine (114)44 and its epimer (+)-1-epi-australine (111)45 constitute two examples in which RCM was used in the construction of the second pyrrole (Scheme 1.25). Both alkaloids
were, together with other australine epimers, isolated from the seeds of *Castanospermum australe*.

![Scheme 1.2](image1)

**Scheme 1.25.** (+)-1-epi-Australine and (+)-australine derived from a similar RCM precursor.

Pyne et al. were the first to use RCM in the synthesis of a tetrahydropyrrolizidine, namely 1-epi-australine 111. Ring-opening of epoxide 115, readily obtained from 3-butynol, with an enantiopure allylic amine provided the desired diallylamine in moderate selectivity (Scheme 1.26). Conversion of the diallylamine into oxazolidinone 116 opened the door to the first RCM cyclization. Portionwise addition of G1 catalyst (30 mol % in total) gave product 117 in 97% yield. When less catalyst was used, significantly lower yields of 117 were obtained. A Cis-dihydroxylation of the 3-pyrroline 117 and an additional five more steps were required to obtain (+)-1-epi-australine (111) as a colorless oil.

![Scheme 1.26](image2)

**Scheme 1.26.** Synthesis of (+)-epi-australine.

Unfortunately, an identical approach failed for the synthesis of (+)-australine (114) since a Mitsunobu ring-closure of the second ring did not take place. A few years later, however, Trost and coworkers published a different route that made an RCM-mediated synthesis of (+)-australine (114) possible. In a similar procedure as described for the synthesis of compound 31,24,25 triolefin 119 was prepared in enantiomerically pure form. Interestingly, application of RCM on unprotected 119 with only 1 mol % of G2 afforded the corresponding product 120 in 77% yield. Next, benzylation of the primary alcohol, followed by selective epoxidation and subsequent opening with benzyl alcohol provided an improved precursor for the second cyclization. Thus, (+)-australine (114) was eventually successfully prepared and isolated as its hydrochloride salt.
Ring closing metathesis in synthesis of natural products

Scheme 1.27. Synthesis of (+)-australine.

In Martin’s synthesis of (+)-hyacinthacine A₂ (123), one of the alkaloids occurring in the bulbs of Muscari armeniacum (Hyacinthaceae), RCM was used for the second ring formation (Scheme 1.28).²⁶ Starting from D-arabinofuranose, only four steps were required to prepare metathesis precursor 122, including reductive amination with allylamine and an intramolecular displacement of the allylic benzoate ester. Ring closing was performed on the corresponding hydrochloride salt of compound 122 in the presence of G1 (16 mol %) in toluene to provide the corresponding trihydroxypyrrolizine in 30% yield (75% based on recovered starting material). (+)-Hyacinthacine A₂ (123) was eventually delivered by concomitant debenzylation and double bond hydrogenation.

Scheme 1.28. Synthesis of (+)-hyacinthacine A₂.

Chang et al. reported a synthesis of the monohydroxypyrrolidine (−)-trachelanthamidine (128) also utilizing RCM to create the second cycle (Scheme 1.29).⁴⁷ The synthesis of this alkaloid, isolated from the plant Trachelanthus korolkovi, commenced with a stereo- and regioselective stepwise [3+2]-annulation reaction of bromoacrylate 124 with sulfonylacacetamide 125 leading in two more steps to compound 126. Preparation of the diene for the metathesis reaction was achieved by subsequent Swern oxidation and Wittig olefination. The pyrrolidizine skeleton 127 was formed upon ring closure, employing G2
(5 mol %), in 81%. Through hydrogenation and subsequent lactam reduction, the authors achieved a synthesis of (−)-trachelantamidine (128) in a total of seven steps.

Scheme 1.29. Synthesis of trachelanthamidine.

1.3. Six-membered nitrogen heterocycles

Alkaloids incorporating six-membered nitrogen heterocycles are abundantly present in nature and occur in a multitude of alkaloid natural product families. Many of these alkaloids exhibit a wide range of diverse biological activities. As a result, extensive research has been devoted to the synthesis of many of the natural products and derivatives. This has led to an enormous variety of synthetic methodology that has been efficiently applied to synthesize many of these alkaloids. Among these methods, metathesis-based processes have played an increasingly important role as will be illustrated in the sequel.

1.3.1 Piperidine alkaloids

1.3.1.1 Piperidines

(−)-Allosedamine (134) and (+)-sedamine (139), two piperidine alkaloids isolated from Lobelia inflate, have been used for the treatment of respiratory disorders such as asthma, bronchitis and pneumonia. While several racemic syntheses have been reported, there are much less asymmetric ones. An enantioselective route to (−)-allosedamine (134) was developed by Raghaven et al., which commenced with addition of lithium compound 130 onto the imine 129 providing the separable allylic amine 131 as a 3:1 mixture of diastereoisomers (Scheme 1.30).48,49 Six additional steps were required to form metathesis precursor 132 from the major isomer 131s. Straightforward RCM (G1, 5 mol %) provided the corresponding heterocycle 133, which upon hydrogenation, deprotection and methylation afforded (−)-allosedamine (134).
Ring closing metathesis in synthesis of natural products

Yadav et al. developed via a similar strategy stereoselective syntheses of both (-)-allosedamine (134) and (+)-sedamine (139), starting from the Sharpless epoxidation product of cinnamyl alcohol (135, Scheme 1.31). The latter compound was converted in a number of steps into a separable diastereomeric mixture of amino alcohols 136a and 136b. N-Allylation gave in both cases the corresponding RCM precursors, which on exposure to the G1 catalyst (20 mol %, benzene, 50 °C) yielded the cyclic compounds 137 and 138 in 90% and 92% yield, respectively. Finally, deprotection and methylation led to (-)-allosedamine (134) and (+)-sedamine (139) via identical procedures.

Scheme 1.30. Synthesis of (-)-allosedamine.

A different approach to synthesize (+)-sedamine (139), reported by Cossy et al., was based on a double enantioselective allyltitanation of the aldehydes 140 and 142 (Scheme 1.32). Next, transformation of the resulting homoalyllic alcohol 143 into amine 144 was accomplished via a Mitsunobu reaction which was in a two-step procedure converted into the RCM precursor 144. Completion of the synthesis was achieved through RCM (catalyst G1, benzene, reflux), followed by hydrogenation of the alkene and deprotection in 52% over four steps.

Scheme 1.31. Synthesis of (-)-allosedamine and (+)-sedamine.
A synthesis of (+)-allosedamine, described by Chang et al. in 2004, started with a hydrolytic kinetic resolution of 146, which in turn was prepared in three steps from (+)-styrene oxide (Scheme 1.33). Subsequent formation of the diallylamine 149 as shown below, followed by G2-catalyzed RCM (10 mol %, benzene, 70 °C) afforded (+)-allosedamine (134).

In 2010, another synthesis of (+)-sedamine (139) and (+)-allosedamine (134) was described by Couture (Scheme 1.34). In this SAMP-based approach the piperidine core structure was prepared from hydrazone 151, that was readily converted into the dienehydrazide 152, the precursor for RCM. Next, ring closure was accomplished by treatment with the G1 catalyst (10 mol %) for 12 hours in refluxing dichloromethane affording, after reduction, the desired natural products.
α-Conhydrine, one of the alkaloids occurring in hemlock, was isolated from the seeds and leaves of the poisonous plant *Conium maculatum*. A synthesis of α-conhydrine (155)\(^5\) started with transformation of prolinol derivative 152 into amino alcohol 153 via a regioselective Baeyer Villiger oxidation of ketone 152 (Scheme 1.35). Compound 153 was then subjected to oxidation and subsequent Wittig olefination to afford RCM precursor 154. Smooth RCM under influence of catalyst G2 (15 mol %, CH\(_2\)Cl\(_2\), reflux) gave the corresponding unsaturated heterocycle in 92% yield, which upon hydrogenation and desulfonylation provided target compound 155.

Another approach to α-conhydrine (155) involved an Overman rearrangement of 156, which was prepared from (S)-glycidol in seven consecutive steps.\(^5\) Deprotection of amine 158, followed by acylation provided RCM precursor 159. Ring-closure under the influence of catalyst G1 (CH\(_2\)Cl\(_2\), reflux) afforded the corresponding unsaturated piperidine in
quantitative yield. Finally, hydrogenation and subsequent MOM deprotection afforded 155 in 42% yield.

Scheme 1.36. Synthesis of (S)-(+)–coniine·HCl and (+)-(β)–conhydrine.

An auxiliary-based synthesis of the related alkaloid (+)-(β)–conhydrine (164) commenced with conversion of enantiopure benzyl-protected 2-hydroxypropionaldehyde into hydrazone 160b (Scheme 1.36). Diastereoselective alkylation and subsequent acylation provided RCM precursor 161b, which upon treatment with G2 (5 mol %, CH2Cl2, rt) led to the corresponding product in 75% yield. Subsequent hydrogenation and deprotection gave (+)-β–conhydrine (164) in a yield of 23% over six steps. Fairly similar procedures were applied in the synthesis of (S)-(+)–coniine (163).

A formal synthesis of (S)-(+)–coniine (163) was developed by Chang et al. in 1999 starting from L-norvaline (164), which was converted into diolefin 165 in several steps. Finally, RCM (G1, CH2Cl2, rt), followed by hydrogenation led to the known intermediate 166 thus completing a formal synthesis.

Scheme 1.37. Synthesis of (S)-(+)–coniine·HCl.

Another approach in the synthesis of functionalized piperidine alkaloids (−)–coniine (169a) and (−)–piperidine (169b) commenced with the imines 167a and 167b using (R)-α-methylbenzylamine as a chiral auxiliary (Scheme 1.38). Consecutive diastereoselective vinylation and N-allylation afforded compounds 168a and 168b as two diastereoisomers (71% de, major isomer shown). RCM (G1, CH2Cl2, rt) gave rise to the corresponding cyclic products in good yields, of which the diastereoisomers were separated via silica gel.
Ring closing metathesis in synthesis of natural products

chromatography. Eventually, straightforward hydrogenation led to the natural products 169a and 169b.

Scheme 1.38. Synthesis of (−)-coniine and (−)-pipercoline.

An auxiliary-mediated approach reported by Agami et al. also led to a synthesis of (−)-β-conhydrine (176, Scheme 1.39).62 This time, (S)-phenylglycinol (170) was used as the starting material, which via Weinreb amide 171 and N,O-acetal 172 was converted into oxazolidinone 173. The latter compound was then diastereoselectively allylated via the corresponding N-acyliminium ion, deprotected and allylated at the nitrogen atom. The resulting diolefin 174 was then subjected to RCM (catalyst G1 (4 mol %), CH₂Cl₂, reflux, 79%) and another four consecutive steps to give (−)-β-conhydrine (176).


Probably, the most well-known alkaloid in *Nicotaiana tabacum* is (S)-nicotine (paragraph 2.2), which plays an important role in modulation of nicotinic acetylcholine receptors (nAChR). However, also related alkaloids have been isolated from the same source, such as the homologous analogues (S)-anabasine (180a) and (S)-anatabine (181a). In 2000, Felpin et al. published a synthesis of the latter alkaloids starting from an asymmetric allylboration of 3-pyridinecarbaldehyde into compound 177.63,64
Scheme 1.40. Synthesis of (S)-anatabine and (S)-N-methylanatabine.

Azide substitution of the alcohol, followed by reduction and functionalization provided RCM precursor 178. Subsequent protonation of the pyridine ring, followed by RCM proceeded uneventfully (G1 catalyst, CH₂Cl₂) to give the ring-closed product 179 that via hydrogenation was both converted into (S)-anabasine (180a) and its methylated counterpart 180b. Alternatively, (S)-anatabine (181a) and its methylated derivative 181b could be directly obtained from the metathesis intermediate 179.

En route to the natural products ent-CP-99,9994 (185) and ent-L-733,060 (186), in 2005 Nakano et al. reported a highly enantioselective palladium-catalyzed asymmetric allylic amination (>99% ee) of the allylic acetate 182 using the ligand L6 (Scheme 1.41). Conversion of the resulting allylic amine 183 with 3-butenolic acid in the presence of DCC followed by RCM (catalyst G2, CH₂Cl₂, reflux, 94%) yielded the piperidinone core structure 184, which was readily converted into the target molecules 185 and 186.

Scheme 1.41. Synthesis of ent-CP-99,9994 and ent-L-733,060.
A synthesis of the sedum alkaloid (−)-sedinine was achieved employing silver(I)-catalyzed allenic hydroxylamine cyclization and ring-closing metathesis to form the bicyclic N,O-acetal 188. Ring opening of this acetal with a silyl enol ether under Lewis acidic conditions was exclusively trans-selective, leading to the natural product 191 after reduction.

Scheme 1.42. Synthesis of (−)-sedinine.

### 1.3.1.2 Piperidine carboxylic acids

A significant number of alkaloids contain the 2-piperidinecarboxylic acid (pipecolic acid) unit as a core structure. Being a proline homologue, the pipecolic acid moiety has been used in many modified peptides and synthetic drugs. For example, naturally occurring 4-hydroxy-2-pipecolic acids have been isolated from various green plants and constitute important chiral building blocks of biologically active molecules such as palinavir. A synthesis of 4-hydroxy-2-pipecolic acid derivatives described by Johnson et al. involved conversion of (S)-192 in the corresponding oxazolidinone, which was N-allylated using allyl bromide and then subjected to G1 (CH₂Cl₂, rt) catalyst to give cyclic product 193. The metathesis product was either readily converted into the protected trans-4-hydroxypipecolic acid derivative 194, but upon elaboration of the side chain also to the natural product (2S,4S)(−)-SS20846A (196).
Baikaiain (200), another example of a natural product containing the piperolic acid core structure, was synthesized in 2000 by Rutjes et al. via a metathesis route. Amidopalladation of methyl propadienyl ether with the enantiopure L-allylglycine derivative 197 provided the RCM precursor 198 in good yield. Cyclization (G1 catalyst, 10 mol %, CH₂Cl₂, rt) afforded the corresponding cyclic N,O-acetal 199, which was readily transformed into the natural product via N-acyliminium mediated reduction with Et₃SiH, followed by deprotection.

A different approach to baikaiain (200) was also reported two years later by Riera et al. Their synthesis commenced with a Sharpless epoxidation of 2,5-hexadienol to give the enantiopure epoxide 201. Subsequent epoxide ring-opening with allylamine and N-Boc-protection afforded the RCM precursor 202, which was readily ring-closed (G1, CH₂Cl₂) in 72% to the tetrahydropyridine derivative. Finally, oxidative cleavage of the diol, followed by Pinnick oxidation led to the N-Boc-protected natural product 203.
1.3.1.3 Piperidones

The 2-(1H)-pyridone ring system is abundantly encountered in a wide variety of naturally occurring alkaloids, but also in synthetic intermediates of piperidine, (iso)quinoline, indolizidone and quinolizidine alkaloids. Plants belonging to genus *Lycopodium* are known to contain alkaloids possessing unique skeletal characteristics and biological activities, such as acetylcholine esterase (AChE) inhibition. One of them is the Phlegmarine-type alkaloid lycoposerramine-V (208). Its synthesis featured the initial formation of cyclohexene 204 from (R)-3-methylcyclohexanone (Scheme 1.46). Removal of the t-Butyldiphenylsilyl group, subsequent Swern oxidation and elaboration of the double bond provided aldehyde 205, which was then converted into quinoline derivative 206. The aldehyde function was in a number of steps transformed into diolefin 207, proceeding via an asymmetric allylation with B-allyldiisopinocampheylborane. Ring closing metathesis (G2, CH2Cl2, rt) proceeded in near quantitative yield and was followed by hydrogenation and lactam reduction to afford the targeted lycoposerramine-V (208).

![Scheme 1.46. Synthesis of lycoposerramine-V.](image)

Pipermethystine is a major constituent of the leaves of *Piper methysticum*, a large shrub indigenous to the Islands of the South Pacific. Its synthesis commenced with butenamide 209, which upon subjection to the G1 catalyst (4 mol %, CH2Cl2, reflux) gave the pyridinone 210 in good yield. Epoxidation of 210, followed by treatment with t-BuOK afforded the allylic alcohol 211, which was enzymatically resolved with a lipase to give the fully protected...
enantiopure (S)-pipermethystine ((S)-213). The non-reacted alcohol (R)-212 was afterwards also converted into (R)-pipermethystine (R)-213 upon esterification with acetic anhydride.

Scheme 1.47. Synthesis of (R)-pipermethystine and (S)-pipermethystine.

1.3.1.4 Polyhydroxypiperidines

In addition to five-membered ring azasugars, a large number of different six-membered ring azasugars exist in nature. Since these compounds resemble the glycopyranosyl cation after protonation of the nitrogen atom, their structures show promising potential in the treatment of several diseases. Two syntheses of six-membered ring azasugars are described in Scheme 1.48, both starting from the protected diacetone glucose derivative 214. After inversion of the free hydroxyl group, compound 215 was converted into RCM precursor 216. G1-mediated ring-closure (CH$_2$Cl$_2$, rt) led to the unsaturated bicyclic intermediate 217 in 90% yield. From there, D-1-deoxyallonojirimycin (218) was prepared via face selective dihydroxylation of the cyclic olefin. In addition, L-1-deoxyallonojirimycin (219) was directly prepared from diacetone glucose derivative 214 according to identical procedures.
Ring closing metathesis in synthesis of natural products

Scheme 1.48. Synthesis of L-1-deoxyallonojirimycin and D-1-deoxyallonojirimycin.

A similar approach to synthesize six-membered ring azasugars was published by Takahata et al. which commenced with a Wittig reaction of the D-serine-derived Garner aldehyde 218. Facile elaboration into metathesis precursor 219, followed by treatment with G1 (CH2Cl2, rt) afforded tetrahydropyridine 220 in virtually quantitative yield. The latter structure was shown to be a good starting point for the preparation of fagomine (222) and its congeners 221 and 223.73

Scheme 1.49. Synthesis of 3-epi-fagomine and 2,4-di-epi-fagomine.

1.3.2 Indolizidine alkaloids

Coniceine (227), a bicyclic alkaloid containing the simplest indolizidine skeleton, has attracted much attention as a building block of indolizidine alkaloids. An early RCM-based synthesis was described by Chang et al. in 2001 (Scheme 1.50).74 It started with the ethyl
ester of proline (224), which was converted in four steps into the RCM precursor 225. Subsequent metathesis under the influence of catalyst G2 (CH$_2$Cl$_2$, rt) provided the corresponding cyclic olefin (226), which is a known intermediate en route to coniceine (227).\textsuperscript{75}

Scheme 1.50. Synthesis of (–)-coniceine.

Another synthesis was reported in 2005 by Génisson et al. who constructed the six-membered indolizidine skeleton via RCM starting from the epoxide 228 (Scheme 1.51). Selective epoxide hydrolysis, followed by alkylation with the triflate of 3-butenol led to diolefin 229 in 72\%. Subsequent RCM (G2 (5 - 10 mol \%), PhMe, 70 °C) afforded the tetrahydropyridine 230 in 66\% yield. Completion of the synthesis enclosed hydrogenolysis followed by ring closure to afford the targeted alkaloid (–)-lentiginosine (231).\textsuperscript{76}

Scheme 1.51. Synthesis of (–)-lentiginosine.

In 2006 Jung et al. reported another synthesis of (–)-lentiginosine (231) starting from the D-xylose-derived olefin 233.\textsuperscript{77} Subjection to chlorosulfonyl isocyanate (CSI) provided the allylic amine 234 in a high diastereoselectivity (syn/anti = 1:26) in 84\% yield. With this compound in hand, the corresponding pyrrolidine was readily formed via intramolecular bromide displacement. Cbz-hydrogenolysis and introduction of the 3-butenyl moiety as described by Génisson led to the RCM precursor 235. Cyclization (catalyst G2, PhMe, 70 °C) proceeded readily in 85\% yield to give the bicyclic skeleton which upon benzyl deprotection and dihydroxylation of the olefin gave (–)-lentiginosine (231).
Ring closing metathesis in synthesis of natural products

Scheme 1.52. Synthesis of (−)-lentiginosine.

A different approach leading to ent-lentiginosine (84) was adopted by Schmidt et al.78 who prepared pyrrolidine 236 in three steps from L-tartrate. N-Acyliminium ion-mediated allylation provided 237 in quantitative yield as a diastereomeric mixture (1:1), which was separated via column chromatography. RCM (G1 (0.4 mol %), CH₂Cl₂, reflux, 12 h) afforded the corresponding indolizidine in 78% yield, which was converted into the natural product via deacetylation and hydrogenation.

Scheme 1.53. Synthesis of (+)-lentiginosine.

In 1994, the tricyclic perhydropyrrolo[2,1]-quinolone lepadiformine (244)79 was isolated from the tunicate Clavelina lepadiformis by Biard et al. and exhibits moderate cytotoxic activity against various tumor cell lines in vitro, as well as high cardiovascular effects in vitro and in vivo. Unfortunately, many synthetic efforts were initially directed to a wrongly assigned structure. However, since 2001 several elegant syntheses have been reported.
of them included RCM of 241 (Scheme 1.54), which was prepared via an Ireland-Claisen rearrangement of amino acid ester 239. Further elaboration provided diolefin 241, which upon RCM (G2, CH2Cl2, 40 °C, 1 h) afforded the bicyclic skeleton 242 in 98% yield. Via an additional five steps, the tricyclic cyanide 243 was prepared from which (−)-lepadiformine (244) could be readily synthesized following known procedures. 

Scheme 1.54. Synthesis of (−)-lepadiformine.

Melodinus alkaloids, also known as meloquinolines, represent a group of monoterpenoid indole alkaloids isolated from certain Apocynacea species, amongst which is (+)-meloscine (251). While in 1989 Overman et al. described a first racemic synthesis of meloscine, it was not until recently that Bach et al. succeeded in synthesizing (+)-meloscine (251) in enantiopure form. Its synthesis started with a [2+2]-photocycloaddition of enone 245 in the presence of the chiral auxiliary A (Scheme 1.55). Ring expansion of cyclobutane 246 into the α-hydroxycyclopentenone 247 was then accomplished by a retro-benzyl ester rearrangement. Further conversion of 247 via 248 provided diolefin 249 which after RCM (catalyst G2 (15 mol %), PhMe, 65 °C) gave the corresponding product 250 in an excellent 95% yield. The latter compound was then transformed in five steps into the targeted natural product (+)-meloscine (251).
Daly et al. isolated numerous alkaloids from the skin of neotropical poison-frogs such as steroidal batrachotoxins, histronicotoxins, gephyrotoxins and pumiliotoxins. One of these alkaloids, (+)-205B (258) possessed an unusual aza-acenaphylene ring system (Scheme 1.56).\textsuperscript{82}

Scheme 1.55. Synthesis of (+)-meloscine.

Scheme 1.56. Synthesis of (−)-205B.
In 2005, Smith et al. published a first total synthesis of alkaloid 205B (258) based on a three component linchpin coupling of compounds 252 - 254, followed by a one-pot sequential cyclization of intermediate 255 to complete the indolizidine core structure 256. Upon treatment with Me₃SiCl in the presence of LHMDS, the corresponding kinetic silyl enol ether was formed, which was then directly subjected to metathesis catalyst G2 (benzene, 65 °C) to provide after an aqueous workup the cyclic ketone 257 in a satisfactory 81% yield. From this aza-acenaphthylene skeleton, (−)-205B (258) was readily synthesized in six steps.

### 1.3.3 Quinolizidine alkaloids

The structure of quinolizidine 233A (264), obtained from skin extracts of poisonous frogs of the genera *Dendrobates* and *Mantella*, was published in 1993. Following up on racemic syntheses, a formal synthesis of enantiopure 264 was reported by Rutjes et al. based on a cationic cyclization of allylic N,O-acetals (Scheme 1.57). The approach commenced with cross metathesis (G5 catalyst, 5 mol %, CH₂Cl₂, reflux) of the enantiopure protected 2-amino-6-heptenoic ester 259 with allyltrimethylsilane to afford the modified side chain via unexpected double bond isomerization. Subsequent amidopalladation with benzyl propadienyl ether gave the allylic N,O-acetal 260, which smoothly cyclized (Sn(OTf)₂ (2 mol %), CH₂Cl₂) to give 261 as a 3:1 mixture of diastereoisomers (major isomer shown). Deprotection, introduction of the second alkene and subsequent RCM (catalyst G2 (5 mol %), CH₂Cl₂, reflux) afforded 262 in 83 % yield. Finally, hydrogenation and reduction of both carbonyl groups provided 263, thereby constituting a formal synthesis of quinolizidine 233A (264).

**Scheme 1.57.** Synthesis of quinolizidine 233A.
In 2005 Honda et al. published a first total synthesis of a quinolizidine alkaloid using RCM as one of the key steps, namely (−)-deoxynupharidine (268). The alkaloid was isolated from plants of the genus Nuphar and exhibited amongst others immunosuppressive activity. Its synthesis commenced with a stereoselective construction of the enantiopure 5,6-disubstituted piperidinone building block 266 by modification and ring expansion of the protected D-pyroglutamic acid derivative 265 (Scheme 1.58). Subsequent RCM of 266 (catalyst G2, PhMe, 60 °C) afforded quinolizidinone 267 in 96% yield, whereafter three consecutive steps led to the natural product itself.

Scheme 1.58. Synthesis of (−)-deoxynupharidine.

Blaauw et al. described a first synthesis of the quinolizidine alkaloid (+)-epiquinamide (272). This compound was isolated from the skin of the Ecuadorian frog Epipedobates tricolor and was claimed to show activity on the nicotinic receptor. The approach started with the efficient conversion of commercially available L-allylsine ethylene acetal (269) in the functionalized pipecolic acid derivative 270. RCM under the influence of catalyst G2 (PHMe, rt), followed by hydrogenation provided the bicyclic skeleton 271 in excellent yield. Further functional group manipulation then provided (+)-epiquinamide (272) in an overall yield of 22% from RCM precursor 270.

Scheme 1.59. Synthesis of (+)-epiquinamide.

The Lythraceae plants produce a large variety of bioactive alkaloids. A number of them comprise the quinolizidine scaffold, such as (−)-lasubine II. Liao et al. described in 2006 a synthesis of (−)-lasubine II (276) involving RCM to construct one of the two rings (Scheme 1.60). Most efforts were directed to an enantioselective synthesis of the functionalized piperidine and RCM precursor 275. This was achieved via S_{N}Z-type cyclization of amino alcohol 274, which in turn was prepared via two sequential Roush asymmetric allylboration steps from the protected amino alcohol 273. RCM under the influence of catalyst [Ru]-I (CH_{2}Cl_{2}, reflux) gave the corresponding ring-closed product in 92% yield, which upon
catalytic hydrogenation in the presence of HF-Et₃N was efficiently converted into (−)-lasubine II (276).

![Scheme 1.60. Synthesis of (−)-lasubine II.](image)

A concise stereoselective route providing access to both enantiomers of the bioactive quinolizidine alkaloid lasubine II has been developed in 2009 by Rutjes et al. The enantioselectivity was introduced by taking advantage of a proline-catalyzed asymmetric Mannich reaction. Next, the bicyclic system was constructed via a diastereoselective Mannich cyclization and subsequent ring-closing metathesis as the key steps.

![Scheme 1.61. Synthesis of (−)-lasubine II.](image)

A synthesis of the highly conjugated pentacyclic quinolizidine alkaloid mitralactonine (282), isolated in 1999 by Takayama et al., shows the usefulness of RCM in constructing polycyclic frameworks. It commenced with a protected tryptamine derivative, which amongst other steps via a Pictet Spengler cyclization was converted into RCM precursor 280. RCM (catalyst G2 (10 mol %), PhMe, 80 °C) proceeded smoothly both on the N-Ts-protected (87%) as well as on the unprotected compound. The tosyl protection, however, was crucial in the next steps involving osmium-catalyzed dihydroxylation and oxidation into the corresponding hydroxyl enone intermediate. TBAF-mediated Ts-deprotection then gave rise to the free indole 281, which is a known precursor for preparing mitralactonine (282).
The sparteine group of alkaloids, abundant in common papilionaceuous plants, is characterized by an asymmetric \textit{exo-endo} rearrangement of bridgehead hydrogen atoms at C6 and C11. (\textpm)-\textalpha-Sparteine, obtained from commercially available \textpm-sparteine by isomerization, has found widespread use as chiral ligand in asymmetric catalysis and asymmetric deprotonation reactions. Therefore a practical stereocontrolled entry into the sparteine core structure would contribute to \textit{exo}-ending the versatility of existing asymmetric methods. An elegant approach was detailed in 2005 by Blakemore \textit{et al.} who identified the tetraoxobispidine (285) as a synthetically versatile scaffold, which could be readily prepared starting from a Knoevenagel condensation of dimethyl malonate (283) with paraformaldehyde (Scheme 1.63). The intermediate was directly treated with ammonia (284), followed by cyclization and subsequent double allylation to provide key intermediate 285. Subsequent Grignard addition resulted in a remarkably regioselective diallylation affording the tetraene and RCM precursor 286. Subjection to the G1 catalyst (4 mol \%, CH$_2$Cl$_2$, rt) provided the tetracyclic structure 287 in 82\% yield. Finally, racemic \textalpha-sparteine (288) was obtained upon global reduction of all olefin, aminal and carbonyl functions.

\textbf{Scheme 1.63.} Synthesis of (\textpm)-\textalpha-isosparteine.

Alkaloids isolated by Rakotoson \textit{et al.} in 1998 from \textit{Galipea officinalis} consisted of several 2-substituted quinolines among which (\textpm)-\textSigma-angustureine (293). A RCM-mediated synthesis...
of this compound started with a Mitsunobu alkylation of sulfonamide 292 with the enantiopure secondary alcohol 289 to give the desired $\alpha,\omega$-diene 288 in 78% yield (Scheme 1.64). With the RCM precursor in hand, subjection to the G2 catalyst (CH$_2$Cl$_2$, 50 °C) gave quinoline 292 in 92% yield. Finally, hydrogenation, deprotection and subsequent methylation provided (+)-(S)-angustureine (293) in 68% yield.\footnote{91}

**Scheme 1.64.** Synthesis of (+)-(S)-angustureine.

In 2012 a novel synthesis of tangutorine based on RCM as key step was published starting from building block 294 which is described in more detail in chapter 7.\footnote{92}

**Scheme 1.65.** Synthesis of (±)-tangutorine.

### 1.4. Seven-membered nitrogen heterocycles

In contrast to the large abundance of RCM examples of five- and six-membered nitrogen heterocycles en route to natural products, RCM to prepare seven-membered rings has been used considerably less frequently.
Scheme 1.66. Synthesis of balanol.

One of the examples concerns a formal synthesis of (–)-balanol 300 (Scheme 1.66). Balanol was first isolated in 1993 from the fungus Verticillium balanoids and is a potent inhibitor of human protein kinase C. Because of its high inhibitory activity, balanol has been a target for a number of synthetic efforts. In 1999, Cook and coworkers published a formal synthesis of balanol (300) based on RCM to form a seven-membered nitrogen heterocycle as a key step.93 The balanol synthesis started with D-serine derivative 296, which via oxazoline 295 was transformed into metathesis precursor 298. Ring closing metathesis using the G1 catalyst (2 × 5 mol %, CH₂Cl₂, reflux) provided the corresponding unsaturated heterocycle in 77% yield, which upon acidic hydrolysis of the oxazoline and hydrogenation with Wilkinson’s catalyst afforded 299, thereby completing the formal synthesis.94

Two years later, Fürstner et al. developed a synthesis of azepine 306 based on a selective Sharpless asymmetric epoxidation of divinylmethanol (Scheme 1.67).95 The resulting epoxide 301 was then regioselectively opened with allylamine to give the corresponding diene. Protection of the secondary amine with a N-Boc-group provided precursor 304 for RCM. Cyclization proceeded in 94% yield using the S1 catalyst (CH₂Cl₂, 30 min, reflux, 94%). Subsequent conversion of the secondary alcohol into the azide, reduction and acylation gave the Boc-protected derivative of 306, which also represents a formal synthesis of balanol.94
Scheme 1.67. Formal synthesis of balanol.

An additional example involves the synthesis of \((-\)-stemoamide \(\text{(311)}\) (Scheme 1.68). In a five-step procedure \(\text{307}\) was synthesized starting from commercially available \((\text{S})\)-pyroglutaminol. Next, a vinyl iodide was installed via a chemoselective iodoboration of the alkyne substituent and subsequently subjected to the Reformatsky reagent derived from ethyl \(\alpha\)-bromoacetate to yield RCM precursor \(\text{308}\).

Scheme 1.68. Synthesis of stemoamide.

By using the \(\text{G2}\) catalyst under high dilution conditions \((c = 0.005 \text{ M})\), azepine \(\text{309}\) was formed in an excellent yield of 92%. Since installation of the C8-hydroxy group via hydroboration was unsuccessful, an alternative was sought in hydrolyzing the ester and exposure to \(\text{CuBr}_2\) on alumina which gave the desired lactone \(\text{308}\). Conjugate hydride addition from the sterically most accessible \(\beta\)-face using \(\text{NiCl}_2\cdot6\text{H}_2\text{O}\) and \(\text{NaBH}_4\), followed by methylation completed the synthesis.

1.5 Eight-membered nitrogen heterocycles

Manzamine A \(\text{(317)}\) has attracted much attention over the past years because of its potent antitumor activity and since it was the first member of a group of similar alkaloids to be isolated in 1986. The combination of the complex and unusual structure of manzamine A
together with its promising biological activity has led to numerous synthetic efforts. One of these comes from Martin et al. involving two cyclizations via RCM (Scheme 1.69). The advanced intermediate 312 was converted by a domino Stille/Diels–Alder reaction into the tricyclic system 313. From there, eight sequential steps were required for installing the two olefinic moieties required for the macrocyclic ring formation (315). This very early RCM macrocyclization was carried out using the G1 catalyst giving rise to the 13-membered ring containing predominantly the Z-olefin (Z/E = 8:1) in a respectable 67% yield. Then, hydrolysis of the cyclic carbamate followed by N-acylation provided diolefin 316, thereby setting the stage for the formation of the eight-membered ring. RCM with the G1 catalyst went in a moderate yield of 26%. Promotion of RCM with the Schrock catalyst (S1) did not improve the yield. Nevertheless, in a few more steps the synthesis of manzamine A (317) could be successfully completed.

Scheme 1.69. Synthesis of manzamine A.

1.6. Purpose and outline of this investigation

Considering the examples of natural products synthesized using RCM to form the heterocycle, as discussed in this chapter, we set out to investigate the metathesis behaviour of α,β-unsaturated dihydroamino acids, thereby generating a general building block for further functionalization. Chapter 2 describes the synthesis of dihydroamino acids from condensation of olefinic amides with a pyruvate followed by RCM, leading to the introduction of substituents at both the allylic and the α-position of the amide. Similarly, condensation of hydroxy-substituted amides followed by intramolecular conjugate addition gives rise to the synthesis of highly functionalized morpholines, as described in Chapter 3. Chapter 4 describes the condensation of more elaborated olefinic amides to optically active 3- and 4-substituted cyclic dehydroamino acids. The application to more elaborated 2-...
substituted pipecolic acids is discussed in Chapter 5 upon intermolecular conjugate addition for the synthesis of trans-substituted derivatives. Moreover, synthesis of cis-substituted variants is described based on reduction of tetrasubstituted cyclic dehydroamino acids. As an extension of this research, asymmetric hydrogenation of the cyclic dehydroamino acids is discussed in Chapter 6. Inspired by the results of RCM on dehydroamino acids, we applied the developed methodology to a synthesis of the natural product tangutorine, which is described in Chapter 7.

1.7 Acknowledgements

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1.8 References


Chapter 1

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Ring closing metathesis in synthesis of natural products

2

Ring closing metathesis of α,β-unsaturated dididehydroamino esters

Abstract

Non-proteinogenic α,β-unsaturated dididehydroamino esters are widespread in nature and exhibit a wide range of biological activities. Many chemists have been inspired by these important bioactivities and also due to their interesting structures have become interested in the development of new enantioselective methodologies for their synthesis. This chapter describes a ring-closing metathesis (RCM)-mediated approach for the formation of cyclic dididehydroamino esters. Drawbacks of a method previously developed in our group, involving alkylation of dididehydroamino esters with enantiopure allylic iodides followed by RCM, included a poor reproducibility of the dididehydroamino ester synthesis, limitations in possibilities to diversify the heterocycles and moderate ee’s of the cyclization precursors. In a new approach, we focused on the condensation of simple unsaturated amines and amides with pyruvates to directly obtain the cyclization precursors (vide infra). While condensation of unsaturated amines appeared to be troublesome leading to low yields, condensation of unsaturated amides proceeded smoothly providing the corresponding α,β-unsaturated dididehydroamino esters in a single transformation. Subsequent RCM led to the formation of the targeted (6-oxo)piperidine carboxylic esters.

Chapter 2

2.1 Introduction

Non-proteinogenic α,β-unsaturated dididehydroamino esters are widespread in nature and exhibit a broad range of biological activities.\(^1\) Inspired by the relevant bioactivities and challenged by their structures, organic chemists continue to develop new methodologies for the synthesis of such molecules. Since ring-closing metathesis (RCM) has been fully integrated in organic synthesis nowadays, we envisioned that RCM might serve as a powerful technique for the construction of cyclic dididehydroamino esters. As exemplified in the first chapter, a variety of functional appendages have already been constructed via this method. For example, as early as in 1992 Grubbs and Fu revealed that RCM could be successfully exploited to form five-, six-, and seven-membered oxygen and nitrogen heterocycles (Scheme 2.1).

Scheme 2.1. Ring-closing metathesis (RCM) of enamides and enol ether double bonds.

While the first examples of olefin metathesis relied on cyclization of neutral and often mono-substituted alkenes, the scope of RCM has steadily been broadened into more highly substituted olefins with both electron-donating and electron-withdrawing groups. Despite the fact that several literature examples illustrate the metathesis opportunities of electron-poor olefins, their scope has remained limited until now.\(^2\) This is most likely due to the fact that electron-poor olefins are less reactive in RCM than regular ones.\(^3\)

Scheme 2.2. Ring-closing metathesis (RCM) of enol ether double bonds.
Ring closing metathesis of α,β-unsaturated didehydroamino esters

Moreover, carbene intermediates of electron-poor olefins are relatively unstable due to the electron-deficient metal carbene bonds. Secondly, after metathesis of the more reactive unhindered olefin, the carbonyl function can chelate to the metal center thereby lowering the rate of catalysis. This effect can sometimes be circumvented by the addition of a Lewis acid (e.g. Ti(OiPr)4). The G2-catalyst, however, is less prone to chelation because of its more electron-rich ruthenium metal center. Ring closing metathesis of electron-rich alkenes, e.g. enol ethers and enamides, to form oxygen- and nitrogen-heterocycles, respectively, is also known. Since the relatively fast reaction of enol ethers leads to a Fischer-type carbene (Scheme 2.2) thereby deactivating the catalyst, ring closing metathesis of enol ethers appeared to be limited. For this reason, enamides were long thought to be unsuitable for metathesis too. In the past years, however, several successful examples of ring closing metathesis on enamides were published.

Previous examples of ring closing metathesis of both electron-rich and electron-poor olefins originating from our group, concerning the metathesis behavior of α-alkoxyacrylates resulted in the formation of a variety of heterocyclic products. Moreover, synthesis and cyclization of α,β-unsaturated didehydroamino acids containing allylic substituents were performed using a similar strategy (Scheme 2.3). Additionally, RCM was successfully used in the cyclization of fluoroolefins as a general strategy for the synthesis of fluorinated (aromatic) heterocycles.

Based on our previous RCM examples on didehydroamino acids, we set out to further determine the scope and limitations of this approach using more elaborate didehydroamino esters as a general entry into functionalized piperidines. A severe drawback of the previously developed method involved the poor reproducibility of the synthesis of the didehydroamino esters. Moreover, the method was rather limited in diversity and the enantiopurity of the didehydroamino esters was not complete. We therefore focused on the condensation of simple unsaturated amines (8, X = H2) and amides (8, X = O) with...

Scheme 2.3. RCM of didehydroamino acids by Hekking et al.
pyruvate esters to directly obtain the cyclization precursors 7 (Scheme 2.4). In case this was successful, this strategy might also be applied on more complex amines and amides. With the objective to prepare \( \alpha,\beta \)-unsaturated didehydroamino esters, we envisaged that this should be possible via condensation of unsaturated amines and amides with ethyl pyruvate under Dean–Stark conditions (PhMe, 110 °C). Imine formation, followed by tautomerization to the more stable enamine (7, \( X = H_2 \)) or enamide (7, \( X = O \)) would then provide the corresponding didehydroamino ester 7 in a single transformation (Scheme 2.4).¹⁵

![Scheme 2.4. RCM approach to functionalized piperidines 6.](image)

### 2.2 \( \alpha,\beta \)-Unsaturated didehydroamino ester precursors for RCM

A preliminary study was performed to synthesize didehydroamino ester 11a from condensation of \( n \)-butylamine (9) with ethyl pyruvate (Scheme 2.5). While TLC showed a rapid consumption of ethyl pyruvate, no clear product was observed. Addition of a drying agent (e.g., sodium sulfate or 4 Å molecular sieves) to the reaction mixture to capture water did not give better results. When the conversion was monitored by \(^1\)H NMR, it was indicated that formation of the unstable imine was already complete within one hour at room temperature, but decomposed on TLC. Subsequent addition of a base, e.g., triethylamine or N,N-diethylaniline, followed by dropwise addition of acetyl or benzoyl chloride afforded the stable unsaturated didehydroamino esters 11a and 11b.

![Scheme 2.5. Condensation of \( n \)-butylamine with ethyl pyruvate.](image)
Encouraged by these results, we decided to use 3-butenylamine (14) and 4-pentenylamine (15) as precursors for the condensation reaction, starting from the commercially available hydrochloric acid salts 12 and 13, respectively (Scheme 2.6). Subjection to 1 equivalent of base (DBU), followed by addition of ethyl pyruvate provided the desired imines. Subsequent addition of triethylamine and acetyl chloride then provided the didehydroamino esters 16 and 17 in yields of 19 and 12%, respectively. In order to raise the yields, several nitrogen protecting groups were investigated. Disappointingly, inducing tautomerization to the enamide could only be achieved by reaction with acid chlorides. Addition of a (strong) base (e.g., LDA, LHMDS, or K$_2$CO$_3$) to the intermediate imine to promote tautomerization in the absence of an acid chloride electrophile only led to decomposition.

Scheme 2.6. Condensation reaction with 3-butenyl- ($n=1$) and 4-pentenylamine ($n=2$).

The low yields and limited scope of nitrogen protecting groups in case of the amines, prompted us to shift our focus to the condensation of amides with ethyl pyruvate. Contrary to the amine condensation, elevated temperatures were required in combination with a catalytic amount of $p$-toluenesulfonic acid (10 mol%) in accordance with results reported (Scheme 2.7).$^{16}$

Scheme 2.7. Condensation reaction of $n$-butylamide (18) with ethyl pyruvate.

More specifically, butanamide (18) was reacted with ethyl pyruvate in the presence of $p$-toluenesulfonic acid (10 mol%) under Dean–Stark conditions in three hours to provide 20 in 18% yield after aqueous workup. The low yield was thought to result from enamide-imine tautomerization, followed by hydrolysis of the imine. Applying a non-aqueous workup,
involving filtration of the reaction mixture through neutral aluminum oxide, followed by column chromatographic purification, on the other hand afforded the α,β-didehydroamino ester 20 in a moderate yield of 51%. The yield of the reaction was even further increased to 83% by applying anhydrous p-toluenesulfonic acid, which was obtained by stirring in concentrated hydrochloric acid and coevaporation with toluene. With this result in hand, the stage was set for the condensation reaction of various unsaturated amides.

Scheme 2.8. Condensation of olefinic amides with ethyl pyruvate.

The olefinic amides 22a-c were readily prepared from the commercially available carboxylic acids 21a-c (Scheme 2.8). Successive chlorination with oxalyl chloride and treatment with ammonia provided the primary amides in pure form after recrystallization from diethyl ether/heptane (1:1). Both condensation of 4-pentenamide (22b) and 5-hexenamide (22c) with ethyl pyruvate were high yielding, condensation of 3-butenamide (22a) on the other hand, led to isomerization of the terminal olefin.

2.3 Ring-closing metathesis of α,β-unsaturated didehydroamino esters

With the precursors 16, 17 and 24b-c in hand, we set out to investigate the behavior of the α,β-didehydroamino esters under metathesis conditions. The first RCM reactions were performed with the first generation Grubbs catalyst (G1, 10 mol%, Table 2.1) in dichloromethane at 40 °C in the presence of 1,4-benzoquinone (10 mol%) to prevent double bond isomerization.\(^{17}\) However, treatment of 16 with G1 did not lead to any ring closure (entry 1). Surprisingly, in the absence of 1,4-benzoquinone only homodimerization was observed together with a substantial amount of starting material. Subjection of enamide 17
to G1 led to similar results (entry 2). Treatment of 16 and 17 with G1 in toluene at 80 °C did not offer any improvement either (entry 3 and 4).

Table 2.1. RCM-mediated generation of five- and six-membered heterocycles.

<table>
<thead>
<tr>
<th>Entry</th>
<th>solvent</th>
<th>T (°C)</th>
<th>Catalyst (10 mol%)</th>
<th>Yield of 25 (%)</th>
<th>Yield of 26 (%)*</th>
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<td>1</td>
<td>CHCl₂</td>
<td>40</td>
<td>G1</td>
<td>–</td>
<td>12</td>
</tr>
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<td>–</td>
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<tr>
<td>8</td>
<td>PhMe</td>
<td>80</td>
<td>G2</td>
<td>–</td>
<td>29</td>
</tr>
</tbody>
</table>

* Yields obtained in the absence of 1,4-benzoquinone

After these unsatisfactory results, we decided to subject diolefin 16 to the more reactive second generation Grubbs catalyst (G2, 10 mol%) under identical conditions. Interestingly, ring closing metathesis with 16 proceeded smoothly leading to the five-membered heterocycle 25a in high yield (entries 5 and 7). On the other hand, Treatment of 17 with G2 only led to multiple products (entries 6 and 8).

Much to our surprise, subjection of 24b to G2 (10 mol%) in toluene gave no reaction at all (Scheme 2.9). Free amines are typically incompatible with metathesis reactions owing to catalyst inhibition by the basic nitrogen. Ring closing metathesis in the presence of amides on the other hand is known, however, previous results in literature suggest that protection of the nitrogen is required for ring closing metathesis to proceed. Attempts to Cbz-protect the nitrogen in the presence of DMAP resulted in the recovery of starting material and reaction with LHMDS at low temperatures only led to decomposition. Interestingly, protection of the amide with a Boc-group (CHCl₂, Boc₂O, DMAP, rt) led to the formation of the desired didehydroamino ester 28 in 85% yield. Disappointingly, the didehydroamino ester remained unreactive toward ring closing metathesis upon treatment with G2 (10 mol%) leading to multiple products upon prolonged reaction times. Since the energetically unfavored s-cis-conformation of the didehydroamino ester is required for cyclization to
proceed, carbamate-protection of the amide probably renders s-cis-trans-isomerization sterically impossible.

![Scheme 2.9](image)

**Scheme 2.9.** Attempted RCM of didehydroamino ester 24b and its Boc-protected derivative 28.

Rather than by introducing a second acyl group on the nitrogen, cis-trans-isomerization might also be influenced by straightforward N-alkylation. Therefore, 24b was treated with LHMDS and benzyl bromide in DMF. Yet, 24b readily decomposed under these basic conditions. By using sodium hydride, 30a was obtained in 34% yield. Due to the moderate yield of the N-benzylation, the more reactive p-methoxybenzyl bromide (PMBBr) was successfully coupled in a yield of 53%. In a later stage, we found that the yield for N-alkylation was substantially increased to 83% via portionwise addition of sodium hydride (five times 0.25 equiv). Furthermore, subjection to p-bromobenzyl bromide also resulted in the desired product 30c. Purification of the latter, however, appeared to be troublesome, resulting in only 23% yield. Upon subjection of the PMB-protected precursors 30b (entry 2) and 30d (entry 3) to RCM, we were pleased to find that 31b was formed smoothly in a yield of 71%, while unfortunately in case of 30d only homodimeric species were observed. The RCM-precursors 30a (entry 2) and 30c (entry 4) reacted similarly, albeit with a slightly lower yield.

**Table 2.2.** RCM of didehydroamino acids

<table>
<thead>
<tr>
<th>Entry</th>
<th>Compound</th>
<th>R</th>
<th>Yield (%)</th>
<th>Compound</th>
<th>R</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>30a</td>
<td>Bn (n = 1)</td>
<td>83</td>
<td>31a</td>
<td>Bn (n = 1)</td>
<td>58a</td>
</tr>
<tr>
<td>2</td>
<td>30b</td>
<td>PMB (n = 1)</td>
<td>53</td>
<td>31b</td>
<td>PMB (n = 1)</td>
<td>71b</td>
</tr>
</tbody>
</table>
Ring closing metathesis of α,β-unsaturated didehydroamino esters

<p>| | | | | |</p>
<table>
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<tr>
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<tbody>
<tr>
<td>3</td>
<td>30c</td>
<td>PBB (n = 1)</td>
<td>23</td>
<td>31c</td>
</tr>
<tr>
<td>4</td>
<td>30d</td>
<td>PMB (n = 2)</td>
<td>79</td>
<td>31d</td>
</tr>
</tbody>
</table>

*Conversion based on 1H NMR. †Isolated yield.

With the 6-oxopiperidine carboxylic ester 31b in hand, we encountered the problem that upon increased concentration of the reaction a mixture of the cyclic structure and its homologous dimeric species (32) were isolated using 10 mol% of G2. When the dimer 32 was subjected to a fresh portion of G2, a full conversion into the heterocycle was observed. In view of this result, the G2-catalyst was then in a new experiment added portionwise (three times 2 mol%), resulting in the formation of the heterocycle 31b as a single product in 71% yield.

Scheme 2.10. Cyclization of didehydroamino ester 30b.

2.4 Introduction of substituents

Having this new method established, the stage was set for condensation of more elaborate, substituted unsaturated amides. At first, we decided to investigate the influence of allylic substituents on the amide. For this purpose, the readily available 3-methyl pent-4-enoiic acid 33a was converted into the corresponding acid chloride by treatment with oxalyl chloride. Careful concentration of the acid chloride and quenching with ammonia yielded the amide 34a in 53% yield. Condensation of 34a with ethyl pyruvate in the presence of p-toluenesulfonic acid afforded 35a in 46% yield as anticipated. Next, alkylation of the nitrogen using PMBBr afforded 36a in a yield of 64%. Finally, ring closing metathesis resulted in the 5-methyl-6-oxopiperidine carboxylic ester 37a in excellent yield (91%). Similar results were obtained from ring closing metathesis of the 2-methyl-substituted derivative 36b, providing cyclic product 37b in 71% yield.
2.5 Synthesis of 1-oxoisoquinoline carboxylic esters

1-Oxoisoquinoline carboxylates (39) are interesting structural entities. They are not only important as building blocks in natural product synthesis (e.g., Marinamide (38), Scheme 2.12), but also play an important role in the synthesis of stereochemically defined ligands. These ligands offer a coordinating environment related to the one present in the Salen ligands, but with chirality stemming from restricted rotation around the biaryl axis, rather than from central asymmetry in a diamine bridge.\(^{19}\)

Stimulated by the previous results, we set out to apply this methodology in a synthetic approach to 1-oxoisoquinoline carboxylates 48 starting from 2-vinylbenzamide 45a. Scheme 2.13 shows the preparation of 45a as well as of its methyl-substituted analogue 45b. Olefins 43a-b were prepared from commercially available 2-formylenzoic acid 41 and 2-acetylbenzoic acid 42 under standard Wittig conditions, following known procedures.\(^{20}\) Due to the low yield of the reaction, the acid was converted into the corresponding methyl ester
prior to olefination. However, in our hands the yield remained moderate. Surprisingly, reaction of methyl esters 43a-b with ammonia did not lead to formation of the amides. Alternatively, the ester was hydrolyzed using potassium hydroxide in dioxane/H₂O to give 44a-b in good yield. Next, the carboxylic acid was converted into the amide using the same two-step procedure that was used previously.

Next, condensation of unsaturated amide 45a with ethyl pyruvate proceeded well, resulting in isolation of the didehydroamino ester 46a in a good yield of 75% (Scheme 2.14). Subsequent PMB-protection followed by RCM using G2 at 80 °C in toluene yielded the 1-oxoisquinoline carboxylic ester 48a in 82%. The condensation of 45b proceeded in a similar fashion as for 45a, resulting in 67% of the desired product. Paramethoxy benzyl protection of 46b, however, proved to be more difficult, resulting in only trace amounts of product 46b (5%). The little product obtained was subjected to RCM using G2. As might have been expected, the less reactive disubstituted alkene did not undergo any RCM. In 2007, the more reactive o-tolyl-imidazolidine catalysts G6 and G7 came onto the market, which were especially developed for ring-closing metathesis of sterically more demanding alkenes. Disappointingly, the didehydroamino ester 47b remained unreactive towards cyclization with the latter catalyst.

2.6 Conclusion

Condensation of unsaturated amines with ethyl pyruvate appeared to be troublesome. The reaction was low yielding and the protection of nitrogen was limited to acid chlorides. Moreover, five-membered nitrogen heterocycles were formed in good yield, while formation of the six-membered analogues failed entirely, leading only to dimerization. Condensation of unsaturated amides with ethyl pyruvate on the other hand proceeded smoothly yielding the desired didehydroamino esters in a single transformation. Although unprotected didehydroamino esters failed to undergo ring-closing metathesis, we were pleased to find that the N-alkylated counterparts underwent smooth ring-closing metathesis with the G2 catalyst to provide the cyclic didehydroamino esters.

Having a new method established, more elaborate unsaturated amides were successfully introduced in order to synthesize 4- and 5-methyl-substituted 6-oxopiperidine carboxylic esters. Finally, the 1-oxoisoulnoline carboxylic ester moiety has been successfully synthesized via the developed method. Unfortunately, the Ru-catalyzed ring closure to tetrasubstituted alkenes was unsuccessful.
2.7 Experimental section

General information

Solvents were distilled from appropriate drying agents prior to use and stored under nitrogen. Chemicals were purchased from Sigma-Aldrich or Acros chemicals and used as received, unless stated otherwise. Reactions were carried out under inert atmosphere of dry nitrogen or argon. Standard syringe techniques were applied for the transfer of dry solvents and air- or moisture-sensitive reagents. Reactions were followed and Rf values are obtained using thin layer chromatography (TLC) on silica gel-coated plates (Merck 60 F254) with the indicated solvent mixture. Detection was performed with UV-light, and/or by charring at ~150 °C after dipping into a solution of either 2% anisaldehyde in ethanol/H2SO4 or (NH4)2MoO4.4H2O (25 g/L) and (NH4)2Ce(SO4)2.2H2O (10 g/L) in 10% H2SO4. IR spectra were recorded on an ATI Mattson Genesis Series FTIR spectrometer, or a Bruker Tensor 27 FTIR spectrometer. NMR spectra were recorded on a Bruker DMX 300 (300 MHz), and a Varian 400 (400 MHz) spectrometer in CDCl3 solutions (unless otherwise reported). Chemical shifts are given in ppm with respect to tetramethylsilane (TMS) as internal standard. Coupling constants are reported as J-values in Hz. Column or flash chromatography was carried out using ACROS silica gel (0.035–0.2H, 2H, J = 6.6 Hz), 1.63 (m, 5H), 1.32 (m, 2H), 1.14 (t, 3H, J = 7.0 Hz), 0.90 (t, 3H, J = 7.3 Hz). 13C NMR (CDCl3, 75 MHz): δ 162.24, 137.68, 126.19, 61.39, 59.92, 46.79, 29.32, 19.53, 13.72, 13.67, 13.34. HRMS (ESI) m/z calcd for C13H18NO3Na (M+Na)+: 236.1263, found: 236.1265.

Ethyl-2-[acetyl(butyl)amino]acrylate (11a)

To a solution of ethyl pyruvate (492 µL, 4.50 mmol) in PhMe (50 mL), was added n-butylamine (445 µL, 1.0 equiv). The reaction was stirred for 3 hours at room temperature and then cooled to 0 °C. Acetyl chloride (320 µL, 1.0 equiv) was added dropwise followed by a slow addition of diethylamine (720 µL, 1.0 equiv). The reaction was stirred for 16 h and then poured onto ice-water. The organic layer was washed with NaCl, dried (MgSO4) and concentrated in vacuo. The residue was purified by column chromatography (EtOAc/heptane 1:1) to give 11a (389 mg, 1.70 mmol, 43%) as a colorless oil. Rf 0.42 (EtOAc/heptane 1:1). FTIR (ATR) 1193, 1628, 1665, 1723, 2957 cm⁻¹. 1H NMR (CDCl3, 400 MHz): δ 6.51 (s, 1 H), 5.74 (s, 1H), 4.30 (q, 2H, J = 7.2 Hz), 3.52-3.46 (m, 2H), 1.97 (s, 3H), 1.54-1.21 (m, 7H), 0.98 (t, 3H, J = 7.2 Hz). 13C NMR (CDCl3, 75 MHz): δ 162.24, 137.68, 126.19, 61.39, 59.92, 46.79, 29.32, 19.53, 13.72, 13.67, 13.34. HRMS (ESI) m/z calcd for C13H18NO3Na (M+Na)+: 236.1263, found: 236.1265.

Ethyl-2-[benzoyl(butyl)amino]acrylate (11b)

To a solution of ethyl pyruvate (492 µL, 4.50 mmol) in PhMe (50 mL), was added n-butylamine (445 µL, 1.0 equiv). The reaction was stirred for 3 hours at room temperature and then cooled to 0 °C. Benzoyl chloride (523 µL, 1.0 equiv) was added dropwise followed by a slow addition of diethylamine (720 µL, 1.0 equiv). The reaction was stirred for 16 h and then poured onto ice-water. The organic layer was washed with NaCl, dried (MgSO4) and concentrated in vacuo. The residue was purified by column chromatography (EtOAc/heptane 1:1) to give 11b (546 mg, 2.57 mmol, 57%) as a colorless oil. Rf 0.46 (EtOAc/heptane 1:1). FTIR (ATR) 1193, 1628, 1665, 1723, 2957 cm⁻¹. 1H NMR (CDCl3, 400 MHz): δ 8.12-7.23 (m, 5H), 6.06 (s, 1H), 5.47 (s, 1H), 4.04 (q, 2H, J = 6.8 Hz), 3.65 (t, 2H, J = 6.6 Hz), 1.63-1.58 (m, 2H), 1.48-1.40 (m, 2H), 1.14 (t, 3H, J = 7.0 Hz), 0.90 (t, 3H, J = 7.3 Hz). 13C NMR (CDCl3, 75 MHz): δ 170.31, 163.54, 140.53, 135.72, 130.01, 129.52, 128.32, 127.50, 61.02, 48.61, 29.23, 19.62, 13.52, 13.32. HRMS (ESI) m/z calcd for C16H12X2Na (M+Na)+: 298.1424, found: 298.1410.

Ethyl-2-[Acetyl(but-3-enyl)amino]acrylate (16)

To a solution of n-butenylamine hydrochloric acid (535 mg, 5.00 mmol) in CH2Cl2 (10 mL) was added DBU (755 µL, 1.0 equiv). The reaction mixture was stirred for 1 hour. Then ethyl pyruvate (545 µL, 1.0 equiv) was added and the reaction was stirred for another 3 hours. The reaction was then cooled to 0 °C and acetyl chloride (355 µL, 1.0 equiv) was added dropwise followed by a slow addition of triethylamine (1395 µL, 10.0 mmol). The reaction was stirred for 16 h and then poured onto ice-water. The organic layer was washed with NaCl, dried (MgSO4) and concentrated in vacuo. The residue was purified by column chromatography (EtOAc/heptane 1:1) to give 16 (389 mg, 1.70 mmol, 43%) as a colorless oil. Rf 0.42 (EtOAc/heptane 1:1). FTIR (ATR) 1193, 1628, 1665, 1723, 2957 cm⁻¹. 1H NMR (CDCl3, 400 MHz): δ 6.51 (s, 1 H), 5.74 (s, 1H), 4.30 (q, 2H, J = 7.2 Hz), 3.52-3.46 (m, 2H), 1.97 (s, 3H), 1.54-1.21 (m, 7H), 0.98 (t, 3H, J = 7.2 Hz). 13C NMR (CDCl3, 75 MHz): δ 162.24, 137.68, 126.19, 61.39, 59.92, 46.79, 29.32, 19.53, 13.72, 13.67, 13.34. HRMS (ESI) m/z calcd for C16H12X2Na (M+Na)+: 298.1424, found: 298.1410.
vacuo. The residue was purified by column chromatography (EtOAc/heptane 1:1) to give 16 (205 mg, 0.97 mmol, 19%) as a colorless oil. Rf 0.36 (EtOAc/heptane 1:1). FTIR (ATR) 1192, 1630, 1667, 1724, 2980 cm⁻¹. ¹H NMR (CDCl₃, 400 MHz): δ 6.48 (s, 1H), 7.57-7.70 (m, 2H), 5.09-5.03 (m, 2H), 4.28 (q, 2H, J = 7.1 Hz), 3.55 (t, 2H, J = 7.4 Hz), 2.29-2.26 (m, 2H), 1.94 (s, 3H), 1.33 (t, 3H, J = 7.1 Hz). ¹³C NMR (CDCl₃, 75 MHz): δ 169.62, 163.21, 144.56, 134.78, 126.70, 116.08, 61.42, 46.23, 31.62, 21.61, 13.73. HRMS (ESI) m/z calcd for C₁₂H₁₅NO₃Na (M+Na)+: 234.1263, found: 234.1265.

**Ethyl-2-[acetyl(pent-4-enyl)amino]acrylate (17)**

To a solution of n-butenylamine (340 mg, 4.0 mmol) in CH₂Cl₂ (10 mL) was added ethyl pyruvate (438 µL, 2.0 equiv) and hydroquinone (81 mg, 10 mol%). The reaction mixture was stirred under Dean-Stark conditions applying vacuum for regulation. After 3 h the reaction was cooled to room temperature and poured over a plug of neutral Al₂O₃. The Al₂O₃ was washed two times with PhMe (25 mL). The organic layer was concentrated in vacuo. The residue was purified by column chromatography (EtOAc/heptane 1:1) to give 17 (162 mg, 0.72 mmole, 18%) as a colorless oil. Rf 0.36 (EtOAc/heptane 1:1). ¹H NMR (CDCl₃, 400 MHz): δ 6.46 (s, 1H), 5.80-5.75 (m, 2H), 5.73 (s, 1H), 5.01-4.96 (m, 2H), 4.28 (q, 2H, J = 7.1 Hz), 3.50 (dt, 2H, J = 7.6 Hz, J = 3.6 Hz), 2.07-2.02 (m, 2H), 1.95 (s, 3H), 1.63-1.58 (m, 2H), 1.32 (t, 3H, J = 7.1 Hz).

**Ethyl-2-(butenylamino)acrylate (20)**

To a solution of 20 (380 mg, 4.5 mmole) in CH₂Cl₂ (25 mL), were added hydroquinone (81 mg, 10 mol%), p-TsOH (86 mg, 10 mol%) and ethyl pyruvate (987 µL, 2.0 equiv). The reaction mixture was stirred under Dean-Stark conditions applying vacuum for regulation. After 3 h the reaction was cooled to room temperature and poured over a plug of neutral Al₂O₃. The Al₂O₃ was washed two times with PhMe (25 mL). The organic layer was concentrated in vacuo. The residue was purified by column chromatography (EtOAc/heptane 1:1) to give 20 (692 mg, 3.7 mmol, 83%) as a colorless oil. Rf 0.76 (EtOAc/heptane 1:1). FTIR (ATR) 1181, 1224, 1512, 1658, 1731, 2958, 3356 cm⁻¹. ¹H NMR (CDCl₃, 400 MHz): δ 7.79 (br. s, 1H), 6.60 (s, 1H), 5.87 (d, 1H, J = 1.5 Hz), 4.29 (q, 2H, J = 7.1 Hz), 2.31-2.28 (m, 2H), 1.73-1.68 (m, 2H), 1.35 (t, 3H, J = 7.1 Hz), 0.98 (t, 3H, J = 7.4Hz). ¹³C NMR (CDCl₃, 75 MHz): δ 171.35, 163.77, 130.63, 107.68, 61.65, 39.08, 18.36, 13.58, 13.45. HRMS (ESI) m/z calcd for C₉H₁₂NO₃Na (M+Na)+: 208.0950, found: 208.0948.

**Ethyl-2-(pent-4-enylamino)acrylate (24b)**

To a solution of 22b (515 mg, 5.2 mmol) in PhMe (50 mL), were added hydroquinone (57.2 mg, 10 mol%), p-TsOH (98.8 mg, 10 mol%) and ethyl pyruvate (1.14 mL, 2.0 equiv). The reaction mixture was stirred under Dean-Stark conditions applying vacuum for regulation. After 3 h the reaction was cooled to room temperature and poured over a plug of neutral Al₂O₃. The Al₂O₃ was washed two times with PhMe (50 mL). The organic layer was concentrated in vacuo. The residue was purified by column chromatography (EtOAc/heptane 1:1) to give 24b (594 mg, 3.02 mmol, 82%) as a colorless oil. Rf 0.75 (EtOAc/heptane 1:1). FTIR (ATR) 1187, 1314, 1512, 1683, 2980, 3355 cm⁻¹. ¹H NMR (CDCl₃, 400 MHz): δ 7.82 (br. s, 1H), 6.60 (s, 1H), 5.88 (d, 1H, J = 1.5 Hz), 5.82-5.79 (m, 1H), 5.07-5.03 (m, 2H), 4.29 (q, 2H, J = 7.1 Hz), 2.46-2.40 (m, 4H), 1.34 (t, 3H, J = 7.1 Hz). ¹³C NMR (CDCl₃, 75 MHz): δ 170.54, 163.61, 136.07, 130.56, 115.29, 107.62, 61.65, 36.24, 28.61, 13.56. HRMS (ESI) m/z calcd for C₁₉H₁₅NO₄Na (M+Na)+: 220.0949, found: 220.0952.

**Ethyl-2-(hex-5-enylamino)acrylate (24c)**

To a solution of 22c (113 mg, 1.0 mmol) in dry PhMe (25 mL), were added hydroquinone (11.0 mg, 10 mol%), p-TsOH (19.0 mg, 10 mol %) and ethyl pyruvate (218 µL, 2.0 equiv). The reaction mixture was stirred under Dean-Stark conditions applying vacuum for regulation. After 3 h the reaction was cooled to room temperature and poured over a plug of neutral Al₂O₃. The Al₂O₃ was washed two times with PhMe (25 mL). The organic layer was concentrated in vacuo. The residue was purified by column chromatography (EtOAc/heptane 1:1) to give 24c (96 mg, 0.45 mmol, 45%) as a colorless oil. Rf 0.78 (EtOAc/heptane 1:1). FTIR (ATR) 1187, 1515, 1683, 2976 cm⁻¹.
Ethyl-1-(acetyl-4,5-dihydro-1H-pyrrole-2-carboxylate (25a)

A solution of 6a (27 mg, 0.13 mmol) in dry PhMe (10 mL) was flushed with nitrogen for 15 min after which the temperature was raised to 80 °C. After 3 h the reaction mixture was stirred at room temperature. After 1 h the reaction was quenched with NH4Cl, extracted with CH2Cl2 (3 × 25 mL), dried (MgSO4) and concentrated in vacuo. The residue was purified by column chromatography (EtOAc/heptane 2:1 to 1:0) to give 25a (21 mg, 0.12 mmol, 89%) as a brown oil. Rf 0.20 (EtOAc/heptane 1:1). FTIR (ATR) 1623, 1700, 1735 cm⁻¹. ¹H NMR (CDCl3, 400 MHz): δ 5.97 (bt s, 1H), 4.98 (d, 1H, J = 10.1 Hz), 4.21 (q, 2H, J = 7.0 Hz), 3.04 (t, 2H, J = 7.4 Hz), 2.40 (dd, 2H, J = 6.8 Hz, J = 13.8 Hz), 1.44 (s, 9H), 1.28 (t, 3H, J = 7.1 Hz). ¹³C NMR (CDCl3, 75 MHz): δ 171.26, 170.94, 137.18, 130.53, 115.19, 107.36, 61.75, 36.44, 32.58, 23.96, 13.63. HRMS (ESI) m/z calcd for C13H15NO3Na (M+Na)+: 234.1090, found: 234.1109.

Ethyl-2-[tert-but oxy(carbonyl-pent-4-enyl)amino]acrylate (28)

To a solution of 24b (200 mg, 0.92 mmol) in dry THF (10 mL), were added Boc₂O (360 mg, 1.6 equiv) and DMAP (120 mg, 1.0 equiv). The reaction mixture was stirred at room temperature. After 1 h the reaction was quenched with NH4Cl, extracted with CH2Cl2 (3 × 25 mL), dried (MgSO4) and concentrated in vacuo. The residue was purified by column chromatography (EtOAc/heptane 1:3) to give 28 (244 mg, 0.082 mmol, 85%) as a colorless oil. Rf 0.47 (EtOAc/heptane 1:3). FTIR (ATR) 1627, 1670, 1735 cm⁻¹. ¹H NMR (CDCl3, 400 MHz): δ 6.43 (s, 1H), 5.86-5.82 (m, 1H), 5.60 (s, 1H), 5.06 (d, 1H, J = 17.2 Hz), 4.98 (d, 1H, J = 10.1 Hz), 4.21 (q, 2H, J = 7.0 Hz), 3.04 (t, 2H, J = 7.4 Hz), 2.40 (dd, 2H, J = 6.8 Hz, J = 13.8 Hz), 1.44 (s, 9H), 1.28 (t, 3H, J = 7.1 Hz). ¹³C NMR (CDCl3, 75 MHz): δ 174.28, 162.63, 151.07, 136.65, 125.13, 114.80, 83.14, 61.025, 36.50, 28.31, 27.34, 13.67. HRMS (ESI) m/z calcd for C15H23NO3Na (M+Na)+: 320.1474, found: 320.1468.

Ethyl-2-[benzyl(pent-4-enyl)amino]acrylate (30a)

To a solution of 24b (50 mg, 0.26 mmol) in dry DMF (10 mL), were added at 0 °C NaH (15.9 mg, 1.25 equiv) and then benzyl bromide (37.0 µL, 1.2 equiv). The reaction mixture was stirred for 1 h and then quenched with H2O (10 mL) and extracted with a mixture of EtOAc/heptane (1:1) (3 × 25 mL). The organic layer was dried (MgSO4) and concentrated in vacuo. The residue was purified by column chromatography (EtOAc/heptane 1:2) to give 30a (42 mg, 0.145 mmol, 57%) as a colorless oil. Rf 0.47 (EtOAc/heptane 1:1). FTIR (ATR) 1180, 1632, 1667, 1724, 2967 cm⁻¹. ¹H NMR (CDCl3, 400 MHz): δ 7.28-7.19 (m, 5H), 6.33 (s, 1H), 5.84-5.79 (m, 1H), 5.38 (s, 1H), 5.03 (d, 1H, J = 0.8 Hz, J = 17.1 Hz), 4.97 (dd, 1H, J = 0.7 Hz, J = 10.2 Hz), 4.70 (s, 2H), 4.23 (q, 1H, J = 7.1 Hz), 2.41 (dd, 2H, J = 6.7 Hz, J = 13.9 Hz), 2.30-2.26 (m, 2H), 1.28 (t, 3H, J = 7.1 Hz). ¹³C NMR (CDCl3, 75 MHz): δ 171.50, 163.27, 138.36, 136.82, 136.70, 131.06, 130.20, 128.50, 127.93, 127.44, 114.70, 61.36, 50.45, 32.76, 28.78, 13.64. HRMS (ESI) m/z calcd for C13H15NO3Na (M+Na)+: 310.1419, found: 310.14237.

Ethyl-2-[(4-methoxybenzyl)pent-4-enyl]amino]acrylate (30b)

To a solution of 24b (95 mg, 0.48 mmol) in dry DMF (5 mL), were added at 0 °C NaH (39 mg, 2.0 equiv) and then PMBBr (171 µL, 2.0 equiv). The reaction mixture was stirred for 1 h and then quenched with H2O (10 mL) and extracted with a mixture of EtOAc/heptane (1:1) (3 × 25 mL). The organic layer was dried (MgSO4) and concentrated in vacuo. The residue was purified by column chromatography (EtOAc/heptane 1:2) to give 30b (115 mg, 0.36 mmol, 76%) as a colorless oil. Rf 0.62 (EtOAc/heptane 1:1). FTIR (ATR) 1172, 1246, 1511, 1663, 2936 cm⁻¹. ¹H NMR (CDCl3, 400 MHz): δ 7.09 (d, 2H, J = 8.0 Hz), 6.82 (d, 2H, J = 8.2 Hz), 6.32 (s, 1H), 5.66-5.60 (m, 1H), 5.19 (s, 1H), 4.84-4.79 (m, 2H), 4.56 (s, 2H), 4.17 (q, 2H, J = 7.0 Hz), 3.77 (s, 3H), 2.14-1.90 (m, 4H), 1.71-1.68 (m, 2H), 1.12 (t, 3H, J = 7.1 Hz). ¹³C NMR (CDCl3, 75 MHz): δ 171.38, 163.30, 158.52, 138.26, 136.85, 129.88, 128.91,
Ethyl-2-[(4-bromobenzoyl)pent-4-enoylamo]acrylate (30c)

To a solution of 24b (60 mg, 0.30 mmol) in dry DMF (3 mL), were added at 0 °C NaH (14 mg, 1.1 equiv) and then PBBBr (84 mg, 1.1 equiv). The reaction mixture was stirred for 1 h and then quenched with H2O (10 mL) and extracted with a mixture of EtOAc/heptane (1:1) (3 × 25 mL). The organic layer was dried (MgSO4) and concentrated in vacuo. The residue was purified by column chromatography (EtOAc/heptane 1:2) to give 30c (108 mg, 0.28 mmol, 89%) as a colorless oil. Rf 0.57 (EtOAc/heptane 1:1). FTIR (ATR) 1180, 1633, 1667, 1725, 2932, 2967 cm⁻¹. ¹H NMR (CDCl₃, 400 MHz): δ 7.40 (d, 2H, J = 7.7 Hz), 7.13 (d, 2H, J = 7.9 Hz), 6.33 (s, 1H), 5.79-5.75 (m, 1H), 5.39 (s, 2H), 5.00 (d, 1H, J = 18.2 Hz), 4.95 (d, 1H, J = 10.7 Hz), 4.62 (s, 2H), 4.21 (q, 2H, J = 7.0 Hz), 2.32-2.27 (m, 4H), 1.27 (t, 3H, J = 7.1 Hz). ¹³C NMR (CDCl₃, 75 MHz): δ 171.58, 163.12, 138.34, 136.69, 135.76, 131.05, 130.20, 127.45, 121.02, 115.40, 114.77, 107.86, 61.47, 49.94, 32.68, 28.72, 13.63. HRMS (ESI) m/z calcd for C₂₅H₂₇BrNO₂Na (M+Na)⁺: 388.05243, found: 388.05311.

Ethyl-2-[(4-methoxybenzoyl)pent-4-enoylamo]acrylate(30d)

To a solution of 24c (187 mg, 0.88 mmol) in dry DMF (9 mL), were added at 0°C NaH (40 mg, 1.1 equiv) and then PMBB (190 µL, 1.5 equiv). The reaction mixture was stirred for 1 h and then another portion of NaH (18 mg, 0.5 equiv) was added. After stirring for another hour, the reaction was quenched with H₂O (10 mL) and extracted with a mixture of EtOAc/heptane (1:1) (3 × 25 mL). The organic layer was dried (MgSO₄) and concentrated in vacuo. The residue was purified by column chromatography (EtOAc/heptane 1:2) to give 30d (248 mg, 0.73 mmol, 83%) as a colorless oil. Rf 0.48 (EtOAc/heptane 1:1). FTIR (ATR) 1175, 1246, 1511, 1663, 1723, 2936 cm⁻¹. ¹H NMR (CDCl₃, 400 MHz): δ 7.09 (d, 2H, J = 8.0 Hz), 6.91 (d, 2H, J = 8.2 Hz), 6.33 (s, 1H), 5.82-5.77 (m, 1H), 5.29 (s, 1H), 4.90-4.96 (m, 2H), 4.56 (s, 2H), 4.12 (q, 2H, J = 7.0 Hz), 3.87 (s, 3H), 2.11-1.94 (m, 4H), 1.27 (t, 3H, J = 7.1 Hz). ¹³C NMR (CDCl₃, 75 MHz): δ 171.94, 163.33, 158.50, 138.32, 137.55, 132.79, 129.75, 129.79, 114.55, 113.25, 61.28, 54.72, 49.73, 32.72, 32.64, 23.88, 13.09. HRMS (ESI) m/z calcd for C₂₅H₂₇NO₂Na (M+Na)⁺: 354.1694, found: 354.1694.

Ethyl-1-(4-methoxybenzyl)-6-oxo-1,4,5,6-tetrahydropyridine-2-carboxylate (31b)

A solution of 30b (170 mg, 0.54 mmol) in dry PhMe (25 mL) was flushed with nitrogen for 15 min after which the temperature was raised to 80°C. At 80°C G2 (5 mol %, 23 mg) was added and the reaction was stirred for 1 h. After 1 h the organic layer was concentrated in vacuo. The residue was purified by column chromatography (EtOAc/heptane 1:2) to give 31b (111 mg, 0.38 mmol, 71%) as a brown oil. Rf 0.34 (EtOAc/heptane 1:1). FTIR (ATR) 1249, 1513, 1677, 1720 cm⁻¹. ¹H NMR (CDCl₃, 400 MHz): δ 7.12 (d, 2H, J = 8.0 Hz), 6.85 (d, 2H, J = 8.0 Hz), 6.31 (t, 1H), 5.06 (s, 2H), 4.17 (q, 2H, J = 7.2 Hz), 3.82 (s, 3H), 2.77-2.68 (m, 2H), 2.45-2.35 (m, 2H), 1.25 (t, 3H, J = 7.0 Hz). ¹³C NMR (CDCl₃, 75 MHz): δ 170.04, 158.32, 133.98, 129.91, 128.77, 120.76, 113.40, 60.83, 54.74, 44.07, 30.55, 19.32, 13.59. HRMS (ESI) m/z calcd for C₁₉H₁₅NO₂Na (M+Na)⁺: 312.1212, found: 312.1204.

Ethyl-2-(3-methyl pent-4-enoylamo)acrylate (35a)

To a solution of 34a (900 mg, 7.96 mmol) in dry PhMe (80 mL), were added p-TsOH (143.1 mg, 10 mol%) and ethyl pyruvate (1.75 mL, 2.0 equiv). The reaction mixture was stirred under Dean-Stark conditions applying vacuum for regulation. After 3 h the reaction was cooled to room temperature and poured over a plug of neutral Al₂O₃. The Al₂O₃ was washed two times with PhMe (25 mL). The organic layer was concentrated in vacuo to give 35a (772 mg, 3.66 mmol, 46%). FTIR (ATR) 1190, 1509, 1685, 2984, 3338 cm⁻¹. ¹H NMR (CDCl₃, 400 MHz): δ 7.77 (br s, 1H), 6.74 (s, 1H), 5.95 (s, 1H), 5.80-5.88 (m, 1H), 5.11-5.00 (m, 2H), 4.27 (q, 2H, J = 7.1 Hz), 2.33-2.25 (m, 2H), 2.10-2.22 (m, 1H), 1.27 (t, 3H, J = 7.1 Hz), 1.14 (d, 3H, J = 6.8 Hz). ¹³C NMR (CDCl₃, 75 MHz): δ 170.11, 163.68, 141.83, 130.50, 112.98, 107.92, 61.71, 44.29, 34.15, 19.22, 13.62. HRMS (ESI) m/z calcd for C₁₉H₁₅NO₂Na (M+Na)⁺: 234.1090, found: 234.1105.

127.49, 114.65, 113.27, 70.97, 61.33, 54.74, 49.77, 32.79, 28.78, 13.64. HRMS (ESI) m/z calcd for C₁₉H₁₅NO₂ (M+H)⁺: 318.1705, found: 318.1689.
Ethyl-2-(2-methyl pent-4-enoylamo) acrylate (35b)

To a solution of 34b (1.0 g, 8.85 mmol) in dry PhMe (90 mL), were added p-TsOH (159.0 mg, 10 mol%) and ethyl pyruvate (1.94 mL, 2.0 equiv). The reaction mixture was stirred under Dean-Stark conditions applying vacuum for regulation. After 3 h the reaction was cooled to room temperature and poured over a plug of neutral Al₂O₃. The Al₂O₃ was washed twice with PhMe (25 mL). The organic layer was concentrated in vacuo to give 35b (803 mg, 3.80 mmol, 43%). FTIR (ATR) 1186, 1314, 1513, 1680, 2974, 3364 cm⁻¹. ¹H NMR (CDCl₃, 400 MHz): 6 7.79 (br s, 1H), 6.77 (s, 1H), 5.91 (s, 1H), 5.89-5.81 (m, 2H), 5.01 (m, 1H), 4.29 (q, 2H, J = 7.1 Hz), 2.74 (ttt, 1H, J = 1.1 Hz, J = 7.0 Hz, J = 14.0 Hz), 2.37 (dd, 1H, J = 7.3 Hz, J = 14.5 Hz), 2.27 (dd, 1H, J = 7.2Hz, J = 14.5 Hz), 1.31 (q, 3H, 7.1 Hz), 1.09 (d, 3H, J = 6.8 Hz). ¹³C NMR (CDCl₃, 75 MHz): 6 174.16, 163.76, 136.84, 130.80, 116.70, 117.97, 107.92, 61.73, 41.77, 37.72, 16.73, 13.63. HRMS (ESI) m/z calcd for C₁₃H₁₇NO₂Na (M+Na)⁺: 324.1106, found: 324.1106.

Ethyl-2-[(4-methoxybenzyl)-(2-methyl pent-4-enol) amino] acrylate (36a)

To a solution of 35a (200 mg, 0.95 mmol) in dry DMF (10 mL), were added at 0°C NaH (39 mg, 1.0 equiv) and then PMBBr (150 µL, 1.1 equiv). The reaction mixture was stirred for 1 h and then quenched with H₂O (10 mL) and extracted with a mixture of EtoAc/heptane (1:1) (3 × 25 mL). The organic layer was dried (MgSO₄) and concentrated in vacuo. The residue was purified by column chromatography (EtoAc/heptane 1:2) to give 36a (231 mg, 0.75 mmol, 68%) as a colorless oil. Rf 0.69 (EtoAc/heptane 1:1). FTIR (ATR) 1177, 1246, 1512, 1662, 1724, 2967 cm⁻¹. ¹H NMR (CDCl₃, 400 MHz): 6 7.13 (d, 2H, J = 8.5 Hz), 6.81 (d, 2H, J = 8.5 Hz), 6.61 (s, 1H), 5.71 (ddd, 1H, J = 7.1, Hz, J = 10.3 Hz, J = 17.3 Hz), 5.44 (s, 1H), 4.96 (d, 1H, J = 17.2 Hz), 4.89 (d, 1H, J = 10.4 Hz), 4.64-4.50 (m, 2H), 4.17 (q, 2H, J = 7.1 Hz), 3.73 (s, 3H), 2.72-2.61 (m, 1H), 2.24 (dd, 1H, J = 7.0 Hz, J = 14.9 Hz), 2.14 (dd, 1H, J = 7.4 Hz, J = 15.0 Hz), 1.23 (t, 3H, J = 7.1 Hz), 0.97 (d, 3H, J = 6.8Hz). ¹³C NMR (CDCl₃, 75 MHz): 6 171.09, 163.08, 158.84, 142.12, 138.10, 129.52, 128.29, 127.43, 112.94, 111.79, 61.35, 53.81, 49.47, 39.94, 34.10, 18.14, 12.55. HRMS (ESI) m/z calcd for C₁₃H₁₇NO₃Na (M+Na)⁺: 354.1681, found: 354.1688.

Ethyl-2-[(4-methoxybenzyl)-2-(methyl pent-4-enyl)amino] acrylate (36b)

To a solution of 35b (200 mg, 0.95 mmol) in dry DMF (10 mL), were added at 0°C NaH (39 mg, 1.0 equiv) and then PMBBr (150 µL, 1.1 equiv). The reaction mixture was stirred for 1 h and then quenched with H₂O (10 mL) and extracted with a mixture of EtoAc/heptane (1:1) (3 × 25 mL). The organic layer was dried (MgSO₄) and concentrated in vacuo. The residue was purified by column chromatography (EtoAc/heptane 1:2) to give 36b (247 mg, 0.80 mmol, 73%) as a colorless oil. Rf 0.73 (EtoAc/heptane 1:1). FTIR (ATR) 1176, 1246, 1512, 1662, 1723, 2967 cm⁻¹. ¹H NMR (CDCl₃, 400 MHz): 6 7.13 (d, 2H, J = 8.1 Hz), 6.80 (d, 2H, J = 8.1 Hz), 6.38 (s, 1H), 5.63-5.52 (m, 1H), 5.41 (s, 1H), 4.94-4.98 (m, 2H), 4.71-4.35 (br s, 2H), 4.22 (q, 2H, J = 7.2 Hz), 3.75 (s, 3H), 2.56-2.49 (m, 1H), 2.33 (dd, 2H, J = 7.2 Hz, J = 15.0 Hz), 1.2 (t, 1H, J = 7.1 Hz), 0.73 (d, 3H, J = 6.8Hz). ¹³C NMR (CDCl₃, 75 MHz): 6 171.18, 163.08, 158.84, 142.30, 138.10, 129.52, 128.29, 127.43, 112.94, 111.79, 61.16, 53.81, 49.47, 39.94, 34.10, 18.14, 12.55. HRMS (ESI) m/z calcd for C₁₃H₁₇NO₃Na (M+Na)⁺: 354.1681, found: 354.1693.

Ethyl-1-(4-methoxybenzyl)-4-methyl-1-oxo-1,4,5,6-tetrahydro pyridine-2-carboxylate (37a)

A solution of 36a (50 mg, 0.14 mmol) in dry PhMe (2 mL) was flushed with nitrogen for 15 min after which the temperature was raised to 80°C. At 80°C G2 (5 mol%, 6 mg) was added and the reaction was stirred for 16 h. After 1 h the organic layer was concentrated in vacuo. The residue was purified by column chromatography (EtoAc/heptane 1:2) to give 37a (35 mg, 0.11 mmol, 91%) as a colorless oil. Rf 0.57 (EtoAc/heptane 1:1). FTIR (ATR) 1249, 1513, 1677, 2720 cm⁻¹. ¹H NMR (CDCl₃, 400 MHz): 6 7.11 (d, 2H, J = 8.3 Hz), 6.88 (d, 2H, J = 8.3 Hz), 6.17 (dd, 1H, J = 0.8 Hz, J = 4.1 Hz), 5.31 (d, 1H, J = 14.9 Hz), 4.97 (d, 1H, J = 14.9 Hz), 4.17 (q, 2H, J = 7.2 Hz), 3.76 (s, 3H), 2.64-2.55 (m, 2H), 2.35-2.20 (m, 1H), 1.27 (t, 3H, J = 7.2 Hz), 1.09 (d, 3H, J = 6.8 Hz). ¹³C NMR (CDCl₃, 75 MHz): 6 169.81, 162.28, 158.34, 132.63, 129.01, 126.57, 113.36, 60.88, 54.73, 44.00, 38.45, 25.99, 18.06, 13.62. HRMS (ESI) m/z calcd for C₁₃H₁₇NO₂Na (M+Na)⁺: 326.1368, found: 326.1368.
A solution of 36b (42 mg, 0.12 mmol) in dry PhMe (2 mL) was flushed with nitrogen for 15 min after which the temperature was raised to 80 °C. At 80 °C G2 (5 mol %, 6 mg) was added and the reaction was stirred for 16 h. After 1 h the organic layer was concentrated in vacuo. The residue was purified by column chromatography (EtOAc/heptane 1:2) to give 37b (27 mg, 0.08 mmol, 71%) as a colorless oil. Rf 0.61 (EtOAc/heptane 1:1). FTIR (ATR) 1249, 1513, 1677, 1720 cm⁻¹. ¹H NMR (CDCl₃, 400 MHz): δ 7.11 (d, 2H, J = 8.3 Hz), 6.88 (d, 2H, J = 8.3 Hz), 6.17 (dd, 1H, J = 0.8 Hz, J = 4.1 Hz), 5.31 (d, 1H, J = 14.9 Hz), 4.97 (d, 1H, J = 14.9 Hz), 4.17 (q, 2H, 7.2 Hz), 3.76 (s, 3H), 2.62-2.51 (m, 2H), 2.34-2.20 (m, 1H), 1.27 (t, 3H, J = 7.2 Hz), 1.09 (d, 3H, J = 6.8 Hz). ¹³C NMR (CDCl₃, 75 MHz): δ 169.81, 162.28, 158.34, 132.63, 129.01, 126.57, 113.36, 60.88, 54.73, 44.00, 38.45, 25.99, 18.06, 13.62. HRMS (ESI) m/z calcld for C₁₂H₂₃NO₄Na (M+Na)⁺: 326.1368, found: 326.1368.

**Methyl-2-vinylbenzoate (43a)**

To a solution of 2-formyl-benzoic acid (4.0 g, 26.7 mmol) in acetone (40 mL) were added K₂CO₃ (11.6 g, 3.0 equiv) and Mel (1.68 mL, 1.0 equiv). The reaction mixture was stirred for 16 h. After 1 h the organic layer was concentrated in vacuo. The residue was then redissolved in CH₂Cl₂ and washed with H₂O₂, dried (MgSO₄) and concentrated in vacuo. The product was purified by column chromatography (EtOAc/heptane 1:2) to give 26 (2.56 g, 15.6 mmol, 58%) as a colorless oil. Rf 0.76 (EtOAc/heptane 1:1). ¹H NMR (CDCl₃, 400 MHz): δ 10.58 (s, 1H), 7.93-7.46 (m, 4H), 3.97 (s, 3H). Data are similar as described in literature.

Next, a solution of MePPh₂Br (14.7 g, 2.15 equiv) in dry THF (20 mL) was added KO'Bu (3.9 g, 1.0 equiv) at 0 °C. After 30 min 41 (2.0 g, 12.2 mmol) in dry THF (30 mL) was added dropwise. The reaction mixture was stirred for another 2 h and then quenched with NH₄Cl extracted with CH₂Cl₂, dried (MgSO₄) and concentrated in vacuo. The product was purified by column chromatography (EtOAc/heptane 1:2) to give 29 (594 mg, 4.01 mmol, 89%) as a colorless oil.

**2-Vinyl benzoic acid (44a)**

To a solution of 43a (744 mg, 4.54 mmol) in a mixture of MeOH/H₂O (1:1, 60 mL) was added KOH (1.29 g, 5.0 equiv) in H₂O (10 mL). The reaction mixture was stirred at room temperature. After 5 h the reaction was quenched by a dropwise addition of concentrated HCl until the solution changed color (blue to yellow). The organic layer was extracted with CH₂Cl₂, dried (MgSO₄) and concentrated in vacuo. The product was purified by column chromatography (EtOAc/heptane 1:1) to give 44a (594 mg, 4.01 mmol, 89%) as a colorless oil. Rf 0.52 (EtOAc/heptane 1:1). ¹H NMR (CDCl₃, 400 MHz): δ 7.78-7.46 (m, 5H), 7.31 (dt, 1H, J = 1.4 Hz, J = 3.4 Hz), 5.65 (dd, 1H, J = 1.4 Hz, J = 17.4 Hz), 3.91 (s, 3H). ¹³C NMR (CDCl₃, 75 MHz): δ 167.36, 139.09, 135.38, 131.62, 129.82, 128.43, 126.72, 126.72, 115.98, 51.60. Data are similar as described in literature.

**2-Vinylbenzamide (45a)**

To a solution of 44a (594 mg, 4.01 mmol) in dry CH₂Cl₂ (40 mL) was added SOCl₂ (438 µL, 1.0 equiv). The reaction mixture was stirred at reflux temperature. After 2 h the reaction was carefully concentrated. The residue was redissolved in THF and dropwise added to a 7 M NH₄/MeOH solution. The reaction was stirred for 2 h and then concentrated in vacuo. The residue was redissolved in cold Et₂O and the product is filtered to give 45a (347 mg, 2.36 mmol, 60%) as a white solid. Rf 0.43 (EtOAc/heptane 1:1). FTIR (ATR) 1397, 1621, 1661, 3168, 3336 cm⁻¹. ¹H NMR (MeOD, 400 MHz): δ 7.63 (d, 1H, J = 7.8 Hz), 7.44-7.37 (m, 2H), 7.29 (dt, 1H, J = 1.2 Hz, J = 7.5 Hz), 7.05 (dd, 1H, J = 11.0 Hz, J = 17.5 Hz), 5.79 (d, 1H, J = 1.1 Hz), 5.74 (d, 1H, J = 1.1 Hz). ¹³C NMR (MeOD, 75 MHz): δ 173.22, 134.94, 134.76, 133.65, 129.33, 126.83, 126.55, 124.97, 114.64. HRMS (ESI) m/z calcld for C₁₂H₁₀NO₄Na (M+Na)⁺: 170.05818, found: 170.05802.
Ethyl-2-[2-vinyl(benzoyl)amino]acrylate (46a)

To a solution of 45a (374 mg, 2.36 mmol) in dry PhMe (25 mL), were added hydroquinone (26.0 mg, 10 mol%), p-TsOH (44.8 mg, 10 mol%) and ethyl pyruvate (388 µL, 1.5 equiv). The reaction mixture was stirred under Dean-Stark conditions applying vacuum for regulation. After 5 h the reaction was cooled to room temperature and poured over a plug of neutral Al₂O₃. The Al₂O₃ was washed twice with PhMe (25 mL). The organic layer was concentrated in vacuo to give 46a (436 mg, 1.77 mmol, 75%). FTIR (ATR) 1187, 1321, 1504, 1677, 2975 cm⁻¹. ¹H NMR (CDCl₃, 400 MHz): δ 8.15 (br s, 1H), 7.25-7.61 (m, 4H), 7.07 (dd, 1H, J = 11.0 Hz, J = 17.4 Hz), 6.77 (s, 1H), 5.78 (s, 1H), 5.73 (d, 1H, J = 17.4 Hz), 5.38 (d, 1H, J = 11.0 Hz), 4.30 (q, 2H, 7.1 Hz), 1.34 (t, 3H, 7.1 Hz). ¹³C NMR (CDCl₃, 75 MHz): δ 167.25, 163.56, 135.98, 134.25, 133.83, 130.95, 130.76, 127.28, 127.08, 126.36, 117.04, 108.45, 61.83, 13.65. HRMS (ESI) m/z calcd for C₁₄H₁₉NO₄Na (M+Na)⁺: 268.0944, found: 268.0937.

Ethyl-2-[(4-methoxybenzyl)(2-vinylbenzoyl)amino]acrylate (47a)

To a solution of 46a (436 mg, 0.177 mmol) in dry DMF (20 mL), were added at 0°C NaH (145 mg, 1.2 equiv) and then PMBBr (409 µL, 1.6 equiv). The reaction mixture was stirred for 1 h and then quenched with H₂O (10 mL) and extracted with a mixture of EtOAc/heptane (1:1) (3 x 25 mL). The organic layer was dried (MgSO₄) and concentrated in vacuo. The residue was purified by column chromatography (EtOAc/heptane 1:2) to give 47a (497 mg, 1.36 mmol, 77%) as a colorless oil. Rᵣ 0.69 (EtOAc/heptane 1:1). FTIR (ATR) 1723, 1654, 1512, 1246, 1177 cm⁻¹. ¹H NMR (CDCl₃, 400 MHz): δ 7.42-6.68 (m, 8H), 6.91 (s, 1H), 5.69 (d, 1H, J = 17.4 Hz), 5.37-5.21 (m, 1H), 5.34 (d, 1H, 11.0 Hz), 5.12 (s, 1H), 4.95 (br s, 2H), 4.09 (q, 2H, J = 7.0 Hz), 3.89 (s, 3H), 1.14 (t, 3H, J = 7.0 Hz). ¹³C NMR (CDCl₃, 75 MHz): δ 169.81, 163.18, 158.63, 138.06, 134.73, 134.66, 133.57, 133.42, 129.93, 128.83, 126.73, 126.58, 125.60, 124.73, 115.76, 113.37, 61.09, 54.77, 49.74, 13.59 HRMS (ESI) m/z calcd for C₁₄H₁₉NO₄Na (M+Na)⁺: 388.1525, found: 388.1522.

Ethyl-2-(4-methoxybenzyl)-1-oxo-1,2-dihydroisouquinoline-3-carboxylate (48a)

A solution of 47a (2.17 g, 6.0 mmol) in dry PhMe (60 mL) was flushed with nitrogen for 15 min after which the temperature was raised to 80 °C. At 80°C G2 (5 mol %, 254 mg) was added and the reaction was stirred for 1 h. After 1 h the organic layer was concentrated in vacuo. The residue was purified by column chromatography (EtOAc/heptane 1:2) to give 48a (1.65 g, 4.92 mmol, 82%) as a brown oil. Rᵣ 0.31 (EtOAc/heptane 1:1). FTIR (ATR) 1249, 1513, 1677, 1770 cm⁻¹. ¹H NMR (CDCl₃, 400 MHz): δ 8.48 (tdd, 1H, J = 0.6Hz, J = 1.3Hz, J = 8.0Hz), 7.72-7.55 (m, 3H), 7.21-7.04 (m, 3H), 7.78 (d, 2H, J = 8.8 Hz), 5.61 (s, 1H), 4.21 (q, 2H, J = 7.1 Hz), 1.26 (q, 3H, J = 7.1 Hz). ¹³C NMR (CDCl₃, 75 MHz): δ 162.61, 162.15, 158.30, 134.06, 132.66, 132.20, 129.47, 128.54, 128.47, 128.21, 126.62, 113.37, 111.94, 61.57, 54.76, 45.93, 13.56. HRMS (ESI) m/z calcd for C₂₀H₁₅NO₃Na (M+Na)⁺: 360.1212, found: 360.1194.

Methyl-2-isopropenyl benzoate (43b)

To a solution of MePPh₂Br (12.85 g, 2.15 equiv) in dry THF (40 mL) was added KO₂Bu (4.0 g, 1.0 equiv) at 0 °C. After 30 min 42 (2.233 g, 12.0 mmol) in dry THF (30 mL) was added dropwise. The reaction mixture was stirred for another 2 h and then quenched with NH₄Cl, extracted with CH₂Cl₂, dried (MgSO₄) and concentrated in vacuo. The product was purified by column chromatography (EtOAc/heptane 1:2) to give 43b (900 mg, 5.11 mmol, 41%) as a colorless oil. Rᵣ 0.78 (EtOAc/heptane 1:2). FTIR (ATR) 1280, 1721 cm⁻¹. ¹H NMR (CDCl₃, 400 MHz): δ 7.78 (ddd, 1H, J = 0.5 Hz, J = 1.4 Hz, J = 7.8 Hz), 7.44 (dt, 1H, J = 1.4 Hz, J = 7.5 Hz), 7.31 (dt, 1H, J = 1.4 Hz, J = 7.5 Hz), 7.24 (ddd, 1H, J = 0.5Hz, J = 1.3Hz, J = 7.6Hz), 5.13-5.05 (m, 1H), 4.84-4.72 (m, 1H), 3.81 (s, 3H), 2.07 (s, 3H). ¹³C NMR (CDCl₃, 75 MHz): δ 167.96, 145.98, 144.69, 131.03, 129.20, 128.77, 126.41, 113.21, 51.54, 23.67. HRMS (ESI) m/z calcd for C₁₁H₁₃NO₂Na (M+Na)⁺: 177.0916, found: 177.0903.
2-Isopropenylbenzoic acid (44b)

To a solution of 43b (600 mg, 3.40 mmol) in a mixture of MeOH/H₂O (1:1, 60 mL) was added KOH (1.29 g, 5.0 equiv) in H₂O (10 mL). The reaction mixture was stirred at room temperature. After 5 h the reaction was quenched by a dropwise addition of concentrated HCl until the solution changed color (blue to yellow). The organic layer was extracted with CH₂Cl₂, dried (MgSO₄) and concentrated in vacuo. The product was purified by column chromatography (EtOAc/heptane 1:2) to give 44b (505 mg, 3.12 mmol, 92%) as a colorless oil. Rf 0.24 (EtOAc/heptane 1:2). 

1H NMR (CDCl₃, 400 MHz): δ 7.78 – 7.64 (m, 4H), 5.68 (d, 1H, J = 8.1 Hz), 5.21 (d, 1H, J = 8.1 Hz), 3.27 (s, 3H).

13C NMR (CDCl₃, 75 MHz): δ 172.16, 146.12, 145.68, 132.00, 130.20, 129.21, 126.53, 113.47, 23.80.

HRMS (ESI) m/z calcd for C₂₀H₁₈NO₄Na (M+Na)⁺: 345.1103, found: 345.1129.

2-Isopropenylbenzamide (45b)

To a solution of 44b (500 mg, 3.10 mmol) in CH₂Cl₂ (30 mL) was added SOCl₂ (338 µL, 1.0 equiv). The reaction mixture was stirred at reflux temperature. After 2 h the reaction was carefully concentrated. The residue was redissolved in THF and dropwise added to a 7 M NH₃/MeOH solution. The reaction was stirred for 2 h and then concentrated in vacuo. The residue was recrystallized from EtOAc/heptane 1:5 to give 45b (150 mg, 0.93 mmol, 30%) as a white solid. Rf 0.31 (EtOAc/heptane 1:1). FTIR (ATR) 1397, 1643, 2359, 2187, 3377 cm⁻¹. 1H NMR (MeOD, 400 MHz): δ 7.74 (ddd, 1H, J = 0.4 Hz, J = 1.5 Hz, J = 7.6 Hz), 7.42 (dt, 1H, J = 1.5 Hz, J = 7.5 Hz), 7.34 (dt, 1H, J = 1.4 Hz, J = 7.6 Hz), 7.22 (ddd, 1H, J = 0.4 Hz, J = 1.4 Hz, J = 7.6 Hz), 6.33 (br s, 1H), 6.14 (br s, 1H), 5.25 (m, 1H), 5.11 (m, 1H), 2.13 (dd, 1H, J = 0.9 Hz, J = 1.5 Hz). 13C NMR (MeOD, 75 MHz): δ 170.54, 146.36, 141.75, 132.30, 130.35, 128.51, 128.37, 127.23, 115.51, 23.93. HRMS (ESI) m/z calcd for C₁₀H₁₁NONa (M+Na)⁺: 184.0738, found: 184.0728.

Ethyl-(2-isopropenylbenzoylamino)acrylate(46b)

To a solution of 45b (100 mg, 0.62 mmole) in dry PhMe (15 mL), were added hydroquinone (9.0 mg, 10 mol %), p-TsOH (12.0 mg, 10 mol %) and ethyl pyruvate (340 µL, 5 equiv). The reaction mixture was stirred under Dean-Stark conditions applying vacuum for regulation. After 5 h the reaction was cooled to room temperature and poured over a plug of neutral Al₂O₃. The Al₂O₃ was washed two times with PhMe (25 mL). The organic layer was concentrated in vacuo to give 46b (57 mg, 1.77 mmol, 34%). FTIR (ATR) 1187, 1321, 1504, 1677, 2975 cm⁻¹. 1H NMR (CDCl₃, 400 MHz): δ 8.15 (br s, 1H), 7.61-7.25 (m, 4H), 7.07 (dd, 1H, J = 11.0 Hz, J = 17.4 Hz), 6.77 (s, 1H), 5.98 (s, 1H), 5.73 (d, 1H, J = 17.4 Hz), 5.38 (d, 3H, J = 11.0 Hz), 4.30 (q, 2H, 7.1 Hz), 1.34 (t, 3H, 7.1 Hz). 13C NMR (CDCl₃, 75 MHz): δ 167.2, 163.5, 144.80, 141.55, 133.29, 131.07, 130.36, 128.08, 128.31, 127.61, 116.34, 108.22, 61.69, 23.69, 13.56. HRMS (ESI) m/z calcd for C₁₄H₁₅NO₃Na (M+Na)⁺: 268.0944, found: 268.0937.
2.8 References


Chapter 2


Ring closing metathesis of α,β-unsaturated didehydroamino esters
Diastereoselective synthesis of substituted morpholines

Abstract

In this project we developed a diastereoselective synthesis of cis-2,5-disubstituted morpholines via intramolecular conjugate addition of β-hydroxylated didehydroamino esters. Two transformations were of critical importance, namely 1) condensation of a (substituted) hydroxy amide with a pyruvate to prepare the β-hydroxy didehydroamino ester, and 2) cyclization to the corresponding morpholine. After this sequence had been successfully developed, substituents were introduced onto the morpholine to determine the scope and limitations of this approach.
3.1 Introduction

3.1.1 Morpholines and their biological relevance

For many years, non-substituted morpholines have been used in organic synthesis as a simple base or as an amine substituent. Hence, the synthesis of substituted morpholine derivatives is relatively unexplored. Nevertheless, C-substituted morpholines show relevant biological activity as antidepressant (1), antioxidant (2), appetite suppressant (3-4), and are also known to exhibit antitumor activity (5) (Scheme 3.1).

![Scheme 3.1. Biologically relevant C-substituted morpholines.](image)

C-Substituted morpholines have been mainly prepared from enantiomerically pure amino acids and the corresponding amino alcohols. The first enantiomerically pure building blocks were reported in 1956 with the synthesis of phendimetrazine (8) derived from a reaction of L-ephedrine (6) with chloroethanol (7) (Scheme 3.2). Since then, syntheses of various C-substituted morpholines have appeared in literature.

![Scheme 3.2. Synthesis of phendimetrazine.](image)
In conjunction with previous morpholine syntheses in our group, in this project we aimed to prepare 2,5-disubstituted morpholines. These types of morpholines are known to show biological activity, e.g. as anti-inflammatory agent (9), GABA<sub>B</sub>-receptor antagonist (10), and as antitumor agent (11) (Scheme 3.3). Generally applicable methods for their synthesis, however, are rare and often lead to diastereomeric mixtures.

**Scheme 3.3.** Biologically active trans-2,5-disubstituted morpholines.

The first diastereoselective synthesis of enantiopure trans-2,5-disubstituted morpholines was reported in 2004 by Myers et al. The synthesis involved nucleophilic ring opening of an enantiopure epoxide (e.g. 12) with an amino alcohol (13). Selective tosylation at nitrogen and the primary alcohol of diol 14 and subsequent cyclization afforded the N-tosyl-protected morpholine 15 as a single diastereoisomer (Scheme 3.4). Although high selectivity was reached in the cyclization, this route lacks some generality because enantiopure epoxides are not commonly commercially available and therefore first need to be prepared.

**Scheme 3.4.** Diastereoselective synthesis of morpholine 15.

Selected examples of cis-disubstituted morpholines include the cis-2,3-disubstituted morpholine Aprepitant (16), a neurokinin-1 receptor antagonist, widely used against Alzheimer’s disease, and the cis-3,5-disubstituted morpholine 17, which is a γ-secretase inhibitor (Scheme 3.5).
Scheme 3.5. Biologically relevant cis-disubstituted morpholines.

Another example of a stereoselective synthesis of cis-disubstituted morpholines was published by Breuning et al. in 2007 (Scheme 3.6). The benzyl-protected amine 18 was reacted with enantiopure epichlorohydrin (19) to obtain the cis-2,5-disubstituted morpholines 20.


In 2011, Medina et al. reported a synthesis of cis-2,5-disubstituted morpholines 21 as potential 3-phosphoinositide-dependent kinase-1 (PDK1) inhibitors (Scheme 3.7).

Scheme 3.7. Cis-2,5-disubstituted morpholines 21.

A more versatile synthesis of enantiomERICALLY pure cis- and trans-2,5-disubstituted morpholines was recently developed in our group starting from enantiopure cyanohydrins.
(22) and amino esters (23) (Scheme 3.8), resulting in complete control over both stereocenters in the resulting morpholines.\(^8\)

![Scheme 3.8. Synthesis of enantio- and diastereomerically pure morpholines 24.](image)

### 3.1.2 Retrosynthesis

We envisaged that the synthesis of 2,5-disubstituted morpholine derivatives might proceed via intramolecular conjugate addition of β-hydroxy-substituted didehydroamino acids and hence should lead to morpholines with new substitution patterns. Retrosynthetically, morpholines of type 25 might therefore be prepared through deprotection-induced cyclization of didehydroamino esters 27, followed by reduction (Scheme 3.9). The didehydroamino esters 27 can be prepared by condensing hydroxyl amide 28 with methyl pyruvate.

![Scheme 3.9. Retrosynthesis of 2,5-disubstituted morpholines.](image)

### 3.2 Synthesis of cyclic amino acids

#### 3.2.1 N-Alkylation of didehydroamino acids

The first attempts to synthesize the required β-hydroxy-substituted didehydroamino acids were based on \(N\)-alkylation of didehydroamino acid 30 which was readily obtained from a condensation reaction of benzyl urethane (29) with ethyl pyruvate. Unfortunately, no conversion was observed and only starting material was recovered. A raise in temperature did not lead to any product formation either. Adding potassium iodide (KI) or
tetrabutylammonium iodide (TBAI) to the reaction mixture, thereby in situ converting the bromide into the corresponding iodide, did result in some formation of 33. Encouraged by these results, 31 was fully converted into its iodinated derivative 32 prior to alkylation.\textsuperscript{14} Alkylation however, was unproductive due to degradation of the iodide.\textsuperscript{15}

Scheme 3.10. Alkylation of didehydroamino ester 30.

Since N-alkylation appeared to be troublesome, the potential of an alternative N-alkylation procedure with chiral epoxides was investigated, similarly as published by Breuning.\textsuperscript{12} Reaction of 30 and 34 could result in the formation of the intermediate 35, which may then undergo intramolecular conjugate addition to the morpholine derivative 36 in a one-pot. To test this hypothesis, N-alkylation of commercially available (S)-phenyloxirane (34) was investigated. Much to our disappointment, the didehydroamino acid appeared to be unreactive towards N-alkylation and only degradation of the didehydroamino acid was observed upon prolonged reaction times (Scheme 3.11).

Scheme 3.11. Synthesis of enantiopure morpholine precursor 36.

### 3.2.2 Condensation of hydroxyl amides with ethyl pyruvate

Since N-alkylation could not be properly achieved, we focused on the preparation of $\beta$-hydroxy-substituted didehydroamino esters by condensation of protected $\beta$-hydroxy amides with ethyl pyruvate. The hydroxy amides were prepared from commercially available amides and esters. Since the stability of the protecting group must comply with the acidic conditions of the condensation reaction, we used several protecting groups with different acid reactivity. At first, the benzoyl-protected amide 38 was prepared in a nearly quantitative yield by substitution of 2-bromoacetamide (37) with benzoic acid in the presence of N,N-diisopropylethylamine (DIPEA) (entry 1, Scheme 3.12).\textsuperscript{16}

In addition, the TBDPS- and PMB-protected derivatives 41 and 43 were prepared from ethyl glycolate (39). Mixing ethyl glycolate with TBDPSCI in the presence of imidazole resulted in ester 40 in 95%,\textsuperscript{17} which was readily converted into the corresponding amide (41) by treatment with ammonia in methanol\textsuperscript{18} and isolated in a moderate yield of 59%, (Scheme 3.12). When ethyl glycolate was reacted in THF with p-methoxybenzyl bromide in the presence of sodium hydride,\textsuperscript{19} PMB-protected 42 was obtained, albeit in a moderate yield of 42%. In an additional step, the ester was converted into amide 43, similar as for amide 41.

With the hydroxy-substituted amides successfully prepared, the next step in the synthesis involved condensation with ethyl pyruvate under Dean–Stark conditions, as depicted in Scheme 3.13.\textsuperscript{20} The protected hydroxy amides 38, 41 and 43 were reacted in refluxing toluene with ethyl pyruvate in the presence of a catalytic amount of p-toluenesulfonic acid. Condensation of 38 led to the desired β-hydroxy0 ydidehydroamino acid 44a in varying yields. This was in sharp contrast to the ether-protected alcohols, which despite a clear full conversion in the condensation of amide 43, only gave trace amounts of products (11%). Probably, both the silyl- and the PMB ether are too acid labile under the acidic condensation conditions.

Scheme 3.13. Condensation to form the didehydroamino esters 44 under Dean Stark conditions.
3.2.3 Intramolecular conjugate addition of β-hydroxy didehydroamino esters

With β-hydroxy didehydroamino ester 44a successfully prepared, cyclization was attempted by hydrolysis of the benzoylester in methanol in the presence of potassium carbonate. Although the hydrolysis was complete within minutes, the resulting alkoxide did not cyclize in a conjugate fashion to morpholine 46 (Scheme 3.14). The amide function of 44a\textsuperscript{21} was then alkylated since we anticipated that forcing the didehydroamino ester into the s-cis conformation might facilitate the cyclization process.

![Scheme 3.14. Synthesis of PMB-protected β-hydroxy didehydroamino acid 45.](image)

Several attempts were undertaken to induce the intramolecular oxa-Michael reaction by deprotection of the alcohol (Scheme 3.15). This was initially performed by dissolving β-hydroxy didehydroamino ester 45 in methanol and treatment with potassium carbonate. A rapid transesterification was observed, but more importantly the simultaneously liberated alkoxide underwent smooth cyclization in an excellent yield of 99% to the morpholine carboxylate 46.

![Scheme 3.15. Synthesis and reaction sequence of the cyclization reaction.](image)

3.3 Synthesis of (2S,5S)-(5-phenylmorpholin-2-yl)methanol

With the synthesis route successfully developed for non-substituted morpholines, a substituent was introduced on the hydroxy amide to increase the biological relevance of the resulting products. This concept was initially validated on enantiopure mandelic acid (47).
Enantiopure mandelic acid was esterified in a mixture of hydrochloric acid in methanol at 70 °C (Scheme 3.16), and stirred in methanolic ammonia to afford the desired hydroxy amide 48. Protection with either acetic anhydride or benzoyl chloride afforded the desired protected hydroxyl amides 49a and 49b in moderate to good yield. According to chiral HPLC-measurements, no racemization occurred (Figure 3.1).

The condensation reaction of hydroxy amides 49a and 49b with methyl pyruvate esters and subsequent PMB-protection led to the corresponding β-hydroxy didehydroamino esters 51a and 51b in good yields (Scheme 3.17).
In sharp contrast to the cyclization of the non-substituted dihydroamino ester 45, the intramolecular oxa-Michael of phenyl-substituted substrate 51a was rather troublesome, resulting in only trace amounts of product. In these attempts, the carboxylic acid was formed as a byproduct, which may prevent the cyclization from occurring. Extensive research on conjugate cyclization of the benzoyl-protected precursor 51b, on the other hand, did result in product formation. Upon addition of 0.5 equivalent of K₂CO₃ and stirring at 50 °C for 4.5 h, an isolated yield of 33% of the cyclic compound (S)-52 was obtained as a single diastereoisomer (Table 3.1). The enantiomer (R)-52 was formed from (R)-51b in a similar yield of 37%, also as a single product.

Table 3.1. Synthesis of the morpholine rings via oxa-Michael addition, both the cis- and trans-configuration.

<table>
<thead>
<tr>
<th>Entry</th>
<th>PG</th>
<th>Solvent</th>
<th>Base</th>
<th>Temperature</th>
<th>Time</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ac</td>
<td>MeOH (wet)</td>
<td>1.0 eq K₂CO₃</td>
<td>rt to 50 °C</td>
<td>10 min</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>Ac</td>
<td>MeOH (CaH₂)</td>
<td>1.0 eq K₂CO₃</td>
<td>rt to 50 °C</td>
<td>16 h</td>
<td>-</td>
</tr>
<tr>
<td>3</td>
<td>Ac</td>
<td>MeOH (dry)</td>
<td>2.5 eq K₂CO₃</td>
<td>rt to 50 °C</td>
<td>16 h</td>
<td>-</td>
</tr>
<tr>
<td>4</td>
<td>Ac</td>
<td>MeOH (dry)</td>
<td>1.0 eq K₂CO₃</td>
<td>rt to 50 °C</td>
<td>40 min</td>
<td>-</td>
</tr>
<tr>
<td>5</td>
<td>Ac</td>
<td>MeOH (dry)</td>
<td>0.2 eq K₂CO₃</td>
<td>rt to 50 °C</td>
<td>4 h</td>
<td>-</td>
</tr>
<tr>
<td>6</td>
<td>Ac</td>
<td>THF</td>
<td>0.95 eq NaOMe</td>
<td>rt</td>
<td>16 h</td>
<td>-</td>
</tr>
<tr>
<td>7</td>
<td>Bz</td>
<td>MeOH (dry)</td>
<td>1.0 eq K₂CO₃</td>
<td>rt to 50 °C</td>
<td>2 h</td>
<td>17%</td>
</tr>
<tr>
<td>8</td>
<td>Bz</td>
<td>MeOH (dry)</td>
<td>0.5 eq K₂CO₃</td>
<td>rt to 50 °C</td>
<td>50 min</td>
<td>24%</td>
</tr>
</tbody>
</table>
Diastereoselective synthesis of substituted morpholines

<table>
<thead>
<tr>
<th></th>
<th>Bz</th>
<th>MeOH (dry)</th>
<th>1.0 eq K₂CO₃</th>
<th>50 °C</th>
<th>2 h</th>
<th>26%</th>
</tr>
</thead>
<tbody>
<tr>
<td>9</td>
<td>Bz</td>
<td>MeOH (dist.)</td>
<td>0.5 eq K₂CO₃</td>
<td>50 °C</td>
<td>4.5 h</td>
<td>33%</td>
</tr>
</tbody>
</table>

The relative configuration of the cyclic amino acids 52 was determined by NMR studies after subsequent ester and lactam reduction (Scheme 3.18). The morpholine derivative 52 was therefore subjected to lithiumaluminum hydride in THF to afford the desired 2,5-disubstituted morpholine 53. ¹³C NMR data revealed a diastereoselectivity of >99%, but the configuration of the second stereocenter could not be determined. Additional COSY, NOESY and HSQC-spectroscopic experiments did not result in conclusive evidence either.

Scheme 3.18. Synthesis of 2,5-disubstituted morpholine 53.

The crystal structure on the other hand showed that the substituents on the morpholine ring were cis-configured, as depicted in Figure 3.3. The ring has adopted a chairlike conformation with the phenyl substituent in the equatorial orientation, while the methanol substituent is axially oriented.

Figure 3.3. Crystal structure of 2,5-disubstituted morpholine 53.

3.4 Diversity of substitution pattern

With the successful incorporation of a phenyl substituent, the stage was set to introduce a larger variety of substituents. Hydroxy amides 56 were synthesized from the enantiopure amino acids 54 in four consecutive steps. An initial three-step procedure, involving 1) diazotation of amino acids 54, 2) conversion into methyl esters, and 3) treatment with ammonia in methanol afforded the hydroxy amides. Finally, the alcohol was protected with a benzoyl group to yield the desired protected hydroxy amides 56 (Scheme 3.19).
Subsequently, condensation with methyl pyruvate, followed by PMB-protection afforded the didehydroamino acids 58 in low to reasonable yields.

\[
\begin{align*}
\text{H}_2\text{N} & \quad \text{H}_2\text{O} \\
\text{R} & \quad 1) \text{H}_2\text{SO}_4 / \text{H}_2\text{O}, \quad \text{NaNO}_2 \quad \text{0} \to \text{rt} \\
\text{H}_2\text{O} & \quad \text{H}_2\text{N} \\
\text{R} & \quad 2) \text{HCl/MeOH} \quad \text{70} \to \text{rt} \\
\text{NH}_2 & \quad \text{MeOH} \\
3) & \quad \text{NH}_2 \quad \text{MeOH}
\end{align*}
\]

\[54a: R = \text{Me} \quad 54b: R = \text{Pr} \quad 54c: R = \text{tBu} \quad 54d: R = \text{Bn} \]

55a: R = Me (93%)*
55b: R = Pr (28%)
55c: R = tBu (45%)
55d: R = Bn (66%)

* derived from methyl (S)-lactate

Next, deprotection of the alcohol allowed cyclization to afford the morpholine derivatives 61 (Scheme 3.20). Although the cyclization appeared to proceed well for all four derivatives, only low yields of 61 were obtained because two side reactions were observed, namely 1) the hydrolysis of the cyclic product 61 leading to acid 62 and 2) ester hydrolysis of 60, which prevents cyclization resulting in byproduct 63. The use of dry methanol did not lead to a substantial increase in product formation either. When the reaction was performed in a non-protic organic solvent, hydrolysis of the methyl ester was prevented, but also the benzoyl ester remained unreactive.

\[
\begin{align*}
\text{BzO} & \quad \text{N} \quad \text{CO}_2\text{Me} \\
\text{R} & \quad \backslash \text{K}_2\text{CO}_3 \quad \text{MeOH} \quad \text{rt to 50} \degree \text{C} \\
& \quad \text{MeOH}
\end{align*}
\]

\[58a: R = \text{Me} (37%) \quad 58b: R = \text{Pr} (75%) \quad 58c: R = \text{tBu} (20%) \quad 58d: R = \text{Bn} (68%) \]


Scheme 3.20. Synthesis of morpholine 61, carboxylic acid 62 and hydrolysed starting compound 63.
3.5 Conclusion

A small set of 2,5-disubstituted morpholines were synthesized via intramolecular conjugate addition of enantiopure β-hydroxy didehydroamino esters. Condensation of hydroxyl amides with pyruvate to the β-hydroxy didehydroamino esters and subsequent hydrolysis of the protected hydroxyl group allowed intramolecular conjugate addition to the morpholine in only three consecutive steps. While a high yield of the non-substituted morpholine was obtained, the yields drastically decreased when substituents were introduced. This might be due to basic hydrolysis of both starting material and product during the reaction.

3.6 Acknowledgements

Suzanne Vissers is kindly thankes for her contribution to this chapter.
Chapter 3

3.7 Experimental section

**General procedure A**
To a 0.1 M solution of the amide in toluene were added methyl pyruvate (2.0 equiv) and p-TsOH (0.1-1 equiv). The reaction was refluxed for 5 h under Dean Stark conditions, during which the reaction mixture was concentrated stepwise to a 0.2 M solution. The mixture was cooled to room temperature and filtrated over Al₂O₃. The residue was washed with toluene and EtOAc. The solvent was removed under reduced pressure and the residue was purified by silica gel column chromatography as indicated.

**General procedure B**
To a 0.1 M solution of the didehydroamino ester in DMF were added PMBBr (1.2 equiv) and NaH (1.25 equiv). The reaction was stirred for 30 min at room temperature, diluted with EtOAc/heptane (1:1) and quenched with H₂O. The mixture was extracted with EtOAc/heptane (1:1) and the combined organic layers were washed with H₂O (2 x 100 mL) and dried over Na₂SO₄. The solvent was removed under reduced pressure and the residue was purified by silica gel column chromatography as indicated.

**General procedure C**
To a 0.1 M solution of the didehydroamino ester in DMF were added BnBr (1.2 equiv) and NaH (1.25 equiv). The reaction was stirred for 30 min at room temperature, diluted with EtOAc/heptane (1:1) and quenched with H₂O. The mixture was extracted with EtOAc/heptane (1:1) and the combined organic layers were washed with H₂O (2 x 100 mL) and dried over Na₂SO₄. The solvent was removed under reduced pressure and the residue was purified by silica gel column chromatography as indicated.

**General procedure D**
To a 0.4 M solution of the methyl ester in MeOH was added liquid NH₃ (50% v/v). The reaction was stirred for 16 h at room temperature, after which the solvent was removed under reduced pressure. The resulting white solid was recrystallized from Et₂O.

**General procedure E**
To a 0.1 M solution of the protected didehydroamino acid in dry MeOH was added K₂CO₃ (10 mol%). The reaction was stirred for 10 min at room temperature. More K₂CO₃ (40 mol%) was added and the mixture was stirred for 40 min at 50 °C. The reaction was cooled to room temperature and stirred with Amberlite IR-120+ for 20 min. After vacuum filtration, the solvent was removed under reduced pressure and the residue was purified by silica gel column chromatography as indicated.
Diastereoselective synthesis of substituted morpholines

General procedure G
A solution of the amino acid in 2 M aqueous H$_2$SO$_4$ was cooled to 0 °C. A 0.5 M solution of NaNO$_2$ (2 equiv) in H$_2$O was added dropwise at 0 °C for 2 h and the reaction was stirred for 16 h at 0 °C. The mixture was stirred for 2 h at room temperature and brought to pH 4 with 50% aqueous NaOH. EtOAc (3 × 100 mL) was added and the mixture was stirred vigorously. The reaction was brought to pH 2 with 2 M aqueous H$_2$SO$_4$, extracted with EtOAc (3 × 100 mL) and the combined organic layers were dried over Na$_2$SO$_4$. The solvent was removed under reduced pressure.

General procedure H
A solution of the alcohol in a 1.2 M solution of hydrochloric acid in methanol was refluxed for 1 h. The reaction was cooled to room temperature and quenched with saturated aqueous NaHCO$_3$. The mixture was extracted with Et$_2$O, the organic layers were washed with H$_2$O (2 × 100 mL) and dried over Na$_2$SO$_4$. The solvent was removed under reduced pressure.

2-Benzoyloxyacetamide (38)
To a solution of 2-bromoacetamide (37, 2.00 g, 14.5 mmol) in DMF (50 mL) were added benzoic acid (3.50 g, 29.0 mmol) and DIPEA (6.29 mL, 36.3 mmol). The solution was stirred for 16 h at room temperature. The reaction was diluted with EtOAc/H$_2$O (1:1) (100 mL) and quenched with saturated aqueous NaHCO$_3$ (100 mL). The mixture was extracted with EtOAc/H$_2$O (1:1) (2 × 100 mL). The organic layer was washed with H$_2$O (2 × 100 mL), with saturated aqueous NaCl (2 × 100 mL) and dried over Na$_2$SO$_4$. The solvent was removed under reduced pressure and the residue was purified by silica gel column chromatography (EtOAc) to provide 2.56 g of acetamide 38 (99%). FTIR (ATR): 711, 1420, 1494, 1612, 1677, 1714, 3188, 3415 cm$^{-1}$. $^1$H NMR (300 MHz, CDCl$_3$): δ 8.08-7.94 (m, 2H), 7.62-7.55 (m, 1H), 7.48-7.31 (m, 2H), 5.94-6.16 (d, 2H, J = 6.1 Hz), 4.83 (s, 2H). $^{13}$C NMR (75 MHz, CDCl$_3$): δ 169.23, 164.74, 133.37, 129.35, 128.23, 62.62. HRMS (ESI) m/z calcd for C$_9$H$_9$NO$_3$Na $[M+Na]^+$: 202.04801, found: 202.04713.

2-(tert-Butyldiphenylsilyl)acetamide (41)
To a solution of ethyl glycolate (2.00 g, 19.2 mmol) in CH$_2$Cl$_2$ (100 mL) were added imidazole (1.57 g, 23.1 mmol), TBSCl (6.8 mL, 28.8 mmol) and DMAP (235 mg, 1.92 mmol). The solution was stirred for 4 h at room temperature, diluted with EtOAc/heptane (1:1) (100 mL) and quenched with H$_2$O (100 mL). The mixture was extracted with EtOAc/heptane (1:1) (2 × 100 mL), and the organic layers were washed with H$_2$O (2 × 100 mL) and dried over Na$_2$SO$_4$. The solvent was removed under reduced pressure and the residue was purified by silica gel column chromatography (EtOAc/heptane 1:1) to provide 3.50 g of acetamide 41 (53%). FTIR (ATR): 606, 839, 1111, 1689, 2923. cm$^{-1}$. $^1$H NMR (300 MHz, CDCl$_3$): δ 8.08-7.94 (m, 2H), 7.62-7.55 (m, 1H), 7.48-7.31 (m, 2H), 5.94-6.16 (d, 2H, J = 4.83 (s, 2H). $^{13}$C NMR (75 MHz, CDCl$_3$): δ 169.23, 212.10827, found: 212.10752.

2-(4-Methoxybenzoyloxy)acetamide (43)
To a solution of ethyl glycolate (1.00 g, 4.46 mmol) in MeOH (60 mL) was added liquid NH$_3$ (10 mL) and the reaction was stirred for 16 h at room temperature. The solvent was removed under reduced pressure. The resulting white solid was redissolved in Et$_2$O, the residue was filtered and the solution was removed under reduced pressure to obtain 43 in 508 mg (58%). FTIR (ATR): 814, 1029, 1097, 1247, 1631, 2937, 3192, 3390 cm$^{-1}$. $^1$H NMR (300 MHz, CDCl$_3$): δ 7.26 (d, 2H, J = 8.7 Hz), 6.90 (d, 2H, J = 8.7 Hz), 6.45 (s, 1H), 6.51 (s, 1H), 3.96 (s, 2H), 4.51 (s, 1H), 3.81 (s, 3H). $^{13}$C NMR (75 MHz, CDCl$_3$):
δ 172.04, 159.25, 129.23, 128.49, 113.55, 72.84, 68.65, 54.88. HRMS (ESI) m/z calcd for C_{10}H_{13}NO_3Na [M+Na]^+: 218.07931, found: 218.07881.

**Ethyl-2-[2-(benzoyloxy)acetylamino]acrylate (44a)**

Acetamide 38 (1.20 g, 6.7 mmol) was reacted according to the general procedure A. Instead of methyl pyruvate, ethyl pyruvate was used. Silica gel column chromatography (EtOAc/heptane 1:1) afforded 424 mg of 44a (23%). FTIR (ATR): 710, 1024, 1265, 1688, 1724, 2902, 3308 cm⁻¹. ¹H NMR (300 MHz, CDCl₃): δ 8.64 (s, 1H), 8.13–7.95 (m, 2H), 7.66–7.51 (m, 3H), 6.68 (s, 1H), 5.99 (d, 1H, J = 1.5 Hz), 4.89 (s, 2H), 4.30 (q, 2H, J = 7.1 Hz), 1.32 (t, 3H, J = 7.1 Hz). ¹³C NMR (300 MHz, CDCl₃): δ 165.26, 164.54, 163.27, 133.37, 132.95, 130.03, 129.56, 128.37, 128.04, 109.14, 62.95, 61.96, 14.66. HRMS (ESI) m/z calcd for C_{14}H_{15}NO_5Na [M+Na]^+: 300.08479, found: 300.08460.

**Ethyl-2-[2-(4-methoxybenzoyloxy)acetylamino]acrylate (44c)**

Amide 43 (436 mg, 2.23 mmol) was reacted according to the general procedure A. Instead of methyl pyruvate, ethyl pyruvate was used. Silica gel column chromatography (EtOAc/heptane 1:1) afforded 70 mg of 44c (11%). FTIR (ATR): 804, 1031, 1096, 1187, 1250, 1323, 1504, 1694, 2963, 3378 cm⁻¹. ¹H NMR (300 MHz, CDCl₃): δ 7.27 (d, 2H, 8.7 Hz), 6.87 (d, 2H, J = 8.7), 6.60 (s, 1H), 5.90 (d, 1H, J = 1.6 Hz), 4.28 (q, 2H, J = 7.1 Hz), 3.98 (s, 2H), 3.78 (s, 2H), 1.30 (t, 3H, J = 7.1 Hz). ¹³C NMR (75 MHz, CDCl₃): δ 168.93, 163.39, 159.68, 131.17, 130.03, 129.24, 112.52, 108.81, 72.45, 69.14, 61.93, 55.03, 13.81. HRMS (ESI) m/z calcd for C_{15}H_{19}NO_5 [M+Na]^+: 316.11609, found: 316.11554.

**Ethyl-2-[(4-benzoyloxy)-2-(4-methoxybenzyl)acetyl]amino]acrylate (45)**

Amide 44a (110 mg, 0.40 mmol) was reacted according to general procedure B. Silica gel column chromatography (EtOAc/heptane 1:1) afforded 115 mg of 45 (73%). FTIR (ATR): 1120, 1180, 1243, 1271, 1687, 1725, 2989 cm⁻¹. ¹H NMR (300 MHz, CDCl₃): δ 8.08–7.96 (m, 2H), 7.55–7.47 (m, 1H), 7.43–7.36 (m, 2H), 7.18 (d, 2H, J = 8.6 Hz), 6.81 (d, 2H, J = 8.6 Hz), 6.38 (s, 1H), 4.81 (s, 2H), 5.53 (s, 1H), 4.67 (s, 2H), 4.20 (q, 2H, J = 7.1 Hz), 3.77 (s, 3H), 3.74 (s, 3H), 1.26 (t, 3H, J = 7.1 Hz). ¹³C NMR (75 MHz, CDCl₃): δ 165.93, 165.64, 162.86, 158.72, 132.85, 130.06, 129.54, 128.92, 127.91, 113.49, 61.6, 61.3, 54.8, 50.2, 13.6. HRMS (ESI) m/z calcd for C_{22}H_{23}NO_6Na [M+Na]^+: 420.14231, found: 420.14271.

**Methyl-4-(4-Methoxybenzyl)-5-oxomorpholine-3-carboxylate (46)**

To a solution of 45 (28.7 mg, 0.072 mmol) in MeOH (1 mL) was added K₂CO₃ (2 mg, 0.014 mmol). The reaction was stirred for 1 h at 50 °C. The mixture was cooled to room temperature and stirred with Amberlite IR-120+ for 20 min. After vacuum filtration, the solvent was removed under reduced pressure and the residue was purified by silica gel column chromatography (EtOAc/heptane 3:1) to provide 20 mg of 46 (99%). FTIR (ATR): 1101, 1246, 1652, 2361 cm⁻¹. ¹H NMR (300 MHz, CD₂OD): δ 7.38 (d, 2H, J = 8.2 Hz), 6.89 (d, 2H, J = 8.2 Hz), 5.35 (d, 1H, 3.8 Hz), 4.21–4.14 (m, 1H), 4.02 (dd, 1H, J = 1.2, J = 2.7 Hz), 3.93 (d, 1H, J = 4.5 Hz), 3.87 (dd, 1H, J = 2.6, J = 4.4 Hz), 3.77 (s, 3H), 3.74 (s, 3H). ¹³C NMR (75 MHz, CD₂OD): δ 169.65, 167.43, 159.12, 129.27, 126.85, 113.37, 66.75, 65.78, 56.95, 53.84, 51.45. HRMS (ESI) m/z calcd for C_{19}H_{19}NO_3Na [M+Na]^+: 302.1004, found: 302.1007.
Diastereoselective synthesis of substituted morpholines

(S)-2-Hydroxy-2-phenylacetamide ((S)-48)

Compound (S)-47 (3.00 g, 18.1 mmol) was reacted according to general procedure D to give 2.44 g of (S)-48 (90%). $[\alpha]^2_D +70.7$ (c 0.02). FTIR (ATR): 700, 1062, 1643, 3259, 3407 cm$^{-1}$. $^1$H NMR (300 MHz, CD$_2$OD): $\delta$ 7.46 (d, J = 6.8 Hz, 2H), 7.32-7.24 (m, 3H), 4.98 (s, 1H). $^{13}$C NMR (75 MHz, CD$_2$OD): $\delta$ 176.73, 139.87, 127.56, 127.25, 126.08, 73.54. HRMS (ESI) m/z calcd for C$_8$H$_9$NO$_2$Na [M+Na]$^+$: 174.05310, found: 174.05202.

(R)-2-Hydroxy-2-phenylacetamide ((R)-48)

Compound (R)-47 (5.88 g, 35 mmol) was reacted according to general procedure D. (R)-48 was obtained in 5.34 g (quant). $[\alpha]^2_D -61.3$ (c 0.02). FTIR (ATR): 695, 1061, 1459, 1620, 2388, 2557, 3309 cm$^{-1}$. $^1$H NMR (300 MHz, CD$_2$OD): $\delta$ 7.45-7.38 (m, 2H), 7.32-7.24 (m, 3H), 4.99 (s, 1H). $^{13}$C NMR (75 MHz, CD$_2$OD): $\delta$ 176.73, 139.84, 127.56, 127.23, 126.13, 73.54. HRMS (ESI) m/z calcd for C$_9$H$_9$NO$_3$Na [M+Na]$^+$: 174.05310, found: 174.05212.

(S)-2-Acetoxy-2-phenylacetamide ((S)-49a)

To a solution of (S)-48 (2.44 g, 16.1 mmol) in CH$_2$Cl$_2$ (80 mL) were added pyridine (20 mL) and Ac$_2$O (20 mL). The mixture was stirred for 16 h at room temperature. The solvents were removed under reduced pressure and the residue was dissolved in CH$_2$Cl$_2$. The reaction was quenched with saturated aqueous NaHCO$_3$ (100 mL) and extracted with CH$_2$Cl$_2$ (100 mL). The organic layer was washed with H$_2$O (2 × 100 mL) and dried over Na$_2$SO$_4$. The solvent was removed under reduced pressure and the residue was purified by silica gel column chromatography (EtOAc) to provide 2.39 g of (S)-49a (77%). $[\alpha]^2_D +31.4$ (c 0.02). FTIR (ATR): 698, 1041, 1227, 1675, 3188, 3373 cm$^{-1}$. $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 7.46-7.39 (m, 2H), 7.35-7.31 (m, 3H), 5.90 (s, 1H), 2.15 (s, 3H). $^{13}$C NMR (75 MHz, CDCl$_3$): $\delta$ 174.64, 139.86, 127.48, 127.25, 126.03, 73.5. HRMS (ESI) m/z calcd for C$_{10}$H$_{11}$NO$_3$Na [M+Na]$^+$: 216.06366, found: 216.06316.

(S)-2-Benzoyloxy-2-phenylacetamide ((S)-49b)

Compound (S)-48 (7.45 g, 49.35 mmol) was reacted according to general procedure E. (S)-49b was obtained in 9.96 g (79%). $[\alpha]^2_D +134.0$ (c 0.02). FTIR (ATR): 698, 1041, 1227, 1675, 3188, 3373 cm$^{-1}$. $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 7.99-8.10 (m, 2H), 7.63-7.37 (m, 8H), 6.34 (s, 1H), 6.20 (s, 1H), 6.02 (s, 1H). $^{13}$C NMR (75 MHz, CDCl$_3$): $\delta$ 170.33, 164.43, 134.75, 133.32, 129.45, 128.74, 128.47, 128.62, 127.07, 75.23. HRMS (ESI) m/z calcd for C$_{15}$H$_{13}$NO$_3$Na [M+Na]$^+$: 278.07931, found: 278.07905.

(R)-2-Benzoyloxy-2-phenylacetamide ((R)-49b)

Substrate (R)-48 (5.43 g, 35.4 mmol) was reacted according to general procedure E. (R)-49b was obtained in 4.1 g (45%). $[\alpha]^2_D +12.8$ (c 0.02). FTIR (ATR): 712, 110, 1270, 1683, 3188, 3347 cm$^{-1}$. $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 7.79-8.10 (m, 2H), 7.57-7.69 (m, 3H), 7.49-7.38 (m, 5H), 6.34 (s, 1H), 6.22 (s, 1H), 5.91 (s, 1H). $^{13}$C NMR (75 MHz, CDCl$_3$): $\delta$ 170.31, 164.43, 134.75, 133.32, 129.45, 134.88, 133.25, 129.44, 128.73, 128.46, 128.26, 127.05, 75.2. HRMS (ESI) m/z calcd for C$_{15}$H$_{14}$NO$_3$ [M+H]$^+$: 256.09737, found: 256.09743.
Ethyl-(S)-2-(2-acetoxy-2-phenylacetylamino)acrylate ((S)-50a)

(S)-49a (1.00 g, 5.18 mmol) was reacted according to the general procedure A. Instead of methyl pyruvate, ethyl pyruvate was used. Silica gel column chromatography (EtOAc/heptane 1:3) afforded 759 mg of (S)-50a (50%). $[\alpha]_{D}^{20} +41.3$ (c 0.02). FTIR (ATR): 810, 1035, 1243, 1521, 1695, 1722 cm$^{-1}$. $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 8.46 (s, 1H), 7.44–7.38 (m, 2H), 7.30–7.24 (m, 3H), 6.53 (s, 1H), 6.07 (s, 1H), 5.84 (d, 1H, J = 1.4 Hz), 4.22 (q, 2H, J = 7.1 Hz), 2.16 (s, 3H), 1.26 (t, 3H, J = 7.1 Hz).

$^{13}$C NMR (75 MHz, CDCl$_3$): $\delta$ 168.0, 165.9, 162.8, 134.0, 129.5, 128.4, 128.2, 128.0, 127.9, 127.2, 126.4, 126.3, 125.3, 124.3, 108.4, 74.6, 61.3, 19.9, 13.0. HRMS (ESI) m/z calcd for C$_{15}$H$_{17}$NO$_5$Na [M+Na]$^+$: 314.10044, found: 314.10101.

Ethyl-(S)-2-(2-benzoxyloxy-2-phenylacetylamino)acrylate ((S)-50b)

Compound (S)-49b (5.00 g, 19.6 mmol) was reacted according to the general procedure A. After vacuum filtration over Al$_2$O$_3$, the solvent was removed under reduced pressure. The product was recrystallized from Et$_2$O and after vacuum filtration, dehydro amino ester (S)-50b was obtained in 2.75 g (41%). $[\alpha]_{D}^{20} +87.1$ (c 0.02). FTIR (ATR): 710, 1095, 1258, 1521, 1695, 1723, 2950, 3062, 3391 cm$^{-1}$. $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 8.80 (s, 1H), 7.99–8.18 (m, 2H), 7.63–7.41 (m, 8H), 6.71 (s, 1H), 6.45 (s, 1H), 5.97 (d, 1H, J = 1.4 Hz), 3.84 (s, 3H).

$^{13}$C NMR (75 MHz, CDCl$_3$): $\delta$ 166.66, 164.25, 163.88, 134.64, 133.30, 133.07, 129.96, 129.75, 129.54, 129.47, 128.84, 128.53, 128.43, 128.32, 128.06, 127.28, 126.81, 109.34, 75.56, 52.64. HRMS (ESI) m/z calcd for C$_{19}$H$_{18}$NO$_5$ [M+H]$^+$: 340.11850, found: 340.11812.

Methyl-(R)-2-(2-benzoxyloxy-2-phenylacetylamino)acrylate ((R)-50b)

Compound (R)-49b (3.74 g, 14.8 mmol) was reacted according to the general procedure A. After vacuum filtration over Al$_2$O$_3$, the solvent was removed under reduced pressure. The solid was dried for 16 h on the freeze dryer. Heptane was added and after vacuum filtration, (R)-50b was obtained in 2.81 g (75%). $[\alpha]_{D}^{20} -9.8$ (c 0.02). FTIR (ATR): 711, 1094, 1257, 1522, 1692, 1723, 2946, 3062, 3391 cm$^{-1}$. $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 8.73 (s, 1H), 8.18–7.98 (m, 2H), 7.62–7.38 (m, 8H), 6.66 (s, 1H), 6.39 (s, 1H), 5.93 (d, 1H, J = 1.4 Hz), 3.84 (s, 3H).

$^{13}$C NMR (75 MHz, CDCl$_3$): $\delta$ 166.67, 164.24, 163.82, 134.62, 133.38, 133.07, 129.96, 129.55, 129.46, 128.83, 128.58, 128.36, 128.05, 127.24, 126.83, 109.33, 75.51, 52.64. HRMS (ESI) m/z calcd for C$_{19}$H$_{18}$NO$_5$ [M+H]$^+$: 340.11850, found: 340.11831.

Ethyl-(S)-2-[(2-acetoxy-2-phenylacetyl)(4-methoxybenzyl)amino]acrylate ((S)-51a)

Compound (S)-50a (380 mg, 1.31 mmol) was reacted according to general procedure B. Silica gel column chromatography (EtOAc/heptane 1:1) afforded 382 mg of (S)-51a (71%). $[\alpha]_{D}^{20} +158.0$ (c 0.02). FTIR (ATR): 711, 1030, 1177, 1233, 1513, 1676, 1727, 2946, 3062, 3391 cm$^{-1}$. $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 7.42–6.91 (m, 10H), 6.40 (s, 1H), 6.16 (s, 1H), 5.36 (s, 2H), 4.01 (t, 2H, J = 7.1 Hz), 3.9 (s, 3H), 2.10 (s, 3H), 1.12 (t, 1H, J = 7.1 Hz). $^{13}$C NMR (75 MHz, CDCl$_3$): $\delta$ 170.11, 167.02, 162.45, 158.61, 158.61, 143.0, 129.86, 129.86, 128.63, 128.22, 128.22, 113.37, 72.92, 61.24, 54.74, 49.76, 20.37, 13.43. HRMS (ESI) m/z calcd for C$_{23}$H$_{25}$NO$_5$Na [M+Na]$^+$: 434.15796, found: 434.15743.
Diastereoselective synthesis of substituted morpholines

Ethyl-(S)-2-[[2-benzoyloxy-2-phenylacetyl][4-methoxybenzyl]amino]acrylate ((S)-51b)

Compound (S)-50b (800 mg, 2.36 mmol) was reacted according to general procedure B. Silica gel column chromatography (EtOAc/heptane 1:3) afforded 700 mg of (S)-51b (65%). [α]D20 +69.9 (c 0.02). FTIR (ATR): 713, 1030, 1174, 1249, 1512, 1677, 1724, 2950, 2997, 3032 cm⁻¹. ¹H NMR (300 MHz, CDCl₃): δ 7.42-6.91 (m, 15H), 6.45 (s, 1H), 6.42 (s, 1H), 3.90 (s, 3H), 3.61 (br, s, 3H). ¹³C NMR (75 MHz, CDCl₃): δ 167.01, 165.53, 163.04, 158.65, 136.06, 132.87, 130.53, 129.93, 129.59, 129.06, 128.85, 128.63, 128.23, 127.87, 113.42, 73.35, 54.76, 51.97, 49.74. HRMS (ESI) m/z calcld for C₂₃H₂₃NO₄Na [M+Na]+: 482.15796, found: 482.15749.

Methyl-(R)-2-[[2-benzoyloxy-2-phenylacetyl][4-methoxybenzyl]amino]acrylate ((R)-51b)

Compound (R)-50b (200 mg, 0.59 mmol) was reacted according to general procedure B. Silica gel column chromatography (EtOAc/heptane 1:3) afforded 150 mg of (R)-51b (56%). [α]D20 +7.2 (c 0.02). FTIR (ATR): 713, 1108, 1174, 1248, 1677, 1724, 2954, 3028 cm⁻¹. ¹H NMR (300 MHz, CDCl₃): δ 7.42-6.91 (m, 15H), 6.45 (s, 1H), 6.42 (s, 1H), 3.90 (s, 3H), 3.61 (br, s, 3H). ¹³C NMR (75 MHz, CDCl₃): δ 167.04, 165.53, 163.05, 158.64, 136.07, 132.82, 130.54, 129.93, 129.55, 129.03, 128.87, 128.69, 128.23, 127.80, 113.46, 73.35, 54.74, 51.98, 49.73. HRMS (ESI) m/z calcld for C₂₃H₂₃NO₄Na [M+Na]+: 482.15796, found: 482.15675.

Methyl-(3R,6S)-4-(4-Methoxybenzyl)-5-oxo-6-phenylmorpholine-3-carboxylate ((3R,6S)-52)

Ester (S)-51b (500 mg, 1.09 mmol) was reacted according to general procedure F. Silica gel column chromatography (EtOAc/heptane 1:1) afforded 92 mg of (3R,6S)-52 (33%). [α]D20 +3.5 (c 0.02). FTIR (ATR): 605, 1246, 1512, 1661, 1749 cm⁻¹. ¹H NMR (300 MHz, CDCl₃): δ 7.42-7.47 (m, 2H), 7.37-7.27 (m, 3H), 7.20 (d, 2H, J = 8.6 Hz), 6.87 (d, 2H, J = 8.7 Hz), 5.47 (d, 1H, J = 14.7 Hz), 5.17 (s, 1H), 4.35 (d, 1H, J = 11.1 Hz), 3.96 (s, 1H), 3.83 (s, 3H), 3.81 (s, 1H), 3.80 (s, 3H), 3.75 (d, 1H, J = 14.7 Hz). ¹³C NMR (75 MHz, CDCl₃): δ 169.84, 167.25, 159.03, 136.67, 129.75, 128.24, 128.03, 127.93, 127.16, 113.83, 80.72, 65.91, 57.04, 54.84, 52.47, 48.15. HRMS (ESI) m/z calcld for C₂₀H₁₆NO₅Na [M+Na]+: 378.13174, found: 378.13092.

(3S,6S)-4-(4-Methoxybenzyl)-6-phenylmorpholin-3-yl)methanol ((3S,6S)-53)

To a solution of (3S,6S)-52 (46 mg, 0.13 mmol) in THF (2 mL) was added LiAlH₄ (25 mg, 0.65 mmol). The mixture was stirred for 16 h at 55 °C. The reaction was quenched with H₂O (33 μL, 1.3 mg/mg LiAlH₄). An aqueous NaOH solution (15% in H₂O, 33 μL, 1.3 mg/mg LiAlH₄) and H₂O (82 μL, 3.25 mg/mg LiAlH₄) were added. The mixture was stirred for 15 min. After vacuum filtration, the solvent was removed under reduced pressure and the residue was purified by silica gel column chromatography (EtOAc/heptane 1:1) to provide 23 mg of (3S,6S)-53 (57%). [α]D20 +1.5 (c 0.02). FTIR (ATR): 700, 1032, 1246, 1511, 2907, 3404 cm⁻¹. ¹H NMR (400 MHz, CDCl₃): δ 7.29-7.26 (m, 7H), 6.87 (d, 2H, J = 8.7 Hz), 4.66 (dd, 1H, J = 2.8, 10.5 Hz), 4.07-4.04 (m, 1H), 4.04-4.00 (m, 1H), 3.97 (d, 1H, J = 13.0 Hz), 3.93-3.87 (m, 1H), 3.87 (d, 1H, J = 13.0 Hz), 3.80 (s, 3H), 3.82-3.79 (m, 1H), 2.91 (dd, 1H, J = 10.6, 13.4 Hz), 2.77-2.73 (m, 1H), 2.67 (dd, 1H, J = 2.8, 13.4 Hz). ¹³C NMR (75 MHz, CDCl₃): δ 158.55, 139.72, 129.96, 129.52, 128.26, 127.93, 127.34, 125.66, 113.44, 74.77, 64.88, 57.95, 57.32, 56.24, 54.87, 52.04. HRMS (ESI) m/z calcld for C₁₉H₂₁NO₅Na [M+Na]+: 336.15756, found: 336.15659.
(S)-2-Hydroxypropionamide ((S)-55a)

Methyl (S)-(+)-lactate (5.0 mL, 52.4 mmol) was reacted according to general procedure D. The product was recrystallized from Et<sub>2</sub>O and after vacuum filtration, (S)-55a was obtained in 4.33 g (93%). [α]<sub>D</sub><sup>0</sup> = −1.6 (c 0.02). FTIR (ATR): 972, 1117, 1642, 2484, 3340 cm<sup>−1</sup>. <sup>1</sup>H NMR (300 MHz, CD<sub>2</sub>OD): δ 4.09 (q, 1H, J = 6.9 Hz), 1.34 (d, 3H, J = 6.9 Hz). 13<sup>C</sup> NMR (75 MHz, CD<sub>2</sub>OD): δ 179.25, 67.12, 19.36. HRMS (ESI) m/z calcd for C<sub>2</sub>H<sub>11</sub>NO<sub>2</sub>[M+Na]<sup>+</sup>: 90.05550, found: 90.05429.

(S)-2-Hydroxy-3-methylbutanamide ((S)-55b)

L-Valine (5.0 g, 43.0 mmol) was reacted according to general procedure G. The crude product (3.92 g, 33.2 mmol) was reacted according to general procedure H. The crude product (4.38 g, 33.2 mmol) was reacted according to general procedure D. The product was recrystallized from Et<sub>2</sub>O and after vacuum filtration, (S)-55b was obtained in 1.39 g (28% over 3 steps). [α]<sub>D</sub><sup>0</sup> = 2.2 (c 0.02). FTIR (ATR): 1022, 1661, 2964, 3331 cm<sup>−1</sup>. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 6.33 (s, 1H), 5.74 (s, 1H), 3.93 (d, 1H, J = 3.3 Hz), 2.09-2.06 (m, 1H), 0.98 (d, 3H, J = 7.0 Hz), 0.83 (d, 3H, J = 6.9 Hz). 13<sup>C</sup> NMR (75 MHz, CDCl<sub>3</sub>): δ 175.66, 75.73, 31.44, 18.65, 15.06. HRMS (ESI) m/z calcd for C<sub>6</sub>H<sub>11</sub>NO<sub>2</sub>[M+Na]<sup>+</sup>: 140.06875, found: 140.06883.

(S)-2-Hydroxy-3-methylpentanamide ((S)-55c)

L-Leucine (4.00 g, 30.5 mmol) was reacted according to general procedure G. The crude product (3.00 g, 22.7 mmol) was reacted according to general procedure H. The crude product (2.67 g, 18.3 mmol) was reacted according to general procedure D. The product was recrystallized from Et<sub>2</sub>O and after vacuum filtration, (S)-55c was obtained in 1.91 g (45% over 3 steps). [α]<sub>D</sub><sup>0</sup> = −37.6 (c 0.02). FTIR (ATR): 973, 1120, 2473, 3343 cm<sup>−1</sup>. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 4.02-3.97 (m, 1H), 1.88-1.83 (m, 1H), 1.56-1.47 (m, 2H), 0.95 (d, 3H, J = 1.3 Hz), 0.93 (d, 3H, J = 1.2 Hz). 13<sup>C</sup> NMR (75 MHz, CDCl<sub>3</sub>): δ 179.47, 69.44, 42.92, 23.77, 22.13, 19.91. HRMS (ESI) m/z calcd for C<sub>8</sub>H<sub>13</sub>NO<sub>2</sub>[M+Na]<sup>+</sup>: 154.08440, found: 154.08442.

(S)-2-Hydroxy-3-phenylpropionamide ((S)-55d)

L-Phenylalanine (10.0 g, 60.5 mmol) was reacted according to general procedure G. The crude product (9.17 g, 55.2 mmol) was reacted according to general procedure H. The product was recrystallized from Et<sub>2</sub>O and after vacuum filtration, (S)-55d was obtained in 4.33 g (72%).

(S)-2-(Benzoyloxy)propionamide ((S)-56a)

Alcohol (S)-55a (4.32 g, 48.6 mmol) was reacted according to general procedure E. After removal of the solvent under reduced pressure, the residue was purified by silica gel column chromatography (MeOH/CH<sub>3</sub>C<sub>2</sub>1:19) to provide 6.74 g of (S)-56a (72%). [α]<sub>D</sub><sup>0</sup> = +77.7 (c 0.02). FTIR (ATR): 710, 1109, 1267, 1681, 3192, 3347 cm<sup>−1</sup>. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 8.01-8.08 (m, 2H), 7.61-7.57 (m, 1H), 7.49-7.43 (m, 2H), 6.21 (s, 2H), 5.47 (q, 1H, J = 6.9 Hz), 1.61 (d, 3H, J = 6.9 Hz). 13<sup>C</sup> NMR (75 MHz, CDCl<sub>3</sub>): δ 172.9, 164.8, 133.2, 129.2, 128.8, 128.2, 127.8, 70.2, 17.2. HRMS (ESI) m/z calcd for C<sub>12</sub>H<sub>13</sub>NO<sub>2</sub>[M+Na]<sup>+</sup>: 216.06366, found: 216.06264.
Diastereoselective synthesis of substituted morpholines

(S)-2-(Benzoyloxy)-3-methylbutanamide ([S]-56b)

Alcohol ([S]-55b (1.37 g, 11.7 mmol) was reacted according to general procedure E. After removal of the solvent under reduced pressure, the residue was purified by silica gel column chromatography (EtOAc/heptane 1:1) to provide 1.54 g of (S)-56b (59%). [α]D20 +17.7 (c 0.02). FTIR (ATR): 710, 1107, 1271, 1678, 2958, 3205, 3347 cm⁻¹. 1H NMR (300 MHz, CDCl₃): δ 8.09-8.02 (m, 2H), 7.58-7.63 (m, 1H), 7.46-7.50 (m, 2H), 6.02 (s, 1H), 5.74 (s, 1H), 5.32-5.25 (m, 1H), 2.42-2.247 (m, 1H), 1.08 (dd, 6H, J = 0.8, 6.9, 13.0 Hz). 13C NMR (75 MHz, CDCl₃): δ 171.94, 165.06, 133.28, 129.33, 128.26, 77.83, 30.27, 18.53, 16.62. HRMS (ESI) m/z calcld for C₁₃H₁₄NO₃Na [M+Na]+: 244.09496, found: 244.0947.

(S)-2-(Benzoyloxy)-3-methylpentanamide ([S]-56c)

Alcohol ([S]-57c (1.88 g, 14.4 mmol) was reacted according to general procedure E. The product was recrystallized from Et₂O and after vacuum filtration, (S)-56c was obtained in 1.86 g (55%). [α]D20 +12.9 (c 0.02). FTIR (ATR): 3330, 3188, 2946, 1679, 3326 cm⁻¹. 1H NMR (300 MHz, CDCl₃): δ 8.09-8.03 (m, 2H), 7.62-7.56 (m, 1H), 7.48-7.44 (m, 2H), 6.06 (s, 1H), 5.86 (s, 1H), 5.45 (dd, 1H, J = 3.7, 9.2 Hz), 1.82-1.88 (m, 3H), 0.97 (dd, 6H, J = 4.9, 6.1 Hz). 13C NMR (75 MHz, CDCl₃): δ 172.6, 165.0, 133.2, 129.3, 128.2, 72.5, 40.3, 24.2, 22.7, 21.3. HRMS (ESI) m/z calcld for C₁₃H₁₂NO₃ [M+H]+: 236.12867, found: 236.12815.

(S)-2-(Benzoyloxy)-3-phenylpropionamide ([S]-56d)

Alcohol ([S]-55d (6.38 g, 38.6 mmol) was reacted according to general procedure E. The product was recrystallized from Et₂O and after vacuum filtration, (S)-56d was obtained in 6.86 g (66%). [α]D20 +7.4 (c 0.02). FTIR (ATR): 710, 1108, 1269, 1679, 2946, 3326 cm⁻¹. 1H NMR (300 MHz, CDCl₃): δ 7.99-7.95 (m, 2H), 7.63 (m, 1H), 7.45-7.42 (m, 2H), 7.25-7.22 (m, 5H), 5.93 (d, 2H, J = 5.5 Hz), 5.65 (dd, 1H, J = 5.2, 6.4 Hz), 3.34 (d, 1H, J = 2.1 Hz), 3.32 (d, 1H, J = 3.2 Hz). 13C NMR (75 MHz, CDCl₃): δ 171.44, 164.75, 135.36, 133.25, 129.28, 129.25, 128.29, 128.05, 126.64, 74.07, 37.21. HRMS (ESI) m/z calcld for C₁₃H₁₂NO₃ [M+H]+: 292.09357.

Methyl-(S)-2-[2-(benzoyloxy)propionylamino]acrylate ([S]-57a)

Compound ([S]-56a (3.50 g, 18.1 mmol) was reacted according to general procedure A. Silica gel column chromatography (EtOAc/heptane 1:1) afforded 413 mg of ([S]-57a (8%). [α]D20 +39.9 (c 0.02). FTIR (ATR): 712, 1110, 1265, 1722, 2946, 3399 cm⁻¹. 1H NMR (300 MHz, CDCl₃): δ 8.71 (br. s, 1H), 8.09 (m, 2H), 7.62-7.58 (m, 1H), 7.45-7.42 (m, 2H), 7.25-7.22 (m, 5H), 5.93 (d, 2H, J = 5.5 Hz), 5.65 (dd, 1H, J = 5.2, 6.4 Hz), 3.34 (d, 1H, J = 2.1 Hz), 3.32 (d, 1H, J = 3.2 Hz). 13C NMR (75 MHz, CDCl₃): δ 170.74, 168.63, 165.42, 164.46, 163.77, 133.28, 132.84, 130.04, 129.38, 129.25, 128.96, 128.62, 128.59, 128.20, 127.96, 127.79, 108.95, 70.63, 68.66, 52.54, 51.83, 17.37, 16.63. HRMS (ESI) m/z calcld for C₁₃H₁₂NO₃Na [M+Na]+: 302.08445, found: 302.08445.

Methyl-(S)-2-[2-(benzoyloxy)-3-methylbutanoyl]amino]acrylate ([S]-57b)

Compound ([S]-56b (1.00 g, 4.52 mmol) was reacted according to general procedure A. Silica gel column chromatography (EtOAc/heptane 1:1) afforded 391.0 mg of ([S]-57b (28%). [α]D20 +53.0 (c 0.02). FTIR (ATR): 608, 711, 1093, 1257, 1693, 1724, 2963, 3399 cm⁻¹. 1H NMR (300 MHz, CDCl₃): δ 8.48 (s, 1H), 8.16-8.10 (m, 2H), 7.62-7.55 (m, 1H), 7.55-7.62 (m, 2H), 6.66 (s, 1H), 5.91 (d, 1H, J = 1.5 Hz), 5.39 (d, 1H, J = 4.2 Hz), 3.78 (s, 3H), 2.42-2.48 (m, 1H), 1.04 (d, 3H, J = 6.7 Hz), 1.00 (d, 3H, J = 6.8 Hz). 13C NMR (75 MHz, CDCl₃): δ 167.84, 164.81, 163.83, 133.26,
Methyl-(S)-2-[2-(benzoyloxy)-3-phenylpropionylamino]acrylate ((S)-57d)

Compound (S)-56d (4.00 g, 14.9 mmol) was reacted according to general procedure A. Silica gel column chromatography (EtOAc/heptane 1:1) afforded 2.18 g of (S)-57d (42%). [α]D 20 +2.4 (c 0.02). FTIR (ATR): 710, 1093, 1260, 1520, 1693, 1723, 2950, 3029, 3391 cm⁻¹. 1H NMR (300 MHz, CDCl₃): δ 8.38 (s, 1H), 8.04-8.00 (m, 2H), 7.61-7.57 (m, 1H), 7.44-7.48 (m, 2H), 7.25-7.21 (m, 5H), 6.67 (s, 1H), 5.91 (d, 1H, J = 1.5 Hz), 5.70 (dd, 1H, J = 5.0, 6.6 Hz), 3.76 (s, 3H), 3.37-3.32 (m, 2H). 13C NMR (75 MHz, CDCl₃): δ 167.44, 164.45, 163.67, 135.09, 133.21, 129.83, 129.35, 129.17, 128.55, 128.23, 128.02, 126.67, 109.18, 74.33, 52.54, 37.48. HRMS (ESI) m/z calcd for C₂₀H₁₉NO₃Na [M+Na]+: 376.11609, found: 376.11550.

Methyl-(S)-2-[(2-benzyloxy)propionyl]-{(4-methoxybenzyl)amino}acrylate ((S)-58a)

Compound (S)-57a (413 mg, 1.49 mmol) was reacted according to general procedure B. Silica gel column chromatography (EtOAc/heptane 1:1) afforded 196 mg of (S)-58a (37%). [α]D 20 +129.9 (c 0.02). FTIR (ATR): 713, 803, 1110, 1246, 1512, 1674, 1721, 2954, 2997 cm⁻¹. 1H NMR (300 MHz, CDCl₃): δ 8.08-8.01 (m, 2H), 7.52-7.49 (m, 1H), 7.42-7.39 (m, 2H), 7.16 (d, 2H, J = 8.4 Hz), 6.80 (d, 2H, J = 8.6 Hz), 6.34 (s, 1H), 5.59 (s, 1H), 5.51 (t, 1H, J = 6.6 Hz), 4.30-5.08 (br, s, 2H), 3.74 (s, 3H), 3.65 (s, 3H), 1.51 (d, 3H, J = 6.7 Hz). 13C NMR (75 MHz, CDCl₃): δ 169.67, 165.25, 163.44, 158.63, 136.47, 132.82, 129.96, 129.47, 129.05, 128.54, 128.04, 127.92, 113.47, 67.35, 54.78, 52.19, 49.75, 16.44. HRMS (ESI) m/z calcd for C₂₁H₂₂O₅Na [M+Na]+: 420.14231, found: 420.14201.

Methyl-(S)-2-[(2-benzyloxy)-3-methylbutanoyl]-{(4-methoxybenzyl)amino}acrylate ((S)-58b)

Compound (S)-57b (391 mg, 1.28 mmol) was reacted according to general procedure B. Silica gel column chromatography (EtOAc/heptane 1:1) afforded 409 mg of (S)-58b (75%). [α]D 20 +93.8 (c 0.02). FTIR (ATR): 712, 807, 1111, 1173, 1248, 1513, 1674, 1723, 2959 cm⁻¹. 1H NMR (300 MHz, CDCl₃): δ 7.52-7.56 (m, 2H), 7.46-7.49 (m, 1H), 7.45-7.41 (m, 2H), 7.17 (d, 2H, J = 8.3 Hz), 6.81 (d, 2H, J = 8.5 Hz), 6.42 (s, 1H), 5.57 (s, 1H), 5.34 (d, 1H, J = 5.7 Hz), 4.36-5.02 (br, s, 2H), 3.78 (s, 3H), 3.73 (s, 3H), 2.27-2.24 (m, 1H), 1.05 (d, 3H, J = 6.7 Hz), 0.99 (d, 3H, J = 6.8 Hz). 13C NMR (75 MHz, CDCl₃): δ 168.44, 165.55, 163.67, 158.63, 136.67, 132.79, 130.06, 129.43, 128.24, 128.22, 127.97, 113.34, 74.83, 54.71, 52.23, 49.74, 29.85, 18.86, 18.66. HRMS (ESI) m/z calcd for C₂₈H₃₈O₅Na [M+Na]+: 462.19166, found: 462.19173.
Diastereoselective synthesis of substituted morpholines

Methyl-(S)-2-[(2-benzoyloxy)-3-phenylpropionyl]-(4-methoxybenzyl)amino]acrylic acid methyl ester ((S)-58d)

Compound (S)-57d (550 mg, 1.56 mmol) was reacted according to general procedure B. Silica gel column chromatography (EtOAc/heptane 1:3) afforded 500 mg of (S)-58d (68%). \([\alpha]_D^{20} +8.2 (c 0.02)\. FTIR (ATR): 712, 1111, 1174, 1249, 1513, 1678, 1723, 2950, 3028 cm\(^{-1}\). \(\delta 8.02-7.95 (m, 2H), 7.55-7.51 (m, 1H), 7.44-7.40 (m, 2H), 7.23-7.20 (m, 8H), 6.81 (d, 2H, J = 8.6 Hz), 6.31 (s, 1H), 5.60 (t, 1H, J = 6.7 Hz), 4.30-5.00 (br. s, 2H), 3.79 (s, 3H), 3.72 (s, 3H), 3.21-3.19 (m, 2H). \(13^C\) NMR (75 MHz, CDCl\(_3\)): \(\delta 168.47, 165.22, 163.54, 158.67, 136.32, 132.73, 130.90, 129.48, 129.04, 128.63, 128.09, 127.92, 127.76, 126.46, 124.88, 113.34, 54.83, 52.22, 49.86, 37.38. HRMS (ESI) m/z calcd for C\(_{28}\)H\(_{28}\)NO\(_6\) [M+H]+: 474.19166, found: 474.19210.

Methyl-(3R,6S)-4-(4-methoxybenzyl)-5-oxo-6-methylmorpholine-3-carboxylate ((3R,6S)-60a)

Compound (S)-58a (98 mg, 0.25 mmol) was reacted according to general procedure F. Silica gel column chromatography (EtOAc/heptane 1:1) afforded 6 mg of (3R,6S)-60a (8%). \([\alpha]_D^{20} -22.0 (c 0.02)\. FTIR (ATR): 610, 1242, 1317, 1638, 1763 cm\(^{-1}\). \(\delta 7.21 (d, 1H, J = 8.1 Hz), 6.90 (d, 2H, J = 8.1 Hz), 5.32 (d, 1H, J = 14.7 Hz), 4.36 (q, 1H, J = 4.3 Hz), 4.18 (d, 1H, J = 11.0 Hz), 4.18 (d, 1H, J = 11.0 Hz), 3.85 (m, 2H), 3.84 (s, 3H), 3.81 (s, 3H), 3.75 (d, 1H, J = 14.7 Hz), 1.48 (d, 2.4 Hz, 3H). \(13^C\) NMR (75 MHz, CDCl\(_3\)): \(\delta 170.25, 170.23, 169.65, 159.48, 130.02, 129.94, 114.23, 74.86, 66.15, 57.52, 55.37, 52.88, 48.34, 18.35 HRMS (ESI) m/z calcd for C\(_{15}\)H\(_{19}\)NO\(_5\)Na [M+Na]+: 326.13256, found: 326.13124.

Methyl-(3R,6S)-4-(4-Methoxybenzyl)-5-oxo-6-benzylmorpholine-3-carboxylate ((3R,6S)-60d)

Compound (S)-58d (120 mg, 0.25 mmol) was reacted according to general procedure F. Silica gel column chromatography (MeOH/CH\(_2\)Cl\(_2\) 1:5) afforded 16 mg of (3R,6S)-60d (24%). \([\alpha]_D^{20} -14.5 (c 0.02)\. FTIR (ATR): 590, 1261, 1329, 1628, 1749 cm\(^{-1}\). \(\delta 6.94-7.61 (m, 9H), 5.31 (d, 1H, J = 14.7 Hz), 5.19 (s, 1H), 4.68 (s, 1H), 4.38 (d, 1H, J = 11.1 Hz), 4.02-3.94 (m, 1H), 3.84 (s, 3H), 3.78 (s, 3H), 3.72 (d, 1H, J = 14.7 Hz). \(13^C\) NMR (300 MHz, CDCl\(_3\)): \(\delta 169.86, 167.25, 159.02, 136.66, 129.78, 128.23, 128.02, 127.97, 127.15, 113.84, 80.77, 65.93, 57.06, 54.82, 52.44, 48.15. HRMS (ESI) m/z calcd for C\(_{19}\)H\(_{29}\)NO\(_5\)Na [M+Na]+: 392.16501, found: 392.16454. [\(\alpha\)]\(_D\) = -14.5.
3.8 References

Synthesis of optically active 2-oxopiperidine carboxylates

Abstract

The piperidine ring system is one of the most common structural subunits in natural products. Moreover, piperidine alkaloids and derivatives thereof are of great interest for the pharmaceutical industry because they exhibit a wide range of biological activities. We realized that enantiopure olefinic amides may represent valuable intermediates en route to highly substituted pipecolic acids as well as more elaborate heterocycles. This chapter describes the synthesis of highly functionalized nitrogen heterocycles by condensation of substituted olefinic amides with a pyruvate. The zinc-mediated ring opening of iodolactones was the key step to provide easy access to enantiopure building blocks.

4.1 Introduction

Pipecolic acid, or 2-piperidinecarboxylic acid, is a non-proteinogenic amino acid, which is encountered in plants and fungi, but also in human physiological fluids and is thought to play an important role in the central inhibitory-aminobutyric acid system. Moreover, pipecolic acid serves as a substrate of some peptides and polyketide synthetases, resulting in the formation of secondary metabolites with interesting pharmacological activities such as the immunosuppressors rapamycin (1), immunomycin (2) and FK506 (3), or the antitumor antibiotic sandramycin (4) (Figure 4.1). It is also a precursor to numerous compounds such as synthetic peptides, local anaesthetics and potential enzyme inhibitors. As a result, stereoselective synthesis of pipecolic acids and derivatives thereof has been of interest to many chemists.

Figure 4.1. Biologically relevant pipecolic acid derivatives.
We realized that the substituted 2-oxopiperidine carboxylic acid 5 as described in Chapter 2 with different substitution patterns, may represent valuable intermediates en route to highly substituted pipecolic acids as well as more elaborate heterocycles (Figure 4.2). Because of their importance in several pharmaceutically relevant structures, we decided to focus our efforts on the synthesis of 4-substituted pipecolic acids. To underline their relevance, a 4-ethylpipecolic acid moiety has been integrated in pyrlymicin (6), which is used in the treatment of bovine metastasis caused by Gram-positive bacteria, specifically *Staphylococcus aureus* and coagulase negative species of *Staphylococcus* and *Streptococcus*. Furthermore, the 4-substituted pipecolic acids LY233053 (7) and selfotel (8) show some potential as NMDA receptor antagonists. Hydroxy-substituted derivatives on the other hand, represent valuable building blocks for more elaborate structures, e.g. clathrotropine (9), and plumerinine (10).

![Figure 4.2. Therapeutically relevant pipecolic acids and derivatives thereof.](image)

While the heterocyclic structures described in Chapter 2 are all racemic, enantiopure variants would increase the biological relevance of the building blocks. Logically, if a similar approach as in Chapter 2 would be followed, i.e. (1) condensation of unsaturated amides with pyruvate, (2) N-alkylation, and (3) cyclization by RCM, a general procedure for the synthesis of enantiopure olefinic amides would be a requisite (Scheme 4.1). Although several syntheses of olefinic amides are known in literature, synthesis of enantiopure variants has remained limited.

For the synthesis of 4-hydroxy-substituted olefinic amides, we envisaged that iodolactones 15 ($R^1 = H, OH, R^2 = OH$) would serve as suitable precursors. Such lactones are readily derived
from the corresponding alcohols (viz. 16) and are known to give a ring-opening in the presence of zinc (Boord reaction), with concomitant formation of a terminal olefin.\textsuperscript{16} Furthermore, derivatives of 14 ($R^1 = H$, $R^2 = NH_2$) might be accessible from the non-proteinogenic amino acid L-allylglycine (17), or from 1,4-addition onto furanone 18 ($R^1 = H$, $R^2 = \text{aliphatic, aromatic}$).

Scheme 4.1. Retrosynthetic approach.

4.2 Hydroxy-substituted olefinic amides

To probe the feasibility of forming hydroxy-substituted unsaturated amides, we decided to focus our attention on the ring-opening of selectively protected ribolactonic acids. Thus, iodide 19 was synthesized in two steps via a reported procedure.\textsuperscript{17} Ring-opening of the iodide went smoothly in the presence of zinc, after which the carboxylic acid 20 was isolated in 53\% yield (Scheme 4.2). Treatment with oxalyl chloride and subsequent quenching with ammonia resulted in formation of amide 21, but the isopropylidene protecting group was cleaved in the process as well. To avoid this deprotection, carboxylic acid 20 was converted into methyl ester 22 by addition of TMSCHN\textsubscript{2}. Disappointingly, again low yields were observed after silica gel purification. The volatility of ester 22, in combination with the problematic acid reactivity of the isopropylidene, led us to search for an alternative protecting group strategy.
Scheme 4.2. Ring-opening of isopropylidene protected ribolactonic acid 19.

Following the procedure of Ireland, \(^{18}\) commercially available ribolactonic acid was reacted with trityl chloride in pyridine at 70 °C to provide 23 in 56% yield together with a substantial amount of starting material. Nevertheless, protection with tert-butyl dimethylsilyl chloride in the presence of imidazole led to the formation of the protected ribolactonic acid 24 in quantitative yield (Scheme 4.3). Next, hydrogenolysis of 24 led to the formation of the primary alcohol 25. This trityl deprotection, however, appeared to be less trivial than anticipated. Acidic removal with hydrochloric acid (0.1 N) led to multiple products, while on the other hand hydrogenolysis (10% Pd/C) in methanol gave no reaction. In sharp contrast, reaction with 10% Pd/C in chloroform, resulted in 25 in a high yield of 80%. Probably, hydrolysis of the trityl group is facilitated by addition of slightly acidic chloroform. Finally, iodolactone 26 was prepared in excellent yield via iodination of the primary alcohol under standard conditions (I\(_2\), PPh\(_3\), imidazole, THF, rt).

Subjection of iodolactone 26 to the previously described zinc-mediated ring-opening protocol, led to the corresponding carboxylic acid in only 27% yield after silica gel purification. Conversion into the methyl ester prior to purification using TMSCHN$_2$, afforded the methyl ester 27 in a moderate yield of 50%, calculated over two steps. Generally, treatment of the methyl ester with an excess of ammonia should convert the ester into the amide. Much to our surprise, however, even in concentrated ammonium hydroxide the ester appeared to be unreactive towards amidation. Subjection to a solution of ammonia (7M) in methanol only led to the recovery of starting material. Gratifyingly, dissolving the methyl ester in liquid ammonia in a sealed tube for eight days at room temperature led to the corresponding amide 28 in 70% isolated yield.

**Scheme 4.4.** Synthesis of the protected olefinic amide 28.

Encouraged by the efficient synthesis of the enantiopure building block 28 via a selective olefination/ring-opening sequence, we decided to apply the same methodology to the corresponding benzylated derivative. Since O-alkylation of lactonic acids in the presence of a strong base is known to be impossible and an imidate coupling in the presence of triflic acid most probably will lead to hydrolysis of the trityl protecting group, we shifted our focus to the ring opening of functionalized 1-O-methyl riboses.

**Scheme 4.5.** Synthesis of amides 35 and 36.

Following a literature procedure,$^{19}$ the iodinated acetal 29 was synthesized in four consecutive steps starting from D-ribose. With the iodide in hand, a zinc-mediated ring-opening should provide aldehyde 31 (Scheme 4.5). Indeed, the aldehyde was formed, albeit...
that high temperatures were required for the reaction to proceed, resulting in only 12% of the aldehyde after silica gel purification. Moreover, the aldehyde rapidly decomposed upon standing at room temperature. In order to enhance the reactivity of the zinc, a catalytic amount of acetic acid was added to the reaction mixture. Although the reaction was now completed within minutes, the yield remained low. Eventually, we found that performing the reaction at room temperature in a H$_2$O/THF-mixture (1:9) increased the yield to 80%. Due to its instability, the aldehyde 31 was immediately oxidized to the more stable carboxylic acid. While the reaction conditions of both the Pinnick and the Jones oxidation were too harsh resulting in decomposition, treatment with the milder oxidant pyridinium dichromate (PDC) resulted in the desired carboxylic acid. Esterification of the acid prior to purification, using TMSCHN$_2$, afforded methyl ester 33 in 89% yield, calculated over two steps. Finally, treatment with ammonia in methanol gave amide 35 in 71% yield. In addition to the synthesis of the disubstituted amide 35, the monosubstituted amide 36 was prepared according to similar procedures (Scheme 4.5). Selective protection of the alcohols and subsequent iodination to the acetal 30 provided the precursor for ring opening. Disappointingly, treatment of 30 with zinc in the presence of a catalytic amount of acetic acid resulted in only 36% yield of 32. A plausible explanation could lie in the volatility of the aldehyde. Oxidation of the crude aldehyde to the carboxylic acid followed by esterification on the other hand yielded the carboxylic ester 34 in 63% yield starting from the iodide 30. Again, treatment of the ester with ammonia provided the amide (36) as described previously.

At this point, having successfully synthesized the hydroxy-substituted olefinic amides 35 and 36, we decided to also synthesize the 2-hydroxy-substituted amide 42 (Scheme 4.6). Although a zinc-mediated ring opening approach of iodinated 3-deoxypentose seemed logical, an additional four steps would be required for its synthesis. Alternatively, the commercially available non-proteinogenic amino acid L-allylglycine (2-amino-4-pentenoic acid, 37) was used. Diazotation in a mixture of THF and methanol (1:1) in the presence of sodium nitrite gave the diazonium salt, which was readily converted into 2-hydroxypent-4-enolic acid (38 upon) loss of nitrogen with full overall retention of stereochemistry. Due to the poor isolated yield (<10%), the crude acid was immediately converted into methyl ester 39. Since this did not improve the yield, the alcohol function was benzylated prior to purification. Formation of the dianion (2.5 equiv of sodium hydride), followed by addition of 1 equiv of benzyl bromide provided 40 in 41% isolated yield (calculated over 2 steps) and a small amount of benzyl ester 41. Although the reaction did not reach completion, additional benzyl bromide only led to an increase of 41. Because of the moderate yield of the reaction, the reaction was repeated with 2.5 equiv of benzyl bromide to give 41, followed by saponification of the benzyl ester with potassium hydroxide. The overall yield was similar,
but since the second pathway required an additional step, the first method had our preference.

Carboxylic acid 40 was successively treated with oxalyl chloride and quenched with ammonia to form amide 42 (Scheme 4.6). Much to our surprise, HPLC-measurements showed that complete racemization had occurred. This was probably caused by ketene formation from the corresponding acid chloride intermediate. To avoid the racemization, carboxylic acid 40 was converted into methyl ester 39. Next, conversion into amide 42 was successfully accomplished by treatment of the ester with ammonia.

![Scheme 4.6](image)

**Scheme 4.6.** Reagents and conditions: a) i: (COCl)$_2$, rt, 2 h, PhMe, ii: NH$_3$, rt, 16 h, MeOH (74%); b) i: TMSCHN$_2$, rt, 10 min, MeOH, ii: NH$_3$, rt, 16 h, MeOH (67%).

### 4.4 Introduction of N-substituents

Since we previously found that secondary amides and carbamates are unreactive toward condensation with ethyl pyruvate (Chapter 2), it was suggested that also protected amines could be introduced as substituents instead of hydroxy groups. This should be possible via conversion of L-allylglycine into the corresponding amide 43, followed by protection of the amine. To this end, L-allylglycine was treated with oxalyl chloride and the reaction was quenched with ammonia to afford the amino amide 43 in 67% yield. In sharp contrast with the 2-hydroxypent-4-enoic acid variants, the stereocenter remained unaffected. In a second transformation, the amine group was protected as carbamate or azide resulting in precursors 44-46 for condensation with ethyl pyruvate (Scheme 4.7).
Synthesis of optically 2-oxopiperidine carboxylate

Scheme 4.7. a) BzCl, NaHCO₃, 0 °C, H₂O; b) CbzCl, Na₂CO₃, 0 °C, acetone; c) TfN₃, Et₃N, CuSO₄, rt, CH₂Cl₂/MeOH/H₂O 3:10:3.

4.5 Introduction of allylic C-substituents

With the oxygen- and nitrogen-substituted olefinic amides successfully synthesized, we envisioned that C4-substituted pipecolic acids (aliphatic, aromatic) could also be readily prepared via the developed methodology. To this end, we explored the possibilities of 1,4-addition onto commercially available 5-hydroxymethylfuran-2-(5H)-one (47) using organocopper reagents. A bulky group on the primary alcohol would then be necessary to maximize the diastereoselectivity. Following literature precedent,²² furanone 47 was initially reacted with trityl chloride in pyridine at room temperature leading to the corresponding product in a moderate yield of 44%. Silylation with the bulky TBDPS-group on the other hand led to the protected furanone 48 in an excellent yield of 89% (Scheme 4.8).

Scheme 4.8. Reagents and conditions: a) R = Et, 'Pr: RMgBr, PhSCu, -30 °C, 10 min, THF; b) R = Ph: PhLi, Cul, TMSCI, -78 °C, 1 h, Et₂O

With the TBDPS-protected furanone 48 in hand, a first conjugate addition was performed with ethylmagnesium bromide in the presence of PhSCu (1 equiv) in THF at -78 °C. Unfortunately, this resulted in multiple products. Most likely, the transmetallation from magnesium to copper did not occur at these low temperatures. For that reason the reaction was repeated at -30 °C. Upon a dropwise addition of the furanone to the cuprate, the reaction was now completed within minutes, resulting in the formation of 49 as a single diastereoisomer in yields ranging from 43-78% yield. In addition, a branched aliphatic
analogue (50) and an aromatic substituted derivative (51) were successfully incorporated. Although 1,4-addition with phenylmagnesium bromide led to low yields, treatment of furanone 48 with phenyllithium in the presence of copper iodide and TMSCl on the other hand, resulted in a high conversion into 51. To probe the feasibility of the sequence to the required olefinic amide, lactone 49 was transformed into the ethyl-substituted olefinic amide 55 in four consecutive steps (desilylation, iodination, ring-opening, amidation) in satisfactory yields (Scheme 4.9).


4.5 Condensation and RCM of optically active amides

With the desired unsaturated amides successfully synthesized, the stage was set for the condensation to the corresponding RCM precursors. First, amide 28 was subjected to ethyl pyruvate under Dean-Stark conditions, as described in Chapter 2. TLC showed a distinct new product, but the reaction was proceeding very slowly. Most likely due to the long reaction time and the additional amount of p-toluenesulfonic acid that was added, eventually only decomposition occurred (e.g., desilylation, elimination, etc) (Table 4.1).

Gratingfyingly, condensation of the O-benzyl-protected amides 35, 36 and 42 with ethyl pyruvate afforded the corresponding dehydroamino esters 57-59. In sharp contrast, condensation of the amine substituted olefinic amides 44-46 did not lead to any product at all. The amides 44 and 45 appeared to be insoluble in toluene and benzene. Condensation in dry ethanol resulted only in recovery of starting material. The azido-protected amide 46 on the other hand decomposed upon heating. Finally, the ethyl-substituted derivative 55 was successfully condensed, providing the dehydroamino ester 63 in 57% yield. 56-63 were then N-protected prior cyclization by treatment with PMBBr in the presence of NaH.
The three hydroxy-substituted didehydroamino esters (64-66) were subjected to ring-closing metathesis conditions using 10 mol% of G2 in toluene at 80 °C. Disappointingly, disubstituted 64 appeared to be unreactive to G2 (Table 4.2). Addition of the more reactive third generation Grubbs catalysts (G6 and G7, see Section 2.5) did also not lead to any product formation either. Chelation of the allylic ether to the metal center of the catalyst could be invoked as a possible explanation for the observed lack of reactivity. However, when the reaction was performed in the presence of Ti(OiPr)₄, a known method for circumventing intramolecular chelation, only decomposition of the starting material was observed. In case of the mono-substituted dehydroamino esters (65, 66), the expected cyclic products were formed in yields of 58 and 88% respectively. This result clearly indicates that the lack of reactivity of 64 is based on steric hindrance of the bulky benzyl groups thereby preventing cis/trans rotation, rather than chelation of the allylic alcohol to the metal complex. Finally, we were pleased to find that reaction of the ethyl-substituted
didehydroamino ester 67 with the second generation Grubbs catalyst G2 in toluene at 80 °C for 2 h resulted in the formation of the cyclic dehydroamino ester 71 in a good yield of 91%.

Table 4.2. Preparation of the cyclic dehydroamino esters 68-71

<table>
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<th>R²</th>
<th>Product</th>
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<td>Et</td>
<td>H</td>
<td>71</td>
<td>91</td>
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</table>

4.6 Conclusions

This chapter shows the scope and limitations for preparing enantiopure C34- and C5-hydroxy- and alkyl-substituted cyclic dehydroamino esters via a condensation/ring-closing metathesis approach. The enantiopure olefinic amides are readily prepared, starting from either 1-O-methylriboses (or its oxidized form) or the unnatural amino acid L-allylglycine. A zinc-mediated ring opening of iodinated pentoses proved to be a useful method for the synthesis of enantiopure olefinic amides. Moreover, a diastereoselective conjugate addition onto furanoses provided enantiopure alkyl- and aryl- amides substituted at the allylic position. Unfortunately, amine-substituted derivatives prepared from L-allylglycine appeared incompatible with the condensation reaction. Finally, RCM of the enantiopure substituted dehydroamino esters proceeded smoothly, yielding the cyclic didehydroamino esters in moderate to good yield.

4.7 Acknowledgements

Peter G. W. Rensen is kindly thanked for his contribution to this chapter. Chiralix BV (Nijmegen, The Netherlands) is kindly acknowledged for providing L-allylglycine.
4.9 Experimental section

General information

For general experimental details, see section 2.7.

(4R,5R)-2,2-Dimethyl-5-vinyl-1,3-dioxolane-4-carboxylic acid (20)

To a solution of 19 (894 mg, 3 mmole) in MeOH (30 mL) Zn (981 mg, 5 equiv.) was added. The mixture was refluxed for 1 h and allowed to cool to rt. Next, it was filtered through Celite and concentrated in vacuo to afford the product 20 (275 mg, 53% yield). $R_f$ 0.04 (EtOAc).

$^1$H NMR (CDCl$_3$, 300 MHz): $\delta$ 5.48 (ddd, 1H, $J = 7.2$ Hz, $J = 10.2$ Hz, $J = 17.1$ Hz), 5.22 (d, 1H, $J = 10.2$ Hz), 4.80 (t, 1H, $J = 7.2$ Hz), 4.69 (d, 1H, $J = 7.2$ Hz), 1.61 (s, 3H), 1.40 (s, 3H). $^{13}$C NMR (CDCl$_3$, 75 MHz): $\delta$ 171.04, 132.42, 117.45, 110.06, 78.05, 76.97, 75.13, 26.53, 25.13. Data are in agreement with literature.

(4R,5R)-Methyl-2,2-dimethyl-5-vinyl-1,3-dioxolane-4-carboxylic acid (22)

To a solution of 20 (70 mg, 0.4 mmole) in MeOH/THF (2 mL, 1:1), TMS-diazomethane 2.0 M in hexane (400 $\mu$L, 2 equiv.) was added. This mixture was stirred for 2 h at rt. Next, it was diluted with EtOAc/H$_2$O (8 mL, 1:1) and the organic layer was washed with $H_2$O (3 x 4 mL) and brine (3 x 3 mL). the organic layer was dried (MgSO$_4$) and purified by column chromatography (EtOAc/heptane, 1:3) to afford 22 (3.7 mg, 5%) as a colorless oil. $R_f$ 0.37 (EtOAc/heptane, 1:3).

$^1$H NMR (CDCl$_3$, 300 MHz): $\delta$ 5.78-5.66 (m, 1H), 5.42 (ddd, 1H, $J = 1.2$ Hz, $J = 1.5$ Hz, $J = 17.1$ Hz), 5.26 (ddd, 1H, $J = 0.9$, 1.5, 10.2 Hz), 4.73 (tt, 1H, $J = 0.9$ Hz, $J = 7.2$ Hz), 4.68 (d, 1H, $J = 7.2$ Hz, 1H), 3.70 (s, 3H), 1.63 (s, 3H), 1.39 (s, 3H). $^{13}$C NMR (CDCl$_3$, 75 MHz): $\delta$ 169.45, 131.67, 118.94, 110.76, 78.33, 77.36, 51.38, 26.53, 25.13. Data are in agreement with literature.

(3R,4S,5R)-3,4-Dihydroxy-5-(trityloxymethyl)dihydrofuran-2(3H)-one (23)

Riboflactonic acid (4.61 g, 34.9 mmole) was dissolved in pyridine (100 mL). To this solution TrtCl (12.66 g, 1.3 eq.) was added and the mixture was heated at 60 °C for 1 d. The reaction was concentrated and CH$_2$Cl$_2$ (200 mL) was added. The solution was washed with brine (3 x 50 mL) and concentrated in vacuo. The crude product was filtered through MeOH (150 mL), filtered over celite, dried (Na$_2$SO$_4$) and concentrated in vacuo. The residue was purified by column chromatography (EtOAc/heptane = 1:2 $\rightarrow$ 1:1) to give 23 (8.5 g, 65% yield) as a white solid. $R_f$ 0.30 (CH$_2$Cl$_2$/MeOH, 6:1).

$^1$H NMR (CDCl$_3$, 200 MHz): $\delta$ 7.47-7.20 (m, 15H), 4.77 (dd, 1H, $J = 0.3$ Hz, 8.4 Hz), 4.42 (t, 1H, $J = 4.5$ Hz, 1H), 4.14 (dd, 1H, $J = 0.9$ Hz, $J = 8.1$ Hz), 3.56 (dd, 1H, $J = 4.5$ Hz, $J = 16.2$ Hz), 3.21 (dd, 1H, $J = 7.5$ Hz, $J = 16.2$ Hz). $^{13}$C NMR (CDCl$_3$, 75 MHz): $\delta$ 176.77, 143.74, 143.33, 142.86, 128.17, 127.93, 127.62, 126.84, 126.68, 126.12, 87.04, 84.05, 73.37, 72.04, 62.47. Data are in agreement with literature.

(3R,4S,5R)-3,4-Bis(tert-butyldimethylsilyloxy)-5-(trityloxymethyl)dihydrofuran-2(3H)-one (24)

Compound 23 (3.25 g, 8.69 mmole) and imidazole (1.2 g, 1.6 eq.) were dissolved in DMF (60 mL). This mixture was cooled to 0 °C and then TBSCI (3.2 g, 1.9 eq.) and DMAP (10 mol%) were added. The resulting mixture was allowed to warm to rt and stirred for 2 d. Next, it was diluted with EtOAc (200 mL), washed with water (3 x 50 mL), dried (Na$_2$SO$_4$) and concentrated in vacuo. The residue was purified by column chromatography (EtOAc/heptane, 1:6) to give 24 (5.37 g, >99% yield) as a yellow oil. $R_f$ 0.41 (EtOAc/heptane, 1:4). $[\alpha]_D^{20} +22.0$ (c 3.39). $^1$H NMR (CDCl$_3$, 300 MHz): $\delta$ 7.43-7.23 (m, 15H), 4.68 (d, 1H, $J = 5.1$ Hz), 4.30 (dt, 1H, $J = 0.9$, 3.3 Hz), 3.97 (dd, 1H, $J = 0.9$ Hz, $J = 5.1$ Hz), 3.61 (dd, 1H, $J = 3.9$ Hz, $J = 11.1$ Hz, 1H), 3.21 (dd, 1H, $J = 2.7$ Hz, $J = 10.8$ Hz), 0.94 (s, 9H), 0.81 (s, 9H), 0.19 (s, 3H), 0.11 (s, 3H), 0.02 (s, 3H), -0.05 (s, 3H). $^{13}$C NMR (CDCl$_3$, 75 MHz): $\delta$ 174.67, 142.63, 128.15, 127.63, 126.96, 87.17, 84.19, 71.62, 69.95, 61.87, 25.44, 25.27, 17.98, 17.65, -5.04, -5.17, -5.35, -5.64. HRMS (ESI) m/z calcd for C$_{36}$H$_{60}$O$_5$Si$_6$ (M+Na$^+$): 641.3085, found: 641.3094.
(3R,4R,5R)-3,4-Bis(tert-butyldimethylsilyloxy)-5-(hydroxymethyl)dihydrofuran-2(3H)-one (25)

Compound 24 (4.0 g, 6.62 mmole) was dissolved in CHCl₃ (50 mL). To this solution a catalytic amount of 10% Pd/C was added. H₂ was bubbled through the solution and the reaction was stirred for 2 d at rt. It was filtered through celite, dried (Na₂SO₄), concentrated in vacuo and purified using column chromatography (EtOAc/heptane, 1:5 → 1:1) to afford 25 (1.12 g, 80% yield) as a white solid. R₁. 0.15 (EtOAc/heptane, 1:5). [α]D²⁰ +36.0 (c 1.63). IR (ATR) 1778, 2846, 2884, 2923, 2958, 3235 cm⁻¹. ¹H NMR (CDCl₃, 300 MHz): δ 4.51 (d, 1H, J = 5.1 Hz), 4.35-4.29 (m, 2H), 3.95 (dd, 1H, J = 3.0 Hz, J = 5.4 Hz, J = 12.6 Hz, 1H), 3.75 (dd, 1H, J = 3.0 Hz, J = 6.6 Hz, J = 12.6 Hz), 2.49 (s, 1H, J = 6.0 Hz), 0.93 (s, 9H), 0.89 (s, 9H), 0.17 (s, 3H), 0.14 (s, 3H), 0.10 (s, 6H). ¹³C NMR (CDCl₃, 75 MHz): δ 174.87, 85.23, 70.96, 70.13, 60.76, 25.38, 25.25, 17.99, 17.73, -5.14, -5.35, -5.63. HRMS (CI) m/z calcd for C₁₇H₃₅O₅Si₃Na (M+Na)⁺: 399.1986. found: 399.1999.

(3R,4R,5S)-3,4-Bis(tert-butyldimethylsilyloxy)-5-(iodomethyl)dihydrofuran-2(3H)-one (26)

Compound 25 (3.2 g, 8.5 mmole) and PPh₃ (2.71 g, 1.2 eq.) were dissolved in THF (75 mL). The solution was heated to 70 °C and a solution of imidazole (963 mg, 1.5 eq.), I₂ (2.9 g, 1.2 eq.) in CH₂Cl₂ (75 mL) were added. After stirring for 3 d at rt, the mixture was diluted with CH₂Cl₂ (15 mL) washed with 10% Na₂SO₄ (15 mL) and brine (15 mL). The organic layer was dried (Na₂SO₄), concentrated in vacuo and purified using column chromatography (EtOAc/heptane = 1:5) to give 26 (1.49 g, 96% yield) as a white wax. R₁. 0.67 (EtOAc/heptane, 1:1). [α]D²⁰ -4.0 (c 0.65). IR (ATR) 512, 1783, 2854, 2928, 2954 cm⁻¹. ¹H NMR (D₂-acetone, 300 MHz): δ 4.84 (dd, 1H, J = 0.3 Hz, J = 4.8 Hz), 4.55 (dd, 1H, J = 1.2 Hz, J = 4.8 Hz), 4.48-4.43 (m, 1H), 3.59 (dd, 1H, J = 7.8 Hz, J = 10.5 Hz), 3.49 (dd, 1H, J = 6.9 Hz, J = 10.5 Hz), 0.95 (s, 9H), 0.91 (s, 9H), 0.20 (s, 3H), 0.19 (s, 3H), 0.17 (s, 3H), 0.16 (s, 3H). ¹³C NMR (CDCl₃, 75 MHz): δ 204.76, 132.93, 128.26, 83.97, 72.58, 69.74, 24.95, 1.34, -5.53, -5.87, -6.08. HRMS (CI) m/z calcd for C₁₇H₃₇O₇Si₃Na: 487.1197. found: 487.1189.

(2R,3R)-Methyl 2,3-bis(tert-butyldimethylsilyloxy)pent-4-enoate (27)

To a solution of 26 (889 mg, 1.83 mmole) in MeOH (20 mL), zinc (1.81 g, 15 equiv.) was added and this mixture was stirred for 2 h at 70 °C. Next, it was filtered through celite and concentrated in vacuo. The residue was filtered through a short plug of silica gel (EtOAc/heptanes, 1:3), concentrated in vacuo and dissolved in MeOH (30 mL). To this solution TMSCH₂N⁺ (2.0 M in hexane) (1.38 mL, 1.5 equiv.) was added and this mixture was stirred for 1 h at rt. The mixture was concentrated in vacuo and purified by column chromatography (EtOAc/heptane, 1:4) to afford 27 (342 mg, 50% yield over 2 steps) as a colorless oil. R₁. 0.71 (EtOAc/heptane, 1:5). [α]D²⁰ +2.6 (c 0.50). IR (ATR) 1749, 2848, 2930, 2958 cm⁻¹. ¹H NMR (CDCl₃, 300 MHz): δ 5.83 (dddd, 1H, J = 6.9 Hz, J = 10.2 Hz, J = 17.1 Hz, 1H), 5.24 (ddd, 1H, J = 1.2 Hz, J = 1.8 Hz, J = 7.4 Hz), 5.16 (ddd, 1H, J = 0.9 Hz, J = 1.8 Hz, J = 10.2 Hz), 4.27 (tt, 1H, J = 1.2 Hz, J = 6.6 Hz, 1H), 3.70 (s, 3H), 0.87 (s, 9H), 0.85 (s, 9H), 0.03 (s, 6H), 0.02 (s, 3H), 0.01 (s, 3H). ¹³C NMR (CDCl₃, 75 MHz): δ 171.94, 137.58, 116.66, 51.29, 35.04, 31.46, 25.28, 25.20, 22.24, 13.65, 0.56, -4.88, -5.58, -5.65. HRMS (ESI) m/z calcd for C₁₇H₃₇O₇Si₃Na: 597.2210. found: 597.2206.

(2R,3R)-2-Bis(tert-butyldimethylsilyloxy)pent-4-enoamide (28)

Compound 27 (337 mg, 0.94 mmole) was dissolved in MeOH (5 mL) and put in a sealed tube. Liquid NH₃ (20 mL) was added, the tube was sealed and the mixture was stirred at 40 °C for 8 days. The tube cooled to -78 °C, opened and allowed to warm to rt. The reaction mixture was concentrated in vacuo and purified by column chromatography (EtOAc/heptane = 1:5) to afford 28 (238 mg, 70% yield) as a colorless oil. R₁. 0.62 (EtOAc/heptane, 1:1). [α]D²⁰ +16.3 (c 0.65). IR (ATR) 1696, 2854, 2919, 2954, 3477 cm⁻¹. ¹H NMR (CDCl₃, 300 MHz): δ 7.44 (s, 1H), 5.83 (ddd, 1H, J = 6.9 Hz, J = 10.2 Hz, J = 17.1 Hz, 1H), 5.16 (ddd, 1H, J = 1.2 Hz, J = 1.8 Hz, J = 27 Hz, 1H), 5.16-5.14 (m, 1H), 4.43-4.47 (m, 1H), 4.20 (d, 1H, J = 2.4 Hz), 0.92 (s, 9H), 0.90 (s, 9H), 0.15 (s, 3H), 0.11 (s, 3H), 0.09 (s, 3H), 0.05 (s, 3H). ¹³C NMR (CDCl₃, 75 MHz): δ 173.76, 135.72, 115.72, 78.44, 76.59, 25.55, 25.44, 17.96, 17.74, -4.97, -5.25, -5.93. HRMS (ESI) m/z calcd for C₁₉H₃₅NO₃Si₃Na: 382.2212. found: 382.2210.
(2S,3S,4R,5R)-3,4-Bis(benzyloxy)-2-(iodomethyl)-5-methoxytetrahydrofuran (29)

The primary alcohol (152 mg, 0.44 mmole) and PPh₃ (140 mg, 0.52 mmole) were dissolved in THF (15 mL). This solution was heated to 70 °C and a solution of imidazole (45 mg, 0.66 mmole), I₂ (135 mg, 0.52 mmole) was added in CH₂Cl₂ (3 mL) was added. After stirring for 3 h at 70 °C the solution was diluted with CH₂Cl₂ (15 mL), washed with 10% Na₂SO₄ (15mL), H₂O (20 mL) and brine (15 mL). The organic layer was dried (Na₂SO₄), concentrated in vacuo and purified using column chromatography (EtOAc/heptane = 1:3). Rᵣ = 0.68 (EtOAc/heptane, 1:1). ¹H NMR (CDCl₃, 300 MHz): δ 7.37-7.28 (m, 10H), 4.93 (s, 1H), 4.66 (d, 2H, J = 12.0 Hz), 4.52 (d, 2H, J = 12.0 Hz), 4.59 (d, 2H, J = 11.7 Hz), 4.46 (d, 2H, J = 11.7 Hz), 4.16 (ddd, 1H, J = 5.1 Hz, J = 5.7 Hz, J = 6.6 Hz, 1H), 3.97-3.89 (m, 2H), 3.37 (s, 3H), 3.32-3.27 (m, 2H). ¹³C NMR (CDCl₃, 75 MHz): δ 137.11, 137.03, 131.75, 131.53, 128.04, 127.97, 127.57, 127.54, 127.47, 105.75, 81.27, 79.88, 79.65, 72.16, 71.89, 54.85, 8.14. Data are in agreement with literature.²⁵

Synthesis of optically 2-oxopiperidine carboxylate

(2R,3S)-2,3-Bis(benzyloxy)pent-4-enoate (31)

To a solution of 29 (1.5 g, 3.3 mmole) in THF/H₂O (9:1) (33 mL), zinc (2.14 g, 10 equiv.) was added together with acetic acid (330 µL) and this mixture was stirred for 1 h at 70 °C. Next, it was filtered over celite and concentrated in vacuo. The organic layer was filtered through celite, dried (Na₂SO₄), concentrated in vacuo and purified using column chromatography (EtOAc/heptane, 1:2) to afford 31 (830 mg, 88%) as a colorless oil. Rᵣ = 0.56 (EtOAc/heptane, 1:1). ¹H NMR (CDCl₃, 75 MHz): δ 7.31-7.22 (m, 10H), 5.88 (ddd, 1H, J = 7.6 Hz, J = 10.5 Hz, J = 17.2 Hz), 5.40-5.55 (m, 2H), 4.77 (d, 1H, J = 11.8 Hz), 4.57 (d, 1H, J = 11.8 Hz), 4.59 (d, 1H, J = 12.0 Hz), 4.44 (d, 1H, J = 12.0 Hz), 4.16 (ddd, 1H, J = 0.9 Hz, J = 4.8 Hz, J = 7.6 Hz), 3.89 (dd, 1H, J = 2.0 Hz, 1H), 3.97 (m, 2H). IR (ATR) 1112, 1747, 2360, 2941 cm⁻¹. HRMS (ESI) m/z calcd for C₂₁H₂₃NO₂S⁻Na (M+Na)⁻: 382.2212, found: 382.2210.

(2R,3S)-2,3-Bis(benzyloxy)pent-4-enoic acid (35)

Methylester 33 (1.63 g, 5.82 mmole) was dissolved in MeOH (5 mL) and put in a sealed tube. Liquid NH₂Cl (20 mL) was added, the tube was sealed and the mixture was stirred at 40 °C for 3 days. The tube was put in a -78 °C bath for 10 min, opened and allowed to warm to rt. The reaction mixture was concentrated in vacuo and purified by column chromatography (EtOAc/heptane, 1:1) to afford 35 (987 mg, 61% yield) as a colorless oil. [α]D²⁰ -7.4 (c 0.005). IR (ATR) 1112, 1747, 2360, 2941 cm⁻¹. ¹H NMR (CDCl₃, 300 MHz): δ 7.34-7.21 (m, 10H), 6.58 (br s, 1H), 5.89 (ddd, 1H, J = 7.5 Hz, J = 11.0 Hz, J = 16.6 Hz), 5.42 (br s), 5.31-5.39 (m, 2H), 4.92 (d, 1H, J = 12.0 Hz), 4.72 (d, 1H, J = 11.9 Hz), 4.63 (d, 1H, J = 12.0 Hz), 4.43 (d, 1H, J = 11.9 Hz), 4.16-4.09 (m, 1H), 4.07 (d, 1H, J = 5.9 Hz). ¹³C NMR (CDCl₃, 75 MHz): δ 170.63, 137.46, 136.69, 134.06, 127.81, 127.54, 127.38, 127.20, 127.10, 119.29, 80.28, 80.24, 72.30, 70.22, 51.46. HRMS (ESI) m/z calcld for C₁₂H₁₃NO₃SNa (M+Na)⁺: 382.2212, found: 382.2210.

(2R,3S)-3-(Benzyloxy)-2-(iodomethyl)-5-methoxytetrahydrofuran (30)

The primary alcohol (3.02 g, 6.32 mmole) and PPh₃ (1.27 g, 1.2 eq.) were dissolved in THF (75 mL). This solution was heated to 70 °C and a solution of imidazole (417 mg, 1.5 eq.), I₂ (1.22 g, 1.2 eq.) in CH₂Cl₂ (75 mL) was added. After stirring for 5 h, the mixture was cooled to room temperature and diluted with CH₂Cl₂ (15 mL), washed with 10% Na₂SO₄ (15mL), H₂O (20 mL)
and brine (15 mL). The organic layer was dried (Na$_2$SO$_4$), concentrated in vacuo and purified using column chromatography (EtOAc/heptane = 1:5) to give 28 (1.08 g, 76% yield) as a white wax. R$_f$ 0.67 (EtOAc/heptane, 1:1). IR (ATR) 1035, 1098, 1209, 1365, 1727, 2907 cm$^{-1}$. $^1$H NMR (CDCl$_3$, 400 MHz): $\delta$ 7.31-7.26 (m, 10H), 5.16 (dd, 1H, J = 2.1 Hz, J = 5.4 Hz), 5.08 (dd, 1H, J = 1.4 Hz, J = 5.6 Hz), 4.61 (d, 1H, J = 12.1 Hz), 4.57 (d, 1H, J = 11.7 Hz), 4.52 (d, 1H, J = 11.7 Hz), 4.51 (d, 1H, J = 12.1 Hz), 4.28 (ddd, 1H, J = 3.2 Hz, J = 6.2 Hz, J = 8.0 Hz), 4.18 (ddd, 1H, J = 3.1 Hz, J = 5.2 Hz, J = 6.8 Hz), 3.98 (q, 1H, J = 4.6 Hz), 3.83 (ddd, 1H, J = 3.0 Hz, J = 4.5 Hz, J = 8.1 Hz), 3.40 (s, 3H), 3.37 (s, 3H), 3.20-3.16 (m, 4H), 2.24-2.19 (m, 3H), 2.03 (ddd, 1H, J = 1.5 Hz, J = 3.0 Hz, J = 14.1 Hz).$^{13}$NMR (CDCl$_3$, 75 MHz): $\delta$ 137.36, 128.00, 105.37, 104.67, 83.70, 81.52, 81.25, 80.75, 71.46, 54.77, 39.41, 38.58, 7.57, 7.50. HRMS (ESI) m/z calcd for C$_{12}$H$_{12}$NO$_3$Na (M+Na)$^+$: 371.0120, found: 371.0103.

Methyl (S)-3-(benzoxyl)pent-4-enoate (34)

To a solution of 30 (1.17 g, 3.36 mmole) in THF/H$_2$O (9:1) (34 mL), zinc (2.18 g, 10 equiv.) was added together with acetic acid (330 £) and this mixture was stirred for 1 h at 70°C. Next, it was filtered through celite, concentrated in vacuo and purified by column chromatography (EtOAc/heptane, 1:2) to afford the aldehyde as a colorless oil. The aldehyde was immediately dissolved in DMF (20 mL), PDC (1096 g, 5 equiv.) was added and this mixture was stirred for 16 h at room temperature. Next, it was filtered over celite and concentrated in vacuo. The mixture was redissolved in MeOH. TMSCHN$_2$ was added until the solution remained yellow. The mixture was again concentrated in vacuo and purified by column chromatography (EtOAc/heptane, 1:1) to afford 34 (1.63 g, 89%) as a colorless oil. R$_f$ 0.38 (EtOAc/heptane, 1:1).

$[^{15}$C]NMR (CDCl$_3$, 75 MHz): $\delta$ 173.1, 300.3 cm$^{-1}$. IR (ATR) 1112, 1747, 2360, 2941 cm$^{-1}$. $^1$H NMR (CDCl$_3$, 400 MHz): $\delta$ 7.31-7.22 (m, 10H), 6.58 (br s, 1H), 5.89 (ddd, 1H, J = 7.5 Hz, J = 11.0 Hz, J = 16.6 Hz), 5.42 (br s, 1H), 3.55-3.29 (m, 2H), 4.92 (d, 1H, J = 12.0 Hz), 4.72 (d, 1H, J = 11.9 Hz), 4.63 (d, 1H, J = 12.0 Hz), 4.43 (d, 1H, J = 11.9 Hz), 4.14-4.07 (m, 1H), 4.07 (d, 1H, J = 5.9 Hz).

(S)-3-(Benzyloxy)pent-4-enoic acid (36)

Methylester 34 (1.63 g, 5.18 mmole) was dissolved in MeOH (5 mL) and put in a sealed tube. Liquid NH$_3$ (20 mL) was added, the tube was sealed and the mixture was stirred at 40 °C for 3 days. The tube was put in a -70 °C bath for 10 min, opened and allowed to warm to rt. The reaction mixture was concentrated in vacuo and purified by column chromatography (EtOAc) to afford 27 (987 mg, 61% yield) as a colorless oil, which was stirred in NH$_3$ for 8 days at 40 °C. The reaction was concentrated in vacuo and purified by column chromatography (CH$_2$Cl$_2$/MeOH) to give 36 (103 mg, 15% yield over 4 steps) as a colorless oil. R$_f$ 0.34 (EtOAc/heptane, 1:1). $[^{15}$C]NMR (CDCl$_3$, 400 MHz): $\delta$ 7.29-7.23 (m, 5H), 7.58 (ddd, 1H, J = 7.4 Hz, J = 10.3 Hz, J = 17.3 Hz), 5.26 (dd, 2H, J = 0.9 Hz, J = 1.7 Hz, J = 10.3 Hz, J = 18.6 Hz), 4.56 (s, 2H), 4.54 (d, 1H, J = 11.7 Hz), 4.37 (d, 2H, J = 11.7 Hz), 4.27-4.18 (m, 1H), 2.50 (dd, 1H, J = 8.4 Hz, J = 14.2 Hz), 2.35 (dd, 1H, J = 5.1 Hz, J = 14.2 Hz).$^{13}$NMR (MeOD, 75 MHz): $\delta$ 173.99, 173.83, 136.88, 127.43, 126.96, 126.70, 126.39, 126.12, 116.41, 77.00, 69.78, 41.34. HRMS (ESI) m/z calcd for C$_{15}$H$_{14}$N$_2$O$_2$Si$_2$Na (M+Na)$^+$: 382.2212, found: 382.2210.

(S)-2-(Benzyloxy)pent-4-enoic acid (40)

To a solution of L-allylglycine (200 mg, 1.72 mmole) in DMF (12 mL), NaH (179.7 mg, 2.5 equiv) was added at 0 °C. The resulting mixture was stirred at 0 °C for 15 min. Then BnBr (210 µL, 1 equiv.) was added. Next, the mixture was stirred at rt for 16 h. The mixture was quenched with H$_2$O (20 mL) and concentrated in vacuo. The resulting oil was dissolved in CH$_2$Cl$_2$ (60 mL) and the salts were filtered off. The solution was dried (Na$_2$SO$_4$) and concentrated in vacuo. The resulting oil was purified using column chromatography (EtOAc/heptane, 1:2) to give 40 (160 mg, 44% yield over 2 steps) as a colorless oil. R$_f$ 0.30 (CH$_2$Cl$_2$/MeOH, 6:1). $[^{15}$C]NMR (CDCl$_3$, 400 MHz): $\delta$ 7.35-7.22 (m, 5H), 5.93-5.79 (m, 1H), 5.12-5.02 (m, 2H), 4.61 (d, 1H, J = 11.7 Hz), 4.53 (d, 1H, J = 11.7 Hz), 3.96 (t, 1H, J = 5.4 Hz), 2.52 (t, 2H, J = 6.6 Hz).$^{13}$NMR (CDCl$_3$, 75 MHz): $\delta$ 176.0, 137.4, 133.5, 127.8, 127.4, 127.1, 116.9, 77.9, 71.4, 44.8, 36.8. HRMS (ESI) m/z calcd for C$_{14}$H$_{21}$O$_3$Na (M+Na)$^+$: 229.0852, found: 229.0841.
(S)-2-(Benzyloxypent-4-enamide (42)

To a solution of 40 (66 mg, 0.32 mmol) in THF/MeOH (3.5 mL, 1:1) was added TMS-diazomethane 2.0 M in hexane (320 µL, 2 equiv.). This mixture was stirred for 2 h at rt, when it was concentrated in vacuo. The resulting oil was purified using column chromatography (EtOAc/heptane, 1:3) to give the methyl ester (47 mg, 67% yield) as a colorless oil. Rf 0.52 (EtOAc/heptane, 1:2). [α]D20 -30.37 (c 0.19). IR (ATR) 3080, 3037, 2920, 2850, cm⁻¹. ¹H NMR (CDCl₃, 300 MHz): δ 7.35-7.69 (m, 7H), 5.89-5.75 (m, 1H), 5.15-5.07 (m, 2H), 4.58 (dd, 2H, J = 68.7, 12.0 Hz), 4.02 (t, 1H, J = 6.3 Hz). ¹³C NMR (CDCl₃, 75 MHz): δ 172.14, 136.95, 132.52, 127.56, 128.06, 127.45, 128.25, 127.45, 127.56, 117.34, 71.86, 51.48, 36.94. HRMS (ESI) m/z calcd for C₃₉H₃₆O₃Na (M+Na)⁺: 221.1189, found: 221.1178.

Then,

To a solution of the methyl ester (47 mg, 0.21 mmol) in MeOH (2 mL) a 7 M solution of NH₄Cl (1.3 g, 20 mmole) was added in MeOH (100 mL) was added followed by NaOH (50 µL). The reaction was warmed to 0 °C and NaHCO₃ (56 mg, 2 equiv) was added together with BzCl (77 µL, 2.0 equiv). The reaction was stirred for 1.5 h and then diluted with EtOAc. The organic layer was washed with brine, dried (MgSO₄) and concentrated in vacuo to afford 44 as a white solid. ¹H NMR (MeOD, 400 MHz): δ 7.27-7.20 (m, 5H), 5.85-5.78 (m, 1H), 5.10-5.02 (m, 2H), 4.61 (d, 1H, J = 12.0 Hz), 4.46 (d, 1H, J = 12.0 Hz), 3.91 (t, 1H, J = 5.9 Hz), 2.45-2.39 (m, 2H). ¹³C NMR (MeOD, 75 MHz): δ 132.72, 127.54, 127.26, 115.16, 78.46, 71.31, 36.42. HRMS (ESI) m/z calcd for C₁₃H₁₅O₃Na (M+Na)⁺: 228.1001, found: 228.0997.

(S)-9H-Fluoren-9-yl)methyl 1-amino-1-oxopent-4-en-2-ylcarbamate (44)

L-allylglycine amide (50 mg, 0.33 mmole) was dissolved in H₂O (3 mL). The reaction was cooled to 0 °C and NaHCO₃ (56 mg, 2 equiv) was added together with BzCl (77 µL, 2.0 equiv). The reaction was stirred for 1.5 h and then diluted with EtOAc. The organic layer was washed with brine, dried (MgSO₄) and concentrated in vacuo to afford 44 as a white solid. ¹H NMR (MeOD, 400 MHz): δ 7.27-7.20 (m, 5H), 5.85-5.78 (m, 1H), 5.10-5.02 (m, 2H), 4.61 (d, 1H, J = 12.0 Hz), 4.46 (d, 1H, J = 12.0 Hz), 3.91 (t, 1H, J = 5.9 Hz), 2.45-2.39 (m, 2H). ¹³C NMR (MeOD, 75 MHz): δ 174.48, 168.23, 133.06, 130.99, 127.67, 126.60, 116.74, 52.70, 35.63. Data are in agreement with literature.

(S)-Benzyl 1-amino-1-oxopent-4-en-2-ylcarbamate (45)

L-allylglycine amide (50 mg, 0.33 mmole) was dissolved in MeOH (2 mL). The reaction was cooled to 0 °C and NaHCO₃ (70 mg, 2 equiv) was added together with CbzCl (57 µL, 1.2 equiv). The reaction was stirred for 2 h and then diluted with EtOAc. The organic layer was washed with H₂O, brine, dried (MgSO₄) and concentrated in vacuo. The residue was purified by column chromatography (EtOAc/heptane, 1:1) to afford 45 (84 mg, 100% yield) as a white solid. ¹H NMR (CDCl₃, 400 MHz): δ 7.41-7.29 (m, 5H), 5.86-5.82 (m, 1H), 5.16 (d, 1H, J = 17.1 Hz), 5.08 (d, 1H, J = 9.5 Hz), 4.62 (dd, 1H, J = 5.4 Hz, J = 8.4 Hz), 2.62-2.56 (m, 2H). ¹³C NMR (CDCl₃, 75 MHz): δ 174.48, 168.23, 133.06, 130.99, 127.67, 126.60, 116.74, 52.70, 35.63. Data are in agreement with literature.

(S)-2-Azidopent-4-enamide (46)

NaN₃ (1.3 g, 20 mmole) was dissolved in CH₂Cl₂ (20 mL) and H₂O (20 mL). The mixture was cooled to 0 °C and Tf₂O (1.66 mL) was added dropwise. The reaction was stirred for 2 h at room temperature and then quenched with NaHCO₃ (40 mL). The layers were separated and teh H₂O-layer was washed with CH₂Cl₂ (20 mL). Then, L-allylglycine amide (500 mg, 3.3 mmole) was dissolved in H₂O (40 mL). CuSO₄ (50 mg) was added together with Et₃N (500 µL). MeOH (100 mL) was added followed by addition of the TfN₃-solution. The reaction was stirred for 2 h. The organic layer was evaporated and the H₂O-layer was extracted with EtOAc (2 x 100 mL). The organic layer was washed with brine, dried (MgSO₄) and concentrated in vacuo. The residue was purified by column chromatography (EtOAc) to afford 46 (337 mg, 72%) as a colorless oil. ¹H NMR (MeOD, 400 MHz): δ 7.58-7.50 (m, 1H), 5.12 (d, 1H, J = 17.1 Hz), 5.08 (d, 1H, J = 9.5 Hz), 3.89 (dd, 1H, J = 5.5 Hz, J = 7.7 Hz), 2.52-2.46 (m, 4H).
(45,55)-5-((Tert butyldiphenylsilyloxy)methyl)-4-ethylidihydrofuran-2(3H)-one (49)

To a solution of PhSCu (47 mg, 0.27 mmole) in THF (1 mL) at -40 °C was dropwise added ethyllmagensium bromide (272 µL, 3 equiv). The reaction was stirred until it changed colour. Then, 48 (96 mg, 0.272 mmole) was added dropwise and the reaction was stirred for another 10 min. The reaction was quenched with NH4Cl (3 mL) and the temperature was raised to room temperature. The solution was diluted with CH2Cl2, filtered over celite, washed with water and dried (MgSO4) concentrated in vacuo and purified by column chromatography (EtOAc/heptane, 1:1) to afford 49 (81 mg, 78%) as a colorless oil. \( \delta \) 7.68, 7.38, 4.28, 3.96, 3.80, 3.65, 3.56, 3.02, 2.76, 2.74, 2.68, 2.58, 2.01, 1.89, 1.06, 0.92, 0.91, 0.87. HRMS (ESI) m/z calcd for C27H22NO3Si: 453.1848, found: 453.1862.

(4R,5S)-5-((Tert butyldiphenylsilyloxy)methyl)-4-isopropylidihydrofuran-2(3H)-one (50)

To a solution of PhSCu (121 mg, 0.70 mmole) in THF (10 mL) at -40 °C was dropwise added isopropylmagnesium bromide (2.1 mL, 3 equiv). The reaction was stirred until it changed colour. Then, 48 (246 mg, 0.70 mmole) was added dropwise and the reaction was stirred for another 10 min. The reaction was quenched with NH4Cl (3 mL) and the temperature was raised to room temperature. The solution was diluted with CH2Cl2, filtered over celite, washed with water and dried (MgSO4) concentrated in vacuo and purified by column chromatography (EtOAc/heptane, 1:1) to afford 50 (214 mg, 77%) as a colorless oil. \( \delta \) 7.68, 7.38, 4.28, 3.96, 3.80, 3.65, 3.56, 3.02, 2.76, 2.74, 2.68, 2.58, 2.01, 1.89, 1.06, 0.92, 0.91, 0.87. HRMS (ESI) m/z calcd for C27H22NO3Si: 453.1848, found: 453.1862.

(4R,5S)-5-((Tert butyldiphenylsilyloxy)methyl)-4-isopropyldihydrofuran-2(3H)-one (51)

To a solution of PhSCu (114 mg, 0.25 mmol) in Et2O (2 mL) at -20 °C was added PhLi (0.5 mmol). After 30 min the solution was cooled to -78 °C and TMSCl (0.25 mmol) and 48 (71 mg, 0.2 mmol) in THF (2 mL) and the reaction was stirred for another 10 min. The reaction was quenched with NH4Cl (3 mL) and the temperature was raised to room temperature. The solution was diluted with CH2Cl2, filtered over celite, washed with water and dried (MgSO4) concentrated in vacuo and purified by column chromatography (EtOAc/heptane, 1:1) to afford 51 (72 mg, 67%) as a colorless oil. \( \delta \) 7.78, 7.35, 4.18, 3.89, 3.27, 3.08, 2.88, 2.58, 2.01, 1.89, 1.06, 0.92, 0.91, 0.87. HRMS (ESI) m/z calcd for C27H22NO3Si: 453.1848, found: 453.1862.

(45,55)-4-Ethyl-5-(hydroxymethyl)dihydrofuran-2(3H)-one (52)

To a solution of 49 (81 mg, 0.21 mmole) in THF (1 mL) at 0 °C was added TBAF (212 µL, 1 equiv) and this mixture was stirred for 2 h. The reaction was quenched with NH4Cl, extracted with CH2Cl2, dried (MgSO4) and concentrated in vacuo and purified by column chromatography (EtOAc/heptane, 1:1) to afford 52 (17 mg, 56%) as a colorless oil. \( \delta \) 7.88, 7.39, 4.25, 3.96, 3.80, 3.27, 2.88, 2.58, 2.01, 1.89, 1.06, 0.92, 0.91, 0.87. HRMS (ESI) m/z calcd for C17H21NO2Na (M+Na+): 167.0684, found: 167.0677.
(4S,5S)-4-Ethyl-5-(iodomethyl)dihydrofuran-2(3H)-one (53)

Compound 52 (40 mg, 0.28 mmole) and PPh₃ (88 mg, 1.2 eq.) were dissolved in THF (3 mL). This solution was heated to 70 °C and a solution of imidazole (29 mg, 1.5 eq.), I₂ (85 mg, 1.2 eq.) in CH₂Cl₂ (2 mL) was added. After stirring for 1 hour at rt, the mixture was diluted with CH₂Cl₂ (15 mL) washed with 10% Na₂S₂O₃ (15mL), H₂O (20 mL) and brine (15 mL). The organic layer was dried (Na₂SO₄), concentrated in vacuo and purified using column chromatography (EtOAc/heptane = 1:1) to give 53 (52 mg, 74% yield) as colorless oil. Rf: 0.81 (EtOAc/heptane, 3:1). [α]D²⁰ +36.9 (c 0.0035). FTIR (ATR) 916, 1707, 2924, 2962 cm⁻¹. ¹H NMR (CDCl₃, 400 MHz): δ 4.12 (dd, 1H, J = 5.2 Hz, J = 10.2 Hz), 3.36 (ddd, 1H, J = 5.1 Hz, J = 10.9 Hz, J = 24.1 Hz), 2.75 (dd, 1H, J = 11.0 Hz, J = 19.8 Hz), 2.28-2.20 (m, 1H), 1.65-1.57 (m, 1H), 1.49-1.42 (m, 1H), 0.97 (t, 3H, J = 7.4 Hz). ¹³C NMR (CDCl₃, 100 MHz): δ 174.90, 82.62, 41.87, 34.05, 26.12, 11.12, 6.54. HRMS (ESI) m/z calcd for C₁₂H₁₂NO₄ (M-H) : 127.0759, found: 127.0759.

(S)-3-Ethylpent-4-enolic acid (54)

To a solution of 53 (372 mg, 1.75 mmole) in MeOH (20 mL), zinc (307 mg, 3.0 equiv.) was added and 10 drops of acetic acid. This mixture was stirred for 2 h at room temperature. Next, it was filtered over celite and concentrated in vacuo and purified by column chromatography (EtOAc/heptane, 1:2) to afford 54 (173 mg, 1.35 mmole, 86%) as a colorless oil. Rf: 0.08 (EtOAc/heptane, 1:2). [α]D²⁰ -12.7 (c 0.01). IR (ATR) 1409, 1631, 1667, 3179, 3351 cm⁻¹. ¹H NMR (MeOD, 400 MHz): δ 5.65-5.58 (m, 1H), 5.05-4.98 (m, 1H), 2.41-2.34 (m, 1H), 1.51-1.45 (m, 1H), 1.36-1.32 (m, 1H), 0.88 (t, 3H, J = 7.4 Hz). ¹³C NMR (CDCl₃, 75 MHz): δ 177.82, 139.99, 114.90, 41.23, 38.91, 26.76, 10.89. HRMS (ESI) m/z calcd for C₁₁H₁₉NO₄ (M-H⁻) : 127.0759, found: 127.0759.

(S)-3-Ethyl-pent-4-enolic acid amide (55)

To a solution of amide 54 (173 mg, 1.37 mmole) in MeOH (4 mL) a 7 M solution of NH₃ in MeOH (3 mL) was added. The mixture was stirred for 4 d at rt, concentrated in vacuo and residue was purified by column chromatography (EtOAc/heptane, 1:1) to afford 55 (110 mg, 67% yield) as a white solid. Rf: 0.08 (EtOAc/heptane, 1:2). [α]D²⁰ -12.7 (c 0.01). IR (ATR) 1409, 1631, 1667, 3179, 3351 cm⁻¹. ¹H NMR (CDCl₃, 400 MHz): δ 5.28 (m, 2H), 5.27 (ddd, 1H, J = 0.9 Hz, J = 1.6 Hz, J = 8.1 Hz), 4.81 (d, 1H, J = 12.0 Hz), 4.74 (d, 1H, J = 11.9 Hz), 4.31 (tdd, 1H, J = 0.9 Hz, J = 2.7 Hz, J = 7.9 Hz), 2.79 (dd, 1H, J = 11.0 Hz, J = 19.8 Hz), 2.28-2.20 (m, 1H), 1.65-1.57 (m, 1H), 1.49-1.42 (m, 1H), 0.97 (t, 3H, J = 7.4 Hz). ¹³C NMR (CDCl₃, 100 MHz): δ 174.90, 82.62, 41.87, 34.05, 26.12, 11.12, 6.54. HRMS (ESI) m/z calcd for C₁₂H₁₂NO₄ (M-H⁻): 127.0759, found: 127.0759.

Ethyl 2-((2S,3S)-2,3-bis(benzyloxy)pent-4-enamido)acrylate (57)

To a solution of amide 35 (310 mg, 1.0 mmole) in PhMe (20 mL), p-TsOH (38 mg, 20 mol%) and ethyl pyruvate (739 µL, 2.0 equiv). The reaction mixture was stirred under Dean-Stark conditions applying vacuum for regulation. After 3 h the reaction was cooled to room temperature and poured over a plug of neutral Al₂O₃. The Al₂O₃ was washed two times with PhMe (25 mL). The organic layer was concentrated in vacuo to give 57 (299 mg, 0.73 mmole, 73%). Rf: 0.67 (EtOAc/heptane 1:1). [α]D²⁰ -17.1 (c 0.505). IR (ATR) 696, 1656, 3188, 3351 cm⁻¹. ¹H NMR (CDCl₃, 400 MHz): δ 9.01 (br s, 1H), 7.33-7.21 (m, 10H), 6.74 (s, 1H), 5.94 (d, 1H, J = 1.6 Hz, J = 7.5 Hz, J = 11.0 Hz, J = 16.6 Hz), 5.33-5.28 (m, 2H), 5.27 (ddd, 1H, J = 0.9 Hz, J = 1.6 Hz, J = 8.1 Hz), 4.81 (d, 1H, J = 12.0 Hz), 4.74 (d, 1H, J = 11.9 Hz), 4.44 (d, 1H, J = 11.9 Hz), 4.31 (tdd, 1H, J = 0.9 Hz, J = 2.7 Hz, J = 7.9 Hz), 4.26 (dq, 2H, J = 1.0 Hz, J = 7.1 Hz), 4.22 (d, 1H, J = 2.7Hz). ¹³C NMR (CDCl₃, 75 MHz): δ 168.16, 163.05, 137.76, 132.87, 130.37, 128.01, 127.86, 127.56, 127.04, 119.49, 108.37, 81.64, 81.52, 73.24, 70.16, 61.57, 13.62. HRMS (ESI) m/z calcd for C₂₉H₂₉NO₄Na (M+Na⁺) : 432.1787, found: 432.1773.

(S)-Ethyl-2-(3-benzoxoy)pent-4-enamido)acrylate (58)

To a solution of amide 36 (65 mg, 0.20 mmole) in PhMe (4 mL), were added p-TsOH (38 mg, 1 eq) and ethyl pyruvate (70 µL, 2.0 equiv). The reaction mixture was stirred under Dean-Stark conditions applying vacuum for regulation. After 3 h the reaction was cooled to room temperature and poured over a plug of neutral Al₂O₃. The Al₂O₃ was washed two times with PhMe (25 mL). The organic layer was concentrated in vacuo. The residue was purified...
by column chromatography (EtOAc/heptane 1:2) to give to give 58 (59 mg, 0.19 mmol, 59%). Rf 0.63 (EtOAc/heptane 1:1). [α]D20 = -12.3 (c 0.033). IR (ATR) 619, 698, 1134, 1187, 1516, 1687, 1731 cm⁻¹. ¹H NMR (CDCl₃, 400 MHz): δ 8.53 (br s, 1H), 7.40-7.31 (m, 5H), 6.58 (s, 1H), 5.89 (d, 1H, J = 1.5 Hz), 5.80 (dd, 1H, J = 7.5 Hz, J = 10.3 Hz, J = 17.3 Hz), 5.32-5.26 (m, 2H), 4.65 (d, 1H, J = 11.7 Hz), 4.47 (d, 1H, J = 11.7 Hz), 4.24 (dq, 1H, J = 1.3 Hz, J = 7.1 Hz), 2.63 (dd, 1H, J = 7.8 Hz, J = 15.0 Hz), 2.56 (dd, 1H, J = 4.1 Hz, J = 15.0 Hz), 1.30 (t, 1H, J = 7.1 Hz). ¹³C NMR (CDCl₃, 75 MHz): δ 168.77, 163.38. 137.26, 136.23, 130.88, 127.88, 127.49, 127.22, 118.01, 108.16, 70.13, 67.56, 61.54, 43.70, 13.64. HRMS (ESI) m/z calcd for C₇H₅NO₅Na (M+Na)+: 326.1368, found: 326.1362.

Ethyl 2-[[(2S,3S)-2,3-bis(benzyloxy)-N-(4-methoxybenzyl)pent-4-enamido]acrylate (64)]

To a solution of 57 (254 mg, 0.62 mmole) in dry DMF (6 mL), were added at 0 °C NaH (45 mg, 1.5 equiv) and then PMBBr (141 µL, 1.2 equiv). The reaction mixture was stirred for 1 h and then quenched with H₂O (10 mL) and extracted with a mixture of EtOAc/heptane (1:1) (3 x 10 mL). The organic layer was dried (MgSO₄) and concentrated in vacuo. To a solution of amide 57 (254 mg, 0.62 mmole) in EtOAc/heptane (2 × 10 mL), were added at 0 °C NaH (45 mg, 1.5 equiv) and then PMBBr (141 µL, 1.2 equiv). The reaction mixture was stirred for 1 h and then quenched with H₂O (10 mL) and extracted with a mixture of EtOAc/heptane (1:1) (3 x 10 mL). The organic layer was dried (MgSO₄) and concentrated in vacuo. To a solution of 57 (254 mg, 0.62 mmole) in dry DMF (2 mL), were added at 0 °C NaH (12.4 mg, 1.2 equiv) and then PMBBr (36 µL, 1.2 equiv). The reaction mixture was stirred for 1 h and then quenched with H₂O (10 mL) and extracted with a mixture of EtOAc/heptane (1:1) (3 x 10 mL). The organic layer was dried (MgSO₄) and concentrated in vacuo. To a solution of amide 57 (254 mg, 0.62 mmole) in dry DMF (2 mL), were added at 0 °C NaH (12.4 mg, 1.2 equiv) and then PMBBr (36 µL, 1.2 equiv). The reaction mixture was stirred for 1 h and then quenched with H₂O (10 mL) and extracted with a mixture of EtOAc/heptane (1:1) (3 x 10 mL). The organic layer was dried (MgSO₄) and concentrated in vacuo.
(S)-Ethyl 2-(3-ethylpent-4-enamido)acrylate (63)

To a solution of amide 55 (52 mg, 0.41 mmole) in PhMe (3 mL), p-TsOH (7.9 mg, 10 mol%) and ethyl pyruvate (90 µL, 2.0 equiv). The reaction mixture was stirred under Dean-Stark conditions applying vacuum for regulation. After 3 h the reaction was cooled to room temperature and poured over a plug of neutral Al₂O₃. The Al₂O₃ was washed two times with PhMe (25 mL). The organic layer was concentrated in vacuo to give 63 (52 mg, 0.23 mmole, 57%). R₆ 0.66 (EtOAc/heptane 1:1). [(α)D]20° +10.3 (c 0.01). IR (ATR) 1188, 1316, 1514, 1686, 2950, 3360 cm⁻¹. ¹H NMR (CDCl₃, 400 MHz): δ 7.75 (s, 1H), 6.66 (s, 1H), 5.87 (d, 1H, J = 1.4 Hz), 5.64 (ddd, 1H, J = 8.3 Hz, J = 10.3 Hz, J = 17.2 Hz), 5.10-5.02 (m, 2H), 4.79 (q, 2H, J = 7.1 Hz), 2.51-2.42 (m, 1H), 2.39 (dd, 1H, J = 5.8 Hz, J = 14.4 Hz), 2.29 (dd, 1H, J = 8.4 Hz, J = 14.4 Hz), 1.34 (t, 1H, J = 7.1 Hz), 0.89 (t, 1H, J = 7.1 Hz). ¹³C NMR (MeOD, 75 MHz): δ 170.24, 163.71, 140.16, 130.50, 115.31, 107.86, 61.70, 42.82, 41.83, 26.92, 13.63, 10.97. HRMS (ESI) m/z calcd for C₁₂H₁₇NO₃Na (M+Na)⁺: 248.1363, found: 248.1270.

(S)-2-[(2-Benzyloxypent-4-enyl)-(4-methoxybenzyl)amino]acrylic acid ethyl ester (66)

To a solution of 59 (14 mg, 0.046 mmole) in dry DMF (2 mL), were added at 0°C NaH (4.5 mg, 2.0 equiv) and then PMBBr (13.2 µL, 2.0 equiv). The reaction mixture was stirred for 1 h and then quenched with H₂O (10 mL) and extracted with a mixture of EtOAc/heptane (1:1) (3 × 10 mL). The organic layer was dried (MgSO₄) and concentrated in vacuo. The residue was purified by column chromatography (EtOAc/heptane 1:2) to give 66 (15 mg, 0.036 mmole, 78%) as a colorless oil. R₆ 0.58 (EtOAc/heptane 1:1). [(α)D]20° -13.5 (c 0.007). IR (ATR) 1169, 1241, 1501, 1666, 1734, 2940 cm⁻¹. ¹H NMR (CDCl₃, 400 MHz): δ 7.25-7.17 (m, 7H), 6.80 (d, 1H, J = 8.2 Hz), 6.21 (s, 1H), 5.12 (s, 1H), 5.10-5.01 (m, 2H), 4.2-4.18 (br s, 2H), 4.51 (d, 1H, 11.5 Hz), 4.59 (d, 1H, 11.5 Hz), 4.11-4.06 (m, 3H), 3.81 (s, 3H), 2.51-2.44 (m, 2H), 1.29 (t, 3H, J = 7.2 Hz). ¹³C NMR (CDCl₃, 75 MHz): δ 170.38, 163.17, 158.63, 137.41, 137.08, 133.37, 130.06, 128.55, 127.75, 127.44, 127.13, 127.09, 117.03, 113.32, 70.58, 61.35, 54.76, 50.07, 36.63, 29.23, 13.60. HRMS (ESI) m/z calcd for C₂₁H₂₂NO₃Na (M+Na)⁺: 446.1943, found: 326.1921.

(S)-Ethyl-2-(3-ethyl-N-(4-methoxybenzyl)pent-4-enamido)acrylate (67)

To a solution of 60 (26 mg, 0.116 mmole) in dry DMF (2 mL), were added at 0°C NaH (11.4 mg, 2.0 equiv) and then PMBBr (33.2 µL, 2.0 equiv). The reaction mixture was stirred for 1 h and then quenched with H₂O (10 mL) and extracted with a mixture of EtOAc/heptane (1:1) (3 × 10 mL). The organic layer was dried (MgSO₄) and concentrated in vacuo. The residue was purified by column chromatography (EtOAc/heptane 1:2) to give 67 (31 mg, 0.090 mmole, 77%) as a colorless oil. R₆ 0.59 (EtOAc/heptane 1:1). [(α)D]20° +5.6 (c 0.056). IR (ATR) 1177, 1248, 1512, 1724 cm⁻¹. ¹H NMR (CDCl₃, 400 MHz): δ 7.17 (d, 2H, J = 8.5 Hz), 6.81 (d, 2H, J = 8.4 Hz), 6.32 (s, 1H), 5.61-5.50 (m, 1H), 5.31 (s, 1H), 5.05-4.97 (m, 1H), 4.69 (d, 1H, J = 15.2 Hz), 4.57 (d, 1H, J = 15.2 Hz), 4.22 (q, 2H, J = 7.2 Hz), 3.78 (s, 3H), 2.56-2.48 (m, 1H), 2.21 (d, 1H, J = 7.3 Hz), 1.28 (t, 1H, J = 7.1 Hz), 0.85 (t, 1H, J = 7.4 Hz). ¹³C NMR (CDCl₃, 75 MHz): δ 172.13, 171.14, 158.49, 140.78, 138.34, 135.10, 129.90, 127.54, 114.35, 113.22, 61.34, 54.76, 49.72, 41.57, 38.57, 26.73, 13.64, 11.06 HRMS (ESI) m/z calcd for C₂₀H₂₁NO₄Na (M+Na)⁺: 368.1838, found: 368.1838.

(S)-5-Benzylxoy-1-(4-methoxybenzyl)-6-oxo-1,4,5,6-tetrahydropyridine-2-carboxylic acid ethyl ester (69)

A solution of 65 (15 mg, 0.036 mmole) in dry PhMe (2 mL) was flushed with nitrogen for 15 min after which the temperature was raised to 80 °C. At 80 °C G2 (10 mol %, 3.0 mg) was added and the reaction was stirred for 1 h. After 1 h the organic layer was concentrated in vacuo. The residue was purified by column chromatography (EtOAc/heptane 1:2) to give 69 (8.2 mg, 0.021 mmole, 58%) as a brown oil. R₆ 0.34 (EtOAc/heptane 1:1). [(α)D]20° -25.3 (c 0.02). FTIR (ATR) 1248, 1512, 1668, 1721, 2950 cm⁻¹. ¹H NMR (CDCl₃, 400 MHz): δ 7.40-7.31 (m, 5H), 7.05 (d, 2H, J = 8.1 Hz), 6.80 (d, 1H, J = 8.2 Hz), 6.21 (t, 1H, J = 2.8 Hz), 5.38 (d, 1H, J = 12.2 Hz), 4.99 (d, 1H, J = 14.7 Hz), 4.82 (d, 1H, J = 12.3 Hz), 4.67 (d, 1H, J = 14.7 Hz), 4.09 (q, 2H, J = 7.2 Hz), 4.02 (t, 1H, J = 4.4 Hz), 3.79 (s, 3H), 2.58-2.51 (m, 2H), 1.12 (t, 3H, J = 7.2 Hz). ¹³C NMR (CDCl₃, 300 MHz): δ 169.43, 161.72, 158.43, 137.16, 132.82, 128.96, 127.98, 127.76.
127.51, 127.40, 127.22, 118.016, 113.45, 113.32, 72.4, 71.92, 60.94, 54.74, 44.47, 26.64, 13.59. HRMS (ESI) m/z calcd for C_{17}H_{21}NO_{4} (M+Na)^+: 418.1630, found: 418.1607.

**(S)-4-(Benzylxoy)-1-(4-methoxybenzyl)-6-oxo-1,4,5,6-tetrahydropyridine-2-carboxylic acid ethyl ester (70)**

A solution of 66 (20 mg, 0.047 mmole) in dry PhMe (2 mL) was flushed with nitrogen for 15 min after which the temperature was raised to 80 °C. At 80 °C G2 (10 mol%, 3.0 mg) was added and the reaction was stirred for 1 h. After 1 h the organic layer was concentrated in vacuo. The residue was purified by column chromatography (EtOAc/heptane 1:2) to give 70 (8.2 mg, 0.021 mmole, 58%) as a brown oil. R_f 0.56 (EtOAc/heptane 1:1). [α]^{20}D = 25.3 (c 0.02). FTIR (ATR) 1248, 1512, 1679, 1724, 2941 cm^{-1}. 

**1H NMR (CDCl$_3$, 400 MHz):** δ 7.35-7.27 (m, 5H), 7.07 (d, 2H, J = 8.8 Hz), 6.71 (d, 2H, J = 8.8 Hz), 6.30 (d, 1H, J = 4.7 Hz), 5.30 (d, 1H, J = 15.1 Hz), 4.87 (d, 1H, J = 15.1 Hz), 4.53 (d, 2H, J = 1.4 Hz), 4.23 (dt, 1H, J = 4.8 Hz, J = 6.0 Hz), 4.15 (q, 2H, J = 7.1 Hz), 3.74 (s, 3H), 2.92 (ddd, 1H, J = 0.7 Hz, J = 5.9 Hz, J = 15.9 Hz), 2.77 (dd, 1H, J = 4.8 Hz, J = 15.9 Hz), 1.21 (t, 3H, J = 7.1 Hz). 

**13C NMR (CDCl$_3$, 75 MHz):** δ 168.62, 162.14, 158.30, 137.15, 135.11, 128.89, 127.96, 127.34, 118.51, 113.32, 69.81, 67.17, 61.19, 54.71, 44.08, 37.57, 13.56. HRMS (ESI) m/z calcd for C_{17}H_{21}NO_{4}Na (M+Na)^+: 418.1630, found: 418.1600.

**(S)-Ethyl-1-(4-methoxybenzyl)-6-oxo-1,4,5,6-tetrahydropyridine-2-carboxylic acid ethyl ester (71)**

A solution of 67 (31 mg, 0.090 mmole) in dry PhMe (2 mL) was flushed with nitrogen for 15 min after which the temperature for 1 h. After 1 h the organic layer was concentrated in vacuo. The residue was purified by column chromatography (EtOAc/heptane 1:2) to give 71 (26 mg, 0.082 mmole, 91%) as a brown oil. R_f 0.41 (EtOAc/heptane 1:1). [α]^{20}D = 16.7 (c 0.02), CDCl$_3$. FTIR (ATR) 1255, 1507, 1683, 1714, 2950 cm^{-1}. 

**1H NMR (CDCl$_3$, 400 MHz):** δ 7.07 (d, 2H, J = 8.8 Hz), 6.79 (d, 2H, J = 8.8 Hz), 6.20 (dd, 1H, J = 0.8 Hz, J = 4.1 Hz), 5.22 (d, 1H, J = 14.9 Hz), 4.19-4.12 (m, 2H), 3.77 (s, 3H), 2.61 (ddd, 1H, J = 1.0 Hz, J = 15.0 Hz, J = 14.6 Hz), 2.46-2.38 (m, 1H), 2.33 (dd, 1H, J = 10.6 Hz, J = 14.6 Hz), 1.47-1.40 (m, 2H), 1.24 (t, 3H, J = 7.1 Hz), 0.93 (t, 3H, J = 7.4 Hz). 

**13C NMR (CDCl$_3$, 75 MHz):** δ 170.00, 158.33, 128.99, 125.36, 113.35, 60.88, 54.73, 44.05, 36.27, 32.62, 25.63, 13.62, 10.71 HRMS (ESI) m/z calcd for C_{18}H_{23}NO_{3}Na (M+Na)^+: 340.1525, found: 340.1523.
4.10 References

21. L-Allylglycine was kindly provided by Chiralix BV.
A stereoselective approach to cis- and trans-3-substituted pipecolic acids

Abstract

3-Substituted pipecolic acid derivatives constitute a common structural subunit of a wide variety of naturally occurring alkaloids and drugs. As a result, we became interested in the synthesis of β-halogenated 2,3-unsaturated dihydropipecolic acids as a general building block for the introduction of substituents in the 3-position. This chapter describes the synthesis of both cis- and trans-3-substituted pipecolic acids. Two different strategies have been developed: (1) a palladium-catalyzed cross-coupling reaction of β-iodinated dihydropipecolic esters for the formation of carbon-carbon bonds and (2) an addition/elimination protocol onto β-iodinated dehydropipecolic esters for the formation of carbon-heteroatom bonds. Hydrogenation of the enamine and reduction of the amide completed the synthesis. A copper-catalyzed 1,4-addition, on the other hand, afforded the trans-substituted derivatives as single products.
5.1 Introduction

Pipecolic acid is one of the most common structural subunits in nature and is found in many natural products (see Chapter 4). The relevance of this ring system has created a continuous interest in short and efficient routes to such highly functionalized building blocks. Considering the synthetic opportunities of the cyclic 2,3-didehydroamino ester building block described in the previous chapter, we dedicated further studies to the synthesis of functionalized pipecolic acids.

A main group of interest is composed of 3-substituted pipecolic acid derivatives, which constitute the common structural subunit of a wide variety of naturally occurring alkaloids and drugs. For example, tetrazomine (1) is an antitumor antibiotic that contains the unusual amino acid cis-3-hydroxypipecolic acid (red) (Figure 5.1). 3-Hydroxypipecolic acids have become synthetically accessible in enantiopure form through asymmetric induction using chiral auxiliaries (chiral imines, enantiopure β-amino alcohols, the Williams lactone and asymmetric catalysis. Via similar asymmetric procedures alkylated, arylated and carboxylated variants have been synthesized over the past decades as well. The examples mentioned above demonstrate the versatility in synthetic pathways and their biological significance. Based on these observations, we aimed to design a novel pathway to increase the availability of pipecolic acid derivatives. Key in this approach are β-halogenated α,β-unsaturated cyclic 2,3-didehydroamino acids, which can be used as general building blocks for the synthesis of functionalized pipecolic acid derivatives via palladium-catalyzed cross-coupling reactions.

![Figure 5.1 tetrazomine.](image)

The viability of palladium-catalyzed cross-coupling reactions using vinyl halides for carbon-carbon bond formation has been widely demonstrated and has found numerous applications in organic synthesis. In particular, Scheme 5.1 shows the application of Suzuki-couplings of β-brominated didehydroamino ester 2 resulting in the Z-substituted didehydroamino esters 3 in good yields. Moreover, Sonogashira couplings of dibrominated didehydroamino
A stereoselective approach to cis- and trans-3-substituted pipecolic acids

Esters 4 have been described for the synthesis of novel amino acids. Synthesis of β-branched cyclic didehydroamino esters, leading to tetrasubstituted alkenes, on the other hand so far has remained unknown.

Scheme 5.1. Synthetic approaches to 3-(di)substituted β-branched didehydroamino esters.

This literature precedent has led us to retrosynthetically derive the targeted cis-3-substituted pipecolic acids 9 from our previously described cyclic didehydroamino esters (Scheme 5.2). The tetrasubstituted alkene 8 is an excellent precursor for the formation of the less common cis-3-substituted pipecolic acids 9. The alkene 8, in turn, is prepared through a palladium-catalyzed cross-coupling reaction of the β-halogenated cyclic didehydroamino ester 7. Finally, 7 is obtained from iodination of the cyclic didehydroamino ester 6, as has been described Chapter 2. In addition, the trans-3-substituted derivative 10 was envisaged to be prepared via a copper-mediated 1,4-addition onto the same didehydroamino ester 6.

Scheme 5.2. Retrosynthetic approach to 3-substituted pipecolic esters.
5.2 Synthesis of iodinated building block 11

En route to the desired 3-substituted piperolic acids, we initially focused our investigations on the formation of the iodinated didehydroamino ester 7, which could then serve as a key building block in palladium-catalyzed cross-coupling reactions. Initial attempts to iodinate enamide 6, involving treatment with the electrophilic reagent N-iodosuccinimide (NIS, 1 equiv) in CH₂Cl₂ provided 7 albeit in only 6% isolated yield after stirring for 16 hours, together with a substantial amount of starting material (Scheme 5.3). An additional amount of reagent did not lead to higher yields. As expected, higher temperatures increased the iodination of the enamide, but also led to electrophilic aromatic substitution on the PMB-group. Interestingly, when the reaction was performed in protic solvents to enhance the solubility of NIS, the corresponding iodohydrin derivative 11 was obtained as a 1:1 diastereomeric mixture.¹⁷

Scheme 5.3. Attempted iodination of didehydroamino ester 6.

Due to these results, we decided to introduce the iodide after removal of the PMB-protecting group. However, deprotection of 6 proved to be somewhat less trivial than expected. Oxidation with ceric ammonium nitrate (CAN) in acetonitrile led to long reaction times, while large excesses of reagents were required, resulting in multiple products. Alternatively, treatment with DDQ in H₂O/CH₂Cl₂ mixtures did not show any conversion at all. Reaction with TFA in CH₂Cl₂ (1:4) at 50 °C on the other hand went smoothly providing 12 in 79% yield (Scheme 5.4). With 12 in hand, iodination was again carried out in CH₂Cl₂ at room temperature, using 1 equiv of NIS. Although the starting material was now fully consumed within minutes, no clear product could be isolated. In the end, we were pleased to find that iodination of 6 in CH₂Cl₂ with NIS (1 equivalent) in the presence of TFA (1 equiv) afforded the desired compound 7, albeit in a moderate yield of only 44%. After extensive optimization, we found that addition of a premixed TFA/NIS solution (1:1, 1 equiv) completely suppressed the undesired electrophilic aromatic substitution, raising the yield to 78%.
Scheme 5.4. Acid-mediated iodination of didehydroamino ester 6.

The same approach was followed to prepare the iodinated isoquinolone 15 (Scheme 5.5). Interestingly, subjection of precursor 14 to the optimized conditions (CH₂Cl₂, NIS/TFA, rt) led to long reaction times, resulting in an inseparable mixture of both iodinated 15 and the undesired electrophilic substitution product 16. A plausible explanation is concealed in the poor nucleophilicity of the enamide due to the conjugation with the aromatic system. A careful and portionwise addition (3 x 0.5 equiv) of the TFA/NIS solution in order to prevent electrophilic aromatic substitution, resulted in 15 in a satisfactory yield of 79%.

Scheme 5.5. Iodination of 1-oxo-1,2-dihydroisoquinoline carboxylate derivative 14.

5.3 Palladium-catalyzed cross-coupling reactions

With the synthesis of vinyl iodide 7 completed, the stage was set for investigation of the palladium-catalyzed cross-coupling reactions. Initially, we focused our attention on Suzuki reactions of iodide 7 with boronic esters. Surprisingly, no product was obtained by treatment of 7 with phenylboronic acid pinacol ester in the presence of Pd(OAc)₂ at 55 °C. In sharp contrast, addition of the more reactive phenylboronic acid resulted in the formation of the tetrasubstituted alkene 17 in 62% yield (Scheme 5.6). In addition, vinyl iodide 7 was exposed to a 3-fluoro-substituted phenylboronic acid and a vinyl-substituted variant yielding the Suzuki products 18 and 19, respectively, in good yields.
In order to determine the scope of the cross-coupling reactions, Heck\textsuperscript{18}, Stille\textsuperscript{19} and Sonogashira\textsuperscript{20} type reactions were also performed (Scheme 5.7). For example, Stille coupling, treating vinyl iodide 7 with tri-n-butylvinylstannane in the presence of Pd(PPh\textsubscript{3})\textsubscript{4}, yielded product 20 in 74%. A Heck-type coupling reaction was also investigated. Surprisingly, several examples of Heck-coupling of acyclic didehydroamino esters with aryl iodides are known in literature,\textsuperscript{21} whereas reactions of β-halogenated didehydroamino esters with activated alkenes are virtually unexplored. Much to our satisfaction, treatment of 7 with ethyl acrylate proceeded well to give 21 in 79% yield. In sharp contrast, Sonogashira coupling with either TMS-acetylene or phenylacetylene remained unsuccessful.

**Scheme 5.6.** Suzuki couplings of vinyl iodide 7.

**Scheme 5.7.** Stille (1), Heck (2) and Sonogashira coupling (3).
5.4 Copper-catalyzed addition/elimination reactions

In addition to palladium-catalyzed cross-coupling methodology, we aimed to introduce heteroatoms via an addition/elimination approach. This method is based on nucleophilic 1,4-addition of nitrogen, oxygen or sulfur onto β-halogenated didehydroamino esters. The alkene could thereby be regained via E1cB-elimination (Scheme 5.8). A nice example in this respect has been described by Matsumoto et al. by addition of a variety of nucleophiles onto highly activated systems, e.g., substituted methyl β-bromo-α-isocyanato acrylates 25 as described in Scheme 5.8. Other examples described in literature for the addition onto less activated systems, e.g., synthesis of azabicyclic structures as well as for intramolecular cyclization preparing substituted oxazoles, imidazoles and thiazoles strengthen this concept.

Scheme 5.8. Nucleophilic addition onto halogenated didehydroamino esters and α-isocyanato acrylates.

When 7 was treated with in situ prepared sodium phenylmethoxide, no clear product could be isolated (Scheme 5.9). This result exemplifies the previously mentioned severe drawback in this carbon-oxygen bond forming process, which is the need for strong bases such as alkoxides which, in combination with the high temperatures, leads to low yields and multiple products.
Nordmann and Buchwald, as well as others, have shown that tertiary alcohols, silanols, and phenols, all lacking $\beta$-hydrogen atoms, can be efficiently coupled with aryl chlorides and bromides under mild conditions using Cu-catalysts. Thus, we explored the possibilities for Ullmann type couplings of iodinated 7. As depicted in Scheme 5.9, treatment of iodide 7 with benzyl alcohol in the presence of copper iodide (10 mol%), 1,10-phenanthroline (20 mol%) and Cs$_2$CO$_3$ at 110 °C led to the formation of 27 in 73% yield. Under similar conditions, both phenol and thiophenol were also successfully introduced to afford 28 and 29 in 77 and 49% yield, respectively (Scheme 5.10).

Scheme 5.9. Proposed mechanism for Ullmann-type reactions.

Scheme 5.10. Ullmann-type reactions of 7 with phenol and thiophenol.
A stereoselective approach to cis- and trans-3-substituted pipecolic acids

With both aromatic alcohols and also thiols successfully incorporated, different amines were screened for nucleophilic addition. Although both primary and secondary aliphatic (n-BuNH₂, BnNH₂, Et₂NH) and aromatic amines (p-anisidine) were to be unsuccessful, leading only to decomposition, primary amides and carbamates on the other hand reacted smoothly to provide the corresponding products 30 and 31, respectively, in very good yields (Scheme 5.10).

5.5 Deprotection and reduction to the 3-substituted pipecolic acids

Since the synthesized β-substituted cyclic didehydroamino esters were intended as precursors for pipecolic ester formation, asymmetric hydrogenation of the olefin was eventually envisaged (Chapter 6). At this stage, a racemic approach was pursued using palladium on carbon in combination with hydrogen. Two pathways were investigated: removal of the PMB-protecting group prior to hydrogenation and vice versa.

![Scheme 5.11. Hydrogenation of β-substituted cyclic didehydroamino ester 33.](image)

Treatment of 17 with TFA at 60 °C for 16 h resulted in the deprotected lactam 33 in 78%. Subsequent hydrogenation was then performed with 10% Pd/C in MeOH at atmospheric pressure. Much to our surprise, reduction led to an inseparable diastereomeric mixture of 34 (cis:trans = 93:7). Since catalytic hydrogenation of olefinic compounds is frequently accompanied by double bond migration, it was assumed that double bond isomerization under these conditions, followed by hydrogenation caused the mixture. In order to lowering the chance for isomerization, the reaction was carried out at higher pressure (60 bar). Interestingly, the diastereoselectivity dropped significantly (d.e. = 56%), suggesting that isomerization of the double bond prior to hydrogenation was even enhanced (Scheme 5.11). Due to these results, we decided to reverse the hydrogenation and deprotection events. While hydrogenation at atmospheric pressure did not show any conversion, hydrogenation at 40 °C and 60 bar using the H-Cube²⁸ hydrogenation reaction resulted in a quantitative conversion into 35 in a completely diastereoselective fashion. Next, the amide was
deprotected under acidic conditions. Full conversion was achieved by stirring for 16 hours in neat TFA at 70 °C, while the stereochemistry was maintained.

Scheme 5.12. Hydrogenation of β-substituted cyclic didehydroamino ester 17.

Finally, reduction of the lactam moiety should be achieved for conversion into the desired 3-substituted pipecolic acid derivatives. At first, the cyclic didehydroamino ester 6 was subjected to BH₃·THF, which only led to degradation of the starting material. Then, the same conditions were applied to the functionalized heterocycles 34 and 35. Although the deprotected heterocycle 34 was fully consumed within minutes according to TLC, multiple products were observed. Reduction of heterocycle 35 on the other hand afforded the cis-3-substituted pipecolic ester 38 in a yield of 71%.

Scheme 5.13. Reduction to β-substituted cyclic didehydroamino esters 36-38.

5.6 Conjugate addition onto α,β-unsaturated cyclic didehydroamino esters

Since with the previous approach only cis-substituted 3-pipecolic acids were accessible, copper-catalyzed 1,4-addition of organometallic reagents onto α,β-unsaturated cyclic
A stereoselective approach to cis- and trans-3-substituted piperolic acids

didehydroamino esters was adopted for the synthesis of trans-substituted 3-piperolic acids. Initially, enamide 6 was reacted with phenylmagnesium bromide in the presence of CuI at −78 °C to avoid 1,2-addition (Scheme 5.14). As a result of the low reaction rate, the temperature was slowly raised to −20 °C, yielding trans-heterocycle 39 in 62% yield in a fully diastereoselective fashion. The selectivity of this reaction can only be explained by the possibility of isomerization of the cis and trans products (see scheme 5.14). Encouraged by these results, other Grignard reagents were reacted with 6 under identical conditions to provide conjugate addition products 40 and 41 with similar yields and selectivities.


Having identified suitable conditions for successful conjugate addition reactions, we decided to take a closer look at an enantioselective version. Although several enantioselective approaches onto conjugated cyclic systems are well described in literature, addition reactions onto cyclic α,β-unsaturated didehydroamino esters are not known. A straightforward approach would involve complexation of copper with a chiral ligand, which after transmetallation with the Grignard reagent should give rise to an enantioselective addition reaction.

Table 5.1. Attempts to enantioselective organocopper addition.
Chapter 5

<table>
<thead>
<tr>
<th>Entry</th>
<th>Temperature</th>
<th>%</th>
<th>D.E.</th>
<th>Reactivity</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>0.1</td>
<td>67</td>
<td>-78 to -10</td>
<td>&gt; 99\textsuperscript{a}</td>
</tr>
<tr>
<td>3</td>
<td>1.1</td>
<td>0</td>
<td>-78 to -10</td>
<td>&gt; 99\textsuperscript{a}</td>
</tr>
<tr>
<td>4</td>
<td>0</td>
<td>76</td>
<td>-78 to -40</td>
<td>&gt; 99\textsuperscript{a}</td>
</tr>
</tbody>
</table>

\textsuperscript{a}determined by chiral HPLC

After stirring the (R,S)-JOSIPHOS (11 mol %) ligand and copper iodide (10 mol %) in dry THF, the cyclic didehydroamino ester 6 was added at -78 °C together with an excess of phenylmagnesium bromide (3 equiv, entry 2). Slowly, the temperature was then raised from -78 to 0 °C. Although the diastereoselectivity remained excellent (d.e. >99%), no enantioselectivity was observed. Surprisingly, when a stoichiometric amount of both copper iodide and the ligand were used in combination with the Grignard reagent (1 equiv, entry 3), also no reaction occurred. Moreover, in the absence of copper, 1,4-addition proceeded well at low temperatures (entry 4), which renders a chiral approach involving organocopper complexes impossible.

Although copper-catalyzed 1,4-additions of Grignard reagents are frequently employed, alternatives based on the use of other metal catalysts (Pd, Ni, Co) or organometallic reagents (R\textsubscript{2}Zn, R\textsubscript{3}Al) have been reported.\textsuperscript{31} Therefore, a coupling with a boronic acid, was briefly investigated.\textsuperscript{32} Treatment of 6 with phenylboronic acid Pd(OAc)\textsubscript{2} and (S,S)-\textsuperscript{i}Pr-DuPHOS as a ligand, however, did not form any product. A zinc-mediated coupling with Et\textsubscript{2}Zn in the presence of Cu(OTf)\textsubscript{2} and (S)-MONOPHOS also only led to the recovery of starting material.

\begin{center}
\includegraphics[width=0.8\textwidth]{scheme5_15.png}
\end{center}

\textbf{Scheme 5.15.} Enantioselective addition attempts onto cyclic didehydroamino ester 6.

### 5.7 Synthesis of 1,3,4-trisubstituted isoquinoline carboxylates

With both cis- and trans-3-substituted piperolic acids successfully synthesized, we decided to apply the same methodology to the 1-oxo-1,2-dihydroisoquinoline 3-carboxylate 15. Remarkably, a palladium-catalyzed Suzuki coupling with phenylboronic acid under the aforementioned conditions proceeded well (Scheme 5.16), while Stille and Sonogashira couplings remained unsuccessful.
A stereoselective approach to cis- and trans-3-substituted pipecolic acids

Scheme 5.16. Suzuki coupling of 1-oxo-1,2-dihydroisoquinoline carboxylate 15.

Deprotection of the 1-oxo-1,2-dihydroisoquinoline carboxylates 14 and 44 led to isomerization to 1-oxo-1,2-dihydroisoquinolines 46a and 46b as depicted in Scheme 5.17. It was suggested that addition of POCl₃ would provide the 1-halogenated derivatives 47a and 47b, giving rise to a precursor for a second Suzuki-coupling to afford 1,3,4-trisubstituted isoquinoline carboxylates. Indeed, when 46a and 46b were treated with POCl₃, chlorides 47a and 47b were obtained in good yield. Finally, subjection of the chlorides to phenylboronic acid in the presence of Pd(OAc)₂ and Na₂CO₃ led to the formation of 48a and 48b after silica gel purification in good yields of 82 and 78%, respectively.

Scheme 5.17. Further conversions of 1-oxo-1,2-dihydroisoquinoline carboxylates 14 and 44.

5.8 Conclusions

After extensive investigations, a general and more widely applicable method for the synthesis of 3-substituted 2,3-didehydropipecolic esters has been developed starting from iodinated didehydroamino esters. Where Suzuki couplings seem to be suitable for the introduction of both (substituted) aromatics and alkenes, the scope of the reaction is broadened by the introduction of terminal alkenes (Stille coupling) and activated alkenes (Heck coupling). Secondly, a variation on the Ullmann-type addition/elimination protocol serves for the introduction of a variety of heteroatoms.
With the method developed, hydrogenation of the alkene and reduction of the amide provides cis-3-substituted pipecolic ester. The trans-3-substituted pipecolic esters were produced by a copper-catalyzed 1,4-addition onto the \( \alpha,\beta \)-unsaturated didehydroamino esters followed by reduction of the lactam.
5.9 Experimental section

General information

For general experimental details, see Section 2.7

Ethyl-3-iodo-1-(4-methoxybenzyl)-6-oxo-1,4,5,6-tetrahydropyridine-2-carboxylate (7)

To a solution of 6 (50 mg, 0.173 mmol) in CH₂Cl₂ (2 mL), was added a mixture of NIS (43 mg, 1.1 equiv) and TFA (13 mL, 1.0 equiv) in CH₂Cl₂ (2 mL) dropwise. The reaction mixture was stirred at rt. After 12 h another equivalent of NIS/TFA mixture was added and the reaction was stirred for three hours. After quenching with aqueous NaHCO₃, the layers were separated. The organic layer was washed with H₂O (50 mL) and brine (50 mL), dried (Na₂SO₄), and concentrated in vacuo. The residue was purified by column chromatography (EtOAc/heptane 1:2) to give 7 (57 mg, 0.137 mmol, 78%) as a colorless oil. Rf 0.67 (EtOAc/heptane 1:1). FTIR (ATR) 1247, 1681, 1727, 2980 cm⁻¹. ¹H NMR (CDCl₃, 400 MHz): δ 7.23 (d, 2H, J = 8.8 Hz), 6.78 (d, 2H, J = 8.8 Hz), 4.82 (d, 1H, J = 14.7 Hz), 4.44 (dd, 1H, J = 4.4 Hz, J = 13.2 Hz), 4.27 (d, 1H, J = 14.7 Hz), 3.97 (dq, 1H, J = 7.1 Hz, J = 10.7 Hz), 3.77 (s, 3H), 2.84 (t, 1H, J = 7.6 Hz). ¹³C NMR (CDCl₃, 75 MHz): δ 168.46, 162.93, 158.66, 137.11, 128.57, 128.38, 113.45, 74.24, 61.67, 54.88, 46.14, 34.65, 31.78, 13.33. HRMS (ESI) m/z calcd for C₁₉H₁₈INO₂Na (M+Na)⁺: 438.0178, found: 438.0172.

Ethyl-2-ethoxy-3-iodo-1-(4-methoxybenzyl)-6-oxopiperidine-2-carboxylate (11)

To a solution of 10 (29 mg, 0.10 mmol) in MeCN/EtOH 2:1 (2 mL), was added NIS (24 mg, 1.1 equiv). The reaction mixture was stirred at 40 °C. After 2 h the reaction was concentrated.

The residue was purified by column chromatography (EtOAc/heptane 1:2) to give 11 (45 mg, 0.098 mmol, 81%) as a colorless oil. Rf 0.67 (EtOAc/heptane 1:1). FTIR (ATR) 1247, 1681, 1727, 2980 cm⁻¹. ¹H NMR (CDCl₃, 400 MHz): δ 7.23 (d, 2H, J = 8.8 Hz), 6.78 (d, 2H, J = 8.8 Hz), 4.82 (d, 1H, J = 14.7 Hz), 4.44 (dd, 1H, J = 4.4 Hz, J = 13.2 Hz), 4.27 (d, 1H, J = 14.7 Hz), 3.97 (dq, 1H, J = 7.1 Hz, J = 10.7 Hz), 3.77 (s, 3H), 3.73 (d, 1H, J = 7.1 Hz, J = 10.7 Hz), 3.72 (q, 1H, J = 7.2 Hz), 3.58 – 3.49 (m, 1H), 3.20-3.27 (m, 1H), 2.86-2.80 (m, 1H), 2.63-2.58 (m, 1H), 2.40-2.36 (m, 1H), 1.23 (t, 1H, J = 7.0 Hz), 1.16 (t, 1H, J = 7.1 Hz). ¹³C NMR (CDCl₃, 75 MHz): δ 170.7, 166.48, 158.31, 129.96, 128.49, 112.85, 91.17, 61.96, 57.05, 54.79, 44.54, 33.61, 29.38, 21.07, 14.26, 13.43. HRMS (ESI) m/z calcd for C₁₃H₁₄EtNO₂Na (M+Na)⁺: 484.0596, found: 484.0597.

Ethyl-4-iodo-2-(4-methoxy-benzyl)-1-oxo-1,2-dihydroisoquinoline-3-carboxylate (15)

To a solution of 14 (500 mg, 1.53 mmol) in CH₂Cl₂ (15 mL), was added a mixture of NIS (172 mg, 0.5 equiv) and TFA (57 µL, 0.5 equiv) in CH₂Cl₂ (2 mL) dropwise. The reaction mixture was stirred at rt. After 3 h and 6 h another 0.5 equivalent of NIS/TFA mixture was added and the reaction was stirred for another 12 h. After quenching with aqueous NaHCO₃, the layers were separated. The organic layer was washed with H₂O (50 mL) and brine (50 mL), dried (Na₂SO₄), and concentrated in vacuo. The residue was purified by column chromatography (EtOAc/heptane 1:2) to give 15 (673 mg, 1.49 mmol, 97%) as a colorless oil. Rf 0.34 (EtOAc/heptane 1:2). FTIR (ATR) 1254, 1654, 1730, 2980 cm⁻¹. ¹H NMR (CDCl₃, 400 MHz): δ 7.09 (d, 2H, J = 8.6 Hz), 6.82 (d, 2H, J = 8.7 Hz), 4.75 (s, 2H), 4.14 (q, 2H, J = 7.2 Hz), 3.78 (s, 3H), 2.84 (t, 1H, J = 7.6 Hz). ¹³C NMR (CDCl₃, 75 MHz): δ 168.44, 162.96, 158.63, 137.17, 128.54, 128.35, 113.47, 74.25, 61.63, 54.88, 46.16, 34.64, 31.78, 13.33. HRMS (ESI) m/z calcd for C₁₇H₁₂INO₂Na (M+Na)⁺: 438.0178, found: 438.0172.

Ethyl-1-(4-methoxy-benzyl)-6-oxo-3-phenyl-1,4,5,6-tetrahydro-pyridine-2-carboxylate (17)

To a solution of 7 (17.5 mg, 0.042 mmol) in EtOH (1 mL), was added a Ph(BOH)₂ (7.2 mg, 1.5 equiv), Pd(OAc)₂ (1 mg, 10 mol%) and Na₂CO₃ (8.3 mg, 0.2 equiv). The reaction mixture was stirred at 55 °C. After 1h H₂O (10 mL) was added and the mixture was extracted with CH₂Cl₂ (2 × 10 mL). The organic layer was dried (Na₂SO₄) and concentrated in vacuo. The residue was purified by column chromatography (EtOAc/heptane 1:2) to give 21 (10 mg, 0.026 mmol, 70%) as a colorless
oil. R, 0.42 (EtOAc/heptane 1:1). FTIR (ATR) 1248, 1678, 2976 cm⁻¹. ¹H NMR (CDCl₃, 400 MHz): δ 7.31-7.21 (m, 4H), 7.11-7.15 (m, 3H), 6.81 (d, 1H, J = 8.8 Hz), 4.87 (s, 3H), 3.79 (q, 2H, J = 7.2 Hz), 3.77 (s, 3H), 2.74-2.67 (m, 4H), 0.74 (t, 3H, J = 7.2 Hz). ¹³C NMR (CDCl₃, 75 MHz): δ 169.27, 163.76, 158.40, 138.75, 128.83, 128.76, 128.51, 127.74, 126.95, 126.55, 125.49, 113.37, 60.80, 54.76, 44.82, 30.58, 26.92, 12.72. HRMS (ESI) m/z calcd for C₂₀H₂₅NO₃Na (M+Na)⁺: 388.1525, found: 388.1538.

**Ethyl-3-(2-fluorobenzyl)-1-(4-methoxybenzyl)-6-oxo-1,4,5,6-tetrahydropyridine-2-carboxylate (18)**

To a solution of 7 (17.5 mg, 0.042 mmol) in EtOH (1 mL), was added a mixture of H₂O (10 mL) and Na₂CO₃ (2 mg, 0.020 mmol). The reaction mixture was stirred at 45 °C. After 2h the reaction mixture was cooled to room temperature, diluted with EtOAc (10 mL), washed with H₂O (10mL), dried (MgSO₄), and concentrated in vacuo. The residue was purified by column chromatography (EtOAc/heptane 1:2) to give 18 (57 mg, 78% yield).

**Ethyl-1-(4-methoxybenzyl)-6-oxo-3-styryl-1,4,5,6-tetrahydropyridine-2-carboxylate (19)**

To a solution of 7 (17.0 mg, 0.044 mmol) in EtOH (1 mL), was added a solution of PhCH=CH(OH)₂ (9.8 mg, 1 equiv), Pd(OAc)₂ (0.01 mg, 10 mol%) and Na₂CO₃ (2 mg, 0.02 equiv). The reaction mixture was stirred at 45 °C. After 1h H₂O (10 mL) was added and the mixture was extracted with CH₂Cl₂ (2 x 10 mL). The organic layer was dried (Na₂SO₄) and concentrated in vacuo. The residue was purified by column chromatography (EtOAc/heptane 1:2) to give 19 (21 mg, 86% yield) as a colorless oil. R, 0.67 (EtOAc/heptane 1:1). FTIR (ATR) 1248, 1678, 2920 cm⁻¹. ¹H NMR (CDCl₃, 400 MHz): δ 7.17-7.27 (m, 1H), 7.12 (d, 2H, J = 8.7 Hz), 6.84-6.94 (m, 3H), 6.81 (d, 2H, J = 8.7 Hz), 4.86 (s, 2H), 3.82 (q, 2H, J = 7.2 Hz), 3.77 (s, 3H), 2.70 (s, 4H), 0.79 (t, 3H, J = 7.2 Hz). ¹³C NMR (CDCl₃, 75 MHz): δ 169.11, 163.67, 163.43, 160.41, 154.56, 140.57, 140.37, 131.15, 129.34, 129.23, 128.64, 128.41, 123.71, 122.36, 122.33, 113.97, 113.78, 113.69, 113.49, 113.41, 113.38, 60.98, 54.77, 44.88, 30.50, 26.69, 12.74. HRMS (ESI) m/z calcd for C₂₀H₂₁NO₃Na (M+Na)⁺: 406.1431, found: 406.1435.

**Ethyl-1-(4-methoxy-benzyl)-6-oxo-3-vinyl-1,4,5,6-tetrahydro-pyridine-2-carboxylate (20)**

To a solution of 16 (16 mg, 0.039 mmol) in DMF (1 mL), were added CuI (0.8 mg, 10 mol%), Pd(PPh₃)₄ (2.1 mg, 10 mol%), CsF (12 mg, 2.0 equiv) and CH₂=CHSnBu₃ (36.2 µL, 3.0 equiv). The reaction mixture was stirred at 45 °C. After 2h the reaction mixture was cooled to room temperature, diluted with EtOAc (10 mL), washed with H₂O (10mL), dried (MgSO₄), and concentrated in vacuo. The residue was purified by column chromatography (EtOAc/heptane 1:1) to give 20 (9 mg, 0.028 mmol, 74%) as a colorless oil. R, 0.58 (EtOAc/heptane 1:1). FTIR (ATR) 1248, 1676, 1722, 2946 cm⁻¹. ¹H NMR (CDCl₃, 400 MHz): δ 7.09 (d, 1H, J = 8.8 Hz), 6.81 (d, 1H, J = 8.8Hz), 6.65 (dd, 1H, J = 10.9 Hz, J = 17.2 Hz), 5.26 (ddd, 2H, J = 0.7 Hz, J = 14.1Hz, J = 11.5 Hz), 4.78 (s, 2H), 4.17 (q, 1H, J = 7.2 Hz), 3.77 (s, 3H), 2.57-2.49 (m, 4H), 1.22 (t, 1H, J = 7.2 Hz). ¹³C NMR (CDCl₃, 75 MHz): δ 169.69, 162.78, 158.45, 131.09, 131.12, 128.48, 123.36, 115.27, 113.44, 61.22, 54.76, 45.63, 30.17, 19.95, 13.46. HRMS (ESI) m/z calcd for C₁₉H₂₀NO₃Na (M+Na)⁺: 338.1368, found: 338.1372.
The residue was purified by column chromatography (EtOAc/heptane 1:1) to give C128.77, 128.60, 128.49, 127.15, 119.16, 113.44, 61.42, 54.77, 45.90, 31.48, 25.97, 13.39. HRMS (ESI) m/z calcd for C21H23NO3Na (M+Na)+: 410.1580, found: 410.1584.

Ethyl-3-benzyloxy-1-(4-methoxybenzyl)-1,4,5,6-tetrahydropyridine-2-carboxylate (27)

To a solution of 11 (15 mg, 0.036 mmol) in PhMe (1 mL), was added BnOH (7.5 µL, 0.2 equiv), CuI (1 mg, 10 mol%), [1,10]phenanthroline (2 mg, 20 mol%), and Cs2CO3 (18 mg, 1.5 equiv). The reaction mixture was stirred at 120 °C. After 24h the reaction mixture was cooled to room temperature, diluted with PhMe (9 mL), filtered and concentrated in vacuo. The residue was purified by column chromatography (EtOAc/heptane 1:1) to give 27 (10 mg, 0.026 mmol, 73%) as a colorless oil. Rf 0.24 (EtOAc/heptane 1:1). FTIR (ATR) 1246, 1512, 1741, 2986 cm−1. 1H NMR (CDCl3, 400 MHz): δ 7.35-7.25 (m, 5H), 7.05 (d, 2H, J = 8.8 Hz), 6.80 (d, 2H, J = 8.8 Hz), 4.82 (s, 2H), 4.78 (s, 2H), 4.15 (q, 2H, J = 6.9 Hz), 3.79 (s, 3H), 2.57-2.52 (m, 2H), 2.45-2.41 (m, 2H). 13C NMR (CDCl3, 75 MHz): δ 168.36, 161.87, 158.39, 149.92, 135.91, 128.87, 128.06, 127.81, 127.22, 119.49, 113.37, 71.47, 50.61, 45.76, 45.25, 30.43, 22.04, 13.60. HRMS (ESI) m/z calcd for C23H25NO3Na (M+Na)+: 418.1630, found: 418.1633.

Ethyl-1-(4-methoxybenzyl)-6-oxo-3-phenoxy-1,4,5,6-tetrahydropyridine-2-carboxylate (28)

To a solution of 7 (15 mg, 0.036 mmol) in PhMe (1 mL), was added PhOH (2.0 equiv, 68 µg), CuI (1 mg, 10 mol%), [1,10]phenanthroline (2 mg, 20 mol%), and Cs2CO3 (18 mg, 1.5 equiv). The reaction mixture was stirred at 120 °C. After 2h the reaction mixture was cooled to room temperature, diluted with PhMe (9 mL), filtered and concentrated in vacuo. The residue was purified by column chromatography (EtOAc/heptane 1:1 to give 28 (11 mg, 0.028 mmol, 77%) as a colorless oil. Rf 0.33 (EtOAc/heptane 1:1). FTIR (ATR) 1246, 1512, 1741, 2986 cm−1. 1H NMR (CDCl3, 400 MHz): δ 7.37-7.25 (m, 5H), 7.13 (d, 2H, J = 8.8 Hz), 6.80 (d, 2H, J = 8.8 Hz), 4.82 (s, 2H), 4.18 (q, 2H, J = 7.2 Hz), 3.79 (s, 3H), 2.52-2.56 (m, 2H), 2.42-2.38 (m, 2H). 13C NMR (CDCl3, 75 MHz): δ 168.16, 162.36, 158.53, 134.94, 133.48, 130.54, 128.77, 128.60, 128.49, 127.15, 119.16, 113.44, 61.42, 54.77, 45.90, 31.48, 25.97, 13.39. HRMS (ESI) m/z calcd for C23H23NO3Na (M+Na)+: 404.1646, found: 404.1643.

Ethyl-1-(4-methoxybenzyl)-6-oxo-3-phenylsulfonyl-1,4,5,6-tetrahydropyridine-2-carboxylate (29)

To a solution of 7 (15 mg, 0.036 mmol) in PhMe (1 mL), was added PhSH (7.5 µL, 0.2 equiv), CuI (1 mg, 10 mol%), [1,10]phenanthroline (2 mg, 20 mol%), and Cs2CO3 (18 mg, 1.5 equiv). The reaction mixture was stirred at 120 °C. After 2h the reaction mixture was cooled to room temperature, diluted with PhMe (9 mL), filtered and concentrated in vacuo. The residue was purified by column chromatography (EtOAc/heptane 1:1 to give 29 (7 mg, 0.018 mmol, 49%) as a colorless oil. Rf 0.67 (EtOAc/heptane 1:1). FTIR (ATR) 1247, 1293, 1512, 1685, 2976 cm−1. 1H NMR (CDCl3, 400 MHz): δ 7.37-7.25 (m, 5H), 7.13 (d, 2H, J = 8.8 Hz), 6.80 (d, 2H, J = 8.8 Hz), 4.82 (s, 2H), 4.18 (q, 2H, J = 7.2 Hz), 3.79 (s, 3H), 2.54-2.49 (m, 2H), 2.40 (m, 2H). 13C NMR (CDCl3, 75 MHz): δ 168.16, 162.36, 158.53, 134.94, 133.48, 130.54, 128.77, 128.60, 128.49, 127.15, 119.16, 113.44, 61.42, 54.77, 45.90, 31.48, 25.97, 13.39. HRMS (ESI) m/z calcd for C23H23NO3Na (M+Na)+: 420.1245, found: 420.1243.
Chapter 5

MHHz: δ 170.06, 163.55, 158.44, 152.21, 143.76, 128.74, 128.11, 127.99, 127.88, 113.51, 66.99, 60.91, 54.72, 46.60, 30.53, 21.09, 13.72. HRMS (ESI) m/z calcd for C_{24}H_{32}N_{2}O_{3}Na (M+Na)^+: 461.1689, found: 461.1689.

Ethyl-3-benzyloamino-1-(4-methoxybenzyl)-6-oxo-1,4,5,6-tetrahydropyridine-2-carboxylate (31)

To a solution of 7 (15 mg, 0.036 mmol) in PhMe (1 mL), was added BzNH₂ (87 mg, 2.0 equiv), Cui (1 mg, 10 mol%), [1,10]-phenanthroline (2 mg, 20 mol%), and Cs₂CO₃ (18 mg, 1.5 equiv). The reaction mixture was stirred at 120 °C. After 2h the reaction mixture was cooled to room temperature, diluted with PhMe (9 mL), filtered and concentrated in vacuo. The residue was purified by column chromatography (EtOAc/heptane 1:4) to give 31 (11 mg, 0.018 mmol, 75%) as a colorless oil. Rₜ 0.67 (EtOAc/heptane 1:1). FTIR (ATR) 1247, 1672, 2950 cm⁻¹. ¹H NMR (CDCl₃, 400 MHz): δ 11.36 (br. s, 1H), 7.89 – 7.84 (m, 2H), 7.55 – 7.51 (m, 1H), 7.49-7.42 (m 2H), 7.03 (d, 2H, J = 8.6 Hz), 6.80 (d, 2H, J = 8.7 Hz), 4.99 (s, 2H), 4.31 (q, 2H, J = 7.2 Hz), 3.77 (s, 3H), 3.38-3.34 (m, 2H), 2.62-2.58 (m, 2H). ¹³C NMR (CDCl₃, 75 MHz):  δ 170.26, 164.97, 164.14, 158.47, 144.64, 133.34, 132.05, 128.72, 128.56, 128.38, 127.04, 113.56, 61.21, 54.72, 46.78, 30.63, 21.93, 13.73. HRMS (ESI) m/z calcd for C_{24}H_{32}N_{2}O_{3}Na (M+Na)^+: 431.1583, found: 431.1560.

Ethyl-6-oxo-3-phenyl-1,4,5,6-tetrahydropyridine-2-carboxylate (33)

A solution of 17 (809 mg, 1.95 mmol) in TFA/CH₂Cl₂ 1:4 (10.0 mL) was stirred for 16 h at 65 °C. After 16 h, the temperature was decreased to 0 °C. The reaction mixture was diluted with CH₂Cl₂ and quenched with NaHCO₃ (aq). The organic layer was washed with H₂O (10 mL), dried over MgSO₄ and concentrated in vacuo. The residue was purified by flash column chromatography (EtOAc/heptane 1:1) affording compound 33 (620 mg, 87%). Rₜ 0.36 (EtOAc/heptane 1:1). FTIR (ATR) 701, 735, 1683, 2915 cm⁻¹. ¹H NMR (CDCl₃, 400 MHz): δ 7.65 (s, 1H), 7.32-7.35 (m, 3H), 7.18-7.15 (m, 2H), 4.01 (q, 2H, J = 7.2 Hz), 2.78-2.74 (m, 2H), 2.65-2.60 (m, 2H), 0.92 (t, 3H, J = 7.1Hz). ¹³C NMR (CDCl₃, 75 MHz):  δ 168.84, 139.10, 128.63, 127.50, 127.25, 127.10, 126.79, 123.19, 61.10, 29.76, 29.25, 12.94. HRMS (ESI) m/z calcd for C_{14}H_{13}NO_{2}Na (M+Na)^+: 268.0950, found: 268.0943.

Ethyl-6-oxo-3-phenylpiperidine-2-carboxylate (34)

A solution of 33 (110 mg, 0.30 mmol) in TFA (3.0 mL) was stirred for 16 h at 65 °C. After 16 h, the temperature was decreased to 0 °C. The reaction mixture was diluted with CH₂Cl₂ and quenched with NaHCO₃ (aq). The organic layer was washed with H₂O (10 mL), dried over MgSO₄ and concentrated in vacuo. The residue was purified by flash column chromatography (EtOAc/heptane 1:1) affording compound 34 (66 mg, 90%). Rₜ 0.36 (EtOAc/heptane 1:1). FTIR (ATR) 604, 1204, 1669, 1736, 2933 cm⁻¹. ¹H NMR (CDCl₃, 400 MHz): δ 7.23-7.22 (m, 5H), 6.32 (br. s, 1H), 4.42 (dd, 1H, J = 1.6 Hz, J = 5.3 Hz), 3.95 (q, 2H, J = 7.1 Hz), 3.62 (dd, 1H, J = 5.2 Hz, J = 11.6 Hz), 2.42 (dd, 1H, J = 6.1 Hz, J = 7.3 Hz), 2.13 (m, 2H), 0.91 (t, 3H, J = 7.1 Hz). ¹³C NMR (CDCl₃, 75 MHz):  δ 171.06, 169.31, 136.82, 128.11, 127.11, 126.79, 61.02, 58.04, 39.47, 28.27, 25.23, 13.20. HRMS (ESI) m/z calcd for C_{14}H_{13}NO_{2}Na (M+Na)^+: 270.1106, found: 270.1114.

Ethyl-1-(4-Methoxybenzyl)-6-oxo-3-phenylpiperidine-2-carboxylate (35)

A solution of 17 (115 mg, 0.32 mmol) in MeOH (3.0 mL) was flushed through the H-cube (40 °C, 60 bar, flowrate 0.05 ml/min). The organic layer was then concentrated in vacuo. The residue was purified by flash column chromatography (EtOAc/heptane 1:1) affording compound 35 (66 mg, 90%). Rₜ 0.27 (EtOAc/heptane 1:1). FTIR (ATR) 1199, 1245, 1512, 1650, 1735, 2928 cm⁻¹. ¹H NMR (CDCl₃, 400 MHz): δ 7.22-7.15 (m, 7H), 6.84 (d, 2H, J = 8.3 Hz), 5.10 (d, 1H, J = 14.7 Hz), 4.11 (d, 1H, J = 5.6 Hz), 3.88 (d, 1H, J = 14.7 Hz), 3.80 (s, 3H), 3.64-3.69 (m, 2H), 3.28-3.25 (m, 1H), 2.83-2.79 (m, 1H), 2.66-2.61 (m, 2H), 1.96-1.90 (m, 1H), 0.81 (t, 1H, J = 7.1 Hz). ¹³C NMR (CDCl₃, 75 MHz): δ 169.74, 169.25, 158.67, 138.35, 129.55, 127.97, 127.01, 113.45, 63.78, 60.40, 54.80, 48.62, 41.84, 31.36, 21.14, 13.15. HRMS (ESI) m/z calcd for C_{24}H_{32}NO_{2}Na (M+Na)^+: 390.1681, found: 390.1681.
Ethyl-1-(4-methoxybenzyl)-3-phenylpiperidine-2-carboxylate (38)

To a cooled solution (0 °C) of cis-35 (12 mg, 0.033 mmol) in THF (1.5 mL) was added BH₃·THF (66 µL, 2 equiv). The solution was stirred for 1 h at room temperature, diluted with CH₂Cl₂ and quenched with NH₄Cl (aq). The organic layer was washed with H₂O (10 mL), dried over MgSO₄ and concentrated in vacuo. The residue was purified by flash column chromatography (EtOAc/heptane 1:2) affording compound 38 (9 mg, 76%). R₆ 0.56 (EtOAc/heptane 1:2). FTIR (ATR) 1178, 1512, 1733, 2359 cm⁻¹. ¹H NMR (CDCl₃, 400 MHz): δ 7.28-7.20 (m, 7H), 6.85 (d, 2H, J = 8.7 Hz), 3.82 (dq, 2H, J = 7.1 Hz, J = 10.8 Hz), 3.84 (s, 3H), 3.71 (d, 1H, J = 5.3 Hz), 3.62 (d, 1H, J = 13.3 Hz), 3.50 (d, 1H, J = 12.7 Hz), 3.14-3.18 (m, 1H), 3.06 (dt, 1H, J = 3.2 Hz, J = 11.7 Hz), 2.65-2.60 (m, 1H), 2.29 (dq, 1H, J = 3.7 Hz, J = 12.7 Hz), 1.86-1.82 (m, 1H), 1.74-1.69 (m, 1H), 1.68-1.64 (m, 1H), 0.87 (t, 1H, J = 7.1 Hz). ¹³C NMR (CDCl₃, 75 MHz): δ 171.16, 164.17, 158.14, 129.44, 127.64, 127.31, 113.13, 66.26, 58.95, 58.64, 54.78, 45.73, 43.98, 24.99, 23.30, 13.48. HRMS (ESI) m/z calcd for C₂₂H₂₆N₂O₃Na (M+Na)⁺: 354.2069, found: 354.2058.

Ethyl-1-(4-methoxybenzyl)-6-oxo-3-phenylpiperidine-2-carboxylate (39)

To a cooled solution (-30 °C) of CuI (118 mg, 0.62 mmol) in Et₂O (0.7 mL), phenylmagnesium bromide (0.1 mL, 0.31 mmol) was added. The solution was stirred for 20 minutes and was cooled to -70 °C. Then compound 6 (45 mg, 0.15 mmol), dissolved in Et₂O (1 mL), was added and the temperature was slowly warmed to -30 °C. The reaction was diluted with Et₂O and quenched with 0.1M HCl. The organic layer was washed with NaHCO₃ (10 mL) and H₂O (10 mL), dried over MgSO₄ and concentrated in vacuo. The residue was purified by flash column chromatography (EtOAc/heptane 1:1) affording compound 39 (34 mg, 62%). R₆ 0.36 (EtOAc/heptane 1:1). FTIR (ATR) 1511, 1649, 1737, 2935 cm⁻¹. ¹H NMR (CDCl₃, 400 MHz): δ 7.21-7.16 (m, 5H), 6.98-6.94 (m, 2H), 6.87-6.80 (m, 2H), 5.39 (d, 1H, J = 14.6 Hz), 4.18 (d, 1H, J = 4.7 Hz), 4.17-4.07 (m, 2H), 3.80 (s, 3H), 3.73 (d, 1H, J = 14.6 Hz), 3.34 (dt, 1H, J = 7.2 Hz, 4.6), 2.57-2.32 (m, 2H), 2.20-2.11 (m, 1H), 2.03-1.92 (m, 1H), 1.18 (t, 3H, J = 7.1 Hz). ¹³C NMR (CDCl₃, 75 MHz): δ 170.91, 169.63, 158.75, 140.36, 130.18, 128.25, 127.86, 126.63, 126.57, 113.45, 63.13, 61.15, 54.87, 48.03, 41.37, 29.45, 25.37, 13.62. HRMS (ESI) m/z calcd for C₂₂H₂₅NO₂Na (M+Na)⁺: 390.1684, found: 390.1681.

Ethyl-3-(2-fluorophenyl)-1-(4-methoxybenzyl)-6-oxo-piperidin-2-carboxylate (40)

To a cooled solution (-30 °C) of Cul (118 mg, 0.62 mmol) in Et₂O (0.7 mL), p-fluorophenylmagnesium bromide (0.3 mL, 0.31 mmol) was added. The solution was stirred for 20 minutes and was cooled to -70 °C. Then compound 6 (45 mg, 0.15 mmol), dissolved in Et₂O (1 mL), was added and the temperature was slowly warmed to -30 °C. The reaction was diluted with Et₂O and quenched with 0.1 M HCl. The organic layer was washed with NaHCO₃ (10 mL) and H₂O (10 mL), dried over MgSO₄ and concentrated under reduced pressure. The residue was purified by flash column chromatography (EtOAc/heptane 1:1) affording compound 40 (26 mg, 45%). R₆ 0.35 (EtOAc/heptane 1:1). FTIR (ATR) 1243, 1511, 1649, 1737, 2936 cm⁻¹. ¹H NMR (CDCl₃, 400 MHz): δ 7.19-7.14 (m, 2H), 6.94-6.80 (m, 4H), 5.42 (d, 1H, J = 14.6 Hz), 4.19-4.06 (m, 3H), 3.80 (s, 3H), 3.67 (d, 1H, J = 14.6 Hz), 3.34 (dt, 1H, J = 7.1, 4.6 Hz), 2.58-2.35 (m, 2H), 2.19-2.09 (m, 1H), 1.99-1.88 (m, 1H), 1.20 (t, 3H, J = 7.1 Hz). ¹³C NMR (CDCl₃, 75 MHz): δ 170.75, 169.46, 161.36 (d, J = 246.1 Hz), 158.84, 136.05 (d, J = 3.1 Hz), 130.03, 128.05 (d, J = 7.9 Hz), 127.74, 115.03 (d, J = 21.3 Hz), 113.55, 63.26, 61.27, 54.85, 48.04, 40.63, 29.47, 25.35, 13.74. HRMS (ESI) m/z calcd for C₂₂H₂₂FNO₂Na (M+Na)⁺: 408.1589, found: 408.1587.

Ethyl-1-(4-methoxybenzyl)-6-oxo-3-vinylpiperidine-2-carboxylate (41)

To a cooled solution (-30 °C) of Cul (31.5 g, 16.6 mmol) in Et₂O (30 mL), a 1M vinylmagnesium bromide solution in THF (8.3 mL, 8.3 mmol) was added. The solution was stirred for 20 minutes and was cooled to -70 °C. Then compound 6 (1.2 g, 4.15 mmol), dissolved in Et₂O (10 mL), was added and the temperature was slowly warmed to -10 °C. The reaction was quenched with 0.1 M HCl and washed with Na₂S₂O₃ (2x40 mL), NaHCO₃ (40 mL) and H₂O (40 mL), dried over MgSO₄ and concentrated in vacuo. The residue was purified by flash column chromatography (EtOAc/heptane 1:1) affording compound 41 (0.95 g, 72%). R₆ 0.41 (EtOAc/heptane 1:1). FTIR (ATR) 1511, 1649, 1738, 2940 cm⁻¹. ¹H NMR (CDCl₃, 400 MHz): δ 7.16 (d, 2H, J = 8.6 Hz), 6.84 (d, 2H, J = 8.7 Hz), 5.69-5.59 (m, 1H), 5.35 (d, 1H, J = 14.7 Hz), 5.08-4.91 (m, 2H), 4.22-4.12 (m, 2H), 3.89 (dd, 1H, J = 3.9, 1.0 Hz), 3.79 (s, 3H), 3.69 (d,
**Chapter 5**

1H, J = 14.7), 2.83-2.77 (m, 1H), 2.54-2.47 (m, 2H), 2.00-1.90 (m, 1H), 1.78-1.71 (m, 1H), 1.26 (t, 3H, J = 7.1 Hz). 13C NMR (CDCl3, 75 MHz): δ 170.98, 169.35, 158.78, 136.23, 129.85, 127.97, 116.33, 113.46, 61.98, 61.25, 54.89, 48.14, 38.65, 28.33, 22.92, 13.78. HRMS (ESI) m/z calcd for C13H12NO3Na (M+Na)+: 340.1537, found: 340.1525.

**Ethyl-3-phenylpiperidine-2-carboxylate (42)**

To a cooled solution (0 °C) of 39 (12 mg, 0.033 mmol) in THF (1.5 mL) was added BH3·THF (66 µL, 2 equiv). The solution was stirred for 1 h at room temperature, diluted with CH2Cl2 and quenched with NH4Cl (aq). The organic layer was washed with H2O (10 mL), dried over MgSO4 and concentrated in vacuo. The residue was purified by flash column chromatography (EtOAc/heptane 1:2) affording compound 42 (9 mg, 73%). Rf 0.56 (EtOAc/heptane 1:2). FTIR (ATR) 1178, 1512, 1733, 2359 cm⁻¹. 1H NMR (CDCl3, 400 MHz): δ 7.50 (d, 2H, J = 8.8 Hz), 7.27 – 7.23 (m, 1H), 6.87 (d, 1H, J = 8.8 Hz), 4.60 (d, 1H, J = 12.9 Hz), 4.38 (d, 1H, J = 13.0 Hz), 4.01 (d, 1H, J = 12.2 Hz), 3.92 (s, 3H), 3.90 (q, 1H, J = 7.7 Hz), 3.38 (dt, 1H, J = 3.9 Hz, J = 12.5 Hz), 3.10-3.06 (m, 1H), 2.77 (dt, 1H, J = 2.7 Hz, J = 14.0 Hz), 2.12-2.09 (m, 1H), 1.70-1.66 (m, 1H), 0.78 (t, 1H, J = 7.1 Hz). (CDCl3, 75 MHz): δ 167.84, 159.34, 139.00, 133.86, 128.07, 127.82, 127.47, 127.18, 123.20, 74.89, 60.09, 54.76, 54.65, 53.37, 39.98, 30.62, 20.08, 12. HRMS (ESI) m/z calcd for C10H13N2O2Na (M+Na)+: 376.1889, found: 376.1876.

**Ethyl-2-(4-methoxybenzyl)-1-oxo-4-phenyl-1,2-dihydroisoquinoline-3-carboxylate (44)**

To a solution of 15 (42 mg, 0.093 mmol) in EtOH (2 mL), was added a PhB(OH)2 (15.9 mg, 1.5 equiv), Pd(OAc)2 (2 mg, 10 mol%) and Na2CO3 (22 mg, 2.0 equiv). The reaction mixture was stirred at 55 °C. After 16 h H2O (10 mL) was added and the mixture was extracted with CH2Cl2 (2 x 10 mL). The organic layer was dried (Na2SO4) and concentrated in vacuo. The residue was purified by column chromatography (EtOAc/heptane 1:2) to give 44 (17 mg, 0.042 mmol, 45%) as a colorless oil. Rf 0.67 (EtOAc/heptane 1:1). FTIR (ATR) 1246, 1512, 1655, 1723, 2976 cm⁻¹. 1H NMR (CDCl3, 400 MHz): δ 8.57-8.53 (m, 1H), 7.62-7.21 (m, 11H), 6.88 (d, 1H, J = 8.6 Hz), 5.45 (s, 2H), 3.76 (s, 3H), 3.67 (q, 2H, J = 7.1 Hz), 0.62 (t, 3H, J = 7.1 Hz). 13C NMR (CDCl3, 75 MHz): δ 163.40, 161.20, 161.13, 155.41, 138.70, 137.74, 135.83, 134.30, 134.18, 132.21, 132.09, 131.98, 130.31, 130.20, 129.27, 128.98, 128.69, 128.55, 128.07, 127.98, 127.88, 127.85, 127.75, 127.67, 127.60, 127.49, 127.38, 126.49, 125.44, 125.37, 118.58, 118.39, 113.34, 111.92, 110.79, 110.32, 61.42, 61.21, 55.91, 55.18, 47.30, 46.47, 12.65, 12.55. HRMS (ESI) m/z calcd for C19H18N2O3Na (M+Na)+: 436.1525, found: 436.1526.

**Ethyl-1-hydroxy isoquinoline-3-carboxylate (46a)**

A solution of 14 (150 mg, 0.44 mmol) in TFA (4 mL) was stirred at 70 °C for 16 h. Then the reaction was diluted with CH2Cl2, washed with NaHCO3, H2O and NaCl (aq). The organic layer was dried over MgSO4 and concentrated in vacuo. The residue was purified by flash column chromatography (EtOAc/heptane 1:1) affording compound 46a (88 mg, 91%). Rf 0.37 (EtOAc/heptane 1:1). FTIR (ATR) 1297, 1650, 29.75, 3075, 3174 cm⁻¹. 1H NMR (CDCl3, 400 MHz): δ 9.02 (br. s, 1H), 8.46 (d, J = 8.0 Hz, 1H), 7.71-7.66 (m, 3H), 7.38 (s, 1H), 4.45 (q, 1H, J = 7.1 Hz), 1.44 (t, 1H, J = 7.1 Hz). 13C NMR (CDCl3, 75 MHz): δ 161.24, 161.20, 135.56, 132.56, 128.86, 127.81, 127.66, 127.45, 110.67, 62.10, 13.76. HRMS (ESI) m/z calcd for C15H12NO3Na (M+Na)+: 240.0637, found: 240.0633.

**Ethyl-1-hydroxy-4-phenyl isoquinoline-3-carboxylate (46b)**

A solution of 44 (75 mg, 0.18 mmol) in TFA (2 mL) was stirred at 70°C for 16 h. Then the reaction was diluted with CH2Cl2, washed with NaHCO3 (aq), H2O and NaCl (aq). The organic layer was dried (MgSO4) and concentrated in vacuo. The residue was purified by flash column chromatography (EtOAc/heptane 1:1) affording compound 46b (32 mg, 61%). Rf 0.26 (EtOAc/heptane 1:1). FTIR (ATR) 766, 1324, 1317, 1730, 2980 cm⁻¹. 1H NMR (CDCl3, 400 MHz): δ 9.34 (br s, 1H), 8.53-8.49 (m, 1H), 7.63 – 7.57 (m, 2H), 7.47-7.43 (m, 3H), 7.27-7.20 (m, 3H), 4.08 (q, 1H, J = 7.1 Hz), 0.91 (t, 1H, J = 7.2 Hz). 13C NMR (CDCl3, 75 MHz): δ 161.82, 160.67, 137.53, 135.27, 129.41, 128.88, 128.58, 127.72, 127.46, 127.36, 127.30, 127.14, 124.30, 110.67, 61.69, 12.86. HRMS (ESI) m/z calcd for C19H13N2O3 (M+Na)+: 316.0950, found: 316.0941.
Ethyl-1-chloro isoquinoline-3-carboxylate (47a)

To a solution of 46a (60 mg, 0.275 mmol) in DMF (2 mL) was added POCl₃ (81 µL, 0.83 mmol). The reaction was stirred at 80 °C for 3 h. Then the reaction was diluted with CH₂Cl₂, washed with NaHCO₃, H₂O and NaCl (aq). The organic layer was dried over MgSO₄ and concentrated in vacuo. The residue was purified by flash column chromatography (EtOAc/heptane 1:3) affording compound 47a (54 mg, 83%). Rf 0.67 (EtOAc/heptane 1:1). FTIR (ATR) 1244, 1774, 2980 cm⁻¹. ¹H NMR (CDCl₃, 400 MHz): δ 8.52 (d, 1H, J = 0.6 Hz), 8.42 – 8.37 (m, 1H), 8.07-8.00 (m, 1H), 7.86-7.80 (m, 2H), 4.53 (q, 2H, J = 7.1 Hz), 1.48 (t, 3H, J = 7.1 Hz). ¹³C NMR (CDCl₃, 75 MHz): δ 177.18, 164.16, 151.41, 140.47, 137.07, 134.80, 133.35, 131.22, 129.28, 127.82, 126.64, 126.09, 61.10, 13.23. HRMS (ESI) m/z calcd for C₁₉H₁₉ClNO₂Na (M+Na)⁺: 334.0611, found: 334.0603.

Ethyl-1-chloro-4-phenyl isoquinoline-3-carboxylate (47b)

To a solution of 46b (32 mg, 0.11 mmol) in DMF (1 mL) was added POCl₃ (33 µL, 0.33 mmol). The reaction was stirred at 80 °C for 3 h. Then the reaction was diluted with CH₂Cl₂, washed with NaHCO₃ (aq), H₂O and NaCl (aq). The organic layer was dried over MgSO₄ and concentrated in vacuo. The residue was purified by flash column chromatography (EtOAc/heptane 1:3) affording compound 47b (25 mg, 0.08 mmol, 73%). Rf 0.67 (EtOAc/heptane 1:1). FTIR (ATR) 766, 1324, 1317, 1730, 2980 cm⁻¹. ¹H NMR (CDCl₃, 400 MHz): δ 8.46-8.41 (m, 1H), 7.78-7.41 (m, 13H), 4.12 (q, 2H, J = 7.1 Hz), 1.04 (t, 3H, J = 7.1 Hz). ¹³C NMR (CDCl₃, 75 MHz): δ 165.40, 150.50, 140.47, 137.07, 134.80, 133.35, 131.22, 129.28, 129.19, 127.82, 126.64, 126.09, 61.10, 13.23. HRMS (ESI) m/z calcd for C₁₉H₁₉ClNO₂Na (M+Na)⁺: 335.0901, found: 335.0900.

Ethyl-1-phenyl isoquinoline-3-carboxylate (48a)

To a solution of 47a (54 mg, 0.228 mmol) in EtOH (3 mL), was added a PhB(OH)₂ (41 mg, 1.5 equiv), Pd(OAc)₂ (8 mg, 10 mol%) and Na₂CO₃ (48 mg, 2.0 equiv). The reaction mixture was stirred at 55 °C. After 16 h H₂O (10 mL) was added and the mixture was extracted with CH₂Cl₂ (2 x 10 mL). The organic layer was dried (Na₂SO₄) and concentrated in vacuo. The residue was purified by column chromatography (EtOAc/heptane 1:2) to give 48a (52 mg, 0.186 mmol, 82%) as a colorless oil. Rf 0.67 (EtOAc/heptane 1:1). FTIR (ATR) 1213, 1240, 1774, 2980 cm⁻¹. ¹H NMR (MeOD, 400 MHz): δ 8.56 (m, 1H), 8.37 (m, 1H), 8.00 (m, 1H), 7.86 (m, 2H), 7.41 (m, 13H), 7.40 (m, 13H), 7.36 (m, 13H), 7.26 (m, 2H), 7.20 (m, 2H), 6.73 (m, 2H), 6.70 (m, 2H), 5.86 (s, 2H), 1.38 (m, 3H). ¹³C NMR (MeOD, 75 MHz): δ 134.38, 131.73, 130.62, 130.56, 129.21, 128.31, 128.16, 127.85, 127.57, 126.85, 125.50, 123.50, 122.64, 61.23, 60.97, 12.74, 12.70. HRMS (ESI) m/z calcd for C₁₉H₁₉NO₂Na (M+Na)⁺: 300.1001, found: 300.1008.

Ethyl-1,4-diphenyl isoquinoline-3-carboxylate (48b)

To a solution of 47b (70 mg, 0.33 mmol) in EtOH (3 mL), was added a PhB(OH)₂ (28 mg, 1.5 equiv), Pd(OAc)₂ (17 mg, 10 mol%) and Na₂CO₃ (36 mg, 2.0 equiv). The reaction mixture was stirred at 55 °C. After 16 h H₂O (10 mL) was added and the mixture was extracted with CH₂Cl₂ (2 x 10 mL). The organic layer was dried (Na₂SO₄) and concentrated in vacuo. The residue was purified by column chromatography (EtOAc/heptane 1:2) to give 48b (92 mg, 0.26 mmol, 78%) as a colorless oil. FTIR (ATR) 1213, 1240, 1712, 2980 cm⁻¹. ¹H NMR (CDCl₃, 400 MHz): δ 8.45-8.40 (m, 1H), 8.17-7.41 (m, 13H), 4.16 (q, 2H, J = 7.1 Hz), 1.07 (t, 3H, J = 7.1 Hz). ¹³C NMR (CDCl₃, 75 MHz): δ 159.81, 156.30, 138.48, 135.89, 129.98, 129.76, 129.56, 128.36, 127.90, 127.76, 127.60, 127.50, 127.26, 126.07, 60.78, 13.21. HRMS (ESI) m/z calcd for C₂₂H₂₃NO₂Na (M+Na)⁺: 376.1313, found: 376.1303.
5.10 References

A stereoselective approach to cis- and trans-3-substituted pipecolic acids

Asymmetric hydrogentation of $\alpha,\beta$-unsaturated cyclic didehydroamino acids

Abstract

Asymmetric catalytic hydrogenation represents one of the most efficient methods to prepare enantiomerically pure compounds via hydrogenation of substituted olefins. Major interest is directed toward the synthesis of enantiomerically pure $\alpha$-amino acids to provide potentially new druglike molecules. The production of highly substituted, non-natural cyclic dehydroamino acids would therefore be of great interest as a starting point for more elaborate structures. While asymmetric hydrogenation of linear dehydroamino acids is commonly known, reduction of the corresponding cyclic derivatives has remained rather unexplored. This chapter describes the asymmetric hydrogenation of cyclic $\alpha,\beta$-unsaturated dehydroamino esters.
6.1 Introduction

Asymmetric catalytic hydrogenation represents one of the most powerful strategies to prepare enantiomerically pure compounds from substituted olefins. Historically, rhodium-catalysed hydrogenation of olefins already dates from 1966, starting with the development of Wilkinson’s catalyst Rh(PPh₃)₃Cl.¹ Only a few years later, the first asymmetric examples appeared in literature, described by Knowles² and Horner³ both using monodentate phosphine ligands (Scheme 6.1).

![Scheme 6.1](attachment:Scheme_6.1.png)

**Scheme 6.1.** First asymmetric hydrogenation reaction by Knowles.

Although the selectivities were rather low, probably caused by the rotational freedom of the rhodium-complexes, these examples for the first time showed the potential of asymmetric hydrogenation. A major improvement in selectivity was not long thereafter achieved by Dang and Kagan using the first bidentate non-P-chiral ligand DIOP (Scheme 6.2), which showed remarkably high ee’s at that time in the hydrogenation of 2-acetamidocinnamic acid.⁴

![Scheme 6.2](attachment:Scheme_6.2.png)

**Scheme 6.2.** Asymmetric hydrogenation using the bidentate ligand DIOP.

Despite the fact that Knowles already showed the potency of using monodentate CAMP (7, Figure 6.1) for the formation of N-acetylphenylalanine with ee’s up to 88%, bidentate P-ligands were generally assumed to induce higher enantioselectivity for a long time. This led to the development and exploration of many chiral bidentate phosphine ligands in
Asymmetric hydrogenation of α,β-unsaturated cyclic didehydroamino acids over the past decades. Preparation of these ligands, however, was often hampered by a lengthy synthesis. This changed with the development of BINAP-based catalytic hydrogenation by Noyori in 1987 (Figure 6.1), for which he was awarded the 2001 Nobel Prize in Chemistry jointly with Knowles and Sharpless. More recently, several other phosphorous-based chiral bidentate ligands, such as bisphosphinates, bisphosphonites and bisphosphites were developed, albeit that they appeared less successful in asymmetric hydrogenation.

![Figure 6.1. Chiral ligands for asymmetric hydrogenation.](image)

In 2000, the groups of Pringle, Reetz, and Feringa/de Vries reported the use of three new classes of monodentate ligands for asymmetric hydrogenation based on BINOL (Figure 6.1). These ligands are readily prepared and induced remarkably high enantioselectivities, comparable to the results obtained with bidentate phosphines in rhodium-catalyzed asymmetric hydrogenation.

**Substrates for hydrogenation**

Many classes of prochiral olefins can be hydrogenated with high enantioselectivity. As an example, hydrogenation of didehydroamino acids leads to the synthesis of enantiopure α-amino acids. The strong demand for the latter compound class led to the development of various effective rhodium-catalysts using different types of ligands. In particular, examples with acyl substituents on the nitrogen atom (viz. 10, R^2 = H) are well preceded in literature and the first examples were reported as early as in 1981. In sharp contrast, tetrasubstituted didehydroamino acids (viz. 10, R^1, R^2 ≠ H) are significantly more difficult to hydrogenate with high enantioselectivity and isolated yields are generally low (Scheme 6.3).
While selective hydrogenation of linear α,β-unsaturated dehydroamino esters is well known, hydrogenation of the corresponding cyclic systems has remained limited to substrates with an acyl group onto the nitrogen heterocycle (Scheme 6.4).\textsuperscript{15}

Given the facile access to tetrasubstituted cyclic dehydroamino esters as described in Chapter 4, the corresponding saturated cyclic amino acids would be readily accessible upon hydrogenation. The latter compounds occur as structural elements in various drugs\textsuperscript{16} and natural products.\textsuperscript{17} We therefore set out to study the asymmetric hydrogenation of cyclic α,β-unsaturated dehydroamino esters.

## 6.2 Asymmetric hydrogenation of tetrasubstituted dehydroamino esters

Over the past years, phosphoramidite ligands as developed by Feringa and Minnaard,\textsuperscript{18,19} have proven their usefulness in asymmetric hydrogenation of a wide range of prochiral olefins, including α,β-unsaturated dehydroamino acids.\textsuperscript{20} Several approaches have been adopted for the synthesis of these ligands. The most common route entails the reaction of phosphoryl chloride intermediate 16 with a secondary amine (17, Scheme 6.5). Their ready accessibility has prompted us to investigate the asymmetric hydrogenation of cyclic dehydroamino acids with Rh(I) in combination with a phosphoramidite ligand library.
Scheme 6.5. Synthesis of phosphoramidites.

The reactions were either performed in an Endeavor synthesizer\textsuperscript{21} or in an autoclave. The Endeavor is a parallel synthesizer containing eight reaction vessels, which can be independently controlled. Hydrogenations can be carefully followed in time by measuring the individual hydrogen uptake. Former studies have shown that the rates of hydrogenation of dehydroamino acids using rhodium-MonoPhos\textsuperscript{TM} are not very high with a hydrogen atmosphere of 1 bar. Initial attempts were therefore performed at a pressure of 25 bar with 0.075 mmol of substrate in 1.5 mL solvent. The experiments were carried out using 5 mol\% of [Rh(COD)\textsubscript{2}]BF\textsubscript{4} and 10 mol \% of ligand.

Hydrogenation of tetrasubstituted alkene 19 in both methanol and dichloromethane using monodentate phosphoramidite ligands (L1-L7) only led to the recovery of starting material (Scheme 6.6). A raise in temperature to 70 °C did not give much conversion either, but instead slow decomposition of the starting material. Disappointingly, hydrogenations using bidentate phosphine ligands (L8-L10) remained unproductive too.
While asymmetric hydrogenation of cyclic dihydroamino esters is only known for \(N\)-heterocycles containing an exocyclic acyl substituent on the nitrogen, we decided to reduce the enamide prior to the hydrogenation (Scheme 6.7). Acidic removal of the PMB protecting group led to the formation of 21, which was immediately protected with a Boc-group to give 23. Then, reduction of the lactam carbonyl to the corresponding hemiaminal, followed by \(N\)-acyliminium ion-mediated triethylsilane reduction provided heterocycle 24 in a moderate yield of 36% over two steps. With both 21 and 24 in hand, we tested their behavior in the hydrogenation. Again, only starting material was recovered.
Asymmetric hydrogenation of α,β-unsaturated cyclic didehydroamino acids


As a next step, we tried to hydrolyze the ester in order to enhance coordination of the didehydroamino carboxylate to the rhodium cation, thereby hopefully enhancing the enantioselectivity. Surprisingly, treatment of 26 with an excess of potassium hydroxide in a mixture of dioxane/H₂O led to decarboxylation together with an unexpected auto-oxidation of the heterocycle to afford 27 in 81% yield (Scheme 6.8).


The reaction was repeated at low temperature in the presence of a stoichiometric amount of more reactive lithium hydroxide to avoid decarboxylation. Indeed, hydrolysis was taking place according to mass measurements, but since the reaction was proceeding slowly, the temperature was raised to room temperature. Full conversion, however, was only reached after stirring the reaction for three days. Again, the oxidized aromatic lactam 27 was isolated as the main product.
6.3 Asymmetric hydrogenation of dihydroamino acids: screening

Since it appeared difficult to hydrogenate the tetrasubstituted alkenes, we decided to investigate the possibility of reducing the dihydroamino esters 28a and 28b. The results of the experiments are summarized in Table 6.1. Although the reaction was not completed in 16 h, we were pleased to find that hydrogenation of 28a proceeded well in dichloromethane at 0.05 M. From entry 2 is also clear that full conversion was obtained at higher concentration (0.2 M). The isoquinoline 28b, on the other hand, was unreactive toward hydrogenation (entries 3 and 4). This was probably due to conjugation of the double bond with both the aromatic ring and the ester, which decreased its reactivity. Apparently, there is a strong solvent effect clearly indicating that reactions in non-protic solvents are more reactive. Unfortunately, the enantioselectivity was rather low in all cases.

Table 6.1. Asymmetric hydrogenation in the Endeavor: solvent screening.

<table>
<thead>
<tr>
<th>entry</th>
<th>substrate</th>
<th>ligand</th>
<th>solvent</th>
<th>product</th>
<th>conversion (%)</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>28a</td>
<td>(S)-L1</td>
<td>CH$_2$Cl$_2$</td>
<td>29a</td>
<td>50</td>
<td>4</td>
</tr>
<tr>
<td>2</td>
<td>28a (0.2 M)</td>
<td>(S)-L1</td>
<td>CH$_2$Cl$_2$</td>
<td>29a</td>
<td>&gt;99</td>
<td>5</td>
</tr>
<tr>
<td>3</td>
<td>28b</td>
<td>(S)-L1</td>
<td>CH$_2$Cl$_2$</td>
<td>29b</td>
<td>0</td>
<td>n.d.</td>
</tr>
<tr>
<td>4</td>
<td>28b (0.2 M)</td>
<td>(S)-L1</td>
<td>CH$_2$Cl$_2$</td>
<td>29b</td>
<td>0</td>
<td>n.d.</td>
</tr>
<tr>
<td>5</td>
<td>28a</td>
<td>(S)-L1</td>
<td>MeOH</td>
<td>29a</td>
<td>24</td>
<td>6</td>
</tr>
<tr>
<td>6</td>
<td>28b</td>
<td>(S)-L1</td>
<td>MeOH</td>
<td>29b</td>
<td>0</td>
<td>n.d.</td>
</tr>
<tr>
<td>7</td>
<td>28a</td>
<td>(S)-L1</td>
<td>EtOAc</td>
<td>29a</td>
<td>53</td>
<td>4</td>
</tr>
<tr>
<td>8</td>
<td>28b</td>
<td>(S)-L1</td>
<td>EtOAc</td>
<td>29b</td>
<td>0</td>
<td>n.d.</td>
</tr>
<tr>
<td>9</td>
<td>28a</td>
<td>(S)-L1</td>
<td>acetone</td>
<td>29a</td>
<td>51</td>
<td>5</td>
</tr>
<tr>
<td>10</td>
<td>28b</td>
<td>(S)-L1</td>
<td>acetone</td>
<td>29b</td>
<td>0</td>
<td>n.d.</td>
</tr>
</tbody>
</table>

Next, we investigated the influence of the amine substituent on the ligand. From the results in Table 6.2 it was concluded that phosphoramidite ligand PipPhos (L2) resulted in a significant decrease in reactivity (entries 1-2). Moreover, the enantiomeric excess was only
5%. In order to increase the selectivity, introduction of chiral amines on the phosphoramidite ligands was investigated. This led, however, to a complete loss of reactivity (entries 3-4). Probably, these ligands are too bulky for the hydrogenation to proceed. In addition, the influence of the ligand backbone was investigated (L5-7). The PipPhos-based ligands L5 and L6 showed a significant decrease in reactivity as compared to PipPhos (entry 2). Phosphoramidites based on TADDOL (L7)²² have also been used, but were ineffective in the hydrogenation of 28a.

Table 6.2. Asymmetric hydrogenation in the Endeavor: ligand screening.

<table>
<thead>
<tr>
<th>entry</th>
<th>substrate</th>
<th>ligand</th>
<th>solvent</th>
<th>product</th>
<th>conversion (%)</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>28a</td>
<td>(S)-L1</td>
<td>CH₂Cl₂</td>
<td>29a</td>
<td>50</td>
<td>4</td>
</tr>
<tr>
<td>2</td>
<td>28a</td>
<td>(S)-L2</td>
<td>CH₂Cl₂</td>
<td>29a</td>
<td>16</td>
<td>5</td>
</tr>
<tr>
<td>3</td>
<td>28a</td>
<td>(S)-L3</td>
<td>CH₂Cl₂</td>
<td>29a</td>
<td>0</td>
<td>n.d.</td>
</tr>
<tr>
<td>4</td>
<td>28a</td>
<td>(S)-L4</td>
<td>CH₂Cl₂</td>
<td>29a</td>
<td>0</td>
<td>n.d.</td>
</tr>
<tr>
<td>5</td>
<td>28a</td>
<td>(S)-L5</td>
<td>CH₂Cl₂</td>
<td>29a</td>
<td>22</td>
<td>4</td>
</tr>
<tr>
<td>6</td>
<td>28a</td>
<td>(S)-L6</td>
<td>CH₂Cl₂</td>
<td>29a</td>
<td>18</td>
<td>3</td>
</tr>
<tr>
<td>7</td>
<td>28a</td>
<td>(S)-L7</td>
<td>CH₂Cl₂</td>
<td>29a</td>
<td>0</td>
<td>n.d.</td>
</tr>
</tbody>
</table>

Despite the fact that the rhodium-phosphoramidite complexes showed high conversions in some cases, the enantioselectivity of the reaction was always low. We therefore decided to shift our focus toward hydrogenation of the dihydroamino esters using bidentate phosphine ligands (Table 6.3). The reactivity was indeed significantly enhanced, leading to a full conversion within one hour, but again the enantioselectivity was low (ee <5%).

Table 6.3. Asymmetric hydrogenation: bidentate phosphine ligands.

<table>
<thead>
<tr>
<th>entry</th>
<th>substrate</th>
<th>ligand</th>
<th>solvent</th>
<th>product</th>
<th>conversion (%)</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Asymmetric hydrogenation of α,β-unsaturated cyclic dihydroamino acids
Finally, we briefly investigated the use of metals other than rhodium. Much to our surprise, both the iridium as well as the ruthenium derivatives appeared to be unreactive in the hydrogenation. A plausible explanation could lie in the stronger coordinating properties of the cationic rhodium species.

Table 6.4. Asymmetric hydrogenation: evaluation of different metals.

<table>
<thead>
<tr>
<th>entry</th>
<th>substrate</th>
<th>catalyst</th>
<th>solvent</th>
<th>ligand</th>
<th>product</th>
<th>conversion (%)</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>28a</td>
<td>[Rh(COD)2]BF4</td>
<td>CH2Cl2</td>
<td>(S)-L8</td>
<td>29a</td>
<td>&gt;99</td>
<td>4</td>
</tr>
<tr>
<td>2</td>
<td>28a</td>
<td>[Ir(COD)Cl]2</td>
<td>CH2Cl2</td>
<td>(R)-L8</td>
<td>29a</td>
<td>&gt;99</td>
<td>5</td>
</tr>
<tr>
<td>3</td>
<td>28a</td>
<td>RuCl2</td>
<td>CH2Cl2</td>
<td>(S,S)-L9</td>
<td>29a</td>
<td>&gt;99</td>
<td>4</td>
</tr>
<tr>
<td>4</td>
<td>28a</td>
<td>[Rh(COD)2]BF4</td>
<td>CH2Cl2</td>
<td>(R,S)-L10</td>
<td>29a</td>
<td>&gt;99</td>
<td>6</td>
</tr>
</tbody>
</table>

6.4 Asymmetric hydrogenation of dihydroamino acids

The previous results let us to conclude that asymmetric hydrogenation of cyclic dihydroamino esters containing an acyl group on the amine substituent was rather difficult, resulting in low enantioselectivities (ee <10%). It was therefore suggested to hydrolyze the ester in order to enhance coordination of the dihydroamino carboxylate to the rhodium cation, thereby hopefully enhancing the enantioselectivity (Scheme 6.9).
Asymmetric hydrogenation of α,β-unsaturated cyclic didehydroamino acids


Treatment of didehydroamino esters 28a and 28b with potassium hydroxide in a mixture of dioxane/H$_2$O (1:1) provided the carboxylic acids 30a and 30b in good yields of 91 and 83%, respectively. Hydrogenation was then investigated using both monodentate phosphoramidite L1 and bidentate phosphonate ligands L8-L10. Since acid 30 was poorly soluble in dichloromethane, the reactions were initially carried out in methanol. Hydrogenation of 30a using MonoPhos™ (L1) gave a slight increase of enantioselectivity of up to 8% ee (Table 6.5, entry 1). The bidentate phosphonate ligand (S,S)-DuPhos (L9) showed similar results (ee = 8%). Much to our satisfaction, subjecting carboxylate 30a to (S)-BINAP (L8) and (R,S)-JosiPhos (L10) led to a significant increase of enantioselectivity to 37% and 39%, respectively (entries 2-4). In contrast, the isoquinoline derivative 30b did not react under any of these circumstances.

Table 6.5. Hydrogenation of cyclic didehydroamino acids 30a: ligand screening.

<table>
<thead>
<tr>
<th>entry</th>
<th>substrate</th>
<th>ligand</th>
<th>solvent</th>
<th>product</th>
<th>Conversion (%)</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>30a</td>
<td>(S)-L1</td>
<td>MeOH</td>
<td>31a</td>
<td>&gt;99</td>
<td>8</td>
</tr>
<tr>
<td>2</td>
<td>30a</td>
<td>(S)-L8</td>
<td>MeOH</td>
<td>31a</td>
<td>&gt;99</td>
<td>37</td>
</tr>
<tr>
<td>3</td>
<td>30a</td>
<td>(S)-L9</td>
<td>MeOH</td>
<td>31a</td>
<td>75</td>
<td>8</td>
</tr>
<tr>
<td>4</td>
<td>30a</td>
<td>(S)-L10</td>
<td>MeOH</td>
<td>31a</td>
<td>73</td>
<td>39</td>
</tr>
</tbody>
</table>

Encouraged by these results, we decided to investigate the solvent effect on hydrogenation with phosphate ligands L8 and L10 (Table 6.6). It became clear that the rhodium-L10 catalyst gave a higher hydrogenation rate than the rhodium-L8 complex. Furthermore, when the
reaction was performed with the rhodium-L8 catalyst in 2-propanol or tert-butyl alcohol, a slightly higher enantioselectivity was obtained (entries 1-3). With H₂O as a co-solvent, the enantioselectivity dropped to 23%. Surprisingly, the highest selectivities were observed when the reaction was performed in toluene. The rate, however, was low, probably due to the poor solubility of the carboxylate.

Table 6.6. Hydrogenation of cyclic dehydroamino acid 30a: solvent screening.

<table>
<thead>
<tr>
<th>entry</th>
<th>solvent</th>
<th>ligand</th>
<th>conversion (%)</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>MeOH</td>
<td>(S)-L8</td>
<td>&gt;99</td>
<td>37</td>
</tr>
<tr>
<td>2</td>
<td>iPrOH</td>
<td>(S)-L8</td>
<td>73</td>
<td>45</td>
</tr>
<tr>
<td>3</td>
<td>tBuOH⁴</td>
<td>(S)-L8</td>
<td>92</td>
<td>43</td>
</tr>
<tr>
<td>4</td>
<td>iPrOH/H₂O (1:1)</td>
<td>(S)-L8</td>
<td>44</td>
<td>23</td>
</tr>
<tr>
<td>5</td>
<td>PhMe</td>
<td>(S)-L8</td>
<td>39</td>
<td>47</td>
</tr>
<tr>
<td>7</td>
<td>CH₂Cl₂</td>
<td>(S)-L8</td>
<td>91</td>
<td>39</td>
</tr>
<tr>
<td>8</td>
<td>MeOH</td>
<td>(R,S)-L10</td>
<td>&gt;99</td>
<td>39</td>
</tr>
<tr>
<td>9</td>
<td>iPrOH</td>
<td>(R,S)-L10</td>
<td>&gt;99</td>
<td>45</td>
</tr>
<tr>
<td>10</td>
<td>tBuOH⁴</td>
<td>(R,S)-L10</td>
<td>&gt;99</td>
<td>44</td>
</tr>
<tr>
<td>11</td>
<td>iPrOH /H₂O (1:1)</td>
<td>(R,S)-L10</td>
<td>&gt;99</td>
<td>31</td>
</tr>
<tr>
<td>12</td>
<td>PhMe</td>
<td>(R,S)-L10</td>
<td>19</td>
<td>49</td>
</tr>
<tr>
<td>13</td>
<td>CH₂Cl₂</td>
<td>(R,S)-L10</td>
<td>&gt;99</td>
<td>36</td>
</tr>
</tbody>
</table>

*Reaction was performed at 25 °C. The ee was determined by HPLC-measurements, using a Chiralpak AD-column upon esterification of the carboxylates with TMSCHN₂.*

Based on the best results observed with (S)-BINAP and (R,S)-JosiPhos, we decided to screen several of these types of ligands. At first, we tested the sterically more demanding rhodium-(S)-tolBINAP catalyst (as compared to (S)-BINAP, Table 6.7, entry 3). The enantioselectivity, however, was comparable as for (S)-BINAP (entry 1). The commercially available ferrocene-based ligands L12-L15 were also screened. While the monodentate ligand L12 showed a significant decrease in enantioselectivity, the bidentate ligands L13-L15 showed comparable results as for (R,S)-JosiPhos.
Asymmetric hydrogenation of α,β-unsaturated cyclic dihydroamino acids

### Table 6.7. Hydrogenation of cyclic dihydroamino acid 30a: ligand screening.

<table>
<thead>
<tr>
<th>entry</th>
<th>ligand</th>
<th>conversion (%)</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>(R)-L8</td>
<td>93</td>
<td>38</td>
</tr>
<tr>
<td>2</td>
<td>(R)-L9</td>
<td>89</td>
<td>37</td>
</tr>
<tr>
<td>3</td>
<td>(S)-L11</td>
<td>91</td>
<td>37</td>
</tr>
<tr>
<td>4</td>
<td>(R,S)-L10</td>
<td>100</td>
<td>39</td>
</tr>
<tr>
<td>5</td>
<td>(R,S)-L12</td>
<td>100</td>
<td>8</td>
</tr>
<tr>
<td>6</td>
<td>(R,S)-L13</td>
<td>100</td>
<td>25</td>
</tr>
<tr>
<td>7</td>
<td>(R,S)-L14</td>
<td>100</td>
<td>33</td>
</tr>
<tr>
<td>8</td>
<td>(R,S)-L15</td>
<td>100</td>
<td>23</td>
</tr>
</tbody>
</table>

### 6.5 Conclusions

Asymmetric hydrogenation of α,β-unsaturated dehydroamino esters appeared to be rather difficult, if not impossible. Although a high turnover rate was observed using the phosphoramidite ligands in combination with Rh(COD)$_2$BF$_4$, enantioselectivity of the reactions remained low. Moreover, the use of metals other than rhodium led to a total loss in reactivity. Enantioselectivity was slightly increased upon hydrogenation with bidentate phosphonate ligands. Reduction of the corresponding isoquinolone derivatives only led to the recovery of starting material.

In sharp contrast, hydrolysis of the dehydroamino ester and subsequent hydrogenation of the resulting acids showed a significant increase in selectivity. While the enantiomeric access was only slightly higher upon using MonoPhos™ and (S,S)-DuPhos, we were pleased to find
that the use of (S)-BINAP and (R,S)-JosiPhos led to an ee of 37% and 39%, respectively. Furthermore, the selectivity was increased to 45% when the reactions were performed in 2-propanol. Disappointingly, screening of a small library of both binaphthyl- and ferrocene phosphonate ligands did not lead to higher ee’s.

Finally, hydrogenation of tetrasubstituted alkenes appeared to be unproductive, resulting solely in the recovery of starting material. Both PMB-deprotection and reduction of the amide prior to reduction did not lead to any conversion at all.

6.6 Acknowledgements

Prof. A.J. Minnaard (Stratingh Institute for Chemistry, University of Groningen) and N. Mrsic are gratefully acknowledged for their hospitality and for their guidance and assistance during the asymmetric hydrogenations.
6.7 Experimental Section

General information

For general experimental details, see section 2.7

General procedure for hydrogenation onto the Endeavor

Reactant A (0.075 mmol) was weighed into the reaction vessel. Five mol % of the catalyst was added together with 6 mol% of the ligand (or 12 mol% in case of the monodenate ligands). The solvent (1.5 mL) was then added and the reaction vessel was closed. Pressure (25 bar) and reaction time (16 h) were set and the reaction was started. After 16 h the reaction vessel was opened and the reaction mixture was poured over a plug of silica. The organic layer was concentrated in vacuo and redissolved in propan-2-ol/hexane 1:10. Enantioselectivity was determined using chiral HPLC on a Chiralpak AD-H column (dimensions: 250 x 46 mm) using UV-detection.

General procedure B for hydrogenation in the autoclave

Reactant A (0.075 mmol) was weighed into the reaction vessel. Five mol % of the catalyst was added together with 6 mol% of the ligand (or 12 mol% in case of the monodenate ligands). The solvent (1.5 mL) was then added and the autoclave was flushed with hydrogen and nitrogen for three times after which the vessel was closed. The pressure was set and the reaction was stirred at room temperature at a magnetic stirring machine. After 16 hours the reaction vessel was opened and the reaction mixture was poured over a plug of silica. The organic layer was concentrated in vacuo and redissolved in propan-2-ol/hexane 1:10. Enantioselectivity was determined using chiral HPLC on a Chiralpak AD-H column (dimensions: 250 x 46 mm) using UV-detection.

Ethyl-6-Oxo-3-phenyl-1,4,5,6-tetrahydropyridine-2-carboxylate (21)

A solution of 19 (809 mg, 1.95 mmol) in TFA/CH₂Cl₂ 1:4 (10.0 mL) was stirred for 16 h at 65 °C. After 16 h, the temperature was decreased to 0 °C. The reaction mixture was diluted with CH₂Cl₂ and quenched with aqueous NaHCO₃. The organic layer was washed with H₂O (10 mL), dried over MgSO₄ and concentrated in vacuo. The residue was purified by flash column chromatography (EtOAc/heptane 1:1) affording compound 21 (620 mg, 87%). Rf = 0.36 (EtOAc/heptane 1:1).

**FTIR (ATR)** 701, 735, 1683, 2915 cm⁻¹.

**1H NMR (CDCl₃, 400 MHz):** δ 7.65 (s, 1H), 7.45 - 7.34 (m, 3H), 7.17 - 7.04 (m, 2H), 4.01 (q, 2H, J = 7.2 Hz), 2.83 - 2.77 (m, 2H), 2.66 - 2.62 (m, 2H), 0.92 (t, 3H, J = 7.1 Hz).

**13C NMR (CDCl₃, 75 MHz):** δ 168.84, 139.10, 128.63, 127.50, 127.25, 127.10, 126.79, 123.19, 61.10, 29.76, 29.25, 12.94. HRMS (ESI) m/z calcd for C₁₄H₁₅NO₃Na (M+Na)⁺: 268.0950, found: 268.0943.

1-Tert-butyl-2-ethyl-6-Oxo-3-phenyl-5,6-dihydro-4H-pyridine-1,2-dicarboxylate (23)

To a solution of 22 (185 mg, 0.76 mmol) in dry CH₂Cl₂ (8 mL) was added DMAP (111 mg, 1.0 equiv) and Boc₂O (246 mg, 1.5 equiv). The reaction mixture was stirred at room temperature for 16 h, quenched with aqueous NH₄Cl and extracted with CH₂Cl₂. The organic layer was washed with H₂O, dried (MgSO₄) and concentrated in vacuo. The residue was purified by column chromatography (EtOAc/heptane 1:2) to give 23 (235 mg, 0.68 mmol, 86%) as a colorless oil. Rf = 0.51 (EtOAc/heptane 1:2). FTIR (ATR) 1149, 1243, 1720, 1785 cm⁻¹. **1H NMR (CDCl₃, 400 MHz):** δ 7.37 - 7.16 (m, 5H), 3.96 (2H, q, J = 7.1 Hz), 2.73-2.68 (m, 4H), 1.51 (s, 9H), 0.91 (t, 3H, J = 7.1 Hz). **13C NMR (CDCl₃, 75 MHz):** δ
1-Tert-butyl-2-ethyl-3-Phenyl-5,6-dihydro-4H-pyridine-1,2-dicarboxylate (24)

A solution of 23 (20 mg, 0.056 mmol) in dry THF (2 mL) was cooled to -78 °C, LiEt₂BH₄ (1.2 equiv, 76 µL) was added and the reaction was stirred for 1 h. After 1 h the reaction was quenched with aqueous NaHCO₃ (5 mL) and the temperature was raised to 0 °C, a drop of H₂O₂ was added and the reaction was stirred for another 20 min. The organic layer was concentrated and redissolved in CH₂Cl₂, dried (MgSO₄) and concentrated in vacuo. The residue was purified by column chromatography (EtOAc/heptane 1:3) to give 24 (11 mg, 0.032 mmol, 57%) as a colorless oil. Rf 0.88 (EtOAc/heptane 1:1). FTIR (ATR) 1247, 1511, 1589, 1657 cm⁻¹. ¹H NMR (CDCl₃ 400 MHz): δ 7.50 (d, 1H, J = 8.5 Hz), 3.87 (br s, 2H), 3.67 (t, 2H, J = 5.4 Hz), 2.44 (t, 2H, J = 6.7 Hz), 1.97 (m, 2H), 1.21 (dt, 1H, J = 0.6 Hz, J = 7.1 Hz).

1-(4-Methoxybenzyl)-5-phenyl-1H-pyridin-2-one (27)

To a solution of 26 (351 mg, 0.85 mmol) in dioxane (8 mL) was added aqueous NaOH (4 mL, 2.5 equiv, 85 mg). After 16 h amberlite IR 120+ was added. The reaction mixture was stirred for another hour and concentrated in vacuo. The residue was purified by column chromatography (10% MeCN/H₂O) to give 27 (240 mg, 0.82 mmol, 96%) as a yellow oil. Rf 0.38 (EtOAc/heptane 1:1). FTIR (ATR) 1247, 1511, 1589, 1657 cm⁻¹. ¹H NMR (CDCl₃ 400 MHz): δ 7.57 (dd, 1H, J = 2.7 Hz, J = 9.4 Hz), 7.47 (dd, 1H, J = 0.5 Hz, J = 2.6 Hz), 7.39-7.23 (m, 5H), 6.86 (d, 2H, J = 8.8 Hz), 6.67 (dd, 1H, J = 0.4 Hz, J = 9.4 Hz), 6.53-6.33 (m, 3H), 6.37 (s, 3H). ¹³C NMR (CDCl₃, 75 MHz): δ 161.47, 159.01, 138.70, 136.02, 133.93, 129.27, 128.55, 127.93, 126.80, 125.29, 120.61, 119.85, 113.85, 54.78, 51.28, 34.96, 31.42, 28.56, 25.98, 25.87, 22.23, 13.66. HRMS (ESI) m/z calcd for C₁₃H₁₂NO₂Na (M+Na)⁺: 354.1681, found: 354.1688.

Ethyl-1-(4-Methoxybenzyl)-6-oxopiperidine-2-carboxylate (29a)

A solution of 28a (40 mg, 0.14 mmol) in MeOH (2 mL) was flushed with nitrogen for 15 min after which 10% Pd/C (10 %/w, 6 mg, 0.082 mmol, 91%) as a colorless oil. Rf 0.41 (EtOAc/heptane 1:1). FTIR (ATR) 1174, 1243, 1511, 1639, 1736, 2946 cm⁻¹. ¹H NMR (CDCl₃, 400 MHz): δ 7.12 (d, 2H, J = 8.5 Hz), 6.84 (d, 2H, J = 8.4 Hz), 5.14 (d, 1H, J = 14.8 Hz), 4.12 (q, 2H, J = 7.1 Hz), 4.04 (dd, 1H, J = 2.8 Hz, J = 5.8 Hz), 3.82 (d, 1H, J = 14.8 Hz), 3.76-3.70 (m, 3H), 2.45-2.41 (m, 2H), 2.09-2.01 (m, 1H), 1.94-1.88 (m, 1H), 1.77-1.72 (m, 2H), 1.21 (dt, 1H, J = 0.6 Hz, J = 7.1 Hz). ¹³C NMR (CDCl₃, 75 MHz): δ 171.06, 171.01, 158.92, 128.92, 114.93, 113.21, 60.91, 58.01, 53.86, 48.07, 30.53, 25.29, 17.16, 12.59. HRMS (ESI) m/z calcd for C₁₅H₁₄NO₃ (M+Na)⁺: 314.1530, found: 314.1601.

Ethyl-2-(4-Methoxybenzyl)-1-oxo-1,2,3,4-tetrahydrosoquinoline-3-carboxylate(29b)

A solution of 28b (20 mg, 0.12 mmol) in MeOH (2 mL) was pumped through the H-cube (flowrate = 1.0 mL/min, P = 10 bar, T = 40 °C). The organic layer was collected and concentrated in vacuo. The residue was purified by column chromatography (EtOAc/heptane 1:2) to give 29b (26 mg, 0.082 mmol, 91%) as a colorless oil. Rf 0.38 (EtOAc/heptane 1:1). FTIR (ATR) 1246, 1511, 1652, 1738, 2937 cm⁻¹. ¹H NMR (CDCl₃, 400 MHz): δ 7.96 (dd, 1H, J = 1.1 Hz, J = 7.7 Hz), 7.44 (dt, 1H, J = 1.4 Hz, J = 7.5 Hz), 7.38-7.31 (m, 1H), 7.26 (d, 1H, J = 8.7 Hz), 7.19 (d, 1H, J = 7.5 Hz), 6.88 (d, 1H, J = 8.7 Hz), 5.24 (d, 1H, J = 14.8 Hz), 4.32 (dd, 1H, J = 2.1 Hz, J = 6.5 Hz), 4.18 (d, 1H, J = 14.7 Hz), 3.99-3.94 (m, 2H), 3.75 (s, 3H), 3.34-3.30 (m, 1H), 3.19 (dd, 1H, J = 2.0 Hz, J = 16.3 Hz), 1.01 (t, 3H, J = 7.1 Hz).
Asymmetric hydrogenation of α,β-unsaturated cyclic dihydroamino acids

$^{13}$C NMR (CDCl$_3$, 300 MHz): $\delta$ 170.27, 134.95, 131.60, 129.00, 128.15, 126.93, 126.67, 126.62, 113.27, 60.81, 56.88, 53.83, 48.63, 30.24, 12.40. HRMS (ESI) m/z calcld for C$_{12}$H$_{23}$NO$_4$ (M+H)$^+$: 340.1525, found: 340.1523.

**1-(4-Methoxybenzyl)-6-oxo-1,4,5,6-tetrahydropyridine-2-carboxylic acid (30a)**

To a solution of 28a (720 mg, 2.49 mmol) in dioxane (20 mL) was added a solution of NaOH (2.5 equiv, 270 mg) in H$_2$O (5 mL). The reaction was stirred for 6 h and neutralized with amberlite IR 120+, filtered and concentrated in vacuo. The residue was purified by column chromatography (10% H$_2$O/MeCN to 25% H$_2$O/MeCN) to give 30a (26 mg, 0.082 mmol, 91%) as a colorless oil.

$R_f$ = 0.28 (10% H$_2$O/MeCN).

$^1$H NMR (CDCl$_3$, 400 MHz): $\delta$ 7.11 (d, 2H, $J = 8.7$ Hz), 6.77 (d, 2H, $J = 8.7$ Hz), 6.09 (t, 1H, $J = 5.0$ Hz), 5.00 (s, 2H), 3.71 (s, 3H), 2.45 (t, 2H, $J = 7.2$ Hz), 2.26-2.20 (m, 2H).

$^{13}$C NMR (CDCl$_3$, 75 MHz): $\delta$ 171.78, 167.47, 158.47, 138.30, 129.60, 128.69, 128.57, 128.47, 116.08, 112.95, 53.77, 44.07, 30.256, 18.57.

HRMS (ESI) m/z calcld for C$_{14}$H$_{15}$NO$_4$Na (M+Na)$^+$: 284.0899, found: 284.0890.

**2-(4-Methoxybenzyl)-1-oxo-1,2-dihydroisoquinoline-3-carboxylic acid (30b)**

To a solution of 28b (573 mg, 1.70 mmol) in dioxane (15 mL) was added a solution of NaOH (2.5 equiv, 102 mg) in H$_2$O (5 mL). The reaction was stirred for 6 h and neutralized with amberlite IR 120+, filtered and concentrated in vacuo. The residue was purified by column chromatography (10% H$_2$O/MeCN to 25% H$_2$O/MeCN) to give 30b (436 mg, 1.41 mmole, 83%) as a colorless oil.

$R_f$ = 0.28 (10% H$_2$O/MeCN).

$^1$H NMR (CDCl$_3$, 400 MHz): $\delta$ 8.31 (d, 1H, $J = 8.4$ Hz), 7.61-7.91 (m, 3H), 7.45 (s, 1H), 7.07 (d, 2H, $J = 8.8$ Hz), 6.82 (d, 2H, $J = 8.8$ Hz), 5.84 (s, 2H), 4.82 (s, 3H).

$^{13}$C NMR (CDCl$_3$, 75 MHz): $\delta$ 166.25, 165.04, 160.96, 136.91, 134.81, 131.69, 130.74, 130.49, 129.38, 129.25, 128.24, 115.42, 114.61, 56.18, 47.91.

HRMS (ESI) m/z calcld for C$_{18}$H$_{15}$NO$_4$ (M+Na)$^+$: 332.0899, found: 332.0886.
6.8 References

Asymmetric hydrogenation of α,β-unsaturated cyclic dihydroamino acids


21 Argonaut Endeavor® catalyst screening system.

A stereoselective total synthesis of tangutorine

Abstract

We herewith describe a novel approach to racemic tangutorine (1) starting from the key building block 5. As shown below, a first disconnection of the pentacyclic tangutorine framework would involve a Bischler-Napieralski cyclization, followed by reduction giving rise to bicyclic precursor 2. Subsequently, quinoline 2 could be derived via RCM from the trans-5,6-disubstituted lactam 3. We were hopeful that the primary iodide 4 would serve as a suitable precursor to deliver 5 via organozinc/copper-mediated coupling with ethyl 2-(bromomethyl)acrylate. Finally, diastereoselective copper-catalyzed 1,4-addition onto 5, followed by some further functionalization was anticipated to lead to iodide 4.

7.1. Introduction

β-Carbolines (e.g. 1, 6 and 7, Figure 7.1), a family of monoterpenoid indole alkaloids, constitute an important class of natural products. They are one of the principal alkaloid groups in the plant kingdom and are biosynthetically derived from the amino acid tryptophan. Some of the alkaloids that are most widely used in medicine belong to this group and contain the yohimbine skeleton (viz. yohimbine (6)). For instance reserpine (7), an antihypertensive drug and one of the first medicinal monoterpenoid agents, has been used for many years to control high blood pressure and to relieve psychotic behaviors. However, due to the many side effects, the use of reserpine as an antipsychotic has been almost completely abandoned nowadays. Despite these disadvantages, many derivatives of reserpine all containing the yohimbine substructure have been synthesized over the past decades in the search for compounds with equal activity, but less undesired side effects.

![Figure 7.1. Monoterpenoid indole alkaloids.](image)

Up till now, nearly 3000 monoterpenoid indole alkaloids with interesting pharmacological properties have been isolated from natural sources. A potentially relevant derivative, (±)-tangutorine (1), was isolated in 1999 by Duan and colleagues from the leaves of the Chinese medical plant *Nitraria tangutorine*. Although tangutorine is structurally related to the yohimbine skeleton, it is the only known β-carboline alkaloid that contains a quinolizidine subunit. Biologically, tangutorine shows interesting effects on the regulation of cell cycle and cellular morphology of HT29, which are human colon cancer cells.

The first total synthesis of tangutorine was reported in 2001 by the group of Jokela. Their synthesis started with preparing dihydroquinolone 8 from 1,3-cyclohexanedione in two steps (Scheme 7.1). The ester substituent was introduced by refluxing the dihydroquinolone with dimethyl carbonate in the presence of sodium hydride and a catalytic amount of methanol. Next, alkylation of the nitrogen with tryptophyl bromide provided the pyridinium salt 9. Reduction with sodium dithionite in a water/methanol mixture in the presence of sodium...
bicarbonate selectively led to cyclic enamine 10. Upon protonation of the double bond, 10 was cyclized via a Pictet-Spengler reaction and subsequently reduced with sodium borohydride in glacial acetic acid. Mesylation of the alcohol, followed by elimination with DBU and reduction of the methyl ester with lithiumaluminum hydride gave tangutorine (1) in 3.2% yield over ten steps.

Scheme 7.1. First total synthesis of tangutorine (1) by Jokela et al.

A different approach was published by Hsung and co-workers, who commenced their synthesis with the protection of tryptamine and subsequent bromination to form the Heck reagent 14 in three consecutive steps (Scheme 7.2). The bromide 14 underwent a Heck reaction with methyl acrylate to give the conjugated ester 16. In the next three steps the ester was reduced and the amine was deprotected. The resulting amine 17 was then condensed with cyclohexa-1,3-dione, followed by oxidation of the alcohol to aldehyde 19. Formation of the iminium ion 20 then initiated an intramolecular aza-[3+3] cycloaddition whereupon two rings were formed simultaneously. In the next four steps the double bonds were diastereoselectively reduced, after which another five steps were required for completion of the synthesis. The total synthesis was completed in 19 steps with an overall yield of 5.5%.
In 2006, a third synthesis was published by Ho et al.\textsuperscript{9} In a nine-step sequence cyclohexa-1,3-dione (18) was reacted with acrolein and the resulting acetal was subsequently converted into aldehyde 23 using lithiumaluminum hydride. The aldehyde was condensed with tryptamine, which directly underwent a Pictet-Spengler reaction, followed by an aza-Michael addition. In order to facilitate the purification, the indole was protected with a Boc-group. The allylic alcohol 25 was introduced under Vilsmeier-Haack conditions (POCl\textsubscript{3}/DMF) to generate the β-chloro α,β-unsaturated aldehyde, followed by sodium borohydride reduction. Finally, Na-naphthalenide was used to dechlorinate 25 providing Boc-protected tangutorine (1) in 3.0% yield over nine steps.

**Scheme 7.2.** Synthesis of tangutorine (1) by Hsung et al.
A stereoselective total synthesis of tangutorine

Scheme 7.3. Synthesis of tangutorine (1) by Ho et al.

During the course of our research, an elegant biomimetic approach to tangutorine (1) was published by the Poupon group. Their synthesis commenced with glutaraldehyde, which under basic conditions dimerized to give an aldehyde/acetal equilibrium between compounds 27 and 28. Elimination of water under acidic conditions, followed by condensation with tryptamine and cyclization to the intermediate amine 30, afforded the pentacycle 31 after a second cyclization. The latter reaction proceeded via an intramolecular Pictet-Spengler reaction, followed by an extended aza-Michael addition in a single transformation, albeit in an inseparable 75:25 mixture. The aldehyde was then reduced with sodium borohydride in the presence of cesium chloride. Finally, recrystallization afforded diastereomerically pure tangutorine (1) in 3.8% yield over six steps.

Scheme 7.4. Synthesis of tangutorine (1) by Poupon.
In our retrosynthetic strategy, we envisaged that two disconnections would be crucial: starting from tangutorine (1), Bischler-Napieralski-mediated ring-opening was envisaged to provide intermediate 32, which in turn, via RCM-induced cleavage of the olefin should provide structure 33. The required side chain was thought to be introduced via a Zn/Cu-mediated coupling onto vinyl-substituted piperidine 34. The latter fragment may be derived from the α,β-unsaturated dehydroamino acid 35 via conjugate addition and reduction of the carboxylic ester.

![Scheme 7.5](image)

**Scheme 7.5.** Retrosynthetic approach to tangutorine.

### 7.2 Synthesis of the quinolizidine precursor of tangutorine

Our forward synthesis commenced with a copper-catalyzed 1,4-addition onto an α,β-unsaturated cyclic dehydroamino ester, which was described in Chapter 5 as a new approach to access trans-5,6-disubstituted 2-oxopiperidine carboxylic esters. Based on this idea, lactam 38 was considered a suitable precursor to enter the quinolizidine substructure of tangutorine (1). Having the trans-5,6-disubstituted 2-oxopiperidine carboxylic esters 38 available, we set out to investigate the potential of organo-zinc/copper couplings with primary iodides, which had to be prepared from ester 38. Reduction of ester 38 using DIBAL-H at −78 °C was unproductive since only starting material was recovered. Use of LiAlH₄ on the other hand gave no product and led to reduction of both the alcohol and amide functions. Gratifyingly, reduction with LiEt₃BH at 0 °C appeared efficient yielding the desired
alcohol 39 in 95%. Conversion into the primary iodide 40 was accomplished in 67% yield using iodine in the presence of triphenylphosphine and imidazole.


With the desired iodide 40 in hand, substitution of the iodide substituent was explored. An organozinc/copper coupling onto iodide 40 was chosen as the method to introduce the second double bond.\textsuperscript{11} To probe the feasibility of this reaction, we decided to test a variety of electrophiles (Table 7.1).

Table 7.1. Organozinc/copper coupling with different electrophiles.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Electrophile</th>
<th>Product</th>
<th>Yield 41 (%)</th>
<th>Yield 42 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>OₚH Cl</td>
<td>41a</td>
<td>–</td>
<td>75</td>
</tr>
<tr>
<td>2</td>
<td>=C=O₂Et</td>
<td>41b</td>
<td>–</td>
<td>39</td>
</tr>
<tr>
<td>3</td>
<td>=C≡CN</td>
<td>41c</td>
<td>–</td>
<td>67</td>
</tr>
<tr>
<td>4</td>
<td>Br=CO₂Et</td>
<td>41d</td>
<td>44</td>
<td>46</td>
</tr>
</tbody>
</table>

Interestingly, organozinc/copper coupling with acid chlorides (entry 1) did not lead to chain extension, but instead resulted in the ring-opened product 42 together with trace amounts of 43.\textsuperscript{12} Moreover, 1,4-addition onto 40 under identical conditions with either ethyl acrylate (entry 2) or acrylonitrile (entry 3) led to similar results. Gratifyingly, reaction of 40 with 2-
bromoethylacrylic acid ethyl ester (S$_2$N$_2$'-type reaction, entry 4) resulted in the RCM-precursor 41d, the anticipated product for construction of the quinoline substructure, albeit in a moderate yield of 42%. In addition, a substantial amount of the ring-opened product 42 was formed.

**Scheme 7.7.** RCM of the quinoline-precursor 41d.

With the dialkene 41d prepared, next a ring-closing metathesis was thought to provide the corresponding isoquinoline product. Treatment of 41d with G2 (10 mol%) indeed yielded quinoline 44 in 89% yield (Scheme 7.9). Without further optimization of the cyclization reaction, initial attempts to complete the synthesis of tangutorine (1) started with PMB-deprotection of 44 followed by N-alkylation with Boc-protected tryptophyl bromide (47). Removal of the PMB-group under acidic conditions (TFA, 70 °C, 16 h) at elevated temperatures proceeded smoothly in 74% yield. In contrast, the resulting secondary amide proved to be unreactive toward alkylation with the aliphatic bromide 47 (Scheme 7.7). Alkylation in the presence of DIPEA at elevated temperatures only led to degradation of the starting material. Attempts to deprotonate the lactam with NaH prior to addition of the bromide were also met with failure. Addition of tetrabutylammonium iodide or potassium iodide did not show any improvement. A raise in temperature on the other hand, only led to degradation.

### 7.3 Bischler-Napieralski cyclizations

As indicated by the previous results, N-alkylation of quinoline 45 appeared less trivial than anticipated. We therefore chose to study introduction of the indole in the linear enamide stage prior to ring-closure (1) and 1,4-addition (2). Since N-alkylation of dehydroamino ester
48 would avoid the PMB-protection/deprotection sequence, it had our preference. However, deprotonation of 48 with NaH in DMF only led to rapid degradation of the starting material (Scheme 7.8). Reaction of 51 under similar conditions did result in N-alkylation, but the isolated yield never exceeded 10%. Remarkable, alkylation involving portionwise addition of NaH (5 times 0.25 equiv) led to a distinct increase in yield of 52 to an acceptable 53%.

Scheme 7.8. N-alkylation with Boc-protected tryptophyl bromide 47.

With the indole successfully incorporated (52), a Bischler-Napieralski cyclization was envisioned to construct the pentacyclic system.14 To promote the selectivity of the reaction, a copper-catalyzed 1,4-addition with vinylmagnesium bromide was performed prior to the cyclization. Indeed, when 53 was reacted with POCl₃ and toluene in CH₂Cl₂ at elevated temperatures, the iminium salt was obtained according to mass spectrometry (ESI). However, the reaction never reached full conversion. Reaction at higher temperatures in toluene on the other hand proceeded smoothly. The crude iminium salt 54 was immediately reduced to the amine upon treatment with sodium borohydride. Reduction led to the Boc-deprotected pentacyle 55 in 78% yield as an inseparable 86:14 mixture of diastereoisomers according to ¹H-NMR (Scheme 7.9).
7.4 Completion of tangutorine

Due to the cleavage of the Boc-group during the Bischler-Napieralski cyclization, reprotection of the tryptophyl moiety would be necessary to complete the synthesis of the quinolizidine moiety (Scheme 7.10).

Scheme 7.10. Completion of the formal synthesis of (+)-tangutorine.
To avoid the reprotection step, the developed 1,4-addition/iodonation/organozinc-copper coupling sequence was successfully applied to convert 53 into the N-tryptophyl substituted cyclic dehydroamino ester 58 (Scheme 7.10) yielding the RCM precursor in three consecutive steps (36%). Again, the ring-opened product was 59 was obtained as major by-product (17%). With 58 in hand, we were pleased to find that RCM (62, 80 °C, 1 h, PhMe) proceeded in a nearly quantitative yield. Subsequently, this time Bischler-Napieralski cyclization proceeded in a completely diastereoselective fashion, as confirmed by 1H-NMR, to the energetically most favourable product. Since in the latter step, the Boc-group was only partially cleaved, pentacycle 61 was further reacted under acidic conditions (TFA/CH2Cl2 1:2) affording the known 62 – a known precursor for tangutorine7 – in a total yield of 45%. Finally, the ester was reduced according to known procedures yielding tangutorine (1) in 82%.15 In overall, tangutorine has been prepared from commercial available chemicals in eleven consecutive steps with an overall yield of 3.0%.

7.5 Conclusions

In conclusion, we have shown that the cyclic dehydroamino ester, described in Chapter 2, can be efficiently converted into tangutorine in eight consecutive steps in an overall yield of 6.5%. The viability of the complete synthesis was proven by N-alkylation of the cyclic dehydroamino ester with Boc-protected tryptophyl bromide prior to quinoline formation. Next, a 1,4-addition using vinylmagnesium bromide followed by chain extension onto the ester provided for the precursor for RCM. This chain extension was accomplished by conversion of the ester into the corresponding iodide, which was then treated with an organozinc/copper coupling sequence. After formation of the quinoline, a Bischler-Napieralski cyclization afforded the pentacycle yielding tangutorine upon reduction of the corresponding ester.

7.6 Acknowledgements

Jaap G.H. Lemmers is gratefully acknowledged for his contribution to this chapter.
7.7 Experimental Section

General information

For general experimental details, see Section 2.7

6-(Hydroxymethyl)-1-(4-methoxybenzyl)-5-vinylpiperidin-2-one (39)

To a cooled solution (0 °C) of compound 38 (0.95 g, 3.0 mmol) in THF (30 mL), LiEt₂BH (9 mL, 9.0 mmol (1 M solution in THF) was added. After 1.5 h stirring at 0 °C another portion of LiEt₂BH (1.5 mL, 1.5 mmol) was added and the reaction was stirred for another 2 h. The reaction was quenched with ice-water (25 mL) and the product was extracted with CH₂Cl₂ (3 x 25 mL), dried over MgSO₄ and concentrated in vacuo. The residue was purified by flash column chromatography (EtOAc/heptane 1:1) affording compound 39 (0.78 g, 95%). Rf 0.41 (DCM/MeOH 9:1). FTIR (ATR) 3376, 2948, 1613, 1512 cm⁻¹. ¹H NMR (CDCl₃, 400 MHz): δ 7.16 (m, 2H), 6.86 (m, 2H), 5.64-5.54 (m, 1H), 5.07-5.00 (m, 3H), 4.25 (d, 1H, J = 14.8 Hz), 3.79 (s, 3H), 3.79-3.73 (m, 1H), 3.64-3.56 (m, 1H), 3.21-3.16 (m, 1H), 2.72-2.63 (m, 1H), 2.58-2.37 (m, 2H), 2.05-1.95 (m, 2H), 1.72-1.60 (m, 1H). ¹³C NMR (CDCl₃, 75 MHz): δ 171.0, 169.9, 138.5, 129.8, 129.3, 128.5, 128.4, 113.7, 113.3, 61.18, 60.65, 54.84, 46.92, 38.34, 30.05, 23.86. HRMS (ESI) m/z calcd for C₁₅H₂₀NO₂Na (M+Na)⁺: 298.1421, found: 298.1419.

6-(Iodomethyl)-1-(4-methoxybenzyl)-5-vinylpiperidin-2-one (40)

To a solution of compound 39 (105 mg, 0.38 mmol) in THF (4 mL), PPh₃ (120 mg, 0.46 mmol) and imidazole (39 mg, 0.57 mmol) were added. The reaction was heated to 70 °C and iodine (116 mg, 0.46 mmol) was added. After 30 minutes the reaction was cooled to room temperature and concentrated in vacuo. The residue was purified by flash column chromatography (EtOAc/heptane 1:1) affording compound 40 (140 mg, 67%). Rf 0.82 (CH₂Cl₂/MeOH 9:1). FTIR (ATR) 2948, 1642, 1512, 1244, 519 cm⁻¹. ¹H NMR (CDCl₃, 400 MHz): δ 7.16 (m, 2H), 6.86 (m, 2H), 5.59-5.49 (m, 1H), 5.51 (d, 1H, J = 15.0 Hz), 5.14-5.04 (m, 2H), 3.80 (s, 3H), 3.75 (d, 1H, J = 15.1 Hz), 3.36-3.33 (m, 2H), 2.94-2.89 (m, 1H), 2.68-2.60 (m, 1H), 2.60-2.41 (m, 2H), 1.95-1.86 (m, 1H), 1.78-1.66 (m, 1H). ¹³C NMR (CDCl₃, 75 MHz): δ 169.96, 158.68, 137.84, 129.12, 127.95, 116.94, 113.73, 57.84, 54.85, 45.48, 41.49, 30.05, 23.24, 9.43. HRMS (ESI) m/z calcd for C₁₅H₂₀INO₃Na (M+Na)⁺: 408.0439, found: 408.0436.

4-[1-(4-Methoxybenzyl)-6-oxo-3-vinylpiperidin-2-yl]-2-methylenetricarbonylacetic acid ethyl ester (41d)

Zinc dust (52.3 mg, 0.8 mmol) was weighed into a schlenk flask, which was dried with a flame and flushed with argon. 1,2-dibromoethane (3.3 μL, 0.04 mmol) in dry DMF (0.3 mL) was added and the flask was heated to 60 °C for 1 hour. TMSCl (0.5 μL, 0.004 mmol) was added and the mixture was stirred at 60 °C for 30 minutes. Compound 40 (50 mg, 0.13 mmol) was dissolved in DMF (0.4 mL), added to the mixture and stirred 10 min at 60 °C. CuCN (11.6 mg, 0.13 mmol) and LiCl (11 mg, 0.26 mmol) were heated to 150 °C under vacuum for 2 hours and cooled to room temperature. Addition of DMF (0.5 mL) formed a soluble CuCN-2LiCl complex. After cooling the organozinc reagent to −55 °C the Cu-complex was added and the solution was warmed to 0 °C. After stirring 10 min at 0 °C the solution was cooled to −55 °C and ethyl 2-(bromomethyl)acrylate (21.8 μL, 0.156 mmol) was added. The solution was slowly warmed to room temperature and stirred over night. The mixture was filtered over celite, diluted with EtOAc, washed with aq. NH₄Cl and brine, dried over MgSO₄ and concentrated in vacuo. The residue was purified by flash column chromatography (EtOAc/heptane 1:1) affording compound 41d (43 mg, 45%). Rf 0.25 (EtOAc/heptane 1:1). FTIR (ATR) 2936, 1712, 1635, 1512, 1245 cm⁻¹. ¹H NMR (CDCl₃, 400 MHz): δ 7.18 (m, 2H), 6.83 (m, 2H), 6.16 (d, 1H, J = 1.2 Hz), 5.60-5.50 (m, 1H), 5.50 (d, 1H, J = 1.2 Hz), 5.42 (d, 1H, J = 14.6 Hz), 5.01-4.92 (m, 2H), 4.23 (q, 2H, J = 7.1 Hz), 3.79 (s, 3H), 3.76 (d, 1H, J = 14.6 Hz), 3.18-3.13 (m, 1H), 2.58-2.45 (m, 2H), 2.44-2.34 (m, 1H), 2.33-2.17 (m, 2H), 2.06-1.95 (m, 1H), 1.90-1.63 (m, 3H), 1.32 (t, 3H, J = 7.1 Hz). ¹³C NMR (CDCl₃, 75 MHz): δ 169.77, 166.35, 158.43, 139.48, 138.46, 129.42, 128.94, 124.86, 115.63, 113.47, 60.34, 58.08, 54.85, 46.04, 39.34, 30.18, 28.99, 27.53, 22.54, 13.82. HRMS (ESI) m/z calcd for C₂₂H₂₃NO₄Na (M+Na)⁺: 394.1997, found: 394.1994.
4-(methoxybenzyl)-4-Vinylhex-5-enamide (42)

This compound was obtained as a side product in the organozinc-coupling. Rₜ 0.43 (EtOAc/heptane 1:1). FTIR (ATR) 3282, 3073, 2930, 1641, 1512, 1246 cm⁻¹. ¹H NMR (CDCl₃, 400 MHz): δ 7.20 (m, 2H), 6.86 (m, 2H), 5.75-5.64 (m, 2H), 5.62 (br. s, 1H), 5.05-4.96 (m, 4H), 4.36 (d, 2H, J = 5.6 Hz), 3.80 (s, 3H), 2.71 (p, 1H, J = 7.4 Hz), 2.19 (t, 2H, J = 7.4 Hz), 1.79 (m, 2H). ¹³C NMR (CDCl₃, 75 MHz): δ 171.95, 158.66, 139.98, 129.95, 128.83, 114.59, 113.65, 54.84, 46.93, 42.64, 33.85, 29.32. HRMS (ESI) m/z calcd for C₃₅H₃₂NO₂Na (M+Na)+: 282.1472, found: 282.1470.

Ethyl-1-(4-methoxybenzyl)-2-oxo-1,2,3,4a,7,8,8a-octahydroquinoline-6-carboxylate (44)

Compound 41d (40 mg, 0.11 mmol) was dissolved in toluene (4 mL) and flushed with argon. Grubbs second generation catalyst (9.2 mg, 0.01 mmol) was added and the solution was heated at 80 °C. After 1 hour the solution was cooled to room temperature and concentrated in vacuo. The residue was purified by flash column chromatography (EtOAc/heptane 1:2:1) affording compound 44 (34 mg, 86%). Rₜ 0.16 (EtOAc/heptane 1:1). FTIR (ATR) 2933, 1708, 1639, 1512, 1244 cm⁻¹. ¹H NMR (CDCl₃, 400 MHz): δ 7.13 (d, 2H, J = 8.8 Hz), 6.84 (d, 2H, J = 8.8 Hz), 6.67 (d, 1H, J = 1.3 Hz), 5.06 (d, 1H, J = 15.4 Hz), 4.42 (d, 1H, J = 15.4 Hz), 4.17 (q, 2H, J = 7.1, Hz), 3.79 (s, 3H), 3.08 (dd, 1H, J = 12.2, 9.8, 2.5 Hz), 2.76-2.59 (m, 2H), 2.55-2.31 (m, 3H), 2.23-2.09 (m, 1H), 2.05-1.97 (m, 1H), 1.60 (m, 1H), 1.42 (m, 1H), 1.27 (t, 3H, J = 7.1 Hz). ¹³C NMR (CDCl₃, 75 MHz): δ 167.0, 166.13, 158.21, 138.74, 129.36, 127.92, 126.77, 113.54, 60.17, 57.65, 54.88, 44.54, 39.50, 32.47, 26.45, 25.94, 24.03, 13.75. HRMS (ESI) m/z calcd for C₇₀H₇₂NO₂Na (M+Na)+: 366.1684, found: 366.1681.

Tert-butyl-3-[2-bromoethyl]indole (47)

To a cooled (0 °C) solution of tryptophyl bromide (1.33 g, 6 mmol), Et₃N (1.6 mL, 12 mmol) and DMAP (147 mg, 1.2 mmol) in DCM (60 mL), a solution of Boc₂O (1.43 g, 6.6 mmol) was added dropwise. The solution was stirred 2 hours at 0 °C, then quenched with H₂O, extracted with DCM, washed with H₂O, dried over MgSO₄ and concentrated under reduced pressure. The residue was purified by flash column chromatography (EtOAc/heptane 1:4) affording compound 48 (1.64 g, 85%). Rₜ 0.67 (EtOAc/heptane 1:1). ¹H NMR (CDCl₃, 400 MHz): δ 8.14 (br. d, 1H, J = 7.4 Hz), 7.52-7.45 (m, 2H), 7.35-7.29 (m, 1H), 7.27-7.21 (m, 1H), 3.62 (t, 2H, J = 7.6 Hz), 3.26 (t, 2H, J = 7.6 Hz), 1.66 (s, 9H).

Ethyl-6-Oxo-1,4,5,6-tetrahydropyridine-2-carboxylate (51)

The cyclic dehydroamino ester 50 (1.04 g, 3.6 mmol) was dissolved in a TFA/CH₂Cl₂ mixture (1:4, 36 mL) and stirred overnight at 50 °C. The reaction was quenched with NaHCO₃ and the organic compound was extracted with CH₂Cl₂, dried over Na₂SO₄ and concentrated in vacuo. The residue was purified by flash column chromatography (EtOAc/heptane 1:1) affording compound 51 (516 mg, 85%). Rₜ 0.14 (EtOAc/heptane 1:1). ¹H NMR (CDCl₃, 400 MHz): δ 7.58 (s, 1H), 6.29-6.26 (m, 1H), 4.29 (q, 2H, J = 7.1 Hz), 2.53-2.50 (m, 4H), 1.33 (t, 3H, J = 7.1 Hz). ¹³C NMR (CDCl₃, 75 MHz): δ 169.25, 161.22, 128.46, 113.53, 61.47, 28.74, 20.33, 13.72.

3-[2-[6-Ethoxy carbonyl-2-oxo-3,4-dihydro-2H-pyridin-1-yl]ethyl]indole-1-carboxylate (52)

Compound 51 (121 mg, 0.72 mmol) was dissolved in DMF (8 mL) and the Boc-protected 3-(3-bromoethyl)indole (347 mg, 1.07 mmol) was added. NaH (45 mg, 0.9 mmol) was gradually added to the mixture over 2.5 h. The reaction was then stirred overnight at room temperature, diluted with EtOAc/heptane 1:1, cooled to 0 °C and quenched with H₂O. The organic layer was extracted, dried over MgSO₄ and concentrated under reduced pressure. The residue was purified by flash column chromatography (EtOAc/heptane 1:1) affording compound 52 (155 mg, 53%). Rₜ 0.40 (EtOAc/heptane 1:1). FTIR (ATR) 2977, 1724, 1678, 1367, 1255, 1157 cm⁻¹. ¹H NMR (CDCl₃, 400 MHz): δ 8.11 (d, 1H, J = 6.1 Hz), 7.62 (d, 1H, J = 7.7 Hz), 7.36 (s, 1H), 7.32-7.20 (m, 2H), 6.27 (t, 1H, J = 5.0 Hz), 4.11 (dq, 2H, J = 7.1, 0.5 Hz), 4.10-4.04 (m, 2H), 3.01-2.95 (m, 2H), 2.50 (t, 2H, J = 7.6 Hz), 2.35-2.26 (m, 2H), 1.66 (s, 9H), 1.25 (dt, 3H, J = 7.1, 0.5 Hz). ¹³C NMR (CDCl₃, 75 MHz): δ 170.14, 162.15, 149.27, 135.14, 134.58, 130.03, 123.84, 122.88, 121.94, 119.95, 118.74, 117.24,
Chapter 7

114.73, 82.93, 60.95, 42.97, 30.47, 27.80, 23.96, 19.45, 13.64. HRMS (ESI) m/z calcd for C_{13}H_{21}N_2O_2Na (M+Na)^+: 435.1898, found: 435.1896.

**Tert-butyl-3-[2-(2-ethoxy carbonyl-6-oxo-3-vinyl pyridin-1-yl)ethyl] indole-1-carboxylate (53)**

To a cooled solution (−30 °C) of Cui (268 mg, 1.41 mmol) in Et_2O (3 mL), a 1M vininylmagnesium bromide solution in THF (707 μL, 0.71 mmol) was added. The solution was stirred for 20 minutes and was cooled to −70 °C. Then compound 52 (155 mg, 0.35 mmol), dissolved in Et_2O (2 mL), was added and the temperature was slowly warmed to −10 °C. The reaction was quenched with 0.1 M HCl and washed with Na_2SO_4 (2×40 mL), NaHCO_3 (10 mL) and H_2O (10 mL), dried over MgSO_4 and concentrated in vacuo. The residue was purified by flash column chromatography (EtOAc/heptane 1:1) affording compound 53 (112 mg, 73%). Rf 0.26 (EtOAc/heptane 1:1). FTIR (ATR) 2977, 1731, 1650, 1454, 1373, 1158 cm⁻¹. ^1H NMR (CDCl_3, 400 MHz): δ 8.12 (d, 1H, J = 7.8 Hz), 7.63 (d, 1H, J = 7.7 Hz), 7.39 (s, 1H), 7.28 (m, 2H), 5.71 (m, 1H), 5.19-5.10 (m, 2H), 4.22 (dq, 2H, J = 7.1, 0.6 Hz), 4.18-4.12 (m, 1H), 3.91 (d, 1H, J = 4.1 Hz), 3.10-2.86 (m, 3H), 2.85-2.77 (m, 1H), 2.56-2.38 (m, 2H), 1.98-1.87 (m, 1H), 1.78-1.69 (m, 1H), 1.66 (s, 9H), 1.27 (dt, 3H, J = 7.1, 0.7 Hz). ^13C NMR (CDCl_3, 75 MHz): δ 171.01, 169.43, 149.26, 136.43, 135.06, 129.93, 123.98, 122.84, 122.13, 118.65, 117.18, 116.44, 114.89, 83.03, 65.06, 61.39, 47.36, 39.24, 28.53, 27.86, 23.20, 22.46, 13.88. HRMS (ESI) m/z calcd for C_{34}H_{32}N_2O_4Na (M+Na)^+: 643.2211, found: 643.2209.

**Ethyl-3-Vinyl-1,2,3,4,6,7,12b-octahydropyrido[2,3-a]quinolizine-4-carboxylate (55)**

Compound 53 (20 mg, 0.045 mmol) was dissolved in toluene (1 mL) and POCl_3 (42 μL, 0.45 mmol) was added. The solution was stirred at 70 °C for 2 hours. The reaction was concentrated under reduced pressure and the residue was dissolved in EtO (1 mL) and cooled to 0 °C. NaBH_4 (3.4 mg, 0.09 mmol) was added and the reaction was stirred for 10 min at 0 °C, diluted with CH_2Cl_2 and quenched with aq. NaHCO_3. The organic layer was separated, dried over MgSO_4 and concentrated in vacuo. The residue was purified by flash column chromatography (EtOAc/heptane 1:2) affording compound 55 (13.0 mg, 68%). Rf 0.48 (EtOAc/heptane 1:1). FTIR (ATR) 3342, 2916, 1717, 1455, 611 cm⁻¹. ^1H NMR (CDCl_3, 400 MHz): δ 7.69 (br. s, 1H), 7.46 (d, 1H, J = 7.8 Hz), 7.30 (d, 1H, J = 7.7 Hz), 7.11 (ddt, 2H, J = 15.9, 7.1, 1.2 Hz), 5.68 (ddd, 1H, J = 17.1, 10.0, 8.7 Hz), 5.04 (dd, 1H, J = 10.2, 1.7 Hz), 4.30-4.20 (m, 2H), 3.40 (br d, 1H, J = 11.4 Hz), 3.06-2.97 (m, 2H), 2.95 (d, 1H, J = 10.3 Hz), 2.76-2.68 (m, 1H), 2.68-2.54 (m, 2H), 2.19-2.11 (m, 1H), 2.03-1.96 (m, 1H), 1.87-1.75 (m, 1H), 1.56-1.44 (m, 1H), 1.30 (t, 3H, J = 7.1 Hz). ^13C NMR (CDCl_3, 300 MHz): δ 167.75, 137.96, 135.53, 133.57, 121.03, 119.07, 117.72, 116.17, 110.22, 108.01, 105.73, 72.64, 60.32, 58.86, 50.73, 44.63, 29.79, 28.39, 21.45, 13.94. HRMS (ESI) m/z calcd for C_{30}H_{27}N_2O_2M+H^+: 325.1918, found: 325.1916.

**Tert-butyl-3-[2-(2-Hydroxymethyl-6-oxo-3-vinyl pyridin-1-yl)ethyl] indole-1-carboxylate (56)**

To a cooled solution (0 °C) of compound 53 (93 mg, 0.21 mmol) in THF (2.5 mL) LiEt_2BH (0.63 mL, 0.63 mmol, 1M solution in THF) was added. After 2.5 hours at 0 °C another equivalent of LiEt_2BH (50 μL, 0.05 mmol) was added and the reaction was stirred for three hours. The reaction was then quenched with ice-water and the product was extracted with CH_2Cl_2, dried over MgSO_4 and concentrated under reduced pressure. The residue was purified by flash column chromatography (EtOAc/heptane 1:1 to CH_2Cl_2 with CH_2Cl_2 10:1) affording compound 56 (74 mg, 88%). Rf 0.35 (CH_2Cl_2/MeOH 9:1). FTIR (ATR) 3322, 1731, 1615, 1455, 1370 cm⁻¹. ^1H NMR (CDCl_3, 400 MHz): δ 8.11 (d, 1H, J = 6.7 Hz), 7.69-7.60 (m, 1H), 7.39 (d, 2H, J = 3.3 Hz), 7.33-7.19 (m, 2H), 5.73-5.55 (m, 1H), 5.16-5.00 (m, 2H), 4.11-4.00 (m, 1H), 4.00-3.64 (m, 2H), 3.32-3.14 (m, 2H), 3.08-2.85 (m, 2H), 2.53-2.40 (m, 2H), 2.39-2.23 (m, 1H), 2.07-1.84 (m, 1H), 1.68-1.57 (m, 10H). ^13C NMR (CDCl_3, 75 MHz): δ 170.75, 170.43, 149.25, 138.57, 138.39, 135.04, 130.02, 130.07, 124.08, 123.94, 122.70, 122.16, 118.85, 118.64, 117.47, 117.33, 115.84, 115.78, 115.54, 114.84, 83.07, 82.99, 62.95, 62.03, 62.03, 61.96, 61.68, 46.06, 45.94, 45.87, 37.85, 37.79, 37.45, 29.44, 29.23, 29.06, 27.84, 23.13, 22.87, 22.73, 22.62. HRMS (ESI) m/z calcd for C_{36}H_{33}N_2O_4Na (M+Na)^+: 421.2106, found: 421.2103.
Tert-butyl-3-{[2-(Iodomethyl)-6-oxo-3-vinyl]pyriderin-1-yl}ethyl]indole-1-carboxylate (57)

Compound 56 (20 mg, 0.125 mmol) was dissolved in THF (2 mL) and PPh₂ (50 mg, 0.19 mmol), imidazole (13 mg, 0.19 mmol) and iodine (48 mg, 0.19 mmol) were added. The resulting reaction mixture was stirred at room temperature for 4 hours. The reaction was diluted with CH₂Cl₂, washed with Na₂S₂O₃ and H₂O, dried over Na₂SO₄ and concentrated under reduced pressure. The residue was purified by flash column chromatography (heptane to EtOAc/heptane 1:3 to 1:2) affording compound 57 (50 mg, 78%). Rₜ 0.80 (CH₂Cl₂/Methanol 9:1). FTIR (ATR) 1975, 1731, 1645, 1455, 1373, 1157 cm⁻¹. ¹H NMR (CDCl₃, 400 MHz): δ 8.13 (d, 1H, J = 7.0 Hz), 7.66 (d, 1H, J = 7.7 Hz), 7.35-7.23 (m, 3H), 5.67-5.56 (m, 1H), 5.23-5.10 (m, 2H), 4.20-2.11 (m, 1H), 3.43-3.37 (m, 1H), 3.36-3.29 (m, 1H), 3.16-2.91 (m, 4H), 2.72-2.64 (m, 1H), 2.55-2.36 (m, 2H), 1.95-1.85 (m, 1H), 1.75-1.63 (m, 10H). ¹³C NMR (CDCl₃, 75 MHz): δ 169.86, 149.23, 137.84, 135.06, 129.97, 124.03, 122.78, 118.64, 117.23, 116.89, 114.85, 83.08, 60.93, 44.95, 40.92, 29.73, 27.85, 22.92, 22.66, 9.34. HRMS (ESI) m/z calc for C₂₃H₂₉N₂O₄Na (M+Na⁺): 531.1123, found: 531.1121.

Tert-butyl-3-{[2-(3-Ethoxycarbonylbut-3-enyl)-6-oxo-3-vinyl]pyriderin-1-yl}ethyl]indole-1-carboxylate (58)

Zinc dust (42 mg, 0.65 mmol) was weighed into a schlenk flask, which was dried with a flame and flushed with argon. 1,2-dibromoethane (2.8 μL, 0.03 mmol) in dry DMF (0.2 mL) was added and the flask was heated to 60 °C for 1 hour. TMSCl (0.41 μL, 0.003 mmol) was added and the mixture was stirred at 60 °C for 30 minutes. Compound 57 (55 mg, 0.11 mmol) was dissolved in DMF (0.3 mL), added to the mixture and stirred 10 min at 60 °C. CuCN (10 mg, 0.11 mmol) and LiCl (9.2 mg, 0.22 mmol) were heated to 150 °C under vacuum for 2 hours and cooled to room temperature. Addition of DMF (0.3 mL) formed a soluble CuCN·2LiCl complex. After cooling the organozinc reagent to ~55 °C the Cu-complex was added and the solution was warmed to 0 °C. After stirring 10 min at 0 °C the solution was cooled to ~55 °C and the ethyl 2-(bromomethyl)acrylate (18.2 μL, 0.13 mmol) was added. The solution was slowly warmed to room temperature and stirred over night. The mixture was filtered over celite, diluted with EtOAc, washed with aq. NH₄Cl and brine, dried over MgSO₄ and concentrated under reduced pressure. The residue was purified by flash column chromatography (EtOAc/heptane 1:1) affording compound 58 (28 mg, 52%). Rₜ 0.27 (EtOAc/heptane 1:1). FTIR (ATR) 2977, 1728, 1637, 1454, 1372, 1158 cm⁻¹. ¹H NMR (CDCl₃, 400 MHz): δ 8.13 (d, 1H, J = 7.0 Hz), 7.66 (d, 1H, J = 7.8 Hz), 7.41 (s, 1H), 7.28 (m, 2H), 6.15 (s, 1H), 5.71 (m, 1H), 5.51 (s, 1H), 5.16-5.06 (m, 2H), 4.19 (q, 2H, J = 6.9 Hz), 4.21-4.12 (m, 1H), 3.19-3.13 (m, 1H), 3.09-2.93 (m, 3H), 2.54-2.44 (m, 2H), 2.40-2.16 (m, 3H), 2.07-1.96 (m, 1H), 1.88-1.68 (m, 4H), 1.66 (s, 9H), 1.28 (t, 3H, J = 7.2 Hz). ¹³C NMR (CDCl₃, 75 MHz): δ 169.54, 166.35, 149.22, 139.36, 138.57, 135.03, 130.04, 124.86, 123.92, 122.87, 122.04, 118.77, 117.34, 115.65, 114.83, 82.98, 61.15, 60.33, 45.59, 38.43, 31.35, 28.63, 27.96, 27.87, 22.64, 22.23, 17.12. HRMS (ESI) m/z calc for C₃₀H₂₉N₂O₂Na (M+Na⁺): 517.2681, found: 517.2678.

Tert-butyl-3-{[2-(4-Vinylhex-5-enyl)amino]ethyl]indole-1-carboxylate (59)

This compound was obtained as a side product in the organozinc-coupling. Rₜ 0.43 (EtOAc/heptane 1:1). FTIR (ATR) 3293, 2976, 1731, 1643, 1377, 1159. ¹H NMR (CDCl₃, 400 MHz): δ 8.14 (d, 1H, J = 7.7 Hz), 7.55 (d, 1H, J = 7.8 Hz), 7.41 (s, 1H), 7.29 (m, 2H), 5.68 (m, 2H), 5.51 (t, 1H, J = 5.5 Hz), 5.04-4.96 (m, 4H), 3.59 (dt, 2H, J = 6.7 Hz, J = 6.6 Hz), 2.91 (t, 2H, J = 6.8 Hz), 2.68 (p, 1H, J = 7.3 Hz), 2.15-2.10 (m, 2H), 1.74 (dt, 2H, J = 7.8 Hz, J = 7.3 Hz), 1.67 (s, 9H). ¹³C NMR (CDCl₃, 75 MHz): δ 172.35, 149.22, 139.95, 135.12, 129.96, 124.12, 122.76, 122.10, 118.49, 117.25, 114.93, 114.52, 83.27, 46.84, 38.65, 33.87, 29.33, 27.86, 24.72. HRMS (ESI) m/z calc for C₂₃H₂₉N₂O₄Na (M+Na⁺): 405.2156, found: 405.2154.
Ethyl-1,2-[1-tert-Butoxy carbonyl-1H-indol-3-yl(ethyl)-2-oxo-1,2,3,4,4a,5,6,8a-octahydroquinoline-7-carboxylate (60)]

Compound 58 (28 mg, 0.056 mmol) was dissolved in toluene (1 mL) and argon was flushed through the solvent. Grubbs catalyst second generation (5 mg, 0.005 mmol) was added and the solution was heated to 80°C. After 1 hour the solution was cooled to room temperature and concentrated in vacuo. The residue was purified by flash column chromatography (EtOAc/heptane 1:1) affording compound 60 (26 mg, 98%).

2,4a,5,6,11b,12,13,13a-Octahydro-1H-4b,11-diazaindeno[2,1-a]phenanthrene-3,11-dicarboxylic acid 11-tert-butyl ester 3-ethyl ester (61)

Compound 60 (26 mg, 0.056 mmol) was dissolved in toluene (1 mL) and POCl₃ (52 μL, 0.56 mmol) was added. The solution was stirred at 70°C for 2 hours when more POCl₃ (27 μL, 0.27 mmol) was added and the reaction was stirred for another hour at 70°C. The reaction was concentrated under reduced pressure and the residue was dissolved in EtOH (1 mL) and cooled to 0°C. NaBH₄ (4.2 mg, 0.11 mmol) was added and the reaction was stirred for 10 min at 0°C, diluted with DCM and quenched with aq. NaHCO₃. The organic layer was extracted, dried over MgSO₄ and the reaction was stirred for 10 min at 0°C, diluted with DCM and quenched with aq. NaHCO₃. The organic layer was extracted, dried over MgSO₄ and the solution was heated to 80°C. After 1 hour the solution was cooled to room temperature and concentrated in vacuo. The residue was purified by flash column chromatography (EtOAc/heptane 1:2) affording compound 61 (11.5 mg, 46%).

Ethyl-1,2,4a,5,6,11b,12,13,13a-Decahydro-4b,11-diazaindeno[2,1-a]phenanthrene-3-carboxylate (62)

Compound 61 (4 mg, 20%) was isolated as a side product of the Bischler-Napieralski reaction with compound 62. Rf 0.54 (EtOAc/heptane 2:1). FTIR (ATR) 2919, 1700, 1648, 1255, 736 cm⁻¹. ¹H NMR (CDCl₃, 400 MHz): δ 7.70 (d, 1H, J = 8.0 Hz), 7.41 (d, 1H, J = 7.2 Hz), 7.29-7.19 (m, 2H), 6.70 (s, 1H), 4.51 (d, 1H, J = 10.9 Hz), 4.21 (q, 1H, J = 7.2 Hz), 3.08-2.95 (m, 2H), 2.87-2.71 (m, 3H), 2.62 (dd, 1H, J = 15.8 Hz, J = 4.2 Hz), 2.39 (t, 2H, J = 10.7 Hz), 2.15-1.97 (m, 3H), 1.90-1.76 (m, 2H), 1.65 (s, 9H), 1.53-1.40 (m, 1H), 1.31 (t, 3H, J = 7.1 Hz). ¹³C NMR (CDCl₃, 75 MHz): δ 166.93, 149.62, 141.83, 136.46, 136.03, 129.47, 128.82, 123.48, 122.14, 117.49, 115.34, 114.57, 83.13, 63.34, 60.06, 58.27, 36.35, 33.33, 30.82, 27.83, 26.86, 25.84, 25.37, 21.57, 13.84. HRMS (ESI) m/z calcd for C₂₇H₃₄N₂O₄ [M+H⁺]: 451.2599, found: 451.2597.

Ethyl-1,2,4a,5,6,11b,12,13,13a-Decahydro-4b,11-diazaindeno[2,1-a]phenanthrene-3-carboxylate (62)

Chapter 7
7.8 References

15. Stereochemistry was confirmed by comparison with the known compound.
16. Due to the instability of the product, it was immediately N-protected.
Summary

The formation of carbon-carbon bonds is a crucial issue in organic synthesis. Out of all methodologies available, the metathesis reaction has over the past decade evolved as one of the most useful tools in this field to rapidly construct the skeleton of carba- and heterocyclic molecules. Only twenty years have elapsed since Grubbs and Fu reported that Schrock’s molybdenum catalyst (S1) could be used to induce efficient cyclization of functionalized α,ω-diene-amines. The key step of the metathesis reaction entails the metal-catalyzed redistribution of two carbon-carbon double bonds by a scission-recombination process. Since then, a wide range of ring-closing metathesis reactions to form nitrogen heterocyclic products have been reported, including applications in the synthesis of natural products using the more general applicable ruthenium catalysts (e.g. G1, G2).

This thesis describes the metathesis behaviour of α,β-unsaturated didehydroamino acids, thereby generating a general cyclic building block for further functionalization. In addition, the diversity of this methodology is demonstrated by the construction of more elaborated heterocycles, including the heterocyclic natural product tangutorine.

Chapter 1 gives an historical overview of RCM used in the synthesis of natural products. It shows that especially five- and six-membered heterocyclic rings are ideal targets for RCM and that applications in larger rings are lacking behind. These applications have been greatly facilitated by the advent of new and more reactive RCM catalysts, thereby continuously widening the range of substrates and increasing the scope of the metathesis processes.

Chapter 2 describes the synthesis of didehydroamino esters from condensation of olefinic amides 1 with a pyruvate followed by RCM, leading to the introduction of substituents at both the allylic and the α-position of the amide.
This chapter focuses on the formation and scope of the condensation of allylic amides with a pyruvate ester to the dehydroamino ester 2. In a second step, ring closure to the didehydroamino ester 4 was accomplished by alkylation of the enamide.

Similarly, condensation of hydroxy-substituted amides followed by intramolecular conjugate addition gives rise to the synthesis of substituted morpholines 8, as described in Chapter 3.

Although condensation of the amides 5 to the dehydroamino esters 7 was straightforward and hydrolysis induced intramolecular conjugate addition was successful (R₁ = H), cyclization of more substituted dehydroamino acids 7 (R₁ ≠ H) appeared difficult to reproduce.

Chapter 4 describes the condensation and RCM of more elaborated olefinic amides to optically active 3- and 4-substituted cyclic dehydroamino acids 14 from enantiomerically pure carbohydrates 9, lactones 10 and amino acids 11.

The application to more elaborated 2-substituted piperolic esters is discussed in Chapter 5 upon intermolecular conjugate addition for the synthesis of trans-substituted derivatives. Moreover, synthesis of cis-substituted variants is described based on reduction of tetrastubstituted cyclic dehydroamino acids.

As an extension of this research, asymmetric hydrogenation of the cyclic dehydroamino acids is discussed in Chapter 6 with an ee up to 45%.
Inspired by the results of RCM on dehydroamino acids, the developed methodology was applied to an eight step synthesis of the natural product tangutorine starting from the cyclic didehydroamino ester 4, which is described in Chapter 7.
Samenvatting

De vorming van koolstof-koolstof bindingen is een cruciale transformatie in de organische synthese. Ondanks dat het pas twintig jaar geleden is dat Grubbs en Fu de Schrock’s molybdeen katalysator (S1) publiceerden die gebruikt kon worden voor de ringsluiting van gefunctionaliseerde α,ω-diene-amines, heeft de metathesereactie zich het laatste decennium ontwikkeld als een van de meest algemeen toepasbare reacties voor de vorming van koolstof- en heterocyclische verbindingen. De belangrijkste stap in deze reactie is de metaal-gekatalyseerde redistributie van twee koolstof-koolstof dubbele bindingen door een recombinaat process. Een grote varieté van ringsluitingsmetathese reacties voor de vorming van stikstof heterocyclische producten is sindsdien gepubliceerd, inclusief applicaties voor de synthese van natuurlijke producten waarbij de commercieel beschikbare ruthenium katalysatoren worden gebruikt (bijvoorbeeld G1, G2)

\[
\text{C=C} \xrightarrow{\text{RCM}} \text{C=C} + \text{C=C}
\]

Dit proefschrift beschrijft de mogelijkheden tot ringsluiting van α,β-onverzadigde dehydroaminozuren voor de vorming van algemene bouwstenen geschikt voor verdere functionalizing. De ontwikkelde synthese is vervolgens toegepast voor de bereiding van gesubstitueerde heterocyclische verbindingen, inclusief de bereiding van de natuurlijke verbinding tangutorine.

Hoofdstuk 1 geeft een historisch overzicht van ringsluitingsmetathese in de synthese van natuurlijke stoffen. Het overzicht laat zien dat met name heterocyclische vijf- en zesringen geschikt zijn om gemaakt te worden door middel van ringsluiting. Sinds de ontwikkeling van de Ruthenium katalysator is het aantal synthesesroutes waarin RCM wordt gebruikt enorm toegenomen door de ontwikkeling van nieuwe, en meer reactieve RCM katalysatoren, waarbij bereik van substraten geschikt voor RCM continue wordt vergroot.

Hoofdstuk 2 beschrijft de synthese van cyclische didehydroamino esters gemaakt door condensatie van gesubstitueerde allylische amides 1 met een pyruvaatester, gevolgd door ringsluiting, voor de introductie van substituenten op zowel de allylische en α-positie van de ring.
Het hoofdstuk beschrijft de ontwikkeling en de algemene toepasbaarheid van de condensatierecactie van allylische amides met een pyruvaat ester voor de vorming van dehydroamino ester 2. In een tweede stap wordt de ring 4 gevormd door ringsluitings metathese, waarbij de noodzaak van alkylering van de stikstof wordt beschreven.

Een vergelijkbare strategie wordt beschreven in hoofdstuk 3 voor de condensatierecactie van hydroxy-gesubstitueerde amides. Een intramoleculaire conjugaat additie leidt vervolgens tot de gesubstitueerde morpholines 8.

Alhoewel condensatierecactie van de amides 5 tot de dehydroamino esters 7 algemeen toepasbaar is en de intramoleculaire conjugaatadditie succesvol (R$_1$ = H), zijn de opbrengsten van de conjugaatadditie voor α-gesubstitueerde hydroxylamides variabel en niet reproduceerbaar.

Hoofdstuk 4 beschrijft de condensatierecactie en ringsluiting van gesubstitueerde, optisch actieve 3- en 4-gesubstitueerde cyclische dehydroaminozuren 14. Enantiomeer zuivere amides 12 zijn gemaakt van suikers 9, lactonen 10 en aminozuren 11.

Hoofdstuk 5 beschrijft de synthese van trans-2-gesubstitueerde pipecol esters 15 via intermoleculaire conjugaatadditie. Cis-2-gesubstitueerde pipecol esters 15 zijn bereid door hydrogeneringsreactie van de enamide.
Een uitbreiding hiervan is beschreven in **hoofdstuk 6**, waarbij een asymmetrische hydrogerningsreactie van de cyclische dehydroaminozuren 18 resulteert in 2-pipecolesters 19 met een ee van 45%.

Geïnspireerd door deze resultaten is de ontwikkelde methodologie toegepast in de synthese van de natuurlijke stof tangutorine. De syntese is beschreven in **hoofdstuk 7** en succesvol voltooid in acht stappen, startend met de cyclische dehydroamino ester 4.
Dankwoord

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Bas
Publications and Patents

Curriculum Vitae

Bas van den Broek was born in Veghel in 1975 and was grown up in Boekel. He attended the Macropedius College in Gemert and graduated in 1996. Then he started a bachelor study in chemistry at the Fontys Hogescholen in Eindhoven of which he received his B.Sc. in 2000. Afterwards he started his Master in chemistry at the Radboud University Nijmegen, where he obtained his M.Sc. in 2003. He performed his master internship in the group of prof. dr. F. P. J. T. Rutjes under guidance of dr. F. L. van Delft. After a short stay at Chiralix, he joined the group of prof. Rutjes as a Ph.D. student. His research was focused on the development of new synthetic strategies for formation of cyclic dehydroamino acids by ring closing metathesis. The results of the project are described in this thesis. Bas is currently working as Senior Researcher at FutureChemistry, focusing at the development of hardware and product development using flow technology.