Copper-Catalyzed 1,2-Methoxy Methoxycarbonylation of Alkenes with Methyl Formate and Synthetic Studies Towards the Total Synthesis of Koumine, Voacafricine A and Voacafricine B

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par

Balázs BUDAÍ

Acceptée sur proposition du jury

Prof. N. Cramer, président du jury
Prof. J. Zhu, directeur de thèse
Prof. T. Soós, rapporteur
Prof. M. Greaney, rapporteur
Prof. J. Waser, rapporteur
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Abstract

The development of an unusual oxidative alkene difunctionalization using methyl formate and synthetic studies towards alkaloid natural products provide the basis of the thesis.

The first chapter details the development of a method that forges methoxycarbonyl radical directly from its most accessible precursor: methyl formate. Although the aforementioned transformation was documented in the literature, no synthetically useful method was developed at the time. We were able to identify conditions that transform methyl formate and simple styrene derivatives to value added β-methoxy alkanoates and cinnamic acid derivatives under copper catalysis. We also demonstrated that by tethering nucleophilic moieties to the styrene substrates, we could access medicinally important heterocycles such as pyrrolidines, tetrahydrofurans and γ-lactones. Our method proved to be scalable on each classes of substrates. Mechanistic studies revealed that methyl formate has an unprecedented double role in the transformation. It acts as a precursor for methoxycarbonyl radical; furthermore, it is the direct source of the β-methoxy function in the synthesis of β-methoxy alkanoates. A ternary β-diketiminato-Cu(I)-styrene complex, fully characterized by NMR spectroscopy and X-ray crystallographic analysis is capable of catalyzing the same transformation. We hypothesize that pre-coordination of electron-rich double bond to copper might play an important role in the polarity-mismatched addition between nucleophilic methoxycarbonyl radical and electron rich olefins.

Synthetic studies toward the total synthesis of koumine is discussed in the second chapter. Our synthetic strategy features an oxidative ring closing, Fukuyama indole synthesis and an enantioselective Diels-Alder cycloaddition for the construction of the core of koumine skeleton. We designed a rapid route to access 1,2-dihydropyridine derivatives and these compounds were examined as dienes in the Diels-Alder cycloaddition reaction. Despite our efforts, we were unable to effect the [4+2] cycloaddition, which eventually lead us to decide to discontinue our campaign.

In chapter three, our synthetic efforts toward voacafricine A and voacafricine B is presented. In our pursuit towards the natural products, we devised and followed a divergent and potentially enantioselective strategy. We successfully developed a synthetic route to reach the key intermediate in five steps. Despite our efforts, we were not able to construct the remaining F ring of the natural product. Our conformational analysis of advanced intermediates suggest that epimerization of the C14 stereocenter potentially unlocks the desired reactivity and enables us to reach the target molecules. Work towards the total synthesis of voacafricine A and voacafricine B is underway and may focus on the conformational manipulation of advanced intermediates to allow the elaboration of the F ring and complete the synthesis.
Resumaziun

Il svilup d’ina difunzionalisaziun d’alchen oxidativa nunusitada cun il diever dal formiat da metil e studis sintetics areguard products natirals alcaloids furman la basa da la tesa.


En chapitel trais vegnan preschentadas nossas stentas sinteticas areguard il voacafricine A ed il voacafricine B. Cun noss sforz visavi ils products natirals avain nus sviluppà e persequità ina strategia divergenta e potenzialmain enantioselectiva. Nus avain sviluppà cun success ina via sintetica per arrivar en tschintg pass a la pli impurtanta mira intermediara. Malgrà nossas stentas n’essan nus betg stai capabels da construir il rintg F dal product natiral. Nossal analisa da conformaziun da products bruts avanzads inditga che l’epimerisaziun dal center da stereo C14 liberescha potenzialmain la reactividad giavischada ed ans pussibilitesa d’obtegnair ils moleculs da finamira. La lavur areguard la sintesa totala dal voacafricine A e dal voacafricine B è en cursa e po sa
concentrar sin la manipulaziun conformaziunala da products bruts avanzads per pussibilitar d’elavurar il rintg F e da cumplettar la sintesa.

Keywords

copper catalysis, olefin functionalization, methyl formate, total synthesis, natural product, alkaloid, koumine, voacafricine A, voacafricine B
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List of Abbreviations

Ac         acetyl
Adams' catalyst PtO₂
aq.        aqueous
Ar         aryl
BINAP      (2,2'-Bis(diphenylphosphino)-1,1'-binaphthyl)
Bn         benzyl
Boc        tert-butyloxycarbonyl
bpy        2,2'-bipyridine
b.r.s.m.   based on recovered starting material
Bu         butyl
Bz         benzoyl
°C         Celsius
c          concentration
CAN        ceric ammonium nitrate
cat.       catalyst
Cbz        carboxybenzyl
COD        1,5-cyclooctadiene
COMU       (1-Cyano-2-ethoxy-2-oxoethyldienaminooxy)dimethylamino-morpholino-carbenium hexafluorophosphate
conc.      concentrated
Cp         cyclopentadienyl
CSA        camphorsulfonic acid
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<td>Cy</td>
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<tr>
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<td>DP</td>
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<td>dr</td>
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<tr>
<td>E</td>
<td>entgegen</td>
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<td>EDC</td>
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<td>electron donating group</td>
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<td>electron withdrawing group</td>
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<td>1-hydroxybenzotriazole</td>
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<tr>
<td>HRMS</td>
<td>high resolution mass spectrometry</td>
</tr>
<tr>
<td>hv</td>
<td>&quot;light&quot;</td>
</tr>
<tr>
<td>Hz</td>
<td>Hertz</td>
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<tr>
<td>IC&lt;sub&gt;50&lt;/sub&gt;</td>
<td>half maximal inhibitory concentration</td>
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<tr>
<td>IBX</td>
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<td>J</td>
<td>coupling constant</td>
</tr>
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<td>montmorillonite</td>
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<tr>
<td>LAH</td>
<td>lithium aluminum hydride</td>
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<tr>
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<td>light emitting diode</td>
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<td>LDA</td>
<td>lithium diisopropyl amine</td>
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<td>meta-perbenzoic acid</td>
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<td>MW</td>
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</tr>
<tr>
<td>NMO</td>
<td>4-methylmorpholine N-oxide</td>
</tr>
<tr>
<td>NMR</td>
<td>nuclear magnetic resonance spectroscopy</td>
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<tr>
<td>nOe</td>
<td>nuclear Overhauser effect</td>
</tr>
<tr>
<td>o</td>
<td>ortho</td>
</tr>
<tr>
<td>p</td>
<td>para</td>
</tr>
<tr>
<td>PCC</td>
<td>pyridinium chlorochromate</td>
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<tr>
<td>PE</td>
<td>petrol ether</td>
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<tr>
<td>Pearmann’s catalyst</td>
<td>Pd(OH)$_2$ on charcoal</td>
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<tr>
<td>Ph</td>
<td>phenyl</td>
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<td>Piv</td>
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<tr>
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<td>pyridine</td>
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<tr>
<td>R</td>
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<td>Red-Al</td>
<td>sodium bis(2-methoxyethoxy)aluminumhydride</td>
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<td>r.t.</td>
<td>room temperature</td>
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<tr>
<td>S</td>
<td>sinister</td>
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<tr>
<td>SAR</td>
<td>structure-activity relationship</td>
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<td>SFC</td>
<td>supercritical fluid chromatography</td>
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<tr>
<td>SM</td>
<td>starting material</td>
</tr>
<tr>
<td>r</td>
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<td>TBAF</td>
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<td>tetrahydrofuran</td>
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<td>Ts / Tosyl</td>
<td>4-toluenesulfonyl</td>
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<td>Description</td>
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<td>-------------</td>
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<td>UV</td>
<td>ultra violet</td>
</tr>
<tr>
<td>W</td>
<td>watt</td>
</tr>
<tr>
<td>Z</td>
<td>zusammen</td>
</tr>
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<td>18-crown-6</td>
<td>1,4,7,10,13,16-hexaoxacyclooctadecane</td>
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<td>Δ</td>
<td>heating</td>
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<td>NMR chemical shift</td>
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Chapter 1 Copper-Catalyzed 1,2-Methoxy Methoxycarbonylation of Alkenes with Methyl Formate

1.1 Introduction

Olefins as abundant feedstock chemicals, one of the largest classes of all naturally occurring raw materials, are key ingredients for the plastics industry, dyes, fine chemicals and medicines. Therefore, there is a huge potential in chemically modifying these compounds, hence accessing new materials that are tailored to our needs. Difunctionalization of olefins has always played a key role in organic synthesis and most likely, it will not change in the near future. Within this field the shared Nobel Prize was awarded to K. Barry Sharpless in 2001 for his pioneering work in the enantioselective epoxidation and dihydroxylation of alkenes.\(^1\) In the past two decades the progress in alkene difunctionalization has not halted, on the contrary, accelerated year-by-year. Stemming from the work of Sharpless, osmium catalyzed alkene aminohydroxylation and diamination strategies have been further developed.\(^2\) Palladium catalyzed alkene difunctionalization became one of the largest branches in the domain and more recently a myriad of transition metal- and photocatalyzed radical-polar crossover transformations have been developed (Scheme 1).\(^3\)

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In recent years, our group has contributed to the field of oxidative alkene difunctionalization. Cyanoalkylative methods have been developed primarily, among these we reported alkene carboetherification, alkyllative epoxidation and alkyllative cyanoetherification without being exhaustive.\(^4\) The development of these methodologies was driven by one common principle. In their respective mechanisms at one point an \(\alpha\)-cyanoalkyl radical is generated and the formed radical is added across a C-C double bond. The incipient radical undergoes oxidation to the corresponding carbocation and this intermediate is trapped by a nucleophile or underwent rearrangement (Scheme 2). Alternatively, radical rebound product of 1.14 with 1.16 would produce 1.17 which may undergo reductive elimination to furnish the product. After exploring multiple transformations in this domain, we were intrigued whether our expertise can be leveraged in the generation of other carbon-centered radicals.

We hypothesized that methoxycarbonyl radicals could also be generated via hydrogen atom abstraction from methyl formate and once this radical is generated a vast array of transformations could be carried out, including alkene functionalization. The generation of alkoxyacarbonyl radical is long known in the literature, although some of their attributes limited their practical use. Starting from the 1970’s the generation of such radicals has been extensively studied, nevertheless the focus was on their physico-chemical properties rather than on their synthetic utility. Subsequently the developed methods for their access necessitated the use of potentially explosive, toxic and corrosive chemicals. Nevertheless, Roberts and later Sander described the physico-chemical properties

\[ \text{[Ref. 5]} \]

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of alkoxycarbonyl radicals by using ESR spectroscopy and step-scan time-resolved infrared spectroscopy.\(^6\) Roberts et al. concluded that alkoxycarbonyl radicals have a predominant \(\sigma\)-character and depending on their alkyl substituent, they may fragment into carbon dioxide and alkyl radical. In a theoretical study (\textit{ab initio} calculations at the UMP2/DZP//UHF/6-311G** level of theory) by Guerra et al. the \(\Theta\)-angle of \(\text{tBuO-C-O}\) bond was calculated to be 128.6° and for a variety of acyl radicals the calculated \(\Theta\)-angle shown a predominant \(sp^2\) character.\(^7\) Sander found that alkoxycarbonyl radicals exhibit lifetimes in the order of several microseconds in carbon tetrachloride. In their system, alkoxycarbonyl radicals decay by chlorine abstraction from the solvent, followed by fragmentation to carbon dioxide and alkyl radical. While benzyloxy carbonyl radicals decarboxylate at rates outside of the detection window of time-resolved step-scan FTIR spectroscopy, tert-butoxycarbonyl and iso-propyloxycarbonyl radicals’ fragmentation to \(\text{CO}_2\) and alkyl radical was detected by the authors. Interestingly, the decarboxylation of the ethoxy carbonyl radical could not be detected by their equipment, presumably due to the formation of less stabilized primary alkyl radical (Scheme 3).

On the one hand, intramolecular addition of alkoxycarbonyl radicals, generated \textit{in situ} by reduction of carbonic acid derivatives (\(\text{ROCOX, X = Cl, SePh, TePh}\)), onto the tethered alkenes is known for years and has been successfully used in the total synthesis of complex natural products.\(^8\) Minisci-type, intermolecular alkoxycarbonylation of electron poor heteroaromatics has also been reported.\(^9\) On the other hand, examples on the difunctionalization of alkenes initiated by addition of alkoxycarbonyl radicals remained rare. In this regard, Taniguchi and co-workers reported the first example of iron phtalocyanine catalyzed oxidative 1,2-hydroxy methoxycarbonylation of alkenes

### Scheme 3 - The physico-chemical properties of alkoxycarbonyl radicals.

<table>
<thead>
<tr>
<th>Geometry</th>
<th>Fragmentation patterns</th>
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</thead>
<tbody>
<tr>
<td>R = H, (\Theta = 126.6^\circ)</td>
<td>R–O' + C=O</td>
</tr>
<tr>
<td>R = Me, (\Theta = 124.6^\circ)</td>
<td>1.22 1.23</td>
</tr>
<tr>
<td>R = NH(_2), (\Theta = 130.8^\circ)</td>
<td>R' + O=C=O</td>
</tr>
<tr>
<td>R = O(\text{tBu}), (\Theta = 128.6^\circ)</td>
<td>1.24 1.25</td>
</tr>
<tr>
<td>R = F, (\Theta = 128.1^\circ)</td>
<td></td>
</tr>
</tbody>
</table>

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using methyl carbazate (1.26) as precursor of methoxycarbonyl radical. Following their landmark achievement, many others have reported oxidative conditions that forges the desired radical from 1.26. Tian and co-workers shown that under palladium catalysis 1.26 is oxidized to methoxycarbonyl radical (1.28) and subsequently used in the functionalization of styrene derivatives. Common point in Tian’s and Taniguchi’s work that both author coupled the radicals to electron rich double bonds. Du and coworkers reported iron- and TBAI-catalyzed oxidative conditions to functionalize acrylamides with alkoxycarbonyl radicals generated from carbazates (Scheme 4).13

**Scheme 4 - The seminal work of Taniguchi demonstrating that methyl carbazate can be a precursor of methoxycarbonyl radical. Tian’s method forges cinnamate derivatives from styrene substrates and Du’s report on the reactivity between 1.28 and electron poor double bonds.**

Regarding the philicity of alkoxycarbonyl radicals, these reports show an apparent contradiction. For comparison, acyl radicals are nucleophilic in nature, they add across electron poor double bonds, regardless of the system in which they are generated.14

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have been known for half-a-century, their philicity may seem somewhat promiscuous. In the presence of a tethered electron rich double bond both oxyacyl and aminoacyl radicals can cyclize. This apparent electrophilic behavior of the radicals is the consequence of entropic favorability of the intramolecular reaction and may not be confused with their philicity. Generally speaking, aminoacyl radicals are classified as nucleophilic radicals. Schiesser and co-workers carried out DFT studies on the philicity of methoxycarbonyl radicals and they characterize them as electrophilic or in certain cases ambiphilic radicals. Eventually, Overman and Slutskyy designed a system in which “naked” alkoxy carbonyl radicals are generated and reacted with electron rich or electron poor alkenes. They demonstrated that 1.28, generated from methyl N-phthalimidoyl oxalate under visible light photoredox conditions, reacted only with electron-poor Michael acceptors to afford 1,4-dicarbonyl compounds and defined 1.28 as nucleophilic, rather than ambiphilic or electrophilic radical proposed previously based on computational studies (Scheme 5).

By surveying the chemistry literature one can find a large number of reports on the generation of alkoxy carbonyl radical. It is puzzling to realize that most of these reports restrict themselves to use hazardous, explosive, toxic or exotic precursors of the desired radical. From the viewpoint of synthetic efficiency and sustainability, methyl formate, produced industrially from CO and MeOH with an annual production of over 700,000 metric tons, would be an ideal precursor of methoxycarbonyl

---

radical 1.28. 20 Since the bond dissociation energy (BDE) of MeOC(O)-H is about 95.4 kcal/mol, it is reasonable to expect that an oxygen centered radical (BDE of tBuO-H: 105.5 kcal/mol) would be able to abstract the hydrogen from methyl formate to generate 1.28. 21 One of the earliest investigation in the field, performed by Urry et al., demonstrated that methyl formate could be a direct precursor of 1.28. Their seminal work showed that heating a mixture of methyl formate, ethylene and di-tbutylperoxide in an autoclave (130 °C, 340-440 p.s.i.) afforded a mixture of homologated alkanoates. 22 The result indicated that both tBuO• and the primary alkyl radical are capable of abstracting a hydrogen from methyl formate. However, the competing oligomerization process rendered the method synthetically insignificant (Scheme 6). Not less than twenty years later was published another protocol for the generation of 1.28 from methyl formate. Tiecco and co-workers employed photolytic conditions for the generation of peroxy radicals from di-tert-butylperoxide, subsequent hydrogen abstraction from methyl formate delivered 1.28. The generated radical underwent homolytic substitution with benzene, furnishing methylbenzoate. Although the set-up was inexpensive, the long reaction time, low yield and lack of generality classifies this method as a proof-of-concept finding, rather than a synthetically valuable transformation (Scheme 6). 23

Scheme 6 - Urry's seminal report showcased that methyl formate could be a direct precursor of methoxycarbonyl radical (1.28). Tiecco’s method for the generation of 1.28 from methyl formate under photolysis. These methods remain as proof-of-concept findings, rather than synthetically valuable transformations.

As we can see, the major challenges of the formation of 1.28 from 1.57 includes the high yielding, selective hydrogen abstraction from 1.57, control over the fate of 1.28 by preventing α- and β-fragmentation or hydrogen atom transfer (HAT) from another molecule. Concerning the design of the hydrogen abstraction process, it is important to discuss here the Kharasch-Sosnovsky reaction. The Kharasch-Sosnovsky reaction is a radical allylic C-H oxidation process that converts allylic C(sp³)-H bonds (BDE = 89 kcal/mol) to allylic esters. The reaction mechanism was investigated and uncovered by Kochi and Zavitsas. The radical chain is initiated by a cuprous salts that reduces a per oxyester to generate the corresponding copper(II) acetate and alkoxy radical. The generated radical abstracts a hydrogen from the weak allylic C-H bond, generating the stabilized allylic radical intermediate and the alcohol. Recombination of the radical and copper(II) acetate delivers the highly reactive copper(III) intermediate which upon reductive elimination forms the product and regenerate copper(I) to propagate the cycle (Scheme 7).

**Scheme 7 - The mechanism of the Kharasch - Sosnovsky reaction.**

In principle, the tert-butoxy radical, generated in the Kharasch-Sosnovsky reaction, is eligible to abstract a hydrogen from methyl formate, however in practice these conditions are mostly limited to abstraction from allylic and benzylic C-H bonds. In recent years, the Kharash-Sosnovksy reaction was extended to aliphatic C-H oxidation and in a similar vein aliphatic C-H amination methods were also reported. First, Warren and co-workers showed that a β-diketiminato Cu(I) complex (1.80) is able to catalyze the oxidation of unactivated C(sp³)-H bonds in the presence of di-tbutylperoxide (1.59) to

form ether products (1.78). It was also shown that related β-diketiminato Cu(I) complexes are capable of catalyzing C-H amination of aliphatic compounds. Hartwig et al. demonstrated that unactivated aliphatic C-H bonds can be oxidized by employing 1.59 and a bis(2-pyridylimino)isoindole Cu(I) complex (1.83), however in this method the alkane substrates are in situ oxidized to alkenes and only then takes the Kharasch-Sosnovsky reaction place. Keeping in mind that unactivated, secondary, aliphatic C-H BDE is approximately 99 kcal/mol and the BDE of MeOC(O)-H is about 95.4 kcal/mol, we were optimistic that a suitable condition can be found for the selective and high-yielding hydrogen abstraction.

\[
\text{Scheme 8 - Modern variants of the Kharasch-Sosnovsky reaction reported by Warren and Hartwig. These methods enable the oxygenation of unactivated C(sp^3)--H bonds}
\]

In summary, methyl formate, the most accessible and benign precursor of methoxycarbonyl radical (1.28), had not been exploited for the radical difunctionalization of olefins at the beginning of our project. Although in the absolute sense 1.28 has been obtained from methyl formate by Urry and Tiecco, the complex product distribution or low yield rendered these transformations synthetically irrelevant. We sought to develop a practical method that uses methyl formate as the direct precursor of 1.28 and transform this knowledge into application in radical chemistry, such as alkene functionalization. In the following chapter the development of this transformation, the exploration of its generality will be presented along with a deeper mechanistic insight into an unprecedented 1,2-methoxy methoxycarbonylation of alkenes using methyl formate.

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1.2 Results and Discussion

1.2.1 Development of the transformation

To address the aforementioned challenges, we sought to develop a non-chain difunctionalization process combining the radical addition reaction with metal-catalyzed transformation. Assuming that the presence of iron salt in Taniguchi’s protocol might be responsible for the apparent contradictory results of Taniguchi and Overman regarding the electronic properties of radical 1.28, a working hypothesis was advanced as shown in Scheme 9. Coordination of electron-rich alkenes to a metal would afford metal-π complex 1.85 with decreased LUMO energy of the double bond, facilitating therefore the addition of nucleophilic 1.28. Functionalization of the carbon-metal bond would then furnish the β-functionalized alkanoates 1.88 with concurrent regeneration of the catalytic species.

![Scheme 9 - Working hypothesis.](image)

In the beginning of our studies, we desired to build on the results of Tiecco and Minisci as they had shown that 1.28 could undergo homolytic substitution on aromatic and heteroaromatic compounds. We attempted to react benzene with methyl formate in the presence of an organic peroxide and a variety of metal salts and ligands under thermal or photolytic conditions. We were not able to observe the formation of methyl benzoate; nevertheless, we observed the consumption of the organic peroxide. We hypothesized that either we do not have the correct set up to reproduce Tiecco’s results or benzene may not be a suitable radical acceptor as the dearomatization-rearomatization process may not be favoured under our reaction conditions. When we switched benzene to α-methylstyrene and heated it in the presence of di-tbutylperoxide (DTBP, 1.59), catalytic amount of copper(II) triflate and methyl formate as solvent, we found that compound 1.90 and 1.91 were formed in 3% and 2% yield respectively. Although the amount of isolated product was insignificant, their mere presence proved us that methoxycarbonyl radical was successfully formed for the first time.

Systematic screening of copper salts, peroxides, ligands and additives was carried out in order to identify the optimal conditions for the transformation. The screening was carried out in an iterative fashion, varying each reaction component one-at-a-time. Here we present the most important observations from the optimization process.

Equation 1 - Proof of concept finding: methoxycarbonyl radical was generated from methyl formate for the first time in our hands.

Initially, \( \textbf{1.90} \) was in the focus as target compound, however, at a later stage, the reaction was followed by gas chromatography and we observed the presence of a transient intermediate that does not respond well for standard TLC staining agents (Equation 2, Table 1). This hidden intermediate was isolated and turned out to be the \( \beta \)-methoxy alkanoate \( \textbf{1.92} \). In our opinion, it was a much more interesting and versatile compound, therefore our efforts were focused on obtaining it in an efficient manner.

Equation 2 - Discovery of a transient intermediate in the formation of \( \textbf{1.90} \) from \( \alpha \)-methylstyrene

The choice of metal salt and ligand are key components in the reaction. We screened a large array of metal salts in the early phase of the project and we found that copper(II) triflate has an outstanding activity in this transformation. On the one hand, copper(II) salts outperformed cuprous salts, furthermore we found that elevated amount of cuprous salts (10 mol\%<) inhibited the reaction. This
latter observation may be the consequence of the fact that higher concentrations of copper(I) facilitates the quenching of tert-butoxy radical to form Cu(III)-OtBu species.\textsuperscript{27,30} On the other hand, the counteranion of copper is another important parameter in the system. Initially, we did not attribute great significance to this factor, but following some control experiments, we found that the \textit{in situ} formed triflic acid is an essential component in the reaction. These experiments will be further detailed under Section 1.2.3.4. The reactivity in transition metal catalysis is regulated by the choice of ligand, and in our case, it was no different. A large array of $N$-ligands, that are known to tolerate oxidative conditions were screened. The majority of commercially available ligands proved ineffective in our transformation and only a select few of them allowed us to isolate \textbf{1.92}. To the author’s greatest fortune, previously gained hands-on experience with diketimine ligands led us to synthesize and try them for our purposes. However, it is noteworthy that when biquinoline-, 1,10-phenanthroline- and salene-type ligands were used we observed the formation of \textbf{1.90} up to 60% yield. Unfortunately, we were not able to find conditions where intermediate \textbf{1.92} could be isolated in good yield as the formation of \textbf{1.90} and \textbf{1.92} in these cases occurred in a quasi-parallel fashion. A possible explanation of this is the existence of a parallel process where the benzylic radical intermediate is directly oxidized by the Cu$^n$L complex to the carbocation and proton elimination delivers \textbf{1.90}. Another reasonable explanation is that these copper complexes are more Lewis acidic and promote methanol elimination at a faster rate than their copper-diketiminato counterparts.

\begin{center}
\[
\text{Scheme 10 - General overview of the ligand classes screened and their respective performance.}
\end{center}

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ligand class</th>
<th>Best yields obtained</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Diketimine</td>
<td>60-83%</td>
</tr>
<tr>
<td>2</td>
<td>Biquinoline</td>
<td>20-60%</td>
</tr>
<tr>
<td>3</td>
<td>Bipyridine</td>
<td>10-40%</td>
</tr>
<tr>
<td>4</td>
<td>1,10-Phenanthroline</td>
<td>30-60%</td>
</tr>
<tr>
<td>5</td>
<td>PyBOX</td>
<td>30%</td>
</tr>
<tr>
<td>6</td>
<td>salene</td>
<td>30-60%</td>
</tr>
</tbody>
</table>

Subsequently a library of variously substituted diketimine ligands was synthesized and as a generalization, we could tell that substitution on the methyl and methylene groups did not alter much the

reaction outcome, however, substitution of the aromatic carbons made significant difference in reactivity.\textsuperscript{31} Ligands bearing 2,6-halo substituents on their aromatic part outperformed all other substitution pattern. As the ligand screening was performed in an iterative fashion by changing other factors as well, we restrict ourselves to present only a summary of results.

![Scheme 11 - Survey of diketimine ligands.](image)

Finally yet importantly, we varied the choice of peroxide to optimize the hydrogen atom abstraction from methyl formate. Although the majority of the optimization work was carried out using di-tertbutyl peroxide, after the first screening it became evident, that peroxoesters are far superior to

\textsuperscript{31}The synthesis of the diketimine ligands is detailed in the experimental section.
peroxoacids, alkyl peroxides and other symmetric peroxides. *Tert*-butylperoxoacetate and *tert*-butylperoxobenzoate (Luperox P©) were the most efficient hydrogen atom abstracting agent. With regard to the reaction temperature, there is no singular best value for the transformation, but within a small window, one can find optimal temperature. The reaction outcome is decided by the sensitive balance between achieving a good conversion and suppressing side reactions. On one hand, higher reaction temperature enables higher conversion even with electron poor substrates, on the other hand, applying lower reaction temperature one can avoid the β-elimination of methanol from electron rich styrene derivatives. Consequently, reactions of electron rich substrates were routinely carried out between 65-75°C, whereas electron poor substrates were reacted at 75°C to 85°C. A reaction of 1.89 as substrate was profiled as the function of temperature and depicted on Scheme 12.

![Scheme 12](image)


\[
\begin{array}{|c|c|c|c|}
\hline
\text{Entry} & \text{Peroxides} & \text{Isolated yield (\%)} & \\
\hline
1 & TBPA & 77 & <5 & <5 \\
2 & di-tertbutylperoxide & 67 & ND & ND \\
3 & Luperox P®, 80°C & 62 & ND & ND \\
4 & Luperox 101®, 90°C & 25 & ND & ND \\
5 & t-butylhydroperoxide, 80°C & 4 & ND & ND \\
6 & mCPBA, 80°C & 20 & 6 & ND \\
7 & Benzoyl peroxide & 12 & ND & ND \\
8 & Dilauroyl-peroxide & 0 & ND & ND \\
9 & Cumene hydroperoxide & 11 & 0 & 0 \\
10 & TBPA, under air & 68 & <5 & ND \\
11 & TBPA, water added & 20 & ND & ND \\
\hline
\end{array}
\]

**Scheme 12** - a) Summary table of the screened peroxides. b) Temperature-dependance chart of the reaction. 1 = tert-butylperoxoacetate

Regarding the temperature dependence of the reaction, it is noteworthy to mention here, that during our efforts to find the optimal temperature we observed the fragmentation of methoxycarbonyl radical to carbon dioxide and methyl radical. When a solution of 1,1-diphenylethylene (1.93) was heated in the presence of 4 equivalents of di-tertbutylperoxide (DTBP), 10 mol% copper(II) triflate
and 20 mol% 1.13 at or above 80°C the side product 1.94 could be isolated from the reaction mixture. This compound is best explained as the product of methyl radical addition onto 1.93, followed by benzylic oxidation or methoxylation/elimination of the radical intermediate.32

**Equation 3 - Formation of 1.94 indicates the fragmentation of methoxycarbonyl radical to methyl radical and carbon dioxide.**

Although methyl formate is an inexpensive, commodity chemical, we found that pentane could also be used as a co-solvent without the deterioration of yield. In contrast, when polar solvents were used as a media, the reaction did not take place. The characteristic light green color of the catalyst complex disappeared when DMF, methanol, ethanol or pyridine was used. In these cases, perhaps the competitive coordination between olefin and solvent to the copper center is the origin of the lack of reactivity.

In conclusion, the optimum conditions consisted of performing the reaction of 1.89 in methyl formate (c 0.1 M) in the presence of tert-butyl peroxycetate (TBPA), a catalytic amount of Cu(OTf)₂ and ligand 1.11 (0.1 equiv) at 75 °C under nitrogen atmosphere. Under these conditions, 1.92 was isolated in 77% yield.

**Equation 4 - The optimized conditions to transform styrene derivatives to b-methoxy alkanoates. Later referred to as “standard conditions”.

---

1.2.2 Generality of the method

With the optimized conditions in hand we began to explore the generality of the method. Terminal alkenes bearing an alkyl and aryl substituent were converted to the corresponding β-methoxy alkanoates (1.96a-h) regardless of the steric and stereoelectronic effects of the substituents. 1,1-diaryl substituted ethylenes participated in the reaction without event (1.96i-t). More importantly, styrenes, known to be highly prone to polymerization in radical processes, were transformed to 3-methoxy-3-arylpropanoates 1.96u-aa in good yields. We note that the presence of strong electron-donating group (OMe) and strong electron-withdrawing group (NO₂) were tolerated in this transformation. A broad range of functional groups such as halides (F, Cl, Br), ester, sulfonamide and nitrile were compatible with the reaction conditions, providing therefore handles for further functionalization. The scalability of the reaction was also examined with the three classes of substrates. To our delight, compounds 1.96a, 1.96i, 1.96u were all formed in comparable yields on gram-scale experiments.

Scheme 13 - Synthesis of β-methoxy alkanoates from styrene derivatives. I = isolated yield of gram-scale experiment ii = reaction was run at 85°C iii = based on recovered starting material
1.2.2.1 Extension to cinnamic ester derivatives

In our preliminary studies, we observed the formation of 1.90 and 1.91 in the reaction mixture. We became interested in optimizing the process, as the conversion of terminal alkenes to α,β-unsaturated esters is a transformation of high importance in the synthesis of complex bioactive compounds. A wide range of bases, Lewis and Brønsted acids were examined in order to promote the in situ β-elimination of methanol from 1.92. A summary of results is shown in Scheme 14. Increasing the temperature and reaction time from the standard conditions promoted the elimination, however without showing any selectivity between products 1.90 and 1.91 (Entry 1). Addition of different bases could not assist efficiently the elimination of methanol. A range of acids was able to catalyze the methanol elimination, but only few were competent to furnish exclusively 1.90. Among these, trifluoromethanesulfonic acid (Entry 9) proved to be the best and afforded, after isolation, product 1.90 in 74% of yield with excellent E/Z selectivity. The elimination process leading to 1.90 was found to proceed in two stages. First, in less than 30 minutes, the elimination of methanol yielded a mixture of 1.90 and 1.91. In the second phase, 1.91 was isomerized to the conjugated system affording exclusively (E)-1.90.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Additives</th>
<th>Total yield</th>
<th>Ratio 1.90:1.91</th>
<th>Yield 1.90</th>
<th>Ratio E/Z</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>No additive</td>
<td>75%</td>
<td>1</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>2</td>
<td>DBU (10 equiv)</td>
<td>17%</td>
<td>0,6</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>3</td>
<td>AlCl₃ (3 equiv)</td>
<td>15</td>
<td>0,9</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>4</td>
<td>BF₃.OEt₂ (3 equiv)</td>
<td>95%</td>
<td>2,7</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>5</td>
<td>Zn(OTf)₂ (3 equiv)</td>
<td>94%</td>
<td>2,9</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>6</td>
<td>Sc(OTf)₃ (3 equiv)</td>
<td>94%</td>
<td>13,2</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>7</td>
<td>MsOH (5 equiv)</td>
<td>96%</td>
<td>14</td>
<td>53%</td>
<td>&gt;20/1</td>
</tr>
<tr>
<td>8</td>
<td>pTSA (5 equiv)</td>
<td>&gt;99%</td>
<td>13</td>
<td>67%</td>
<td>&gt;20/1</td>
</tr>
<tr>
<td>9</td>
<td>TfOH (2 equiv)</td>
<td>&gt;99%</td>
<td>&gt;20</td>
<td>77% (74%)³</td>
<td>&gt;20/1</td>
</tr>
</tbody>
</table>

Scheme 14 - Optimization of the synthesis of cinnamic ester derivatives. Ratios and yields were determined by GC-FID using toluene as internal standard. ³ = isolated yield

The work presented in section 1.2.2.1 was performed by Alexandre Leclaire as the theme of his Master thesis.
Under optimized conditions, the \( \alpha,\beta \)-unsaturated ester 1.90 was isolated in good yield with excellent \( E/Z \) selectivity. \( \alpha \)-Methyl styrene and its derivatives with different electronic properties were converted to the corresponding \( \beta,\beta \)-disubstituted \( \alpha,\beta \)-unsaturated esters (1.98a-g) with high synthetic efficiency. 1,1-Diaryl substituted ethylenes were similarly transformed to the homologated esters (1.98h-j) (Scheme 15).

\[ \text{Scheme 15 - Conversion of styrenes to cinnamic acid derivatives.} \]

### 1.2.2.2 Extention to obtain functionalized heterocycles from styrene derivatives

To further extend the application scope of this protocol, methoxycarbonylative cycloetherification, lactonization and cycloamination were examined. Gratifyingly, heating a methyl formate solution of 4-phenylpent-4-en-1-ol (1.99a) under standard conditions readily furnished a mixture of 2,2-disubstituted tetrahydrofuran 1.100a and ester 1.101. A brief optimization showed us that 1.100a can be obtained in one-step from alkene 1.99a in good yield. A sample of results with the screened Brønsted- and Lewis acids is shown below (Error! Reference source not found.). Following the acid screening, we settled with 0.1 equivalent of [0.1 M] aqueous \( \text{H}_2\text{SO}_4 \) solution as additive, as it not only promoted the cyclization with high efficiency, but also proved to be equally efficient with ester (1.104a-g) and tosylamide (1.104a-e) substrates. It is important to note that other Lewis- and Brønsted acids could also promote the transformation with comparable efficiency.
Table 2 - A brief screening of acidic additives showed that 1.100a can be obtained in high yield using dilute aqueous sulfuric acid in catalytic amount.

As it is illustrated in Scheme 16 the substrates, regardless of their electronic properties, were converted to the corresponding heterocycles. However, the presence of OMe group led in general to the corresponding products with reduced yields, due to the instability of the resulting heterocycles.
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Scheme 16 - One-pot conversion of styrenes to functionalized tetrahydrofurans, \(\gamma\)-lactones and pyrrolidines.

1.2.2.3 Limitations of the method

Sometimes the limitation of a method tells more than its applicability and as every chemical reaction, this transformation has its weaknesses too. Probably the first thing the reader noticed that simple aliphatic alkanes and alkynes are not presented as substrates. The principal problem with these substrates is that no good conversion could be achieved with them. It could be for multiple reasons, but we believe that the stabilization of the radical intermediate or the low affinity to the copper catalyst could be behind the problem. In a similar vein, internal alkenes refused to react under our conditions, regardless of them being styrene derivatives or not. We hypothesise that steric congestion around the reactive site hinders the access of the copper catalyst to the \(\pi\)-bond. The two following arguments further support this theory. First, we observed longer reaction times and lower yields with compound 1.96f and 1.96g, furthermore, when 1.109 was subjected to the reaction conditions the substrate remained intact. Second, \textit{ortho}-substitution on aromatic substituents were not tolerated either, regardless of their size or stereoelectronic effect (Scheme 17).
If we take a closer look at the substrate scope, we can see that the stereoelectronic effects of the substituents has little effect on the obtained yield, at the same time, the extremes are not well tolerated. Placing multiple, strong electron donating group on the aryl substituents would facilitate the elimination of methanol from the product and we routinely observed with these substrates the preference toward cinnamic ester formation. On the other hand, electron-withdrawing substituents are better tolerated and even nitrile and nitro substituents allowed us to obtain the product in decent yield. Nevertheless, these reactions required to be run at elevated temperatures and an additional aryl substituent on the olefin was necessary to effect the transformation.

**1.2.3 Mechanism**

**1.2.3.1 Experiments with radical probes**

To gain insight into the reaction mechanism, a series of control experiments were carried out. As it would be expected, the reaction did not proceed in the absence of copper catalyst. Submitting 1-(1-cyclopropylvinyl)benzene \(1.112\) to the standard conditions afforded homoallylic methyl ether \(1.113\) in 27% yield (Equation 5). Should the radical intermediate \(1.115\) be involved, the formation of 1,2- dihydronaphthalene \(1.114\) would be expected. The fact that \(1.114\) was not detected suggested that the reaction might proceed through an organometallic species \(1.116\) rather than the radical intermediate \(1.115\). Although intermediate \(1.116\) could in principle undergo homolytic cleavage to afford homoallylic radical \(1.115\) and Cu(II) species, the reductive elimination of \(1.116\) was apparently kinetically faster to provide methyl ether \(1.113\) instead.\(^{34}\)

\[\text{Scheme 17 - Substrates that failed to react under the developed conditions.}\]

Alternatively, carbocupration of the olefin with the in situ generated Cu(II)-COOMe specie, subsequent β-C-elimination and reductive elimination would also deliver 1.113. Although we did not find a similar precedent in the literature, intramolecular carbocupration of olefins and intermolecular carbocupration of strained cyclopropenes is documented in the literature.\textsuperscript{35}

1.2.3.2 Crossover experiments: determination of the origin of the methoxy group

We were intrigued by the origin of the methoxy group on the β-methoxy alkanoates, therefore we designed experiments to better understand the elemental steps leading to these products. First, we probed the reaction by adding various external nucleophiles to the media under standard conditions (ethanol, isopropanol, butanol, methyl amine, diethylamine). To our surprise, we could not observe the incorporation of any of these externally added nucleophiles and we suspected the reaction may not proceed through a carbocationic intermediate. In order to confirm our hypothesis we designed a crossover experiment with deuterium labelled methanol and methyl formate. Performing the 1,2-methoxy methoxycarbonylation on 1.89 in the presence of CD\textsubscript{3}OD (2.0 equiv) under otherwise standard conditions afforded compounds 1.92 and 1.117 in a 10 to 1 ratio. Conversely, performing the same reaction in HCOOCD\textsubscript{3} in the presence of MeOH (2.0 equiv) afforded 1.119 and 1.120 in a ratio of 1 to 10 (Scheme 18). The results of these two crossover experiments suggested that both methoxycarbonyl and methoxy groups came from methyl formate and that the formation of C-O bond did not go through a cationic intermediate. In addition, reaction of 1.92 with HCOOCD\textsubscript{3} under standard conditions led also to the formation of a small amount of 1.17 via most probably the ionization of 1.92 to carbocation followed by nucleophilic trapping. We hypothesized that this pathway could also account for the formation of the minor products 1.117 and 1.119 in the crossover experiments.

1.2.3.3 The role of carbon monoxide in the reaction

The measurement of CO concentration was done by a GfG GMA200-R carbon monoxide detector. The background CO concentration in the air of our laboratory is between 0-1 ppm. In order to determine whether carbon monoxide was generated under the reaction conditions, we prepared two reaction mixtures and their headspace was measured with the CO detector. The two reaction mixtures (Sample 1 and Sample 2) were prepared according to general procedure B (see Experimental) using compound 1.89 as substrate. Sample 1 was kept at room temperature for one hour and then the cap was removed for the CO measurement. The detector showed no increase in CO concentration compared to the background level. Sample 2 was heated at 75°C for one hour and then the cap was removed for the CO measurement. The detector showed a dramatic increase in the CO concentration up to and above the limit of detection at 340 ppm. The screen of the CO detector was recorded during the measurements and the video files are accessible in the supporting information of the published article.36 The detection of the in situ formed carbon monoxide was an important step ahead in understanding the mechanism. First of all, it is in accordance with the result of the crossover experiments, presented in Section 1.2.3.2. If we assume, that the methoxy group at the benzylic position of the product is delivered as depicted on Scheme 24, then the CO elimination may be a

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A reversible process. In line with this mechanistic hypothesis, the yield of 1.92 was reduced to 28% when the reaction was performed under CO atmosphere under otherwise identical conditions.

Scheme 19 - When the reaction is run under CO atmosphere the product formation is inhibited.

1.2.3.4 Synthesis of a ternary β-diketiminato-Cu(I)-styrene complex

Since fragmentation of the cyclopropyl methyl radical was a kinetically fast process, the aforementioned results implied that the alkene-Cu complex might be formed before radical addition. Gratifyingly, stirring a pentane solution of styrene and the β-diketiminato Cu(I) (μ-benzene) complex 1.124, synthesized according to Warren, afforded a new complex 1.125 whose structure was fully established by spectroscopic and X-ray single crystal structure analysis (Scheme 20).

Scheme 20 - Synthesis of a ternary β-diketiminato-Cu(I)-styrene complex

A series of control experiments showed that in the presence of an equal amount of Cu(OTf)₂ or TfOH, 1.125 was a competent catalysts for the methoxy methoxycarbonylation of 1.89 under otherwise standard conditions. These experiments highlight that the in situ formed triflic acid under standard conditions is essential in the transformation. It is hard to prove the exact role of the acid, but it might facilitate the reductive elimination process.
<table>
<thead>
<tr>
<th>Entry</th>
<th>Additive</th>
<th>Conversion</th>
<th>XX</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>-</td>
<td>&lt;10%</td>
<td>nd</td>
</tr>
<tr>
<td>2</td>
<td>Cu(OTf)₂ (10%)</td>
<td>100%</td>
<td>63%</td>
</tr>
<tr>
<td>3</td>
<td>NaOTf (20%)</td>
<td>0%</td>
<td>nd</td>
</tr>
<tr>
<td>4</td>
<td>TfOH (0.1 mol%)</td>
<td>0%</td>
<td>nd</td>
</tr>
<tr>
<td>5</td>
<td>TfOH (1 mol%)</td>
<td>15%</td>
<td>10%</td>
</tr>
<tr>
<td>6</td>
<td>TfOH (10 mol%)</td>
<td>100%</td>
<td>75%</td>
</tr>
</tbody>
</table>

Scheme 21 - Control experiments that show the catalytic activity of 1.125 and the necessity of trifluoromethanesulfonic acid.

1.2.3.5 Kinetic study experiments

Finally, we designed a series of experiments to measure the relative rates of the 1,2-methoxy methoxycarbonylation of variously substituted styrene derivatives. A schematic representation of the experimental design is shown on Scheme 22—detailed description can be found in the Experimental section. First, a homogenous solution of all components but the substrate was prepared in a round bottom flask. The mixture was briefly heated to pre-activate the catalyst, cooled to room temperature and once the substrate was added to it, the obtained mixture was divided into smaller reaction vials. The vials were inserted into a hotplate pre-heated at 65°C and counting from then, each minute a vial was submerged into liquid nitrogen. The content of the vials was analysed by GC-FID technique using toluene as an internal standard.
The designed experiments to determine the relative rates of 1,2-methoxy methoxycarbonylation of styrene derivatives provided us with data that shows the increased reaction rate of electron rich styrenes compared to electron deficient styrenes. As it is shown below in the graphs the relative rate of the reaction increases as the more electron rich substrates were utilized. We attempted to carry out the same experiment with 4-methoxystyrene, but to our dismay the reaction rate in this case was too high to obtain a good regression line and coherent data. Although the obtained information is seemingly against the radical polarity-match principle knowing that the methoxycarbonyl radical 1.28 is characterized as nucleophilic, we surmise that the increased electron density on the styrene double bond facilitates the rapid coordination to the Cu(I) center, hence accelerating the radical addition and subsequently the observed rate of the reaction.
1.2.3.6 Proposed mechanism

On the basis of the results of these control experiments, a possible reaction pathway is depicted in Scheme 24. Coordination of LCu(I) (1.126) to electron-rich alkenes (1.128) would afford Cu(I)-π complex 1.129 that would react with nucleophilic methoxycarbonyl radical 1.28, in situ generated from methyl formate by hydrogen abstraction. Radical rebound of adduct 1.130 with 1.28 would produce the Cu(III) intermediate 1.131 which might be in equilibrium with methoxy complex 1.132. Reductive elimination of the latter would then furnish the β-methoxy alkanoates 1.133 with concurrent regeneration of the Cu(I) specie.

Scheme 24 - Proposed mechanism of the 1,2-methoxy methoxycarbonylation of alkenes with methyl formate.
1.3 Conclusion

In summary, methyl formate was successfully exploited for the first time in a synthetically useful Cu-catalyzed difunctionalization of alkenes. Acting as a donor of both methoxycarbonyl and methoxy groups, methyl formate transforms styrene and its derivatives to value-added β-methoxy alkanoates, cinnamates as well as medicinally important five-membered heterocycles. It was believed that “the reaction of alkyl radicals is synthetically significant only when the olefinic double bond is conjugated with electron-withdrawing groups owing to the nucleophilic character of the alkyl radical”. While the statement is correct in absolute sense, the landscape is changing and the transition metal-catalyzed difunctionalization of electron-rich alkenes involving addition of nucleophilic alkyl radical is seen in the recent literature. We surmised that pre-coordination of electron rich double bond to metal might play an important role in accelerating these polarity mismatched additions and could have general implications in designing novel radical-based transformations.

Chapter 2  Synthetic Studies Toward the Total Synthesis of Koumine

2.1 Introduction

Koumine (2.1) is a monoterpene indole alkaloid, which belongs to the Gelsemium family. The genus is a source of more than 120 alkaloids, which are sorted into six classes: koumine, humantenine, sarpagine, gelsemine, gelsedine and yohimbine. The biogenetic route toward the six classes is hypothesised to stem from one common intermediate, strictosidine (2.7), which is the Pictet-Spengler condensation product of tryptamine (2.8) and secologanin (2.9) (Figure 1).

Figure 1 - The six classes of Gelsemine alkaloids and their common biogenetic precursor, strictosidine.

The Gelsemium alkaloids have rich literature, which reaches further than the scope of this work, here we will restrict ourselves to discuss the koumine type alkaloids. The koumine subclass consists

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of fourteen alkaloids, all isolated from *Gelsemium elegans*. 2.1 was first isolated from *Gelsemium elegans* Benth., in 1931. The structure was elucidated by single-crystal X-ray diffraction in 1981 by Riche et al., and the absolute stereochemistry was established by the semi-synthesis from vo- basine. Although the *Gelsemium* alkaloids are a particularly wide class of natural products, none of them have succumbed to total synthesis until the late eighties’ and only three member of the koumine subclass has ever been synthetically prepared. A plausible reason for the apparent difficulty of their synthesis may be the cage-like structure of these natural products, a particularly challenging motif in synthetic organic chemistry. If we take a closer look at the structure of koumine on Figure 3, we can see the cage formed by the bottom of the isoquinuclidine core and flanked by the tetrahydropyran motif. From another point of view, a [3.3.1] bicyclic system serves as the core of the skeleton, interlinked by aminomethylene and oxymethylene units (Figure 3). This pattern is unique to the koumine subclass of *Gelsemium* alkaloids and there is no other known compound features the above mentioned bicyclic system. The reason for choosing koumine as target roots in these structural features and our motivation was further increased by the lack of efficient synthetic route at the time.

![Figure 2 – The numbering of koumine](image)

![Figure 3 - Representation of the koumine skeleton from different angles. The cage-like structure renders the scaffold an exceptionally challenging target for synthetic organic chemists.](image)

### 2.1.1 Bioactivity

The genus *Gelsemium*, comprises three species in Asia (*Gelsemius elegans*) and North America (*G. rankinii* and *G. sempervirens*), has been utilized for centuries in traditional Chinese medicine and folk medicine for the treatment of migraines, sciatica, neuralgia, various types of sores and cancer. Despite their known healing properties, their toxicity has also been recognized and multiple cases

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of intoxication from extracts of *Gelsemium elegans* has been reported, resulting in dizziness, difficulty of respiration and even coma.\(^{43}\) Renewed interest in these alkaloids has led to the discovery of more efficient chromatographic separation methods of the crude plant extract enabling detailed studies of the bioactivity of the isolated alkaloids.\(^{39,44}\) It has been shown that koumine (2.1) has moderate toxicity with an LD₅₀ = 99 mg/kg (i.p. injection, mice), in stark contrast with many other *Gelsemium* alkaloids.\(^{45}\) Pharmacological studies have shown the analgesic, antianxiety and anti-stress effects of 2.1 at 0.28-2 mg/kg, 0.4 mg /kg and 2.4 mg/kg in mice, respectively.\(^{39}\) The antitumour activity of koumine was examined against various cancer cell lines, however, the relatively high minimal active concentration of koumine calls into question its potential as a therapeutic agent.\(^{39}\)

### 2.1.2 Biosynthesis

The koumine type *Gelsemium* alkaloids is thought to originate from strictosidine (2.7), the Pictet-Spengler condensation product of tryptamine (2.8) and secologanin (2.9). β-Glucosidase mediates the liberation of the aldehyde function of 2.7 and subsequent steps achieve a net reductiveamination delivering geissoschizine (2.10), a Corynanthe-type alkaloid. Upon intramolecular bond formation between C5 and C16 atoms and reduction of the ester function, E-koumidine (2.11), member of the Sarpagine-type *Gelsemine* alkaloids is formed. Allylic oxidation of 2.11 and subsequent C/D ring cleavage would give the hypothetic biogenetic precursor 2.13. Intramolecular Sₙ₂’ substitution connecting the C7 and C20 atoms would deliver koumine (2.1) (Scheme 25).\(^{46}\) Based on this proposed biosynthetic route, 11-methoxykoumine was synthesized from the 11-methoxy analogue of 2.13 by Sakai et al.\(^{52}\)

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2.1.3 Previous total syntheses

The first total synthesis of koumine (2.1) was reported by Magnus and co-workers in 1989. Although the obtained alkaloid was antipodal to the natural product, it does not lessen the achievement, especially if we consider that their work constituted the first synthetic entry to the Gelsemium alkaloid family. Based on the results of Yoneda and Cook, starting from natural (L)-tryptophan they reach the bicyclic intermediate (+)-2.16 in seven steps.\(^4\) Debenzylation of (+)-2.16 under transfer hydrogenation conditions, followed by decarboxymethylation under acidic conditions delivered (+)-2.17. In the next phase of the synthesis the quinuclidine skeleton was elaborated. The obtained ketone (+)-2.17 was N-propargylated and subsequent transformation to the acetylenic ester furnished the precursor of the quinuclidine intermediate (+)-2.18. First, the silyl-enol ether was converted to the ketone and the obtained product was subjected to a catalytic amount of pyrrolidinium trifluoroacetate in refluxing benzene. The intramolecular Michael addition yielded the desired (+)-E-2.20 and its geometric isomer as a minor product. The carbonyl group of (+)-E-2.20 was homologated via Tebbe olefination and hydroboration. Reduction of the ester and N-debenzylation delivered the key intermediate of the synthetic route ((+)-2.21). Fragmentation of (+)-2.21 by treatment with methyl chloroformate generated intermediate (+)-2.22 bearing a benzylic carbocation stabilized by the indole moiety. The incipient charged specie was trapped by the hydroxyl group to form (+)-2.23. Treatment of (+)-2.23 with LiAlH₄ furnished 18-hydroxytaberpsychnine ((+)-2.24). (+)-2.24 was then converted to (+)-koumine ((+)-2.1) by treatment with SeO₂/H₂O₂. The complete sequence is shown of Scheme 26. The last transformation of the total synthesis starting from (+)-2.24 has a


pivotal role in the sequence and can be considered as the key step of the work. Actually, Liu and co-workers reported in 1986 the semi-synthesis of koumine from (+)-taberpsychnine (18-deoxy-2.24) by its treatment with SeO₂ in acidic conditions.\textsuperscript{49} Magnus also intercepted (+)-taberpsychnine as an intermediate towards (+)-koumidine and mentions that the formal total synthesis of 2.1 is achieved. However, as they were able to access (+)-2.24, which can be considered as the transient intermediate of Liu’s semi-synthesis, by applying Liu’s selenium mediated conditions to (+)-2.24 they accessed koumine. Magnus’ synthesis from (+)-18-hydroxytaberpsychnine ((+)-2.24) is somewhat better than the route from (+)-taberpsychnine in terms of overall yield, but in all likelihood the primary reason behind pursuing this alternative route was to establish this work as the first total synthesis of (+)-koumine ((+)-2.1).

\textsuperscript{49} Liu, Z.; Yu, Q. \textit{Youji Huaxue} 1986, 6, 36.
The formal total synthesis of 2.1 was disclosed by Takayama featuring a gold (I) catalysed 6-exo-dig cyclization as key step. The synthesis is described from azabicyclononane (+)-2.27, which was prepared in four steps from cyclooctadiene as reported by Rassat. The substrate ([−]-2.28) of the key cyclization reaction was accessed in six steps. In their initial investigation of the 6-exo-dig cyclization, the propargyl alcohol group on [−]-2.28 was masked as a methoxymethyl ether and performing the gold (I) carbene complex catalysed cyclization process yielded significant quantity of the undesired 7-endo-dig product. By changing the O-protecting group to the bulky trityl moiety ([−]-2.28), the authors could isolate [−]-2.30 in 85% yield accompanied by 15% of the 7-endo-dig cyclization product. Functional group interconversions delivered the bicyclic ketone [−]-2.31, which was converted

Scheme 26 - The first total synthesis of (+)-koumine ([+]-2.1) reported by Magnus et al.
to (+)-2.32 via Fischer indole synthesis with 1-benzyl-1-phenylhydrazine, followed by hydroboration and N-debenzylation. The obtained product ((+)-2.32) corresponds to the 11-demethoxy analogue of Sakai’s intermediate from which he accessed 11-methoxykoumine.\textsuperscript{52} Following Sakai’s procedure from (+)-2.22, (-)-koumine can be obtained in 4 steps (Scheme 27).

\begin{center}
\textbf{Scheme 27 - Formal total synthesis of (-)-koumine reported by Takayama and co-workers.}
\end{center}

Recently, Kerr disclosed the racemic formal total synthesis of koumine.\textsuperscript{53} They designed an efficient, 11-step synthetic route to access (19Z)-taberpsychine (2.47), which can be converted to koumine according to the semi-synthetic studies reported by Liu in 1987.\textsuperscript{54} The synthesis commences with a


hydrostannylation-Stille coupling sequence of alkyne \textbf{2.37}. The obtained lactone is then converted to hydroxylamine \textbf{2.42} in three steps. \textit{In situ} Boc-deprotection and condensation of \textbf{2.43} delivered nitrene intermediate \textbf{2.44}, which upon heating underwent intramolecular [3+2] cycloaddition to construct the bicyclic key intermediate (\textbf{2.45}) in 23% yield. Functional group interconversion delivered \textbf{2.46}, which was the junction point in their divergent synthetic strategy to access four \textit{Gelsemine} alkaloids. Treatment of \textbf{2.46} with boron trifluoride-ether complex, followed by reductive amination with formaldehyde furnished (19Z)-taberspsychine (\textbf{2.47}), precursor of koumine. Although the authors did not disclose their procedure and spectrum of koumine, according to Liu, treatment of \textbf{2.47} with selenium dioxide in the presence of sulphuric acid yields the racemic mixture of \textbf{2.1}.\textsuperscript{54}

![Scheme 28 - Formal total synthesis of (−)-koumine by Kerr.](image)

The extremely limited synthetic access to koumine type \textit{Gelsemium} alkaloids renders the above-mentioned works remarkable achievements of the synthetic community. The temporal analysis of the three synthesis highlights the philosophical evolution of synthetic organic chemists in the past decades. Magnus’ initial report comprises of 19 steps to access the antipode of \textbf{2.1} from \textit{L}-tryptophan. The overall yield of the sequence is 0.6%, labelling the feat a symbolic success rather than a practical synthetic solution. The next synthetic entry, which waited almost three decades, was published by Takayama and co-workers. The 23-step sequence to (−)-koumine (\textbf{2.1}) may be longer than Magnus’ route, the achieved synthetic efficiency compensates for its length. Starting from cyclooctadiene the natural product was obtained in 3% overall yield, demonstrating the efficiency-centered
mindset of chemists in the 21st century and the advancement of synthetic methods in the past decades. Finally, the 12-step sequence disclosed by Kerr is the closest to represent what we call today an ideal synthesis. The sequence is short, scalable and the used materials are inexpensive. Although the synthesis is racemic and the obtained overall yield falls short of Takayama’s with 1.5%, in practice the shorter sequence, hence higher attainable throughput compensates for the lower efficiency.

Above the purely synthetic considerations, we would like to introduce the reader to our perspective of the strategic advancement in the total synthesis of koumine. We witnessed the remarkable evolution of the total synthesis of koumine type Gelsemine alkaloids in the past three decades. While it is correct in the absolute sense, since there was no significant advancement in the construction of the koumine skeleton, we challenge the statement. The key step in each of the previously described total syntheses is actually the rearrangement from taberpsychine derivatives (2.24, 2.34 and 2-47) to koumine described by Liu et al. in the 1980s. Therefore, the synthetic advancement described above is mainly related to the construction of the taberpsychine framework and not of the distinct koumine skeleton. Only Kerr’s work includes a genuinely new strategy toward the koumine skeleton, albeit only saturated isodihydrokoumine derivatives can be accessed *via* that pathway. The discovery of novel strategies for the construction of the koumine skeleton would enable us to access the numerous members of the koumine type alkaloids that has never been made before. Moreover, such strategy could potentially pave the way to the synthesis of new-to-nature secondary metabolites bearing the koumine skeleton.

### 2.1.4 Retrosynthetic plan

Our synthetic strategy was based on the enantioselective formation of the isoquinuclidine core. To this end, we dissected the [2.2.2] bicycle into a 1,2-dihydropyridine and a dienophile fragment. The 1,2-dihydropyridine fragment could be derived from a functionalized pyridine and an aniline derivative via cross coupling. Once the isoquinuclidine core is formed *via* enantioselective Diels-Alder cycloaddition, functional group interconversions will lead to an isocyanide-, primary alcohol- and a halide equivalent-bearing intermediate (2.49). The indolenine ring will be constructed by Fukuyama indole synthesis and the obtained 2-stannyl indolenine would be coupled with the masked halide, marked with X. Oxidative ring closure would form the tetrahydropyran moiety and deliver the natural product (Scheme 29).
Scheme 29 - Our retrosynthesis of koumine, featuring Fukuyama indole synthesis and an enantioselective Diels-Alder cycloaddition as the key steps.
2.2 Results and Discussion

This section is divided into three parts. In Section 2.2.1 we detail the route scouting up until the phenylpyridine intermediates. In section 2.2.2 our study of the intermolecular Diels-Alder is presented. Finally, section 2.2.3 details the attempts toward the intramolecular Diels-Alder cycloadditions for the construction of the isoquinuclidine core of the target molecule.

2.2.1 Route scouting to the phenylpyridine intermediate

In this chapter we discuss the first phase of the total synthesis. The principal goal here is to design a robust, scalable, short and inexpensive route to phenylpyridine 2.55. Such a route in hand enables us to synthesize in sufficient amount the precursors for the key step of the total synthesis, the enantioselective Diels-Alder cycloaddition. It was important to design a flexible route that enables us to obtain derivatives of the phenylpyridine, thereby increasing our freedom in finding the ideal substrate for the cycloaddition (Figure 4).

![Figure 4 – Schematic synthetic plan of the desired phenylpyridine intermediate from commercially available starting materials.](image)

2.2.1.1 Synthetic route A

In the design of the first few steps of the total synthesis we kept in mind that implementing robust reactions will pay dividends when the scale of these steps will have to be increased later on. Therefore we examined a route starting from inexpensive phenylboronic acid (2.62) and 4-aminopyridine (2.64) for the construction of the phenylpyridine intermediate 2.60. The retrosynthesis of 2.60 is shown on Figure 5.

![Figure 5 - Retrosynthetic plan of phenylpyridine 2.60, starting from inexpensive starting materials.](image)
Nitration of phenylboronic acid (2.62), catalyzed by urea is an extremely vigorous, nonetheless reliable reaction reported by Johnson.\(^{55}\) The reaction proved to be reproducible and scalable. The desired coupling partner 2.67 was obtained under iron-mediated reduction from 2.66.\(^{56}\) The relative simplicity of these reactions would suggest that compound 2.67 is an easily accessible, commercial reagent. However, purification of the crude mixture obtained from the reduction of 2.66 proved to be surprisingly difficult. After careful examination we found that the mixture of compounds obtained after the reduction are the dimer, trimer and oligomer of 2.67. The mixture was used as is in the following steps.

\[
\begin{align*}
\text{B(OH)}_2 & \quad \text{HNO}_3, \text{urea (cat.)} \\
2.62 & \quad \text{Ac}_2\text{O}, -15^\circ\text{C} \\
& \quad \text{54\%} \\
\text{O}_2\text{N} & \quad \text{Fe powder, cc,HCl} \\
\text{B(OH)}_2 & \quad \text{EtOH, H}_2\text{O}, 50^\circ\text{C} \\
2.66 & \quad \text{45\%} \\
\text{H}_2\text{N} & \quad \text{B(OH)}_2 \\
2.67 & \quad \text{(2.71)}
\end{align*}
\]

The preparation of the pyridine coupling partner commenced with pivaloylation of 2.64 and subsequent directed \textit{ortho}-lithiation of 2.68. The organometallic intermediate (2.69) was quenched with DMF and subsequent hydrolysis furnished aldehyde 2.70.\(^{57}\) Wittig olefination and basic hydrolysis delivered the precursor of the desired coupling partner (2.71).\(^{58,59}\) To our dismay, we were not able to convert 2.71 to 4-halogeno-3-vinylpyridine in good yield. After surveying the literature, we found that 4-chloro-3-vinylpyridine is reported to be extremely prone to decomposition and has to be prepared right before use.\(^{60}\) Other 4-halogeno-3-vinylpyridines are not reported in the literature, which may be another indicator of their surprisingly high sensitivity.

\(^{56}\) Youjun, Z.; Feng, Z.; Wei, L.; Jia, L.; Shana, C. \textit{Patent number: CN103214489B}
2.2.1.2 Synthetic route B

Motivated by the potential rapid access to phenylpyridine 2.74, we devised a route leveraging that pyridinephosphonium salts can act as pseudoarylhalides in cross coupling reactions. The method to obtain heteroarylphosphonium salts and their utility in cross coupling reactions was developed by McNally and co-workers.\textsuperscript{61,62} The synthetic plan to access 2.74 in delineated on Figure 6.

![Scheme 30 - Synthetic sequence to obtain the desired 4-halogeno-3-vinylpyridine coupling partner. Unfortunately the last step only provided the product in traces, therefore the route was abandoned.](image)

**Figure 6 - Retrosynthetic plan of phenylpyridine 2.74.**

First, we synthesized boronic acid 2.75 from aniline. According to reported procedures, 2.75 was prepared by directed ortho-lithiation of Boc-protected aniline (2.79) and subsequent quenching


\textsuperscript{62} Zhang, X.; McNally, A. Angew. Chem. - Int. Ed. \textbf{2017}, \textit{56} (33), 9833–9836.
with trimethyl borate.\textsuperscript{63} Although the reaction was robust and reproducible, the purification of the crude reaction mixture posed a significant challenge on gram scale. From the crude mixture the reaction yield was estimated to be around 60\%, upon flash column chromatography it dropped below 10\% and the remaining mass could not be recovered. Various solid phases and eluents were examined to improve the purification by chromatography without success. Eventually, our attention was drawn to the work of Hall, describing the “phase-switching” synthesis of boronic acid tagged molecules.\textsuperscript{64} The method exploits the ability of sorbitol to complex and transfer boronic acids reversibly from an organic solvent to water by varying the pH. Applying the reported procedure for the isolation of 2.75 we were already able to double the isolated yield (22\%). After successful optimization of the purification procedure with special regard to the acidification step, we were able to isolate 2.75 in 52\% yield at multigram scale.

\begin{center}
\textbf{Figure 7 - Scalable process for the synthesis of boronic acid 2.75 from aniline.}
\end{center}

The preparation of 2.77 commenced with Wittig olefination of 2.78 to obtain 2.80 in 80\% yield. Subsequent activation of 2.80 with triflic anhydride and treatment with triphenylphosphine delivered 2.77. These steps leading 2.80 and 2.77 were scalable without the deterioration of the yield.


Conversion of 2.77 to 2.74 could be performed in two ways.\textsuperscript{61,62} Nickel-mediated cross coupling with an arylboronic acid partner could deliver the desired phenylpyridine 2.74. Alternatively, a nucleophilic attack on the phosphor atom by an organolithium compound and subsequent ligand coupling would also furnish the desired compound. In order to assess these options we synthetized the necessary SIPr·HCl ligand (2.84) in 3 steps according to a reported procedure (Scheme 31).\textsuperscript{62}

Disappointingly, when we applied the reported conditions to our substrate (2.77) and boronic acid partner (2.75) we could not observe the formation of the desired product (2.74).\textsuperscript{62} We hypothesized that the ortho substituents on the aryl rings may impede the reductive elimination to occur. To test this idea, p-tolyboronic acid was subjected to the reaction conditions as it was the authors’ primary choice of substrate and bears no ortho substituents. In either case we did not observe the formation of the desired products. Perhaps the vinyl moiety coordinating to the nickel complex rendered the process unproductive (Scheme 32).
Nucleophilic attack on the P-center of arylphosphonium salt followed by ligand coupling to form C(sp2)-O, C(sp2)-S and C(sp2)-C bonds was reported by McNally and co-workers. They demonstrated the breadth of the scope with regard to alcoholate and thiaoalcoholate nucleophilic coupling partners, however, only two examples were reported with organolithium coupling partners for the construction of carbon-carbon bonds. We prepared aryllithium intermediate and attempted its addition to 2.77. A variety of solvents, temperatures, addition rates and concentrations were examined, our results are summarized in Table 3. When the reported procedure was followed and the temperature was kept under -40 °C we observed minimal conversion and the desired product was not formed (Table 3, Entry 1 and 2). We detected the formation of 2.74 when highly diluted stock solutions were used and the temperature was elevated above -10 °C. By following a reverse addition order at room temperature in high dilution, we could obtain full conversion and the desired product was isolated in 10% yield (Table 3, Entry 7). However, when reverse addition was used the starting material was consumed even at lower temperatures, indicating a side reaction which was absent when the normal addition order was followed (Table 3, Entry 5 and 6). Further variations of the conditions did not improve the yield of 2.74, therefore we abandoned this synthetic strategy.
2.2.1.3 Synthetic route C

The potential rapid access to 2.74 motivated us to attempt the synthesis of the pyridine coupling partner via deprotonation at the C4 position of pyridine derivatives. First, we attempted the selective deprotonation of 2.80 with three different bases and quenched the obtained intermediates with deuterium oxide at cryogenic temperatures. Deprotonation with LDA lead to non-selective deprotonation on the aromatic ring. Treatment of 2.80 with Lochmann-Schlosser base induced the rapid decomposition of the starting material, perhaps via Chichibabin type oligomerization as it is a common side reaction in pyridine metalation reactions. When 2.80 was treated with boron trifluoride-ether complex, to activate the aromatic ring and block the coordinating nitrogen lone pair, and TMPMgCl, partial deprotonation at the C2 position was observed (Scheme 33).

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Chapter 2 - Synthetic Studies Toward the Total Synthesis of Koumine

Scheme 33 - Attempts for the selective para-deprotonation of 3-vinylpyridine.

We turned our attention to Knochel’s one-pot metolation-cross coupling sequence for the arylation of pyridine derivatives. Starting from 3-cyanopyridine or ethyl-3-picolinate, we were not able to isolate the desired compounds in good yield (Equation 6). It is worth to mention, that the quality of the freshly made TMP-MgCl is essential to effect the metellation step. To this end, we surveyed different preparation and titration methods and we found that Knochel’s preparative procedure combined with the reverse Watson-Eastham titration is the best method to obtain high quality TMP-MgCl solution with accurately determined concentration.

Equation 6 - Survey of substrates for Knochel’s one-pot metolation-cross coupling sequence. Although the metolation of the heterocycles was successful, we were not able to effect the subsequent cross-couling step with 2.89.

2.2.1.4 Synthetic route D

After these initial failures we better understood the reactivity of the pyridine and the aniline compounds and we devised a synthesis that overcomes the weaknesses of the previous routes. On the one hand, we have already developed a large scale synthesis of boronic acid 2.75. Since it was a promising substrate for the planned cross coupling reaction we did not modify this part of the synthesis. On the other hand, the synthesis of the pyridine fragment was more problematic. We learned that 4-halogeno-3-vinylpyridines are notoriously unstable, therefore we wanted to form it in a fast reaction under mild conditions. We also experienced that the installation of the halogen or metal at the para position of pyridine is particularly difficult. We hypothesized that starting from a 4-

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halogeno pyridine and subsequent installation of the functionality at the 3-position of the aromatic ring may overcome the instability issues we faced earlier. Meta-deprotonation of 2.91 with LDA, followed by trapping with DMF and aqueous work-up delivered 2.92. As we knew that the olefination of the aldehyde function would furnish an unstable product and 2.92 is an excellent electrophilic substrate for Suzuki-Miyaura coupling, we decided to first form the biaryl intermediate. Under standard Suzuki-Miyaura coupling conditions we obtained 2.93 in 85% yield in the hemiacetal form.

Scheme 34 - Revised route to phenylpyridine 2.93.

Olefination of 2.93 would deliver the desired phenylpyridine 2.74. To this end, Wittig- and Petasis-Tebbe olefination proved to be the best methods, however, even in forced conditions, we were not able to surpass 60% conversion and 50% yield.

Scheme 35 - Wittig olefination of 2.93 proved difficult, however, Petasis-Tebbe olefination provided us with a temporary solution.

In order to support the front end of the synthesis the Petasis-Tebbe olefination served as a temporary solution, but it was evident that a better answer had to be found for this problem. It was logical to exchange the order of steps: first convert 2.92 to 4-chloro-3-vinylpyridine (2.94) by Wittig olefination and only then perform the Suzuki-Miyaura coupling. Wittig olefination of 2.92 delivered 2.94 smoothly, which was immediately subjected to cross coupling after purification. By applying standard Suzuki-Miyaura coupling conditions to 2.94 and 2.75 we could not isolate 2.74 in good yield (Table 4, Entry 1). Part of the reason may be the less electron poor pyridine ring, compared to
2.92, impeding the oxidative addition of Pd⁰. The steric hindrance constituted by the two ortho-substituents of the coupling partners (2.94, 2.75) may hamper the reductive elimination process. Fu and Buchwald independently developed phosphine ligands that enables the oxidative addition to electron rich aryl chlorides and allows the coupling of ortho-substituted aromatic rings.⁷⁰ Their ligands were surveyed for the cross coupling of 2.94 and 2.75 and we found that performing the reaction in the presence of 0.5 mol% Pd₂dba₃, 1 mol% tri-cyclohexylphosphine and 3 equivalents of potassium fluoride in THF leads to the formation of 2.74 in 80% yield (Table 4, Entry 7). In comparison with other ligands, we assume that tri-cyclohexylphosphine has the optimal balance between electronic and steric requirements for the cross coupling. As a strong electron donor and bulky ligand, it favors the dissociation from palladium to form highly reactive monophosphine complex, which readily undergoes oxidative addition with 2.94. At the same time, the cyclohexyl unit is not too bulky to hinder the transmetalation-reductive elimination sequence joining the two ortho-substituted aryl units. The most electron-rich and sterically hindered ligand, tri-tertbutylphosphine, was also evaluated and fell short in performance compared to PCy₃ (Table 4, Entry 5). At last, the catalyst to ligand ratio was fine-tuned. We found that when higher ligand-to-metal ratio was used palladium black formed over prolonged reaction times, whereas when only a slight excess of ligand was used the system remained stable and delivered the product in good yield (Table 4, Entry 7).

\[
\begin{align*}
\text{Cl} & \quad \text{Cl} \\
\text{2.92} & \quad \text{2.94} \\
\text{2.74}
\end{align*}
\]

\(\text{Cl} \quad \text{Cl} \quad \text{N} \quad \text{N} \quad \text{H}_{\text{Boc}} \quad \text{BocH}_{\text{N}} \quad \text{conditions}
\]

Chapter 2 - Synthetic Studies Toward the Total Synthesis of Koumine

Table 4 - Optimization summary of the Suzuki-Miyaura cross-coupling reaction.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Pd-source (2.5 mol%)</th>
<th>Ligand (5 mol%)</th>
<th>Base</th>
<th>Solvent</th>
<th>Temperature</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1*</td>
<td>Pd(OAc)$_2$</td>
<td>PPh$_3$</td>
<td>K$_2$CO$_3$</td>
<td>DME / H$_2$O</td>
<td>100 °C</td>
<td>low conversion</td>
</tr>
<tr>
<td>2</td>
<td>Pd(OAc)$_2$</td>
<td>JohnPhos</td>
<td>KF</td>
<td>EtCN / H$_2$O (1:1)</td>
<td>100 °C</td>
<td>40% conv., 20% yield</td>
</tr>
<tr>
<td>3</td>
<td>Pd(OAc)$_2$</td>
<td>SPhos</td>
<td>K$_2$PO$_4$</td>
<td>THF / H$_2$O (4:1)</td>
<td>65 °C</td>
<td>72% conv., 41% yield</td>
</tr>
<tr>
<td>4</td>
<td>Pd(OAc)$_2$</td>
<td>CyJohnPhos</td>
<td>KF</td>
<td>DMSO</td>
<td>60 °C</td>
<td>60% conv., 30% yield</td>
</tr>
<tr>
<td>5</td>
<td>Pd$_2$dba$_3$</td>
<td>Pt' Bu$_3$</td>
<td>KF</td>
<td>THF</td>
<td>60 °C</td>
<td>70% conv. in 3 days; 50% yield</td>
</tr>
<tr>
<td>6</td>
<td>Pd$_2$dba$_3$</td>
<td>PCy$_3$</td>
<td>KF</td>
<td>THF</td>
<td>65 °C</td>
<td>82% conv., 60% yield</td>
</tr>
<tr>
<td>7**</td>
<td>Pd$_2$dba$_3$</td>
<td>PCy$_3$</td>
<td>KF</td>
<td>THF</td>
<td>65 °C</td>
<td>100% conv., 80% yield</td>
</tr>
</tbody>
</table>

* = 10 mol% ligand ** = 0.5 mol% Pd$_2$dba$_3$; 1.2 mol% PCy$_3$

It is worth to mention that with our method, 2.94 can be obtained from 4-chloropyridine in 62% overall yield, which is a significant improvement compared to the best reported yield (21%) in the literature. With this efficient and scalable route to 2.74 in hand, we proceeded to the second phase of the total synthesis, i.e. the preparation of 1,2-dihydropyridines and their examination as substrates for the Diels-Alder cycloaddition will be detailed in the following two sections.
2.2.2 Synthesis of 1,2-dihydropyridine derivatives and the investigation of the intermolecular Diels-Alder cycloaddition

2.2.2.1 Synthesis of 1,2-dihydropyridines

The first synthesis of a dihydropyridine was reported by Hantzsch in 1882, but the surge of interest in the scaffold waited until the isolation of NADH and the discovery of its biological role in oxidation-reduction reactions. From the five theoretically possible isomers of dihydropyridine, the 1,2- and the 1,4-structures are the most prevalent in the literature with an emphasis on the latter. They can be synthesized “bottom-up” from smaller molecules or “top-down” by reducing pyridine derivatives. It is difficult to summarize the promiscuous reactivity and selectivity patterns in the reduction of activated pyridines, but there are five major factors observed by us and others:

1. 1-electron and 2-electron reduction process give 1,4- and 1,2-reduction, respectively.
2. Hard nucleophiles prefer to attack the C2 position, whereas soft nucleophiles attack the C4 position of the pyridine ring.
3. N-acylpyridinium and N-carbamoylpyridinium salts are equally reactive, a large activating group may prevent reaction at the C2 position.
4. Bulky nucleophiles and reducing agents preferentially give 1,4-reduction product.
5. Pre-existing substituents on the pyridine can alter the site of attack and the substituent’s electronic effects typically outweigh sterical considerations.

With this information in mind we focused on hard, hydridic reducing agents and compact activating groups. Therefore we examined the methods disclosed by Fowler and Sundberg, using methyl chloroformate as activating agent. When sodium borohydride or lithium borohydride was used we obtained 2.95 as a single product (Table 5, Entry 1 and 2). Lithium tri-tert-butoxyaluminum hydride gave low conversion and the 1,4-reduction product (2.96) was preferentially formed (Table 5, Entry 3). The latter compound proved to be too air sensitive for isolation, therefore it was assigned relying on the benchmark NMR values published by Sundberg. In our hands, the conditions shown in Table 5, Entry 1 were reproducible, however, performing the reaction on gram scale was problematic. Solubility issues and a tendency for runaways were the main obstacles in obtaining 2.95 in good

---

71 Hantzsch, A. Justus Liebigs Ann. Chem. 1882, 14, 1058
yield. We found that adding chloroform as a co-solvent eliminates the solubility issue, but also propagates the formation of the 2.96. Minimizing the amount of chloroform and by designing an air-free work-up protocol, we were able to obtain gram quantities of 2.95 in a reproducible manner.

\[
\text{BocHN} \quad \text{reductant} \quad \text{CICOOMe} \quad \text{solvent} \quad -78^\circ \text{C} \\
\text{2.74} \quad \Delta \quad \text{BocHN} \quad \text{2.95} \quad \text{2.96}
\]

<table>
<thead>
<tr>
<th>Entry</th>
<th>Reductant</th>
<th>Solvent / T(°C)</th>
<th>Yield of 2.95</th>
<th>Yield of 2.96</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>NaBH₄</td>
<td>MeOH / THF, -78 °C</td>
<td>75%</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>LiBH₄</td>
<td>MeOH / THF, -78 °C</td>
<td>70%</td>
<td>-</td>
</tr>
<tr>
<td>3</td>
<td>Li(OtBu)₃AlH</td>
<td>MeOH / THF, -78 °C</td>
<td>traces</td>
<td>30%</td>
</tr>
<tr>
<td>4ᵃ</td>
<td>NaBH₄</td>
<td>MeOH / CHCl₃ (1:1), -78 °C</td>
<td>60%</td>
<td>13%</td>
</tr>
<tr>
<td>5ᵃ</td>
<td>NaBH₄</td>
<td>MeOH / EtOAc (1:1), -78 °C</td>
<td>45%</td>
<td>18%</td>
</tr>
<tr>
<td>6ᵃ</td>
<td>NaBH₄</td>
<td>MeOH / CHCl₃ / Et₂O (4:1:1), -78 °C</td>
<td>85%</td>
<td>4%</td>
</tr>
</tbody>
</table>

ᵃ = reactions performed on at least 500 mg scale

Table 5 - Summary of the development of a scalable synthesis of 1,2-dihydropyridines.

In the literature, Diels-Alder cycloaddition between N-carbamoyl-1,2-dihydropyridines and dienophiles is well documented, but an important drawback is that generally the reaction requires high temperatures and gives moderate to good yields.⁷⁵ To overcome this potential limitation we desired to prepare N-alkyl-1,2-dihydropyridines, highly electron rich dienes. These compounds are scarcely represented in the literature, perhaps due to their notoriously air-sensitive and reactive nature. To this end, we based our initial study on the work of Fowler, who was able to isolate N-methyl-1,2-dihydropyridine by reducing N-carbamoyl-1,2-dihydropyridine with LiAlH₄.⁷³ After multiple attempts, by varying the solvent, temperature and mode of addition we were not able to observe the formation of 2.97 or 2.98 (Equation 7).

Equation 7 - Our attempts to convert 2.95 to N-alkyl-1,2-dihydropyridines was unsuccessful following Fowler’s method.

We revised our strategy and decided to activate the pyridine by N-methylation and attempt the selective 1,2-reduction of the obtained pyridinium salt. We examined reported activation conditions with methyl iodide, methyl triflate and Meerwein’s salt at various temperatures, eventually the latter reagent dissolved in DCM at 0 °C successfully transformed 2.74 to the pyridinium salt 2.99. We reduced 2.99 to the corresponding 1,2-dihydropyridine 2.97 in excellent yield and purity, by applying Kutney’s reduction method in basic media. The key to success was the rigorously inert condition combined with an elaborate air-free work-up procedure developed by us.

Scheme 36 - The conversion of 2.74 to the highly reactive 2.97 in two steps in 90% yield. The key to success in the reduction process was the rigorous exclusion of air and the development of an inert work-up procedure.

2.2.2.2 The intermolecular Diels-Alder cycloaddition

There were multiple possibilities to effect the desired Diels-Alder cycloaddition and these options are schematically presented on Scheme 37. In order to obtain the correct adduct, the ideal dienophile would be an electron deficient cis alkene (2.104) which undergoes polarity matched, endo cycloaddition. Alternatively, trans-alkenes (2.101) are an amenable option, if polarity matched, exo cycloaddition is effected and the stereocenter bearing the wrong configuration in the product (2.102) is epimerized at a later stage. In this work we did not pursue the latter option, but we kept in mind the concept while analyzing our reactions. As a third alternative, ynals (2.105) can also be

used as dienophiles in the planned cycloaddition, as the formed bicyclic enone (2.106) can be regioselectively reduced to the desired product (Scheme 37).

Scheme 37 - Analysis of the possible scenarios in the Diels-Alder cycloaddition.

The cyclic dienophile 2.109, reported by Tsuji, was prepared in two steps starting from δ-valerolactone (2.107). The linear Z-dienophile (2.114), reported by Jacobi, was prepared in four steps from homopropargyl alcohol (Scheme 38).  

---

With 2.109 and 2.114 in hand, we attempted the cycloaddition under thermal-, Lewis acid- and Brønsted acid-catalysed conditions. We screened thermal conditions from 18 °C up to 175 °C in a broad range of degassed solvents, but all we could observe was lack of reactivity or slow decomposition of 2.95. The Lewis- and Brønsted-acids were in part chosen based on previous reports and the following selection was surveyed: MgCl₂, MgBr₂, Mg(OTf)₂, AlCl₃, TfN[Al(Me)Cl]₂, AlEt₂Cl, Al(OTf)₃, Sc(OTf)₃, TiCl₄, TiOIPr₄, FeBr₅, FeCl₃, NiBr₂, Ni(OTf)₂, ZnCl₂, ZnBr₂, Zn(OTf)₂, GaCl₃, Ga(OTf)₃, Y(OTf)₃, ZrCl₄, InBr₃, SnCl₄, Sn(NTf₂)₄, La(OTf)₃, CeCl₃, Ce(OTf)₃, Yb(OTf)₃, Lu(OTf)₃, Hf(OTf)₄, Bi(OTf)₃, trifluoroacetic acid, triflic acid, dry hydrochloric acid, triflimide, triflamide, camphorsulfonic acid, PTSA, 3,5-dinitrobenzoic acid, chiral phosphoric acids 2.117, 2.118 and finally chiral phosphoramidate 2.119. These catalysts were screened at 10 mol% loading, in degassed DCE, toluene and xylene, between 18 °C and 80 °C. If we observed conversion at 18 °C we attempted the reaction at cryogenic temperatures. If we observed partial or low conversion at 80 °C, we elevated the temperature until a reaction took place. Following this protocol, we screened the above-mentioned catalysts, however, we could not isolate adducts of 2.95 with the dienophiles (Scheme 39).

---

We turned our attention to ynal dienophiles, as they are more reactive than their olefin counterparts, furthermore they allow us the use of iminium catalysis, as the isomerization of cis double bond is not a concern with ynals. We prepared 2.120 by the oxidation of 2.112 with Dess-Martin periodinane. The preparation of propiolaldehyde (2.122) was much more difficult. The procedure described in the trustworthy Organic Synthesis journal was not feasible for us, due to the safety regulation imposed by EPFL on the use of chromium (VI) oxide. Preparation of the needed CrO$_3$ could have been an option, if the precursors would have not been excessively regulated by the same body. After all, we attempted the deprotection of commercially available 2.123 under reported conditions, without success – although propiolaldehyde was not isolated, but used in situ in these cases. We also tried the oxidation of propargyl alcohol with PDC and modified Swern-conditions,

---

reported by Corey and Kumar, respectively.\textsuperscript{83} In our hands, none of these procedures yielded pro-
piolaldehyde (2.122). Eventually, 2.122 was prepared by iron catalysed aerobic oxidation reported
by Ma.\textsuperscript{84} The method is economical and reproducible even on larger scales (Scheme 40).

![Scheme 40 - Preparation of dienophile 2.120 and 2.122.]

With ynal 2.120 and 2.122 in hand, we moved on to attempt the Diels-Alder cycloaddition. We
screened non-catalysed conditions between 18 °C and 60 °C in toluene using an excess of the ynals,
but we could not observe the formation of adducts. The Lewis-acids we surveyed included: MgCl\(_2\),
MgBr\(_2\), Mg(O Tf)\(_2\), AlCl\(_3\), Al(O Tf)\(_3\), Sc(O Tf)\(_3\), TiCl\(_4\), FeBr\(_2\), FeCl\(_3\), NiBr\(_2\), Ni(O Tf)\(_2\),
ZnCl\(_2\), ZnBr\(_2\), Zn(O Tf)\(_2\), GaCl\(_3\), Ga(O Tf)\(_3\), Y(O Tf)\(_3\), ZrCl\(_4\), InBr\(_3\), SnCl\(_4\), Sn(NTf\(_2\))\(_2\), La(O Tf)\(_3\),
CeCl\(_3\), Ce(O Tf)\(_3\), Yb(O Tf)\(_3\), Lu(O Tf)\(_3\), Hf(O Tf)\(_4\) and Bi(O Tf)\(_3\). These catalysts were screened at 10 mol% loading, in degassed DCE and tolu-
ene, between -20 °C and 60 °C. Following the previously described screening protocol, we could not
isolate adducts of 2.95 and the dienophiles. At this point, we turned our attention to iminium catal-
ysis develope\textsuperscript{d} by Macmillan and Nakano\textsuperscript{d} and we also tested activated oxazaborolidine catalysts
reported by Corey.\textsuperscript{85} After the successful preparation of the organocatalysts, following the original

procedures, we examined the Diels-Alder cycloaddition using dihydropyridine \( 2.95 \) and ynals \( 2.120 \) and \( 2.122 \). Aminoalcohol \( 2.126, 2.127 \) correspond to Nakano’s first generation- and \( 2.128 \) correspond to Nakano’s second generation organocatalysts. These aminoalcohols were developed to promote enantioselective Diels-Alder cycloaddition between 1,2-dihydropyridines and \( \alpha,\beta \)-unsaturated aldehydes. Macmillan’s first and second generation organocatalysts (\( 2.129, 2.130, 2.131 \)), shown on Scheme 41, are benchmark organocatalysts for enantioselective Diels-Alder reaction and has been featured in several total synthesis. Running the reaction under the originally reported conditions did not yield product in any case. Increasing the concentration, temperature or catalyst loading led to the decomposition of the ynal partners (Scheme 41).

---


Scheme 41 - The attempted Diels-Alder cycloadditions between 2.95 and ynals were unsuccessful. We believe that the low electron density in the diene system is the source of low reactivity of 2.95.

After running hundreds of unsuccessful attempts for the cycloaddition of 2.95 and various dienophiles, we went back to the drawing board. The main issue was not the mere absence of the desired product. We were concerned by the low reactivity of 2.95 and the lack of informative feedback from the many experiments we ran. In other words, the above presented reactions did not produce any
side products that show informative chemical shifts in NMR analysis of the reaction mixture, therefore we could not determine where the side reactions lead in the rare case when 2.95 reacted at all. Having said that, the path to be followed was clear. The reactivity of 2.95 had to be increased in order to better understand its chemistry and subsequently find conditions that deliver the cycloadduct. Accordingly, we prepared the electron rich diene 2.97 (described in Section 2.2.2.1), which not only proved to be more reactive, but also challenged my practical skills during the preparation and the following test reactions. When α,β-unsaturated aldehyde 2.114 and lactone 2.109 were tested under thermal-, Lewis acid- and Brønsted-acid-catalysed conditions we observed the rapid decomposition of 2.97 or the isomerisation of the enone double bond to the E-configuration. No adduct was formed in either case. When we surveyed ynal 2.120 and 2.122 as dienophile partners in similar conditions, vigorous reaction leading to decomposition was observed. Out of the frying pan into the fire, now the diene partner 2.97 had too high reactivity, preventing us from drawing conclusions from the experiments. Nevertheless, we still had hope in the organocatalysts developed by Macmillan and Nakano. Eventually we gained control on the reactivity and when catalytic amount of 2.131 was used at -78 °C in toluene, we observed the formation of the Michael-adduct 2.135 which was isolated in 23% yield. Similarly, we were able to catalyse the reaction between 2.97 and 2.122, however in this case the formed product was too sensitive for isolation and the structure was postulated from the crude mixture (Scheme 42).

![Scheme 42 - Under iminium catalysis the 1,2-dihydropyridine 2.97 acted as an enamine nucleophile and delivered a Michael adduct with 2.120 and 2.122.](image)

On the one hand, we were glad to have isolated a meaningful product after several months of effort; on the other hand, the structure of 2.135 and 2.137 suggested that Diels-Alder cycloaddition between the desired carbon atoms is not likely to occur with these substrates. This result prompted us...
to devise a new strategy featuring an intramolecular cycloaddition, where such side reaction could be prevented by appropriate design.

2.2.3 The intramolecular Diels-Alder cycloaddition

After the failure with the intermolecular Diels-Alder strategy, we planned to tether the diene and dienophile together, thereby disabling the non-productive Michael addition witnessed in the Section 2.2.2.2. Our retrosynthetic plan is delineated on Scheme 43.

**Scheme 43 – Revised synthetic strategy toward koumine, featuring an intramolecular Diels-Alder cycloaddition.**

2.2.3.1 Synthesis of tetherable 1,2-dihydropyridines

Having 2.74 in hand, we originally planned to execute a simple hydroboration-oxidation of the double bond, thereby temporarily masking the vinyl moiety as a tether for the attachment of the dienophile. We surveyed borane-DMS, borane-THF, borane-trimethylamine, catecholborane and 9-BBN for the hydroboration reaction. We found that reacting 2.74 with 9-BBN followed by oxidation with hydrogen peroxide lead to the desired product 2.141. However, we faced reproducibility issues on larger scale and more importantly we were not able to identify conditions for the purification of alcohol 2.141. Despite all our efforts, we could not continue the synthesis with the obtained mixture and had to find another route to access 2.141 (Equation 8).
Equation 8 - Hydroboration of 2.74 delivered the desired alcohol, however the difficult purification procedure led us to abandon this route of accessing 2.141.

In order to access 2.141 the alcohol tether can also be installed prior to the formation of phenylpyridine 2.74. Knowing that 2.94 is notoriously difficult to handle, we ruled out its hydroboration as an option. We synthesized 2.148 by the homologation of 2.92 in 2 steps. Benzoyl protection of the alcohol 2.148 and Suzuki coupling delivered the desired phenylpyridine intermediate 2.150. Basic hydrolysis of the benzoyl ester delivered 2.151 quantitatively. Applying our previously developed method for the selective 1,2-reduction of activated pyridines we obtained 2.152 in 40% yield (Scheme 44).

Scheme 44 - Synthetic sequence leading to 2.152. The obtained diene is now equipped with a tether which will be used for linking the dienophile partner. The tether also functions as the masked vinyl group of the natural product.
2.2.3.2 Preparation of the tethered diene-dienophile Diels-Alder precursors

Our next task was the preparation of the dienophiles and their subsequent attachment to 2.152. To this end, we set 2.153, 2.154 and 2.155 as target compounds (Scheme 45).

![Structure of the target molecules](image)

Scheme 45 - Structure of the targeted dienophiles, equipped with an attachment point for their tethering to 2.152.

2.156 was prepared according to the protocol disclosed by Fu and co-workers. 88 2.156 was obtained alongside an inseparable allene side-product, which was carried on, as it did not interfere with the following transformations. The obtained alkyne was converted to the corresponding cis-alkene via hydrogenation with Lindlar catalyst. The partial hydrogenation was not an obvious transformation and in the single successful condition we found, the desired product 2.158 readily lactonized to 2.159 upon concentration. The attempted hydrolysis of 2.159 lead to non-desired alkene isomerization to form the thermodynamically stable 2.160 (Scheme 46).

![Scheme 46 - Synthetic effort toward our first targeted dienophile 2.153. Disappointingly, spontaneous lactonizations of 2.158 prevented us from moving forward to 2.153.](image)

Although the result was discouraging, we devised another plan to access **2.154** and **2.155**. Hydrolysis of **2.161** to glutaric acid (**2.162**), followed by treatment with boiling acetic anhydride and subsequent methanolysis delivered **2.163**.\(^8^9\) Although the obtained monoester was utilized earlier by several research groups, none of them could assign the exact position of the double bond. Since it was of decisive importance to us, we analysed the product by single crystal X-ray diffraction and found that the double bond is in conjugation with the carboxylic acid function. For our purposes, this result meant that the obtained compound had the double bond at the wrong position, as we could not directly couple it to **2.152** (Scheme 47).

\[
\begin{align*}
\text{O-} & & \text{O-} & & \text{OCH}_3 \\
\text{MeO-} & & \text{O-} & & \text{O-} \\
\text{MeO-} & & \text{O-} & & \text{O-} \\
\text{NaOH / H}_2\text{O, r.t.} & & 82\% & & \text{O-} \\
\text{MeO-} & & \text{O-} & & \text{O-} \\
\text{Ac}_2\text{O, 150°C} & & 25\text{ min} & & \text{MeOH} \\
\text{2.161} & & 2.162 & & \text{crude mixture} \\
\end{align*}
\]

\[
\begin{align*}
\text{MeOOC} & & \text{HOOC} \\
\text{MeOH} & & \text{sublimation} \\
\text{O-} & & \text{O-} \\
\text{2.163} & & 40\% \\
\end{align*}
\]

\[
\begin{align*}
\text{O-} & & \text{O-} \\
\text{MeO-} & & \text{O-} \\
\text{MeO-} & & \text{O-} \\
\text{2.154} & & 20\% \\
\end{align*}
\]

*Scheme 47 - Synthesis of the cyclic unsaturated anhydride 2.154 and their methanolysis to afford 2.163.*

From another point of view, the X-ray crystallographic analysis proved that the nucleophilic attack of an alcohol selectively occurs at the saturated side of **2.154**, meaning that if we use alcohol **2.152** we could, in principle, directly attach the diene and dienophile. We were able to isolate **2.154** as a white crystalline solid via sublimation from the crude reaction mixture. With the anhydride **2.154** and alcohols **2.152, 2.151** in hand, we attempted their linking under various conditions. Initially, thermal conditions were tested without success. We observed the rapid decomposition of the anhydride when **2.151** was used as substrate or the reaction was run in the presence of a catalytic amount of 4-dimethylaminopyridine. Control experiments showed that pyridine alone catalyses the decomposition of **2.154**, therefore we converted **2.151** to its hydrochloride salt before submitting it to the reaction conditions. Trauner et al. reported the selective opening of a similar cyclic anhydride using HOBt as activating agent, however, in their protocol the alcohol partner was used in

large excess. To our dismay, the use of HOBt or HOAt as activators yielded no product (Table 6, Entry 4 and 5).⁹⁰

![Chemical structures](image)

**Table 6 - Summary of our attempts to acylate 2.152 with 2.154.**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Anhydride 2.154</th>
<th>Catalyst</th>
<th>Temperature</th>
<th>Conversion</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2 equiv</td>
<td>-</td>
<td>r.t. to 100°C</td>
<td>0%</td>
</tr>
<tr>
<td>2</td>
<td>10 equiv</td>
<td>-</td>
<td>r.t. to 100°C</td>
<td>0%</td>
</tr>
<tr>
<td>3</td>
<td>2-50 equiv</td>
<td>DMAP 5%</td>
<td>r.t. to 50°C</td>
<td>0%</td>
</tr>
<tr>
<td>4</td>
<td>10-50 equiv</td>
<td>HOAt (5-200 mol%)</td>
<td>-20°C to 50°C</td>
<td>0%</td>
</tr>
<tr>
<td>5</td>
<td>10-50 equiv</td>
<td>HOBt (5-200 mol%)</td>
<td>-20°C to 50°C</td>
<td>0%</td>
</tr>
</tbody>
</table>

Although our efforts to acylate 2.152 and 2.151·HCl with 2.154 in thermal and catalytic conditions proved futile, we believed that increasing the nucleophilicity of the hydroxyl group of the dienes may be a solution to this problem. Treatment of 2.151 with sodium hydride and subsequent addition of 2.154 surprisingly did not result in product formation nor in observable conversion (Equation 9).

Chapter 2 - Synthetic Studies Toward the Total Synthesis of Koumine

Equation 9 - Formation of the alcoholate of 2.151, followed by treatment with anhydride 2.154 did not result in acylation to our surprise.

We suspected that the methylene group of 2.154 bears significant acidity, and it may be deprotonated by the alcoholate and exist as the enolate form in the reaction conditions. To test our hypothesis, we dissolved 2.154 in methanol-$d_4$ and monitored the solution by NMR spectroscopy. Indeed, the methylene protons fully exchanged with deuterium in the course of hours at neutral pH, proving that the acidity of these protons falls in the range of the pKa of methanol.

Finally, we designed a sequence starting from 2.163 to attempt “switching” between the ester and carboxylic acid functionality. 2.163 was treated with alkylating agent 2.166 in the presence of catalytic amount of boron trifluoride – ether complex to furnish 2.167. Attempts to selectively hydrolyse the methyl ester 2.167 resulted in the isomerization of the double bond to its $E$-configuration, which rendered the molecule useless for us (Scheme 48).

Scheme 48 - Attempt on the synthesis of tetherable dienophile 2.155.

As it is often the case in organic chemistry, the simplest looking compounds can be the hardest to make and it appeared to be the case in the synthesis of the dienophile partners. The above described difficulties related to the tethering process eventually led us to abandon the intramolecular Diels-Alder strategy.
2.3 Conclusion

In summary, we developed an efficient and flexible route to functionalized \( N \)-carbamoyl-1,2-dihydropyridines and \( N \)-alkyl-1,2-dihydropyridines. Our study provides an insight into the underexplored reactivity of these compounds and the peculiar nature of the intermediates leading to them. Disappointingly, we were not able to effect the key Diels-Alder cycloaddition between the above mentioned 1,2-dihydropyridines and \( \alpha,\beta \)-unsaturated carbonyl compounds. Although our synthetic battle to conquer the natural product was fruitless, the journey has been an indispensable experience for my development as a chemist. We hope that this study will help researchers in the future to avoid the pitfalls we encountered and will serve as an important lesson to those who aspire to synthesize the elusive natural product, koumine.
Chapter 3  Towards the Total Synthesis of Voacafricine A and Voacafricine B

3.1  Introduction

Voacafricine A (3.1) and voacafricine B (3.2) were isolated in 2018 from the fruits of *Voacanga africana* (Apocynaceae), a small tree native to tropical Africa. The plant has been a source of a large number of alkaloids, most of them belonging to the *Iboga* family, such as ibogaine, voacangine, voacristine and 19-epi-voacristine among others. Voacafricines A and B have unique architecture. Their 6/5/6/5/6/5 skeleton embedding five heterocycles is unprecedented among natural products. Moreover, 3.1 and 3.2 exist in zwitterionic form of a carboxylate and a quaternary ammonium moiety. Alkaloids bearing a quaternary ammonium centre are rare in nature, however, many alkaloids have been transformed to their ammonium salts via *N*-alkylation and used successfully as catalysts in enantioselective transformations. The total synthesis of quaternary ammonium bearing alkaloids often exhibit unique challenges and many of them has been in the crosshairs of organic chemists.

![Structure of voacafricine A and voacafricine B](image)

**Figure 8 - The structure and numbering of voacafricine A and voacafricine B.**

3.1.1  Bioactivity and biosynthesis

The naturally occurring alkaloids bearing quaternerized nitrogen atom often display antibacterial activity. The extract of plants harboring berberine, chelerythrine and ageloxime D have been used in traditional and folk medicine for centuries against bacterial infections and other diseases. In Ivory Coast the extracts of *Voacanga africana* is traditionally used to treat ulcers, carious teeth,

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92 Ha, M. W.; Park, H. In *Sustainable Catalysis: Without Metals or Other Endangered Elements, Part 2*; 2015; 77, 82–134.


diarrhea, microbial infection and the extracts of the seeds are used to cure gonorrhea and tooth decay in Cameroon. Most medical applications of the plant is related to its antimicrobial activity. The natural abundance of voacafricines is fairly low. Luo and co-workers could isolate 105 mg of 3.1 and 7.5 mg of 3.2 starting from 3 kg of dried and powdered fruit of *Voacanga africana*. The authors tested these compounds against four bacterial strains: *Staphylococcus aureus*, *Escherichia coli*, *Salmonella typhi* and *Bacillus subtilis*. In comparison with two known, naturally occuring antimicrobial agent, berberine and fibrauretine, 3.1 and 3.2 showed higher activity against *Staphylococcus aureus* with a minimum inhibitory concentration (MIC) of 3.12 µg/mL. Moreover, 3.2 efficiently suppressed the growth of *Salmonella typhi* at a MIC value of 0.78 µg/mL (Table 7).

<table>
<thead>
<tr>
<th>Sample</th>
<th>3.1</th>
<th>3.2</th>
<th>berberine</th>
<th>fibrauretine</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Staphylococcus aureus</em></td>
<td>3.12</td>
<td>3.12</td>
<td>6.25</td>
<td>25</td>
</tr>
<tr>
<td><em>Escherichia coli</em></td>
<td>&gt;100</td>
<td>50</td>
<td>25</td>
<td>25</td>
</tr>
<tr>
<td><em>Salmonella typhi</em></td>
<td>6.25</td>
<td>0.78</td>
<td>3.12</td>
<td>3.12</td>
</tr>
<tr>
<td><em>Bacillus subtilis</em></td>
<td>25</td>
<td>50</td>
<td>12.5</td>
<td>25</td>
</tr>
</tbody>
</table>

*Table 7 - Antibiotic activity of voacafricine A and voacafricine B against various bacterial strains. Comparison with berberine and fibrauretine highlights the potency of voacafricine alkaloids against S. aureus and S. typhi.*

The common biogenetic precursor of voacafricine A and B (3.1, 3.2) is believed to be 19-epi-voacristine (3.3), which is the major alkaloid of *Voacanga africana*. 3.3 undergoes dehydration to forge a C-C double bond between C19 and C20 atoms. Hydration of the alkene moiety and oxidation at the C18 position delivers the hypothetical intermediate 3.5. Indole-assisted cleavage of the C16-C21 bond and subsequent trapping of the conjugated iminium cation by the N4 atom furnishes 3.7. Epoxidation of the enamine double bond, followed by cycloetherification constructs the F ring of the natural products. Saponification of the ester moiety of 3.9 delivers 3.2, which undergoes reduction at the C20 position to furnish 3.1 (Scheme 49).

3.1.2 Retrosynthetic plan

When we embarked on the total synthesis of voacafricine A and B, we desired to build a strategy that would allow us to access both alkaloids (3.1, 3.2) from a common intermediate. Such strategy would be ideal if it allows enantioselective synthesis and avoids the handling of highly polar quaternary ammonium intermediates. Along these lines, we devised the following plan. In a retrosynthetic sense, the C3-N4 bond of the natural products is broken first, eliminating the issues related to the handling of charged intermediates. The F ring of the alkaloids can be constructed from a 7-membered α-ketolactam (3.12). Key compound 3.12 is the common intermediate towards voacafricine A and voacafricine B and it can be synthesised from 3.13 via opening of the enamine ring with a suitable nucleophilic reagent, followed by lactamization between C21 and N4. The synthesis of optically active 3.13 can be performed via enantioselective Pictet-Spengler reaction between 5-methoxytryptamine and 3.15, followed by in situ condensation. As the two carbonyl groups of 3.15 are prochiral, successful desymmetrization of the molecule would result in the correct installation of two stereocenters into 3.13. The C2-symmetric diketone can be accessed in one step from inexpensive chemicals, according to Tanaka and co-workers (Scheme 50).99

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Chapter 3 - Towards the Total Synthesis of Voacafricine A and Voacafricine B

Scheme 50 - Retrosynthetic analysis of the Voacafricine alkaloids.
3.2 Results and Discussion

This section is divided into three parts, in accordance with the synthetic strategy delineated on Scheme 50. In section 3.2.1, the route until the key \(\alpha\)-ketolactam intermediate 3.12 is described. There, the emphasis is on the Pictet-Spengler reaction and the liberation of the \(\alpha\)-keto moiety of the key intermediate 3.12. The following two sections detail the routes toward the two voacafricine alkaloids starting from \(\alpha\)-ketolactam 3.12.

3.2.1 Route to the key intermediate

3.2.1.1 Initial phase: cascade cyclization via Pictet-Spengler reaction

According to the synthetic plan shown in section 3.1.2, we began the project with the synthesis of diketone 3.15. Building on Tanaka’s reported procedure for the construction of dihydropyranos from secondary aldehydes and pyruvate esters, we set compound 3.20 and 3.24 as our first targets.\(^99\) Following Brindle’s method we prepared aldehyde 3.18 and submitted it to Tanaka’s conditions using ethyl pyruvate as reaction partner.\(^100\) We could not isolate the desired product (3.20), but the self-condensation products of 3.19 (3.21, 3.22). We hypothesized that \(\alpha\)-unsubstituted aldehydes may not be suitable for this transformation due to their low steric bulk around their carbonyl group, hence having a higher propensity to condense with the catalyst and rest in their corresponding enamine form. To address this issue, we prepared the analogue of 3.18 with the large tert-butylidiphenylsilyl O-protecting group (3.23), according to Reisman and Matsuoka.\(^101,102\) The obtained bulky, primary aldehyde 3.23, was submitted to Tanaka’s conditions using ethyl pyruvate as reactant. Self-condensation products of 3.19 accounted for the majority of the isolated mass, however the desired diketone (3.24) was also isolated in 14% yield. The linear and cyclic forms of 3.24 were in rapid equilibrium and their co-existence compromised their accurate assignment by NMR spectroscopy, but mass spectrometric analysis confirmed their identity (Scheme 51). Due to the inefficient synthesis of 3.24 and its cumbersome analysis we decided to switch to \(\alpha\)-branched aldehydes as substrates for the construction of the desired diketone.

To our delight, when commercially available 2,2-dimethoxyacetaldehyde (3.25) was reacted with 3.19 in the presence of catalytic amount of (S)-β-proline, the desired dihydropyran was obtained in 85% yield (Equation 10).

With the diketone equivalent 3.26 in hand, we moved forward to the Pictet-Spengler cyclization between 3.26 and 5-methoxytryptamine (3.14). As a starting point, we tested conditions for the Pictet-Spengler reaction developed in our lab and conditions reported by others for similar cyclizations (Table 8).103,104 The condition developed in our laboratory, shown in Table 8, Entry 1, provided 3.28 in similar efficiency to Jacobsen’s conditions (103 a) Piemontesi, C.; Wang, Q.; Zhu, J. J. Am. Chem. Soc. 2016, 138 (35), 11148–11151.; b) Piemontesi, C. Alkaloids , Macrocycles and Heterocycles : Interplay between Methodological Development and Total Synthesis, Ecole Polytechnique Federale de Lausanne, 2018. 104 a) Klausen, R. S.; Kennedy, C. R.; Hyde, A. M.; Jacobsen, E. N. J. Am. Chem. Soc. 2017, 139, 12299-12309. b) Magnus, P.; Gazzard, L.; Hobson, L.; Payne, A. H.; Rainey, T. J.; Westlund, N.; Lynch, V. Tetrahedron 2002, 58 (17), 3423–3443.; c)
Table 8, Entry 2). Furthermore, we measured 10% enantiomeric excess in the product, which was a promising preliminary result. The Pictet-Spengler reaction resulted mainly in the formation of the anti-diastereoisomer, when the starting materials were refluxed in hexafluoroisopropanol (Table 8, Entry 5). In order to elucidate the relative stereochemistry of 3.27 and 3.28 we conducted $^1$H-$^1$H nuclear Overhauser effect spectroscopical measurements. Unfortunately, the observed NOE effects could not allow us to distinguish these two diastereomers. Eventually, their relative configuration was established later by analysing the single crystals of 3.43 by X-ray diffraction spectroscopy.

Table 8 - Evaluation of reported methods for the Pictet-Spengler cyclization.

Of mechanistic importance, we wondered whether 3.27 and 3.28 arose from each other or they are formed via distinct reaction pathways. If one of the products is the precursor of the other, then the epimerization can occur via formation of the conjugated enolate of the $\alpha,\beta$-unsaturated ester moiety, alternatively via enamine/iminium tautomerization and followed by ring-opening and subsequent transannular cyclization (Scheme 52).

Scheme 52 - The two possible epimerization mechanisms between 3.27 and 3.28: a) epimerization via the formation of an extended enolate; b) transannular ring opening-closing pathway.

To test this possibility, we ran the control experiments shown on Scheme 53. While 3.28 could not be transformed to 3.27, we could isolate 3.28 when 3.27 was subjected to a catalytic amount of benzoic acid in toluene. According to the prevalence of transannular ring opening of similar structures in the literature of alkaloid chemistry, the epimerization likely occurs via that mechanism; however, the mechanism shown on Scheme 52/a, cannot be ruled out. If the enantiopure 3.27 and 3.28 is isolated, then by epimerizing enantiopure 3.27 in the presence of catalytic amount of benzoic acid in toluene, it would be possible to deduce which is the operating mechanism. This finding also shows that the kinetic product of the Pictet-Spengler reaction is 3.27 and the thermodynamic product is 3.28.

Scheme 53 - Control experiments show that 3.28 can arise from the epimerization of 3.27.
Of strategic importance, compound 3.27 has the relative configuration matching with the natural products', however we chose to continue with 3.28 for multiple reasons. First of all, compound 3.28 was obtained in higher yield and the C14 stereocenter can be epimerized later on in the synthesis. Furthermore, we desired to obtain the natural products enantioselectively. The conditions affording 3.28 feature apolar media and lower temperatures, in stark contrast with the conditions that yielded 3.27. High temperatures and polar solvents, such as HFIP, are generally detrimental for the development of asymmetric transformations. Finally, we were aware of one of the potential shortcomings of our proposed synthetic plan, namely the stereocontrol over the nucleophilic addition onto the ketone of 3.30 for the introduction of the F ring of the natural products. A 1,3-repulsive interaction between the incoming nucleophile and the up-facing dimethoxyacetal substituent in 3.30 could hamper the desired Si-face attack on the ketone. Having the R-configuration at C14 could actually help in attaining good stereocontrol during the installation of ring F (Figure 9). From another point of view, if organometallic nucleophiles will be used, chelation to the methoxy group may direct the nucleophilic addition from the Si-face of ketone 3.30.

![Figure 9](image-url)  
*Figure 9 - Although compound 3.27 has the correct relative configuration towards the natural products, one of the potential pitfalls is shown above. The stereocontrol over the planned 1,2-addition onto the ketone moiety can be compromised by the upward pointing dimethoxyacetal group, preventing the desired Si-face attack of the nucleophile.*

### 3.2.1.2 Enamine ring opening and synthesis of α-oximinolactams

The next important milestone to reach was the construction of the 7-membered lactam ring (as in 3.12). Although the apparent stability of the enamine ring of 3.28 was somewhat worrying, a brief screening of reported methods for the transamination of stable enamines provided us with a condition to access 3.34.\(^\text{105}\) Lehn and co-workers demonstrated that the rate of transamination catalysed by lanthanide ions increases linearly with a decrease in ionic radius, making scandium(III) the

most efficient catalyst in the group. Based on their results, we examined the enamine ring opening with various amines in the presence of catalytic amount of scandium(III) triflate and found that hydroxylamines are excellent reactants for the transimination process (Table 9, Entry 5). Brønsted acid-catalysed transimination resulted in less clean reaction and modest yields (Table 9, Entry 4), while hydrazines and hydrolytic conditions failed to open the 6-membered enamine cycle (Table 9, Entry 1-3).

<table>
<thead>
<tr>
<th>Entry</th>
<th>Condition</th>
<th>T (°C)</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Hydrazine, MS 4 Å, MeOH</td>
<td>r.t. to 65 °C</td>
<td>no conversion</td>
</tr>
<tr>
<td>2</td>
<td>MeOH, DOWEX 50x8</td>
<td>r.t. to 65 °C</td>
<td>no conversion</td>
</tr>
<tr>
<td>3</td>
<td>N,N-dimethylhydrazine, MeOH, AcOH (20 mol%)</td>
<td>r.t. to 65 °C</td>
<td>no conversion</td>
</tr>
<tr>
<td>4</td>
<td>NH₂OMe*HCl, MeOH, MS 4 Å</td>
<td>65 °C</td>
<td>full conversion, &lt;40% yield</td>
</tr>
<tr>
<td>5</td>
<td>NH₂OMe*HCl, Huenig’s base, Sc(OTf)₃ (15 mol%), CHCl₃</td>
<td>65 °C</td>
<td>90% conv., 60% yield</td>
</tr>
</tbody>
</table>

Table 9 - Summary of the surveyed conditions for opening the enamine ring of 3.28.

Formation of the 7-membered lactam ring necessitated the activation of the α-oximinoester group. The activation may be done in situ or can be performed on the free carboxylic acid after saponification. First, we attempted the direct lactamization between the ester and amine. After surveying the literature we found that thermal and Brønsted acid-catalysed methods are the most utilized, however, just a handful of cases dealt with hindered amines and α-oximino esters. In our hands, these conditions led to decomposotion of the starting material (Table 10, Entry 1-3). Aubé reported the synthesis of twisted amides by employing cesium carbonate in acetonitrile as solvent; their method did not yield our desired product.¹⁰⁶ Watson developed a catalytic system for the amidation of unactivated esters, using trifluoroethanol, however under their conditions we could not observe the consumption of 3.34.¹⁰⁷ A variety of nucleophilic activators were tested, such as potassium cyanide, potassium thiocyanate and pyridine.

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sodium azide, L-hydroxyproline (HYP), 1,5,7-triazabicyclo[4.4.0]dec-5-ene (TBD), 4-dimethylamino-pyridine (DMAP) and N-hydroxysuccinimide (NHS).\textsuperscript{108} Among these, to our surprise, HYP, DMAP and NHS catalysed the reverse transimination and we were able to isolate enamine 3.28, the precursor of our starting material (Table 10, Entry 8, 10 and 11). Porco and co-workers developed a catalytic system for the preparation of amides from simple esters and amines under group IV metal catalysis. They found that Zr(OtBu)\textsubscript{4} gives the best results when used in conjunction with a catalytic amount of additive, such as HOBT, HOAT or HYP.\textsuperscript{109} Their method was thoroughly examined for our purposes; however, our efforts to convert 3.34 to lactam 3.35 remained fruitless (Table 10, Entries 12-14).

![Chemical structures](image)

**Table 10 - Summary of the surveyed conditions for the direct lactamization of 3.34:**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Condition</th>
<th>T (°C)</th>
<th>Conversion</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Toluene, MS4Å</td>
<td>110 °C</td>
<td>~80% conv.</td>
<td>decomposition</td>
</tr>
<tr>
<td>2</td>
<td>Dioxane, PTSA\textsubscript{anh.} (30 mol%)</td>
<td>60 °C</td>
<td>10-20%</td>
<td>acetal deprotection, decomposition</td>
</tr>
<tr>
<td>3</td>
<td>Dioxane, HCl\textsubscript{anh.} (30 mol%)</td>
<td>60 °C</td>
<td>10-20%</td>
<td>acetal deprotection, decomposition</td>
</tr>
<tr>
<td>4</td>
<td>Cs\textsubscript{2}CO\textsubscript{3}, MeCN</td>
<td>60 °C</td>
<td>0%</td>
<td>-</td>
</tr>
<tr>
<td>5</td>
<td>CF\textsubscript{3}CH\textsubscript{2}OH, K\textsubscript{3}PO\textsubscript{4}, THF</td>
<td>reflux</td>
<td>0%</td>
<td>-</td>
</tr>
<tr>
<td>6</td>
<td>KCN (1 eq.), MeCN</td>
<td>r.t.-60 °C</td>
<td>0%</td>
<td>-</td>
</tr>
<tr>
<td>7</td>
<td>NaN\textsubscript{3}, EtOH</td>
<td>70 °C</td>
<td>0%</td>
<td>-</td>
</tr>
<tr>
<td>8</td>
<td>HYP, DCE</td>
<td>50 °C</td>
<td>40%</td>
<td>3.28 forms slowly</td>
</tr>
<tr>
<td>9</td>
<td>TBD, THF</td>
<td>60 °C</td>
<td>0%</td>
<td>-</td>
</tr>
<tr>
<td>10</td>
<td>DMAP, DCM</td>
<td>reflux</td>
<td>40%</td>
<td>3.28 forms slowly</td>
</tr>
<tr>
<td>11</td>
<td>NHS, DCE</td>
<td>50 °C</td>
<td>full conversion</td>
<td>50% yield of 3.28</td>
</tr>
<tr>
<td>12</td>
<td>Zr(OtBu)\textsubscript{4} / HOAT, toluene</td>
<td>80°C</td>
<td>full conversion</td>
<td>decomposition</td>
</tr>
<tr>
<td>13</td>
<td>Zr(OtBu)\textsubscript{4} / HOBt, toluene</td>
<td>80°C</td>
<td>full conversion</td>
<td>decomposition</td>
</tr>
<tr>
<td>14</td>
<td>Zr(OtBu)\textsubscript{4} / HYP, toluene</td>
<td>80°C</td>
<td>&lt;20%</td>
<td>-</td>
</tr>
</tbody>
</table>


We turned our attention to the more conventional route to the desired lactam via selective ester hydrolysis of 3.34 and activation of the resulting carboxylic acid for lactamization. Standard hydrolytic methods employing alkali and alkaline earth metal hydroxides failed to deliver 3.37. Lithium hydroperoxide, a strong nucleophilic agent, failed to convert 3.34 to the free (peroxo)acid. We examined methods to access the carboxylic acid via nucleophilic substitution. Tin-based reagents were explored next for the liberation of the carboxylic moiety. Trimethyltinhydroxide and bis(tributyltin) oxide (BBTO), reported by Nicolaou and Mascaretti, respectively, are capable of displacing non-hindered alkyl groups from ester function. Eventually, heating a mixture of 3.34 in the presence of 2 equivalents of BBTO in toluene yielded 3.36 in good yield. The obtained tributyltin acetate did not lactamize when treated with peptide coupling reagents and the removal of the tin residue was not a trivial task (Scheme 54).

![Scheme 54](image)

Scheme 54 - Compound 3.34 was hydrolysed by treatment with BBTO in refluxing toluene. The obtained stannyl acetate could not be converted to the corresponding acid via trivial transformations.

Treatment of 3.36 with trimethylaluminum or sodium hydroxide did not result in Sn-O bond cleavage. Commercially available fluoride sources alone, such as KF, TBAF, TASF, CsF, HF-amine complexes and HF, were unable to liberate the free acid either. After numerous attempts and careful analysis, we were able to identify that Oláh’s reagent buffered with potassium fluoride is capable of cleaving the tin-oxygen bond. Neutralization of the excess hydrogen fluoride by pyridine, followed by solvent exchange and addition of HOBt and EDCl at 0 °C resulted in the formation of the desired

product 3.35 in moderate yield. Reaching lactam 3.35 was a bittersweet victory, because the tedious procedure and poor scalability of the method eventually led us to abandon this pathway (Scheme 55).

Scheme 55 - Meticulous optimization of the destannylation allowed us to obtain the free acid 3.37, which was converted to the desired lactam under peptide coupling conditions. Unfortunately, the method did not prove scalable.

The optimization of the conversion of 3.36 to lactam 3.35 was underway, when we began the preparation of the methyl ester derivative of 3.34 (3.41). We hoped that the methyl α-oximinoester 3.41 yields to standard, basic hydrolytic conditions and allows us the preparation of the seven-membered lactam (3.49) in a more efficient and scalable manner. The synthesis of 3.41 was performed without event, except that the catalyst loading at the transimination step had to be decreased to 5 mol% to prevent side reactions (Scheme 56).

Scheme 56 - Synthesis of the dimethylester 3.41.
As expected, the hydrolysis of the methyl ester 3.41 was significantly easier and after a brief screening of conditions we found that lithium hydroxide in a four-to-one mixture of methanol and water at 0 °C can hydrolyse the α-oximino ester of 3.41 selectively. The obtained amino acid was freeze-dried and subjected to the next step without further purification. In order to obtain the best possible yield for the lactamization step, we surveyed systems that were successfully utilized on similar scaffolds or known to be beneficial when hindered amines were to be coupled.\textsuperscript{115} After a series of screenings, we found that TATU, HATU and COMU coupling reagents are essentially interchangeable for the lactamization, when the reaction was run in the presence of an excess amount of Huenig’s base in DMF as solvent. Moreover, we found that lowering the temperature to 0 °C was crucial for obtaining yields between 65-70% over two steps. Recrystallization of 3.43 provided us with single crystals eligible for X-ray diffractional analysis. The measurements confirmed the relative configuration the two C(sp\(^3\)) stereocenters and the geometry of the oxime double bond. As shown on Scheme 57, the seven-embered lactam ring bears a bent, boat-like shape, positioning the oxime moiety parallel to the ester function. The oxime’s C=N double bond is 74° off-phase from the lactam carbonyl’s π-bond (Scheme 57).

\textbf{Scheme 57 - Brief optimization allowed us to access the seven-membered lactam 3.43 from 3.41 in 68% yield. Single crystal X-ray diffraction analysis showed the peculiar conformation of the obtained product, confirmed the relative configuration the two C(sp\(^3\)) stereocenters and the geometry of the oxime double bond.}

3.2.1.3 Studies on the conversion of $\alpha$-oximino lactams to $\alpha$-ketolactams: deoximation of oximes and oxime ethers

With the seven-membered $\alpha$-oximino lactam 3.43 in hand, we proceeded to the unmasking of the latent ketone from the oxime moiety. A myriad of methods are reported to effect deoximation and these are categorized into three groups: hydrolytic, reductive and oxidative deoximation. The scope of the reported methods predominantly cover alkyl- and aryl-substituted aldoximes and ketoximes. $O$-alkyloximes are less represented in the three categories, while $O$-acyloximes are known substrates for reductive methods. Oximes in conjugation with olefins and carbonyl groups are scarcely represented as substrates, due to their increased stability. Nevertheless, we remained optimistic that deoximation of 3.43 could be performed and the key intermediate (3.44) toward the Voacafri-cine alkaloids would be isolated.

Hydrolytic methods were first examined. We tested various sacrificial aldehydes to effect transoximation, but our starting material’s oxime function remained untouched under these conditions (Table 11, Entries 1-5). Transition metal-catalysed hydrolytic deoximation was reported by Shi and Liu, with copper(II) chloride and ruthenium(III) chloride respectively; these conditions were unable to unmask the latent ketone function (Table 11, Entries 6 and 7). In a number of cases, we had observed the conversion of the dimethoxyacetal function to aldehyde; these conditions were later revisited (see Scheme 58). A summary of the examined conditions are presented in Table 11.

---


A broad range of reported, reductive deoximation methods was surveyed. Low-valent metals, such as zinc, titanium(III) and molybdenum, are able to reduce oxime to the corresponding imine via SET processes. Spontaneous hydrolysis of the imine intermediate delivers the desired ketone.\footnote{Ryu, I.; Kuriyama, H.; Miyazato, H.; Minakata, S.; Komatsu, M.; Yoon, J.-Y.; Kim, S. Bull. Chem. Soc. Jpn. 2004, 77 (7), 1407–1408.; Stepanov, A. V; Veselovsky, V. V. Russ. Chem. Bull. 2002, 51 (2), 359–361.; Nitta, M.; Iino, Y. Bull. Chem. Soc. Jpn. 1986, 59 (7), 2365–2367.} The original reported methods and their variations were survey on \ref{eq:3.43}, however, we could not observe the formation of the desired product. Raney nickel is another strong reductant, capable of cleaving the N-O bond of oximes. Curran and co-workers reported the selective transformation of oximes to ketones using Raney nickel. Unfortunately, their conditions left \ref{eq:3.43} intact even when the highly active, freshly prepared W6 and W7 variants of Raney nickel were employed (Table 12, Entries 6-9). Hydrogenation under high pressure and temperature could not effect the sought-after transformation, therefore we deemed \ref{eq:3.43} a dead-end of the total synthesis (Table 12, Entry 11).
Deprotection of the dimethoxyacetal function of 3.43 was a common issue with the above presented attempts for the deoximation, therefore we converted 3.43 to 3.46 in two steps to overcome this chemoselectivity issue. The obtained alcohol 3.46 was then subjected to the conditions that resulted in acetal deprotection or decomposition, however, 3.46 resisted and the desired product was not formed (Scheme 58).

**Table 12 - Summary of the surveyed reductive methods for the deoximation of 3.43.**
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Scheme 58 - Synthesis of alcohol 3.46 and its examination for deoximation with reductive and hydrolytic conditions.

The unsuccessful deoximation attempts prompted us to move toward other oxime derivatives. Deoximation starting from simple oximes has more widespread literature, therefore we set 3.49 as target compound. When we performed the synthetic sequence that delivered 3.43, by switching O-methylhydroxylamine to hydroxylamine we found that the hydrolysis of intermediate 3.48 was not feasible. Perhaps the deprotonated oxime rendered the conjugated system electron rich or the formation of the dianionic product was not favored, either way, 3.49 could not be prepared via the same synthetic sequence (Scheme 59).

Scheme 59 - The synthetic sequence leading to oxime ether 3.43 could not be recycled for the preparation of 3.49.

With the linear oxime 3.48 in hand, we Boc-protected the secondary aliphatic nitrogen and run a quick survey of conditions to see if deoximation could occur on 3.48 as a test substrate. To our surprise, when 3.48 was reduced with zinc in acidic media, enamine 3.40 was isolated. It may meant
that deoximation occurred, but due to concurrent Boc-deprotection the resulting ketone cyclized back to the enamine form. Another possibility is that Boc-deprotection occurred first and transimination resulted in the formation of 3.40. We surveyed conditions for the unmasking of the ketone while preventing the deprotection of the amine, but we were not able to observe the desired acyclic ketone even in trace amounts (Scheme 60).

Changing the hydroxylamine source to 3.53 allowed us to synthesize 3.49 by adding only one step to the sequence. We chose para-methoxybenzyl protecting group, because it gave us a broader choice of deprotection methods, than simple benzyl group. Initially we followed the procedure of Yang, to access the hydroxylamine 3.53, but we found that the formation and expansion of a polymeric side product rendered the method dangerous to run above 3 gram scale. When hydrazine was replaced with N-methylhydrazine, the polymeric product was not observed and 3.53 could be synthesized on multigram scale. The debenzylation of 3.56 was first examined via reductive methods and we found that ethylsilane in combination with Pearlman’s catalyst delivers 3.49 in quantitative yield. Performing the reaction above milligram scale necessitated the dilution of the reaction mixture to allow complete dissolution of the starting material. 3.56 was examined for deoximation and to this end we tested the conditions presented in Table 11 and Table 12, but we were not able to detect the formation of the desired ketone (Scheme 61).

Scheme 60 - When we subjected linear oxime 3.48 to zinc mediated reduction under acidic conditions, we observed the formation of enamine 3.40 in low yield. The formation of 3.40 is more likely to demonstrate a Boc-deprotection-transimination sequence, than true deoximation.

We began to examine the deoximation of 3.49 with hydrolytic methods. Oppolzer and Szántay reported methods for the hydrolysis of α-oximinolactams to α-ketolactams by treatment with refluxing formalin in the presence of Brønsted acid catalyst.\textsuperscript{120} Deoximation can also occur by treatment with CS\textsubscript{2} in the presence of Barton’s base.\textsuperscript{121} Unfortunately, neither of these methods furnished the desired ketone (Table 13, Entries 1-3). The reductive deoximation methods, which were discussed earlier in Table 12, were examined on oxime 3.49. Delightfully, we were able to reduce the starting material, however, an unexpected dilactam (3.57) was isolated as the single product in most cases. A reasonable explanation for the formation of 3.57 can be that the C=N double bond of the oxime moiety is reduced first and the hydrogen atoms were delivered exclusively on the Si-face of the oxime. The face selectivity of the reduction is in accord with our initial analysis shown on Figure 9. The resulting amine (or hydroxylamine) readily lactonized with the proximal ester group to form 3.57. Oxidative methods lead to decomposition of the starting material (Table 13, Entries 10, 11 and 12).


The preparation of multigram quantities of α-oximinolactam 3.49 relied on the scalable preparation of O-PMB protected hydroxylamine 3.53 (Scheme 61). Gabriel synthesis using hydrazine for the liberation of 3.53 was not scalable, due to the formation of a polymeric, sponge-like side product, which disabled stirring and cooling of the reaction mixture. In order to overcome this issue, we ran Gabriel synthesis with different hydrazine derivatives and parallel to that, we examined commercially available O-benzylhydroxylamine to substitute 3.53. Eventually, we found that the preparation of 3.53 via Gabriel synthesis with N-methlyhydrazine is scalable and O-benzylhydroxylamine is a good alternative to 3.53 for the enamine ring opening (Scheme 62).

**Table 13 - Summary of conditions surveyed for the deoximation of 3.49.**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Condition</th>
<th>Temperature</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>formalin&lt;sub&gt;aq.&lt;/sub&gt; / HCl&lt;sub&gt;cc.&lt;/sub&gt; (7:2)</td>
<td>70 °C</td>
<td>decomposition</td>
</tr>
<tr>
<td>2</td>
<td>PTSA, paraformaldehyde, AcOH</td>
<td>70 °C</td>
<td>decomposition</td>
</tr>
<tr>
<td>3</td>
<td>CS&lt;sub&gt;2&lt;/sub&gt;, Barton’s base, MeCN</td>
<td>0 °C - 70 °C</td>
<td>no conversion</td>
</tr>
<tr>
<td>4</td>
<td>Raney Ni (W2, freshly prepared), H&lt;sub&gt;2&lt;/sub&gt;, H&lt;sub&gt;3&lt;/sub&gt;BO&lt;sub&gt;3&lt;/sub&gt; (5.7 equiv), acetone (2.7 equiv), THF/MeOH/water (7:7:1)</td>
<td>18 °C</td>
<td>3.57, single product</td>
</tr>
<tr>
<td>5</td>
<td>Raney Ni (W2, freshly prepared), H&lt;sub&gt;2&lt;/sub&gt;, H&lt;sub&gt;3&lt;/sub&gt;BO&lt;sub&gt;3&lt;/sub&gt; (5.7 equiv), acetone (2.7 equiv), THF/MeOH/water (7:7:1)</td>
<td>18 °C</td>
<td>3.57, single product</td>
</tr>
<tr>
<td>6</td>
<td>Raney Ni (W6, freshly prepared), H&lt;sub&gt;2&lt;/sub&gt;, H&lt;sub&gt;3&lt;/sub&gt;BO&lt;sub&gt;3&lt;/sub&gt; (5.7 equiv), acetone (2.7 equiv), THF/MeOH/water (7:7:1)</td>
<td>18 °C - 60 °C</td>
<td>no conversion</td>
</tr>
<tr>
<td>7</td>
<td>TiCl&lt;sub&gt;3&lt;/sub&gt;, NH&lt;sub&gt;4&lt;/sub&gt;OAc buffered to pH=5</td>
<td>18 °C</td>
<td>3.57, single product</td>
</tr>
<tr>
<td>8</td>
<td>Zn*, AcOH:THF:water (3:1:1), 37 °C</td>
<td>37 °C</td>
<td>3.57, single product</td>
</tr>
<tr>
<td>9</td>
<td>CAN, MeOH</td>
<td>-30 °C</td>
<td>decomposition</td>
</tr>
<tr>
<td>10</td>
<td>DMP, wet DCM</td>
<td>0 °C</td>
<td>no conversion</td>
</tr>
</tbody>
</table>
The excessive use of palladium for the conversion of 3.56 to 3.49 prompted us to seek a safer and economic synthesis. With 3.59 in hand, we set up a rapid screening of conditions for debenzylation (Table 14). We found that the conditions used for the debenzylation of 3.56, provided 3.49 in quantitative yield from 3.59 (Table 14, Entry 1). The vigorous reaction between triethylsilane and the catalyst led us to try 1,4-cyclohexadiene (1,4-CHD), a safer hydrogen donor, for the deoximation. The expected oxime (3.49) was obtained in reduced yield, but the formation of a side product raised our curiosity and upon isolation we found that the coveted α-ketolactam 3.44 was obtained.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Reductant</th>
<th>Temperature</th>
<th>Conversion</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Pearlmann's catalyst</td>
<td>TES</td>
<td>50 °C</td>
<td>100%</td>
<td>quant., 3.49</td>
</tr>
<tr>
<td>2</td>
<td>Pd/C</td>
<td>TES</td>
<td>50 °C</td>
<td>100%</td>
<td>quant., 3.49</td>
</tr>
<tr>
<td>3</td>
<td>Pearlmann's catalyst</td>
<td>1,4-cyclohexadiene</td>
<td>50 °C</td>
<td>100%</td>
<td>3:2 ratio between 3.49 and 3.44</td>
</tr>
</tbody>
</table>

Table 14 - A short survey of reductive conditions for the debenzylation of 3.59. Unexpectedly, with the conditions at Entry 3 we were able to isolate the sought-after α-ketolactam 3.44.

Immediately after this finding, we set up a control experiment to understand whether the N-O bond or the O-C bond is cleaved first in 3.59. We submitted 3.49 to the same conditions and repeated the
deoximation of 3.59 on the same scale, parallelly. Oxime 3.49 remained intact under these conditions leading us to the conclusion that the N-O bond was cleaved first upon the deoximation of 3.59 and 3.49 is not an intermediate toward 3.44 (Scheme 63).

Scheme 63 - Control experiments determined that oxime 3.49 is not an intermediate in the formation of ketone 3.44 from 3.59.

In the optimization our task was to identify conditions that favor the cleavage of the N-O bond versus the O-C bond. While keeping the catalyst we surveyed a variety of hydrogen donors, such as 1,3-CHD, cyclohexene, tetratin, diphenylsilane, phenylsilane, ethylsilane, polymethylhydrosiloxane, sodium formate and ammonium formate, but none of these reductants delivered 3.44 even in trace amount. Similar results were obtained upon the screening for alternative catalyst and solvent systems. We found that the catalyst loading could not be lower than 70 mol%, the pressure must be kept as high as possible and the optimum temperature of the deoximation is 110 °C. Due to these restrictions, the method was not scalable due significant yield-loss and finding appropriate, reproducible conditions to run the reaction at larger scales was a tedious task. Using a sealed vessel in a microwave reactor allowed us to obtain a detailed image of the reaction’s pressure profile and have control over the remaining parameters. The major difficulties included the spontaneous and unpredictable pressure rises in the vessel, inconsistent yields and low throughput caused by the low capacity of the microwave reactor. Eventually, after a series of trial and errors we found a condition which consistently keeps the pressure below the limit of our microwave reactor (20 bar), thereby preventing auto-shutdown of the reaction. Another important factor was the fast temperature ramp to 110 °C using microwave irradiation at 300 Watts. We found that the majority of the side product (3.49) is formed in the period of the ramping, between 60-100 °C. In this particular case, to reach
an even faster ramp, a microwave flow reactor may have been an excellent choice to avoid the issues related to slow temperature build-up. Pre-stirring the mixture was crucial to ensure even dispersion of the four-phase system before irradiation, thereby preventing rapid pressure build-up, runaway reaction and explosion.\textsuperscript{122} The headspace of the sealed vessel was maximized by using the minimal amount of solvent in the reactor. The measure had to be taken due to the occasional pressure jumps occurred during the reaction. A larger headspace served as a safety volume, mitigating the effects of rapid hydrogen generation and pressure build-up. Finally, we paid great attention to the inertization of the headspace and the proper cleaning of glassware after each reaction. Eventually, the obtained method served as the major source of \textbf{3.44} and proved reproducible and safe after dozens of runs (Equation 11).

\textbf{Equation 11 - The optimized conditions for the synthesis of the key intermediate 3.44.}

3.2.1.4 Studies on the conversion of $\alpha$-oximino lactams to $\alpha$-ketolactams: deoximation of $O$-acyloximes

By reducing \textbf{3.59} under transfer hydrogenation conditions to $\alpha$-ketolactam \textbf{3.44} we had access to the key intermediate of the total synthesis, however, the low yield and time-consuming procedure motivated us to seek a better alternative for the synthesis of ketolactam. To this end, we synthesized various $O$-acyloxime derivatives whose weak N-O bond can be cleaved and subsequently converted to carbonyl compounds (Equation 12).

\textsuperscript{122} The four-phases were \textbf{3.59}, methanol, Pearlman’s catalyst and 1,4-CHD. \textbf{3.59} was only soluble in boiling methanol at 5.3 M concentration. 1,4-CHD is immiscible with methanol.
Chapter 3 - Towards the Total Synthesis of Voacaficine A and Voacaficine B

Equation 12 - Synthesis of O-acyloxime derivatives 3.66-3.70.

O-acyloximes can be converted to organometallic species by oxidative addition, iminyl radicals can be obtained by single electron transfer (SET) process and upon two consecutive SET process iminato metal intermediates can be obtained.\(^{123,124}\) When O-acetyl oxime 3.66 and O-benzoyloxime 3.67 were subjected to the conditions that resulted in the reduction of oxime 3.49 to 3.57 (Table 13) the same bicyclic lactam 3.57 was obtained as the single product. We examined iron pentacarbonyl and dicobalt octacarbonyl for the reduction of 3.66 and 3.67, according to the reports of Nitta and Mukai, however, the ketone was not formed under these conditions.\(^{125}\) Corey reported the deoximation of ketoximes with \textit{in situ} generated chromium(II) acetate, unfortunately we were not able to observe the removal of the oxime using their protocol.\(^{126}\) Submitting 3.66-3.68 to transfer hydrogenative conditions resulted in the formation of bicyclic lactam as the sole product. We hypothesized that increasing the electron withdrawing effect of the O-acyl group decreases the BDE of the N-O bond of the oxime, thereby facilitating its cleavage. Copper and iron catalyzed double SET processes are capable of converting O-acyloximes to iminato metal complexes, which can be hydrolyzed to ketones. Based on reported procedures and our own in-house experience, we screened copper and iron salts that are known to catalyze such transformations.\(^{123,124k-m}\) Copper(II) triflate, tetrakis(acetonitrile)copper(I) tetrafluorophosphate, copper(I) iodide, copper(I) bromide, copper(II)

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acetate and iron(III) chloride was surveyed with various solvents and additives, but to our dismay the decomposition of the starting material or the lack of reactivity was observed in all cases. Nevado and co-workers disclosed the generation of iminyl radicals from 4-trifluoromethylbenzoylloximes. Applying their conditions to 3.68 resulted in the formation of a peculiar compound, which we were not able to unambiguously assign by standard analytic methods and were not able to obtain single crystals either. Our proposed structure is nevertheless shown below (Table 15).

![Structure Diagram]

Narasaka and co-workers reported the oxidative insertion of palladium to the N-O bond of perfluorobenzoylloximes and utilized it for the development of Heck type aminations, today called Narasaka-Heck cyclization. Building on their seminal work, Fürstner and Bower disclosed similar methods for the synthesis of N-heterobicyclic scaffolds. As our purpose was not to carry out Narasaka-Heck cyclization, but the hydrolysis of the intermediate organometallic complex, these methods were examined using stoichiometric quantities of palladium for the deoximation of O-perfluorobenzoyl oxide 3.70. When the reactions were run under 50 °C the starting material remained intact in every case. Upon reaching 60 °C, the insertion of palladium rapidly took place followed by vigorous reaction. Although the desired ketone (3.44) was detected in some cases (Table 16, Entry 1 and 3) we were not able to significantly increase the yield.

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Chapter 3 - Towards the Total Synthesis of Voacafricine A and Voacafricine B

Table 16 - Surveyed conditions to perform oxidative insertion of palladium into the weak N-O bond of O-acyloximes 3.69 and 3.70.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Condition</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3.70</td>
<td>Pd$_2$dba$_3$ (1 equiv), P(3,5-(CF$_3$)$_2$)C$_6$H$_3$)$_3$ (1 equiv), TEA, DMF, 60 °C</td>
<td>decomp., traces of 3.44</td>
</tr>
<tr>
<td>2</td>
<td>3.69, 3.70</td>
<td>Pd(OAc)$_2$ (1 equiv), P(o-tolyl)$_3$ (1 equiv), TEA, DMF, 60 °C</td>
<td>decomposition</td>
</tr>
<tr>
<td>3</td>
<td>3.70</td>
<td>Pd$_2$dba$_3$ (1 equiv), P(tBu)$_3$ (1 equiv), TEA, DMF, 60 °C</td>
<td>decomp., traces of 3.44</td>
</tr>
<tr>
<td>4</td>
<td>3.69, 3.70</td>
<td>Pd$_2$dba$_3$, P(o-tolyl)$_3$ (1 equiv), HCOONa, DMF, 60 °C</td>
<td>decomposition</td>
</tr>
</tbody>
</table>

Although we were not able to develop a method for the high-yielding synthesis of our key intermediate 3.44, we were able to prepare it with sufficient throughput and continue our pursuit to voacafricine A and voacafricine B. The following two sections detail our journey towards the two natural products, starting from compound 3.44.
3.2.2 Towards the total synthesis of voacafricine A

The synthetic plan leading to voacafricine A, starting from the key intermediate (3.44) and junction point of the total synthesis, is shown on Scheme 64. First, we wanted to homologate the ketone unit of 3.44 via Wittig olefination or Knoevenagel condensation. The obtained olefinic product is converted to the protected alcohol 3.73 by sequential reduction of the C-C double bond and the ester function. Selective, partial reduction of the lactam allows the in situ formation of an iminium intermediate, which is trapped by the tethered alcohol to construct the F ring of 3.74. Conversion of the acetal moiety to aldehyde function, followed by epimerization and reduction leads to the precursor of the natural product. Saponification of the methyl ester and activation of the alcohol by sulfonylation leads to the quaternization of the N4 nitrogen atom, delivering voacafricine A (Scheme 64).

The homologation of the ketone group of 3.44 was first examined by Wittig olefination. To this end, we synthesized 3.80 and 3.81 according to reported literature procedures. Various bases and solvents were surveyed for the generation of the phosphor ylides, however we could not convert 3.44 to the desired olefins with these reagents. We hypothesized that 3.44 may be deprotonated by the phosphor ylides and rest in their enolate form under these conditions. To address this possibility, we applied Masamune’s conditions and tried neutral phosphoranylidene reagents, but even under

\[ \text{Scheme 64 - Synthetic plan towards voacafricine A.} \]

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refluxing conditions in methanol of THF, we could not detect the formation of the sought-after olefin (Scheme 65).\textsuperscript{130}  

![Scheme 65 - We were not able to homologate ketone 3.44 by Wittig olefination.](image)

Knoevenagel condensation with Meldrum’s acid and monomethyl malonate was next attempted. The classic conditions employing pyrrolidine acetate left 3.44 untouched. Running the reactions at elevated temperatures resulted in the deprotection of the dimethoxy acetal function and when Ti(IV)-mediated Knoevenagel condensation was attempted we observed only the decomposition of the nucleophilic partners (Scheme 66).

Another possible pathway towards voacafricine A is diastereoselective reduction of $\textbf{3.44}$ to the alcohol, followed by $\text{SN}_2$ substitution to forge the bond between C20 and C19. Based on our previous results on the reduction of $\alpha$-oximino lactams and $O$-acyloximes (see Sections 3.2.1.3 and 3.2.1.4) and the three-dimensional structure of $\textbf{3.43}$ and $\textbf{3.59}$ in their solid state (Scheme 57, Scheme 62) we hypothesized that the ketone moiety of $\textbf{3.44}$ would be selectively attacked by a hydride nucleophile on the $\text{Si}$-face. Activation of the obtained alcohol by sulfonylation followed by nucleophilic substitution, for example with dimethyl malonate, would furnish a promising intermediate towards voacafricine A (Scheme 67).
When 3.44 was treated with sodium borohydride in dry methanol, we observed the formation of hemiacetal 3.92. Under Luche reduction conditions, the same product was formed. The structure of 3.92 can be rationalized by initial formation of ketal 3.89 with trace amount of water, which undergoes lactonization with the proximal ester group. The increased reactivity of the lactone yielded towards sodium borohydride reduction furnishing 3.91. When ketone 3.44 was treated with sodium borohydride in anhydrous THF or a one-to-one mixture of anhydrous DCE and MTBE, we observed the formation of the same product albeit in reduced yield (3.92) (Scheme 68).

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Surprisingly, the reduction of $3.44$ with sodium borohydride resulted in the formation of a bicyclic hemiacetal ($3.92$). The proposed mechanism presumes the presence of a trace amount of water in the reaction mixture.

Although Wittig-olefination, Knoevenagel-condensation and reduction with sodium borohydride did not transform $3.44$ to our target molecules, there is still a myriad of options to advance this compound to the natural product. As the route discovery toward the other alkaloid, voacafricine B, was carried out in a parallel fashion and we obtained encouraging results on that terrain, our attention was drawn away from this pathway. In the following section, our synthetic battle with voacafricine B is detailed, decorated with another collection of unexpected transformations and uncommon chemical structures.
3.2.3 Towards the total synthesis of voacaficine B

Starting from the key intermediate 3.44, there were multiple options to choose from towards the synthesis of voacaficine B (3.2). Reformatsky reaction performed on 3.44 and global reduction of the obtained triester 3.93 delivers the pentacyclic intermediate 3.94 as shown on Scheme 69, Path A. Oxidation of the primary alcohol (3.94), followed by acetal deprotection, epimerization and aldehyde reduction leads to the precursor of voacaficine B (3.96). Quaternarization of the aliphatic amine is achieved by activation of the obtained alcohol by mesylation and subsequent intramolecular nucleophilic substitution. Alternatively the F ring can be installed by 1,2-addition of a Grignard reagent to 3.44, followed by selective lactam reduction-alcohol deprotection as shown on Scheme 69, Path B. The obtained pentacyclic intermediate 3.98 can be converted to the natural product following the above described end-game strategy (Scheme 69).

Following “Path A”, the Reformatsky reaction was examined first. When we subjected ketone 3.44 to ethyl bromoacetate in the presence of activated zinc in THF, we were able to observe the for-
mation of the zinc enolate, but the reaction was sluggish and we could not isolate the desired product. We examined different ways for the activation of zinc without success.\textsuperscript{132} Fukuzawa and co-workers reported the samarium (II) diiodide-mediated Reformatsky reaction between \(\alpha\)-bromo-esters and aldehydes.\textsuperscript{133} When we applied their protocol to \textbf{3.44}, we could observe the scission of the N4-C21 amide bond. To realize the 1,2-addition to ketone \textbf{3.44}, Grignard reagents were next surveyed. As an effort to increase the convergency of the synthesis we wanted to prepare \textbf{3.102} Grignard reagent. Although there is no reported procedure for the preparation of similar Grignard reagent, we were surprised that haloether \textbf{3.102} underwent rapid decomposition upon oxidative addition of elemental magnesium presumably \textit{via} elimination of the OTBS group (Scheme 70).

![Scheme 70 - Preparation of Grignard reagent 3.102 proved more difficult than expected. Eventually we switched to a longer sequence to reach our targets.](image-url)

After multiple attempts we opted for a longer, but theoretically feasible sequence: 1,2-addition of vinylmagnesium chloride onto the ketone and subsequent hydration of the alkene could equally give us access to the needed motif. When \textbf{3.44} was treated with vinylmagnesium bromide at cryogenic temperatures, the starting material simply underwent \(\alpha\)-deprotonation and remained intact. Imamoto and Knochel, in their seminal works, detailed the preparation of organolanthanide reagents for selective 1,2-addition onto carbonyl compounds bearing acidic protons.\textsuperscript{134,135} When the exact protocol of Imamoto was utilized, we did not observe the consumption of the starting material (Table 17, Entry 1). Increasing the equivalents or using a one-to-three ratio between the cerium (III) and vinylmagnesium bromide furnished spiro compound \textbf{3.105} in good yield. Knochel’s method delivered the same product (Table 17, Entry 5), when the temperature was decreased \textbf{3.44} remained untouched (Table 17, Entry 4).

Chapter 3 - Towards the Total Synthesis of Voacafricine A and Voacafricine B

Table 17 - Summary of the attempted 1,2-additions of vinylmetal reagents to 3.44. An unexpected rearrangement delivered compound 3.105 as the single product.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Condition</th>
<th>Temperature</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>CeCl₃ (1.5 equiv), vinylMgBr (1.5 equiv)</td>
<td>-78°C - r.t.</td>
<td>no conversion</td>
</tr>
<tr>
<td>2</td>
<td>CeCl₃ (3 equiv), vinylMgBr (3 equiv)</td>
<td>-78°C</td>
<td>3.105</td>
</tr>
<tr>
<td>3</td>
<td>CeCl₃ (3 equiv), vinylMgBr (9 equiv)</td>
<td>-78°C</td>
<td>3.105</td>
</tr>
<tr>
<td>4</td>
<td>LaCl₃ * 2 LiCl (1.1 equiv), vinylMgBr (1.1 equiv)</td>
<td>-78°C</td>
<td>no conversion</td>
</tr>
<tr>
<td>5</td>
<td>LaCl₃ * 2 LiCl (1.1 equiv), vinylMgBr (1.1 equiv)</td>
<td>r.t.</td>
<td>3.105</td>
</tr>
</tbody>
</table>

A plausible mechanistic explanation for the formation of 3.105 is shown on Scheme 71. The lanthanide salt promotes the enolization of the ketone moiety, which initiates transannular Dieckmann condensation with the proximal ester group. The formed bicyclic diketone cannot enolize as it would be against Bredt’s rule. The lanthanum salt forms a coordination complex with the 1,2-dicarbonyl unit and subsequent attack of the vinyl nucleophile results in the formation of intermediate 3.108. Retro-aldol reaction fragments the bicyclic system delivering the isolated product 3.105 (Scheme 71).
The allylation of ketone 3.44 is another alternative to introduce the required two-carbon unit for the construction of ring F. Treatment of 3.44 with allylmagnesium chloride in THF led to the allyl derivative of the previously isolated spiro compound 3.105 (3.111) (Table 18, Entry 1). When the reaction was run according to Imamoto’s protocol the same product was isolated (Table 18, Entry 2).\textsuperscript{134} Ishihara reported a practical zinc-catalyzed 1,2-addition of Grignard reagents to ketones and aldimines.\textsuperscript{136} The zinc-catalyzed 1,2-allylation of 3.44 lead to complex reaction mixture and the desired product could not be detected (Table 18, Entry 3 and 4).

Chapter 3 - Towards the Total Synthesis of Voacafricine A and Voacafricine B

Table 18 - Summary of Grignard allylation conditions surveyed for the preparation of 3.110.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Condition</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>allyl-MgCl (1.5 equiv), THF, 18 °C</td>
<td>clean conversion to 3.111</td>
</tr>
<tr>
<td>2</td>
<td>CeCl3 (1.5 equiv), allyl-MgCl (1.5 equiv), THF, 18 °C</td>
<td>clean conversion to 3.111</td>
</tr>
<tr>
<td>3</td>
<td>ZnCl2 (1.1 equiv), allyl-MgCl (1.1 equiv), THF, 18 °C</td>
<td>complex mixture obtained</td>
</tr>
<tr>
<td>4</td>
<td>ZnCl2 (0.1 equiv), allyl-MgCl (1.3 equiv), THF, 18 °C</td>
<td>low conversion, complex mixture</td>
</tr>
</tbody>
</table>

Allyltrimethylsilane, allyltributyltin and allylpinacolboronate are well known, mild reagents used for 1,2-allylmetalation of aldehydes. The ketone function of 3.44 is activated by the neighboring amide group and the reactivity of such carbonyl unit is comparable with aldehydes’. We examined 3.112, 3.113 and 3.114 for the allylation reaction under thermal conditions and in the presence of catalytic amount of Lewis acids between -78 °C and 40 °C in chloroform. The surveyed catalysts included TiCl4, SnCl4, Mg(OTf)2, Sc(OTf)3, In(OTf)3, Tf2NH and Montmorillonite K10. To our dismay, none of these conditions furnished the 1,2-allylation product 3.110 (Equation 13).

Equation 13 – The allylation of 3.44 was unsuccessful when 3.112, 3.113 and 3.114 reagents were used.

As the efforts towards the installation of the F ring via the originally outlined Reformatsky and Grignard reaction failed, we turned our attention to Mukaiyama aldol addition using ketene acetals for
the implementation of the two-carbon unit onto 3.44. We prepared ketene acetal 3.115 according to a reported procedure and screened a variety of Lewis acid catalysts for the Mukaiyama aldol reaction (Table 19). The selected catalysts, presented in Table 19, were examined between –60 °C to 18 °C and we found that scandium triflate, indium triflate and boron trifluoride ether complex were capable of catalyzing the transformation. Among these, scandium (III) triflate delivered 3.117 with the highest yield as a single diastereoisomer, however, simultaneous acetal deprotection could not be prevented (Table 19).

![Chemical structure images](image)

Table 19 - The survey of Lewis acid catalysts for the Mukaiyama aldol reaction led us to identify scandium (III) triflate as an efficient catalyst, however, deprotection of the acetal function could not be prevented.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Lewis acid (20 mol%)</th>
<th>Temperature</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>BF₃ OEt₂ (2.5 equiv)</td>
<td>-60 °C to 18 °C</td>
<td>no conversion</td>
</tr>
<tr>
<td>2</td>
<td>BF₃ OEt₂ (4.5 equiv)</td>
<td>18 °C</td>
<td>20% yield of 3.117</td>
</tr>
<tr>
<td>3</td>
<td>ZnBr₂</td>
<td>-60 °C to 18 °C</td>
<td>no conversion</td>
</tr>
<tr>
<td>4</td>
<td>Cu(OTf)₂</td>
<td>-60 °C to 18 °C</td>
<td>decomposition of 3.44</td>
</tr>
<tr>
<td>5</td>
<td>CuCl₂</td>
<td>-60 °C to 18 °C</td>
<td>acetal deprot.</td>
</tr>
<tr>
<td>6</td>
<td>Sc(OTf)₃</td>
<td>18 °C</td>
<td>70% yield of 3.117</td>
</tr>
<tr>
<td>7</td>
<td>In(OTf)₃</td>
<td>18 °C</td>
<td>15% yield of 3.117</td>
</tr>
<tr>
<td>8</td>
<td>MgI₂</td>
<td>-60 °C to 18 °C</td>
<td>no conversion</td>
</tr>
<tr>
<td>9</td>
<td>SnCl₂</td>
<td>-60 °C to 18 °C</td>
<td>decomposition</td>
</tr>
</tbody>
</table>

To our surprise, the expected silyl shift from the ketene acetal to the formed β-alcoholate did not take place, instead, the alcoholate trapped the carboxonium ion forming the rare oxetane-orthoester compound 3.120 as shown on Scheme 72. Perhaps the relatively large –OTBS group prevented the arrangement to the six-membered transition state, thereby allowing the formation of the ox-

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etane moiety. Although an excess of ketene acetal was used, the unmasked aldehyde did not undergo aldol condensation, showcasing the highly selective addition to the activated ketone function (Scheme 72).

![Scheme 72 - The proposed mechanism for the formation of 3.120 and illustration of the expected 1,5-silyl shift.](image)

As we could not prevent the simultaneous acetal deprotection, we decided to prepare more reactive ketene acetals to allow milder conditions, thereby sparing the dimethoxy acetal function. We hypothesised that a smaller silyl protecting group may allow the formation of a six-membered transition state for the 1,5-silyl shift, therefore we prepared 3.121 according to a literature procedure.\textsuperscript{139} Based on our previous results and literature precedents we selected an array of Lewis acids and bases for our survey to find a potential catalyst.\textsuperscript{138,140} Scandium triflate was by far the most potent catalyst for the Mukaiyama aldol reaction between 3.44 and 3.121 (Table 19), however, when 3.121 was utilized it proved ineffective. Among the other Lewis acids screened, magnesium bromide stood out, but yttrium triflate, cerium triflate and indium triflate also catalyzed the transformation (Table 20, Entries 7-10). Our survey of reported Lewis base catalyzed methods was fruitless (Table 20, Entries 11-13).\textsuperscript{140} We continued the optimization of the Mukaiyama aldol reaction by varying the counteranion of the magnesium ion and we found that magnesium triflate and magnesium iodide are

\begin{flushleft}
\end{flushleft}
equally potent catalysts, but on larger scale the triflate salt delivered more consistent results. Thor-ough optimization of the remaining reaction parameters resulted in a method, which converts 3.44 in very good yield to 3.123 even on gram scale (Table 20, Entry 17). 3.123 was obtained as a single
diastereoisomer, but the relative geometry surrounding the oxetane moiety was difficult to assign.
Based on the observed exclusive Si-face selective attack on the oxime C-N double bond by various
reducing agents (see sections 3.2.1.3 and 3.2.1.4), we surmise that the oxygen in the oxetane ring
is pointing down as a result of the Si-face selective attack of ketene acetal reagent. Spin-spin corre-
lation between the methyl ether of 3.123 and the methylene hydrogens at C5 was measured using
nuclear Overhauser effect spectroscopy. Our analysis suggests the relative configuration of 3.123 is
as shown below.

Table 20 - Summary of the early catalyst screening and optimization of the Mukaiyama aldol reaction for the
synthesis of 3.123.
The removal of the TMS protecting group of 3.123 and opening of the oxetane ring turned out to be more difficult than expected. The silyl protecting group resisted to acidic conditions, even treatment with 1 M hydrogen chloride solution did not result in deprotection. Various fluoride sources were surveyed and we found that tetrabutylammonium fluoride efficiently converts 3.123 to its open chain form (3.122), however we were not able to isolate the formed product due to its high sensitivity. The crude residue was highly contaminated with tetrabutylammonium residue and when it was subjected to the next step, we routinely observed the decomposition of 3.122. Eventually, we found that treatment of 3.123 with anhydrous cesium fluoride in DMF followed by aqueous work-up delivered 3.122 in acceptable purity and good yield (~70-80%), although further purification was not possible due to the sensitivity of the product. In an ideal scenario, global reduction of 3.122 delivers directly the pentacyclic product 3.124 as it was reported using similar scaffolds.\textsuperscript{141} When 3.122 was treated with DIBAL-H, LiBH\textsubscript{4} or NaBH\textsubscript{4} spiro compound 3.128 was formed as the single product.

\begin{center}
\begin{tikzpicture}
\node at (0,0) {3.123};
\node at (3,0) {3.122};
\node at (6,0) {3.124};
\node at (0,-1) {\textbf{Scheme 73 - Our attempts to reduce intermediate 3.122 with hydridic reagents were not successful.}};
\end{tikzpicture}
\end{center}

A plausible explanation for the formation of 3.128 is shown on Scheme 74. The hydridic reducing agent first deprotonates the free alcohol and the alcoholate initiates retro-Aldol reaction to furnish 3.44. Enolization followed by Dieckmann condensation with the proximal ester group leads to the bicyclic diketone 3.107. Hydrolysis of the activated lactam and retro-Claisen condensation furnishes the isolated product (3.128).

Converting ester 3.122 to the free acid (3.129) via basic hydrolysis or nucleophilic substitution could allow us to selectively reduce the free acid in the presence of the ester and amide functions. To this end, we examined the hydrolysis of 3.122 with alkalimetal hydroxides, lithium hydroperoxide and sodium propanethiolate (Scheme 75). Disappointingly the formation of the free acid was not observed even at elevated temperatures; instead the rearrangement to spiro 3.128 was the prevalent transformation that took place.
Scheme 75 - Disappointingly our efforts to hydrolyse the primary methyl ester of 3.122 resulted in a rearrangement to 3.128.

Protection of the tertiary alcohol seemed to be the only viable way to proceed. Classic conditions for the mild silylation of the hindered hydroxyl group did not yield the desired protected alcohol (3.130), only the 2,6-lutidine-promoted rearrangement to 3.128 (as on Scheme 74) was observed as shown in Table 21.

Table 21 - Our attempts for the protection of the in situ generated tertiary alcohol were fruitless. Rearrangement to 3.128 was observed when 2,6-lutidine was used as base.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Silylating reagent</th>
<th>Condition</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>TMSOTf (1 equiv)</td>
<td>2,6-lutidine (1.2 equiv), DCM, -78 °C</td>
<td>major product is 3.128</td>
</tr>
<tr>
<td>2</td>
<td>TMSOTf (1.5 equiv)</td>
<td>TEA (2 equiv), THF, -78 °C</td>
<td>complex mixture was obtained</td>
</tr>
<tr>
<td>3</td>
<td>TMSCl (1 equiv)</td>
<td>imidazole (2.5 equiv), DMF, 0 °C to r.t.</td>
<td>complex mixture was obtained</td>
</tr>
<tr>
<td>4</td>
<td>TESOTf (1 equiv)</td>
<td>2,6-lutidine (1.2 equiv), DCM, -78 °C</td>
<td>major product is 3.128</td>
</tr>
<tr>
<td>5</td>
<td>TESOTf (1 equiv)</td>
<td>TEA (2 equiv), THF, -78 °C</td>
<td>complex mixture was obtained</td>
</tr>
</tbody>
</table>

The oxetane-orthoester function of 3.123 can be regarded as a protected surrogate of 3.122. Our plan to leverage this function is as follows: selective, partial reduction of the lactam to hemiaminal 3.131 followed by the *in situ* oxetane ring opening/orthoester deprotection with cesium fluoride leads to intermediate 3.132. Acidic treatment elicits the iminium intermediate 3.133, which is trapped by the tethered methyl ester. Reduction of the lactone 3.134 leads to the formation of the pentacyclic target compound as shown on Scheme 76.
Methods for the selective reduction of amides to aldehydes have been known for more than half-a-century, but due to their lack of generality, typically a two-step activation-reduction protocol is followed in total synthesis.\textsuperscript{142} We set out this latter strategy to follow for the synthesis of our target molecule. After screening various activating agents, we found that triflic anhydride is able to activate the hindered tertiary amide moiety of 3.123. Survey of the literature precedents pointed out that 2- and 3-substituted pyridines are especially well suited as bases for such a transformation and a rapid screening uncovered that 2-chloropyridine and 3-cyanopyridine are excellent additives for the studied reaction (Table 22, Entries 4 and 5).\textsuperscript{143}


We found that the combination of triflic anhydride with 2-chloropyridine or 3-cyanopyridine in acetonitrile can convert 3.123 to the carboximidate 3.136.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Condition</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Meerwein’s salt (1 equiv), DCM, 0 °C</td>
<td>no conversion</td>
</tr>
<tr>
<td>2</td>
<td>MeOTf (1.1 equiv), DCM, 0 °C</td>
<td>no conversion</td>
</tr>
<tr>
<td>3</td>
<td>Tf₂O (1.1 equiv), DTBMP (1.2 equiv), MeCN, 0 °C</td>
<td>decomposition</td>
</tr>
<tr>
<td>4</td>
<td>Tf₂O (1.1 equiv), 3-CN-Py (1.2 equiv), MeCN, -20 °C to 18 °C</td>
<td>full conversion to 3.136</td>
</tr>
<tr>
<td>5</td>
<td>Tf₂O (1.1 equiv), 2-Cl-Py (1.2 equiv), MeCN, -20 °C to 18 °C</td>
<td>full conversion to 3.136</td>
</tr>
<tr>
<td>6</td>
<td>Tf₂O (1.1 equiv), 2-F-Py (1.2 equiv), DCM, -78 °C to 0 °C</td>
<td>3.136 is formed at lower yield</td>
</tr>
</tbody>
</table>

Table 22 - We found that the combination of triflic anhydride with 2-chloropyridine or 3-cyanopyridine in acetonitrile can convert 3.123 to the carboximidate 3.136.

Charette and co-workers developed protocols to reduce activated amides to aldehydes using triflic anhydride as activator and ethylsilane as reducing agent. We tried to reduce 3.136 according to their protocols, moreover, we surveyed other reducing agents, such as phenylsilane, sodium cyanoborohydride and sodium borohydride. Using the latter reagent 3.136 was cleanly converted to a mixture of two compounds whose structure was not assigned, but we could exclude them as potentially interesting scaffolds. We also tried to trap the activated amide group with the in situ liberated ester function and reduce the intermediate in situ. Unfortunately, this approach did not furnish the desired product (Table 23).
Aldehydes, enamines or hemiaminals can be obtained from tertiary amides by the catalytic hydrosilylation of amides in the presence of transition metals. Buchwald, Nagashima and Adolfsson reported the titanium, iridium, molybdenum and potassium tert-butoxyde catalyzed hydrosilylation of tertiary amides.\textsuperscript{145} Although the partial reduction of a tertiary amide bearing a quaternary carbon centre adjacent to the nitrogen atom is not reported to date, we examined these reported procedures; however, none of these methods were able to transform compound \textbf{3.123}. Brown reported the stoichiometric and partial reduction of amides to aldehydes using lithium tri-tert-butoxyaluminum hydride.\textsuperscript{146} Surprisingly, neither the commercial, nor the freshly prepared reagent was able to reduce \textbf{3.123}. Chiba and co-workers reported selective amide reduction using a mixture of sodium hydride and sodium iodide as a suspension in THF at 40 °C. To our dismay, rapid decomposition of \textbf{3.123} ensued when Chiba’s conditions were employed. Finally, Georg reported the selective reduction of tertiary amides to aldehydes with Schwartz reagent.\textsuperscript{147} Subjecting \textbf{3.123} to four equivalents of Schwartz reagent in THF at 18 °C, cleanly afforded a new product (Table 13).

\begin{table}
\centering
\begin{tabular}{|c|c|c|}
\hline
Entry & Condition & Result \\
\hline
1 & TES, DCM & no reaction \\
2 & Hantzsch ester in DCM & no reaction \\
3 & NaBH\textsubscript{3}CN / THF & no reaction \\
4 & PhMe\textsubscript{2}SiH in DCM & no reaction \\
5 & NaBH\textsubscript{4} in MeOH & full conv., 1:1 mixture of two products \\
6 & CsF in DMF & complex mixture \\
7 & TBAF in THF & complex mixture \\
\hline
\end{tabular}
\caption{Summary of surveyed conditions for the reduction of 3.136.}
\end{table}


Initially, we had a hard time to unambiguously assign the structure of the major product of the reduction with Schwartz reagent. After thorough inspection and much debate, we settled with the structure shown in Table 24. It is important to note that we took this assignment with reserve, due to some inconsistencies with chemical shifts and long range heteronuclear correlations. However, mechanistically the assigned structure made the most sense among the initially proposed variants. The assignment implies that Schwartz reagent reduced the tertiary lactam to the aldehyde and the orthoester to alcohol, while the tertiary methyl ester was converted to orthoester. The oxidation state of the carbon skeleton was perfect for our purposes. In theory, conversion of the orthoester 3.140 to the carboxylic acid 3.141, followed by hemiaminal formation hypothetically leads us to the desired pentacyclic scaffold without the need to perform any additional redox transformation (Scheme 77).
Following our hypothesis, we surmised that subjecting 3.140 to acidic conditions may result in spontaneous desilylation-cyclization cascade, however, we could not realize this transformation. We believed that if we were able to reduce the labile hemiacetal group we obtain a compound which is easier to characterize. Even better, if we subject 3.140 to the slightly acidic conditions of reductive amination we may be able to initiate a cascade collapse of the orthoester unit followed by intramolecular reductive amination. We were able to quickly identify such conditions to transform 1.140 to another new product in high yield. The proposed structure of 3.142 is shown on Equation 14.

Although the reduction of C21 was successful, we knew that the obtained product is not the sought-after tetracyclic product. Therefore, we wanted to see whether collapsing the orthoester function using a fluoride source leads us to 3.135. To our greatest surprise, treatment of the presumed orthoesters 3.140 and 3.142 with cesium fluoride in DMF or tetrabutylammonium fluoride in THF led to the formation of the spirocyclic product 3.128 in both cases (Scheme 78).
Now we had clear evidence that the proposed structures of \textbf{3.140} and \textbf{3.142} were wrong. We prepared a larger quantity of the presumed orthoesters and subjected those to further NMR experiments, including nuclear Overhauser effect spectroscopy. On Scheme 79 we highlighted the observed key NOE interactions and our revised structures of \textbf{3.140} and \textbf{3.142}. The three dimensional illustration of \textbf{3.142} in Scheme 79/c) demonstrates how the spiro-spiro ring system brings C18 and C19 to the proximity of C5 and C6. The previously dubious chemical shifts and long range heteronuclear correlations are now in accordance with the proposed structures and the assignment is further supported by the particularly intense NOE interactions of the highlighted protons. An additional interesting observation was the slow shift of the trimethylsilyl group from the tertiary alcohol to the hemiacetal’s hydroxyl group when \textbf{3.140} was kept as a CDCl$_3$ solution (Scheme 79).
In order to provide a reasonable explanation for the formation of 3.140, we first proof checked the purity of the Schwartz reagent as it tends to convert to zirconocene dihydride upon standing. The latter is a significantly stronger reducing agent, capable of reducing dichloromethane to methyl chloride.\textsuperscript{148} Our bottle contained a small amount (<5%) of unidentified impurity, but it was absent from

zirconocene dihydride. In the literature the scope of reactivity of the Schwartz reagent is well documented. While it converts tertiary amides to aldehydes among other transformations, it cannot reduce aromatic and aliphatic esters.\textsuperscript{149} With this in mind, the following mechanism is proposed for the formation of \textit{3.140}. In the first step, the lactam is reduced by one equivalent of Schwartz reagent. Coordination of zirconium (IV) to the lone pairs of the adjacent oxygen mediates the retro-[2+2] addition to liberate the ketene acetal. Enolization and Dieckmann condensation forges the bicyclic diketone intermediate \textit{3.147}. Enolization of the ketone is prohibited as it would violate Bredt’s rule, the activated carbonyl group undergoes Mukaiyama aldol addition with the previously released ketene acetal to forge \textit{3.148}. The charged intermediate is reduced by Schwartz reagent and the tertiary alcoholate initiates retro-aldol fragmentation of the bicyclic system to deliver intermediate \textit{3.150}. Sequential ketalization leads to intermediate \textit{3.152}, which upon 1,5-silyl shift is converted to the aldehyde \textit{3.153}. The aldehyde is reduced with the third equivalent of Schwartz reagent and subsequent transacetalization delivers the isolated product \textit{3.140}. Subjecting \textit{3.140} to one equivalent of sodium cyanoborohydride in acidic conditions results in the reduction of the latent aldehyde to furnish \textit{3.142} (Scheme 80).

The above detailed mechanism may explain the formation of **3.128** upon the treatment of **3.123** with lithium aluminumhydride (Table 24, Entry 7). However, it remains difficult to explain the survival of the ketone unit. Most likely it stays in the (hemi)ketal form and only upon exposure to silica gel or aqueous work-up is the ketone liberated. While the reduction with Schwartz reagent results in the formation of a stable and isolable hemiketal (**3.140**), the hypothetic (hemi)ketal precursor of **3.128** could not be isolated or observed in any form.
3.3 Conclusion

In our pursuit towards the voacafricine alkaloids we devised and followed a divergent and potentially enantioselective strategy. We successfully developed a synthetic route to reach the key $\alpha$-ketolactam intermediate $\text{3.44}$ in 5-steps. The sequence begins with a Pictet-Spengler cyclization followed by spontaneous condensation to furnish $\text{3.40}$. Our preliminary experiments indicated that the transformation can be rendered enantioselective and further optimization can potentially lead to reach high stereoselectivity. The robust sequence leading to the $\alpha$-oximinolactam intermediate ($\text{3.59}$) allowed us to access hands on a wide array of oxime derivatives and our studies on their deoxymation led to identifying conditions for the unmasking of the elusive ketone $\text{3.44}$. With this key intermediate in hand we were able to explore its chemistry en route to voacafricine A and voacafricine B. Despite our efforts, we were not able to construct ring F, the last key motif in the natural products (Scheme 81).
We hypothesize that the boat conformation of the seven-membered lactam ring in 3.123 was the major source of our troubles in installing the F ring. On the one hand, the boat conformation aligned the α-keto unit proximal to the ester function, thereby facilitating reaction between the two functional groups. On the other hand, upon Si-face selective 1,2-addition of nucleophiles onto the ketone, the generated alcolholate ended up in a sterically inaccessible position, in a “cage”, preventing any further transformation at the oxygen centre.
We hypothesize that controlling the conformation of the lactam ring is the key to progress with the total synthesis. Epimerization of the C14 stereocenter can potentially change the conformation of the lactam ring and change the reactivity of the crucial oxetane-orthoester moiety.

We surmise, that control over the conformation of the lactam ring is predominantly governed by the pseudo-axial dimethoxyacetal group. Liberation of the aldehyde followed by α-epimerization-reduction sequence could potentially change the conformation and thereby the reactivity of the molecule. Furthermore, the epimerization would set the C14 stereocenter to the correct configuration, as observed in the natural products. Both conformation of the lactam ring can be leveraged, if the epimerization step is performed on 3.123, as this compound is obtained as the exclusive diastereoisomer of the Mukaiyama aldol reaction (Scheme 82). Work towards the total synthesis of voacafricine A and voacafricine B are underway and may focus on the conformational manipulation of the seven-membered lactam ring to allow the elaboration of the F ring and complete the synthesis.
Chapter 3 - Towards the Total Synthesis of Voacaficine A and Voacaficine B
Chapter 4  Experimental part

General Information

Reagents and solvents were purchased from commercial sources (Aldrich, Acros, Merck, Fluka and VWR international) and preserved under argon. Sensitive compounds were stored in a desiccator or glove box if required. Reagents were used without further purification unless otherwise noted. All reactions were performed under argon (or nitrogen) unless otherwise noted. When needed, glassware was dried overnight in an oven (T > 100 °C) or in vacuo with a heat gun (T > 200 °C).

When solvents are indicated as dry they were purchased as such, either distilled prior to use or were dried by a passage through a column of anhydrous alumina or copper using a Puresolv MD 5 from Innovative Technology Inc., based on the Grubb’s design. Flash column chromatography was performed using Silicycle P60 silica: 230-400 mesh (40-63 μm) silica. Reactions were monitored using Merck Kieselgel 60F254 aluminum or glass backed plates. TLC’s were visualized by UV fluorescence (254 nm) then one of the following: KMnO4, Seebach’s reagent, phosphomolybdic acid, ninhydrin, pancaldi, p-anisaldehyde or vanillin.

NMR spectra were recorded on a Brüker Avance III-400, Brüker Avance-400, Bruker Avance II-800 or Brüker DRX-400 spectrometer at room temperature. 1H frequency is at 400.13 MHz, 13C frequency is at 100.62 MHz. Chemical shifts (δ) were reported in parts per million (ppm) relative to residual solvent peaks rounded to the nearest 0.01 ppm for proton and 0.1 ppm for carbon (ref: CHCl3 [1H: 7.26 ppm, 13C: 77.16 ppm], C6D6 [1H: 7.16 ppm, 13C: 128.39 ppm], MeOH [1H: 3.31 ppm, 13C: 49.0 ppm]). Coupling constants (J) were reported in Hz to the nearest 0.1 Hz. Peak multiplicity was indicated as follows s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet) and br (broad). Attribution of peaks was done using the multiplicities and integrals of the peaks. When needed, a COSY, HSQC and HMBC experiments were used to confirm the attribution.

IR spectra were recorded in a Jasco FT/IR-4100 spectrometer outfitted with a PIKE technology MIRacleTM ATR accessory as neat films compressed onto a Zinc Selenide window. The spectra are reported in cm⁻¹. Abbreviations used are: w (weak), m (medium), s (strong) and br (broad).

Mass spectra were obtained by using a Waters ACQUITY H-class UPLC/MS ACQ-SQD by electron ionization (EI positive and negative) or a Finnigan TSQ7000 by electrospray ionization (ESI+). The accurate masses were measured by the mass spectrometry service of the EPFL by ESI-TOF using a QTOF Ultima from Waters.

Melting points are uncorrected and were recorded on a Stuart SMP30 melting point apparatus.
GC-MS/FID experiments were performed on a Perkin Elmer Clarus 580 GC-FID instrument and Perkin Elmer Clarus SQ 8 mass spectrometer. For quantitative measurements toluene was used as internal standard.

For all general procedures the order of addition of reagents has to be respected.

When a rigorously inert and dry atmosphere was needed the reaction was carried out in a PureLab HE 4GB 2500 Glove-box System from Innovative Technologies inc.
4.1 Experimental procedures and characterization data for Chapter 1

4.1.1 Synthesis and characterization of diketimine ligands

2,6-dichloro-N-((2Z,4E)-4-((2,6-dichlorophenyl)imino)pent-2-en-2-yl)aniline (1.L1)

2,6-dichloro-N-((2Z,4E)-4-((2,6-dichlorophenyl)imino)pent-2-en-2-yl)aniline was prepared according to a literature procedure.¹

Yield: 62%, White solid

¹H NMR (400 MHz, CDCl₃) δ 12.15 (s, 1H), 7.32 (d, J = 8.0 Hz, 4H), 7.00 (t, J = 8.1 Hz, 2H), 5.07 (s, 1H), 1.84 (s, 6H).

¹³C NMR (101 MHz, CDCl₃) δ 162.8, 140.9, 131.5, 128.3, 125.9, 95.6, 21.1.

IR (νmax, cm⁻¹) 2955 (m), 1629 (s), 1548 (s), 1434 (s), 1370 (m), 1287 (m), 1191 (m), 1072 (w), 1024 (m), 908 (w), 876 (w), 846 (w), 817 (w), 778 (m), 729 (m), 681 (m), 656 (s)

HRMS (ESI/QTOF) m/z calcd for C₁₇H₁₅Cl₄N₂⁺ [M + H]⁺ 386.9984; Found 386.9991.

2,6-dibromo-N-((2Z,4E)-4-((2,6-dibromophenyl)imino)pent-2-en-2-yl)aniline (1.L2)

2,6-dibromo-N-((2Z,4E)-4-((2,6-dibromophenyl)imino)pent-2-en-2-yl)aniline was prepared according to a literature procedure.¹
Yield: 69%, grey solid

Melting point: 95-96°C

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 12.05 (s, 1H), 7.54 (d, $J = 8.0$ Hz, 4H), 6.86 (t, $J = 8.0$ Hz, 2H), 5.05 (s, 1H), 1.83 (s, 6H).

$^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 162.6, 143.5, 132.1, 126.9, 121.6, 94.9, 21.2.

IR $\nu$ (cm$^{-1}$) 2917 (w), 2358 (w), 1622 (s), 1543 (s), 1426 (s), 1275 (m), 1189 (m), 771 (m), 724 (s).

HRMS (ESI): m/z calcd for C$_{17}$H$_{15}$Br$_4$N$_2^+$ ([M + H]$^+$): 562.7963; found: 562.7960.

$N$-((2Z,4E)-4-((2,6-diisopropylphenyl)imino)pent-2-en-2-yl)-2,6-diisopropylaniline (1.L3)

$N$-((2Z,4E)-4-((2,6-diisopropylphenyl)imino)pent-2-en-2-yl)-2,6-diisopropylaniline was prepared according to a literature procedure.$^2$ The spectroscopic data were consistent with those previously reported in the literature.$^2$

4-methoxy-$N$-((2Z,4E)-4-((4-methoxyphenyl)imino)pent-2-en-2-yl)aniline (1.L4)

was prepared according to a literature procedure.REF The spectroscopic data were consistent with those previously reported in the literature. REF

2-methoxy-$N$-((2Z,4E)-4-((2-methoxyphenyl)imino)pent-2-en-2-yl)aniline (1.L5)
2-methoxy-N-((2Z,4E)-4-((2-methoxyphenyl)imino)pent-2-en-2-yl)aniline was prepared according to a literature procedure.\textsuperscript{1,3}

All spectroscopic data matched with the reported values.\textsuperscript{3}

Yield: 15\%, yellow oil

\textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}) δ 12.72 (s, 1H), 7.06 – 6.95 (m, 4H), 6.94 – 6.84 (m, 4H), 4.93 (s, 1H), 3.78 (s, 6H), 1.98 (s, 6H).

\textsuperscript{13}C NMR (101 MHz, CDCl\textsubscript{3}) δ 160.1, 151.4, 135.5, 123.7, 123.2, 120.6, 111.5, 98.1, 55.9, 21.3.

IR ν (cm\textsuperscript{-1}) 2958 (w), 1596 (m), 1549 (s), 1481 (m), 1280 (s), 1143 (s), 1042 (m), 850 (m), 752 (m).

HRMS (ESI): m/z calcd for C\textsubscript{19}H\textsubscript{23}N\textsubscript{2}O\textsubscript{2} ([M + H]\textsuperscript{+}): 311.1759; found: 311.1757.

3-methoxy-N-((2Z,4E)-4-((3-methoxyphenyl)imino)pent-2-en-2-yl)aniline (1.L6)

3-methoxy-N-((2Z,4E)-4-((3-methoxyphenyl)imino)pent-2-en-2-yl)aniline was prepared according to a literature procedure.\textsuperscript{4}

\textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}) δ 12.60 (s, 1H), 7.19 (t, \textit{J} = 8.0 Hz, 2H), 6.62 (ddd, \textit{J} = 8.3, 2.6, 1.0 Hz, 2H), 6.56 (ddd, \textit{J} = 7.8, 2.0, 0.9 Hz, 2H), 6.52 (t, \textit{J} = 2.2 Hz, 2H), 4.87 (s, 1H), 3.79 (s, 6H), 2.01 (s, 6H), 1.54 (s, 2H).

\textsuperscript{13}C NMR (101 MHz, CDCl\textsubscript{3}) δ 160.26, 159.70, 147.19, 129.63, 115.30, 109.00, 108.48, 97.62, 55.44, 21.09.
IR: ν (cm$^{-1}$) 2958 (w), 1596 (m), 1549 (s), 1481 (m), 1280 (s), 1143 (s), 1042 (m), 850 (m), 752 (m).

**HRMS (ESI):** m/z calcd for ([M + H]$^+$): 311.1754; found: 311.1754.

$N$-((2Z,4E)-4-(phenylimino)pent-2-en-2-yl)aniline (1.L7)

$N$-((2Z,4E)-4-(phenylimino)pent-2-en-2-yl)aniline was prepared according to a literature procedure.$^4$ The spectroscopic data were consistent with those previously reported in the literature.$^4$

2-chloro-$N$-((2Z,4E)-4-((2-chlorophenyl)imino)pent-2-en-2-yl)aniline (1.L8)

2-chloro-$N$-((2Z,4E)-4-((2-chlorophenyl)imino)pent-2-en-2-yl)aniline was prepared according to a literature procedure.$^1$ The spectroscopic data were consistent with those previously reported in the literature.$^5$

2-bromo-$N$-((2Z,4E)-4-((2-bromophenyl)imino)pent-2-en-2-yl)aniline (1.L9)
2-bromo-N-((2Z,4E)-4-((2-bromophenyl)imino)pent-2-en-2-yl)aniline was prepared according to a literature procedure.\textsuperscript{1} The spectroscopic data were consistent with those previously reported in the literature.\textsuperscript{5}

\textbf{4-(trifluoromethyl)-N-((2Z,4E)-4-((4-(trifluoromethyl)phenyl)imino)pent-2-en-2-yl)aniline (1.L10)}

\begin{center}
\includegraphics[width=0.3\textwidth]{1.L10}
\end{center}

4-(trifluoromethyl)-N-((2Z,4E)-4-((4-(trifluoromethyl)phenyl)imino)pent-2-en-2-yl)aniline was prepared according to a literature procedure.\textsuperscript{6} The spectroscopic data were consistent with those previously reported in the literature.\textsuperscript{6}

\textbf{N-((2Z,4Z)-1,1,5,5,5-hexafluoro-4-(phenylimino)pent-2-en-2-yl)aniline (1.L11)}

\begin{center}
\includegraphics[width=0.3\textwidth]{1.L11}
\end{center}

\(\text{TiCl}_4\) (1.1 mL, 10 mmol) in 10 mL of toluene was added dropwise to a solution of aniline (7.3 mL, 80 mmol) in 50 mL of toluene. The resulting mixture was stirred at 90 °C for 30 min followed by the addition of 1,1,5,5,5-hexafluoroacetylacetone (1.41 mL, 20 mmol). The reaction mixture was stirred overnight, poured into dilute Na\textsubscript{2}CO\textsubscript{3} solution, and extracted with methylene chloride. The organic phase was dried over Na\textsubscript{2}SO\textsubscript{4} and the volatiles were removed under vacuum. The residue was dissolved in ether and treated with concentrated hydrochloric acid at 0 °C. Subsequently, the white precipitate was removed by filtration. The filtrate was washed with dilute Na\textsubscript{2}CO\textsubscript{3} solution, dried over anhydrous Na\textsubscript{2}SO\textsubscript{4}, and evaporated. The crude product was purified by column chromatography on silica gel with petroleum ether as the eluent.
Yield: 20%, yellow oil

All the spectroscopic data matched with the reported values.\(^4\)

\(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 12.07 (s, 1H), 7.35 (t, \(J = 7.9\) Hz, 4H), 7.22 (t, 2H), 7.07 (d, \(J = 7.8\) Hz, 4H), 5.90 (s, 1H).

\(^{13}\)C NMR (101 MHz, CDCl\(_3\)) \(\delta\) 149.2 (q, \(J = 29.8\) Hz), 142.8, 128.9, 125.9, 122.9, 119.2 (q, \(J = 283.6\) Hz), 88.9 (sept, \(J = 4.8\) Hz).

2-chloro-N-((2Z,4Z)-4-((2-chlorophenyl)imino)-1,1,5,5,5-hexafluoropent-2-en-2-yl)aniline (1.L12)

2-chloro-N-((2Z,4Z)-4-((2-chlorophenyl)imino)-1,1,5,5,5-hexafluoropent-2-en-2-yl)aniline was prepared according to a literature procedure.\(^7\) The spectroscopic data were consistent with those previously reported in the literature.\(^7\)

2,6-dichloro-N-((2Z,4Z)-4-((2,6-dichlorophenyl)imino)-1,1,5,5,5-hexafluoropent-2-en-2-yl)aniline (1.L13)

Step 1

To a mixture of 2,6-dichloroaniline (6.48 g, 0.04 mol) and 15% HCl (40 mL), NaNO\(_2\) (3.31 g, 0.048 mol) in H\(_2\)O (50 mL) was added dropwise at 0°C. After the completion of addition, the reaction mixture was stirred at this temperature for 30 min. A solution of sodium azide (4.22 g, 0.065 mol in 15 mL H\(_2\)O) was added dropwise to the reaction mixture at 0°C. After addition the reaction mixture was maintained at 0°C for 1 h. The product was extracted by using ethyl acetate followed by washing...
with water up to neutral pH. Organic layer was dried with anhydrous sodium sulfate and then concentrated by distillation to afford as yellow oil. The crude mixture was passed through silica gel with hexane to obtain 6.9 g light yellow oil.

**Step 2**

Under a nitrogen atmosphere a chilled (-35°C) solution of 2,6-dichlorophenylazide (1 g, 5.32 mmol) in 2 mL of THF was added slowly to a chilled (-35°C) solution trimethylphosphine (5.32 mL of a 1.0 M solution in THF, 5.32 mmol). Rapid gas evolution was observed. The yellow solution was allowed to stand for 20 minutes at room temperature. All volatiles were removed from the crude product in vacuo. The product was used as is for the following steps.

**Step 3**

Under a nitrogen atmosphere, the product of **Step 2** in 3 mL toluene and 1,1,1,5,5,5-hexafluoropentadione (0.748 ml, 5.27 mmol) in 3 mL of toluene were added together inside a glass pressure vessel. The pressure vessel was sealed and heated for 108 hours at 100 °C. The brown reaction was concentrated to remove all volatiles. The brown remaining oil was purified via column chromatography using 30:1 hexane:toluene as the mobile phase. The first, bright yellow fraction was collected. Crystallization from methanol at -20 °C afforded bright yellow crystals in 6% yield over three steps (269 mg; 0.543 mmol).

The spectroscopic data were consistent with those previously reported in the literature.\(^8\)

\[ N-((2Z,4E)-4-((2,6-dimethylphenyl)imino)-3-methylpent-2-en-2-yl)-2,6-dimethylaniline (1.L14) \]

\[ N-((2Z,4E)-4-((2,6-dimethylphenyl)imino)-3-methylpent-2-en-2-yl)-2,6-dimethylaniline \] was prepared according to a literature procedure.\(^7\) The spectroscopic data were consistent with those previously reported in the literature.\(^7\)

Yield: 17% (white amorphous solid)

Melting point: 55°C

\(^1\)H NMR (400 MHz, CDCl\(_3\)) \( \delta \) 7.02 (d, \( J = 7.5 \) Hz, 5H), 6.89 (t, \( J = 7.5 \) Hz, 2H), 2.02 (s, 12H), 1.76 (s, 6H), 1.59 (d, \( J = 7.0 \) Hz, 3H).
$^{13}$C NMR (101 MHz, CDCl$_3$) δ 171.43, 148.64, 128.18, 128.13, 125.79, 122.97, 55.80, 18.69, 18.29, 18.24, 15.72, 93

IR: ν (cm$^{-1}$) 2915 (w), 2360 (s), 1607 (m), 1531 (s), 1466 (m), 1268 (w), 1212 (w), 987 (w), 763 (s).


4.1.2 General procedure A for the synthesis of the starting materials

Methyltriphenylphosphonium bromide (0.12 mmol) was added to a flame-dried round-bottom flask, evacuated, backfilled with nitrogen three times, and suspended in Et$_2$O (0.30 M). To this vigorously stirred heterogeneous solution was added KOTBu (0.12 mmol) at 0°C and the reaction was allowed to stir at room temperature for 30 min until a bright yellow heterogeneous mixture was achieved. The resulting suspension was cooled to 0 °C, and the appropriate ketone/aldehyde (0.1 mmol) was added slowly so as to avoid flash boiling of the ethereal solvent. Upon complete addition, the cooling bath was removed, and the reaction was allowed to stir for ~15 h before filtering through Celite and concentrating. The crude material was purified by silica gel column chromatography using hexane as eluent.

Prop-1-en-2-ylbenzene (1.89)

Prop-1-en-2-ylbenzene was purchased from Sigma Aldrich.

1-methyl-4-(prop-1-en-2-yl)benzene (1.95b)
1-methyl-4-(prop-1-en-2-yl)benzene was purchased from Sigma Aldrich.

\[
\text{1-methyl-3-(prop-1-en-2-yl)benzene (1.95c)}
\]

1-methyl-3-(prop-1-en-2-yl)benzene was prepared according to general procedure A. The spectroscopic data were consistent with those previously reported in the literature.\(^9\)

\[
\text{1-fluoro-4-(prop-1-en-2-yl)benzene (1.95d)}
\]

1-fluoro-4-(prop-1-en-2-yl)benzene was prepared according to general procedure A. The spectroscopic data were consistent with those previously reported in the literature.\(^10\)

\[
\text{But-1-en-2-ylbenzene (1.95e)}
\]
But-1-en-2-ylbenzene was prepared according to general procedure A. The spectroscopic data were consistent with those previously reported in the literature.\(^9\)

\[(3\text{-methylbut-1-en-2-yl})\text{benzene (1.95f)}\]

(3-methylbut-1-en-2-yl)benzene was prepared according to general procedure A. The spectroscopic data were consistent with those previously reported in the literature.\(^{11}\)

\[(1\text{-cyclohexylvinyl})\text{benzene (1.95g)}\]

(1-cyclohexylvinyl)benzene was prepared according to general procedure A. The spectroscopic data were consistent with those previously reported in the literature.\(^9\)

\[4\text{-methyl-N-(2-phenylallyl)benzenesulfonamide (1.95h)}\]
4-methyl-N-(2-phenylallyl)benzenesulfonamide was prepared from alpha-methylstyrene in a two-step process. Alpha-methylstyrene was brominated according to a reported procedure. To a solution of alpha-methylstyrene (4.6 g, 39 mmol, 1.0 equiv) in 6 mL CHCl₃ was added NBS (8.0 g, 45 mmol, 1.15 equiv). The mixture was stirred and heated to reflux for 4 h. Then the reaction mixture was concentrated and petroleum ether was added. The precipitate that had formed was filtered off and then the organic layer was dried over Na₂SO₄ and concentrated under vacuo. The crude product was purified by column chromatography (petroleum ether) to give the allylbromide (7.1 g, 36 mmol, 92% yield) as a colorless liquid.

To a solution of the above obtained allyl bromide (500 mg, 2.54 mmol, 1 equiv) in MeCN (8 mL) at 80 °C were added K₂CO₃ (690 mg, 5.07 mmol, 2.0 equiv), KI (42 mg, 0.25 mmol, 10 mol %) and TsNH₂ (856 mg, 5.07 mmol, 2.0 equiv). The mixture was stirred at reflux for 8 hours. After successive filtration and purification by flash column chromatography on silica gel (petroleum ether-ethyl acetate, 4:1), 4-methyl-N-(2-phenylallyl)benzenesulfonamide (533 mg, 73% yield) was obtained as an orange amorphous solid. All spectroscopic data matched with the reported values.

**Ethene-1,1-diyl dibenzene (1.95i)**

Ethene-1,1-diyl dibenzene was purchased from SigmaAldrich.

**1-nitro-4-(1-phenylvinyl)benzene (1.95j)**
1-nitro-4-(1-phenylvinyl)benzene was prepared according to literature procedure.\textsuperscript{14} The spectroscopic data were consistent with those previously reported in the literature.\textsuperscript{15}

\chem{4,4'-(ethene-1,1-diyil)bis(fluorobenzene)} (1.95k)

4,4\textsuperscript{'-}(ethene-1,1-diyl)bis(fluorobenzene) was prepared according to general procedure A. The spectroscopic data were consistent with those previously reported in the literature.\textsuperscript{9}

\chem{4,4'-(ethene-1,1-diyil)bis(chlorobenzene)} (1.95l)

4,4\textsuperscript{'-}(ethene-1,1-diyl)bis(chlorobenzene) was prepared according to general procedure A. The spectroscopic data were consistent with those previously reported in the literature.\textsuperscript{9}

\chem{1-chloro-3-(1-phenylvinyl)benzene} (1.95m)
1-chloro-3-(1-phenylvinyl)benzene was prepared according to a literature procedure.\(^9\)

Styrene (1\textit{u}), 1-methyl-4-vinylbenzene (1\textit{v}) and 1-methoxy-4-vinylbenzene (1\textit{w}) were purchased from Sigma Aldrich or TCI Co. Ltd.

\textbf{1-fluoro-4-(1-phenylvinyl)benzene (1.95n)}

1-fluoro-4-(1-phenylvinyl)benzene was prepared according to a literature procedure.\(^9\)

\textbf{1-bromo-4-(1-phenylvinyl)benzene (1.95o)}

1-bromo-4-(1-phenylvinyl)benzene was prepared according to a literature procedure.\(^9\)

\textbf{Ethyl 4-(1-phenylvinyl)benzoate (1.95p)}
1-bromo-4-(1-phenylvinyl)benzene was prepared according to literature procedure. The spectroscopic data were consistent with those previously reported in the literature.

4-(1-phenylvinyl)benzonitrile (1.95q)

4-(1-phenylvinyl)benzonitrile was prepared according to literature procedure. The spectroscopic data were consistent with those previously reported in the literature.

1-(1-phenylvinyl)-4-(trifluoromethyl)benzene (1.95r)

1-(1-phenylvinyl)-4-(trifluoromethyl)benzene was prepared according to literature procedure. The spectroscopic data were consistent with those previously reported in the literature.

1-(1-phenylvinyl)-3-(trifluoromethyl)benzene (1.95s)
1-(1-phenylvinyl)-3-(trifluoromethyl)benzene was prepared according to a literature procedure.\textsuperscript{9}

1-methyl-3-(1-phenylvinyl)benzene (1.95t)

1-(1-phenylvinyl)-3-(trifluoromethyl)benzene was prepared according to a literature procedure.\textsuperscript{9}

1,2-dimethoxy-4-vinylbenzene (1.95x)

1,2-dimethoxy-4-vinylbenzene was prepared according to general procedure A. The spectroscopic data were consistent with those previously reported in the literature.\textsuperscript{19}

Styrene (1.95u), 4-methylstyrene (1.95v), 4-methoxystyrene (1.95w), 1-Fluoro-4-vinylbenzene (1.95y), 1-chloro-4-vinylbenzene (1.95z) and 1-bromo-4-vinylbenzene (1.95aa) were purchased from Sigma Aldrich or TCI Co. Ltd.
4.1.3 General procedure B for the synthesis of beta-methoxy esters 1.96a – 1.96aa

Glassware and stirring bar were stored in the oven and the reaction was carried out under inert atmosphere and dry conditions.\(^{150}\) Into a Pyrex 10 mL sealed tube was prepared a solution of copper(II) triflate (9 mg, 0.025 mmol, 0.1 equiv), \(\text{L}1\) (9.7 mg, 0.025 mmol, 0.1 equiv) and 2.5 mL of dry, degassed methyl formate. The solution was stirred at room temperature for 3 minutes or until the solution was homogeneous and had dark green color. The substrate (1) (0.25 mmol, 1 equiv) and tert-butyl-peracetate (319 µL, 1 mmol, 50% solution in mineral spirits, Sigma Aldrich\(^{®}\)) was added to the reaction mixture. The sealed tube was placed into a preheated metallic block heater at the indicated temperature for the indicated time (see Table 26, Table 25 and Table 27). The reaction mixture was cooled to room temperature with an ice-bath and was diluted with diethyl ether. The organic phase was washed with 2.5 M ammonium acetate, saturated sodium bicarbonate solution and with brine. The combined aqueous phases were extracted 3 times with ether and the organic phases were combined, dried over anhydrous \(\text{Na}_2\text{SO}_4\) and concentrated under reduced pressure. The crude mixture must not be stored for long time. The obtained crude mixture was purified by flash column chromatography (\(\text{SiO}_2\), petroleum ether/ether 10/1 \(\rightarrow\) 8/1, unless otherwise noted). Dry-loading has to be avoided, toluene was used for the dissolution of the crude mixture and their introduction onto the column.

**Gram scale procedure for the synthesis of methyl 3-methoxy-3-phenylbutanoate (2a)**

![Chemical structure](image)

Glassware and stirring bar were stored in the oven and the reaction was carried out under inert atmosphere and dry conditions. Into a 100 mL pressure resistant round bottomed flask was prepared a solution of copper(II) triflate (153 mg, 0.42 mmol, 0.05 equiv), \(\text{L}1\) (164 mg, 0.42 mmol, 0.05 equiv) and 60 mL of dry, degassed methyl formate. The solution was stirred at room temperature for 3 minutes or until the solution became homogeneous and had dark green color. \(\alpha\)-Methyl styrene (\(\text{1.89}\)) (1.0 g, 8.47 mmol, 1 equiv) and tert-butyl peracetate (5.4 mL, 16.9 mmol, 2 equiv, 50% solution in mineral spirits, Sigma Aldrich\(^{®}\)) was added to the reaction mixture. The sealed tube

\(^{150}\) Reaction can also be carried out under air, but there is a loss of yield around 10%.
was placed into a preheated oil bath at 75 °C for 30 min. The reaction mixture was cooled to room temperature with an ice-bath and was added a solution of copper(II) triflate (153 mg, 0.42 mmol, 0.05 equiv), 1.L1 (164 mg, 0.42 mmol, 0.05 equiv), tert-butyl peracetate (5.4 mL, 16.9 mmol, 2 equiv, 50% solution in mineral spirits, Sigma Aldrich®) and 10 mL of dry, degassed methyl formate. The flask was placed back into the oil bath at 75 °C and was stirred for an additional hour. The reaction mixture was then cooled to room temperature with an ice-bath and the organic phase was washed with 2.5 M ammonium acetate, saturated sodium bicarbonate solution and with brine. The combined aqueous phases were extracted 3 times with ether and the organic phases were combined, dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The crude mixture must not be stored for long time. The obtained crude mixture was purified by flash column chromatography (SiO₂, petroleum ether/ethyl acetate/triethylamine 100/3.5/0.2). Dry-loading has to be avoided, toluene was used for the introduction. Rf (petroleum ether/ethyl acetate 10/1)=0.42. Yield (1.96a): 1.27 g (72%) yellow oil.

**Gram scale procedure for the synthesis of methyl 3-methoxy-3,3-diphenylpropanoate (1.96i)**

Glassware and stirring bar were stored in the oven and the reaction was carried out under inert atmosphere and dry conditions. Into a 100 mL pressure resistant round bottomed flask was prepared a solution of copper(II) triflate (100 mg, 0.28 mmol, 0.05 equiv), 1.L1 (108 mg, 0.28 mmol, 0.05 equiv) and 45 mL of dry, degassed methyl formate. The solution was stirred at room temperature for 3 minutes or until the solution became homogeneous and had dark green color. Ethene-1,1-diyl dibenzene (1.95i) (1.0 g, 5.55 mmol, 1 equiv) and tert-butyl peracetate (3.54 mL, 11.1 mmol, 2 equiv, 50% solution in mineral spirits, Sigma Aldrich®) was added to the reaction mixture. The sealed tube was placed into a preheated oil bath at 65 °C for 1 h. The reaction mixture was cooled to room temperature with an ice-bath and was added a solution of copper(II) triflate (100 mg, 0.28 mmol, 0.05 equiv), 1.L1 (108 mg, 0.28 mmol, 0.05 equiv), tert-butyl peracetate (3.54 mL, 11.1 mmol, 2 equiv, 50% solution in mineral spirits, Sigma Aldrich®) and 10 mL of dry, degassed methyl formate. The flask was placed back into the oil bath at 65 °C and was stirred for two additional hours. The reaction mixture was then cooled to room temperature with an ice-bath and the organic phase was washed with 2.5 M ammonium acetate, saturated sodium bicarbonate solution and with brine. The
combined aqueous phases were extracted 3 times with ether and the organic phases were combined, dried over anhydrous Na$_2$SO$_4$ and concentrated under reduced pressure. The crude mixture must not be stored for long time. The obtained crude mixture was purified by flash column chromatography (SiO$_2$, petroleum ether/ethylacetate/triethylamine 100/3.1/0.25). Dry-loading has to be avoided, toluene was used for the introduction. Rf (petroleum ether/ethyl acetate 10/1)=0.40. Yield (1.96i): 1.08 g (72%) yellow oil.

**Gram scale procedure for the synthesis of methyl 3-methoxy-3-phenylpropanoate (2u)**

Glassware and stirring bar were stored in the oven and the reaction was carried out under inert atmosphere and dry conditions. Into a 100 mL pressure resistant round bottomed flask was prepared a solution of copper(II) triflate (174 mg, 0.96 mmol, 0.05 equiv), 1.11 (187 mg, 0.96 mmol, 0.05 equiv) and 75 mL of dry, degassed methyl formate. The solution was stirred at room temperature for 3 minutes or until the solution became homogeneous and had dark green color. Styrene (1.95u) (1.0 g, 9.61 mmol, 1 equiv) and tert-butyl peracetate (6.1 mL, 19.2 mmol, 2 equiv, 50% solution in mineral spirits, Sigma Aldrich®) was added to the reaction mixture. The sealed tube was placed into a preheated oil bath at 65 °C for 1 h. The reaction mixture was cooled to room temperature with an ice-bath and was added a solution of copper(II) triflate (174 mg, 0.96 mmol, 0.05 equiv), 1.11 (187 mg, 0.96 mmol, 0.05 equiv), tert-butyl peracetate (6.1 mL, 19.2 mmol, 2 equiv, 50% solution in mineral spirits, Sigma Aldrich®) and 10 mL of dry, degassed methyl formate. The flask was placed back into the oil bath at 65 °C and was stirred for two additional hours. The reaction mixture was then cooled to room temperature with an ice-bath and the organic phase was washed with 2.5 M ammonium acetate, saturated sodium bicarbonate solution and with brine. The combined aqueous phases were extracted 3 times with ether and the organic phases were combined, dried over anhydrous Na$_2$SO$_4$ and concentrated under reduced pressure. The crude mixture must not be stored for long time. The obtained crude mixture was purified by flash column chromatography (SiO$_2$, petroleum ether/ether 25/1). Dry-loading has to be avoided, toluene was used for the introduction. Yield (1.96u): 1.03 g (53%) yellow oil.
<table>
<thead>
<tr>
<th>Structure</th>
<th>Temperature (°C)</th>
<th>Reaction time (h)</th>
<th>Isolated yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.96a</td>
<td>75 °C</td>
<td>1</td>
<td>77%</td>
</tr>
<tr>
<td>1.96b</td>
<td>75 °C</td>
<td>1</td>
<td>79%</td>
</tr>
<tr>
<td>1.96c</td>
<td>75 °C</td>
<td>1</td>
<td>76%</td>
</tr>
<tr>
<td>1.96d</td>
<td>75 °C</td>
<td>1</td>
<td>73%</td>
</tr>
<tr>
<td>1.96e</td>
<td>75 °C</td>
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<td>70%</td>
</tr>
<tr>
<td>1.96f</td>
<td>75 °C</td>
<td>1</td>
<td>58%</td>
</tr>
<tr>
<td>1.96g</td>
<td>75 °C</td>
<td>1</td>
<td>59%</td>
</tr>
<tr>
<td>1.96h</td>
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Table 25 - Alpha-alkylstyrene derivatives
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<th>Temperature (°C)</th>
<th>Reaction time (h)</th>
<th>Isolated yield (%)</th>
</tr>
</thead>
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<tr>
<td>1.96i</td>
<td><img src="image1" alt="Structure 1.96i" /></td>
<td>65 °C</td>
<td>2</td>
<td>70%</td>
</tr>
<tr>
<td>1.96j</td>
<td><img src="image2" alt="Structure 1.96j" /></td>
<td>85 °C</td>
<td>1</td>
<td>69%</td>
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<td><img src="image3" alt="Structure 1.96n" /></td>
<td>75 °C</td>
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<td>83%</td>
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<td>1.96o</td>
<td><img src="image4" alt="Structure 1.96o" /></td>
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<td>67%</td>
</tr>
<tr>
<td>1.96p</td>
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</tr>
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<td>1.96q</td>
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<td>68%</td>
</tr>
<tr>
<td>1.96r</td>
<td><img src="image7" alt="Structure 1.96r" /></td>
<td>65 °C</td>
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<td>57%</td>
</tr>
<tr>
<td>1.96s</td>
<td><img src="image8" alt="Structure 1.96s" /></td>
<td>75 °C</td>
<td>1</td>
<td>62%</td>
</tr>
<tr>
<td>1.96t</td>
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<td>65 °C</td>
<td>2</td>
<td>44%</td>
</tr>
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</table>
Chapter 4 - Experimental part

| 1.96k | \[
\begin{align*}
\text{MeO}-\text{COOMe} \\
\text{F} & \quad \text{F}
\end{align*}
\] | 75 °C | 1.5 | 67% |
| 1.96l | \[
\begin{align*}
\text{MeO}-\text{COOMe} \\
\text{Cl} & \quad \text{Cl} & \quad \text{Cl}
\end{align*}
\] | 75 °C | 1.5 | 54% |
| 1.96m | \[
\begin{align*}
\text{MeO}-\text{COOMe} \\
\text{Cl} & \quad \text{Cl}
\end{align*}
\] | 75 °C | 1.5 | 60% |

Table 26 – 1,1-diarylethylene derivatives
<table>
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<tr>
<th>##</th>
<th>Structure</th>
<th>Temperature (°C)</th>
<th>Reaction time (h)</th>
<th>Isolated yield (%)</th>
</tr>
</thead>
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<td>1</td>
<td>58%</td>
</tr>
<tr>
<td>1.96v</td>
<td><img src="image2" alt="Structure" /></td>
<td>65 °C</td>
<td>2</td>
<td>66%</td>
</tr>
<tr>
<td>1.96w</td>
<td><img src="image3" alt="Structure" /></td>
<td>65 °C</td>
<td>1</td>
<td>60%</td>
</tr>
<tr>
<td>1.96x</td>
<td><img src="image4" alt="Structure" /></td>
<td>65 °C</td>
<td>1</td>
<td>63%</td>
</tr>
<tr>
<td>1.96y</td>
<td><img src="image5" alt="Structure" /></td>
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<td>54%</td>
</tr>
<tr>
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</tr>
<tr>
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<td>65 °C</td>
<td>3</td>
<td>53%</td>
</tr>
</tbody>
</table>

*Table 27 - Styrene derivatives*
Methyl 3-methoxy-3-phenylbutanoate (1.96a)

Yield: 77% (40 mg), yellow oil

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.41 – 7.32 (m, 4H), 7.29 – 7.24 (m, 1H), 3.57 (s, 3H), 3.08 (s, 3H), 2.83 (d, $J = 13.7$ Hz, 1H), 2.73 (d, $J = 13.7$ Hz, 1H), 1.73 (s, 3H).

$^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 170.9, 143.7, 128.4, 127.5, 126.2, 77.9, 51.6, 50.7, 47.7, 23.1.

All the spectroscopic data were in accordance with those reported in the literature.²⁰

Methyl 3-methoxy-3-(p-tolyl)butanoate (1.96b)

Yield: 79% (44 mg), colorless oil

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.30 – 7.26 (m, 2H), 7.20 – 7.12 (m, 2H), 3.59 (s, 3H), 3.08 (s, 3H), 2.83 (d, $J = 13.7$ Hz, 1H), 2.73 (d, $J = 13.7$ Hz, 1H), 2.34 (s, 3H), 1.72 (s, 3H).

$^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 171.0, 140.7, 137.1, 129.1, 126.2, 77.7, 51.6, 50.6, 47.7, 23.2, 21.2.

IR $\nu$ (cm$^{-1}$) 2943 (w), 2827 (w), 1738 (s), 1436 (m), 1329 (m), 1190 (m), 1159 (m), 1092 (s), 1062 (s), 819 (m).

HRMS (ESI/QTOF): m/z calcd for C$_{13}$H$_{18}$NaO$_3$ ([M + Na]$^+$): 245.1154; found: 245.1156.

Methyl 3-methoxy-3-(m-tolyl)butanoate (1.96c)
Yield: 76% (42 mg), colorless oil

$^1$H NMR (400 MHz, Acetone-$d_6$) $\delta$ 7.26 – 7.17 (m, 3H), 7.10 – 7.06 (m, 1H), 3.51 (s, 3H), 3.02 (s, 3H), 2.80 (d, $J = 13.9$ Hz, 1H), 2.75 (t, $J = 13.9$ Hz, 1H), 2.34 (s, 3H), 1.68 (s, 3H).

$^{13}$C NMR (101 MHz, Acetone) $\delta$ 170.9, 145.0, 138.3, 128.8, 128.6, 127.6, 124.1, 78.2, 51.3, 50.4, 47.2, 23.9, 21.6.

IR $\nu$ (cm$^{-1}$) 2940 (w) 1738 (s), 1434 (m), 1332 (m), 1160 (m), 810 (m).

HRMS (ESI/QTOF): m/z calcd for C$_{13}$H$_{18}$NaO$_3$ ([M + Na]$^+$): 245.1154; found: 245.1150.

Methyl 3-(4-fluorophenyl)-3-methoxybutanoate (1.96d)

Yield: 73% (41 mg), colorless oil

$^1$H NMR (400 MHz, C$_6$D$_6$) $\delta$ 7.11 – 7.06 (m, 2H), 6.82 – 6.76 (m, 2H), 3.20 (s, 3H), 2.83 (s, 3H), 2.70 (d, $J = 13.9$ Hz, 1H), 2.59 (d, $J = 13.9$ Hz, 1H), 1.59 (s, 3H).

$^{13}$C NMR (101 MHz, C$_6$D$_6$) $\delta$ 170.4, 162.8 (d, $J = 245.2$ Hz), 140.4 (d, $J = 3.2$ Hz), 128.8 (d, $J = 8.1$ Hz), 115.5 (d, $J = 21.2$ Hz), 77.7, 51.3, 50.4, 47.9, 23.5.

IR $\nu$ (cm$^{-1}$) 2952 (w), 2338 (w), 1739 (s), 1603 (w), 1509 (s), 1225 (s), 1162 (s), 1088 (m), 1059 (m), 838 (s).

HRMS (ESI/QTOF): m/z calcd for C$_{12}$H$_{15}$FNaO$_3$ ([M + Na]$^+$): 249.0903; found: 249.0901.
Chapter 4 - Experimental part

Methyl 3-methoxy-3-phenylpentanoate (1.96e)

\[
\text{Et} \overset{\text{OMe}}{\text{COOMe}} \text{Ph}
\]

Yield: 70% (40 mg), colorless oil

The analytical data were in accordance with those reported in the literature.\textsuperscript{21}

\(^1\text{H NMR}\) (400 MHz, \(\text{C}_6\text{D}_6\)) \(\delta 7.31 – 7.27\) (m, 2H), \(7.20 – 7.12\) (m, 2H), \(7.10 – 7.03\) (m, 1H), \(3.20\) (s, 3H), \(2.99\) (s, 3H), \(2.81\) (d, \(J = 13.8\) Hz, 1H), \(2.76\) (d, \(J = 13.8\) Hz, 1H), \(2.13\) (dq, \(J = 14.7, 7.4\) Hz, 1H), \(1.98\) (dq, \(J = 14.6, 7.4\) Hz, 1H), \(0.79\) (t, \(J = 7.4\) Hz, 3H).

\(^{13}\text{C NMR}\) (101 MHz, \(\text{C}_6\text{D}_6\)) \(\delta 170.5, 143.8, 128.7, 127.6, 127.2, 80.9, 51.3, 50.2, 41.5, 30.2, 8.3\).

HRMS (ESI/QTOF): m/z calcd for \(\text{C}_{13}\text{H}_{18}\text{NaO}_3\) ([M + Na]\(^+\)): 245.1154; found: 245.1154.

Methyl 3-methoxy-4-methyl-3-phenylpentanoate (1.96f)

\[
\text{Et} \overset{\text{OMe}}{\text{COOMe}} \text{Ph}
\]

The analytical data were in accordance with those reported in the literature.\textsuperscript{22}

Yield: 58% (34 mg), colorless oil

\(^1\text{H NMR}\) (400 MHz, \(\text{C}_6\text{D}_6\)) \(\delta 7.21 – 7.06\) (m, 5H), \(3.34\) (s, 3H), \(3.20\) (s, 3H), \(2.98\) (d, \(J = 13.9\) Hz, 1H), \(2.76\) (d, \(J = 13.9\) Hz, 1H), \(2.50\) (hept, \(J = 6.8\) Hz, 1H), \(0.90\) (d, \(J = 6.8\) Hz, 3H), \(0.83\) (d, \(J = 6.8\) Hz, 3H).

\(^{13}\text{C NMR}\) (101 MHz, \(\text{C}_6\text{D}_6\)) \(\delta 170.8, 140.4, 128.5, 128.1, 127.5, 84.1, 51.5, 51.4, 38.2, 36.5, 18.7, 17.4\).

Methyl 3-cyclohexyl-3-methoxy-3-phenylpropanoate (1.96g)
Yield: 59% (41 mg), colorless oil

\(^1\text{H NMR}\) (400 MHz, CDCl\textsubscript{3}) \(\delta 7.38 - 7.29\) (m, 2H), \(7.29 - 7.20\) (m, 3H), 3.70 (s, 3H), 3.28 (s, 3H), 3.24 (d, \(J = 14.1\) Hz, 1H), 2.95 (d, \(J = 14.1\) Hz, 1H), 2.01 (m, 1H), 1.93 – 1.80 (m, 2H), 1.75 – 1.60 (m, 2H), 1.58 – 1.49 (m, 1H), 1.33 – 1.10 (m, 2H), 0.95 – 0.79 (m, 1H), 0.69 – 0.49 (m, 2H).

\(^{13}\text{C NMR}\) (101 MHz, CDCl\textsubscript{3}) \(\delta 171.2, 140.2, 127.6, 127.6, 127.0, 83.5, 51.8, 51.1, 46.3, 37.4, 28.6, 26.9, 26.8, 26.5, 26.5.\)

\(\text{IR } \nu\) (cm\(^{-1}\)) 2929 (w), 2853 (w), 1737 (s), 1445 (m), 1328 (w), 1175 (s), 1069 (m), 1009 (w), 704 (s).

\(\text{HRMS (ESI/QTOF)}\): m/z calcd for \(\text{C}_{17}\text{H}_{24}\text{NaO}_3\) ([M + Na]\(^+\)): 299.1623; found: 299.1625.

**Methyl 3-methoxy-4-((4-methylphenyl)sulfonamido)-3-phenylbutanoate (1.96h)**

Yield: 59% (57 mg), orange amorphous solid

\(^1\text{H NMR}\) (400 MHz, CDCl\textsubscript{3}) \(\delta 7.70 - 7.69\) (m, 2H), \(7.36 - 7.24\) (m, 7H), 4.76 (t, \(J = 6.4\) Hz, 1H), 3.63 (dd, \(J = 12.6, 7.9\) Hz, 1H), 3.56 (s, 3H), 3.39 (dd, \(J = 12.6, 5.0\) Hz, 1H), 3.02 (s, 3H), 2.95 (s, 2H), 2.41 (s, 3H).

\(^{13}\text{C NMR}\) (101 MHz, CDCl\textsubscript{3}) \(\delta 170.5, 143.5, 139.7, 136.8, 129.9, 128.9, 128.3, 127.3, 126.5, 79.1, 52.0, 50.7, 48.2, 40.4, 21.7.

\(\text{IR } \nu\) (cm\(^{-1}\)) 3282 (w), 2955 (w), 1734 (w), 1438 (w), 1333 (m), 1163 (s), 1092 (m), 703 (m), 667 (m).

\(\text{HRMS (ESI/QTOF)}\): m/z calcd for \(\text{C}_{19}\text{H}_{23}\text{NNaO}_5\) ([M + Na]\(^+\)): 400.1195; found: 400.1194.
Methyl 3-methoxy-3,3-diphenylpropanoate (1.96i)

Yield: 70% on 0.25 mmol scale, 72% (1.06 g) on 1 gram scale, yellow oil

$^1\text{H NMR}$ (400 MHz, CDCl$_3$) $\delta$ 7.41 – 7.25 (m, 8H), 7.25 – 7.14 (m, 2H), 3.42 (s, 3H), 3.36 (s, 2H), 3.19 (s, 3H).

$^{13}\text{C NMR}$ (101 MHz, CDCl$_3$) $\delta$ 170.4, 144.3, 128.1, 127.3, 127.0, 81.9, 51.5, 51.1, 41.7.

IR $\nu$ (cm$^{-1}$) 2949 (w), 1735 (m), 1447 (m), 1325 (m), 1234 (m), 1197 (m), 1149 (m), 1076 (m), 699 (s).

HRMS (ESI): m/z calcd for C$_{17}$H$_{19}$O$_3^+$ ([M + H]$^+$): 271.1329; found: 271.1328.

Methyl 3-methoxy-3-(4-nitrophenyl)-3-phenylpropanoate (1.96j)

Yield: 69% (53 mg), colorless oil

$^1\text{H NMR}$ (400 MHz, CDCl$_3$) $\delta$ 8.15 – 8.10 (m, 2H), 7.55 – 7.49 (m, 2H), 7.37 – 7.31 (m, 2H), 7.33 – 7.23 (m, 3H), 3.50 (d, $J = 13.6$ Hz, 1H), 3.47 (s, 3H), 3.35 (d, $J = 13.6$ Hz, 1H), 3.22 (s, 3H).

$^{13}\text{C NMR}$ (101 MHz, CDCl$_3$) $\delta$ 169.7, 152.6, 146.8, 142.4, 128.8, 128.7, 128.2, 127.6, 127.1, 123.2, 81.5, 51.7, 51.2, 41.1.

IR $\nu$ (cm$^{-1}$) 2928 (w), 1740 (s), 1444 (w), 1241 (w), 1100 (m), 910 (m), 732 (s).

HRMS (ESI): m/z calcd for C$_{17}$H$_{18}$NO$_5^+$ ([M + H]$^+$): 316.1180; found: 316.1175.
Methyl 3,3-bis(4-fluorophenyl)-3-methoxypropanoate (1.96k)

Yield: 67% (51 mg), colorless oil

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.30 – 7.24 (m, 4H), 6.99 (t, $J$ = 8.7 Hz, 4H), 3.45 (s, 3H), 3.31 (s, 2H), 3.17 (s, 3H).

$^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 170.0, 162.1 (d, $J$ = 246.5 Hz), 140.0 (d, $J$ = 3.3 Hz), 128.8 (d, $J$ = 8.1 Hz), 115.0 (d, $J$ = 21.4 Hz), 81.2, 51.7, 51.0, 41.8.

IR $\nu$ (cm$^{-1}$) 2948 (w), 1740 (s), 1604 (m), 1507 (s), 1324 (w), 1226 (s), 1160 (s), 1084 (w), 1027 (w), 835 (s).

HRMS (ESI): m/z calcd for C$_{17}$H$_{17}$F$_2$O$_3$ + ([M + H]$^+$): 307.1141; found: 307.1042.

Methyl 3,3-bis(4-chlorophenyl)-3-methoxypropanoate (1.96l)

Yield: 54% (46 mg), colorless oil

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.30 – 7.19 (m, 8H), 3.45 (s, 3H), 3.30 (s, 2H), 3.17 (s, 3H).

$^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 169.8, 142.5, 133.4, 128.4, 81.1, 51.7, 51.1, 41.3.
**IR** $\nu$ (cm$^{-1}$) 2944 (w), 1740 (s), 1491 (m), 1435 (m), 1328 (m), 1229 (m), 1194 (m), 1150 (m), 1091 (s), 1015 (s), 817 (s), 960 (w)

**HRMS (ESI):** $m/z$ calcd for C$_{17}$H$_{17}$Cl$_2$O$_3$ $^+$ ([M + H]$^+$): 339.0549; found: 339.0546

**Methyl 3-(3-chlorophenyl)-3-methoxy-3-phenylpropanoate (1.96m)**

Yield: 60% (45 mg), colorless oil

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.37 (s, 1H), 7.36 – 7.08 (m, 8H), 3.45 (s, 3H), 3.38 (d, $J = 13.3$ Hz, 1H), 3.31 (d, $J = 13.3$ Hz, 1H), 3.19 (s, 3H).

$^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 170.0, 146.9, 143.4, 134.1, 129.3, 128.3, 127.7, 127.4, 127.0, 127.0, 125.2, 81.5, 51.6, 51.1, 41.4.

**IR** $\nu$ (cm$^{-1}$) 2955 (w), 2833 (w), 1740 (s), 1480 (m), 1444 (m), 1190 (m), 1160 (s), 1101 (s)

**HRMS (ESI/QTOF) m/z:** Calcd for C$_{17}$H$_{17}$ClNaO$_3$ $^+$ ([M + Na]$^+$) 327.0758; found 327.0768.

**Methyl 3-(4-fluorophenyl)-3-methoxy-3-phenylpropanoate (1.96n)**

Yield: 83% (60 mg), colorless oil

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.33 – 7.23 (m, 6H), 6.97 (t, $J = 8.7$ Hz, 2H), 3.44 (s, 3H), 3.37 (d, $J = 13.2$ Hz, 1H), 3.31 (d, $J = 13.2$ Hz, 1H), 3.18 (s, 3H).
\[^{13}\text{C NMR}\] (101 MHz, CDCl\(_3\)) \(\delta\) 170.2, 162.0 (d, \(J = 246.0\) Hz), 143.9, 140.4 (d, \(J = 3.2\) Hz), 128.7 (d, \(J = 8.1\) Hz), 128.3, 127.6, 127.1, 114.9 (d, \(J = 21.3\) Hz), 81.6, 51.6, 51.1, 41.7.

\[\text{IR } \nu\ (\text{cm}^{-1})\] 2952 (w), 1740 (s), 1517 (s), 1325 (w), 1202 (s), 1158 (s), 1084 (w), 830 (s).

\[\text{HRMS (ESI/QTOF) } m/z:\] Calcd for C\(_{17}\)H\(_{17}\)FNaO\(_3\) [\([M + Na]^+\)] 311.1059; found 311.1058.

**Methyl 3-(4-bromophenyl)-3-methoxy-3-phenylpropanoate (1.96o)**

Yield: 67\% (58 mg), colorless oil

\[^{1}\text{H NMR}\] (400 MHz, CDCl\(_3\)) \(\delta\) 7.43-7.40 (m, 2H), 7.36 – 7.24 (m, 5H), 7.22 – 7.18 (m, 2H), 3.46 (s, 3H), 3.38 (d, \(J = 13.3\) Hz, 1H), 3.30 (d, \(J = 13.3\) Hz, 1H), 3.19 (s, 3H).

\[^{13}\text{C NMR}\] (101 MHz, CDCl\(_3\)) \(\delta\) 170.2, 143.8, 143.5, 131.2, 128.7, 128.4, 127.7, 127.0, 121.3, 81.5, 51.7, 51.1, 41.4.

\[\text{IR } \nu\ (\text{cm}^{-1})\] 2949 (w), 2830 (w), 1737 (s), 1487 (m), 1436 (m), 1324 (m), 1244 (w), 1197 (m), 1150 (s), 1076 (s), 1010 (m), 701 (m).

**HRMS (ESI):** m/z calcd for C\(_{18}\)H\(_{18}\)BrO\(_3\) [\([M + H]^+\)]: 349.0434; found: 349.0432.

**Ethyl 4-(1,3-dimethoxy-3-oxo-1-phenylpropyl)benzoate (1.96p)**

Yield: 63\% (54 mg), colorless oil
\[ ^1H \text{ NMR} \ (400 \text{ MHz, } \text{CDCl}_3) \delta 7.95 - 7.91 \ (m, 2H), 7.39 - 7.36 \ (m, 2H), 7.30 - 7.20 \ (m, 5H), 4.35 \ (q, J = 7.1 \text{ Hz, } 2H), 3.44 \ (s, 3H), 3.43 \ (d, J = 13.3 \text{ Hz, } 1H), 3.35 \ (d, J = 13.4 \text{ Hz, } 1H), 3.20 \ (s, 3H), 1.36 \ (t, J = 7.1 \text{ Hz, } 3H). \]

\[ ^{13}C \text{ NMR} \ (101 \text{ MHz, } \text{CDCl}_3) \delta 170.1, 166.6, 149.8, 143.4, 129.4, 129.4, 128.4, 127.7, 127.1, 126.8, 81.8, 61.0, 51.6, 51.2, 41.4, 14.5. \]

IR \( \nu \ \text{(cm}^{-1} \text{)} \) 2951 (w), 1737 (m), 1716 (s), 1275 (s), 1106 (m).

HRMS (ESI): m/z calcd for C\text{20}H\text{23}O\text{5}+ ([M + H]+): 343.1540 ; found: 343.1839.

**Methyl 3-(4-cyanophenyl)-3-methoxy-3-phenylpropanoate (1.96q)**

Yield: 68\% (50 mg), colorless oil

\[ ^1H \text{ NMR} \ (400 \text{ MHz, } \text{CDCl}_3) \delta 7.60 - 7.55 \ (m, 2H), 7.49 - 7.43 \ (m, 2H), 7.37 - 7.32 \ (m, 2H), 7.30 - 7.26 \ (m, 3H), 3.46 \ (s, 3H), 3.46 \ (d, J = 13.5 \text{ Hz, } 1H), 3.31 \ (d, J = 13.5 \text{ Hz, } 1H), 3.20 \ (s, 3H). \]

\[ ^{13}C \text{ NMR} \ (101 \text{ MHz, } \text{CDCl}_3) \delta 169.6, 150.4, 142.4, 131.7, 128.5, 128.0, 127.3, 127.0, 118.9, 110.8, 81.4, 51.6, 51.1, 41.0. \]

IR \( \nu \ \text{(cm}^{-1} \text{)} \) 2949 (w), 2227 (m), 1737 (s), 1446 (m), 1440 (m), 1328 (m), 1235 (m), 1200 (m), 1150 (s), 1080 (m), 1025 (m), 835 (m), 702 (s)

HRMS (nanochip-ESI/LTQ-Orbitrap) m/z: Calcd for C\text{18}H\text{17}NNaO\text{3}+ ([M+Na]+): 318.1101; found 318.1096.

**Methyl 3-methoxy-3-phenyl-3-(4-(trifluoromethyl)phenyl)propanoate (1.96r)**
Yield: 57% (48 mg), colorless oil

$^1$H NMR (400 MHz, Acetone-$d_6$) $\delta$ 7.66 – 7.57 (m, 4H), 7.42 – 7.32 (m, 4H), 7.31 – 7.20 (m, 1H), 3.57 (d, $J$ = 13.8 Hz, 1H), 3.52 (d, $J$ = 13.8 Hz, 1H), 3.40 (s, 3H), 3.22 (s, 3H).

$^{13}$C NMR (101 MHz, Acetone-$d_6$) $\delta$ 169.2, 150.0, 143.6, 128.2 (q, $J$ = 32.0 Hz), 128.2, 127.4, 127.3, 126.9, 124.6 (q, $J$ = 3.9 Hz), 124.5 (q, $J$ = 271.2 Hz), 81.4, 50.5, 50.3, 40.4.

IR $\nu$ (cm$^{-1}$) 2952 (w), 1738 (m), 1437 (w), 1326 (s), 1164 (m), 1119 (s), 1069 (s), 1019 (m).

HRMS (ESI/QTOF) $m/z$ calcld for C$_{18}$H$_{17}$F$_3$NaO$_3$ (+[M + Na]$^+$): 361.1022; found 361.1020.

Methyl 3-methoxy-3-phenyl-3-(3-(trifluoromethyl)phenyl)propanoate (1.96s)

Yield: 62% (50 mg) colorless oil

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.70 (s, 1H), 7.50 – 7.46 (m, 1H), 7.44 – 7.37 (m, 2H), 7.36 – 7.25 (m, 5H), 3.45 (d, $J$ = 13.2 Hz, 1H), 3.44 (s, 3H), 3.32 (d, $J$ = 13.4 Hz, 1H), 3.21 (s, 3H).

$^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 170.0, 146.1, 143.1, 130.5, 130.3 (q, $J$ = 32.2 Hz), 128.5, 128.5, 127.9, 127.2, 124.3 (q, $J$ = 272.2 Hz), 124.1 (q, $J$ = 3.8 Hz), 123.4 (q, $J$ = 3.9 Hz), 81.6, 51.7, 51.2, 41.5.

IR $\nu$ (cm$^{-1}$) 2952 (w), 2833 (w), 2350 (w), 1740 (m), 1733 (m), 1438 (m), 1331 (s), 1167 (s), 1125 (s), 1077 (m), 702 (m).


Methyl 3-methoxy-3-phenyl-3-(m-toly1)propanoate (1.96t)
Yield: 44% (31 mg), colorless oil

\(^1\text{H NMR}\) (400 MHz, CDCl\(_3\)) \(\delta\) 7.34 – 7.03 (m, 9H), 3.43 (s, 3H), 3.37 (d, \(J = 13.3\) Hz, 1H), 3.34 (d, \(J = 13.3\) Hz, 1H), 3.19 (s, 3H), 2.31 (s, 3H).

\(^{13}\text{C NMR}\) (101 MHz, CDCl\(_3\)) \(\delta\) 170.5, 144.5, 144.2, 137.7, 128.1, 128.1, 128.0, 127.7, 127.2, 127.0, 124.2, 81.9, 51.6, 51.1, 41.7, 21.8.

\(\text{IR } \nu\) (cm\(^{-1}\)) 2950 (w), 2828 (w), 2356 (w), 1738 (s), 1447 (m), 1326 (m), 1195 (m), 1079 (m), 1035 (w), 793 (w), 750 (w), 702 (s).

HRMS (ESI): \(m/z\) calcd for C\(_{18}\)H\(_{20}\)NaO\(_3\)\(^+\) ([M + Na]\(^+\)): 307.1310; found: 307.1310.

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**Methyl 3-methoxy-3-phenylpropanoate (1.96u)**

Yield: 58% (28 mg), 53% on gram scale (1.03 g) yellow oil

\(^1\text{H NMR}\) (400 MHz, CDCl\(_3\)) \(\delta\) 7.39 – 7.28 (m, 5H), 4.64 (dd, \(J = 9.2, 4.5\) Hz, 1H), 3.69 (s, 3H), 3.22 (s, 3H), 2.81 (dd, \(J = 15.4, 9.3\) Hz, 1H), 2.58 (dd, \(J = 15.4, 4.5\) Hz, 1H).

\(^{13}\text{C NMR}\) (101 MHz, CDCl\(_3\)) \(\delta\) 171.6, 140.7, 128.8, 128.2, 126.7, 80.2, 57.0, 51.9, 43.5.

\(\text{IR } \nu\) (cm\(^{-1}\)) 2824 (w), 1739 (s), 1436 (m), 1198 (m), 1158 (s), 1105 (s), 702 (s).
HRMS (ESI/QTOF): \( m/z \) calcd for \( C_{12}H_{16}NaO_3 \) ([\( M + Na \]^+) : 217.0841; found: 217.0843.

**Methyl 3-methoxy-3-(p-tolyl)propanoate (1.96v)**

\[
\begin{align*}
\text{Yield: } & 66\% (34 \text{ mg}), \text{ colorless oil} \\
^1H \text{ NMR (400 MHz, CDCl}_3) & \delta 7.23 - 7.21 (m, 2H), 7.18 - 7.16 (m, 2H), 4.60 (dd, } J = 9.2, 4.6 \text{ Hz, 1H),} \\
& 3.69 (s, 3H), 3.21 (s, 3H), 2.81 (dd, } J = 15.3, 9.3 \text{ Hz, 1H}), 2.56 (dd, } J = 15.3, 4.6 \text{ Hz, 1H}), 2.35 (s, 3H).
\end{align*}
\]

\( ^{13}C \text{ NMR (101 MHz, CDCl}_3) \delta 171.7, 137.9, 137.6, 129.4, 126.7, 80.0, 56.9, 51.9, 43.5, 21.3. \)

IR \( \nu (\text{cm}^{-1}) \) 2931 (w), 1739 (s), 1436 (m), 1158 (m), 1103 (s), 819 (m).

HRMS (ESI/QTOF): \( m/z \) calcd for \( C_{13}H_{18}NaO_3 \) ([\( M + Na \]^+) : 231.0997; found: 231.0993.

**Methyl 3-methoxy-3-(4-methoxyphenyl)propanoate (1.96w)**

\[
\begin{align*}
\text{Yield: } & 60\% (33 \text{ mg}), \text{ colorless oil} \\
^1H \text{ NMR (400 MHz, CDCl}_3) & \delta 7.27 - 7.24 (m, 2H), 6.91-6.88 (m, 2H), 4.58 (dd, } J = 9.1, 4.8 \text{ Hz, 1H),} \\
& 3.81 (s, 3H), 3.68 (s, 3H), 3.19 (s, 3H), 2.81 (dd, } J = 15.3, 9.1 \text{ Hz, 1H}), 2.56 (dd, } J = 15.3, 4.8 \text{ Hz, 1H}).
\end{align*}
\]

\( ^{13}C \text{ NMR (101 MHz, CDCl}_3) \delta 171.7, 159.5, 132.6, 128.0, 114.1, 79.7, 56.8, 55.4, 51.9, 43.5. \)

IR \( \nu (\text{cm}^{-1}) \) 2935 (w), 1738 (s), 1613 (m), 1513 (s), 1247 (s), 1160 (s), 1101 (s), 834 (m).

HRMS (ESI): \( m/z \) calcd for \( C_{13}H_{16}NaO_4 \) ([\( M + Na \]^+) : 247.0946; found: 247.0946.
Methyl 3-(3,4-dimethoxyphenyl)-3-methoxypropanoate (1.96x)

Yield: 63% (40 mg), colorless oil

$^{1}H$ NMR (400 MHz, CDCl$_3$) $\delta$ 6.86 – 6.80 (m, 3H), 4.56 (dd, $J$ = 9.2, 4.7 Hz, 1H), 3.87 (s, 3H), 3.86 (s, 3H), 3.67 (s, 3H), 3.19 (s, 3H), 2.79 (dd, $J$ = 15.2, 9.2 Hz, 1H), 2.55 (dd, $J$ = 15.2, 4.7 Hz, 1H).

$^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 171.6, 149.4, 148.9, 133.1, 119.3, 111.0, 109.2, 80.0, 56.8, 56.0, 51.9, 43.5.

IR v (cm$^{-1}$) 2936 (w), 2835 (w), 1737 (s), 1514 (s), 1258 (s), 1027 (s).

HRMS (ESI/QTOF): m/z calcd for C$_{13}$H$_{18}$NaO$_5$ ([M + Na]$^+$): 277.1052; found: 277.1051.

Methyl 3-(4-fluorophenyl)-3-methoxypropanoate (1.96y)

The analytical data were in accordance with those reported in the literature.\[23\]

Yield: 54% (27 mg), colorless oil

$^{1}H$ NMR (400 MHz, Acetone-$d_6$) $\delta$ 7.43 – 7.38 (m, 1H), 7.17 – 7.10 (m, 1H), 4.62 (dd, $J$ = 9.1, 5.0 Hz, 1H), 3.61 (s, 1H), 3.15 (s, 2H), 2.81 – 2.70 (m, 1H), 2.57 (ddd, $J$ = 15.4, 5.0, 1.5 Hz, 0H).

$^{13}$C NMR (126 MHz, Acetone-$d_6$) $\delta$ 171.3, 163.22 (d, $J$ = 243.9 Hz), 137.94 (d, $J$ = 3.1 Hz), 129.47 (d, $J$ = 8.2 Hz), 115.96 (d, $J$ = 21.5 Hz). 80.1, 56.7, 51.6, 43.6.
Methyl 3-(4-chlorophenyl)-3-methoxypropanoate (1.96z)

The analytical data were in accordance with those reported in the literature.\textsuperscript{23}

**Yield:** 45\% (26 mg), colorless oil

\textsuperscript{1}H NMR (400 MHz, C\textsubscript{6}D\textsubscript{6}) δ 7.05 (d, J = 8.4 Hz, 2H), 6.86 (d, J = 8.3 Hz, 2H), 4.52 (dd, J = 9.0, 4.7 Hz, 1H), 3.30 (s, 3H), 2.95 (s, 3H), 2.70 (dd, J = 15.5, 9.0 Hz, 1H), 2.28 (dd, J = 15.6, 4.7 Hz, 1H).

\textsuperscript{13}C NMR (101 MHz, C\textsubscript{6}D\textsubscript{6}) δ 171.0, 140.1, 134.2, 129.3, 128.0, 56.9, 51.6, 43.7.

methyl 3-(4-bromophenyl)-3-methoxypropanoate (1.96aa)

The analytical data were in accordance with those reported in the literature.\textsuperscript{23}

**Yield:** 53\% (36 mg), colorless oil

\textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}) δ 7.51 – 7.47 (m, 2H), 7.23 – 7.20 (m, 2H), 4.60 (dd, J = 8.9, 4.8 Hz, 1H), 3.68 (s, 3H), 3.21 (s, 3H), 2.79 (dd, J = 15.4, 8.9 Hz, 1H), 2.54 (dd, J = 15.5, 4.9 Hz, 1H).

\textsuperscript{13}C NMR (101 MHz, CDCl\textsubscript{3}) δ 171.3, 139.8, 131.9, 128.5, 122.1, 79.6, 57.1, 52.0, 43.3.
### 4.1.4 General procedure C for the synthesis of cinnamic acid derivatives 1.98a-j

In a sealed tube were added Cu(OTf)$_2$ (0.025 mmol, 0.10 equiv, 9.0 mg) and 1.11 (9.7 mg, 0.025 mmol, 0.10 equiv) under inert atmosphere (glove box). Degassed methyl formate (2.4 mL, [0.1 M]) was added followed by TBPA [319 μL (50 % wt in mineral oils), 1.0 mmol, 4.0 equiv] and the tube was removed from the glove box. Finally the starting material 1.97a-j (0.25 mmol, 1.0 equiv) and toluene (10 μL as internal reference) were quickly added using Hamilton syringe. The reaction mixture was heated at 75 °C for the indicated time (T1). The reaction was monitored by GC-FID/MS.

After completion, the reaction mixture was cooled down with an ice-bath and TfOH (44 μL, 0.5 mmol, 2 equiv) was added. The reaction turned instantaneously from yellow/brown to orange and then brown/black. After being stirred at 75 °C for the indicated time (T2), the reaction mixture was cooled down with an ice-bath, diluted with EtOAc and washed successively with NH$_4$OAc (to remove copper salts), NaHCO$_3$ and brine. The aqueous layer was then extracted with EtOAc (x3). The combined organic layer was dried over Na$_2$SO$_4$ and concentrated under vacuum (rotary evaporator followed by Schlenk line) to afford an oil with dark residues.

CH$_2$Br$_2$ (10 μL) was added as internal reference and the crude was dissolved in CDCl$_3$ for NMR quantification. The crude was purified by flash column chromatography using silica gel (column Ø= 1 cm, 12 cm of SiO$_2$, dry loading) using a mixture 80/1 petroleum ether/EtOAc as eluent to afford the desired product.

<table>
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<th>##</th>
<th>Structure</th>
<th>Reaction time (h)</th>
<th>Isolated yield (%)</th>
</tr>
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<td>Elimination (T2)</td>
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<td>Substrate</td>
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<td>Yield (%)</td>
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</tr>
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</tr>
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</table>

*Table 28 - Substrate scope for the cinnamic ester derivatives.*
Synthesis of \((E)\)-methyl cinnamate (1.98a)

\[
\text{Yield: 62\% (25.2 mg), orange/brown solid}
\]

\(^{1}\text{H NMR}\) (CDCl\(_3\), 400 MHz): \(\delta 7.70 (d, J = 16.0 \text{ Hz}, 1\text{H}), 7.54-7.52 (m, 2\text{H}), 7.39-7.38 (m, 3\text{H}), 6.45 (d, J = 16.0 \text{ Hz}), 3.81 (s, 3\text{H})\)

\(^{13}\text{C NMR}\) (CDCl\(_3\), 100 MHz): \(\delta 167.6, 145.0, 134.5, 130.4, 129.0, 128.2, 117.9, 51.9\)

The spectroscopic data were consistent with those previously reported in the literature.\(^{24}\)

Synthesis of \((E)\)-methyl 3-(4-fluorophenyl)prop-2-enoate (1.98b)

\[
\text{Yield: 58\% (30.1 mg), orange/brown solid (0.29 mmol scale)}
\]

\(^{1}\text{H NMR}\) (CDCl\(_3\), 400 MHz): \(\delta 7.66 (d, J = 16.0 \text{ Hz}, 1\text{H}), 7.52-7.49 (m, 2\text{H}), 7.10-7.05 (m, 2\text{H}), 6.37 (d, J = 16.0 \text{ Hz}, 1\text{H}), 3.81 (s, 3\text{H})\)

\(^{13}\text{C NMR}\) (CDCl\(_3\), 100 MHz): \(\delta 167.4, 164.0 (d, J_{\text{C-F}} = 251.3 \text{ Hz}), 143.7, 130.8 (d, J_{\text{C-F}} = 3.4 \text{ Hz}), 130.1 (d, J_{\text{C-F}} = 8.5 \text{ Hz}), 117.7 (d, J_{\text{C-F}} = 2.2 \text{ Hz}), 116.2 (d, J_{\text{C-F}} = 21.9 \text{ Hz}), 51.9\)

The spectroscopic data were consistent with those previously reported in the literature.\(^{24}\)

Synthesis of \((E)\)-methyl 3-(4-methoxyphenyl)prop-2-enoate (1.98c)

\[
\text{Yield: 64\% (30.8 mg), yellow solid}
\]

\(^{1}\text{H NMR}\) (CDCl\(_3\), 400 MHz): \(\delta 7.65 (d, J = 16.0 \text{ Hz}, 1\text{H}), 7.48 (d, J = 8.7 \text{ Hz}, 2\text{H}), 6.91 (d, J = 8.7 \text{ Hz}, 2\text{H}), 6.31 (d, J = 16.0 \text{ Hz}, 1\text{H}), 3.84 (s, 3\text{H}), 3.79 (s, 3\text{H})\)
$^{13}$C NMR (CDCl$_3$, 100 MHz): $\delta$ 168.0, 161.6, 144.7, 129.9, 127.3, 115.5, 114.5, 55.6, 51.8

The spectroscopic data were consistent with those previously reported in the literature.$^{24}$

**Synthesis of (E)-methyl 3-phenylbut-2-enoate (1.98d)**

Yield: 74% (32.7 mg), yellow oil

$^1$H NMR (CDCl$_3$, 400 MHz): $\delta$ 7.49-7.46 (m, 2H), 7.40-7.36 (m, 3H), 6.15 (q, $J = 1.1$ Hz, 1H), 3.76 (s, 3H), 2.59 (d, $J = 1.1$ Hz, 3H)

$^{13}$C NMR (CDCl$_3$, 100 MHz): $\delta$ 167.4, 156.0, 142.3, 129.2, 128.6, 126.4, 116.8, 51.2, 18.1

The spectroscopic data were consistent with those previously reported in the literature.$^{25}$

**Synthesis of (E)-methyl 3-(4-fluorophenyl)but-2-enoate (1.98e)**

Yield: 69% (33.4 mg), yellow oil

$^1$H NMR (CDCl$_3$, 400 MHz): $\delta$ 7.48-7.43 (m, 2H), 7.09-7.03 (m, 2H), 6.10 (q, $J = 1.3$ Hz, 1H), 3.76 (s, 3H), 2.56 (d, $J = 1.3$ Hz, 3H)

$^{13}$C NMR (CDCl$_3$, 100 MHz): $\delta$ 167.3, 163.5 (d, $J_{C-F} = 249.1$ Hz), 154.8, 138.3 (d, $J_{C-F} = 3.3$ Hz), 128.3 (d, $J_{C-F} = 8.3$ Hz), 116.8, 115.6 (d, $J_{C-F} = 21.6$ Hz), 51.3, 18.2

The spectroscopic data were consistent with those previously reported in the literature.$^{26}$
Synthesis of (E)-methyl 3-(4-methoxyphenyl)but-2-enoate (1.98f)

Yield: 51% (29.3 mg), white/beige solid

$^1$H NMR (CDCl$_3$, 400 MHz): $\delta$ 7.47-7.43 (m, 2H), 6.92-6.88 (m, 2H), 6.11 (q, $J = 1.2$ Hz, 1H), 3.83 (s, 3H), 3.74 (s, 3H) 2.57 (d, $J = 1.2$ Hz, 3H)

$^{13}$C NMR (CDCl$_3$, 100 MHz): $\delta$ 167.6, 160.6, 155.4, 134.4, 127.8, 115.0, 114.0, 55.5, 51.2, 17.8

The spectroscopic data were consistent with those previously reported in the literature.$^{27}$

Synthesis of (E)-methyl 3-(4-methylphenyl)but-2-enoate (1.98g)

Yield: 79% (37.6 mg), yellow solid

$^1$H NMR (CDCl$_3$, 400 MHz): $\delta$ 7.39 (d, $J = 8.0$ Hz, 2H), 7.19 (d, $J = 8.0$ Hz, 2H), 6.14 (q, $J = 0.9$ Hz, 1H), 3.75 (s, 3H), 2.57 (d, $J = 0.9$ Hz, 1H), 2.37 (s, 3H)

$^{13}$C NMR (CDCl$_3$, 100 MHz): $\delta$ 167.5, 155.9, 139.4, 139.3, 129.4, 126.4, 116.0, 51.2, 21.3, 18.0

The spectroscopic data were consistent with those previously reported in the literature.$^{28}$

Synthesis of methyl 3,3’-diphenylprop-2-enoate (1.98h)

Yield: 76% (45.3 mg), yellow/orange oil
Chapter 4 - Experimental part

$^1$H NMR (CDCl$_3$, 400 MHz): δ 7.41-7.29 (m, 8H), 7.25-7.20 (m, 2H), 6.38 (s, 1H), 3.62 (s, 3H)

$^{13}$C NMR (CDCl$_3$, 100 MHz): δ 166.5, 157.2, 140.9, 138.9, 129.6, 129.2, 128.5, 128.0, 116.9, 51.4

The spectroscopic data were consistent with those previously reported in the literature.$^{26}$

**Synthesis of methyl 3,3’-bis(4-fluorophenyl)prop-2-enoate (1.98i)**

Yield: 64% (22.0 mg), yellow solid (0.125 mmol scale)

$^1$H NMR (CDCl$_3$, 400 MHz): δ 7.31-7.22 (m, 2H), 7.22-7.15 (m, 2H), 7.13-6.97 (m, 4H), 6.31 (s, 1H), 3.63 (s, 3H)

$^{13}$C NMR (CDCl$_3$, 100 MHz): δ 166.3, 163.8 (d, $J_{C-F} = 250.6$ Hz), 163.0 (d, $J_{C-F} = 247.9$ Hz), 155.1, 137.0 (d, $J_{C-F} = 3.1$ Hz), 134.5 (d, $J_{C-F} = 3.5$ Hz), 131.2 (d, $J_{C-F} = 8.2$ Hz), 130.4 (d, $J_{C-F} = 8.5$ Hz), 117.0, 115.7 (d, $J_{C-F} = 21.8$ Hz), 115.2 (d, $J_{C-F} = 21.6$ Hz), 51.5

HRMS (ESI/QTOF) m/z: Calcd for C$_{16}$H$_{13}$F$_2$O$_2$+ [M + H]$^+$ 275.0878; found 275.0880

IR $\nu$ (cm$^{-1}$): 2162 (m), 1723 (s), 1601 (s), 1508 (s), 1436 (w), 1265 (w), 1225 (s), 1157 (s), 836 (s), 722 (s)

Mp: 54.6-56.5 °C
Synthesis of methyl 3,3’-bis(4-methylphenyl)prop-2-enoate (1.98j)

Yield: 57% (19.0 mg), white/slightly yellow solid (0.125 mmol scale)

$^1$H NMR (CDCl$_3$, 400 MHz): $\delta$ 7.24-7.16 (m, 4H), 7.16-7.07 (m, 4H), 6.31 (s, 1H), 3.62 (s, 3H), 2.40 (s, 3H), 2.36 (s, 3H)

$^{13}$C NMR (CDCl$_3$, 100 MHz): $\delta$ 166.7, 157.6, 139.8, 138.4, 138.1, 136.1, 129.3, 129.2, 128.7, 128.5, 115.7, 51.3, 21.6, 21.4

The spectroscopic data were consistent with those previously reported in the literature.$^{29}$

1.99a-f, 1.102a-g and 1.103a-e were prepared according to a literature procedure.$^{30,31}$ All the spectroscopical data for compound 1.99a-f, 1.102a-g and 1.103a-e matched with the reported values.$^{30,31}$

4.1.5 General procedure D for the synthesis of substituted heterocycles 1.100a-f, 1.104a-g and 1.105a-e

Glassware and stirring bar were stored in the oven and the reaction was carried out under inert atmosphere and dry conditions.151 Into a Pyrex 10 mL sealed tube was prepared a solution of copper(II) triflate (9 mg, 0.025 mmol, 0.1 equiv), 1.L1 (9.7 mg, 0.025 mmol, 0.1 equiv) and 2.5 mL of dry, degassed methyl formate. The solution was stirred at room temperature for 3 minutes or until the solution is homogeneous and has dark green colour. The starting material (1.99a-f, 1.102a-g, 1.103a-e) (0.25 mmol, 1 equiv) and tert-butyl-peracetate (319 $\mu$L, 1 mmol, 50% solution in mineral spirits, Sigma Aldrich®) was added to the reaction mixture. The sealed tube was placed into a preheated metallic block heater at 75 °C for 1 hour. The reaction mixture was cooled to room temperature and 0.1 M sulfuric acid was added (0.025 mL, 0.025 mmol, 0.1 equiv) and the sealed tube was placed back to the metallic block heater at 75 °C for the indicated time (see Table S). The reaction mixture

$^{151}$ Reaction can also be carried out under air, but there is a loss of yield around 5%.
was cooled to room temperature with an ice-bath and was diluted with diethyl ether. The organic phase was washed with 2.5 M ammonium acetate, saturated sodium bicarbonate solution and with brine. The combined aqueous phases were extracted 3 times with ether and the organic phases were combined, dried over NaSO₄ and concentrated under reduced pressure. It is important not to store the crude mixture for long time. The obtained crude mixture was purified by flash column chromatography (SiO₂, petroleum ether/ethyl acetate 10/1 to 5/1) unless otherwise stated. Dry-loading has to be avoided toluene was used instead.

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*Table S5 - Substrate scope of tetrahydrofuran, γ-lactone and pyrrolidine products.*
Methyl 2-(2-phenyltetrahydrofuran-2-yl)acetate (1.100a)

Yield: 75% (41 mg), colorless oil. Eluent system used for flash column chromatography: toluene with 0.1% 2-propanol.

$^1$H NMR (400 MHz, CDCl$_3$) δ 7.41 – 7.37 (m, 1H), 7.32 (ddd, $J = 7.9, 6.7, 1.2$ Hz, 1H), 7.26 – 7.21 (m, 1H), 4.01 (dt, $J = 7.9, 7.0$ Hz, 0H), 3.90 (td, $J = 8.1, 5.6$ Hz, 1H), 3.57 (s, 1H), 2.85 (dd, $J = 16.7, 14.0$ Hz, 1H), 2.81 (dd, $J = 14.1, 1.1$ Hz, 1H), 2.43 (dt, $J = 12.4, 8.3$ Hz, 1H), 2.30 (ddd, $J = 12.5, 7.8, 4.9$ Hz, 1H), 2.02 – 1.91 (m, 1H), 1.84 – 1.73 (m, 1H).

$^{13}$C NMR (201 MHz, CDCl$_3$) δ 170.9, 145.9, 128.3, 127.0, 125.2, 84.7, 68.1, 51.7, 47.0, 37.4, 25.5.

IR: ν (cm$^{-1}$) 2950 (w), 1736 (s), 1437 (w), 1335 (w), 1176 (m), 1169 (m), 1058 (s).


Methyl 2-(2-(p-tolyl)tetrahydrofuran-2-yl)acetate (1.100b)

Yield: 58% (34 mg), colorless oil. Eluent system used for flash column chromatography: petroleum ether – toluene (3:2) with 0.2% THF.
Methyl 2-(2-(4-fluorophenyl)tetrahydrofuran-2-yl)acetate (1.100c)

Yield: 77% (42 mg), colorless oil. Eluent system used for flash column chromatography: petroleum ether – toluene (3:2) with 0.1% 2-propanol.

\[ ^{1}H\text{ NMR} (800 \text{ MHz, } CD_{6}) \delta 7.21 – 7.18 (m, 2H), 6.82 – 6.79 (m, 2H), 3.77 – 3.73 (m, 1H), 3.55 (td, J = 8.0, 5.7 Hz, 1H), 3.22 (s, 3H), 2.64 (s, 2H), 2.29 (dt, J = 12.4, 8.1 Hz, 1H), 1.96 (ddd, J = 12.8, 7.9, 5.2 Hz, 1H), 1.56 (dddd, J = 13.3, 11.0, 7.9, 5.4 Hz, 1H), 1.40 – 1.33 (m, 1H).

\[ ^{13}C\text{ NMR} (201 \text{ MHz, } CD_{6}) \delta 170.2, 162.9, 161.7, 142.4, 142.4, 127.4, 127.4, 115.2, 115.1, 115.1, 115.0, 84.4, 67.7, 50.9, 47.0, 37.2, 25.6.

IR: \( \nu (\text{cm}^{-1}) \): 2955 (w), 2873 (w), 1735 (s), 1424 (s), 1424, 1274, 1274, 115.2, 115.1, 115.1, 115.0, 84.4, 67.7, 50.9, 47.0, 37.2, 25.6.

HRMS (ESI/QTOF) m/z: Calcd for C_{13}H_{15}FNaO_3^+ ([M + Na]^+) : 261.0897; found 261.0902.
Methyl 2-(2-(4-cyanophenyl)tetrahydrofuran-2-yl)acetate (1.100d)

Yield: 62% (38 mg), yellow oil.

$^1$H NMR (400 MHz, Acetone-$d_6$) $\delta$ 7.75 – 7.70 (m, 2H), 7.66 – 7.61 (m, 2H), 4.04 – 3.92 (m, 1H), 3.87 (td, $J = 8.0$, 5.7 Hz, 1H), 3.49 (s, 3H), 2.89 (d, $J = 14.4$ Hz, 1H), 2.84 (d, $J = 14.5$ Hz, 1H), 2.50 (dt, $J = 12.6$, 7.9 Hz, 1H), 2.21 (ddd, $J = 12.8$, 7.9, 5.5 Hz, 1H), 2.07 – 1.96 (m, 1H) 1.85 – 1.69 (m, 1H).

$^{13}$C NMR (101 MHz, Acetone-$d_6$) $\delta$ 170.4, 152.9, 132.6, 127.2, 119.4, 111.2, 85.1, 68.6, 51.4, 46.5, 38.5, 25.9.

IR: $\nu$ (cm$^{-1}$): 2953 (w), 2871 (w), 2227 (m), 1735 (s), 1607 (w), 1435 (m), 1349 (m), 1204 (m), 1171 (s), 1062 (s), 1022 (m), 837 (m)

HRMS (ESI/QTOF) m/z: Calcd for C$_{14}$H$_{15}$NNaO$_3$ $^+$ ([M + Na]$^+$): 268.0944; found 268.0949.

Methyl 2-(2-(4-methoxyphenyl)tetrahydrofuran-2-yl)acetate (1.100e)

Yield: 47% (29 mg) colorless oil.

$^1$H NMR (400 MHz, C$_6$D$_6$) $\delta$ 7.39 – 7.34 (m, 2H), 6.83 – 6.77 (m, 2H), 3.85 – 3.78 (m, 1H), 3.70 – 3.63 (m, 1H), 3.30 (s, 3H), 3.25 (s, 3H), 2.78 (s, 2H), 2.39 (dt, $J = 12.2$, 8.2 Hz, 1H), 2.16 (ddd, $J = 12.6$, 8.0, 5.0 Hz, 1H), 1.68 – 1.57 (m, 1H), 1.54 – 1.42 (m, 1H).

$^{13}$C NMR (201 MHz, C$_6$D$_6$) $\delta$ 170.8, 159.5, 138.9, 127.2, 114.2, 84.9, 67.9, 55.1, 51.2, 47.6, 37.4, 26.0.
**IR** $\nu$ (cm$^{-1}$): 2955 (w), 2880 (w), 2836 (w), 1735 (s), 1610 (m), 1461 (m), 1439 (m), 1297 (m), 1249 (s), 1175 (s), 1058 (m), 1034 (s), 834 (m)

**HRMS (ESI/QTOF)** m/z: Calcd for $C_{14}H_{18}NaO_4^+$ ([M + Na]$^+$): 273.1097; found 273.1099.

**Methyl 2-(2-(m-tolyl)tetrahydrofuran-2-yl)acetate (1.100f)**

![Chemical structure of methyl 2-(2-(m-tolyl)tetrahydrofuran-2-yl)acetate](image)

**Yield:** 57% (34 mg), light yellow oil

**$^1$H NMR** ($400$ MHz, CDCl$_3$) $\delta$ 7.23 – 7.15 (m, 3H), 7.04 (dt, $J$ = 6.7, 1.6, 0.8 Hz, 1H), 4.04 – 3.98 (m, 1H), 3.89 (td, $J$ = 8.1, 5.7 Hz, 1H), 3.58 (s, 3H), 2.84 (d, $J$ = 14.0 Hz, 1H), 2.80 (d, $J$ = 14.0 Hz, 1H), 2.43 (dt, $J$ = 12.4, 8.2 Hz, 1H), 2.35 (s, 3H), 2.29 (ddd, $J$ = 12.6, 7.8, 5.0 Hz, 1H), 2.01 – 1.90 (m, 1H), 1.79 (dq, $J$ = 12.2, 7.9, 6.6 Hz, 1H).

**$^{13}$C NMR** (101 MHz, CDCl$_3$) $\delta$ 170.9, 145.9, 137.8, 128.2, 127.7, 125.8, 122.2, 84.7, 68.1, 51.6, 46.9, 37.3, 25.5, 21.7.

**IR** $\nu$ (cm$^{-1}$) 2922 (s), 1738 (s), 1441 (m), 1200 (m), 1163 (m), 1257 (m), 1061 (s), 916 (m)

**HRMS (ESI/QTOF)** m/z: Calcd for $C_{14}H_{18}O_3^+$ ([M + Na]$^+$): 257.1148; found 257.1150.

**Methyl 2-(5-oxo-2-phenyltetrahydrofuran-2-yl)acetate (1.104a)**

![Chemical structure of methyl 2-(5-oxo-2-phenyltetrahydrofuran-2-yl)acetate](image)

**Yield:** 75% (44 mg), yellow oil
$^{1}$H NMR (400 MHz, CDCl$_3$) δ 7.43 – 7.36 (m, 4H), 7.37 – 7.29 (m, 1H), 3.63 (s, 3H), 3.00 (d, $J$ = 15.5 Hz, 1H), 2.97 (d, $J$ = 15.5 Hz, 1H), 2.94 – 2.83 (m, 1H), 2.74 – 2.57 (m, 2H), 2.54 – 2.43 (m, 1H).

$^{13}$C NMR (101 MHz, CDCl$_3$) δ 176.2, 169.5, 142.8, 128.3, 124.6, 86.0, 52.0, 46.3, 33.4, 28.7

IR: $\nu$ (cm$^{-1}$): 2964 (w), 1701 (s), 1398 (m), 1214 (m), 1139 (m)

HRMS (ESI/QTOF): m/z calcd for C$_{13}$H$_{15}$O$_4$ ([M + H]*): 235.0970; found: 235.0972.

Methyl 2-(5-oxo-2-($p$-tolyl)tetrahydrofuran-2-yl)acetate (1.104b)

![Chemical structure of methyl 2-(5-oxo-2-($p$-tolyl)tetrahydrofuran-2-yl)acetate]

Yield: 70% (43 mg), colorless oil

$^{1}$H NMR (400 MHz, CDCl$_3$) δ 7.27 (d, $J$ = 8.1 Hz, 2H), 7.18 (d, $J$ = 8.0 Hz, 2H), 3.63 (s, 3H), 3.00 (d, $J$ = 15.5 Hz, 1H), 2.95 (d, $J$ = 15.3 Hz, 1H), 2.88 – 2.80 (m, 1H), 2.72 – 2.55 (m, 2H), 2.52 – 2.43 (m, 1H), 2.35 (s, 3H).

$^{13}$C NMR (101 MHz, CDCl$_3$) δ 176.2, 169.6, 139.8, 138.1, 129.5, 124.6, 86.1, 52.0, 46.4, 33.4, 28.7, 21.2.

IR: $\nu$ (cm$^{-1}$): 2950 (w), 1778 (s), 1736 (s), 1435 (m), 1369 (w), 1222 (m), 1189 (s), 1160 (s), 1081 (m), 791 (m), 708 (m)

HRMS (ESI/QTOF) m/z: Calcd for C$_{14}$H$_{16}$NaO$_4$* ([M + Na]*): 271.0941; found 271.0945.
Chapter 4 - Experimental part

**Methyl 2-(2-(4-fluorophenyl)-5-oxotetrahydrofuran-2-yl)acetate (1.104c)**

Yield: 70% (44 mg), colorless oil.

$^1$H NMR (400 MHz, CDCl$_3$) δ 7.40 – 7.35 (m, 2H), 7.09 – 7.03 (m, 2H), 3.62 (s, 3H), 2.99 (d, $J = 15.5$ Hz, 1H), 2.94 (d, $J = 15.5$ Hz, 1H), 2.86 (ddd, $J = 12.4, 9.3, 8.1$ Hz, 1H), 2.69 (ddd, $J = 16.8, 9.2, 4.5$ Hz, 1H), 2.59 (ddd, $J = 12.4, 9.3, 4.5$ Hz, 1H), 2.48 (ddd, $J = 17.1, 9.3, 8.1$ Hz, 1H).

$^{13}$C NMR (101 MHz, CDCl$_3$) δ 175.8, 169.4, 163.7, 161.3, 138.5, 138.5, 126.7, 126.6, 115.8, 115.6, 85.6, 77.5, 77.2, 76.8, 52.0, 46.4, 33.5, 28.6.

IR: ν (cm$^{-1}$): 2930 (w), 1777 (s), 1736 (s), 1441 (m), 1286 (s), 1165 (s), 890 (w).

HRMS (ESI/QTOF) m/z: [M + Na]$^+$ Calcd for C14H16NaO4+ 271.0941; Found 271.0945.

**Methyl 2-(2-(4-cyanophenyl)tetrahydrofuran-2-yl)acetate (1.104d)**

Yield: 69% (44 mg), orange oil

$^1$H NMR (400 MHz, CDCl$_3$) δ 7.72 – 7.64 (m, 2H), 7.55 – 7.50 (m, 2H), 3.61 (s, 3H), 3.01 (d, $J = 15.8$ Hz, 1H), 2.96 (d, $J = 15.8$ Hz, 1H), 2.89 (ddd, $J = 10.9, 9.6, 6.6$ Hz, 1H), 2.78 – 2.68 (m, 1H), 2.61 – 2.43 (m, 2H).

$^{13}$C NMR (101 MHz, CDCl$_3$) δ 175.3, 168.9, 147.9, 132.7, 125.7, 118.3, 112.4, 85.1, 52.1, 45.8, 33.5, 28.3.
IR ν (cm⁻¹): 2949 (w), 2936 (w), 2232 (w), 1781 (s), 1739 (s), 1611 (w), 1437 (m), 1368 (w), 1163 (s), 1060 (m), 1010 (m).

HRMS (ESI/QTOF) m/z: Calcd for C_{14}H_{13}NNaO_{4}⁺ ([M + Na]⁺): 282.0737; found 282.0745.

Methyl 2-(2-(4-methoxyphenyl)-5-oxotetrahydrofuran-2-yl)acetate (1.104e)

Yield: 44% (30 mg), containing 4% of elimination product, colorless oil

¹H NMR (400 MHz, Acetone-\(d_6\)) δ 7.38 – 7.34 (m, 2H), 6.96 – 6.92 (m, 2H), 3.80 (s, 3H), 3.55 (s, 3H), 3.07 (d, \(J = 15.5\) Hz, 1H), 3.02 (d, \(J = 15.5\) Hz, 1H), 2.92 – 2.78 (m, 1H), 2.69 – 2.54 (m, 2H), 2.49 – 2.40 (m, 1H).

¹³C NMR (101 MHz, Acetone-\(d_6\)) δ 176.2, 170.0, 160.1, 136.2, 126.8, 114.5, 86.2, 55.5, 51.7, 46.4, 34.0, 28.9.

IR ν (cm⁻¹) 2960 (w), 2365 (m), 2339 (m), 1751 (m), 1738 (s), 1605 (m), 1511 (s), 1435 (m), 1251 (s), 1169 (s), 1030 (m), 909 (m), 833 (m), 739 (s).

HRMS (ESI/QTOF) m/z: Calcd for C_{14}H_{16}NaO_{5}⁺ ([M + Na]⁺): 287.0890; found 287.0890.
Methyl 2-{5-oxo-2-(m-tolyl)tetrahydrofuran-2-yl}acetate (1.104f)

Yield: 47% (30 mg) colorless oil

^1H NMR (400 MHz, Acetone-\textit{d}_6) \(\delta\) 7.30 – 7.24 (m, 2H), 7.24 – 7.19 (m, 1H), 7.16 – 7.11 (m, 1H), 3.56 (s, 3H), 3.09 (d, \(J = 15.6\) Hz, 1H), 3.02 (d, \(J = 15.6\) Hz, 1H), 2.90 (ddd, \(J = 12.4, 9.4, 7.6\) Hz, 1H), 2.66 (ddd, \(J = 16.8, 9.4, 4.9\) Hz, 1H), 2.55 (ddd, \(J = 12.3, 9.4, 4.8\) Hz, 1H), 2.44 (ddd, \(J = 17.0, 9.4, 7.7\) Hz, 1H), 2.35 (s, 3H).

^13C NMR (101 MHz, Acetone-\textit{d}_6) \(\delta\) 176.2, 170.0, 144.5, 138.8, 129.2, 126.0, 122.5, 86.2, 51.7, 46.2, 34.1, 28.8, 21.5.

IR \(\nu\) (\text{cm}^{-1}) 2949 (w), 2924 (w), 1779s, 1735 (s), 1435 (m), 1363(w), 1241 (m), 1186 (s), 1165 (s), 1061 (m), 1002 (m), 936 (m), 890 (w), 791 (m), 708 (m).

HRMS (ESI/QTOF) m/z: Calcd for \(\text{C}_{14}\text{H}_{16}\text{NaO}_4\) ([M + Na]⁺): 271.0941; found 271.0945.

Methyl 2-{2-(3-chlorophenyl)-5-oxotetrahydrofuran-2-yl}acetate (1.104g)

Yield: 68%, (45 mg), colorless oil

^1H NMR (400 MHz, CDCl\textit{3}) \(\delta\) 7.39 (m, 1H), 7.34 – 7.25 (m, 3H), 3.63 (s, 3H), 2.99 (d, \(J = 15.7\) Hz, 1H), 2.94 (d, \(J = 15.7\) Hz, 1H), 2.87 (ddd, \(J = 11.6, 9.6, 7.5\) Hz, 1H), 2.70 (ddd, \(J = 17.1, 9.5, 3.9\) Hz, 1H), 2.62 – 2.44 (m, 2H).

^13C NMR (101 MHz, CDCl\textit{3}) \(\delta\) 175.7, 169.2, 144.9, 134.9, 130.2, 128.5, 125.1, 122.9, 85.3, 52.1, 46.1, 33.4, 28.5.
IR ν (cm\(^{-1}\)) 2961 (w), 1782 (s), 1737 (s), 1596 (w), 1574 (w), 1437 (w), 1362 (w), 1238 (m), 1194 (s), 1163 (s), 1057 (m), 790 (m).

HRMS (ESI/QTOF) \(m/z\): Calcd for C\(_{13}\)H\(_{13}\)ClNaO\(_4\)\(^+\) ([M + Na]\(^+\)): 291.0395; found 291.0402.

**Methyl 2-(2-phenyl-1-tosylpyrrolidin-2-yl)acetate (1.105a)**

![Methyl 2-(2-phenyl-1-tosylpyrrolidin-2-yl)acetate](image)

**Yield:** 69% (64 mg) orange amorphous solid

\(^1\)H NMR (400 MHz, C\(_6\)D\(_6\)) \(\delta\) 7.42 (d, \(J = 8.2\) Hz, 2H), 7.29 – 7.25 (m, 2H), 7.07 – 6.98 (m, 3H), 6.69 (d, \(J = 8.0\) Hz, 2H), 3.63 (d, \(J = 16.4\) Hz, 1H), 3.57 (dt, \(J = 8.9, 7.5\) Hz, 1H), 3.47 (d, \(J = 16.4\) Hz, 1H), 3.41 (dt, \(J = 8.9, 6.3\) Hz, 1H), 3.26 (s, 3H), 2.62 (dt, \(J = 12.9, 8.3\) Hz, 1H), 1.95 (dt, \(J = 12.7, 6.1\) Hz, 1H), 1.89 (s, 3H), 1.48 – 1.41 (m, 2H).

\(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.33 – 7.23 (m, 4H), 7.24 – 7.20 (m, 3H), 7.15 – 7.09 (m, 2H), 3.73 – 3.63 (m, 2H), 3.59 (s, 3H), 3.41 (d, \(J = 16.3\) Hz, 1H), 2.74 (dt, \(J = 13.1, 8.1\) Hz, 1H), 2.38 (s, 3H), 2.27 (dt, \(J = 12.9, 6.3\) Hz, 1H), 1.95 – 1.91 (m, 2H).

\(^13\)C NMR (101 MHz, CDCl\(_3\)) \(\delta\) 171.5, 144.2, 142.6, 137.9, 129.2, 128.2, 127.2, 127.0, 126.4, 70.1, 51.6, 50.0, 42.4, 42.1, 23.0, 21.6.

IR ν (cm\(^{-1}\)) 2955 (w), 2360 (w), 1741 (m), 1441 (w), 1334 (s), 1153 (s), 1090 (s), 1009 (m), 815 (m), 659 (s).

HRMS (ESI/QTOF) \(m/z\): Calcd for C\(_{20}\)H\(_{23}\)NNaO\(_5\)\(^+\) ([M + Na]\(^+\)): 396.1240; found 396.1250.

**Methyl 2-(2-(p-tolyl)-1-tosylpyrrolidin-2-yl)acetate (1.105b)**
Yield: 51% (49 mg), white amorphous solid

$^1$H NMR (400 MHz, C$_6$D$_6$) $\delta$ 7.45 – 7.40 (m, 2H), 7.24 – 7.17 (m, 2H), 6.88 – 6.82 (m, 2H), 6.74 – 6.68 (m, 2H), 3.68 (d, $J = 16.3$ Hz, 1H), 3.58 (dt, $J = 8.9$, 7.4 Hz, 1H), 3.45 (d, $J = 16.4$ Hz, 1H), 3.46 – 3.40 (m, 1H), 2.63 (dt, $J = 12.9$, 8.1 Hz, 1H), 2.09 (s, 3H), 2.01 (dt, $J = 12.7$, 6.2 Hz, 1H), 1.92 (s, 3H), 1.53 – 1.45 (m, 2H).

$^{13}$C NMR (101 MHz, C$_6$D$_6$) $\delta$ 171.5, 142.4, 142.3, 139.5, 136.8, 129.4, 129.2, 127.8, 127.1, 70.4, 51.4, 50.4, 43.1, 42.3, 23.2, 21.4, 21.2.

IR: $\nu$ (cm$^{-1}$): 2949 (w), 1741 (m), 1437 (w), 1333 (s), 1153 (s), 1092 (m), 1007 (m), 814 (m), 664 (m).

HRMS (APPI/LTQ-Orbitrap) m/z: Calcd for C$_{20}$H$_{24}$NO$_{4}$S$^+$ ([M + H]$^+$): 374.1421; found 374.1413.

Methyl 2-(2-(4-fluorophenyl)-1-tosylpyrrolidin-2-yl)acetate (1.105c)

Yield: 42% (41 mg), white amorphous solid

$^1$H NMR (400 MHz, C$_6$D$_6$) $\delta$ 7.39 – 7.35 (m, 2H), 7.08 – 7.02 (m, 2H), 6.71 – 6.63 (m, 4H), 3.57 (d, $J = 16.4$ Hz, 1H), 3.55 (dt, $J = 8.9$, 7.3 Hz, 1H), 3.38 – 3.32 (m, 1H), 3.33 (d, $J = 4.9$ Hz, 1H), 3.26 (s, 3H), 2.54 (ddd, $J = 13.1$, 8.7, 7.5 Hz, 1H), 1.90 (s, 3H), 1.85 (ddd, $J = 12.9$, 7.3, 5.3 Hz, 1H), 1.47 – 1.35 (m, 2H).

$^{13}$C NMR (101 MHz, C$_6$D$_6$) $\delta$ 171.3, 162.5 (d, $J = 245.7$ Hz), 142.6, 140.9 (d, $J = 3.2$ Hz), 139.3, 129.5, 129.1 (d, $J = 7.9$ Hz), 127.7, 115.1 (d, $J = 21.3$ Hz), 69.8, 51.4, 50.3, 43.1, 42.4, 23.1, 21.4.
IR \( \tilde{\nu} \) (cm\(^{-1}\)): 2952 (w), 2924 (w), 1738 (m), 1602 (w), 1439 (w), 1336 (m), 1230 (m), 1154 (s), 1096 (m), 1013 (m), 842 (w), 817 (m), 661 (m).

HRMS (LTQ-Orbitrap) \( m/z \): Calcd for C\(_{19}\)H\(_{21}\)FNO\(_4\)S\(^+\) ([M + H]\(^+\)): 378.1170; found 378.1170.

**Methyl 2-(2-(m-tolyl)-1-tosylpyrrolidin-2-yl)acetate (1.105d)**

Yield: 55\% (53 mg), light yellow oil

\(^1\)H NMR (400 MHz, CDCl\(_3\)) \(7.27 – 7.23\) (m, 2H), \(7.15 – 7.07\) (m, 4H), \(7.01 – 6.99\) (m, 1H), \(6.91 – 6.89\) (m, 1H), \(3.73\) (dt, \(J = 9.0, 7.2\) Hz, 1H), \(3.65 – 3.56\) (m, 1H), \(3.61\) (d, \(J = 16.1\) Hz, 1H), \(3.61\) (s, 3H), \(3.41\) (d, \(J = 16.1\) Hz, 1H), \(2.74\) (dt, \(J = 13.1, 7.8\) Hz, 1H), \(2.46 – 2.29\) (m, 1H), \(2.36\) (s, 3H), \(2.29 – 2.20\) (m, 1H), \(2.17\) (s, 3H), \(2.01 – 1.90\) (m, 2H).

\(^{13}\)C NMR (101 MHz, CDCl\(_3\)) \(\delta\) 171.6, 143.9, 142.4, 137.9, 137.6, 129.1, 128.0, 128.0, 127.4, 127.0, 123.5, 69.8, 51.7, 50.2, 42.6, 42.2, 23.0, 21.7, 21.5.

IR \( \tilde{\nu} \) (cm\(^{-1}\)) \(2950\) (w), \(1738\) (m), \(1439\) (w), \(1336\) (m), \(1206\) (m), \(1155\) (s), \(1095\) (m), \(1006\) (m), \(876\) (w), \(813\) (w), \(788\) (w), \(704\) (m), 661 (s).

HRMS (nanochip-ESI/LTQ-Orbitrap) \( m/z \): Calcd for C\(_{21}\)H\(_{26}\)NO\(_4\)S\(^+\) ([M + H]\(^+\)): 388.1577; found 388.1571.

**Methyl 2-(2-(3-chlorophenyl)-1-tosylpyrrolidin-2-yl)acetate (1.105e)**
Yield: 45% (46 mg), colorless oil

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.32 – 7.27 (m, 2H), 7.25 – 7.21 (m, 1H), 7.20 – 7.17 (m, 2H), 7.16 – 7.12 (m, 2H), 7.07 (m, 1H), 3.74 (dt, $J = 9.1$, 7.2 Hz, 1H), 3.65 – 3.59 (m, 1H), 3.62 (d, $J = 16.4$ Hz, 1H), 3.62 (s, 3H), 3.38 (d, $J = 16.4$ Hz, 1H), 2.75 (dt, $J = 13.2$, 7.8 Hz, 1H), 2.38 (s, 3H), 2.21 (ddd, $J = 13.3$, 7.4, 5.8 Hz, 1H), 2.01 – 1.91 (m, 2H).

$^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 171.2, 146.1, 143.0, 137.6, 134.2, 129.4, 129.3, 127.4, 127.0, 126.8, 124.7, 69.4, 51.8, 50.2, 42.3, 42.2, 23.0, 21.6.

IR $\nu$ (cm$^{-1}$) 2954 (w), 1738 (m), 1337 (s), 1156 (s), 1096 (m), 910 (m), 733 (m), 665 (m).

HRMS (ESI/QTOF) m/z: Calcd for C$_{20}$H$_{22}$ClINaO$_4$S$^+$ ([M + Na]$^+$): 430.0850; found 430.0853.

**Synthesis of d$_3$-methyl formate (1.118)**

A mixture of 13.80 g (0.3 mol) of formic acid, 9.60 g (0.3 mol) of d$_4$-methanol, and 1 mL of boron trifluoride methanol complex (0.00758 mol) was placed into a 100 mL reaction flask equipped with a magnetic stirrer and a distillation set up with Vigreux column and a receiving flask cooled to about 0 °C. The reaction flask was immersed in a silicon bath at 55–60° and heated with stirring. The ester began to distill almost immediately at 27 °C. In about 1 hour, 9 g of 1.118 was collected and the boiling point rose to 29 °C. The temperature of the bath was increased to 70 °C and within 2 hours additional 7 g of ester was obtained. The obtained liquid was washed with saturated sodium bicarbonate solution, brine and dried over sodium sulfate. The total yield was 15 g (82%).

Colorless liquid

Boiling point: 29 °C

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 11.63 (s, 1H).

$^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 161.1, 49.2 (sept, $J = 22.4$ Hz).
Methyl 6-hydroxy-3-methoxy-3-phenylhexanoate (1.101)

Yield: 15.4 mg (25%), colorless oil

$^1$H NMR (400 MHz, $C_6D_6$) δ 7.55 (s, 1H), 7.26 – 7.23 (m, 2H), 7.20 – 7.11 (m, 1H), 7.09 – 7.04 (m, 1H), 3.85 (t, $J = 6.6$ Hz, 1H), 3.34 – 3.19 (m, 1H), 3.19 (s, 3H), 3.15 – 2.99 (m, 1H), 2.95 (s, 3H), 2.73 (d, $J = 14.0$ Hz, 1H), 2.69 (d, $J = 14.0$ Hz, 1H), 2.11 (ddd, $J = 14.0$, 11.1, 5.5 Hz, 1H), 1.89 (ddd, $J = 14.0$, 11.2, 5.1 Hz, 1H), 1.50 – 1.41 (m, 2H).

$^{13}$C NMR (101 MHz, $C_6D_6$) δ 170.3, 160.7, 143.5, 127.8, 127.0, 80.1, 64.1, 51.3, 50.2, 42.1, 33.7, 23.4

Methyl-d3 3-(methoxy-d3)-3-phenylbutanoate (1.120)

The compound was prepared according to General procedure B by using d$_3$-methyl formate as solvent instead of methyl formate.

Yield: 66%, yellow oil

$^1$H NMR (400 MHz, CDCl$_3$) δ 7.42 – 7.33 (m, 4H), 7.32 – 7.23 (m, 1H), 2.84 (d, $J = 13.7$ Hz, 1H), 2.74 (d, $J = 13.7$ Hz, 1H), 1.74 (s, 3H).

$^{13}$C NMR (101 MHz, CDCl$_3$) δ 170.9, 143.8, 128.5, 127.5, 126.3, 77.8, 50.9 (sept, $J = 22.4$ Hz ), 49.9 (sept, $J = 21.6$ Hz), 47.8, 23.2.

IR ν (cm$^{-1}$) 2929 (w), 2209 (w), 2068 (w), 1735 (s), 1448 (w), 1332 (m), 1197 (m), 1114 (s), 1088 (s), 767 (m), 702 (m).
HRMS (ESI/QTOF): m/z calcd for C_{11}H_{10}D_{3}O_{3} ([M – CD_{3}]^{+}): 196.1053; found: 196.1054.

Methyl (E)-6-methoxy-3-phenylhex-3-enoate (1.113)

Yield: 27% (contains 5% Z-isomer), yellow oil

$^{1}H$ NMR (400 MHz, Chloroform-\text{d}) $\delta$ 7.41 – 7.35 (m, 2H), 7.34 – 7.27 (m, 2H), 7.25 – 7.21 (m, 1H), 5.99 (t, $J = 7.2$ Hz, 1H), 3.65 (s, 3H), 3.54 (s, 2H), 3.50 (t, $J = 6.8$ Hz, 2H), 3.37 (s, 3H), 2.51 (q, $J = 6.9$ Hz, 2H).

$^{13}C$ NMR (101 MHz, CDCl$_3$) $\delta$ 171.9, 142.1, 134.1, 128.8, 128.5, 128.3, 127.2, 126.1, 72.0, 58.8, 52.1, 36.0, 29.8.

IR: $\nu$ (cm$^{-1}$) 2928 (w), 2364 (w), 1735 (s), 1435 (m), 1319 (m), 1255 (m), 1160 (s), 1113 (s), 1017 (m), 871 (w), 759 (m), 697 (m).

HRMS (ESI/QTOF) m/z: Calcd for C_{14}H_{18}NaO_{3}$^+$ ([M + Na]$^+$): 257.1148; found 257.1154.

$\{[\text{Cl}_{2}\text{NN}]\text{Cu}\}_2\text{(benzene)}$ (1.124)

The title compound was prepared according to a literature procedure and all the spectroscopic data matched with the reported values.$^{32}$
\[ \{[\text{Cl}_2\text{NN}]\text{Cu}\}_2\text{(styrene)} \] (1.125)

Procedure (in the glovebox): Dissolve \([\text{Cl}_2\text{NN}]\text{Cu(I)}\{\text{benzene}\}\) complex (21 mg, 0.04 mmol, 1 equiv) in degassed C\(_6\)D\(_6\) and add styrene (4 \(\mu\)L, 0.04 mmol, 1 equiv). Mix it (in the NMR tube) for 5 minutes, while the poison-green solution turns into dark brown.

Procedure (in the glovebox): Into a suspension of \([\text{Cl}_2\text{NN}]\text{Cu(I)}\{\text{benzene}\}\) (260 mg, 0.5 mmol, 1 equiv) in pentane (8 mL) was added styrene (56 \(\mu\)L, 0.5 mmol, 1 equiv) at room temperature. The sand-brown slurry was stirred overnight and subsequent filtration provided the pure product as a white solid (73\% yield, 200 mg). The mother liquor was let to evaporate to ~2 mL and upon cooling to -20 °C after 12 hours the product precipitated from the mother liquor as white pointy crystals. The obtained crystals were eligible for single crystal X-ray diffraction analysis.

CCDC deposition number: 1900564

\(^1\)H NMR (400 MHz, C\(_6\)D\(_6\)) \(\delta\) 7.15 – 6.91 (m, 4H), 6.91 – 6.85 (m, 3H), 6.74 – 6.70 (m, 2H), 6.39 (t, \(J = 8.0\) Hz, 2H), 4.97 (s, 1H), 4.85 (dd, \(J = 14.9, 9.5\) Hz, 1H), 3.45 (dd, \(J = 14.9, 1.0\) Hz, 1H), 3.35 (dd, \(J = 9.5, 1.0\) Hz, 1H), 1.69 (s, 6H).

\(^{13}\)C NMR (101 MHz, C\(_6\)D\(_6\)) \(\delta\) 165.0, 148.2, 138.4, 131.0 (br), 128.9, 128.8, 127.4, 125.7, 124.7, 96.6, 94.8, 69.0, 23.3.
Comparative NMR spectrum of [[Cl2NN]Cu](styrene) (1.125) and styrene in C6D6
4.2 Experimental procedures and characterization data for Chapter 2

(2-aminophenyl)boronic acid (2.67)

\[
\begin{align*}
\text{B(OH)}_2 & \quad \text{HNO}_3, \text{urea (cat.)} \quad \text{Ac}_2\text{O}, -15^\circ\text{C} \\
2.65 & \quad \text{O}_2\text{N} \\
2.66 & \quad \text{Fe powder, oc.HCl} \quad \text{EtOH, H}_2\text{O, 50}^\circ\text{C} \\
& \quad \text{45\%} \\
2.67 & \\
& \quad \text{54\%}
\end{align*}
\]

(2-aminophenyl)boronic acid was prepared according to a literature procedure.\textsuperscript{33,34} The spectroscopic data were consistent with those previously reported in the literature.

\[
\begin{align*}
\text{N-(3-formylpyridin-4-yl)pivalamide (2.70)}
\end{align*}
\]

\[
\begin{align*}
\text{N-(3-formylpyridin-4-yl)pivalamide was prepared according to a literature procedure.}\textsuperscript{35} \text{ The spectroscopic data were consistent with those previously reported in the literature.}
\end{align*}
\]

\[
\begin{align*}
\text{N-(3-vinylpyridin-4-yl)pivalamide (2.71)}
\end{align*}
\]

\[
\begin{align*}
\text{Methyltriphenylphosphonium bromide (2.07 g, 5.08 mmol) was dissolved in THF (15 mL) and chilled to 0 °C. Potassium tert-butoxide (652 mg, 5.08 mmol) was added over 5 min. The mixture was stirred for 30 min, and then 2.70 (1.00 g, 4.9 mmol) was added dropwise as a [0.1 M] solution in THF. The}
\end{align*}
\]
mixture was stirred an additional 30 min at 0 °C, and then the reaction was warmed to 18°C over one hour. The reaction was quenched via addition of saturated aqueous NH4Cl (10 mL). Obtained mixture was extracted with Et2O (3 × 20 mL). The combined organic phase was dried over MgSO4, the solids were removed via filtration and rinsed several times with additional ether and concentrated. The residue was purified by flash chromatography on silica gel (petroleum – ethyl acetate 3:2 → 1:1) to afford 2.71 as an amorphous solid (734 mg, 65% yield).

\[ ^1H \text{NMR} (400 \text{ MHz, Chloroform-}d) \delta 8.46 (d, J = 0.8 \text{ Hz, 1H}), 8.44 (d, J = 5.7 \text{ Hz, 1H}), 8.25 (d, J = 5.7 \text{ Hz, 1H}), 6.69 (dd, J = 17.5, 11.1 \text{ Hz, 1H}), 5.72 (dd, J = 17.6, 1.2 \text{ Hz, 1H}), 5.64 (dd, J = 11.2, 1.1 \text{ Hz, 1H}), 1.32 (s, 9H). \]

\[ ^{13}\text{C NMR} (101 \text{ MHz, CDCl}_3) \delta 149.9, 149.1, 148.6, 130.0, 119.4, 117.7, 109.8, 39.3, 28.0 \]

HRMS (APCI/QTOF) m/z: [M + H]\(^+\) Calcd for C\(_{12}\)H\(_{17}\)N\(_2\)O\(^+\) 205.1335; Found 205.1336.

IR (\(\nu_{\text{max}}\), cm\(^{-1}\)) 2978 (w), 1711 (s), 1583 (m), 1522 (m), 1450 (s), 1376 (m), 1254 (s), 1158 (s)

**3-vinylpyridin-4-amine (2.72)**

Compound 2.71 (730 mg, 3.57 mmol) was dissolved in 10 ml methanol and 1N aqueous NaOH. The solution was refluxed for 2 hours and then water and ethyl acetate was added to the reaction mixture. The organic layer was washed with water and brine and the organic phase was dried with sodium sulphate. The solids were removed via filtration, followed by concentration under vacuum. The residue was purified by flash chromatography on silica gel (ethyl acetate – methanol triethyl amine 1000:50:5) to afford 2.72 (258 mg, 60% yield). The spectroscopic data were consistent with those previously reported in the literature.\(^{36}\)
tert-butyl phenylcarbamate (2.79)

2.79 was prepared according to a literature procedure. The spectroscopic data were consistent with those previously reported in the literature.

(2-((tert-butoxycarbonyl)amino)phenyl)boronic acid (2.75)

Under argon atmosphere, a solution of tert-butyllithium in n-pentane (220 mL, 2.62 M, 572 mmol) was added to Boc-aniline (50 g, 260 mmol) in dry Et₂O (1000 mL) at -10°C. After stirring the mixture for 3.5 h at -10°C, trimethyl borate (87 mL, 780 mmol) was added over 10 seconds under efficient, rapid stirring. The resulting viscous mixture was allowed to warm up to room temperature and stirred for another 15 h. The mixture was quenched with half-saturated ammonium chloride (200 mL). The aqueous phase was extracted with DCM (4x150 mL). The combined organic layers were dried over sodium sulfate and after the removal of the solids via filtration; the crude mixture was concentrated to ~500 mL. The organic phase was extracted with solution A (see below) (5x70 ml). The combined aqueous phases were acidified with 5 N HCl to pH=5 and was extracted with ethyl acetate (4x70 ml). The combined aqueous phases were further acidified with 5 N HCl to pH=2 and was extracted with ethyl acetate (4x70 ml). The combined aqueous phases were further acidified with 5 N HCl to pH=0-1 and was extracted with ethyl acetate (4x70 ml). The combined organic phases were concentrated under vacuo. 2.75 is obtained in 52% yield (32 grams) as a light yellow solid.

“Solution A” is prepared by measuring 184 grams of D-sorbitol into a 1 liter Erlenmeyer flask and dissolving it in aqueous [1 N] Na₂CO₃ such that the volume of the obtained solution reaches 1 liter. The final concentration of the solution is 1 N with regard to D-sorbitol and Na₂CO₃. The solution can be stored at 18 °C for at least 6 months without deterioration of performance.
The spectroscopic data were consistent with those previously reported in the literature.\(^3\)\(^8\)

\[
\text{triphenyl(3-vinylpyridin-4-yl)-l5-phosphaneyl trifluoromethanesulfonate (2.77)}
\]

Methyltriphenylphosphonium bromide (21.7 g, 60.7 mmol) was dissolved in THF (70 mL) and chilled to 0 °C. Sodium hydride (60% in paraffin, 2.43 g, 60.7 mmol) was added over 5 min. The mixture was stirred for 1 h 30 min, and then the temperature was increased to 60 °C. \(\text{2.78} \) (5 g, 47 mmol) was added at such a pace that the yellow color of the phosphor-ylide remained visible at all times. The mixture was stirred an additional 5 min at 60 °C, and then the reaction was cooled to 18°C. The reaction was quenched via addition of saturated aqueous ammonium chloride solution. The obtained mixture was extracted with Et₂O (3 × 20 mL). The combined organic phase was dried over Na₂SO₄, the solids were removed via filtration and rinsed several times with additional ether and concentrated. The residue was purified by flash chromatography on silica gel (petroleum ether with 1% triethylamine 4:1 → 1:4) to afford \(\text{2.77}\) as a colorless liquid (3.96 g, 80% yield). The spectroscopic data were consistent with those previously reported in the literature.\(^3\)\(^9\)

An oven dried 100 ml round bottom flask equipped with a stir bar was charged with \(\text{2.80} \) (500 mg, 4.76 mmol) and placed under a nitrogen atmosphere. CH₂Cl₂ (47 ml) was added, the reaction vessel cooled to –78 °C and Tf₂O (789 µl, 1.34 g, 4.76 mmol) was added dropwise over 5 minutes. The reaction was stirred for 30 minutes before finely crushed PPh₃ (1.37 g, 5.23 mmol) was added in one portion. The reaction was subjected to three rapid cycles of vacuum/nitrogen backfill and was stirred for a further 30 minutes at –78 °C. 1,8-Diazabicyclo[5.4.0]undec-7-ene (710 µl, 4.76 mmol) was added dropwise via syringe, the cooling bath was removed and the reaction was allowed to warm to room temperature while stirring (approximately 15–30 minutes). The reaction mixture was quenched with H₂O (approximately the same volume as CH₂Cl₂) and the mixture was transferred to a separatory funnel. The mixture was diluted CH₂Cl₂ and the resulting organic layer was washed three times with H₂O. The organic layer was dried (MgSO₄), filtered and concentrated \textit{in vacuo} to approximately 5 mL. An excess of chilled Et₂O (0 °C) was added to the concentrated solution that was then placed in a –20 °C refrigerator for 12 hours. The resulting suspension was filtered on a frit,
the solid washed with chilled Et$_2$O (0 °C) and dried \textit{in vacuo} to provide the pure phosphonium salt as a light beige solid (1.64 g, 67%).

$^1$H NMR (400 MHz, Chloroform-$d$) $\delta$ 9.15 (d, $J = 6.5$ Hz, 1H), 8.86 (s, 1H), 7.94 – 7.88 (m, 3H), 7.79 (td, $J = 7.8$, 3.8 Hz, 6H), 7.72 – 7.66 (m, 6H), 7.26 – 7.20 (m, 1H), 6.20 (dd, $J = 17.0$, 11.0 Hz, 1H), 5.84 (d, $J = 17.1$ Hz, 1H), 5.24 (d, $J = 11.0$ Hz, 1H).

$^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 150.1, 149.1, 136.3, 136.3, 134.7, 134.6, 131.4, 131.2, 130.5, 130.5, 123.3, 116.6, 115.7.

$^{31}$P NMR (162 MHz, CDCl$_3$) $\delta$ 21.8.

HRMS (ESI/QTOF) m/z: [M]+ Calcd for C$_{25}$H$_{21}$NP$^+$ 366.1406; Found 366.1406.

IR (v$_{\text{max, cm}^{-1}}$) 1440 (m), 1264 (s), 1224 (m), 1150 (m), 1106 (m), 1073 (w), 1030 (s), 758 (w), 725 (m), 715 (m), 689 (m)

1,3-bis(2,6-diisopropylphenyl)-4,5-dihydro-1H-imidazol-3-ium chloride (2.84)

1,3-bis(2,6-diisopropylphenyl)-4,5-dihydro-1H-imidazol-3-ium chloride was prepared according to a literature procedure. The spectroscopic data were consistent with those previously reported in the literature.  

4-chloronicotinaldehyde (2.92)
4-chloronicotinaldehyde was prepared according to a literature procedure. The spectroscopic data were consistent with those previously reported in the literature.

**tert-butyl (2-(3-(dihydroxymethyl)pyridin-4-yl)phenyl)carbamate (2.93)**

2.92 (320 mg, 2.26 mmol), 2.75 (535 mg, 2.26 mmol) and triphenylphosphine (92.6 mg 0.226 mmol) were dissolved in 1,2-dimethoxyethane (4 mL). 4.8 mL of a 2M K₂CO₃ (2.7 equiv) aqueous solution were added and the mixture was purged with argon. Palladium acetate (20 mg, 0.056 mmol) was added and the mixture was refluxed for 18 hours. The two phases were then separated and the aqueous phase was extracted with ethyl acetate. The combined organic phases were washed with water and brine and were dried over MgSO₄. After evaporation of the solvent, the oily residue was purified by flash column chromatography (hexane - aceton 3:2) to afford 595 mg (85%) of 2.93. The compound absorbs light at 354 nm, which facilitates observation with TLC. Please note that the compound was isolated as a 1:1 mixture of two isomers of 2.93, hence the higher number of peaks in the ¹³C NMR spectrum.

**¹H NMR** (400 MHz, Chloroform-δ) δ 8.73 (s, 1H), 8.64 (d, J = 5.5 Hz, 1H), 7.90 (dd, J = 7.8, 1.5 Hz, 1H), 7.80 (dd, J = 11.2, 6.9 Hz, 2H), 7.69 – 7.62 (m, 1H), 7.31 – 7.26 (m, 1H), 6.94 (s, 1H), 1.57 (s, 9H).

**¹³C NMR** (101 MHz, CDCl₃) δ 152.6, 150.2, 148.8, 137.5, 135.0, 132.3, 132.2, 132.1, 130.3, 128.7, 128.6, 125.3, 125.3, 124.6, 124.4, 123.3, 117.0, 83.1, 83.1, 74.5, 28.4.

**HRMS** (ESI/QTOF) m/z: [M – H₂O]⁺ Calcd for C₁₇H₁₉N₂O₃⁺ 299.1396; Found 299.1393.
**IR** ($\nu_{\text{max}}, \text{cm}^{-1}$) 2978 (m), 1703 (s), 1606 (m), 1481 (s), 1329 (s), 1254 (m), 1157 (s), 1119 (m), 1045 (m), 1012 (m), 785 (w), 758 (s), 721 (m), 696 (m)

**tert-butyl (2-(3-vinylpyridin-4-yl)phenyl)carbamate (2.74)**

Methyltriphenylphosphonium bromide (1.39 g, 3.88 mmol) was dissolved in diethyl ether (10 mL) and chilled to 0 °C. Potassium tert-butoxide (435 mg, 3.88 mmol) was added in one portion. The mixture was stirred for 30 min. 2.92 (500 mg, 3.53 mmol) was added dropwise. TLC analysis indicated the end of the reaction and upon completion it was quenched via addition of saturated aqueous ammonium chloride solution. The obtained mixture was extracted with Et$_2$O (3 × 50 mL). The combined organic phases were dried over Na$_2$SO$_4$, the solids were removed via filtration and rinsed several times with additional ether and concentrated. The residue was purified by flash chromatography on silica gel (petrolether – ether with 1% triethylamine 4:1 → 1:4) to afford 2.77 as a slightly volatile colorless liquid. The product was immediately subjected to the next step. The spectroscopic data were consistent with those previously reported in the literature.$^{36}$

In a glovebox, into a pressure flask was measured (2-((tert-butoxycarbonyl)amino)phenyl)boronic acid (975 mg, 4.12 mmol, 1.5 equiv), 2.94 (477 mg, 3.43 mmol, 1 equiv), KF (656 mg, 11.3 mmol, 3.3 equiv), PCy$_3$ (80 mg, 0.29 mmol, 8.4 mol%) and was added 3 ml THF (on large scale 15 ml / g of 2.95). Tris(dibenzylideneacetone)dipalladium(0) (94 mg, 0.1 mmol, 6 mol%) was added finally to the mixture, the cap was sealed and was warmed to 60 °C while vigorous stirring. When TLC indicated the consumption of the starting material, the reaction mixture was diluted with diethyl ether and filtered through a pad of silica gel with copious washings, concentrated and purified by flash column chromatography (hexane:acetone 4:1). 2.74 was obtained as a beige amorphous solid (784 mg, 77% yield).

$^1$H NMR (400 MHz, Chloroform-$d$) δ 8.91 (s, 1H), 8.59 (d, $J = 5.3$ Hz, 1H), 7.92 (d, $J = 8.2$ Hz, 1H), 7.46 (ddd, $J = 8.6, 7.4, 1.7$ Hz, 1H), 7.37 (d, $J = 5.2$ Hz, 1H), 7.20 (td, $J = 7.5, 1.2$ Hz, 1H), 7.13 (dd, $J = 7.6,$
1.7 Hz, 1H), 6.45 (dd, J = 17.7, 11.2 Hz, 1H), 5.96 (s, 1H), 5.87 (d, J = 17.6 Hz, 1H), 5.41 (d, J = 11.2 Hz, 1H), 1.40 (s, 9H).

$^{13}$C NMR (101 MHz, CDCl$_3$) δ 152.8, 145.3, 144.7, 135.3, 133.8, 131.1, 130.3, 129.9, 127.9, 126.1, 124.3, 122.0, 119.5, 81.2, 28.3.

HRMS (ESI/QTOF) m/z: [M + H]$^+$ Calcd for C$_{18}$H$_{23}$N$_2$O$_2$ $^+$ 297.1598; Found 297.1598.

IR ($\nu_{max}$, cm$^{-1}$) 2979 (w), 2360 (m), 1722 (s), 1585 (m), 1522 (m), 1446 (m), 1294 (m), 1240 (m), 1159 (s), 1043 (m), 1022 (m), 916 (w), 835 (m), 796 (w), 717 (s)

methyl 4-((tert-butoxycarbonyl)amino)phenyl)-3-vinylpyridine-1(2H)-carboxylate (2.95)

To a solution of NaBH$_4$ (76 mg, 2 mmol, 1.2 equiv) in methanol (1 ml) at -78°C was added a solution of tert-butyl (2-(3-vinylpyridin-4-yl)phenyl)carbamate (500 mg, 1.68 mmol, 1 equiv) in CHCl$_3$ (250 ul) dropwise. Methyl chloroformate (155 ul, 1 mmol, 1.2 equiv) in ether (125 ul) was added dropwise to the reaction mixture. The reaction was kept at -78°C for 1 hour under vigorous stirring and was warmed to r.t. Full conversion was observed after 6 h at r.t., the volatiles were evaporated under Ar atm. and the crude mixture was purified with flash column chromatography (hexane : ether 9:1) to yield 513 mg of light yellow solid (85%).

$^1$H NMR (400 MHz, Chloroform-$d$) δ 8.04 (d, J = 8.3 Hz, 1H), 7.30 (dt, J = 8.6, 4.5 Hz, 1H), 7.05 – 7.02 (m, 2H), 6.89 (d, J = 7.8 Hz, 1H), 6.32 (s, 1H), 6.21 (dd, J = 17.5, 11.1 Hz, 1H), 5.26 – 5.05 (m, 3H), 4.68 (d, J = 16.1 Hz, 1H), 4.55 (d, J = 15.9 Hz, 1H), 3.87 (d, J = 7.3 Hz, 3H), 1.49 (s, 9H).

$^{13}$C NMR (101 MHz, CDCl$_3$) δ 153.0, 135.9, 132.4, 129.6, 128.8, 127.9, 127.2, 126.3, 125.0, 123.0, 119.8, 114.4, 113.6, 108.0, 80.8, 53.7, 43.5, 28.5.

HRMS (APCI/QTOF) m/z: [M + H]$^+$ Calcd for C$_{20}$H$_{25}$N$_2$O$_4$ $^+$ 357.1809; Found 357.1815.

IR ($\nu_{max}$, cm$^{-1}$) 2978 (w), 2360 (m), 2339 (m), 2297 (w), 1711 (s), 1583 (m), 1522 (m), 1448 (s), 1367 (m), 1244 (s), 1159 (s), 1049 (m), 1026 (m)
2.74 (296 mg, 1 mmol) was dissolved in dichloromethane (10 ml) at 0 °C and trimethyloxonium tetrafluoroborate (163 mg, 1 mmol) was added to the solution in one portion. The reaction mixture was stirred at 0 °C for 24 hours. The volatiles were removed under vacuum and 2.99 was obtained as yellow crystalline solid. (353 mg, 99% yield)

**1H NMR** (400 MHz, Chloroform-d) δ 8.88 (s, 1H), 8.57 (d, J = 6.3 Hz, 1H), 7.72 – 7.64 (m, 2H), 7.45 – 7.39 (m, 1H), 7.18 (t, J = 7.5 Hz, 1H), 7.10 (d, J = 7.6 Hz, 1H), 6.60 (s, 1H), 6.34 (dd, J = 17.6, 11.2 Hz, 1H), 6.09 (d, J = 17.5 Hz, 1H), 5.49 (d, J = 11.2 Hz, 1H), 5.28 (s, 1H), 4.40 (s, 3H), 1.33 (s, 9H).

**13C NMR** (101 MHz, CDCl₃) δ 153.4, 153.3, 142.9, 142.6, 137.1, 135.6, 131.1, 129.6, 129.4, 129.0, 126.9, 124.8, 124.1, 122.9, 81.0, 48.3, 28.1.

**IR** (νmax, cm⁻¹) 2976 (w), 2931 (w), 1718 (m), 1662 (m), 1583 (m), 1516 (m), 1448 (m), 1390 (m), 1367 (m), 1302 (m), 1240 (m), 1159 (s), 1047 (m), 1024 (m), 754 (m)

**HRMS** (APCI/QTOF) m/z: [M]+ Calcd for C₁₉H₂₅N₂O₂⁺ 311.1754; Found 311.1755.

**tert-butyl (2-(1-methyl-3-vinyl-1,2-dihydropyridin-4-yl)phenyl)carbamate (2.97)**

Use degassed solvents and inert atmosphere. Prepare a mixture of ether (2 ml), MeOH (075 ml) and 2.1 M NaOH(aq.) (1.25 ml) and add NaBH₄ (46 mg). Add N-methylpyridinium salt (398 mg) as a solution (1 ml ether + 0.5 ml MeOH) at once while vigorously stirring the mixture at r.t. After exactly
5 min, check TLC (DM91 and HE11) for starting materiel. Multiple product will appear on TLC as a result of decomposition on exposure to air.

Work-up: Add water and ether to the reaction mixture if it is run at small scale and separate the layers using a syringe (20 ml). The organic phase should remain in the syringe and it was washed two times with 2.1M NaOH (aq.) – in the syringe. Into another syringe filled with basic alumina (grade 1) the organic phase was transferred and subsequently filtered (LCMS syringe filter: 22um, d=40 mm) into a tared and inertized rb-flask. The basic alumina was washed four times with degassed ether transferred into the round bottomed flask. The volatiles were evaporated under inert atmosphere. 270 mg (87%) dark yellow oil was obtained.

\[
{^1}H \text{ NMR (400 MHz, Chloroform-d)} \quad \delta \ 8.07 (d, J = 8.4 \ Hz, 1H), \ 7.08 – 6.96 (m, 2H), \ 6.59 (s, 1H), \ 6.21 (q, J = 6.4, 5.6 \ Hz, 2H), \ 4.86 (d, J = 11.0 \ Hz, 1H), \ 4.78 (d, J = 17.4 \ Hz, 1H), \ 4.57 (d, J = 6.9 \ Hz, 1H), \ 4.18 (d, J = 12.6 \ Hz, 1H), \ 4.11 (d, J = 12.7 \ Hz, 1H), \ 2.86 (s, 3H), \ 1.49 (s, 9H).
\]

HRMS (APCI/QTOF) m/z: [M + H]^+ Calcd for C_{19}H_{25}N_{2}O_{2}^+ 313.1911; Found 313.1915.

5,6-dihydro-2H-pyran-2-one (2.109)

5,6-dihydro-2H-pyran-2-one was prepared according to a literature procedure. The spectroscopic data were consistent with those previously reported in the literature.

(Z)-5-((tert-butyldimethylsilyl)oxy)pent-2-enal (2.114)
(Z)-5-(( tert-butyldimethylsilyl)oxy)pent-2-enal was prepared according to a literature procedure. The spectroscopic data were consistent with those previously reported in the literature.

5-(( tert-butyldimethylsilyl)oxy)pent-2-ynal (2.120)

Propiolaldehyde (2.122)

Propiolaldehyde was prepared according to a literature procedure. The spectroscopic data were consistent with those previously reported in the literature.
tert-butyl (2-((tert-butyldimethylsilyl)oxy)-1-oxopent-2-en-yl)-1-methyl-3-vinyl-1,2-dihydropyridin-4-yl)phenyl)carbamate (2.135)

To a solution of 2.97 (100 mg, 0.32 mmol, 1.00 equiv.) in toluene (3.2 mL) at –78 ºC was added catalyst 2.131 (15 mg, 0.0330 mmol) in one portion. The resulting solution was stirred at –78 ºC for 10 minutes before adding 2.120 (102 mg, 0.48 mmol). The solution was stirred at –78 ºC for 24 hours. When TLC analysis indicated the end of the reaction, ethyl acetate and water was added to the reaction mixture and the aqueous phase was extracted with ethyl acetate three times. The combined organic phases were washed with brine and dried on sodium sulphate. The solids were removed by filtration and the volatiles were removed under vacuum. The crude residue was purified by flash column chromatography by using argon instead of pressurized air (hexane – ethyl acetate 4:1). The combined fractions containing the desired product were concentrated in inert atmosphere to obtain 38 mg (23 mg) of 2.135.

**1H NMR (400 MHz, Benzene-d$_6$)** $\delta$ 9.11 (s, 1H), 8.81 (d, $J = 8.4$ Hz, 1H), 7.24 – 7.20 (m, 1H), 6.97 (s, 1H), 6.90 – 6.81 (m, 2H), 6.40 (dt, $J = 17.2$, 8.6 Hz, 2H), 5.58 (s, 1H), 5.46 (d, $J = 13.8$ Hz, 1H), 4.90 – 4.83 (m, 1H), 4.75 (d, $J = 11.1$ Hz, 1H), 3.76 (td, $J = 10.0$, 3.9 Hz, 1H), 3.64 (ddd, $J = 9.9$, 5.2, 4.1 Hz, 1H), 3.43 (d, $J = 13.7$ Hz, 1H), 2.48 (ddd, $J = 14.5$, 9.9, 5.2 Hz, 1H), 2.33 (s, 3H), 1.58 (s, 9H), 0.97 (s, 9H), 0.05 (s, 3H), 0.05 (s, 3H).

**13C NMR (101 MHz, C$_6$D$_6$)** $\delta$ 188.0, 160.0, 153.2, 149.6, 148.4, 144.4, 139.5, 138.1, 136.6, 135.7, 129.6, 129.5, 128.9, 122.8, 119.8, 114.8, 80.7, 66.3, 62.5, 48.9, 45.8, 40.4, 28.6, 26.5, -4.8, -4.9.

**HRMS (ESI/QTOF) m/z:** [M + H]$^+$ Calcd for C$_{30}$H$_{45}$N$_2$O$_4$Si$^+$ 525.3143; Found 525.3141.

**IR (ν$_{max}$ cm$^{-1}$)** 2937 (w), 2856 (w), 2362 (w), 2159 (m), 1729 (m), 1594 (s), 1519 (m), 1446 (m), 1398 (m), 1237 (m), 1158 (s), 1082 (m), 934 (m), 898 (m), 838 (s), 775 (s)
Chapter 4 - Experimental part

4-chloro-3-(2-methoxyvinyl)pyridine (2.147)

To a suspension of methoxymethyltriphenylphosphonium chloride (30 g, 88.8 mmol) in THF at 0 °C was added KOTBu (9.85 g, 88.8 mmol) portionwise and was stirred at room temperature for 40 min. The mixture was cooled to 0 °C and was added 4-chloronicotinaldehyde (8.4 g, 60 mmol) dropwise as a concentrated solution in THF. After 30 min, an aliquot was taken to NMR to determine the full consumption of the starting material. The mixture was concentrated under vacuo, was added water and EtOAc and the organic phase was extracted 3x with EtOAc. The organic phase was dried over Na$_2$SO$_4$, filtered and concentrated under reduced pressure. The crude mixture was added cold diethyl ether, suspended and filtered through glass frit to remove the excess triphenylphosphine oxide. After evaporation of the volatiles the crude mixture was purified by FCC (petrol ether : ethyl acetate 3:2 → petrol ether : ethyl acetate 3:2 + 2% triethylamine ). -2.147 was isolated as an inseparable mixture of geometric isomers (E/Z 7:4) in 85% yield (8.5 g).

$^1$H NMR (400 MHz, Chloroform-$d$) δ 9.23 (s, 1H), 8.56 (s, 1H), 8.27 (d, $J$ = 5.3 Hz, 1H), 8.24 (d, $J$ = 5.3 Hz, 1H), 7.68 (ddd, $J$ = 12.0, 7.6, 1.4 Hz, 1H), 7.58 – 7.52 (m, 1H), 7.46 (ddd, $J$ = 8.6, 5.3, 2.3 Hz, 2H), 7.26 (dt, $J$ = 5.4, 2.8 Hz, 3H), 7.10 (d, $J$ = 13.1 Hz, 1H), 6.35 (d, $J$ = 7.0 Hz, 1H), 5.96 (d, $J$ = 13.0 Hz, 1H), 5.53 (d, $J$ = 7.1 Hz, 1H), 3.83 (d, $J$ = 0.7 Hz, 4H), 3.76 (s, 4H).

$^{13}$C NMR (101 MHz, CDCl$_3$) δ 151.5, 151.4, 150.5, 147.4, 147.0, 146.9, 141.2, 140.6, 132.2, 132.1, 132.0, 132.0, 131.3, 130.4, 128.7, 128.5, 124.5, 124.2, 98.6, 97.9, 61.1, 56.8.

HRMS (ESI/QTOF) m/z: [M + H]$^+$ Calcd for C$_8$H$_9$ClNO$^+$ 170.0367; Found 170.0373.

IR ($\nu_{max}$, cm$^{-1}$) 2935 (w), 2360 (w), 1639 (s), 1570 (m), 1545 (m), 1468 (m), 1400 (m), 1308 (w), 1284 (m), 1242 (s), 1194 (m), 1151 (m), 1126 (m), 1099 (s), 1076 (m), 995 (w), 939 (m), 823 (m), 717 (m)
2-(4-chloropyridin-3-yl)ethan-1-ol (2.148)

To a mixture of TFA (20 ml) and DCM (20 ml) was added 4-chloro-3-(2-methoxyvinyl)pyridine (1 g, 5.9 mmol) at 0°C. After 15 min the cooling bath was removed and the reaction was kept at room temperature until full consumption of the starting material. The volatiles were evaporated and the crude mixture was diluted with ethyl acetate and was washed with NaHCO₃ solution. The aqueous phase was added Na₂CO₃ solution and was extracted twice with ethyl acetate. The combined organic phases were dried over Na₂SO₄, filtered and concentrated under vacuum. The obtained yellow oil was the pure product and as it was unstable, it was transferred directly to the next step (NaBH₄ reduction to 2-(4-chloropyridin-3-yl)ethyl benzoate).

To the solution of crude 2-(4-chloropyridin-3-yl)acetaldehyde (starting from 1 g 2-(4-chloropyridin-3-yl)acetaldehyde) and methanol MeOH (20 ml) was added NaBH₄ (227 mg, 6 mmol) portionwise at 0°C. After 1 h at 0°C, the reaction mixture was concentrated and was added aq. NH₄Cl (sat.). The aqueous phase was extracted with ethyl acetate (3x) and the combined organic phases were washed with brine, dried over Na₂SO₄, filtered and concentrated under reduced pressure. The obtained residue was purified by flash column chromatography (hexane/ethylacetate 1:1). (710 mg, 76%; on 10 g scale 7.3 g was isolated, 79%)

¹H NMR (400 MHz, Chloroform-d) δ 8.46 (d, J = 3.0 Hz, 1H), 8.32 (d, J = 5.2 Hz, 1H), 7.29 (d, J = 5.3 Hz, 1H), 3.90 (t, J = 6.5 Hz, 2H), 3.01 (t, J = 6.5 Hz, 2H).

¹³C NMR (101 MHz, CDCl₃) δ 151.9, 148.6, 132.0, 128.5, 124.5, 61.3, 34.0.

HRMS (nanochip-ESI/LTQ-Orbitrap) m/z: [M + H]⁺ Calcd for C₇H₉ClNO⁺ 158.0367; Found 158.0369.

IR (νmax, cm⁻¹) 3249 (w), 2367 (w), 2861 (w), 1579 (m), 1558 (m), 1473 (m), 1439 (m), 1403 (m), 1177 (m), 1122 (m), 1082 (s), 1050 (s), 829 (m), 797 (m), 725 (m), 695 (s)
Chapter 4 - Experimental part

2-(4-chloropyridin-3-yl)ethyl benzoate (2.149)

To a solution of 2-(4-chloropyridin-3-yl)ethan-1-ol (2.53 g, 16 mmol, 1 equiv), triethylamine (6.5 ml, 46.5 mmol, 2.9 equiv), DMAP (20 mg, 0.1 mol%) and DCM (80 ml) at 0 °C was added dropwise benzoyl chloride (1.98 ml, 17 mmol, 1.05 equiv). The cooling bath was removed and after consumption of starting material the mixture was added brine. The aqueous layer was washed with DCM 3x and the combined organic phases was washed with brine 2x. The organic phase was dried over Na2SO4, filtered and concentrated under vacuo. The crude mixture was purified with FCC (hexane - ethyl acetate 3:1) affording 4.31 g (98%) of white solid. TLC (hexane/ethylacetate 1:1) Rf(2.149)= 0.66 Rf(2.148)=0.1

1H NMR (400 MHz, Chloroform-d) δ 8.55 (s, 1H), 8.40 (d, J = 5.3 Hz, 1H), 8.02 – 7.95 (m, 2H), 7.58 – 7.52 (m, 1H), 7.42 (t, J = 7.7 Hz, 2H), 7.33 (d, J = 5.3 Hz, 1H), 4.57 (t, J = 6.5 Hz, 2H), 3.24 (t, J = 6.5 Hz, 2H).

13C NMR (101 MHz, CDCl₃) δ 166.5, 152.0, 149.3, 144.1, 133.2, 131.9, 130.0, 129.8, 129.7, 128.6, 124.7, 63.2, 30.4.

IR (ν_max, cm⁻¹) 2966 (w), 2360 (w), 2023 (w), 1718 (s), 1680 (w), 1556 (w), 1473 (w), 1454 (w), 1313 (w), 1273 (s), 1111 (m), 1082 (w), 822 (w), 712 (m)

HRMS (ESI/QTOF) m/z: [M + H]^+ Calcd for C_{14}H_{13}ClNO₂⁺ 262.0629; Found 262.0630.

2-(4-(2-((tert-butoxycarbonyl)amino)phenyl)pyridin-3-yl)ethyl benzoate (2.150)

In a glovebox, into a pressure flask was measured (2-((tert-butoxycarbonyl)amino)phenyl)boronic acid (225.6 mg, 0.95 mmol, 1.5 equiv), 2-(4-chloropyridin-3-yl)ethan-1-ol (100 mg, 0.63 mmol, 1
equiv), KF (121.65 mg, 2.1 mmol, 3.3 equiv), PCy₃ (15 mg, 53.3 umol, 8.4 mol%) and was added 3 ml THF (on large scale 15 ml / g pyridine). Tris(dibenzyldieneacetone)dipalladium(0) (17.43 mg, 19.04 umol, 6 mol%) was added finally to the mixture, the cap was sealed and was warmed to 60 °C while vigorous stirring. When TLC indicated the consumption of the starting material, the reaction mixture was diluted with diethyl ether and filtered through a pad of silica gel with copious washings, concentrated and purified by flash column chromatography (hexane:ethylacetate 3:2). 2.150 was obtained as a white amorphous solid (182 mg, 69% yield).

^1H NMR (400 MHz, Chloroform-­d) δ 8.70 (s, 1H), 8.59 (d, J = 4.9 Hz, 1H), 8.10 (d, J = 8.3 Hz, 1H), 7.96 – 7.90 (m, 2H), 7.54 (ddt, J = 8.0, 6.9, 1.4 Hz, 1H), 7.46 – 7.37 (m, 3H), 7.18 – 7.15 (m, 1H), 7.14 – 7.08 (m, 2H), 6.06 (s, 1H), 4.35 (ddd, J = 11.0, 7.0, 6.1 Hz, 1H), 4.27 (ddd, J = 11.0, 6.8, 6.2 Hz, 1H), 3.01 (dt, J = 14.4, 6.5 Hz, 1H), 2.88 (dt, J = 14.4, 6.6 Hz, 1H), 1.42 (s, 9H).

^13C NMR (101 MHz, CDCl₃) δ 166.4, 152.8, 152.0, 148.9, 146.1, 135.3, 133.2, 132.5, 130.0, 129.7, 129.6, 129.4, 128.6, 128.5, 127.9, 125.3, 123.6, 120.8, 81.1, 64.1, 30.0, 28.3.

HRMS (ESI/QTOF) m/z: [M + H]^+ Calcd for C₂₅H₂₇N₂O₄^+ 419.1965; Found 419.1964.

Tert-butyl (2-(3-(2-hydroxyethyl)pyridin-4-yl)phenyl)carbamate (2.151)

Prepare a solution of water (80 ml), methanol (80 ml) and NaOH (1.8 g, 32 mmol, 2 equiv). To this solution 2.150 (4.62 g, 11 mmol) was added and stirred overnight at 18 °C. After TLC indicated the full consumption of the starting material the reaction mixture was diluted with water and was extracted with ethyl acetate three times. The combined organic phases were dried over sodium sulfate, filtered and concentrated under reduced pressure. The crude mixture was purified by flash column chromatography (EtOAc → EtOAc:MeOH 9:1). 3.47 g of pure 2.151 was obtained as a white foam (quantitative yield).

^1H NMR (400 MHz, Chloroform-d) δ 8.66 (s, 1H), 8.53 (d, J = 4.9 Hz, 1H), 8.00 (d, J = 8.3 Hz, 1H), 7.40 (td, J = 8.3, 7.8, 1.7 Hz, 1H), 7.17 – 7.11 (m, 2H), 7.07 (dd, J = 7.6, 1.7 Hz, 1H), 6.23 (s, 1H), 3.78 – 3.64 (m, 2H), 2.80 (dt, J = 14.1, 7.0 Hz, 1H), 2.69 (dt, J = 14.2, 5.9 Hz, 1H), 1.42 (s, 9H).

^13C NMR (101 MHz, CDCl₃) δ 153.2, 150.9, 147.2, 147.1, 135.2, 133.7, 129.3, 129.1, 125.0, 123.6, 122.0, 80.6, 61.8, 33.4, 28.2.
HRMS (ESI/QTOF) m/z: [M + H]+ Calcd for C_{18}H_{23}N_{2}O_{3}+ 315.1703; Found 315.1709.

IR (ν_{max}, cm^{−1}) 2971 (s), 1704 (s), 1585 (s), 1521 (s), 1445 (s), 1367 (s), 1242 (s), 1158 (s), 1102 (m), 1074 (s), 1057 (s), 1026 (s)

Methyl 4-((tert-butoxycarbonyl)amino)phenyl)-3-(2-hydroxyethyl)pyridine-1(2H)-carboxylate (2.152)

To a solution of methanol (4.56 ml) and sodium borohydride (174 mg, 4.58 mmol) at -78°C was added dropwise a solution of chloroform (1 ml) and tert-butyl (2-((3-(2-hydroxyethyl)pyridin-4-yl)phenyl)carbamate (1.2 g, 3.8 mmol). After stirring at -78°C for 10 min, methyl chloroformate (355 μl, 4.58 mmol) dissolved in ether (490 μl) was added dropwise to the cooled mixture while maintaining the temperature under -70°C and the obtained light orange colored mixture was stirred at this temperature for 30 min. The cooling bath was removed and the reaction mixture was stirred at 20°C for 2 hours. If TLC does not indicate the completion of the reaction, the mixture was put into a 40°C water bath and was stirred for an additional 2 hours. Without this step full conversion may not be achieved. Upon completion, the reaction was quenched with water and was extracted 3 times with ethyl acetate. The combined organic layer was washed with brine, dried over sodium sulfate and the volatiles were removed under vacuum. The obtained crude product was purified with flash column chromatography (petrol ether : ethyl acetate 3:1 to 3:2) (785 mg, 40%)

^1H NMR (400 MHz, Chloroform-d) δ 7.95 (d, J = 8.1 Hz, 1H), 7.33 – 7.18 (m, 2H), 7.19 – 7.11 (m, 1H), 7.05 – 6.98 (m, 2H), 6.86 – 6.68 (m, 1H), 5.24 – 4.88 (m, 1H), 4.63 – 4.28 (m, 2H), 3.82 (s, 3H), 3.81 – 3.60 (m, 2H), 2.35 (s, 1H), 2.27 (dt, J = 14.5, 7.3 Hz, 1H), 2.10 (dt, J = 14.4 Hz, 1H), 1.50 (s, 9H).

^13C NMR (101 MHz, CDCl₃) δ 159.0, 154.3, 152.5, 141.1, 138.1, 133.2, 131.5, 122.7, 121.9, 121.5, 117.6, 109.7, 80.4, 61.0, 53.4, 51.1, 31.4, 28.2

IR (ν_{max}, cm^{−1}) 2978 (m), 1703 (s), 1606 (m), 1481 (m), 1329 (s), 1254 (m), 1157 (s), 1119 (m), 1045 (m), 1012 (m), 785 (w), 758 (s), 721 (m), 696 (m)
Ethyl 5-hydroxypent-3-ynoate (2.156)

Ethyl 5-hydroxypent-3-ynoate was prepared according to a literature procedure. The spectroscopic data were consistent with those previously reported in the literature.

(E)-pent-2-enedioic acid (2.162)

(E)-pent-2-enedioic acid was prepared according to a literature procedure. The spectroscopic data were consistent with those previously reported in the literature.

2H-pyran-2,6(3H)-dione (2.154)

2H-pyran-2,6(3H)-dione was prepared according to a literature procedure. The spectroscopic data were consistent with those previously reported in the literature.

(Z)-5-methoxy-5-oxopent-2-enoic acid (2.163)
(Z)-5-methoxy-5-oxopent-2-enoic acid was prepared according to a literature procedure. The spectroscopic data were consistent with those previously reported in the literature.

1-(tert-butyl) 5-methyl (Z)-pent-2-enedioate (2.167)

To a stirred solution of (Z)-5-methoxy-5-oxopent-2-enoic acid (480 mg, 3.3 mmol, 1 equiv) in dry THF (6.6 ml) a solution of tert-butyl-2,2,2,-trichloroimidate (2.9 g, 13.3 mmol, 4 equiv) in cyclohexane (13 ml) was added dropwise at room temperature, followed by addition of BF3*OEt2 (<5 µl). After stirring the mixture at room temperature for 30 min, TLC (HE41) indicated the consumption of the starting material. The volatiles were evaporated under reduced pressure and the crude mixture was purified by flash column chromatography (hexane : ether 20:1). The pure product was obtained as a colorless oil. The spectroscopic data were consistent with those previously reported in the literature.

$^1$H NMR (400 MHz, Chloroform-d) δ 6.38 (dt, $J = 11.5$, 6.9 Hz, 1H), 5.84 (dt, $J = 11.5$, 2.0 Hz, 1H), 3.74 (dd, $J = 6.9$, 2.0 Hz, 2H), 3.71 (s, 3H), 1.47 (s, 9H).

$^{13}$C NMR (101 MHz, CDCl3) δ 171.8, 165.5, 138.9, 124.0, 80.8, 52.1, 33.9, 28.3.
4.3 Experimental procedures and characterization data for Chapter 3

4.3.1 Experimental procedures and spectroscopical data of the synthetic sequence leading to the most advanced intermediate 3.123

The synthetic sequence leading to the closest intermediate (3.123) to voacaficine B (3.2) is shown below. In this section the experimental details of this synthetic sequence is discussed first. The protocols and analytical data related to all other compounds can be found in section 4.3.2.

Scheme 83 - Synthetic sequence leading to the most advanced intermediate of the total synthesis.
dimethyl 4-(dimethoxymethyl)-2-hydroxy-3,4-dihydro-2H-pyran-2,6-dicarboxylate (3.39)

\[
\begin{align*}
\text{MeO} & \quad \text{OMe} \\
\text{1 equiv. } 3.26 & \quad + \quad \text{CO}_2 \text{Me} \\
\text{3 equiv. } 3.38 & \quad \xrightarrow{\text{(S)-β-Pro (6 mol%) MeCN, rt, 81\%}} \quad \text{MeO} \quad \text{OMe} \\
\text{3.39} & \quad \text{OMe}
\end{align*}
\]

Dimethyl 4-(dimethoxymethyl)-2-hydroxy-3,4-dihydro-2H-pyran-2,6-dicarboxylate was prepared according to a literature procedure.\(^{49}\) The spectroscopic data were consistent with those previously reported in the literature.\(^{49}\)

dimethyl 2-(dimethoxymethyl)-9-methoxy-1,2,7,12-tetrahydroindolo[2,3-a]quinolizine-4,12b(6H)-dicarboxylate (3.40)

\[
\begin{align*}
\text{MeO} & \quad \text{H} \\
\text{3.14} & \quad + \quad \text{MeO} \quad \text{OMe} \\
\text{3.39} & \quad \xrightarrow{\text{BzOH (20 mol%) toluene, rt, MS 4 Å }} \quad \text{MeO} \quad \text{OMe} \\
\text{3.40} & \quad \text{OMe}
\end{align*}
\]

3.39 (20 g, 69 mmol) and 3.14 (13.1 g, 69 mmol) was dissolved in toluene (600 ml). Molecular sieve (51.7 g, 4 Å) and benzoic acid (1.68 g, 13.8 mmol) was added to the solution and the heterogenous mixture was stirred until TLC analysis indicated the consumption of the starting materials. The molecular sieves were removed by filtration and the organic phase was washed with NaHCO\(_3\) solution. The organic phase was dried with Na\(_2\)SO\(_4\) and concentrated under vacuo. The crude residue was purified by flash column chromatography (hexane-ether 1:1) to yield 3.40 as a light yellow foam (22 g, 72%)
**Chapter 4 - Experimental part**

**1H NMR** (400 MHz, Chloroform-\textit{d}) \( \delta \) 8.11 (s, 1H), 7.27 – 7.22 (m, 1H), 6.90 (d, \( J = 2.5 \) Hz, 1H), 6.84 (dd, \( J = 8.8, 2.5 \) Hz, 1H), 5.83 (dd, \( J = 2.6, 1.1 \) Hz, 1H), 4.05 (d, \( J = 7.7 \) Hz, 1H), 3.92 – 3.85 (m, 1H), 3.84 (s, 4H), 3.83 (s, 3H), 3.75 (s, 3H), 3.39 – 3.33 (m, 1H), 3.35 (s, 3H), 3.28 (s, 3H), 2.67 (ddd, \( J = 15.4, 10.5, 4.8 \) Hz, 1H), 2.59 (dd, \( J = 4.3, 2.8 \) Hz, 1H), 2.53 (ddd, \( J = 13.2, 4.8, 2.1 \) Hz, 1H), 2.37 (ddd, \( J = 9.8, 7.7, 5.2, 2.6 \) Hz, 1H), 2.17 (dd, \( J = 13.4, 9.6 \) Hz, 1H).

**13C NMR** (101 MHz, CDCl\textit{3}) \( \delta \) 173.1, 165.8, 154.3, 138.7, 131.8, 127.2, 115.7, 112.6, 112.2, 111.9, 105.9, 100.7, 63.5, 56.1, 54.4, 53.4, 53.2, 52.3, 45.7, 33.6, 32.9, 20.4.

**IR** (\( \nu_{\text{max}} \), cm\textsuperscript{-1}) 3365 (w), 2949 (w), 2833 (w), 1722 (s), 1626 (m), 1485 (m), 1458 (m), 1437 (m), 1373 (m), 1246 (s), 1217 (s), 1119 (s), 1068 (s), 1049 (m), 1022 (m), 719 (m)

**HRMS** (ESI/QTOF) m/z: [M + H\textsuperscript{+}] Calcd for C\textsubscript{23}H\textsubscript{29}N\textsubscript{2}O\textsubscript{7} 445.1969; Found 445.1976.

**Methyl 4-((benzoyloxy)imino)-2-(dimethoxymethyl)-10-methoxy-5-oxo-2,3,4,5,8,13-hexahydro-1H-azepino[1′,2′:1,2]pyrido[3,4-b]indole-13b(7H)-carboxylate (3.59)**

To a solution of compound **3.40** (3 g, 6.75 mmol) in dry methanol (70 ml) was added O-benzylhydroxylamine (761 \( \mu \)L, 7.4 mmol) and Sc(OTf)\textsubscript{3} (166 mg, 0.337 mmol). The obtained mixture was refluxed until TLC analysis indicated the consumption of the starting materials. The solution was concentrated under vacuum to \( \sim 35 \) ml and was diluted with ethyl acetate and water. The two phases were then separated and the aqueous phase was extracted with ethyl acetate three times. The combined organic phases were washed with water and brine and were dried over Na\textsubscript{2}SO\textsubscript{4}. The solids were removed via filtration and the organic phase was concentrated under vacuo. The oily residue was purified by flash column chromatography (hexane – ether 2:3) to afford **3.58** as a yellow foam of about 90% purity. The obtained material was directly transferred to the next step.
\[^{1}\text{H} \text{NMR}\] (400 MHz, Chloroform-\(d\)) \(\delta\) 7.89 (s, 1H), 7.42 – 7.28 (m, 5H), 7.24 – 7.16 (m, 2H), 6.94 (d, \(J = 2.5\) Hz, 1H), 6.84 (dd, \(J = 8.8\), 2.5 Hz, 1H), 5.27 (d, \(J = 12.2\) Hz, 1H), 5.18 (d, \(J = 12.1\) Hz, 1H), 4.61 (dt, \(J = 12.9\), 4.7 Hz, 1H), 4.18 (d, \(J = 6.1\) Hz, 1H), 3.84 (s, 3H), 3.65 – 3.55 (m, 1H), 3.29 (s, 3H), 3.27 (s, 6H), 2.90 – 2.84 (m, 2H), 2.80 (dd, \(J = 14.2\), 11.4 Hz, 1H), 2.66 (dd, \(J = 19.0\), 12.9 Hz, 1H), 2.55 (ddd, \(J = 18.9\), 3.8, 1.5 Hz, 1H), 2.36 (s, 1H), 2.33 – 2.26 (m, 1H), 2.19 – 2.08 (m, 1H).

\[^{13}\text{C} \text{NMR}\] (101 MHz, CDCl\(_3\)) \(\delta\) 172.5, 165.3, 155.9, 154.6, 137.1, 131.8, 131.7, 129.2, 128.8, 128.5, 128.4, 128.3, 126.5, 125.4, 113.2, 112.2, 110.1, 106.6, 100.6, 77.3, 63.8, 56.0, 54.4, 54.4, 53.6, 40.3, 35.4, 33.9, 26.2, 20.5.

To the methanolic (100 ml) solution of the obtained 3.58, aqueous LiOH ([1 N], 20 ml) was added dropwise at 0 °C. The obtained mixture was stirred until TLC analysis indicated the consumption of the starting material. NaHSO\(_4\) (2.4 g, 20 mmol) was dissolved and the methanol was removed under vacuo. The obtained heterogenous residue was freeze-dried overnight to yield the crude aminoacid as a light orange powder.

The obtained amino acid was dissolved in DMF (40 ml) and was added Hüning’s base (2.21 ml, 13.4 mmol). The solution was cooled to 0 °C and solution of TATU (2.15 g, 6.7 mmol)* in DMF (12 ml) was added dropwise over 20 minutes. The cooling bath was removed and the reaction mixture was quenched with water when TLC analysis indicated the consumption of the starting material. The obtained mixture was extracted with ethyl acetate (5 x 20 mL). The combined organic phase was washed with 10% aqueous lithium chloride solution, brine and dried over Na\(_2\)SO\(_4\). After evaporation of the solvent, the oily residue was purified by flash column chromatography (toluene – ethyl acetate 85:15) to afford 1.1 g of 3.59 as a white crystalline solid.

* TATU can be substituted with HATU or COMU peptide coupling agents without any decrease in synthetic efficiency.

The single-crystal x-ray diffraction structure and .cif file is available upon request.

\[^{1}\text{H} \text{NMR}\] (400 MHz, Chloroform-\(d\)) \(\delta\) 7.89 (s, 1H), 7.42 – 7.28 (m, 5H), 7.24 – 7.16 (m, 2H), 6.94 (d, \(J = 2.5\) Hz, 1H), 6.84 (dd, \(J = 8.8\), 2.5 Hz, 1H), 5.27 (d, \(J = 12.2\) Hz, 1H), 5.18 (d, \(J = 12.1\) Hz, 1H), 4.61 (dt, \(J = 12.9\), 4.7 Hz, 1H), 4.18 (d, \(J = 6.1\) Hz, 1H), 3.84 (s, 3H), 3.65 – 3.55 (m, 1H), 3.29 (s, 3H), 3.27 (s, 6H), 2.90 – 2.84 (m, 2H), 2.80 (dd, \(J = 14.2\), 11.4 Hz, 1H), 2.66 (dd, \(J = 19.0\), 12.9 Hz, 1H), 2.55 (ddd, \(J = 18.9\), 3.8, 1.5 Hz, 1H), 2.36 (s, 1H), 2.33 – 2.26 (m, 1H), 2.19 – 2.08 (m, 1H).

\[^{13}\text{C} \text{NMR}\] (101 MHz, CDCl\(_3\)) \(\delta\) 172.5, 165.3, 155.9, 154.6, 137.1, 131.8, 131.7, 129.2, 128.8, 128.5, 128.4, 128.3, 126.5, 125.4, 113.2, 112.2, 110.1, 106.6, 100.6, 77.3, 63.8, 56.0, 54.4, 54.4, 53.6, 40.3, 35.4, 33.9, 26.2, 20.5.
**IR** ($\nu_{\text{max}}$, cm$^{-1}$) 2926 (s), 2854 (s), 1740 (s), 1689 (s), 1660 (s), 1454 (s), 1361 (s), 1339 (m), 1271 (s), 1240 (s), 1217 (s), 1171 (s), 1116 (s), 1062 (s), 1038 (s), 968 (s), 909 (s), 801 (s), 729 (s)

**HRMS** (ESI/QTOF) m/z: [M + H]$^+$ Calcd for C$_{29}$H$_{34}$N$_3$O$_7$ $^+$ 539.2391; Found 536.2395.

Methyl 2-(dimethoxymethyl)-10-methoxy-4,5-dioxo-2,3,4,5,8,13-hexahydro-1H-aze-pino[1',2':1,2]pyrido[3,4-b]indole-13b(7H)-carboxylate (3.44)

![Chemical structure diagram]

**BEWARE:** deviating from the exact protocol can lead to accident, hence the experimental procedure need to be followed exactly as written.

The CEM Discover SP microwave reactor, equipped with an attenuator for 10 ml vessel, was programmed the following method:

- Dynamic program
- Power ($\mu\lambda$.) = 300 W
- Time (Time) = 1 hour 15 minutes
- Temperature ($T^\circ$) = 110 °C
- Pre-stirring (PreMix) = 1 min
- Stirring speed (Stirring): HIGH
- Cooling = ON (snowflake sign)
- Pressure limit = 20 bar
- Upper limit of power (PowerMAX) = OFF

When the reactor is ready and the method is saved, the reaction vessel can be prepared.

To an acid-washed and oven-dried 10 mL vial made for the CEM Discover SP microwave reactor equipped with a stirring bar was added 3.59 (300 mg, 0.56 mmol) and Pearlman’s catalyst (20% Pd
on charcoal containing 50% water from ABCR, 550 mg, 0.39 mmol). The vial was thoroughly inertized with argon using a Schlenk apparatus. The vessel can be prepared in a glovebox alternatively. Methanol was added to the solids and the mixture was stirred to ensure the free movement of the stirring bar. Once the larger blocks of the solids were crushed into powder by the stirring bar (~10 min), freshly distilled 1,4-cyclohexadiene (533 µL, 5.6 mmol) was added to the mixture and the vial was immediately introduced to the attenuator cavity of the CEM Discover SP microwave reactor and the method was loaded. We process is repeated 5 to 10 times and the content of the vials was diluted with methanol and combined to an Erlenmeyer flask equipped with a stirbar. By gentle heating the combined heterogenous mixture was brought to boiling, while being stirred, and the hot mixture was filtered on a glass fritted funnel. It is important to wash the solids with additional methanol three times, to avoid them getting in contact with air and to immediately neutralize it. The filtrate was added toluene (20 ml/vessel) and concentrated under vacuo. The obtained solid residue is purified with flash column chromatography (toluene – tetrahydrofuran 950:150) to obtain 3.44 as a yellow foam (670 mg / 10 batches, 27%).

\( ^1H \text{NMR} \) (800 MHz, Chloroform-\( d \)) \( \delta \) 7.30 (dd, \( J = 8.8, 0.6 \) Hz, 1H), 6.98 (d, \( J = 2.4 \) Hz, 1H), 6.90 (dd, \( J = 8.8, 2.4 \) Hz, 1H), 4.37 (d, \( J = 6.2 \) Hz, 1H), 3.88 (s, 3H), 3.87 (s, 5H), 3.61 (dt, \( J = 7.8, 6.6 \) Hz, 2H), 3.48 (s, 3H), 3.43 (s, 3H), 3.41 (tt, \( J = 6.5, 2.7 \) Hz, 1H), 3.20 (t, \( J = 7.5 \) Hz, 2H), 2.65 (dd, \( J = 19.0, 6.7 \) Hz, 1H), 2.53 (dd, \( J = 19.0, 2.4 \) Hz, 1H).

\( ^{13}C \text{NMR} \) (201 MHz, CDCl\( _3 \)) \( \delta \) 209.3, 161.2, 156.8, 155.5, 154.5, 135.2, 130.6, 128.1, 127.3, 114.2, 112.7, 111.2, 106.1, 99.4, 56.0, 54.8, 54.8, 53.7, 43.3, 39.8, 37.1, 24.9.

\( \text{IR} \) (\( \nu_{\text{max}}, \text{cm}^{-1} \)) 2922 (s), 2362 (s), 2337 (s), 1747 (s), 1653 (s), 1429 (m), 1244 (m), 1201 (m), 1157 (m), 1120 (m), 1047 (m), 968 (m), 914 (m)

\( \text{HRMS} \) (ESI/QTOF) m/z: \([\text{M} + \text{H}]^+ \) Calcd for C\(_{22}\)H\(_{27}\)N\(_2\)O\(_7\) \( 431.1813 \); Found 431.1814.

**Methyl 2-{dimethoxymethyl}-4',10-dimethoxy-5-oxo-4'-(trimethylsilyloxy)-2,3,8,13-tetrahydro-1H,5H-spiro[azepino[1',2':1,2]pyrido[3,4-b]indole-4,2'-oxetane]-13b(7H)-carboxylate (3.123)**
To a solution of 3.44 (100 mg, 0.23 mmol) in chloroform (1.1 ml, [0.2 M]), was added Mg(OTf)\(_2\) (22.5 mg, 0.069 mmol, 30 mol%) at 18 °C. The reaction mixture was stirred until complete dissolution of the catalyst and ((1-methoxyvinyl)oxy)trimethylsilane (340 mg, 2.3 mmol) was added dropwise over 15 minutes. When TLC analysis indicated the consumption of the starting material, the reaction mixture was diluted with chloroform and water. The aqueous phase was separated and washed with chloroform three times. The combined organic phases were washed with water and brine and were dried over Na\(_2\)SO\(_4\). After evaporation of the solvent, a light yellow solid was obtained with a purity of 92-98%. Further purification is possible with flash column chromatography (hexane-ethylacetate, 4:1) to obtain 3.123 as light yellow foam (117 mg, 87%).

\(^{1}H\) NMR (400 MHz, Chloroform-\text{d}) \(\delta\) 7.72 (s, 1H), 7.21 (d, \(J = 8.6\) Hz, 1H), 6.93 (d, \(J = 2.5\) Hz, 1H), 6.83 (dd, \(J = 8.7, 2.5\) Hz, 1H), 4.24 (d, \(J = 6.7\) Hz, 1H), 3.86 (s, 3H), 3.83 (s, 3H), 3.57 (s, 3H), 3.45 (d, \(J = 16.0\) Hz, 1H), 3.36 – 3.36 (m, 4H), 3.35 – 3.35 (m, 4H), 3.20 – 3.11 (m, 1H), 2.81 – 2.75 (m, 1H), 2.75 – 2.68 (m, 1H), 2.65 – 2.56 (m, 2H), 2.06 – 2.00 (m, 1H), 1.80 – 1.67 (m, 2H), 0.05 (s, 9H).

\(^{13}C\) NMR (101 MHz, CDCl\(_3\)) \(\delta\) 170.8, 170.6, 154.1, 135.7, 132.0, 127.7, 116.0, 111.9, 111.6, 109.5, 107.0, 100.7, 95.4, 72.1, 56.1, 54.9, 52.8, 52.2, 51.6, 51.3, 44.0, 41.6, 40.5, 38.3, 37.7, 20.9, 1.4.

IR (\(\nu_{\text{max}}, \text{cm}^{-1}\)) 2952 (m), 1738 (s), 1628 (w), 1593 (w), 1529 (w), 1483 (m), 1456 (m), 1439 (m), 1350 (m), 1315 (m), 1277 (m), 1252 (s), 1213 (s), 1173 (s), 1153 (s), 1095 (s), 1066 (s), 1045 (s), 966 (m), 908 (m), 883 (s), 847 (s), 760 (m), 723 (m), 654 (s)

HRMS (ESI/QTOF) m/z: [M + H]\(^{+}\) Calcd for C\(_{28}\)H\(_{43}\)N\(_2\)O\(_9\)Si\(^{+}\) 577.2576; Found 577.2581.
4.3.2 Experimental procedures and spectroscopical data of all other intermediates and side products

Diethyl 4-(dimethoxymethyl)-2-hydroxy-3,4-dihydro-2H-pyran-2,6-dicarboxylate (3.26)

Diethyl (2S,4S)-4-(dimethoxymethyl)-2-hydroxy-3,4-dihydro-2H-pyran-2,6-dicarboxylate as prepared according to a literature procedure.49 The spectroscopic data were consistent with those previously reported in the literature.49

Diethyl 2-(dimethoxymethyl)-9-methoxy-1,2,7,12-tetrahydroindolo[2,3-a]quinolizine-4,12b(6H)-dicarboxylate (3.28)

3.26 (500 mg, 1.57 mmol) and 3.14 (270 mg, 1.42 mmol) was dissolved in a mixture of DCE (4 ml) and toluene (4 ml). Molecular sieve (1.2 g, 4 Å) and benzoic acid (35 mg, 0.29 mmol) was added to the solution and the heterogenous mixture was stirred until TLC analysis indicated the consumption of the starting materials. The molecular sieves were removed by filtration and the organic phase was washed with NaHCO₃ solution. The organic phase was dried with Na₂SO₄ and concentrated under vacuo. The crude residue was purified by flash column chromatography (hexane-ether 1:1) to yield 3.28 as a light yellow foam (523 mg, 75%)

¹H NMR (400 MHz, Chloroform-d) δ 8.08 (s, 1H), 7.25 (d, J = 8.8 Hz, 1H), 6.91 (d, J = 2.4 Hz, 1H), 6.84 (dd, J = 8.8, 2.5 Hz, 1H), 5.77 – 5.75 (m, 1H), 4.29 (q, J = 6.9 Hz, 2H), 4.20 (dddd, J = 17.9, 10.8, 7.1, 3.7 Hz, 2H),
4.07 (d, J = 7.7 Hz, 1H), 3.89 (ddd, J = 14.6, 4.9, 2.6 Hz, 1H), 3.84 (s, 3H), 3.36 (s, 3H), 3.41 – 3.28 (m, 1H), 3.28 (s, 3H), 2.66 (ddd, J = 15.6, 10.7, 4.8 Hz, 1H), 2.60 – 2.48 (m, 2H), 2.37 (dddd, J = 9.7, 7.5, 4.8, 2.4 Hz, 1H), 2.17 (dd, J = 13.3, 9.6 Hz, 1H), 1.34 (t, J = 7.1 Hz, 3H), 1.27 (t, J = 7.0 Hz, 4H).

$^{13}$C NMR (101 MHz, CDCl$_3$) δ 172.6, 165.4, 154.3, 139.1, 131.9, 127.3, 114.7, 112.5, 112.2, 111.9, 106.0, 100.6, 63.4, 62.2, 61.2, 56.1, 54.4, 53.3, 45.5, 33.6, 32.9, 20.4, 14.4, 14.3.

HRMS (ESI/QTOF) m/z: [M + H]$^+$ Calcd for C$_{25}$H$_{33}$N$_2$O$_7$ 473.2282; Found 473.2281.

IR (ν$_{max}$, cm$^{-1}$) 3352 (m), 2979 (m), 2928 (m), 2833 (m), 2257 (m), 2162 (m), 1719 (s), 1631 (m), 1485 (m), 1460 (s), 1371 (m), 1264 (s), 1220 (s), 1156 (s), 1074 (s), 1055 (s), 1030 (s), 973 (m), 675 (s)

Diethyl 2-(dimethoxymethyl)-9-methoxy-1,2,7,12-tetrahydroindolo[2,3-a]quinolizine-4,12b(6H)-dicarboxylate (3.27)

A solution of 3.26 (500 mg, 1.57 mmol) and 3.14 (270 mg, 1.42 mmol) in 1,1,1,3,3,3-hexafluoropropan-2-ol (3 ml) was refluxed until TLC analysis indicated the consumption of the starting materials (~1.5 day). The reaction mixture was concentrated under vacuo and the crude residue was purified by flash column chromatography (hexane-ether 3:2) to yield 3.27 as a dark brown amorphous solid (371 mg, 59%).

$^1$H NMR (400 MHz, CDCl$_3$) δ $^1$H NMR (400 MHz, Chloroform-d) δ 8.10 (s, 1H), 7.22 (d, J = 8.8 Hz, 1H), 6.94 (d, J = 2.5 Hz, 1H), 6.84 (dd, J = 8.8, 2.5 Hz, 1H), 5.95 (t, J = 2.0 Hz, 1H), 4.38 – 4.24 (m, 3H), 4.17 – 4.04 (m, 2H), 4.08 (d, J = 7.1 Hz, 1H), 3.85 (s, 4H), 3.61 (dt, J = 12.2, 4.8 Hz, 1H), 3.39 (s, 3H), 3.36 (s, 3H), 3.15 (ddd, J = 12.4, 8.3, 4.2 Hz, 1H), 2.96 – 2.88 (m, 1H), 2.82 – 2.71 (m, 1H), 2.71 – 2.62 (m, 2H), 1.85 – 1.73 (m, 1H), 1.35 (t, J = 7.1 Hz, 3H), 1.21 (t, J = 7.1 Hz, 3H).

$^{13}$C NMR (101 MHz, CDCl$_3$) δ 172.7, 165.2, 154.3, 140.4, 132.0, 131.5, 127.1, 115.5, 112.6, 111.9, 110.3, 106.5, 100.8, 63.7, 62.1, 61.2, 56.1, 54.3, 53.5, 46.2, 35.9, 32.0, 21.9, 14.4, 14.3.

IR (ν$_{max}$, cm$^{-1}$) 2937 (m), 2724 (s), 1626 (s), 1485 (s), 1458 (s), 1439 (s), 1252 (s), 1217 (s), 1120 (s), 962 (s), 916 (s), 733 (s)

HRMS (ESI/QTOF) m/z: [M + H]$^+$ Calcd for C$_{25}$H$_{33}$N$_2$O$_7$ 473.2282; Found 473.2287.
Ethyl (E)-1-(2-(dimethoxymethyl)-5-ethoxy-4-(hydroxyimino)-5-oxopentyl)-6-methoxy-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-1-carboxylate

To a solution of compound 3.27 (3.2 g, 6.75 mmol) in dry methanol (70 ml) was added hydroxylamine hydrochloride (2.11 g, 31 mmol) and Sc(OTf)$_3$ (322 mg, 0.675 mmol). The obtained mixture was refluxed until TLC analysis indicated the consumption of the starting materials. The solution was concentrated under vacuum to ~35 ml and was diluted with ethyl acetate and water. The two phases were then separated and the aqueous phase was extracted with ethyl acetate three times. The combined organic phases were washed with water and brine and were dried over Na$_2$SO$_4$. The solids were removed via filtration and the organic phase was concentrated under vacuo. The oily residue was purified by flash column chromatography (hexane – ethyl acetate 1:1) to afford 3.48 as a yellow foam (2.21 g, 65%).

$^1$H NMR (400 MHz, Chloroform-d) $\delta$ 8.26 (s, 1H), 7.22 (d, $J = 8.7$ Hz, 1H), 6.91 (d, $J = 2.3$ Hz, 1H), 6.82 (dd, $J = 8.8$, 2.4 Hz, 1H), 4.28 (q, $J = 7.2$ Hz, 2H), 4.26 – 4.14 (m, 2H), 3.96 (d, $J = 3.6$ Hz, 1H), 3.84 (s, 3H), 3.22 (s, 2H), 3.08 (s, 1H), 3.02 (s, 2H), 2.79 (dd, $J = 13.6$, 7.7 Hz, 2H), 2.72 – 2.59 (m, 2H), 2.42 (dd, $J = 14.7$, 3.3 Hz, 1H), 2.13 (s, 1H), 1.81 (dd, $J = 14.8$, 6.4 Hz, 1H), 1.56 (dt, $J = 14.2$, 7.2 Hz, 1H), 1.32 (t, $J = 7.2$ Hz, 3H), 1.29 – 1.25 (m, 4H).

$^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 164.1, 154.1, 152.9, 131.8, 131.5, 127.1, 112.3, 111.9, 111.8, 107.9, 100.6, 63.0, 62.2, 61.8, 56.1, 55.4, 41.2, 41.0, 37.9, 35.0, 27.0, 24.0, 21.7, 20.9, 17.6, 17.4, 14.8, 14.4, 14.3, 14.3.

IR (v$_{max}$, cm$^{-1}$) 3329 (m), 2931 (m), 2834 (m), 1724 (s), 1487 (m), 1458 (s), 1375 (m), 1297 (m), 1264 (m), 1216 (s), 1155 (s), 1140 (s), 1118 (s), 1081 (s), 1066 (s), 1026 (s), 981 (m), 859 (m)

HRMS (ESI/QTOF) m/z: [M + H]$^+$ Calcd for C$_{25}$H$_{36}$N$_3$O$_8$ $^+$ 506.2497; Found 506.2508.
Chapter 4 - Experimental part

**Ethyl (E)-1-(2-(dimethoxymethyl)-5-ethoxy-4-(methoxyimino)-5-oxopentyl)-6-methoxy-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-1-carboxylate (3.41)**

To a solution of compound **3.27** (3.2 g, 6.75 mmol) in **dry** methanol (70 ml) was added O-methylhydroxylamine (2.54 g, 30 mmol) and Sc(OTf)$_3$ (166 mg, 0.338 mmol). The obtained mixture was refluxed until TLC analysis indicated the consumption of the starting materials. The solution was concentrated under vacuum to ~35 ml and was diluted with ethyl acetate and water. The two phases were then separated and the aqueous phase was extracted with ethyl acetate three times. The combined organic phases were washed with water and brine and were dried over Na$_2$SO$_4$. The solids were removed via filtration and the organic phase was concentrated under vacuo. The oily residue was purified by flash column chromatography (hexane – ethyl acetate 2:1) to afford **3.34** as a yellow foam (2.14 g, 61%).

**$^1$H NMR** (400 MHz, Chloroform-$_d$) δ 8.20 (s, 1H), 7.22 (d, $J = 8.7$ Hz, 1H), 6.92 (d, $J = 2.4$ Hz, 1H), 6.82 (dd, $J = 8.7, 2.4$ Hz, 1H), 4.30 (q, $J = 7.1$ Hz, 2H), 4.24 – 4.14 (m, 2H), 3.98 (s, 3H), 3.89 (d, $J = 3.7$ Hz, 1H), 3.84 (s, 3H), 3.20 (s, 3H), 3.02 (s, 3H), 2.79 – 2.63 (m, 2H), 2.36 (dd, $J = 14.9, 3.9$ Hz, 1H), 2.18 (td, $J = 6.9, 3.5$ Hz, 1H), 1.73 (dd, $J = 14.7, 6.0$ Hz, 1H), 1.33 (t, $J = 7.1$ Hz, 3H), 1.28 (t, $J = 7.2$ Hz, 3H).

**$^{13}$C NMR** (101 MHz, CDCl$_3$) δ 174.4, 163.9, 154.0, 131.4, 127.2, 112.1, 111.7, 108.0, 100.6, 63.0, 62.9, 61.9, 61.7, 56.1, 55.3, 41.2, 38.0, 34.9, 27.3, 24.0, 22.2, 14.4, 14.4.

**IR** ($v_{max}$, cm$^{-1}$) 3394 (w), 2941 (w), 2833 (w), 1723 (s), 1482 (m), 1456 (m), 1373 (w), 1297 (m), 1215 (s), 1152 (m), 1122 (m), 1079 (m), 1047 (s), 933 (w)

**HRMS** (ESI/QTOF) m/z: [M + H]$^+$ Calcd for C$_{26}$H$_{38}$N$_3$O$_8$+ 520.2653; Found 520.2664.
To a solution of compound 3.40 (1 g, 2.25 mmol) in dry methanol (23 ml) was added O-methylhydroxylamine hydrochloride (751 mg, 9 mmol) and Sc(OTf)$_3$ (56 mg, 0.112 mmol). The obtained mixture was refluxed until TLC analysis indicated the consumption of the starting materials. The solution was concentrated under vacuum to ~12 ml and was diluted with ethyl acetate and water. The two phases were then separated and the aqueous phase was extracted with ethyl acetate three times. The combined organic phases were washed with water and brine and were dried over Na$_2$SO$_4$. The solids were removed via filtration and the organic phase was concentrated under vacuo. The oily residue was purified by flash column chromatography (hexane – ethyl acetate 3:2 $\rightarrow$ 1:1) to afford 3.41 as a yellow foam (862 mg, 78%).

$^1$H NMR (400 MHz, Chloroform-d) $\delta$ 8.18 (s, 1H), 7.22 (d, $J$ = 8.7 Hz, 1H), 6.92 (d, $J$ = 2.4 Hz, 1H), 6.82 (dd, $J$ = 8.8, 2.5 Hz, 1H), 3.97 (s, 3H), 3.91 (d, $J$ = 3.7 Hz, 1H), 3.84 (d, $J$ = 1.2 Hz, 6H), 3.74 (s, 3H), 3.21 (s, 3H), 3.21 – 2.98 (m, 1H), 3.04 (s, 3H), 2.81 – 2.58 (m, 4H), 2.37 (dd, $J$ = 14.8, 3.6 Hz, 1H), 2.14 (qq, $J$ = 6.9, 3.6, 2.9 Hz, 1H), 1.72 (dd, $J$ = 14.8, 6.1 Hz, 1H).

$^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 174.9, 164.4, 154.1, 152.5, 132.3, 131.4, 127.2, 112.2, 112.1, 111.7, 108.1, 100.6, 63.1, 63.0, 56.1, 55.3, 55.3, 52.8, 52.7, 41.2, 37.8, 34.9, 27.5, 22.1.

IR (vmax, cm$^{-1}$) 2943 (w), 2833 (w), 1726 (m), 1485 (w), 1452 (w), 1437 (m), 1294 (w), 1213 (m), 1144 (m), 1120 (m), 1045 (m), 1001 (w), 972 (w), 908 (s), 833 (w), 796 (w), 729 (s)

HRMS (ESI/QTOF) m/z: [M + H]$^+$ Calcd for C$_{24}$H$_{34}$N$_3$O$_8$ + 492.2340; Found 492.2342.
To the methanolic (100 ml) solution of 3.41 (1.8 g, 3.66 mmol), aqueous LiOH ([1 N], 7.33 ml) was added dropwise at 0 °C. The obtained mixture was stirred until TLC analysis indicated the consumption of the starting material. NaHSO₄ (880 mg, 7.33 mmol) was dissolved and the methanol was removed under vacuo. The obtained heterogenous residue was freeze-dried overnight to yield the crude aminoacid (3.42) as a light orange powder.

The obtained amino acid (3.42) was dissolved in DMF (40 ml) and was added Hünig’s base (2.34 ml, 14.2 mmol). The solution was cooled to 0 °C and solution of HATU (2.7 g, 7.1 mmol)* in DMF (12 ml) was added dropwise over 20 minutes. The cooling bath was removed and the reaction mixture was quenched with water, when TLC analysis indicated the consumption of the starting material. The obtained mixture was extracted with ethyl acetate (5 × 20 mL). The combined organic phase was washed with 10% aqueous lithium chloride solution, brine and dried over Na₂SO₄. After evaporation of the solvent, the oily residue was purified by flash column chromatography (hexane – ethyl acetate 3:2 → 1:1) to afford 3.43 (1.05 g, 65%) as a white crystalline solid.

*HATU can be substituted with TATU or COMU peptide coupling agents without any decrease in synthetic efficiency.

The single-crystal x-ray diffraction structure and .cif file is available upon request.
$^1$H NMR (400 MHz, Chloroform-$d$) $\delta$ 8.37 – 8.17 (m, 1H), 7.21 (d, $J$ = 8.8 Hz, 1H), 6.95 (d, $J$ = 2.4 Hz, 1H), 6.84 (ddd, $J$ = 8.8, 2.5, 1.4 Hz, 1H), 4.70 (dt, $J$ = 13.0, 4.5 Hz, 1H), 4.01 (dd, $J$ = 6.0, 1.4 Hz, 1H), 3.98 (s, 3H), 3.83 (s, 3H), 3.56 (s, 3H), 3.53 – 3.44 (m, 1H), 3.26 (s, 3H), 2.90 – 2.81 (m, 1H), 2.63 (d, $J$ = 19.0, 13.1 Hz, 1H), 2.49 (dd, $J$ = 18.9, 3.6, 1.6 Hz, 1H), 2.29 (ddd, $J$ = 14.2, 5.0, 1.5 Hz, 1H), 2.20 – 2.06 (m, 1H).

$^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 172.6, 165.1, 155.6, 154.5, 131.7, 126.4, 113.1, 112.1, 109.8, 106.6, 100.5, 63.7, 62.9, 55.9, 54.5, 54.3, 53.9, 40.1, 35.0, 33.9, 25.9, 20.5.

IR ($\nu_{\max}$, cm$^{-1}$) 3296 (w), 2939 (w), 2833 (w), 1734 (m), 1643 (s), 1595 (w), 1487 (m), 1456 (m), 1427 (m), 1404 (m), 1263 (m), 1238 (m), 1217 (s), 1173 (m), 1128 (m), 1043 (s), 966 (w), 895 (m), 847 (w), 735 (m), 719 (w), 692 (w).

HRMS (ESI/QTOF) m/z: [M + H]$^+$ Calcd for C$_{23}$H$_{30}$N$_3$O$_7$ 460.2078; Found 460.2085.

Methyl (E)-2-(hydroxymethyl)-10-methoxy-4-(methoxyimino)-5-oxo-2,3,4,5,8,13-hexahydro-1H-azepino[1',2':1,2]pyrido[3,4-b]indole-13b(7H)-carboxylate (3.46)

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

To a solution of 3.43 (46 mg, 0.1 mmol) in acetonitrile (1600 μL) was added dropwise a solution of copper(II) chloride dihydrate (34 mg, 0.2 mmol) in distilled water (400 μL) under vigorous stirring. The obtained mixture was heated at 75 °C until TLC analysis indicated the consumption of the starting material (~30 min). The reaction mixture was diluted with saturated solution of NaHCO$_3$ and ethyl acetate. The two phases were then separated and the aqueous phase was extracted with ethyl acetate three times. The combined organic phases were washed with water and brine and were dried over Na$_2$SO$_4$. The obtained dark brown residue is the pure aldehyde 3.45, no further purification is needed. 3.45 tend to decompose upon contact with silica gel, therefore it was transferred immediately to the next step.
$^1$H NMR (400 MHz, Chloroform-\textit{d}) $\delta$ 9.69 (s, 1H), 7.93 (s, 1H), 7.23 (d, $J = 8.8$ Hz, 1H), 6.95 (d, $J = 2.5$ Hz, 1H), 6.88 (dd, $J = 8.8$, 2.4 Hz, 1H), 4.48 (dt, $J = 12.9$, 5.1 Hz, 1H), 4.01 (s, 3H), 4.04 – 3.96 (m, 1H), 3.85 (s, 3H), 3.81 – 3.73 (m, 1H), 3.61 (s, 3H), 3.11 (dd, $J = 14.3$, 9.8 Hz, 1H), 2.88 (dt, $J = 8.5$, 5.1 Hz, 3H), 2.72 (s, 1H), 2.53 – 2.47 (m, 1H).

$^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 199.7, 172.1, 154.8, 153.5, 131.8, 130.9, 126.5, 113.6, 112.4, 110.8, 100.7, 63.8, 63.2, 56.1, 54.1, 43.9, 40.9, 38.8, 34.2, 23.9, 20.6.

The crude residue obtained from the previous step (3.45) is dissolved in methanol (1 ml) at 0 °C. upon complete homogenization, sodium borohydride (5.7 mg, 0.15 mmol) was added in one portion. When TLC analysis indicated the consumption of the starting material, saturated aqueous solution of ammonium chloride and ethyl acetate was added to the reaction mixture. The two phases were separated and the aqueous phase was extracted with ethyl acetate three times. The combined organic phases were washed with water and brine and were dried over Na$_2$SO$_4$. The obtained crude residue was purified by flash column chromatography (hexane – ethyl acetate, 3:7) to obtain 3.46 (36 mg, 87%) as an amorphous white solid.

$^1$H NMR (400 MHz, Chloroform-\textit{d}) $\delta$ 7.96 (s, 1H), 7.21 (d, $J = 8.8$ Hz, 1H), 6.96 (d, $J = 2.5$ Hz, 1H), 6.86 (dd, $J = 8.8$, 2.5 Hz, 1H), 4.66 (dt, $J = 13.0$, 4.6 Hz, 1H), 3.99 (s, 3H), 3.85 (s, 3H), 3.61 (d, $J = 6.2$ Hz, 2H), 3.59 (s, 3H), 3.55 (dd, $J = 7.6$, 5.5 Hz, 1H), 2.91 – 2.86 (m, 2H), 2.82 (d, $J = 15.0$ Hz, 1H), 2.59 (dd, $J = 18.7$, 12.7 Hz, 1H), 2.52 – 2.45 (m, 1H), 2.33 – 2.27 (m, 1H), 2.12 – 1.98 (m, 1H).

$^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ 172.8, 165.4, 155.7, 154.7, 131.7, 126.6, 113.3, 112.3, 110.1, 100.7, 100.6, 66.1, 63.9, 60.6, 56.0, 54.0, 40.3, 37.2, 33.9, 27.1, 20.6.

IR ($\nu_{\text{max}}$, cm$^{-1}$) 2952 (m), 1789 (m), 1731 (m), 1439 (m), 1239 (m), 1215 (m), 1151 (m), 1119 (m), 718 (s)

HRMS (ESI/QTOF) m/z: [M + Na]$^+$ Calcd for C$_{18}$H$_{22}$F$_3$NNaO$_5$ $^{\text{412.1342}}$; Found 412.1343.
Methyl 1-((E)-2-(dimethoxymethyl)-4-(hydroxyimino)-5-methoxy-5-oxopentyl)-6-methoxy-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-1-carboxylate (3.48)

To a solution of compound 3.40 (1 g, 2.25 mmol) in dry methanol (23 ml) was added hydroxylamine hydrochloride (625 mg, 9 mmol) and Sc(OTf)₃ (56 mg, 0.112 mmol). The obtained mixture was refluxed until TLC analysis indicated the consumption of the starting materials. The solution was concentrated under vacuum to ~12 ml and was diluted with ethyl acetate and water. The two phases were then separated and the aqueous phase was extracted with ethyl acetate three times. The combined organic phases were washed with water and brine and were dried over Na₂SO₄. The solids were removed via filtration and the organic phase was concentrated under vacuo. The oily residue was purified by flash column chromatography (hexane – ethyl acetate 1:1 → 1:2) to afford 3.48 as a yellow foam (795 mg, 74%).

**¹H NMR** (400 MHz, Chloroform-d) δ 8.39 (s, 1H), 7.22 (d, J = 8.7 Hz, 1H), 6.91 (d, J = 2.5 Hz, 1H), 6.82 (dd, J = 8.7, 2.5 Hz, 1H), 3.97 (d, J = 3.8 Hz, 1H), 3.84 (s, 3H), 3.81 (s, 3H), 3.71 (s, 3H), 3.23 (s, 3H), 3.22 (s, 1H), 3.10 – 3.06 (m, 1H), 3.04 (s, 3H), 2.82 – 2.69 (m, 2H), 2.62 (dt, J = 15.3, 3.8 Hz, 1H), 2.41 (dd, J = 14.8, 3.5 Hz, 1H), 2.16 (qt, J = 5.8, 3.2 Hz, 1H), 1.83 (dd, J = 14.8, 6.3 Hz, 1H).

**¹³C NMR** (101 MHz, CDCl₃) δ 174.7, 164.7, 154.0, 152.5, 131.9, 131.5, 127.1, 112.3, 111.8, 108.0, 100.6, 63.0, 56.0, 55.4, 55.3, 53.6, 52.9, 52.6, 41.2, 37.8, 34.9, 27.0, 21.8.

**IR** (ν_max, cm⁻¹) 2935 (m), 2370 (s), 2341 (s), 1730 (s), 1537 (m), 1487 (s), 1456 (s), 1441 (s), 1304 (s), 1265 (s), 1215 (s), 1136 (s), 1016 (s), 665 (s)

**HRMS** (ESI/QTOF) m/z: [M + H]^+ Calcd for C_{23}H_{32}N_{3}O_{8}^+: 478.2184; Found 478.2193.
2-(tert-butyl) 1-methyl 1-(E)-2-(dimethoxymethyl)-4-(hydroxyimino)-5-methoxy-5-oxopentyl)-6-methoxy-1,3,4,9-tetrahydro-2H-pyrido[3,4-b]indole-1,2-dicarboxylate (3.50)

To a solution of 3.48 (250 mg, 0.52 mmol) in DCM (5.2 ml) was added di-tert-butyl dicarbonate (137 mg, 0.63 mmol). The obtained solution was sonicated for 1 hour or until TLC analysis indicated the consumption of the starting materials. The reaction mixture was diluted with DCM and water. The two phases were then separated and the aqueous phase was extracted with DCM three times. The combined organic phases were washed with water and brine and were dried over Na$_2$SO$_4$. The solids were removed via filtration and the organic phase was concentrated under vacuo. 3.50 was obtained as a yellow foam in quantitative yield.

$^1$H NMR (400 MHz, Chloroform-d) $\delta$ 8.20 (s, 1H), 7.22 (d, $J = 8.7$ Hz, 1H), 6.92 (d, $J = 2.5$ Hz, 1H), 6.82 (dd, $J = 8.8$, 2.5 Hz, 1H), 3.93 (d, $J = 3.3$ Hz, 1H), 3.86 (s, 3H), 3.84 – 3.82 (m, 4H), 3.72 (s, 3H), 3.17 (s, 3H), 3.03 (s, 3H), 2.94 (dd, $J = 13.2$, 6.4 Hz, 1H), 2.81 – 2.73 (m, 2H), 2.63 – 2.56 (m, 1H), 2.39 (dd, $J = 14.8$, 3.2 Hz, 1H), 2.10 (tp, $J = 6.4$, 3.1 Hz, 1H), 1.70 (dd, $J = 14.8$, 6.6 Hz, 1H), 1.53 (s, 9H).

$^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 174.8, 163.8, 158.7, 154.0, 151.0, 131.9, 131.4, 127.1, 112.4, 112.3, 111.7, 108.1, 100.6, 84.7, 63.1, 56.0, 55.7, 55.0, 53.0, 52.8, 41.3, 37.3, 35.5, 28.8, 27.7, 21.9.

IR (v$_{max}$, cm$^{-1}$) 3390 (w), 2951 (w), 2929 (w), 2835 (w), 1780 (m), 1732 (s), 1485 (m), 1456 (m), 1439 (m), 1369 (m), 1242 (s), 1215 (s), 1151 (s), 1066 (m), 1020 (m), 912 (m), 835 (m), 796 (m), 758 (m), 731 (s)

HRMS (ESI/QTOF) m/z: [M + H]$^+$ Calcd for C$_{28}$H$_{40}$N$_3$O$_{10}$ $^+$ 578.2708; Found 578.2718.
O-(4-methoxybenzyl)hydroxylamine was prepared according to a literature procedure, with the exception of using \( N \)-methylhydrazine instead of hydrazine in the protocol.\(^5\) The spectroscopic data were consistent with those previously reported in the literature.\(^5\)

**methyl (\( E \))-2-(dimethoxymethyl)-4-(hydroxyimino)-10-methoxy-5-oxo-2,3,4,5,8,13-hexahydro-1H-azepino[1',2':1,2]pyrido[3,4-b]indole-13b(7H)-carboxylate (3.49)**

To a solution of compound 3.40 (2.41 g, 5.44 mmol) in dry methanol (55 ml) was added O-(4-methoxybenzyl)hydroxylamine (1 g, 6.53 mmol) and Sc(OTf)\(_3\) (133 mg, 0.270 mmol). The obtained mixture was refluxed until TLC analysis indicated the consumption of the starting materials. The solution was concentrated under vacuum to \(~25\) ml and was diluted with ethyl acetate and water. The two phases were then separated and the aqueous phase was extracted with ethyl acetate three times. The combined organic phases were washed with water and brine and were dried over Na\(_2\)SO\(_4\). The solids were removed via filtration and the organic phase was concentrated under vacuo. The oily residue was purified by flash column chromatography (hexane – ethyl acetate 1:1) to afford 3.54 as a white foam (2.1 g, 65%).
1H NMR (400 MHz, Chloroform-d) δ 8.16 (s, 1H), 7.28 – 7.18 (m, 2H), 7.14 (d, J = 8.1 Hz, 2H), 6.93 (s, 1H), 6.84 (dd, J = 8.8, 2.3 Hz, 1H), 6.75 (d, J = 8.0 Hz, 2H), 5.12 (dd, J = 11.6, 1.3 Hz, 2H), 3.84 (s, 3H), 3.84 (s, 3H), 3.77 (s, 3H), 3.70 (s, 3H), 3.14 (s, 4H), 3.10 – 2.93 (m, 1H), 2.87 (s, 3H), 2.77 – 2.62 (m, 3H), 2.61 – 2.53 (m, 0H), 2.37 (td, J = 14.8 Hz, 1H), 2.09 – 2.05 (m, 1H), 1.73 – 1.51 (m, 2H).

13C NMR (101 MHz, CDCl3) δ 175.0, 164.6, 159.8, 154.2, 131.5, 130.5, 130.5, 128.5, 127.2, 113.9, 113.9, 112.2, 111.8, 108.3, 108.2, 100.7, 63.1, 56.1, 55.4, 55.3, 55.1, 52.7, 41.2, 37.8, 34.8, 28.1, 24.0.

IR (νmax, cm⁻¹) 2931 (w), 2835 (w), 2362 (m), 2337 (m), 1724 (m), 1612 (w), 1514 (m), 1441 (m), 1298 (w), 1246 (m), 1215 (m), 1178 (m), 1119 (m), 1030 (m), 1001 (m), 845 (w), 812 (w), 758 (s)

HRMS (ESI/QTOF) m/z: [M + H]+ Calcd for C₃₁H₄₀N₃O₉+ 598.2759; Found 598.2761.

To the methanolic (17 ml) solution of 3.54 (800 mg, 1.34 mmol), aqueous LiOH ([1 N], 3.35 ml) was added dropwise at 0 °C. The obtained mixture was stirred until TLC analysis indicated the consumption of the starting material. NaHSO₄ (402 mg, 3.35 mmol) was dissolved and the methanol was removed under vacuo. The obtained heterogenous residue was freeze-dried overnight to yield the crude aminoacid (3.55) as a light yellow powder.

The obtained amino acid (3.55) was dissolved in DMF (15 ml) and was added Hüning’s base (856 µL, 5.2 mmol). The solution was cooled to 0 °C and solution of HATU (0.989 g, 2.6 mmol)* in DMF (4 ml) was added dropwise over 20 minutes. The cooling bath was removed and the reaction mixture was quenched with water, when TLC analysis indicated the consumption of the starting material. The obtained mixture was extracted with ethyl acetate (5 × 20 mL). The combined organic phase was washed with 10% aqueous lithium chloride solution, brine and dried over Na₂SO₄. After evaporation of the solvent, the oily residue was purified by flash column chromatography (hexane – ethyl acetate 1:1) to afford 3.56 (552 mg, 73%) as a white powder.

*HATU can be substituted with TATU or COMU peptide coupling agents without any decrease in synthetic efficiency.

1H NMR (400 MHz, CDCl₃) δ 7.89 (s, 1H), 7.32 (d, J = 8.3 Hz, 2H), 7.20 (d, J = 8.8 Hz, 1H), 6.94 (d, J = 2.4 Hz, 1H), 6.94 – 6.80 (m, 4H), 5.20 (d, J = 11.7 Hz, 1H), 5.10 (d, J = 11.2 Hz, 1H), 4.62 (dt, J = 13.0, 4.7 Hz, 1H), 4.16 (d, J = 6.1 Hz, 1H), 3.84 (s, 4H), 3.79 (s, 4H), 3.65 – 3.55 (m, 1H), 3.33 (s, 3H), 3.28 (s, 3H), 3.26 (s, 3H), 2.89 – 2.85 (m, 2H), 2.82 – 2.75 (m, 1H), 2.62 – 2.49 (m, 2H), 2.29 (dd, J = 14.1, 4.6 Hz, 1H), 2.18 – 2.06 (m, 1H).
\( ^{13} \text{C NMR} \) (101 MHz, CDCl\(_3\)) \( \delta \) 172.5, 165.3, 159.7, 155.6, 154.6, 131.8, 131.7, 130.5, 129.2, 126.5, 113.9, 113.2, 112.2, 110.1, 106.6, 100.6, 77.1, 63.8, 60.5, 56.0, 55.4, 54.4, 54.3, 53.7, 40.3, 35.4, 33.9, 26.2, 20.6, 14.3.

IR (\( \nu_{\text{max}}, \ \text{cm}^{-1} \)) 2935 (w), 1736 (m), 1666 (s), 1512 (m), 1458 (m), 1435 (m), 1385 (m), 1246 (s), 1217 (m), 1176 (m), 1144 (m), 1088 (m), 1032 (m), 908 (s), 812 (w), 729 (s)

HRMS (ESI/QTOF) m/z: [M + H]^+ Calcd for C\(_{30}\)H\(_{36}\)N\(_3\)O\(_8\) 566.2494; Found 566.2496.

To a solution of 3.56 (565 mg, 1 mmol) in methanol (70 ml) was added Pearlman’s catalyst (20% on Pd on charcoal containing 50% water from ABCR, 700 mg, 1 mmol) under Ar atmosphere. The mixture was heated to reflux under vigorous stirring and triethylsilane (1.61 ml, 10 mmol) was added dropwise over 10 minutes. When TLC analysis indicated the consumption of the starting material, the reaction mixture was filtered and concentrated under vacuo. Recrystallization of the crude residue from methanol afforded 3.49 (441 mg, quant.) as a white powder.

\( ^{1} \text{H NMR} \) (400 MHz, Aceton-\( d_6 \)) \( \delta \) 9.90 (s, 1H), 7.27 (d, \( J = 8.8 \) Hz, 1H), 7.03 (d, \( J = 2.5 \) Hz, 1H), 6.77 (dd, \( J = 8.8, 2.5 \) Hz, 1H), 5.62 (s, 1H), 4.69 (ddd, 8.8, 4.7, 3.8 Hz, 1H), 4.30 (d, \( J = 5.6 \) Hz, 1H), 3.49 (s, 3H), 3.46 – 3.34 (m, 1H), 3.34 (s, 3H), 3.32 (s, 3H), 3.32 (s, 3H), 2.72 (dd, \( J = 18.5, 13.3 \) Hz, 1H), 2.38 (dd, \( J = 18.6, 3.5, 1.7 \) Hz, 1H), 2.34 – 2.28 (m, 1H), 2.95 – 2.77 (m, 2H).

\( ^{13} \text{C NMR} \) (101 MHz, Acetone) \( \delta \) 172.8, 165.7, 156.5, 155.2, 133.4, 133.0, 127.3, 113.2, 113.0, 109.8, 107.7, 101.0, 64.6, 55.8, 55.0, 54.6, 53.8, 41.8, 40.1, 35.2, 35.0, 25.5, 24.4, 21.3, 21.2, 17.8, 14.9.

IR (\( \nu_{\text{max}}, \ \text{cm}^{-1} \)) 3373 (s), 3248 (s), 2925 (s), 1730 (s), 1639 (s), 1612 (s), 1485 (s), 1454 (s), 1435 (s), 1410 (s), 1263 (s), 1242 (s), 1217 (s), 1155 (m), 1065 (s), 1047 (s), 1014 (m), 968 (s), 841 (m), 816 (m), 796 (m)

HRMS (ESI/QTOF) m/z: [M + Na]^+ Calcd for C\(_{22}\)H\(_{27}\)N\(_3\)NaO\(_7\) 468.1741; Found 468.1738.

2-(dimethoxymethyl)-10-methoxy-1,2,3,4,8,13-hexahydro-5H,7H-4,13b-(epiminomethano)azepino[1',2':1,2]pyrido[3,4-b]indole-5,14-dione (3.57)
**3.57** was isolated as a side product and it was formed under various starting materials and reductive conditions. Only one example of those conditions is presented here, but all other procedures are available upon request.

To a solution of **3.66** (50 mg, 0.1 mmol) in glacial acetic acid (1 ml) was added activated zinc powder (335 mg, 5.1 mmol). The solution was stirred at 18 °C until TLC analysis indicated the consumption of the starting material. The reaction mixture was added plenty of ethyl acetate and the solution was filtered through celite and a short pad of silica gel. The volatiles were removed and **3.57** (40 mg, quantitative) was obtained as a white solid in quantitative yield.

**1H NMR** (400 MHz, Chloroform-d) δ 8.64 (s, 1H), 7.27 (d, J = 8.6 Hz, 1H), 6.95 (d, J = 2.4 Hz, 1H), 6.86 (dd, J = 8.8, 2.4 Hz, 1H), 6.75 (s, 1H), 4.82 – 4.75 (m, 1H), 4.11 (t, J = 6.2 Hz, 1H), 4.07 (d, J = 5.0 Hz, 1H), 3.85 (s, 3H), 3.31 (s, 6H), 3.19 (d, J = 24.4 Hz, 1H), 3.16 – 3.06 (m, 1H), 2.92 – 2.82 (m, 2H), 2.40 – 2.34 (m, 1H), 2.27 – 2.06 (m, 3H), 1.51 – 1.42 (m, 1H).

**13C NMR** (101 MHz, CDCl3) δ 172.4, 169.0, 154.4, 132.9, 132.7, 126.6, 112.7, 112.6, 109.2, 107.0, 100.7, 60.7, 56.1, 55.2, 54.7, 53.8, 38.5, 36.0, 34.2, 29.4, 20.1.

**IR (νmax, cm⁻¹)** 3357 (m), 2925 (m), 2835 (m), 1653 (s), 1487 (m), 1454 (s), 1431 (s), 1361 (s), 1296 (m), 1273 (s), 1217 (s), 1159 (s), 1130 (s), 1095 (s), 1080 (s), 1065 (s), 970 (m), 933 (m), 825 (m), 796 (m), 737 (m), 723 (s)

**HRMS (ESI/QTOF) m/z:** [M + Na]+ Calcd for C_{21}H_{25}N_{3}NaO_{5}^{+} 422.1686; Found 422.168.
Methyl (E)-4-(acetoxyimino)-2-(dimethoxymethyl)-10-methoxy-5-oxo-2,3,4,5,8,13-hexahydro-1H-azepino[1',2':1,2]pyrido[3,4-b]indole-13b(7H)-carboxylate (3.66)

**General procedure E:**

To a solution of 3.49 (124 mg, 0.278 mmol) in DCM (30 ml, [0.01M]) was added triethylamine (97 µL, 0.695 mmol) and N,N-dimethylaminopyridine (3.4 mg, 0.028 mmol). Upon complete dissolution of the starting materials, acetic anhydride (31 µL, 0.334 mmol) was added dropwise. The obtained mixture was stirred at 18 °C until TLC analysis indicated the consumption of the starting materials. The reaction mixture was quenched with H₂O (approximately the same volume as CH₂Cl₂) and the mixture was transferred to a separatory funnel. The mixture was diluted CH₂Cl₂ and the resulting organic layer was washed three times with H₂O. The organic layer was dried (MgSO₄), filtered and the volatiles were removed under vacuum. The crude residue was purified by flash column chromatography (petrol ether – ethyl acetate 4:1) to afford 3.66 (135 mg, quantitative) as a yellow foam.

**¹H NMR** (400 MHz, Chloroform-d) δ 7.96 (s, 2H), 7.22 (d, J = 8.8 Hz, 1H), 6.95 (d, J = 2.4 Hz, 1H), 6.87 (dd, J = 8.7, 2.5 Hz, 1H), 4.55 (dt, J = 12.9, 4.9 Hz, 1H), 4.20 (d, J = 5.7 Hz, 1H), 3.84 (s, 3H), 3.72 – 3.65 (m, 1H), 3.61 (s, 3H), 3.31 (s, 3H), 3.29 (s, 3H), 2.91 – 2.88 (m, 2H), 2.81 (s, 2H), 2.64 (ddd, J = 18.6, 4.2, 1.6 Hz, 1H), 2.37 (ddd, J = 14.3, 4.5, 1.6 Hz, 1H), 2.23 (s, 3H), 2.20 – 2.07 (m, 1H).

**¹³C NMR** (101 MHz, CDCl₃) δ 172.4, 167.9, 163.6, 163.1, 154.7, 131.7, 131.3, 126.5, 113.4, 112.3, 110.3, 106.2, 100.6, 63.9, 56.0, 54.6, 54.3, 40.4, 38.7, 35.4, 33.8, 26.8, 20.5, 19.7.

**IR** (νmax, cm⁻¹) 2939 (m), 2835 (w), 1778 (m), 1738 (m), 1651 (s), 1626 (s), 1514 (m), 1489 (m), 1458 (m), 1427 (m), 1381 (m), 1263 (m), 1236 (s), 1217 (s), 1190 (s), 1146 (m), 1065 (s), 964 (m), 939 (m), 889 (m), 723 (m)

**HRMS** (ESI/QTOF) m/z: [M + Na]⁺ Calcd for C₂₆H₂₉N₃NaO₈⁺ 510.1847; Found 510.1849.
Methyl (E)-2-(dimethoxymethyl)-10-methoxy-5-oxo-4-(((4-(trifluoromethyl)benzoyl)oxy)imino)-2,3,4,5,8,13-hexahydro-1H-azepino[1',2':1,2]pyrido[3,4-b]indole-13b(7H)-carboxylate (3.68)

3.68 was prepared according to general procedure E.

$^1$H NMR (400 MHz, Chloroform-d) $\delta$ 8.18 (d, $J = 8.1$ Hz, 2H), 7.77 (d, $J = 8.2$ Hz, 2H), 7.22 (d, $J = 8.8$ Hz, 1H), 6.96 (d, $J = 2.5$ Hz, 1H), 6.88 (dd, $J = 8.8$, 2.5 Hz, 1H), 4.57 (dt, $J = 12.9$, 4.9 Hz, 1H), 4.24 (d, $J = 5.6$ Hz, 1H), 3.85 (s, 3H), 3.75 (dt, $J = 12.8$, 6.3 Hz, 1H), 3.67 (s, 3H), 3.34 (s, 3H), 3.33 (s, 3H), 2.92 (ddd, $J = 8.9$, 6.6, 3.5 Hz, 3H), 2.88 – 2.77 (m, 2H), 2.40 (ddd, $J = 14.4$, 4.5, 1.6 Hz, 1H), 2.20 (tt, $J = 10.4$, 5.8 Hz, 1H).

$^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 172.4, 164.9, 163.4, 161.7, 154.8, 135.31 (q, $J = 32.9$ Hz), 131.8, 131.7, 131.2, 130.4, 126.5, 125.89 (d, $J = 3.9$ Hz), 123.62 (q, $J = 541.9$, 270.6, 193.4 Hz), 113.5, 112.3, 110.4, 106.1, 100.7, 63.9, 56.0, 54.9, 54.6, 54.5, 40.5, 35.6, 33.9, 26.8, 20.5.

IR (v$_{max}$, cm$^{-1}$) 2939 (m), 2835 (w), 1778 (m), 1738 (m), 1651 (s), 1626 (s), 1514 (m), 1489 (m), 1458 (m), 1427 (m), 1381 (m), 1263 (m), 1236 (s), 1217 (s), 1190 (s), 1146 (m), 1065 (s), 964 (m), 939 (m), 889 (m), 723 (m)

HRMS (ESI/QTOF) m/z: [M + Na]$^+$ Calcd for C$_{30}$H$_{30}$F$_3$N$_3$NaO$_8$ $^+$ 640.1877; Found 640.1882.
Methyl (E)-2-(dimethoxymethyl)-10-methoxy-5-oxo-4-((pivaloyloxy)imino)-2,3,4,5,8,13-hexahydro-1H-azepino[1',2':1,2]pyrido[3,4-b]indole-13b(7H)-carboxylate (3.69)

3.69 was prepared according to general procedure E.

$^1\text{H NMR}$ (400 MHz, Chloroform-$d$) $\delta$ 8.03 (s, 0H), 7.22 (d, $J = 13.2$ Hz, 1H), 6.98 (d, $J = 2.5$ Hz, 0H), 6.89 (dd, $J = 8.8$, 2.5 Hz, 0H), 4.57 (dt, $J = 13.0$, 4.9 Hz, 0H), 4.24 (d, $J = 5.8$ Hz, 0H), 3.87 (s, 2H), 3.73 (ddd, $J = 13.1$, 7.2, 5.7 Hz, 0H), 3.63 (s, 1H), 3.34 (s, 1H), 3.33 (s, 1H), 2.94 – 2.88 (m, 1H), 2.87 – 2.78 (m, 1H), 2.66 (ddd, $J = 18.3$, 4.3, 1.6 Hz, 0H), 2.44 – 2.39 (m, 0H), 2.32 – 2.24 (m, 0H), 2.22 – 2.12 (m, 0H), 1.33 (s, 4H).

$^{13}\text{C NMR}$ (101 MHz, CDCl$_3$) $\delta$ 173.9, 172.2, 163.6, 163.6, 154.6, 131.7, 131.3, 126.4, 113.3, 112.3, 110.2, 106.2, 100.6, 68.6, 63.9, 56.0, 54.8, 54.3, 40.3, 38.9, 35.3, 33.7, 27.3, 26.6, 21.5, 20.4.

IR ($\nu_{\text{max}}$, cm$^{-1}$) 3284 (m), 2941 (w), 2833 (m), 1763 (s), 1738 (s), 1655 (s), 1483 (s), 1458 (s), 1427 (s), 1263 (s), 1217 (s), 1173 (s), 1128 (s), 1090 (s), 1020 (m), 972 (m), 912 (s), 847 (m), 806 (m), 741 (s), 723 (s), 661 (m)

HRMS (ESI/QTOF) m/z: [M + H]$^+$ Calcd for C$_{27}$H$_{36}$F$_3$N$_3$O$_8$ $^+$ 530.2497; Found 530.2507.
methyl (E)-2-(dimethoxymethyl)-10-methoxy-5-oxo-4-(((perfluorobenzoyl)oxy)imino)-2,3,4,5,8,13-hexahydro-1H-azepino[1',2':1,2]pyrido[3,4-b]indole-13b(7H)-carboxylate (3.70)

3.70 was prepared according to general procedure E.

$^1$H NMR (800 MHz, Chloroform-$d$) $\delta$ 7.90 (s, 1H), 7.22 (d, $J = 8.7$ Hz, 1H), 6.95 (d, $J = 2.5$ Hz, 1H), 6.87 (dd, $J = 8.8$, 2.4 Hz, 1H), 4.51 (dt, $J = 13.0$, 5.0 Hz, 1H), 4.20 (d, $J = 5.7$ Hz, 1H), 3.85 (s, 3H), 3.77 (ddd, $J = 12.8$, 7.5, 5.1 Hz, 1H), 3.66 (s, 3H), 3.30 (s, 3H), 3.29 (s, 3H), 2.92 – 2.90 (m, 1H), 2.90 – 2.85 (m, 1H), 2.79 (dd, $J = 14.6$, 11.3 Hz, 1H), 2.70 (ddd, $J = 18.6$, 4.2, 1.7 Hz, 1H), 2.42 (ddd, $J = 14.5$, 4.3, 1.7 Hz, 1H), 2.18 – 2.12 (m, 1H).

$^{13}$C NMR (201 MHz, CDCl$_3$) $\delta$ 172.2, 165.8, 162.9, 154.7, 145.75 (brd, $J = 259.8$ Hz), 143.93 (brd, $J = 261.9$ Hz), 137.95 (brd, $J = 254.3$ Hz), 131.7, 131.0, 126.4, 113.5, 112.3, 110.5, 106.40 (dd, $J = 15.0$, 3.8 Hz), 106.1, 100.6, 64.1, 56.0, 54.8, 54.7, 54.4, 40.5, 35.4, 33.7, 27.3, 24.0, 20.5.

IR ($v_{\text{max}}$, cm$^{-1}$) 3325 (w), 2925 (w), 2850 (w), 1766 (m), 1738 (m), 1653 (m), 1523 (m), 1500 (s), 1458 (m), 1421 (m), 1325 (m), 1265 (m), 1240 (m), 1217 (s), 1188 (s), 1082 (m), 1003 (m), 885 (m), 849 (w)

HRMS (ESI/QTOF) m/z: [M + Na]$^+$ Calcd for C$_{29}$H$_{26}$F$_5$N$_3$NaO$_8$ $^+$ 662.1532; Found 662.1525.
Methyl 2’(dimethoxymethyl)-9’-methoxy-3-oxo-2’,3’,7’,12’-tetrahydro-1’H-spiro[aziridine-2,4’-indolo[2,3-a]quinolizine]-12b’(6’H)-carboxylate (3.71)

The proposed 3.71 was prepared following the procedure disclosed by Nevado and co-workers

\(^1\text{H NMR}\) (400 MHz, Chloroform-\(d\)) \(\delta\) 8.09 (s, 0H), 7.26 (s, 1H), 6.95 (d, \(J = 2.2\) Hz, 1H), 6.91 (dd, \(J = 8.8, 2.4\) Hz, 1H), 4.33 (dt, \(J = 13.1, 3.9\) Hz, 1H), 4.19 (d, \(J = 9.0\) Hz, 0H), 3.86 (s, 1H), 3.83 (s, 1H), 3.74 – 3.61 (m, 1H), 3.39 (s, 1H), 3.23 (s, 1H), 3.15 – 3.03 (m, 1H), 2.94 – 2.83 (m, 2H), 2.43 (dd, \(J = 13.0, 6.4\) Hz, 1H), 2.39 – 2.33 (m, 1H), 2.25 – 2.05 (m, 2H).

\(^{13}\text{C NMR}\) (101 MHz, CDCl\(_3\)) \(\delta\) 170.7, 169.2, 154.7, 132.4, 131.4, 126.8, 113.6, 112.4, 109.7, 105.5, 100.9, 74.3, 69.0, 56.1, 55.3, 53.3, 52.1, 36.6, 32.8, 32.1, 26.0, 21.4.

\(\text{IR} (\nu_{\text{max}}, \text{cm}^{-1})\) 2926 (s), 2854 (s), 1740 (s), 1689 (s), 1660 (s), 1486 (s), 1454 (s), 1435 (s), 1361 (s), 1339 (m), 1271 (s), 1240 (s), 1217 (s), 1171 (s), 1116 (s), 1062 (s), 1038 (s), 968 (s), 909 (s), 801 (s), 729 (s)

\(\text{HRMS (ESI/QTOF) m/z: [M + H]^+}\) Calcd for C\(_{22}\)H\(_{28}\)N\(_3\)O\(_6\)^+ 430.1973; Found 430.1982.
2-(dimethoxymethyl)-4-hydroxy-10-methoxy-1,2,3,4,8,13-hexahydro-5H,7H-4,13b-(epoxymethano)azepino[1',2':1,2]pyrido[3,4-b]indol-5-one (3.92)

To a solution of 3.44 (50 mg, 0.116 mmol) in dry methanol (1 ml) was added sodium borohydride (9 mg, 0.23 mmol) in one portion. The obtained mixture was stirred at 18 °C until TLC analysis indicated the consumption of the starting material. The obtained mixture was diluted with ethyl acetate and 10% aqueous ammonium chloride solution. The two phases were then separated and the aqueous phase was extracted with ethyl acetate three times. The combined organic phases were washed with water and brine and were dried over Na₂SO₄. After evaporation of the solvent, the oily residue was purified by flash column chromatography (hexane – ethyl acetate 4:1) to afford 3.92 (42 mg, 90%) as a colorless oil.

¹H NMR (400 MHz, Chloroform-d) δ 9.06 (s, 1H), 7.21 (d, J = 8.7 Hz, 1H), 6.90 (d, J = 2.5 Hz, 1H), 6.82 (dd, J = 8.7, 2.5 Hz, 1H), 4.98 – 4.91 (m, 1H), 4.41 (d, J = 16.6 Hz, 1H), 4.30 (d, J = 3.9 Hz, 1H), 4.16 (d, J = 16.6 Hz, 1H), 3.82 (s, 3H), 3.44 (s, 6H), 2.89 – 2.72 (m, 3H), 2.66 – 2.61 (m, 1H), 2.52 – 2.37 (m, 2H), 2.35 – 2.24 (m, 2H).

¹³C NMR (101 MHz, CDCl₃) δ 166.4, 154.3, 135.5, 132.4, 127.2, 112.5, 112.2, 111.7, 107.2, 103.5, 100.6, 67.5, 61.1, 56.8, 55.5, 40.0, 39.2, 38.5, 35.6, 21.4.

IR (ν max, cm⁻¹) 3323 (w), 2937 (w), 2833 (w), 1734 (m), 1633 (s), 1458 (s), 1435 (s), 1348 (m), 1074 (s), 1017 (s), 1063 (s), 1041 (s), 960 (m), 912 (s), 852 (m), 825 (m), 795 (m), 756 (m), 731 (s), 681 (s)

HRMS (ESI/QTOF) m/z: [M + H]⁺ Calcd for C₂₁H₂₇N₂O₆⁺ 403.1863; Found 403.1866.

1-(4-(dimethoxymethyl)-6'-methoxy-2-oxo-4',9'-dihydrospiro[cyclopentane-1,1'-pyrido[3,4-b]indol]-2'(3'H)-yl]but-3-ene-1,2-dione (3.105)
Following Imamoto’s procedure\textsuperscript{52}, to an over-dried flask was added dry CeCl\textsubscript{3} (51 mg, 0.21 mmol) and dry THF (600 \( \mu \)L) and stirred overnight. The obtained viscous solution was cooled to -78 °C and was added a solution of \textbf{3.44} (30 mg, 0.07 mmol) in THF (300 \( \mu \)L). The solution was stirred for an additional hour before vinylmagnesium bromide (1M in THF, 210 \( \mu \)L, 210 mmol) was added at -78 °C at such a pace that the internal temperature did not exceed -70 °C. The obtained mixture was stirred until TLC analysis indicated the consumption of the starting materials. The reaction mixture was diluted with ethyl acetate and water. The two phases were then separated and the aqueous phase was extracted with ethyl acetate three times. The combined organic phases were washed with water and brine and were dried over Na\textsubscript{2}SO\textsubscript{4}. After evaporation of the solvent, the oily residue was purified by flash column chromatography (hexane – ethyl acetate 5:1) to afford \textbf{3.105} (20 mg, 70%) as a colorless oil.

\textbf{1H NMR} (800 MHz, Chloroform-\( d \)) \( \delta \) 9.27 (s, 1H), 7.18 (d, \( J = 8.7 \) Hz, 1H), 6.91 (d, \( J = 2.4 \) Hz, 1H), 6.84 (dd, \( J = 8.7, 2.4 \) Hz, 1H), 6.56 (d, \( J = 17.8 \) Hz, 1H), 6.48 (dd, \( J = 17.8, 10.6 \) Hz, 1H), 6.39 (d, \( J = 10.6 \) Hz, 1H), 4.47 (d, \( J = 2.7 \) Hz, 1H), 3.91 (ddd, \( J = 13.0, 4.8, 1.9 \) Hz, 1H), 3.84 (s, 3H), 3.61 (s, 3H), 3.60 (s, 3H), 3.44 (ddd, \( J = 12.9, 11.9, 3.7 \) Hz, 1H), 3.23 – 3.18 (m, 1H), 2.92 (ddd, \( J = 14.9, 11.8, 4.8 \) Hz, 1H), 2.85 – 2.75 (m, 3H), 2.68 – 2.61 (m, 2H).

\textbf{13C NMR} (201 MHz, CDCl\textsubscript{3}) \( \delta \) 210.2, 191.7, 165.7, 154.4, 137.3, 134.2, 133.4, 131.5, 126.5, 112.0, 108.5, 108.1, 100.5, 66.5, 56.6, 56.4, 56.1, 44.3, 36.4, 35.8, 34.1, 21.7.

\textbf{IR} (\( \nu_{\text{max}}, \text{cm}^{-1} \)) 3326 (m), 2925 (m), 1749 (s), 1733 (m), 1685 (s), 1635 (s), 1489 (s), 1457 (s), 1438 (s), 1218 (s), 1185 (s), 1177 (s), 1124 (s), 1046 (s), 918 (m), 718 (s)

\textbf{HRMS} (ESI/QTOF) m/z: [M + Na]\textsuperscript{+} Calcd for C\textsubscript{23}H\textsubscript{26}N\textsubscript{2}O\textsubscript{6}Na\textsuperscript{+} 449.1683; Found 449.1687.

\textbf{1-((1S,4R)-4-(dimethoxymethyl)-6'-methoxy-2-oxo-4',9'-dihydrospiro[cyclopentane-1,1'-pyrido[3,4-b]indol]-2'(3'H)-yl)pent-4-ene-1,2-dione (3.111)}
Following Imamoto’s procedure\textsuperscript{52}, to an over-dried flask was added dry CeCl\textsubscript{3} (51 mg, 0.21 mmol) and dry THF (600 mL) and stirred overnight. The obtained viscous solution was cooled to -78 °C and was added a solution of 3.44 (30 mg, 0.07 mmol) in THF (300 mL). The solution was stirred for an additional hour before allylmagnesium bromide (1M in THF, 210 mL, 210 mmol) was added at -78 °C at such a pace that the internal temperature did not exceed -70 °C. The obtained mixture was stirred until TLC analysis indicated the consumption of the starting materials. The reaction mixture was diluted with ethyl acetate and water. The two phases were then separated and the aqueous phase was extracted with ethyl acetate three times. The combined organic phases were washed with water and brine and were dried over Na\textsubscript{2}SO\textsubscript{4}. After evaporation of the solvent, the oily residue was purified by flash column chromatography (hexane – ethyl acetate 6:1) to afford 3.111 (17 mg, 56%) as a brown oil.

\textsuperscript{1}H NMR (400 MHz, Chloroform-\textit{d}) \(\delta\) 9.16 (s, 1H), 7.17 (d, \(J = 8.8\) Hz, 1H), 6.92 (d, \(J = 2.4\) Hz, 1H), 6.84 (dd, \(J = 8.7, 2.5\) Hz, 1H), 5.99 (ddt, \(J = 17.2, 10.4, 6.0\) Hz, 1H), 5.45 (dq, \(J = 17.2, 1.4 \) Hz, 1H), 5.35 (dq, \(J = 10.4, 1.1\) Hz, 1H), 4.86 – 4.76 (m, 2H), 4.44 (d, \(J = 2.8\) Hz, 1H), 4.13 – 4.08 (m, 1H), 3.86 – 3.82 (m, 4H), 3.60 (s, 3H), 3.58 (s, 3H), 3.48 – 3.40 (m, 1H), 3.37 – 3.26 (m, 1H), 3.24 – 3.10 (m, 1H), 3.05 (ddd, \(J = 16.1, 11.7, 4.8\) Hz, 1H), 2.88 – 2.84 (m, 1H), 2.81 (d, \(J = 9.9\) Hz, 1H), 2.73 (d, \(J = 8.9\) Hz, 1H), 2.70 – 2.58 (m, 2H).

\textsuperscript{13}C NMR (101 MHz, CDCl\textsubscript{3}) \(\delta\) 209.0, 192.5, 161.9, 160.8, 154.5, 133.6, 131.7, 130.8, 126.6, 120.6, 112.7, 112.1, 109.0, 108.3, 100.7, 67.1, 66.6, 56.7, 56.4, 56.2, 44.8, 36.6, 36.2, 34.4, 30.0, 21.8.

IR (\(\nu_{\text{max}}, \text{cm}^{-1}\)) 2931 (m), 1801 (m), 1749 (s), 1655 (s), 1599 (m), 1487 (m), 1448 (s), 1350 (m), 1302 (m), 1273 (s), 1215 (s), 1182 (s), 1134 (s), 1119 (s), 1080 (s), 1012 (s), 910 (s), 822 (m), 793 (m), 733 (s), 692 (m)

HRMS (ESI/QTOF) m/z: [M + K]\textsuperscript{+} Calcd for C\textsubscript{24}H\textsubscript{28}N\textsubscript{2}KO\textsubscript{6}\textsuperscript{+} 479.1584; Found 479.1603.
methyl 4'-(tert-butyldimethylsilyl)oxy)-2-formyl-4'-isopropoxy-10-methoxy-5-oxo-2,3,8,13-tetrahydro-1H,5H-spiro[azepino[1',2':1,2]pyrido[3,4-b]indole-4,2'-oxetane]-13b(7H)-carboxylate (3.117)

To a solution of 3.44 (40 mg, 0.092 mmol) in THF (1 ml) was added Sc(OTf)$_3$ (9.1 mg, 0.019 mmol) at 18 °C. After complete dissolution of the catalyst, freshly distilled tert-butyl((1-isopropoxyvinyl)oxy)dimethylsilane (201 mg, 0.9 mmol) was added dropwise, while maintaining the internal temperature at 18 °C. The obtained mixture was stirred until TLC analysis indicated the consumption of the starting materials. The reaction mixture was diluted with ethyl acetate and water. The two phases were then separated and the aqueous phase was extracted with ethyl acetate three times. The combined organic phases were washed with water and brine and were dried over Na$_2$SO$_4$. After evaporation of the solvent, the oily residue was purified by flash column chromatography (hexane – ethyl acetate 3:1) to afford 3.117 (39 mg, 70%) as a yellow foam.

$^1$H NMR (400 MHz, Chloroform-$d$) $\delta$ 9.78 (d, $J = 1.7$ Hz, 1H), 7.74 (s, 1H), 7.17 (d, $J = 8.7$ Hz, 1H), 6.93 (d, $J = 2.5$ Hz, 1H), 6.83 (dd, $J = 8.7$, 2.4 Hz, 1H), 4.94 (p, $J = 6.3$ Hz, 1H), 3.86 (d, $J = 1.2$ Hz, 4H), 3.84 (s, 4H), 3.61 (dd, $J = 15.5$, 6.1 Hz, 1H), 3.44 (d, $J = 16.3$ Hz, 1H), 3.33 – 3.24 (m, 1H), 3.16 (ddd, $J = 15.4$, 11.8, 5.8 Hz, 1H), 2.88 – 2.77 (m, 2H), 2.66 – 2.57 (m, 1H), 2.61 (d, $J = 16.2$ Hz, 1H), 2.22 (ddd, $J = 13.2$, 5.8, 2.1 Hz, 1H), 2.17 (d, $J = 2.3$ Hz, 1H), 2.11 (dd, $J = 13.1$, 11.4 Hz, 1H), 1.98 (dd, $J = 13.2$, 11.7 Hz, 1H), 1.18 (d, $J = 6.3$ Hz, 3H), 1.14 (d, $J = 6.3$ Hz, 3H), 0.75 (s, 8H), 0.21 (s, 3H), -0.09 (s, 3H).

$^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 202.4, 170.9, 169.3, 154.2, 134.1, 131.9, 127.5, 116.1, 112.3, 111.8, 109.8, 100.7, 95.4, 71.8, 68.5, 56.0, 52.7, 48.3, 42.5, 41.3, 39.7, 38.5, 25.8, 21.9, 21.9, 21.1, 17.7, -2.8, -3.2.

IR ($\nu_{\text{max}}$, cm$^{-1}$) 2927 (s), 2921 (s), 1766 (s), 1728 (s), 1460 (s), 1369 (s), 1259 (s), 1215 (s), 1171 (s), 1151 (s), 1109 (s), 1068 (s), 1030 (s), 966 (s), 912 (s), 881 (s), 835 (s), 783 (s), 742 (s), 729 (s), 696 (s), 685 (s), 663 (s)

HRMS (ESI/QTOF) m/z: [M + H]$^+$ Calcd for C$_{31}$H$_{46}$N$_2$O$_8$Si$^+$ 601.2945; Found 601.2947.
methyl -2-(dimethoxymethyl)-4-hydroxy-10-methoxy-4-(2-methoxy-2-oxoethyl)-5-oxo-2,3,4,5,8,13-hexahydro-1H-azepino[1′,2′:1,2]pyrido[3,4-b]indole-13b(7H)-carboxylate (3.122)

To a solution of anhydrous CsF (66 mg, 0.43 mmol) in DMF (1 ml) was added dropwise a solution of 3.123 (25 mg, 0.043 mmol) in DMF (200 μL) at 18 °C. The mixture was stirred until TLC analysis indicated the consumption of the starting material. The reaction mixture was diluted with ethyl acetate and water. The two phases were then separated and the aqueous phase was extracted with ethyl acetate three times. The combined organic phases were washed with water and brine and were dried over Na₂SO₄. After evaporation of the solvent, the obtained crude residue could not be purified further.

¹H NMR (500 MHz, Chloroform-d) δ 8.20 (s, 1H), 7.17 (d, J = 8.7 Hz, 1H), 6.93 (d, J = 2.5 Hz, 1H), 6.82 (dd, J = 8.8, 2.5 Hz, 1H), 4.36 (d, J = 4.2 Hz, 1H), 3.84 (s, 4H), 3.50 (s, 3H), 3.49 (s, 3H), 3.45 – 3.33 (m, 1H), 3.27 – 3.22 (m, 1H), 3.01 – 2.94 (m, 1H), 2.93 – 2.81 (m, 3H), 2.75 – 2.59 (m, 1H), 2.49 – 2.39 (m, 3H).

HRMS (ESI/QTOF) m/z: [M + H]^+ Calcd for C$_{25}$H$_{33}$N$_2$O$_9$^+ 505.2181; Found 505.2177.

IR (ν$_{max}$, cm$^{-1}$) 2951 (m), 2935 (m), 2831 (m), 1737 (s), 1661 (s), 1627 (m), 1487 (m), 1455 (s), 1437 (s), 1388 (m), 1361 (m), 1295 (m), 1258 (s), 1216 (s), 1177 (s), 1170 (s), 1124 (s), 1096 (s), 1073 (s), 1064 (s), 1029 (s), 989 (m), 970 (m)
4-(dimethoxymethyl)-6'-methoxy-2',3',4',9'-tetrahydriop[3,4-b]indol-2-one (3.128)

3.128 was isolated as a side product and it was formed under various starting materials and reductive conditions. Only one example of those conditions is presented here, but all other procedures are available upon request.

To a stirred solution of 3.123 (20 mg, 0.034 mmol) in THF (0.3 ml) was added LiAlH₄ (1.4 mg, 1 equiv) at 18 °C. The mixture was stirred until TLC analysis indicated the consumption of the starting material. The reaction mixture was diluted with ethyl acetate and water. The two phases were then separated and the aqueous phase was extracted with ethyl acetate three times. The combined organic phases were washed with water and brine and were dried over Na₂SO₄. After evaporation of the solvent, the obtained crude residue was purified with flash column chromatography (hexane – ethyl acetate 2:3) to afford 3.128 (6.21 mg, 52%) as a colorless oil.

¹H NMR (800 MHz, Chloroform-d) δ 8.01 (s, 1H), 7.16 (d, J = 8.7 Hz, 1H), 6.93 (d, J = 2.4 Hz, 1H), 6.81 (dd, J = 8.7, 2.5 Hz, 1H), 4.34 (d, J = 4.6 Hz, 1H), 3.84 (s, 4H), 3.48 (s, 3H), 3.47 (s, 3H), 3.28 (td, J = 18.8, 17.7, 11.4 Hz, 1H), 3.16 (dt, J = 13.6, 4.8 Hz, 1H), 2.97 – 2.91 (m, 1H), 2.83 (dd, J = 18.8, 8.9 Hz, 1H), 2.79 – 2.75 (m, 2H), 2.41 – 2.35 (m, 2H), 2.29 – 2.23 (m, 1H).

¹³C NMR (101 MHz, CDCl₃) δ 212.5, 154.3, 133.5, 132.9, 131.4, 127.6, 112.3, 111.8, 111.4, 108.0, 100.7, 77.4, 63.2, 56.1, 55.8, 55.0, 40.2, 38.1, 38.0, 34.6, 22.4.

IR (νmax cm⁻¹) 2934 (s), 2835 (m), 1735 (s), 1456 (s), 1215 (s), 1124 (s), 1074 (s), 1058 (s)

HRMS (ESI/QTOF) m/z: [M + H]⁺ Calcd for C₁₉H₂₅N₂O₄⁺ 345.1809; Found 345.1809.
In a glovebox, to a stirred suspension of Schwartz reagent (36 mg, 4 equiv) in THF (0.3 ml) was added a solution of 3.123 (20 mg, 0.034 mmol) in THF (0.2 ml). The mixture was stirred until TLC analysis indicated the consumption of the starting material. The reaction mixture was directly introduced to a preparative TLC plate and was eluted with ethyl acetate three times to afford 3.140 (15 mg, 79%) as a colorless oil.

$^1$H NMR (400 MHz, Chloroform-d) $\delta$ 8.08 (s, 1H), 7.75 (s, 1H), 7.25 – 7.20 (m, 2H), 6.96 – 6.93 (m, 2H), 6.86 – 6.81 (m, 2H), 5.13 (d, $J = 10.9$ Hz, 1H), 4.93 (s, 1H), 4.24 (dd, $J = 8.0$, 5.9 Hz, 2H), 4.14 (ddd, $J = 8.7$, 6.3, 2.9 Hz, 1H), 4.02 – 3.90 (m, 3H), 3.87 – 3.85 (m, 6H), 3.72 (dt, $J = 13.7$, 3.6 Hz, 2H), 3.41 (d, $J = 1.7$ Hz, 6H), 3.36 (d, $J = 3.9$ Hz, 6H), 3.33 – 3.23 (m, 2H), 2.92 – 2.76 (m, 2H), 2.75 – 2.57 (m, 3H), 2.47 – 2.31 (m, 3H), 2.24 – 1.81 (m, 6H), 1.73 (t, $J = 12.5$ Hz, 1H), 1.65 (s, 1H), 0.12 (s, 9H), 0.04 (s, 9H).

$^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 154.0, 154.0, 135.3, 132.0, 131.9, 128.2, 127.9, 127.7, 127.5, 127.2, 114.9, 113.9, 111.8, 111.7, 111.6, 109.0, 107.4, 106.8, 101.9, 100.5, 100.5, 100.0, 97.4, 73.2, 72.4, 66.5, 65.8, 56.0, 56.0, 55.2, 54.4, 53.9, 44.6, 41.7, 41.2, 38.2, 37.9, 37.8, 33.8, 31.6, 20.8, 20.3, 1.7, 1.6.

IR ($\nu_{max}$, cm$^{-1}$) 2936 (m), 1484 (s), 1457 (s), 1438 (m), 1331 (m), 1323 (m), 1283 (s), 1273 (m), 1250 (s), 1216 (s), 1177 (s), 1157 (s), 1130 (s), 1077 (s), 1068 (s), 1044 (s), 984 (m), 974 (s), 966 (s), 922 (s), 912 (s), 902 (m), 888 (s), 881 (s), 867 (s), 843 (s), 823 (m), 759 (m), 748 (m), 734 (s), 719 (s), 686 (m)

HRMS (APPI/QTOF) m/z: [M + H]$^+$ Calcd for C$_{26}$H$_{41}$N$_2$O$_8$Si$^+$ 536.2627; Found 536.2636.

2-(4'-dimethoxymethyl)-6-methoxy-4''-((trimethylsilyl)oxy)-2,3,4,9-tetrahydrodispiro[pyrido[3,4-b]indole-1,1'-cyclopentane-2',2''-[1,3]dioxolan]-4''-yl)ethan-1-ol (3.142)
To a solution of 3.140 (15 mg, 0.028 mmol) in DCE was added acetic acid (1.6 μL, 0.028 mmol) and NaBH₃CN (2.11 mg, 0.033 mmol) at 18 °C. The solution was stirred until TLC analysis indicated the consumption of the starting material. The reaction mixture was directly introduced to a preparative TLC plate and was eluted with ethyl acetate to afford 3.140 (9 mg, 79%) as a colorless oil.

**1H NMR** (400 MHz, Chloroform-d) δ 7.45 (s, 1H), 7.09 (d, J = 8.7 Hz, 1H), 6.79 (d, J = 2.5 Hz, 1H), 6.70 (dd, J = 8.7, 2.4 Hz, 1H), 4.10 (d, J = 6.1 Hz, 1H), 3.72 (s, 3H), 3.65 – 3.59 (m, 1H), 3.57 – 3.51 (m, 1H), 3.48 – 3.42 (m, 1H), 3.24 – 3.21 (m, 6H), 3.16 (s, 2H), 2.67 (dt, J = 17.3, 8.8 Hz, 1H), 2.54 – 2.41 (m, 2H), 2.29 (ddd, J = 12.7, 6.1, 2.1 Hz, 1H), 2.03 – 1.93 (m, 1H), 1.86 – 1.77 (m, 1H), 1.66 (t, J = 12.5 Hz, 1H), -0.00 (s, 9H).

**13C NMR** (101 MHz, CDCl₃) δ 154.2, 132.0, 127.6, 114.2, 111.8, 111.6, 109.4, 107.0, 100.7, 99.4, 72.2, 64.1, 58.8, 56.1, 54.9, 53.4, 43.9, 42.1, 38.4, 37.7, 20.8, 1.8.

**IR (ν_max, cm⁻¹)** 3344 (w), 2935 (m), 1483 (m), 1458 (m), 1439 (m), 1356 (m), 1315 (m), 1275 (m), 1252 (s), 1215 (s), 1153 (s), 1132 (s), 1043 (s), 964 (m), 931 (m), 910 (m), 881 (s), 845 (s), 756 (m), 735 (s), 719 (s), 654 (m)

**HRMS (APPI/QTOF) m/z:** [M + H]+ Calcd for C₂₆H₄₁N₂O₇Si⁺ 521.2683; Found 521.2714.
Bibliography of experimental part


(44) Ritchie, S.; Goodenowe, D.; Khan, M. A. Hydroxy fatty acid compounds and uses thereof for disease treatment and diagnosis, Phenomenone Discoveries Inc, WO 2011/011882 Al. **2011**
(45) Liu, J.; Ma, S. *Synth.* **2013**, *45* (12), 1624–1626.


# EDCH Requirements

## EDCH Course Credits

<table>
<thead>
<tr>
<th>Course Name</th>
<th>Credit</th>
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<tr>
<td>Synergism between the Art of total Synthesis and High Level Strategic Design - Summer</td>
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<tr>
<td>Synergism between the Art of total Synthesis and High Level Strategic Design - Winter</td>
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<tr>
<td>Perspectives in Modern Organic Chemistry (OCS)</td>
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<tr>
<td>Perspectives in Modern Organic Chemistry (OCS)</td>
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<tr>
<td>Frontiers in Organic Synthesis. Part II Synthesis of carbo- and heterocycles</td>
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<tr>
<td>Frontiers in Organic Synthesis. Towards Sustainable Chemistry</td>
<td>2</td>
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<tr>
<td>Swiss Summer School 2017 - Oral Presentation</td>
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<tr>
<td>Swiss Summer School 2019 - Poster Presentation</td>
<td>2</td>
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<td><strong>Total</strong></td>
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## EDCH Teaching Hours

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<tr>
<th>Course Name</th>
<th>Hours</th>
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<tr>
<td>Organic chemistry laboratory work - Practical work (2016-2017)</td>
<td>140</td>
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<tr>
<td>Master project in Molecular &amp; Biological Chemistry - Project mentorship (2016-2017)</td>
<td>56</td>
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<tr>
<td>Organic functions and reactions II - Exercises (2017-2018)</td>
<td>123</td>
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<tr>
<td>Organic chemistry laboratory work - Practical work (2017-2018)</td>
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<tr>
<td>Organic functions and reactions II - Exercises (2018-2019)</td>
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<tr>
<td>Organic functions and reactions II - Exam correction (2018-2019)</td>
<td>24</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>606</strong></td>
</tr>
</tbody>
</table>
Balázs Budai

Address: Route Cantonale 39B
1025, St. Sulpice, Switzerland
Phone: +41 (0)78 619 6985
E-mail: balazs.budai@epfl.ch

Date of birth: 24 June 1991
Google Scholar: Balazs Budai
ORCID: 0000-0002-6275-0339

Education

6/2016 – 8/2020 PhD in Organic Chemistry (EPFL, Switzerland)
Advisor: Prof. Jieping Zhu
Topics: Copper catalyzed olefin difunctionalization and total synthesis of alkaloid natural products.

9/2014 – 5/2016 Master of Science (EPFL, Switzerland)
Advisor: Prof. Phil S. Baran (The Scripps Research Institute, CA, USA)
Program: Molecular and Biological Chemistry, GPA: 5.65/6
Thesis title: “Studies toward the formal hydroamination of unactivated olefins”

9/2010 – 1/2014 Bachelor of Science (Budapest University of Technology and Economics, Hungary)
Advisor: Prof. György Kalaus (MTA-BME)
Program: Chemical Engineering in Pharmaceutical Industry, Excellent with Highest Honors, GPA 4.75/5
Thesis title: “Studies toward the total synthesis of minovincinine and its O-acylated derivatives. Discovery of an unexpected transformation and its application to the semi-synthesis of catharoseumine.”

Research Experience

PhD in Organic Chemistry – 4 years, advisor: Prof. Jieping Zhu, EPFL
• Developed a copper-catalyzed oxidative olefin 1,2-difunctionalization with methyl formate.
• Unprecedented mechanism shows double role of methyl formate in the process.
• Synthetic studies toward the total synthesis of koumine, voacaficine A and voacaficine B.

Master thesis – 6 months, advisor: Prof. Phil S. Baran, The Scripps Research Institute
• Methodology studies on olefin hydroamination with aliphatic nitro compounds.

Semester project – 6 months, Prof. Jieping Zhu, EPFL
• Synthetic studies toward the total synthesis of Peganumine A.

Bachelor thesis – 1.5 years, advisor: Prof. György Kalaus (MTA-BME)
• Developed a semi-synthetic route to a novel alkaloid, catharoseumine.
• Synthetic studies toward minovincinine and its O-acylated derivatives. Development of the first synthetic route to catharoseumine.

Volunteer internship in Drug Research – 6 months, advisor: Csaba Szántay, Jr., PhD, DSc, Richter Gedeon Plc.
• Developed an NMR technique for elucidating the location of PEG-lation on a therapeutic protein.

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1 Hungarian Academy of Sciences - Budapest University of Technology and Economics Alkaloid Chemistry Research Group
Teaching Experience

- Mentorship of Alexandre Leclair (master student) during his thesis work (6 months)
- Laboratory teaching assistant at Organic Reactions and Functions 1. – Practical work (2x10 students, 2 semester)
- Teaching assistant at Organic Reactions and Functions 2. – Lectures and exercises (60 students, 2 semester)

9/2010 – 1/2014, Budapest University of Technology and Economics
- Teaching assistant at Organic Chemistry 2. & Advanced course (30 students, 1 semester)
- Teaching assistant at Structure Elucidation in Organic Chemistry (12 students, 1 semester)
- Prepared high school students for university application in chemistry and mathematics

Publications


Awards

2019 Dec EPF Lausanne Teaching Excellence Award
2019 Aug Helvetica Chimica Acta - Swiss Chemical Society Best Poster Presentation Award (SCS Summer School)
2014 Jan Bachelor of Science degree - Excellent with Highest Honours
2013 Aug Richter Gedeon Plc.’s Prize for outstanding internship work
2010 June District Mayoral Laudation for exceptional results in studies and sports

Languages and Skills

English Fluent – Cambridge Advanced C1 certificate
French Intermediate – level B1
Hungarian Native
Softwares ChemDraw, MestreNova, ELN, MS Office, Matlab, Mercury, Sparky, Chenomx, ChemSketch, Mendeley, Zotero
Hardware GC-FID/MS: Perkin Elmer Clarus580 GC and SQ 8 MS
UPLC-MS: Waters Acquity UPLC H-Class and SQ MS