On the application of asymmetric transition metal catalyzed allylic substitutions:

Studies on the total synthesis of the natural metastasis inhibitor camporidine A and synthesis of novel opines

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Abstract

The present work deals with the synthesis of the piperidine alkaloid camporidine A, which was isolated from the gut bacteria of the ant species *camponotus kiusiuensis*. Due to its interesting 6/5/3 tricyclic structure and the discovered anti-metastatic activity, this natural product represents a challenging target molecule for organic synthesis. In particular, the focus was on the introduction of the stereocenters, which could be established by asymmetric Ir-catalyzed allylic substitutions. The central bicyclic system, which also appears in many camporidine-related structures, could be prepared by ring-closing metathesis, 1,3-dipolar cycloaddition of a nitrone intermediate and subsequent reductive cleavage of the *N-O* bond. Further functionalizations were also investigated using a test system.

In addition, the synthesis of novel opines based on phenylalanine and tyrosine was investigated. With the help of an asymmetric Pd-catalyzed *N*-allylation and subsequent ozonolysis, the targeted opines could be produced in a highly stereoselective fashion in just a few steps. This way, reference compounds with known absolute configuration could be provided for the analytical assignment of opines in organisms.

Kurzzusammenfassung

Die vorliegende Arbeit befasst sich mit der Synthese des Piperidin Alkaloids Camporidine A, welches aus den Darmbakterien der Ameisenspezies *camponotus kiusiuensis* isoliert wurde. Aufgrund seiner interessanten 6/5/3 tricyclischen Struktur und der entdeckten anti-metastatischen Aktivität, stellt dieser Naturstoff ein herausforderndes Zielmolekül für die organische Synthese dar. Insbesondere lag der Fokus auf der Einführung der Stereozentren, welche durch asymmetrische Ir-katalysierte allylische Substitutionen aufgebaut werden konnten. Das zentrale bicyclische System, welches auch in vielen Camporidine-verwandten Strukturen auftaucht, konnte durch Ringschlussmetathese, 1,3-dipolare Cycloaddition eines Nitron-Intermediats und anschließender reduktiver Spaltung der *N-O* Bindung hergestellt werden. Weitere Funktionalisierungen konnten anhand eines Testsystems ebenfalls betrachtet werden.

Des Weiteren wurde die Synthese neuartiger Opine auf Basis von Phenylalanin und Tyrosin untersucht. Mit Hilfe einer asymmetrischen Pd-katalysierten *N*-Allylierung und anschließender Ozonolyse konnte das Opin-Motiv stereoselektiv in nur wenigen Schritten hergestellt werden. Auf diese Weise konnten Referenzverbindungen mit bekannter absoluter Konfiguration für die analytische Zuordnung von Opinen in Organismen bereitgestellt werden.

Vorwort

An erster Stelle möchte ich mich herzlich bei meinem Doktorvater Prof. Dr. Hans-Günther Schmalz bedanken. Schon seit meiner Bachelorarbeit, gefolgt von meiner Masterarbeit und meiner Promotion, hat er mich immer unterstützt und gefördert. Ich habe die Freiheiten in der Forschung im Arbeitskreis und die Möglichkeit eigene Ideen umzusetzen sehr wertgeschätzt. Dennoch war es immer möglich Problemstellungen mit ihm zu diskutieren und Lösungsansätze zu entwickeln, so dass ich jedes Mal mit neuen Ratschlägen, Ideen und vor allem Motivation ins Labor zurückgekehrt bin.

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schrumpfenden Arbeitskreises immer erhalten blieb. Dabei möchte ich allen voran meiner Labornachbarin Mira Scheithe danken. Vielen Dank fürs Zuhören, für jeglichen fachlichen, aber auch vor allem emotionalen Beistand und für das Bestreiten aller Hochs und Tiefs im Medizinermodul! Außerdem bedanke ich mich bei meinem ehemaligen Laborkollegen Dr. Bernhard Krause. Du hast mir den Start in die Promotion durch deine fachliche Expertise und die lustige und entspannte Atmosphäre (besonders durch deine Witze) im Labor sehr erleichtert. Ich möchte mich auch bei Marvin Schwamborn, Tobias Wilzcek, Dr. Dominik Albat und Felix Blüm für die chemischen Diskussionen, die lustigen Gespräche und die auflockernden Kickerrunden in der Kaffeepause bedanken. Es war mir eine Freude mit euch zusammenzuarbeiten!

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1 Introduction

Throughout history, natural products have always played a crucial role in the context of drug development. Already in ancient medicine, many well-known drugs have been used as therapeutics. For instance, in 5000 BC extracts from the willow bark were known to reduce inflammation and to ease pain. The active ingredient in the extract was salicin (**1**), a predecessor of aspirin (**2**, Figure 1). Nowadays, the latter is one of the most prominent drugs marketed by *Bayer*. Although aspirin (**2**) is a synthetic salicylate, the core structure is derived from nature and underlines the tremendous influence of natural products in medicine.[1]

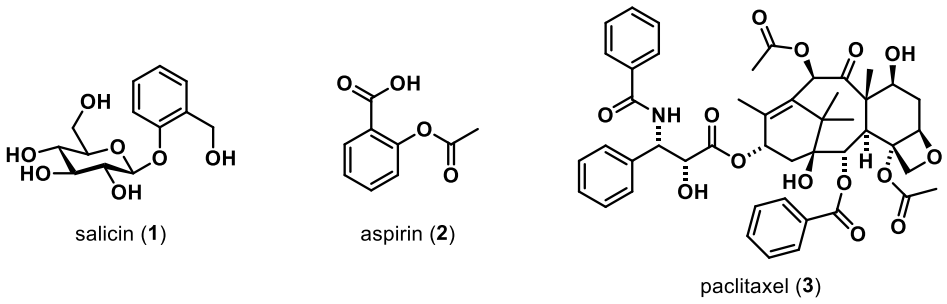


Figure 1: Example of natural products and their derivatives that are marketed as successful drugs.

In the period from 1981 to 2019, natural products, their derivatives, mimetics or natural product pharmacophores accounted for the majority of the approved drugs.[2] Especially in anti-cancer therapy, natural products serve as a highly potent source for pharmaceuticals. 57% of all approved anti-cancer drugs from 1946 to 2019 were natural compounds, their derivatives or mimetics.[2, 3] One of the most famous examples of highly effective natural products is the anti-cancer therapeutic paclitaxel (Taxol©, **3**) which is an approved drug against breast and ovarian cancer (Figure 1).[4]

The main reason for the success of natural products as pharmaceuticals is their special features compared to conventional synthetic molecules with regard to scaffold diversity and molecular complexity. Nature has “optimized” those substrates over hundred millions of years to fulfil particular biological functions.[5] For example, many known natural products are used in nature to interfere with the regulation of defence mechanisms or serve in the interaction with other organisms. This explains the high relevance of natural products in the drug development against infectious diseases and cancer.[6]

Due to the manifold important applications of natural products and their often challenging molecular scaffolds, chemists have become interested in developing access to these compounds, making the total synthesis a highly intriguing field in organic chemistry. This not only leads to the development of new synthetic strategies and methodologies but is also immensely

important for the pharmaceutical industry. Since the access to natural products is often limited,[6] the synthetic access to those products is vital to meet the challenge of the ever increasing drug demand.

Part 1: Studies on the total synthesis of the natural metastasis inhibitor camporidine A

2 Theoretical background

2.1 The compound class of [4.3.0] piperidine alkaloids

Piperidine alkaloids constitute an interesting compound class bearing several structural challenges condensed in a small molecule. To date, the library of this particular class of compounds has been relatively small, but more and more structural analogues have been isolated in the last decades.[7] Some examples for [4.3.0] piperidine alkaloids are depicted in Figure 2.

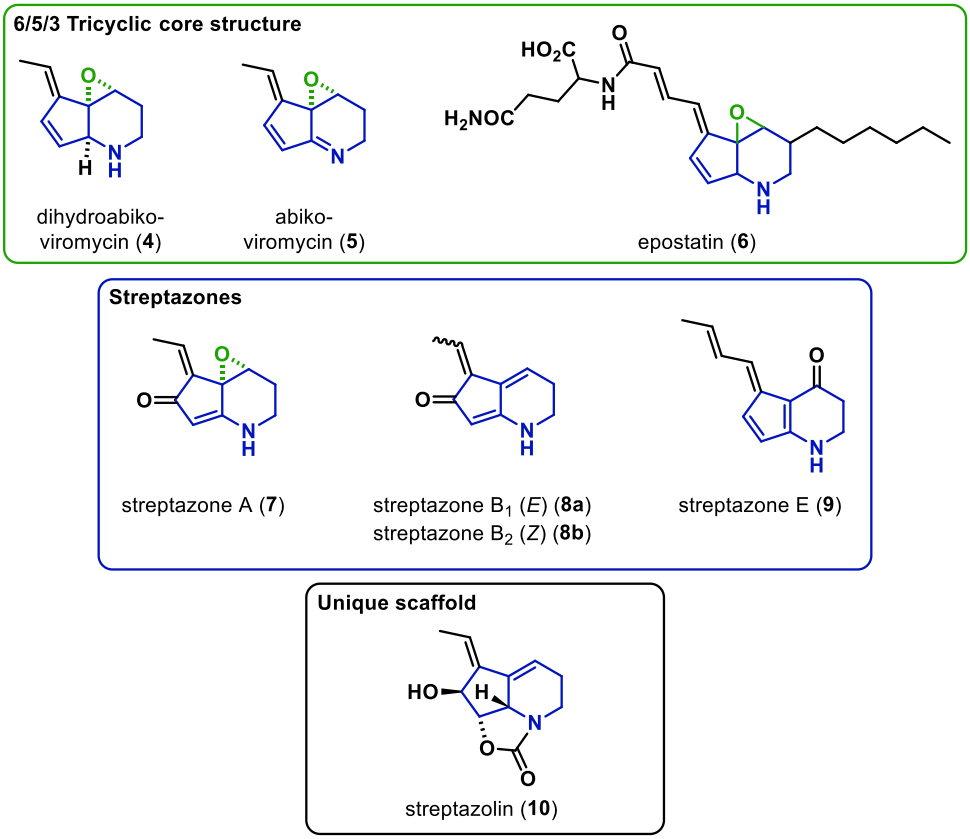


Figure 2: Selected examples for [4.3.0] piperidine alkaloids.

All these compounds share the bicyclic core motif consisting of a fused cyclopentane and piperidine moiety (marked in blue). However, several variations can be noted. Dihydroabikoviromycin (**4**), abikoviromycin (**5**), epostatin (**6**) and streptazone A (**7**) expand the core motif by an epoxide functionality forming a 6/5/3 tricyclic structure. In addition, epostatin (**6**) features an alkyl side chain, an elongated unsaturated side chain and a glutamine peptide bond representing the most expanded piperidine alkaloid system so far.[7]

Many isolated piperidine alkaloids are known under the name “streptazones”. These molecules exhibit an enaminone (as in streptazone A (**7**) and streptazone $B_{1/2}$ (**8**)) or a transposed enaminone motif (as in streptazone E (**9**)). Additionally, streptazone E (**9**) bears an elongated unsaturated side chain.[7]

Another interesting member of the piperidine alkaloids is streptazoline (**10**). In the past years, streptazoline (**10**) has attracted a lot of attention from organic synthesis groups due to its rather unusual scaffold including an exocyclic ethylidene unit and a urethane moiety.[7] Overall, six total syntheses of streptazoline (**10**) have been described so far, which will be further elucidated in the subsequent part (see Chapter 2.1.2).[8-13]

The piperidine alkaloids represent not only synthetically challenging small molecules, but some of those compounds also possess promising biological activities. For example, antibacterial and antifungal activities were described for dihydroabikoviromycin (**4**).[7, 14] Streptazone A (**6**) was reported to act in a cytotoxic way against several cancer cell lines.[15] Epostatin (**7**) is a potential dipeptidyl peptidase II (DPP-II) inhibitor.[16, 17] DPPs play a crucial role in the regulation of signaling by peptide hormones. Although the physiological role of DPP-II has not yet been fully understood, it is assumed that DPP-II is involved in cell differentiation processes and in cell death protection.[18] Moreover, the alkaloid **7** displayed weak antibacterial and antifungal properties.[7, 16] These are just few of the many examples to emphasize the interest in this compound class.

2.1.1 Camporidine A

In 2019, two new [4.3.0] piperidine alkaloids were isolated by the research group of *Oh*. Camporidine A (**11**) and its structural analogue camporidine B (**12**) were both extracted from the gut bacterium *streptomyces* of the carpenter ant *camponotus kiusiuensis* (Figure 3).[19]

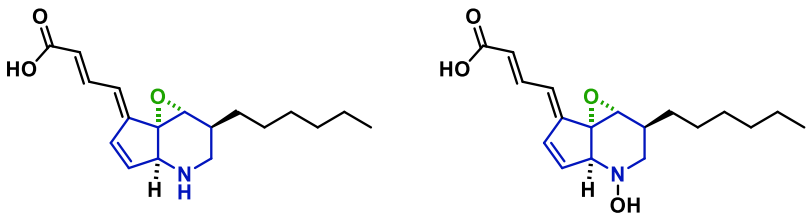


*Figure 3: Structures of camporidine A (**11**) and camporidine B (**12**).*

The structures resemble epostatin (**6**) featuring the same 6/5/3 tricyclic core motif, an unsaturated C_4-side chain and a hexyl side chain. Whereas the absolute configuration for epostatin (**6**) was not determined, *Oh et al.* were able to solve the relative and absolute

configuration of camporidine A (**11**) and B (**12**) by ^{1}H-NOE experiments and comparison of the experimental and calculated ECD-spectra.[19]

Besides structural elucidation, *Oh and co-workers* also investigated the bioactivity of camporidine A (**11**) and B (**12**). While camporidine B (**12**) was unactive or weakly active in all reported assays, camporidine A (**11**) exhibited interesting biological properties emphasizing the necessity of the amine functionality for active binding and interfering.[19]

Since antibacterial and antifungal properties were reported for dihydroabikoviromycin (**4**),[14] the activity of camporidine A (**11**) against pathogenic bacteria and fungi was tested. However, no significant activity was observed, only minimal inhibitory concentrations (MIC) of 64 µM were reported.[19] Moreover, the antiproliferative activity of piperidine alkaloid **11** was investigated. Therefore, the compound's antiproliferative effect was tested on a variety of human cancer cell lines and a human breast epithelial cell line. No cytotoxic activity of camporidine A (**11**) could be identified in any of the cell lines. However, these observations led to experiments on the anti-metastatic properties of alkaloid **11**. Here, the cell migration was examined by wound healing assays performed against MDA-MB-231 human breast cancer cells. Additionally, cell invasion assays were performed. Both experiments showed an inhibitory effect of camporidine A (**11**) in a concentration-dependent manner (Table 1).[19]

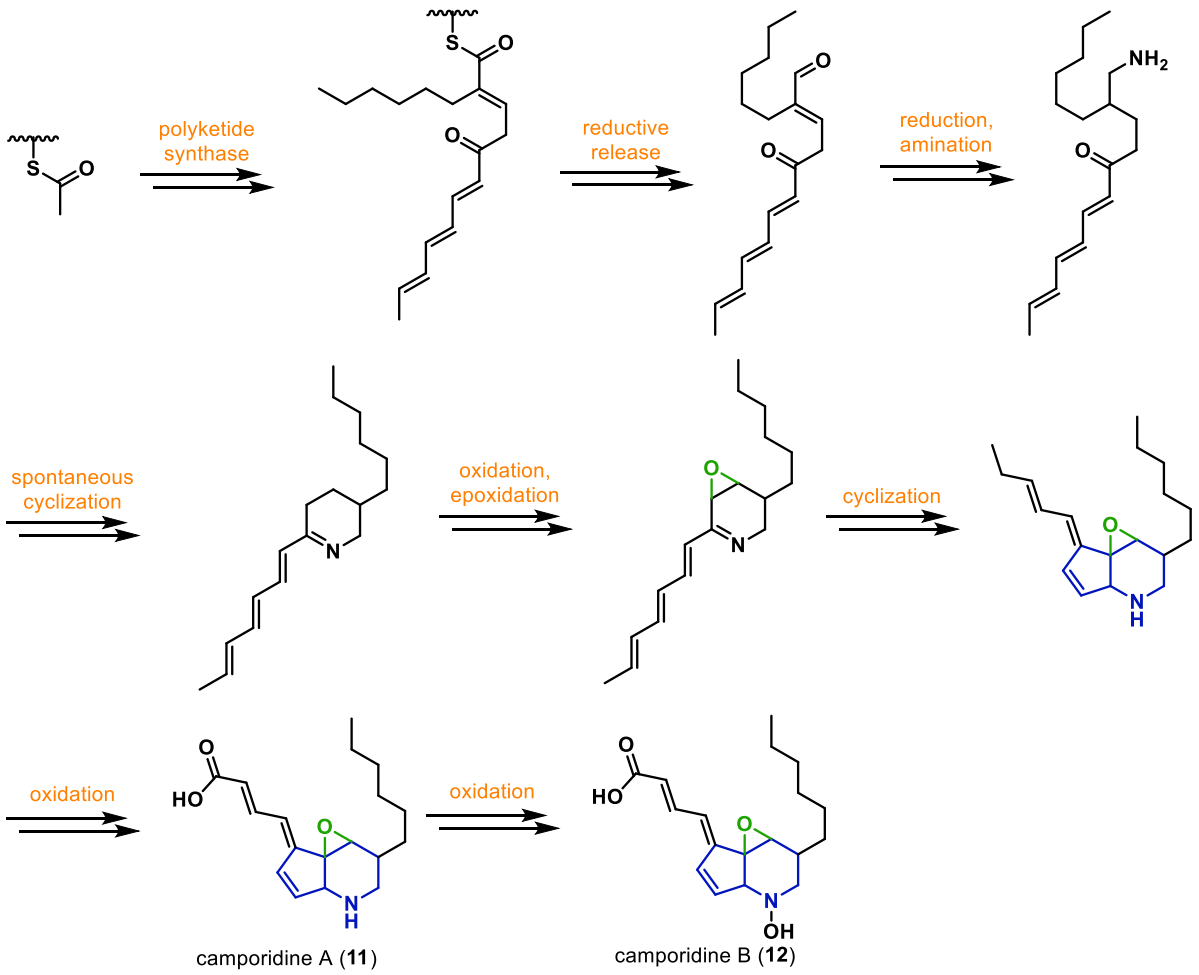
*Table 1: Overview of the determined suppression of cell migration and invasion for camporidine A (**11**).[19]*

Assay	Observed suppression in relation to concentration of 11	
	20 µM	**40 µM**
Cell migration	50%	73%
Cell invasion	20%	36%

By applying a concentration of 40 µM, cell migration decreased by 73% and cell invasion by 36%, proving an anti-metastatic activity. However, the targeted inhibitory pathways leading to the observed effect have not been investigated yet.[19]

In addition to the anti-metastatic property, an anti-inflammatory effect was reported. Mouse macrophages were treated with camporidine A (**11**) leading to a suppression of nitric oxide production induced by lipopolysaccharide with a half maximal inhibitory concentration (IC_{50}) of 16.9 µM.[19]

Besides investigating the bioactivity, *Oh et al.* hypothesized a biosynthetic pathway for the natural products **11** and **12** (Scheme 1).[19]

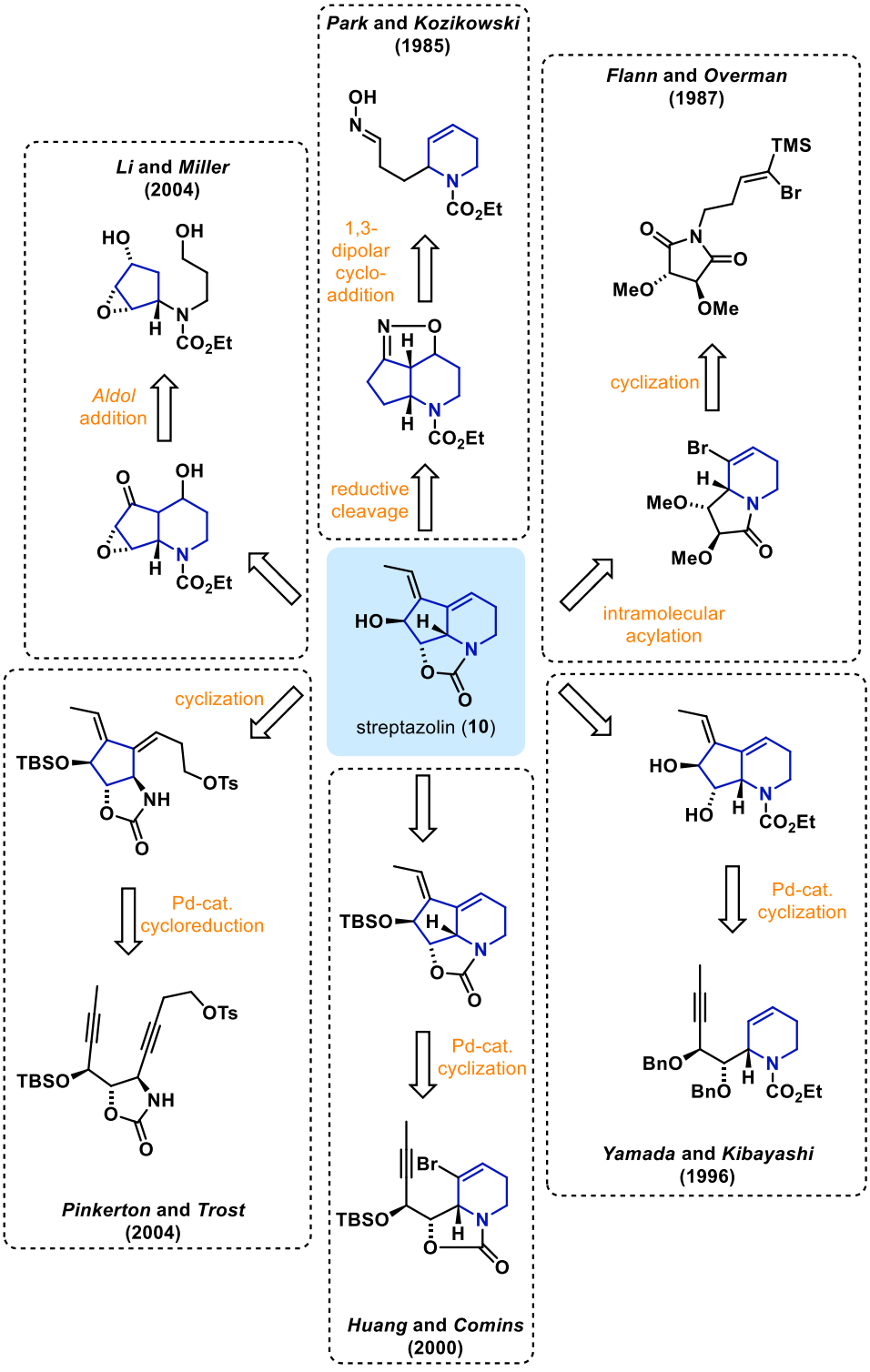


*Scheme 1: Proposed biosynthesis of camporidine A (**11**) and B (**12**).*[19]

Although the biosynthetic pathways for streptazones,[7, 15, 20] streptazoline (**10**)[21] and abikoviromycin (**5**)[7] have already been described, the establishment of the tricyclic camporidine core motif, which is also found in epostatin (**6**) and dihydroabikoviromycin **(4)**, has not yet been reported. Since the biosynthetic pathway for streptazone E (**9**) has been proposed by *Ohnishi et al.*,[20] *Oh and co-workers* suggested a similar pathway for camporidines **11** and **12** due to the structural similarity.[19] It is hypothesized that a polyketide synthase (PKS) system is responsible for the formation of a precursor of the natural product **11**. Upon reductive release of this precursor, the key steps in the biosynthetic pathway include spontaneous *Schiff* base formation, epoxidation and cyclization.[19] The cyclization, which leads to the establishment of the 6/5/3 tricyclic core motif, is supposed to proceed *via* an ene-reaction, however, the final re-formation of the epoxide remains elusive.[7] Although the biosynthesis has been studied and a few total syntheses of [4.3.0] piperidine alkaloids have been accomplished so far, a total synthesis of camporidine A (**11**) has not yet been reported.

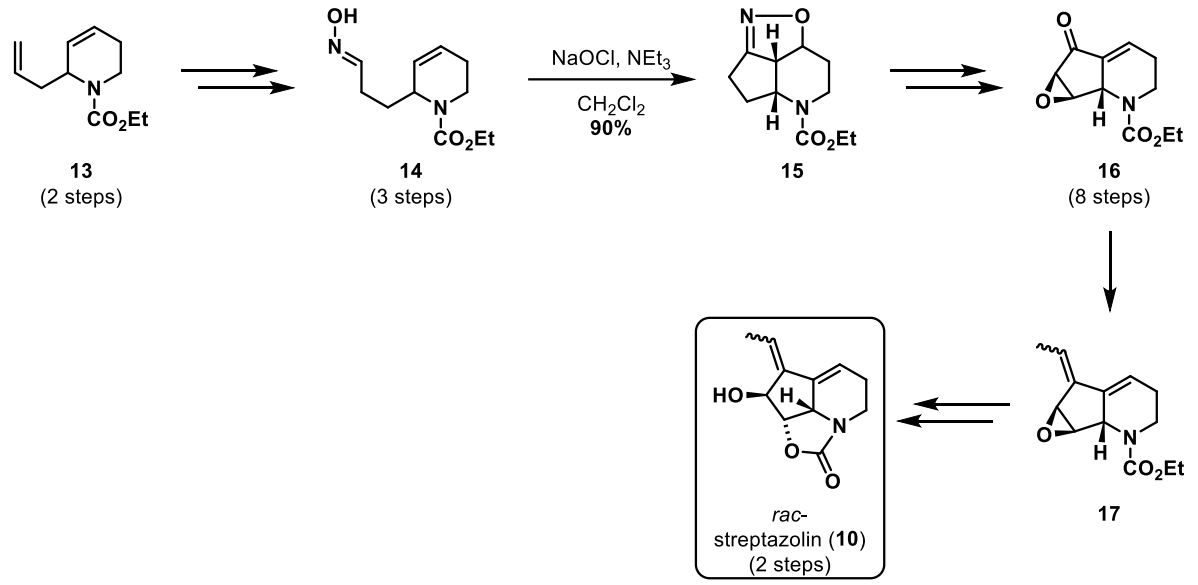
2.1.2 Total syntheses of streptazolin

As stated before, streptazolin (**10**) is one of the best-known examples of [4.3.0] piperidine alkaloids, which was first isolated from *streptomyces viridochromogenes* in 1981 by *Drautz* and *Zahner*.[22] Due to its unusual scaffold, it has gained a lot of attention in the field of total synthesis. Up to date, six total syntheses of the natural product **10** have been published (Scheme 2).



*Scheme 2: Overview of accomplished total syntheses of streptazolin (**10**) highlighting the key strategies to form the central [4.3.0] bicyclic structure.*[7]

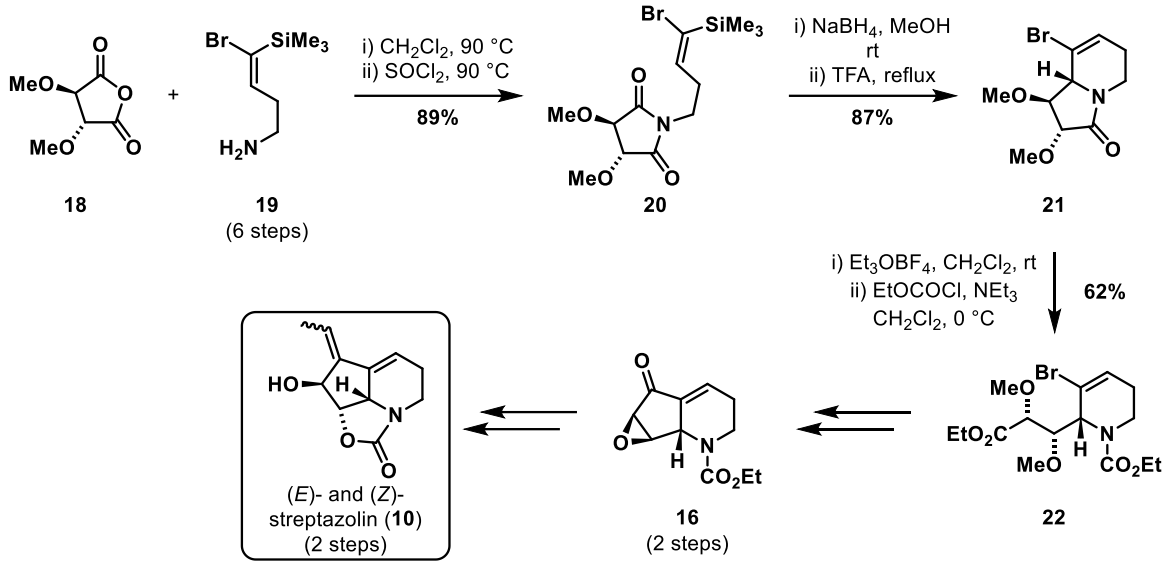
Interestingly, a variety of different strategies were used to accomplish the total synthesis of streptazolin (**10**). The first racemic total synthesis of the natural product was published by *Park* and *Kozowski* in 1985 (Scheme 3).[8]



*Scheme 3: Racemic total synthesis of streptazolin (**10**) reported by Park and Kozikowski.[8, 23]*

Starting from allyl-substituted tetrahydropyridine **13**, the aza-analogue of a *Ferrier*-type reaction,[23] the corresponding oxime **14** was generated. The key step of the synthesis is a 1,3-dipolar cycloaddition of a nitrile oxide to establish the bicyclic core structure **15**. After reductive cleavage of the isoxazoline motif **15**, dehydrobromination, epoxidation and elimination, epoxide **16** was provided. Consecutive *Wittig* reaction generated the (*E*)- and (*Z*)-isomers of olefin **17**. Treatment of substrate **17** with NaOAc and NaOMe led to the racemic synthesis of streptazolin (**10**) in overall 17 steps. This was not only the first described total synthesis of the natural product, but also helped elucidating the stereochemistry of streptazolin (**10**) assigning the (*Z*)-olefin as the naturally occurring isomer.[8]

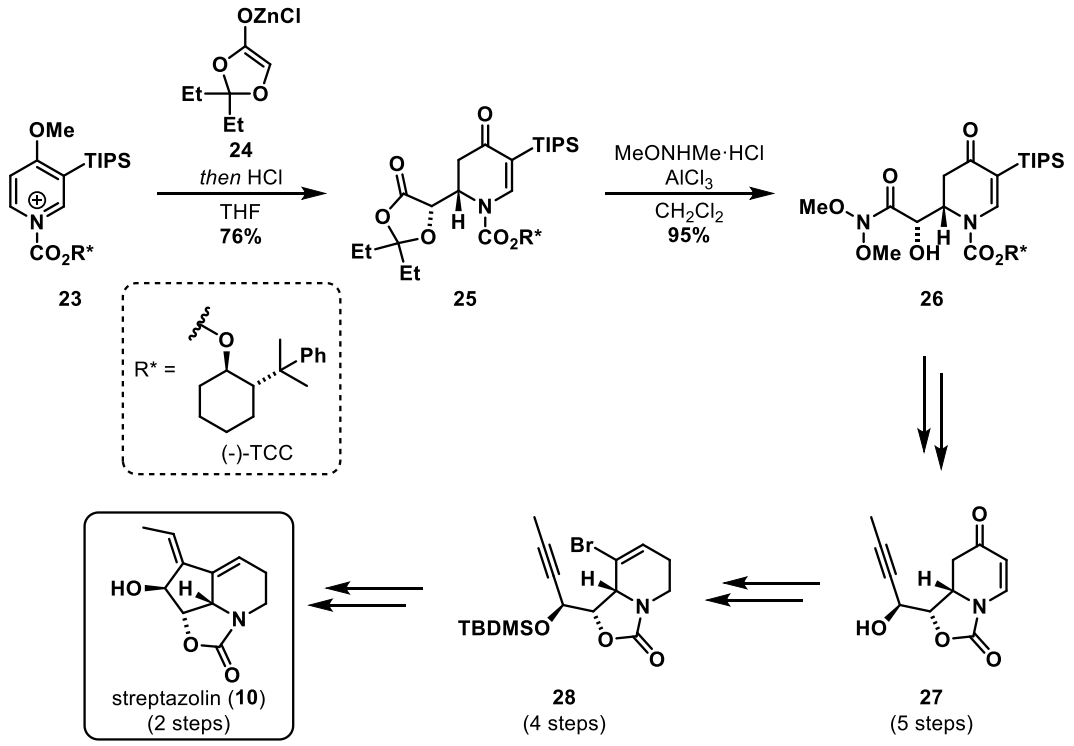
The first non-racemic synthesis was reported by *Flann* and *Overman* in 1987.[9] The approach was based on using the chiral pool (Scheme 4).



*Scheme 4: First non-racemic synthesis of streptazolin (**10**) reported by Flann and Overman.[9]*

Anhydride **18** was implemented, which is derived from L-tartaric acid in a three-step synthesis. It already includes the correct stereochemistry of the substituents attached to the cyclopentane moiety of streptazolin (**10**). The tetrahydropyridine unit in substrate **21** was established by reacting anhydride **18** and bromo vinylsilane **19** to afford amide **20**. Subsequently, substrate **20** was reduced and cyclized to tetrahydropyridine **21** under acidic conditions. The desired diastereoselectivity was induced by the bulky TMS group in *Z*-position. Next, the amide bond was cleaved and the formed amine trapped by ethyl chloroformate to afford ester **22**. After halogen-lithium exchange, a cyclization occurred and after cleavage of the methyl protection groups, the desired epoxide **16** was provided. The last steps of the total synthesis referred to the reported sequence of *Park* and *Kozikowski*[8] affording streptazolin (**10**) in 15 steps. However, the selectivity of the *Wittig* reaction introducing the vinylidene side chain was challenging as the undesired (*E*)-isomer of streptazolin (**10**) was obtained as the main product in a 2:1 (*E*/*Z*) ratio.[9]

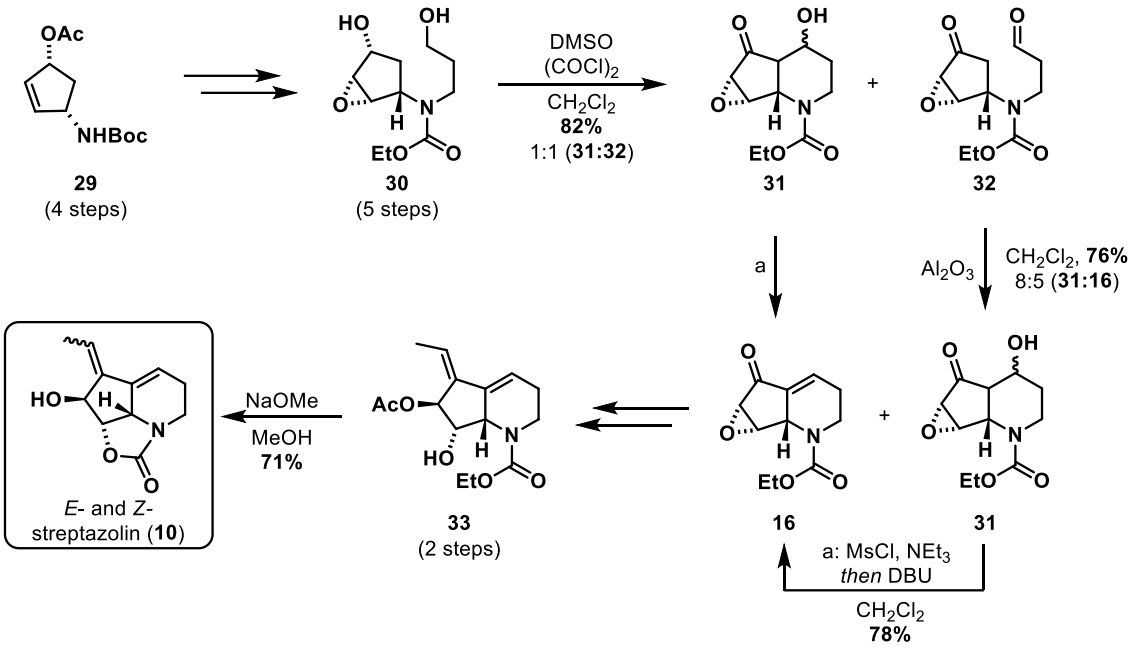
From 1996 to 2004, the natural product **10** was again of high interest, as four new non-racemic total syntheses were reported. Here, *Yamada* and *Kibashi*[10], *Huang* and *Comins*[11] and *Pinkerton* and *Trost*[13] followed a similar strategy in which the central cyclopentane unit was built up by a Pd-catalyzed cyclization (see Scheme 2). *Yamada* and *Kibashi*, as well as *Pinkerton* and *Trost*, made once again use of the natural chiral pool to establish the desired stereochemistry of streptazolin (**10**) by using L-tartaric acid and D-mannitol diacetonide, respectively.[10, 13] Interestingly, *Huang* and *Comins* followed an auxiliary-mediated approach to induce stereoselectivity (Scheme 5).[11]



*Scheme 5: Auxiliary-mediated total synthesis of streptazolin (**10**) reported by Huang and Comins.*[11]

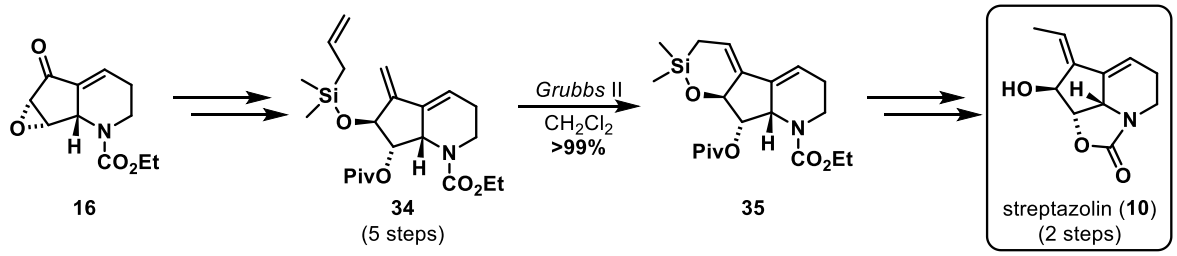
Their total synthesis is based on the use of enantiopure *N*-acyldihydropyridones in which *trans*-2-(*α*-cumyl)cyclohexanol ((-)-TCC) was implemented as the chiral auxiliary. Metal enolate addition of zinc organyle **24** to acylpyridinium **23** established the 2-substituted pyridine **25** in a diastereoselective fashion. Dihydopyridone **25** was then converted to the corresponding *Weinreb* amide **26**. Next, a reaction sequence followed to afford bicylic carbamate **27**. Here, a propinyl group was introduced, a *Luche* reduction was performed, the carbamate was established, the stereocenter of the alcohol was inverted employing *Mitsunobu* conditions and the TIPS group was removed. Side reactions of the enone moiety were prevented in this reaction sequence by the bulky TIPS group. To afford vinyl bromide **28**, substrate **27** was brominated and the enaminone functionality was reduced. The tricylic core structure of streptazolin (**10**) was established through an intramolecular Pd-catalyzed *Heck*-type cyclization. After silylether deprotection, streptazolin (**10**) was provided in 13 linear steps and with high stereocontrol.[11]

The latest total synthesis of streptazolin (**10**) was published by *Li* and *Miller* in 2004. In contrast to the previously reported total syntheses, *Li* and *Miller* established the central tetrahydropyridine by an aldol condensation (Scheme 6).[12]



*Scheme 6: Total synthesis of streptazolin (**10**) reported by Li and Miller.[12]*

The synthesis starts from enantiopure aminocyclopentene **29** prepared by chemoenzymatic transformations from *N*-Boc-hydroxylamine in four steps. The alcohol **30** was obtained in five steps *via* a reductive amination sequence, carbamate formation and epoxidation. By applying *Swern* oxidation conditions, the precursor **32** for the aldol condensation was obtained along with the aldol product **31**. Next, the precursor **32** was treated with Al_2O_3 resulting in the formation of the aldol addition product **31** and the aldol condensation product **16**. Conversion of aldol product **31** to **16** was accomplished by mesylation and base-initiated elimination. As previously reported by *Park* and *Kozikowski*, enone **16** was transformed through a *Wittig* reaction and by epoxide opening to streptazolin precursor **33**, from which streptazolin (**10**) was afforded after cyclic carbamate formation in overall 14 steps. However, the *E*/*Z*-selectivity of the *Wittig* reaction was problematic as both *E*- and *Z*-streptazolin (**10**) were obtained.[12] Although the isomers were separable by HPLC, *Li* and *Miller* aimed for a more convenient and selective approach (Scheme 7).[24]

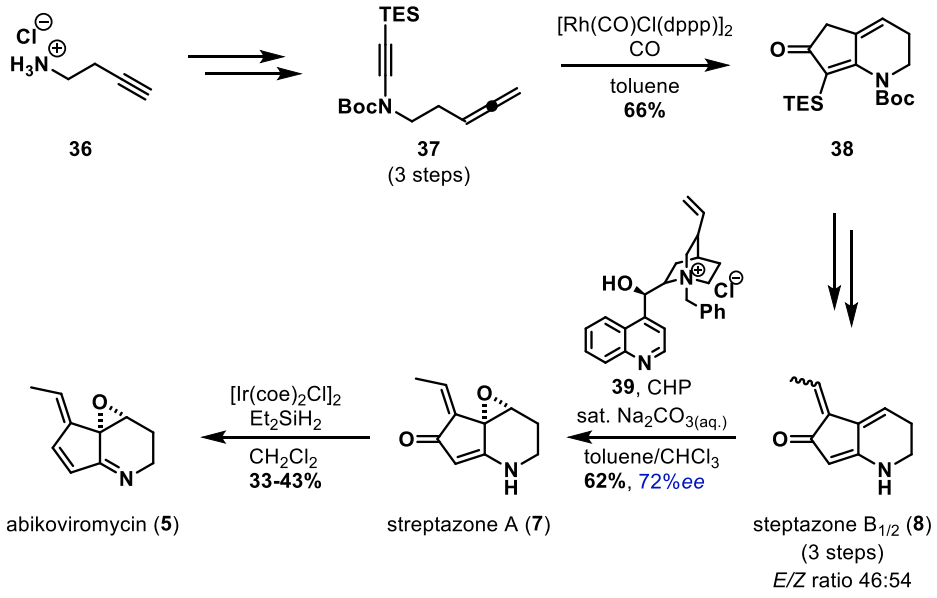


*Scheme 7: Alternative final steps of the total synthesis of streptazolin (**10**) reported by Li and Miller.[24]*

Alternatively, enone **16** could be transformed to allylsilane **34** by *Wittig* reaction and epoxide opening. The key step was the silicon-tethered ring closing metathesis (RCM) to establish the desired *Z*-geometry of the ethylidene side chain. After protodesylilation and carbamate formation, (*Z*)-streptazolin (**10**) was obtained in overall 16 steps.[24]

2.1.3 Total syntheses of other [4.3.0] piperidine alkaloids

Besides streptazolin (**10**), very few other piperidine alkaloids were explored synthetically. The research group of *Poulsen* has focussed on the synthesis of this challenging compound class and published the first asymmetric syntheses of streptazone A (**7**), streptazone $B_{1/2}$ (**8**) and abikoviromycin (**5**) in 2021 (Scheme 8).[25]



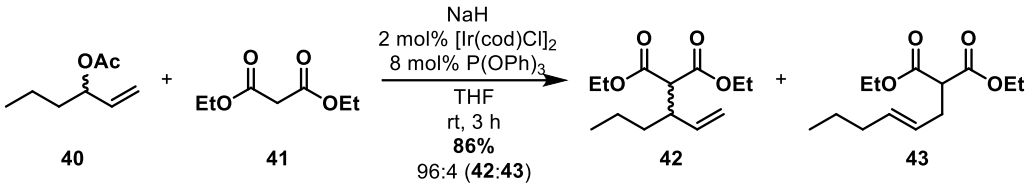
*Scheme 8: Total synthesis of streptazone $B_{1/2}$ (**8**), streptazone A (**7**) and abikoviromycin (**5**) reported by Poulsen et al.*[25]

Here, a very convenient strategy was applied to establish the piperidine alkaloid core structure that could be converted into the different natural products by simple transformations starting from but-3-yn-1-amine hydrochloride (**36**). The amine **36** was converted to TES-alkyne **37** in three steps through a *Crabbé* homologation and addition of TES-bromoacetylene. An intramolecular allene-ynamide *Pauson-Khand* cyclization served as the key transformation to establish the [4.3.0] bicyclic core motif **38**. The ethylidene group was installed by addition of acetaldehyde and dehydration. Subsequent treatment with TFA delivered the desilylated natural product streptazone B (**8**) in just 7 steps. Since the ethylidene formation was unselective, both the (*E*)- and *(Z)*-isomer of streptazone B (**8**) were obtained. However, the isomers were separable by column chromatography. Next, cumene hydroperoxide (CHP) was proven to be a suitable epoxidation reagent in combination with the organocatalyst **39**, a chiral cinchona-based phase transfer

catalyst, to obtain streptazone A (**7**). After reduction of the enaminone system with an iridium-diethylsilane system, abikoviromycin (**5**) was obtained in this reaction sequence.[25] Although a variety of [4.3.0] piperidine alkaloids have been isolated, the described substrates are the only reported synthetic approaches towards this compound class. Until now, the access to many isolated [4.3.0] piperidine alkaloids remains to be explored despite their high pharmacological potential.

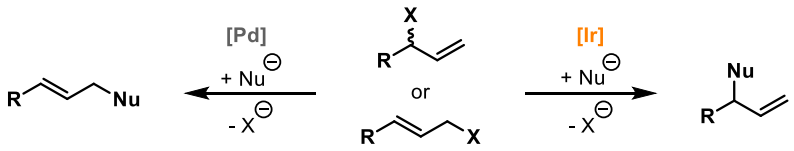
2.2 Asymmetric Iridium-catalyzed allylic substitution

Transition metal-catalyzed carbon-carbon or carbon-heteroatom bond formations have become a highly valuable tool in organic synthesis. In many synthetic strategies towards chiral substrates, the stereocontrolled introduction of a stereogenic center is of crucial importance making asymmetric allylic substitution reactions (also known as *Tsuji-Trost* reactions) an immensely valuable method.[26-28] Most *Tsuji-Trost*-type reactions rely on the implementation of a Pd-catalyst, but catalysts based on other transition metals, such as Mo[29], Ru[30, 31], Rh[32] and Ni[33] have also been used successfully. Furthermore, Ir-based catalysts were found to be highly effective, which was first reported by *Takeuchi* and *Kashio* in 1997 (Scheme 9).[34]



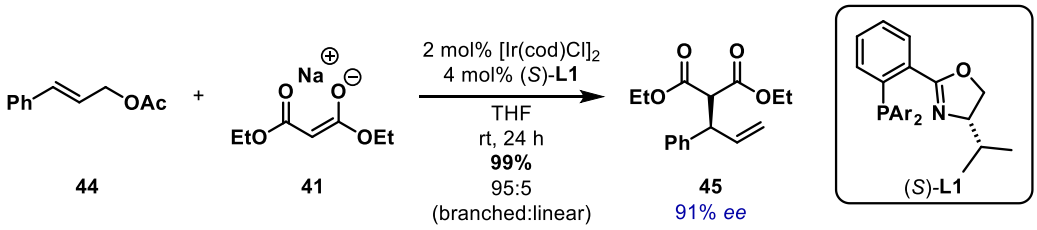
Scheme 9: First Ir-catalyzed allylic substitution reported by Takeuchi and Kashio.[34]

Interestingly, the Ir-catalyzed allylic substitution of racemic acetate **40** and malonic ester **41** mainly yielded the branched product **42**.[34] In contrast, Pd-catalyzed reactions preferably form the linear product **43** (Scheme 10).[35]



Scheme 10: Comparison of Pd- and Ir-catalyzed allylic substitutions.

The unique regioselectivity of Ir-catalyzed allylic substitutions raises the question about the possibility of enantioselective transformations. Only shortly after *Takeuchi* and *Kashio*, the first asymmetric Ir-catalyzed reaction was published by *Janssen* and *Helmchen* (Scheme 11).[36]



Scheme 11: First enantioselective Ir-catalyzed allylic substitution reported by Janssen and Helmchen.[36]

The conversion of linear acetate **44** and malonate **41** to the branched product **45** was achieved with high regioselectivity, as expected for Ir-catalyzed reactions. Moreover, a highly enantioselective transformation was accomplished with the use of the chiral PHOX-ligand (*S*)-**L1**

in combination with $[Ir(cod)Cl]_2$.[36] Today, a variety of ligand systems could be implemented in the Ir-catalyzed allylic substitution. In particular, phosphoramidite ligands established by the *Feringa* group have developed to a useful and widely applicable ligand system (Figure 4). Originally, the *Feringa* group developed those ligand systems for asymmetric Cu-catalysis,[37, 38] however, the research groups of *Helmchen* and *Hartwig* quickly implemented these ligands in the field of asymmetric Ir-catalysis.[39, 40] The most prominent and widely applicable ligand is phosphoramidite (*S,S,S*)-**L2**, which is also referred to as the *Feringa* ligand.[37]

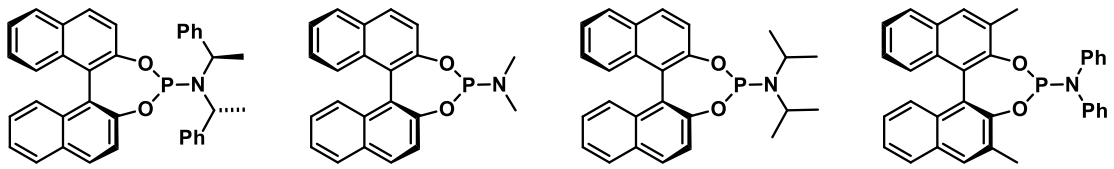
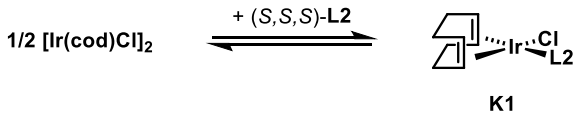


Figure 4: Selected phosphoramidite ligands developed by Feringa et al.[37, 38]

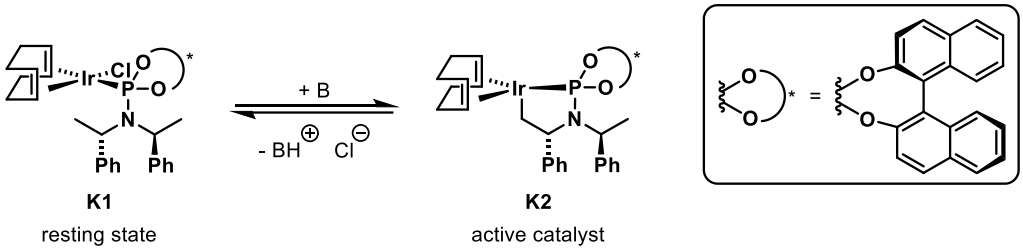
2.2.1 Mechanism

The mechanism of the Ir-catalyzed allylic substitution was extensively investigated by the research group of *Hartwig*. Initial studies showed that the catalyst system consisting of $[Ir(cod)Cl]_2$ and *Feringa* ligand (*S,S,S*)-**L2** formed the square planar complex **K1** (Scheme 12).[41]



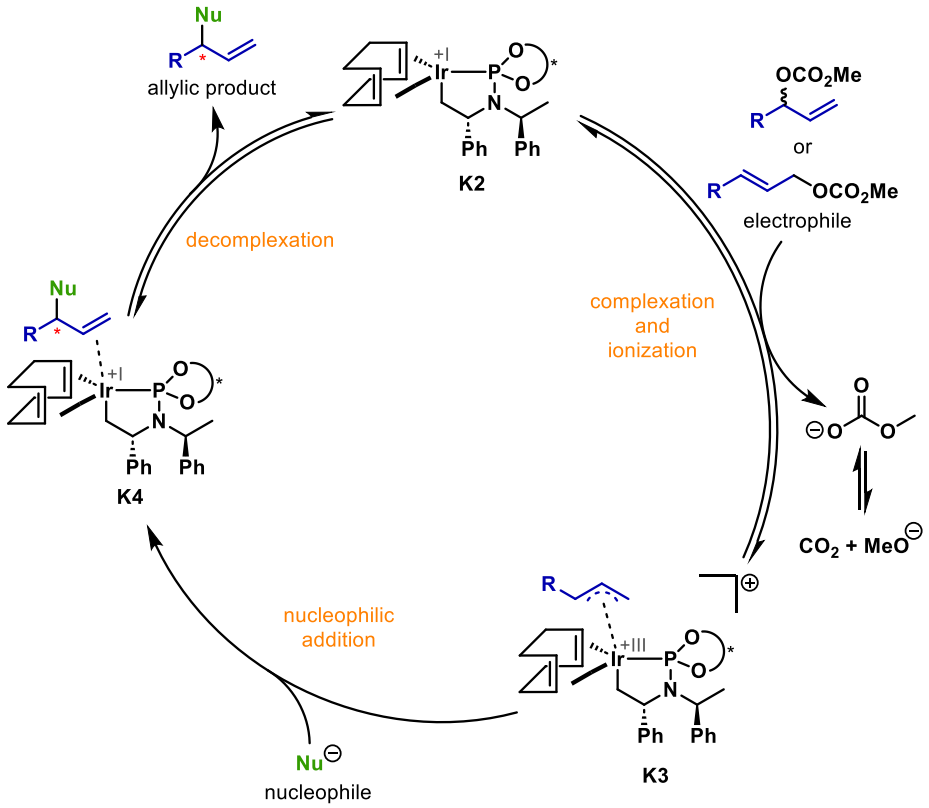
*Scheme 12: Formation of square-planar complex **K1**.*[41]

Hartwig and co-workers were able to isolate complex **K1** and analyse the catalyst species by means of NMR spectroscopy and X-ray diffraction. Furthermore, the isolated complex was directly tested in an Ir-catalyzed allylic substitution using methyl cinnamyl carbonate as the electrophile. However, the addition of the carbonate to complex **K1** was not observed, implying that **K1** is not the active catalytic species. Thus, complex **K1** was described as the resting state of the catalyst instead.[41] Further experiments showed that the active catalytic species is formed *via* a base-induced *C-H* activation to generate the cyclometalated complex **K2** (Scheme 13).[42, 43]



Scheme 13: Formation of the active catalytic species.[43]

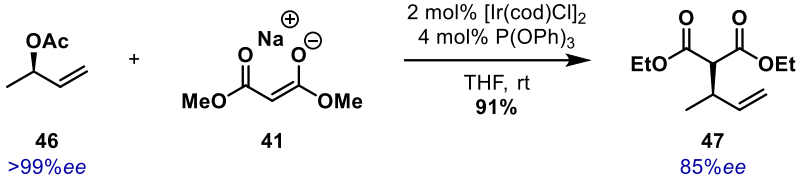
The 16 valence electrons (VE) complex **K2** is usually formed *in situ*. If the nucleophile used in the reaction is basic enough, it can already induce the formation of the active catalytic species without an additional base. Otherwise, non-nucleophilic bases, e.g. 1,5,7-triaza-bicylo[4.4.0]dec-5-ene (TBD) or DBU, are well suited for the *C-H* activation.[43] With complex **K2** in hand, the catalytic cycle can proceed (Scheme 14).



Scheme 14: Catalytic cycle of the Ir-catalyzed allylic substitution.

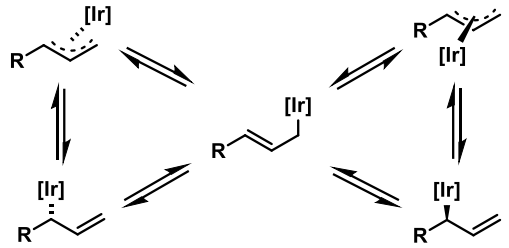
First, the active catalytic species **K2** undergoes complexation and ionization. In this step, the carbonate electrophile is coordinated, subsequently releases a carbonate anion, which potentially decomposes to CO_2 and methanolate, generating allyl-metal-intermediate **K3**. The ionization step proceeds in a S_N2'-type fashion. Upon nucleophilic addition, intermediate **K4** is formed releasing the chiral allylic product and regenerating the active catalyst **K2** in the decomplexation step.[42, 43] The crucial step determining the configuration of the product is the

complexation and ionization sequence. In order to study the configurational stability of allyl-metal-intermediates, *Helmchen* and *co-workers* examined the reaction of chiral acetate **46** (Scheme 15).[39]



*Scheme 15: Ir-catalyzed allylic substitution performed with chiral acetate **46**, in which the stereoinformation is retained by a double inversion mechanism.*[39]

Interestingly, the product retained the stereochemistry implying that the reaction proceeds through a double inversion process. First, the stereocenter is inverted by substitution to afford a *σ*-allyl-iridium complex. Nevertheless, the Ir-complex may isomerize upon *σ*-*π*-*σ*-rearrangement (Scheme 16). This racemization proceeds rather slow for Ir-complexes in comparison to other species, e.g. Pd-complexes. Further reaction with the nucleophile proceeds fast and inverts the stereocenter again leading to the overall retained stereoinformation.[39] The same reaction mechanism has also been postulated for Rh-catalyzed reactions.[44]



Scheme 16: Possible σ-π-σ-isomerization of allyl-irdium complexes.[39]

For the configurational outcome of the reaction, the position of the substituent R is decisive. Several research groups have investigated the formation of *π*-allyl-iridium complexes of type **K3** for different catalytic systems. By means of X-ray diffraction and kinetic studies, it was proven that the complex of type **K3a** is predominantly formed (Figure 5).[43, 45-48] In this case, the substituent R is aligned opposite to the BINOL and the cod-unit avoiding any steric hindrance.

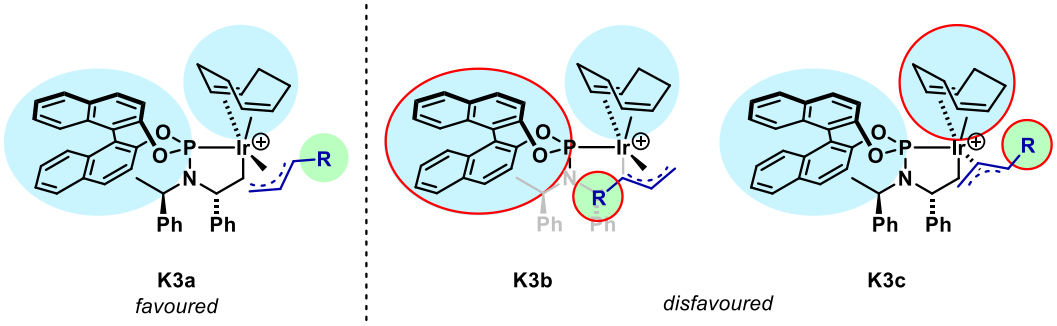


*Figure 5: Favoured configuration of allyl-iridium complex **K3a**, in which the substituent R is aligned in the less hindered position forced by the bulky BINOL unit and the cod ligand in comparison to the disfavoured π-allyl-iridium complexes **K3b** and **K3c**.*[46]

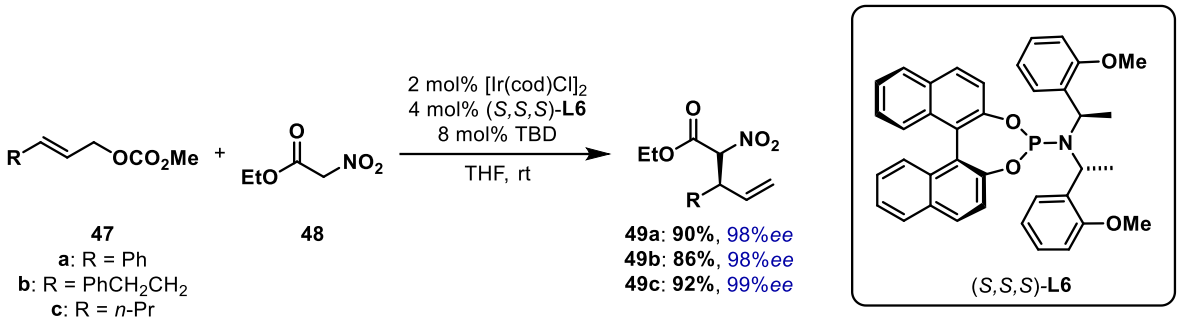
In 2015, *Hartwig* and *co-workers* tried to elucidate the regioselectivity of the Ir-catalyzed reaction by kinetic studies and DFT calculations. Therefore, a catalytic system consisting of $[Ir(cod)Cl]_2$ and a $P(OPh)_3$-derived ligand was examined. The study showed that the favoured formation of the branched product is neither driven by the Ir-C bond length, nor by the increased partial charge, nor by the stability of the resulting *π*-complex. Instead, DFT calculations supported the hypothesis that the nucleophile interacts with the hydrogen atoms of the cod-ligand. These interactions lead to the favoured formation of the branched product.[49] However, *Helmchen et al.* could not verify these interactions for their allylic amination systems.[43, 50] Therefore, a general explanation for the observed regioselectivity remains elusive.

Besides the typical catalyst system of $[Ir(cod)Cl]_2$ and *Feringa*-type ligands, *Helmchen and co-workers* showed that $[Ir(dbcot)Cl]_2$ (dbcot = dibenzocyclooctatetraene) is a valuable alternative to $[Ir(cod)Cl]_2$. The use of $[Ir(cod)Cl]_2$ is limited since the complex is oxygen-sensitive and not heat-stable. In comparison, Ir-complexes bearing the dbcot-ligand were found to be superior. *Helmchen et al.* were able to conduct allylic alkylations with $[Ir(dbcot)Cl]_2$ under elevated temperature and even under air. Furthermore, the dbcot-ligand is a better electron-acceptor and exhibits an even stronger coordination to Ir than the cod-ligand. The regioselectivity of allylic alkyl substrates in particular was improved by the use of $[Ir(dbcot)Cl]_2$.[51]

2.2.2 Substrate scope

The substrate scope of the Ir-catalyzed allylic substitution is extremely versatile. As far as nucleophiles are concerned, a variety of substrates were used in these reactions, whereby not only *C*-nucleophiles, but also *N*-, *O*- and *S*-nucleophiles were successfully utilized.[35] As the range of nucleophiles is immense, only a few selected examples of *C*- and *N*-nucleophiles will be highlighted in this chapter.

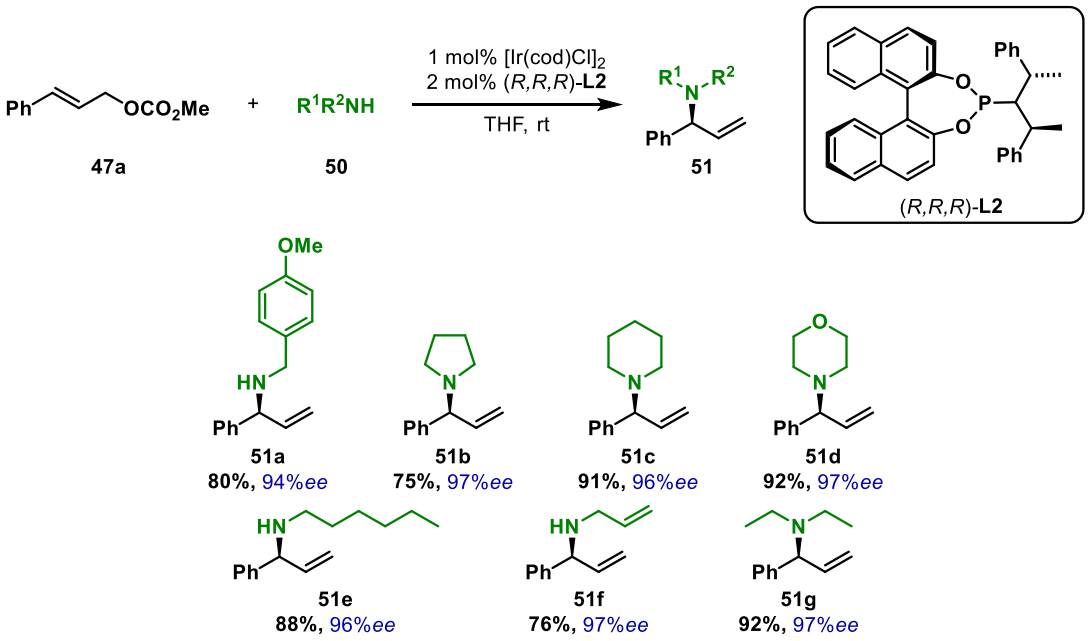
Malonates are mostly used as *C*-nucleophiles (Scheme 9, Scheme 11),[35] which can be classified as stabilized enolates. Among these stabilized enolates, also malononitrile[52] and sulfonylacetic esters[53] can be found in the literature. Moreover, Ir-catalyzed allylic substitutions work well with unstabilized esters[54] and ketone enolates, such as silyl enol ethers[55], aldehydes[56, 57], enamines[58] and electron-rich arenes[59-61]. One example to highlight in the context of applied *C*-nucleophiles are aliphatic nitro compounds. The latter are interesting intermediates in organic synthesis due to their versatile reactivity. For example, nitro compounds allow an easy access to the corresponding amines. In 2006, *Dahnz* and *Helmchen* reported the first Ir-catalyzed allylic substitution with aliphatic nitronates (Scheme 17).[62]



*Scheme 17: Ir-catalyzed allylic substitution of ethyl nitroacetate (**48**) described by Dahnz and Helmchen.[62]*

Linear carbonates of type **47** and ethyl nitroacetate (**48**) underwent Ir-catalyzed substitution in high yields and enantioselectivities. *Dahnz* and *Helmchen* had originally aimed to convert nitromethane itself, however, only inseparable product mixtures were obtained. Therefore, ethyl nitroacetate (**48**), a convenient equivalent of nitromethane, was used. Decarboxylation of the products of type **49** can be performed under *Krapcho* conditions. This method opens access to chiral nitro building blocks for organic synthesis.[62]

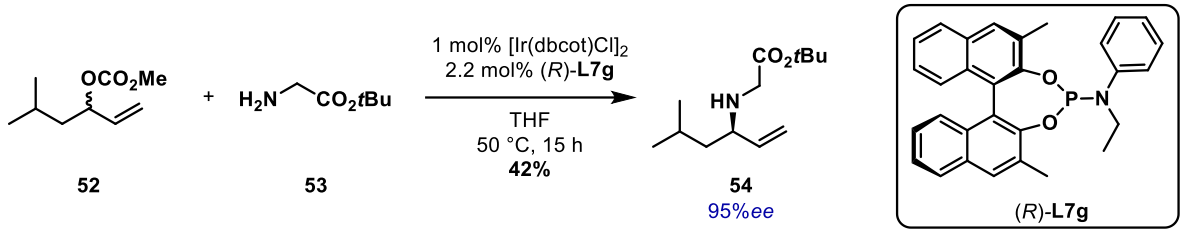
The first Ir-catalyzed allylic amination was published by *Hartwig and co-workers* in 2002. High yields and enantioselectivities between 94%*ee* and 97%*ee* were achieved with several aliphatic primary and secondary amines using the *Feringa* ligand **L2** (Scheme 18). An external base is not necessarily needed, as the applied amines are basic enough to induce the formation of the activated complex **K2**. Furthermore, experiments showed that THF is the solvent of choice for the reaction with regard to optimal reaction rate and enantioselectivity.[40]



Scheme 18: First asymmetric Ir-catalyzed aminations with various N-nucleophiles reported by Ohmura and Hartwig.[40]

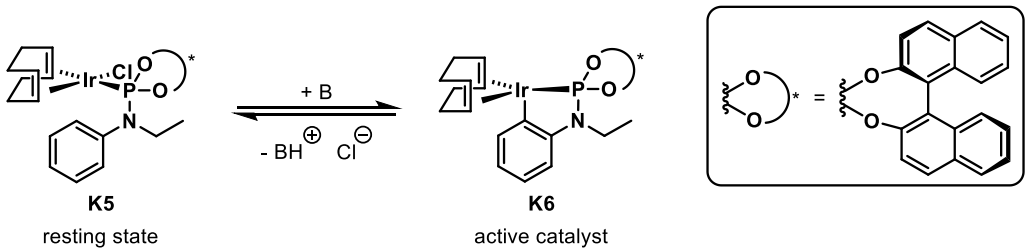
Besides aliphatic amines, arylamines were implemented as well.[63] Another interesting approach was the application of amino acids as chiral pronucleophiles, which was published by the research group of *Marsden*.[64]

As far as the electrophiles are concerned, allylic acetates or carbonates were found to be suitable substrates.[35] However, investigations by the research group of *Takeuchi* showed that allylic acetates tend to be less reactive as compared to allylic carbonates in Ir-catalysis.[65] Therefore, carbonates are implemented more often. Interestingly, linear carbonates are found more frequently in the literature than their branched analogues, although both substrates are applicable in the Ir-catalysis. This is due to the fact that the Ir-catalyzed reaction proceeds stereospecifically. Therefore, branched racemic substrates were found to yield low enantioselectivities in most cases[66, 67], whereas the enantioenriched branched electrophiles afford products in high enantio- and regioselectivity (see Scheme 15).[39] In 2022, the research group of *Schmalz* showed that highly enantioselective allylic aminations with racemic branched carbonates are possible with an optimized ligand system (Scheme 19).[68]



*Scheme 19: Highly enantioselective transformation of racemic branched carbonate **52** and tert-butyl glycinate (**53**) reported by Schmalz et al.[68]*

Using the catalyst system of $[Ir(dbcot)Cl]_2$ and phosphoramidite **L7g** provided the selective transformation of carbonate *rac*-**52** and *tert*-butyl glycinate (**53**) to allylic amine **54** with 95%*ee*.[68] It should be noted that ligands of type **L7** follow a slightly different *C-H* activation than described before (Scheme 20).[69]

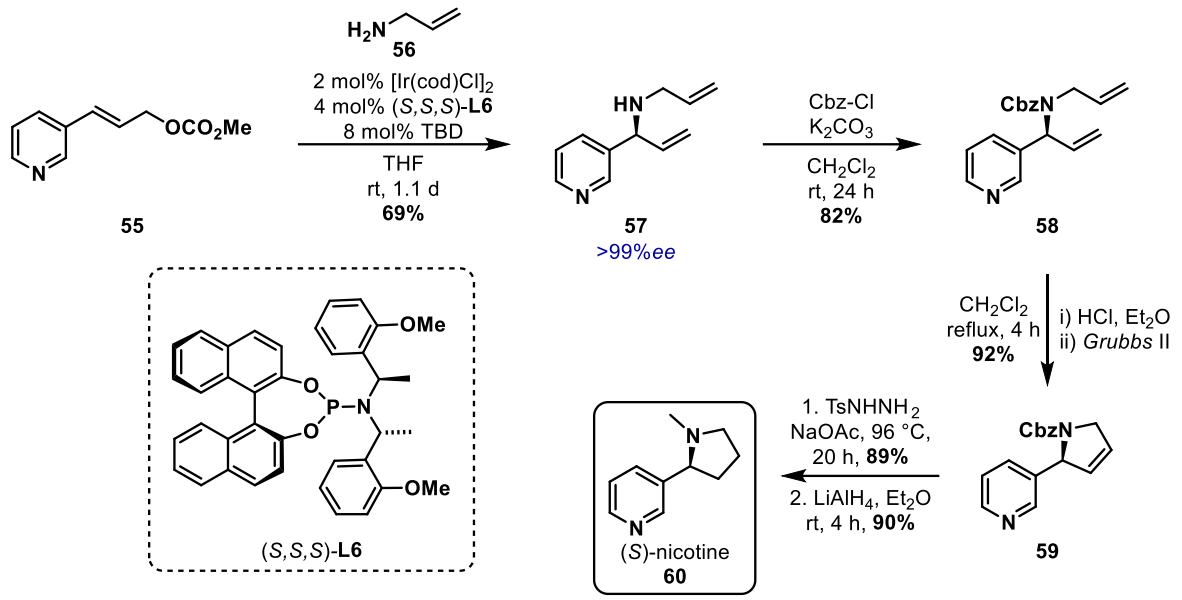


*Scheme 20: Formation of the active catalytic species **K6** for ligands of type **L7**, where a C(sp²)-H activation is preferred over a C(sp³)-H activation.[68, 69]*

Although the building block **54** was applied in the specific context of the synthesis of ProMs (proline-derived modules),[68] the developed methodology could also be applicable to other nucleophiles. Compared to their linear analogues, racemic branched carbonates are often more easily accessible, which would simplify the overall synthesis.[68]

2.2.3 Applications in total synthesis of natural products and biologically active compounds

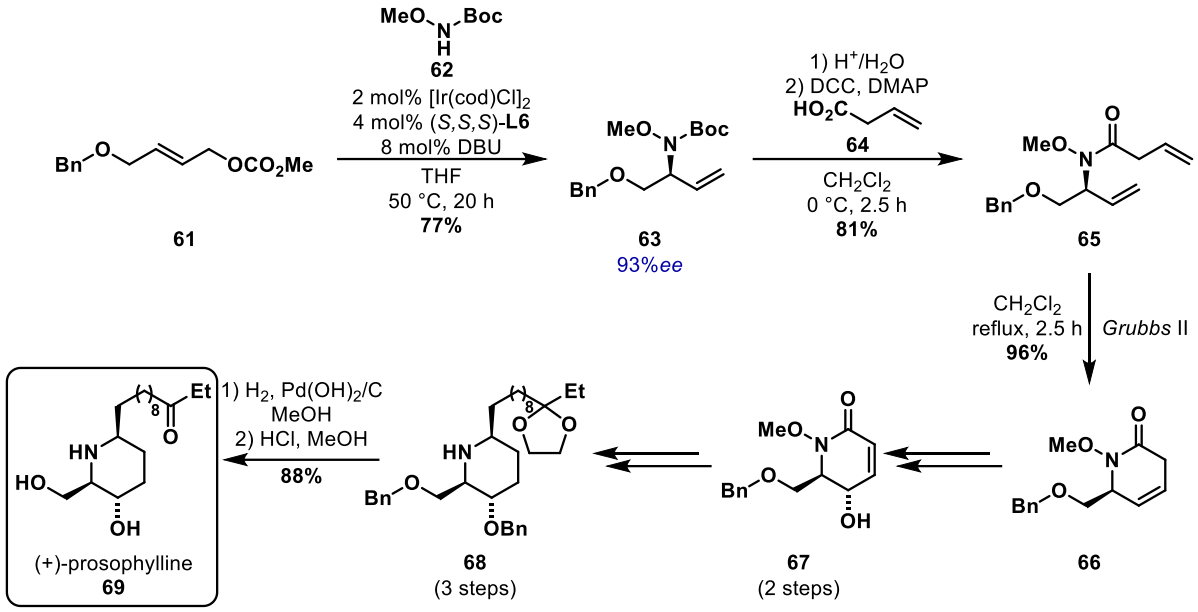
Ir-catalyzed allylic substitution displays an extremely versatile and worthy tool in the synthesis of natural products due to the high enantio- and regioselectivity, as well as a huge substrate scope. Since allylic compounds are generated, the enantioselective Ir-catalysis is often implemented in a reaction sequence prior to olefin metathesis.[39] For example, *Helmchen and co-workers* established an easy access to tobacco alkaloids, such as nicotine (**60**), by Ir-catalyzed allylic amination with high enantiomeric excess (Scheme 21).[70]



*Scheme 21: Total synthesis of (S)-nicotine (**60**) reported by Helmchen et al.*[70]

Besides the commonly known addictive characteristics of nicotine (**60**), the natural product and its analogues also exhibit therapeutic effects on diseases associated with the nervous system, e.g. *Alzheimer's* and *Parkinson's* disease. *Helmchen et al.* demonstrated that the Ir-catalyzed allylic amination is readily applicable in the synthetic procedure affording allylic amine **57** in >99%*ee*. After protection of the amine functionality, a ring closing metathesis was performed which provided the pyrrolidine motif of nicotine (**60**). The latter was obtained after treatment with $TsNHNH_2$ and $LiAlH_4$ in just six linear steps.[70]

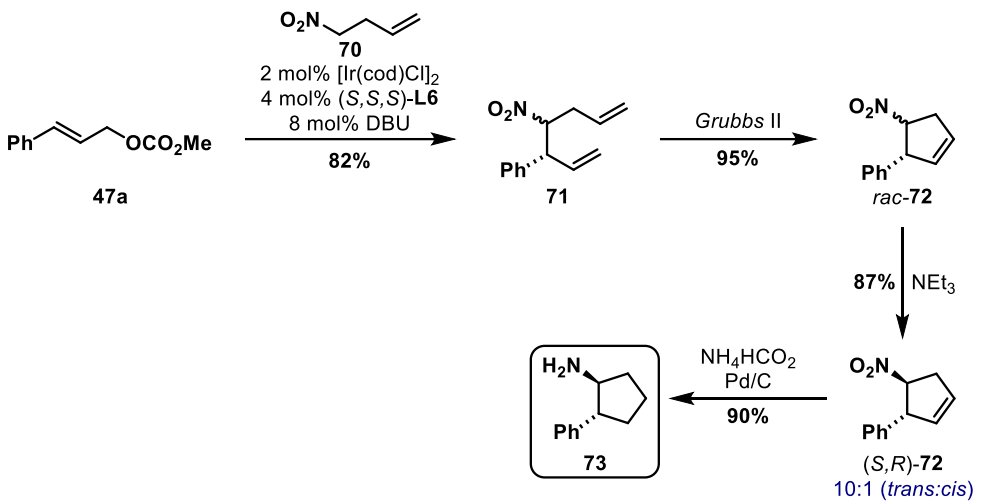
Not only pyrrolidines, also piperidine motifs are easily accessible *via* an Ir-catalyzed allylic amination and RCM sequence. One example is the total synthesis of (+)-prosophylline (**69**), a piperidine alkaloid with analgesic, antibiotic and anaesthetic properties[71], as shown in Scheme 22.[72]



*Scheme 22: Total synthesis of (+)-prosophylline (**69**) reported by Helmchen et al.*[72, 73]

The total synthesis started with an Ir-catalyzed allylic amination to provide allylic amine **63** in 93%*ee*. After acidic removal of the Boc-protection group and acylation with vinylacetic acid (**64**), diene **65** was afforded. Piperidone **66** was generated *via* ring closing metathesis and further functionalized by epoxidation and base-catalyzed elimination to obtain the substituted piperidone **67**.[73] After benzyl-protection, a *Grignard* reaction was used to introduce the aliphatic side chain in substrate **68**. Reduction of the double bond and deprotection provided the natural product (+)-prosophylline (**69**).[72]

Of course, not only allylic aminations were applied in natural product synthesis, but also allylic substitutions with *C*-nucleophiles. *Helmchen et al.* used their described reaction conditions for the enantioselective introduction of aliphatic nitro compounds (see Scheme 17) to synthesize (*S,R*)-*trans*-2-phenylcyclopentanamine (**73**),[62] a potential antidepressant (Scheme 23).[74]



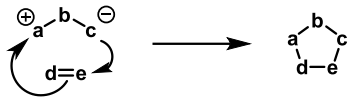
*Scheme 23: Synthesis of (S,R)-trans-2-phenylcyclopentanamine (**73**) reported by Dahnz and Helmchen.[62]*

Here, the Ir-catalyzed allylic substitution provided the enantioselective transformation to diene **71**, which was reacted to cyclopentane **72**. By treatment with NEt_3, the diastereomeric mixture of **72** was equilibrated to the thermodynamically more stable and desired *trans*-product **72** in high excess. After subsequent reduction, the biologically active compound **73** was obtained in just four steps.[62]

These are just a few examples of accomplished syntheses with the use of asymmetric Ir-catalyzed allylic substitutions. In the literature, many more syntheses based on this strategy can be found.[35, 75, 76] However, the examples demonstrate that the combination of Ir-catalyzed allylic substitutions and ring closing metathesis provide a convenient access to cyclic compounds in an enantioselective fashion. The pyrrolidine and piperidine motifs in particular are often found in alkaloids, therefore depicting an interesting method in the total synthesis of alkaloid natural products.

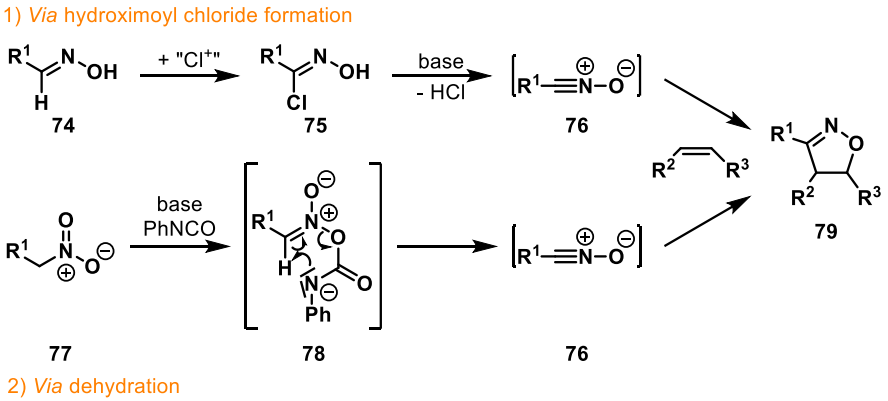
2.3 1,3-Dipolar cycloaddition

1,3-Dipolar cycloadditions were originally introduced by *Huisgen*, who described them as reactions of a 1,3-dipole with a dipolarophile (Scheme 24).



Scheme 24: Schematic representation of the 1,3-dipolar cycloaddition reported by Huisgen.[77]

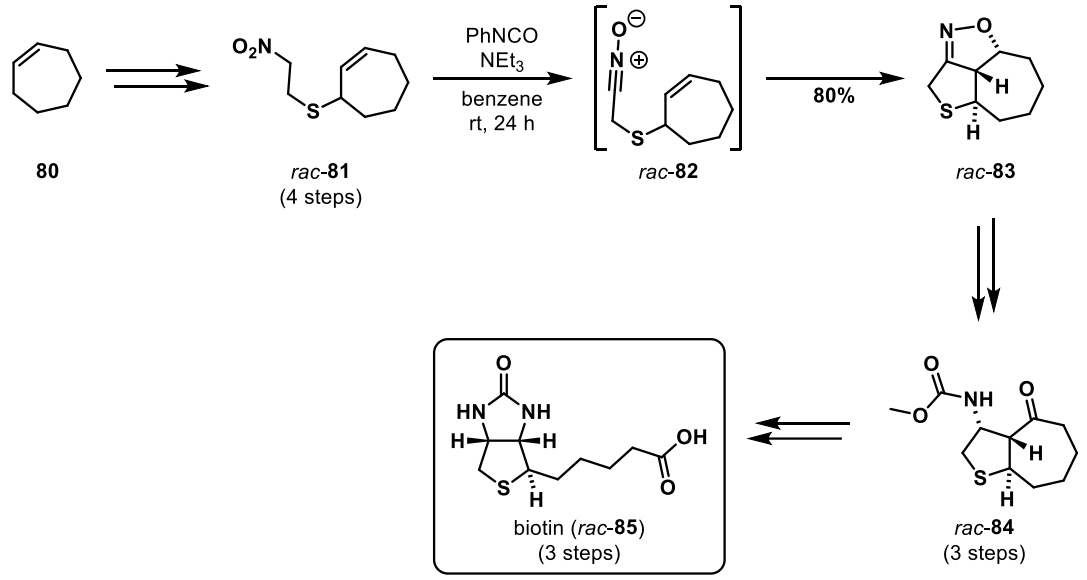
Here, 1,3-dipoles consist of a three-atomic structure with a sextet formula (type a-b-c), in which atom a is formally positively charged and atom c possesses a negative charge and an unshared electron pair. The dipolarophile (type d-e) is a multiple bond system that forms a five-membered ring in combination with the 1,3-dipole.[77] Today, 1,3-dipolar cycloadditions have emerged as a versatile tool in organic synthesis. The most prominent example for these is the click reaction, in which the concept of 1,3-dipolar cycloadditions is exploited and was even awarded the nobel prize in 2022. In 2001, *Sharpless* reported the first click reaction of an azide (1,3-dipole) and an alkyne (dipolarophile) under copper catalysis.[78] Together with *Meldal*[79] and *Bertozzi*[80], the click reaction was developed into a popular methodology for the easy linkage of molecular building blocks proceeding selectively and even under physiological conditions. Besides click reactions, 1,3-dipolar cycloadditions in general are also widely used in natural product synthesis. An example has already been highlighted in a previous chapter, in which the total synthesis of streptazolin (**10**) by *Park* and *Kozikowski* has been described (see Scheme 3). *Park* and *Kozikowski* synthesized an oxime, which was transformed *in situ* to the nitrile oxide. The latter directly underwent a 1,3-dipolar cycloaddition to form an isoxazoline.[8] Since isoxazolines are common precursors in organic synthesis due to their versatile reactivity[81], 1,3-dipolar cycloadditions are often performed using nitrile oxides (**76**) as the 1,3-dipole. Nitrile oxides (**76**) can be easily generated *in situ* through two different pathways (Scheme 25).[82]



*Scheme 25: Possible pathways to generate nitrile oxides of type **76**.*[82]

First, it is possible to form nitrile oxides **76** from the corresponding oximes **74** *via* hydroximoyl chloride **75** formation. Electrophilic chlorination generates the hydroximoyl chloride **75**, which subsequently is converted to the desired nitrile oxide **76** after base-treatment under the release of HCl. As chlorinating agents, *N*-chlorosuccinimide (NCS)[83] and NaOCl[84] can be used or a modern methodology using catalytic amounts of hypervalent iodine reagents in combination with a stochiometric oxidant[85] can be applied. Second, nitrile oxides **76** can be generated from nitro compounds **77** by dehydration using phenyl isocyanate.[86] With nitrile oxide **76** in hand, the isoxazoline **79** is formed by addition of a dipolarophile.

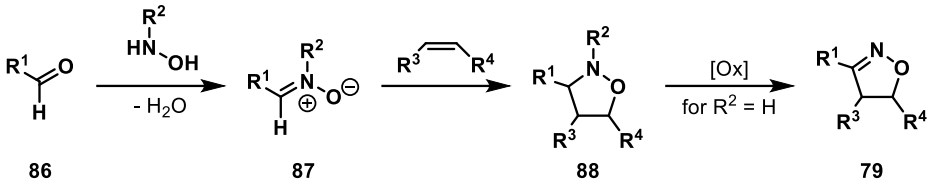
This methodology is often used in natural product synthesis. A very prominent example for the application of 1,3-dipolar cycloadditions with nitrile oxides is the racemic synthesis of biotin (**85**) by *Confalone et al.* (Scheme 26).[87]



*Scheme 26: Racemic synthesis of biotin (**85**) reported by Confalone et al.*[87]

The nitrile oxide **82** was prepared *in situ via* dehydration of nitro compound *rac*-**81** leading to key structure **83** by an intramolecular 1,3-dipolar cycloaddition. After reductive cleavage of the isoxazoline motif, acetylation and oxidation, substrate **84** was synthesized. Conversion to biotin (**85**) was achieved by oxime generation, *Beckmann* rearrangement and basic hydrolysis.[87]

Due to their simple accessibility and easy handling, nitrones (**87**) are frequently implemented in the 1,3-dipolar cycloaddition instead of nitrile oxides of type **76**. Nitrones (**87**) are synthesized by condensation of aldehydes or ketones with *N*-alkyl or -aryl hydroxylamines (Scheme 27). In contrast to nitrile oxides, nitrones are stable and can be even isolated, purified and stored.[82] 1,3-Dipolar cycloaddition provides the isoxazolidine structure **88** that can be easily converted to *β*-amino acids, *β*-amino alcohols, *β*-lactams or to isoxazolines **79** by further oxidation.[88]

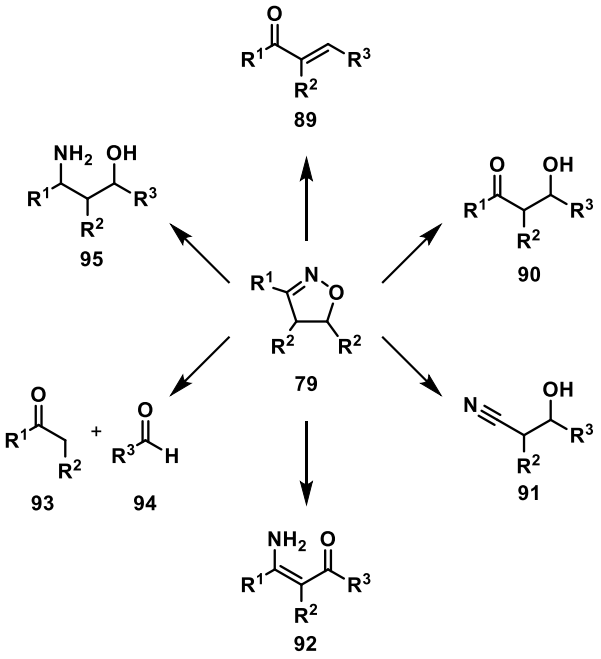


Scheme 27: Preparation of nitrones and their 1,3-dipolar cycloaddition products.[82]

Unsubstituted nitrones **87** (R^2 = H) are the tautomers of oximes **74**. They can also be generated by heating in order to induce a 1,2-hydrogen shift as proposed by *Grigg*.[89] However, strong heating is required which might raise the question about the stability of other functional moieties incorporated in the molecule during the process. The application of *N*-alkyl or *N*-aryl nitrones **87** ($R^2 \neq$ H) is more common.[90, 91] Interestingly, the regioselectivity of the cycloaddition can be predicted relatively well according to frontier orbitals interaction and electronic effects of the substituted 1,3-dipole and dipolarophile.[92] The application span of 1,3-dipolar cycloadditions of nitrones in organic synthesis has been well exploited with numerous examples of successful synthetic protocols.[82, 90, 91, 93, 94]

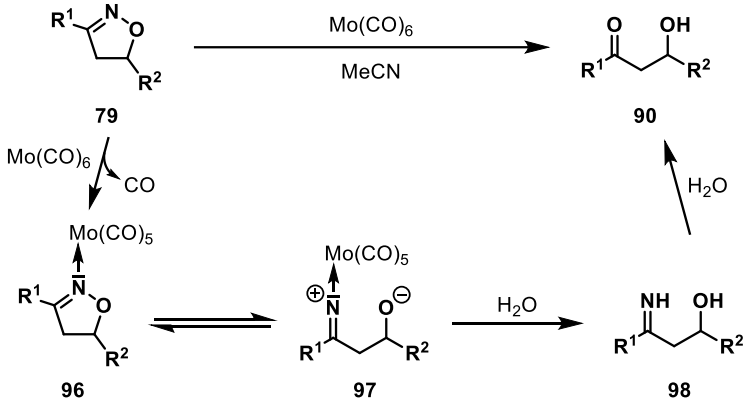
2.3.1 Cleavage of isoxazolines

The structural motif of isoxazolines **79** displays a versatile building block in organic synthesis. As shown in the previous examples of those motifs in natural product synthesis (see Scheme 3, Scheme 26), the establishment of isoxazolines is often linked to a subsequent cleavage. Depending on the used reagent, various carbonyl compounds, hydroxyimines, aminoketones and aminoalcohols can be generated (Scheme 28).[81] Due to the numerous possible transformations of isoxazolines **79**, only the most relevant ones for the course of this work will be explained, which are the transformations to enones **89** and to β-hydroxyketones **90**.



*Scheme 28: Overview of possible transformations of the isoxazoline motif **79**.[81]*

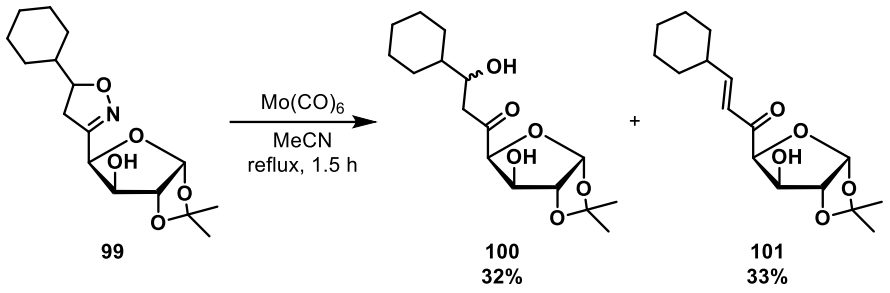
Enones of type **89** can be obtained by reductive cleavage initiated by molybdenum-based complexes, e.g. $Mo(CO)_6$. This methodology was developed by *Nitta* and *Kobayashi*, who reported the *N-O* bond cleavage of isoxazoles with $Mo(CO)_6$ and water.[95] Later, *Simoni and co-workers* applied this strategy to isoxazolines **79** (Scheme 29).[96]



*Scheme 29: Molybdenum-mediated N-O bond cleavage of isoxazoline **79**.[96]*

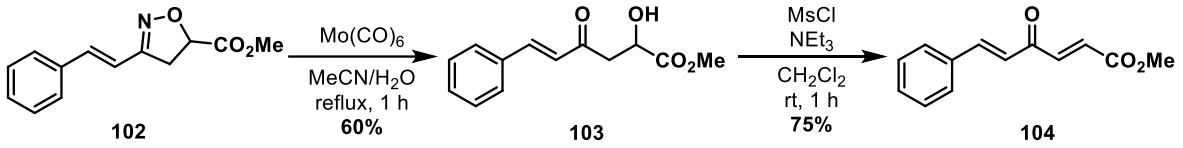
Heating of disubstituted isoxazolines **79** with $Mo(CO)_6$ in acetonitrile resulted in a smooth transformation to *β*-hydroxyketones of type **90**. *Simoni et al.* proposed that the reductive cleavage is initiated by a *N-Mo* coordination facilitating the ring opening to afford complex **97**. In the presence of water, the *β*-hydroxyimine **98** is formed first, which further reacts to the *β*-hydroxyketone **90**.[96] In the literature, many examples are known in which *β*-hydroxyketone **90** directly undergoes elimination to form enone **89**. Since the reductive cleavage with $Mo(CO)_6$ requires heating, the elimination might already occur within the reaction sequence depending on

the substitution pattern of **90**.[97] For example, the research group of *Accorso* studied the reductive opening of glycosyl-substituted isoxazolines **99** yielding a 1:1 product mixture of the *β*-hydroxyketone **100** and the elimination product **101** (Scheme 30).[98]



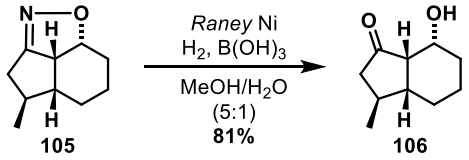
*Scheme 30: Reductive N-O bond cleavage of glycosyl-substituted isoxazolines **99** reported by Accorso et al.[98]*

If the enone is not formed during the reductive cleavage, the *β*-hydroxyketone can be subjected to elimination conditions. As an example, a procedure by *Simoni et al.* is described in which the elimination product **104** was formed by treatment with methane sulfonyl chloride and NEt_3 (Scheme 31).[99]



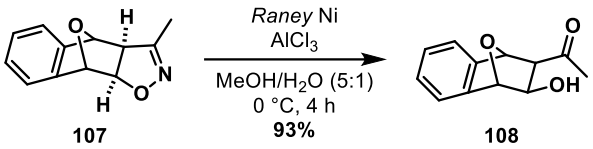
Scheme 31: Reaction sequence of reductive N-O bond cleavage and subsequent elimination.[99]

In addition to $Mo(CO)_6$ there are many other well-suited reagents for reductive cleavage to provide *β*-hydroxyketones of type **90**. For instance, *Raney* Ni is a convenient alternative. Suitable reaction conditions were extensively studied by *Curran*, who described a combination of *Raney* Ni, H_2 and $B(OH)_3$ as the most efficient reducing system (Scheme 32).[100, 101]



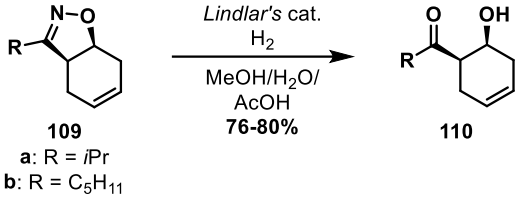
*Scheme 32: Raney Ni-mediated reductive cleavage of isoxazoline **105**.[100]*

$B(OH)_3$ was utilized as an additional *Lewis* acid, which is supposed to coordinate to the alkoxy-functionality after isoxazoline ring opening (see Scheme 29, structure **97**) and H_2 served as hydrogen source. However, the use of external H_2 is not mandatory. *Tam and co-workers* have reported that their carbobicycle-fused isoxazolines of type **107** undergo smooth *N-O* bond cleavage just with *Raney* Ni and $AlCl_3$ under aqueous conditions (Scheme 33).[81]



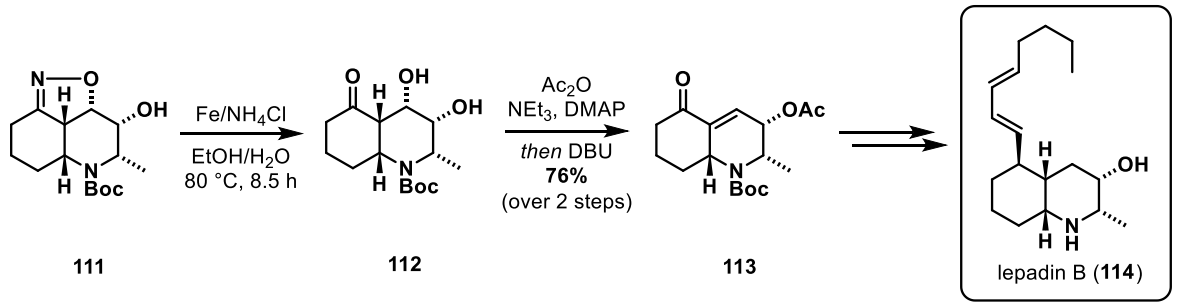
Scheme 33: Reductive cleavage with Raney Ni and $AlCl_3$.[81]

Moreover, Pd-based catalysts can be used to generate *β*-hydroxyketones. For instance, reductive *N-O* bond cleavages employing the *Lindlar's* catalyst ($Pd/CaCO_3$ poisoned with Pb) have been described (Scheme 34).[102]



Scheme 34: Example for a Pd-mediated reductive cleavage.[102]

Alternatively, iron in combination with ammonium chloride can be used to provide the *β*-hydroxyketone structure. As an example, a procedure by *Tong and co-workers* is shown in Scheme 35. In the course of the total syntheses of lepadins, the reductive cleavage of isoxazoline **111** was applied to establish building block **113**. Further transformations provided e.g. lepadin B (**114**), a substituted bicyclic piperidine alkaloid.[103]

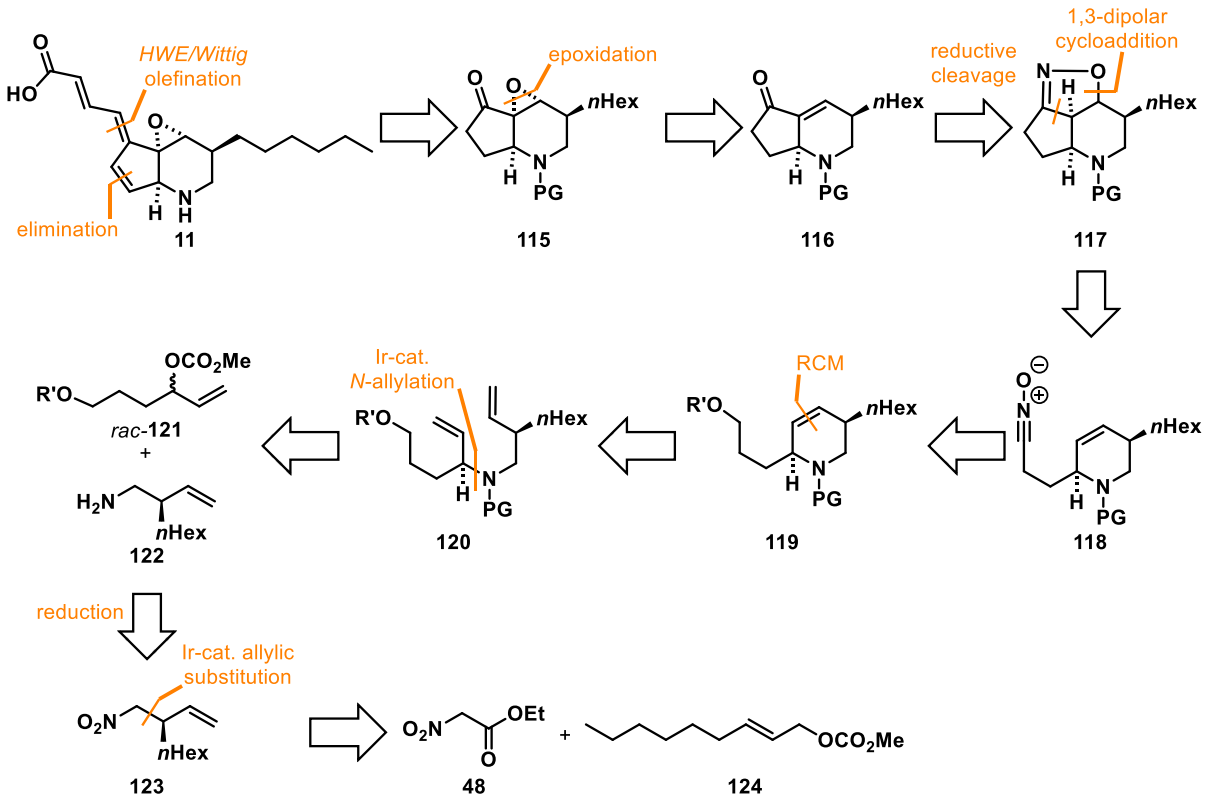


*Scheme 35: Reductive cleavage of isoxazoline **111** in the total synthesis of lepadin B (**114**).[103]*

The examples given are just a few selected possible transformations. However, they underline the utility of isoxazoline motifs as versatile building blocks in organic synthesis.[97]

3 Concept and motivation

Since camporidine A (**11**) is a structurally interesting and synthetically challenging molecule with promising anti-inflammatory and anti-metastatic activity,[19] this natural product is an attractive target compound for organic synthesis. The structure of camporidine A (**11**) is reminiscent of an elongated amino acid analogue, a research topic that is also being investigated in the *Schmalz* group with a particular focus on polycyclic amino acid derivatives with regard to their synthesis and biological activities. Strategies towards a total synthesis of camporidine A (**11**) have already been examined by *Tobias Wilczek*, however, none of them proved suitable. For example, the establishment of the camporidine core structure *via* imino-*Diels-Alder* reaction or *via* an aza-*Michael*/aldol sequence was considered, but did not yield the desired target structure **11**.[104] Therefore, a new retrosynthetic strategy was developed (Scheme 36).



*Scheme 36: Retrosynthetic analysis of camporidine A (**11**).*

Camporidine A (**11**) should be established by late-stage introduction of the unsaturated side chain *via HWE* or *Wittig* olefination and generation of the double bond in the cyclopentene unit by elimination from intermediate **115**. The tricylic motif **115** should be synthesized by epoxidation of enone **116** as the desired diastereomer by substrate control. Enone **116** can be regarded as the central core motif of camporidine A (**11**), which is thought to be formed by reductive cleavage of isoxazoline **117**. The latter could be generated from the corresponding nitrile oxide **118** *via* 1,3-dipolar cycloaddition, which marks an important key reaction in this strategy. The approach

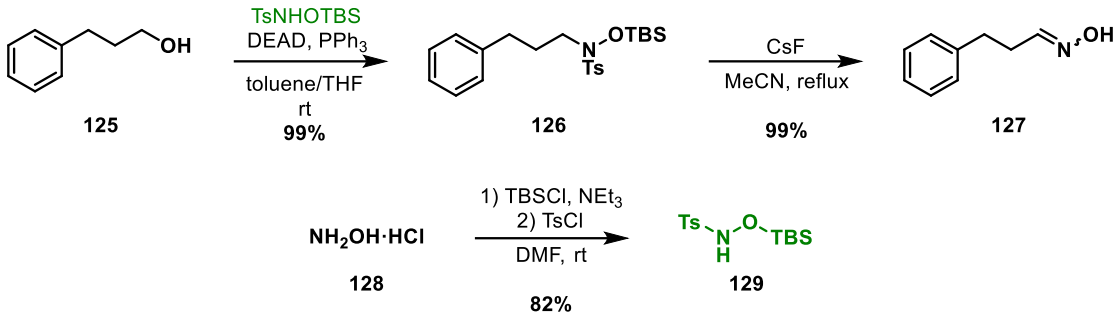
using a 1,3-dipolar cycloaddition and a subsequent reductive cleavage has already been successfully applied in the total synthesis of streptazolin (**10**) by *Park* and *Kozikowski* (see Scheme 3).[105] Nitrile oxides can be derived for example from aldehydes, so a protected aldehyde or alcohol of type **119** is planned to be used. The aza-cyclohexene motif in substrate **119** should be formed by ring closing metathesis performed on allylic amine **120**. To render the allylation diastereoselective, an asymmetric Ir-catalyzed allylic amination of racemic carbonate **121** and amine **122** is envisaged, which represents another important key step in this sequence. Prior to reduction of nitro compound **123**, which provides the amine **122**, another stereoselective reaction is necessary. Here, a second Ir-catalyzed substitution should be applied using ethyl nitroacetate (**48**) and linear carbonate **124** as the corresponding starting materials.

The total synthesis of camporidine A (**11**) would not only provide access to a synthetically challenging molecule with interesting reaction sequences but would also help in the further analysis of the molecule. On the one hand, the molecular structure and the absolute configuration could be validated. So far, the isolated natural product has only been analyzed by NMR and mass spectrometry and the configuration has been determined according to 1D NOE correlations and ECD spectra.[19] Therefore, the analytics lack a crystal structure that would validate the proposed constitution and configuration. On the other hand, a synthetic access to camporidine A (**11**) would provide more material for biological tests to further analyze the biological activity, with additional emphasis on the mechanism of action explaining the detected anti-metastatic and anti-inflammatory activity.

4 Results and discussion

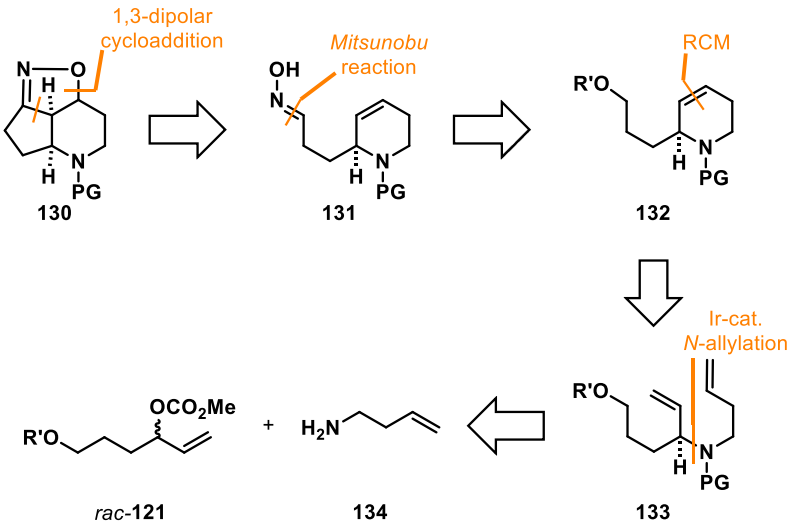
4.1 Synthetic approach *via* oxime formation

Since one of the envisioned key steps in the retrosynthesis of camporidine A (**11**) was the 1,3-dipolar cycloaddition, a decision had to be made as to which precursor should be chosen for the isoxazoline motif. Based on a literature procedure by *Fukuyama et al.* (Scheme 37),[106] the use of an alcohol that can be easily converted to the oxime prior to isoxazoline formation was considered.



*Scheme 37: Two-step synthesis of oxime **127** from alcohol **125** via Mitsunobu reaction with protected hydroxylamine **129** and protecting group removal described by Fukuyama et al.*[106]

The simple two-step protocol includes a *Mitsunobu* reaction with protected hydroxylamine **129**, followed by desilylative elimination of *p*-toluenesulfinate **126** with the use of CsF to provide oxime **127** in excellent yield.[106] Applying this reaction sequence to the synthesis of camporidine A (**11**) results in the retrosynthetic approach towards isoxazoline motif **130** shown in Scheme 38.



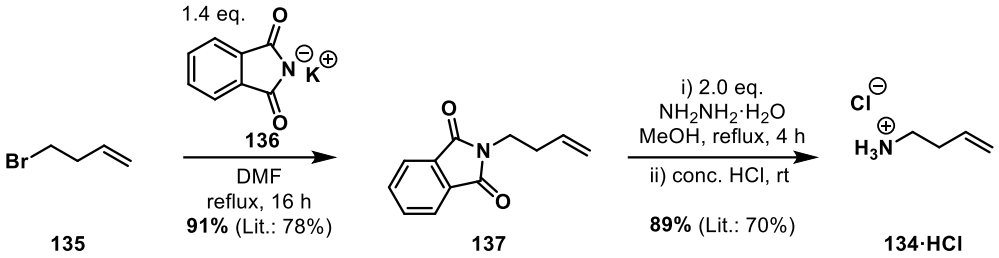
*Scheme 38: Retrosynthetic approach towards key motif **130** by oxime generation.*

A test system without the *n*-hexyl side chain was selected to investigate the envisioned reaction steps. The isoxazoline **130** should be derived from oxime **131**, which can be generated *via* the described *Mitsunobu* reaction from protected alcohol **132**. Ring closing metathesis and

Ir-catalyzed allylic amination would lead to racemic carbonate **121** and homoallyl amine **134** as the simplified starting materials.

4.1.1 Investigations on the Ir-catalyzed allylic amination

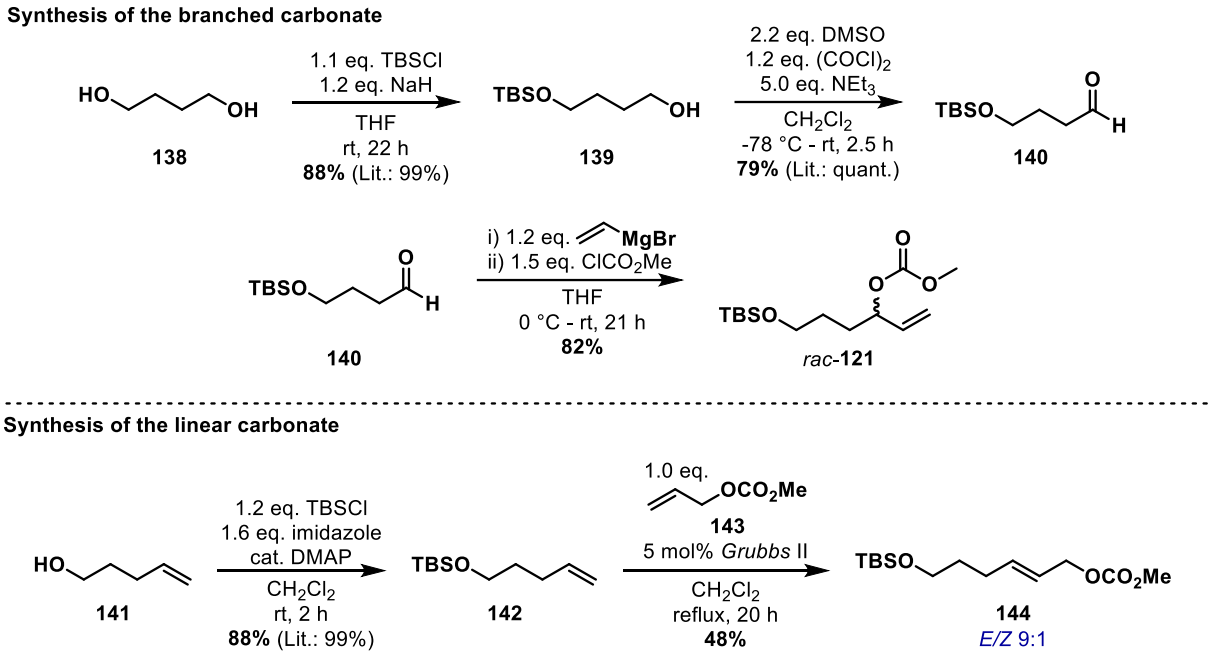
The first step of the synthesis towards isoxazoline motif **130** was the Ir-catalyzed allylic amination with homo-allylamine **134**. The synthesis of amine **134** was accomplished following a literature-known two-step procedure, which provided the hydrochloride **134·HCl** in 81% overall yield (Scheme 39).[107]



*Scheme 39: Two-step synthesis of amine hydrochloride **134·HCl** as reported by Miller et al.[107]*

The procedure corresponds to a standard *Gabriel* synthesis. The potassium salt of phthalimide (**136**) was *N*-alkylated with 4-bromo-1-butene (**135**) to form *N*-alkylphthalimide **137**. By treatment with hydrazine hydrate, the phthalimide **137** was cleaved to afford the desired homoallyl amine as its hydrochloride **134·HCl**. Since the hydrochloride **134·HCl** was easy to handle, it was considered to directly apply substrate **134·HCl** in the catalysis instead of the free amine.

Moreover, suitable carbonates of type **121** had to be synthesized. Since the free alcohol must be formed in the course of the synthesis, which then reacts further to form oxime **131**, an easily removable protecting group for the hydroxyl function must be chosen to avoid side reactions. Thus, a silyl protecting group should be implemented, as it can be cleaved under mild conditions. In addition to branched carbonate *rac*-**121**, the linear analogue **144** was synthesized in order to investigate the reaction outcome of the Ir-catalysis with regard to the nature of the carbonate (Scheme 40).

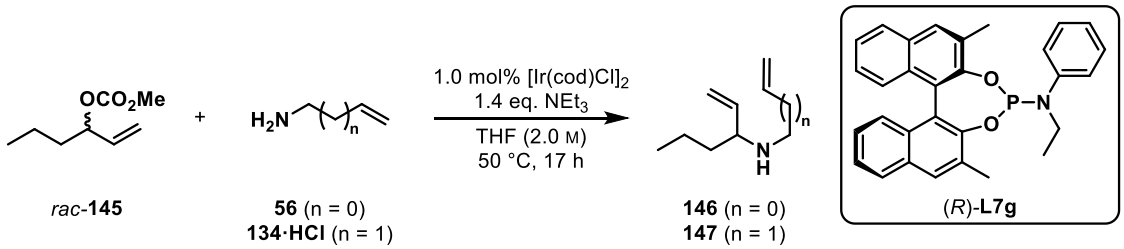


*Scheme 40: Accomplished syntheses of the branched and linear carbonates rac-**121** and **144**.*[108-110]

The branched carbonate *rac*-**121** was provided in three steps starting from 1,4-butanediol (**138**). After monosilylation, the TBS-protected substrate **139** was afforded in 88% yield.[108] Next, a *Swern* oxidation was performed to obtain aldehyde **140**.[109] Finally, aldehyde **140** was reacted with vinyl magnesium bromide and subsequently treated with methyl chloroformate in a one-pot procedure yielding racemic carbonate *rac*-**121** in 57% over three steps.

Pent-4-enol (**141**) was used as the starting material for the synthesis of the corresponding linear analogue **144**. Following a procedure by *Stang* and *White*, the alcohol **141** was TBS-protected in 88% yield.[110] An olefin metathesis was then performed by reacting compound **142** with allyl methyl carbonate **143** catalyzed by *Grubbs* II complex. The linear carbonate **144** was afforded in 48% yield and overall in 42% over two steps. The low yield of the olefin metathesis can be attributed to side reactions, as homo-couplings of the substrates can occur. With the starting materials in hand, the Ir-catalyzed allylic amination was examined (Table 2).

*Table 2: Overview of the tested reaction conditions for the Ir-catalyzed allylic amination applied on carbonate rac-**145** and amines **56** and **134·HCl**.*



rac-**145**

56 (n = 0)
134·HCl (n = 1)

146 (n = 0)
147 (n = 1)

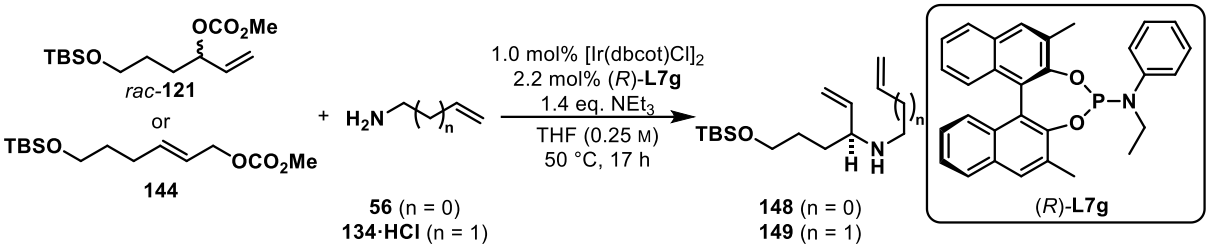
(*R*)-**L7g**

Entry	Amine	Deviation from standard conditions	Product	Yield[a]	Isolated yield
1	**56**	-	*rac*-**146**	74%	-
2	**134·HCl**	-	*rac*-**147**	23%	-
3	**134·HCl**	1.0 mol% $[Ir(dbcot)Cl]_2$, 2.9 mol% (*R*)-**L7g**, THF (0.25 M)	(*S*)-**147**	81%	25%

a: The yield was determined by GC-MS.

Before applying the synthesized carbonates *rac*-**121** and **144**, carbonate *rac*-**145** was reacted with readily available allyl amine (**56**) as a simplified system to test the intended reaction sequence (Table 2, entry 1). Catalytic amounts of $[Ir(cod)Cl]_2$ and stoichiometric amounts of NEt_3 were used. The use of a chiral phosphoramidite was dispensed with, as the focus in the first experiments lied on the applicability of the amine nucleophile. The test reaction provided the desired allylic amine **146** in a good yield of 74% determined by GC-MS. Subsequently, allyl amine (**56**) was exchanged by the synthesized amine **134·HCl** (Table 2, entry 2). Applying the previous reaction conditions afforded the product **147** of the allylic amination in 23% yield. The addition of chiral ligand (*R*)-**L7g** significantly enhanced the yield (Table 2, entry 3). The applied reaction conditions correspond to the Ir-catalysis conditions developed in the *Schmalz* group. The combination of $[Ir(dbcot)Cl]_2$ and phosphoramidite **L7g** proved to be a powerful method for the *N*-allylation of the hydrochlorides of amino esters.[68] The conditions were easily transferable to the nucleophile **134·HCl**, increasing the yield to 81%. Isolation of product **147** only afforded 25% yield, which was caused by difficulties in the purification of the free amine and volatility of the product. The enantiomeric excess could not be determined *via* chiral GC-MS and had to be evaluated in a later stage of the synthesis. However, the small screening validated that amine **134·HCl** was readily applicable to the reaction conditions of the Ir-catalyzed *N*-allylation. Therefore, the approved reaction conditions were transferred to the synthesized carbonates *rac*-**121** and **144** (Table 3).

*Table 3: Overview of the results for the tested carbonates rac-**121** and **144** in the Ir-catalyzed allylic amination.*

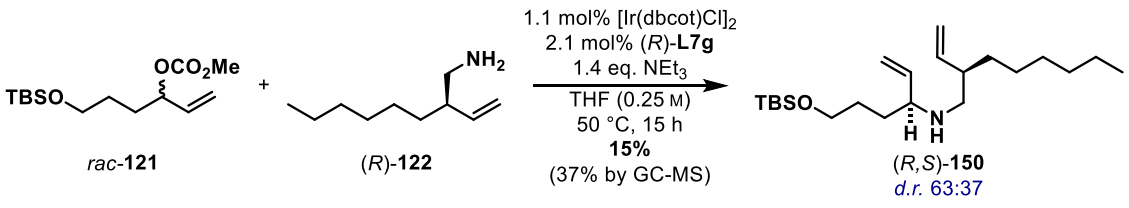


Entry	Carbonate	Amine	Result
1	**144**	**56**	No conversion
2	*rac*-**121**	**56**	**148**, 67%[a] (41%)[b]
3	*rac*-**121**	**134·HCl**	**149**, 95%[a] (51%)[b]

a: Determined by GC-MS; b: Isolated yield.

First, the influence of the nature of the carbonate was examined by reacting the branched racemic carbonate **121** and the linear carbonate **144** with allyl amine (**56**). Interestingly, no conversion of the starting materials was detected for linear carbonate **144** (Table 3, entry 1), whereas the reaction with the branched carbonate *rac*-**121** delivered diolefin **148** in 41% isolated yield (Table 3, entry 2). This implies that the catalytic system of $[Ir(dbcot)Cl]_2$ and (*R*)-**L7g** favours and accelerates complexation and ionization of the branched substrate rather than that of the linear one. It can be assumed that steric and electronic effects are responsible for the lack of formation of a π-allyl complex for linear carbonate **144**. The replacement of amine **56** by **134·HCl** delivered the target structure **149** in 95% yield according to GC-MS and in moderate isolated yield of 51% (Table 3, entry 3).

Since the Ir-catalyzed *N*-allylation worked well for the test system, the reaction sequence was transferred to the real system of camporidine A (**11**). Thus, chiral alkyl amine (*R*)-**122** was implemented for test purposes (Scheme 41). The enantioselective synthesis of allylic amine (*R*)-**122** will be discussed in a subsequent section (see Chapter 4.3.1).



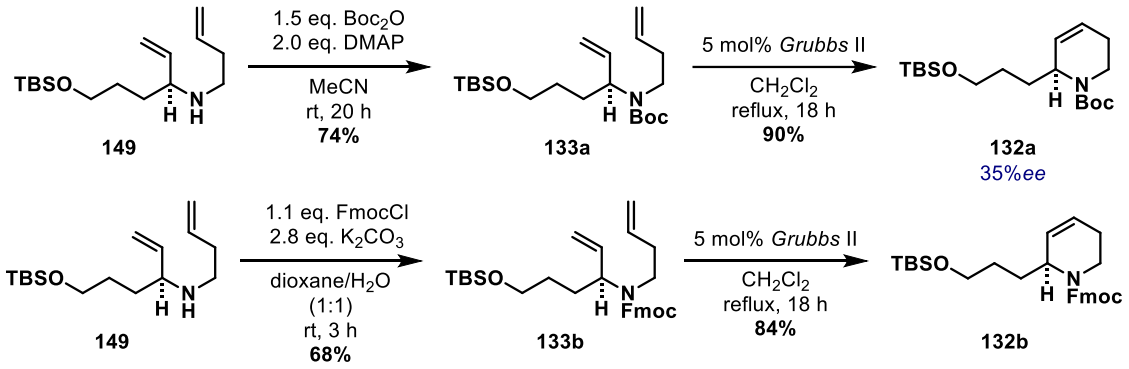
*Scheme 41: Tested Ir-catalyzed allylic amination with amine (R)-**122**. The diastereomeric ratio was determined by NMR.*

Allylic amine **150** was isolated in 15% yield with a moderate diastereomeric ratio of 63:37 in the first trial. Although the yield was not satisfactory due to incomplete conversion of the starting material, it was shown that the Ir-catalysis is suitable for the planned system and provides the

desired diastereomer (*R,S*)-**150** in excess. Of course, conversion, yield and diastereoselectivity can be improved by variation of the ligand system, concentration and temperature. However, the purpose of the experiment was achieved, and the attention was focussed on developing the next steps of the synthesis.

4.1.2 Investigations on the synthesis towards the oxime motif

Next, the reaction steps to generate oxime motif **131** were investigated. As the allylic amine **149** has already been successfully synthesized, the ring closing metathesis should be examined to deliver aza-cyclohexene motif **132**. Prior to RCM, a *N*-protecting group was introduced to avoid side reactions of the nucleophilic amine (Scheme 42).

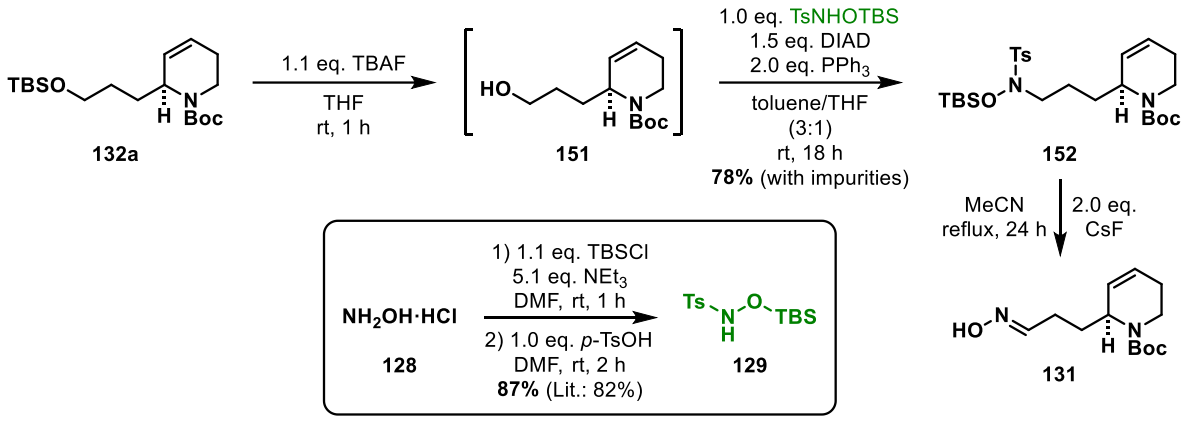


*Scheme 42: Synthesis of Boc- and Fmoc-protected amines **132a** and **132b**.*

Boc and Fmoc groups were introduced as suitable amine protecting groups under standard conditions, which afforded the protected amines **133a** and **133b** in 74% and 68% yield, respectively. A ring closing metathesis was then carried out with catalytic amounts of *Grubbs* II catalyst, which proceeded without any problems. The desired cyclic amine **132a** was obtained in 90% yield. At this stage, it was possible to separate the enantiomers *via* chiral GC-MS by detecting an enantiomeric excess of 35%. For Fmoc-protected amine **132b**, which was obtained in 84% yield by RCM, the enantiomeric excess could not be determined. However, the detected ratio for substrate **132a** is only a guide value to represent the enantioselectivity of the previous Ir-catalyzed allylic amination. Improvements of the reaction conditions for the asymmetric catalysis would be needed to increase enantioselectivity. Nevertheless, reinvestigations on the catalysis were disregarded, as the reaction conditions for the Ir-catalysis would have to be adjusted for the expanded system of camporidine A (**11**) with regard to the diastereoselectivity of the reaction.

The synthesized substrate **132a** was then subjected to TBS cleavage (Scheme 43). The obtained alcohol **151** was of sufficient purity to be directly reacted *via Mitsunobu* reaction with

O-TBS-*N*-hydroxylamine (**129**) according to the described procedure by *Fukuyama et al.* (see Scheme 37).[106]



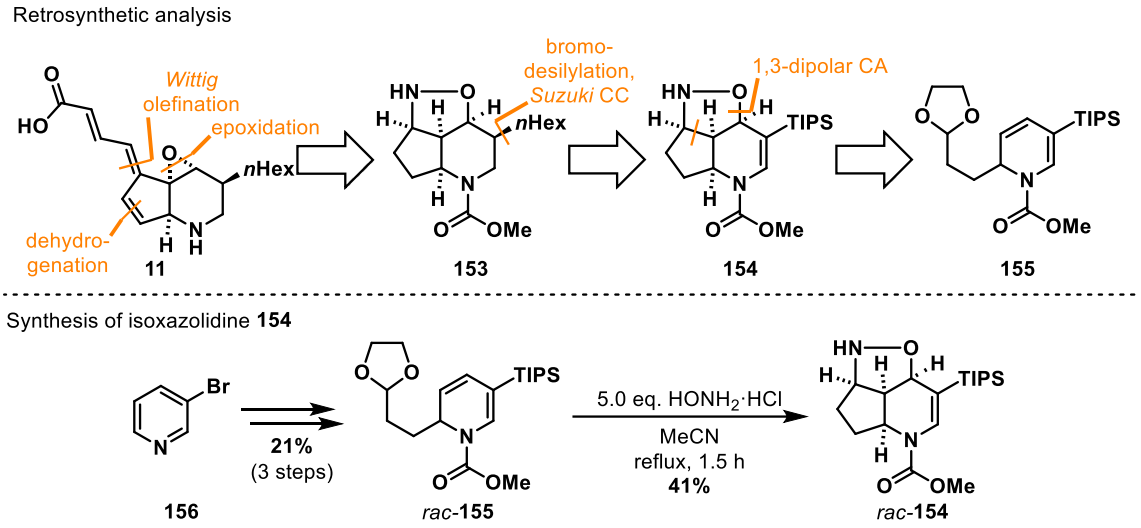
*Scheme 43: Attempted synthesis of oxime **131**.*

Originally, DEAD was used in the procedure by *Fukuyama et al.*,[106] however, it was replaced by DIAD in our approach due to its safer handling. The procedure provided compound **152** in 78% yield over two steps. It should be noted that the yield includes impurities by an unknown compound that could not be removed. It is possible that side reactions occur during the *Mitsunobu* reaction in which DIAD acts as a nucleophile attacking the activated alcohol. Nevertheless, compound **152** was subjected to desilylative elimination with CsF for test purposes. NMR measurements clearly indicated the removal of the TBS group, which speaks in favour of the synthesis of oxime **131**. However, impurities from the tosyl group were observed. Thus, the elimination of the protecting group only proceeded in parts. Also, GC-MS measurements revealed an intense peak with fragments corresponding to the desired oxime **131** in addition to impurities. The analytical data would correspond to a yield of 55% for the oxime **131**. Even after further attempts to purify the oxime **131**, the impurities remained.

Due to the difficulties in purification and the unsatisfactory yield, further optimizations and investigations of this route were not pursued. At the same time, another synthetic approach towards the isoxazoline motif **130** was established that delivered more promising results, which will be elucidated in the subsequent chapter.

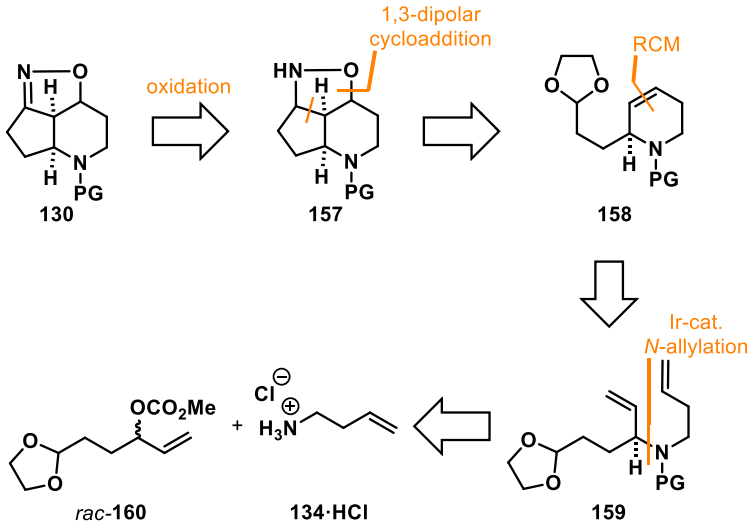
4.2 Synthetic approach *via* isoxazolidine formation

Based on a reaction sequence that *Tobias Wilczek* attempted during the investigation of possible synthetic approaches towards camporidine A (**11**),[104] the formation of the central bicyclic core structure *via* generation of an isoxazolidine was considered (Scheme 44).



*Scheme 44: Retrosynthetic analysis and accomplished synthesis of isoxazolidine **154** by Tobias Wilczek.*[104]

In the attempted approach, the key step was the oxime formation *via* acetal deprotection and reaction with hydroxylamine hydrochloride that directly underwent 1,3-dipolar cycloaddition in one step. Although the approach provided the isoxazolidine motif **154** in 41% yield, the considered system presented some difficulties. For example, substrate *rac*-**155** tended to form an aromatic co-product in which the pyridine system was restored. Furthermore, the synthesis only delivered the racemic mixture of isoxazolidine *rac*-**154**.[104] Therefore, this approach was combined with the described enantioselective allylic amination approach in the course of this work (Scheme 45).

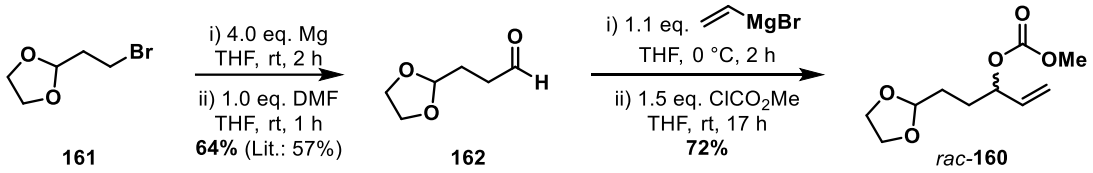


*Scheme 45: Retrosynthetic analysis of isoxazoline **130** via isoxazolidine **157**.*

Regarding the unalkylated test system, the isoxazoline **130** should be established by oxidation from the corresponding isoxazolidine **157**. According to the presented procedure by *Tobias Wilczek*,[104] intermediate **157** should be generated from the acetal-protected aldehyde **158**. As in the previously described approach towards oxime **131**, aza-cyclohexene **158** should be established *via* ring closing metathesis from diolefin **159**. The stereoselective transformation towards the protected allylic amine **159** should be accomplished by an asymmetric Ir-catalyzed allylic amination of homoallyl amine **134·HCl** and racemic carbonate **160**.

4.2.1 Investigations on the Ir-catalyzed allylic amination

Prior to investigations on the applicability of the reaction conditions for the Ir-catalyzed allylic amination, the corresponding carbonate *rac*-**160** was synthesized. Here, a two-step procedure starting from bromo ethyldioxolane **161** was applied (Scheme 46).

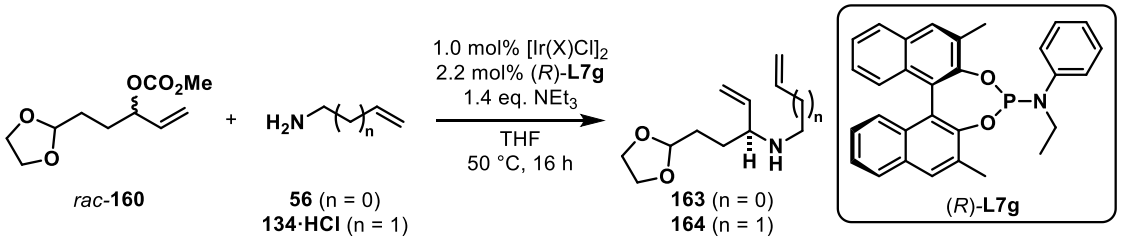


*Scheme 46: Synthesis of racemic carbonate **160**.[111]*

Following a literature procedure by *Lucchesini*,[111] bromo ethyldioxolane **161** was transformed into the corresponding *Grignard* reagent and reacted with DMF. Upon aqueous workup, aldehyde **162** was obtained in 64% yield. It should be noted that the reaction outcome was highly dependent on the quality of the purchased dioxolane **161**. In most cases, a reproducible yield of 64% for aldehyde **162** was achieved. However, with some batches of **161**, the yield dropped to 10-20%. Even replacing the old THF and DMF bottles, which might draw water over time, and distillation of dioxolane **161** could not improve the result. Only with a new batch of **161**, the former results could be reproduced. It is therefore likely that the starting material has partially decomposed, as it is temperature-labile. Moreover, the concentration of the generated *Grignard* reagent was always lower than expected. For example, a concentration of 0.43 M was determined by titration, while the calculated maximum concentration would have been 1.0 M. In addition to partially decomposed starting material or decomposed *Grignard* reagent, it is possible that the generated *Grignard* reagent partially reacts with unreacted dioxolane **161** to form a dimerized product.[104] However, the *Grignard* reagent was always generated in excess so that the yield of compound **162** could be improved to 64%.

With aldehyde **162** in hand, the substrate was reacted with vinyl magnesium bromide and methyl chloroformate in a one-pot procedure providing the desired racemic carbonate **160** in 46% yield over two steps. Thus, carbonate *rac*-**160** could be tested in the Ir-catalyzed *N*-allylation with allyl amine (**56**) and the previously synthesized hydrochloride **134·HCl** (Table 4).

*Table 4: Results of the Ir-catalyzed N-allylation of racemic carbonate **160** and amines **56** and **134·HCl**.*



Entry	Amine	$[Ir(X)Cl]_2$	Concentration	Result
1	**56**	cod	2.3 M	*rac*-**163**, 93%[a] (43%)[b]
2	**56**	dbcot	0.25 M	(*R*)-**163**, >99%[a] (34%)[b]
3	**134·HCl**	dbcot	0.25 M	(*R*)-**164**, >99%[a] (38%)[b]

a: Determined by GC-MS; b: Isolated yield.

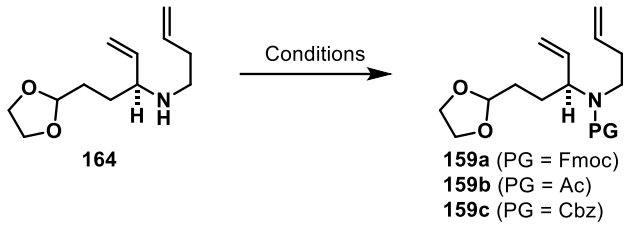
First, racemic carbonate **160** was tested in combination with allyl amine (**56**). The use of catalytic amounts of $[Ir(cod)Cl]_2$ already showed a successful conversion to allylic amine *rac*-**163** in 93% yield according to GC-MS (Table 4, entry 1). The addition of chiral ligand (*R*)-**L7g** provided the diolefin **163** in >99% yield according to GC-MS and in 34% isolated yield (Table 4, entry 2). Transferring these conditions to the synthesized homoallyl amine **134·HCl** afforded the targeted amine **164** in >99% yield by GC-MS (Table 4, entry 3). The isolated yield of 38% was again in the same range as for substrate **163**. This can be attributed to the difficult purification of free amines by column chromatography, which could not be improved even by using ultrapure silica gel and addition of NEt_3 to the eluent mixture.

Similar to the synthesized amine **149** (see Table 3), it was not possible to determine the enantiomeric excess of the product **164** at this stage. Thus, the enantioselectivity of the Ir-catalysis had to be evaluated at a later stage of the synthesis sequence.

4.2.2 Forward synthesis towards the isoxazoline motif

Subsequently, the obtained allylic amine **164** was protected. Since the removal of the acetal group might require acidic conditions, appropriate candidates, e.g. Fmoc-, Ac- or Cbz-protecting groups, were considered (Table 5).

*Table 5: Overview of synthesized protected amines of type **159**.*

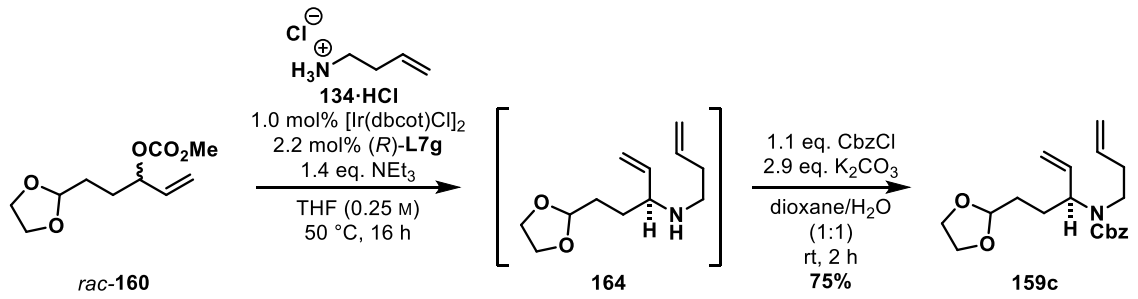


Entry	Conditions	Result
1	1.1 eq. FmocCl, 2.8 eq. K_2CO_3, dioxane/H_2O (1:1), rt, 1.5 h	**159a**, 90%[a]
2	1.1 eq. AcCl, 1.2 eq. pyridine, CH_2Cl_2, rt, 22 h	**159b**, 61%[a]
3	1.1 eq. CbzCl, 2.9 eq. K_2CO_3, dioxane/H_2O (1:1), rt, 2 h	**159c**, 85%[a]

a: Isolated yield.

All three protecting groups were successfully introduced providing the protected amines **159a-c** in good yields. Fmoc- and Cbz-protected amines **159a** and **159c** were isolated in yields of 90% and 85%, respectively (Table 5, entry 1 and 3). Only for Ac-protected amine **159b** a moderate yield of 61% was obtained (Table 5, entry 2).

Since the isolation of amine **164** was rather problematic and led to a decrease in yield, a direct protection of the crude product was considered. This was performed for the Cbz-protected analogue **159c**, in which the crude amine **164** was directly subjected to protecting conditions without previous isolation (Scheme 47).

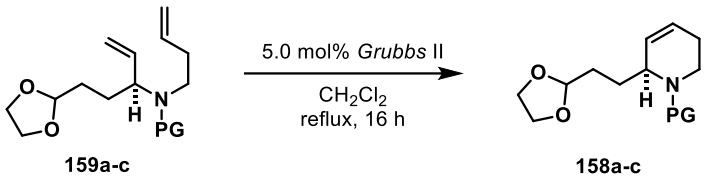


*Scheme 47: Synthesis of Cbz-protected amine **159c** without isolation of the free allylic amine **164**.*

The two-step sequence provided Cbz-protected amine **159c** in 75% yield. In comparison, the overall yield of this sequence with isolation of the allylic amine **164** only afforded the desired product **159c** in 32% yield over two steps. Therefore, the overall yield was significantly enhanced by the illustrated approach.

Subsequently, the protected amines **159a-c** were subjected to RCM conditions. Since the standard conditions using *Grubbs* II catalyst and CH_2Cl_2 proved to be well suited for the TBS-analogues **133a** and **133b**, the same conditions were applied to the acetal-system (Table 6).

Table 6: Results of the performed ring closing metathesis with regard to the implemented protecting groups.



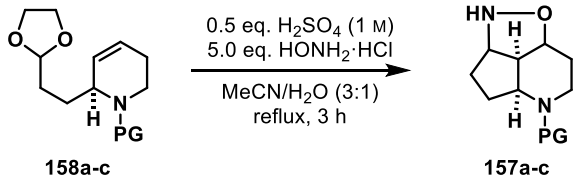
Entry	Protecting group (PG)	Result
1	Fmoc	**158a**, 74%[a]
2	Ac	**158b**, 73%[a]
3	Cbz	**158c**, 81%[a]

a: Isolated yield.

The ring closing metathesis worked well for all synthesized allylic amines **159a-c**, with the corresponding aza-cyclohexene motifs **158a-c** obtained in 73-81% yield. Furthermore, it was possible to separate the enantiomers *via* chiral HPLC at this stage of the synthesis. In case of the Cbz-protected analogue **158c**, a successful separation was achieved, yielding an enantiomeric excess of 42%. This result demonstrated that the conditions of the Ir-catalyzed allylic amination were suitable to provide one enantiomer in excess, although the enantioselectivity obtained is improvable. However, the purpose of the test system was fulfilled and further investigations on the Ir-catalyzed allylic amination of the test system were disregarded.

Based on the observed reaction by *Tobias Wilczek*, in which acetal-protected substrate *rac*-**155** directly underwent 1,3-dipolar cycloaddition after deprotection of the aldehyde and oxime formation in just one step (see Scheme 44),[104] the reaction conditions were transferred to the system examined in this work (Table 7).

Table 7: Overview of the results of the one-step oxime formation and 1,3-dipolar cycloaddition with regard to the implemented protecting group.

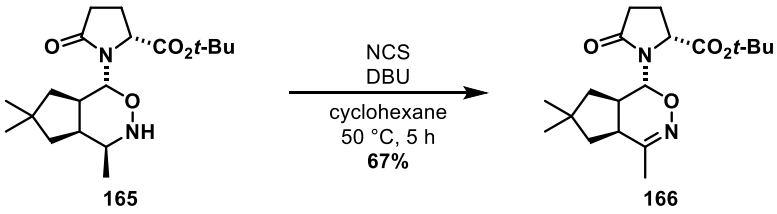


Entry	Protecting group (PG)	Result
1[a]	Fmoc	**157a**, 71%[c]
2[a]	Ac	**157b**, 77%[c]
3[a]	Cbz	**157c**, >99%[c]
4[b]	Cbz	**157c**, 90%[c]

a: Reactions were performed on a 0.20 mmol scale; b: Reactions were performed on a 2.2 mmol scale; c: Isolated yield.

Additionally, 1 M H_2SO_4 was added to accelerate the removal of the acetal-protecting group. The applied reaction conditions afforded the isoxazolidines **157a-c** in 71% up to quantitative yield, which is a drastically improved result compared to the dihydropyridine system **155** (see Scheme 44). Therefore, the 1,3-dipolar cycloaddition worked even better for the structures of type **158**, as the major source for the reduced yield, the formation of an aromatic side product, was eliminated. Moreover, the applied compounds **158a-c** were quite polar, thus, they were easily dissolved in the MeCN/H_2O solvent mixture. Cbz-protected compound **158c** in particular afforded the isoxazolidine **157c** in an excellent yield of >99% on a 0.26 mmol scale (Table 7, entry 3). On a larger scale of 2.2 mmol, the yield slightly decreased to 90% (Table 7, entry 4). It should be noted that the isoxazolidines **157a-c** were obtained as a mixture of diastereomers and rotamers according to NMR, which were not separable by column chromatography. As the Cbz-protecting group proved to be the most suitable choice, only the forward synthesis of isoxazolidine **157c** was further investigated. The Cbz-analogues not only provided the best yields in the synthetic sequences but were also easy-to-handle substrates. Compared to the acetyl-protected analogue **157b**, which is a compound of high polarity that was not soluble in all organic solvents, Cbz-isoxazolidine **157c** was also soluble in less polar organic solvents and therefore more suitable for the investigation of the upcoming reaction steps.

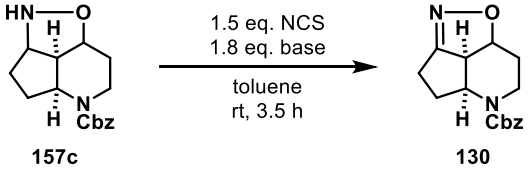
With isoxazolidine **157c** in hand, the central bicyclic core structure of the camporidine A test system has already been established in just four reaction steps. Subsequently, the oxidation to isoxazoline **130** was examined. The reaction conditions used by *Streith and co-workers* for isoxazolidine **165** seemed suitable as the oxidation was achieved under mild conditions using NCS and DBU (Scheme 48).[112]



*Scheme 48: Synthesis of isoxazoline **166** via oxidation of isoxazolidine **165** with NCS and DBU described by Streith et al.*[112]

The transformation proceeds *via* chlorination and subsequent elimination of HCl under basic conditions. These reaction conditions were transferred to isoxazolidine **157c** (Table 8). Since a pre-experiment on the solubility of isoxazolidine **157c** revealed a poor solubility of the compound in cyclohexane, it was directly exchanged for the slightly more polar solvent toluene, which still permits removal of the formed succinimide salt by filtration.

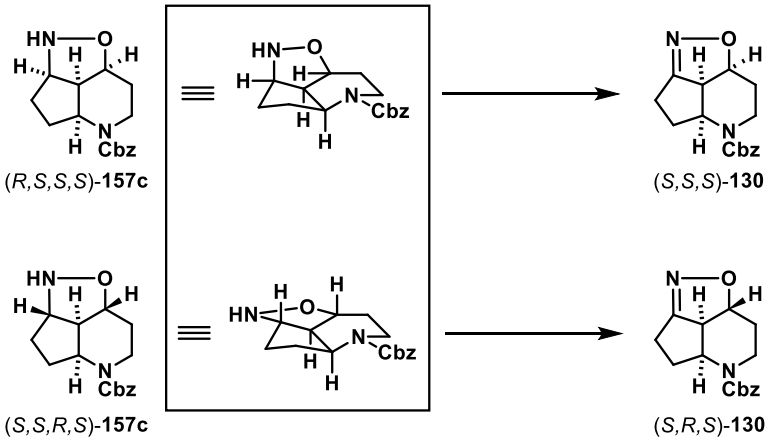
*Table 8: Results of the oxidation of isoxazolidine **157c** to isoxazoline **130**.*



Entry	Base	Yield
1[a]	DBU	25%
2[a]	DABCO	86%
3[b]	DABCO	80%

A: Reaction was performed on 0.07 mmol scale; b: Reaction was performed on 0.7 mmol scale.

The first attempt using NCS and DBU on isoxazolidine **157c** on a small scale provided the desired isoxazolidine motif **130** in 25% yield (Table 8, entry 1). Unfortunately, full conversion of the starting material **157c** was not achieved. Therefore, DBU was replaced by DABCO, another non-nucleophilic base. The exchange led to full conversion of the starting material and an isolated yield of 86% for isoxazoline **130** (Table 8, entry 2). The reaction conditions were successfully transferred to a larger scale of 0.7 mmol with a slightly decreased yield of 80% (Table 8, entry 3). Due to the previous observations indicating a diastereomeric mixture of isoxazolidine **157c**, it is assumed that isoxazoline **130** also consisted as a diastereomeric mixture (Scheme 49).



*Scheme 49: Proposed formation of two distinct diastereomers of isoxazolidine **157c** and isoxazoline **130**.*

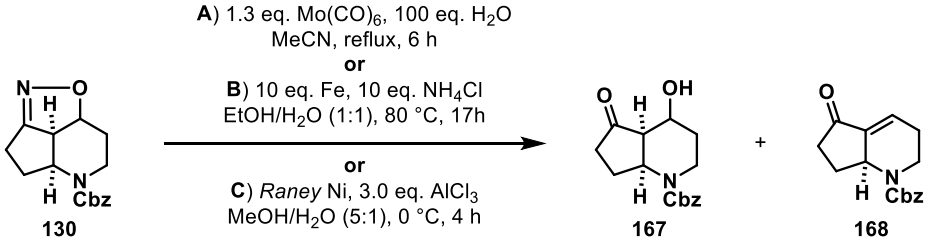
Based on the molecular structure, it is supposed that two distinct diastereomers of isoxazolidine **157c** are formed, the (*R,S,S,S*)- and the (*S,S,R,S*)-analogue. As stated previously, NMR measurements indicated a mixture of diastereomers and rotamers for **157c**. Further oxidation to isoxazoline **130** would therefore lead to the formation of the (*S,S,S*)- and the (*S,R,S*)-isomers. However, the diastereomeric ratio could not be identified by NMR and GC-MS measurements and had to be evaluated in a subsequent step.

The results show that the envisioned reaction sequence was well transferable to the test system. The isoxazoline motif **130** was synthesized in just five steps with an overall yield of 44%, which paved the way for further reaction steps.

4.2.3 Synthesis of the core motif *via* reduction/elimination

Since the establishment of isoxazoline **130** was used to form the bicyclic motif of the camporidine structure, the next step to be investigated was the reductive cleavage of the *N-O* bond to provide enone **168** after imine hydrolysis. Originally, a reductive cleavage using $Mo(CO)_6$ was planned, as it is possible to directly synthesize the elimination product of *β*-hydroxyketones under these conditions.[98] However, the reaction of compound **130** with $Mo(CO)_6$ on a small test scale did not deliver the desired product, only traces of the enone **168** could be detected according to GC-MS (Table 9, entry 1). Therefore, other reductive cleavage conditions were tested in which the formation of the *β*-hydroxyketone **167** was expected.

*Table 9: Overview of the tested reaction conditions and results of the reductive cleavage of isoxazoline **130**.*



Entry	Conditions	Result
1[a]	A	Inseparable mixture, traces of **168** detected *via* GC-MS
2[a]	B	Full conversion, only **168** detected *via* GC-MS
3[b]	B	42% **167**, 34% **168**
4[b]	C	66% **167**, 12% **168**
5[c]	C	62% **167**, 12% **168**

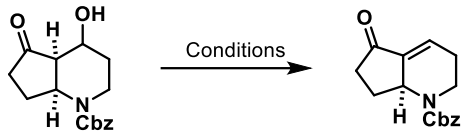
a: Reactions were performed on a 5 mg scale, the outcome was only evaluated by GC-MS and TLC; b: Reactions were performed on an 18 mg scale, products were isolated and analyzed by NMR; c: Reaction was performed on a 1 mmol (300 mg) scale.

In a small-scale experiment, the use of a combination of Fe and NH_4Cl led to full conversion of the starting material according to TLC and GC-MS (Table 9, entry 2). Interestingly, GC-MS measurements only revealed a product peak with fragments corresponding to enone **168**. However, the formation of *β*-hydroxyketone **167** cannot be excluded as the elimination of H_2O might occur during the heating process of the GC-MS measurement. Therefore, the reaction was repeated on a slightly larger scale which allowed isolation of the products. Indeed, the *β*-hydroxyketone **167** was obtained in 42% yield along with 34% of the elimination product **168**

(Table 9, entry 3). Moreover, isoxazoline **130** was reacted with *Raney* Ni and the *Lewis* acid $AlCl_3$, resulting in a full conversion of the starting material (Table 9, entry 4). Analysis of the isolated substrates revealed that 66% of *β*-hydroxyketone **167** were synthesized. As a side product, enone **168** was isolated in 12% yield. The reaction outcome was nearly identically reproducible on a 1 mmol scale (Table 9, entry 5).

Since the reductive cleavage with *Raney* Ni delivered one major product in good yield and a slightly higher overall yield of **167** and **168** compared to using Fe, the combination of *Raney* Ni and $AlCl_3$ was applied in the reaction sequence. Therefore, the elimination of the hydroxyl functionality to form enone **168** was examined (Table 10).

*Table 10: Overview of the tested reaction conditions and selected results for the cleavage of alcohol **167** to form enone **168**.*



167 168

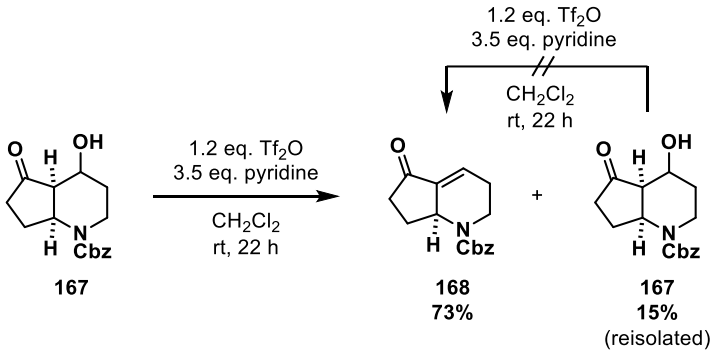
Entry	Reagents	Solvent	Conditions	Ratio 167:168[a]
1	1.2 eq. MsCl, 2.0 eq. NEt_3, 0.2 eq. DMAP	CH_2Cl_2	rt, 17 h	54:46
2	1.2 eq. MsCl, 2.0 eq. NEt_3, 0.2 eq. DMAP	CH_2Cl_2	reflux, 2 d	52:48
3	i) 4.0 eq. Ac_2O, 4.0 eq. NEt_3, 0.4 eq. DMAP ii) 5.0 eq. DBU	CH_2Cl_2	rt-reflux, 4 d	55:45
4	1.1 eq. PPh_3, 1.2 eq. I_2, 2.0 eq. DBU	CH_2Cl_2	rt-reflux, 4 d	100:0
5	1.1 eq. PPh_3, 1.3 eq. DIAD	toluene	rt-reflux, 7 d	decomp.
6	1.2 eq. *p*-TsOH·H_2O	toluene	50 °C, 21 h	24:76; decomp. products
7	1.1 eq. Tf_2O, 3.5 eq. pyridine	CH_2Cl_2	0 °C-rt, 22 h	24:76

a: The ratio was determined by NMR.

For example, *β*-hydroxyketone **167** was reacted with MsCl to form the *O*-mesylated intermediate. Base-induced elimination should provide the desired product **168**. Reaction at room temperature led to the formation of 46% of compound **168** according to NMR, however, full conversion of the starting material was not achieved (Table 10, entry 1). Heating the reaction mixture to reflux did not lead to a significant change in the ratio of starting material to product (Table 10, entry 2). Subsequently, the *β*-hydroxyketone **167** was reacted with Ac_2O under basic conditions. Additionally, five equivalents of DBU were added to accelerate the cleavage of the acetylated analogue of **167**. Similar to the previous experiments, the determined ratio did not exceed 55:45 (Table 10, entry 3). Moreover, *Appel*-type conditions were examined in which the hydroxyl functionality is substituted by iodine under the release of triphenylphosphine oxide. Since

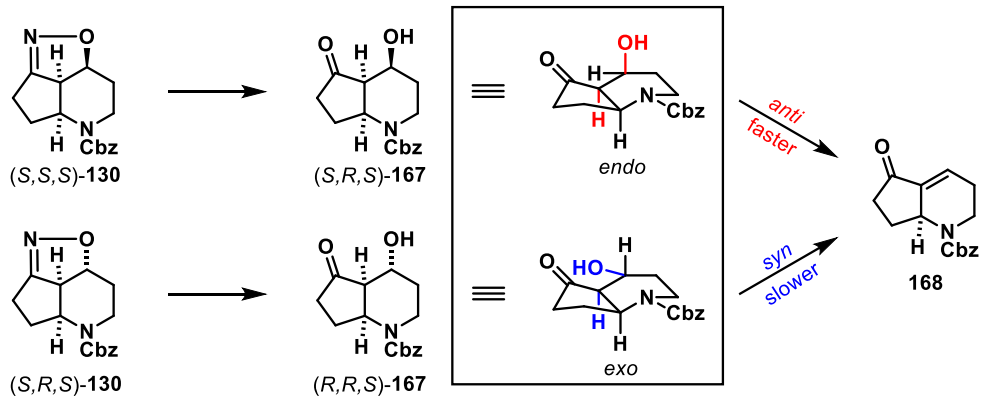
halogens display good leaving groups, the desired cleavage to **168** should be facilitated. Unfortunately, no product formation was detected according to NMR (Table 10, entry 4). Furthermore, *Mitsunobu*-type conditions were used to generate an oxygen-phosphine species. The elimination should be favoured and accelerated by the formation and release of triphenylphosphine oxide, but only decomposition products were detected (Table 10, entry 5). Next, *p*-toluenesulfonic acid was used as an acidic catalyst for dehydration. Under these conditions the desired product **168** was formed in excess, with only 24% of the starting material remaining (Table 10, entry 6). However, the NMR measurements showed that in addition to product formation, the material decomposed under the given conditions. Thus, *β*-hydroxyketone **167** was reacted with triflic anhydride under basic conditions. Here, a ratio of 24:76 was identified without the formation of decomposition products (Table 10, entry 7). The results imply that full conversion of the starting material was not reachable under the given conditions due to limits by decomposition upon heating.

The best reaction conditions using Tf_2O and pyridine were repeated on a slightly larger scale to allow isolation of the product. The desired elimination product **168** was obtained in 73% yield, which is similar to the observed ratio *via* NMR (Scheme 50).



*Scheme 50: Synthesis of the elimination product **168** from β-hydroxyketone **167** obtained from the reductive cleavage and application of the reaction conditions to reisolated **167** from the elimination procedure.*

Alcohol **167** could be reisolated in minor amounts from the reaction mixture. Surprisingly, it was not possible to repeat the reaction on reisolated *β*-hydroxyketone **167**. This outcome led to the assumption that the two diastereomers of **167** exhibited different reactivities towards the elimination (Scheme 51).



*Scheme 51: Depending on the diastereomer of **167**, the reaction proceeds as an anti- or syn-elimination.*

Following the reaction sequence from the isoxazoline **130**, where it is assumed that two distinct diastereomers were formed (see Scheme 49), the reductive cleavage would lead to the formation of (*S,R,S*)- and (*R,R,S*)-**167**. For the *endo*-analogue, the hydrogen and the leaving group are in *anti*-position, whereas the two substituents are in *syn*-position for the *exo*-analogue. It is assumed that the elimination proceeds according to an E_2-mechanism. Therefore, the process is concerted, in which deprotonation and removal of the leaving group occur simultaneously. In these reaction types, the *anti*-elimination is favoured because the repulsion between the electrons of the examined *C-H* bond and the electron pairs of the leaving group is lower. It was therefore assumed that the *endo*-diastereomer of **167** reacted easily to the desired enone **168**, while the *exo*-diastereomer of **167** did not or only partially reacted. This would provide an explanation for the incomplete conversion of **167** in the elimination screening (see Table 10) and the unreactive behaviour of reisolated alcohol **167** when re-subjected to the elimination conditions. To prove this hypothesis, the obtained *β*-hydroxyketone **167** was analyzed by HPLC after reductive cleavage, where two major diastereomers of **167** could be separated, indicating a ratio of 69:31 of *endo*-**167** to *exo*-**167**. It must be noted that the *β*-hydroxyketone **167** already reacted partially to enone **168** in the reductive elimination step, therefore, the determined ratio does not provide an insight on the diastereomeric ratio of the previous intermediates. The reisolated substrate **167** was also subjected to HPLC. It was expected that only one diastereomer should be detected. However, it was not possible to obtain a pure signal of **167**. Instead, the HPLC measurements indicated a product mixture. Reinvestigations of the NMR measurements revealed that reisolated compound **167** was always obtained as an inseparable product mixture of triflated and untriflated **167**. These results make it difficult to draw conclusions. To validate the hypothesis that *exo*-**167** is less reactive, conditions for *syn* eliminations, e.g. by using the *Burgess'* reagent, could be tested. Due to the impurities of the reisolated alcohol **167**, further tests were not considered. Besides, it is possible that the elimination proceeds *via* an E_1cb instead of an E_2 mechanism. Here, the stereocenter of the *β*-hydroxyketone **167** would be irrelevant and the

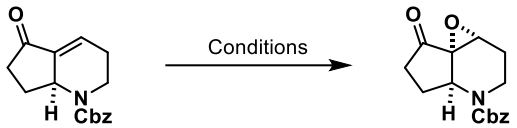
reaction simply reaches its limits due to decomposition and formation of impurities during heating. Unfortunately, a general explanation could not be identified.

Still, the desired enone **168** was isolated in an overall yield of 60%. Thus, the core structure of the test system of camporidine A (**11**) was successfully established, paving the way for further functionalization of the molecule.

4.2.4 Functionalization of the core motif

With the core motif **168** in hand, further functionalizations of this structure were investigated, starting with the screening of reaction conditions for the epoxidation (Table 11).

*Table 11: Results of the applied epoxidation conditions to substrate **168**.*



168 **169**

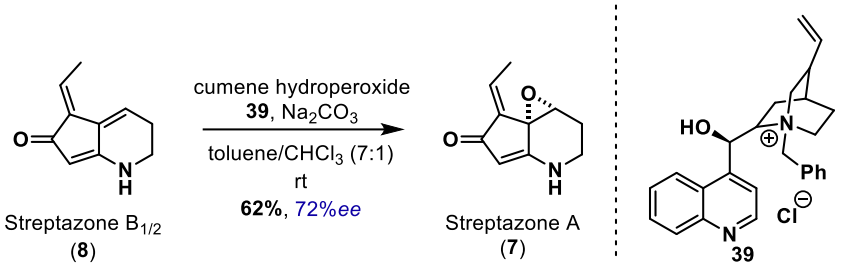
Entry	Reagent	Solvent	Conditions	Result
1	1.5 eq. *m*CPBA	CH_2Cl_2	0 °C-reflux, 20 h	traces of **169**, mostly **168**
2	1.2 eq. *t*BuOOH, 1.2 eq. DBU	CH_2Cl_2	0 °C-reflux, 20 h	traces of **169**, mostly **168**
3	1.6 eq. oxone, 5.9 eq. $NaHCO_3$	acetone/H_2O (2:1)	0 °C-reflux, 2 d	no conversion
4	5.0 eq. H_2O_2, 4.9 eq. 1 M NaOH	MeOH	0 °C-rt, 21 h	decomposition
5	10 eq. cumene hydroperoxide, sat. aq. Na_2CO_3	toluene/CH_2Cl_2 (7:1)	rt, 16 h	no conversion
6	5.1 + cat. amounts of TBAB	toluene/CH_2Cl_2 (7:1)	rt, 16 h	94% of **169**
7[a]	5.1 + cat. amounts of TBAB	toluene/CH_2Cl_2 (7:1)	rt, 16 h	88% of **169**

a: Experiment was performed on a 0.2 mmol (55 mg) scale. All other test reactions were performed on a 10 mg scale.

Since it was assumed that the epoxidation will most likely proceed stereoselective due to the favoured *cis*-conformation of the bicyclic [4.3.0] motif, the use of chiral epoxidation reagents was disregarded. Instead, classical epoxidation reagents such as *m*CPBA, *t*BuOOH and oxone were applied (Table 11, entry 1-3). However, the approaches did not lead to conversion of the substrate

168, only traces of the product could be detected *via* TLC and GC-MS. Moreover, the use of hydrogen peroxide resulted in decomposition of the material (Table 11, entry 4).

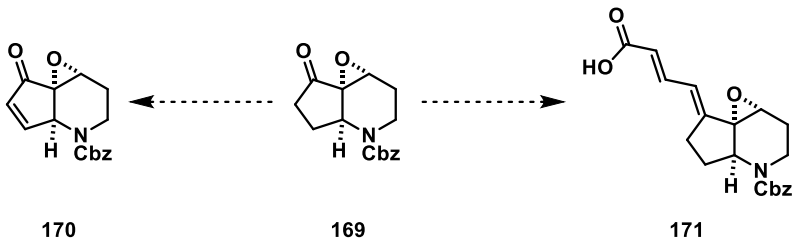
Inspired by a reaction sequence applied by *Poulsen and co-workers* in their total synthesis of streptazone A (**7**), in which cumene hydroperoxide and the chiral organocatalyst **39** were utilized for a stereoselective epoxidation (Scheme 52),[25] the reaction conditions they used were transferred to test system **168**. However, no conversion of the starting material was observed in this test either (Table 11, entry 5).



*Scheme 52: Epoxidation procedure towards streptazone A (**7**), reported by Poulsen and co-workers.[25]*

Taking a closer look at the reaction conditions of *Poulsen et al.*,[25] it is clear that the catalyst **39** was used as a phase transfer catalyst. Therefore, catalytic amounts of TBAB were added to the reaction mixture, leading to a successful epoxidation with an isolated yield of 94% for epoxide **169** (Table 11, entry 6). The reaction conditions were also applicable to an increased scale of 0.2 mmol, obtaining 88% of the desired epoxide **169** (Table 11, entry 7). The obtained NMR spectrum did not indicate a mixture of diastereomers, which already implies that only one favoured diastereomer was formed.

With the tricyclic system **169** in hand, further functionalizations should be evaluated. On the one hand, the implementation of the unsaturated side chain *via Wittig* or *Horner-Wadsworth-Emmons* olefination should be investigated. On the other hand, suitable reaction conditions for the introduction of the double bond in the cyclopentene motif were regarded (Scheme 53).

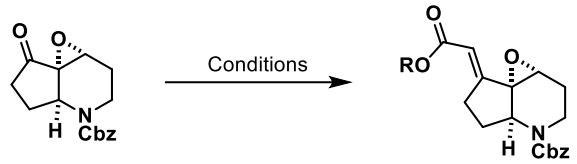


*Scheme 53: Regarded functionalizations of the tricyclic motif **169**.*

First, the olefination sequence was examined. Here, the *Wittig* and *HWE* reagents **172**-**174** were used for testing, as they were readily available in our laboratories (Table 12). In case of the *Wittig*

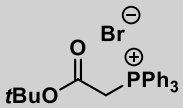
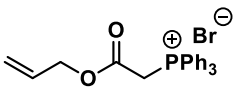
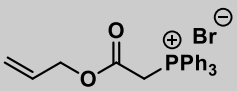
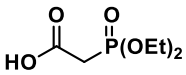
reagents **172** and **173**, the substrates were first subjected to basic conditions with NaOH. After workup, the crude products were directly applied to the *Wittig* olefination conditions.

*Table 12: Screening of reaction conditions for the olefination of substrate **169**.*



169

175a (R = *t*Bu)
175b (R = allyl)
175c (R = H)

Entry	*Wittig*/*HWE* reagent	Conditions	Result
1[a]	1.8 eq.  **172**	CH_2Cl_2, 0 °C-reflux, 30 h	1:1 (**169**:**175a**)[b], isolated with major impurities
2[a]	1.7 eq.  **173**	THF, 0 °C-40 °C, 42 h	2:3 (**169**:**175b**)[b], 53% isolated product
3	4.8 eq.  **173**	4.6 eq. KO*t*Bu, THF, rt-55 °C, 18 h	full conversion, 91% of **175b** isolated
4	1.9 eq.  **174**	3.7 eq. KHMDS, THF, rt-65 °C, 3 d	no conversion

a: The phosphonium bromides were activated by treatment with NaOH (1 M) prior to *Wittig* olefination; b: The ratio was determined by GC-MS.

The reaction of reagent **172** with epoxide **169** in CH_2Cl_2 afforded a mixture of the starting material and the desired product **175a** in a ratio of 1:1 (Table 12, entry 1). Full conversion of the starting material could not be achieved under the described conditions. Moreover, product **175a** was only isolated with major impurities, which indicates an instability of the compound. By using allyl ester **173** and replacing CH_2Cl_2 with THF, the ratio could be increased to 2:3, and the product **175b** was isolated as the pure compound in 53% yield (Table 12, entry 2). An *in situ* activation approach of the phosphonium bromide **173** with KO*t*Bu made it possible to completely convert the starting material and isolate olefin **175b** in 91% yield (Table 12, entry 3). Lastly, *HWE* olefination conditions were applied using reagent **174**, which was activated *in situ* by KHMDS (Table 12, entry 4). However, the reaction did not provide the desired product **175c**. Instead, the starting material was

reisolated. The first reaction screening on the olefination conditions implies that a *Wittig* olefination is more suitable for the examined system. Comparing the two tested esters **172** and **173**, the allyl ester **173** proved to be superior and led to a higher conversion to the product.

Furthermore, the obtained unsaturated ester **175b** was analyzed by means of NMR with special emphasis on the NOE correlations. Interestingly, the spectroscopic analysis revealed that only the desired (*E*)-isomer of **175b** was obtained. It can be assumed that the electronic repulsion between the ester moiety and the epoxide is responsible for this (Figure 6).

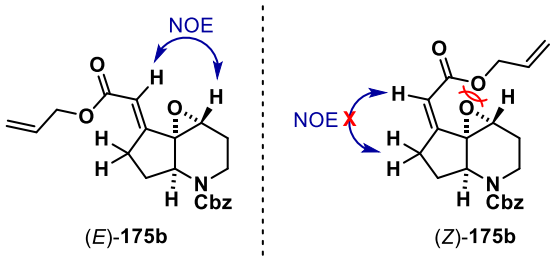
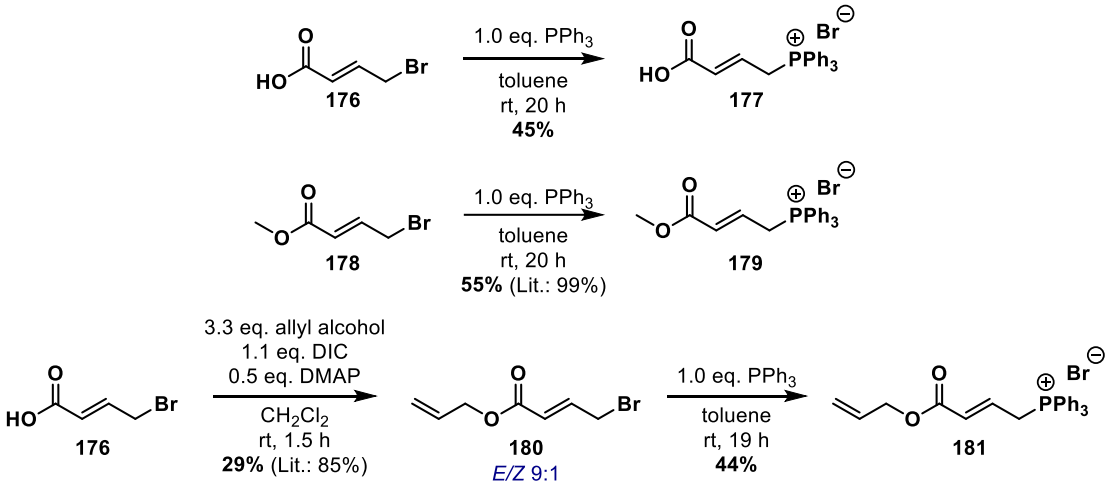


*Figure 6: Analysis of the NOE correlations revealed that (E)-**175b** was obtained (left), whereas the NOE correlation for the (Z)-isomer was not detected (right).*

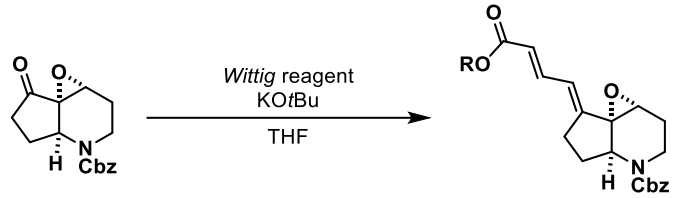
Since the *Wittig* olefination worked for the test system, similar reaction conditions were applied to the elongated unsaturated side chain. Thus, phosphonium bromides **177**, **179** and **181** were synthesized from their corresponding bromo esters by reaction with PPh_3 (Scheme 54),[113, 114] providing the products in moderate yields.



*Scheme 54: Synthesis of phosphonium bromides **177, 179** and **181**.[113, 114]*

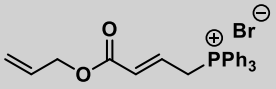
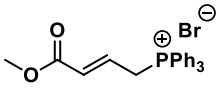
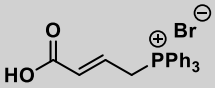
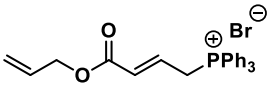
With the elongated phosphonium bromides in hand, the *Wittig* olefination was reinvestigated (Table 13).

Table 13: Screening of different phosphonium bromides in the Wittig olefination.



169

182a (R = allyl)
182b (R = Me)
171 (R = H)

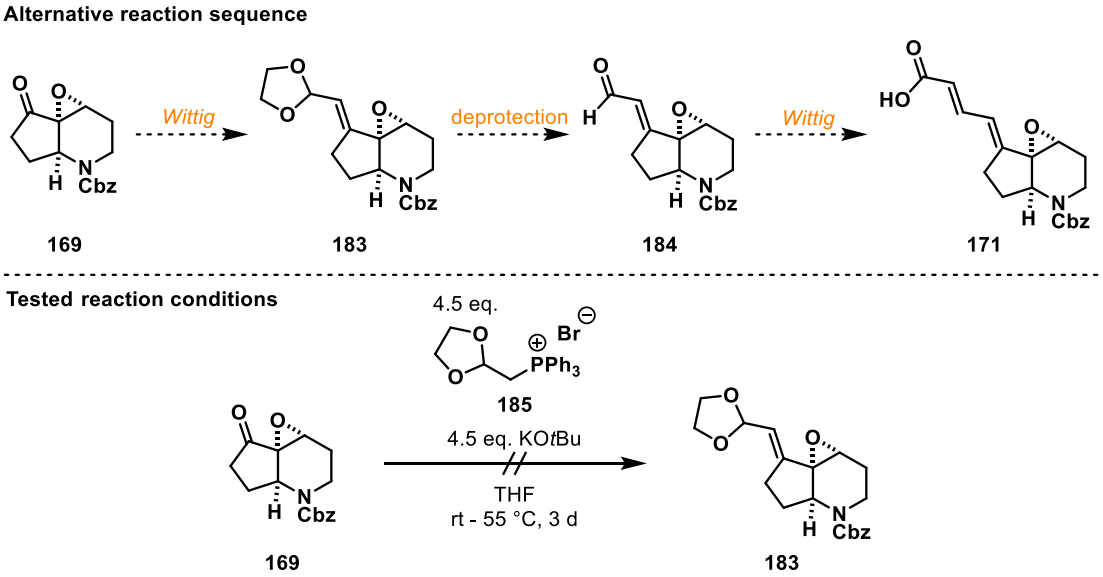
Entry	*Wittig* reagent	KO*t*Bu	Conditions	Result
1[a]	 1.7 eq. **181**	/	0 °C-rt, 20 h	decomposition
2	 5.8 eq. **179**	5.8 eq.	rt-55 °C, 2 d	no conversion
3	 4.0 eq. **177**	8.0 eq.	rt-55 °C, 22 h	decomposition
4	 5.8 eq. **181**	6.0 eq.	rt-55 °C, 2 d	23% of **182a**

a: The phosphonium bromides were activated by treatment with NaOH (1 M) prior to *Wittig* olefination; b: The ratio was determined by GC-MS.

First, the elongated *Wittig* reagent **181** was subjected to basic conditions and the crude ylide was directly applied to the *Wittig* reaction (Table 13, entry 1). However, only decomposition products were obtained. Thus, the *in situ* activation of the *Wittig* reagent with KO*t*Bu was applied to phosphonium bromides **177**, **179** and **181**. For the methyl ester **179**, no conversion of ketone **169** was observed (Table 13, entry 2). In case of the free acid **177**, only decomposition of the starting material was detected (Table 13, entry 3). Only the allyl ester **181** delivered a successful transformation to **182a** with an isolated yield of 23% (Table 13, entry 4). Therefore, it can be assumed that the allyl group has a stabilizing effect on the system, probably through π-interactions within the side chain that prevent interference with the epoxy functionality. Unfortunately, full conversion of the starting material could not be reached in combination with the elongated reagent **181**, as the system is more demanding. As for the first test with the activated ylide of **181** (Table 13, entry 1), the obtained *Wittig* reagent was probably extremely unstable. This would also provide an explanation for the observed decomposition and the low isolated yield of **182a** in the *in situ* approach. Upon activation by base, the obtained phosphonium ylide of **181** can possibly react *via Diels-Alder* reaction forming a γ-lactone which might be even

cleaved upon heating or by the basic conditions. However, a side-product that would confirm this hypothesis was not isolated.

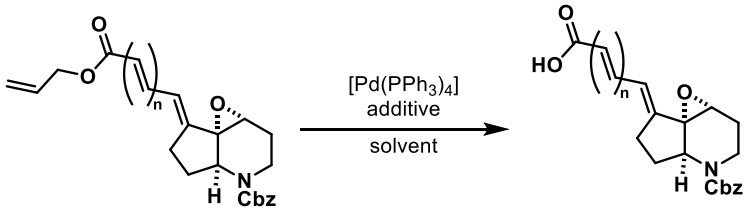
Another possibility was to carry out two consecutive *Wittig* reactions that would provide the unsaturated side chain of compound **171** (Scheme 55).



Scheme 55: Alternative reaction sequence with two consecutive Wittig olefinations (upper scheme) and the tested reaction conditions (lower scheme).

Here, the acetal-protected phosphonium bromide **185** would provide a possible reagent. However, applying reagent **185** to the reaction conditions previously used did not lead to any conversion of the starting material **169**. Therefore, the best result in this screening was the use of allyl ester **181**, which provided the unsaturated side chain in product **182a**. As reported for the test analogue **175**, analysis of the NMR spectra with special regard to NOE correlations and coupling constants showed that the desired (*E,E*)-isomer **182a** was predominantly obtained. Since the allyl ester has to be cleaved in the total synthesis of camporidine A (**11**), suitable conditions were examined (Table 14).

Table 14: Overview of the tested reaction conditions for the allyl ester cleavage.



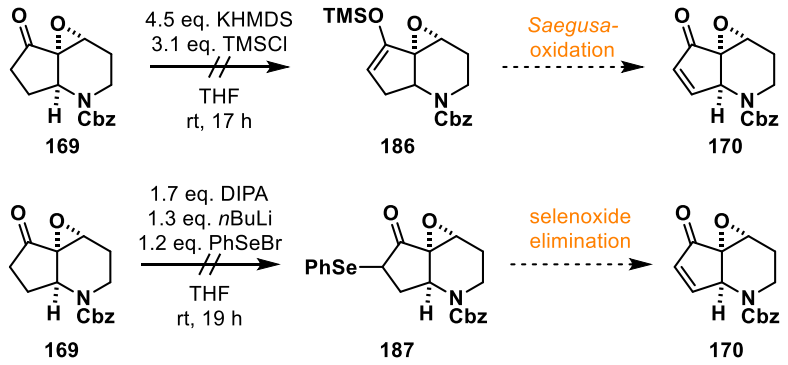
175b (n = 0)
182a (n = 1)

175c (n = 0)
171 (n = 1)

Entry	Substrate	[$Pd(PPh_3)_4$]	Additive	Solvent	T	t	Result
1	**175b**	4.4 mol%	2.0 eq. PhSiH	CH_2Cl_2	rt	2 d	decomposition
2	**175b**	8.7 mol%	5.0 eq. morpholine	THF	rt-80 °C	4 d	decomposition
3	**182a**	1.0 mol%	9.9 eq. 1,3-dimethyl-barbituric acid	CH_2Cl_2	rt-50 °C	2 d	decomposition, traces of **171**

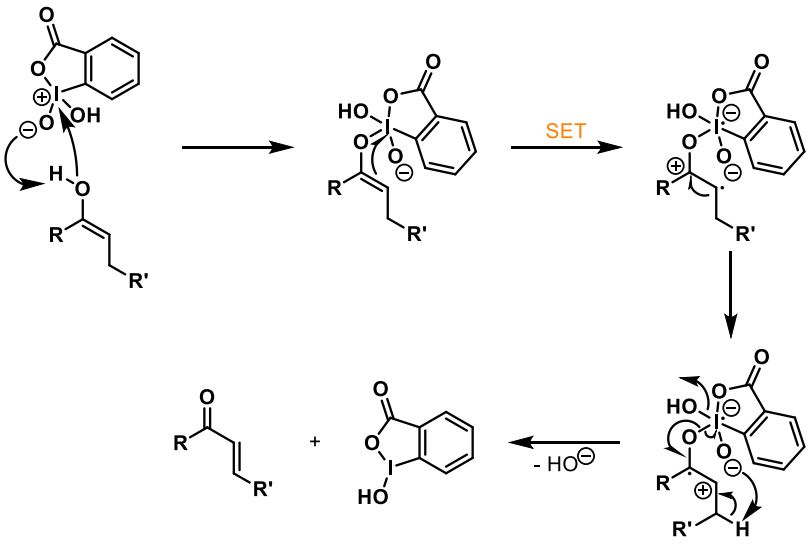
In general, allyl esters are cleaved under Pd-catalysis with the use of an allyl scavenger. Phenylsilane, morpholine and 1,3-dimethylbarbituric acid were applied as examples of potential scavengers. Unfortunately, all tested conditions led to decomposition of the starting material, which indicates an instability of the carboxylic acids **175c** and **171**. Traces of the desired product could only be detected in one experiment according to GC-MS (Table 14, entry 3). Further investigations would be necessary, e.g. by reinvestigating other ester functionalities and its cleavages, to examine if the decomposition is caused by the allyl ester cleavage conditions or by a general instability of the formed allylic epoxides **175c** and **171**.

Apart from investigations on the introduction of the unsaturated side chain, examinations on the generation of the double bond providing the cyclopentenone motif **170** were made. Initially, the introduction of the double bond *via Saegusa* oxidation or selenoxide elimination was considered (Scheme 56).



*Scheme 56: Attempted synthesis of precursors **186** and **187** for the Saegusa oxidation (upper scheme) and the selenoxide elimination (lower scheme).*

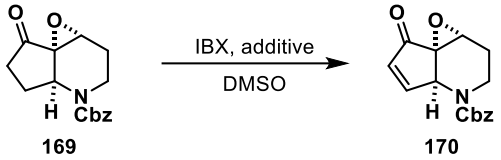
For the *Saegusa* oxidation it was necessary to generate the corresponding silyl enol ether **186**. By applying standard conditions using TMSCl and KHMDS, it was not possible to provide enol ether **186**. Furthermore, the reaction led to decomposition of the starting material **169**, which can be attributed to the lability of the epoxide moiety. Subsequently, the selenoxide elimination approach was investigated. Therefore, the epoxide **169** was reacted with LDA, which was generated *in situ* from DIPA and *n*BuLi, and phenylselenyl bromide. However, here too the reaction only led to decomposition of the starting material. In the search for a milder method, a selective oxidation towards enones with IBX was considered (Scheme 57).



Scheme 57: Mechanism of the oxidation of enones with IBX.[115]

This approach was developed by *Nicolaou and co-workers*.[115, 116] The mechanism proceeds by enolization of the starting material, followed by single electron transfer (SET) and subsequent rearrangement of the radical to establish the desired enone motif.[115] This mild and selective method was applied to the test system **169** (Table 15).

*Table 15: Overview of the results for the IBX-mediated oxidation towards enone **170**.*

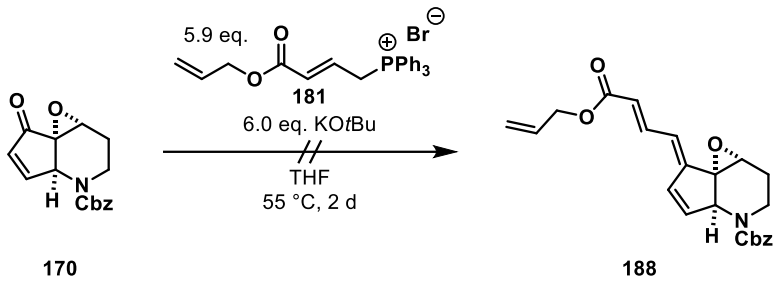


169 170

Entry	IBX	Additive	T	t	Result
1	1.4 eq.	-	65 °C	23 h	no conversion
2	1.4 eq.	-	75 °C	18 h	decomposition
3	4.2 eq.	3.8 eq. MPO	rt-55 °C	21 h	82% of **170**

The use of the standard conditions by *Nicolaou* with IBX in DMSO at 65 °C[116] did not lead to any conversion of the starting material **169** (Table 15, entry 1). When the temperature was increased to 75 °C, decomposition of epoxide **169** was observed (Table 15, entry 2). *Nicolaou and co-workers* reported that the addition of 4-methylpyridine-*N*-oxide (MPO) accelerates the reaction by forming an activated IBX·*N*-oxide complex.[115] Therefore, the latter was added to the oxidation of **169**, which provided enone **170** in 82% yield (Table 15, entry 3).

Subsequently, the former evaluated *Wittig* olefination was applied to enone **170**. The synthesized compound **170** was reacted with phosphonium bromide **181** under basic conditions (Scheme 58). However, the desired product **188** was not formed. Instead, decomposition of the starting material was detected and only remains of the *Wittig* reagent and phosphonium oxide species were isolated.



170 188

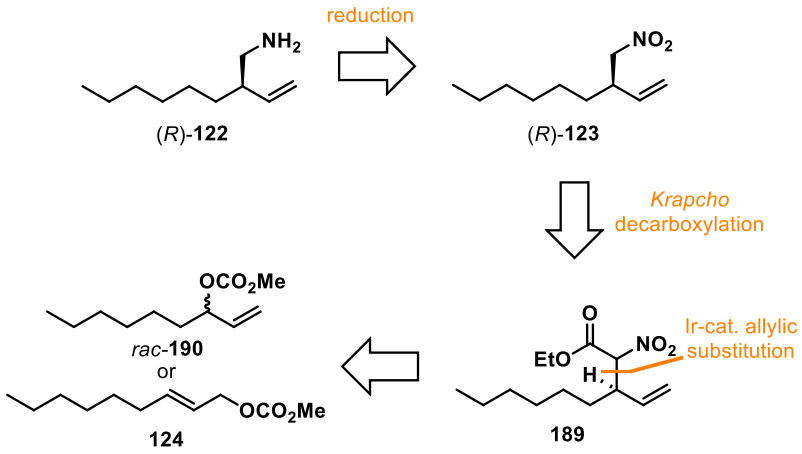
*Scheme 58: Attempted Wittig olefination of enone **170**.*

Overall, the forward synthesis of the test system proved to be quite successful in the formation of core motif **168**. Further functionalizations were achieved, but additional investigations are necessary to complete the remaining synthetic steps. Especially the removal of the allyl ester remains a major challenge, which makes further evaluation of other protected carboxylic acids or allyl scavengers necessary.

4.3 Forward synthesis towards camporidine A

4.3.1 Synthesis of the chiral amine building block *via* Ir-catalyzed allylic substitution

Since the forward synthesis *via* isoxazolidine formation appeared to be a promising approach for the establishment of the camporidine test system, the synthetic procedure should be transferred to camporidine A (**11**). It was therefore necessary to synthesize the corresponding alkylated amine (*R*)-**122** enantioselectively for the implementation into the Ir-catalyzed allylic amination (Scheme 59).

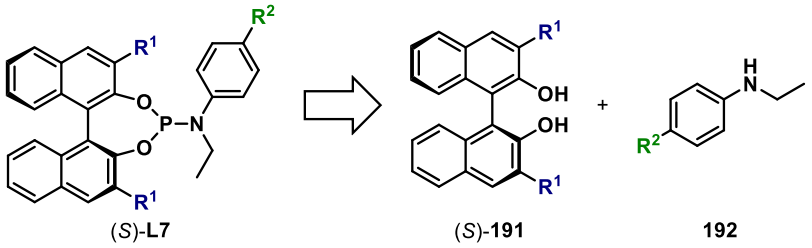


*Scheme 59: Retrosynthetic analysis of amine (R)-**122**.*

The key reaction towards amine (*R*)-**122** should be an Ir-catalyzed allylic substitution. The use of chiral phosphoramidite ligands should render the reaction stereoselective. Therefore, suitable phosphoramidite ligands had to be synthesized.

4.3.1.1 Synthesis of chiral phosphoramidite ligands

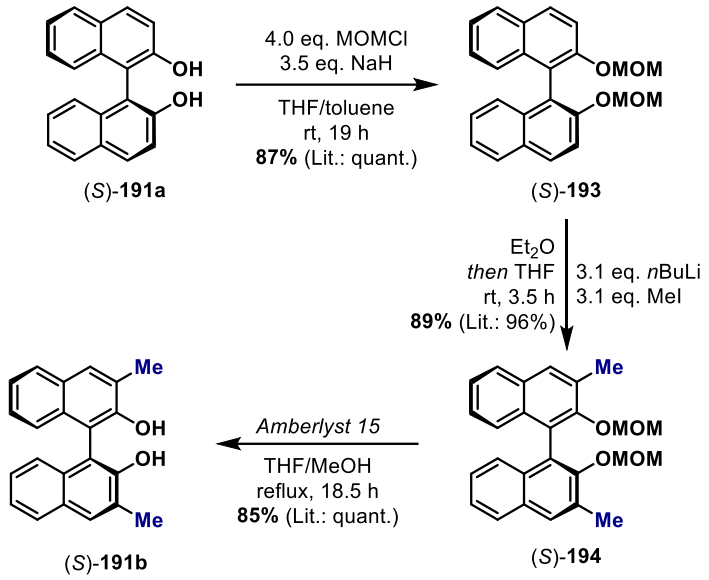
In addition to the standard *Feringa* ligand **L2**, asymmetric phosphoramidite ligands of type **L7**, which were developed in the *Schmalz* group,[117] should be synthesized from the BINOL motif **191** and amines of type **192** (Scheme 60). Based on the literature, it was estimated that the use of the (*S*)-ligands would provide the desired stereochemistry of the product (*R*)-**123**.[62, 68, 117]



*Scheme 60: Retrosynthetic analysis of phosphoramidite ligand **L7**.*

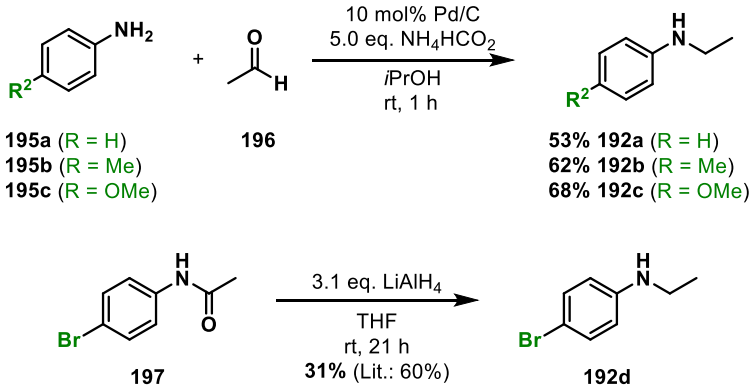
First, the BINOL motif **191** was established, for which the use of BINOL (**191a**) and dimethylated BINOL **191b** was considered. The dimethylated species **191b** could be obtained by

MOM-protection of the hydroxyl functionalities, ortholithiation and subsequent methylation and cleavage of the MOM group with the use of *Amberlyst 15* (Scheme 61). The synthetic sequence provided the desired BINOL **191b** in 66% overall yield.



*Scheme 61: Synthesis of dimethylated BINOL (S)-**191b**.*[118]

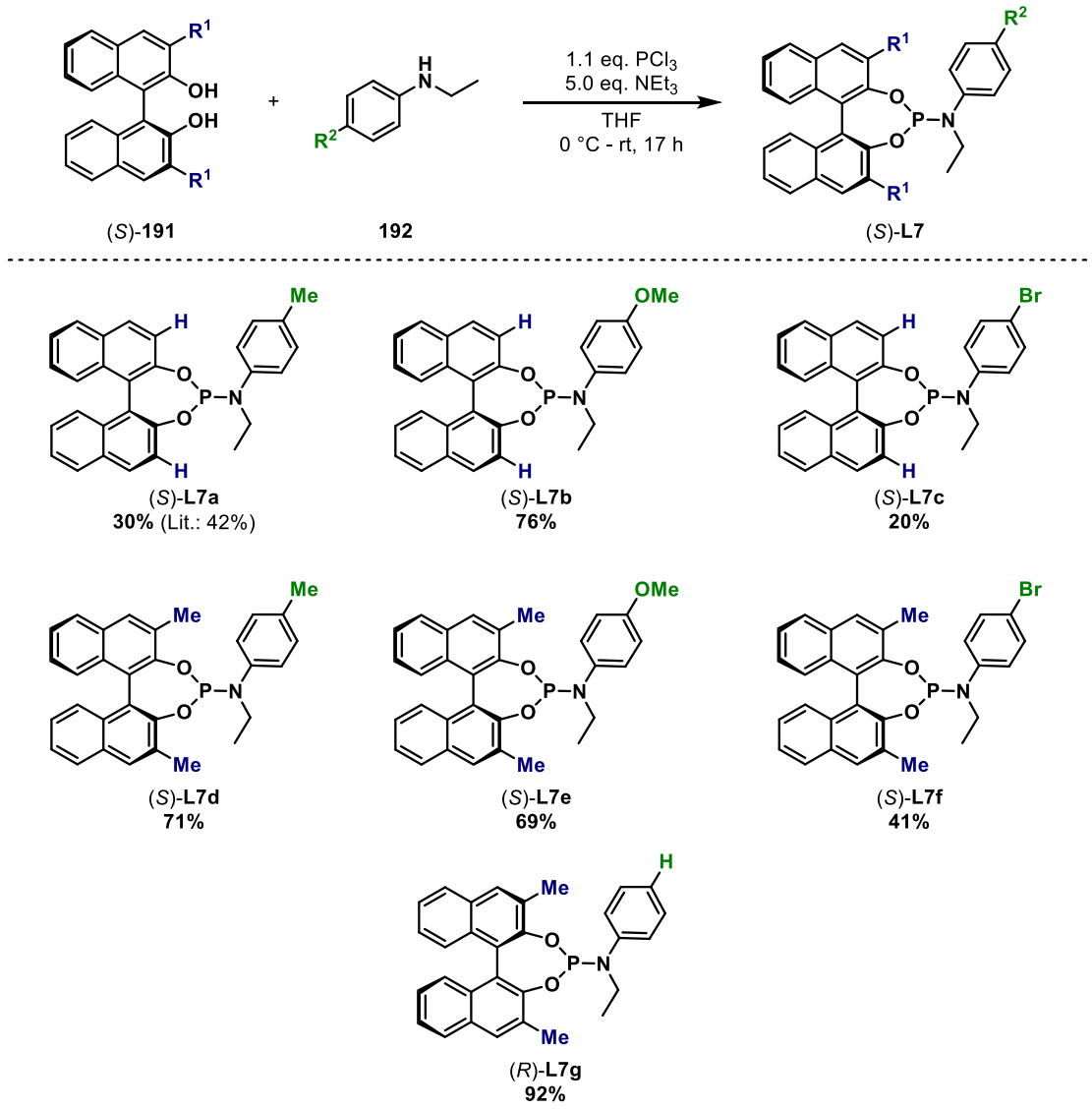
Moreover, a variety of amines of type **192** were generated (Scheme 62). The focus was on the implementation of different *para*-substituents in order to study the influence of their electronic effects.



*Scheme 62: Synthesis of para-substituted N-ethyl-aniline derivates of type **192**.*[119, 120]

Two procedures were applied for the synthesis of the substituted *N*-ethyl-aniline derivatives of type **192**. Following a procedure by *Byun et al.*,[119] a reductive monoalkylation was performed on aniline derivatives **195a-c** with the use of acetaldehyde (**196**) and a reducing system of Pd/C and ammonium formate. *N*-Ethyl-amines **192a-c** were obtained in moderate yields of 53-68%. Regarding bromo-substituted derivative **192d**, a procedure by *Al-Horani et al.* was applied,[120] in which the reduction of the commercially available amide **197** was directly subjected to reducing conditions. The desired target structure **192d** was provided in 31% yield using $LiAlH_4$.

With the desired BINOL and amine building blocks in hand, the corresponding phosphoramidite ligands **L7** were synthesized. The combination of dimethyl BINOL **191b** or BINOL (**191a**) and amines **192a-d**, based on the synthetic protocol established in the *Schmalz* group,[68, 117] provided seven ligands (Scheme 63).

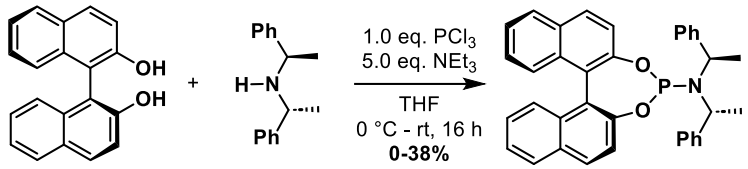


*Scheme 63: Overview of the synthesized phosphoramidite ligands of type **L7**. Ligand **L7g** was only synthesized as its (R)-enantiomer, the (S)-analogue was readily available in stock.*

It should be noted that the use of a fresh bottle of PCl_3 was crucial for a successful reaction outcome as the ligands of type **L7** are extremely labile towards acidic conditions. Since PCl_3 tends to release HCl over time, this can lead to decomposition of the established ligands. Moreover, a decomposition of the ligands was observed during purification by column chromatography in some cases, indicating that the used silica gel was too acidic. By using ultrapure silica gel, it was possible to increase the yield of most ligands.

In addition to the phosphoramidite ligand motifs developed by *Dominik Albat*,[117] the *Feringa* ligand (*S,S,S*)-**L2** was synthesized from (*S*)-BINOL (**191a**) and (*S,S*)-amine **198**. Following a standard procedure by *Alexakis and co-workers*,[121] the amine **198** was first reacted with PCl_3 and NEt_3, generating an activated amine species that further reacts with BINOL (**191a**) to the desired ligand (*S,S,S*)-**L2**. Unfortunately, the yield of 38% was rather unsatisfactory. Moreover, the synthesis was not always reproducible. In some experiments, a decreased yield of about 10% or even no product formation at all was obtained. This led to the assumption that the problems in reproducibility derived from the reagents and solvents used in the reaction (Table 16).

*Table 16: Overview of the regarded deviations from the standard conditions to increase the yield of Feringa ligand (S,S,S)-**L2**.*



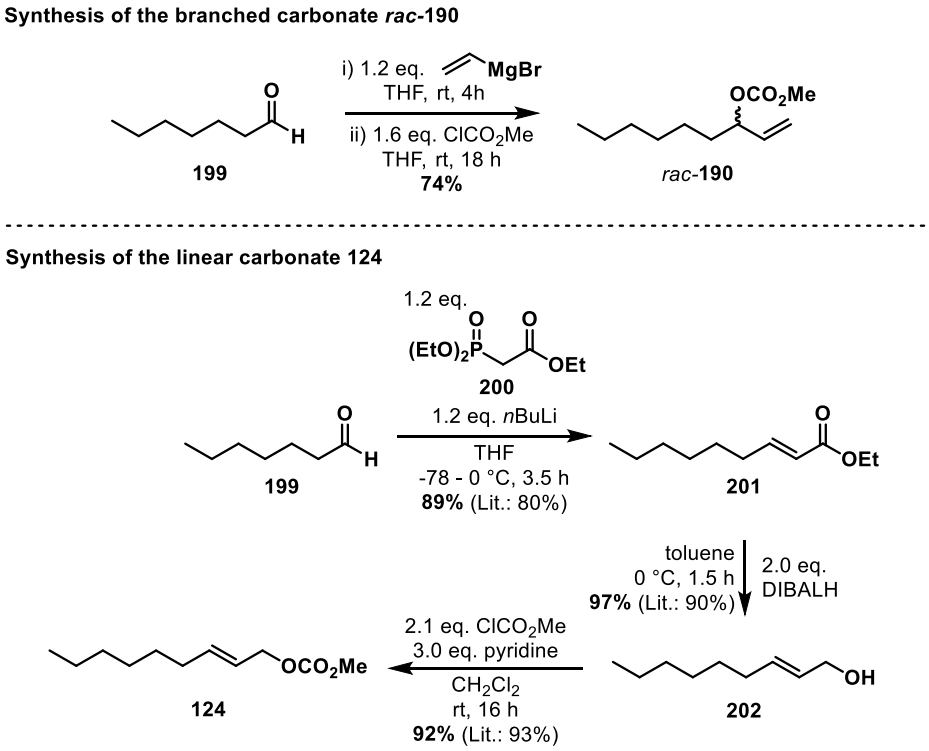
(*S*)-**191a** (*S,S*)-**198** (*S,S,S*)-**L2**

Entry	Deviation from standard conditions	Yield
1	New NEt_3	0%
2	New PCl_3	15%
3	New PCl_3	8%
4	New THF	0%
5	CH_2Cl_2	91%

Therefore, freshly purchased batches of NEt_3, PCl_3 and THF were used in the reaction. However, none of these reagents and solvents had a positive impact on the yield (Table 16, entry 1-4). Since it was reported in the literature that the *Feringa* ligand **L2** could also be synthesized in CH_2Cl_2,[122] the solvent was replaced (Table 16, entry 5). This led to an enhanced and reproducible yield of 91%, which underlines that the solvent has a major influence on the reaction.

4.3.1.2 Synthesis of suitable carbonates

In order to study the influence of the use of linear and branched carbonates on the enantioselectivity of the Ir-catalyzed allylic substitution, the branched carbonate *rac*-**190** and the linear analogue **124** were synthesized (Scheme 64).



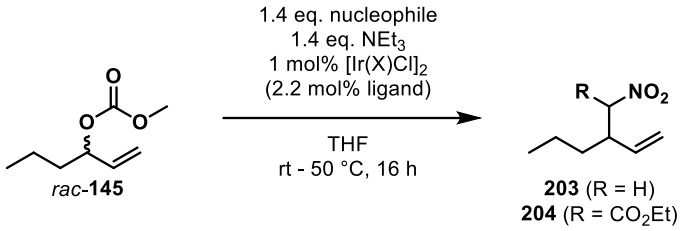
*Scheme 64: Synthesis of the branched and linear carbonates rac-**190** and **124**.*[72, 123]

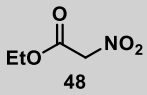
The racemic branched carbonate **190** was synthesized in a simple one-pot procedure starting from heptanal (**199**). Heptanal (**199**) was first reacted with vinyl magnesium bromide. The generated alcohol was trapped by methyl chloroformate to provide the desired carbonate *rac*-**190** in 74% yield. The corresponding linear carbonate **124** was synthesized *via* three steps from heptanal (**199**). Transformation to the olefin **201** was accomplished by reacting aldehyde **199** with phosphonoacetate **200** according to a *Horner-Wadsworth-Emmons* olefination. Subsequent ester reduction with DIBALH and reaction with methyl chloroformate delivered the desired carbonate **124** in a very good overall yield of 79%.[72, 123]

4.3.1.3 Ir-catalyzed allylic substitution

Prior to analysis of the catalysis with the use of the synthesized carbonates and ligands, standard reaction conditions for the allylic substitution were applied on a test system. Here, the simplified carbonate *rac*-**145** was tested. The experiments focussed on the use of possible nucleophiles for the transformation to the nitro compound. Initially, an attempt was made to use nitromethane directly as the nucleophile, which would provide the desired nitro compound in just one step. However, nitromethane was extremely reactive leading to an inseparable mixture of different products and decomposition products. The desired nitro compound **203** could not be identified in both experiments (Table 17, entry 1 and 2).

Table 17: Overview of the results for the Ir-catalyzed allylic substitution with regard to the nucleophile used.



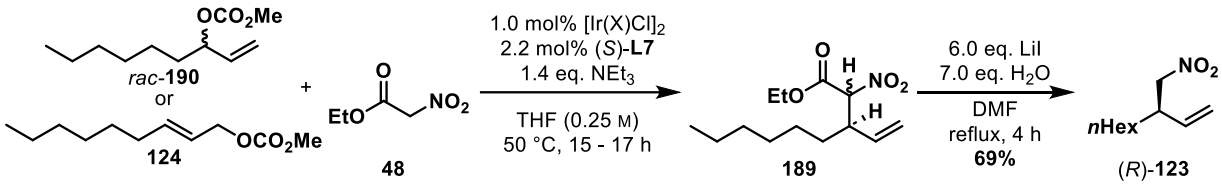
Entry	Nucleophile	$[Ir(X)Cl]_2$	Ligand	Concentration	Result
1	$MeNO_2$	cod	-	2.0 M	Product mixture, decomp.
2	$MeNO_2$	dbcot	(*S*)-**L7g**	0.25 M	Product mixture, decomp.
3	 **48**	cod	-	2.0 M	*rac*-**204**, >99%[a] (47%)[b]

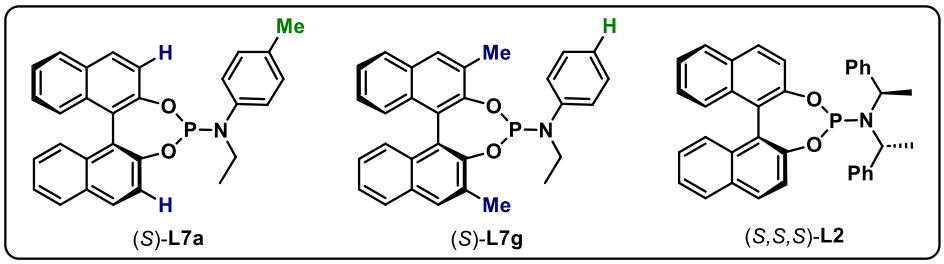
a: Yield determined by GC-MS; b: Isolated yield.

The same observations have also been reported by *Dahnz* and *Helmchen*, who regarded the Ir-catalyzed substitution towards compounds of type **203**.[62] The use of ethyl nitroacetate (**48**) as a nitromethane equivalent proved to be superior. In a test reaction with carbonate *rac*-**145**, full conversion of the starting material was observed by TLC and GC-MS, and 47% of aliphatic nitro compound **204** were isolated (Table 17, entry 3). The ester moiety can be easily removed by *Krapcho* decarboxylation.[62]

The Ir-catalyzed allylic amination was transferred to the synthesized carbonates *rac*-**190** and **124**. First, the phosphoramidites of type **L7** should be used in the synthesis of aliphatic nitro compound **123**, which would increase the substrate scope of this ligand class. Since the work by *Dominik Albat* has shown that the phosphoramidites **L7a** and **L7g** were the most efficient ligands for allylic aminations to date, the first experiments concentrated on the use of these two ligands. Furthermore, the influence of the Ir-precursor was studied (Table 18).

Table 18: Overview of the Ir-catalysis screening with regard to conversion, yield and enantiomeric excess.





Entry	Carbonate	$[Ir(X)Cl]_2$	Ligand	Conversion[a]	Yield of 189	*ee* of (*R*)-123[b]
1	*rac*-**190**	dbcot	**L7g**	>99%	68%	43%
2	*rac*-**190**	cod	**L7g**	65%[c]	35%	62%
3	*rac*-**190**	dbcot	**L7a**	>99%	54%	45%
4	*rac*-**190**	cod	**L7a**	>99%	61%	43%
5	*rac*-**190**	dbcot	**L2**	73%	44%	27%
6	**124**	cod	**L7a**	15%	0%	-

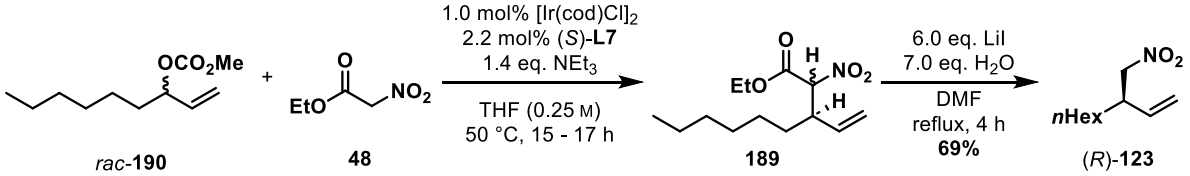
a: The conversion was determined by GC-MS; b: The enantiomeric excess was determined after *Krapcho* decarboxylation *via* chiral GC-MS; c: The reaction was run for three days.

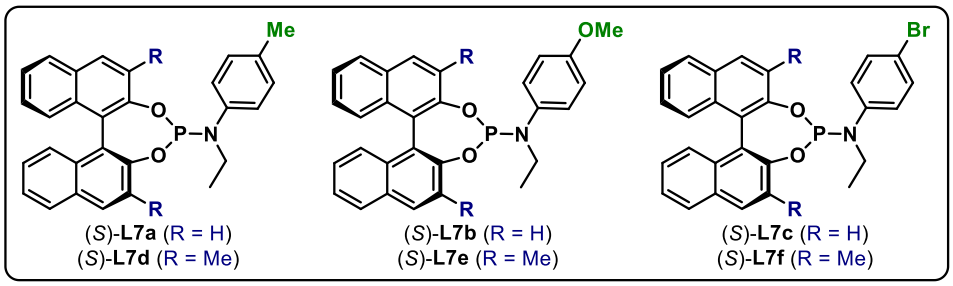
Using branched carbonate *rac*-**190**, $[Ir(dbcot)Cl]_2$ and chiral ligand (*S*)-**L7g**, a successful conversion to allylic substrate **189** was identified, isolating 68% of the desired product. Analysis of the enantiomeric excess after *Krapcho* decarboxylation revealed a value of 43%*ee* (Table 18, entry 1). By changing the Ir-complex precursor to $[Ir(cod)Cl]_2$, the enantiomeric excess could be increased to 62% (Table 18, entry 2). Repetition of the experiments with ligand (*S*)-**L7a** led to enantioselectivities of 45%*ee* and 43%*ee* for $[Ir(dbcot)Cl]_2$ and $[Ir(cod)Cl]_2$, respectively (Table 18, entry 3 and 4). Interestingly, the superior effect of using $[Ir(cod)Cl]_2$ in combination with (*S*)-**L7g** could not be confirmed in this trial. Since the best enantiomeric excess was achieved with **L7g**, it was assumed that the methyl-substituted BINOL motif has a positive influence on the enantioselectivity, which is possibly attributed to steric effects. However, further validation for this hypothesis was necessary. In addition to the asymmetric phosphoramidite ligands of type **L7**, the *Feringa* ligand **L2** was applied for test purposes in combination with $[Ir(dbcot)Cl]_2$. This catalytic system yielded the lowest enantiomeric excess of 27% (Table 18, entry 5). Furthermore, the reaction conditions regarded were transferred to linear carbonate **124**. In this experiment, only 15% conversion of the starting material was detected, the product **189** could not be isolated

(Table 18, entry 6). The outcome is in accordance with the reported data by *Dominik Albat*, who identified phosphoramidites of type **L7** to be superior ligands for branched electrophiles.[117]

For further analysis of the influence of the phosphoramidite ligands on the enantioselectivity of the allylic substitution, all synthesized ligands were screened (Table 19).

Table 19: Overview of the reaction outcome for the Ir-catalyzed allylic substitution with regard to the used phosphoramidite ligand.





Entry	Ligand	Conversion[a]	Yield[a]	Isolated yield	*ee* of (*R*)-123[b]
1	**L7a**	>99%	88%	61%	43%
2	**L7d**	>99%	73%	53%	70%
3	**L7b**	>99%	88%	50%	62%
4	**L7e**	>99%	97%	60%	39%
5	**L7c**	>99%	87%	60%	52%
6	**L7f**	>99%	86%	70%	59%

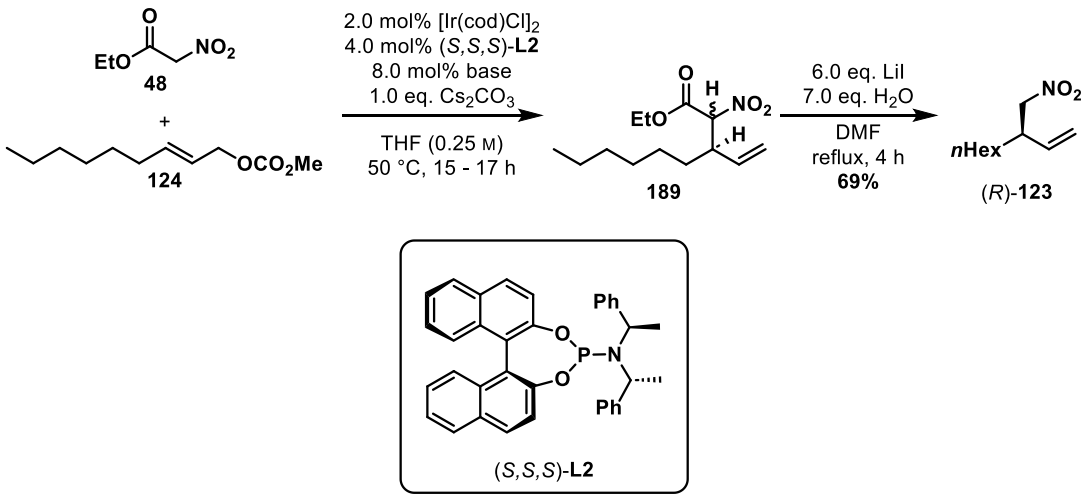
a: The conversion was determined by GC-MS; b: The enantiomeric excess was determined after *Krapcho* decarboxylation *via* chiral GC-MS.

The hypothesis that the phosphoramidites including the dimethylated BINOL motif **191b** are superior in comparison to their unsubstituted BINOL analogues could be validated for the ligand pairs **L7a/d** (Table 19, entry 1 and 2) and **L7c/f** (Table 19, entry 5 and 6). A significant increase of the enantiomeric excess was observed in particular for the *para*-toluidine-based ligand **L7d**, which reached 70%*ee*. Only for the anisidine-based ligands **L7b/e** an inverse behaviour was detected (Table 19, entry 3 and 4). Here, a higher enantioselectivity of 62%*ee* was observed for the unmethylated ligand **L7b**. Since the *para*-methoxy substituent bears the strongest electronic influence exhibiting a mesomeric effect in comparison to the methyl- and bromo-substituted systems considered, which have minor positive and negative inductive effects, the electronic effect seems to be greater than the steric effect in this case. This is supported by the observation for the methylated ligand **L7e**, for which a decrease in enantioselectivity to 39%*ee* was observed.

Steric and electronic effects compete with each other and work against each other, which leads to the diminishment. Thus, matching electronic and steric influence might increase the enantiomeric excess for the system. However, this would require a greater library of ligands to be screened.

Since the Ir-catalyzed allylic substitution with $[Ir(cod)Cl]_2$ and ligand (*S*)-**L7d** has so far been the best result with 70%*ee*, further approaches were analyzed to increase the enantioselectivity. Since *Dahnz* and *Helmchen* reported a similar allylic substitution with ethyl nitroacetate (**48**) in combination with linear carbonates and *Feringa*-type ligands (see Scheme 17),[62] their reaction conditions were transferred to linear carbonate **124** (Table 20).

Table 20: Overview of the reaction outcome of the Ir-catalyzed allylic substitution applying the reaction conditions developed by Dahnz and Helmchen.[62]



Entry	Base	Conversion[a]	Isolated yield	*ee* of (*R*)-123[b]
1	TBD	>99%	86%	95%
2	TBD	52%	Mixture of **124** and **189**	-
3	TBD	0%	-	-
4[c]	TBD	>99%	68%	4%
5	DBU	>99%	89%	98%

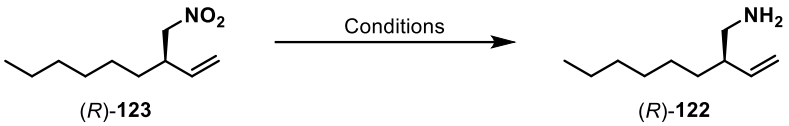
a: The conversion was determined by GC-MS; b: The enantiomeric excess was determined after *Krapcho* decarboxylation *via* chiral GC-MS; c: Instead of linear carbonate **124**, the branched analogue *rac*-**190** was used.

The use of $[Ir(cod)Cl]_2$ in combination with *Feringa* ligand (*S,S,S*)-**L2** and TBD provided the desired nitro compound (*R*)-**123** after *Krapcho* decarboxylation in an excellent enantioselectivity of 95%*ee* (Table 20, entry 1). This procedure was reproducible many times until the conversion significantly diminished after a couple of months, even though the same reaction conditions were used. The decrease in yield was caused by impurities of water in the used TBD, which led to decomposition of the Ir-complex and the phosphoramidite ligand (Table 20, entry 2 and 3). TBD was therefore replaced by DBU, which has the advantage that it can be easily purified by

distillation prior to its usage. In fact, DBU could even increase the enantiomeric excess to 98%*ee* (Table 20, entry 5). This result was perfectly reproducible and could be applied to an increased scale of 10 mmol. Furthermore, it can be stated that the application of the reaction conditions by *Dahnz* and *Helmchen*[62] on branched carbonate *rac*-**190** led to full conversion of the starting material, but afforded the product (*R*)-**123** in just 4%*ee* (Table 20, entry 4). This is in accordance with reports in the literature, which state that low enantioselectivities are obtained with the branched analogues due to the stereospecificity of the Ir-catalyzed allylic substitution.[66, 67] Especially in the case of the phosphoramidites of type **L7**, the conversion of branched racemic carbonates was reported to proceed in high enantioselectivity.[68, 117]

As the desired nitro compound (*R*)-**123** was generated in good yield and excellent enantiomeric excess, the reduction to aliphatic amine (*R*)-**122** was examined (Table 21).

*Table 21: Overview of the applied reaction conditions for the reduction of nitro compound **123**.*



(*R*)-**123** (*R*)-**122**

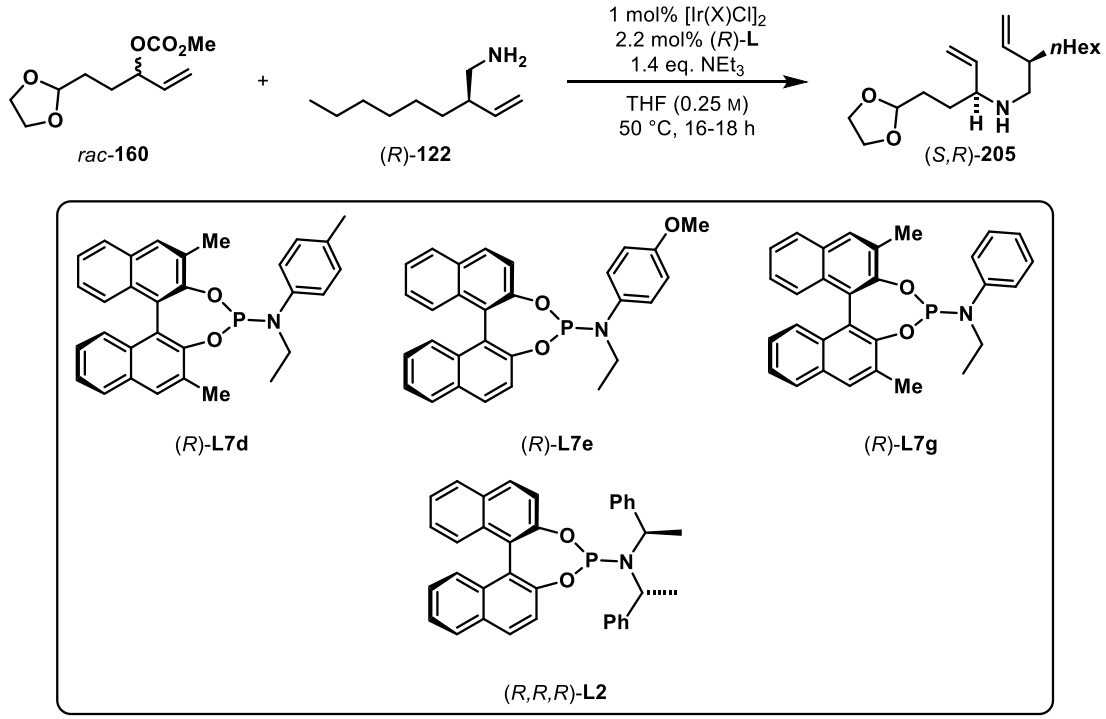
Entry	Reagent	Solvent	Conditions	Result
1	42 eq. Zn, 21 eq. conc. HCl	MeOH	rt, 30 min	decomposition
2	3.9 eq. $LiAlH_4$	Et_2O	0 °C-rt, 23 h	36% of (*R*)-**122**
3	20 mol% Pd/C, 2.5 eq. NH_4HCO_2	EtOH	reflux, 2 d	no conversion
4	30 eq. Zn, 40 eq. AcOH	*i*PrOH	rt, 2 h	97% of (*R*)-**122**

Initially, standard conditions for the reduction with the use of Zn and HCl were applied, but the conditions were too harsh and led to the decomposition of the starting material (Table 21, entry 1). $LiAlH_4$ was then used as a reducing agent, which afforded 36% of the desired amine (*R*)-**122** (Table 21, entry 2). The use of Pd/C and ammonium formate did not lead to any conversion of the starting material (Table 21, entry 3). Zn and AcOH were then used as a reducing system. This transformation was very successful and the desired amine (*R*)-**122** was obtained in 97% yield (Table 21, entry 4). In advantage, the reaction delivered the amine **122** in very good purity, further purification was not necessary.

4.3.2 Investigations on the Ir-catalyzed allylic amination

Subsequently, the next step in the forward synthesis, the Ir-catalyzed *N*-allylation, was examined with regard to the diastereoselectivity. Since the reaction conditions for the unalkylated test system have already been established (see Table 4), the same conditions were applied to racemic carbonate **160** and chiral amine (*R*)-**122**. Based on the previous screening on the Ir-catalyzed allylic substitution, the (*R*)-analogues of ligands **L7d** and **L7e**, which gave the best results, were synthesized and tested in the allylic amination. In addition, the standard phosphoramidite ligand **L7g** developed by *Dominik Albat*[117] and the *Feringa* ligand **L2** were used and the Ir-catalysis was investigated with special regard to the diastereomeric ratio (Table 22).

Table 22: Overview of the results of the Ir-catalyzed N-allylation with regard to the influence of the ligand and Ir-complex on the conversion, yield and diastereomeric ratio.

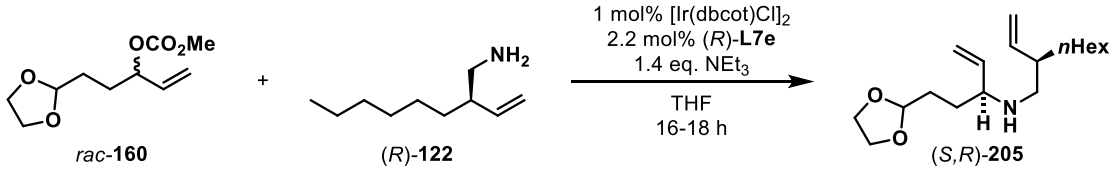


Entry	Ligand	$[Ir(X)Cl]_2$	Conversion[a]	Isolated yield[b]	*d.r.*[c]
1	**L7d**	cod	28%	29%	67:33
2	**L7d**	dbcot	88%	31%	74:26
3	**L7e**	cod	78%	34%	76:24
4	**L7e**	dbcot	34%	32%	95:5
5	**L7g**	cod	79%	15%	58:42
6	**L7g**	dbcot	81%	18%	65:35
7	**L2**	dbcot	47%	23%	70:30

a: The conversion was determined by GC-MS; b: The amine (*S,R*)-**205** was isolated as a diastereomeric mixture; c: The diastereomeric ratio was determined by NMR.

Overall, the results of the screening imply that $[Ir(dbcot)Cl]_2$ is superior to $[Ir(cod)Cl]_2$ for this transformation. Direct comparison of ligands **L7d**, **e** and **g** with cod or dbcot as co-ligands revealed that higher diastereomeric ratios were obtained for $[Ir(dbcot)Cl]_2$ (Table 22, entry 2, 4 and 6). This can be attributed to a higher steric and electronic impact of the dbcot-ligand. In most cases, the use of $[Ir(dbcot)Cl]_2$ led to a higher conversion of the starting material, however, an inverse behaviour was identified in combination with **L7e** (Table 22, entry 3 and 4). Here, only 34% conversion was observed with the dbcot co-ligand. Furthermore, ligands including a substituted aniline motif, **L7d** and **e**, delivered increased diastereoselectivity (Table 22, entry 2 and 4) in comparison to unsubstituted derivative **L7g** and *Feringa* ligand **L2** (Table 22, entry 6 and 7). Therefore, it can be hypothesized that the positive inductive and mesomeric effects of the methyl- and the methoxy-substituent have beneficial effects on the stereoselectivity that favour the formation of the desired diastereomer. In particular, an excellent diastereomeric ratio of 95:5 was detected with methoxy-substituted ligand **L7e** (Table 22, entry 4). But as the conversion was rather unsatisfactory, the reaction conditions were optimized in terms of concentration and temperature (Table 23).

*Table 23: Overview of the results of the Ir-catalyzed N-allylation with regard to the concentration of rac-**160** in THF and reaction temperature.*



Entry	Concentration	Temperature	Conversion[a]	Yield	*d.r.*[b]
1	0.25 M	50 °C	78%	24%	79:21
2[c]	0.25 M	50 °C	>99%	42%	85:15
3	0.25 M	70 °C	>99%	30%	68:32
4	0.10 M	70 °C	73%	28%	79:21
5	0.10 M	50 °C	60%	20%	91:9
6[d]	0.05 M	50 °C	59%	20%	92:8

a: The conversion was determined by GC-MS; b: The diastereomeric ratio was determined by NMR; c: The reaction was performed on a 0.8 mmol scale and stirred for 3 d; d: The reaction mixture was stirred for 2 d.

First, an attempt was made to reproduce the previously observed best reaction outcome (Table 22, entry 4). Unfortunately, the excellent diastereomeric ratio of 95:5 could not be repeated in the second try. Instead, a ratio of 79:21 was obtained together with a higher conversion of 78% (Table 23, entry 1). This result proved to be reproducible, indicating that a mistake in isolation or in the reaction procedure led to the former result. On a slightly larger scale and by increasing the reaction time, it was even possible to obtain reliably >99% conversion of the starting material and

a diastereomeric ratio of 85:15 (Table 23, entry 2). By increasing the temperature to 70 °C, the diastereomeric ratio diminished to 68:32. Due to the elevated temperature, it is likely that the allyl-iridium complex undergoes a faster *σ*-*π*-*σ* rearrangement prior to the nucleophilic attack decreasing the stereoselectivity of the reaction. By simultaneous decrease in concentration, the diastereoselectivity could be increased again to 79:21 (Table 23, entry 4). However, better results were obtained at 50 °C where a ratio of 91:8 was reached (Table 23, entry 5). Further dilution to 0.05 M only slightly increased the ratio to 92:8 (Table 23, entry 6). Although the diastereomeric ratios for low concentrations were better, the conversion significantly suffered, as no more than 60% conversion of the starting material could be reached at a reaction temperature of 50 °C. Therefore, the reaction conditions reported in Table 23, entry 2 (0.25 M, 50 °C), were mostly used.

In all experiments, the diastereomeric ratio could be analyzed based on NMR measurements, which is exemplarily shown in Figure 7.

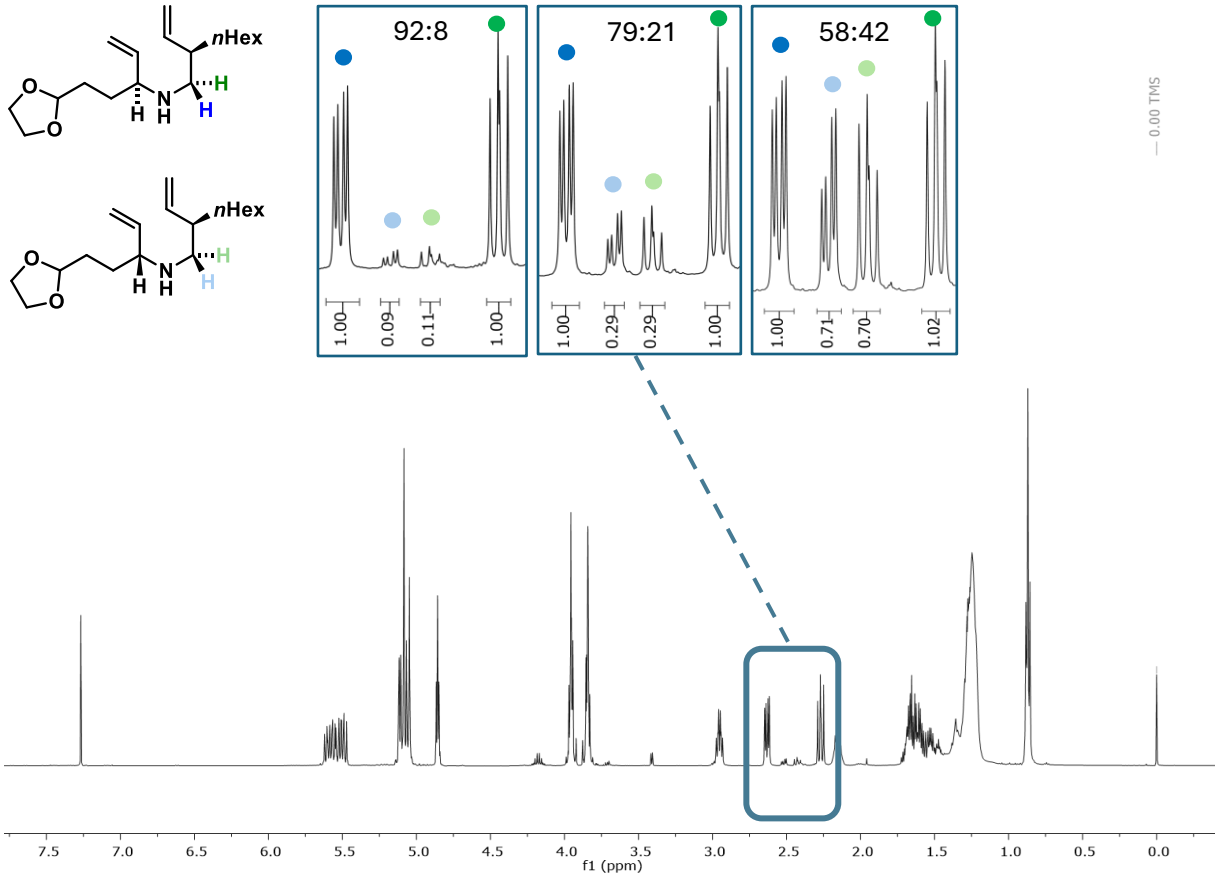


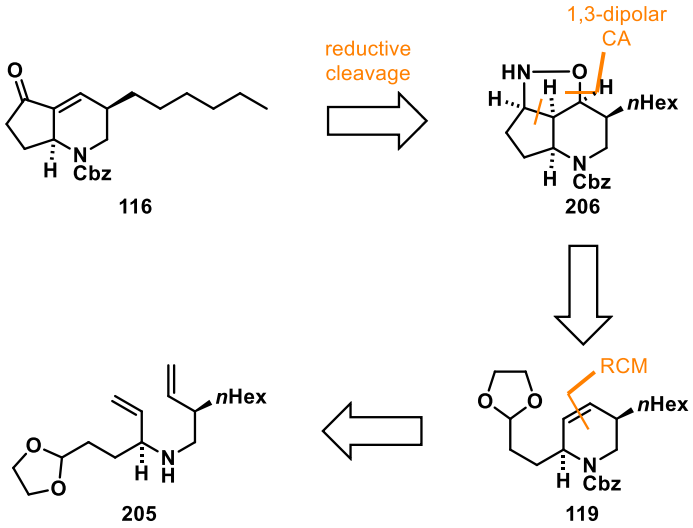
*Figure 7: ^{1}H NMR ($CDCl_3$, 500 MHz) of allylic amine **205** with regard to the diastereomeric ratio, which can be determined by the integration of the signals of the diastereotopic protons.*

The diastereotopic protons marked in Figure 7 can be split into four distinguished signals. Each proton can be attributed to a signal, one for the desired (*R,S*)-diastereomer, the other for the (*S,S*)-analogue. The ratio of the two diastereomers was determined reliably by integration of the signals.

With a reproducible and reliable method towards allylic amine **205** in hand, the next steps in the forwards synthesis were transferred to the camporidine system.

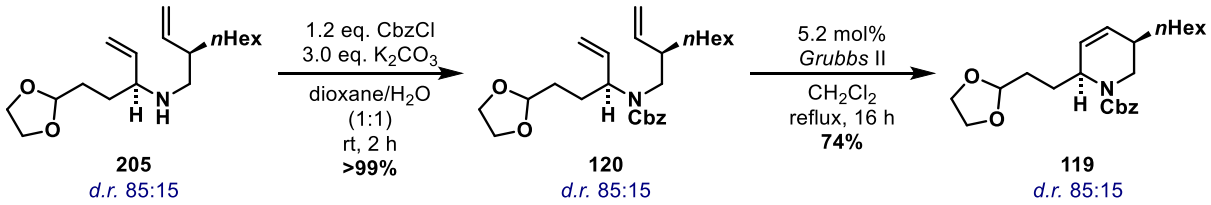
4.3.3 Synthesis towards the core structure of camporidine A

Since the forward synthesis worked well on the non-alkylated test system, the same steps should be applied on allylic amine **205** in order to establish the desired core motif **116** of camporidine A (Scheme 65).



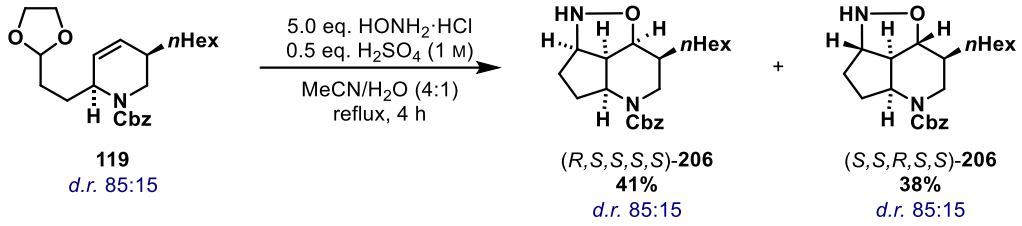
*Scheme 65: Retrosynthetic analysis of the camporidine A core motif **116**.*

First, the allylic amine **205** was Cbz-protected under standard conditions affording the protected amine **120** in quantitative yield (Scheme 66). Reacting the diolefin **120** with *Grubbs* II catalyst delivered the desired aza-cyclohexene motif **119** in a yield of 74%. It should be noted that the reactions were performed with the diastereomeric mixture of **205**. Upon workup of the substrate **119**, it was not possible to separate the isomers.



*Scheme 66: Synthesis of protected amine **119** from allylic amine **205** via Cbz-protection and RCM.*

The 1,3-dipolar cycloaddition procedure was then carried out. The reaction of substrate **119** with hydroxylamine hydrochloride under acidic conditions gave an overall yield of 79% for the desired isoxazolidine **206** (Scheme 67).



119
d.r. 85:15

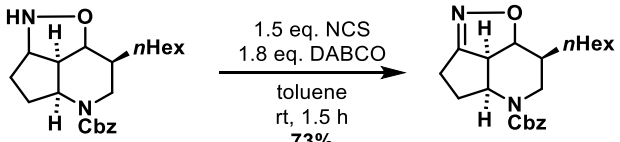
(*R,S,S,S,S*)-**206**
41%
d.r. 85:15

(*S,S,R,S,S*)-**206**
38%
d.r. 85:15

*Scheme 67: Synthesis of isoxazolidine **206**. The determined diastereomeric ratios refer to the established stereocentre in the Ir-catalyzed allylic amination.*

In this reaction step, it was possible to isolate two distinct diastereomers. Based on ^{1}H-NOE correlations, the isolated diastereomers were identified as the (*R,S,S,S,S*)- and the (*S,S,R,S,S*)-analogues of **206**, indicating that the 1,3-dipolar cycloaddition occurred from both faces of the molecule in an almost equal ratio. Analysis of the diastereomers *via* GC-MS revealed that both consisted of a diastereomeric mixture in a ratio of 85:15. This is in accordance with the determined diastereomeric ratio for the established stereocenter in allylic amine **205** by Ir-catalyzed allylic amination. Unfortunately, it was not possible to separate the diastereomers any further.

Since the stereochemistry of the isoxazolidine motif was not relevant for the upcoming reaction steps, as the functional groups were intended to be removed, both diastereomers of **206** were reacted in the next step. The isoxazolidine **206** was oxidized using NCS and DABCO to obtain isoxazoline **117** in 73% yield (Scheme 68).

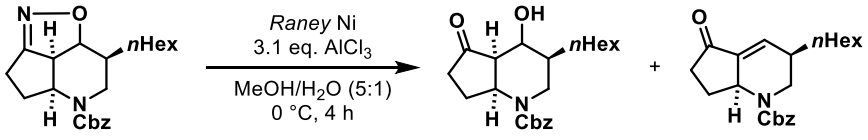


206
d.r. 85:15

117
d.r. 85:15

*Scheme 68: Synthesis of isoxazoline **117**.*

Subsequently, the isoxazoline **117** was reacted *via* a reductive cleavage with the use of *Raney* Ni and $AlCl_3$ as a supporting *Lewis* acid. As for the test system (see Table 9), these conditions afforded a mixture of the desired enone **116** and the corresponding *β*-hydroxyketone **207** in a moderate overall yield (Scheme 69).



117

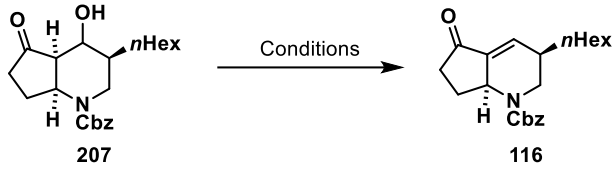
207
54%

116
11%

*Scheme 69: Reductive cleavage of isoxazoline **117**.*

The moderate yield of 54% for the alcohol **207** can be attributed to the difficult purification of the product. During column chromatography, product loss of **207** was partly observed. The isolated product **207** was analyzed by NMR and GC-MS, but a reliable insight on the diastereomeric ratio of the established stereocentre of the hydroxyl functionality could not be provided. Subsequently, *β*-hydroxyketone **207** was subjected to the previously applied elimination conditions for test system **167** (see Table 10). Surprisingly, the reaction conditions did not work as expected, as only minor amounts of the elimination product **116** were formed. A ratio of starting material **207** to enone **116** of 77:23 was determined based on NMR measurements (Table 24, entry 1). Thus, other reaction conditions were regarded.

*Table 24: Overview of the regarded reaction conditions for the elimination towards enone **116**.*



207 **116**

Entry	Reagents	Solvent	Conditions	Ratio 207:116[a]
1	1.1 eq. Tf_2O, 3.5 eq. pyridine	CH_2Cl_2	0 °C – rt, 22 h	77:23
2	2.6 eq. $HCl_{(aq.)}$ (1 M)	THF	rt – 60 °C, 6.5 h	91:9
3	2.0 eq. *Burgess'* reagent	THF	rt – 60 °C, 25 h	100:0
4	70 eq. $SOCl_2$	pyridine	0 °C - rt, 2.5 h	n.d., decomposition, traces of **116**
5	1.1 eq. Tf_2O, 3.5 eq. pyridine	CH_2Cl_2	35 °C, 22 h	n.d., 81%[b] of **116**

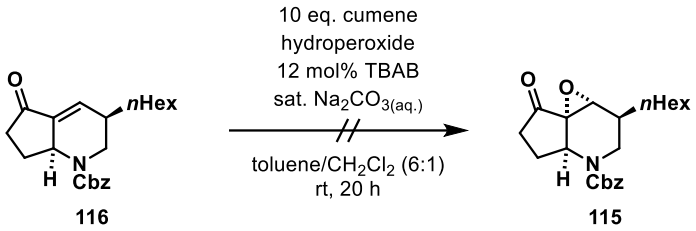
a: The ratio was determined by NMR; b: Isolated yield.

An elimination under acidic conditions was then attempted (Table 24, entry 2). Even when heated to 60 °C, no significant conversion of the starting material could be detected. NMR analysis illustrated that a ratio of 91:9 was obtained. Furthermore, substrate **207** was reacted with *Burgess'* reagent which depicts a mild dehydration reagent (Table 24, entry 3). However, no conversion was observed and only starting material was recovered from the reaction. It should be noted that the *Burgess'* reagent is used for *syn*-eliminations, which would imply that the *β*-hydroxyketone **207** would only partially react depending on the stereochemistry of the hydroxyl functionality. The reaction conditions were examined at a time where the exact stereochemistry of the isoxazolidine **206** and thus the stereochemistry of *β*-hydroxyketone **207** had not yet been identified. Since the previous approaches had not worked, it was suspected that the *syn*-arrangement of the hydroxyl group and the relevant hydrogen might be the reason. Moreover, a reaction of **207** with $SOCl_2$ in pyridine was tested (Table 24, entry 4). These conditions seemed to be too harsh for the system under consideration as mostly decomposition of the starting material and only traces of the

product **116** were detected after 2.5 hours reaction time. As the initial conditions still provided the most promising results, they were re-investigated (Table 24, entry 5). This time, the reaction mixture was heated to 35 °C, which according to TLC led to full conversion of the starting material, and 81% of the desired elimination product were isolated. In contrast to the unalkylated test system **168**, none of the *β*-hydroxyketone **207** was reisolated. This indicates that the hexyl side chain has a positive influence on the elimination towards substrate **116**, which marks the sterically less hindered product. Thus, the *syn*- or *anti*-arrangement of the hydroxyl group has no or only minor influence on the elimination step. It must be noted that the diastereomeric ratio of **116** could not be determined by GC-MS, nor by NMR due to a mixture of diastereomers and rotamers that could not be distinguished.

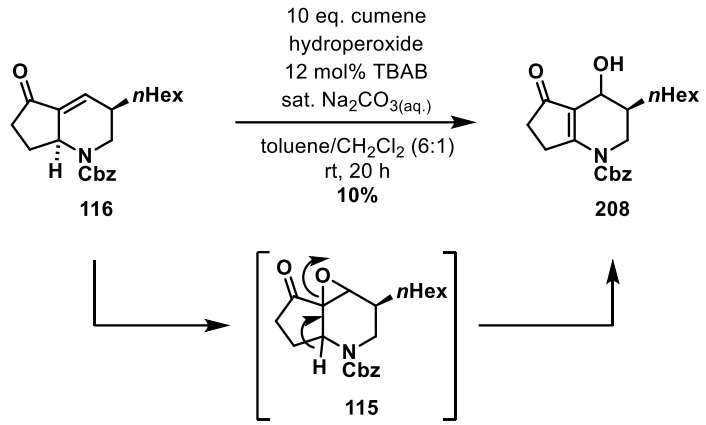
4.3.4 Functionalization of the core structure

With the core motif **116** of camporidine A (**11**) in hand, the functionalizations of the central structure should be examined. Therefore, the substrate **116** was subjected to epoxidation conditions using the previously established procedure (Scheme 70).



*Scheme 70: Epoxidation of enone **116**.*

Contrary to the expectations, the reaction did not deliver the desired epoxide **115**, although complete conversion of the starting material was indicated. Further examinations and workup of the crude product revealed mainly decomposition products along with one isolated substrate. According to the analytical data, the isolated product was identified as enaminone **208** (Scheme 71).



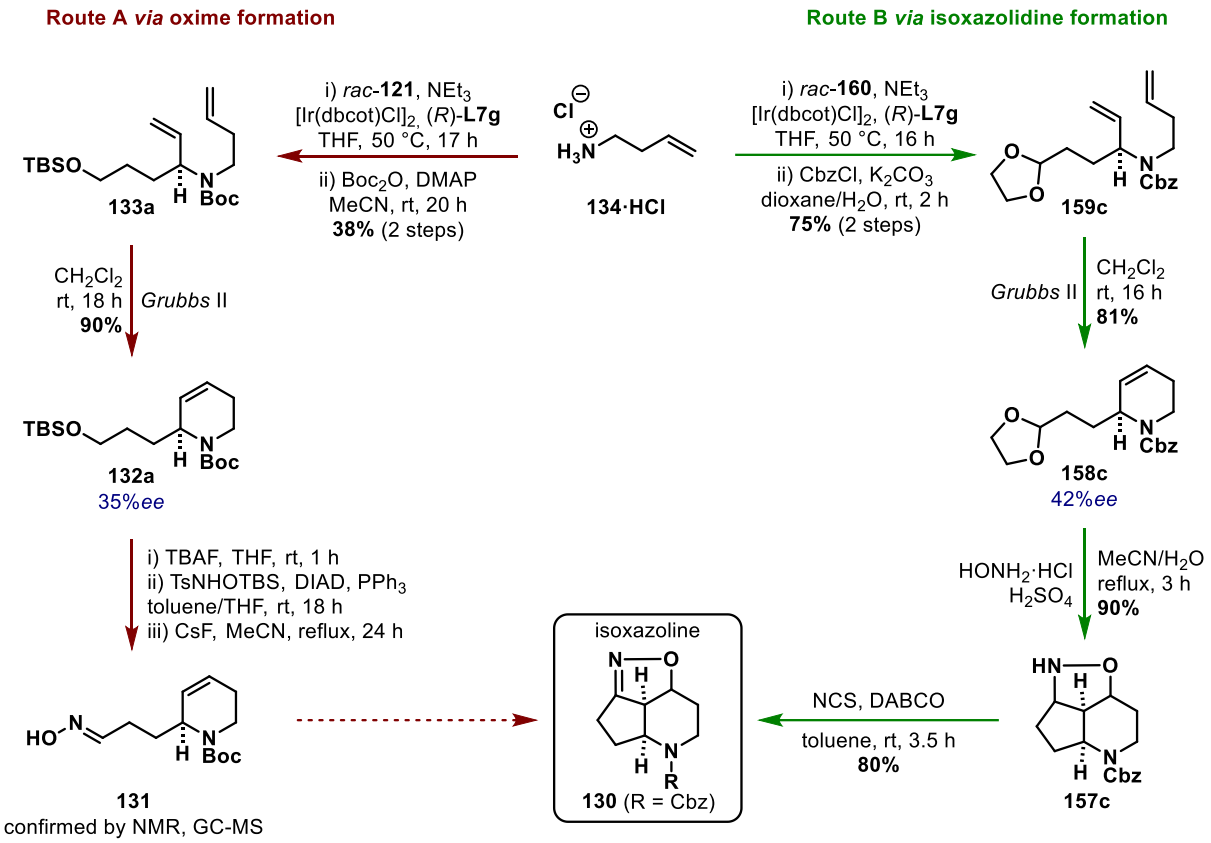
*Scheme 71: Synthesis of enaminone **208** via epoxide formation.*

It is assumed that the formation of the product **208** proceeds *via* the generation of the desired epoxide **115**. However, the substrate directly underwent epoxide opening by formation of the double bond to obtain enaminone **208**, indicating that epoxide **115** is rather instable. Unfortunately, the stereochemistry of the final product **208** remained unclear as only minor amounts were isolated. Due to the instability of the epoxide, most of the material decomposed. Since the epoxide could be isolated in very good yields for the test system **168** without any further reaction or decomposition being observed, it is assumed that the alkyl chain has a stronger impact on the ring strain than expected. The formation of the epoxide appears to lead to a strained system that tends to form the more stable product **208**, including an enaminone motif that is highly stabilized by delocalization of π-electrons.

Since the epoxidation procedure did not afford the desired target structure **115**, further functionalizations were disregarded. Additional evaluation would be necessary in order to find suitable reaction conditions that would provide the target motifs in the total synthesis of camporidine A (**11**). Still, the studied approach illustrates a promising strategy in the stereoselective synthesis of [4.3.0] piperidine alkaloids with remaining challenges in the final functionalization towards camporidine A (**11**).

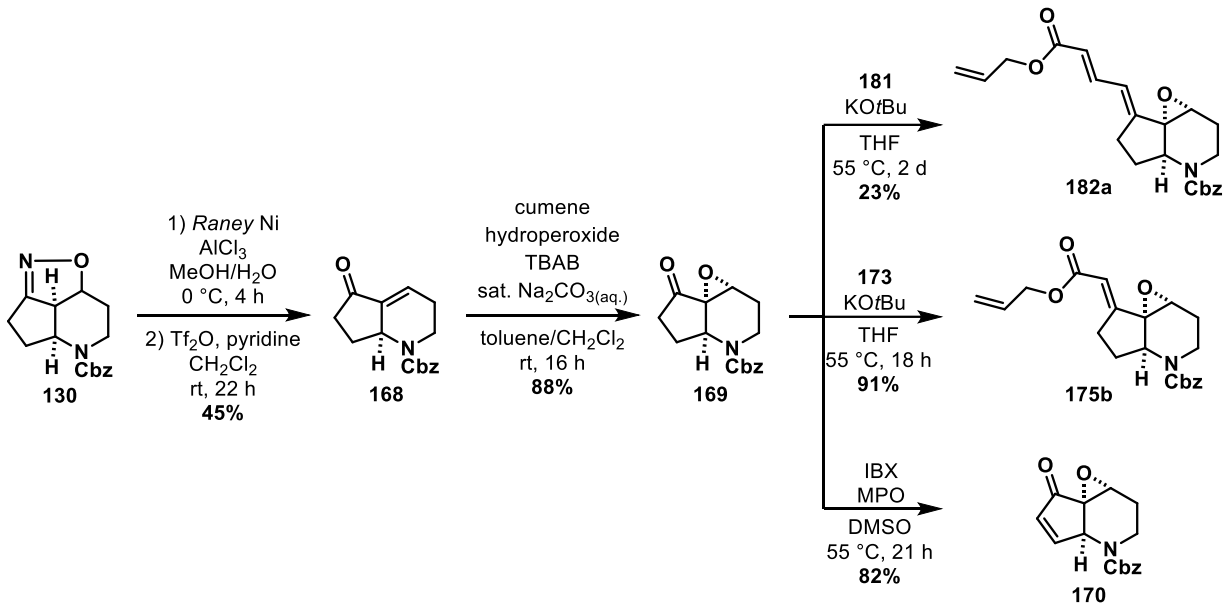
5 Summary and outlook

The synthetic strategy discussed provided a convenient and promising approach towards the enone core motif **116** of camporidine A (**11**) including several challenging key transformations. By first regarding an unalkylated test system, two different strategies in the establishment of the isoxazoline motif were developed (Scheme 72).



*Scheme 72: Overview of the regarded synthetic routes towards isoxazoline **130**.*

First, a synthetic approach *via* the formation of oxime **131** was tested. Unfortunately, the isolation of pure oxime **131** was challenging. Therefore, further reaction steps towards the isoxazoline motif were not pursued, as the second regarded synthetic route was more successful. Here, it was possible to generate the aza-cyclohexene motif **158c** in three steps in 61% yield and in an enantiomeric excess of 42%. Further improvements might be possible by examining the reaction conditions of the Ir-catalyzed *N*-allylation with regard to the ligand system used, reaction temperature and concentration. Followed by the key transformation, which includes the removal of the acetyl group under acidic conditions, condensation with hydroxylamine and 1,3-dipolar cycloaddition of the formed oxime, and subsequent oxidation, the isoxazoline **130** was provided in five steps. By reductive cleavage and subsequent elimination of the *β*-hydroxyketone **167**, it was possible to generate the enone core motif **168** for the test system (Scheme 73).

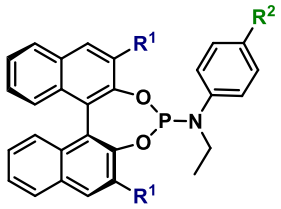


*Scheme 73: Synthesis of core motif **168** and accomplished functionalizations.*

With key structure **168** in hand, several functionalizations were regarded. First, the compound **168** was successfully epoxidized to give **169**. Tests on the *Wittig* olefination revealed that only the allyl-protected ester yielded the expected products **182a** and **175b**, respectively. However, the removal of the allyl group could not be accomplished. By screening a greater variety of phosphonium bromides with other protection groups for the carboxylic acid, it might be possible to simplify the cleavage of the ester and transfer the olefination conditions to epoxy-enone **170**, which was obtained from **169** by IBX/4-methyl-pyridine-*N*-oxide (MPO) oxidation. Since the allyl ester was the only successfully generated olefin, it might be interesting to study a greater variety of carboxylic ester analogues, e.g. the benzyl protected ester. Moreover, silyl esters or the 1,1-dimethylallyl analogue of **181** could be interesting to test. The exchange of the phosphonium bromide could lead in particular for the elongated system **182a** to an increased yield. However, the deprotection of the carboxylic ester would remain the major challenge, as most esters, e.g. allyl esters and benzyl esters, require hydrolysis conditions that previously seemed to be unsuitable.

In addition to the challenges in the late stage of the synthesis, the reaction sequence was transferred to the real system of camporidine A (**11**). To synthesize the required chiral amine (*R*)-**122**, several phosphoramidite ligands were generated and tested in the asymmetric Ir-catalyzed allylation (Table 25). Seven asymmetric phosphoramidite ligands of type **L7** were synthesized, of which **L7b**,**c**,**e** and **f** were literature unknown.

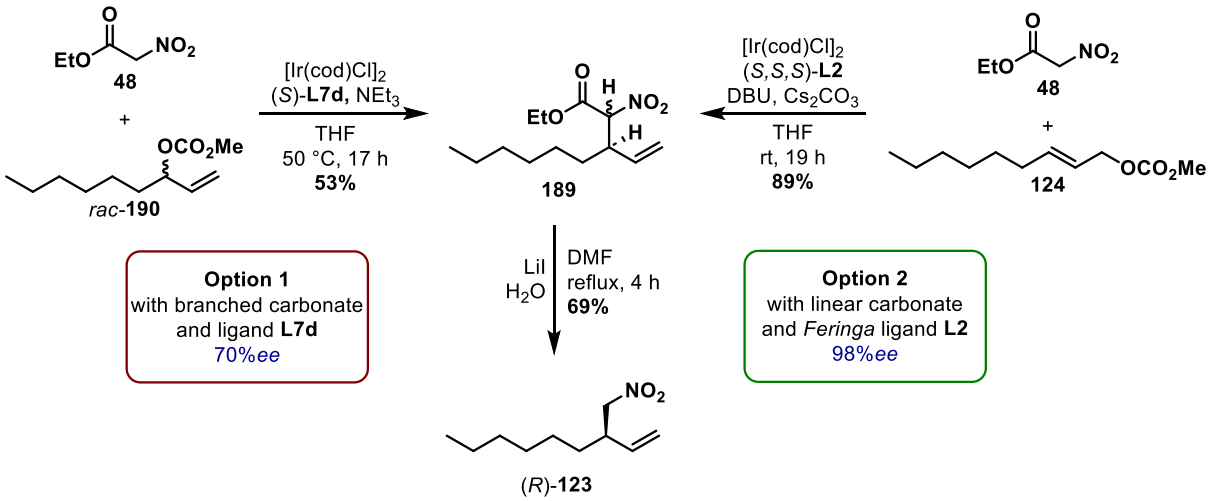
*Table 25: Overview of the synthesized phosphoramidite ligands of type **L7**.*



(*S*)-**L7**

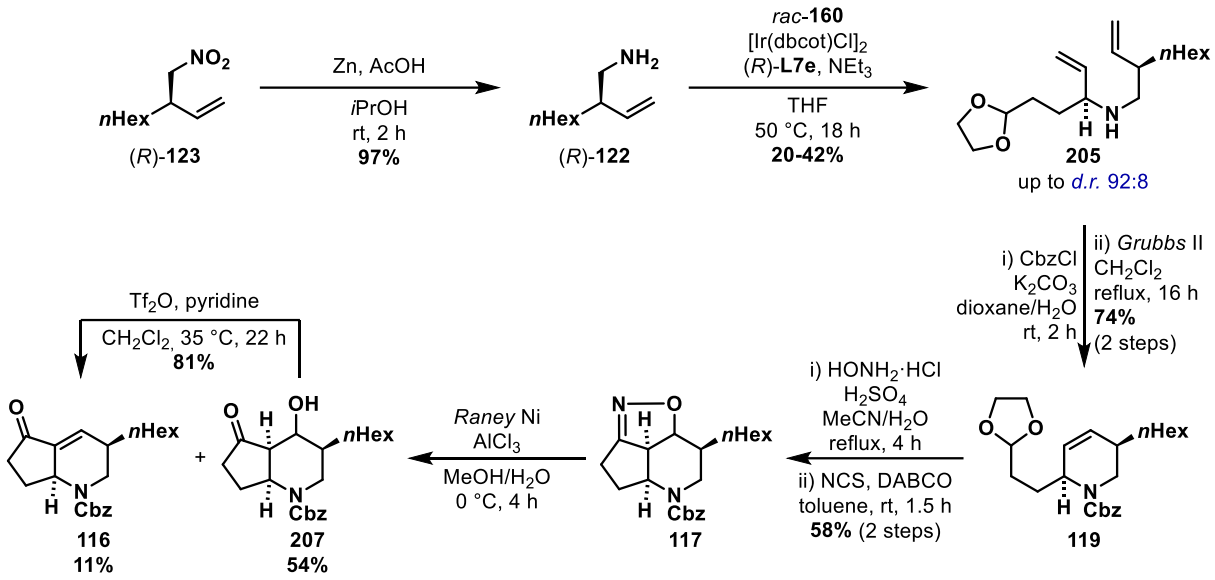
L7	R^1	R^2	L7	R^1	R^2
L7a	H	Me	**L7d**	Me	Me
L7b	H	OMe	**L7e**	Me	OMe
L7c	H	Br	**L7f**	Me	Br
			L7g	Me	H

The phosphoramidite ligands were subjected to the Ir-catalyzed allylic substitution. Here, the branched and the linear carbonates *rac*-**190** and **124** were both reacted with ethyl nitroacetate (**48**) as a suitable nitromethane equivalent. The two reactions provided the desired product **189**, which could be further transformed to nitro compound (*R*)-**123** by *Krapcho* decarboxylation (Scheme 74)**.** These examinations revealed that the use of the linear carbonate **124** in combination with $[Ir(cod)Cl]_2$ and *Feringa* ligand **L2** was superior, as the enantiomeric excess could be optimized to 98%.



*Scheme 74: Overview of the best results for the asymmetric Ir-catalyzed allylic substitution with branched carbonate rac-**190** and linear carbonate **124**.*

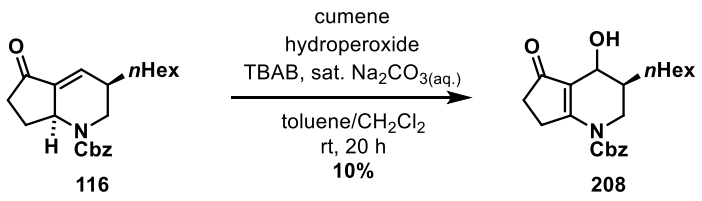
By investigating suitable conditions for the reduction of nitro compound (*R*)-**123**, the desired amine (*R*)-**122** was obtained, which paved the way for the upcoming reaction steps towards camporidine A (**11**, Scheme 75).



*Scheme 75: Accomplished forward synthesis towards core motif **116** in the total synthesis of camporidine A (**11**).*

A special emphasis was drawn to the stereoselective Ir-catalyzed allylation of amine (*R*)-**122** to the diolefin **205**. By applying [Ir(dbcot)Cl]$_2$ in combination with ligand (*R*)-**L7e** and optimization of the reaction conditions, it was possible to obtain the targeted product **205** in a diastereomeric ratio of up to 92:8. After Cbz protection, ring closing metathesis, 1,3-dipolar cycloaddition and oxidation, the isoxazoline key intermediate **117** was successfully obtained. Reductive cleavage of the *N-O* bond, hydrolysis and subsequent elimination provided the enone **116** in ten steps and an overall yield of 5.9%. As for the test system, direct Cbz-protection of the crude amine **205** could even increase the yield. In addition, the reductive cleavage step, which is linked to a significant loss of product due to the difficult purification of *β*-hydroxyketone **207**, leaves space for further optimizations.

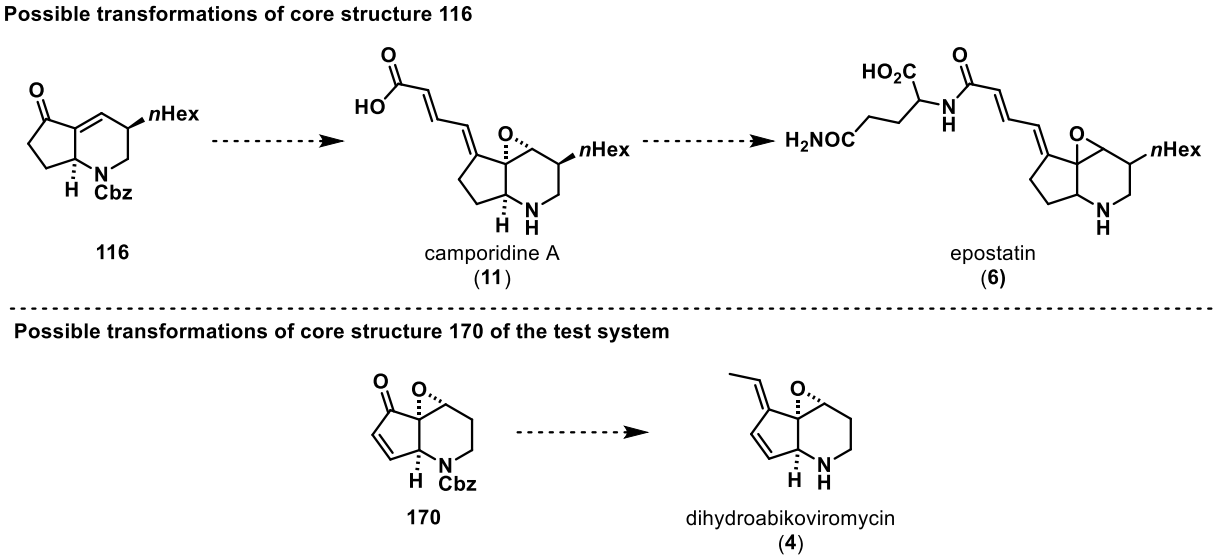
First experiments aiming at the further functionalizations of **116** under the established epoxidation conditions were not successful and resulted in the formation of enaminone **208** *via* a hydrogen elimination and subsequent epoxide opening (Scheme 76).



*Scheme 76: Result of the attempted epoxidation of enone **116**.*

Since the epoxidation on enone **116** did not work under the established conditions, further methodologies towards the target molecule camporidine A (**11**) remain an interesting challenge for future investigations.

Although the total synthesis of camporidine A (**11**) has not been accomplished, the investigations led to a reliable synthesis of the enone core motif **116** in a diastereoselective fashion. Key transformations were the Ir-catalyzed allylic substitutions, ring closing metathesis and the 1,3-dipolar cycloaddition of a nitrone intermediate to build up the bicyclic core structure. With some optimizations and reinvestigations, it would still be possible to generate camporidine A (**11**) according to this approach, which could be used to further elucidate the bioactivity of the natural product and related analogues. Apart from certain challenges in the functionalization, our synthetic approach provides a convenient strategy in the synthesis of [4.3.0] piperidine alkaloid motifs. The approach could not only provide access to camporidine A (**11**), but also to epostatin (**6**) or, as far as the test system is concerned, to dihydroabikoviromycin (**4**) to which a synthetic access has not been published yet (Scheme 77).



*Scheme 77: Overview of [4.3.0] piperidine alkaloids that could be derived from the synthesized core motif **116** and the functionalized test system **170**.*

Part 2: Synthesis of novel opines

6 Theoretical background

6.1 The compound class of opines

Substances, which are characterized by the linkage of two amino acids *via* a common nitrogen atom, are classified as opines.[124] These naturally occurring compounds represent a subclass of peptides that are found in a variety of organisms.[124, 125] The name “opine” is derived from the first isolated compound D(+)-octopine (**209**), an *N*-(carboxyalkyl)-amino acid isolated from the common octopus (*octopus vulgaris*).[126] It is formed by condensation and subsequent reductive amination of pyruvate and L-arginine with the help of specific NADP(H)-dehydrogenases.[124] Today, many other condensation compounds of pyruvate and different amino acids have been identified, e.g. strombine (**210**)[127], alanopine (**211**)[127], *β*-alanopine (**212**)[128] and seropine (**213**)[124]. In addition to the pyruvate condensation products, a second class of opines derived from *α*-ketoglutarate was discovered.[124] Here, the first example of this opine subclass was nopaline (**214**), which was found in the cactus *opuntia vulgaris*.[129] Other prominent examples are cucumopine (**215**)[130] and succinamopine[131] (**216**, Figure 8).

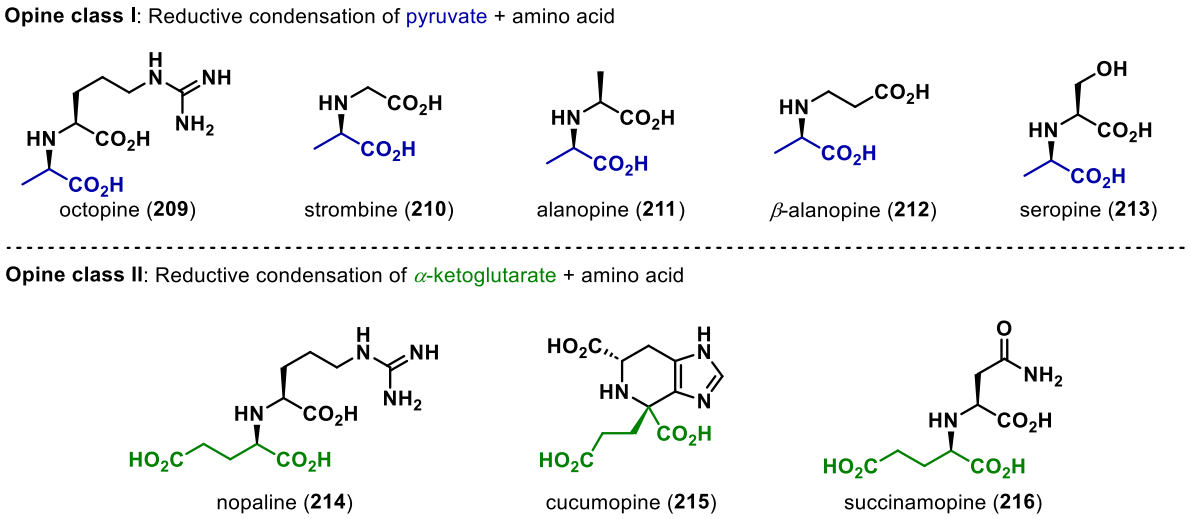


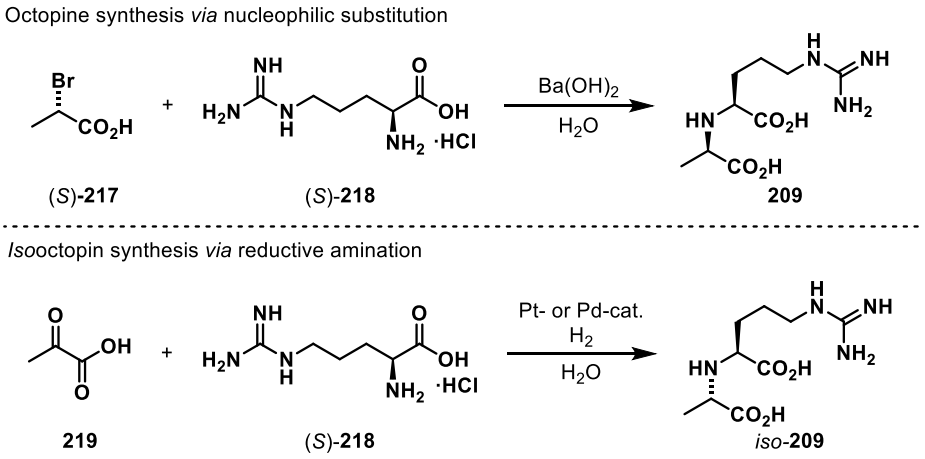
Figure 8: Overview of selected opines which can be divided into class I and II.

In many cases, the appearance of opine motifs in plants is linked to proliferative plant diseases, e.g. crown gall and hairy root, indicating a parasitic infestation by *agrobacteria tumefaciens* and *agrobacteria rhizogenes*.[125] These bacteria cause the expression of T-DNA genes by transferring plasmid fragments into the plant cell and integrating them into its DNA, which leads to the development of diseases. In addition, the expressed T-DNA genes cause the production of opines that serve as nutrients for the *agrobacteria*, as the plant is not able to metabolize those uncommon substrates.[124]

Furthermore, opines were found as metabolites in the gram-negative bacteria *straphylococcus aureus* and *pseudomonas aeruginosa*.[132-134] These bacteria make use of opines as metallophores for the transport of transition metals.[132] This strategy helps the bacteria to survive under metal scarce conditions as transition metals are crucial micronutrients.[135] Since the metallophores serve as means of transport to overcome the permeability barrier of outer membranes, the exploitation of the mechanisms might be interesting for new antibiotic therapies similar to the "Trojan horse" strategy.[135, 136] Thus, opines do not only depict interesting structural motifs that are versatile metabolites in a variety of organisms, but they are also compounds of interest in the development of future therapeutic strategies.

6.1.1 Synthesis of opines

As octopine (**209**) was the first opine to be discovered, several research groups investigated the synthesis of the uncommon compound to provide more insight on the structural elucidation and chemical and physical properties. In 1937, *Akashi* reported the first synthesis of octopine (**209**) from arginine (**218**) and *α*-bromopropionic acid (**217**) under basic conditions (Scheme 78).[137] The synthesis was further optimized by *Herbst* and *Swart*[138] and later by the research group of *Greenstein*, who reported that a mole ratio of L-arginin:*α*-bromopropionic acid:$Ba(OH)_2$ of 1:2:4 afforded the best results with regard to conversion.[139]

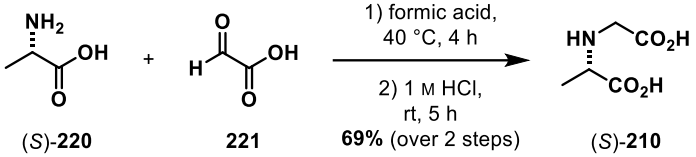


Scheme 78: Synthetic strategies towards octopine and its diastereomer iso-octopin.

However, the synthesis of the desired isomer **209** can only be achieved by applying enantiopure (*S*)-**217** and L-arginine (**218**). Otherwise, a mixture of diastereomers is obtained, which can be separated as their picrate and flavinate derivatives.[138, 139] A second strategy was published in 1939 by *Knoop* and *Martius* who reported the conversion of pyruvic acid (**219**) and arginine carbonate using PtO_2 and H_2.[140] Originally, *Knoop* and *Martius* stated that the reductive amination approach

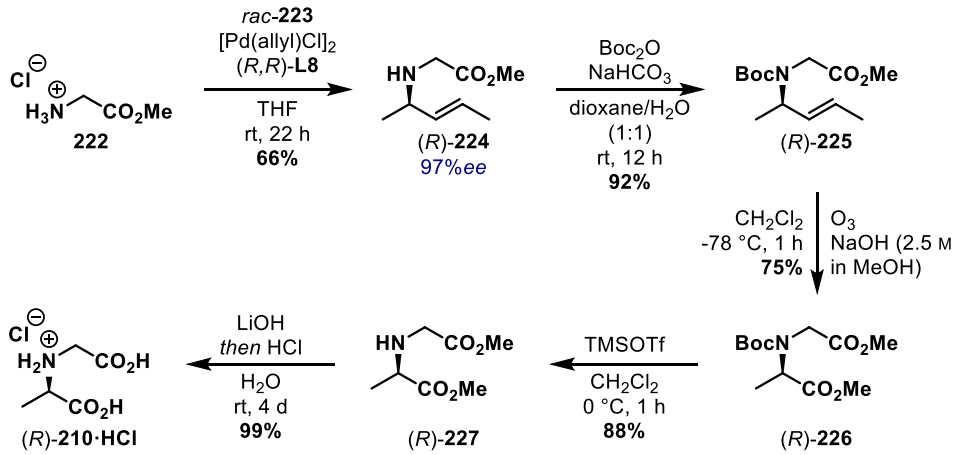
yielded octopine (**209**), but *Herbst* and *Swart* revised that the procedure predominantly afforded the diastereomer *iso*-octopine (*iso*-**209**).[138]

In addition to the described approaches above, *Wickberg and co-workers* published a synthetic strategy towards opines by monocarboxymethylation of primary amines describing the synthesis of (*S*)-strombine (**210**). A *Leuckart-Wallach*-type reaction of L-alanine (**220**) and glyoxylic acid (**221**) in formic acid provided *N*-formyl strombine. Subsequent hydrolysis afforded (*S*)-strombine (**210**) in 69% overall yield (Scheme 79). Partial racemization for optical active substrates was observed due to a possible tautomerization of the imine intermediate.[141]



*Scheme 79: Synthesis of (S)-strombine (**210**) according to Wickberg and co-workers.[141]*

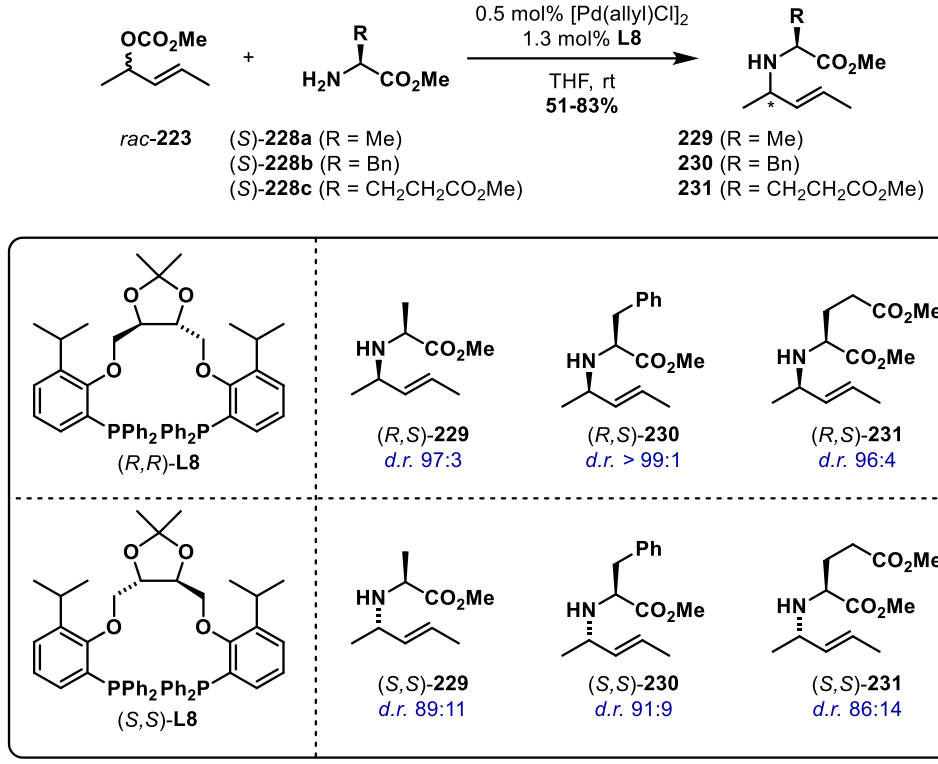
Although the described syntheses show that the structural motif of opines can be obtained by easy transformations, they lack stereoselectivity. In most examples, racemic mixtures of opines were obtained or the use of enantiopure starting materials was crucial. Thus, the research group of *Schmalz* implemented an asymmetric Pd-catalyzed transformation to provide the opine motif in an enantioselective fashion (Scheme 80).[142]



*Scheme 80: Synthetic approach towards strombine hydrochloride (**210·HCl**).[142]*

The synthesis of (*R*)-strombine hydrochloride (**210·HCl**) is shown as an example. First, a Pd-catalyzed *N*-allylation was performed affording allylic amine (*R*)-**224** with high enantioselectivity. After Boc-protection of the amine, substrate (*R*)-**225** was subjected to ozonolysis to provide diester (*R*)-**226**, which already contains the structural motif of pyruvate-derived opines. Removal of the Boc-protection group and subsequent ester cleavage afforded the desired target structure (*R*)-**210·HCl** in good yields. The key reaction is the

Pd-catalyzed allylic amination using a catalytic system of $[Pd(allyl)Cl]_2$ and *Medi*Phos ligand **L8**, which was also used for the synthesis of other opine precursors, e.g. in the synthesis of alanopine (**211**) (Scheme 81).[142]



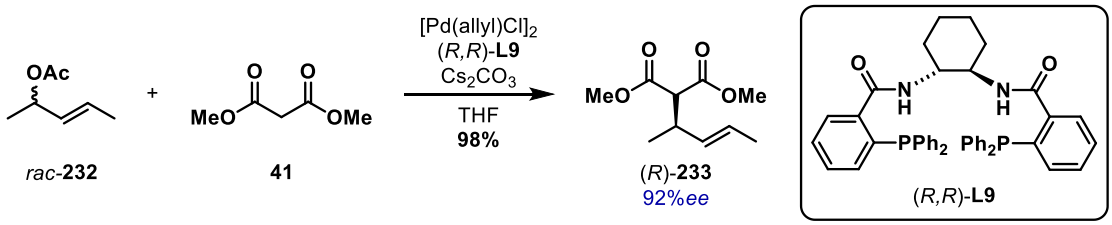
Scheme 81: Overview of accomplished Pd-catalyzed N-allylations in the course of opine syntheses.[142]

The results implied that the strategy is well suited for different amino acids with high diastereoselectivity. However, a minor *matched/mismatched* effect was observed, thus, the formation of the (*S,S*)-diastereomers with (*S,S*)-**L8** proceeded less selective yielding slightly lower diastereomeric ratios.[142] Overall, the use of the Pd-catalyzed allylic amination depicts a powerful method in the stereoselective synthesis of the interesting compound class of opines.

6.2 Pd-catalyzed allylic substitutions

6.2.1 Mechanism

Metal-catalyzed allylic substitutions have become a versatile tool in organic synthesis, allowing stereoselective transformations of a variety of allylic substrates under mild reaction conditions. As previously stated (see Chapter 2.2), various metals can be used in allylic substitutions, such as Ir, Rh, Ru and many more. However, Pd-based catalysts are the most prominent and versatile examples, as they have been recognized in the *Tsuji-Trost* reaction.[26] The eponyms of the reaction were significantly involved in the development of the methodology of allylic substitutions. Whereas *Tsuji* reported the first achiral allylic substitution[143], *Trost* made enormous efforts to establish an asymmetric transformation.[27, 28, 144, 145] This led to the development of the *Trost* ligand **L9**, which can be readily used in numerous Pd-catalyzed allylic substitutions (Scheme 82).[27, 28, 146, 147]

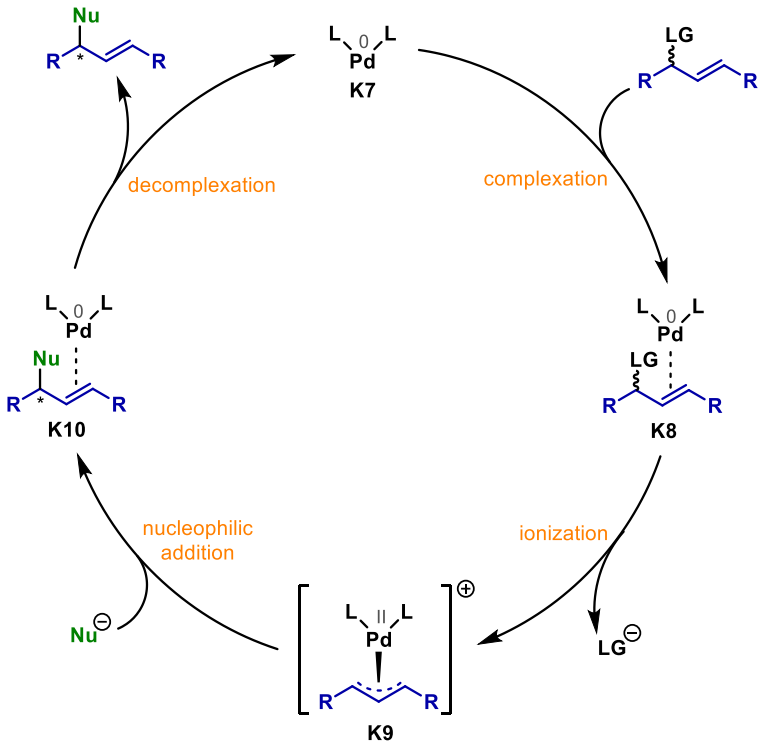


*Scheme 82: Example for a Pd-catalyzed allylic substitution using the Trost ligand **L9**.[146]*

For example, *Trost and co-workers* described the enantioselective transformation of allylic acetate *rac*-**232** and dimethyl malonate (**41**) to allylic product (*R*)-**233** in 92%*ee*.[146] The catalytic system of [Pd(allyl)Cl]$_2$ and *Trost* ligand **L9** can be used in amounts of 2.5 mol% and 7.5 mol%, respectively, generating the active catalytic species *in situ*.[146]

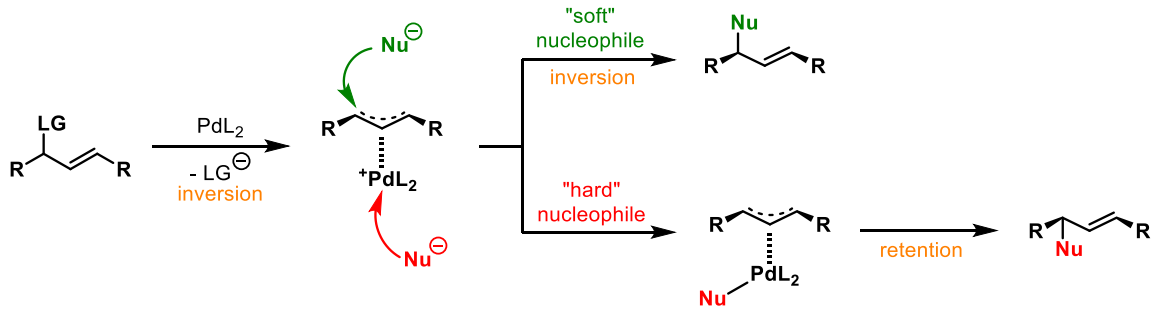
The reaction mechanism and thus the regio- and stereoselectivity was extensively studied by the research group of *Trost*.[27, 28] Mechanistically, a distinction has to be made between "symmetric electrophiles", such as acetate **232**, which form a symmetric π-allyl-complex, and "unsymmetric electrophiles". For the latter, regioselectivity issues and the formation of linear allylic substrates (see Scheme 10) have to be taken into account.[148] In this thesis, only the mechanism and stereoselectivity with "symmetric electrophiles" will be discussed.

As presented in Scheme 83, the first step in the catalytic cycle is marked by coordination of the allylic substrate to the active catalytic species **K7** to form π-allyl complex **K8**. Followed by the ionization step, the leaving group (LG) is removed and the oxidized Pd intermediate **K9** is obtained. Next, the nucleophile (Nu) is introduced leading to the formation of η^2-olefin complex **K10**. After release of the chiral allylic product by decomplexation, the active catalytic species **K7** is regenerated.[27, 28]



Scheme 83: Catalytic cycle of Pd-catalyzed allylic substitutions.[27]

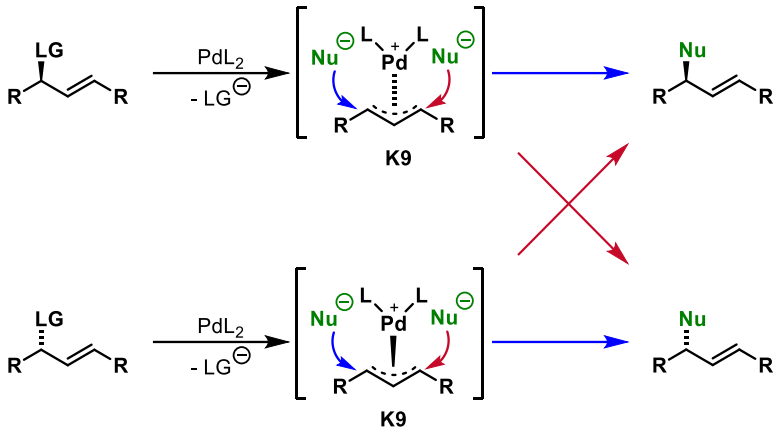
The ionization step always proceeds with inversion of the stereoinformation. However, the nature of the nucleophile determines from which face of the π-system the nucleophilic attack occurs (Scheme 84).[27, 28]



Scheme 84: Influence of the nucleophile on face of the nucleophilic attack in the Pd-catalyzed allylic substitution.[28]

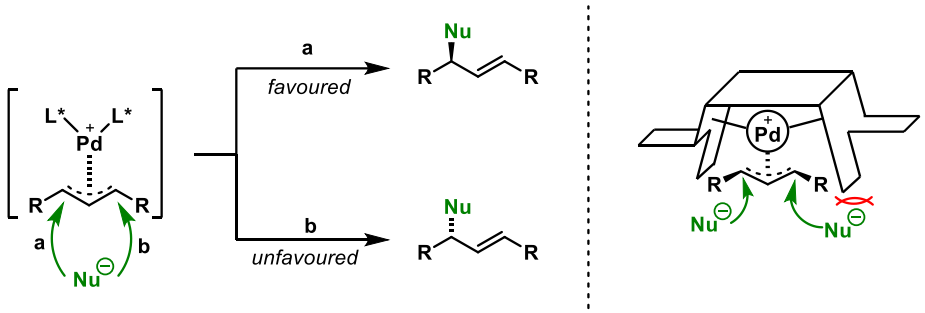
When analyzing the nucleophilic attack, a distinction must be made between “soft” and “hard” nucleophiles. “Soft” nucleophiles can also be referred to as “stabilized” nucleophiles, which are often derived from conjugate acids with a $pK_a < 25$. For example, malonic esters, amides, amines and alkoxides are included in this group. “Soft” nucleophiles directly add to the π-allyl system from the *exo* face leading to a second inversion. In contrast, “hard” or “unstabilized” nucleophiles undergo transmetallation by attack at the Pd-centre, after which the nucleophile is transferred to the π-allyl system from the *endo* face while retaining the stereochemistry. Examples for “hard” nucleophiles are *Grignard* reagents, hydride donors and alkylzinc halides.[27, 28]

The use of allylic electrophiles in combination with an achiral Pd-catalyst leads to the formation of complex **K9** (Scheme 85). Upon nucleophilic attack of a "soft" nucleophile from the *exo* face that can occur at two possible positions, both enantiomers are formed.[27, 28]



*Scheme 85: Formation of the meso-complex **K9** and subsequent nucleophilic addition.*[27, 28]

Complex **K9** is a *meso*-structure with two enantiotopic carbon atoms. The use of chiral ligands renders the enantiotopic carbon atoms diastereotopic. Thus, regioselectivity issues have to be taken into account, as the position of the nucleophilic attack is crucial to achieve the formation of exclusively one enantiomer. Influenced by steric and electronic effects deriving from the chiral ligand, the addition proceeds regioselectively providing the favoured enantiomer (Scheme 86).[27, 28]



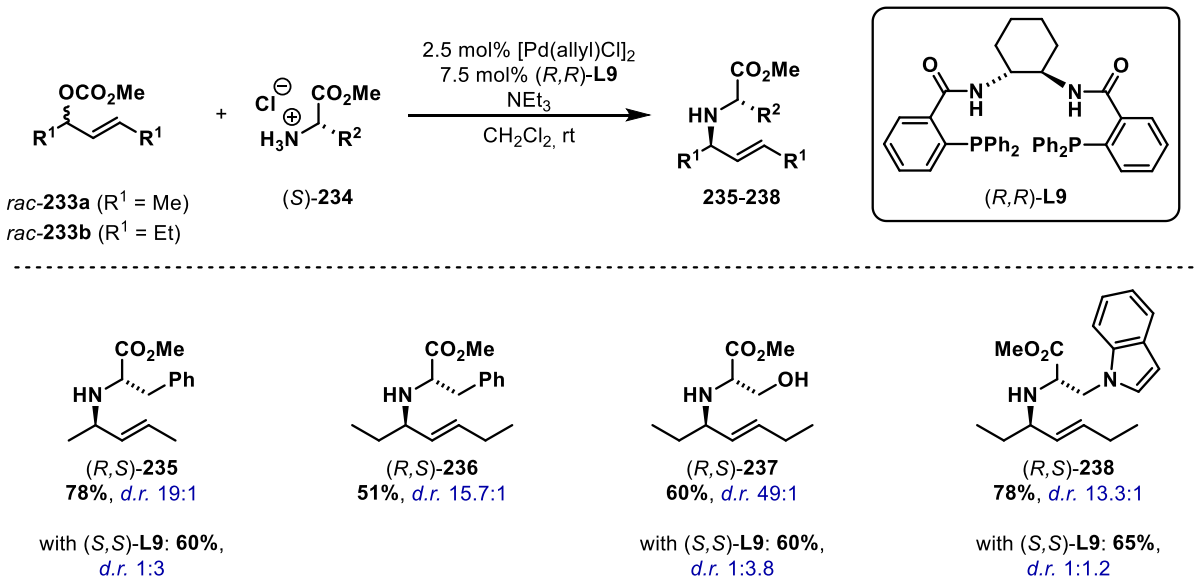
Scheme 86: Depending on the position of the nucleophilic attack on the meso-complex, the stereochemical outcome of the reaction is determined (left). By implementing chiral ligands, the nucleophilic attack proceeds regioselectively due to steric and electronic effects (right, schematic drawing).[27]

6.2.2 Pd-catalyzed allylic amination with amino esters

Pd-catalyzed allylic substitutions can be performed with a variety of different nucleophiles. The application of numerous *N*-nucleophiles in Pd-catalyzed allylic aminations in particular has proven to be a powerful tool in organic synthesis. For example, many total syntheses using this methodology have been reported to establish secondary and tertiary amines in natural products in a stereoselective fashion.[26] Furthermore, it has already been shown that Pd-catalyzed

N-allylations can be used for the synthesis of opines (see Scheme 81), using amino esters as suitable nucleophiles.[142] However, many other *N*-nucleophiles, e.g. aliphatic amines[149, 150], phthalimides[151] and aryl amines[152, 153], were readily applicable in this reaction sequence.[26] As the focus of this chapter lies on the structural motif of opines, the use of amino acid derivatives as nucleophiles will be further elucidated.

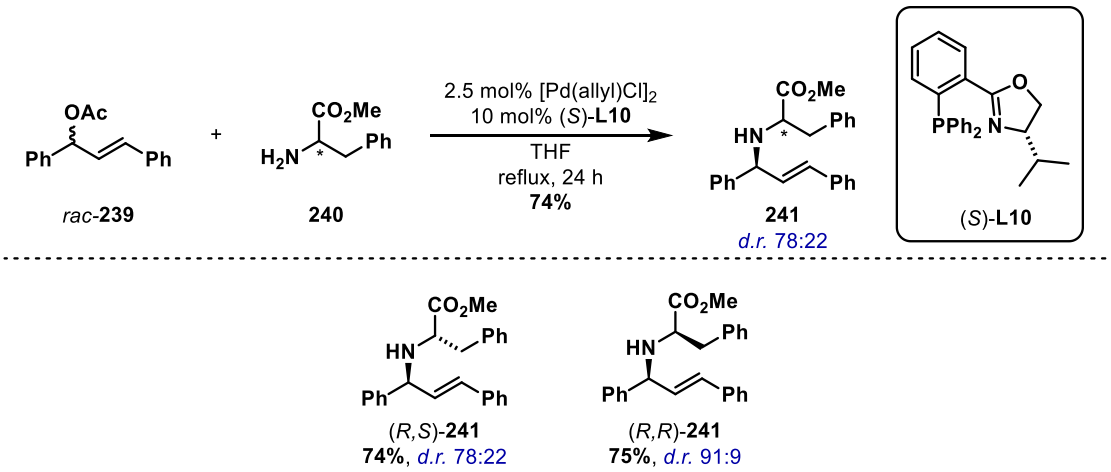
The first application of amino esters as nucleophiles in Pd-catalyzed *N*-allylations was reported by *Trost* in 1998. With the use of the *Trost* ligand **L9**, successful conversions of allylic carbonates of type *rac*-**233** and hydrochlorides of amino esters (*S*)-**234** were observed (Scheme 87).[154]



Scheme 87: The Pd-catalyzed allylic amination with hydrochlorides of amino esters, first reported by Trost et al. The diastereomeric ratios are given as (R,S):(S,S).[154]

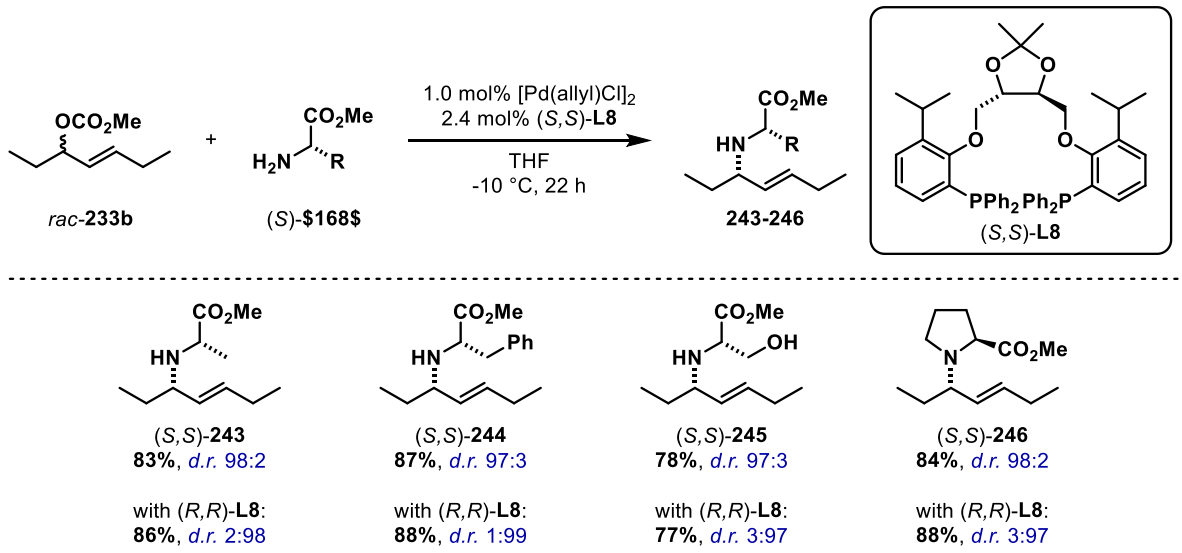
Good diastereoselectivities were achieved with (*R,R*)-**L9**, predominantly forming the (*R,S*)-substrates **235**-**238**. The formation of the (*S,S*)-diastereomers was favoured using the enantiomeric ligand (*S,S*)-**L9**, however, a significant loss in diatereoselectivities was observed. The lower ratios can be attributed to *matched/mismatched* effects. For ligand (*S,S*)-**L9**, the ligand favours the formation of the unfavoured diastereomer of the substrate control. Still, the catalyst dominates the influence on the diastereoselectivity obtaining mainly the (*S,S*)-products.[154]

In the same year, *Humphries* reported a Pd-catalyzed *N*-allylation of racemic acetate **239** and amino esters with the use of chiral PHOX-ligand **L10**. As an example, the reactions with (*S*)- and (*R*)-phenylalanine methyl ester (**240**) are depicted in Scheme 88. For this system, *matched/mismatched* effects were also observed. Whereas the D-amino esters delivered good diastereomeric ratios, a loss of diastereoselectivity was observed for L-amino esters.[155]



*Scheme 88: Reaction of allylic acetate rac-**239** and phenylalanine methyl ester (**240**) reported by Humphries and co-workers.[155]*

In the course of the synthesis of proline-derived modules (ProMs), the research group of *Schmalz* also applied the asymmetric Pd-catalyzed *N*-allylation of amino esters.[156] Here, C_2-symmetric diphosphine ligands (*Medi*Phos), which were developed in the *Schmalz* group,[157] were applied. The use of ligand **L8** with L-amino esters **242** provided the desired (*S,S*)- and (*R,S*)-allylic amines **243**-**246** in excellent diastereomeric ratios (Scheme 89).[156]



*Scheme 89: Overview of selected products synthesized via Pd-catalyzed allylic amination of amino esters with the use of MediPhos ligand **L8** reported by the research group of Schmalz.[156] Diastereomeric ratios are given as (S,S):(R,S).*

Beside the very good yields and observed stereoselectivity, no *matched/mismatched* effect for (*S,S*)- and (*R,R*)-**L8** were reported identifying *Medi*Phos ligand **L8** as a most suitable chiral ligand for these allylic aminations.[156] Moreover, the research group of *Schmalz* applied *Medi*Phos ligand **L8** in the asymmetric synthesis of opines, as already described in Scheme 81. Here, only minor *matched/mismatched* effects were reported.[142]

7 Concept

Methylglyoxal (MG) is a reactive carbonyl species found in all biological organisms, as it is formed by spontaneous degradation of numerous metabolites that can occur in the course of metabolic pathways, e.g. during the amino acid metabolism or glycolysis.[158, 159] The formed MG is removed from the cell by the glyoxalase system for detoxification by transforming it mainly to L-lactate.[160] However, MG partly escapes detoxification by reacting with biopolymers to form irreversible modifications, which are referred to as advanced glycation end products (AGEs).[159, 161] It is assumed that these AGEs are highly involved in the development of age-related diseases, such as diabetes[160], cancer[162] and neurodegenerative diseases[163], as AGEs are able to alter or even disrupt essential protein functions.[161] Well-known examples for MG adducts are the L-arginine-derived metabolites MG-H1 (**247**) and CEA (**248**).[164, 165] However, there is no additional insight into the metabolite adducts. Furthermore, the role of MG-adducts in the development of age-related diseases has not been fully elucidated yet.

Therefore, *Katrine Arnkjær* and *Mogens Johannsen* from the *Aarhus University* performed reactivity-based metabolomics experiments to identify MG-derived adducts in cells. Here, cell cultures were exposed to ^{12}C-MG and ^{13}C-MG. After lysis of the cells, the metabolites were analyzed by means of mass spectrometry (LG-qTOF-MS). Potential MG adducts were identified by comparison of the ^{12}C-MG and ^{13}C-MG mass data, searching for identical retention times and similar peak intensities for mass differences of 3.01 Da (Figure 9).

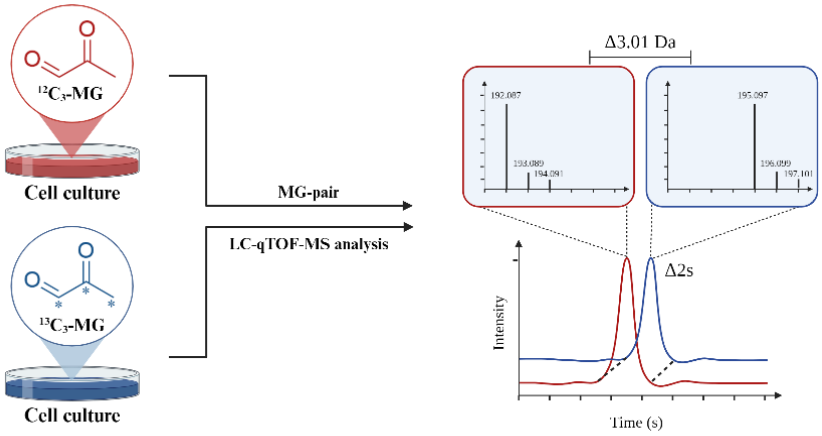


Figure 9: Schematic illustration of the identification of MG adduct pairs.

The featured pairs can be additionally identified from the volcano plot, wherein the adducts extracted from the cells exposed with ^{12}C-MG and ^{13}C-MG are shown (Figure 10). Beside the already well known adducts MG-H1 (**247**) and CEA (**248**), additional adducts derived from amino acids were found. For example, *N*-carboxyethyl phenylalanine (*N*-CE-Phe, **249**) and

N-carboxyethyl tyrosine (*N*-CE-Tyr, **250**) were identified by analysis of mass spectrometry fragments.

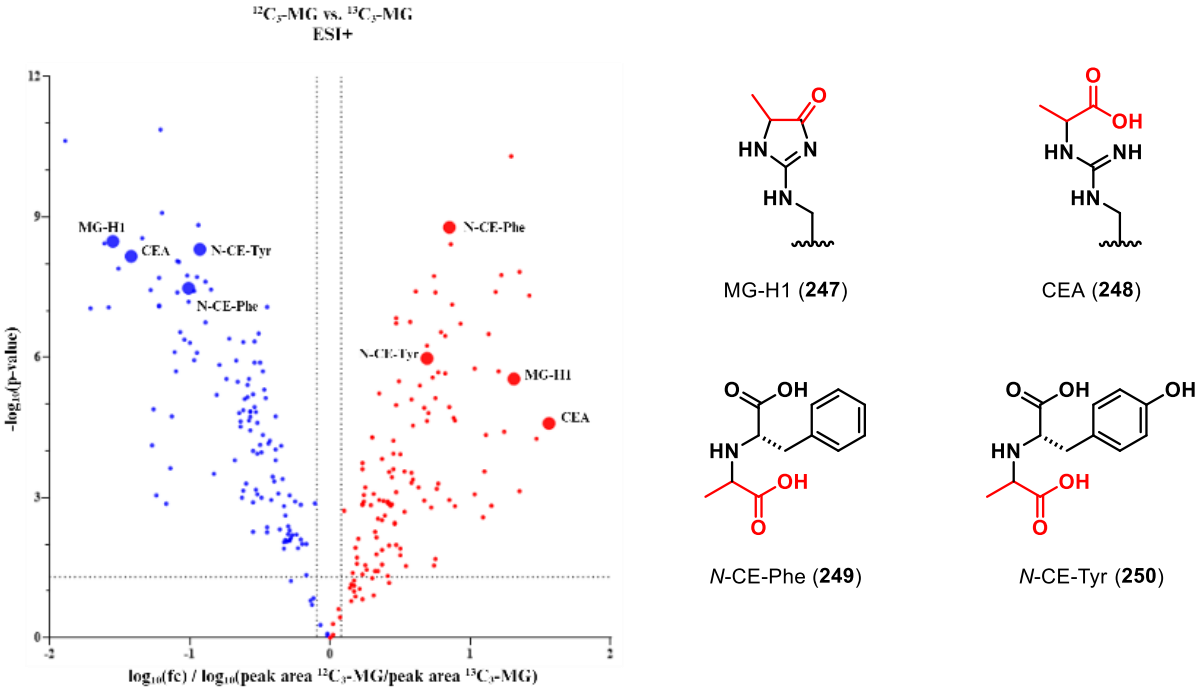


*Figure 10: Volcano plot of the found MG-adducts in ^{12}C-MG- and ^{13}C-MG-exposed cells. Among these, MG-H1 (**247**), CEA (**248**), N-CE-Phe (**249**) and N-CE-Tyr (**250**) were identified as expressed MG-adducts.*

In order to validate the findings of the opine structures **249** and **250** as MG-related metabolites, the diastereomeric mixture of **249** was synthesized. The LC-qTOF-MS data of the diastereomeric mixture was compared to the cell sample and the spiked cell sample, illustrating that the MG-exposed cell delivered one specific diastereomer (Figure 11).

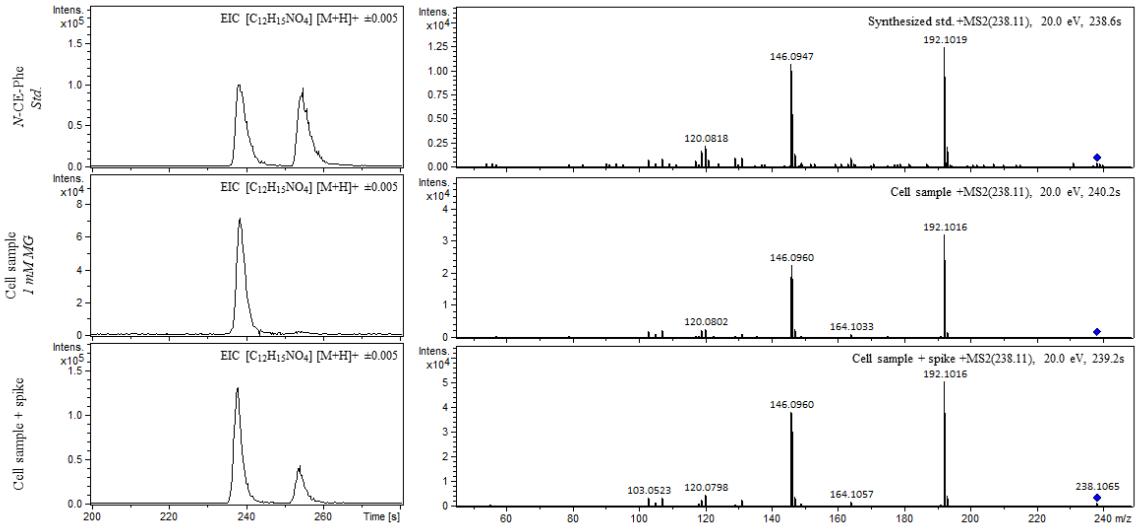
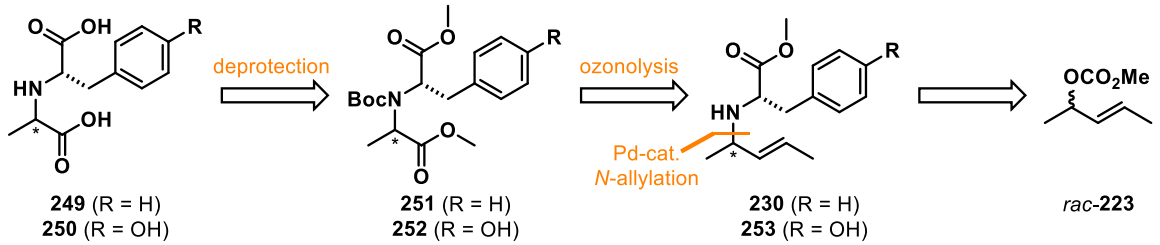


*Figure 11: Extracted ion chromatograms and MS spectra of the synthesized diastereomeric mixture of **249** (top), the cell sample (middle) and the spiked cell sample (bottom).*

However, the stereochemistry of the obtained diastereomers of metabolites **249** and **250** remained unclear. Since a general protocol for the diastereoselective synthesis of opine structures has already been established in the *Schmalz* group (see Scheme 80),[142] the protocol should be transferred to the MG-adducts **249** and **250** (Scheme 90).



*Scheme 90: Retrosynthetic analysis of opines **249** and **250**.*

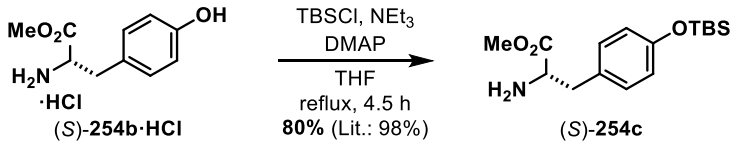
N-CE-Phe (**249**) and *N*-CE-Tyr (**250**) can be derived from their protected forms **251** and **252**, respectively. These diesters can be generated from the allylic amines **230** and **253**. By applying an asymmetric Pd-catalyzed *N*-allylation, the allylic amines **230** and **253** can be provided in a diastereoselective fashion starting from racemic carbonate **223** and the (*S*)-configurated phenylalanine or tyrosine ester. Depending on the enantiomer of the ligand used in the Pd-catalyzed *Tsuji-Trost* reaction, both diastereomers (*R,S*)-**249**/**250** and (*S,S*)-**249**/**250** should be synthesized. The synthesis of the pure stereoisomers of **249** and **250** would help to validate the stereochemistry of the detected isomer in the cell sample, which is crucial for further elucidation of the formation of these substrates and their biological function.

8 Results and discussion

8.1 Stereocontrolled synthesis of allylic amines by Pd-catalyzed *N*-allylation

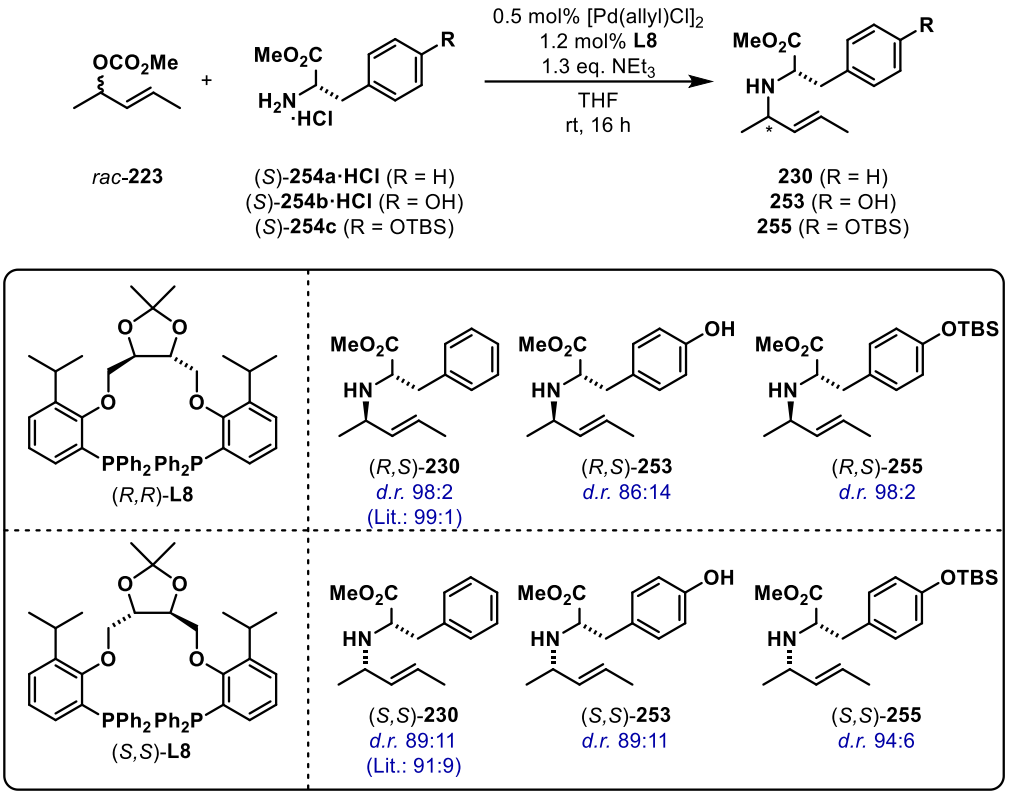
According to the described procedure developed in the *Schmalz* labs (see Scheme 81),[142] a Pd-catalyzed *N*-allylation should be applied to synthesize allylic amines **230** and **253** diastereoselectively (see Scheme 90).

Allylic carbonate *rac*-**223** serves as the electrophile in the reaction, which can be synthesized in one step from crotonaldehyde.[142] Commercially available hydrochlorides of L-amino esters should be used as nucleophiles, like the (*S*)-phenylalanine methyl ester (**254a·HCl**) and the (*S*)-tyrosine methyl ester (**254b·HCl**). Since the unprotected alcohol of the tyrosine moiety of compound **254b·HCl** might function as a competing nucleophile, the TBS-protected tyrosine analogue (*S*)-**254c** should also be considered. Thus, the hydrochloride of the tyrosine methyl ester ((*S*)-**254b·HCl**) was reacted with TBSCl under standard basic conditions to obtain TBS-protected tyrosine derivative (*S*)-**254c** in 80% yield (Scheme 91).



*Scheme 91: Synthesis of the TBS-protected tyrosine derivative (S)-**254c**.[166]*

With the three L-amino esters in hand, the asymmetric Pd-catalyzed allylic amination was examined (Scheme 92). Since the (*R,S*)- and the (*S,S*)-diastereomers of the allylic amines were to be synthesized, both enantiomers of the *Medi*Phos ligand **L8** were used in combination with $[Pd(allyl)Cl]_2$. Additionally, stoichiometric amounts of NEt_3 were added in order to transform the hydrochlorides (*S*)-**254a·HCl** and (*S*)-**254b·HCl** to the free amines *in situ*. Moreover, the use of NEt_3 accelerates the formation of the active catalytic Pd-complex.

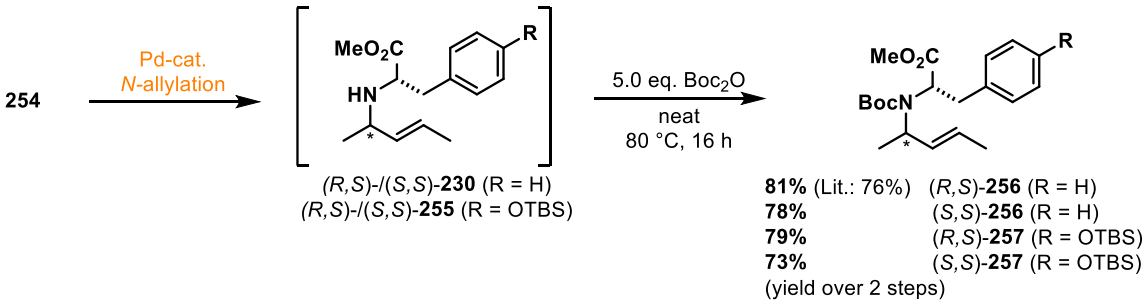


*Scheme 92: Overview of the performed Pd-catalyzed allylic aminations with the enantiomers of chiral MediPhos ligand **L8**. The diastereomeric ratios of the obtained allylic amines were analyzed by GC-MS.*

The (*R,S*)- and (*S,S*)-diastereomers of the allylic amines **230**, **253** and **255** were obtained in very good to excellent diastereoselectivities, however, *matched/mismatched* effects were observed. For the transformation of phenylalanine derivative **254a·HCl** with *Medi*Phos (*R,R*)-**L8**, an excellent diastereomeric ratio of 98:2 was obtained (*matched*). Applying *Medi*Phos (*S,S*)-**L8** to the same substrates yielded a decreased diastereomeric ratio of 89:11 for allylic amine (*S,S*)-**230** (*mismatched*). For the other substrates, only minor deviations in diastereoselectivity were detected. In case of TBS-protected tyrosine derivative **255**, high diastereomeric ratios of 98:2 and 94:6 were obtained with (*R,R*)- and (*S,S*)-**L8**, respectively. The ratios determined for allylic amines **230** and **255** indicate that the formation of the (*R,S*)-products is favoured by substrate control, thus, slightly higher diastereomeric ratios were afforded with (*R,R*)-**L8**. This is also in accordance with the diastereoselectivities reported in the literature.[142] Interestingly, the *N*-allylation of unprotected tyrosine derivative **254b·HCl** yielded slightly higher diastereomeric ratios of 89:11 in combination with (*S,S*)-**L8** compared to the use of (*R,R*)-**L8** (*d.r.* 86:14). This implies that the hydroxyl functionality interacts with the ligand system, possibly through hydrogen bonding, which supports the formation of (*S,S*)-allylic amine **253**.

Due to the problematic purification of free amines by column chromatography, the crude products **230** and **255** of the Pd-catalyzed *N*-allylation were directly subjected to Boc-protection

conditions (Scheme 93). Since the obtained diastereomeric ratios for amine **253** were not as good as for its TBS-protected alternative **255** and possible side reactions of the hydroxyl functionality in future reaction steps should be circumvented, substrate **253** was not regarded any further.



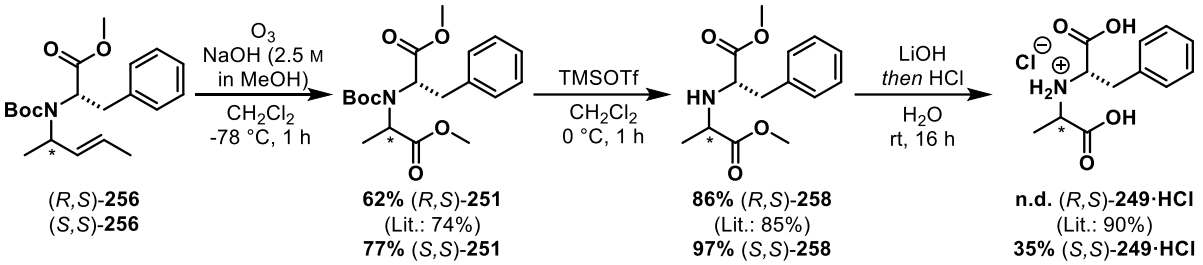
*Scheme 93: Boc-protection of crude allylic amines **230** and **255**.*

The corresponding Boc-amines **256** and **257** were obtained in very good yields of 73%-81% over two steps. The diastereomers could be separated by column chromatography affording the pure (*R,S*)- and (*S,S*)-products. The Boc-protection does not only simplify the purification of the amines, it also crucial for the upcoming steps of the reaction sequence circumventing possible side reactions.

8.2 Synthesis of opines

8.2.1 Synthesis of the phenylalanine-derived opine

Following the procedure already developed for (*R,S*)-*N*-CE-Phe (**249**),[142] the reaction sequence was repeated for (*R,S*)-**256** and transferred to its diastereomer (*S,S*)-**256** (Scheme 94).



(*R,S*)-**256**
(*S,S*)-**256**

62% (*R,S*)-**251**
(Lit.: 74%)
77% (*S,S*)-**251**

86% (*R,S*)-**258**
(Lit.: 85%)
97% (*S,S*)-**258**

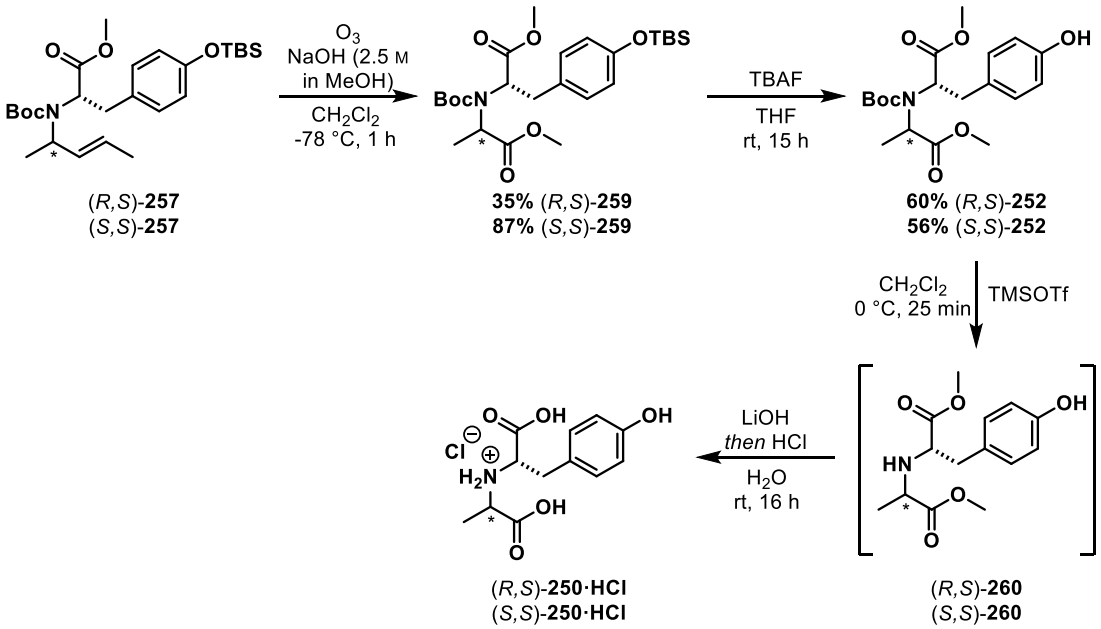
n.d. (*R,S*)-**249·HCl**
(Lit.: 90%)
35% (*S,S*)-**249·HCl**

*Scheme 94: Synthesis of (R,S)- and (S,S)-**249·HCl**.*

The Boc-protected allylic amine **256** was subjected to oxidizing ozonolysis conditions providing diesters (*R,S*)- and (*S,S*)-**251** in 62% and 77% yield, respectively. Substrate **251** already provides the structural motif of opines. The Boc-protection group was then removed using TMSOTf, obtaining both diastereomers of amine **258** in very good yields. Finally, amine **258** was reacted with LiOH to cleave the methyl ester and subsequently treated with HCl. The latter facilitates isolation of the opine structure **249** as the corresponding hydrochloride. Unfortunately, the yield for (*R,S*)-**249·HCl** could not be determined and for (*S,S*)-**249·HCl** only a low yield of 35% was obtained. This can be attributed to solubility problems of the target compound **249**. Purification of the compound was attempted by recrystallization with H_2O, however, opines (*R,S*)- and (*S,S*)-**249** were only partly soluble even upon heating. Therefore, the (*S,S*)-diastereomer **249** was obtained as a pure compound, albeit in low yield, and the (*R,S*)-diastereomer **249** could not be completely purified, as it was even less soluble. The impurities derive from LiCl formed in the reaction sequence. Still, hydrochloride (*S,S*)-**249·HCl** was obtained in sufficient purity for analysis by MS and NMR measurements. Furthermore, HPLC measurements revealed that (*R,S*)- and (*S,S*)-**249·HCl** were obtained as the pure diastereomers.

8.2.2 Synthesis of the tyrosine-derived opine

The performed procedure for phenylalanine-derived opine **249** was transferred to the synthesis of tyrosine-derived opine **250** (Scheme 95), which is unknown in the literature.

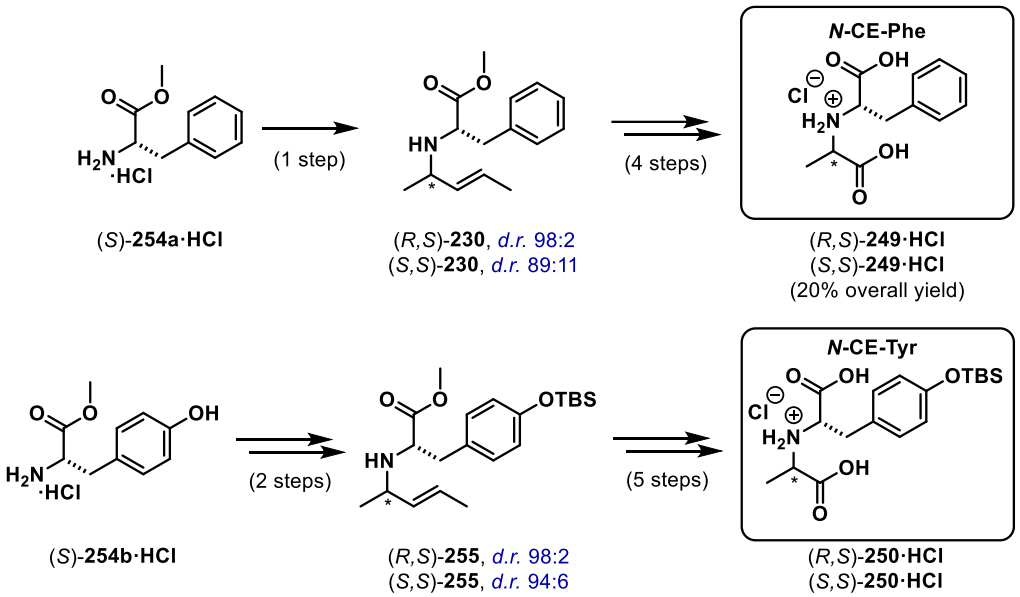


*Scheme 95: Synthesis of (R,S)- and (S,S)-**250·HCl**.*

Overall, the reaction sequence was easily transferrable to tyrosine derivative **250**. Ozonolysis of Boc-protected allylic amine (*S,S*)-**257** afforded diester (*S,S*)-**259** in 87% yield. The same reaction conditions were applied to the (*R,S*)-diastereomer **257**, however, only 35% of the desired diester (*R,S*)-**259** were isolated, although full conversion of the starting material was observed by TLC. The reaction outcome was even reproducible in a second trial. This implies that the (*R,S*)-diastereomer **257** is less stable than (*S,S*)-**257** towards oxidizing conditions. Standard deprotection conditions using TBAF were applied to remove the silyl protecting group, which afforded the unprotected tyrosine-derivatives (*R,S*)- and (*S,S*)-**252** in 60% and 56% yield, respectively. The moderate yields can be explained by problematic purification *via* column chromatography due to the unprotected hydroxyl functionality. Subsequently, Boc- and methyl ester-cleavage afforded the desired target structures (*R,S*)- and (*S,S*)-**250·HCl**. The two reaction steps were performed without purification of the amine **260** to avoid product loss. As described for the analogue **249·HCl**, the recrystallization with H_2O proved to be equally difficult. Therefore, the obtained solids were washed with cold H_2O and dried under vacuum, yielding the tyrosine-derived opines (*R,S*)- and (*S,S*)-**250·HCl** as single diastereomers with minor impurities by LiCl.

9 Summary and outlook

The synthesis of target motif *N*-CE-Phe (**249**) was successfully accomplished in good yields over just five reaction steps (Scheme 96). The phenylalanine-derivative (*R,S*)-**249·HCl** was obtained according to a literature procedure developed in the *Schmalz* group, which could be easily transferred to the (*S,S*)-analogue of **249·HCl** by using different enantiomers of *Medi*Phos **L8**. Moreover, the hydrochloride of *N*-CE-Tyr (**250·HCl**) was obtained by the same procedure in seven steps including additional TBS protection and deprotection.



*Scheme 96: Accomplished syntheses of N-CE-Phe (**249**) and N-CE-Tyr (**250**).*

Particular emphasis was placed on the asymmetric Pd-catalyzed *N*-allylation, which provided the allylic amines **230** and **255** in very good to excellent diastereomeric ratios. Although minor *matched/mismatched* effects were observed, the selectivity for the *mismatched* case of (*S,S*)-**230** and *Medi*Phos (*S,S*)-**L8** was still very good reaching a diastereoselective ratio of 89:11. The results underline the utility of asymmetric Pd-catalyzed allylic substitutions for the stereoselective formation of allylic amines. In combination with ozonolysis, this strategy depicts a powerful tool to establish opine motifs in a stereoselective fashion.

However, the overall yield of most opines could not be determined due to problems in the final purification by recrystallization. The difficulties derived from poor solubility of the synthesized hydrochlorides **249·HCl** and **250·HCl**. Therefore, the target structures were obtained including minor amounts of LiCl in sufficient purity, which was confirmed by NMR and HPLC measurements. It is possible that an acid-base extraction after ester cleavage with LiOH would be a more favourable alternative to direct treatment with HCl. Furthermore, ion exchange or reverse phase chromatography could be performed to provide the pure material. Only the

hydrochloride of (*S,S*)-*N*-CE-Phe (**249·HCl**) could be purified by recrystallization, affording the target compound in an overall yield of 20% over five steps.

Since the substrates *N*-CE-Phe (**249**) and *N*-CE-Tyr (**250**) were synthesized to gain insight into the stereochemistry of these opine structures formed in cells, the samples were passed on to *Katrine Arnkjær* and *Mogens Johannsen* for further analysis. The diastereomerically pure substrates **249** and **250** were subjected to LC-qTOF-MS and compared to the cell sample (Figure 12).

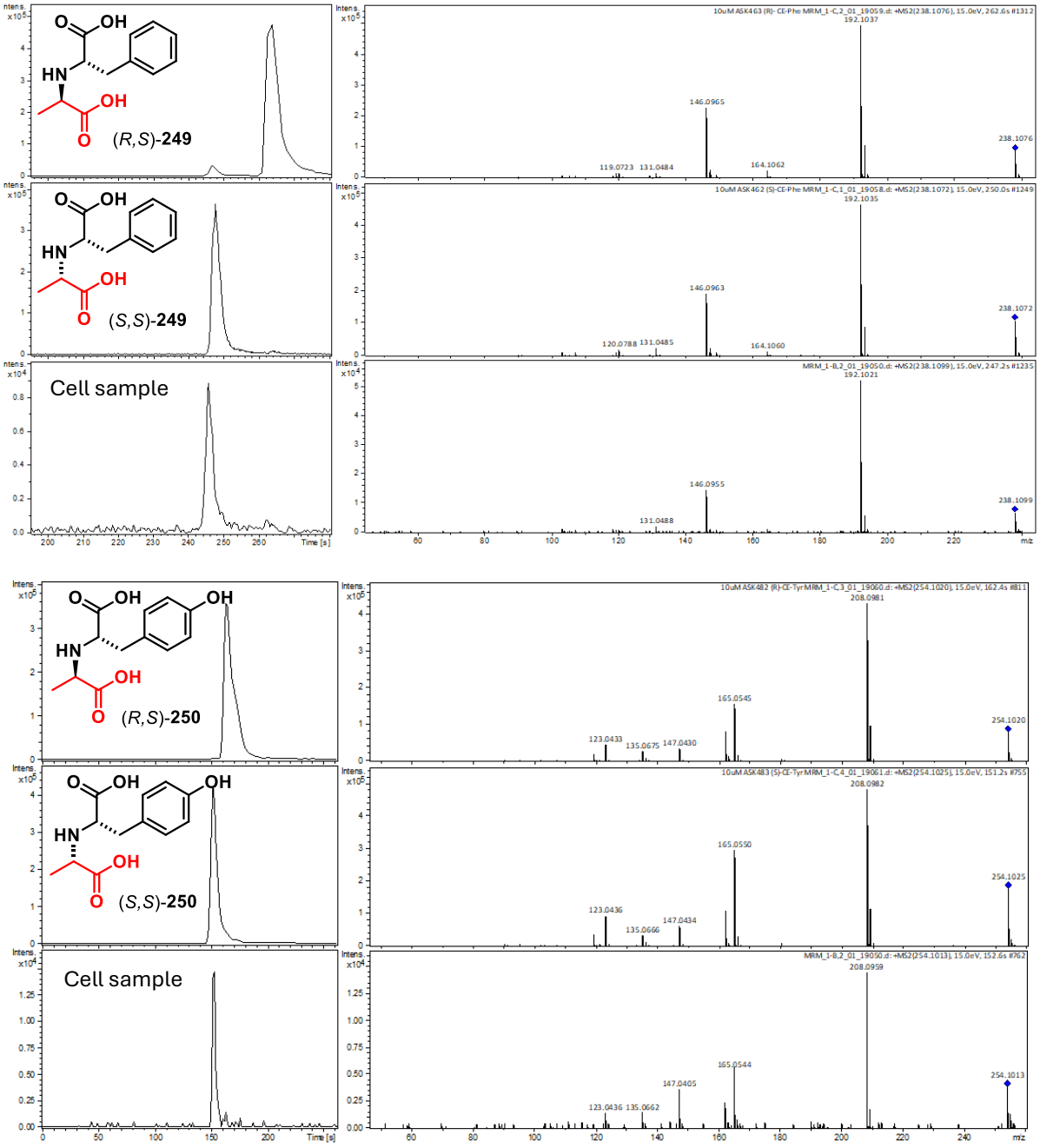


*Figure 12: Extracted ion chromatograms and MS spectra of the synthesized diastereomerically pure substrates N-CE-Phe (**249**) and N-CE-Tyr (**250**) and the corresponding cell samples confirming the (S,S)-configuration of the natural samples.*

The measurements indicated that the (*S,S*)-diastereomers of **249** and **250** were isolated from the cells. As the stereochemistry of *N*-CE-Phe (**249**) and *N*-CE-Tyr (**250**) has been elucidated, the formation of these MG-derived metabolites can be discussed. Furthermore, the question of the biological function of these new opine structures remains. From a synthetic point of view, the procedure developed for the synthesis of opine motifs proved to be a versatile tool that can be used for various amino esters.

10 Experimental part

10.1 General methods

General conditions

If not stated different, reactions were performed under an argon atmosphere with *Linde*® Argon 4.6 (99.996%, <1 ppm H_2O, <1 ppm O_2) using the *Schlenk* technique. The glass equipment was heated under vacuum with a propane-butane blowtorch gun and flushed with argon before usage. Solids were transferred under an argon counter current *via* a funnel. Liquids were added *via* a septum using syringes, which were rendered inert by flushing with argon three times. Solvents were removed under reduced pressure using a *Büchi* rotary evaporator at 40 °C water bath temperature. Residual solvents were dried under vacuum pressure with an oil pump.

Solvents and reagents

Commercially available reagents were obtained from common commercial sources, e.g. *Sigma Aldrich*, *Alfa Aesar*, *Acros Organics*, *TCI*, *BLDpharm* and *Carbolution*, and were used without further purification. In case of air- and moisture-sensitive reactions, solvents were distilled before usage. Dichloromethane was freshly distilled over calcium hydride under an argon atmosphere. Tetrahydrofuran and diethyl ether were distilled over sodium and benzophenone under an argon atmosphere. Other absolute solvents like DMF, toluene and MeOH were directly used from commercially available sources. DBU was purified by distillation. The concentration of *n*BuLi was determined before usage by titration of *N*-benzyl benzamide, according to a procedure by *Burchat*.[167]

Chromatography

For TLC analysis, silica gel 60 F_{254} plates with a thickness of 0.25 mm by *Merck* were used. The corresponding analytes were detected under UV-light or by potassium permanganate stain (3.00 g $KMnO_4$, 20.0 g K_2CO_3, 5.00 mL 5% NaOH-solution in 300 mL H_2O). Purification by column chromatography was carried out with silica gel 60 Å (35-70 µm) by the company *Acros*. The solvents used and the corresponding mixing ratios of the mobile phase are given in fractions of volume for each experiment.

NMR-spectroscopy

NMR-spectra were recorded on a *Bruker* Avance II 300 (^{1}H: 300 MHz, ^{13}C: 75 MHz), Avance III 499 (^{1}H: 500 MHz; ^{13}C: 126 MHz), Avance III 500 (^{1}H: 500 MHz, ^{13}C: 126 MHz) or Avance II+ 600 (^{1}H: 600 MHz, ^{13}C: 151 MHz, ^{31}P: 202 MHz). All spectra were measured at room temperature in common deuterated solvents, e.g. $CDCl_3$, DMSO-d_6, MeOD-d_4 and D_2O, and referenced to the internal standard TMS (0 ppm) in case of proton spectra or to the solvent signal for carbon spectra. The chemical shifts are reported in parts per million (ppm) and the coupling constants *J* are given in Hertz (Hz). The multiplicities are given by s = singlet, d = doublet, t = triplet, q = quartet and m = multiplet. The assignment of the signals was done by using recorded 2D-spectra or according to reported literature. Diastereotopic protons are marked as “a” and “b”. Rotamers are indicated as “rot1” and “rot2”. If a mixture of diastereomers and rotamers was obtained, proton signals are marked with ‘, ‘’, ‘’’. The corresponding ^{13}C-signals are summarized.

Gas chromatography with mass detector (GC-MS)

GC-MS measurements were conducted on an *Agilent HP6890* system combined with a mass detector (MSD) *5937N*. Hydrogen was used as the carrier gas with a flow rate of 1.7 mL/min and a pressure of 0.3 bar. As the capillary tube, an *Agilent 19091S-4335 HP-5 MS* (30 m · 0.25 mm · 0.25 µm) was used. The intensities were reported relative to the peak with the highest intensity (100%). For measurements the temperature program 50300M (50 °C for 2 min, 25 °C /min to 300 °C, 320 °C for 2 min) was used.

Gas chromatography with chiral stationary phase (GC-FID)

The separation of enantiomers was conducted using an *Agilent Technologies 7890B* with a flame ionization detector (FID). Hydrogen was used as a carrier gas. The used capillary tube, flow rate, temperature program and retention times of the enantiomer are reported in the depicted chromatograms.

High performance liquid chromatography (HPLC)

The separation of some enantiomers and diastereomers was conducted using high performance liquid chromatography on a *Merck-Hitachi I*. The used columns, solvent mixtures and retention times of the substrates are reported in the depicted chromatograms.

High resolution mass spectrometry

High resolution mass spectra were recorded on a *THERMO Scientific LTQ Orbitrap XL* using the electrospray ionisation method (ESI). For the spray voltage a value of 3.4 kV was applied. The capillary voltage and the tube lens voltage had a value of 3.0 V.

Fourier-transformed infrared spectroscopy (FT-IR)

Infrared (IR) spectra were measured on a *PerkinElmer* Spectrum Two FT-IR spectrometer with the aid of the attenuated total reflectance (ATR) technique. The wave numbers v are reported in cm^{-1}. The intensities are defined as w = weak, m = medium, s = strong and br = broad.

Optical rotation

The specific optical rotations $[\alpha]_\lambda$ of the samples were measured on an *Anton Paar* MCP 200. The experiments were conducted at 20.0 °C measuring the optical rotation at the following wavelengths: 365 nm, 436 nm, 546 nm, 579 nm, 589 nm. The cuvette length was 10 cm. The concentrations are reported in g/100 mL.

Melting point

Melting points of obtained solids were measured in an open glass capillary using a *Büchi B545* with a heat rate of 2 °C/min. The measured melting points are uncorrected.

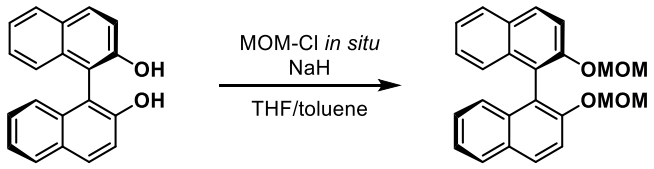
Ozonolysis

For ozonolysis an *Ozon-Generators-Modell 500* by *Fischer* was used. Ozon was generated by applying a current strength of 110 mA and oxygen volume flow of 60 L/h.

10.2 Synthetic procedures

10.2.1 Synthesis of phosphoramidite ligands

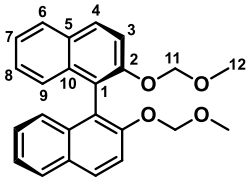
10.2.1.1 Synthesis of (*R*)-2,2'-bis(methoxymethoxy)-1,1'-binaphthalene (193)



(*R*)-**191a** (*R*)-**193**

MOM-Cl was prepared *in situ* according to a literature procedure by *Berliner and Belecki*.[168] An argon-flooded flask equipped with a reflux condenser was charged with 6.50 mL (73.5 mmol, 4.19 eq.) of dimethoxymethane, catalytic amounts of $ZnBr_2$ and 19 mL dry toluene. While cooling with a reflux condenser, 5.00 mL (70.1 mmol, 3.99 eq.) of acetyl chloride were slowly added and the reaction mixture was stirred for 4 h at rt.

A separate argon-flooded *Schlenk* flask was charged with 2.47 g (61.7 mmol, 3.52 eq.) of NaH (60%) suspended in 88 mL dry THF. 5.02 g (17.6 mmol, 1.00 eq.) of (*R*)-BINOL (**191a**) were added in portions and the reaction mixture was stirred for 30 min. The prepared MOM-Cl solution was added *via* a dropping funnel and the reaction mixture was stirred at rt. After 19 h, full consumption of the starting material was indicated by TLC and the reaction was slowly terminated by adding 25 mL sat. aq. NH_4Cl solution. The organic solvent was removed under reduced pressure. The remaining aqueous phase was diluted with H_2O and extracted three times with 50 mL CH_2Cl_2. The combined organic layers were washed with 70 mL sat. aq. NaCl-solution, dried over $MgSO_4$ and the solvent was removed under reduced pressure. The crude product was recrystallized from *n*-hexane/CH_2Cl_2 to afford 5.74 g (15.3 mmol, 87%, Lit.[118]: quant.) of MOM-BINOL (*R*)-**193** as colourless crystals.



M($C_{24}H_{22}O_4$) 374.44 g/mol.

R_f (SiO_2, *c*-Hex/EtOAc 10:1) = 0.33.

Melting point 101-102 °C (Lit.[169]: 104-105 °C).

^{1}H NMR (300 MHz, $CDCl_3$), δ [ppm] = 7.93 (d, $^3J_{HH}$ = 9.0 Hz, 2H, H-4), 7.85 (d, $^3J_{HH}$ = 8.1 Hz, 2H, H-6), 7.56 (d, $^3J_{HH}$ = 9.0 Hz, 2H, H-3), 7.32 (ddd, $^3J_{HH}$ = 8.1, 6.5 Hz, $^4J_{HH}$ = 1.5 Hz, 2H, H-7), 7.26-7.11 (m, 4H, H-8, H-9), 5.07 (d, $^3J_{HH}$ = 6.8 Hz, 2H, H-11a), 4.96 (d, $^3J_{HH}$ = 6.8 Hz, 2H, H-11b), 3.13 (s, 6H, H-12).

^{13}C NMR (75 MHz, $CDCl_3$), δ [ppm] = 152.8 (C-2), 134.1 (C-10), 130.0 (C-5), 129.5 (C-4), 128.0 (C-6), 126.4 (C-7), 125.7 (C-8), 124.2 (C-3), 121.4 (C-1), 117.4 (C-9), 95.3 (C-11), 55.9 (C-12).

FT-IR ATR, v [cm^{-1}] = 3054 (w), 2999 (w), 2952 (w), 2902 (w), 2849 (w), 2825 (w), 2787 (w), 2114 (w), 1942 (w), 1759 (w), 1621 (w), 1592 (w), 1507 (m), 1477 (w), 1463 (m), 1445 (w), 1432 (w), 1403 (w), 1356 (w), 1331 (w), 1299 (w), 1272 (w), 1261 (w), 1239 (s), 1196 (m), 1161 (m), 1146 (s), 1088 (m), 1068 (m), 1032 (s), 1010 (s), 958 (w), 920 (s), 910 (m), 897 (m), 870 (w), 823 (m), 809 (s), 787 (w), 776 (m), 766 (m), 754 (s), 704 (w), 688 (m), 666 (w), 651 (w), 636 (w), 614 (m), 574 (w), 536 (w), 503 (w), 451 (w), 440 (w), 412 (w).

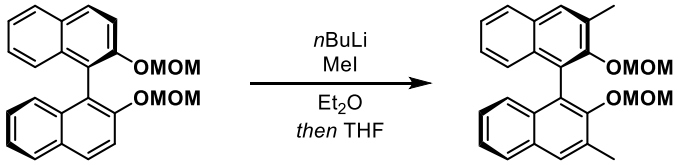
GC-MS m/z (%) = 374 (26, [M]), 330 (7), 313 (13), 298 (33), 284 (17), 269 (100), 253 (27), 239 (62), 215 (11), 156 (15), 134 (10), 120 (30), 96 (22), 75 (15), 50 (17).

$[\alpha]_\lambda^{20}$ *S*-enantiomer: (0.33 g/100 mL in $CHCl_3$): $[\alpha]_{365}$ = -751 °, $[\alpha]_{436}$ = -250 °, $[\alpha]_{546}$ = -111 °, $[\alpha]_{579}$ = -93 °, $[\alpha]_{589}$ = -88 °.

R-enantiomer: (0.345 g/100 mL in $CHCl_3$): $[\alpha]_{365}$ = 740 °, $[\alpha]_{436}$ = 246 °, $[\alpha]_{546}$ = 113 °, $[\alpha]_{579}$ = 97 °, $[\alpha]_{589}$ = 93 °.

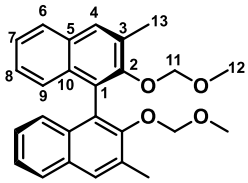
The analytical data is in accordance with the literature.[169]

10.2.1.2 Synthesis of (*R*)-2,2'-bis(methoxymethoxy)-3,3'-dimethyl-1,1'-binaphthalene (194)



(*R*)-**193** (*R*)-**194**

Following a procedure by *Chong et al.*,[118] an argon-flooded *Schlenk* flask was charged with 3.01 g (8.04 mmol, 1.00 eq.) of MOM-BINOL (*R*)-**193** and 110 mL dry Et_2O. To the solution, 12.0 mL (24.7 mmol, 3.08 eq.) of *n*BuLi (2.06 M in THF) were slowly added and the reaction mixture was stirred for 3 h at rt. Then, 50 mL dry THF were added and the reaction mixture was stirred for 30 min at rt. Upon ice bath cooling, 1.80 mL (28.9 mmol, 3.60 eq.) of MeI were added and the reaction mixture was stirred at rt. After indicating full conversion by TLC after 25 min, the reaction was terminated by the addition of 40 mL H_2O and 40 mL sat. aq. NH_4Cl-solution. The aqueous phase was extracted twice with 80 mL EtOAc. The combined organic phases were washed with 80 mL sat. aq. NaCl-solution, dried over $MgSO_4$ and the solvent was removed under reduced pressure. The crude product was purified by column chromatography (SiO_2, *c*-Hex/EtOAc 15:1) to afford 2.87 g (7.14 mmol, 89%, Lit.[118]: 96%) of Me-MOM-BINOL (*R*)-**194** as a light yellow solid.



M ($C_{26}H_{26}O_4$) 402.49 g/mol.

R_f (SiO_2, *c*-Hex/EtOAc 10:1) = 0.51.

Melting point 90-92 °C (Lit.[170]: 90-92 °C).

^{1}H NMR (300 MHz, $CDCl_3$), δ [ppm] = 7.81-7.79 (m, 4H, H-4, H-6), 7.36 (ddd, $^3J_{HH}$ = 8.1, 5.7 Hz, $^4J_{HH}$ = 2.3 Hz, 2H, H-7), 7.24-7.13 (m, 4H, H-8, H-9), 4.59 (d, $^3J_{HH}$ = 5.9 Hz, 2H, H-11a), 4.47 (d, $^3J_{HH}$ = 5.9 Hz, 2H, H-11b), 2.83 (s, 6H, H-12), 2.58 (s, 6H, H-13).

^{13}C NMR (75 MHz, $CDCl_3$), δ [ppm] = 153.4 (C-2), 133.2 (C-10), 131.8 (C-3), 131.1 (C-5), 129.9 (C-4), 127.3 (C-6), 126.3 (C-8), 125.7 (C-9), 125.5 (C-1), 125.0 (C-7), 98.8 (C-11), 56.6 (C-12), 18.0 (C-13).

FT-IR ATR, ν [cm^{-1}] = 3672 (w), 3053 (w), 2956 (w), 2940 (w), 2829 (w), 1912 (w), 1689 (w), 1626 (w), 1596 (w), 1499 (w), 1461 (w), 1445 (w), 1426 (m), 1395 (w), 1377 (w), 1357 (m), 1334 (w), 1287 (w), 1260 (w), 1237 (m), 1207 (m), 1180 (w), 1151 (s), 1104 (m), 1097 (m), 1062 (s), 1037 (m), 969 (s), 940 (m), 914 (s), 897 (m), 878 (s), 845 (w), 784 (w), 753 (s), 741 (s), 722 (m), 700 (m),

679 (w), 666 (w), 644 (w), 625 (w), 608 (w), 572 (w), 544 (w), 530 (m), 476 (w), 457 (w), 444 (w), 427 (w), 404 (w).

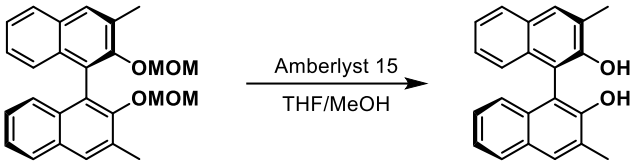
GC-MS *m/z* (%) = 402 (12, [M]), 388 (6), 358 (9), 340 (8), 326 (100), 311 (34), 298 (74), 283 (50), 268 (22), 252 (32), 239 (26), 224 (6), 207 (13), 189 (15), 170 (9), 152 (8), 141 (9), 126 (12), 115 (18), 105 (6), 90 (6), 71 (6), 56 (11).

$[\alpha]_\lambda^{20}$ *S*-enantiomer: (0.42 g/100 mL in $CHCl_3$): $[\alpha]_{365}$ = 881 °, $[\alpha]_{436}$ = 490 °, $[\alpha]_{546}$ = 254 °, $[\alpha]_{579}$ = 218 °, $[\alpha]_{589}$ = 208 °.

R-enantiomer: (0.39 g/100 mL in $CHCl_3$): $[\alpha]_{365}$ = -876 °, $[\alpha]_{436}$ = -481 °, $[\alpha]_{546}$ = -256 °, $[\alpha]_{579}$ = -215 °, $[\alpha]_{589}$ = -208 °.

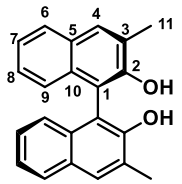
The analytical data is in accordance with the literature.[170]

10.2.1.3 Synthesis of (*R*)-3,3'-dimethyl-[1,1'-binaphthalene]-2,2'-diol (191b)



(*R*)-**194** (*R*)-**191b**

Following a procedure by *Chong et al.*[118], an argon-flooded *Schlenk* flask was charged with 2.35 g (5.84 mmol, 1.00 eq.) of BINOL-substrate (*R*)-**194** and 3.01 g *Amberlyst 15* suspended in 120 mL dry THF/MeOH (1:1). The reaction mixture was heated to reflux. After 18.5 h, full conversion was indicated by TLC. The suspension was filtered and the solvent of the filtrate was removed under reduced pressure. The crude product was recrystallized from *n*-hexane/CH_2Cl_2 to afford 1.56 g (4.96 mmol, 85%, Lit.[118]: quant.) of the desired product (*R*)-**191b** as colourless crystals.



M ($C_{22}H_{18}O_2$) 314.38 g/mol.

R_f (SiO_2, *c*-Hex/EtOAc 10:1) = 0.50.

Melting point 204-205 °C (Lit.[118]: 201-202 °C).

^{1}H NMR (300 MHz, $CDCl_3$), δ [ppm] = 7.83-7.77 (m, 4H, H-4, H-6), 7.32 (ddd, $^3J_{HH}$ = 8.1, 6.9 Hz, $^4J_{HH}$ = 1.2 Hz, 2H, H-7), 7.22 (ddd, $^3J_{HH}$ = 8.2, 6.9 Hz, $^4J_{HH}$ = 1.2 Hz, 2H, H-8), 5.07 (s, 2H, *O*H), 2.50 (s, 6H, H-11).

^{13}C NMR (75 MHz, $CDCl_3$), δ [ppm] = 152.2 (C-2), 132.3 (C-10), 130.9 (C-4), 129.6 (C-5), 127.7 (C-6), 127.2 (C-3), 126.5 (C-8), 124.2 (C-9), 124.1 (C-7), 110.6 (C-1), 17.1 (C-11).

FT-IR ATR, v [cm^{-1}] = 3672 (w), 3544 (w), 3514 (m), 3055 (w), 2972 (w), 2943 (w), 2911 (w), 1926 (w), 1625 (w), 1602 (w), 1506 (m), 1460 (w), 1448 (m), 1425 (m), 1385 (m), 1360 (m), 1309 (w), 1289 (w), 1262 (w), 1214 (s), 1194 (s), 1159 (m), 1142 (s), 1095 (s), 1035 (m), 1023 (m), 1007 (m), 949 (w), 931 (w), 884 (m), 865 (w), 852 (w), 780 (m), 747 (s), 691 (m), 672 (m), 605 (s), 550 (w), 525 (w), 451 (m), 442 (m), 407 (m).

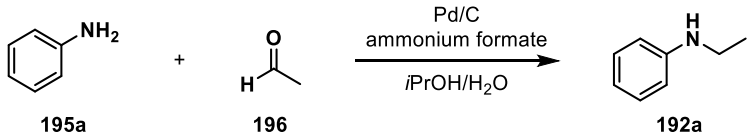
GC-MS *m/z* (%) = 314 (100, [M]), 296 (9), 281 (<5), 270 (7), 254 (12), 239 (13), 228 (9), 215 (11), 195 (<5), 178 (<5), 157 (9), 141 (9), 128 (33), 115 (13), 102 (<5), 88 (<5), 77 (11), 63 (5), 51 (5).

$[\alpha]_\lambda^{20}$ *S*-enantiomer: (0.49 g/100 mL in $CHCl_3$): $[\alpha]_{365}$ = -554 °, $[\alpha]_{436}$ = -133 °, $[\alpha]_{546}$ = -46 °, $[\alpha]_{579}$ = -37 °, $[\alpha]_{589}$ = -34 °.

R-enantiomer: (0.365 g/100 mL in $CHCl_3$): $[\alpha]_{365}$ = 518 °, $[\alpha]_{436}$ = 123 °, $[\alpha]_{546}$ = 46 °, $[\alpha]_{579}$ = 39 °, $[\alpha]_{589}$ = 37 °.

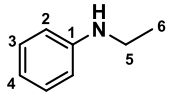
The analytical data is in accordance with the literature.[118]

10.2.1.4 Synthesis of *N*-ethylaniline (192a)



195a **196** **192a**

Following a procedure by *Byun et al.*[119], a round-bottom flask was charged with 526 mg (0.494 mmol, 9.81 mol%) of Pd/C (10 *w*%) suspended in 45 mL *i*PrOH. A solution of 1.60 g (25.4 mmol, 5.12 eq.) ammonium formate in 4.6 mL H_2O was added and stirred for 15 min at rt. At 0 °C, 0.46 mL (5.04 mmol, 1.02 eq.) of aniline (**195a**) and 0.28 mL (4.96 mmol, 1.00 eq.) of acetaldehyde (**196**) were added and the reaction mixture was stirred at rt. After 1 h, full conversion was indicated by TLC. The suspension was filtered over celite, washed with CH_2Cl_2 and the solvent was removed under reduced pressure. The crude product was purified by column chromatography (SiO_2, *c*-Hex/EtOAc 30:1) to afford 355 mg (2.63 mmol, 53%, Lit.[119]: 91%) of the desired product **192a** as a yellow oil.



M ($C_8H_{11}N$) 121.18 g/mol.

R_f (SiO_2, *c*-Hex/EtOAc 10:1) = 0.32.

^{1}H NMR (500 MHz, $CDCl_3$), δ [ppm] = 7.20-7.13 (m, 2H, H-3), 6.69 (tt, $^3J_{HH}$ = 7.4 Hz, $^4J_{HH}$ = 1.0 Hz, 1H, H-4), 6.60-6.58 (m, 2H, H-2), 3.50 (s, 1H, *N*H), 3.14 (q, $^3J_{HH}$ = 7.1 Hz, 2H, H-5), 1.24 (t, $^3J_{HH}$ = 7.1 Hz, 3H, H-6).

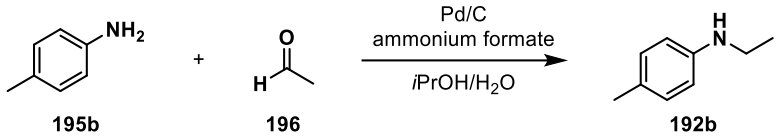
^{13}C NMR (126 MHz, $CDCl_3$), δ [ppm] = 148.6 (C-1), 129.3 (C-3), 117.3 (C-4), 112.8 (C-2), 38.6 (C-5), 15.0 (C-6).

FT-IR ATR, ν [cm^{-1}] = 3402 (br), 3052 (w), 3021 (w), 2969 (w), 2928 (w), 2872 (w), 1918 (w), 1824 (w), 1761 (w), 1602 (s), 1505 (s), 1480 (m), 1381 (w), 1319 (m), 1279 (m), 1257 (m), 1179 (m), 1146 (m), 1099 (w), 1028 (w), 930 (w), 868 (w), 746 (s), 691 (s), 617 (w).

GC-MS *m/z* (%) = 121 (100, [M]), 106 (100), 77 (97), 51 (65).

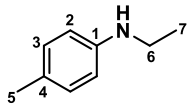
The analytical data is in accordance with the literature.[119]

10.2.1.5 Synthesis of *N*-ethyl-4-methylaniline (192b)



195b 196 192b

Following a procedure by *Byun et al.*[119], a round-bottom flask was charged with 321 mg (0.30 mmol, 10.1 mol%) of Pd/C (10%) suspended in 20 mL *i*PrOH. A solution of 953 mg (15.1 mmol, 5.06 eq.) ammonium formate in 2.0 mL H_2O was added and the mixture was stirred at rt for 20 min. Under ice bath cooling, 320 mg (2.99 mmol, 1.00 eq.) of *p*-toluidine (**195b**) and 0.17 mL (3.01 mmol, 1.01 eq.) of acetaldehyde (**196**) were added and the reaction mixture was stirred at rt. After 1 h, full conversion of the starting material was indicated by TLC. The suspension was filtered over a pad of celite, washed with CH_2Cl_2 and the solvent was removed under reduced pressure. The remaining oil was diluted with 40 mL CH_2Cl_2 and washed three times with 20 mL sat. aq. NaCl-solution. The organic phase was dried over $MgSO_4$ and the solvent was removed under reduced pressure. The crude product was purified by column chromatography (SiO_2, *c*-Hex/EtOAc 10:1) to afford 252 mg (1.84 mmol, 62%, Lit.[119]: 71%) of the desired amine **192b** as an orange-yellow oil.



M ($C_9H_{13}N$) 135.21 g/mol.

R_f (SiO_2, *c*-Hex/EtOAc 10:1) = 0.58.

^{1}H NMR (300 MHz, $CDCl_3$), δ [ppm] = 6.97 (d, $^3J_{HH}$ = 8.2 Hz, 2H, H-3), 6.53 (d, $^3J_{HH}$ = 8.4 Hz, 2H, H-2), 3.29 (s, 1H, *N*H), 3.12 (q, $^3J_{HH}$ = 7.1 Hz, 2H, H-6), 2.23 (s, 3H, H-5), 1.22 (t, $^3J_{HH}$ = 7.1 Hz, 3H, H-7).

^{13}C NMR (75 MHz, $CDCl_3$), δ [ppm] = 146.3 (C-1), 129.8 (C-3), 126.5 (C-4), 113.1 (C-2), 38.9 (C-6), 20.5 (C-5), 15.1 (C-7).

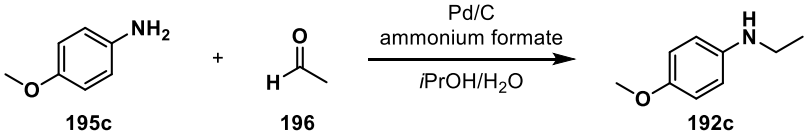
FT-IR ATR, v [cm^{-1}] = 3398 (w), 3016 (w), 2969 (w), 2921 (w), 2868 (w), 2733 (w), 1864 (w), 1748 (w), 1618 (m), 1519 (s), 1482 (m), 1449 (w), 1405 (w), 1378 (w), 1317 (m), 1302 (m), 1275 (m), 1252 (m), 1182 (m), 1146 (m), 1121 (w),

1109 (w), 1058 (w), 986 (w), 931 (w), 803 (s), 705 (w), 560 (w), 507 (m), 414 (m).

GC-MS *m/z* (%) = 135 (42, [M]), 120 (100), 106 (6), 91 (21), 77 (10), 51 (3).

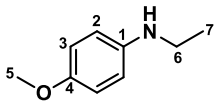
The analytical data is in accordance with the literature.[119]

10.2.1.6 Synthesis of *N*-ethyl-4-methoxyaniline (192c)



195c 196 192c

Following a procedure by *Byun et al.*[119], a round-bottom flask was charged with 318 mg (0.299 mmol, 9.90 mol%) of Pd/C (10 *w*%) suspended in 22 mL *i*PrOH. A solution of 948 mg (15.0 mmol, 4.98 eq.) ammonium formate in 2.2 mL H_2O was added and stirred at rt for 20 min. At 0 °C, 372 mg (3.02 mmol, 1.00 eq.) of *p*-anisidine (**195c**) and 0.17 mL (3.01 mmol, 1.00 eq.) of acetaldehyde (**196**) were added and the reaction mixture was stirred at rt. After 1 h, full conversion of the starting material was indicated by TLC. The suspension was filtered over celite, washed with CH_2Cl_2 and the solvent was removed under reduced pressure. The remaining crude oil was diluted with 40 mL CH_2Cl_2 and washed three times with 20 mL sat. aq. NaCl-solution. The organic layer was dried over $MgSO_4$ and the solvent was removed under reduced pressure. The crude product was purified by column chromatography (SiO_2, *c*-Hex/EtOAc 10:1) to afford 309 mg (2.04 mmol, 68%) of the desired amine **192c** as a light-yellow oil.



M ($C_9H_{13}NO$) 151.21 g/mol.

R_f (SiO_2, *c*-Hex/EtOAc 10:1) = 0.23.

^{1}H NMR (300 MHz, $CDCl_3$), δ [ppm] = 6.77 (d, $^3J_{HH}$ = 8.9 Hz, 2H, H-3), 6.57 (d, $^3J_{HH}$ = 8.9 Hz, 2H, H-2), 3.73 (s, 3H, H-5), 3.19 (s, 1H, *N*H), 3.09 (q, $^3J_{HH}$ = 7.1 Hz, 2H, H-6), 1.22 (t, $^3J_{HH}$ = 7.1 Hz, 3H, H-7).

^{13}C NMR (75 MHz, $CDCl_3$), δ [ppm] = 152.1 (C-4), 142.9 (C-1), 115.0 (C-3), 114.2 (C-2), 55.9 (C-5), 39.5 (C-6), 15.1 (C-7).

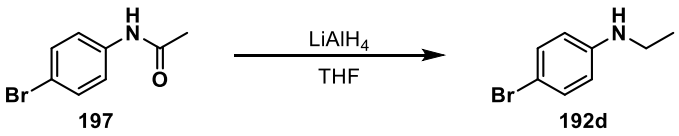
FT-IR ATR, ν [cm^{-1}] = 3385 (w), 3029 (w), 2967 (w), 2933 (w), 2902 (w), 2873 (w), 2831 (w), 2061 (w), 1844 (w), 1618 (w), 1509 (s), 1483 (m), 1464 (m), 1453 (m), 1407 (w), 1375 (w), 1352 (w), 1307 (w), 1296 (w), 1269 (w), 1248 (m),

1231 (s), 1179 (m), 1146 (m), 1104 (w), 1035 (m), 1004 (w), 931 (w), 815 (s), 754 (m), 714 (s), 641 (w), 578 (m), 518 (m), 416 (w).

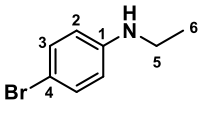
GC-MS *m/z* (%) = 151 (52, [M]), 136 (100), 122 (6), 108 (17), 94 (4), 80 (8), 53 (6).

The analytical data is in accordance with the literature.[171]

10.2.1.7 Synthesis of 4-bromo-*N*-ethylaniline (192d)



Following a procedure by *Al-Horani et al.*[120], an argon-flooded *Schlenk* flask was charged with 1.07 g (5.05 mmol, 1.00 eq.) of acetamide **197** dissolved in 25 mL dry THF. At 0 °C, 6.40 mL (15.4 mmol, 3.05 eq.) of $LiAlH_4$ (2.4 M in THF) were slowly added and stirring was continued at rt. After 21 h, full conversion of the starting material was indicated by TLC and the reaction mixture was diluted with 20 mL THF. Upon ice bath cooling, H_2O was slowly added until the gas evolution stopped. After the addition of 5 mL NaOH-solution (10%) and 15 mL H_2O, the suspension was filtered over a pad of celite and the solvent was removed under reduced pressure. The remaining oil was diluted with 50 mL CH_2Cl_2 and washed with 50 mL sat. aq. NaCl-solution. The organic phase was dried over $MgSO_4$ and the solvent was removed under reduced pressure. The crude product was purified by column chromatography (SiO_2, *c*-Hex/EtOAc 30:1) to afford 310 mg (1.55 mmol, 31%, Lit.[120]: 60%) of *N*-ethyl-4-bromoaniline (**192d**) as a yellow oil.



M ($C_8H_{10}BrN$) 200.08 g/mol.

R_f (SiO_2, *c*-Hex/EtOAc 10:1) = 0.46.

^{1}H NMR (300 MHz, $CDCl_3$), δ [ppm] = 7.23 (d, $^3J_{HH}$ = 8.9 Hz, 2H, H-3), 6.45 (d, $^3J_{HH}$ = 8.9 Hz, 2H, H-2), 3.54 (s, 1H, *N*H), 3.10 (q, $^3J_{HH}$ = 7.1 Hz, 2H, H-5), 1.23 (t, $^3J_{HH}$ = 7.1 Hz, 3H, H-6).

^{13}C NMR (75 MHz, $CDCl_3$), δ [ppm] = 147.5 (C-1), 132.0 (C-3), 114.3 (C-2), 108.7 (C-4), 38.6 (C-5), 14.8 (C-6).

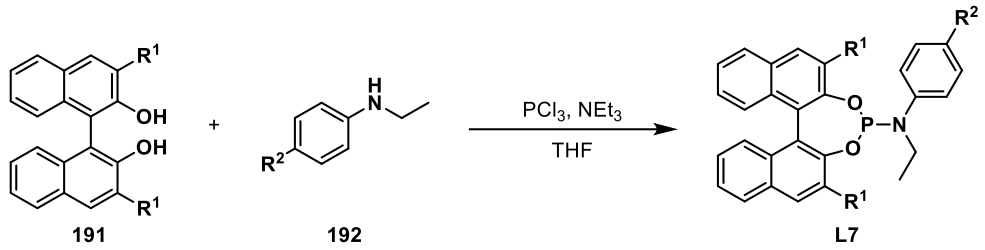
FT-IR ATR, ν [cm^{-1}] = 3671 (w), 3408 (w), 3022 (w), 2969 (w), 2928 (w), 2872 (w), 2575 (w), 1864 (w), 1735 (w), 1595 (s), 1496 (s), 1449 (m), 1398 (m), 1383 (w), 1356 (w), 1317 (m), 1293 (m), 1280 (m), 1252 (m), 1177 (m), 1147 (m),

1113 (w), 1098 (w), 1073 (m), 998 (m), 931 (w), 809 (s), 751 (w), 694 (m), 644 (m), 632 (m), 502 (s), 427 (m).

GC-MS *m/z* (%) = 200 (5, [M]), 199 (45), 186 (95), 184 (100), 172 (5), 170 (5), 155 (5), 118 (10), 105 (20), 91 (10), 81 (5), 78 (10), 76 (13), 65 (13), 63 (20), 50 (18).

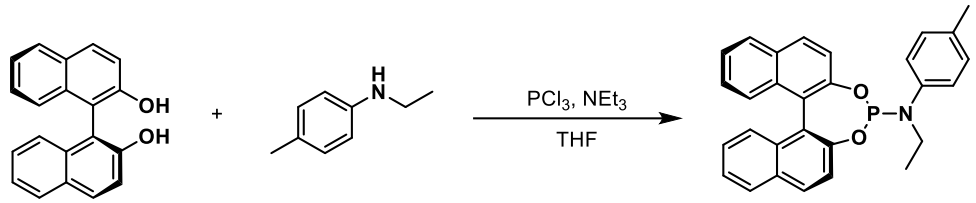
The analytical data is in accordance with the literature.[120]

10.2.1.8 Ligands: General protocol (GP1)



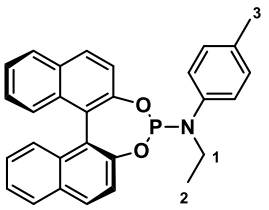
Following a procedure by *Albat*,[117] an argon-flooded *Schlenk* flask was charged with PCl_3 (1.10 eq.) diluted in dry THF (10.0 mL/mmol BINOL **191**). At 0 °C, NEt_3 (5.00 eq.) was added and the mixture was stirred for 10 min. Then, amine **192** (1.10 eq.) was added. After 3 h at 0 °C, BINOL **191** (1.00 eq.) was added and the reaction mixture was stirred at rt. After indication of full consumption of the starting materials by TLC, Et_2O (67.5 mL/mmol BINOL **191**) was added and the reaction mixture was stirred for another hour. The suspension was filtered over a pad of celite, washed with Et_2O and the solvent was removed under reduced pressure. The crude product was purified by column chromatography.

10.2.1.9 Synthesis of *O,O'*-(1,1'-Dinaphthyl-2,2'-diyl)-*N*,*N*-ethyl-3-methylphenyl phosphoramidite (L7a)



(*S*)-**191a** **192b** (*S*)-**L7a**

According to **GP1**, 121 mg (0.42 mmol, 1.00 eq.) of (*S*)-BINOL (**191a**), 62.0 mg (0.46 mmol, 1.10 eq.) of amine **192b**, 40.1 µL (0.46 mmol, 1.10 eq.) of PCl_3 and 0.29 mL (2.09 mmol, 4.96 eq.) of NEt_3 were reacted in 4.0 mL dry THF at rt for 16 h. The crude product was purified by column chromatography (SiO_2, *c*-Hex/toluene 10:1 → 5:1) to afford 57 mg (0.13 mmol, 30%, Lit.[68]: 42%) of phosphoramidite ligand (*S*)-**L7a** as a colourless foam.



M ($C_{29}H_{24}NO_2P$) 449.49 g/mol.

R_f (SiO_2, *c*-Hex/toluene 5:1) = 0.58.

Melting point 157-158 °C.

^{1}H NMR (500 MHz, $CDCl_3$), δ [ppm] = 7.97 (d, $^3J_{HH}$ = 8.8 Hz, 1H, H_{Ar}), 7.92-7.89 (m, 3H, H_{Ar}), 7.55 (d, $^3J_{HH}$ = 8.8 Hz, 1H, H_{Ar}), 7.44-7.39 (m, 4H, H_{Ar}), 7.34 (d, $^3J_{HH}$ = 8.5 Hz, 1H, H_{Ar}), 7.30-7.22 (m, 2H, H_{Ar}), 7.20-7.12 (m, 4H, H_{Ar}), 3.20 (dqd, $^2J_{HH}$ = 14.1 Hz, $^3J_{HH}$ = 11.8 Hz, $^3J_{HP}$ = 3.0 Hz, 1H, H-1a), 2.99 (dqd, $^2J_{HH}$ = 14.0 Hz, $^3J_{HH}$ = 11.7 Hz, $^3J_{HP}$ = 2.2 Hz, 1H, H-1b), 2.33 (s, 3H, H-3), 0.79 (t, $^3J_{HH}$ = 7.0 Hz, 3H, H-2).

^{13}C NMR (126 MHz, $CDCl_3$), δ [ppm] = 150.0 (C_{qAr}), 149.5 (C_{qAr}), 140.4 (C_{qAr}), 134.6 (C_{qAr}), 133.0 (C_{qAr}), 132.8 (C_{qAr}), 131.6 (C_{qAr}), 130.9 (C_{qAr}), 130.5 (CH_{Ar}), 130.1 (CH_{Ar}), 129.9 (2 CH_{Ar}), 128.5 (CH_{Ar}), 128.4 (CH_{Ar}), 127.2 (CH_{Ar}), 127.1 (CH_{Ar}), 126.2 (CH_{Ar}), 126.2 (CH_{Ar}), 126.1 (CH_{Ar}), 126.0 (CH_{Ar}), 125.0 (CH_{Ar}), 124.7 (CH_{Ar}), 124.2 (C_{qAr}), 122.7 (C_{qAr}), 122.2 (CH_{Ar}), 122.1 (CH_{Ar}), 41.3 (C-1), 21.0 (C-3), 14.6 (C-2).

^{31}P NMR (202 MHz, $CDCl_3$), δ [ppm] = 143.3.

FT-IR ATR, ν [cm^{-1}] = 3672 (w), 3051 (w), 3000 (w), 2977 (w), 2926 (w), 2875 (w), 1916 (w), 1890 (w), 1739 (w), 1646 (w), 1618 (w), 1589 (w), 1509 (m), 1466 (m), 1430 (w), 1405 (w), 1378 (w), 1357 (w), 1330 (w), 1306 (w), 1270 (w),

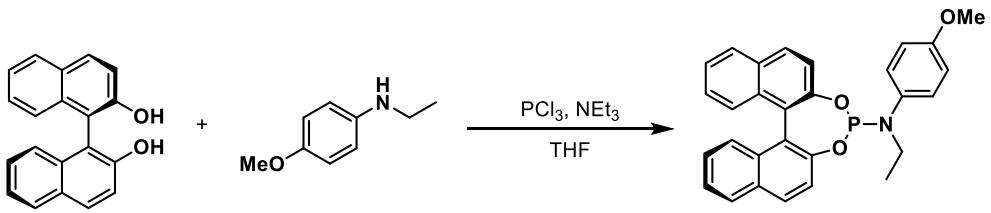
1249 (w), 1228 (s), 1203 (m), 1183 (w), 1167 (m), 1158 (m), 1140 (w), 1114 (w), 1093 (w), 1066 (m), 1027 (w), 1017 (w), 984 (w), 964 (w), 947 (s), 940 (s), 899 (m), 863 (w), 852 (w), 824 (s), 814 (s), 799 (s), 788 (s), 777 (m), 767 (s), 750 (s), 743 (s), 715 (m), 695 (m), 684 (m), 654 (w), 642 (m), 630 (m), 593 (m), 567 (m), 559 (s), 538 (w), 523 (s), 506 (m), 482 (w), 467 (w), 440 (m), 418 (w), 408 (w).

HR-MS (ESI) Calcd. $[M+H]^+$: 450.1617, found: 450.1622; calcd. $[M+Na]^+$: 472.1437, found: 472.1442.

$[\alpha]_\lambda^{20}$ (0.27 g/100 mL in $CHCl_3$): $[\alpha]_{365}$ = -1416 °, $[\alpha]_{436}$ = 148 °, $[\alpha]_{546}$ = 193 °, $[\alpha]_{579}$ = 178 °, $[\alpha]_{589}$ = 173 °.

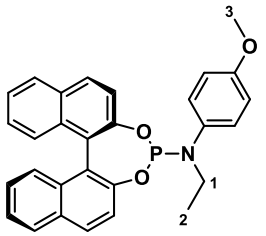
The analytical data is in accordance with the literature.[68]

10.2.1.10 Synthesis of *O,O'*-(1,1'-Dinaphthyl-2,2'-diyl)-*N,N*-ethyl-3-methoxy phenyl-phosphoramidite (L7b)



(*R*)-**191a** **192c** (*R*)-**L7b**

According to **GP1**, 174 mg (0.608 mmol, 1.00 eq.) of BINOL ((*R*)-**191a**), 103 mg (0.681 mmol, 1.12 eq.) of amine **192c**, 57.8 µL (0.661 mmol, 1.09 eq.) of PCl_3 and 0.43 mL (3.09 mmol, 5.07 eq.) of NEt_3 were reacted in 6.0 mL dry THF at rt for 17 h. The crude product was purified by column chromatography (SiO_2, *c*-Hex/toluene 5:1 → 2:1) to afford 216 mg (0.464 mmol, 76%) of phosphoramidite ligand (*R*)-**L7b** as a colourless foam.



M ($C_{29}H_{24}NO_3P$) 465.49 g/mol.

R_f (SiO_2, *c*-Hex/toluene 1:1) = 0.31.

Melting point 164-165 °C.

^{1}H NMR (500 MHz, $CDCl_3$), δ [ppm] = 7.97 (d, $^3J_{HH}$ = 8.8 Hz, 1H, H_{Ar}), 7.93-7.89 (m, 3H, H_{Ar}), 7.55 (d, $^3J_{HH}$ = 8.8 Hz, 1H, H_{Ar}), 7.45-7.39 (m, 4H, H_{Ar}), 7.33 (d, $^3J_{HH}$ = 8.5 Hz, 1H, H_{Ar}), 7.30-7.21 (m, 4H, H_{Ar}), 6.86 (d, $^3J_{HH}$ = 8.8 Hz, 2H, H_{Ar}), 3.79

(s, 3H, H-3), 3.19 (dqd, $^{2}J_{HH}$ = 14.1 Hz, $^{3}J_{HH}$ = 11.7 Hz, $^{3}J_{HP}$ = 3.4 Hz, 1H, H-1a), 2.94 (dqd, $^{2}J_{HH}$ = 14.0 Hz, $^{3}J_{HH}$ = 11.6 Hz, $^{3}J_{HP}$ = 2.7 Hz, 1H, H-1b), 0.78 (t, $^{3}J_{HH}$ = 7.0 Hz, 3H, H-2).

^{13}C NMR (126 MHz, $CDCl_3$), δ [ppm] = 157.5 (C_{qAr}), 150.0 (C_{qAr}), 149.5 (C_{qAr}), 135.7 (C_{qAr}), 135.5 (C_{qAr}), 133.0 (C_{qAr}), 131.6 (C_{qAr}), 130.8 (C_{qAr}), 130.5 (CH_{Ar}), 130.0 (CH_{Ar}), 128.6 (CH_{Ar}), 128.6 (CH_{Ar}), 128.5 (CH_{Ar}), 128.4 (CH_{Ar}), 127.2 (CH_{Ar}), 127.1 (CH_{Ar}), 126.2 (CH_{Ar}), 126.2 (CH_{Ar}), 125.0 (CH_{Ar}), 124.7 (CH_{Ar}), 124.2 (C_{qAr}), 122.6 (C_{qAr}), 122.2 (CH_{Ar}), 122.1 (2 CH_{Ar}), 114.5 (CH_{Ar}), 55.6 (C-3), 42.1 (C-1), 14.7 (C-2).

^{31}P NMR (202 MHz, $CDCl_3$), δ [ppm] = 143.0.

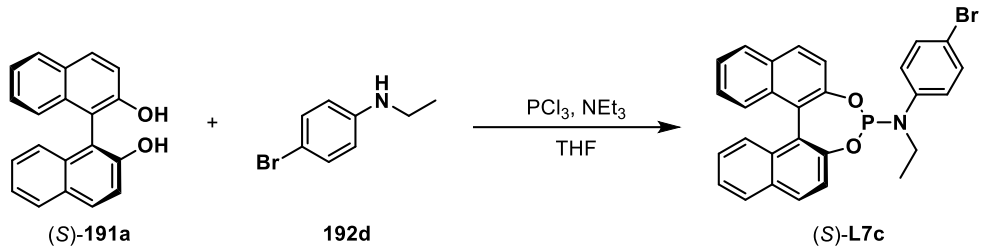
FT-IR ATR, ν [cm^{-1}] = 3672 (w), 2977 (w), 2928 (w), 2873 (w), 1917 (w), 1734 (w), 1618 (w), 1588 (w), 1508 (s), 1466 (m), 1443 (w), 1431 (w), 1404 (w), 1378 (w), 1357 (w), 1329 (m), 1306 (w), 1270 (w), 1242 (m), 1227 (s), 1202 (m), 1167 (m), 1141 (w), 1110 (w), 1094 (w), 1067 (s), 1034 (m), 984 (w), 948 (s), 940 (s), 901 (m), 865 (w), 852 (w), 818 (s), 799 (s), 788 (s), 777 (s), 767 (s), 752 (s), 744 (s), 722 (w), 696 (m), 685 (m), 630 (s), 593 (m), 569 (m), 559 (s), 539 (m), 525 (m), 506 (m), 478 (w), 467 (w), 440 (w), 411 (w).

HR-MS (ESI) Calcd. $[M+H]^+$: 466.1567, found: 466.1572; calcd. $[M+Na]^+$: 488.1386, found: 488.1392.

$[\alpha]_\lambda^{20}$ *S*-enantiomer: (0.26 g/100 mL in $CHCl_3$): $[\alpha]_{365}$ = -657 °, $[\alpha]_{436}$ = 380 °, $[\alpha]_{546}$ = 300 °, $[\alpha]_{579}$ = 269 °, $[\alpha]_{589}$ = 260 °.

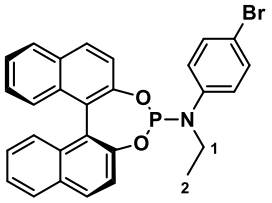
R-enantiomer: (0.19 g/100 mL in $CHCl_3$): $[\alpha]_{365}$ = 1267 °, $[\alpha]_{436}$ = -132 °, $[\alpha]_{546}$ = -169 °, $[\alpha]_{579}$ = -155 °, $[\alpha]_{589}$ = -151 °.

10.2.1.11 Synthesis of *O,O'*-(1,1'-Dinaphthyl-2,2'-diyl)-*N,N*-ethyl-3-bromo phenyl-phosphoramidite (L7c)



(*S*)-**191a** **192d** (*S*)-**L7c**

According to **GP1**, 85 mg (0.297 mmol, 1.00 eq.) of (*S*)-BINOL (**191a**), 64 mg (0.320 mmol, 1.08 eq.) of amine **192d**, 28.0 µL (0.320 mmol, 1.08 eq.) of PCl_3 and 0.20 mL (1.46 mmol, 4.90 eq.) of NEt_3 were reacted in 3.0 mL dry THF at rt for 18 h. The crude product was purified by column chromatography (SiO_2, *c*-Hex/toluene 30:1 → 10:1) to afford 30 mg (58.3 µmol, 20%) of phosphoramidite ligand **L7c** as a colourless foam.



M ($C_{28}H_{21}BrNO_2P$) 514.36 g/mol.

R_f (SiO_2, *c*-Hex/toluene 30:1) = 0.29.

Melting point 131-135 °C.

^{1}H NMR (500 MHz, $CDCl_3$), δ [ppm] = 7.99 (d, $^3J_{HH}$ = 8.8 Hz, 1H, H_{Ar}), 7.92 (d, $^3J_{HH}$ = 8.3 Hz, 2H, H_{Ar}), 7.89 (d, $^3J_{HH}$ = 8.7 Hz, 1H, H_{Ar}), 7.54 (d, $^3J_{HH}$ = 8.8 Hz, 1H, H_{Ar}), 7.45-7.39 (m, 5H, H_{Ar}), 7.37-7.23 (m, 4H, H_{Ar}), 7.15 (dd, $^3J_{HH}$ = 8.7, 1.1 Hz, 2H, H_{Ar}), 3.25 (dqd, $^2J_{HH}$ = 14.2 Hz, $^3J_{HH}$ = 7.1 Hz, $^3J_{HP}$ = 3.3 Hz, 1H, H-1a), 3.06 (dqd, $^2J_{HH}$ = 14.1 Hz, $^3J_{HH}$ = 7.1 Hz, $^3J_{HP}$ = 2.7 Hz, 1H, H-1b), 0.82 (t, $^3J_{HH}$ = 7.0 Hz, 3H, H-2).

^{13}C NMR (126 MHz, $CDCl_3$), δ [ppm] = 149.7 (C_{qAr}), 149.2 (C_{qAr}), 142.6 (C_{qAr}), 132.9 (C_{qAr}), 132.7 (C_{qAr}), 132.2 (2 CH_{Ar}), 131.6 (C_{qAr}), 130.9 (C_{qAr}), 130.6 (CH_{Ar}), 130.2 (CH_{Ar}), 128.5 (CH_{Ar}), 128.5 (CH_{Ar}), 127.2 (CH_{Ar}), 127.1 (CH_{Ar}), 126.6 (CH_{Ar}), 126.5 (CH_{Ar}), 126.4 (CH_{Ar}), 126.3 (CH_{Ar}), 125.1 (CH_{Ar}), 124.9 (CH_{Ar}), 124.2 (C_{qAr}), 122.6 (C_{qAr}), 122.0 (CH_{Ar}), 121.9 (CH_{Ar}), 117.5 (C_{qAr}), 40.9 (C-1), 14.5 (C-2).

^{31}P NMR (202 MHz, $CDCl_3$), δ [ppm] = 142.8.

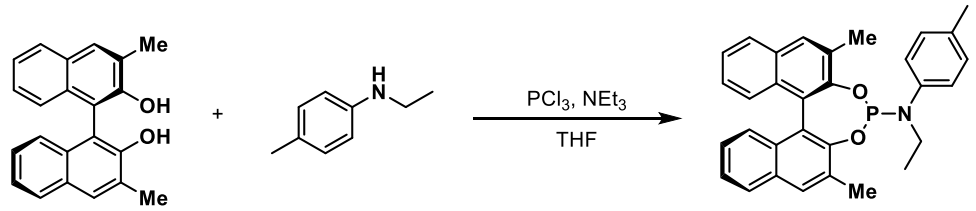
FT-IR ATR, ν [cm^{-1}] = 3054 (w), 2969 (w), 2926 (w), 1904 (w), 1734 (w), 1619 (w), 1587 (w), 1506 (w), 1486 (m), 1462 (m), 1431 (w), 1401 (w), 1371 (w), 1359 (w), 1325 (m), 1269 (w), 1224 (s), 1202 (m), 1156 (m), 1126 (w), 1086 (w),

1065 (s), 1008 (w), 982 (m), 943 (s), 890 (m), 865 (w), 851 (w), 818 (s), 800 (s), 780 (s), 765 (m), 748 (s), 698 (s), 682 (m), 657 (w), 637 (m), 628 (s), 600 (m), 578 (m), 556 (s), 537 (m), 516 (s), 490 (m), 474 (m), 446 (w), 432 (w), 415 (m).

HR-MS (ESI) Calcd. $[M+H]^+$: 514.0566, found: 514.0568.

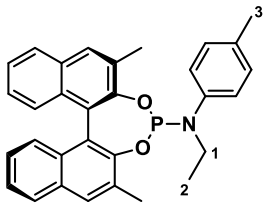
$[\alpha]_\lambda^{20}$ *S*-enantiomer: (0.28 g/100 mL in $CHCl_3$): $[\alpha]_{365}$ = -1104 °, $[\alpha]_{436}$ = 174 °, $[\alpha]_{546}$ = 130 °, $[\alpha]_{579}$ = 122 °, $[\alpha]_{589}$ = 119 °.

10.2.1.12 Synthesis of *O,O'*-(3,3'-Dimethyl-(1,1'-dinaphthyl)-2,2'-diyl)-*N,N*-ethyl-3-methyl-phenylphosphoramidite (L7d)



(*R*)-**191b** **192b** (*R*)-**L7d**

According to **GP1**, 213 mg (678 µmol, 1.00 eq.) of (*R*)-BINOL **191b**, 104 mg (0.769 mmol, 1.13 eq.) of amine **192b**, 64.7 µL (0.740 mmol, 1.09 eq.) of PCl_3 and 0.47 mL (3.37 mmol, 4.97 eq.) of NEt_3 were reacted in 7.0 mL dry THF at rt for 16 h. After purification by column chromatography (SiO_2, *c*-Hex/toluene 5:1 → 2:1) 230 mg (0.482 mmol, 71%) of phosphoramidite ligand **L7d** were afforded as a colourless foam.



M ($C_{31}H_{28}NO_2P$) 477.54 g/mol.

R_f (SiO_2, *c*-Hex/toluene 5:1) = 0.28.

Melting point 88-90 °C.

^{1}H NMR (500 MHz, $CDCl_3$), δ [ppm] = 7.84-7.82 (m, 3H, H_{Ar}), 7.77 (s, 1H, H_{Ar}), 7.37 (q, $^3J_{HH}$ = 8.0 Hz, 2H, H_{Ar}), 7.34 (d, $^3J_{HH}$ = 8.5 Hz, 1H, H_{Ar}), 7.26-7.13 (m, 7H, H_{Ar}), 3.19 (dqd, $^2J_{HH}$ = 14.2 Hz, $^3J_{HH}$ = 11.8 Hz, $^3J_{HP}$ = 2.4 Hz, 1H, H-1a), 3.01 (dqd, $^2J_{HH}$ = 14.0 Hz, $^3J_{HH}$ = 11.7 Hz, $^3J_{HP}$ = 1.9 Hz, 1H, H-1b), 2.63 (s, 3H, CH_3), 2.56 (s, 3H, CH_3), 2.33 (s, 3H, H-3), 0.79 (t, $^3J_{HH}$ = 7.0 Hz, 3H, H-2).

^{13}C NMR (126 MHz, $CDCl_3$), δ [ppm] = 149.3 (C_{qAr}), 148.7 (C_{qAr}), 140.9 (C_{qAr}), 140.7 (C_{qAr}), 133.9 (C_{qAr}), 131.8 (C_{qAr}), 131.7 (C_{qAr}), 131.4 (C_{qAr}), 130.8 (C_{qAr}), 130.5

(C_{qAr}), 130.3 (C_{qAr}), 129.9 (CH_{Ar}), 129.9 (2 CH_{Ar}), 129.6 (CH_{Ar}), 127.7 (CH_{Ar}), 127.6 (CH_{Ar}), 127.1 (CH_{Ar}), 127.0 (CH_{Ar}), 125.2 (CH_{Ar}), 124.9 (CH_{Ar}), 124.7 (CH_{Ar}), 124.5 (CH_{Ar}), 124.4 (CH_{Ar}), 124.3 (CH_{Ar}), 122.6 (C_{qAr}), 40.5 (C-1), 20.9 (C-3), 18.0 (CH_3), 17.6 (CH_3), 14.5 (C-2).

^{31}P NMR (202 MHz, $CDCl_3$), δ [ppm] = 140.6.

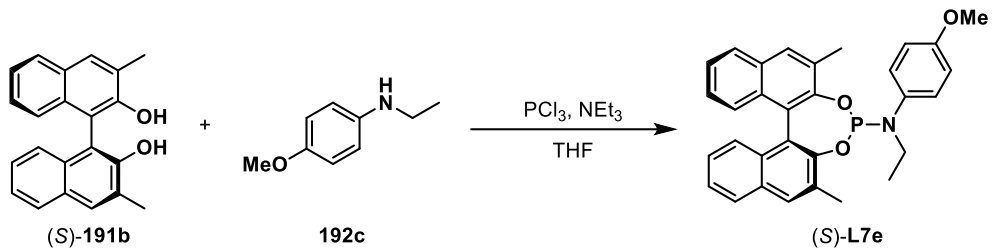
FT-IR ATR, v [cm^{-1}] = 3672 (w), 2978 (w), 2926 (w), 2875 (w), 1890 (w), 1734 (w), 1619 (w), 1589 (m), 1509 (m), 1466 (m), 1431 (w), 1407 (w), 1378 (w), 1358 (w), 1331 (m), 1306 (w), 1270 (w), 1249 (w), 1228 (s), 1203 (m), 1183 (w), 1167 (m), 1141 (w), 1114 (w), 1092 (m), 1066 (s), 1018 (w), 985 (w), 947 (s), 900 (m), 863 (m), 852 (w), 824 (m), 814 (s), 799 (s), 788 (s), 777 (s), 767 (s), 750 (s), 743 (s), 716 (m), 695 (m), 684 (m), 630 (m), 592 (m), 568 (m), 559 (m), 538 (w), 523 (s), 506 (m), 482 (w), 467 (w), 440 (w), 418 (w), 408 (w).

HR-MS (ESI) Calcd. $[M+H]^+$: 478.1930, found: 478.1928; calcd. $[M+Na]^+$: 500.1750, found: 500.1749.

$[\alpha]_\lambda^{20}$ *S*-enantiomer: (0.27 g/100 mL in $CHCl_3$): $[\alpha]_{365}$ = -1449 °, $[\alpha]_{436}$ = 219 °, $[\alpha]_{546}$ = 175 °, $[\alpha]_{579}$ = 162 °, $[\alpha]_{589}$ = 158 °.

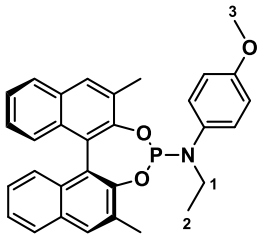
R-enantiomer: (0.305 g/100 mL in $CHCl_3$): $[\alpha]_{365}$ = 525 °, $[\alpha]_{436}$ = -346 °, $[\alpha]_{546}$ = -264 °, $[\alpha]_{579}$ = -235 °, $[\alpha]_{589}$ = -227 °.

10.2.1.13 Synthesis of *O,O'*-(3,3'-Dimethyl-(1,1'-dinaphthyl)-2,2'-diyl)-*N,N*-ethyl-3-methoxyphenylphosphoramidite (L7e)



(*S*)-**191b** **192c** (*S*)-**L7e**

According to **GP1**, 189 mg (0.601 mmol, 1.00 eq.) of (*S*)-BINOL **191b**, 100 mg (0.661 mmol, 1.10 eq.) of amine **192c**, 57.8 µL (0.661 mmol, 1.10 eq.) of PCl_3 and 0.46 mL (3.31 mmol, 5.50 eq.) of NEt_3 were reacted in 7.0 mL dry THF at rt for 15 h. The crude product was purified by column chromatography (SiO_2, *c*-Hex/toluene 2:1) to afford 205 mg (0.415 mmol, 69%) of phosphoramidite ligand **L7e** as a colourless foam.



M ($C_{31}H_{28}NO_3P$) 493.54 g/mol.

R_f (SiO_2, *c*-Hex/toluene 1:1) = 0.37.

Melting point 78-83 °C.

^{1}H NMR (500 MHz, $CDCl_3$), δ [ppm] = 7.83 (s, 1H, H_{Ar}), 7.82 (s, 2H, H_{Ar}), 7.77 (s, 1H, H_{Ar}), 7.37 (qd, $^3J_{HH}$ = 8.0, $^4J_{HH}$ = 1.1 Hz, 2H, H_{Ar}), 7.33 (d, $^3J_{HH}$ = 8.5 Hz, 1H, H_{Ar}), 7.27-7.13 (m, 5H, H_{Ar}), 6.87 (d, $^3J_{HH}$ = 8.8 Hz, 2H, H_{Ar}), 3.79 (s, 3H, H-3), 3.19 (dqd, $^2J_{HH}$ = 14.2 Hz, $^3J_{HH}$ = 7.0 Hz, $^3J_{HP}$ = 2.6 Hz, 1H, H-1a), 2.99 (dqd, $^2J_{HH}$ = 13.9 Hz, $^3J_{HH}$ = 7.0 Hz, $^3J_{HP}$ = 2.2 Hz, 1H, H-1b), 2.63 (s, 3H, CH_3), 2.59 (s, 3H, CH_3), 0.78 (t, $^3J_{HH}$ = 7.0 Hz, 3H, H-2).

^{13}C NMR (126 MHz, $CDCl_3$), δ [ppm] = 157.0 (C_{qAr}), 149.4 (C_{qAr}), 148.8 (C_{qAr}), 136.2 (C_{qAr}), 136.0 (C_{qAr}), 131.8 (C_{qAr}), 131.4 (C_{qAr}), 130.8 (C_{qAr}), 130.5 (C_{qAr}), 130.3 (C_{qAr}), 129.9 (CH_{Ar}), 129.6 (CH_{Ar}), 127.7 (CH_{Ar}), 127.6 (CH_{Ar}), 127.2 (CH_{Ar}), 127.1 (CH_{Ar}), 127.1 (CH_{Ar}), 127.0 (CH_{Ar}), 125.2 (CH_{Ar}), 125.2 (CH_{Ar}), 124.9 (CH_{Ar}), 124.7 (CH_{Ar}), 124.2 (C_{qAr}), 122.5 (C_{qAr}), 114.6 (2 CH_{Ar}), 55.6 (C-3), 41.4 (C-1), 18.1 (CH_3), 17.6 (CH_3), 14.6 (C-2).

^{31}P NMR (202 MHz, $CDCl_3$), δ [ppm] = 140.3.

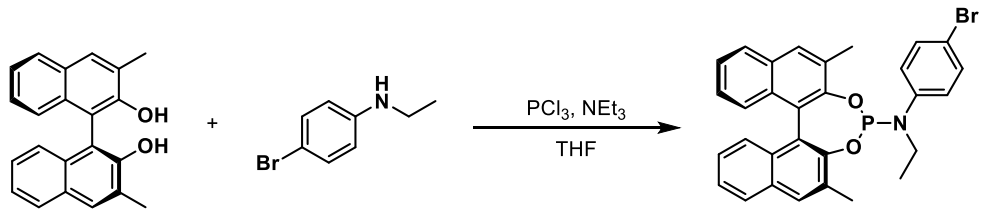
FT-IR ATR, ν [cm^{-1}] = 3672 (w), 2980 (w), 2932 (w), 2876 (w), 1944 (w), 1735 (w), 1589 (w), 1506 (s), 1465 (m), 1445 (w), 1431 (w), 1414 (m), 1377 (w), 1332 (w), 1314 (w), 1230 (s), 1214 (s), 1181 (m), 1159 (m), 1150 (m), 1112 (w),

1102 (m), 1089 (m), 1070 (m), 1032 (m), 984 (w), 958 (m), 949 (m), 901 (s), 894 (s), 864 (m), 826 (s), 814 (m), 799 (m), 790 (s), 778 (s), 766 (s), 752 (s), 742 (s), 722 (m), 697 (m), 684 (m), 664 (w), 641 (m), 631 (m), 626 (m), 612 (w), 592 (m), 568 (s), 559 (m), 539 (m), 526 (s), 520 (s), 506 (m), 487 (w), 463 (m), 432 (w), 419 (w), 407 (w).

HR-MS (ESI) Calcd. $[M+H]^+$: 494.1880, found: 494.1877; calcd. $[M+Na]^+$: 516.1699, found: 516.1697.

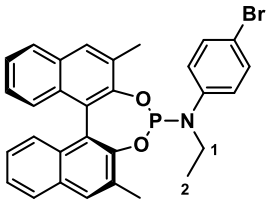
$[\alpha]_\lambda^{20}$ *S*-enantiomer: (0.26 g/100 mL in $CHCl_3$): $[\alpha]_{365}$ = -569 °, $[\alpha]_{436}$ = 381 °, $[\alpha]_{546}$ = 293 °, $[\alpha]_{579}$ = 263 °, $[\alpha]_{589}$ = 253 °.

10.2.1.14 Synthesis of *O,O'*-(3,3'-Dimethyl-(1,1'-dinaphthyl)-2,2'-diyl)-*N,N*-ethyl-3-bromophenylphosphoramidite (L7f)



(*S*)-**191b** **192d** (*S*)-**L7f**

According to **GP1**, 93 mg (0.296 mmol, 1.00 eq.) of (*S*)-BINOL **191b**, 64 mg (0.320 mmol, 1.08 eq.) of amine **192d**, 28.0 µL (0.320 mmol, 1.08 eq.) of PCl_3 and 0.20 mL (1.46 mmol, 4.92 eq.) of NEt_3 were reacted in 3.0 mL dry THF at rt for 18 h. The crude product was purified by column chromatography (SiO_2, *c*-Hex/toluene 20:1 → 3:1) to afford 65.0 mg (0.120 mmol, 41%) of phosphoramidite ligand **L7f** as a colourless foam.



M ($C_{30}H_{25}BrNO_2P$) 542.41 g/mol.

R_f (SiO_2, *c*-Hex/toluene 30:1) = 0.38.

Melting point 75-76 °C.

^{1}H NMR (500 MHz, $CDCl_3$), δ [ppm] = 7.84-7.82 (m, 2H, H_{Ar}), 7.76 (s, 1H, H_{Ar}), 7.43-7.36 (m, 4H, H_{Ar}), 7.32 (d, $^3J_{HH}$ = 8.4 Hz, 1H, H_{Ar}), 7.27-7.21 (m, 2H, H_{Ar}), 7.18-7.14 (m, 4H, H_{Ar}), 3.23 (dqd, $^2J_{HH}$ = 14.2 Hz, $^3J_{HH}$ = 7.1 Hz, $^3J_{HP}$ = 2.7 Hz, 1H, H-1a), 3.04 (dqd, $^2J_{HH}$ = 13.9 Hz, $^3J_{HH}$ = 7.0 Hz, $^3J_{HP}$ = 1.9 Hz, 1H, H-1b), 2.62 (s, 3H, CH_3), 2.48 (s, 3H, CH_3), 0.81 (t, $^3J_{HH}$ = 7.0 Hz, 3H, H-2).

^{13}C NMR (126 MHz, $CDCl_3$), δ [ppm] = 149.0 (C_{qAr}), 148.4 (C_{qAr}), 143.0 (C_{qAr}), 142.8 (C_{qAr}), 132.2 (2 CH_{Ar}), 131.8 (C_{qAr}), 131.7 (C_{qAr}), 131.5 (C_{qAr}), 130.9 (C_{qAr}), 130.3 (C_{qAr}), 130.1 (CH_{Ar}), 129.8 (CH_{Ar}), 127.7 (CH_{Ar}), 127.7 (CH_{Ar}), 127.1 (CH_{Ar}), 127.0 (CH_{Ar}), 125.4 (CH_{Ar}), 125.3 (CH_{Ar}), 125.1 (CH_{Ar}), 124.9 (CH_{Ar}), 124.8 (CH_{Ar}), 124.8 (CH_{Ar}), 124.3 (C_{qAr}), 122.6 (C_{qAr}), 116.6 (C_{qAr}), 40.1 (C-1), 17.9 (CH_3), 17.6 (CH_3), 14.4 (C-2).

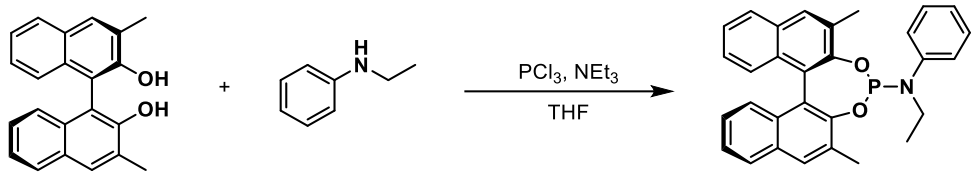
^{31}P NMR (202 MHz, $CDCl_3$), δ [ppm] = 140.0.

FT-IR ATR, v [cm^{-1}] = 3054 (w), 2972 (w), 2924 (w), 1735 (w), 1587 (w), 1501 (w), 1487 (m), 1460 (w), 1447 (w), 1412 (w), 1377 (w), 1362 (w), 1333 (w), 1235 (s), 1210 (m), 1181 (w), 1159 (w), 1147 (w), 1102 (m), 1086 (m), 1064 (m), 1041 (m), 1005 (w), 951 (w), 903 (s), 887 (m), 862 (m), 818 (w), 778 (s), 766 (m), 745 (s), 730 (m), 697 (m), 662 (w), 641 (w), 628 (m), 613 (w), 594 (m), 573 (m), 565 (m), 552 (w), 515 (s), 476 (w), 463 (w), 435 (w), 405 (w).

HR-MS (ESI) Calcd. $[M+H]^+$: 542.0879, found: 542.0880; calcd. $[M+Na]^+$: 564.0698, found: 564.0700.

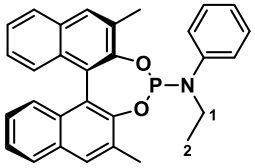
$[\alpha]_\lambda^{20}$ *S*-enantiomer: (0.41 g/100 mL in $CHCl_3$): $[\alpha]_{365}$ = -797 °, $[\alpha]_{436}$ = 250 °, $[\alpha]_{546}$ = 165 °, $[\alpha]_{579}$ = 152 °, $[\alpha]_{589}$ = 148 °.

10.2.1.15 Synthesis of *O,O'*-(3,3'-Dimethyl-(1,1'-dinaphthyl)-2,2'-diyl)-*N,N*-ethyl-phenyl-phosphoramidite (L7g)



(*R*)-**191b** **192a** (*R*)-**L7g**

According to **GP1**, 313 mg (0.996 mmol, 1.00 eq.) of (*R*)-Me-BINOL **191b** were reacted with 150 mg (1.11 mmol, 1.11 eq.) of amine **192a**, 96.2 µL (1.10 mmol, 1.10 eq.) of PCl_3 and 0.70 mL (5.02 mmol, 5.04 eq.) of NEt_3 in 2.00 mL dry THF at rt for 17 h. The crude product was purified by column chromatography (SiO_2, *c*-Hex/toluene 2:1) to afford 424 mg (0.915 mmol, 92%, Lit.[117]: 81%) of the desired phosphoramidite ligand **L7g** as a colourless foam.



M ($C_{30}H_{26}NO_2P$) 463.52 g/mol.

R_f (SiO_2, *c*-Hex/toluene 2:1) = 0.34.

Melting point 175-176 °C.

^{1}H NMR (500 MHz, $CDCl_3$), δ [ppm] = 7.84-7.83 (m, 2H, 2·H_{Ar}), 7.78 (m, 1H, H_{Ar}), 7.41-7.32 (m, 5H, 5·H_{Ar}), 7.31-7.26 (m, 2H, 2·H_{Ar}), 7.25-7.10 (m, 6H, 6·H_{Ar}), 3.24 (dqd, $^2J_{HH}$ = 14.2 Hz, $^3J_{HH}$ = 7.1 Hz, $^3J_{HP}$ = 2.5 Hz, 1H, H-1a), 3.07 (dqd, $^2J_{HH}$ = 13.9 Hz, $^3J_{HH}$ = 6.9 Hz, $^3J_{HP}$ = 1.8 Hz, 1H, H-1b), 2.63 (s, 3H, CH_3), 2.54 (s, 3H, CH_3), 0.82 (t, $^3J_{HH}$ = 7.0 Hz, 3H, H-2).

^{13}C NMR (126 MHz, $CDCl_3$), δ [ppm] = 149.3 (C_{qAr}), 148.7 (C_{qAr}), 143.8 (C_{qAr}), 143.5 (C_{qAr}), 131.9 (C_{qAr}), 131.5 (C_{qAr}), 130.9 (C_{qAr}), 130.5 (C_{qAr}), 130.3 (C_{qAr}), 130.0 (CH_{Ar}), 129.7 (CH_{Ar}), 129.2 (CH_{Ar}), 128.4 (CH_{Ar}), 127.7 (CH_{Ar}), 127.6 (CH_{Ar}), 127.1 (CH_{Ar}), 127.1 (CH_{Ar}), 125.5 (CH_{Ar}), 125.3 (CH_{Ar}), 125.2 (CH_{Ar}), 125.0 (CH_{Ar}), 124.7 (CH_{Ar}), 124.3 (C_{qAr}), 124.3 (C_{qAr}), 123.9 (CH_{Ar}), 123.8 (CH_{Ar}), 122.6 (CH_{Ar}), 40.2 (C-1), 18.0 (CH_3), 17.6 (CH_3), 14.6 (C-2).

^{31}P NMR (202 MHz, $CDCl_3$), δ [ppm] = 140.6.

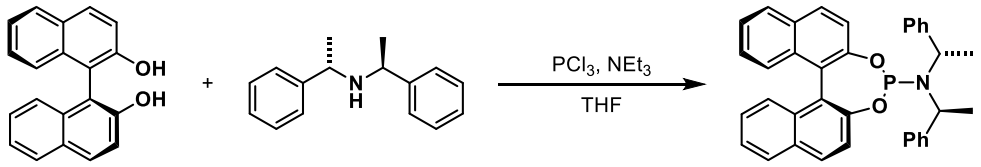
FT-IR ATR, ν [cm^{-1}] = 3055 (w), 2974 (w), 2925 (w), 1735 (w), 1597 (w), 1490 (w), 1461 (w), 1412 (w), 1376 (w), 1334 (w), 1234 (m), 1210 (m), 1181 (w), 1148 (w), 1102 (m), 1090 (m), 1064 (w), 1041 (w), 952 (m), 903 (m), 888 (m), 777 (m), 744 (m), 695 (m), 660 (w), 640 (w), 627 (w), 612 (w), 570 (m), 539 (w), 516 (m).

HRMS (ESI) Calcd. $[M+H]^+$: 464.17739, found: 464.17692; calcd. $[M+Na]^+$: 486.15934, found: 486.15835.

$[\alpha]_\lambda^{20}$ (0.19 g/100 mL in $CHCl_3$): $[\alpha]_{365}$ = 486 °, $[\alpha]_{436}$ = -431 °, $[\alpha]_{546}$ = -320 °, $[\alpha]_{579}$ = -285 °, $[\alpha]_{589}$ = -275 °.

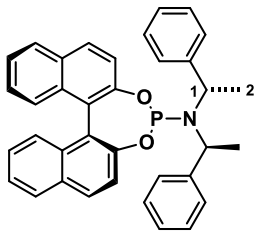
The analytical data is in accordance with the literature.[117]

10.2.1.16 Synthesis of *O,O'*-(1,1'-Dinaphthyl-2,2'-diyl)-*N,N*-di-1-phenylethyl-phosphoramidite (L2)



(*S*)-**191a** (*S,S*)-**205** (*S,S,S*)-**L2**

Following a procedure by *Mezzetti et al.*,[122] an argon-flooded *Schlenk* flask was charged with 87.5 µL (1.00 mmol, 1.01 eq.) of PCl_3 in 10 mL dry CH_2Cl_2 and was cooled to 0 °C. 0.70 mL (5.02 mmol, 5.08 eq.) of NEt_3 and 0.23 mL (1.01 mmol, 1.02 eq.) of (*S,S*)-amine **205** were added, respectively, and the reaction mixture was stirred at rt for 4 h. Then, 283 mg (0.988 mmol, 1.00 eq.) of (*S*)-BINOL (**191a**) were added. Full conversion of the starting material was indicated by TLC after 20 h. Then, 10 mL Et_2O were added. After another hour stirring at rt, the suspension was filtered over celite, washed with Et_2O and the solvent was removed under reduced pressure. The crude product was purified by column chromatography (SiO_2, *c*-Hex/toluene 5:1) to afford 483 mg (0.896 mmol, 91%, Lit.[122]: 87%) of the desired product **L2** as a colourless foam.



M ($C_{36}H_{30}NO_2P$) 539.62 g/mol.

R_f (SiO_2, *c*-Hex/toluene 30:1) = 0.54.

Melting point 81-83 °C.

^{1}H NMR (500 MHz, $CDCl_3$), δ [ppm] = 7.99 (d, $^3J_{HH}$ = 8.4 Hz, 1H, H_{Ar}), .7.91 (d, $^3J_{HH}$ = 8.2 Hz, 1H, H_{Ar}), 7.80 (d, $^3J_{HH}$ = 8.6 Hz, 1H, H_{Ar}), 7.72 (d, $^3J_{HH}$ = 8.9 Hz, 1H, H_{Ar}), 7.56 (d, $^3J_{HH}$ = 8.7 Hz, 1H, H_{Ar}), 7.41-7.38 (m, 1H, H_{Ar}), 7.36-7.33 (m, 3H, H_{Ar}), 7.27-7.20 (m, 4H, H_{Ar}), 7.21-7.14 (m, 9H, H_{Ar}), 4.41 (dq, $^3J_{HP}$ = 11.0 Hz, $^3J_{HH}$ = 7.0 Hz, 2H, H-1), 1.68 (2·s, 6H, H-2).

^{13}C NMR (126 MHz, $CDCl_3$), δ [ppm] = 150.7 (C_{qAr}), 150.6 (C_{qAr}), 149.9 (C_{qAr}), 143.2 (C_{qAr}), 138.0 (C_{qAr}), 133.0 (C_{qAr}), 132.9 (C_{qAr}), 131.5 (C_{qAr}), 130.6 (CH_{Ar}), 130.5 (C_{qAr}), 129.7 (CH_{Ar}), 129.2 (CH_{Ar}), 128.4 (CH_{Ar}), 128.4 (CH_{Ar}), 128.2 (CH_{Ar}), 128.1 (CH_{Ar}), 127.9 (CH_{Ar}), 127.3 (CH_{Ar}), 126.8 (CH_{Ar}), 126.0 (CH_{Ar}), 125.5 (CH_{Ar}), 124.9 (CH_{Ar}), 124.5 (CH_{Ar}), 122.5 (CH_{Ar}), 121.3 (CH_{Ar}), 54.6 (C-1), 23.2 (C-2), 23.1 (C-2).

^{31}P NMR (202 MHz, $CDCl_3$), δ [ppm] = 150.5.

FT-IR ATR, ν [cm^{-1}] = 3058 (w), 3027 (w), 2970 (w), 2930 (w), 1735 (w), 1618 (w), 1590 (w), 1495 (w), 1463 (w), 1430 (w), 1404 (w), 1371 (w), 1326 (w), 1271 (w), 1229 (m), 1201 (w), 1155 (w), 1114 (w), 1069 (m), 1049 (w), 1015 (w), 982 (w), 946 (m), 924 (m), 865 (w), 818 (m), 799 (w), 784 (m), 746 (m), 694 (m), 656 (w), 626 (w), 609 (w), 590 (w), 558 (w), 522 (w).

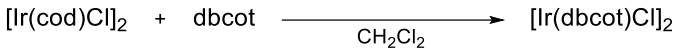
HRMS (ESI) Calcd. $[M+H]^+$: 540.20869, found: 540.20836; calcd. $[M+Na]^+$: 562.19064, found: 562.18960.

$[\alpha]_\lambda^{20}$ (0.345 g/100 mL in $CHCl_3$): $[\alpha]_{365}$ = -1192 °, $[\alpha]_{436}$ = -79 °, $[\alpha]_{546}$ = 15 °, $[\alpha]_{579}$ = 18 °, $[\alpha]_{589}$ = 18 °.

The analytical data is in accordance with the literature.[122]

10.2.2 Synthesis of Iridium-complexes

10.2.2.1 Synthesis of $[Ir(dbcot)Cl]_2$

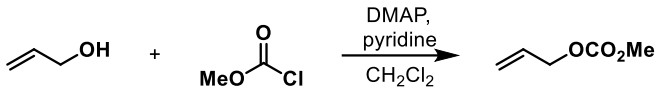


An argon-flooded *Schlenk* flask was charged with 255 mg (0.379 mmol, 1.00 eq.) of $[Ir(cod)Cl]_2$ dissolved in 6 mL dry CH_2Cl_2. 152 mg (0.744 mmol, 1.96 eq.) of dbcot were added and the reaction mixture was stirred at rt for 50 min. Then, CH_2Cl_2 was removed under reduced pressure. To the yellow solid, 2 mL CH_2Cl_2 and 8 mL *n*-hexane were added, the solid was filtered off and washed with cold *n*-hexane. After drying, the desired complex was obtained as a yellow solid in quantitative yield (327 mg, 0.379 mmol, Lit.[172]: 65%).

M($C_{32}H_{24}Ir_2Cl_2$) 863.87 g/mol.

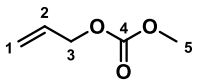
10.2.3 Synthesis of carbonates for Ir-catalysis

10.2.3.1 Synthesis of allyl methyl carbonate (143)



261 **262** **143**

Following a procedure by *Trost et al.*[173], an argon-flooded *Schlenk* flask was charged with 0.68 mL (10.0 mmol, 1.00 eq.) of allyl alcohol (**261**) dissolved in 50 mL dry CH_2Cl_2. At 0 °C, 247 mg (2.02 mmol, 0.20 eq.) of DMAP and 3.20 mL (39.7 mmol, 3.97 eq.) of pyridine were added. After 25 min, 2.30 mL (29.7 mmol, 2.97 eq.) of methyl chloroformate (**262**) were slowly added and stirring was continued at rt. After 21 hours, full consumption of the starting material was indicated *via* TLC and 30 mL HCl (1 M) were added. The organic layer was washed with 40 mL H_2O and 40 mL sat. aq. NaCl-solution, dried over $MgSO_4$ and the solvent was removed under reduced pressure. Allyl methyl carbonate (**143**) (940 mg, 8.10 mmol, 81%, Lit.[173]: 94%) was obtained as a colourless oil that could be used without further purification.



M ($C_5H_8O_3$) 116.12 g/mol.

R_f (SiO_2, *c*-Hex/EtOAc 10:1) = 0.53.

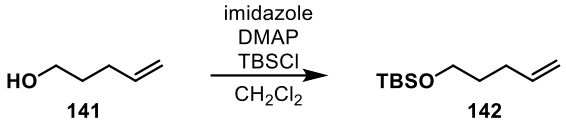
^{1}H NMR (300 MHz, $CDCl_3$), δ [ppm] = 5.94 (ddt, $^3J_{HH}$ = 17.1, 10.5, 5.7 Hz, 1H, H-2), 5.24-5.39 (m, 2H, H-1), 4.63 (dt, $^3J_{HH}$ = 5.7 Hz, $^4J_{HH}$ = 1.3 Hz, 2H, H-3), 3.78 (s, 3H, H-5).

^{13}C NMR (126 MHz, $CDCl_3$), δ [ppm] = 155.7 (C-4), 131.7 (C-2), 118.9 (C-1), 68.5 (C-3), 54.9 (C-5).

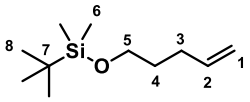
FT-IR ATR, ν [cm^{-1}] = 3090 (w), 2960 (w), 1747 (s), 1651 (w), 1587 (w), 1444 (m), 1365 (m), 1294 (m), 1252 (s), 1082 (w), 966 (m), 927 (m), 791 (m), 645 (w), 555 (w).

The analytical data is in accordance with the literature.[173]

10.2.3.2 Synthesis of *tert*-butyldimethyl(pent-4-en-1-yloxy)silane (142)



Following a procedure by *Stang and White*[110], an argon-flooded *Schlenk* flask was charged with 1.00 mL (9.68 mmol, 1.00 eq.) of 4-penten-1-ol (**141**) dissolved in 15 mL dry CH_2Cl_2 and cooled to 0 °C. 1.83 g (12.1 mmol, 1.25 eq.) of TBSCl, 1.08 g (15.9 mmol, 1.64 eq.) of imidazole and 71 mg (0.58 mmol, 0.06 eq.) of DMAP were added and stirring was continued at rt. Full consumption of the starting material was indicated *via* TLC after 2 h. The white suspension was filtered over a short silica pad and eluted with 150 mL *c*-Hex/EtOAc (100:1). The solvent of the filtrate was removed under reduced pressure to afford 1.70 g (8.49 mmol, 88%, Lit.[110]: 99%) of the compound **142** as a colourless oil, which could be used without further purification.



M ($C_{11}H_{24}OSi$) 200.397 g/mol.

R_f (SiO_2, *c*-Hex/EtOAc 10:1) = 0.69.

^{1}H NMR (300 MHz, $CDCl_3$), δ [ppm] = 5.82 (ddt, $^3J_{HH}$ = 16.9, 10.2, 6.6 Hz, 1H, H-2), 4.91-5.07 (m, 2H, H-1), 3.62 (t, $^3J_{HH}$ = 6.5 Hz, 2H, H-5), 2.05-2.16 (m, 2H, H-3), 1.61 (dt, $^3J_{HH}$ = 13.6, 6.6 Hz, 2H, H-4). 0.90 (s, 9H, H-8), 0.05 (s, 6H, H-6).

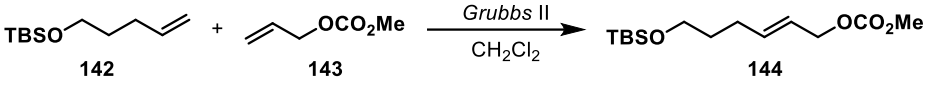
^{13}C NMR (75 MHz, $CDCl_3$), δ [ppm] = 138.9 (C-1), 114.7 (C-2), 62.7 (C-5), 32.2 (C-3), 30.2 (C-4), 26.1 (C-8), 18.5 (C-7), -5.1 (C-6).

FT-IR ATR, v [cm^{-1}] = 3080 (w), 2955 (w), 2930 (m), 2888 (w), 2858 (m), 2739 (w), 1642 (w), 1472 (w), 1444 (w), 1388 (w), 1362 (w), 1255 (m), 1098 (s), 1034 (w), 1006 (w), 939 (w), 911 (m), 833 (s), 773 (s), 718 (m), 662 (m).

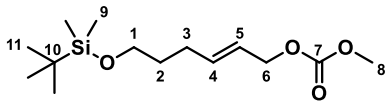
GC-MS *m/z* (%) = 143 (68), 113 (17), 101 (12), 89 (20), 75 (100), 59 (8), 41 (7).

The analytical data is in accordance with the literature.[110]

10.2.3.3 Synthesis of (*E*)-6-((*tert*-butyldimethylsilyl)oxy)hex-2-en-1-yl methyl carbonate (144)



An argon-flooded flask equipped with a reflux condenser was charged with 0.53 mL (4.67 mmol, 1.00 eq.) of allyl methyl carbonate (**143**) dissolved in 30 mL dry CH_2Cl_2. Then, 1.00 g (5.01 mmol, 1.07 eq.) of substrate **142** and 191 mg (0.225 mmol, 4.82 mol%) of *Grubbs* II catalyst were added and the reaction mixture was heated to reflux. After 20 h, full consumption of the starting material was indicated by TLC. The solvent was removed under reduced pressure. The crude product was purified by column chromatography (SiO_2, *c*-Hex/EtOAc 10:1) to afford the desired product **144** (646 mg, 2.24 mmol, 48%, *E*/*Z* 9:1) as an orange oil.



M ($C_{14}H_{28}O_4Si$) 288.46 g/mol.

R_f (SiO_2, *c*-Hex/EtOAc 5:1) = 0.48.

^{1}H NMR (600 MHz, $CDCl_3$, mixture of *E*/*Z*-isomers), δ [ppm] = 5.86-5.80 (m, 0.9H, H-4), 5.71-5.65 (m, 0.1H, H-4'), 5.63-5.55 (m, 1H, H-5), 4.69 (dd, $^3J_{HH}$ = 6.9 Hz, $^4J_{HH}$ = 1.2 Hz, 0.2H, H-6'), 4.57 (dd, $^3J_{HH}$ = 6.6 Hz, $^4J_{HH}$ = 1.0 Hz, 1.8H, H-6), 3.78 (s, 3H, H-8), 3.60 (t, $^3J_{HH}$ = 6.3 Hz, 2H, H-1), 2.18 (q, $^3J_{HH}$ = 6.6 Hz, 0.2H, H-3'), 2.13 (q, $^3J_{HH}$ = 7.2 Hz, 1.8H, H-3), 1.64-1.58 (m, 2H, H-2), 0.89 (s, 9H, H-11), 0.04 (s, 6H, H-9).

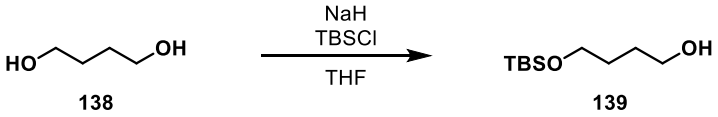
^{13}C NMR (151 MHz, $CDCl_3$, mixture of *E*/*Z*-isomers), δ [ppm] = 155.8 (C-7), 137.1 (C-4), 135.5 (C-4'), 123.6 (C-5), 123.3 (C-5'), 68.8 (C-6), 63.8 (C-6'), 62.5 (C-1), 54.8 (C-8), 32.5 (C-2'), 32.0 (C-2), 28.7 (C-3), 26.1 (C-11), 24.0 (C-3'), 18.5 (C-10), -5.2 (C-9).

FT-IR ATR, ν [cm^{-1}] = 2954 (m), 2930 (m), 2896 (w), 2857 (m), 2058 (w), 1749 (s), 1695 (m), 1442 (m), 1383 (w), 1254 (s), 1099 (s), 1006 (m), 945 (m), 834 (s), 774 (s), 733 (m), 662 (m).

HR-MS (EI) Calcd. $[M\text{-}C_2H_3O_2]^+$: 229.1624, found: 229.1981; calcd. $[M\text{-}C_4H_6O_3]^+$: 186.1440, found: 186.1349.

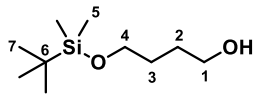
GC-MS *m/z* (%) = 155 (10), 133 (26), 101 (<5), 81 (100), 59 (10), 41 (6).

10.2.3.4 Synthesis of 4-((*tert*-butyldimethylsilyl)oxy)butan-1-ol (139)



138 139

Following a literature procedure by *Li et al.*[108], an argon-flooded *Schlenk* flask was charged with 1.44 g (36.1 mmol, 1.18 eq.) of NaH (60%) suspended in 50 mL dry THF. While cooling to 0 °C, 2.70 mL (30.6 mmol, 1.00 eq.) of 1,4-butandiol (**138**) were added and the reaction mixture was stirred at rt for 2 h. Then, 5.00 g (33.2 mmol, 1.08 eq.) TBSCl dissolved in 10 mL dry THF were added at 0 °C and stirring was continued at rt overnight. After 17 h, full consumption of the starting material was indicated by TLC and the reaction was terminated by the addition of 100 mL sat. aq. K_2CO_3-solution. The aqueous phase was extracted three times with 40 mL MTBE. The combined organic layers were dried over Na_2SO_4 and the solvent was removed under reduced pressure. The crude product was purified by column chromatography (SiO_2, *c*-Hex/EtOAc 2:1) to afford 5.52 g (27.0 mmol, 88%, Lit.[108]: 99%) of the mono-protected alcohol **139** as a colourless oil.



M ($C_{10}H_{24}SiO_2$) 204.39 g/mol.

R_f (SiO_2, *c*-Hex/EtOAc 2:1) = 0.31.

^{1}H NMR (300 MHz, $CDCl_3$), δ [ppm] = 3.66-3.59 (m, 4H, H-1, H-4), 2.76 (s, 1H, *O*H), 1.65-1.40 (m, 4H, H-2, H-3), 0.88 (s, 9H, H-7), 0.04 (s, 6H, H-5).

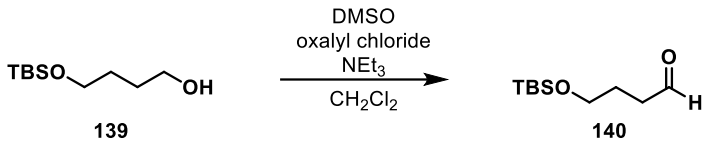
^{13}C NMR (75 MHz, $CDCl_3$), δ [ppm] = 63.4, 62.8 (C-1, C-4), 30.2, 29.9 (C-2, C-3), 26.0 (C-7), 18.4 (C-6), -5.3 (C-5).

FT-IR ATR, v [cm^{-1}] = 3339 (br), 2953 (m), 2929 (m), 2901 (m), 2857 (m), 1472 (m), 1464 (m), 1388 (m), 1254 (m), 1095 (s), 1067 (s), 1006 (m), 833 (s), 773 (s), 661 (m).

GC-MS *m/z* (%) = 147 (6), 105 (85), 75 (100), 55 (15).

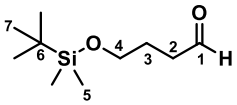
The analytical data is in accordance with the literature.[108]

10.2.3.5 Synthesis of 4-((*tert*-butyldimethylsilyl)oxy)butanal (140)



139 140

Following a literature procedure by *Wünsch et al.*[109], an argon-flooded *Schlenk* flask was charged with 1.80 mL (27.1 mmol, 2.22 eq.) of dry DMSO diluted in 24 mL dry CH_2Cl_2. The solution was cooled to -78 °C and 1.20 mL (14.0 mmol, 1.15 eq.) of oxalyl chloride were added. After stirring for 10 min, 36 mL dry CH_2Cl_2 and 2.50 g (12.2 mmol, 1.00 eq.) of alcohol **139** were added. After 1 h, 8.50 mL (61.0 mmol, 4.99 eq.) of NEt_3 were added and stirring was continued at -78 °C for 40 min and then for another 40 min at rt. The reaction mixture was washed once with 50 mL H_2O and twice with 20 mL aq. $KHSO_4$-solution (5%). The aqueous phase was extracted twice with 40 mL CH_2Cl_2. The combined organic layers were dried over $MgSO_4$ and the solvent was removed under reduced pressure. The crude product was purified by column chromatography (SiO_2, *c*-Hex/EtOAc 5:1) to afford 1.96 g (9.70 mmol, 79%, Lit.[109]: quant.) of aldehyde **140** as a light-yellow oil.



M ($C_{10}H_{22}SiO_2$) 202.37 g/mol.

R_f (SiO_2, *c*-Hex/EtOAc 5:1) = 0.48.

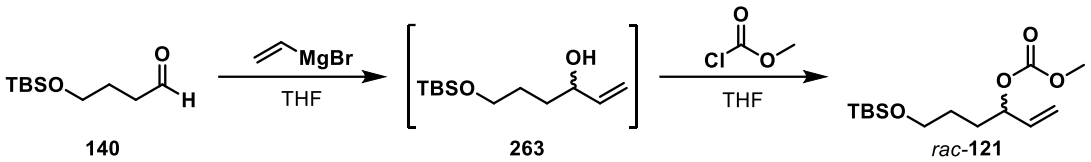
^{1}H NMR (300 MHz, $CDCl_3$), δ [ppm] = 9.77 (t, $^3J_{HH}$ = 1.7 Hz, 1H, H-1), 3.63 (t, $^3J_{HH}$ = 6.0 Hz, 2H, H-4), 2.48 (td, $^3J_{HH}$ = 7.1, 1.7 Hz, 2H, H-2), 1.88-1.80 (m, 2H, H-3), 0.87 (s, 9H, H-7), 0.02 (s, 6H, H-5).

^{13}C NMR (75 MHz, $CDCl_3$), δ [ppm] = 202.7 (C-1), 62.2 (C-4), 40.9 (C-2), 26.0 (C-7), 25.6 (C-3), 18.4 (C-6), -5.3 (C-5).

FT-IR ATR, ν [cm^{-1}] = 2954 (m), 2930 (m), 2887 (m), 2858 (m), 2715 (w), 1727 (s), 1472 (m), 1389 (m), 1254 (s), 1096 (s), 1006 (m), 939 (w), 833 (s), 774 (s), 662 (m).

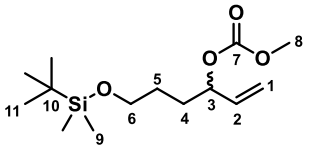
The analytical data is in accordance with the literature.[109]

10.2.3.6 Synthesis of 6-((*tert*-butyldimethylsilyl)oxy)hex-1-en-3-yl methyl carbonate (121)



140 263 *rac*-121

An argon-flooded *Schlenk* flask was charged with 812 mg (4.01 mmol, 1.00 eq.) of aldehyde **140** dissolved in 4.0 mL dry THF. The solution was cooled to 0 °C and 4.80 mL (4.80 mmol, 1.20 eq.) of vinyl magnesium bromide (1 M in THF) were added and stirring was continued at rt. After 3 h, full consumption of the starting material was indicated by TLC, the reaction mixture was cooled to 0 °C and 0.47 mL (6.02 mmol, 1.50 eq.) of methyl chloroformate were added. Stirring was continued at rt overnight. After 16 h, full consumption of the alcohol **263** was indicated by TLC and the reaction was terminated by adding 10 mL sat. aq. NH_4Cl-solution. The aqueous phase was extracted three times with 10 mL EtOAc. The combined organic layers were dried over $MgSO_4$ and the solvent was removed under reduced pressure. The crude product was purified by column chromatography (SiO_2, *c*-Hex/EtOAc 50:1) to afford 951 mg (3.30 mmol, 82%) of the carbonate *rac*-**121** as a light-yellow oil.



M ($C_{14}H_{28}O_4Si$) 288.46 g/mol.

R_f (SiO_2, *c*-Hex/EtOAc 50:1) = 0.19.

^{1}H NMR (500 MHz, $CDCl_3$), δ [ppm] = 5.80 (ddd, $^3J_{HH}$ = 17.2, 10.5, 6.7 Hz, 1H, H-2), 5.32-5.20 (m, 2H, H-1), 5.21 (q, $^3J_{HH}$ = 10.5 Hz, 1H, H-3), 3.77 (s, 3H, H-8), 3.66-3.59 (m, 2H, H-6), 1.77-1.69 (m, 2H, H-4), 1.58-1.52 (m, 2H, H-5), 0.89 (s, 9H, H-11), 0.04 (s, 6H, H-9).

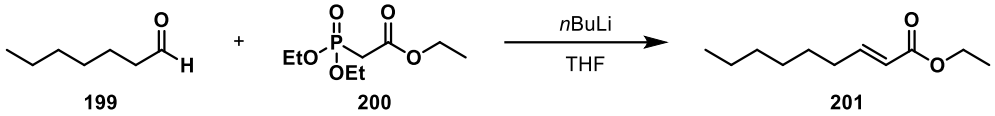
^{13}C NMR (75 MHz, $CDCl_3$), δ [ppm] = 155.4 (C-7), 136.1 (C-2), 117.6 (C-1), 79.1 (C-3), 62.7 (C-6), 54.7 (C-8), 30.8 (C-4), 28.3 (C-5), 26.1 (C-11), 18.4 (C-10), -5.2 (C-9).

FT-IR ATR, ν [cm^{-1}] = 3088 (w), 2955 (m), 2930 (m), 2887 (m), 2858 (m), 1748 (s), 1463 (m), 1442 (m), 1389 (w), 1259 (s), 1096 (s), 986 (m), 937 (m), 833 (s), 774 (s), 661 (m).

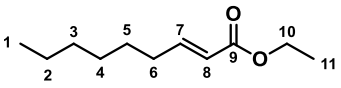
GC-MS *m/z* (%) = 155 (13), 133 (19), 101 (6), 81 (100), 59 (12), 41 (7).

The analytical data is in accordance with the literature.[174]

10.2.3.7 Synthesis of ethyl (*E*)-non-2-enoate (201)



Following a procedure by *Wang and Lowary*,[175] an argon-flooded *Schlenk* flask was charged with 1.70 mL (8.53 mmol, 1.20 eq.) of triethyl phosphonoacetate (**200**) dissolved in 34 mL dry THF and the solution was cooled to -78 °C. After the addition of 2.80 mL (8.68 mmol, 1.23 eq.) of *n*BuLi (3.10 M in hexane), the reaction mixture was stirred at 0 °C for 40 min. Then, 1.00 mL (7.09 mmol, 1.00 eq.) of heptanal (**199**) were added and the reaction mixture was stirred at 0 °C. After 3 h, full consumption of the starting material was indicated by TLC and the reaction mixture was terminated by adding 20 mL H_2O. The aqueous phase was extracted three times with 20 mL EtOAc. The combined organic layers were washed with 50 mL sat. aq. NaCl-solution, dried over $MgSO_4$ and the solvent was removed under reduced pressure. The crude product was purified by column chromatography (SiO_2, *c*-Hex/EtOAc 50:1 → 20:1) to afford 1.15 g (6.30 mmol, 89%, Lit.[175]: 82%) of the ester **201** as a colourless oil.



M ($C_{10}H_{18}O_2$) 170.25 g/mol.

R_f (SiO_2, *c*-Hex/EtOAc 20:1) = 0.48.

^{1}H NMR (300 MHz, $CDCl_3$), δ [ppm] = 6.97 (dt, $^3J_{HH}$ = 15.6, 7.0 Hz, 1H, H-7), 5.81 (dt, $^3J_{HH}$ = 15.6 Hz, $^4J_{HH}$ = 1.6 Hz, 1H, H-8), 4.18 (q, $^3J_{HH}$ = 7.1 Hz, 2H, H-10), 2.19 (qd, $^3J_{HH}$ = 7.2 Hz, $^4J_{HH}$ = 1.5 Hz, H-6), 1.52-1.20 (m, 11H, H-2, H-3, H-4, H-5, H-11), 0.96-0.81 (m, 3H, H-1).

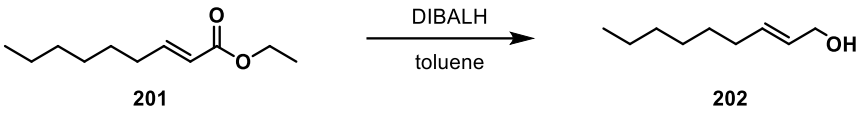
^{13}C NMR (75 MHz, $CDCl_3$), δ [ppm] = 166.8 (C-9), 149.5 (C-8), 121.3 (C-7), 60.2 (C-10), 32.3, 31.7, 28.9, 28.1, 22.6 (C-2, C-3, C-4, C-5, C-6), 14.4 (C-11), 14.1 (C-1).

FT-IR ATR, ν [cm^{-1}] = 2957 (w), 2927 (m), 2857 (w), 1721 (s), 1654 (m), 1465 (w), 1367 (m), 1308 (m), 1264 (m), 1220 (m), 1194 (m), 1167 (s), 1125 (m), 1096 (w), 1043 (m), 976 (m), 847 (w), 809 (w), 725 (w), 711 (w), 475 (w).

GC-MS *m/z* (%) = 169 (7), 157 (6), 139 (48), 127 (10), 115 (15), 109 (15), 101 (34), 96 (30), 88 (24), 81 (18), 69 (58), 61 (7), 55 (100).

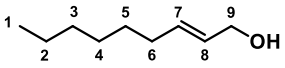
The analytical data is in accordance with the literature.[123]

10.2.3.8 Synthesis of (*E*)-non-2-en-1-ol (202)



201 **202**

Following a procedure by *Yadav and Babu*[123], an argon-flooded *Schlenk* flask was charged with 1.29 g (7.02 mmol, 1.00 eq.) of ester **201** dissolved in 14 mL dry toluene and the solution was cooled to 0 °C. Then, 14.0 mL (14.0 mmol, 1.99 eq.) of DIBALH (1 M in hexanes) were added and stirring was continued at 0 °C. After 1.5 h, full consumption of the starting material was indicated by TLC and the reaction was terminated by adding 30 mL H_2O while warming to rt. The reaction mixture was diluted with 60 mL EtOAc and washed with 40 mL 1 M HCl. The aqueous phase was extracted three times with 30 mL EtOAc. The combined organic layers were washed with 50 mL H_2O and 50 mL sat. aq. NaCl-solution, dried over Na_2SO_4 and the solvent was removed under reduced pressure. The desired alcohol **202** was obtained as a colourless oil (972 mg, 6.83 mmol, 97%, Lit.[123]: 90%) and could be used without further purification.



M ($C_9H_{18}O$) 142.24 g/mol.

R_f (SiO_2, *c*-Hex/EtOAc 20:1) = 0.11.

^{1}H NMR (300 MHz, $CDCl_3$), δ [ppm] = 5.76 (m, 2H, H-7, H-8), 4.12-4.05 (m, 2H, H-9), 2.14-1.96 (m, 2H, H-6), 1.47-1.18 (m, 8H, H-2, H-3, H-4, H-5), 0.97-0.82 (m, 3H, H-1).

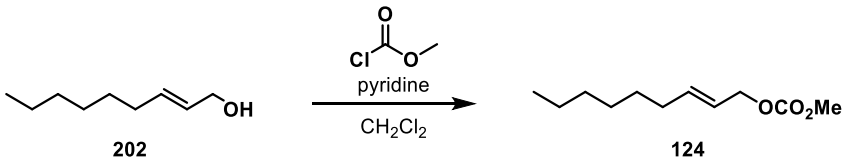
^{13}C NMR (75 MHz, $CDCl_3$), δ [ppm] = 133.6 (C-8), 129.0 (C-7), 63.9 (C-9), 32.3, 31.8, 29.2, 29.0, 22.7 (C-2, C-3, C-4, C-5, C-6), 14.2 (C-1).

FT-IR ATR, ν [cm^{-1}] = 3317 (br), 2957 (m), 2923 (s), 2855 (s), 1670 (w), 1458 (m), 1394 (m), 1378 (m), 1226 (w), 1088 (m), 1047 (m), 1003 (s), 967 (s), 909 (w), 834 (w), 724 (m).

GC-MS *m/z* (%) = 124 (10), 95 (23), 81 (29), 67 (32), 57 (100).

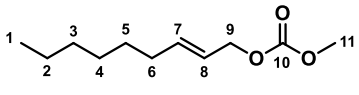
The analytical data is in accordance with the literature.[123]

10.2.3.9 Synthesis of (*E*)-methyl non-2-en-1-yl carbonate (124)



202 124

Following a procedure by *Helmchen et al.*[72], an argon-flooded *Schlenk* flask was charged with 7.56 g (53.1 mmol, 1.00 eq.) of alcohol **202** dissolved in 130 mL dry CH_2Cl_2. After the addition of 13.0 mL (161 mmol, 3.04 eq.) of pyridine, the reaction mixture was cooled to 0 °C and 8.50 mL (110 mmol, 2.07 eq.) of methyl chloroformate were added. The resulting white suspension was stirred at rt. After 16 h, full consumption of the starting material was indicated by TLC and the reaction was terminated by the addition of 100 mL sat. aq. NaCl-solution. The aqueous phase was extracted three times with 100 mL EtOAc. The combined organic layers were washed with 150 mL HCl (1 M), dried over $MgSO_4$ and the solvent was removed under reduced pressure. The crude product was purified by column chromatography (SiO_2, *c*-Hex/EtOAc 30:1) to afford 9.80 g (49.0 mmol, 92%, Lit.[72]: 93%) of the linear carbonate **124** as a colourless oil.



M ($C_{11}H_{20}O_3$) 200.28 g/mol.

R_f (SiO_2, *c*-Hex/EtOAc 30:1) = 0.26.

^{1}H NMR (300 MHz, $CDCl_3$), δ [ppm] = 5.82 (dtt, $^3J_{HH}$ = 15.6, 6.6 Hz, $^4J_{HH}$ = 1.1 Hz, 1H, H-7), 5.58 (dtt, $^3J_{HH}$ = 15.4, 6.5 Hz, $^4J_{HH}$ = 1.4 Hz, 1H, H-8), 4.57 (dq, $^3J_{HH}$ = 6.6 Hz, $^4J_{HH}$ = 1.0 Hz, 2H, H-9), 3.78 (s, 3H, H-11), 2.14-1.97 (m, 2H, H-6), 1.45-1.21 (m, 8H, H-2, H-3, H-4, H-5), 0.94-0.84 (m, 3H, H-1).

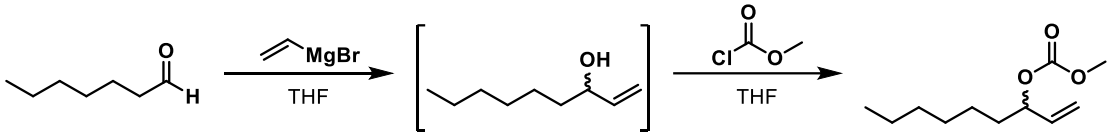
^{13}C NMR (75 MHz, $CDCl_3$), δ [ppm] = 155.8 (C-10), 137.7 (C-7), 123.2 (C-2), 68.8 (C-9), 54.8 (C-11), 32.3 (C-6), 31.8 (C-5), 28.9, 28.9 (C-3, C-4), 22.7 (C-2), 14.2 (C-1).

FT-IR ATR, ν [cm^{-1}] = 2957 (m), 2927 (m), 2857 (m), 2163 (w), 1747 (s), 1673 (w), 1442 (m), 1380 (m), 1253 (s), 1112 (w), 1045 (w), 968 (m), 943 (s), 899 (m), 792 (m), 724 (w).

GC-MS *m/z* (%) = 129 (9), 124 (28), 117 (6), 109 (16), 95 (25), 89 (<5), 81 (44), 67 (75), 59 (41), 54 (100).

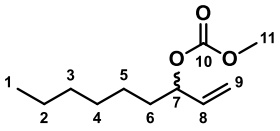
The analytical data is in accordance with the literature.[72]

10.2.3.10 Synthesis of methyl non-1-en-3-yl carbonate (190)



199 **264** *rac*-**190**

An argon-flooded *Schlenk* flask was charged with 5.60 mL (40.0 mmol, 1.00 eq.) of heptanal (**199**) diluted in 40 mL dry THF and the solution was cooled to 0 °C. Then, 48.0 mL (48.0 mmol, 1.20 eq.) of vinyl magnesium bromide (1 M in THF) were added and stirring was continued at rt. After 4 h, full consumption of the starting material was indicated by TLC, the reaction mixture was cooled to 0 °C and 4.80 mL (62.0 mmol, 1.60 eq.) of methyl chloroformate were added. Stirring was continued at rt overnight. Full consumption of the alcohol **264** was indicated by TLC after 18 h. The reaction mixture was quenched with 60 mL sat. aq. NH_4Cl-solution. The aqueous phase was extracted three times with 75 mL EtOAc. The combined organic layers were washed with 100 mL sat. aq. NaCl-solution, dried over $MgSO_4$ and the solvent was removed under reduced pressure. The crude product was purified by column chromatography (SiO_2, *c*-Hex/EtOAc 20:1) to afford 5.94 g (29.7 mmol, 74%) of the carbonate *rac*-**190** as a colourless oil.



M ($C_{11}H_{20}O_3$) 200.28 g/mol.

R_f (SiO_2, *c*-Hex/EtOAc 20:1) = 0.22.

^{1}H NMR (300 MHz, $CDCl_3$), δ [ppm] = 5.79 (ddd, $^3J_{HH}$ = 17.2, 10.5, 6.8 Hz, 1H, H-8), 5.29 (dt, $^3J_{HH}$ = 17.3 Hz, $^4J_{HH}$ = 1.1 Hz, 1H, H-9a), 5.20 (dt, $^3J_{HH}$ = 10.8 Hz, $^4J_{HH}$ = 1.1 Hz, 1H, H-9b), 5.05 (q, $^3J_{HH}$ = 6.8 Hz, 1H, H-7), 3.77 (s, 3H, H-11), 1.75-1.54 (m, 2H, H-6), 1.38-1.28 (m, 8H, H-2, H-3, H-4, H-5), 0.87 (t, $^3J_{HH}$ = 6.9 Hz, 3H, H-1).

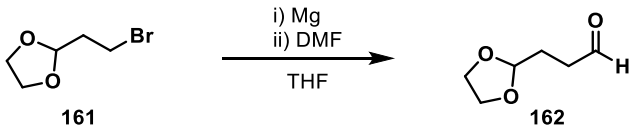
^{13}C NMR (75 MHz, $CDCl_3$), δ [ppm] = 155.4 (C-10), 136.2 (C-8), 117.3 (C-9), 79.2 (C-11), 57.6 (C-7), 34.3, 31.7, 29.1, 25.0, 22.6 (C-2, C-3, C-4, C-5, C-6), 14.1 (C-1).

FT-IR ATR, ν [cm^{-1}] = 3087 (w), 2956 (w), 2929 (w), 2859 (w), 2200 (w), 1747 (s), 1648 (w), 1584 (w), 1442 (m), 1378 (w), 1338 (w), 1258 (s), 1199 (w), 1128 (w), 1080 (w), 1058 (w), 989 (w), 933 (m), 859 (w), 792 (m), 725 (w), 685 (w), 663 (w), 561 (w), 477 (w).

GC-MS *m/z* (%) = 130 (9), 115 (36), 95 (46), 71 (100), 55 (63), 41 (99).

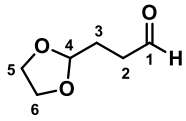
The analytical data is in accordance with the literature.[176]

10.2.3.11 Synthesis of 3-(1,3-dioxolan-2-yl)propanal (162)



161 162

Following a procedure by *Lucchesini*[111], an argon-flooded flask equipped with a reflux condenser was charged with 2.94 g (121 mmol, 4.08 eq.) of Mg suspended in 100 mL dry THF and 7.00 mL (59.6 mmol, 2.01 eq.) of 1,3-bromoethyldioxolane (**161**). Since the reaction was strongly exothermic, evaporation of the solvent was circumvented by cooling with a reflux condenser. After 2 h, the *Grignard* reagent was cooled to 0 °C and 2.30 mL (29.7 mmol, 1.00 eq.) of dry DMF were added. Stirring was continued at rt. After 1 h, full consumption of the starting material was indicated by TLC and the reaction was terminated by the addition of 60 mL aq. citric acid-solution (20%) upon cooling to 0 °C. The aqueous phase was extracted three times with 80 mL EtOAc. The combined organic phases were washed with 100 mL sat. aq. NaCl-solution, dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure. The crude product was purified by column chromatography (SiO_2, *c*-Hex/EtOAc 3:1 → 2:1 → 1:1) to afford 2.48 g (19.1 mmol, 64%, Lit.[111]: 57%) of aldehyde **162** as a colourless oil.



M ($C_6H_{10}O_3$) 130.14 g/mol.

R_f (SiO_2, *c*-Hex/EtOAc 2:1) = 0.26.

^{1}H NMR (300 MHz, $CDCl_3$), δ [ppm] = 9.76 (t, $^3J_{HH}$ = 1.7 Hz, 1H, H-1), 4.97 (t, $^3J_{HH}$ = 3.9 Hz, 1H, H-4), 4.04-3.90 (m, 4H, H-5, H-6), 2.54 (td, $^3J_{HH}$ = 7.1, 1.7 Hz, 2H, H-2), 2.05 (td, $^3J_{HH}$ = 7.1, 3.9 Hz, 2H, H-3).

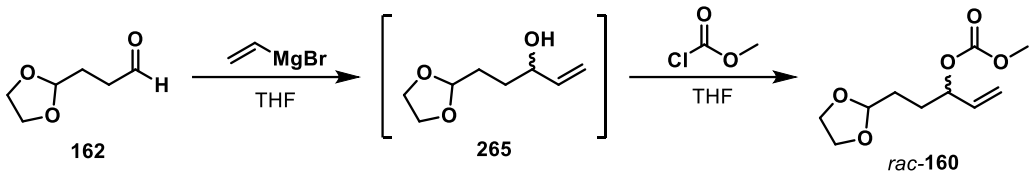
^{13}C NMR (75 MHz, $CDCl_3$), δ [ppm] = 201.7 (C-1), 104.5 (C-4), 65.1 (C-5, C-6), 37.7 (C-2), 26.3 (C-3).

FT-IR ATR, ν [cm^{-1}] = 2950 (m), 2885 (m), 2729 (w), 1721 (s), 1438 (w), 1395 (m), 1374 (m), 1242 (m), 1214 (w), 1139 (s), 1092 (m), 1034 (s), 943 (s), 838 (m), 727 (w), 709 (w), 659 (w), 608 (w), 489 (m).

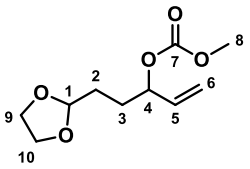
GC-MS *m/z* (%) = 129 ([M]$^+$, 2), 99 (<5), 85 (8), 73 (100), 57 (13).

The analytical data is in accordance with the literature.[177]

10.2.3.12 Synthesis of 5-(1,3-dioxolan-2-yl)pent-1-en-3-yl methyl carbonate (160)



An argon-flooded *Schlenk* flask was charged with 580 mg (4.46 mmol, 1.00 eq.) of aldehyde **162** dissolved in 4.6 mL dry THF. The solution was cooled to 0 °C and 5.00 mL (5.00 mmol, 1.12 eq.) of vinyl magnesium bromide (1 M in THF) were added. After 2 h, full consumption of the starting material was indicated by TLC, the reaction mixture was cooled to 0 °C and 0.51 mL (6.58 mmol, 1.48 eq.) of methyl chloroformate were added. The reaction mixture was stirred at rt for 17 h, after which full consumption of the alcohol **265** was indicated by TLC. The reaction was terminated by the addition of 20 mL sat. aq. NH_4Cl-solution. The aqueous phase was extracted three times with 15 mL EtOAc. The combined organic phases were washed with 30 mL sat. aq. NaCl-solution, dried over $MgSO_4$ and the solvent was removed under reduced pressure. The crude product was purified by column chromatography (SiO_2, *c*-Hex/EtOAc 5:1 → 3:1) to afford 691 mg (3.20 mmol, 72%) of the carbonate *rac*-**160** as a yellow oil.



M ($C_6H_{10}O_3$) 216.23 g/mol.

R_f (SiO_2, *c*-Hex/EtOAc 2:1) = 0.41.

^{1}H NMR (500 MHz, $CDCl_3$), δ [ppm] = 5.80 (ddd, $^3J_{HH}$ = 17.2, 10.5, 6.7 Hz, 1H, H-5), 5.32 (dt, $^3J_{HH}$ = 17.2 Hz, $^4J_{HH}$ = 1.2 Hz, 1H, H-6a), 5.23 (dt, $^3J_{HH}$ = 10.5 Hz, $^4J_{HH}$ = 1.1 Hz, 1H, H-6b), 5.11 (q, $^3J_{HH}$ = 6.7 Hz, 1H, H-4), 4.89 (t, $^3J_{HH}$ = 4.3 Hz, 1H, H-1), 3.98-3.94 (m, 2H) and 3.87-3.83 (m, 2H, H-9, H-10), 3.77 (s, 3H, H-8), 1.86-1.70 (m, 4H, H-2, H-3).

^{13}C NMR (126 MHz, $CDCl_3$), δ [ppm] = 155.3 (C-7), 135.8 (C-5), 117.9 (C-6), 104.0 (C-1), 78.1 (C-4), 65.1 (C-9, C-10), 54.7 (C-8), 29.3 (C-2), 28.4 (C-3).

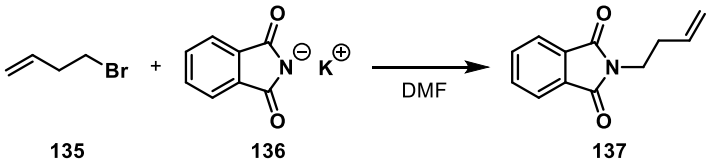
FT-IR ATR, ν [cm^{-1}] = 2956 (m), 2884 (m), 2765 (w), 1745 (s), 1647 (w), 1443 (m), 1413 (w), 1339 (w), 1260 (s), 1139 (s), 1085 (m), 1030 (s), 991 (m), 938 (s), 860 (m), 791 (s), 710 (w), 685 (w), 525 (w), 480 (w).

HRMS (EI) calcd. $[M-H]^+$: 215.09140, found: 215.09119.

GC-MS *m/z* (%) = 215 ($[M]^+$, 8), 141 (20), 125 (5), 99 (48), 73 (100), 55 (43).

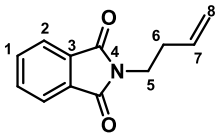
10.2.4 Synthesis of the amine building blocks

10.2.4.1 Synthesis of 2-(but-3-en-1-yl)isoindoline-1,3-dione (137)



135 136 137

Following a procedure by *Miller et al.*[107], an argon-flooded flask equipped with a reflux condenser was charged with 5.00 mL (49.3 mmol, 1.00 eq.) of 4-bromobutene (**135**) and 13.0 g (70.0 mmol, 1.42 eq.) of potassium phthalimide (**136**) dissolved in 50 mL dry DMF . The reaction mixture was heated to reflux. After 16 h, full consumption of the starting material was indicated by TLC. The reaction mixture was cooled to rt and diluted with 100 mL EtOAc. The organic phase was washed with 100 mL sat. aq. NH_4Cl-solution and 100 mL sat. aq. $NaHCO_3$-solution, dried over $MgSO_4$ and the solvent was removed under reduced pressure. The obtained crude product was purified by column chromatography (SiO_2, *c*-Hex/EtOAc 5:1 → 3:1) to afford 8.99 g (44.7 mmol, 91%, Lit.[107]: 78%) of the desired phthalimide **137** as a colourless solid.



M ($C_{12}H_{11}NO_2$) 201.225 g/mol.

R_f (SiO_2, *c*-Hex/EtOAc 5:1) = 0.26.

Melting point 51-52 °C (Lit.[178]: 52-53 °C).

^{1}H NMR (300 MHz, $CDCl_3$), δ [ppm] = 7.87-7.81 (m, 2H, H-2), 7.74-7.69 (m, 2H, H-1), 5.80 (ddt, $^3J_{HH}$ = 17.1, 10.2, 6.9 Hz, 1H, H-7), 5.10-5.00 (m, 2H, H-8), 3.78 (t, $^3J_{HH}$ = 7.1 Hz, 2H, H-5), 2.45 (qt, $^3J_{HH}$ = 7.0 Hz, $^4J_{HH}$ = 1.2 Hz, 2H, H-6).

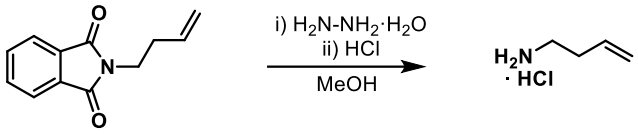
^{13}C NMR (75 MHz, $CDCl_3$), δ [ppm] = 168.4 (C-4), 134.5 (C-7), 133.9 (C-2), 132.1 (C-8), 123.2 (C-1), 117.6 (C-3), 37.4 (C-5), 32.9 (C-6).

FT-IR ATR, ν [cm^{-1}] = 3064 (w), 3002 (w), 2976 (w), 2942 (w), 1972 (w), 1927 (w), 1875 (w), 1832 (w), 1769 (m), 1694 (s), 1642 (m), 1466 (m), 1397 (s), 1362 (m), 1333 (m), 1255 (m), 1176 (m), 1055 (s), 999 (m), 936 (s), 867 (m), 798 (m), 721 (s), 713 (s), 651 (m), 612 (m), 530 (s).

GC-MS *m/z* (%) = 201 ([M], 100), 162 (42), 148 (15), 130 (44), 104 (38), 76 (32), 55 (12).

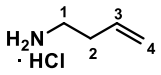
The analytical data is in accordance with the literature.[179]

10.2.4.2 Synthesis of but-3-en-1-amine hydrochloride (134·HCl)



137 **134·HCl**

Following a procedure by *Miller et al.*[107], an argon-flooded flask equipped with a reflux condenser was charged with 5.40 g (26.9 mmol, 1.00 eq.) of homoallyl phthalimide **137** and 1.80 mL (37.1 mmol, 1.38 eq.) of hydrazine monohydrate dissolved in 200 mL absolute methanol. The reaction mixture was heated to reflux. After 4 h, full consumption of the starting material was indicated. The reaction mixture was cooled to 0 °C and 15 mL conc. HCl were added and stirred for another hour at rt. The solvent was removed under reduced pressure. The resulting white slurry was triturated with $CHCl_3$ and filtered over a short pad of celite. The solvent of the filtrate was removed under reduced pressure to afford 2.57 g (23.9 mmol, 89%, Lit.[107]: 70%) of hydrochloride **134·HCl** as a colourless solid that could be used without further purification.



M (C_4H_9N·HCl) 107.58 g/mol.

Melting point 168-170 °C (Lit.[180]: 168-171 °C).

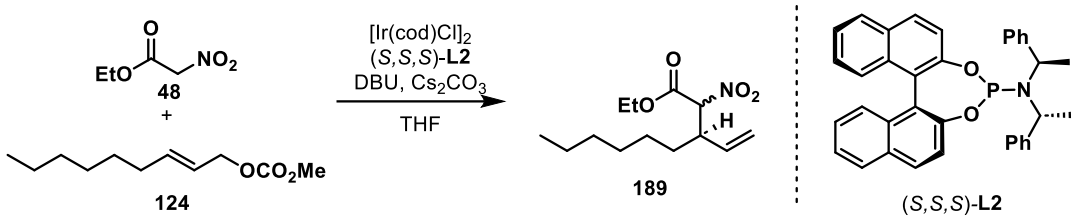
^{1}H NMR (300 MHz, DMSO-d_6), δ [ppm] = 8.02 (s, 3H, NH_2·HCl), 5.87-5.73 (m, 1H, H-3), 5.17-5.07 (m, 2H, H-4), 2.82 (t, $^3J_{HH}$ = 7.3 Hz, 2H, H-1), 2.38-2.30 (m, 2H, H-2).

^{13}C NMR (75 MHz, DMSO-d_6), δ [ppm] = 134.0 (C-3), 117.5 (C-4), 37.9 (C-1), 31.0 (C-2).

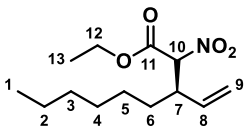
FT-IR ATR, ν [cm^{-1}] = 3084 (m), 3001 (s), 2981 (s), 2914 (s), 1645 (m), 1591 (m), 1508 (s), 1420 (w), 1386 (w), 1274 (w), 1125 (m), 1043 (m), 991 (m), 911 (s), 786 (m), 631 (m).

The analytical data is in accordance with the literature.[180]

10.2.4.3 Synthesis of ethyl (3*R*)-2-nitro-3-vinylnonanoate (189)



Following a procedure by *Dahnz and Helmchen*[62], an argon-flooded *Schlenk* flask was charged with 137 mg (0.204 mmol, 2.04 mol%) of $[Ir(cod)Cl]_2$, 216 mg (0.400 mmol, 4.00 mol%) of the *Feringa* ligand (*S,S,S*)-**L2**, 0.12 mL (0.804 mmol, 8.04 mol%) of DBU and 10 mL dry THF. The reaction mixture was stirred at rt for two hours. Then, 2.00 g (10.0 mmol, 1.00 eq.) of carbonate **124**, 1.50 mL (13.5 mmol, 1.35 eq.) of ethyl nitroacetate (**48**) and 3.29 g (10.1 mmol, 1.01 eq.) of Cs_2CO_3 were added. The reaction mixture was stirred at rt for 19 h after which full consumption of the starting material was indicated by TLC and GC-MS. The mixture was diluted with 80 mL EtOAc and 80 mL sat. NH_4Cl-solution. The aqueous phase was extracted three times with 50 mL EtOAc. The combined organic layers were washed with 100 mL sat. aq. NaCl-solution, dried over $MgSO_4$ and the solvent was removed under reduced pressure. The crude product was purified by column chromatography (SiO_2, *c*-Hex/EtOAc 30:1) to afford 2.30 g (2.91 mmol, 89%) of the desired product **189** as a yellow oil.



M ($C_{13}H_{23}NO_4$) 257.33 g/mol.

R_f (SiO_2, *c*-Hex/EtOAc 10:1) = 0.42.

^{1}H NMR (500 MHz, $CDCl_3$, mixture of diastereomers), δ [ppm] = 5.75-5.54 (m, 1H, H-8), 5.23-5.17 (m, 2H, H-9), 5.07 (d, $^3J_{HH}$ = 8.4 Hz, 0.5H, H-10a), 5.02 (d, $^3J_{HH}$ = 8.4 Hz, 0.5H, H-10b), 4.32-4.21 (m, 2H, H-12), 3.06-2.93 (m, 1H, H-7), 1.44-1.26 (m, 13H, H-2, H-3, H-4, H-5, H-6, H-13), 0.88 (t, $^3J_{HH}$ = 7.0 Hz, 3H, H-1).

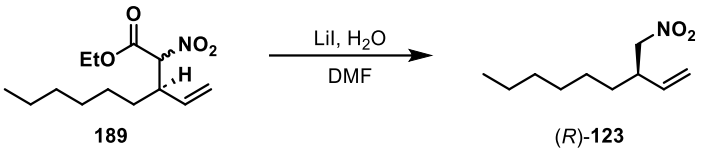
^{13}C NMR (126 MHz, $CDCl_3$, mixture of diastereomers), δ [ppm] = 163.7/163.5 (C-11z), 135.1 (C-8a), 134.5 (C-8b), 120.1 (C-9), 91.8/91.5 (C-10), 63.0/62.8 (C-12), 45.5 (C-7), 31.7 (C-3), 30.9/30.6 (C-6), 29.0/28.9 (C-4), 26.9/26.8 (C-5), 22.7 (C-2), 14.2 (C-13), 14.1 (C-1).

FT-IR ATR, v [cm^{-1}] = 3084 (w), 2957 (m), 2929 (m), 2859 (m), 1751 (s), 1643 (w), 1560 (s), 1466 (m), 1421 (w), 1373 (m), 1303 (m), 1197 (m), 1180 (m), 1096 (m), 1022 (m), 996 (m), 927 (m), 860 (m), 793 (w), 671 (m), 612 (w), 443 (w).

HRMS (ESI) Calcd. $[M+H]^+$: 258.17000, found: 258.17034; calcd. $[M+Na]^+$: 280.15193, found: 280.15235.

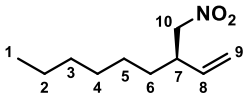
GC-MS *m/z* (%) = 211 (6), 183 (23), 167 (9), 153 (37), 127 (28), 109 (42), 95 (65), 81 (100), 55 (95).

10.2.4.4 Synthesis of (*R*)-3-(nitromethyl)non-1-ene (123)



189 (*R*)-**123**

Following a procedure by *Dahnz and Helmchen*[62], an argon-flooded flask equipped with a reflux condenser was charged with 2.28 g (8.86 mmol, 1.00 eq.) of substrate **189**, 7.12 g (53.2 mmol, 6.00 eq) of LiI, 1.10 mL (61.1 mmol, 6.89 eq.) of H_2O, catalytic amounts of 3,5-di*tert*butyl hydroquinone and 30 mL dry DMF. The reaction mixture was heated to reflux. After 4 h, full consumption of the starting material was indicated by TLC and the reaction mixture was cooled to rt. The solution was diluted with 80 mL EtOAc and 100 mL H_2O. The aqueous layer was extracted three times with 50 mL EtOAc. The combined organic layers were washed with 100 mL sat. aq. NaCl-solution, dried over $MgSO_4$ and the solvent was removed under reduced pressure. The crude product was purified by column chromatography (SiO_2, *c*-Hex/EtOAc 10:1) to afford 1.19 g (6.10 mmol, 69%, 98%*ee*) of the desired product (*R*)-**123** as a yellow oil.



M ($C_{10}H_{19}NO_2$) 185.27 g/mol.

R_f (SiO_2, *c*-Hex/EtOAc 20:1) = 0.40.

^{1}H NMR (500 MHz, $CDCl_3$), δ [ppm] = 5.59 (ddd, $^3J_{HH}$ = 16.7, 10.6, 8.7 Hz, 1H, H-8), 5.16-5.12 (m, 2H, H-9), 4.36 (dd, $^2J_{HH}$ = 11.6 Hz, $^3J_{HH}$ = 6.2 Hz, 1H, H-10a), 4.28 (dd, $^2J_{HH}$ = 11.6 Hz, $^3J_{HH}$ = 8.7 Hz, 1H, H-10b), 2.90-2.82 (m, 1H, H-7), 1.40-1.23 (m, 10H, H-2, H-3, H-4, H-5, H-6), 0.88 (t, $^3J_{HH}$ = 6.9 Hz, 3H, H-1).

^{13}C NMR (126 MHz, $CDCl_3$), δ [ppm] = 136.8 (C-8), 118.4 (C-9), 80.1 (C-10), 43.0 (C-7), 31.8 (C-3), 26.1 (C-5), 26.7 (C-4), 22.7 (C-2), 14.2 (C-1).

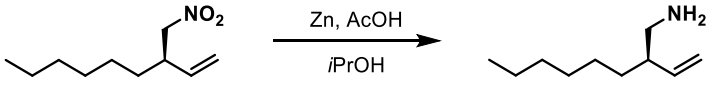
FT-IR ATR, v [cm^{-1}] = 3084 (w), 2957 (m), 2928 (m), 2858 (m), 1652 (w), 1551 (s), 1459 (m), 1433 (m), 1422 (m), 1378 (s), 1181 (m), 967 (m), 923 (m), 724 (m), 683 (m), 614 (w).

HRMS (EI) Calcd. $[M+H]^+$: 186.1489, found: 186.1487.

GC-MS *m/z* (%) = 109 (12), 95 (34), 69 (77), 55 (100), 41 (77).

$[\alpha]_\lambda^{20}$ (0.495 g/100 mL in $CHCl_3$): $[\alpha]_{365}$ = -367 °, $[\alpha]_{436}$ = -5.0 °, $[\alpha]_{546}$ = -0.6 °, $[\alpha]_{579}$ = -0.5 °, $[\alpha]_{589}$ = -0.5 °.

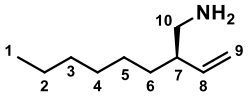
10.2.4.5 Synthesis of (*R*)-2-vinyloctan-1-amine (122)



(*R*)-**123** (*R*)-**122**

A round-bottom flask was charged with 11.3 g (173 mmol, 30.2 eq.) of Zn dust suspended in 57 mL *i*PrOH. At 0 °C, 1.06 g (5.73 mmol, 1.00 eq.) of nitroalkene **123** and 14.0 mL (245 mmol, 42.8 eq.) of AcOH were added and the reaction mixture was stirred at rt. After 2.5 h, full consumption of the starting material was indicated by TLC. The suspension was filtered over a pad of celite, washed with EtOAc and the solvent was removed under reduced pressure. The crude product was dissolved in 50 mL EtOAc and 30 mL sat. aq. $NaHCO_3$-solution. The aqueous phase was extracted three times with 20 mL EtOAc. The combined organic layers were washed with 50 mL sat. aq. NaCl-solution, dried over Na_2SO_4 and the solvent was removed under reduced pressure. The amine (*R*)-**122** (860 mg, 5.54 mmol, 97%) was obtained as an orange oil and could be used without further purification.

M ($C_{10}H_{21}N$) 155.29 g/mol.



R_f (SiO_2, CH_2Cl_2/MeOH 10:1) = 0.13.

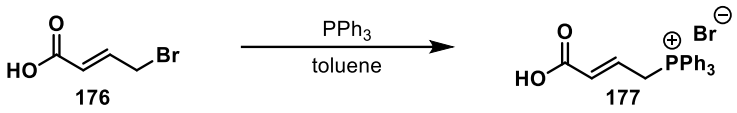
^{1}H NMR (500 MHz, $CDCl_3$), δ [ppm] = 5.52 (ddd, $^3J_{HH}$ = 17.1, 10.3, 8.9 Hz, 1H, H-8), 5.15-5.03 (m, 2H, H-9), 2.71 (dd, $^2J_{HH}$ = 12.6 Hz, $^3J_{HH}$ = 4.6 Hz, 1H, H-10a), 2.51 (dd, $^2J_{HH}$ = 12.6 Hz, $^3J_{HH}$ = 8.8 Hz, 1H, H-10b), 2.02 (ddq, $^3J_{HH}$ = 13.2, 8.9, 4.7 Hz, 1H, H-7), 1.49 (s, 2H, NH_2), 1.37-1.21 (m, 10H, H-2, H-3, H-4, H-5, H-6), 0.88 (t, $^3J_{HH}$ = 7.0 Hz, 3H, H-1).

^{13}C NMR (126 MHz, $CDCl_3$), δ [ppm] = 141.2 (C-8), 116.5 (C-9), 48.0 (C-7), 46.2 (C-10), 32.4 (C-6), 31.9 (C-3), 29.5 (C-4), 27.2 (C-5), 22.7 (C-2), 14.2 (C-1).

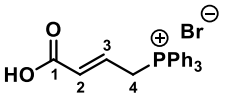
FT-IR	ATR, v [cm^{-1}] = 3076 (m), 2956 (s), 2924 (s), 2856 (s), 2116 (w), 1639 (m), 1558 (s, br), 1467 (s), 1401 (s), 1379 (s), 1332 (m), 1045 (m), 995 (m), 914 (s), 783 (w), 753 (w), 724 (m), 684 (m), 648 (m), 617 (m), 467 (m).
HRMS (EI)	Calcd. $[M+H]^+$: 156.1747, found: 156.1747; calcd. $[M-H]^+$: 154.1509, found: 154.1589.
GC-MS	*m/z* (%) = 156 ($[M]^+$, 7), 138 (11), 84 (13), 70 (100), 54 (67).
$[\alpha]_\lambda^{20}$	(0.437 g/100 mL in $CHCl_3$): $[\alpha]_{365}$ = -883 °, $[\alpha]_{436}$ = 1.4 °, $[\alpha]_{546}$ = 1.1 °, $[\alpha]_{579}$ = 1.1 °, $[\alpha]_{589}$ = 0.8 °.

10.2.5 Synthesis of *Wittig*-reagents

10.2.5.1 Synthesis of (*E*)-(3-carboxyallyl)triphenylphosphonium bromide (177)



Following a procedure by *Olsson et al.*,[113] an argon-flooded *Schlenk* flask was charged with 1.97 g (7.51 mmol, 1.00 eq.) of PPh_3 dissolved in 19 mL dry toluene. Then, 1.26 g (7.63 mmol, 1.02 eq.) of (*E*)-bromobutenoic acid (**176**) were slowly added. The resulting yellow suspension was stirred at rt for 19 h. The suspension was filtered over a *Büchner* funnel. The solid was washed with *n*-hexane and dried under vacuum to afford 1.43 g (3.35 mmol, 45%) of the desired product **177** as a colourless solid.



M ($C_{22}H_{20}BrO_2P$) 427.28 g/mol.

Melting point 201-203 °C.

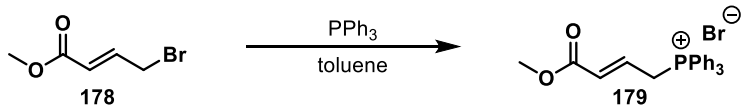
^{1}H NMR (300 MHz, DMSO-d_6, mixture of *E/Z*-isomers), δ [ppm] = 12.67 (s, 1H, *O*H), 7.96-7.90 (m, 3H, H_{Ar}), 7.83-7.76 (m, 12H, H_{ar}), 6.57 (dq, $^3J_{HH}$ = 13.8, 7.4 Hz, 1H, H-3), 6.04 (dd, $^3J_{HH}$ = 15.4, 4.9 Hz, 1H, H-2), 4.89 (dd, $^3J_{HH}$ = 17.4, 7.6 Hz, 2H, H-4).

^{13}C NMR (126 MHz, DMSO-d_6, mixture of *E/Z*-isomers), δ [ppm] = 165.5 (C-1), 135.5 (CH_{Ar}), 134.5 (C-3), 133.7 (CH_{Ar}), 133.3 (C-2), 130.3 (CH_{Ar}), 125.5 (C_{qAr}), 118.0 (C_{qAr}), 117.4 (C_{qAr}), 25.3/24.9 (C-4).

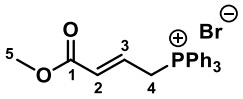
FT-IR ATR, v [cm^{-1}] = 3036 (br), 2886 (w), 2849 (w), 2773 (w), 1710 (s), 1639 (w), 1586 (w), 1484 (w), 1436 (m), 1367 (m), 1323 (w), 1307 (w), 1238 (w), 1195 (m), 1184 (m), 1158 (m), 1056 (w), 1030 (w), 997 (w), 982 (m), 880 (w), 855 (w), 826 (m), 785 (w), 753 (m), 741 (s), 722 (s), 687 (s), 674 (m), 652 (w), 632 (m), 615 (w), 551 (w), 533 (s), 507 (s).

The analytical data is in accordance with the literature.[181]

10.2.5.2 Synthesis of (*E*)-(4-methoxy-4-oxobut-2-en-1-yl)triphenylphosphonium bromide (179)



Following a procedure by *Olsson et al.*[113], an argon-flooded *Schlenk* flask was charged with 1.98 g (7.55 mmol, 1.01 eq.) of PPh_3 dissolved in 19 mL dry toluene. Then, 1.10 mL (7.48 mmol, 1.00 eq.) of (*E*)-bromobutenoic methylester (**178**) were slowly added and the reaction mixture was stirred at rt for 19 h. The suspension was filtered over a *Büchner* funnel. The solid was washed with *n*-hexane and dried under vacuum to afford 1.80 g (4.08 mmol, 55%, Lit.[113]: 99%) of the desired phosphonium bromide **179** as a pale-yellow solid.



M ($C_{23}H_{22}BrO_2P$) 441.30 g/mol.

Melting point 159-160 °C.

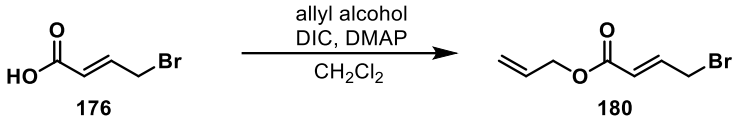
^{1}H NMR (300 MHz, $CDCl_3$, mixture of *E/Z*-isomers), δ [ppm] = 7.91-7.69 (m, 15H, H_{Ar}), 6.82-6.66 (m, 1H, H-3), 6.48 (dd, $^3J_{HH}$ = 15.5, 4.8 Hz, 1H, H-2), 5.26 (dd, $^3J_{HH}$ = 16.8, 8.0 Hz, 2H, H-4), 3.66 (s, 3H, H-5).

^{13}C NMR (126 MHz, $CDCl_3$, mixture of *E/Z*-isomers), δ [ppm] = 165.6 (C-1), 135.4 (CH_{Ar}), 134.1 (CH_{Ar}), 132.8/132.2 (C-3), 130.7 (CH_{Ar}), 130.6 (CH_{Ar}), 128.6 (C-2), 118.0 (C_{qAr}), 117.3 (C_{qAr}), 52.0 (C-5), 28.1/27.7 (C-4).

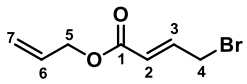
FT-IR ATR, ν [cm^{-1}] = 3037 (w), 2884 (w), 2841 (w), 2771 (w), 1711 (s), 1651 (w), 1586 (w), 1485 (w), 1435 (m), 1367 (w), 1328 (m), 1281 (m), 1250 (w), 1234 (m), 1214 (m), 1192 (m), 1154 (m), 1110 (s), 1052 (m), 1032 (m), 994 (m), 981 (m), 929 (w), 880 (w), 856 (w), 843 (w), 773 (w), 759 (m), 744 (m), 722 (s), 686 (s), 666 (m), 615 (w), 536 (s), 508 (s).

The analytical data is in accordance with the literature.[113]

10.2.5.3 Synthesis of allyl (*E*)-4-bromobut-2-enoate (180)



Following a procedure by *Ihsen et al.*[114], an argon-flooded *Schlenk* flask was charged with 1.16 g (7.03 mmol, 1.00 eq.) of (*E*)-bromobutenoic acid (**176**) dissolved in 14 mL dry CH_2Cl_2. Then, 1.60 mL (23.4 mmol, 3.33 eq.) of allyl alcohol, 1.20 mL (7.75 mmol, 1.10 eq.) of DIC and 428 mg (3.50 mmol, 0.50 eq.) of DMAP were added. The reaction mixture was stirred at rt. After 19 h, full consumption of the starting material was indicated by TLC. The reaction mixture was diluted with 20 mL EtOAc and 20 mL sat. aq. NaCl-solution. The aqueous phase was extracted three times with 10 mL EtOAc. The combined organic layers were dried over Na_2SO_4 and the solvent was removed under reduced pressure. The crude product was purified by column chromatography (SiO_2, *c*-Hex/EtOAc 10:1) to afford 422 mg (2.06 mmol, 29%, *E/Z* 9:1, Lit.[114]: 85%) of the desired allyl ester **180** as a light-yellow oil.



M ($C_7H_9BrO_2$) 205.05 g/mol.

^{1}H NMR (500 MHz, $CDCl_3$, mixture of *E/Z*-isomers), δ [ppm] = 7.04 (dt, $^3J_{HH}$ = 15.2, 7.4 Hz, 1H, H-3), 6.14 (d, $^3J_{HH}$ = 15.4 Hz, 0.1H, H-2'), 6.06 (d, $^3J_{HH}$ = 15.4 Hz, 0.9H, H-2), 5.95 (ddt, $^3J_{HH}$ = 16.5, 11.1, 5.7 Hz, 1H, H-6), 5.34 (d, $^3J_{HH}$ = 18.2 Hz, 1H, H-7a), 5.26 (d, $^3J_{HH}$ = 10.4 Hz, 1H, H-7b), 4.66 (d, $^3J_{HH}$ = 5.7 Hz, 2H, H-5), 4.18 (dd, $^3J_{HH}$ = 6.0 Hz, $^4J_{HH}$ = 1.5 Hz, 0.2H, H-4'), 4.02 (dd, $^3J_{HH}$ = 7.4 Hz, $^3J_{HH}$ = 1.0 Hz, 1.8H, H-4).

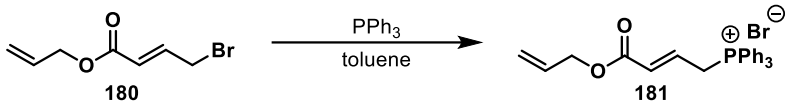
^{13}C NMR (126 MHz, $CDCl_3$, mixture of *E/Z*-isomers), δ [ppm] = 165.2 (C-1), 142.3 (C-3), 132.0 (C-6), 124.4/123.9 (C-2), 118.6 (C-7), 65.5 (C-5), 42.6/29.2 (C-4).

FT-IR ATR, ν [cm^{-1}] = 3086 (w), 3022 (w), 2947 (w), 2884 (w), 1718 (s), 1653 (m), 1437 (w), 1416 (w), 1362 (m), 1313 (m), 1289 (m), 1271 (m), 1210 (m), 1186 (s), 1134 (m), 1097 (w), 1065 (w), 1018 (m), 974 (s), 933 (m), 886 (w), 843 (w), 722 (m), 669 (w), 581 (m), 509 (w).

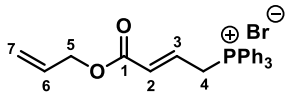
GC-MS *m/z* (%) = 149 (100), 111 (13), 68 (50).

The analytical data is in accordance with the literature.[114]

10.2.5.4 Synthesis of (*E*)-(4-(allyloxy)-4-oxobut-2-en-1-yl)triphenylphosphonium bromide (181)



Following a procedure by *Olsson et al.*,[113] an argon-flooded *Schlenk* flask was charged with 406 mg (1.55 mmol, 1.00 eq.) of PPh_3 dissolved in 4.0 mL dry toluene. Then, 317 mg (1.55 mmol, 1.00 eq.) of allyl ester **180** were slowly added and the reaction mixture was stirred at rt for 19 h. The suspension was filtered over a *Büchner* funnel. The solid was washed with *n*-hexane and was vacuum-dried to afford 316 mg (0.676 mmol, *E/Z* 7:3, 44%) of phosphonium bromide **181** as a colourless solid.



M ($C_{25}H_{24}BrO_2P$) 467.34 g/mol.

Melting point 181-182 °C.

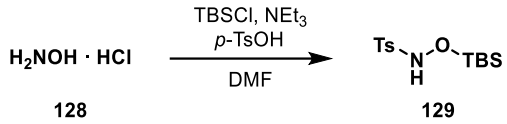
^{1}H NMR (500 MHz, $CDCl_3$, mixture of *E/Z*-isomers), δ [ppm] = 8.52 (dd, $^3J_{HH}$ = 23.0, 16.7 Hz, 0.3H, H-2'), 7.90-7.86 (m, 5H, H_{Ar}), 7.83-7.79 (m, 3H), 7.72-7.78 (m, 7H, H_{Ar}), 6.78-6.64 (m, 1H, H-3), 6.51 (dd, $^3J_{HH}$ = 15.4, 4.8 Hz, 1H, H-2), 5.92-5.82 (m, 1H, H-6), 5.34-5.19 (m, 3.4H, H-4, H-7), 4.58-4.56 (m, 1.85H, H-5), 4.37 (dt, $^3J_{HH}$ = 5.7, 1.2 Hz, 0.15H, H-5'), 4.06 (ddd, $^3J_{HH}$ = 6.7 Hz, $^4J_{HH}$ = 2.6, 1.5 Hz, 0.6H, H-4').

^{13}C NMR (126 MHz, $CDCl_3$, mixture of *E/Z*-isomers), δ [ppm] = 169.8/164.8 (C-1), 154.2/132.9 (C-3), 135.4 (CH_{Ar}), 135.3 (CH_{Ar}), 134.3 (CH_{Ar}), 134.2 (CH_{Ar}), 134.1 (CH_{Ar}), 134.0 (CH_{Ar}), 131.8/131.7 (C-6), 130.7 (CH_{Ar}), 130.6 (CH_{Ar}), 130.4/130.3/114.3/113.6 (C-2), 118.9/118.5 (C-7), 118.0 (C_{qAr}), 117.8 (C_{qAr}), 117.3 (C_{qAr}), 66.0/65.5 (C-5), 39.0/27.7 (C-4).

FT-IR ATR, ν [cm^{-1}] = 3045 (w), 2989 (w), 2875 (w), 2765 (w), 2186 (w), 1710 (m), 1648 (m), 1588 (w), 1489 (w), 1437 (m), 1402 (w), 1365 (w), 1321 (m), 1240 (m), 1199 (m), 1153 (m), 1112 (m), 1075 (m), 1055 (m), 996 (m), 987 (m), 978 (m), 941 (m), 923 (m), 887 (m), 837 (w), 790 (w), 756 (m), 720 (s), 704 (m), 687 (s), 669 (m), 640 (m), 616 (w), 561 (w), 536 (s), 503 (s).

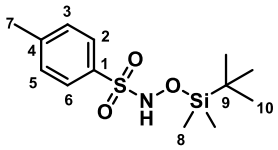
10.2.6 Synthesis of building blocks for the approach *via* oxime formation

10.2.6.1 Synthesis of *N*-((*tert*-butyldimethylsilyl)oxy)-4-methylbenzenesulfonamide (129)



128 129

Following a procedure by *Fukuyama et al.*[106], an argon-flooded *Schlenk* flask was charged with 702 mg (10.1 mmol, 1.11 eq.) of hydroxylamine hydrochloride (**128**) dissolved in 30 mL dry DMF. At 0 °C, 1.54 g (10.2 mmol, 1.12 eq.) of TBSCl and 6.50 mL (46.6 mmol, 5.13 eq.) of NEt_3 were added. The reaction mixture was stirred at rt for 1 h. Upon ice bath cooling 1.74 g (9.10 mmol, 1.00 eq.) of *p*-TsOH were added. After stirring at rt for 2 h, full consumption of the starting material was indicated by TLC. Then, 50 mL *n*-hexane and 50 mL H_2O were added consecutively. The aqueous phase was extracted twice with 25 mL *n*-hexane. The combined organic layers were washed twice with 25 mL H_2O and 25 mL 10% citric acid solution, dried over $MgSO_4$ and the solvent was removed under reduced pressure. The desired product **129** (2.38 g, 7.91 mmol, 87%, Lit.[106]: 82%) was obtained as a colourless oil and was used without further purification.



M ($C_{13}H_{23}NO_3SSi$) 301.48 g/mol.

R_f (SiO_2, *c*-Hex/EtOAc 10:1) = 0.13.

^{1}H NMR (300 MHz, $CDCl_3$), δ [ppm] = 7.71 (d, $^3J_{HH}$ = 8.2 Hz, 2H, H-3, H-5), 7.24 (d, $^3J_{HH}$ = 8.0 Hz, 2H, H-2, H-6), 6.56 (s, 1H, *N*H), 2.36 (s, 3H, H-7), 0.80 (s, 9H, H-10), 0.09 (s, 6H, H-8).

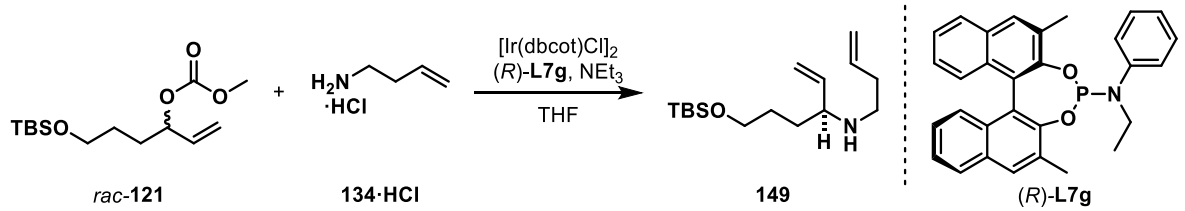
^{13}C NMR (75 MHz, $CDCl_3$), δ [ppm] = 144.8 (C-1), 133.3 (C-4), 129.6, 129.0 (C-2, C-3, C-5, C-6), 25.9 (C-10), 21.8 (C-7), 18.0 (C-9), -5.3 (C-8).

FT-IR ATR, v [cm^{-1}] = 3375 (w), 3253 (w), 3157 (w), 2972 (w), 2927 (w), 2883 (w), 1696 (w), 1569 (m), 1495 (w), 1452 (w), 1383 (w), 1345 (m), 1291 (w), 1181 (m), 1161 (s), 1123 (s), 1092 (s), 1033 (m), 1007 (m), 985 (m), 906 (m), 851 (m), 813 (s), 704 (m), 668 (s), 543 (s).

GC-MS *m/z* (%) = 231 (5), 189 (88), 173 (<5), 147 (100), 133 (42), 117 (32), 101 (5), 73 (73), 57 (12).

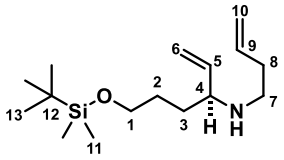
The analytical data is in accordance with the literature.[182]

10.2.6.2 Synthesis of (*S*)-*N*-(but-3-en-1-yl)-6-((*tert*-butyldimethylsilyl)oxy)hex-1-en-3-amine (149)



rac-**121** **134·HCl** **149** (*R*)-**L7g**

An argon-flooded head space vial was charged with 6.1 mg (7.1 µmol, 1.00 mol%) of $[Ir(dbcot)Cl]_2$ and 7.7 mg (16.6 µmol, 2.36 mol%) of ligand (*R*)-**L7** dissolved in 1.0 mL dry THF. After stirring at rt for 20 min, 203 mg (0.704 mmol, 1.00 eq.) of carbonate *rac*-**121** were added. After another 15 min, 1.4 mL dry THF, 0.14 mL (1.00 mmol, 1.43 eq.) of NEt_3 and 104 mg (0.967 mmol, 1.37 eq.) of amine **134·HCl** were added, respectively. The reaction mixture was heated to 50 °C in a heating block. After 16 h, full consumption of the starting material was indicated by TLC. Quadrasil© was added. The suspension was stirred at rt for 15 min, then, filtered over a pad of celite, washed with MTBE and the solvent was removed under reduced pressure. The crude product was purified by column chromatography (SiO_2, *c*-Hex/EtOAc/NEt_3 2:1:0.01) to afford 119 mg (0.420 mmol, 60%) of amine **149** as a yellow oil.



M ($C_{16}H_{33}NOSi$) 283.53 g/mol.

R_f (SiO_2, *c*-Hex/EtOAc 2:1) = 0.16.

^{1}H NMR (600 MHz, $CDCl_3$), δ [ppm] = 5.76 (ddt, $^3J_{HH}$ = 17.1, 10.2, 6.9 Hz, 1H, H-9), 5.59-5.52 (m, 1H, H-5), 5.11-5.01 (m, 4H, H-6, H-10), 3.59 (t, $^3J_{HH}$ = 6.2 Hz, 2H, H-1), 2.97 (td, $^3J_{HH}$ = 8.2, 7.0, 3.6 Hz, 1H, H-4), 2.69 (dt, $^2J_{HH}$ = 11.5 Hz, $^3J_{HH}$ = 7.0 Hz, 1H H-7a), 2.54 (dt, $^2J_{HH}$ = 11.5 Hz, $^3J_{HH}$ = 6.8 Hz, 1H, H-7b), 2.25-2.20 (m, 2H, H-8), 1.56-1.38 (m, 4H, H-2, H-3), 0.88 (s, 9H, H-13), 0.03 (s, 6H, H-11).

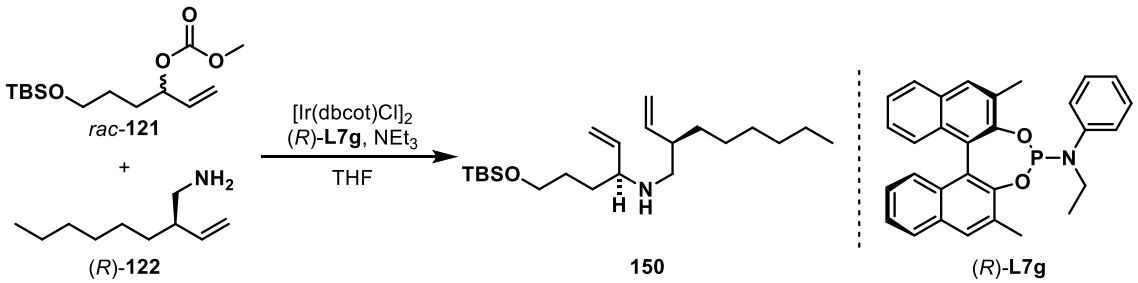
^{13}C NMR (151 MHz, $CDCl_3$), δ [ppm] = 141.5 (C-5), 136.7 (C-9), 116.4 (C-6), 116.0 (C-10), 63.3 (C-1), 62.0 (C-4), 46.4 (C-7), 34.5 (C-8), 32.0 (C-3), 29.4 (C-2), 26.1 (C-13), 18.5 (C-12), -5.2 (C-11).

FT-IR ATR, ν [cm^{-1}] = 3676 (w), 3077 (w), 2954 (m), 2929 (m), 2901 (m), 2857 (m), 1751 (w), 1720 (w), 1640 (w), 1463 (m), 1472 (m), 1414 (w), 1388 (w), 1361 (w), 1254 (m), 1097 (s), 993 (m), 914 (m), 833 (s), 773 (s), 713 (m), 679 (m), 661 (m), 550 (w).

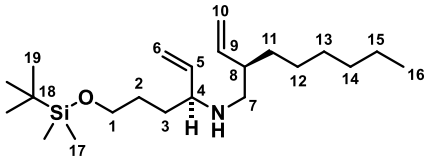
HRMS (EI) Calcd. [M-CH_3]: 268.20912, found: 268.20898; Calcd. [M-*t*Bu]: 226.16272, found: 226.16196.

GC-MS *m/z* (%) = 268 (<5), 242 (22), 226 (9), 155 (4), 125 (9), 110 (100), 96 (8), 81 (50), 55 (7), 41 (<5).

10.2.6.3 Synthesis of (*R*)-*N*-((*S*)-6-((*tert*-butyldimethylsilyl)oxy)hex-1-en-3-yl)-2-vinyloctan-1-amine (150)



An argon-flooded head space vial was charged with 3.4 mg (3.94 µmol, 1.14 mol%) of $[Ir(dbcot)Cl]_2$ and 3.4 mg (7.34 µmol, 2.12 mol%) of ligand (*R*)-**L7g** dissolved in 1.0 mL dry THF. After stirring at rt for 20 min, 100 mg (0.347 mmol, 1.00 eq.) of carbonate *rac*-**121** were added. After another 15 min, 0.4 mL dry THF, 67.7 µL (0.486 mmol, 1.40 eq.) of NEt_3 and 77.0 mg (0.496 mmol, 1.43 eq.) of amine (*R*)-**122** were added, respectively. The reaction mixture was heated to 50 °C in a heating block for 16 h. Then, Quadrasil© was added. The suspension was stirred at rt for 15 min, filtered over a pad of celite, washed with MTBE and the solvent was removed under reduced pressure. The crude product was purified by column chromatography (SiO_2, *c*-Hex/EtOAc 10:1) to afford 19.0 mg (51.7 µmol, 15%, *d.r.* 63:37) of amine **150** as a yellow oil.



M ($C_{22}H_{45}NOSi$) 367.69 g/mol.

R_f (SiO_2, *c*-Hex/EtOAc 2:1) = 0.55.

^{1}H NMR (500 MHz, $CDCl_3$, mixture of diastereomers), δ [ppm] = 5.63-5.46 (m, 2H, H-5, H-9), 5.12-5.02 (m, 4H, H-6, H-10), 3.59 (t, $^3J_{HH}$ = 6.0 Hz, 2H, H-1), 2.98-2.89 (m, 1H, H-4), 2.63 (dd, $^2J_{HH}$ = 11.1 Hz, $^3J_{HH}$ = 4.5 Hz, 0.6H, H-7a), 2.51 (dd, $^2J_{HH}$ = 11.6 Hz, $^3J_{HH}$ = 4.5 Hz, 0.3H, H-7a‘), 2.42 (dd, $^2J_{HH}$ = 11.6 Hz, $^3J_{HH}$ = 9.3 Hz, 0.3H, H-7b‘), 2.26 (dd, $^2J_{HH}$ = 11.1 Hz, $^3J_{HH}$ = 9.3 Hz, 0.7H,

H-7b), 2.19-2.14 (m, 1H, H-8), 1.57-1.18 (m, 14H, H-2, H-3, H-11, H-12, H-13, H-14, H-15), 0.90-0.85 (m, 12H, H-16, H-19), 0.03 (s, 6H, H-17).

^{13}C NMR (126 MHz, $CDCl_3$, mixture of diastereomers), δ [ppm] = 142.0/142.0 (C-5), 141.8/141.6 (C-10), 116.3/116.2 (C-6), 115.9 (C-9), 63.3/63.3 (C-1), 62.5/61.5 (C-4), 52.0/51.2 (C-7), 44.9/44.4 (C-8), 33.2 (C-11), 32.0 (C-3), 31.9 (C-12), 29.5 (C-2), 29.4 (C-13), 27.2 (C-14), 26.1 (C-19), 22.8 (C-15), 18.5 (C-18), 14.2 (C-16), -5.1 (C-17).

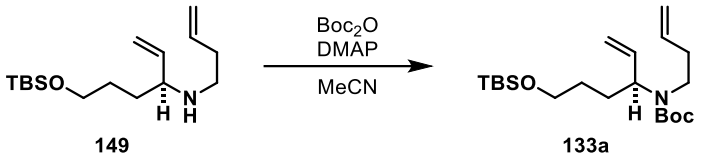
FT-IR ATR, v [cm^{-1}] = 3076 (w), 2955 (m), 2927 (s), 2856 (m), 1640 (w), 1470 (m), 1463 (m), 1407 (w), 1388 (w), 1361 (w), 1323 (w), 1254 (m), 1098 (s), 995 (m), 914 (s), 833 (s), 813 (m), 774 (s), 723 (m), 678 (m), 662 (m).

HRMS (ESI) Calcd. $[M+H]^+$: 368.33432, found: 368.33423; Calcd. $[M+Na]^+$: 390.31626, found: 390.31623.

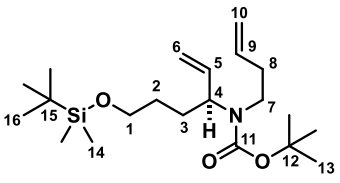
GC-MS *m/z* (%) = 367 ([M], 2), 352 (14), 310 (23), 242 (100), 212 (5), 194 (15), 155 (3), 110 (48), 81 (23), 55 (6).

$[\alpha]_\lambda^{20}$ (0.285 g/100 mL in $CHCl_3$): $[\alpha]_{436}$ = -7.2 °, $[\alpha]_{546}$ = -3.5 °, $[\alpha]_{579}$ = -2.6 °, $[\alpha]_{589}$ = -2.3 °.

10.2.6.4 Synthesis of *tert*-butyl (*S*)-but-3-en-1-yl(6-((*tert*-butyldimethylsilyl)oxy)hex-1-en-3-yl)carbamate (133a)



An argon-flooded *Schlenk* tube was charged with 200 mg (0.705 mmol, 1.00 eq.) of amine **149** dissolved in 1.4 mL dry MeCN. Then, 172 mg (1.41 mmol, 1.98 eq.) of DMAP and 224 mg (1.03 mmol, 1.46 eq.) of Boc_2O were added and the reaction mixture was stirred at rt. After 19.5 h, full consumption of the starting material was indicated by TLC and the solvent was removed under reduced pressure. The crude product was purified by column chromatography (SiO_2, *c*-Hex/EtOAc 4:1) to afford 199 mg (0.519 mmol, 74%) of the Boc-protected amine **133a** as a yellow oil.



M ($C_{21}H_{41}NO_3Si$) 383.65 g/mol.

R_f (SiO_2, *c*-Hex/EtOAc 2:1) = 0.82.

^{1}H NMR (500 MHz, $CDCl_3$), δ [ppm] = 5.88-5.79 (m, 1H, H-5), 5.74 (ddd, $^3J_{HH}$ = 17.0, 9.9, 4.8 Hz, 1H, H-9), 5.14-4.98 (m, 4H, H-6, H-10), 4.56-4.21 (m, 1H, H-4), 3.62 (t, $^3J_{HH}$ = 6.2 Hz, 2H, H-1), 3.10-3.02 (m, 2H, H-7), 2.30-2.25 (m, 2H, H-8), 1.70-1.57 (m, 2H, H-3), 1.54-1.51 (m, 2H, H-2), 1.46 (s, 9H, H-13), 0.89 (s, 9H, H-16), 0.04 (s, 6H, H-14).

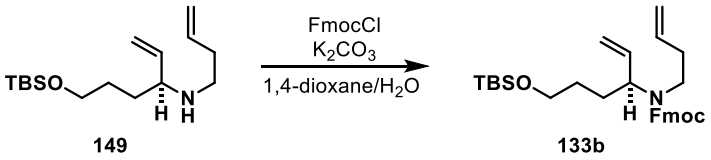
^{13}C NMR (126 MHz, $CDCl_3$), δ [ppm] = 155.8 (C-11), 138.2 (C-5), 135.9 (C-9), 116.2 (C-6, C-10), 79.6 (C-12), 63.0 (C-1), 57.4 (C-4), 44.1 (C-7), 31.2 (C-8), 29.8 (C-2), 28.6 (C-13), 27.0 (C-3), 26.1 (C-16), 18.5 (C-15), -5.1 (C-14).

FT-IR ATR, v [cm^{-1}] = 3080 (w), 2954 (m), 2930 (m), 2895 (m), 2858 (m), 1692 (s), 1642 (w), 1472 (m), 1462 (m), 1404 (m), 1365 (m), 1293 (m), 1253 (m), 1213 (w), 1173 (s), 1138 (m), 1099 (s), 996 (m), 970 (m), 916 (m), 833 (s), 774 (s), 733 (m), 661 (m), 615 (w), 460 (w).

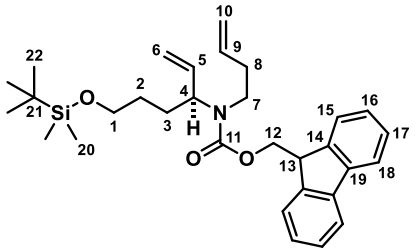
HRMS (ESI) Calcd. $[M+Na]^+$: 406.27479, found: 406.27498.

GC-MS *m/z* (%) = 270 (14), 242 (14), 184 (6), 172 (32), 154 (9), 125 (<5), 110 (36), 81 (27), 57 (100).

10.2.6.5 Synthesis of (9*H*-fluoren-9-yl)methyl (*S*)-but-3-en-1-yl(6-((*tert*-butyldimethylsilyl)-oxy)hex-1-en-3-yl)carbamate (133b)



A round-bottom flask was charged with 56 mg (0.198 mmol, 1.00 eq.) of amine **149** and 76 mg (0.550 mmol, 2.78 eq.) of K_2CO_3 dissolved in 0.9 mL H_2O. At 0 °C, a solution of 57 mg (0.220 mmol, 1.11 eq.) FmocCl in 0.90 mL 1,4-dioxane was added and the reaction mixture was warmed to rt. After 3 h, full consumption of the starting material was indicated by TLC. The reaction mixture was diluted with 10 mL CH_2Cl_2 and 10 mL H_2O. The aqueous phase was extracted twice with 10 mL CH_2Cl_2. The combined organic layers were washed with 20 mL sat. aq. NH_4Cl-solution and 20 mL sat. aq. NaCl-solution, respectively, dried over $MgSO_4$ and the solvent was removed under reduced pressure. The crude product was purified by column chromatography (SiO_2, *c*-Hex/EtOAc 10:1 → 5:1) to afford 68.0 mg (0.134 mmol, 68%) of the Fmoc-protected amine **133b** as a yellow oil.



M ($C_{31}H_{43}NO_3Si$) 505.77 g/mol.

R_f (SiO_2, *c*-Hex/EtOAc 10:1) = 0.34.

^{1}H NMR (500 MHz, $CDCl_3$, mixture of rotamers), δ [ppm] = 7.76 (d, $^3J_{HH}$ = 7.5 Hz, 2H, H-18), 7.59 (d, $^3J_{HH}$ = 7.4 Hz, 2H, H-15), 7.39 (t, $^3J_{HH}$ = 7.4 Hz, 2H, H-17), 7.31 (t, $^3J_{HH}$ = 7.4 Hz, 2H, H-16), 5.77-5.53 (m, 2H, H-5, H-9), 5.18-4.35 (m, 4H, H-6, H-10), 4.62-4.39 (m, 3H, H-4, H-12), 4.23 (t, $^3J_{HH}$ = 5.7 Hz, 1H, H-13), 3.61-3.50 (m, 2H, H-1), 3.17-2.92 (m, 2H, H-7), 2.30-2.26 (m, 0.7H, H-8^{rot1}), 2.05-2.00 (m, 1.3H, H-8^{rot2}), 1.74-1.21 (m, 4H, H-2, H-3), 0.88 (s, 9H, H-22), 0.04 (s, 6H, H-20).

^{13}C NMR (126 MHz, $CDCl_3$, mixture of rotamers), δ [ppm] = 156.5 (C-11), 144.3 (C-19), 141.6 (C-14), 137.6 (C-5), 135.4 (C-9), 127.7 (C-17), 127.2 (C-16), 124.9 (C-15), 120.1 (C-18), 116.6 (C-6), 116.4 (C-10), 66.7 (C-12), 62.9 (C-1), 58.5 (C-4), 47.7 (C-13), 43.5 (C-7), 34.3 (C-8), 29.6 (C-2), 27.9 (C-3), 26.1 (C-22), 18.5 (C-21), -5.2 (C-20).

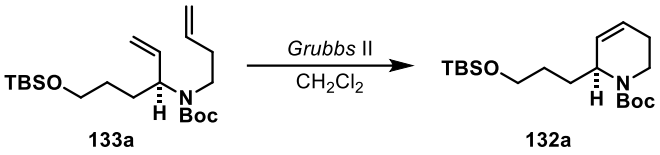
FT-IR ATR, ν [cm^{-1}] = 3070 (w), 2952 (m), 2929 (m), 2895 (m), 2856 (m), 1697 (s), 1674 (s), 1641 (m), 1610 (w), 1471 (m), 1463 (m), 1450 (s), 1414 (s), 1361

(w), 1286 (m), 1252 (s), 1208 (m), 1095 (s), 993 (m), 917 (m), 834 (s), 773 (s), 759 (s), 734 (s), 662 (m), 621 (m), 569 (m), 470 (w), 426 (m).

HRMS (ESI) Calcd. $[M+Na]^+$: 528.29044, found: 528.28981.

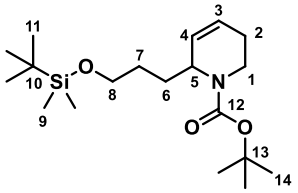
GC-MS *m/z* (%) = 448 (3), 270 (3), 211 (5), 178 (100), 152 (6), 127 (3), 89 (6), 75 (15), 55 (8).

10.2.6.6 Synthesis of *tert*-butyl (*S*)-6-(3-((*tert*-butyldimethylsilyl)oxy)propyl)-3,6-dihydropyridine-1(2*H*)-carboxylate (132a)



133a 132a

An argon-flooded flask equipped with a reflux condenser was charged with 166 mg (0.433 mmol, 1.00 eq.) of amine **133a**, 17.9 mg (21.1 µmol, 4.87 mol%) of *Grubbs* II catalyst dissolved in 4.4 mL dry CH_2Cl_2. The reaction mixture was heated to reflux. After 18 h, full consumption of the starting material was indicated by TLC and Quadrasil© was added. After stirring at rt for 15 min, the suspension was filtered over celite, washed with CH_2Cl_2 and the solvent was removed under reduced pressure. The crude product was purified by column chromatography (SiO_2, *c*-Hex/EtOAc 10:1) to afford 138 mg (0.388 mmol, 90%, 35%*ee*) of the desired product **132a** as a yellow oil.



M ($C_{21}H_{41}NO_3Si$) 383.65 g/mol.

R_f (SiO_2, *c*-Hex/EtOAc 10:1) = 0.33.

^{1}H NMR (500 MHz, $CDCl_3$), δ [ppm] = 5.85-5.74 (m, 1H, H-3), 5.71 (m, 1H, H-4), 4.44-3.99 (m, 2H, H-5, H-1a), 3.61 (t, $^3J_{HH}$ = 6.8 Hz, 2H, H-8), 2.85-2.76 (m, 1H, H-1b), 2.23-2.16 (m, 1H, H-2), 1.93-.190 (m, 1H, H-2‘), 1.66-1.53 (m, 4H, H-6, H-7), 1.45 (s, 9H, H-14), 0.88 (s, 9H, H-11), 0.04 (s, 6H, H-9).

^{13}C NMR (126 MHz, $CDCl_3$), δ [ppm] = 154.9 (C-12), 128.9 (C-4), 125.5 (C-3), 79.6 (C-13), 63.2 (C-8), 52.3 (C-5), 36.2 (C-1), 29.7 (C-6), 29.7 (C-7), 28.6 (C-14), 26.1 (C-11), 25.1 (C-2), 18.5 (C-10), -5.1 (C-9).

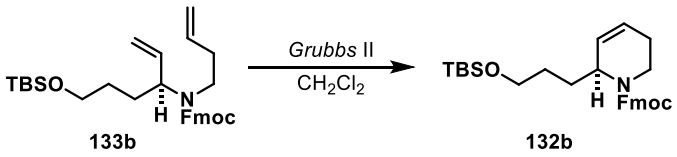
FT-IR ATR, v [cm^{-1}] = 2954 (m), 2929 (m), 2901 (m), 2858 (m), 1693 (s), 1652 (w), 1473 (m), 1462 (m), 1416 (m), 1364 (m), 1316 (m), 1276 (m), 1248 (m), 1171

(s), 1150 (m), 1102 (s), 1051 (m), 1007 (m), 938 (w), 896 (w), 834 (s), 773 (s), 704 (m), 661 (m).

HRMS (EI) Calcd. [M-O*t*Bu]: 282.18892, found: 282.18845.

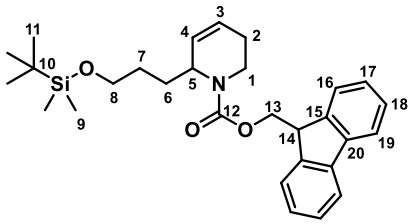
GC-MS *m/z* (%) = 282 (6), 242 (32), 224 (9), 198 (11), 169 (12), 141 (5), 126 (100), 97 (15), 82 (52), 57 (41).

10.2.6.7 Synthesis of (9*H*-fluoren-9-yl)methyl (*S*)-6-(3-((*tert*-butyldimethylsilyl)oxy)-propyl)-3,6-dihydropyridine-1(2*H*)-carboxylate (132b)



133b 132b

An argon-flooded flask equipped with a reflux condenser was charged with 304 mg (0.601 mmol, 1.00 eq.) of amine **133b**, 25.3 mg (29.8 µmol, 4.96 mol%) of *Grubbs* II-catalyst dissolved in 6.0 mL dry CH_2Cl_2. The reaction mixture was heated to reflux. After 18 h, full consumption of the starting material was indicated by TLC and Quadrasil© was added. After stirring at rt for 15 min, the suspension was filtered over celite, washed with CH_2Cl_2 and the solvent was removed under reduced pressure. The crude product was purified by column chromatography (SiO_2, *c*-Hex/EtOAc 20:1→10:1) to afford 240 mg (0.502 mmol, 84%) of the desired product **132b** as a yellow oil.



M ($C_{29}H_{39}NO_3Si$) 477.72 g/mol.

R_f (SiO_2, *c*-Hex/EtOAc 10:1) = 0.24.

^{1}H NMR (500 MHz, $CDCl_3$, mixture of rotamers), δ [ppm] = 7.76 (d, $^3J_{HH}$ = 7.5 Hz, 2H, H-19), 7.58 (d, $^3J_{HH}$ = 7.4 Hz, 2H, H-16), 7.40 (t, $^3J_{HH}$ = 7.4 Hz, 2H, H-18), 7.31 (t, $^3J_{HH}$ = 7.4 Hz, 2H, H-17), 5.82-5.77 (m, 1H, H-3), 5.69-5.63 (m, 1H, H-4), 4.59-4.39 (m, 2.5H, H-1a^{rot1}, H-13), 4.25-4.01 (m, 2.5H, H-1b^{rot1}, H-5, H14), 3.61-3.52 (m, 2H, H-8), 3.03-2.79 (m, 1H, H-1^{rot2}), 2.21- 2.13 (m, 1H, H-2a), 1.95-1.92 (m, 1H, H-2b), 1.65-1.41 (m, 4H, H-6, H-7), 0.89 (s, 9H, H-11), 0.04 (s, 6H, H-9).

^{13}C NMR (126 MHz, $CDCl_3$, mixture of rotamers), δ [ppm] = 155.6/155.3 (C-12), 144.3 (C-15), 141.5 (C-20), 129.3/128.4 (C-4), 127.8 (C-18), 127.2 (C-17), 125.5/125.1 (C-3), 125.0 (C-16), 120.1 (C-19), 67.2/67.0 (C-13), 63.1/62.9

(C-8), 52.4/52.2 (C-5), 47.9 (C-14), 37.5/37.1 (C-1), 30.8/30.2 (C-6), 29.4 (C-7), 26.1 (C-11), 25.2/24.8 (C-2), 18.5 (C-10), -5.1 (C-9).

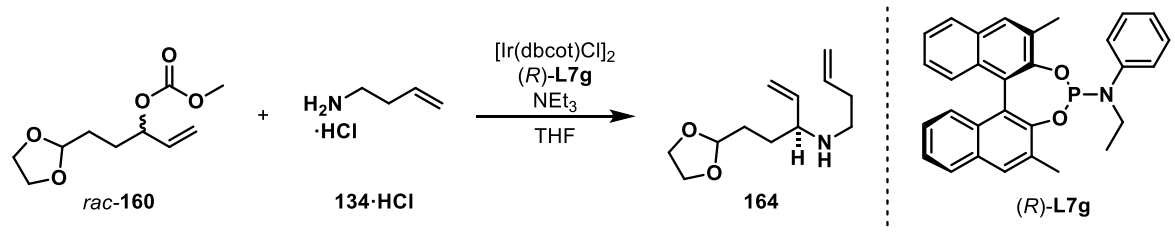
FT-IR ATR, v [cm^{-1}] = 3064 (w), 3026 (w), 2951 (m), 2927 (m), 2895 (w), 2855 (m), 2336 (w), 2127 (w), 1908 (w), 1717 (w), 1610 (w), 1471 (m), 1462 (m), 1449 (m), 1431 (m), 1361 (m), 1321 (m), 1251 (m), 1207 (w), 1095 (s), 1006 (m), 938 (m), 892 (m), 833 (s), 813 (m), 778 (s), 731 (s), 706 (m), 663 (m), 583 (w), 564 (w), 492 (w).

HRMS (ESI) calcd. $[M+H]^+$: 478.27720, found: 478.27800; calcd. $[M+Na]^+$: 500.25914, found: 500.25978.

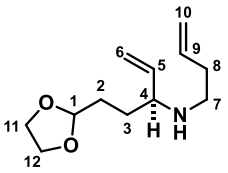
GC-MS *m/z* (%) = 180 (60), 165 (100), 152 (6), 139 (3), 115 (3), 89 (4), 76 (3).

10.2.7 Synthesis of building blocks for the test system for the approach *via* isoxazolidine formation

10.2.7.1 Synthesis of (*S*)-*N*-(but-3-en-1-yl)-5-(1,3-dioxolan-2-yl)pent-1-en-3-amine (164)



An argon-flooded flask equipped with a reflux condenser was charged with 18.3 mg (27.2 µmol, 1.03 mol%) of $[Ir(dbcot)Cl]_2$ and 26.2 mg (56.5 µmol, 2.14 mol%) of the phosphoramidite ligand (*R*)-**L7g** dissolved in 5.0 mL dry THF. After stirring at rt for 20 min, 572 mg (2.65 mmol, 1.00 eq.) of carbonate *rac*-**160** were added. After another 20 min, 5.0 mL dry THF, 0.52 mL (3.73 mmol, 1.41 eq.) NEt_3 and 398 mg (3.70 mmol, 1.40 eq.) of amine **134·HCl** were added consecutively. The reaction mixture was heated to 50 °C under reflux. Full consumption of the starting material was indicated by TLC after 16 h. Quadrasil was added and the suspension stirred at rt for another 15 min. The suspension was filtered over a pad of celite, washed with MTBE and the solvent was removed under reduced pressure. The crude product was purified by column chromatography (SiO_2, EtOAc/NEt_3 1:0.01) to afford 212 mg (1.00 mmol, 38%) of the desired amine **164** as a yellow oil.



M ($C_{11}H_{21}NO_2$) 211.31 g/mol.

R_f (SiO_2, EtOAc) = 0.15.

^{1}H NMR (600 MHz, $CDCl_3$), δ [ppm] = 5.77 (ddt, $^3J_{HH}$ = 17.1, 10.2, 6.9 Hz, 1H, H-9), 5.57 (ddd, $^3J_{HH}$ = 16.6, 10.7, 8.2 Hz, 1H, H-5), 5.14-5.00 (m, 4H, H-6, H-10), 4.86 (t, $^3J_{HH}$ = 4.6 Hz, 1H, H-1), 3.99-3.91 (m, 2H, H-11a, H-12a), 3.87-3.81 (m, 2H, H-11b, H-12b), 3.05-2.98 (m, 1H, H-4), 2.69 (dt, $^2J_{HH}$ = 11.5 Hz, $^3J_{HH}$ = 6.9 Hz, 1H, H-7a), 2.56 (dt, $^2J_{HH}$ = 11.5 Hz, $^3J_{HH}$ = 6.8 Hz, 1H, H-7b), 2.23 (qt, $^3J_{HH}$ = 6.8 Hz, $^4J_{HH}$ = 1.3 Hz, 2H, H-8), 1.78-1.59 (m, 3H, H-2, H-3a), 1.56-1.46 (m, 1H, H-3b), 1.28 (s, 1H, *N*H).

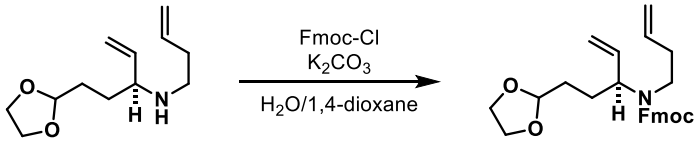
^{13}C NMR (151 MHz, $CDCl_3$), δ [ppm] = 141.1 (C-5), 136.7 (C-9), 116.4 (C-6), 116.3 (C-10), 104.5 (C-1), 65.0 (C-11, C-12), 61.8 (C-4), 46.3 (C-7), 34.4 (C-8), 30.5 (C-2), 29.7 (C-3).

FT-IR ATR, v [cm^{-1}] = 3076 (w), 2926 (w), 2882 (m), 1640 (m), 1475 (m), 1437 (m), 1413 (m), 1363 (m), 1316 (w), 1215 (m), 1127 (s), 1033 (s), 994 (s), 967 (m), 942 (m), 912 (s), 710 (m), 684 (m), 644 (m), 523 (m).

HRMS (ESI) Calcd. $[M+H]^+$: 212.16451, found: 212.16420.

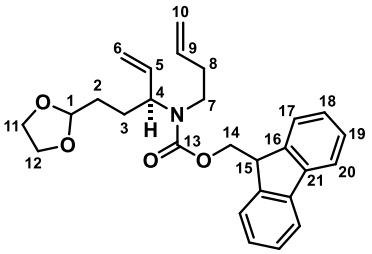
GC-MS *m/z* (%) = 192 (5), 170 (47), 139 (23), 124 (5), 110 (82), 96 (12), 73 (100), 55 (30).

10.2.7.2 Synthesis of (9*H*-fluoren-9-yl)methyl (*S*)-(5-(1,3-dioxolan-2-yl)pent-1-en-3-yl)(but-3-en-1-yl)carbamate (159a)



164 **159a**

55.0 mg (0.260 mmol, 1.00 eq.) of amine **164** were dissolved in 1.2 mL 1,4-dioxane. A solution of 101 mg (0.731 mmol, 2.81 eq.) of K_2CO_3 in 1.2 mL H_2O were added and the solution was cooled to 0 °C. Then, 71.0 mg (0.274 mmol, 1.05 eq.) of Fmoc-Cl were added and the reaction mixture was warmed up to rt. After 1.5 h full consumption of the starting material was indicated by TLC. The reaction mixture was diluted with 10 mL CH_2Cl_2 and 10 mL H_2O. The aqueous phase was extracted twice with 5 mL CH_2Cl_2. The combined organic layers were washed with 10 mL sat. aq. NH_4Cl-solution and 10 mL sat. aq. NaCl-solution, dried over $MgSO_4$ and the solvent was removed under reduced pressure. The crude product was purified by column chromatography (SiO_2, *c*-Hex/EtOAc 5:1) to afford 101 mg (0.233 mmol, 90%) of the desired Fmoc-protected amine **159a** as a light-yellow oil.



M ($C_{27}H_{31}NO_4$) 433.55 g/mol.

R_f (SiO_2, *c*-Hex/EtOAc 5:1) = 0.26.

^{1}H NMR (500 MHz, $CDCl_3$, mixture of rotamers), δ [ppm] = 7.75 (d, $^3J_{HH}$ = 7.5 Hz, 2H, H-20), 7.58 (d, $^3J_{HH}$ = 8.0 Hz, 2H, H-17), 7.39 (t, $^3J_{HH}$ = 7.7 Hz, 2H, H-19), 7.32 (t, $^3J_{HH}$ = 8.3 Hz, 2H, H-18), 5.84-5.67 (m, 1H, H-5), 5.61-5.45 (m, 1H, H-9), 5.17-4.71 (m, 5H, H-1, H-6, H-10), 4.60-4.42 (m, 2.5H, H-4^{rot1}, H-14), 4.23 (t, $^3J_{HH}$ = 5.6 Hz, 1H, H-15), 4.15-4.10 (m, 0.5H, H-4^{rot2}), 3.98-3.90 (m, 2H, H-11a, H-12a), 3.88-3.81 (m, 2H, H-11b, H-12b), 3.20-2.91 (m, 2H, H-7),

2.8-2.25 (m, 0.8H, H-8^{rot1}), 2.11-1.97 (m, 1.2H, H-8^{rot2}), 1.81-1.47 (m, 4H, H-2, H-3).

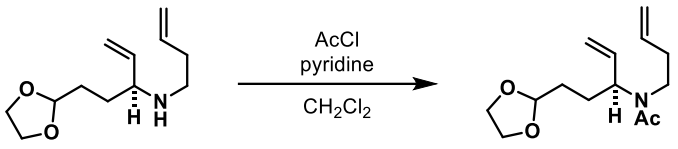
^{13}C NMR (126 MHz, $CDCl_3$, mixture of rotamers), δ [ppm] = 156.4 (C-13), 144.5/144.3 (C-16), 141.7/141.6 (C-21), 137.2 (C-5), 135.6/135.4 (C-9), 127.7 (C-19), 127.2 (C-18), 124.9/124.8 (C-17), 120.2/120.1 (C-20), 116.9 (C-6), 116.4 (C-10), 104.2 (C-1), 66.7 (C-14), 65.4 (C-11, C-12), 58.6 (C-4), 50.5/47.7 (C-15), 43.6 (C-7), 34.3 (C-8), 30.7 (C-2). 25.6 (C-3).

FT-IR ATR, v [cm^{-1}] = 3068 (w), 2952 (w), 2884 (w), 1690 (s), 1641 (m), 1611 (w), 1476 (m), 1450 (m), 1415 (s), 1286 (m), 1208 (m), 1179 (m), 1137 (s), 1085 (m), 1032 (m), 997 (m), 916 (s), 759 (s), 737 (s), 671 (m), 648 (m), 621 (m), 570 (m), 540 (m).

HRMS (ESI) calcd. $[M+H]^+$: 434.23259, found: 434.23312; calcd. $[M+Na]^+$: 456.21453, found: 456.21485.

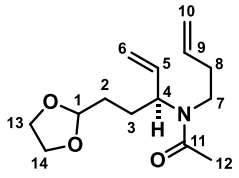
GC-MS *m/z* (%) = 196 (14), 178 (38), 165 (100), 139 (8), 115 (5), 89 (<5), 63 (<5).

10.2.7.3 Synthesis of (*S*)-*N*-(5-(1,3-dioxolan-2-yl)pent-1-en-3-yl)-*N*-(but-3-en-1-yl) acetamide (159b)



164 159b

An argon-flooded *Schlenk* flask was charged with 101 mg (0.477 mmol, 1.00 eq.) of amine **164** dissolved 0.5 mL dry CH_2Cl_2. At 0 °C, 46.1 µL (0.572 mmol, 1.20 eq.) of pyridine and 35.7 µL (0.501 mmol, 1.05 eq.) of AcCl were added. The reaction mixture was warmed to rt. After 22 h, full consumption of the starting material was indicated by TLC. The reaction mixture was diluted with 5 mL CH_2Cl_2 and 5 mL sat. aq. $NaHCO_3$-solution. The aqueous phase was extracted three times with 5 mL CH_2Cl_2. The combined organic layers were washed with 10 mL sat. aq. NaCl-solution, dried over $MgSO_4$ and the solvent was removed under reduced pressure. The crude product was purified by column chromatography (SiO_2, *c*-Hex/EtOAc 1:1 → 1:2) to afford 74.0 mg (0.292 mmol, 61%) of the desired acetate-protected amine **159b** as a light-yellow oil.



M ($C_{14}H_{23}NO_3$) 253.34 g/mol.

R_f (SiO_2, *c*-Hex/EtOAc 1:1) = 0.15.

^{1}H NMR (500 MHz, $CDCl_3$, mixture of rotamers), δ [ppm] = 5.90-5.68 (m, 2H, H-5, H-9), 5.24-4.98 (m, 4H, H-6, H-10), 4.93-4.87 (m, 1.5H, H-1, H-4^{rot1}), 4.24 (q, $^3J_{HH}$ = 6.2 Hz, 0.5H, H-4^{rot2}), 4.01-3.93 (m, 2H, H-13a, H-14a), 3.90-3.81 (m, 2H, H-13b, H-14b), 3.29 (ddd, $^2J_{HH}$ = 13.6 Hz, $^3J_{HH}$ = 10.8, 5.3 Hz, 0.5H, H-7a^{rot1}), 3.24-3.16 (m, 1H, H-7b), 3.12 (ddd, $^2J_{HH}$ = 13.5 Hz, $^3J_{HH}$ = 10.7, 5.3 Hz, 0.5H, H-7a^{rot2}), 2.42-2.24 (m, 2H, H-8), 2.12 (s, 3H, H-12), 1.88-1.56 (m, 4H, H-2, H-3).

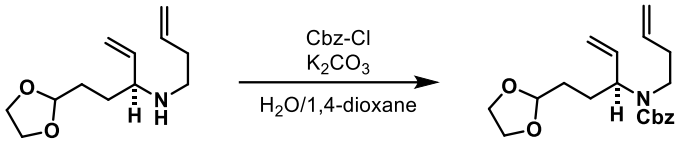
^{13}C NMR (126 MHz, $CDCl_3$, mixture of rotamers), δ [ppm] = 170.9/170.8 (C-11), 137.4/137.0 (C-5), 135.9/134.5 (C-9), 117.3/117.2 (C-6), 117.1/116.2 (C-10), 104.2/104.0 (C-1), 65.2/65.1/65.0 /C-13, C-14), 60.3/56.3 (C-4), 45.1/42.2 (C-7), 35.1/33.5 (C-8), 30.8/30.5 (C-2), 26.2/25.5 (C-3), 22.4/22.2 (C-12).

FT-IR ATR, v [cm^{-1}] = 3079 (w), 2957 (w), 2884 (w), 2764 (w), 1739 (w), 1635 (s), 1448 (m), 1415 (s), 1365 (w), 1290 (w), 1251 (w), 1229 (w), 1178 (w), 1140 (m), 1033 (m), 1000 (m), 967 (w), 919 (m), 806 (w), 769 (w), 709 (w), 613 (w).

HRMS (ESI) calcd. $[M+H]^+$: 254.17507, found: 254.17514; calcd. $[M+Na]^+$: 276.15701, found: 276.15712.

GC-MS *m/z* (%) = 252 ($[M]^+$, <5), 212 (35), 181 (9), 166 (17), 139 (47), 110 (89), 73 (100), 55 (30).

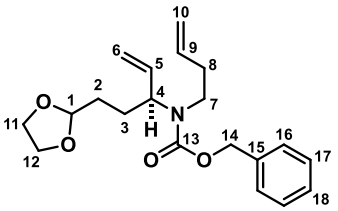
10.2.7.4 Synthesis of benzyl (*S*)-(5-(1,3-dioxolan-2-yl)pent-1-en-3-yl)(but-3-en-1-yl)-carbamate (159c)



164 159c

A round-bottom flask was charged with 102 mg (0.482 mmol, 1.00 eq.) of amine **164** dissolved in 2.4 mL 1,4-dioxane. A solution of 195 mg (1.41 mmol, 2.93 eq.) K_2CO_3 in 2.4 mL H_2O was added and the solution was cooled to 0 °C. Then, 69.4 µL (0.496 mmol, 1.03 eq.) of Cbz-Cl were added and the reaction mixture was warmed to rt. After 2 h, full consumption of the starting material was indicated by TLC. The reaction mixture was diluted with 20 mL CH_2Cl_2 and 10 mL H_2O. The aqueous phase was extracted twice with 10 mL CH_2Cl_2. The combined organic layers were washed with 20 mL sat. aq. NH_4Cl-solution, 20 mL sat. aq. NaCl-solution, dried over $MgSO_4$ and the solvent was removed under reduced pressure. The crude product was purified by column chromatography (SiO_2, *c*-Hex/EtOAc 5:1) to afford 141 mg (0.408 mmol, 85%) of Cbz-protected amine **159c** as a yellow oil.

Note: By reacting the crude amine **164** according to the described procedure the overall yield was increased to 75% over two steps.



M ($C_{20}H_{27}NO_4$) 345.44 g/mol.

R_f (SiO_2, *c*-Hex/EtOAc 5:1) = 0.32.

^{1}H NMR (600 MHz, $CDCl_3$, mixture of rotamers), δ [ppm] = 7.37-7.34 (m, 4H, H-16, H-17), 7.33-7.28 (m, 1H, H-18), 5.88-5.68 (m, 2H, H-5, H-9), 5.20-5.11 (m, 4H, H-6, H-14), 5.05-4.96 (m, 2H, H-10), 4.91-4.84 (m, 1H, H-1), 4.56-4.37 (m, 1H, H-4), 3.97-3.92 (m, 2H, H-11a, H-12a), 3.86-3.81 (m, 2H, H-11b, H-12b), 3.20-3.13 (m, 2H, H-7), 2.37-2.27 (m, 2H, H-8), 1.81-1.72 (m, 2H, H-3), 1.70-1.63 (m, 2H, H-2).

^{13}C NMR (151 MHz, $CDCl_3$, mixture of rotamers), δ [ppm] = 156.4 (C-13), 137.5/137.3 (C-5), 137.0 (C-15), 135.6/135.5 (C-9), 128.7/128.6 (C-16, C-17), 128.0/127.9 (C-18), 117.0/116.8 (C-10), 116.5 (C-6), 104.2 (C-1), 67.1 (C-14), 65.0 (C-11, C-12), 58.7 (C-4), 43.7 (C-7), 34.7/33.5 (C-8), 30.8 (C-2), 26.8/25.7 (C-3).

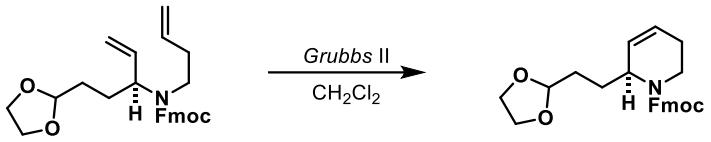
FT-IR ATR, v [cm^{-1}] = 3068 (w), 3032 (w), 2954 (w), 2884 (w), 1810 (w), 1744 (w), 1694 (s), 1641 (w), 1498 (w), 1466 (m), 1413 (m), 1369 (w), 1285 (m), 1213 (m), 1179 (m), 1135 (s), 1077 (m), 1028 (m), 997 (m), 966 (m), 942 (m), 916 (s), 824 (w), 769 (m), 736 (m), 698 (s), 608 (w).

HRMS (ESI) Calcd. $[M+H]^+$: 346.20128, found: 346.20146; calcd. $[M+Na]^+$: 368.18323, found: 368.18305.

GC-MS *m/z* (%) = 346 ($[M+H]^+$, <5), 304 (<5), 230 (<5), 186 (<5), 154 (<5), 139 (11), 120 (<5), 91 (100), 73 (53), 55 (9).

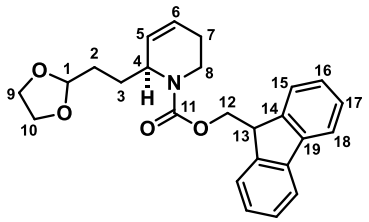
$[\alpha]_\lambda^{20}$ (0.353 g/100 mL in $CHCl_3$): $[\alpha]_{365}$ = -49 °, $[\alpha]_{436}$ = -21 °, $[\alpha]_{546}$ = -11 °, $[\alpha]_{579}$ = -9.4 °, $[\alpha]_{589}$ = -9.1 °.

10.2.7.5 Synthesis of (9*H*-fluoren-9-yl)methyl (*S*)-6-(2-(1,3-dioxolan-2-yl)ethyl)-3,6-dihydropyridine-1(2*H*)-carboxylate (158a)



159a **158a**

An argon-flooded flask equipped with a reflux condenser was charged with 81 mg (0.187 mmol, 1.00 eq.) of Fmoc-protected amine **159a** and 7.7 mg (9.07 µmol, 4.85 mol%) of *Grubbs* II catalyst. The solids were dissolved in 2.0 mL dry CH_2Cl_2 and the reaction mixture was heated to reflux. After 18 h, full consumption of the starting material was indicated by TLC. Quadrasil© was added and the mixture was stirred at rt for 15 min. The suspension was filtered over a pad of celite, washed with CH_2Cl_2 and the solvent was removed under reduced pressure. The crude product was purified by column chromatography (SiO_2, *c*-Hex/EtOAc 3:1) to afford 56 mg (0.14 mmol, 74%) of the desired product **158a** as a light-yellow oil.



M ($C_{20}H_{27}NO_4$) 345.44 g/mol.

R_f (SiO_2, *c*-Hex/EtOAc 3:1) = 0.22.

^{1}H NMR (600 MHz, $CDCl_3$, mixture of rotamers), δ [ppm] = 7.76 (d, $^3J_{HH}$ = 7.5 Hz, 2H, H-18), 7.58 (d, $^3J_{HH}$ = 7.2 Hz, 2H, H-15), 7.39 (t, $^3J_{HH}$ = 7.4 Hz, 2H, H-17), 7.31 (t, $^3J_{HH}$ = 7.5 Hz, 2H, H-16), 5.85-5.77 (m, 1H, H-5), 5.70-5.62 (m, 1H, H-6), 4.89-4.77 (m, 1H, H-1), 4.57-4.40 (m, 2.5H, H-4^{rot1}, H-12), 4.28-4.14 (m, 2H, H-4^{rot2}, H-8a^{rot1}, H-13), 4.05-4.00 (m, 0.5H, H-8a^{rot2}), 3.97-3-92 (m, 2H, H-9a, H-10a), 3.85-3.81 (m, 2H, H-9b, H-10b), 2.99-2.84 (m, 1H, H-8b), 2.23-2.08 (m, 1H, H-7a), 1.96-1.90 (m, 1H, H-7b), 1.81-1.65 (m, 2H, H-2), 1.60-1.57 (m, 2H, H-3).

^{13}C NMR (151 MHz, $CDCl_3$, mixture of rotamers), δ [ppm] = 155.5 (C-11), 144.3 (C-19), 141.5 (C-14), 128.9/128.0 (C-6), 127.8 (C-17), 127.2 (C-16), 125.9/125.3 (C-5), 125.1 (C-15), 120.1 (C-18), 104.3 (C-1), 67.2 (C-12), 65.04 (C-9, C-10), 52.1 (C-4), 47.6 (C-13), 37.5/37.1 (C-8), 30.5 (C-3), 28.5/28.0 (C-2), 25.2/24.8 (C-7).

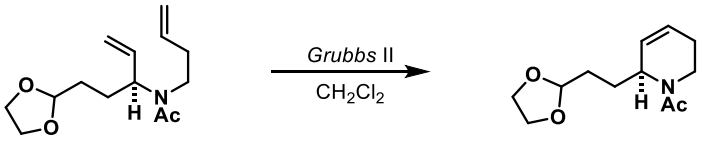
FT-IR ATR, v [cm^{-1}] = 3037 (w), 2653 (w), 2887 (w), 1695 (s), 1653 (w), 1450 (m), 1426 (m), 1356 (w), 1330 (w), 1314 (w), 1274 (w), 1244 (m), 1199 (m), 1140

(m), 1110 (m), 1054 (m), 1029 (m), 969 (w), 944 (w), 894 (w), 758 (m), 740 (m), 708 (w), 621 (w), 570 (w), 540 (w).

HRMS (ESI) Calcd. $[M+H]^+$: 406.20128, found: 406.20178; calcd. $[M+Na]^+$: 428.18323, found: 428.18334.

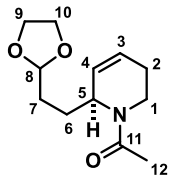
GC-MS *m/z* (%) = 178 (100), 152 (9), 126 (<5), 98 (<5), 76 (9), 50 (6).

10.2.7.6 Synthesis of (*S*)-1-(6-(2-(1,3-dioxolan-2-yl)ethyl)-3,6-dihydropyridin-1(2*H*)-yl)ethan-1-one (158b)



159b 158b

An argon-flooded flask equipped with a reflux condenser was charged with 74.0 mg (0.292 mmol, 1.00 eq.) of acetate-protected amine **159b** and 13.1 mg (15.4 µmol, 5.28 mol%) of *Grubbs* II catalyst. The solids were dissolved in 3.0 mL dry CH_2Cl_2 and the reaction mixture was heated to reflux. After 17 h, full consumption of the starting material was indicated by TLC. Quadrasil© was added and the mixture was stirred at rt for 15 min. The suspension was filtered over a pad of celite, washed with CH_2Cl_2 and the solvent was removed under reduced pressure. The crude product was purified by column chromatography (SiO_2, *c*-Hex/EtOAc 1:2 → 0:1) to afford 48 mg (0.21 mmol, 73%) of the desired product **158b** as a light-yellow oil.



M ($C_{12}H_{19}NO_3$) 225.29 g/mol.

R_f (SiO_2, *c*-Hex/EtOAc 1:2) = 0.09.

^{1}H NMR (500 MHz, $CDCl_3$, mixture of rotamers), δ [ppm] = 5.91-5.84 (m, 0.4H, H-3^{rot2}), 5.81-5.77 (m, 0.6H, H-3^{rot1}), 5.73-5.69 (m, 1H, H-4), 4.93-4.87 (m, 1.6H, H-5^{rot1}, H-8), 4.64 (dd, $^3J_{HH}$ = 12.5, 6.0 Hz, 0.4H, H-1a), 4.17-4.11 (m, 0.4H, H-5^{rot2}), 4.00-3.92 (m, 2H, H-9a, H-10a), 3.90-3.81 (m, 2H, H-9b, H-10b), 3.70 (dd, $^3J_{HH}$ = 13.8, 5.6 Hz, 0.6H, H-1a^{rot1}), 3.23 (ddd, $^3J_{HH}$ = 13.8, 12.2 Hz, $^4J_{HH}$ = 3.9 Hz, 0.6H, H-1b^{rot1}), 2.70 (td, $^3J_{HH}$ = 12.5, 4.2 Hz, 0.4H, H-1^{rot2}), 2.27-2.17 (m, 1H, H-2a), 2.11 (2·s, 3H, H-12), 2.05-1.93 (m, 1H, H-2b), 1.80-1.64 (m, 4H, H-6, H-7).

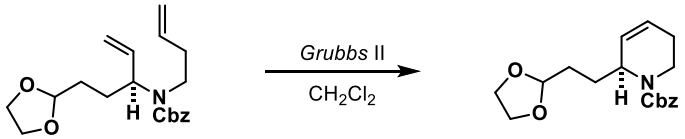
^{13}C NMR (126 MHz, $CDCl_3$, mixture of rotamers), δ [ppm] = 169.3/169.0 (C-11), 129.3/127.4 (C-4), 126.8/124.6 (C-3), 104.3/104.1 (C-8), 65.1/65.0 (C-9, C-10), 54.3/46.7 (C-5), 40.0/34.5 (C-1), 30.4/30.3 (C-6), 28.8/27.8 (C-7), 25.8/25.0 (C-2), 22.0/21.8 (C-12).

FT-IR ATR, v [cm^{-1}] = 3032 (w), 2955 (w), 2926 (w), 2888 (w), 1657 (m), 1629 (s), 1427 (s), 1367 (w), 1338 (w), 1314 (w), 1251 (w), 1200 (w), 1139 (m), 1067 (w), 1052 (m), 1035 (m), 971 (m), 944 (m), 917 (w), 883 (w), 762 (w), 714 (w), 590 (w).

HRMS (ESI) Calcd. $[M+H]^+$: 226.14377, found: 226.14362; calcd. $[M+Na]^+$: 248.12571, found: 248.12560.

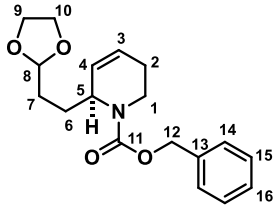
GC-MS *m/z* (%) = 182 (15) 124 (44), 109 (<5), 82 (100), 55 (11).

10.2.7.7 Synthesis of benzyl (*S*)-6-(2-(1,3-dioxolan-2-yl)ethyl)-3,6-dihydropyridine-1(2*H*)-carboxylate (158c)



159c **158c**

An argon-flooded flask equipped with a reflux condenser was charged with 480 mg (1.39 mmol, 1.00 eq.) of substrate **159c** and 59.4 mg (70.0 µmol, 5.08 mol%) of *Grubbs* II catalyst dissolved in 14 mL dry CH_2Cl_2 and the reaction mixture was heated to reflux. Full consumption of the starting material was indicated after 17 h. After cooling to rt, Quadrasil© was added and the mixture was stirred at rt for 15 min. The suspension was filtered over a pad of celite, washed with CH_2Cl_2 and the solvent was removed under reduced pressure. The crude product was purified by column chromatography (SiO_2, *c*-Hex/EtOAc 5:1 → 3:1) to afford 358 mg (1.13 mmol, 81%) of the desired product **158c** as a yellow oil.



M ($C_{18}H_{23}NO_4$) 317.39 g/mol.

R_f (SiO_2, *c*-Hex/EtOAc 5:1) = 0.18.

^{1}H NMR (600 MHz, $CDCl_3$, mixture of rotamers), δ [ppm] = 7.37-7.34 (m, 4H, H-14, H-15), 7.33-7.29 (m, 1H, H-16), 5.85-5.79 (m, 1H, H-3), 5.71-5.63 (m, 1H, H-4), 5.25 (d, $^4J_{HH}$ = 2.3 Hz, 2H, H-12), 4.93-4.78 (m, 1H, H-8), 4.57-4.40 (m,

1H, H-5), 4.27-4.07 (m, 1H, H-1a), 3.95-3.81 (m, 4H, H-11, H-12), 3.02-2.86 (m, 1H, H-1b), 2.30-2.13 (m, 1H, H-2a), 2.01-1.88 (m, 1H, H-2b), 1.82-1.64 (m, 4H, H-6, H-7).

^{13}C NMR (151 MHz, $CDCl_3$, mixture of rotamers), δ [ppm] = 155.5 (C-11), 137.1/136.9 (C-13), 128.6 (C-14, C-15), 128.1 (C-16), 127.9 (C-4), 125.8/125.3 (C-3), 104.3 (C-8), 67.3/67.1 (C-12), 65.1 (C-9, C-10), 52.1 (C-5), 37.5/37.0 (C-1), 30.5 (C-7), 28.5/28.1 (C-6), 25.3/24.9 (C-2).

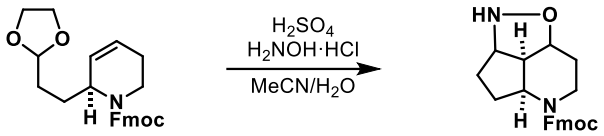
FT-IR ATR, v [cm^{-1}] = 3032 (w), 2931 (w), 2884 (m), 1693 (s), 1653 (m), 1586 (w), 1497 (w), 1454 (m), 1424 (s), 1357 (m), 1331 (m), 1313 (m), 1274 (m), 1244 (m), 1198 (m), 1138 (m), 1105 (s), 1053 (m), 1024 (s), 969 (m), 944 (m), 891 (m), 790 (w), 735 (m), 697 (s), 635 (w), 602 (w), 587 (w), 559 (w), 530 (w).

HRMS (ESI) Calcd. $[M+H]^+$: 318.16998, found: 318.17022; calcd. $[M+Na]^+$: 340.15193, found: 340.15222.

GC-MS *m/z* (%) = 317 ([M], <5), 216 (27), 184 (11), 172 (43), 138 (11), 122 (<5), 91 (100), 73 (9), 45 (<5).

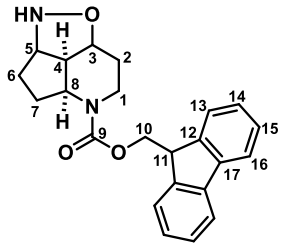
$[\alpha]_\lambda^{20}$ (0.295 g/100 mL in $CHCl_3$): $[\alpha]_{365}$ = 198 °, $[\alpha]_{436}$ = 122 °, $[\alpha]_{546}$ = 71 °, $[\alpha]_{579}$ = 62 °, $[\alpha]_{589}$ = 60 °.

10.2.7.8 Synthesis of (9*H*-fluoren-9-yl)methyl (2a[1]*S*,7a*S*)-octahydro-4-oxa-3,7-diazacyclopenta[cd]indene-7(2*H*)-carboxylate (157a)



158a 157a

A round-bottom flask equipped with a reflux condenser was charged with 56.0 mg (0.138 mmol, 1.00 eq.) of acetal **158a** in 1.05 mL MeCN. 48.0 mg (0.691 mmol, 5.01 eq.) of hydroxylamine hydrochloride, 0.4 mL H_2O and 69.0 µL (69.0 µmol, 0.50 eq.) of H_2SO_4 (1 M) were added consecutively. The reaction mixture was heated to reflux. After 3.5 h, full consumption of the starting material was indicated by TLC. The reaction mixture was quenched with 5 mL sat. aq. $NaHCO_3$-solution. The aqueous phase was extracted three times with 5 mL EtOAc. The combined organic layers were washed with 10 mL sat. aq. NaCl-solution, dried over $MgSO_4$ and the solvent was removed under reduced pressure. The crude product was purified by column chromatography (SiO_2, *c*-Hex/EtOAc 3:1 → 2:1) to afford 37.0 mg (98.3 µmol, 71%) of the desired product **157a** as a colourless oil.



M ($C_{23}H_{24}N_2O_3$) 376.46 g/mol.

R_f (SiO_2, *c*-Hex/EtOAc 3:1) = 0.15.

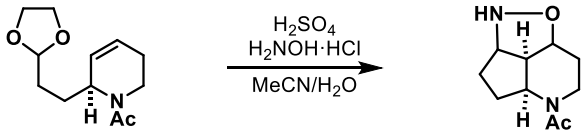
^{1}H NMR (500 MHz, $CDCl_3$, mixture of diastereomers), δ [ppm] = 7.76 (d, $^3J_{HH}$ = 7.5 Hz, 2H, H-16), 7.57 (d, $^3J_{HH}$ = 7.4 Hz, 2H, H-13), 7.48-7.45 (m, 0.25H, H-5), 7.40 (t, $^3J_{HH}$ = 7.4 Hz, 2H, H-15), 7.31 (t, $^3J_{HH}$ = 7.5 Hz, H-14), 7.28-7.23 (m, 0.5H, H-5'), 6.81-6.75 (m, 0.25H, H-5''), 6.53-6.48 (m, 0.25H, H-5'''), 5.82 (q, $^3J_{HH}$ = 6.7 Hz, 1H, H-3), 5.73-5.63 (m, 0.5H, H-4), 5.62-5.50 (m, 0.5H, H-4'), 4.65-4.40 (m, 2.5H, H-8, H-10), 4.29-4.20 (m, 1H, H-11), 4.20-4.03 (m, 0.5H, H-1a), 4.07-3.93 (m, 1H, H-1a', H-8'), 3.00-2.73 (m, 1H, H-1b), 2.51-2.34 (m, 0.5H, H-6'), 2.30-2.06 (m, 2H, H-2', H-6), 2.00-1.86 (m, 1.5H, H-2), 1.83-1.66 (m, 1H, H-7a), 1.61-1.39 (m, 1H, H-7b).

^{13}C NMR (126 MHz, $CDCl_3$, mixture of diastereomers), δ [ppm] = 155.5 (C-9), 151.9/151.7 (C-5), 144.2 (C-12), 141.5 (C-17), 127.8 (C-15), 127.3 (C-4), 127.2 (C-14), 125.1 (C-3), 124.8 (C-13), 120.1 (C-16), 67.3/66.7 (C-10), 51.9/51.8 (C-8), 47.6 (C-11), 37.5/37.0 (C-1), 30.6 (C-7), 25.1/24.8 (C-2), 21.9/21.7 (C-6).

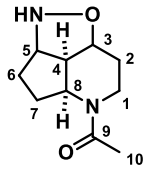
FT-IR ATR, v [cm^{-1}] = 3320 (br), 3065 (w), 3037 (w), 2922 (w), 2247 (w), 1911 (w), 1676 (s), 1609 (w), 1581 (w), 1528 (w), 1470 (m), 1449 (s), 1428 (s), 1356 (m), 1331 (m), 1274 (m), 1243 (m), 1199 (m), 1147 (m), 1111 (m), 1057 (m), 1024 (m), 1007 (w), 906 (m), 813 (w), 782 (m), 758 (s), 735 (s), 710 (s), 674 (m), 646 (m), 621 (m), 569 (m), 540 (m).

GC-MS *m/z* (%) = 178 (100), 152 (8), 139 (<5), 126 (3), 113 (3), 89 (9), 75 (9), 63 (11), 50 (9).

10.2.7.9 Synthesis of 1-((2a[1]*S*,7a*S*)-octahydro-4-oxa-3,7-diazacyclo- penta[cd]inden-7(2*H*)yl)ethan-1-one (157b)



A round-bottom flask equipped with a reflux condenser was charged with 48 mg (0.21 mmol, 1.00 eq.) of acetal **158b** in 1.6 mL MeCN. 74 mg (1.1 mmol, 5.00 eq.) of hydroxylamine hydrochloride, 0.55 mL H_2O and 0.11 mL (0.110 mmol, 0.50 eq.) of H_2SO_4 (1 M) were added consecutively. The reaction mixture was heated to reflux. After 3.5 h, full consumption of the starting material was indicated by TLC. The reaction mixture was quenched with 5 mL sat. aq. $NaHCO_3$-solution. The aqueous phase was extracted three times with 5 mL EtOAc. The combined organic layers were washed with 10 mL sat. aq. NaCl-solution, dried over $MgSO_4$ and the solvent was removed under reduced pressure. The crude product was purified by column chromatography (SiO_2, EtOAc) to afford 32.0 mg (0.163 mmol, 77%) of the desired product **157b** as a colourless oil.



M ($C_{10}H_{16}N_2O_2$) 196.25 g/mol.

R_f (SiO_2, EtOAc) = 0.14.

^{1}H NMR (500 MHz, $CDCl_3$, mixture of diastereomers and rotamers), δ [ppm] = 7.45 (2·t, $^3J_{HH}$ = 5.6 Hz, 0.6H, H-5, H-5'), 6.77 (t, $^3J_{HH}$ = 5.5 Hz, 0.3H, H-5''), 6.73 (t, $^3J_{HH}$ = 5.5 Hz, 0.1H, H-5'''), 5.93-5.87 (m, 0.3H, H-3'), 5.85-5.78 (m, 0.7H, H-3), 5.75-5.67 (m, 1H, H-4), 4.95-4.89 (m, 0.7H, H-8), 4.66 (dt, $^3J_{HH}$ = 11.6, 5.6 Hz, 0.3H, H-1a'), 4.18-4.08 (m, 0.3H, H-8'), 3.77-3.68 (m, 0.7H, H-1a),

3.26-3.19 (m, 0.7H, H-1b), 2.75-2.65 (m, 0.3H, H-1b'), 2.53-2.37 (m, 1H, H-6a), 2.34-2.18 (m, 2H, H-2a, H-6b), 2.13-2.11 (m, 3H, H-10), 2.08-1.94 (m, 1H, H-2b), 1.93-1.71 (m, 2H, H-7).

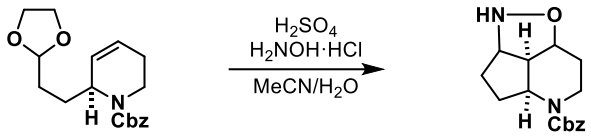
^{13}C NMR (126 MHz, $CDCl_3$, mixture of diastereomers and rotamers), δ [ppm] = 169.6/169.5/169.4 (C-9), 152.2/151.6/151.0/150.5 (C-5), 128.8/128.7/127.0 (C-4), 127.3/125.1/125.0 (C-3), 54.3/53.8/49.8/49.7 (C-8), 40.2/40.1/34.7 (C-1), 31.1/30.5/29.9 (C-7), 26.6/26.4/25.8/24.9 (C-2), 22.0/21.9 (C-6), 22.0/21.8 (C-10).

FT-IR ATR, v [cm^{-1}] = 3239 (br), 3094 (w), 3035 (w), 2923 (w), 2240 (w), 1656 (w), 1607 (s), 1425 (s), 1369 (m), 1338 (m), 1312 (m), 1277 (m), 1242 (m), 1200 (m), 1143 (w), 1101 (w), 1053 (w), 1034 (w), 1001 (m), 971 (w), 916 (m), 798 (m), 758 (m), 725 (s), 645 (m), 588 (m).

HRMS (ESI) Calcd. $[M+H]^+$: 197.12845, found: 197.12858; calcd. $[M+Na]^+$: 219.11040, found: 219.11029.

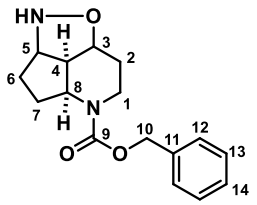
GC-MS *m/z* (%) = 178 (<5), 135 (17), 124 (26), 96 (15), 82 (100), 67 (12), 54 (14).

10.2.7.10 Synthesis of benzyl (2a[1]*S*,7a*S*)-octahydro-4-oxa-3,7-diazacyclopenta[cd]indene-7(2*H*)-carboxylate (157c)



158c 157c

A round-bottom flask equipped with a reflux condenser was charged with 685 mg (2.16 mmol, 1.00 eq.) of acetal **158c** and 745 mg (10.7 mmol, 4.97 eq.) of hydroxylamine hydrochloride dissolved in 21.9 mL MeCN/H_2O (3:1). After the addition of 1.10 mL (1.10 mmol, 0.51 eq.) of H_2SO_4 (1 M), the reaction mixture was heated to reflux. Full consumption of the starting material was indicated after 3 h and the reaction mixture was cooled to rt. Then, it was diluted with 10 mL EtOAc and 15 mL sat. aq. $NaHCO_3$-solution. The aqueous phase was extracted twice with 10 mL EtOAc. The combined organic layers were washed with 20 mL sat. aq. NaCl-solution, dried over Na_2SO_4 and the solvent was removed under reduced pressure. The crude product was purified by column chromatography (SiO_2, *c*-Hex/EtOAc 2:1) to afford 561 mg (1.95 mmol, 90%) of the desired product **157c** as a light-yellow oil.



M ($C_{16}H_{20}N_2O_3$) 288.35 g/mol.

R_f (SiO_2, *c*-Hex/EtOAc 1:1) = 0.47.

^{1}H NMR (500 MHz, $CDCl_3$, mixture of diastereomers and rotamers), δ [ppm] = 7.49-7.45 (m, 0.25H, H-5), 7.39-7.29 (m, 5H, H-12, H-13, H-14), 7.21-7.18 (m, 0.25H, H-5'), 6.81-6.75 (m, 0.25H, H-5''), 6.69-6.63 (m, 0.25H, H-5'''), 5.90-5.78 (m, 1H, H-3), 5.75-5.58 (m, 1H, H-4), 5.18-5.12 (m, 2H, H-10), 4.60-4.37 (m, 1H, H-8), 4.30-4.06 (m, 1H, H-1a), 3.03-2.82 (m, 1H, H-1b), 2.58-2.14 (m, 3H, H-2a, H-6), 2.03-1.89 (m, 1H, H-2b), 1.84-1.70 (m, 2H, H-7).

^{13}C NMR (126 MHz, $CDCl_3$, mixture of diastereomers and rotamers), δ [ppm] = 155.5 (C-9), 151.8/151.5 (C-5), 137.0/136.8 (C-11), 128.7 (C-12, C-13), 128.2 (C-14), 127.9 (C-4), 126.2/125.8 (C-3), 67.4/67.2 (C-10), 52.0/51.7 (C-8), 37.5/37.0 (C-1), 30.6/30.2 (C-7), 26.6/26.5/25.2/24.8 (C-2), 21.9 (C-6).

FT-IR ATR, v [cm^{-1}] = 3347 (br), 3091 (w), 3066 (w), 3032 (w), 2924 (m), 2902 (m), 2087 (w), 1674 (s), 1651 (m), 1587 (w), 1498 (w), 1425 (s), 1394 (m), 1357 (m), 1334 (m), 1311 (m), 1274 (m), 1242 (s), 1198 (s), 1148 (m), 1106 (s),

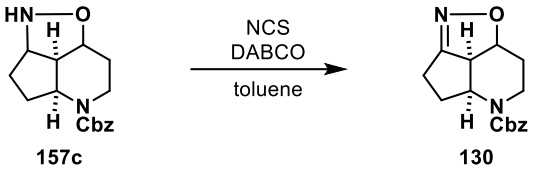
1080 (m), 1057 (s), 1024 (s), 962 (m), 913 (m), 828 (w), 753 (m), 734 (m), 697 (s), 635 (m), 621 (m), 602 (m), 587 (m), 558 (m).

HRMS (ESI) Calcd. $[M+H]^+$: 289.15467, found: 289.15499; calcd. $[M+Na]^+$: 311.13661, found: 311.13694.

GC-MS *m/z* (%) = 216 (21), 172 (20), 135 (<5), 105 (<5), 91 (100), 80 (12), 65 (14), 54 (6).

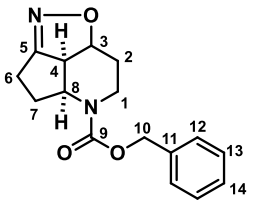
$[\alpha]_\lambda^{20}$ (0.23 g/100 mL in $CHCl_3$): $[\alpha]_{436}$ = 133 °, $[\alpha]_{546}$ = 75 °, $[\alpha]_{579}$ = 65 °, $[\alpha]_{589}$ = 63 °.

10.2.7.11 Synthesis of benzyl (2a¹*S*,7a*S*)-1,2a¹,4a,5,6,7a-hexahydro-4-oxa-3,7-diazacyclopenta[cd]indene-7(2*H*)-carboxylate (130)



157c **130**

An argon-flooded *Schlenk* flask was charged with 200 mg (0.694 mmol, 1.00 eq.) of isoxazolidine **157c** dissolved in 7.0 mL dry toluene. Consecutively, 138 mg (1.03 mmol, 1.49 eq.) of NCS and 152 mg (1.24 mmol, 1.79 eq.) of DABCO were added. After 3 h at rt, full consumption of the starting material was indicated by TLC. The suspension was filtered over a pad of celite, washed with EtOAc and the solvent was removed under reduced pressure. The crude product was purified by column chromatography (SiO_2, *c*-Hex/EtOAc 2:1) to afford 159 mg (0.56 mmol, 80%) of isoxazoline **130** as a colourless oil.



M ($C_{16}H_{18}N_2O_3$) 286.33 g/mol.

R_f (SiO_2, *c*-Hex/EtOAc 1:1) = 0.26.

^{1}H NMR (600 MHz, $CDCl_3$), δ [ppm] = 7.39-7.31 (m, 5H, H-12, H-13, H-14), 5.17-5.11 (m, 2H, H-10), 4.81 (dt, $^3J_{HH}$ = 9.6, 2.1 Hz, 1H, H-3), 4.33 (t, $^3J_{HH}$ = 7.3 Hz, 1H, H-8), 4.05-3.93 (m, 2H, H-1a, H-4), 3.08 (t, $^3J_{HH}$ = 13.1 Hz, 1H, H-1b), 2.66-2.60 (m, 1H, H-7a), 2.54-2.49 (m, 1H, H-6a), 2.44-2.36 (m, 1H, H-6b), 2.29-2.20 (m, 1H, H-7b), 1.90-1.86 (m, 1H, H-2a), 1.64-1-58 (m, 1H, H-2b).

^{13}C NMR (151 MHz, $CDCl_3$), δ [ppm] = 168.1 (C-5), 155.5 (C-9), 136.6 (C-11), 128.7 (C-13), 128.3 (C-14), 128.1 (C-12), 75.9 (C-3), 67.5 (C-10), 53.7 (C-4), 48.4 (C-8), 38.2 (C-7), 36.7 (C-1), 29.5 (C-2), 20.4 (C-6).

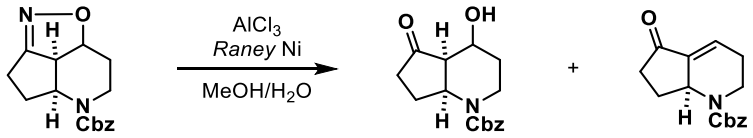
FT-IR ATR, v [cm^{-1}] = 3032 (w), 2953 (w), 1689 (s), 1586 (w), 1454 (w), 1409 (m), 1352 (m), 1316 (m), 1278 (m), 1251 (m), 1202 (m), 1166 (w), 1114 (m), 1059 (m), 1039 (m), 1004 (m), 978 (w), 913 (w), 887 (w), 844 (m), 817 (m), 733 (m), 697 (m), 599 (w), 550 (w).

HRMS (ESI) Calcd. $[M+H]^+$: 287.13902, found: 287.13940; calcd. $[M+Na]^+$: 309.12096, found: 309.12129.

GC-MS *m/z* (%) = 232 (<5), 188 (9), 151 (<5), 91 (100), 65 (9), 51 (<5), 39 (<5).

$[\alpha]_\lambda^{20}$ (0.33 g/100 mL in $CHCl_3$): $[\alpha]_{365}$ = 211 °, $[\alpha]_{436}$ = 128 °, $[\alpha]_{546}$ = 74 °, $[\alpha]_{579}$ = 65 °, $[\alpha]_{589}$ = 62 °.

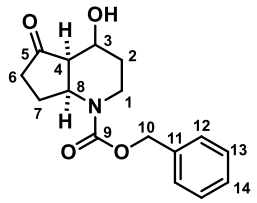
10.2.7.12 Synthesis of benzyl (4a*R*,7a*S*)-4-hydroxy-5-oxooctahydro-1*H*-cyclopenta-[b]pyridine-1-carboxylate (167)



130 167 168

An argon-flooded *Schlenk* flask was charged with 313 mg (1.09 mmol, 1.00 eq.) of isoxazoline **130** dissolved in 53 mL MeOH/H_2O (5:1). After cooling to 0 °C, 435 mg (3.62 mmol, 3.00 eq.) of $AlCl_3$ were added. The reaction mixture was stirred for 10 min until 3.27 g of *Raney* Ni were added. After 4 h, full consumption of the starting material was indicated by TLC. The reaction mixture was warmed to rt, filtered over a pad of celite, washed with MeOH and the solvent was removed under reduced pressure. The remaining oil was diluted with 50 mL CH_2Cl_2 and washed with 30 mL H_2O. The aqueous phase was extracted twice with 20 mL CH_2Cl_2. The combined organic layers were washed with 50 mL sat. aq. NaCl-solution, dried over Na_2SO_4 and the solvent was removed under reduced pressure. The crude product was purified by column chromatography (SiO_2, *c*-Hex/EtOAc 2:1→1:1) to afford 195 mg (0,674 mmol, 62%) of *β*-hydroxyketone **167** and 31 mg (0.11 mmol, 12%) of enone **168**.

167



M ($C_{16}H_{19}NO_4$) 289.33 g/mol.

R_f (SiO_2, *c*-Hex/EtOAc 1:1) = 0.21.

^{1}H NMR (500 MHz, $CDCl_3$), δ [ppm] = 7.40-7.30 (m, 5H, H-12, H-13, H-14), 5.21-5.13 (m, 2H, H-10), 4.72 (dd, $^3J_{HH}$ = 10.1, 8.5 Hz, 1H, H-8), 4.44-4.41 (m, 1H, H-3), 3.99 (ddd, $^2J_{HH}$ = 13.4 Hz, $^3J_{HH}$ = 4.4, 3.0 Hz, 1H, H-1a), 3.38 (td, $^2J_{HH}$ = 13.2 Hz, $^3J_{HH}$ = 2.7 Hz, 1H, H-1b), 2.44-2.14 (m, 5H, H-4, H-6, H-7), 1.88 (s, 1H, *O*H), 1.80 (dq, $^2J_{HH}$ = 13.9 Hz, $^3J_{HH}$ = 2.8 Hz, 1H, H-2a), 1.65 (td, $^2J_{HH}$ = 13.9 Hz, $^3J_{HH}$ = 4.6, 2.3 Hz, 1H, H-2b).

^{13}C NMR (126 MHz, $CDCl_3$), δ [ppm] = 218.4 (C-5), 155.7 (C-9), 136.7 (C-11), 128.7 (C-13), 128.3 (C-14), 128.1 (C-12), 67.5 (C-10), 65.1 (C-3), 51.7 (C-8), 49.4 (C-4), 38.6 (C-6), 33.2 (C-1), 31.4 (C-2), 25.8 (C-7).

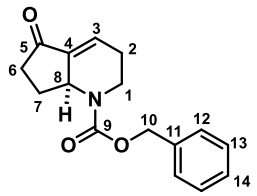
FT-IR ATR, v [cm^{-1}] = 3439 (br), 3032 (w), 2953 (w), 1739 (m), 1670 (s), 1587 (w), 1498 (w), 1427 (s), 1349 (s), 1306 (m), 1280 (m), 1224 (s), 1189 (m), 1153 (m), 1138 (m), 1097 (m), 1046 (m), 996 (m), 971 (m), 910 (m), 875 (m), 851 (w), 823 (w), 767 (m), 731 (s), 697 (s), 647 (w), 547 (m).

HRMS (ESI) Calcd. $[M+H]^+$: 290.13868, found: 290.13905; calcd. $[M+Na]^+$: 312.12063, found: 312.12103.

GC-MS *m/z* (%) = 273 (<5), 200 (5), 182 (8), 138 (<5), 110 (6), 91 (100), 77 (5), 65 (17), 51 (5).

$[\alpha]_\lambda^{20}$ (0.275 g/100 mL in $CHCl_3$): $[\alpha]_{365}$ = 76 °, $[\alpha]_{436}$ = 61 °, $[\alpha]_{546}$ = 38 °, $[\alpha]_{579}$ = 34 °, $[\alpha]_{589}$ = 33 °.

168



M ($C_{16}H_{17}NO_3$) 271.32 g/mol.

R_f (SiO_2, *c*-Hex/EtOAc 1:1) = 0.38.

^{1}H NMR (500 MHz, $CDCl_3$), δ [ppm] = 7.41-7.32 (m, 5H, H-12, H-13, H-14), 6.94 (dt, $^3J_{HH}$ = 7.0, 3.2 Hz, 1H, H-3), 5.26-5.15 (m, 2H, H-10), 4.62-4.57 (m, 1H, H-8), 4.24-4-09 (m, 1H, H-1a), 2.84-2.76 (m, 1H, H-1b), 2.45-2.20 (m, 4H, H-2, H-6), 1.63-1.51 (m, 2H, H-7).

^{13}C NMR (126 MHz, $CDCl_3$), δ [ppm] = 202.2 (C-5), 175.0 (C-4), 155.8 (C-9), 136.6 (C-11), 131.9 (C-3), 128.7 (C-13), 128.4 (C-14), 128.2 (C-12), 67.6 (C-10), 55.1 (C-8), 38.7 (C-1), 36.5 (C-6), 27.9 (C-7), 25.3 (C-2).

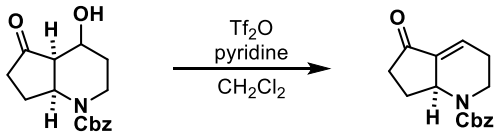
FT-IR ATR, v [cm^{-1}] = 3064 (w), 3032 (w), 2939 (w), 2900 (w), 2251 (w), 2092 (w), 1742 (w), 1722 (m), 1694 (s), 1659 (s), 1606 (w), 1536 (w), 1498 (w), 1455 (w), 1415 (s), 1349 (m), 1313 (m), 1279 (m), 1265 (s), 1208 (s), 1197 (s), 1172 (m), 1139 (w), 1103 (s), 1056 (m), 1041 (m), 1029 (m), 962 (m), 916 (m), 889 (m), 851 (w), 815 (m), 758 (m), 754 (m), 735 (m), 697 (s), 645 (m), 617 (m), 607 (m), 581 (w), 551 (m), 526 (m).

HRMS (ESI) Calcd. $[M+Na]^+$: 294.11006, found: 294.10976.

GC-MS *m/z* (%) = 271 ([M], <5), 227 (<5), 199 (6), 180 (9), 136 (<5), 108 (8), 91 (100), 65 (12), 52 (8).

$[\alpha]_\lambda^{20}$ (0.76 g/100 mL in $CHCl_3$): $[\alpha]_{365}$ = -52.9 °, $[\alpha]_{436}$ = 2.2 °, $[\alpha]_{546}$ = 7.7 °, $[\alpha]_{579}$ = 7.5 °, $[\alpha]_{589}$ = 7.4 °.

10.2.7.13 Synthesis of benzyl (*S*)-5-oxo-2,3,5,6,7,7a-hexahydro-1*H*-cyclopenta[b]-pyridine-1-carboxylate (168)

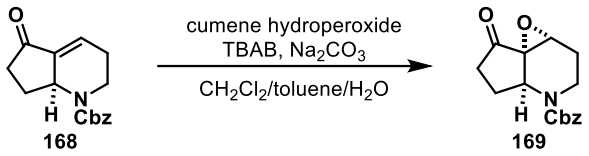


167 168

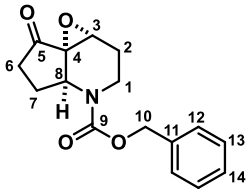
An argon-flooded *Schlenk* flask was charged with 38 mg (0.13 mmol, 1.00 eq.) of *β*-hydroxyketone **167** dissolved in 0.7 mL dry CH_2Cl_2 and 37.0 µl (0.459 mmol, 3.50 eq.) of pyridine. After cooling to 0 °C, 24.2 µl (0.144 mmol, 1.10 eq.) of Tf_2O were added and the reaction mixture was stirred at rt for 16 h. The reaction was terminated with H_2O. The aqueous phase was extracted three times with 5 mL CH_2Cl_2. The combined organic layers were dried over Na_2SO_4 and the solvent was removed under reduced pressure. The crude product was purified by column chromatography (SiO_2, *c*-Hex/EtOAc 2:1 → 1:1) to afford 26.0 mg (95.8 µmol, 73%) of the desired product **168** as a yellow oil.

The analytical data for substrate **168** was reported in the above-mentioned procedure.

10.2.7.14 Synthesis of benzyl (1a*R*,4a*S*,7a*S*)-7-oxohexahydrocyclopenta[b]- oxireno[2,3-c]pyridine-4(1a*H*)-carboxylate (169)



A round-bottom flask was charged with 55.0 mg (0.203 mmol, 1.00 eq.) of enone **168** dissolved in 2.1 mL CH_2Cl_2/toluene (6:1). Then, 2.0 mL sat. aq. Na_2CO_3-solution, 0.37 mL (2.00 mmol, 9.87 eq.) of cumene hydroperoxide (80% in cumene) and 7.2 mg (22 µmol, 11.0 mol%) of TBAB were added. The reaction mixture was stirred at rt. After 16 h, full consumption of the staring material was indicated by TLC. The reaction mixture was diluted with 15 mL CH_2Cl_2 and 10 mL sat. aq. NaCl-solution. The aqueous phase was extracted three times with 10 mL CH_2Cl_2 each. The combined organic layers were dried over Na_2SO_4 and the solvent was removed under reduced pressure. The crude product was purified by column chromatography (SiO_2, *c*-Hex/EtOAc 3:1) to afford 51.0 mg (0.178 mmol, 88%) of epoxide **169** as a colourless oil.



M ($C_{16}H_{17}NO_4$) 287.32 g/mol.

R_f (SiO_2, *c*-Hex/EtOAc 2:1) = 0.24.

^{1}H NMR (400 MHz, $CDCl_3$), δ [ppm] = 7.42-7.29 (m, 5H, H-12, H-13, H-14), 5.25-5.09 (m, 2H, H-10), 4.60 (dd, $^3J_{HH}$ = 11.0, 7.2 Hz, 1H, H-8), 3.68-3.60 (m, 1H, H-1a), 3.49 (dd, $^3J_{HH}$ = 3.9, 2.0 Hz, 1H, H-3), 3.38-3.20 (m, 1H, H-1b), 2.86-2.63 (m, 1H, H-7a), 2.55 (dd, $^2J_{HH}$ = 19.3 Hz, $^3J_{HH}$ = 8.6 Hz, 1H, H-6a), 2.42 (ddd, $^2J_{HH}$ = 19.4 Hz, $^3J_{HH}$ = 12.6, 9.2 Hz, 1H, H-6b), 2.14-2.04 (m, 1H, H-2a), 2.03 -1.93 (m, 1H, H-2b), 1.93 -1.81 (m, 1H, H-7b).

^{13}C NMR (101 MHz, $CDCl_3$), δ [ppm] = 209.7 (C-5), 156.1 (C-9), 136.3 (C-11), 128.8 (C-13), 128.4 (C-14), 128.2 (C-12), 67.8 (C-10), 61.5 (C-4), 57.8 (C-3), 51.7 (C-8), 35.8 (C-1), 35.5 (C-6), 25.0 (C-2), 23.9 (C-7).

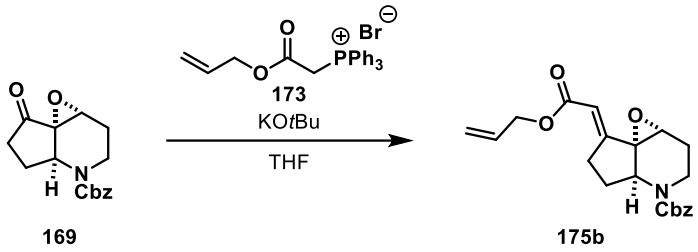
FT-IR ATR, ν [cm^{-1}] = 3064 (w), 3032 (w), 2955 (w), 2884 (w), 1752 (m), 1693 (s), 1586 (w), 1468 (w), 1429 (m), 1405 (m), 1330 (m), 1282 (m), 1214 (s), 1185 (m), 1145 (m), 1103 (m), 1046 (m), 1028 (m), 967 (m), 923 (m), 898 (m), 874 (m), 810 (m), 754 (m), 734 (m), 698 (s), 621 (w), 596 (m), 556 (m), 523 (m).

HRMS (ESI) Calcd. $[M+Na]^+$: 310.10498, found: 310.10527.

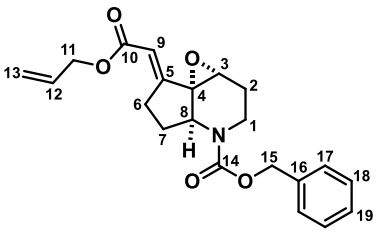
GC-MS *m/z* (%) = 287 ([M], <5), 258 (<5), 195 (9), 181 (8), 152 (<5), 137 (<5), 91 (100), 65 (15), 51 (6), 39 (8).

$[\alpha]_{\lambda}^{20}$ (0.205 g/100 mL in $CHCl_3$): $[\alpha]_{365}$ = -192 °, $[\alpha]_{436}$ = -34 °, $[\alpha]_{546}$ = -4.7 °, $[\alpha]_{579}$ = -1.8 °, $[\alpha]_{589}$ = -1.5 °.

10.2.7.15 Synthesis of benzyl (1a*R*,4a*S*,7a*S*,*E*)-7-(2-(allyloxy)-2-oxoethylidene)-hexahydro-cyclopenta[b]oxireno[2,3-c]pyridine-4(1a*H*)-carboxylate (175b)



An argon-flooded head space vial was charged with 32.3 mg (0.288 mmol, 4.60 eq.) of KO*t*Bu and 133 mg (0.301 mmol, 4.80 eq.) of phosphonium bromide **173** dissolved in 0.33 mL dry THF. The suspension was stirred at rt for 15 min. Then, 18.0 mg (62.7 µmol, 1.00 eq.) of epoxide **169** dissolved in 0.3 mL dry THF were added. The reaction mixture was heated to 55 °C in a heating block. After 18 h, full consumption of the starting material was indicated by TLC. The reaction mixture was diluted with 10 mL EtOAc and 10 mL H_2O. The aqueous phase was extracted three times with 5 mL EtOAc. The combined organic layers were washed with 15 mL sat. aq. NaCl-solution, dried over $MgSO_4$ and the solvent was removed under reduced pressure. The crude product was purified by column chromatography (SiO_2, *c*-Hex/EtOAc 4:1 → 2:1) to afford 21.0 mg (56.9 µmol, 91%) of the desired product **175b** as a colourless oil.



M ($C_{21}H_{23}NO_5$) 369.42 g/mol.

R_f (SiO_2, *c*-Hex/EtOAc 1:1) = 0.62.

^{1}H NMR (600 MHz, $CDCl_3$), δ [ppm] = 7.39-7.30 (m, 5H, H-17, H-18, H-19), 5.93 (ddt, $^3J_{HH}$ = 17.2, 10.5, 5.7 Hz, 1H, H-12), 5.69 (t, $^3J_{HH}$ = 2.7 Hz, 1H, H-9), 5.32 (dq, $^3J_{HH}$ = 17.2 Hz, $^4J_{HH}$ = 1.5 Hz, 1H, H-13a), 5.23 (dq, $^3J_{HH}$ = 10.4 Hz, $^4J_{HH}$ = 1.3 Hz, 1H, H-13b), 5.18-5.10 (m, 2H, H-15), 4.61 (dq, $^3J_{HH}$ = 5.7 Hz, $^4J_{HH}$ = 1.5 Hz, 2H, H-11), 4.44 (dd, $^3J_{HH}$ = 11.5, 7.2 Hz, 1H, H-8), 3.76-3-62 (m, 1H, H-1a), 3.27-3.24 (m, 1H, H-3), 3.20-3.11 (m, 2H, H-1b, H-6a), 2.81 (dddd, $^2J_{HH}$ = 20.3 Hz, $^3J_{HH}$ = 11.8, 8.7 Hz, $^4J_{HH}$ = 3.1 Hz, 1H, H-6b), 2.42-2.38 (m, 1H,

H-7a), 2.10-2.03 (m, 1H, H-2a), 2.01-1.94 (m, 1H, H-2b), 1.80-1.70 (m, 1H, H-7b).

^{13}C NMR (151 MHz, $CDCl_3$), δ [ppm] = 165.9 (C-10), 160.0 (C-5), 156.1 (C-14), 136.6 (C-16), 132.4 (C-12), 128.7 (C-18), 128.3 (C-19), 128.1 (C-17), 118.3 (C-13), 111.8 (C-9), 67.6 (C-15), 64.9 (C-11), 63.4 (C-4), 61.6 (C-3), 53.6 (C-8), 35.5 (C-1), 28.1 (C-6), 26.3 (C-7), 25.1 (C-2).

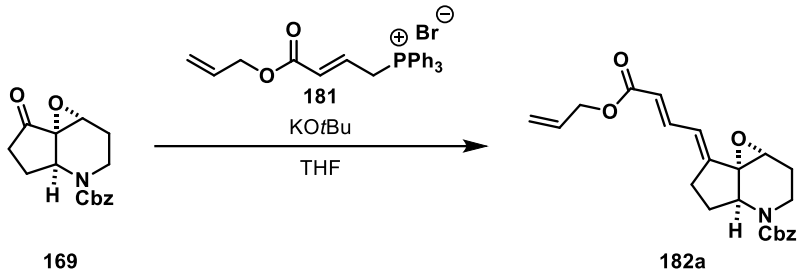
FT-IR ATR, v [cm^{-1}] = 3066 (w), 2927 (w), 2103 (w), 1698 (s), 1665 (m), 1587 (w), 1498 (w), 1430 (m), 1363 (m), 1336 (m), 1262 (m), 1210 (m), 1164 (m), 1145 (m), 1128 (m), 1101 (m), 1027 (m), 976 (m), 923 (m), 902 (m), 861 (m), 814 (w), 766 (m), 734 (m), 697 (m), 648 (w), 608 (w), 586 (w), 554 (w).

HRMS (ESI) Calcd. $[M+Na]^+$: 392.14684, found: 392.14702.

GC-MS *m/z* (%) = 278 (8), 260 (5), 234 (5), 205 (6), 178 (6), 121 (5), 91 (100), 65 (15).

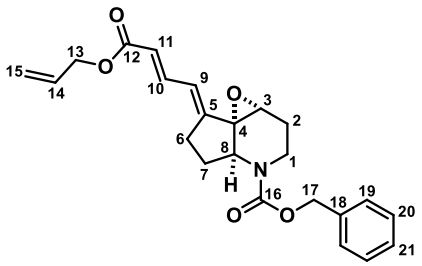
$[\alpha]_\lambda^{20}$ (0.09 g/100 mL in $CHCl_3$): $[\alpha]_{365}$ = 33 °, $[\alpha]_{436}$ = 20 °, $[\alpha]_{546}$ = 15 °, $[\alpha]_{579}$ = 15 °, $[\alpha]_{589}$ = 14 °.

10.2.7.16 Synthesis of benzyl (1a*R*,4a*S*,7a*S*,*E*)-7-((*E*)-4-(allyloxy)-4-oxobut-2-en-1-ylidene)-hexahydrocyclopenta[b]oxireno[2,3-c]pyridine-4(1a*H*)-carboxylate (182a)



169 182a

An argon-flooded reaction vial was charged with 35.0 mg (0.312 mmol, 5.98 eq.) of KO*t*Bu and 141 mg (0.302 mmol, 5.78 eq.) of phosphonium bromide **181** dissolved in 0.27 mL dry THF. The yellow suspension was stirred at rt for 1.5 h. Then, 15.0 mg (52.2 µmol, 1.00 eq.) of epoxide **169** dissolved in 0.25 mL dry THF were added and the reaction mixture was heated to 80 °C in a heating block. After 2 d, full consumption of the starting material was indicated by TLC. The reaction mixture was diluted with 8 mL EtOAc and 5 mL H_2O. The aqueous phase was extracted three times with 5 mL EtOAc. The combined organic layers were washed with 15 mL sat. aq. NaCl-solution, dried over $MgSO_4$ and the solvent was removed under reduced pressure. The crude product was purified by column chromatography (SiO_2, *c*-Hex/EtOAc 2:1 → 1:1) to afford 4.7 mg (11.9 µmol, 23%) of the desired allyl ester **182a** as a colourless oil.



M ($C_{23}H_{25}NO_5$) 395.46 g/mol.

R_f (SiO_2, *c*-Hex/EtOAc 1:1) = 0.68.

^{1}H NMR (600 MHz, $CDCl_3$), δ [ppm] = 7.42-7.31 (m, 6H, H-10, H-19, H-20, H-21), 6.01-5.91 (m, 2H, H-9, H-14), 5.86 (d, $^3J_{HH}$ = 15.3 Hz, 1H, H-11), 5.33 (dq, $^3J_{HH}$ = 17.2 Hz, $^4J_{HH}$ = 1.5 Hz, 1H, H-15a), 5.24 (dq, $^3J_{HH}$ = 10.4 Hz, $^3J_{HH}$ = 1.2 Hz, 1H, H-15b), 5.17-5.11 (m, 2H, H-17), 4.65 (dt, $^3J_{HH}$ = 5.7 Hz, $^4J_{HH}$ = 1.4 Hz, 2H, H-13), 4.43 (dd, $^3J_{HH}$ = 11.5, 7.0 Hz, 1H, H-8), 3.82-3.63 (m, 1H, H-1a), 3.30-3.25 (m, 1H, H-3), 3.23-3.09 (m, 1H, H-1b), 2.81-2.76 (m, 1H, H-6a), 2.66-2.55 (m, 1H, H-6b), 2.45-2.33 (m, 1H, H-7a), 2.07-2.04 (m, 1H, H-2a), 1.96 (ddd, $^3J_{HH}$ = 15.1, 11.0, 4.1 Hz, 1H, H-2b), 1.82-1.71 (m, 1H, H-7b).

^{13}C NMR (151 MHz, $CDCl_3$), δ [ppm] = 166.9 (C-12), 156.1 (C-16), 149.1 (C-5), 140.2 (C-10), 136.6 (C-18), 132.4 (C-14), 128.7 (C-20), 128.3 (C-21), 128.1 (C-19),

121.1 (C-11), 119.2 (C-9), 118.3 (C-15), 67.5 (C-17), 65.2 (C-13), 63.2 (C-4), 61.4 (C-3), 54.1 (C-8), 35.6 (C-1), 26.1 (C-7), 25.6 (C-6), 25.3 (C-2).

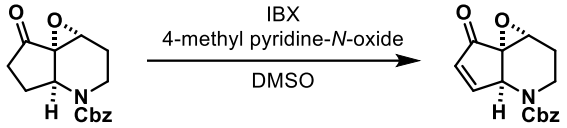
FT-IR ATR, v [cm^{-1}] = 3092 (w), 3031 (w), 2937 (w), 2879 (w), 1702 (s), 1647 (w), 1617 (w), 1498 (w), 1427 (w), 1331 (w), 1257 (m), 1210 (m), 1138 (m), 1028 (w), 986 (w), 927 (w), 900 (w), 753 (w), 699 (w), 543 (w).

HRMS (ESI) Calcd. $[M+Na]^+$: 418.16249, found: 418.16296.

GC-MS *m/z* (%) = 288 (6), 244 (12), 188 (12), 152 (6), 91 (100), 65 (17).

$[\alpha]_\lambda^{20}$ (0.15 g/100 mL in $CHCl_3$): $[\alpha]_{365}$ = -1590 °, $[\alpha]_{436}$ = 25 °, $[\alpha]_{546}$ = 17 °, $[\alpha]_{579}$ = 16 °, $[\alpha]_{589}$ = 16 °.

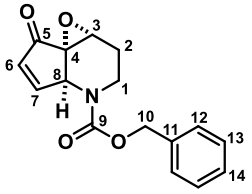
10.2.7.17 Synthesis of benzyl (1a*R*,4a*S*,7a*S*)-7-oxo-2,3,4a,7-tetrahydro-cyclopenta[b]-oxireno[2,3-c]pyridine-4(1a*H*)-carboxylate (170)



169 **170**

A reaction vial was charged with 59.9 mg (0.214 mmol, 4.10 eq.) of IBX and 20.2 mg (0.185 mmol, 3.54 eq.) of 4-methyl pyridine-*N*-oxide dissolved in 0.52 mL DMSO. The solution was stirred at rt for 1.5 h. Then, the reagent solution was added to a vial containing 15.0 mg (52.2 µmol, 1.00 eq.) of epoxide **169** and the reaction mixture was heated to 55 °C in a heating block. After 21 h, full consumption of the starting material was indicated by TLC. The reaction mixture was diluted with 8 mL EtOAc and 5 mL H_2O. The aqueous phase was extracted three times with 5 mL EtOAc. The combined organic layers were washed with 10 mL sat. aq. NaCl-solution, dried over $MgSO_4$ and the solvent was removed under reduced pressure. The crude product was purified by column chromatography (SiO_2, *c*-Hex/EtOAc 2:1) to afford 12.2 mg (42.8 µmol, 82%) of the desired product **170** as a colourless oil.

Note: The sample contains minor amounts of IBX (<25%).



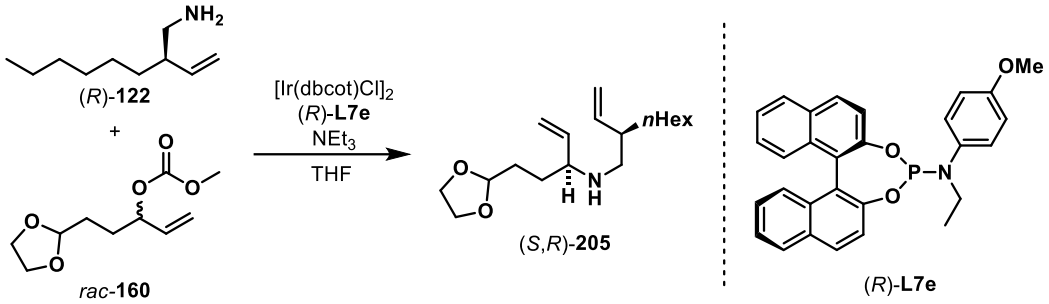
M ($C_{16}H_{15}NO_4$) 285.30 g/mol.

R_f (SiO_2, *c*-Hex/EtOAc 1:1) = 0.39.

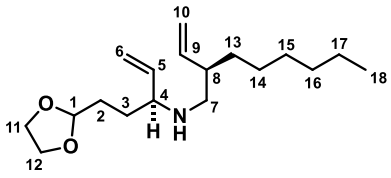
^{1}H NMR	(500 MHz, $CDCl_3$), δ [ppm] = 8.09-7.98 (m, 1H, H-7), 7.39-7.35 (m, 5H, H-12, H-13, H-14), 6.50 (dd, $^{3}J_{HH}$ = 6.6, 1.8 Hz, 1H, H-6), 5.22-5.12 (m, 2H, H-10), 4.94-4.86 (m, 1H, H-8), 3.64-3.57 (m, 2H, H-1a, H-3), 3.36-3.27 (m, 1H, H-1b), 2.16-2.07 (m, 1H, H-2a), 1.95-1.86 (m, 1H, H-2b).
^{13}C NMR	(126 MHz, $CDCl_3$), δ [ppm] = 198.2 (C-5), 160.6 (C-7), 155.8 (C-9), 136.0 (C-6), 134.8 (C-11), 128.8 (C-13), 128.6 (C-14), 128.3 (C-12), 68.0 (C-10), 61.1 (C-4), 57.5 (C-3), 55.2 (C-8), 38.5 (C-1), 25.3 (C-2).
FT-IR	ATR, v [cm^{-1}] = 3065 (w), 3033 (w), 2965 (w), 2932 (w), 1698 (s), 1585 (w), 1498 (w), 1455 (m), 1414 (m), 1344 (m), 1286 (m), 1272 (m), 1245 (m), 1215 (s), 1143 (m), 1101 (m), 1016 (m), 968 (m), 904 (m), 826 (m), 814 (m), 738 (m), 697 (s), 665 (m), 634 (m), 598 (m), 567 (m).
HRMS (ESI)	Calcd. $[M+H]^+$: 286.10738, found: 286.10780; calcd. $[M+Na]^+$: 308.08933, found: 308.08957.
GC-MS	*m/z* (%) = 284 ($[M]^+$, <5), 269 (<5), 224 (<5), 170 (<5), 91 (100), 65 (11).
$[\alpha]_{\lambda}^{20}$	(0.205 g/100 mL in $CHCl_3$): $[\alpha]_{365}$ = -165 °, $[\alpha]_{436}$ = 62 °, $[\alpha]_{546}$ = 39 °, $[\alpha]_{579}$ = 35 °, $[\alpha]_{589}$ = 34 °.

10.2.8 Forward synthesis on camporidine system

10.2.8.1 Synthesis of (*R*)-*N*-((*S*)-5-(1,3-dioxolan-2-yl)pent-1-en-3-yl)-2-vinyloctan-1-amine (205)



An argon-flooded head space vial was charged with 7.1 mg (8.22 µmol, 1.02 mol%) of $[Ir(dbcot)Cl]_2$ and 9.4 mg (19.7 µmol, 2.43 mol%) of (*R*)-**L7e** dissolved in 2.0 mL dry THF. After stirring at rt for 25 min, 175 mg (0.809 mmol, 1.00 eq.) of carbonate *rac*-**160** were added. After another 25 min, 6.0 mL dry THF, 0.16 mL (1.15 mmol, 1.42 eq.) of NEt_3 and 175 mg (1.13 mmol, 1.39 eq.) of amine (*R*)-**122** were added. The head space vial was capped and heated to 50 °C for 3 d. After cooling to rt, Quadrasil© was added and stirred for 15 min. The suspension was filtered over celite, washed with MTBE and the solvent was removed under reduced pressure. The crude product was purified by column chromatography (SiO_2, *c*-Hex/EtOAc 1:1) to afford 100 mg (0.338 mmol, 42%, 85:15 *d.r.*) of allylic amine (*S,R*)-**205** as a yellow oil.



M ($C_{18}H_{33}NO_2$) 295.47 g/mol.

R_f (SiO_2, *c*-Hex/EtOAc 2:1) = 0.08.

^{1}H NMR (500 MHz, $CDCl_3$, mixture of diastereomers), δ [ppm] = 5.63-5.46 (m, 2H, H-5, H-9), 5.13-5.02 (m, 4H, H-6, H-10), 4.86 (t, $^3J_{HH}$ = 4.6 Hz, 1H, H-1), 3.99-3.93 (m, 2H, H-11a, H-12a), 3.89-3.81 (m, 2H, H-11b, H-12b), 2.95 (td, $^3J_{HH}$ = 8.1, 5.3 Hz, 1H, H-4), 2.63 (dd, $^2J_{HH}$ = 11.2 Hz, $^3J_{HH}$ = 4.6 Hz, 0.85H, H-7a), 2.52 (dd, $^2J_{HH}$ = 11.5 Hz, $^3J_{HH}$ = 4.6 Hz, 0.15H, H-7a'), 2.42 (dd, $^2J_{HH}$ = 11.5 Hz, $^3J_{HH}$ = 9.2 Hz, 0.1H, H-7b'), 2.27 (dd, $^2J_{HH}$ = 11.1 Hz, $^3J_{HH}$ = 9.2 Hz, 0.9H, H-7b), 2.18-2.11 (m, 1H, H-8), 1.73-1.47 (m, 4H, H-2, H-3), 1.41-1.18 (m, 10H, H-13, H-14, H-15, H-16, H-17), 0.87 (t, $^3J_{HH}$ = 6.9 Hz, 3H, H-18).

^{13}C NMR (126 MHz, $CDCl_3$, mixture of diastereomers), δ [ppm] = 142.0 (C-9), 141.4 (C-5), 116.3 (C-6, C-10), 104.6 (C-1), 65.0 (C-11, C-12), 62.5 (C-4), 51.9 (C-7), 44.9 (C-8), 33.1 (C-13), 31.9 (C-16), 30.5 (C-2), 29.8 (C-3), 29.5 (C-14), 27.2 (C-15), 22.8 (C-17), 14.2 (C-18).

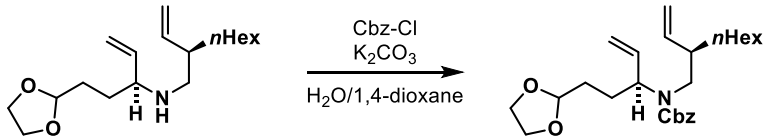
FT-IR ATR, v [cm^{-1}] = 3676 (w), 3075 (w), 2955 (m), 2924 (s), 2872 (m), 2856 (m), 1639 (w), 1456 (m), 1413 (m), 1378 (w), 1314 (w), 1231 (w), 1127 (s), 1037 (s), 995 (s), 965 (m), 942 (m), 913 (s), 724 (m), 680 (m), 567 (w), 515 (m).

HRMS (ESI) Calcd. $[M+H]^+$: 296.25841, found: 296.25839; calcd. $[M+Na]^+$: 318.24035, found: 318.24051.

GC-MS *m/z* (%) = 294 ($[M]^+$, <5), 235 (<5), 210 (18), 194 (12), 170 (54), 139 (43), 112 (100), 97 (15), 73 (49), 55 (58).

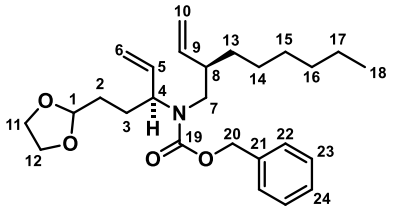
$[\alpha]_\lambda^{20}$ (0.275 g/100 mL in $CHCl_3$): $[\alpha]_{436}$ = -11.3 °, $[\alpha]_{546}$ = -5.5 °, $[\alpha]_{579}$ = -4.2 °, $[\alpha]_{589}$ = -4.5 °.

10.2.8.2 Synthesis of benzyl ((*S*)-5-(1,3-dioxolan-2-yl)pent-1-en-3-yl)((*R*)-2-vinyloctyl)-carbamate (120)



(*S,R*)-**205** (*S,R*)-**120**

A round-bottom flask was charged with 36 mg (0.12 mmol, 1.00 eq.) of amine (*S,R*)-**205** dissolved in 0.85 mL 1,4-dioxane and a solution of 50 mg (0.36 mmol, 2.97 eq.) K_2CO_3 in 0.85 mL H_2O was added. At 0 °C, 20.4 µl (0.146 mmol, 1.20 eq.) of Cbz-Cl was slowly added and stirring was continued at rt. After 2 h, full consumption of the starting material was indicated by TLC. The reaction mixture was diluted with 5 mL CH_2Cl_2 and 3 mL H_2O were added. The aqueous phase was extracted twice with 5 mL CH_2Cl_2. The combined organic layers were washed with sat. aq. NH_4Cl-solution and sat. aq. NaCl-solution, respectively, dried over $MgSO_4$ and the solvent was removed under reduced pressure. The desired product **120** (53 mg, 0.12 mmol, quant. yield) was obtained as a yellow oil, which could be used without further purification.



M ($C_{26}H_{39}NO_4$) 429.60 g/mol.

R_f (SiO_2, *c*-Hex/EtOAc 2:1) = 0.64.

^{1}H NMR (500 MHz, $CDCl_3$, mixture of diastereomers and rotamers), δ [ppm] = 7.36-7.30 (m, 5H, H-22, H-23, H-24), 6.07-5.77 (m, 1H, H-5), 5.63-5.36 (m, 1H, H-9), 5.14-5.11 (m, 4H, H-6, H-20), 5.02-4.78 (m, 3H, H-1, H-10), 4.25-4.12 (m, 1H, H-4), 3.98-3.89 (m, 2H, H-11a, H-12a), 3.86-3.79 (m, 2H,

H-11b, H-12b), 3.28-3.04 (m, 2H, H-7), 2.39-2.33 (m, 1H, H-8), 1.90-1.60 (m, 4H, H-2, H-3), 1.39-1.07 (m, 10H, H-13, H-14, H-15, H-16, H-17), 0.87 (t, $^{3}J_{HH}$ = 6.9 Hz, 3H, H-18).

^{13}C NMR (126 MHz, $CDCl_3$, mixture of diastereomers and rotamers), δ [ppm] = 156.5 (C-19), 141.0 (C-9), 137.8 (C-5), 137.0 (C-21), 128.5 (C-22, C-23), 128.0 (C-24), 116.7 (C-6), 116.1 (C-10), 104.3/104.1 (C-1), 67.1 (C-20), 65.0 (C-11, C-12), 60.4 (C-4), 50.5 (C-7), 44.8 (C-8), 33.5/32.8 (C-13), 32.5/32.4/32.2 (C-14), 31.9 (C-16), 30.9/30.8 (C-2), 29.8/29.5/29.4/29.0 (C-15), 27.2/26.8 (C-3), 22.8 (C-17), 14.2 (C-18).

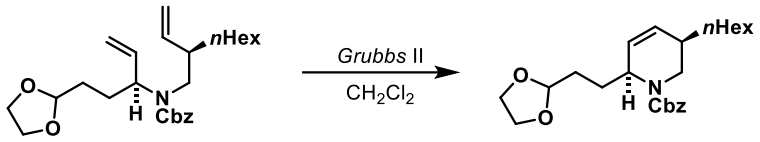
FT-IR ATR, v [cm^{-1}] = 2957 (m), 2926 (s), 2858 (m), 2101 (w), 1734 (s), 1711 (m), 1636 (w), 1464 (m), 1393 (m), 1369 (m), 1241 (m), 1159 (s), 1140 (m), 1110 (m), 1095 (m), 1066 (m), 1036 (s), 975 (w), 864 (w), 768 (w), 724 (w).

HRMS Calcd. $[M+H]^+$: 430.29519, found: 430.29543; calcd. $[M+Na]^+$: 452.27713, found: 452.27711.

GC-MS *m/z* (%) = 429 (<5, [M]), 304 (9), 260 (<5), 230 (7), 186 (<5), 168 (<5), 139 (29), 110 (5), 91 (100), 73 (11), 55 (<5).

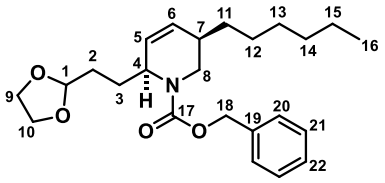
$[\alpha]_{\lambda}^{20}$ (0.305 g/100 mL in $CHCl_3$): $[\alpha]_{365}$ = -31 °, $[\alpha]_{436}$ = -19 °, $[\alpha]_{546}$ = -8 °, $[\alpha]_{579}$ = -6 °, $[\alpha]_{589}$ = -5 °.

10.2.8.3 Synthesis of benzyl (3*R*,6*S*)-6-(2-(1,3-dioxolan-2-yl)ethyl)-3-hexyl-3,6-dihydropyridine-1(2*H*)-carboxylate (119)



(*S,R*)-**120** (*S,R*)-**119**

An argon-flooded flask equipped with a reflux condenser was charged with 448 mg (1.043 mmol, 1.00 eq.) of Cbz-protected amine (*S,R*)-**120** dissolved in 10 mL dry CH_2Cl_2 and 46.0 mg (54.2 µmol, 5.20 mol%) of *Grubbs* II catalyst were added. The reaction mixture was heated to reflux. After 16 h, full consumption of the starting material was indicated by TLC. The reaction mixture was cooled to rt, Quadrasil© was added and the suspension was stirred at rt for 40 min. Then, the suspension was filtered over celite, washed with CH_2Cl_2 and the solvent was removed under reduced pressure. The crude product was purified by column chromatography (SiO_2, *c*-Hex/EtOAc 5:1) to afford 308 mg (0.767 mmol, 74%) of the desired product (*S,R*)-**119** as a pale-yellow oil.



M ($C_{24}H_{35}NO_4$) 401.55 g/mol.

R_f (SiO_2, *c*-Hex/EtOAc 5:1) = 0.26.

^{1}H NMR (500 MHz, $CDCl_3$, mixture of diastereomers and rotamers), δ [ppm] = 7.40-7.28 (m, 5H, H-20, H-21, H-22), 5.72-5.57 (m, 2H, H-5, H-6), 5.15-5.11 (m, 2H, H-18), 4.92-4-78 (m, 1H, H-1), 4.53-4.40 (m, 1H, H-4), 4.23 (dd, $^2J_{HH}$ = 12.9 Hz, $^3J_{HH}$ = 4.9 Hz, 0.5H, H-8a), 4.09 (dd, $^2J_{HH}$ = 12.9 Hz, $^3J_{HH}$ = 4.9 Hz, 0.5H, H-8b), 4.13-4.07 (m, 2H, H-9a, H-10a), 3.96-3.80 (m, 2H, H-9b, H-10b), 2.57-2.45 (m, 1H, H-8'), 2.30-2.11 (m, 1H, H-7), 1.78-1.62 (m, 4H, H-2, H-3), 1.39-1.14 (m, 10H, H-11, H-12, H-13, H-14, H-15), 0.88 (t, $^3J_{HH}$ = 6.7 Hz, 3H, H-16).

^{13}C NMR (126 MHz, $CDCl_3$, mixture of diastereomers and rotamers), δ [ppm] = 155.5/155.3 (C-17), 136.9 (C-19), 131.3/130.8 (C-6), 128.6 (C-20, C-21), 128.1/128.0 (C-22), 127.8/127.4 (C-5), 104.4/104.3 (C-1), 67.3/67.0 (C-18), 65.0 (C-9, C-10), 52.3/52.1/52.0 (C-4), 43.3/43.0 (C-8), 35.0/34.6 (C-7), 33.2/33.0 (C-11), 31.9 (C-14), 30.6/30.5 (C-2), 29.6/26.5 (C-12), 28.5/28.1 (C-3), 26.6/26.5 (C-13), 22.7 (C-15), 14.2 (C-16).

FT-IR ATR, v [cm^{-1}] = 3066 (w), 3030 (w), 2955 (m), 2925 (s), 2856 (m), 1699 (s), 1587 (w), 1498 (w), 1455 (m), 1424 (s), 1378 (m), 1357 (m), 1333 (m), 1233

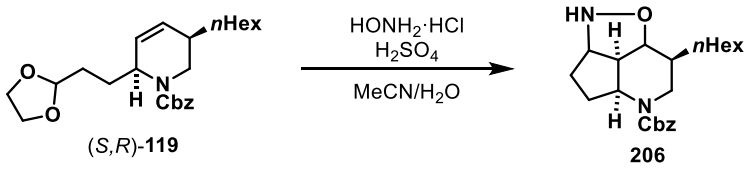
(m), 1185 (m), 1138 (m), 1104 (m), 1028 (m), 966 (m), 943 (m), 916 (m), 765 (m), 751 (m), 730 (m), 698 (m), 582 (w).

HRMS Calcd. $[M+H]^+$: 402.26389, found: 402.26414; calcd. $[M+Na]^+$: 424.24583, found: 424.24615.

GC-MS *m/z* (%) = 401 ([M], <5), 300 (14), 256 (50), 222 (14), 91 (100), 73 (9).

$[\alpha]_\lambda^{20}$ (0.115 g/100 mL in $CHCl_3$): $[\alpha]_{365}$ = 77 °, $[\alpha]_{436}$ = 49 °, $[\alpha]_{546}$ = 30 °, $[\alpha]_{579}$ = 27 °, $[\alpha]_{589}$ = 26 °.

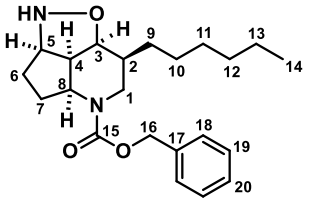
10.2.8.4 Synthesis of benzyl (2a¹*S*,5*S*,7a*S*)-5-hexyloctahydro-4-oxa-3,7-diazacyclo-penta-[cd]indene-7(2*H*)-carboxylate (206)



(*S,R*)-**119** **206**

A round-bottom flask equipped with a reflux condenser was charged with 348 mg (0.867 mmol, 1.00 eq.) of acetal (*S,R*)-**119** dissolved in 8.7 mL MeCN/H_2O (4:1). Then, 301 mg (4.33 mmol, 5.00 eq.) of hydroxylamine hydrochloride and 0.43 mL (0.430 mmol, 0.50 eq.) of H_2SO_4 (1 M) were added and the reaction mixture was heated to reflux. After 4 h, full consumption of the starting material was indicated by TLC. The reaction mixture was quenched with 10 mL sat. aq. $NaHCO_3$-solution. The aqueous phase was extracted three times with 10 mL EtOAc. The combined organic layers were washed with 20 mL sat. aq. NaCl-solution, dried over Na_2SO_4 and the solvent was removed under reduced pressure. The crude product was purified by column chromatography (SiO_2, *c*-Hex/EtOAc 6:1 → 4:1) to afford 122 mg (0.328 mmol, 38%) of (*R,S,S,S,S*)-**206** and 133 mg (0.357 mmol, 41%) of (*S,S,R,S,S*)-**206.**

(*R,S,S,S,S*)-**206**



M ($C_{22}H_{32}N_2O_3$) 372.51 g/mol.

R_f (SiO_2, *c*-Hex/EtOAc 2:1) = 0.50.

¹H NMR (500 MHz, $CDCl_3$, mixture of diastereomers and rotamers), δ [ppm] = 7.47-7.45 (m, 0.3H, H-5), 7.36-7.30 (m, 5H, H-18, H-19, H-20), 7.20-7.09 (m, 0.4H, H-5'), 6.80-6.74 (m, 0.15H, H-5''), 6.64 (t, $^3J_{HH}$ = 5.6 Hz, 0.15H,

H-5'''), 5.87-5.79 (m, 0.2H, H-4'), 5.72-5.57 (m, 1.9H, H-3, H-4), 5.20-5.10 (m, 2H, H-16), 4.55-4.50 (m, 0.5H, H-8), 4.45-4.38 (m, 0.5H, H-8'), 4.27-4.22 (m, 0.5H, H-1a), 4.14-4.08 (m, 0.5H, H-1a'), 4.03-3.98 (m, 0.1H, H-1b), 3.05-2.98 (m, 0.2H, H-1b'), 2.55-2.43 (m, 1.7H, H-1b'', H-6a), 2.30-2.18 (m, 2H, H-2, H-6b), 1.73 (dt, $^{3}J_{HH}$ = 14.9 Hz, 8.3 Hz, 2H, H-7), 1.60 (s, 1H, *N*H), 1.36-1.16 (m, 10H, H-9, H-10, H-11, H-12, H-13), 0.88 (t, $^{3}J_{HH}$ = 6.9 Hz, 3H, H-14).

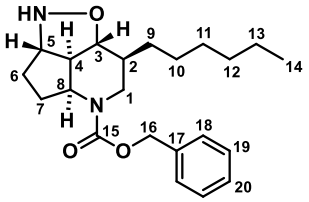
^{13}C NMR (126 MHz, $CDCl_3$, mixture of diastereomers and rotamers), δ [ppm] = 155.4 (C-15), 151.9/151.5 (C-5), 136.9/136.8 (C-17), 131.6/131.2 (C-4), 128.6 (C-19), 128.3/128.2 (C-18), 127.8 (C-20), 127.0/126.9 (C-3), 67.4/67.1 (C-16), 52.1/51.8 (C-8), 43.1/43.0 (C-1), 35.0/34.6 (C-2), 33.2/33.0 (C-9), 31.9 (C-12), 30.8/30.6 (C-7), 29.6 (C-10), 26.6 (C-11), 22.8 (C-13), 22.0 (C-6), 14.2 (C-14).

FT-IR ATR, ν [cm^{-1}] = 3356 (br), 3066 (w), 2954 (m), 2924 (m), 2855 (m), 1695 (s), 1678 (s), 1587 (w), 1498 (w), 1455 (m), 1427 (s), 1378 (w), 1357 (m), 1334 (m), 1274 (m), 1232 (m), 1217 (m), 1161 (m), 1103 (m), 1028 (m), 969 (m), 914 (m), 824 (w), 764 (m), 728 (m), 697 (s), 601 (m), 584 (m).

HRMS (ESI) Calcd. $[M+H]^+$: 373.24857, found: 373.24928; calcd. $[M+Na]^+$: 395.23051, found: 395.23081.

GC-MS *m/z* (%) = 300 (17), 256 (48), 219 (6), 164 (<5), 91 (100), 65 (10).

$[\alpha]_\lambda^{20}$ (0.32 g/100 mL in $CHCl_3$): $[\alpha]_{436}$ = 56 °, $[\alpha]_{546}$ = 31 °, $[\alpha]_{579}$ = 26 °, $[\alpha]_{589}$ = 25 °.



(*S*,*S*,*R*,*S*,*S*)-**206**

R_f (SiO_2, *c*-Hex/EtOAc 2:1) = 0.41.

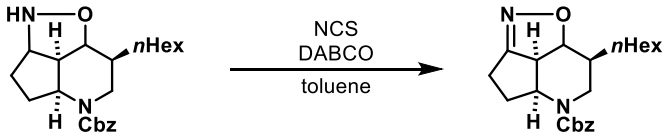
^{1}H NMR (500 MHz, $CDCl_3$, mixture of diastereomers and rotamers), δ [ppm] = 7.51-7.44 (m, 0.3H, H-5), 7.39-7.29 (m, 5H, H-18, H-19, H-20), 7.16-7.03 (m, 0.4H, H-5'), 6.79-6.75 (m, 0.15H, H-5''), 6.67-6.61 (m, 0.15H, H-5'''), 5.88-5.78 (m, 0.3H, H-4'), 5.74-5.55 (m, 1.7H, H-3, H-4), 5.18-5.10 (m, 2H, H-16), 4.52-4.42 (m, 1H, H-8), 4.29-4.21 (m, 0.4H, H-1a), 4.15-4.07 (m, 0.5H, H-1a'), 4.03-3.98 (m, 0.2H, H-1b), 3.07-2.96 (m, 0.3H, H-1b'),

2.58-2.35 (m, 1.5H, H-1b'', H-6a), 2.34-2.13 (m, 1.9H, H-2, H-6b), 2.03-1.95 (m, 0.2H, H-2'), 1.81-1.66 (m, 2H, H-7), 1.60 (s, 1H, *N*H), 1.36-1.16 (m, 10H, H-9, H-10, H-11, H-12, H-13), 0.88 (t, $^{3}J_{HH}$ = 6.9 Hz, 3H, H-14).

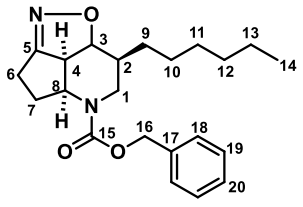
^{13}C NMR (126 MHz, $CDCl_3$, mixture of diastereomers and rotamers), δ [ppm] = 155.4 (C-15), 151.8/151.4 (C-5), 137.1/136.9 (C-17), 131.6/131.2 (C-4), 128.6 (C-19), 128.3/128.1 (C-18), 127.8 (C-20), 127.0/126.9 (C-3), 67.4/67.3/67.1 (C-16), 52.1/ 51.8 (C-8), 43.3/43.0/41.1 (C-1), 34.9/34.6 (C-2), 33.1/32.9 (C-9), 31.9 (C-12), 30.9/30.6/30.5 (C-7), 29.5 (C-10), 26.6/26.5 (C-11), 22.7 (C-13), 22.0 (C-6), 14.2 (C-14).

$[\alpha]_{\lambda}^{20}$ (0.30 g/100 mL in $CHCl_3$): $[\alpha]_{436}$ = 27 °, $[\alpha]_{546}$ = 14 °, $[\alpha]_{579}$ = 12 °, $[\alpha]_{589}$ = 11 °.

10.2.8.5 Synthesis of benzyl (2a^{1}*S*,5*S*,7a*S*)-5-hexyl-1,2a^{1},4a,5,6,7a-hexahydro-4-oxa-3,7-diazacyclopenta[cd]indene-7(2*H*)-carboxylate (117)



An argon-flooded *Schlenk* flask was charged with 251 mg (0.674 mmol, 1.00 eq.) of isoxazolidine **206** dissolved in 7.0 mL dry toluene. Then, 137 mg (1.03 mmol, 1.52 eq.) of NCS and 150 mg (1.23 mmol, 1.82 eq.) of DABCO were added and the reaction mixture was stirred at rt. After 1.5 h, full consumption of the starting material was indicated by TLC and 5 mL Et_2O were added to the reaction mixture. After stirring at rt for another hour, the suspension was filtered over celite, washed with EtOAc and the solvent was removed under reduced pressure. The crude product was purified by column chromatography (SiO_2, *c*-Hex/EtOAc 3:1) to afford 182 mg (0.492 mmol, 73%) of the desired isoxazoline **117** as a pale-yellow oil.



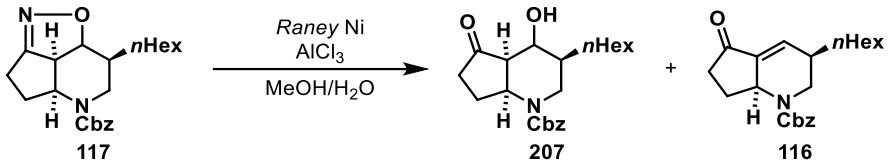
M ($C_{22}H_{30}N_2O_3$) 370.49 g/mol.

R_f (SiO_2, *c*-Hex/EtOAc 2:1) = 0.30.

^{1}H NMR (500 MHz, $CDCl_3$, mixture of diastereomers and rotamers), δ [ppm] = 7.38-7.31 (m, 5H, H-18, H-19, H-20), 5.21-5.09 (m, 2H, H-16), 4.75 (dd, $^{3}J_{HH}$ = 11.2 Hz, 6.4 Hz, 0.8H, H-3), 4.46 (ddd, $^{3}J_{HH}$ = 11.1 Hz, 2.9 Hz, $^{4}J_{HH}$ = 1.3 Hz, 0.2H, H-3'), 4.28-4.20 (m, 1H, H-8), 4.05-3.94 (m, 1H, H-4),

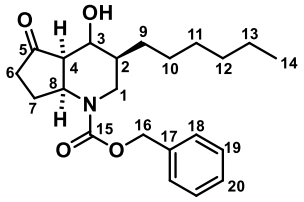
	3.91-3.81 (m, 0.6H, H-1a), 3.75 (dd, $^{2}J_{HH}$ = 12.5 Hz, $^{3}J_{HH}$ = 4.0 Hz, 0.2H, H-1a'), 3.22 (dd, $^{2}J_{HH}$ = 13.9 Hz, $^{3}J_{HH}$ = 2.4 Hz, 0.2H, H-1b'), 2.82-2.72 (m, 0.9H, H-1b), 2.67-2.22 (m, 4H, H-6, H-7), 1.50-1.43 (m, 1H, H-2), 1.42-1.15 (m, 10H, H-9, H-10, H-11, H-12, H-13), 0.89-0.86 (m, 3H, H-14).
^{13}C NMR	(151 MHz, $CDCl_3$, mixture of diastereomers and rotamers), δ [ppm] = 169.0/168.6 (C-5), 155.7 (C-15), 136.7 (C-17), 128.7 (C-18, C-19), 128.3/128.1/128.0 (C-20), 77.8/77.6 (C-3), 67.6/67.5/67.3 (C-16), 55.2/53.3 (C-4), 49.1/48.7 (C-8), 41.5/41.3/40.3 (C-1), 39.2/37.8 (C-2), 38.5/37.3 (C-7), 31.8 (C-12), 29.5/29.4 (C-9), 28.0 (C-11), 26.9 (C-10), 22.8 (C-13), 20.3/19.7 (C-6), 14.2 (C-14).
FT-IR	ATR, v [cm^{-1}] = 3064 (w), 2954 (m), 2926 (m), 2856 (m), 2328 (w), 2091 (w), 1694 (s), 1586 (w), 1497 (w), 1455 (m), 1407 (s), 1350 (m), 1315 (m), 1287 (m), 1240 (m), 1215 (m), 1176 (m), 1111 (s), 1078 (m), 1057 (m), 1028 (m), 1002 (w), 969 (w), 926 (w), 864 (m), 841 (m), 824 (m), 768 (m), 734 (m), 697 (s), 600 (m), 551 (w).
HRMS (ESI)	Calcd. $[M+H]^+$: 371.23292, found: 371.23323; calcd. $[M+Na]^+$: 393.21486, found: 393.21515.
GC-MS	*m/z* (%) = 316 (5), 272 (14), 241 (<5), 191 (<5), 91 (100), 65 (9).
$[\alpha]_\lambda^{20}$	(0.405 g/100 mL in $CHCl_3$): $[\alpha]_{365}$ = 133.2 °, $[\alpha]_{436}$ = 70.0 °, $[\alpha]_{546}$ = 36.5 °, $[\alpha]_{579}$ = 31.8 °, $[\alpha]_{589}$ = 30.4 °.

10.2.8.6 Synthesis of benzyl (3*S*,4a*R*,7a*S*)-3-hexyl-4-hydroxy-5-oxooctahydro-1*H*-cyclopenta[b]pyridine-1-carboxylate (207)



117 207 116

An argon-flooded *Schlenk* flask was charged with 176 mg (0.475 mmol, 1.00 eq.) of isoxazoline **117** dissolved in 24 mL MeOH/H_2O (5:1). At 0 °C, 194 mg (1.46 mmol, 3.06 eq.) of $AlCl_3$ were added. After 20 min, 1.56 g of *Raney* Ni were added and the reaction mixture was stirred at 0 °C. After 4 h, full consumption of the starting material was indicated by TLC. The suspension was filtered over a pad of celite, washed with MeOH and the solvent was removed under reduced pressure. The crude product was purified by column chromatography (SiO_2, *c*-Hex/EtOAc 3:1) to afford 96 mg (0.257 mmol, 54%) of *β*-hydroxyketone **207** and 19 mg (53.5 µmol, 11%) of enone **116**.



<u>207</u>

M ($C_{22}H_{31}NO_4$) 373.49 g/mol.

R_f (SiO_2, *c*-Hex/EtOAc 2:1) = 0.41.

^{1}H NMR (500 MHz, $CDCl_3$, mixture of diastereomers and rotamers), δ [ppm] = 7.40-7.30 (m, 5H, H-18, H-19, H-20), 5.24-5.10 (m, 2H, H-16), 4.81-4.62 (m, 1H, H-8), 4.26 (t, $^3J_{HH}$ = 3.4 Hz, 0.8H, H-3), 4.14 (q, $^3J_{HH}$ = 3.6 Hz, 0.2H, H-3'), 3.99-3.77 (m, 1H, H-1a), 3.46 (dd, $^2J_{HH}$ = 13.6 Hz, $^3J_{HH}$ = 2.9 Hz, 0.2H, H-1b'), 3.13-2.93 (m, 0.8H, H-1b), 2.46-2.08 (m, 5H, H-4, H-6, H-7), 1.92 (d, $^3J_{HH}$ = 4.1 Hz, 0.2H, H-7'), 1.69-1.63 (m, 1H, *O*H, H-2'), 1.49-1.42 (m, 0.9H, H-2), 1.39-1.16 (m, 10H, H-9, H-10, H-11, H-12, H-13), 0.88 (t, $^3J_{HH}$ = 6.8 Hz, 3H, H-14).

^{13}C NMR (126 MHz, $CDCl_3$, mixture of diastereomers and rotamers), δ [ppm] = 219.3/218.3 (C-5), 156.2/155.6 (C-15), 136.8 (C-17), 128.7 (C-19), 128.2 (C-18), 128.1 (C-20), 69.4/67.8 (C-3), 67.4 (C-16), 51.7 (C-8), 50.5/46.2 (C-4), 40.5/39.2 (C-2), 38.7 (C-6), 38.2/36.7 (C-1), 31.9 (C-12), 29.5 (C-9), 29.1 (C-11), 26.6 (C-10), 28.2/27.4/25.8 (C-7), 22.7 (C-13), 14.2 (C-14).

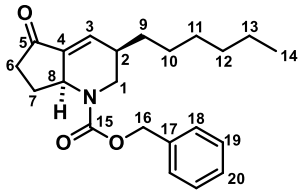
FT-IR ATR, v [cm^{-1}] = 3434 (br), 3034 (w), 2954 (w), 2925 (m), 2856 (m), 2087 (w), 1742 (m), 1673 (s), 1587 (w), 1498 (w), 1455 (m), 1429 (m), 1400 (m), 1346 (m), 1282 (m), 1265 (m), 1215 (m), 1190 (m), 1131 (m), 1098 (m), 1029 (m), 997 (m), 969 (m), 918 (m), 850 (w), 804 (w), 767 (m), 732 (m), 696 (s), 646 (w), 618 (w), 576 (w), 551 (m).

HRMS (ESI) Calcd. $[M+Na]^+$: 396.21453, found: 396.21468.

GC-MS *m/z* (%) = 356 (<5), 341 (<5), 316 (<5), 191 (16), 133 (14), 91 (100), 67 (29).

$[\alpha]_\lambda^{20}$ (0.3 g/100 mL in $CHCl_3$): $[\alpha]_{365}$ = -101.0 °, $[\alpha]_{436}$ = -18.4 °, $[\alpha]_{546}$ = -0.6 °, $[\alpha]_{579}$ = 1.7 °, $[\alpha]_{589}$ = 1.8 °.

116



M ($C_{22}H_{29}NO_3$) 355.48 g/mol.

R_f (SiO_2, *c*-Hex/EtOAc 2:1) = 0.51.

^{1}H NMR (500 MHz, $CDCl_3$, mixture of diastereomers and rotamers), δ [ppm] = 7.41-7.30 (m, 5H, H-18, H-19, H-20), 6.99 (dd, $^3J_{HH}$ = 7.1 Hz, $^4J_{HH}$ = 3.3 Hz, 0.5H, H-3), 6.76 (t, $^{3,4}J_{HH}$ = 2.6 Hz, 0.5H, H-3'), 5.31-5.14 (m, 2H, H-16), 4.64-4.57 (m, 1H, H-8), 4.28-4.11 (s, 0.5H, H-1a), 3.99 (d, $^3J_{HH}$ = 12.7 Hz, 0.5H, H-1b), 2.90 (dd, $^3J_{HH}$ = 12.9 Hz, $^4J_{HH}$ = 3.1 Hz, 0.5H, H-1b'), 2.74-2.58 (m, 1H, H-7a), 2.51-2.20 (m, 3.5H, H-1a', H-2, H-6), 1.56 (dt, $^2J_{HH}$ = 20.3 Hz, $^3J_{HH}$ = 10.4 Hz, 1H, H-7b), 1.49-1.16 (m, 10H, H-9, H-10, H-11, H-12, H-13), 0.90-0.86 (m, 3H, H-14).

^{13}C NMR (126 MHz, $CDCl_3$, mixture of diastereomers and rotamers), δ [ppm] = 202.7 (C-5), 156.3 (C-15), 138.6 (C-4), 136.7 (C-17), 136.6/136.1 (C-3), 128.7/128.7 (C-19), 128.3/128.3 (C-20), 128.2/128.1 (C-18), 67.5 (C-16), 55.0 (C-8), 44.4/43.0 (C-1), 36.8/36.6 (C-6), 35.9/35.6 (C-2), 32.0/31.8 (C-12), 31.8/31.5 (C-9), 29.4/29.3 (C-10), 27.8 (C-7), 26.7 (C-11), 22.7/22.7 (C-13), 14.2 (C-14).

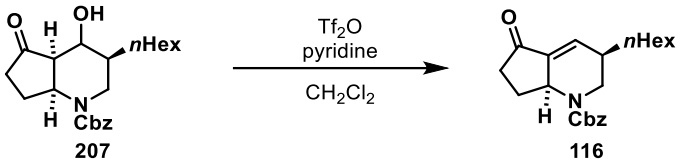
FT-IR ATR, v [cm^{-1}] = 3034 (w), 2954 (w), 2925 (m), 2855 (w), 1704 (m), 1607 (m), 1498 (w), 1456 (m), 1410 (m), 1394 (m), 1338 (m), 1248 (m), 1203 (m), 1150 (m), 1066 (m), 1028 (m), 976 (m), 914 (w), 828 (w), 752 (m), 697 (m), 579 (m).

HRMS (ESI) Calcd. $[M+H]^+$: 356.22202, found: 356.22226; calcd. $[M+Na]^+$: 378.20397, found: 378.20428.

GC-MS *m/z* (%) = 355 ([M], <5), 281 (8), 264 (7), 192 (8), 133 (6), 91 (100), 65 (13).

$[\alpha]_\lambda^{20}$ (0.15 g/100 mL in $CHCl_3$): $[\alpha]_{436}$ = -29.1 °, $[\alpha]_{546}$ = -7.3 °, $[\alpha]_{579}$ = -2.7 °, $[\alpha]_{589}$ = -2.7 °.

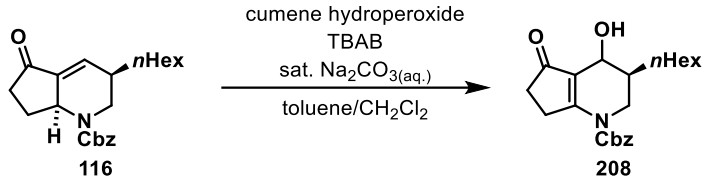
10.2.8.7 Synthesis of benzyl (3*R*,7a*S*)-3-hexyl-5-oxo-2,3,5,6,7,7a-hexahydro-1*H*-cyclopenta-[b]pyridine-1-carboxylate (116)



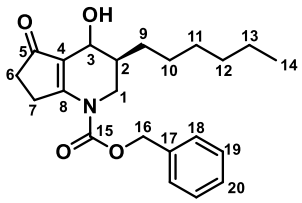
An argon-flooded reaction vial was charged with 13.0 mg (34.8 µmol, 1.00 eq.) of *β*-hydroxyketone **207** dissolved in 0.18 mL dry CH_2Cl_2. At 0 °C, 9.84 µL (0.122 mmol, 3.50 eq.) of pyridine and 6.44 µL (38.3 µmol, 1.10 eq.) of Tf_2O were added. The reaction vial was capped and heated to 35 °C in a heating block. Full consumption of the starting material was indicated *via* TLC after 22 h. The reaction mixture was diluted with 8 mL CH_2Cl_2 and 10 mL H_2O. The aqueous phase was extracted three times with 5 mL CH_2Cl_2. The combined organic layers were washed with 15 mL sat. aq. NaCl-solution, dried over Na_2SO_4 and the solvent was removed under reduced pressure. The crude product was purified by column chromatography (SiO_2, *c*-Hex/EtOAc 4:1) to afford 10.0 mg (28.1 µmol, 81%) of enone **116** as a colourless oil.

The analytics of substrate **116** are given in the above-mentioned procedure.

10.2.8.8 Synthesis of benzyl (3*S*)-3-hexyl-4-hydroxy-5-oxo-2,3,4,5,6,7-hexahydro-1*H*-cyclopenta[b]pyridine-1-carboxylate (208)



A round-bottom flask was charged with 38.0 mg (0.107 mmol, 1.00 eq.) of enone **116** dissolved in 1.05 mL toluene/CH_2Cl_2 (6:1). Then, 2.1 mL sat. aq. Na_2CO_3-solution, 0.20 mL (1.08 mmol, 10.1 eq.) of cumene hydroperoxide (80% in cumene) and 4.2 mg (13.0 µmol, 12.2 mol%) of TBAB were added, respectively. The reaction mixture was stirred at rt. After 20 h, full consumption of the starting material was indicated by TLC. The reaction mixture was diluted with 5 mL CH_2Cl_2 and 5 mL sat. aq. NaCl-solution. The aqueous phase was extracted three times with 5 mL CH_2Cl_2. The combined organic layers were dried over Na_2SO_4 and the solvent was removed under reduced pressure. The crude product was purified by column chromatography (SiO_2, *c*-Hex/EtOAc 2:1) to afford 3.9 mg (10.5 µmol, 10%) of substrate **208** as a colourless oil.



M ($C_{22}H_{29}NO_4$) 371.48 g/mol.

R_f (SiO_2, *c*-Hex/EtOAc 2:1) = 0.16.

^{1}H NMR (600 MHz, $CDCl_3$, mixture of diastereomers and rotamers), δ [ppm] = 7.40-7.26 (m, 5H, H-18, H-19, H-20), 5.30-5.23 (m, 2H, H-16), 4.83 (d, $^3J_{HH}$ = 4.8 Hz, 0.4H, H-3'), 4.52 (d, $^3J_{HH}$ = 6.4 Hz, 0.6H, H-3), 3.90-3.80 (m, 1H, H-1a), 3.70-3.62 (m, 0.6H, H-1b), 3.60-3.56 (m, 0.4H, H-1b'), 3.25-3.11 (m, 2H, H-7), 2.54-2.44 (m, 2H, H-6), 2.05-1.96 (m, 1H, H-2), 1.53-1.46 (m, 1H, H-9a), 1.31-1.24 (m, 8H, H-10, H-11, H-12, H-13), 1.14 (dtd, $^3J_{HH}$ = 14.1, 9.1, 5.1 Hz, 1H, H-9b), 0.87 (t, $^3J_{HH}$ = 7.1 Hz, 3H, H-14).

^{13}C NMR (126 MHz, $CDCl_3$, mixture of diastereomers and rotamers), δ [ppm] = 205.9 (C-5), 170.2 (C-8), 152.9 (C-15), 134.9 (C-17), 129.1/129.0 (C-19), 128.7/128.6 (C-18), 125.2 (C-20), 119.2 (C-4), 78.8/71.3 (C-3), 69.2/69.2 (C-16), 47.4/47.0 (C-1), 34.8 (C-2), 34.2/34.2 (C-6), 31.8/31.8 (C-12), 29.4/29.4 (C-9), 29.3/29.0 (C-7), 27.2 (C-11), 27.1 (C-10), 22.8/22.7 (C-13), 14.2 (C-14).

FT-IR ATR, v [cm^{-1}] = 3335 (br), 3034 (w), 2954 (w), 2928 (m), 2857 (w), 1732 (m), 1693 (m), 1598 (m), 1498 (w), 1466 (w), 1411 (m), 1392 (m), 1340 (m), 1300

(m), 1245 (m), 1204 (s), 1152 (m), 1101 (w), 1028 (w), 976 (w), 828 (w), 766 (w), 699 (w), 671 (w), 606 (w), 548 (w).

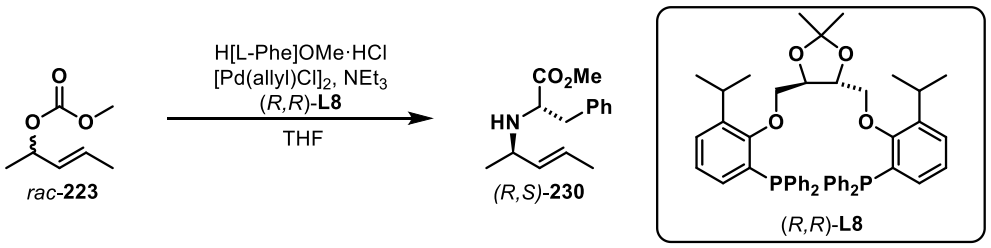
HRMS (ESI) Calcd. $[M+H]^+$: 372.21693, found: 372.21721; calcd. $[M+Na]^+$: 394.19888, found: 394.19888.

GC-MS *m/z* (%) = 369 (<5), 355 (20), 315 (<5), 295 (6), 277 (100), 222 (18), 183 (12), 147 (15), 133 (8), 91 (17), 77 (30).

$[\alpha]_\lambda^{20}$ (0.14 g/100 mL in $CHCl_3$): $[\alpha]_{365}$ = -40 °, $[\alpha]_{436}$ = -8.6 °, $[\alpha]_{546}$ = -6.2 °, $[\alpha]_{579}$ = -4.5 °, $[\alpha]_{589}$ = -3.8 °.

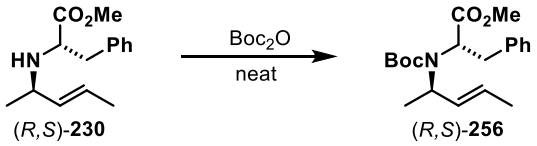
10.2.9 Synthesis of opines: phenylalanine-derivative

10.2.9.1 Synthesis of methyl *N*-(*tert*-butoxycarbonyl)-*N*-((*E*)-pent-3-en-2-yl)-L-phenylalaninate (256)



An argon-flooded *Schlenk* flask was charged with 3.90 mg (10.7 µmol, 0.51 mol%) of $[Pd(allyl)Cl]_2$ and 19.0 mg (24.8 µmol, 1.19 mol%) (*R,R*)-*Medi*Phos ligand **L8** dissolved in 1.0 mL dry THF. After stirring at rt for 20 min, 300 mg (2.08 mmol, 1.00 eq.) of carbonate *rac*-**223** were added. After another 20 min, 0.38 mL (2.73 mmol, 1.31 eq.) of NEt_3 and 583 mg (2.70 mmol, 1.30 eq.) of H[L-Phe]OMe·HCl were added, respectively. Full conversion of the starting material was indicated by TLC after 16 hours. Quadrasil$^{(R)}$ was added and the suspension was stirred for one hour at rt. The reaction mixture was filtered over celite, washed with EtOAc and the solvent was removed under reduced pressure. The crude product was directly used within the next step. The diastereomeric ratio was determined by GC-MS (*d.r.* 98:2).

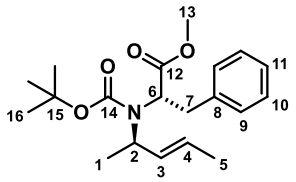
The corresponding amine (*S,S*)-**230** was obtained by reacting 296 mg (2.05 mmol, 1.00 eq.) of carbonate *rac*-**223**, 587 mg (2.72 mmol, 1.33 eq.) of H[L-Phe]OMe·HCl, 0.38 mL (2.73 mmol, 1.33 eq.) of NEt_3, 3.8 mg (10.4 µmol, 0.51 mol%) of $[Pd(allyl)Cl]_2$ and 18.8 mg (24.5 µmol, 1.19 mol%) of (*S,S*)-*Medi*Phos ligand **L8** in 1.0 mL dry THF. The crude product was directly used within the next step. The diastereomeric ratio was determined by GC-MS (*d.r.* 89:11).



The crude product of (*R,S*)-**230** was reacted with 2.26 g (10.4 mmol, 4.97 eq.) of Boc_2O in a head space vial at 80 °C. After 18 hours, full conversion was indicated by TLC. The reaction mixture was diluted with 30 mL EtOAc, 20 mL H_2O and a crystal of DMAP was added. The mixture was stirred for two hours at rt. Then, the aqueous phase was extracted three times with 10 mL EtOAc. The combined organic layers were washed with 40 mL sat. aq. NaCl-solution, dried over $MgSO_4$ and the solvent was removed under reduced pressure. The crude product was purified by column

chromatography (SiO_2, *c*-Hex/EtOAc 20:1 → 15:1) to afford 589 mg (1.70 mmol, 81% over two steps) of the desired product **256** as a light-yellow oil.

(*R*,*S*)-**256**:



M($C_{20}H_{29}NO_4$) 347.46 g/mol.

R_f (SiO_2, *c*-Hex/EtOAc 5:1) = 0.41.

^{1}H NMR (500 MHz, $CDCl_3$) δ [ppm] = 7.30-7.26 (m, 2H, H-10), 7.24-7.19 (m, 1H, H-11), 7.16 (d, $^3J_{HH}$ = 7.4 Hz, 2H, H-9), 5.40 (dt, $^3J_{HH}$ = 15.7, 8.0 Hz, 1H, H-4), 4.69-4.64 (m, 0.6H, H-2a), 4.50 (d, $^3J_{HH}$ = 15.6 Hz, 1H, H-3), 4.36-4.31 (m, 0.2H, H-2b), 3.90-3.85 (m, 0.2H, H-6b), 3.80-3.72 (m, 0.7H, H-6a), 3.71 (s, 3H, H-13), 3.42 (dd, $^3J_{HH}$ = 14.0, 6.0 Hz, 1H, H-7a), 3.31-3.26 (m, 0.2H, H-7b'), 3.10 (dd, $^3J_{HH}$ = 13.8, 8.3 Hz, 0.7H, H-7b), 1.50-1.49 (m, 12H, H-5, H-16), 1.14 (d, $^3J_{HH}$ = 6.8 Hz, 3H, H-1).

^{13}C NMR (126 MHz, $CDCl_3$) δ [ppm] = 172.7 (C-12), 154.8 (C-14), 139.2 (C-8), 131.7 (C-3), 130.0 (C-9), 128.4 (C-10), 127.0 (C-4), 126.5 (C-11), 80.7 (C-15), 57.9 (C-6), 52.4 (C-2), 52.2 (C-13), 37.9 (C-7), 28.6 (C-16), 18.1 (C-5), 16.4 (C-1).

FT-IR (ATR) ν [cm^{-1}] = 3029 (w), 2975 (w), 2951 (w), 2935 (w), 1742 (m), 1691 (s), 1605 (w), 1497 (w), 1434 (m), 1415 (m), 1366 (m), 1288 (m), 1254 (m), 1161 (s), 1100 (m), 1080 (m), 1055 (m), 1021 (m), 977 (m), 919 (w), 898 (w), 852 (w), 775 (m), 977 (m), 700 (s), 615 (w), 581 (w), 564 (w).

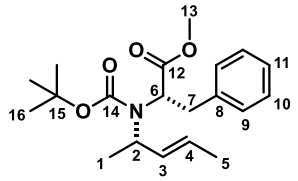
GC-MS *m/z* (%) = 291 (17), 232 (18), 188 (6), 172 (<5), 156 (32), 139 (<5), 120 (21), 91 (55), 69 (100), 53 (17).

HRMS (ESI) calcd. $[M+H]^+$: 348.21693, found: 348.21709; calcd. $[M+Na]^+$: 370.19888, found: 370.19868.

$[\alpha]_\lambda^{20}$ (0.235 g/100 mL in $CHCl_3$): $[\alpha]_{365}$ = -202.7 °, $[\alpha]_{436}$ = -126.8 °, $[\alpha]_{546}$ = -73.1 °, $[\alpha]_{579}$ = -63.5 °, $[\alpha]_{589}$ = -60.4 °.

(*S,S*)-**256**:

The corresponding Boc-protected amine (*S,S*)-**256** was obtained by reacting the crude product of *(S,S)*-**230** with 2.24 g (10.2 mmol, 4.99 eq.) of Boc_2O. The crude product was purified by column chromatography (SiO_2, *c*-Hex/EtOAc 30:1) to afford 553 mg (1.59 mmol, 78% over two steps) of the desired product **256**.



M($C_{20}H_{29}NO_4$) 347.46 g/mol.

R_f (SiO_2, *c*-Hex/EtOAc 5:1) = 0.42.

^{1}H NMR (500 MHz, $CDCl_3$) δ [ppm] = 7.31-7.26 (m, 2H, H-10), 7.21-7.15 (m, 3H, H-9, H-11), 5.54 (d, $^3J_{HH}$ = 15.6 Hz, 1H, H-3), 5.42-5.33 (m, 1H, H-4), 4.68-4.49 (m, 0.8H, H-2), 4.33-4.20 (m, 0.2H, H-2'), 4.02-3.93 (m, 0.3H, H-6'), 3.84-3.76 (m, 0.7H, H-6), 3.71 (s, 3H, H-13), 3.50-3.40 (m, 1H, H-7a), 3.28-3.10 (m, 1H, H-7b), 1.63 (d, $^3J_{HH}$ = 6.4 Hz, 3H, H-5), 1.48 (s, 9H, H-16), 1.14(d, $^3J_{HH}$ = 6.9 Hz, 0.4H, H-1'), 0.68-0.62 (m, 2.7H, H-1).

^{13}C NMR (126 MHz, $CDCl_3$) δ [ppm] = 172.4 (C-12), 154.7 (C-14), 139.2 (C-8), 131.6 (C-3), 129.9 (C-9), 128.5 (C-10), 126.6 (C-11), 126.5 (C-4), 80.6 (C-15), 58.7 (C-6), 52.7 (C-2), 52.2 (C-13), 37.8 (C-7), 28.6 (C-16), 18.0 (C-5), 16.8 (C-1).

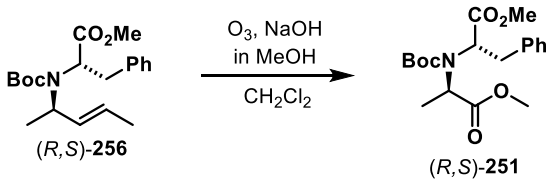
FT-IR (ATR) v [cm^{-1}] = 3029 (w), 2975 (w), 2951 (w), 2935 (w), 1742 (m), 1691 (s), 1605 (w), 1497 (w), 1434 (m), 1415 (m), 1366 (m), 1288 (m), 1254 (m), 1161 (s), 1100 (m), 1080 (m), 1055 (m), 1021 (m), 977 (m), 919 (w), 898 (w), 852 (w), 775 (m), 977 (m), 700 (s), 615 (w), 581 (w), 564 (w).

GC-MS *m/z* (%) = 291 (15), 247 (<5), 232 (15), 206 (<5), 188 (6), 156 (33), 120 (17), 91 (45), 69 (100).

HRMS (ESI) calcd. $[M+H]^+$: 348.21693, found: 348.21709; calcd. $[M+Na]^+$: 370.19888, found: 370.19868.

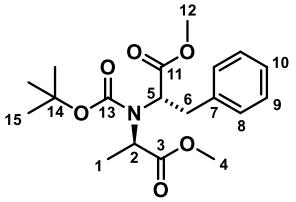
$[\alpha]_\lambda^{20}$ (0.15 g/100 mL in $CHCl_3$): $[\alpha]_{365}$ = -454.2 °, $[\alpha]_{436}$ = -276.2 °, $[\alpha]_{546}$ = -152.5 °, $[\alpha]_{579}$ = -131.3 °, $[\alpha]_{589}$ = -124.5 °.

10.2.9.2 Synthesis of methyl *N*-(*tert*-butoxycarbonyl)-*N*-(-1-methoxy-1-oxopropan-2-yl)-L-phenylalaninate (251)



A round-bottom flask was charged with 194 mg (0.558 mmol, 1.00 eq.) of Boc-protected amine (*R,S*)-**256** dissolved in 35 mL CH_2Cl_2. After adding 2.30 mL 2.5 M NaOH in MeOH, the reaction mixture was cooled to -78 °C and ozone was introduced. Full consumption of the starting material was indicated after 1.5 hours. Then, O_2 was introduced for 20 minutes. The reaction mixture was warmed to rt and 30 mL CH_2Cl_2 and H_2O each were added. The aqueous phase was extracted three times with 50 mL CH_2Cl_2. The combined organic layers were washed with 70 mL sat. aq. NaCl-solution, dried over $MgSO_4$ and the solvent was removed under reduced pressure. The crude product was purified by column chromatography (SiO_2, *c*-Hex/EtOAc 10:1) to afford 127 mg (0.348 mmol, 62%) of the diester **251** as a light-yellow oil.

(*R,S*)-**251**:



M($C_{19}H_{27}NO_6$) 365.43 g/mol.

R_f (SiO_2, *c*-Hex/EtOAc 5:1) = 0.32.

^{1}H NMR (500 MHz, $CDCl_3$, mixture of rotamers) δ [ppm] = 7.28 (dd, $^3J_{HH}$ = 13.5, 4.0 Hz, 4H, H-8, H-9), 7.21 (dt, $^3J_{HH}$ = 8.7 Hz, $^4J_{HH}$ = 4.3 Hz, 1H, H-10), 4.92 (dd, $^3J_{HH}$ = 9.5, 5.5 Hz, 0.5 H, H-5^{rot1}), 4.62 (q, $^3J_{HH}$ = 7.1 Hz, 0.4H, H-2^{rot2}), 4.27 (dd, $^3J_{HH}$ = 8.3, 4.8 Hz, 0.4H, H-5^{rot2}), 4.15 (q, $^3J_{HH}$ = 6.9 Hz, 0.5H, H-2^{rot1}), 3.69-3.59 (m, 6H, H-4, H-12), 3.44 (dd, $^3J_{HH}$ = 13.8, 8.4 Hz, 0.5H, H-6a^{rot1}), 3.25 (dd, $^3J_{HH}$ = 13.8, 9.5 Hz, 0.5H, H-6a^{rot2}), 3.13 (dt, $^3J_{HH}$ = 13.9, 4.6 Hz, 1H, H-6b), 1.45 (2·s, 9H, H-15), 1.37 (d, $^3J_{HH}$ = 7.0 Hz, 3H, H-1).

^{13}C NMR (126 MHz, $CDCl_3$, mixture of rotamers) δ [ppm] = 172.7/172.5 (C-3), 171.8 (C-11), 154.3 (C-13), 138.9/137.6 (C-7), 129.7/129.5 (C-8), 128.5 (C-9), 126.6 (C-10), 81.6 (C-14), 59.9/59.5 (C-5), 54.0/53.6 (C-2), 52.2/52.1 (C-4 and C-12), 37.8/36.4 (C-6), 28.4 (C-15), 16.3/15.5 (C-1).

FT-IR (ATR) ν [cm^{-1}] = 3029 (w), 2978 (w), 2951 (w), 2075 (w), 1995 (w), 1741 (s), 1698 (s), 1605 (w), 1455 (m), 1421 (m), 1367 (m), 1278 (m), 1220 (s), 1159

(s), 1101 (m), 1068 (m), 1013 (m), 987 (m), 971 (m), 883 (w), 848 (w), 775 (m), 749 (m), 700 (m), 564 (w), 520 (w).

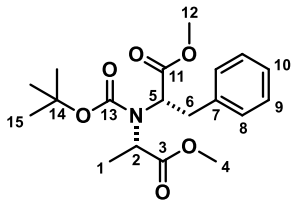
GC-MS *m/z* (%) = 306 (<5), 264 (<5), 232 (5), 206 (61), 174 (100), 146 (38), 131 (15), 114 (35), 91 (45), 76 (17), 57 (94).

HRMS (ESI) calcd. $[M+H]^+$: 366.19111, found: 366.19136; calcd. $[M+Na]^+$: 388.17306, found: 388.17300.

$[\alpha]_\lambda^{20}$ (0.44 g/100 mL in $CHCl_3$): $[\alpha]_{365}$ = -159.6 °, $[\alpha]_{436}$ = -93.7 °, $[\alpha]_{546}$ = -50.5 °, $[\alpha]_{579}$ = -43.5 °, $[\alpha]_{589}$ = -41.5 °.

(*S,S*)-**251**:

The corresponding (*S,S*)-diester **251** was obtained by reacting 193 mg (0.555 mmol, 1.00 eq.) of allylic amine (*S,S*)-**256** and 2.30 mL 2.5 M NaOH in MeOH in 35 mL CH_2Cl_2. The crude product was purified by column chromatography (SiO_2, *c*-Hex/EtOAc 10:1) to afford 157 mg (0.420 mmol, 77%) of the desired product (*S,S*)-**251** as a yellow oil.



M($C_{19}H_{27}NO_6$) 365.43 g/mol.

R_f (SiO_2, *c*-Hex/EtOAc 5:1) = 0.24.

^{1}H NMR (500 MHz, $CDCl_3$, mixture of rotamers) δ [ppm] = 7.31-7.27 (m, 2H, H-9), 7.25-7.20 (m, 3H, H-8, H-10), 4.76 (t, $^3J_{HH}$ = 7.7 Hz, 0.5H, H-5^{rot1}), 4.41 (q, $^3J_{HH}$ = 6.8 Hz, 0.5H, H-2^{rot1}), 4.28-4.22 (m, 0.5H, H-5^{rot2}), 4.13 (q, $^3J_{HH}$ = 6.8 Hz, 0.5H, H-2^{rot2}), 3.79-3.61 (m, 6H, H-4, H-12), 3.39 (dd, $^2J_{HH}$ = 14.0 Hz, $^3J_{HH}$ = 6.1 Hz, 0.5H, H-6a^{rot1}), 3.32-3.26 (m, 0.5H, H-6a^{rot2}), 3.12 (td, $^3J_{HH}$ = 14.4, 7.7 Hz, 1H, H-6b), 1.45 (s, 9H, H-15), 1.25 (d, $^3J_{HH}$ = 7.6 Hz, 2H, H-1^{rot1}), 0.93 (d, $^3J_{HH}$ = 7.0 Hz, 1H, H-1^{rot2}).

^{13}C NMR (126 MHz, $CDCl_3$, mixture of rotamers) δ [ppm] = 172.1 (C-3), 171.2 (C-11), 154.2 (C-13), 138.2/137.4 (C-7), 129.8/129.5 (C-8), 128.6/128.5 (C-9), 126.9/126.8 (C-10), 81.6/81.5 (C-14), 60.0/59.5 (C-5), 53.9 (C-2), 52.3/52.2 (C-4), 52.1/52.0 (C-12), 37.2/36.3 (C-6), 28.4/28.2 (C-15), 16.5/15.2 (C-1).

FT-IR (ATR) ν [cm^{-1}] = 3029 (w), 2978 (w), 2951 (w), 2075 (w), 1995 (w), 1741 (s), 1698 (s), 1605 (w), 1455 (m), 1421 (m), 1367 (m), 1278 (m), 1220 (s), 1159

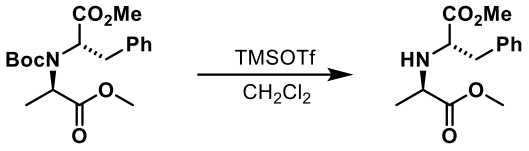
(s), 1101 (m), 1068 (m), 1013 (m), 987 (m), 971 (m), 883 (w), 848 (w), 775 (m), 749 (m), 700 (m), 564 (w), 520 (w).

GC-MS *m/z* (%) = 306 (<5), 264 (<5), 232 (5), 206 (61), 174 (100), 146 (38), 131 (15), 114 (35), 91 (45), 76 (17), 57 (94).

HRMS (ESI) calcd. $[M+H]^+$: 366.19111, found: 366.19136; calcd. $[M+Na]^+$: 388.17306, found: 388.17300.

$[\alpha]_\lambda^{20}$ (0.405 g/100 mL in $CHCl_3$): $[\alpha]_{365}$ = -428.4 °, $[\alpha]_{436}$ = -250.9 °, $[\alpha]_{546}$ = -139.8 °, $[\alpha]_{579}$ = -121.2 °, $[\alpha]_{589}$ = -116.1 °.

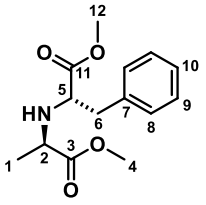
10.2.9.3 Synthesis of methyl (1-methoxy-1-oxopropan-2-yl)-L-phenylalaninate (258)



(*R,S*)-**251** (*R,S*)-**258**

An argon-flooded *Schlenk* flask was charged with 108 mg (0.296 mmol, 1.00 eq.) of substrate (*R,S*)-**251** dissolved in 1.50 mL dry CH_2Cl_2. At 0 °C, 65.1 µL (0.355 mmol, 1.20 eq.) of TMSOTf were added. After 20 minutes at 0 °C, full consumption of the starting material was observed by TLC. The reaction was quenched with 10 mL sat. aq. $NaHCO_3$-solution. The aqueous phase was extracted five times with 10 mL CH_2Cl_2. The combined organic layers were dried over $MgSO_4$ and the solvent was removed under reduced pressure. The crude amine (*R,S*)-**258** (68.0 mg, 0.256 mmol, 86%) was used without further purification.

<u>(*R,S*)-**258**:</u>



M($C_{14}H_{19}NO_4$) 265.31 g/mol.

R_f (SiO_2, *c*-Hex/EtOAc 5:1) = 0.15.

^{1}H NMR (500 MHz, $CDCl_3$) δ [ppm] = 7.31-7.26 (m, 2H, H-9), 7.23-7.18 (m, 3H, H-8, H-10), 3.67 (s, 3H, H-12), 3.63 (s, 3H, H-4), 3.53 (t, $^3J_{HH}$ = 6.8 Hz, 1H, H-5), 3.28 (q, $^3J_{HH}$ = 6.9 Hz, 1H, H-2), 3.00-2.89 (m, 2H, H-6), 2.26 (s, 1H, *N*H), 1.23 (d, $^3J_{HH}$ = 7.0 Hz, 3H, H-1).

^{13}C NMR (126 MHz, $CDCl_3$) δ [ppm] = 175.2 (C-3), 174.5 (C-11), 137.5 (C-7), 129.4 (C-8), 128.5 (C-9), 126.8 (C-10), 61.3 (C-5), 56.3 (C-2), 52.0, 51.9 (C-4 and C-12), 40.1 (C-6), 18.6 (C-1).

FT-IR (ATR) ν [cm^{-1}] = 3335 (w), 3087 (w), 3063 (w), 3029 (w), 2979 (w), 2952 (w), 2075 (w), 1734 (s), 1703 (w), 1604 (w), 1453 (m), 1435 (m), 1375 (w), 1200 (s), 1155 (s), 1078 (m), 1056 (m), 1031 (m), 1018 (m), 982 (m), 849 (w), 747 (m), 700 (s), 628 (w), 596 (w), 543 (w).

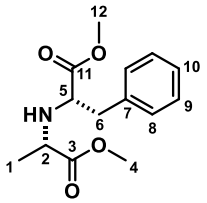
GC-MS *m/z* (%) = 265 ([M], <5), 206 (62), 174 (100), 146 (67), 131 (15), 114 (68), 91 (85), 55 (35).

HRMS (ESI) calcd. $[M+H]^+$: 266.13868, found: 266.13865; calcd. $[M+Na]^+$: 288.12063, found: 288.12069.

$[\alpha]_\lambda^{20}$ (0.04 g/100 mL in $CHCl_3$): $[\alpha]_{365}$ = -81.3 °, $[\alpha]_{436}$ = -44.2 °, $[\alpha]_{546}$ = -12.5 °, $[\alpha]_{579}$ = -10.8 °, $[\alpha]_{589}$ = -10.0 °.

(*S,S*)-**258**:

The corresponding (*S,S*)-amine **258** was obtained by reacting 114 mg (0.312 mmol, 1.00 eq.) of diester (*S,S*)-**251** and 68.6 µL (0.374 mmol, 1.20 eq.) of TMSOTf in 1.6 mL dry CH_2Cl_2. The desired product (*S,S*)-**258** was afforded as a yellow oil (80.0 mg, 0.302 mmol, 97%) and was used without further purification.



M($C_{14}H_{19}NO_4$) 265.31 g/mol.

R_f (SiO_2, *c*-Hex/EtOAc 5:1) = 0.09.

^{1}H NMR (500 MHz, $CDCl_3$) δ [ppm] = 7.32-7.29 (m, 2H, H-9), 7.25-7.19 (m, 3H, H-8, H-10), 3.66 (s, 3H, H-12), 3.63 (s, 3H, H-4), 3.60 (dd, $^3J_{HH}$ = 7.7, 6.4 Hz, 1H, H-5), 3.37 (q, $^3J_{HH}$ = 7.0 Hz, 1H, H-2), 3.03 (dd, $^2J_{HH}$ = 13.5 Hz, $^3J_{HH}$ = 6.3 Hz, 1H, H-6a), 2.92 (dd, $^2J_{HH}$ = 13.5 Hz, $^3J_{HH}$ = 7.8 Hz, 1H, H-6b), 1.85 (s, 1H, *N*H), 1.27 (d, $^3J_{HH}$ = 7.0 Hz, 3H, H-1).

^{13}C NMR (126 MHz, $CDCl_3$) δ [ppm] = 175.3 (C-3), 174.5 (C-11), 136.9 (C-7), 129.3 (C-8), 128.6 (C-10), 61.2 (C-5), 55.1 (C-2), 52.0 (C-4 and C-12), 39.8 (C-6), 19.3 (C-1).

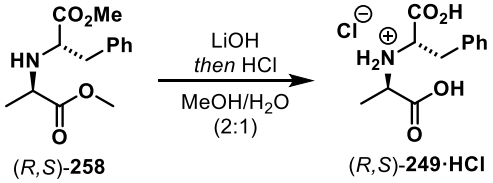
FT-IR (ATR) ν [cm^{-1}] = 3335 (w), 3087 (w), 3063 (w), 3029 (w), 2979 (w), 2952 (w), 2075 (w), 1734 (s), 1703 (w), 1604 (w), 1453 (m), 1435 (m), 1375 (w), 1200 (s), 1155 (s), 1078 (m), 1056 (m), 1031 (m), 1018 (m), 982 (m), 849 (w), 747 (m), 700 (s), 628 (w), 596 (w), 543 (w).

GC-MS *m/z* (%) = 265 ([M], <5), 206 (62), 174 (100), 146 (67), 131 (15), 114 (68), 91 (85), 55 (35).

HRMS (ESI) calcd. $[M+H]^+$: 266.13868, found: 266.13865; calcd. $[M+Na]^+$: 288.12063, found: 288.12069.

$[\alpha]_\lambda^{20}$ (0.23 g/100 mL in $CHCl_3$): $[\alpha]_{365}$ = -13.8 °, $[\alpha]_{436}$ = -7.4 °, $[\alpha]_{546}$ = -2.9 °, $[\alpha]_{579}$ = -2.3 °, $[\alpha]_{589}$ = 0.1 °.

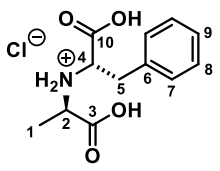
10.2.9.4 Synthesis of (*S*)-1-carboxy-*N*-(1-carboxyethyl)-2-phenylethan-1-aminium chloride (249·HCl)



(*R,S*)-**258** (*R,S*)-**249·HCl**

A round-bottom flask was charged with 44.0 mg (0.166 mmol, 1.00 eq.) of amine (*R,S*)-**258** dissolved in 0.90 mL MeOH/H_2O (2:1) and 19.0 mg (0.793 mmol, 4.78 eq.) of LiOH were added. The reaction mixture was stirred at rt for 16.5 hours until full conversion of the starting material was confirmed by TLC. 1 N HCl was added until the mixture reached pH 1. The solvent was removed under reduced pressure. The crude product was recrystallized from H_2O to obtain the desired product (*R,S*)-**249·HCl**.

Note: The product contained LiCl.



(*R,S*)-**249·HCl**:

M($C_{12}H_{16}ClNO_4$) 273.71 g/mol.

^{1}H NMR (500 MHz, D_2O) δ [ppm] = 7.46-7.35 (m, 5H, H-7, H-8, H-9), 4.00 (t, $^3J_{HH}$ = 6.5 Hz, 1H, H-4), 3.73 (q, $^3J_{HH}$ = 7.0 Hz, 1H, H-2), 3.33-3.19 (m, 2H, H-5), 1.51 (d, $^3J_{HH}$ = 7.1 Hz, 3H, H-1).

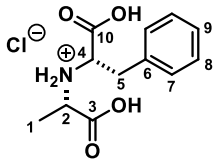
^{13}C NMR (126 MHz, D_2O) δ [ppm] = 173.9 (C-3), 172.6 (C-10), 134.8 (C-6), 129.2, 129.1 (C-7 and C-8), 127.7 (C-9), 61.5 (C-4), 56.6 (C-2), 35.8 (C-5), 14.2 (C-1).

FT-IR (ATR) ν [cm^{-1}] = 3370 (br), 3066 (w), 3028 (w), 1854 (w), 1901 (w), 1729 (m), 1613 (s), 1557 (m), 1493 (m), 1427 (m), 1386 (m), 1335 (m), 1294 (m), 1276 (m), 1148 (m), 1099 (m), 1075 (m), 1039 (m), 1004 (m), 948 (m), 865 (m), 836 (m), 773 (m), 745 (m), 699 (s), 606 (s), 552 (s), 540 (s).

HRMS (ESI) calcd. $[M\text{-}Cl]^+$: 238.10738, found: 238.10742.

(*S,S*)-**249·HCl**:

The corresponding (*S,S*)-opine **249·HCl** was obtained by reacting 58.0 mg (0.219 mmol, 1.00 eq.) of (*S,S*)-amine **258** with 26.0 mg (1.09 mmol, 4.96 eq.) of LiOH in 1.2 mL MeOH/H_2O (2:1). The crude product was recrystallized from H_2O to afford 21 mg (77 µmol, 35%) of the desired product (*S,S*)-**249·HCl** as a colourless solid.



M($C_{12}H_{16}ClNO_4$) 273.71 g/mol.

^{1}H NMR (500 MHz, D_2O) δ [ppm] = 7.49-7.32 (m, 5H, H-7, H-8, H-9), 4.09 (t, $^3J_{HH}$ = 6.9 Hz, 1H, H-4), 3.73 (q, $^3J_{HH}$ = 7.2 Hz, 1H, H-2), 3.27 (h, $^3J_{HH}$ = 7.3 Hz, 2H, H-5), 1.54 (d, $^3J_{HH}$ = 7.2 Hz, 3H, H-1).

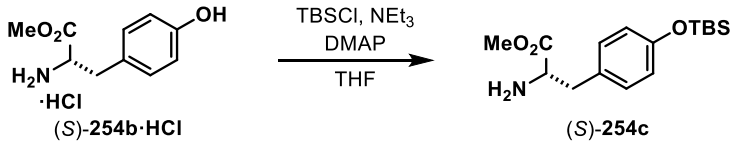
FT-IR (ATR) ν [cm^{-1}] = 3370 (br), 3066 (w), 3028 (w), 1854 (w), 1901 (w), 1729 (m), 1613 (s), 1557 (m), 1493 (m), 1427 (m), 1386 (m), 1335 (m), 1294 (m), 1276 (m), 1148 (m), 1099 (m), 1075 (m), 1039 (m), 1004 (m), 948 (m), 865 (m), 836 (m), 773 (m), 745 (m), 699 (s), 606 (s), 552 (s), 540 (s).

HRMS (ESI) Calcd. $[M\text{-}Cl]^+$: 238.10738, found: 238.10742.

Due to solubility issues no ^{13}C-spectrum could be recorded.

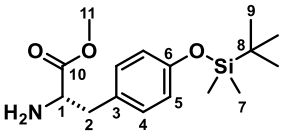
10.2.10 Synthesis of opines: tyrosine-derivative

10.2.10.1 Synthesis of methyl (*S*)-2-amino-3-(4-((*tert*-butyldimethylsilyl)-oxy)phenyl)-propanoate (254)



(*S*)-**254b·HCl** (*S*)-**254c**

A argon-flooded flask equipped with a reflux condenser was charged with 1.00 g (4.32 mmol, 1.00 eq.) H[L-Tyr]OMe·HCl (**254b·HCl**) dissolved in 22 mL dry THF. 1.80 mL (12.9 mmol, 2.99 eq.) of NEt_3, 1.68 g (11.1 mmol, 2.58 eq.) of TBSCl and 97.0 mg (0.794 mmol, 18.4 mol%) of DMAP were added, respectively. The reaction mixture was heated to reflux for 4.5 hours until full conversion was indicated by TLC. After cooling to rt, the reaction was terminated by the addition of 20 mL sat. aq. NH_4Cl-solution. The aqueous phase was extracted three times with 20 mL EtOAc. The combined organic layers were washed with 40 mL sat. aq. NaCl-solution, dried over $MgSO_4$ and the solvent was removed under reduced pressure. The crude product was purified by column chromatography (SiO_2, *c*-Hex/EtOAc 1:1) to afford 1.06 g (3.43 mmol, 80%, Lit.[166]: 98%) of the desired product (*S*)-**254c** as a light-yellow oil.



M($C_{16}H_{27}NO_3Si$) 309.48 g/mol.

R_f (SiO_2, *c*-Hex/EtOAc 1:1) = 0.14.

^{1}H NMR (500 MHz, $CDCl_3$) δ [ppm] = 7.04 (d, $^3J_{HH}$ = 8.4 Hz, 2H, H-4), 6.77 (d, $^3J_{HH}$ = 8.4 Hz, 2H, H-5), 3.72-3.66 (m, 4H, H-1, H-11), 3.00 (dd, $^2J_{HH}$ = 13.6 Hz, $^3J_{HH}$ = 5.3 Hz, 1H, H-2a), 2.80 (dd, $^2J_{HH}$ = 13.6 Hz, $^3J_{HH}$ = 7.8 Hz, 1H, H-2b), 1.47 (s, 2H, *N*H_2), 0.98 (s, 9H, H-9), 0.18 (s, 6H, H-7).

^{13}C NMR (126 MHz, $CDCl_3$) δ [ppm] = 175.7 (C-10), 154.7 (C-6), 130.3 (C-4), 129.8 (C-3), 120.3 (C-5), 56.1 (C-1), 52.1 (C-11), 40.5 (C-2), 25.8 (C-9), 18.3 (C-8), -4.3 (C-7).

FT-IR (ATR) ν [cm^{-1}] = 3382 (w), 3211 (w), 3031 (w), 2954 (m), 2930 (m), 2887 (w), 2858 (m), 2092 (w), 1893 (w), 1739 (m), 1673 (m), 1609 (m), 1509 (s), 1472 (m), 1442 (m), 1390 (w), 1362 (m), 1335 (w), 1252 (s), 1196 (m), 1170 (m), 1102 (m), 1008 (m), 912 (s), 837 (s), 780 (s), 688 (m), 632 (w), 534 (m).

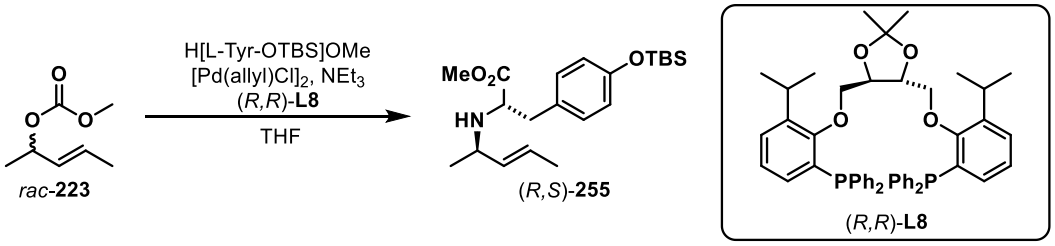
GC-MS *m/z* (%) = 309 ([M], <5), 250 (7), 221 (100), 207 (16), 165 (27), 151 (14), 135 (5), 107 (8), 91 (15), 73 (33), 57.

HRMS (ESI) calcd. $[M+H]^+$: 310.18330, found: 310.18354; calcd. $[M+Na]^+$: 332.16524, found: 332.16577.

$[\alpha]_\lambda^{20}$ (0.285 g/100 mL in $CHCl_3$): $[\alpha]_{365}$ = -137.8 °, $[\alpha]_{436}$ = -79.7 °, $[\alpha]_{546}$ = -42.6 °, $[\alpha]_{579}$ = -36.7 °, $[\alpha]_{589}$ = -34.4 °.

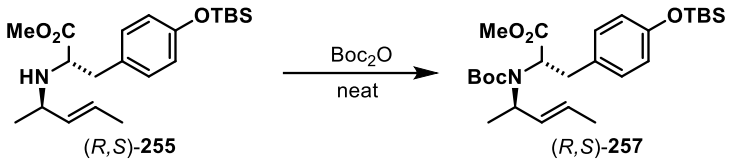
The analytical data is in accordance with the literature.[182]

10.2.10.2 Synthesis of methyl (*S*)-2-((*tert*-butoxycarbonyl)((*E*)-pent-3-en-2-yl)amino)-3-(4-((*tert*-butyldimethylsilyl)oxy)phenyl)propanoate (257)



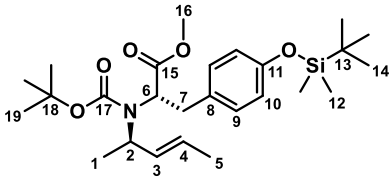
An argon-flooded *Schlenk* flask was charged with 2.10 mg (5.74 µmol, 0.79 mol%) of $[Pd(allyl)Cl]_2$ and 6.80 mg (8.87 µmol, 1.22 mol%) (*R,R*)-*Medi*Phos ligand **L8** dissolved in 0.37 mL dry THF. After stirring at rt for 20 min, 105 mg (0.728 mmol, 1.00 eq.) of carbonate *rac*-**223** were added. After another 20 min, 296 mg (0.956 mmol, 1.31 eq.) of H[L-Tyr-OTBS]OMe were added. Full conversion of the starting material was indicated by TLC after 18 hours. Quadrasil© was added and the suspension was stirred for one hour at rt. The reaction mixture was filtered over celite, washed with EtOAc and the solvent was removed under reduced pressure. The crude product was directly used within the next step. The diastereomeric ratio was determined by GC-MS (*d.r.* 98:2).

The corresponding amine (*S,S*)-**255** was obtained by reacting 112 mg (0.777 mmol, 1.00 eq.) of carbonate *rac*-**223**, 298 mg (0.963 mmol, 1.24 eq.) of H[L-Tyr-OTBS]OMe, 1.9 mg (5.19 µmol, 0.67 mol%) of $[Pd(allyl)Cl]_2$ and 6.6 mg (8.61 µmol, 1.11 mol%) of (*S,S*)-*Medi*Phos ligand **L8** in 0.37 mL dry THF. The crude product was directly used within the next step. The diastereomeric ratio was determined by GC-MS (*d.r.* 94:6).



The crude product of (*R,S*)-**255** was reacted with 790 mg (3.62 mmol, 4.97 eq.) of Boc_2O in a head space vial at 80 °C. After 16 hours, full conversion was indicated by TLC. The reaction mixture was diluted with 10 mL EtOAc, 30 mL H_2O and a crystal of DMAP was added. The mixture was stirred for four hours at rt. Then, the aqueous phase was extracted three times with 30 mL EtOAc. The combined organic phases were washed with 50 mL sat. aq. NaCl-solution, dried over $MgSO_4$ and the solvent was removed under reduced pressure. The crude product was purified by column chromatography (SiO_2, *c*-Hex/EtOAc 25:1 → 20:1) to afford 274 mg (0.574 mmol, 79% over two steps) of the desired product (*R,S*)-**257** as a light-yellow oil.

(*R,S*)-**257**:



M($C_{26}H_{43}NO_5Si$) 477.72 g/mol.

R_f (SiO_2, *c*-Hex/EtOAc 5:1) = 0.53.

^{1}H NMR (500 MHz, $CDCl_3$, mixture of rotamers) δ [ppm] = 7.00 (d, $^3J_{HH}$ = 7.9 Hz, 2H, H-9), 6.75 (d, $^3J_{HH}$ = 8.4 Hz, 2H, H-10), 5.47-5.32 (m, 1H, H-4), 4.68-4.25 (m, 2H, H-2, H-3), 3.89-3.83 (m, 0.2H, H-6^{rot2}), 3.76-3.67 (m, 3.7H, H-6^{rot1}, H-16), 3.32 (dd, $^2J_{HH}$ = 13.9 Hz, $^3J_{HH}$ = 5.3 Hz, 1H, H-7a), 3.24-3.18 (m, 0.2H, H-7b^{rot2}), 3.04 (dd, $^2J_{HH}$ = 12.8 Hz, $^3J_{HH}$ = 8.7 Hz, 0.6H, H-7b^{rot1}), 1.52 (d, $^3J_{HH}$ = 6.0 Hz, 3H, H-5), 1.48 (s, 9H, H-19), 1.14 (d, $^3J_{HH}$ = 6.7 Hz, 3H, H-1), 0.98 (s, 9H, H-14), 0.18 (2·s, 6H, H-12),

^{13}C NMR (126 MHz, $CDCl_3$, mixture of rotamers) δ [ppm] = 172.3 (C-15), 154.8 (C-17), 154.4 (C-11), 131.8 (C-3), 131.8 (C-8), 131.0 (C-9), 127.0 (C-4), 119.9 (C-10), 80.6 (C-18), 58.0 (C-6), 52.5 (C-2), 52.1 (C-16), 37.0 (C-7), 28.6 (C-19), 25.8 (C-14), 18.4 (C-13), 18.1 (C-5), 16.4 (C-1), -4.3 (C-12).

FT-IR (ATR) ν [cm^{-1}] = 2955 (w), 2931 (w), 2859 (w), 1743 (m), 1694 (s), 1610 (w), 1510 (s), 1472 (w), 1450 (m), 1413 (m), 1365 (m), 1313 (w), 1292 (m), 1252 (s), 1221 (m), 1162 (s), 1103 (w), 1057 (m), 1019 (m), 980 (m), 913 (s), 886 (w), 838 (m), 801 (m), 778 (s), 733 (m), 688 (m), 655 (w), 635 (w), 613 (w), 585 (w), 530 (w).

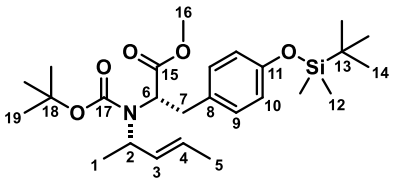
GC-MS *m/z* (%) = 421 (<5), 336 (<5), 292 (42), 236 (12), 221 (100), 192 (<5), 156 (11), 135 (<5), 107 (6), 88 (17), 73 (26), 57 (33).

HRMS (ESI) calcd. $[M+Na]^+$: 500.28027, found: 500.28026.

$[\alpha]_\lambda^{20}$ (0.315 g/100 mL in $CHCl_3$): $[\alpha]_{365}$ = -141.7 °, $[\alpha]_{436}$ = -85.6 °, $[\alpha]_{546}$ = -49.3 °, $[\alpha]_{579}$ = -49.3 °, $[\alpha]_{589}$ = -43.2 °.

(*S,S*)-**257**:

The corresponding Boc-protected amine (*S,S*)-**257** was obtained by reacting the crude product of (*S,S*)-**255** with 857 mg (3.93 mmol, 5.05 eq.) of Boc_2O. The crude product was purified by column chromatography (SiO_2, *c*-Hex/EtOAc 25:1→20:1) to afford 271 mg (0.567 mmol, 73% over two steps) of the desired product **257**.



M($C_{26}H_{43}NO_5Si$) 477.72 g/mol.

R_f (SiO_2, *c*-Hex/EtOAc 5:1) = 0.56.

^{1}H NMR (500 MHz, $CDCl_3$, mixture of rotamers) δ [ppm] = 7.02 (d, $^3J_{HH}$ = 8.1 Hz, 2H, H-9), 6.75 (d, $^3J_{HH}$ = 8.4 Hz, 2H, H-10), 5.53 (d, $^3J_{HH}$ = 14.6 Hz, 1H, H-4), 5.42-5.34 (m, 1H, H-3), 4.72-4.49 (m, 0.8H, H-2^{rot1}), 4.28-4.20 (m, 0.2H, H-2^{rot2}) 3.95-3.89 (m, 0.2H, H-6^{rot2}), 3.76-3.68 (m, 3.8H, H-6^{rot1}, H-16), 3.43-3.00 (m, 2H, H-7), 1.63 (d, $^3J_{HH}$ = 6.4 Hz, 3H, H-5), 1.48 (s, 9H, H-19), 0.97 (s, 9H, H-14), 0.66-0.54 (m, 3H, H-1), 0.16 (2·s, 6H, H-12).

^{13}C NMR (126 MHz, $CDCl_3$, mixture of rotamers) δ [ppm] = 172.7 (C-15), 154.5 (C-17), 131.9 (C-4), 130.9 (C-9), 126.8 (C-3), 120.2 (C-10), 80.6 (C-18), 58.8 (C-6), 52.6 (C-2), 52.2 (C-16), 36.7 (C-7), 28.6 (C-19), 25.9 (C-14), 18.4 (C-5), 18.0 (C-1), 17.0 (C-13), -4.3 (C-12).

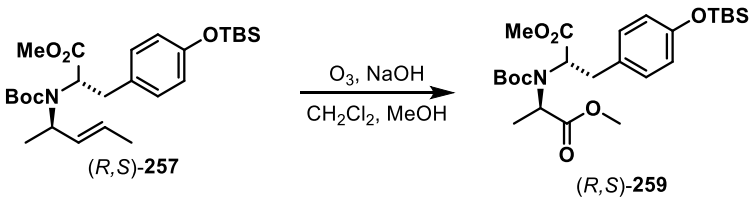
FT-IR (ATR) ν [cm^{-1}] = 2955 (w), 2931 (w), 2859 (w), 1743 (m), 1694 (s), 1610 (w), 1510 (s), 1472 (w), 1450 (m), 1413 (m), 1365 (m), 1313 (w), 1292 (m), 1252 (s), 1221 (m), 1162 (s), 1103 (w), 1057 (m), 1019 (m), 980 (m), 913 (s), 886 (w), 838 (m), 801 (m), 778 (s), 733 (m), 688 (m), 655 (w), 635 (w), 613 (w), 585 (w), 530 (w).

GC-MS *m/z* (%) = 421 (5), 336 (<5), 292 (100), 236 (24), 221 (92), 192 (<5), 156 (14), 135 (<5), 107 (6), 88 (17), 73 (26), 57 (33).

HRMS (ESI) calcd. $[M+Na]^+$: 500.28027, found: 500.28026.

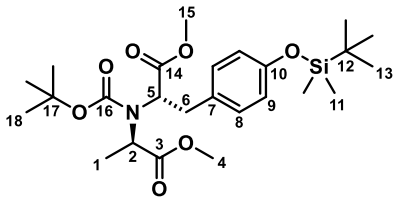
$[\alpha]_\lambda^{20}$ (0.32 g/100 mL in $CHCl_3$): $[\alpha]_{365}$ = -350.1 °, $[\alpha]_{436}$ = -209.7 °, $[\alpha]_{546}$ = -115.7 °, $[\alpha]_{579}$ = -100.4 °, $[\alpha]_{589}$ = -95.7 °.

10.2.10.3 Synthesis of methyl (*S*)-2-((*tert*-butoxycarbonyl)(-1-methoxy-1-oxopropan-2-yl)amino)-3-(4-((*tert*-butyldimethylsilyl)oxy)phenyl)propanoate (259)



A round-bottom flask was charged with 242 mg (0.507 mmol, 1.00 eq.) of Boc-protected amine (*R,S*)-**257** dissolved in 25 mL CH_2Cl_2. After adding 2.00 mL 2.5 M NaOH in MeOH, the reaction mixture was cooled to -78 °C and ozone was introduced. Full consumption of the starting material was indicated after one hour. Then, O_2 was introduced for 20 minutes. The reaction mixture was warmed to rt and 20 mL CH_2Cl_2 and H_2O each were added. The aqueous phase was extracted three times with 20 mL CH_2Cl_2. The combined organic layers were washed with 50 mL sat. aq. NaCl-solution, dried over $MgSO_4$ and the solvent was removed under reduced pressure. The crude product was purified by column chromatography (SiO_2, *c*-Hex/EtOAc 10:1) to afford 88 mg (0.18 mmol, 35%) of diester (*R,S*)-**259** as a light-yellow oil.

(*R,S*)-**259**:



M($C_{25}H_{41}NO_7Si$) 495.69 g/mol.

R_f (SiO_2, *c*-Hex/EtOAc 5:1) = 0.35.

^{1}H NMR (500 MHz, $CDCl_3$, mixture of rotamers) δ [ppm] = 7.09-7.07 (m, 2H, H-8), 6.80-6.71 (m, 2H, H-9), 4.74 (t, $^3J_{HH}$ = 9.3, 5.8 Hz, 0.6H, H-5^{rot1}), 4.64-4.61 (m, 0.2H, H-2^{rot2}), 4.47 (q, $^3J_{HH}$ = 6.9 Hz, 0.4H, H-2^{rot1}), 4.19-4-14 (m, 0.8H, H-2^{rot3}, H-5^{rot2}), 4.10-4.07 (m, 0.2H, H-2^{rot4}), 3.77-3.65 (m, 6H, H-4, H-15), 3.36-3.26 (m, 0.5H, H-6^{rot2}), 3.23-2.97 (m, 1.5H, H-6^{rot1}), 1.53-1.35 (m, 9H,

H-18), 1.23-1.18 (m, 2H, H-1^{rot1}), 0.97 (s, 9H, H-13), 0.87 (d, $^{3}J_{HH}$ = 7.0 Hz, 1H, H-1^{rot2}), 0.17 (6H, H-11).

^{13}C NMR (126 MHz, $CDCl_3$, mixture of rotamers) δ [ppm] = 172.6/172.5 (C-3), 171.9/171.8 (C-14), 154.4/154.4 (C-10), 154.2/154.2 (C-16), 130.6/130.5 (C-8), 130.4/130.1 (C-7), 120.1/120.0 (C-9), 81.5/81.4 (C-17), 60.4/59.7 (C-5), 54.2/53.6 (C-2), 52.2/52.2/52.2/52.0 (C-4 and C-15), 37.0/36.7 (C-6), 28.4 (C-18), 25.8 (C-13), 18.3 (C-12), 16.3/15.5 (C-1), -4.3 (C-11).

FT-IR (ATR) ν [cm^{-1}] = 2953 (m), 2932 (m), 2899 (w), 2859 (m), 2080 (w), 1741 (s), 1700 (s), 1610 (w), 1510 (s), 1472 (m), 1433 (m), 1367 (m), 1252 (s), 1228 (s), 1159 (s), 1103 (m), 1068 (m), 1052 (m), 1016 (m), 991 (w), 969 (w), 911 (s), 838 (s), 803 (m), 779 (s), 732 (w), 687 (m), 655 (w), 634 (w), 588 (w), 544 (w).

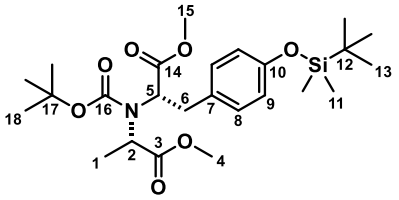
GC-MS *m/z* (%) = 336 (11), 276 (<5), 251 (<5), 221 (56), 174 (100), 146 (9), 114 (30), 91 (11), 73 (32), 55 (9).

HRMS (ESI) calcd. $[M+H]^+$: 496.27251, found: 496.27297; calcd. $[M+Na]^+$: 518.25445, found: 518.25410.

$[\alpha]_\lambda^{20}$ (0.2 g/100 mL in $CHCl_3$): $[\alpha]_{365}$ = -239.8 °, $[\alpha]_{436}$ = -141.7 °, $[\alpha]_{546}$ = -76.8 °, $[\alpha]_{579}$ = -66.2 °, $[\alpha]_{589}$ = -63.5 °.

(*S,S*)-**259**:

The corresponding (*S,S*)-diester **259** was obtained by reacting 241 mg (0.504 mmol, 1.00 eq.) of allylic amine (*S,S*)-**257** and 2.00 mL 2.5 M NaOH in MeOH in 25 mL CH_2Cl_2. The crude product was purified by column chromatography (SiO_2, *c*-Hex/EtOAc 15:1) to afford 216 mg (0.436 mmol, 87%) of the desired product (*S,S*)-**259** as a yellow oil.



M($C_{25}H_{41}NO_7Si$) 495.69 g/mol.

R_f (SiO_2, *c*-Hex/EtOAc 5:1) = 0.29.

^{1}H NMR (500 MHz, $CDCl_3$, mixture of rotamers) δ [ppm] = 7.17-7.08 (m, 2H, H-8), 6.75 (dd, $^{3}J_{HH}$ = 8.2 Hz, $^{4}J_{HH}$ = 2.8 Hz, 2H, H-9), 4.86 (dd, $^{3}J_{HH}$ = 9.3, 5.8 Hz, 0.6H, H-5^{rot1}), 4.55 (q, $^{3}J_{HH}$ = 7.0 Hz, 0.4H, H-2^{rot2}), 4.22 (dd, $^{3}J_{HH}$ = 8.0, 5.1 Hz,

0.4H, H-5^{rot2}), 4.13 (q, $^{3}J_{HH}$ = 6.9 Hz, 0.6H, H-2^{rot1}), 3.63 (2·s, 6H, H-4, H-15), 3.35 (dd, $^{2}J_{HH}$ = 14.0 Hz, $^{3}J_{HH}$ = 8.4 Hz, 0.5H, H-6^{rot2}), 3.21-2.98 (m, 1.5H, H-6^{rot1}), 1.44 (2·s, 9H, H-18), 1.35 (d, $^{3}J_{HH}$ = 7.0 Hz, 3H, H-1), 0.97 (s, 9H, H-13), 0.17 (6H, H-11).

^{13}C NMR (126 MHz, $CDCl_3$, mixture of rotamers) δ [ppm] = 172.2 (C-3), 171.5/171.4 (C-14), 154.6/154.5 (C-10), 154.4/154.3 (C-16), 130.9/130.8 (C-8), 130.5/130.0 (C-7), 120.3/120.2 (C-9), 81.6/81.4 (C-17), 59.9/59.3 (C-5), 53.6/53.5 (C-2), 52.5/52.3/52.11/52.0 (C-4 and C-15), 36.3/35.5 (C-6), 28.5/28.4 (C-18), 25.8 (C-13), 18.4 (C-12), 16.6/15.2 (C-1), -4.3 (C-11).

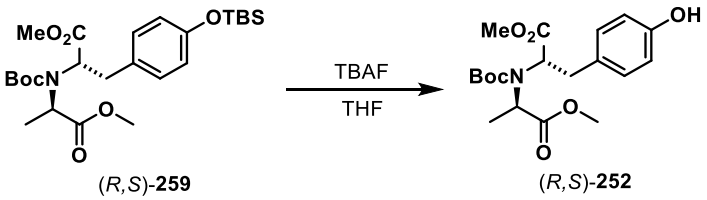
FT-IR (ATR) ν [cm^{-1}] = 2953 (m), 2932 (m), 2899 (w), 2859 (m), 2080 (w), 1741 (s), 1700 (s), 1610 (w), 1510 (s), 1472 (m), 1433 (m), 1367 (m), 1252 (s), 1228 (s), 1159 (s), 1103 (m), 1068 (m), 1052 (m), 1016 (m), 991 (w), 969 (w), 911 (s), 838 (s), 803 (m), 779 (s), 732 (w), 687 (m), 655 (w), 634 (w), 588 (w), 544 (w).

GC-MS *m/z* (%) = 336 (11), 276 (<5), 251 (<5), 221 (56), 174 (100), 146 (9), 114 (30), 91 (11), 73 (32), 55 (9).

HRMS (ESI) calcd. $[M+H]^+$: 496.27251, found: 496.27297; calcd. $[M+Na]^+$: 518.25445, found: 518.25410.

$[\alpha]_\lambda^{20}$ (0.23 g/100 mL in $CHCl_3$): $[\alpha]_{365}$ = -377.2 °, $[\alpha]_{436}$ = -215.2 °, $[\alpha]_{546}$ = -117.3 °, $[\alpha]_{579}$ = -100.9 °, $[\alpha]_{589}$ = -96.1 °.

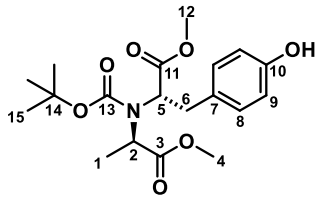
10.2.10.4 Synthesis of methyl *N*-(*tert*-butoxycarbonyl)-*N*-(1-methoxy-1-oxopropan-2-yl)-L-tyrosinate (252)



(*R,S*)-**259** (*R,S*)-**252**

An argon-flooded *Schlenk* flask was charged with 78.0 mg (0.157 mmol, 1.00 eq.) of Boc-protected amine (*R,S*)-**259** dissolved in 0.16 mL dry THF. At 0 °C, 0.47 mL (0.470 mmol, 2.99 eq.) of TBAF (1 M in THF) were added and the reaction mixture was stirred at rt. After 15 h, full conversion was indicated by TLC. The reaction was terminated by the addition of 5 mL H_2O. The aqueous phase was extracted three times with 5 mL CH_2Cl_2. The combined organic layers were washed with 10 mL sat. aq. NaCl-solution, dried over Na_2SO_4 and the solvent was removed under reduced pressure. The crude product was purified by column chromatography (SiO_2, *c*-Hex/EtOAc 4:1→2:1) to afford 36.0 mg (94.4 µmol, 60%) of the desired product (*R,S*)-**252** as a colourless oil.

(*R,S*)-**252**:



M($C_{25}H_{41}NO_7Si$) 495.69 g/mol.

R_f (SiO_2, *c*-Hex/EtOAc 5:1) = 0.35.

^{1}H NMR (500 MHz, $CDCl_3$, mixture of rotamers) δ [ppm] = 7.18-7.12 (m, 2H, H-8), 6.75 (dd, $^3J_{HH}$ = 8.3 Hz, $^2J_{HH}$ = 4.2 Hz, 2H, H-9), 4.90-4.79 (m, 1H, H-5), 4.63 (q, $^3J_{HH}$ = 7.0 Hz, 0.5H, H-2^{rot1}), 4.20-4.14 (m, 0.5H, H-2^{rot2}), 3.76-3.56 (m, 6H, H-4, H-12), 3.37 (dd, $^2J_{HH}$ = 13.9 Hz, $^3J_{HH}$ = 8.6 Hz, 0.5H, H-6b^{rot1}), 3.17 (dd, $^2J_{HH}$ = 13.7 Hz, $^3J_{HH}$ = 9.7 Hz, 0.5H, H-6b^{rot2}), 3.04 (dd, $^2J_{HH}$ = 13.9 Hz, $^3J_{HH}$ = 5.1 Hz, 0.4H, H-6a^{rot2}), 2.99 (dd, $^2J_{HH}$ = 13.9 Hz, $^3J_{HH}$ = 7.1 Hz, 0.6H, H-6a^{rot1}), 1.45 (2·s, 9H, H-15), 1.38 (d, $^3J_{HH}$ = 6.8 Hz, 3H, H-1).

^{13}C NMR (126 MHz, $CDCl_3$, mixture of rotamers) δ [ppm] = 172.2 (C-3), 171.3 (C-12), 154.7/154.4 (C-13), 130.9/130.6 (C-8), 130.0 (C-10), 129.1 (C-7), 115.4 (C-9), 81.7 (C-14), 60.0/59.5 (C-5), 53.8/53.5 (C-2), 52.2 (C-4, C-12), 36.2/35.5 (C-6), 28.5/28.4 (C-15), 16.7/15.3 (C-1).

FT-IR (ATR) ν [cm^{-1}] = 3397 (br), 2979 (w), 2952 (w), 1739 (s), 1698 (s), 1679 (s), 1615 (m), 1596 (w), 1517 (m), 1434 (s), 1394 (m), 1368 (m), 1224 (s), 1157

(s), 1104 (m), 1071 (m), 1017 (m), 991 (m), 969 (m), 911 (w), 885 (w), 849 (m), 836 (m), 825 (m), 799 (m), 773 (m), 735 (s), 702 (m), 592 (m), 538 (m).

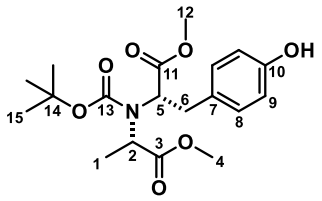
GC-MS *m/z* (%) = 280 (5), 248 (<5), 222 (28), 204 (5), 178 (100), 163 (9), 148 (15), 107 (42), 77 (9), 57 (50).

HRMS (ESI) calcd. $[M+H]^+$: 382.18603, found: 382.18630; calcd. $[M+Na]^+$: 404.16797, found: 404.16809.

$[\alpha]_\lambda^{20}$ (0.035 g/100 mL in $CHCl_3$): $[\alpha]_{365}$ = 2.9 °, $[\alpha]_{436}$ = 5.7 °, $[\alpha]_{546}$ = 21.0 °, $[\alpha]_{579}$ = 23.8 °, $[\alpha]_{589}$ = 29.5 °.

(*S,S*)-**252**:

The corresponding (*S,S*)-analogue **252** was obtained by reacting 166 mg (0.335 mmol, 1.00 eq.) of diester (*S,S*)-**259** with 1.00 mL (1.00 mmol, 2.99 eq.) of TBAF (1 M in THF) in 0.34 mL dry THF. The crude product was purified by column chromatography (SiO_2, *c*-Hex/EtOAc 5:1) to afford 71 mg (0.19 mmol, 56%) of the desired product (*S,S*)-**252**.



M($C_{25}H_{41}NO_7Si$) 495.69 g/mol.

R_f (SiO_2, *c*-Hex/EtOAc 5:1) = 0.35.

^{1}H NMR (500 MHz, $CDCl_3$, mixture of rotamers) δ [ppm] = 7.07 (dd, $^3J_{HH}$ = 15.3 Hz, $^4J_{HH}$ = 8.1 Hz, 2H, H-8), 6.75 (m, 2H, H-9), 5.35 (s, 1H, *O*H), 4.78 (t, $^3J_{HH}$ = 7.7 Hz, 0.5H, H-5^{rot1}), 4.46 (q, $^3J_{HH}$ = 6.9 Hz, 0.5H, H-2^{rot1}), 4.20-4.13 (m, 1H, H-2^{rot2}, H-5^{rot2}), 3.73-3.61 (m, 6H, H-4, H-12), 3.31 (dd, $^2J_{HH}$ = 14.1 Hz, $^3J_{HH}$ = 5.9 Hz, 0.4H, H-6b^{rot2}), 3.20 (dd, $^2J_{HH}$ = 13.9 Hz, $^3J_{HH}$ = 8.5 Hz, 0.6H, H-6a^{rot1}), 3.07 (dd, $^2J_{HH}$ = 13.8 Hz, $^3J_{HH}$ = 8.5 Hz, 0.4H, H-6a^{rot2}), 2.99 (dd, $^2J_{HH}$ = 13.9 Hz, $^3J_{HH}$ = 7.1 Hz, 0.6H, H-6b^{rot1}), 1.45 (2·s, 9H, H-15), 1.30 (d, $^3J_{HH}$ = 6.9 Hz, 1.7H, H-1^{rot1}), 0.93 (d, $^3J_{HH}$ = 7.1 Hz, 1.3H, H-1^{rot2}).

^{13}C NMR (126 MHz, $CDCl_3$, mixture of rotamers) δ [ppm] = 172.2 (C-3), 171.3 (C-12), 154.8/154.4 (C-13), 130.9/130.6 (C-8), 130.0 (C-10), 129.0 (C-7), 115.4 (C-9), 81.7 (C-14), 60.0/59.5 (C-5), 53.8/53.5 (C-2), 52.3/52.2 (C-4, C-12), 36.2/35.5 (C-6), 28.4 (C-15), 16.7/15.2 (C-1).

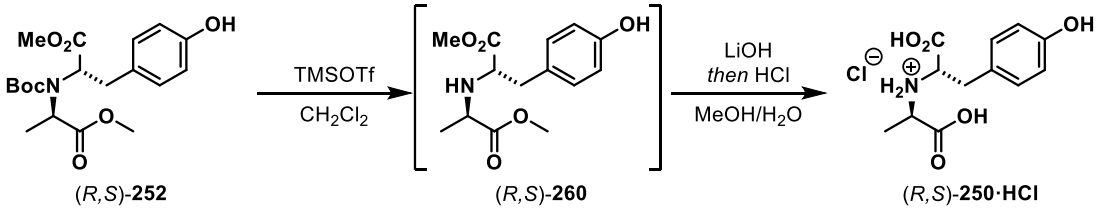
FT-IR (ATR) ν [cm^{-1}] = 3397 (br), 2979 (w), 2952 (w), 1739 (s), 1698 (s), 1679 (s), 1615 (m), 1596 (w), 1517 (m), 1434 (s), 1394 (m), 1368 (m), 1224 (s), 1157 (s), 1104 (m), 1071 (m), 1017 (m), 991 (m), 969 (m), 911 (w), 885 (w), 849 (m), 836 (m), 825 (m), 799 (m), 773 (m), 735 (s), 702 (m), 592 (m), 538 (m).

GC-MS *m/z* (%) = 280 (5), 248 (<5), 222 (28), 204 (5), 178 (100), 163 (9), 148 (15), 107 (42), 77 (9), 57 (50).

HRMS (ESI) calcd. $[M+H]^+$: 382.18603, found: 382.18630; calcd. $[M+Na]^+$: 404.16797, found: 404.16809.

$[\alpha]_\lambda^{20}$ (0.62 g/100 mL in $CHCl_3$): $[\alpha]_{365}$ = -391.8 °, $[\alpha]_{436}$ = -231.3 °, $[\alpha]_{546}$ = -128.8 °, $[\alpha]_{579}$ = -111.5 °, $[\alpha]_{589}$ = -106.5 °.

10.2.10.5 Synthesis of (*S*)-1-carboxy-*N*-(1-carboxyethyl)-2-(4-hydroxyphenyl)-ethan-1-aminium chloride (250·HCl)

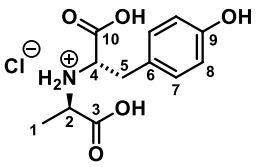


(*R,S*)-**252** (*R,S*)-**260** (*R,S*)-**250·HCl**

An argon-flooded *Schlenk* flask was charged with 36.0 mg (94.4 µmol, 1.00 eq.) of Boc-protected amine (*R,S*)-**252** dissolved in 0.47 mL dry CH_2Cl_2. At 0 °C, 20.7 µL (0.113 mmol, 1.20 eq.) of TMSOTf were added and the reaction mixture was stirred at rt for 25 minutes until full conversion was indicated by TLC. The reaction was quenched with 5 mL sat. aq. $NaHCO_3$-solution. The aqueous phase was extracted three times with 10 ml CH_2Cl_2. The combined organic layers were dried over $MgSO_4$ and the solvent was removed under reduced pressure to afford 25 mg (89 µmol, 94%) of amine **260** which was directly used within the next step.

A round-bottom flask was charged with 25 mg (89 µmol, 1.00 eq.) of amine (*R,S*)-**260** and 10.0 mg (0.418 mmol, 4.70 eq.) of LiOH dissolved in 0.45 mL MeOH/H_2O (2:1). After stirring at rt for 16 h, full conversion was indicated by TLC and 1 N HCl was added until pH 1 was reached. The solvent was removed under reduced pressure. The resulting solid was washed with cold H_2O to afford the desired product (*R,S*)-**250·HCl** as a colourless solid.

Note: The product contains LiCl.



(*R,S*)-**250·HCl**:

M($C_{12}H_{16}ClNO_5$) 289.71 g/mol.

^{1}H NMR (500 MHz, D_2O) δ [ppm] = 7.22 (d, $^3J_{HH}$ = 8.6 Hz, 2H, H-7), 6.90 (d, $^3J_{HH}$ = 8.6 Hz, 2H, H-8), 4.02 (t, $^3J_{HH}$ = 6.6 Hz, 1H, H-4), 3.75 (q, $^3J_{HH}$ = 7.3 Hz, 1H, H-5), 3.24-3.17 (m, 2H, H-5), 1.44 (d, $^3J_{HH}$ = 7.3 Hz, 3H, H-1).

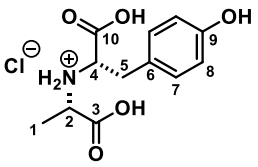
FT-IR (ATR) ν [cm^{-1}] = 3377 (br), 3160 (m), 3021 (w), 2821 (w), 2507 (w), 1742 (m), 1614 (m), 1595 (m), 1557 (m), 1515 (m), 1470 (m), 1436 (m), 1385 (m), 1332 (m), 1304 (m), 1252 (m), 1222 (s), 1174 (m), 1158 (m), 1134 (m), 1105 (m), 1054 (m), 1013 (m), 969 (m), 931 (w), 875 (m), 841 (m), 819 (m), 786 (m), 764 (m), 739 (m), 714 (m), 653 (m), 620 (m), 577 (s), 561 (s), 525 (s).

HRMS (ESI) calcd. $[M\text{-}Cl]^+$: 254.10230, found: 254.10247.

Due to solubility issued no ^{13}C-spectrum could be recorded.

(*S,S*)-**250·HCl**:

The corresponding (*S,S*)-amine **250·HCl** was obtained by reacting 71.0 mg (0.186 mmol, 1.00 eq.) of amine *(S,S)*-**252** and 40.9 µL (0.223 mmol, 1.20 eq.) of TMSOTf in 0.90 mL dry CH_2Cl_2. The crude product was directly used within the next step and reacted with 22.0 mg (0.919 mmol, 4.94 eq.) of LiOH in 0.93 mL MeOH/H_2O (2:1) to afford the desired product (*S,S*)-**250·HCl** as a colourless solid.



Note: The product contains LiCl.

M($C_{12}H_{16}ClNO_5$) 289.71 g/mol.

^{1}H NMR (500 MHz, D_2O) δ [ppm] = 7.22 (d, $^3J_{HH}$ = 8.6 Hz, 2H, H-7), 6.90 (d, $^3J_{HH}$ = 8.6 Hz, 2H, H-8), 4.03 (t, $^3J_{HH}$ = 6.9 Hz, 1H, H-4), 3.81 (q, $^3J_{HH}$ = 7.3 Hz, 1H, H-2), 3.19 (qd, $^3J_{HH}$ = 14.6, 6.9 Hz, 2H, H-5), 1.52 (d, $^3J_{HH}$ = 7.2 Hz, 3H, H-1).

^{13}C NMR (126 MHz, D_2O) δ [ppm] = 190.8 (C-3, C-10), 154.9 (C-9), 130.8 (C-7), 129.2 (C-6), 115.8 (C-8), 62.6 (C-4), 57.1 (C-2), 35.3 (C-5), 15.5 (C-1).

FT-IR (ATR) ν [cm^{-1}] = 3377 (br), 3160 (m), 3021 (w), 2821 (w), 2507 (w), 1742 (m), 1614 (m), 1595 (m), 1557 (m), 1515 (m), 1470 (m), 1436 (m), 1385 (m), 1332

(m), 1304 (m), 1252 (m), 1222 (s), 1174 (m), 1158 (m), 1134 (m), 1105 (m), 1054 (m), 1013 (m), 969 (m), 931 (w), 875 (m), 841 (m), 819 (m), 786 (m), 764 (m), 739 (m), 714 (m), 653 (m), 620 (m), 577 (s), 561 (s), 525 (s).

HRMS (ESI) calcd. $[M\text{-}Cl]^+$: 254.10230, found: 254.10247.

11 References

[1] A. Zhang, A. L. Demain, *Natural Products - Drug Discovery and Therapeutic Medicine*, Humana Press, Totowa, New Jersey, **2005**.

[2] D. J. Newman, G. M. Cragg, *J. Nat. Prod.* **2020**, *83*, 770-803.

[3] D. J. Newman, *Natl. Sci. Rev.* **2022**, *9*, nwac206.

[4] G. M. Cragg, J. M. Pezzuto, *Med. Princ. Prac.* **2016**, *25*, 41-59.

[5] A. G. Atanasov, B. Waltenberger, E.-M. Pferschy-Wenzig, T. Linder, C. Wawrosch, P. Uhrin, V. Temml, L. Wang, S. Schwaiger, E. H. Heiss, *Biotechnol. Adv.* **2015**, *33*, 1582-1614.

[6] A. G. Atanasov, S. B. Zotchev, V. M. Dirsch, I. E. Orhan, M. Banach, J. M. Rollinger, D. Barreca, W. Weckwerth, R. Bauer, E. A. Bayer, M. Majeed, A. Bishayee, V. Bochkov, G. K. Bonn, N. Braidy, F. Bucar, A. Cifuentes, G. D'Onofrio, M. Bodkin, M. Diederich, A. T. Dinkova-Kostova, T. Efferth, K. El Bairi, N. Arkells, T.-P. Fan, B. L. Fiebich, M. Freissmuth, M. I. Georgiev, S. Gibbons, K. M. Godfrey, C. W. Gruber, J. Heer, L. A. Huber, E. Ibanez, A. Kijjoa, A. K. Kiss, A. Lu, F. A. Macias, M. J. S. Miller, A. Mocan, R. Müller, F. Nicoletti, G. Perry, V. Pittalà, L Rastrelli, M. Ristow, G. L. Russo, A. S. Silva, D. Schuster, H. Sheridan, K. Skalicka-Woźniak, L Skaltsounis, E. Sobarzo-Sánchez, D. S. Bredt, H. Stuppner, A. Sureda, N. T. Tzvetkov, R. A. Vacca, B. B. Aggarwal, M. Battino, F. Giampieri, M. Wink, J.-L. Wolfender, J. Xiao, A. W. K. Yeung, G. Lizard, M. A. Popp, M. Heinrich, I. Berindan-Neagoe, M. Stadler, M. Daglia, R. Verpoorte, C. T. Supuran, the International Natural Product Sciences Taskforce, *Nat. Rev. Drug Discov.* **2021**, *20*, 200-216.

[7] G. J. Wørmer, T. B. Poulsen, *Synlett* **2022**, *33*, 637-654.

[8] A. P. Kozikowski, P. U. Park, *J. Am. Chem. Soc.* **1985**, *107*, 1763-1765.

[9] C. J. Flann, L. E. Overman, *J. Am. Chem. Soc.* **1987**, *109*, 6115-6118.

[10] H. Yamada, S. Aoyagi, C. Kibayashi, *J. Am. Chem. Soc.* **1996**, *118*, 1054-1059.

[11] S. Huang, D. L. Comins, *Chem. Commun.* **2000**, *7*, 569-570.

[12] F. Li, N. C. Warshakoon, M. J. Miller, *J. Org. Chem.* **2004**, *69*, 8836-8841.

[13] B. M. Trost, C. K. Chung, A. B. Pinkerton, *Angew. Chem. Int. Ed.* **2004**, *43*, 4327-4329.

[14] J. Holmalahti, O. Raatikainen, A. von Wright, H. Laatsch, A. Spohr, O. K. Lyngbergn J. Nielsen, *J. Appl. Microbiol.* **1998**, *85*, 61-68.

[15] C. Puder, P. Krastel, A. Zeeck, *J. Nat. Prod.* **2000**, *63*, 1258-1260.

[16] T. Akiyama, S. Harada, F. Kojima, N. Kojima, M. Hamada, Y. Muraoka, T. Aoyagi, T. Takeuchi *J. Antibiot.* **1998**, *51*, 253-260.

[17] T. Akiyama, R. Sawa, H. Naganawa, Y. Muraoka, T. Aoyagi, T. Takeuchi, *J. Antibiot.* **1998**, *51*, 372-373.

[18] M.-B. Maes, S. Scharpé, I. De Meester, *Clin. Chim. Acta* **2007**, *380*, 31-49.

[19] S.-H. Hong, Y. H. Ban, W. S. Byun, D. Kim, Y.-J. Jang, J. S. An, B. Shin, S. K. Lee, J. Shin, Y. J. Yoon, D.-C. Oh, *J. Nat. Prod.* **2019**, *82*, 903-910.

[20] S. Ohno, Y. Katsuyama, Y. Tajima, M. Izumikawa, M. Takagi, M. Fujie, N. Satoh, K. Shin-ya, Y. Ohnishi, *ChemBioChem* **2015**, *16*, 2385-2391.

[21] M. Mayer, R. Thiericke, *J. Org. Chem.* **1993**, *58*, 3486-3489.

[22] H. Drautz, H. Zähner, E. Kupfer, W. Keller-Schierlein, *Helv. Chim. Acta* **1981**, *64*, 1752-1765.

[23] A. P. Kozikowski, P. U. Park, *J. Org. Chem.* **1984**, *49*, 1674-1676.

[24] F. Li, M. J. Miller, *J. Org. Chem.* **2006**, *71*, 5221-5227.

[25] G. J. Wørmer, N. L. Villadsen, P. Nørby, T. B. Poulsen, *Angew. Chem.* **2021**, *133*, 10615-10619.

[26] O. Pàmies, J. Margalef, S. Cañellas, J. James, E. Judge, P. J. Guiry, C. Moberg, J.-E. Bäckvall, A. Pfaltz, M. A. Pericàs, M. Diéguez, *Chem. Rev.* **2021**, *121*, 4373-4505.

[27] B. M. Trost, M. L. Crawley, *Chem. Rev.* **2003**, *103*, 2921-2944.

[28] B. M. Trost, D. L. Van Vranken, *Chem. Rev.* **1996**, *96*, 395-422.

[29] C. Moberg, *Molybdenum-Catalyzed Asymmetric Allylic Alkylations* (in *Organic Reactions*), Wiley & Sons Ltd, New Jersey, **2014**.
[30] B. M. Trost, M. Rao, A.P. Dieskau, *J. Am. Chem. Soc.* **2013**, *135*, 18697-18704.
[31] N. Kanbayashi, K. Hosoda, M. Kato, K. Takii, T.-A. Okamura, K. Onitsuka, *Chem. Commun.* **2015**, *51*, 10895-10898.
[32] M. B. Thoke, Q. Kang, *Synthesis* **2019**, *51*, 2585-2631.
[33] D. Ghorai, À. Cristòfol, A. W. Kleij, *Eur. J. Inorg. Chem.* **2022**, *2*, e202100820.
[34] R. Takeuchi, M. Kashio, *Angew. Chem. Int. Ed.* **1997**, *36*, 263-265.
[35] Q. Cheng, H.-F, Tu, C. Zheng, J.-P. Qu, G. Helmchen, S.-L. You, *Chem. Rev.* **2019**, *119,* 1855-1969.
[36] J. P. Janssen, G. Helmchen, *Tetrahedron Lett.* **1997**, *38*, 8025-8026.
[37] B. L. Feringa, M. Pineschi, L. A. Arnold, R. Imbos, A. H. de Vries, *Angew. Chem. Int. Ed.* **1997**, *36*, 2620-2623.
[38] A. H. de Vries, A. Meetsma, B. L. Feringa, *Angew. Chem. Int. Ed.* **1996**, *35*, 2374-2376.
[39] G. Helmchen, A. Dahnz, P. Dübon, M. Schelwies, R. Weihofen, *Chem. Commun.* **2007**, *7*, 675-691.
[40] T. Ohmura, J. F. Hartwig, *J. Am. Chem. Soc.* **2002**, *124*, 15164-15165.
[41] C. A. Kiener, C. Shu, C. Incarvito, J. F. Hartwig, *J. Am. Chem. Soc.* **2003**, *125*, 14272-14273.
[42] J. F. Hartwig, L. M. Stanley, *Acc. Chem. Res.* **2010**, *43*, 1461-1475.
[43] J. A. Raskatov, C. Spiess, C. Gnamm, K. Brödner, F. Rominger, G. Helmchen, *Chem. Eur. J.* **2010**, *16*, 6601-6615.
[44] D. K. Leahy, P. A. Evans, *Modern Rhodium-Catalyzed Organic Reactions*, Wiley-VCH, Weinheim, **2005**.
[45] B. Bartels, C. García-Yebra, F. Rominger, G. Helmchen, *Eur. J. Inorg. Chem.* **2002**, *10*, 2569-2586.
[46] S. T. Madrahimov, D. Markovic, J. F. Hartwig, *J. Am. Chem. Soc.* **2009**, *131*, 7228-7229.
[47] S. Spiess, J. A. Raskatov, C. Gnamm, K. Brödner, G. Helmchen, *Chem. Eur. J.* **2009**, *15*, 11087-11090.
[48] W.-B. Liu, C. Zheng, C.-X. Zhou, L.-X. Dai, S.-L. You, *J. Am. Chem. Soc.* **2012**, *134*, 4812-4821.
[49] S. T. Madrahimov, Q. Li, A. Sharma, J. F. Hartwig, *J. Am. Chem. Soc.* **2015**, *137*, 14968-14981.
[50] J. A. Raskatov, M. Jäkel, B. F. Straub, F. Rominger, G. Helmchen, *Chem. Eur. J.* **2012**, *18*, 14314-14328.
[51] S. Spiess, C. Welter, G. Franck, J. P. Tacquet, G. Helmchen, *Angew. Chem. Int. Ed.* **2008**, *47*, 7652-7655.
[52] S. Foerster, O. Tverskoy, G. Helmchen, *Synlett* **2008**, *18*, 2803-2806.
[53] M. Gärtner, G. Satyanarayana, S. Förster, G. Helmchen, *Chem. Eur. J.* **2013**, *19*, 400-405.
[54] W. Chen, J. F. Hartwig, *J. Am. Chem. Soc.* **2012**, *134*, 15249-15252.
[55] T. Graening, J. F. Hartwig, *J. Am. Chem. Soc.* **2005**, *127*, 17192-17193.
[56] S. Krautwald, M. A. Schafroth, D. Sarlah, E. M. Carreira, *J. Am. Chem. Soc.* **2014**, *136*, 3020-3023.
[57] T. Sandmeier, S. Krautwald, H. F. Zipfel, E. M. Carreira, *Angew. Chem. Int. Ed.* **2015**, *54*, 14363-14367.
[58] D. J. Weix, J. F. Hartwig, *J. Am. Chem. Soc.* **2007**, *129*, 7720-7721.
[59] Q.-L. Xu, L.-X. Dai, S.-L. You, *Org. Lett.* **2012**, *14*, 2579-2581.
[60] C.-X. Zhuo, W.-B. Liu, Q.-F. Wu, S.-L. You, *Chem. Sci.* **2012**, *3*, 205-208.
[61] W.-B. Liu, H. He, L.-X. Dai, S.-L. You, *Org. Lett.* **2008**, *10*, 1815-1818.
[62] A. Dahnz, G. Helmchen, *Synlett* **2006**, *5*, 697-700.
[63] C. Shu, A. Leitner, J. F. Hartwig, *Angew. Chem. Int. Ed.* **2004**, *43*, 4797-4800.
[64] P. Tosatti, J. Horn, A. J. Campbell, D. House, A. Nelson, S. P. Marsden, *Adv. Synth. Cat.* **2010**, *352*, 3153-3157.

[65] R. Takeuchi, N. Ue, K. Tanabe, K. Yamashita, N. Shiga, *J. Am. Chem. Soc.* **2001**, *123*, 9525-9534.
[66] D. Polet, A. Alexakis, K. Tissot-Croset, C. Corminboeuf, K. Ditrich, *Chem. Eur. J.* **2006**, *12*, 3596-3609.
[67] B. Bartels, G. Helmchen, *Chem. Commun.* **1999**, *8*, 741-742.
[68] D. Albat, A. Köcher, J. Witt, H.-G. Schmalz, *Eur. J. Org. Chem.* **2022**, *12*, e202200188.
[69] X. Zhang, W.-B. Liu, Q. Cheng, S.-L. You, *Organometallics* **2016**, *35*, 2467-2472.
[70] C. Welter, R. M. Moreno, S. Streiff, G. Helmchen, *Org. Biomol. Chem.* **2005**, *3*, 3266-3268.
[71] C. Ande, S. Dubbu, A. K. Verma, Y. D. Vankar, *Tetrahedron Lett.* **2018**, *59*, 1879-1895.
[72] M. Jäkel, J. Qu, T. Schnitzer, G. Helmchen, *Chem. Eur. J.* **2013**, *19*, 16746-16755.
[73] M. Gärtner, M. Jäkel, M. Achatz, C. Sonnenschein, O. Tverskoy, G. Helmchen, *Org. Lett.* **2011**, *13*, 2810-2813.
[74] W. McGrath, W. Kuhn, *Arch. Int. Pharmacodyn. Ther.* **1968**, *172*, 405-413.
[75] J. Qu, G. Helmchen, *Acc. Chem. Res.* **2017**, *50*, 2539-2555.
[76] L. Mohammadkhani, M. M. Heravi, *Chem. Rec.* **2021**, *21*, 29-68.
[77] R. Huisgen, *Angew. Chem. Int. Ed.* **1963**, *2*, 565-598.
[78] H. C. Kolb, M. Finn, K. B. Sharpless, *Angew. Chem. Int. Ed.* **2001**, *40*, 2004-2021.
[79] C. W. Tornøe, C. Christensen, M. Meldal, *J. Org. Chem.* **2002**, *67*, 3057-3064.
[80] N. J. Agard, J. M. Baskin, J. A. Prescher, A. Lo, C. R. Bertozzi, *ACS Chem. Biol.* **2006**, *1*, 644-648.
[81] J. R. Nagireddy, G. K. Tranmer, E. Carlson, W. Tam, *Beilstein J. Org. Chem.* **2014**, *10*, 2200-2205.
[82] T. Hashimoto, K. Maruoka, *Chem. Rev.* **2015**, *115*, 5366-5412.
[83] K.-C. Liu, B. R. Shelton, R. K. Howe, *J. Org. Chem.* **1980**, *45*, 3916-3918.
[84] D. E. Kizer, R. B. Miller, M. J. Kurth, *Tetrahedron Lett.* **1999**, *40*, 3535-3538.
[85] A. Yoshimura, K. R. Middleton, A. D. Todora, B. J. Kastern, S. R. Koski, A. V. Maskaev, V. V. Zhdankin, *Org. Lett.* **2013**, *15*, 4010-4013.
[86] T. Mukaiyama, T. Hoshino, *J. Am. Chem. Soc.* **1960**, *82*, 5339-5342.
[87] P. N. Confalone, E. D. Lollar, G. Pizzolato, M. R. Uskokovic, *J. Am. Chem. Soc.* **1978**, *100*, 6291-6292.
[88] K. V. Gothelf, K. A. Jørgensen, *Chem. Commun.* **2000**, *16*, 1449-1458.
[89] R. Grigg, S. Thianpantangul, *J. Am. Chem. Soc. Perk. Trans. 1* **1984**, 653-656.
[90] M. S. Singh, S. Chowdhury, S. Koley, *Tetrahedron* **2016**, *72*, 1603-1644.
[91] M. Berthet, T. Cheviet, G. Dujardin, I. Parrot, J. Martinez, *Chem. Rev.* **2016**, *116*, 15235-15283.
[92] P. N. Confalone, E. M. Huie, *The [3 + 2] Nitrone–Olefin Cycloaddition Reaction* (in *Organic Reactions*), Wiley & Sons Ltd, New Jersey, **2004**.
[93] M. Breugst, H.-U. Reissig, *Angew. Chem. Int. Ed.* **2020**, *59*, 12293-12307.
[94] C. Nájera, J. M. Sansano, *Org. Biomol. Chem.* **2009**, *7*, 4567-4581.
[95] M. Nitta, T. Kobayashi, *Chem. Commun.* **1982**, *15*, 877-878.
[96] P. G. Baraldi, A. Barco, S. Benetti, S. Manfredini, D. Simoni, *Synthesis* **1987**, *3*, 276-278.
[97] J. R. Nagireddy, M.-A. Raheem, J. Haner, W. Tam, *Curr. Org. Synth.* **2011**, *8*, 659-700.
[98] L. I. Gelabert, M. L. Fascio, N. B. D'Accorso, *J. Heterocycl. Chem.* **2003**, *40*, 341-344.
[99] P. G. Baraldi, R. Bazzanini, A. Bigoni, S. Manfredini, D. Simoni, G. Spalluto, *Synthesis* **1993**, *12*, 1206-1208.
[100] D. P. Curran, P. B. Jacobs, *Tetrahedron Lett.* **1985**, *26*, 2031-2034.
[101] D. P. Curran, *J. Am. Chem. Soc.* **1983**, *105*, 5826-5833.
[102] S. H. Jeong, S. H. Jeong, H. J. Seong, S. O. Kim, *Bull. Kor. Chem. Soc.* **1996,** *17*, 2-4.
[103] F. Ma, C. He, E. Wang, R. Tong, *Org. Lett.* **2021**, *23*, 6583-6588.
[104] T. Wilczek, *Contributions to the development of new agents for tumor therapy: Synthesis of 7,19-epoxysteroids as well as precursors of the natural product camporidine A*, Universität zu Köln, Köln, **2023**.

[105] A. P. Kozikowski, P. U. Park, *J. Am. Chem. Soc.* **1985**, *107*, 1763-1765.
[106] K. Kitahara, T. Toma, J. Shimokawa, T. Fukuyama, *Org. Lett.* **2008**, *10*, 2259-2261.
[107] B. R. McNaughton, K. M. Bucholtz, A. Camaaño-Moure, B. L. Miller, *Org. Lett.* **2005**, *7*, 733-736.
[108] A. H. F. Lee, A. S. C. Chan, T. Li, *Tetrahedron* **2003**, *59*, 833-839.
[109] M. Wünsch, D. Schröder, T. Fröhr, L. Teichmann, S. Hedwig, N. Janson, C. Belu, J. Simon, S. Heidemeyer, P. Holtkamp, J. Rudlof, L. Klemme, A. Hinzmann, B. Neumann, H.-G. Stammler, N. Sewald, *Beilstein J. Org. Chem.* **2017**, *13*, 2428-2441.
[110] E. M. Stang, M. C. White, *J. Am. Chem. Soc.* **2011**, *133*, 14892-14895.
[111] F. Lucchesini, *Tetrahedron* **1992**, *48*, 9951-9966.
[112] M. Joubert, A. Defoin, C. Tarnus, J. Streith, *Synlett* **2000**, *9*, 1366-1368.
[113] H. Gradén, J. Hallberg, N. Kann, T. Olsson, *J. Comb. Chem.* **2004**, *6*, 783-788.
[114] J. Ihsen, U. Spitz, D. Shabat, O. Green, N. Hananya, *Long Wavelength Emitting Chemiluminescent Probes*, WO2019224339A1, **2019**.
[115] K. C. Nicolaou, D. L. F. Scott, T. Montagnon, S. T. Harrison, *Angew. Chem. Int. Ed.* **2002**, *41*, 996-1000.
[116] K. C. Nicolaou, T. Montagnon, P. S. Baran, Y. L. Zhong, *J. Am. Chem. Soc.* **2002**, *124*, 2245-2258.
[117] D. Albat, *Stereoselektive Palladium- und Iridium-katalysierte N-Allylierung von Aminosäureestern und die Synthese von PPII-Sekundärstrukturmimetika als Metastase-Inhibitoren*, Universität zu Köln, Köln, **2021**.
[118] T. R. Wu, L. Shen, J. M. Chong, *Org. Lett.* **2004**, *6*, 2701-2704.
[119] E. Byun, B. Hong, K. A. De Castro, M. Lim, H. Rhee, *J. Org. Chem.* **2007**, *72*, 9815-9817.
[120] R. A. Al-Horani, A. Y. Mehta, U. R. Desai, *Eur. J. Med. Chem.* **2012**, *54*, 771-783.
[121] M. Vuagnoux-d'Augustin, A. Alexakis, *Chem. Eur. J.* **2007**, *13*, 9647-9662.
[122] I. S. Mikhel, H. Rüegger, P. Butti, F. Camponovo, D. Huber, A. Mezzetti, *Organometallics* **2008**, *27*, 2937-2948.
[123] V. K. Yadav, K. G. Babu, *Tetrahedron* **2003**, *59*, 9111-9116.
[124] T. Matveeva, L. Otten, *Phytochemistry* **2021**, *189*, 112813.
[125] Y. A. Dessaux, A. Petit, J. Tempe, *Phytochemistry* **1993**, *34***,** 31-38.
[126] K. Morizawa, *Acta Scholae Medicinalis Universitatis in Kioto* **1927**, *9*, 285-298.
[127] J. H. Fields, A. K. Eng, W. D. Ramsden, P. W. Hochaka, B. Weinstein, *Arch. Biochem. Biophys.* **1980**, *201***,** 110-114.
[128] M. Sato, M Takahara, N. Nanno, Y. Sato, W. R. Ellington, *Comp. Biochem. Physiol. B* **1987**, *88*, 803-806.
[129] A. Goldmann, D. Thomas, G. Morel, *CR Acad. Sci. Paris* **1969**, *268*, 852-854.
[130] E. Davioud, A. Petit, M. E. Tate, M. H. Ryder, J. Tempé, *Phytochemistry* **1988**, *27*, 2429-2433.
[131] W. S. Chilton, J. Tempé, M. Matzke, M. D. Chilton, *J. Bacteriol.* **1984**, *157*, 357-62.
[132] N. O. Gomez, A. Tetard, L. Ouerdane, C. Laffont, C. Brutesco, G. Ball, R. Lobinski, Y. Denis, P. Plésiat, C. Llanes, *Mol. Microbiol.* **2021**, *115*, 84-98.
[133] J. S. McFarlane, J. Zhang, S. Wang, X. Lei, G. R. Moran, A. L. Lamb, *J. Biol. Chem.* **2019**, *294*, 17988-18001.
[134] G. Ghssein, C. Brutesco, L. Ouerdane, C. Fojcik, A. Izaute, S. Wang, C. Hajjar, R. Lobinski, D. Lemaire, P. Richaud, *Science* **2016**, *352*, 1105-1109.
[135] J. Zhang, T. Zhao, R. Yang, I. Siridechakorn, S. Wang, Q. Guo, Y. Bai, H. C. Shen, X. Lei, *Chem. Sci.* **2019**, *10*, 6635-6641.
[136] R. Liu, P. A. Miller, S. B. Vakulenko, N. K. Stewart, W. C. Boggess, M. J. Miller, *J. Med. Chem.* **2018**, *61*, 3845-3854.
[137] S. Akashi, *J. Biochem. (Japan)* **1937**, *25*, 281-290.
[138] R. M. Herbst, E. A. Swart, *J. Org. Chem.* **1946**, *11*, 368-377.
[139] N. Izumiya, R. Wade, M. Winitz, M. C. Otey, S. M. Birnbaum, R. J. Koegel, J. P. Greenstein, *J. Am. Chem. Soc.* **1957**, *79*, 652-658.

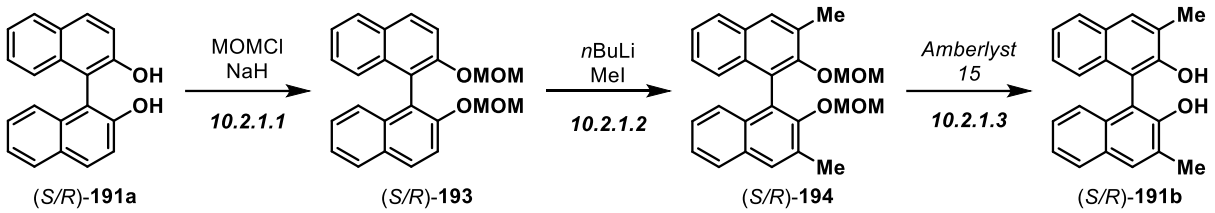
[140] F. Knoop, C. Martius, *Z. Physiol. Chem.* **1939**, *258*, 238-242.
[141] J. Kihlberg, R. Bergman, B. Wickberg, *Acta Chem. Scand. B* **1983**, *37*, 911-916.
[142] D. Albat, J.-M. Neudörfl, H.-G. Schmalz, *Eur. J. Org. Chem.* **2021**, *14*, 2099-2102.
[143] J. Tsuji, H. Takahashi, M. Morikawa, *Tetrahedron Lett.* **1965**, *6*, 4387-4388.
[144] B. M. Trost, P.E. Strege, *J. Am. Chem. Soc.* **1977**, *99*, 1649-1651.
[145] B. M. Trost, T. J. Dietsch, *J. Am. Chem. Soc.* **1973**, *95*, 8200-8201.
[146] B. M. Trost, A. C. Krueger, R. C. Bunt, J. Zambrano, *J. Am. Chem. Soc.* **1996**, *118*, 6520-6521.
[147] B. M. Trost, *Chem. Pharm. Bull.* **2002**, *50*, 1-14.
[148] B. M. Trost, F. D. Toste, *J. Am. Chem. Soc.* **1999**, *121*, 4545-4554.
[149] S. Soriano, M. Escudero-Casao, M. I. Matheu, Y. Díaz, S. Castillón, *Adv. Synth. Cat.* **2016**, *358*, 4057-4066.
[150] S. Soriano, M. Azzouz, J. Llaveria, P. Marcé, M. I. Matheu, Y. Díaz, S. Castillón, *J. Org. Chem.* **2016**, *81*, 5217-5221.
[151] B. M. Trost, T. Zhang, *Angew. Chem. Int. Ed.* **2008**, *47*, 3759-3761.
[152] X. Wang, P. Guo, Z. Han, X. Wang, Z. Wang, K. Ding, *J. Am. Chem. Soc.* **2014**, *136*, 405-411.
[153] L. Hu, A. Cai, Z. Wu, A. W. Kleij, G. Huang, *Angew. Chem.* **2019**, *131*, 14836-14844.
[154] B. M. Trost, T. L. Calkins, C. Oertelt, J. Zambrano, *Tetrahedron Lett.* **1998**, *39*, 1713-1716.
[155] M. E. Humphries, B. P. Clark, J. M. J. Williams, *Tetrahedron Asymmetry* **1998**, *9*, 749-751.
[156] S. Dohmen, M. Reiher, D. Albat, S. Akyol, M. Barone, J.-M. Neudörfl, R. Kühne, H.-G. Schmalz, *Chem. Eur. J.* **2020**, *26*, 3049-3053.
[157] M. Dindaroğlu, S. Akyol Dinçer, H.-G. Schmalz, *Eur. J. Org. Chem.* **2014**, *20*, 4315-4326.
[158] I. Allaman, M. Bélanger, P. J. Magistretti, *Front. Neurosci.* **2015**, *9*, 23.
[159] R. Kold-Christensen, M. Johannsen, *Trends Endocrinol. Metab.* **2020**, *31*, 81-92.
[160] D. E. M. Maessen, C. D. A. Stehouwer, C. G. Schalkwijk, *Clin. Sci.* **2015**, *128*, 839-861.
[161] C. Ott, K. Jacobs, E. Haucke, A. N. Santos, T. Grune, A. Simme, *Redox Biol.* **2014**, *2*, 411-429.
[162] J. Bellier, M.-J. Nokin, E. Lardé, P. Karoyan, O. Peulen, V. Castronovo, A. Bellahcène, *Diabetes Res. Clin. Pract.* **2019**, *148*, 200-211.
[163] V. I. Muronetz, A. K. Melkinova, Z. N. Seferbekova, K. V. Barinova, E. V. Schmalhausen *Biochemistry (Mosc.)* **2017**, *82*, 874-886.
[164] P. J. Thornalley, S. Battah, N. Ahmed, N. Karachalias, S. Agalou, R. Babaei-Jadidi, A. Dawnay, *Biochem. J.* **2003**, *375*, 581-592.
[165] S. W. T. Lai, E. Lopez Gonzalez, T. Zoukari, P. Ki, S. C. Shuck, *Chem. Res. Toxicol.* **2022**, *35*, 1720-1746.
[166] N. Riache, C. Bailly, A. Deville, L. Dubost, B. Nay, *Eur. J. Org. Chem.* **2010**, *28*, 5402-5408.
[167] A. F. Burchat, J. M. Chong, N. Nielsen, *J. Organomet. Chem.* **1997**, *542*, 281-283.
[168] M. A. Berliner, K. Belecki, *J. Org. Chem.* **2005**, *70*, 9618-9621.
[169] S. Beckendorf, O. G. Mancheño, *Synthesis* **2012**, *44*, 2162-2172.
[170] Y. Xu, G. C. Clarkson, G. Docherty, C. L. North, G. Woodward, M. Wills, *J. Org. Chem.* **2005**, *70*, 8079-8087.
[171] T. Ikawa, Y. Fujita, T. Mizusaki, S. Betsuin, H. Takamatsu, T. Maegawa, Y. Monguchi, H. Sajiki, *Org. Biomol. Chem.* **2012**, *10*, 293-304.
[172] D. R. Anton, R. H. Crabtree, *Organometallics* **1983**, *2*, 621-627.
[173] B. M. Trost, J. R. Miller, C. M. Hoffman, *J. Am. Chem. Soc.* **2011**, *133*, 8165-8167.
[174] Y. Zhou, B. Breit, *Chem. Eur. J.* **2017**, *23*, 18156-18160.
[175] L. Wang, T. L. Lowary, *Org. Lett.* **2020**, *22*, 9633-9637.
[176] C. Shen, X. Lu, J. Zhang, L. Ding, Y. Sun, G. Zhong, *Chem. Commun.* **2019**, *55*, 13582-13585.
[177] L.-H. Shiu, Y.-L. Li, C.-L. Li, C.-Y. Lao, Chen, C.-H. Yu, R.-S. Liu, *J. Org. Chem.* **1999**, *64*, 7552-7558.
[178] X.-M. Chen, X.-S. Ning, Y.-B. Kang, *Org. Lett.* **2016**, *18*, 5368-5371.

[179] Z. Al Shuhaib, D. H. Davies, M. Dennis, D. M. Evans, M. D. Fletcher, H. Franken, P. Hancock, J. Hollinshead, I. Jones, K. Kähm, P. J. Murphy, R. Nash, D. Potter, R. Rowles, *Tetrahedron* **2014**, *70*, 4412-4419.
[180] A. Koziara, K. Osowska-Pactwicka, S. Zawadzki, A. Zwierzak, *Synthesis* **1985**, *2*, 202-204.
[181] M. Spacek, J. Drahonovsky, J. Stanek, M. Cerny, K. Jezek, V. Votava, *Production of Phosphonium Salts*, CS228058B1, **1982**.
[182] S. Bruckner, M. Weise, R. Schobert, *J. Org. Chem.* **2018**, *83*, 10805-10812.

12 Overview of reaction sequences

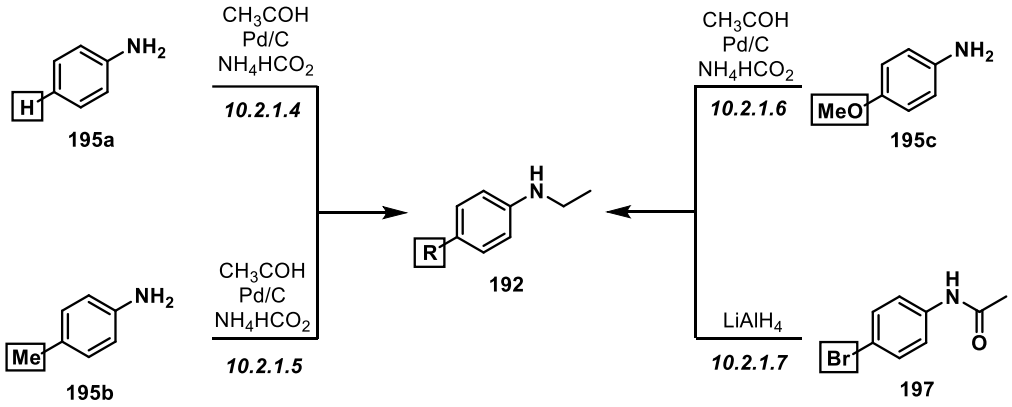
12.1 Phosphoramidite ligands

Synthesis of phosphoramidite ligands – substituted BINOL motif (Chapter 4.3.1.1)



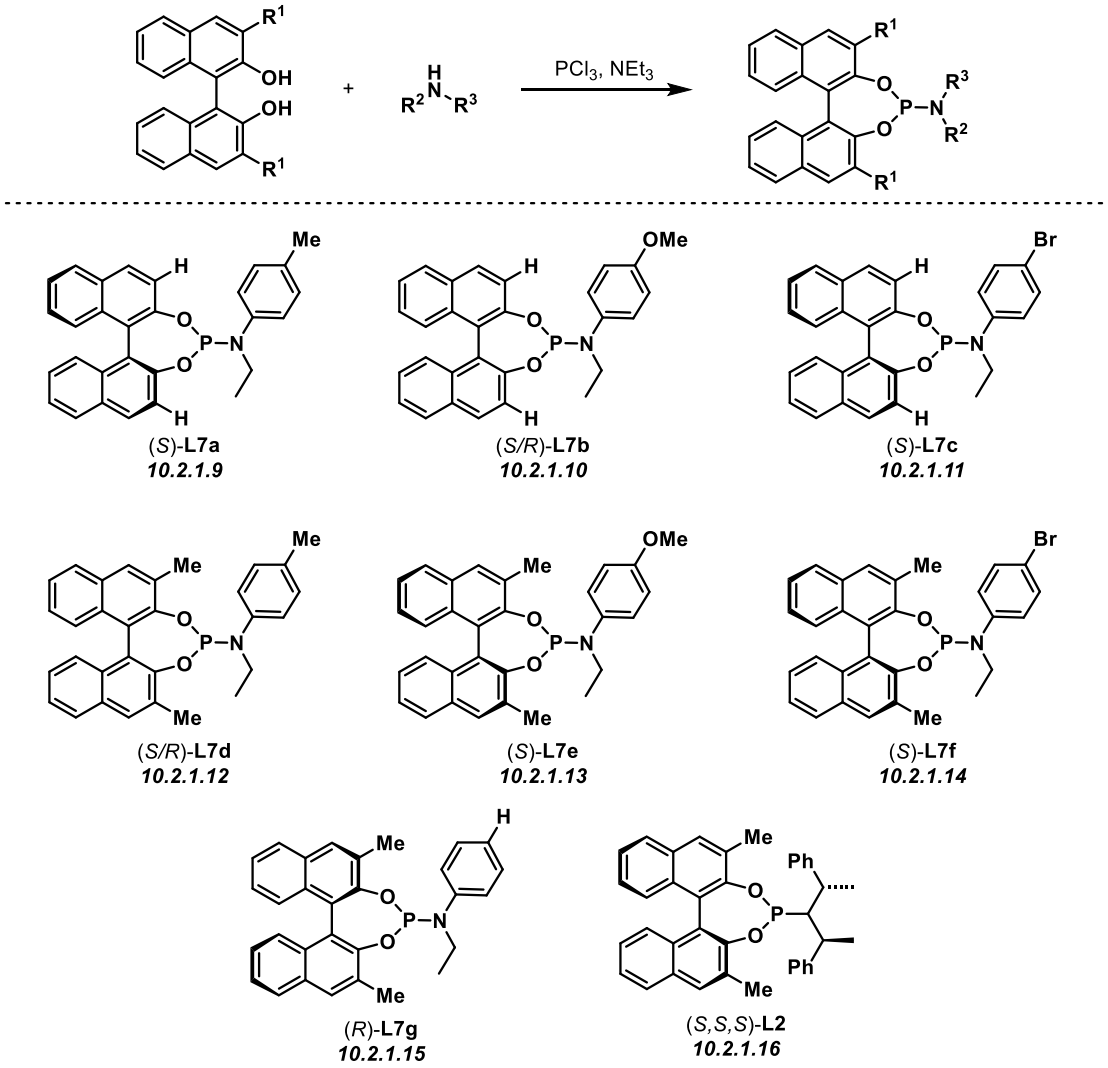
*Scheme 97: Synthesis of dimethyl BINOL **191b**.*

Synthesis of phosphoramidite ligands – aniline building blocks (Chapter 4.3.1.1)



*Scheme 98: Synthesis of substituted aniline-derived building blocks of type **192**.*

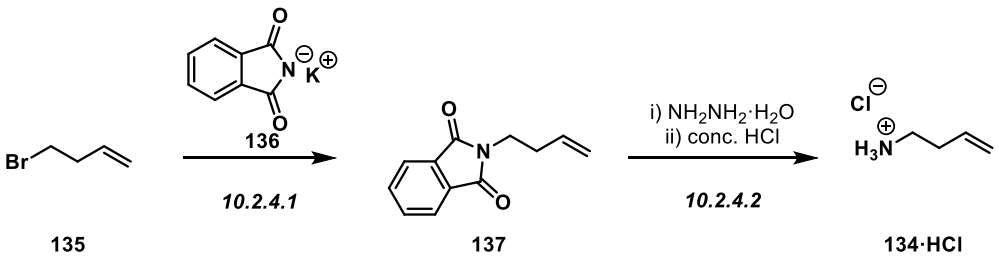
Synthesis of phosphoramidite ligands (Chapter 4.3.1.1)



Scheme 99: Overview of the synthesized phosphoramidite ligands.

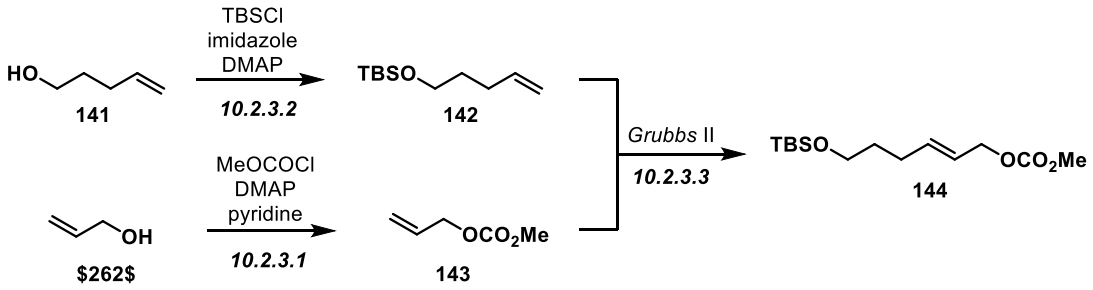
12.2 Synthesis towards camporidine A – test system

Synthesis of the amine building block (Chapter 4.1.1)

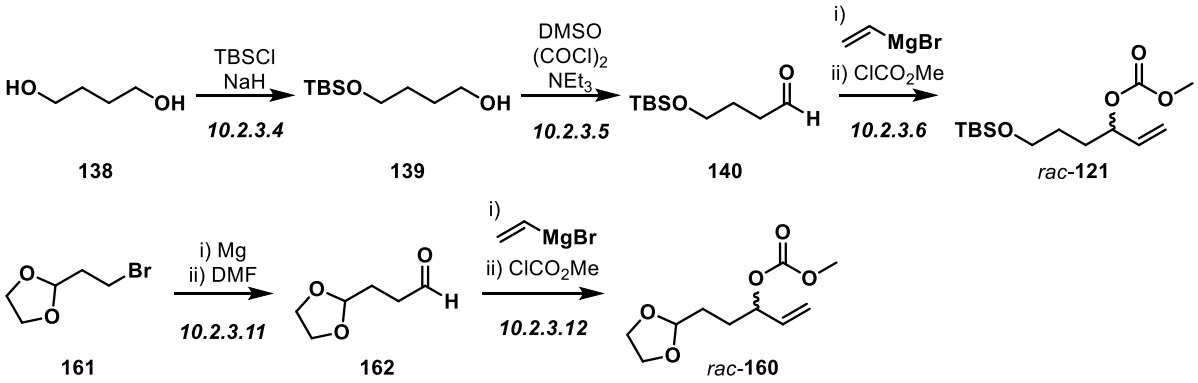


*Scheme 100: Synthesis of the simplified amine building block **134·HCl**.*

Synthesis of carbonates (Chapter 4.1.1 and 4.2.1)

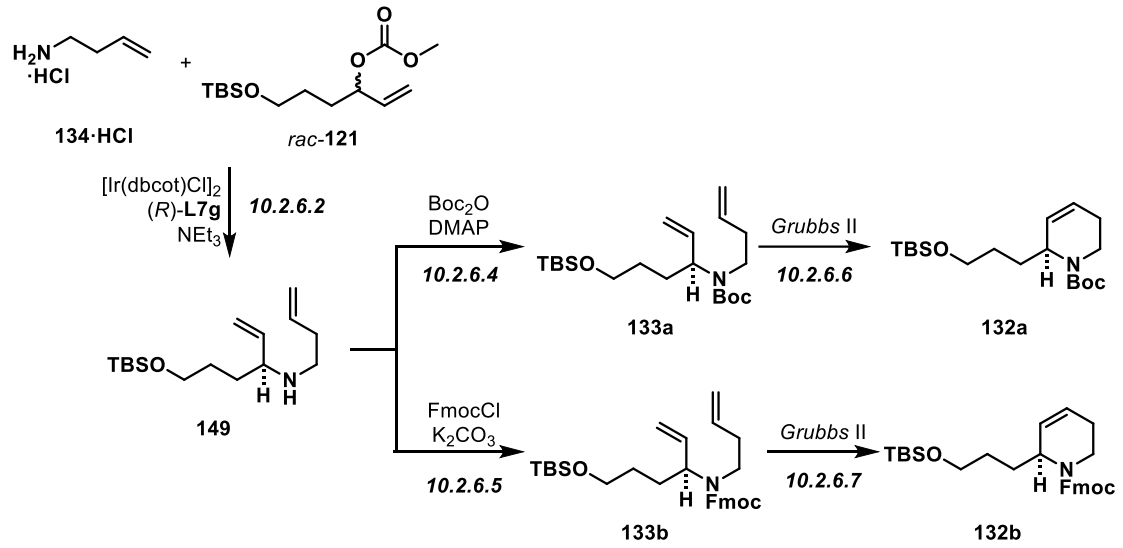


*Scheme 101: Synthesis of linear carbonate **144**.*



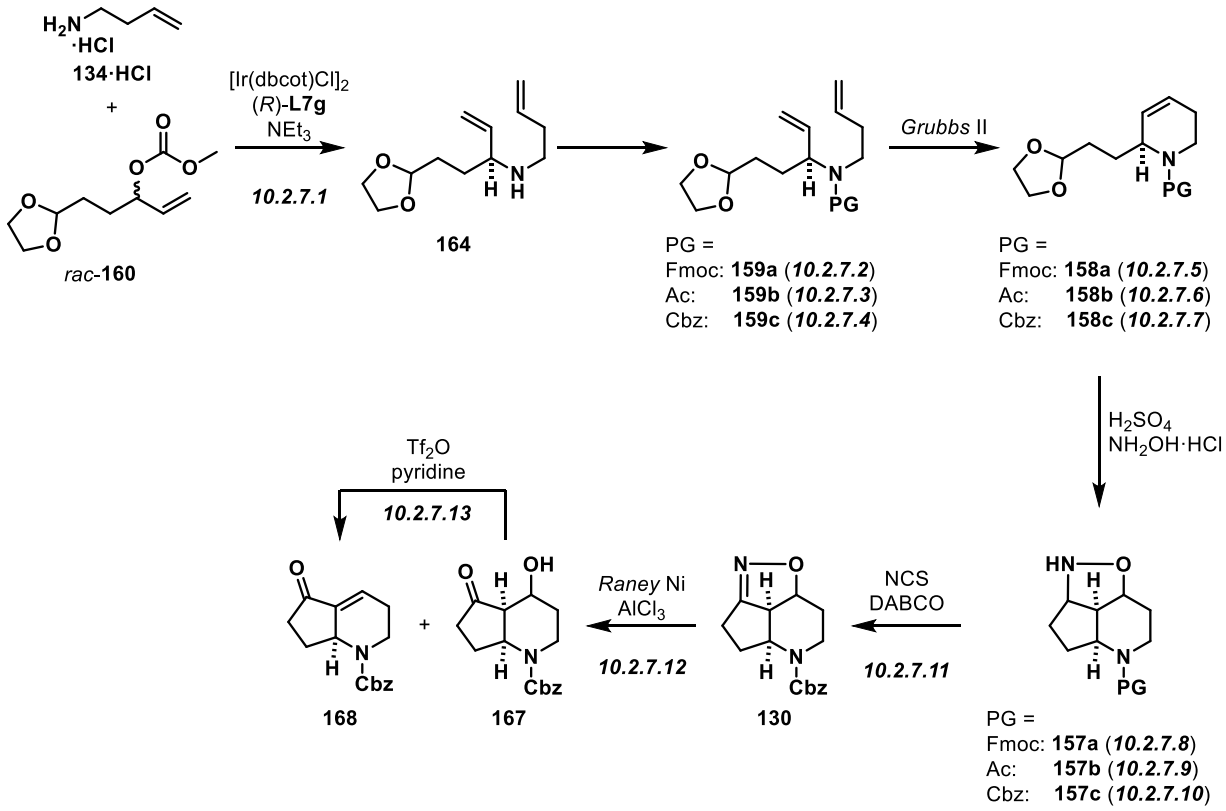
*Scheme 102: Synthesis of branched carbonates rac-**121** and rac-**160**.*

Forward synthesis – attempted *Mitsunobu* approach (Chapter 4.1.1 and 4.1.2)



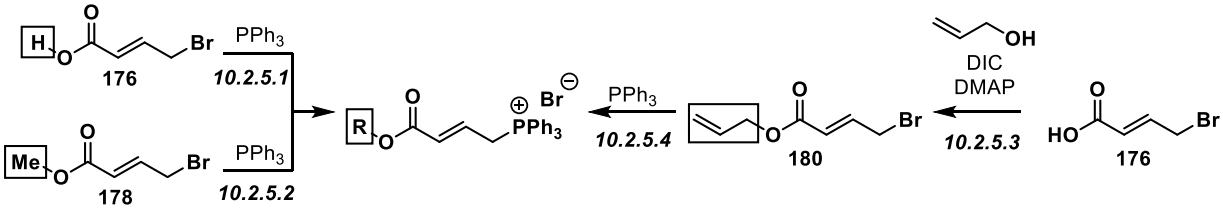
*Scheme 103: Synthesis of protected amines **132**.*

Synthesis of the enone core structure (Chapter 4.2.2 and 4.2.3)



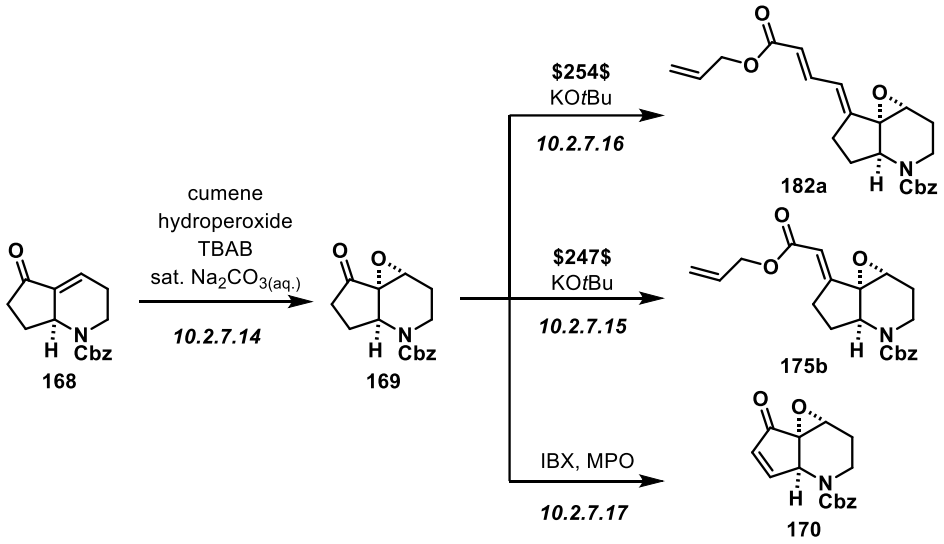
*Scheme 104: Synthetic sequence towards enone core structure **168**.*

Synthesis of *Wittig* reagents (Chapter 4.2.4)



Scheme 105: Synthesis of phosphonium bromides for the Wittig olefination.

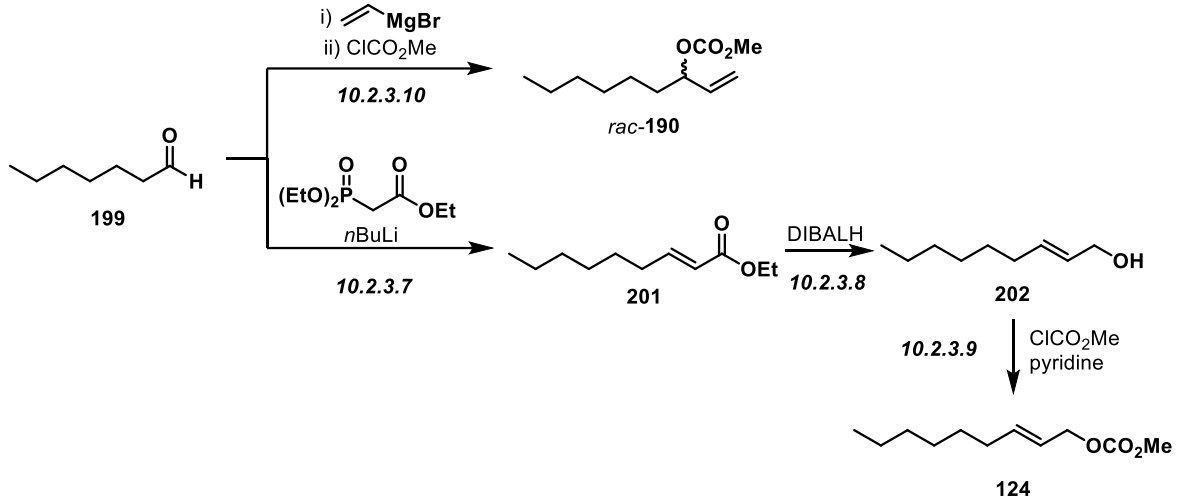
Functionalization of the enone core structure (Chapter 4.2.4)



*Scheme 106: Accomplished functionalizations of the enone core structure **168**.*

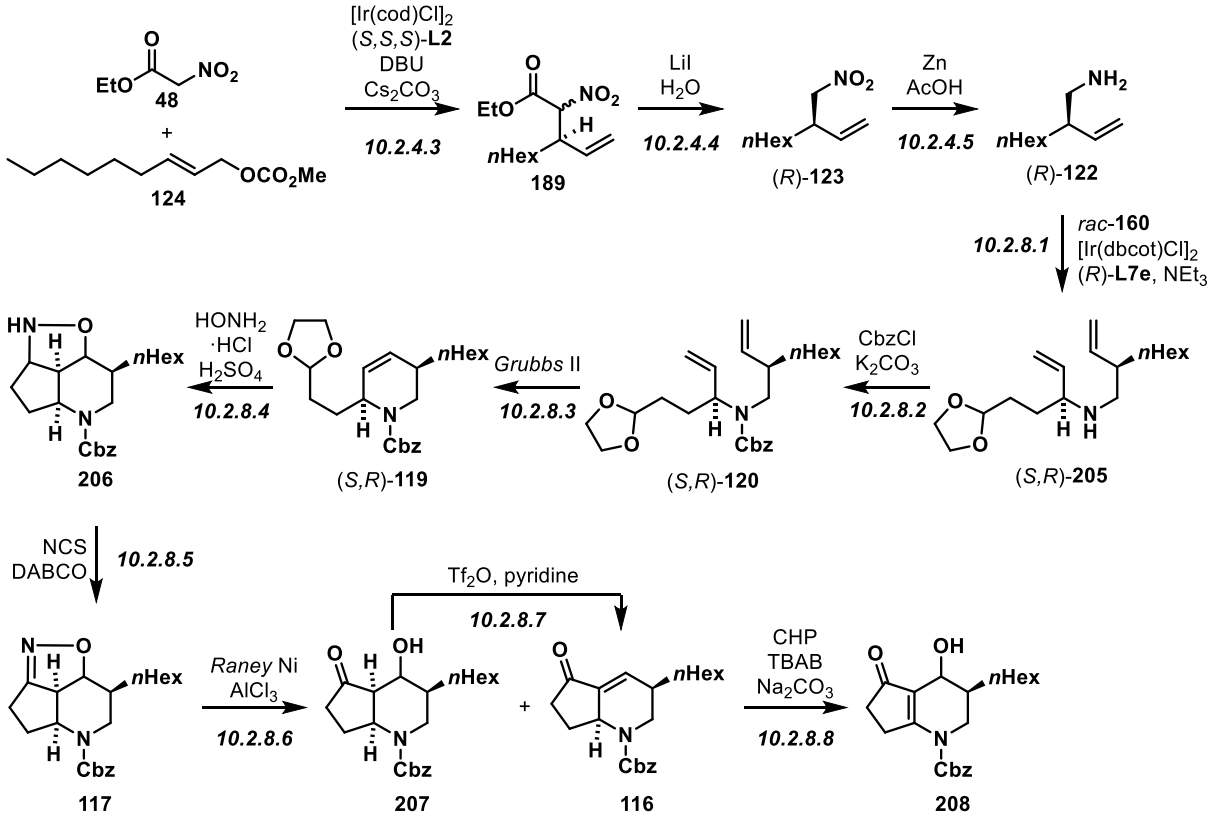
12.3 Synthesis towards camporidine A

Synthesis of carbonates (Chapter 4.3.1.2)



*Scheme 107: Synthesis of branched carbonate rac-**190** and linear carbonate **124**.*

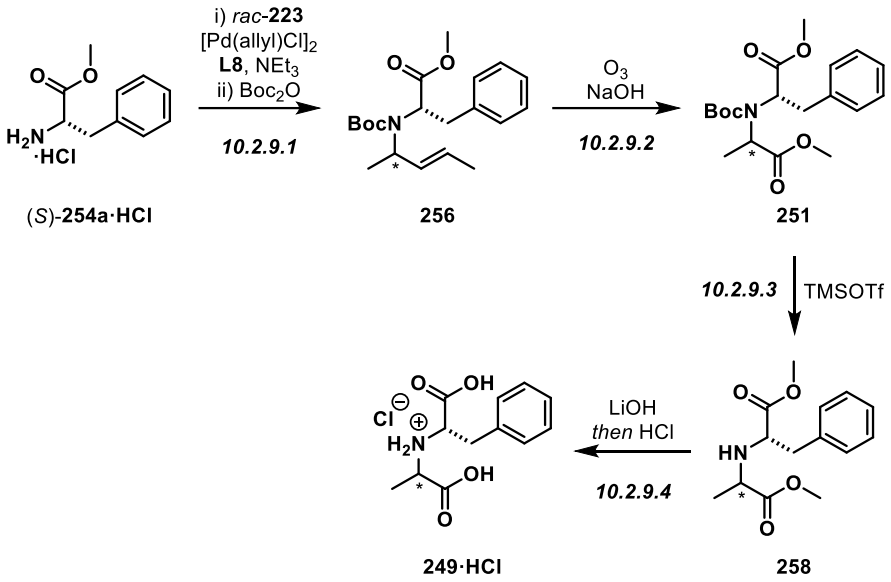
Forward synthesis (Chapter 4.3)



*Scheme 108: Synthetic sequences of the forward synthesis towards camporidine A (**11**).*

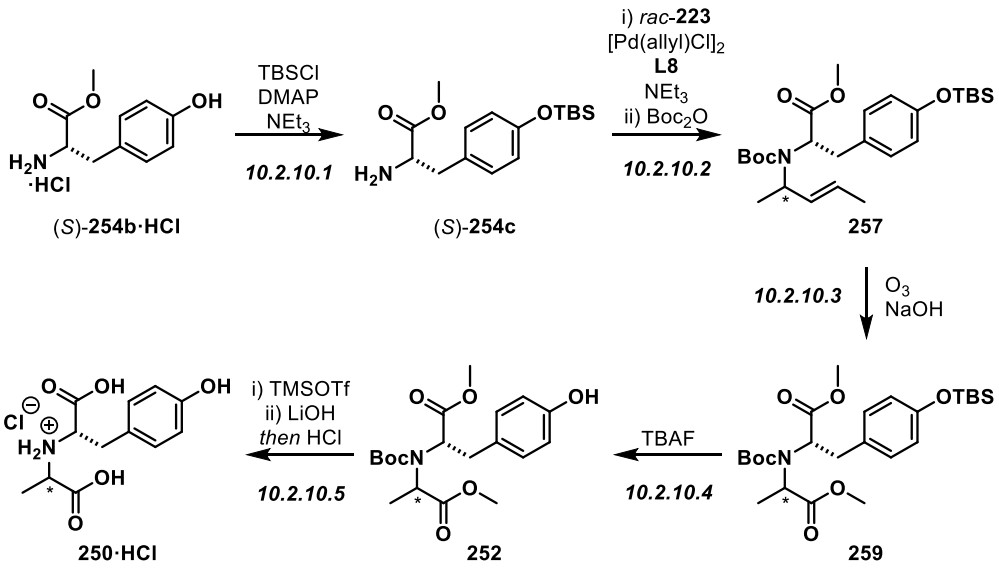
12.4 Synthesis of opines

Synthesis of *N*-CE-Phe (Chapter 8.1 and 8.2.1)



*Scheme 109: Synthesis of N-CE-Phe (**249·HCl**).*

Synthesis of *N*-CE-Tyr (Chapter 8.1 and 8.2.2)



*Scheme 110: Synthesis of N-CE-Tyr (**250·HCl**).*

13 Appendix

13.1 List of abbreviations

Ac	Acetate
AGE	Advanced glycation end products
aq.	aqueous
BINOL	1,1'-Bi-2-naphthol
Boc	*tert*-Butyloxycarbonyl
CA	Cycloaddition
cat.	catalyzed
Cbz	Benzyloxycarbonyl
CC	Cross coupling
CE	Carboxyethyl
CEA	Carboxyethyl-arginine
c-Hex	Cyclohexane
CHP	Cumene hydroperoxide
cod	1,5-Cyclooctadiene
conc.	Concentrated
conv.	Conversion
d.r.	diastereomeric ratio
DABCO	1,4-Diazabicyclo[2.2.2]octane
dbcot	Dibenzo[a,e]cyclooctatetraene
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DEAD	Diethyl azodicarboxylate
decomp.	Decomposition
DFT	Density functional theory
DIAD	Diisopropyl azodicarboxylate
DIBALH	Diisobutylaluminium hydride
DIC	*N,N'*-Diisopropylcarbodiimide
DIPA	Diisopropylamine
DMAP	4-Dimethylaminopyridine
DMF	Dimethylformamide
DMSO	Dimethyl sulfoxide
DNA	Deoxyribonucleic acid
e.g.	*exempli gratia*
ECD	Electronic circular dichroism
ee	enantiomeric excess
eq.	equivalents
et al.	*et alii*
Fmoc	Fluorenylmethoxycarbonyl
GC	Gas chromatography
HPLC	High-performance liquid chromatography
HWE	*Horner-Wadsworth -Emmons*
IBX	2-Iodoxybenzoic acid
KHMDS	Potassium bis(trimethylsilyl)amide
LC	Liquid chromatography
LDA	Lithium diisopropylamide
LG	Leaving group
Lit.	Literature
*m*CPBA	*meta*-Chloroperoxybenzoic acid
MG	Methylglyoxal

MOM	Methoxymethyl
MPO	4-Methyl-pyridine-*N*-oxide
MS	Mass spectrometry
Ms	Mesyl
MTBE	Methyl *tert*-butyl ether
n.d.	not determined
NADP(H)	Nicotinamide Adenine Dinucleotide Phosphate Hydrogen
NCS	*N*-Chlorosuccinimide
*n*Hex	*n*-Hexyl
NMR	Nuclear magnetic resonance
NOE	Nuclear *Overhauser* effect
Nu	Nucleophile
PG	Protecting group
Phe	Phenylalanine
PHOX	Phosphinooxazolines
PKS	Polyketide synthase
qTOF	quadrupole Time-of-Flight
quant.	quantitative
RCM	Ring closing metathesis
R_f	Retention factor
rt	room temperature
sat.	saturated
SET	Single electron transfer
TBAB	Tetrabutylammonium bromide
TBAF	Tetrabutylammonium fluoride
TBD	1,5,7-Triazabicyclo[4.4.0]dec-5-ene
TBS	*tert*-Butyl(dimethyl)silyl
TCC	*trans*-2-(*α*-Cumyl)cyclohexanol
T-DNA	Transferred deoxyribonucleic acid
Tf	Triflate
THF	Tetrahydrofuran
TLC	Thin layer chromatography
TMS	Tetramethylsilane
Ts	Tosyl
Tyr	Tyrosine
VE	Valence electron

13.2 Selected NMR spectra

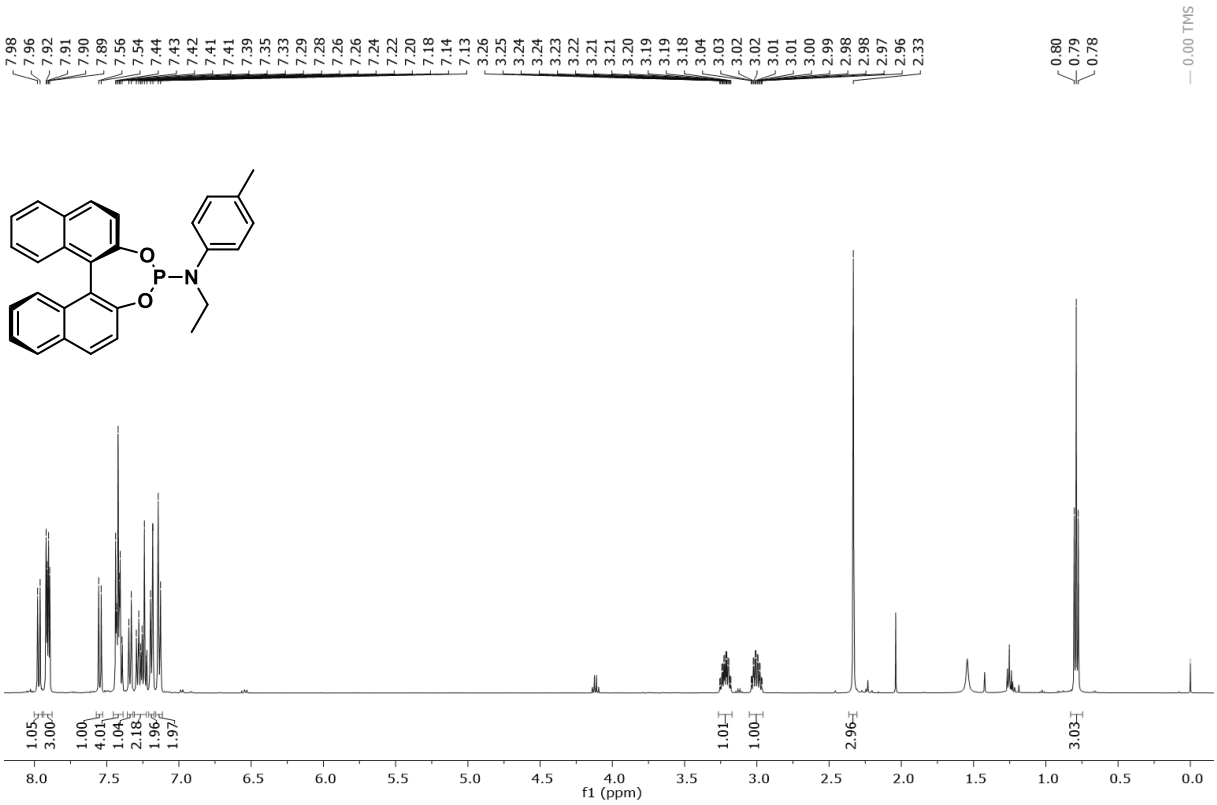


*Figure 13: ^{1}H NMR (500 MHz, $CDCl_3$) of O,O‘-(1,1‘-Dinaphthyl-2,2‘-diyl)-N,N-ethyl-3-methylphenyl phosphoramidite (**L7a**).*

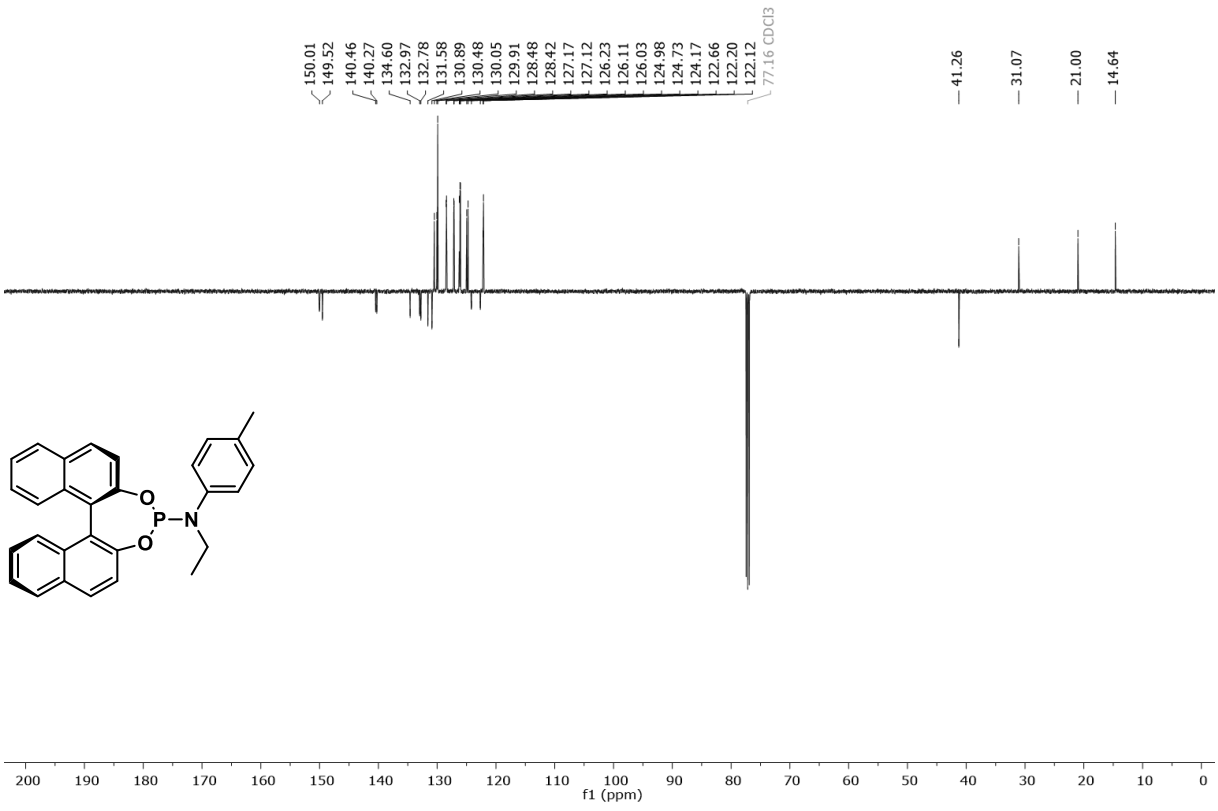


*Figure 14: ^{13}C NMR (126 MHz, $CDCl_3$) of O,O‘-(1,1‘-Dinaphthyl-2,2‘-diyl)-N,N-ethyl-3-methylphenyl phosphoramidite (**L7a**).*

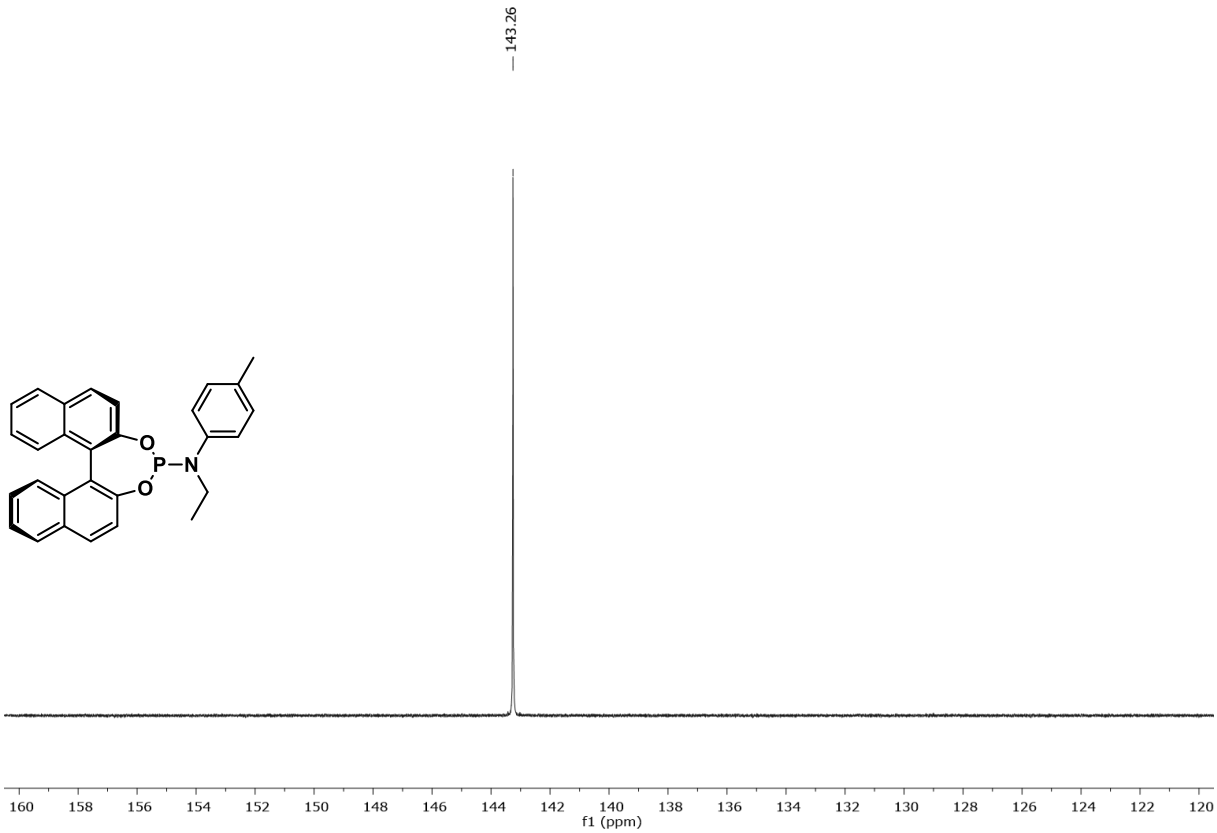


*Figure 15: ^{31}P NMR (202 MHz, $CDCl_3$) of O,O'-(1,1'-Dinaphthyl-2,2'-diyl)-N,N-ethyl-3-methylphenyl phosphoramidite (**L7a**).*

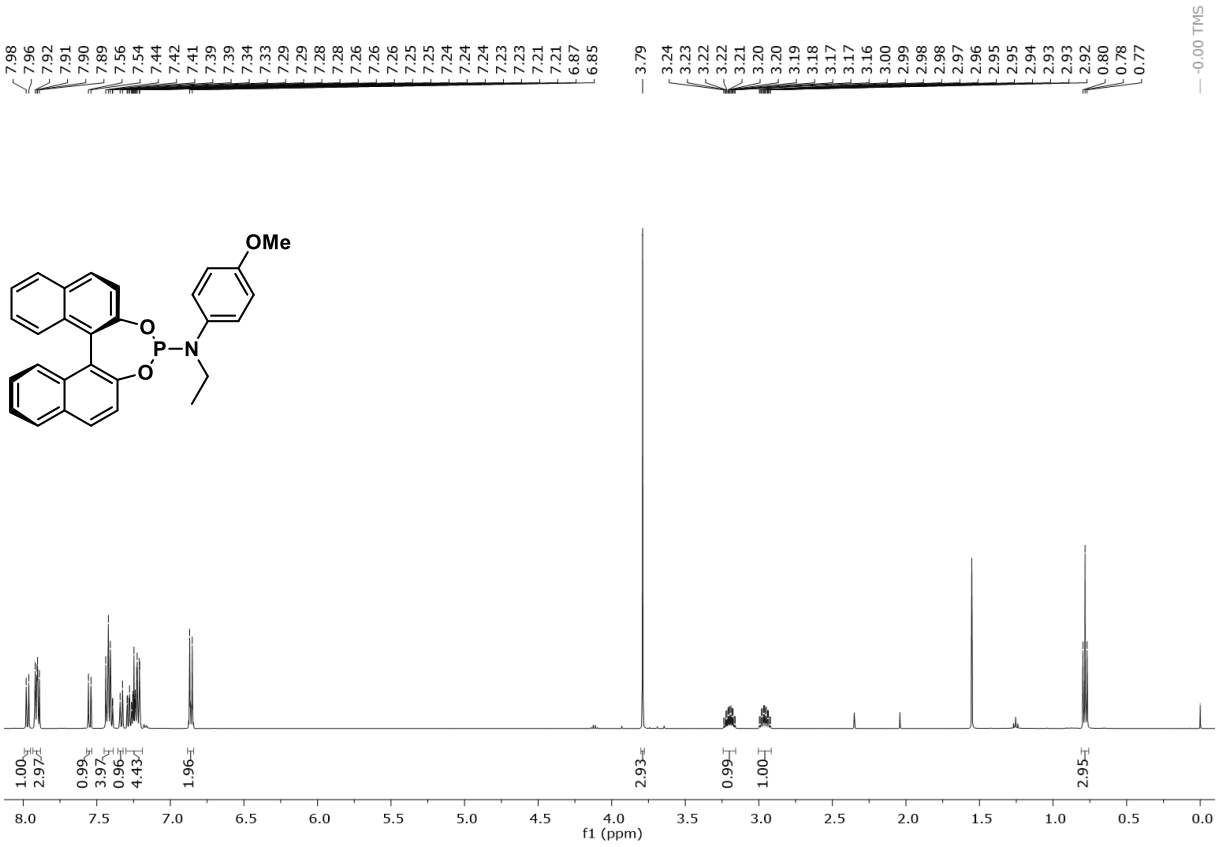


*Figure 16: ^{1}H NMR (500 MHz, $CDCl_3$) of O,O'-(1,1'-Dinaphthyl-2,2'-diyl)-N,N-ethyl-3-methoxyphenyl phosphoramidite (**L7b**).*

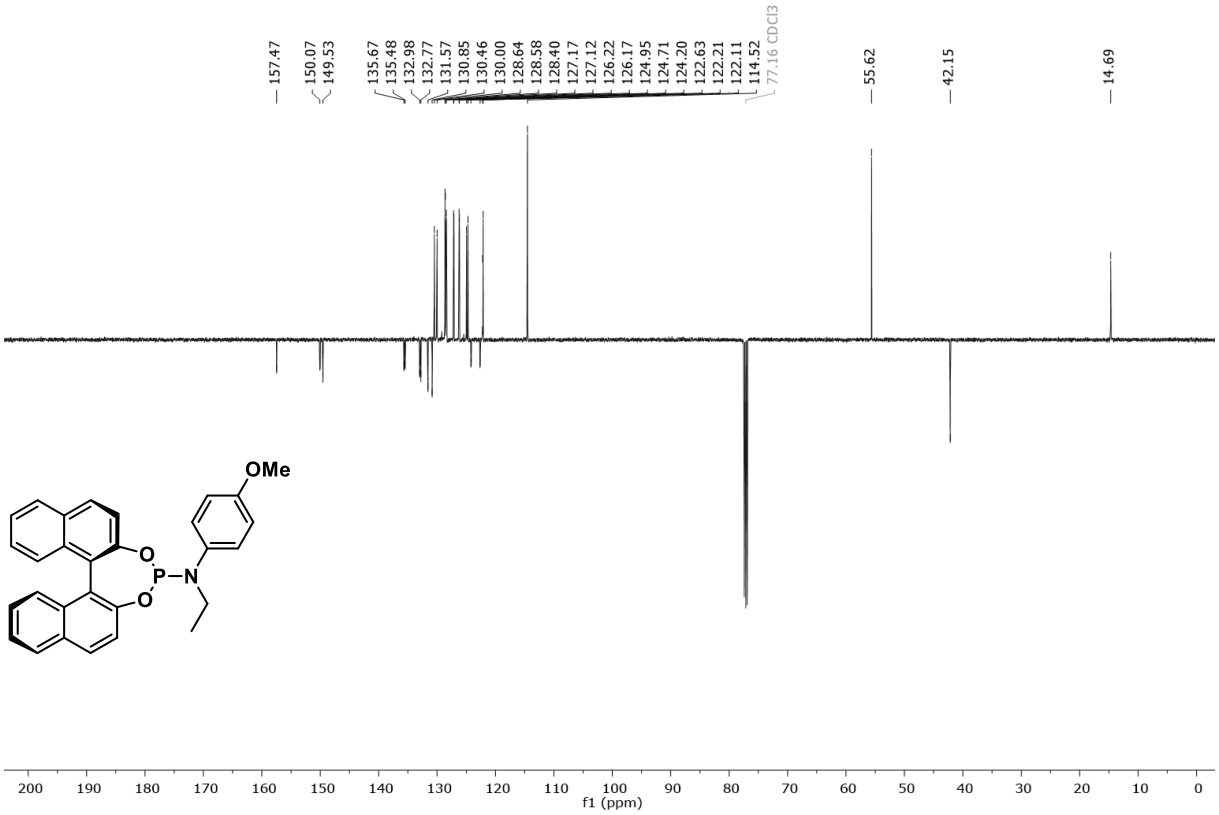


*Figure 17: ^{13}C NMR (126 MHz, $CDCl_3$) of O,O'-(1,1'-Dinaphthyl-2,2'-diyl)-N,N-ethyl-3-methoxyphenyl phosphoramidite (**L7b**).*

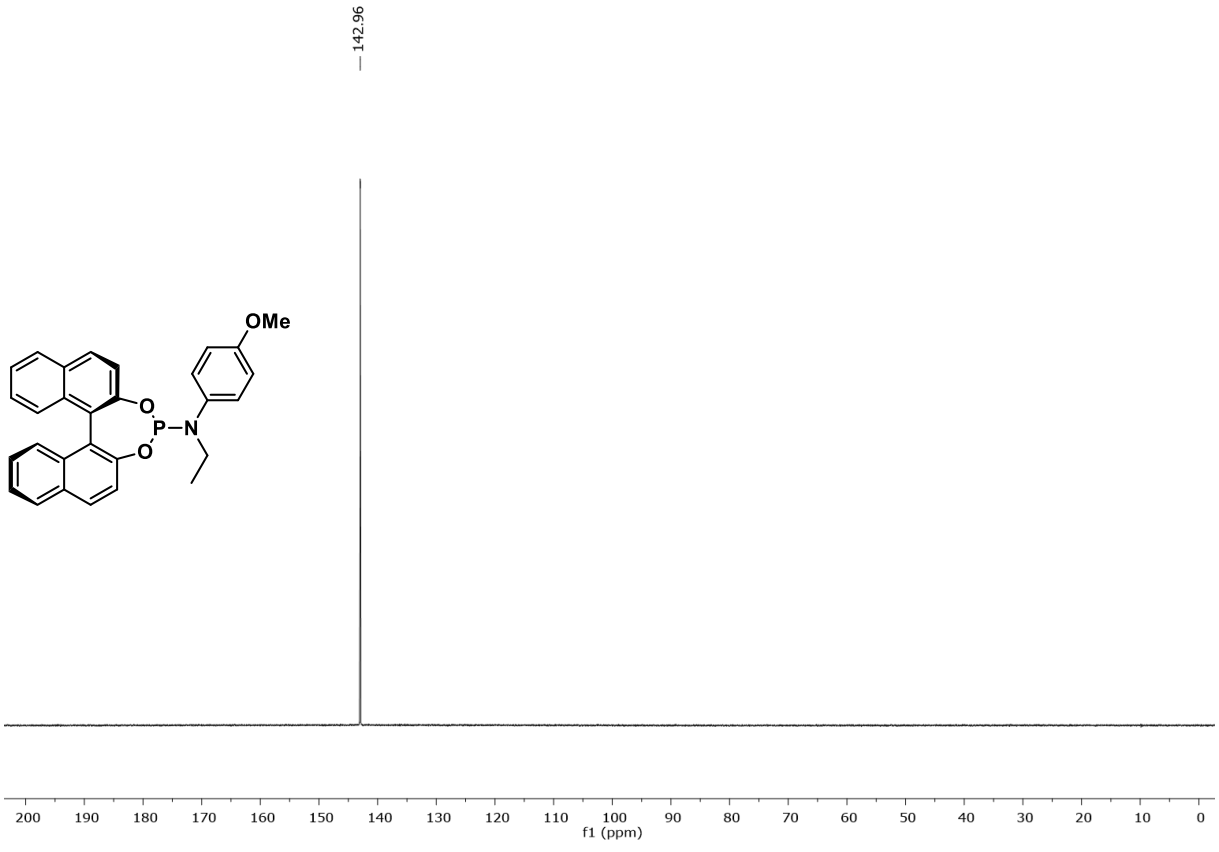


*Figure 18: ^{31}P NMR (202 MHz, $CDCl_3$) of O,O'-(1,1'-Dinaphthyl-2,2'-diyl)-N,N-ethyl-3-methoxyphenyl phosphoramidite (**L7b**).*

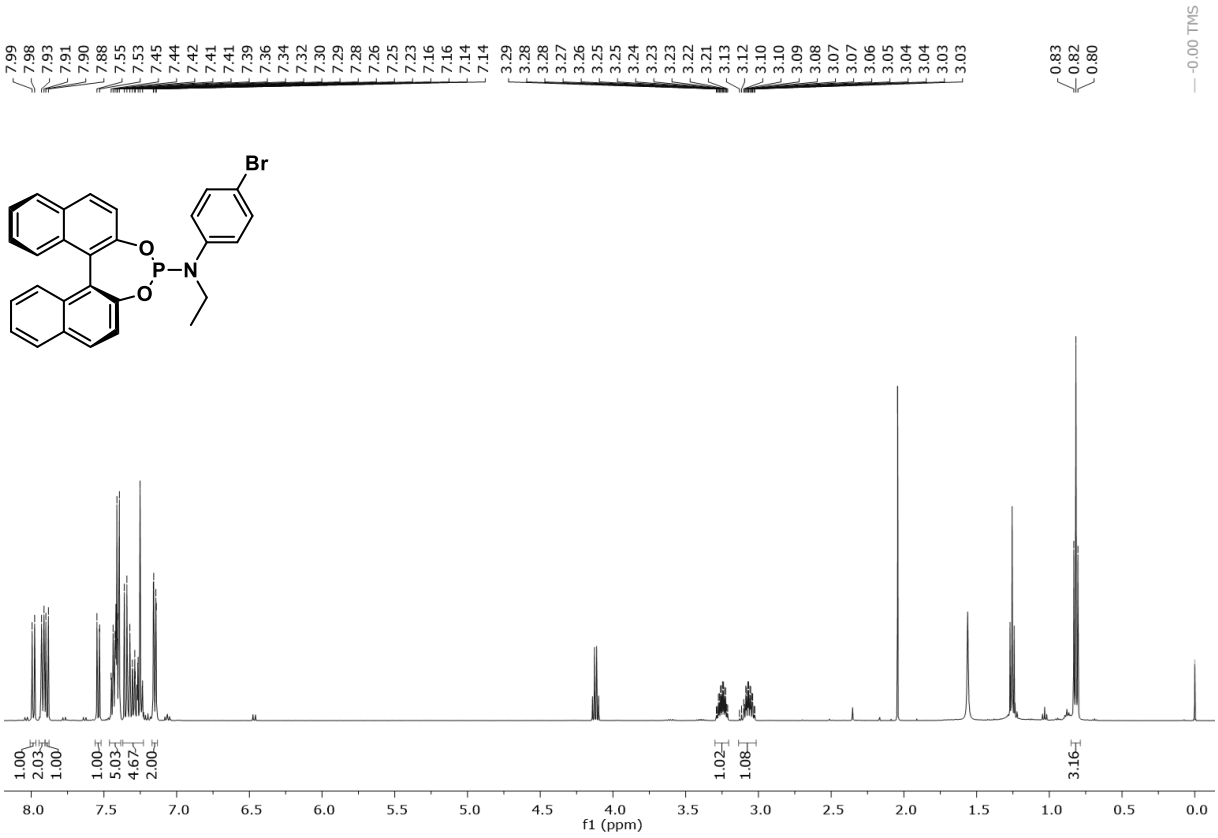


*Figure 19: ^{1}H NMR (500 MHz, $CDCl_3$) of O,O'-(1,1'-Dinaphthyl-2,2'-diyl)-N,N-ethyl-3-bromophenyl phosphoramidite (**L7c**).*

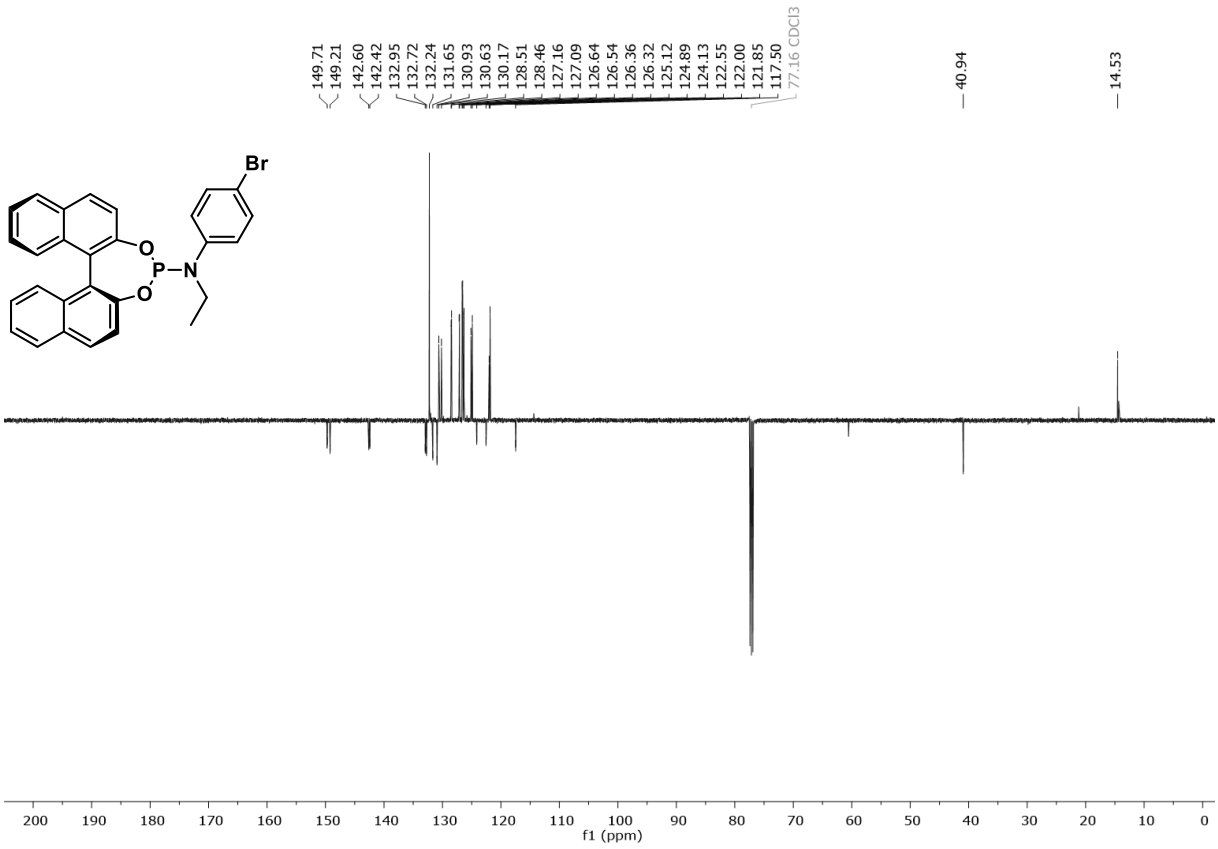


*Figure 20: ^{13}C NMR (126 MHz, $CDCl_3$) of O,O'-(1,1'-Dinaphthyl-2,2'-diyl)-N,N-ethyl-3-bromophenyl phosphoramidite (**L7c**).*

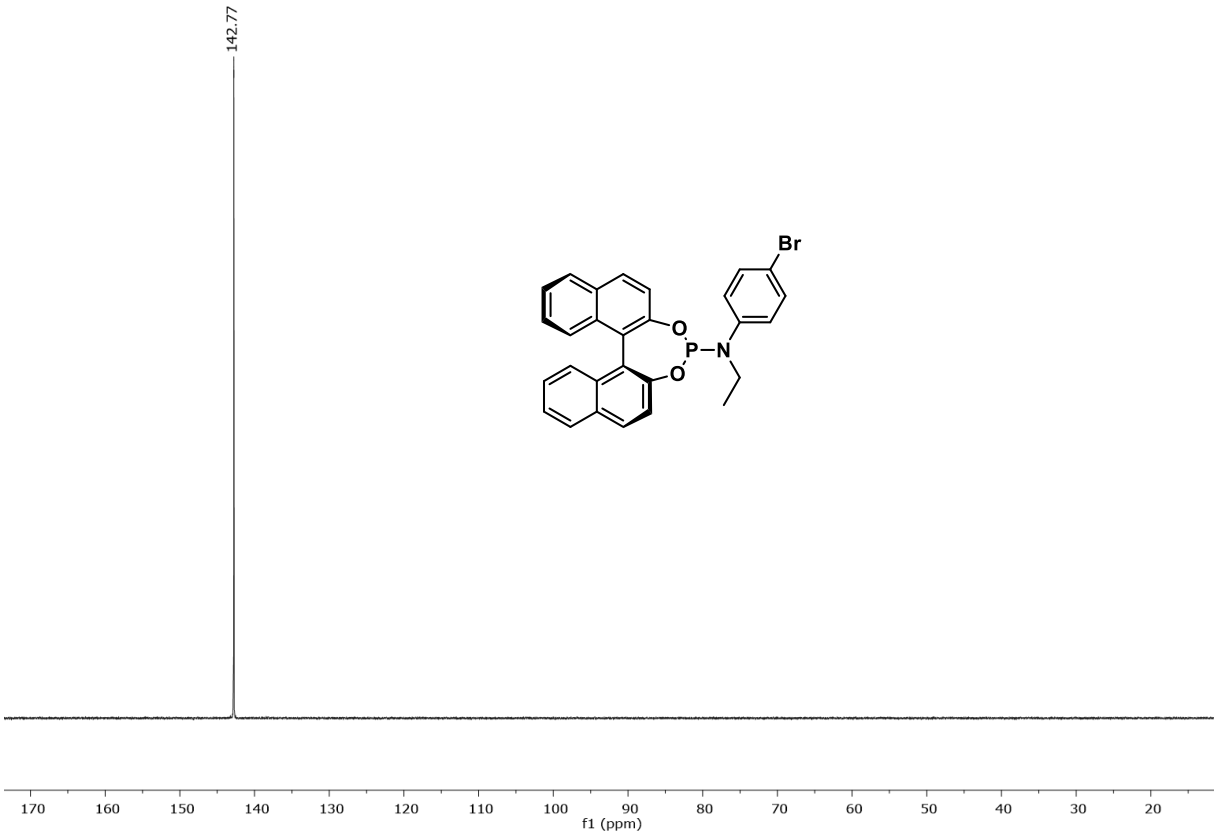


*Figure 21: ^{31}P NMR (202 MHz, $CDCl_3$) of O,O‘-(1,1‘-Dinaphthyl-2,2‘-diyl)-N,N-ethyl-3-bromophenyl phosphoramidite (**L7c**).*

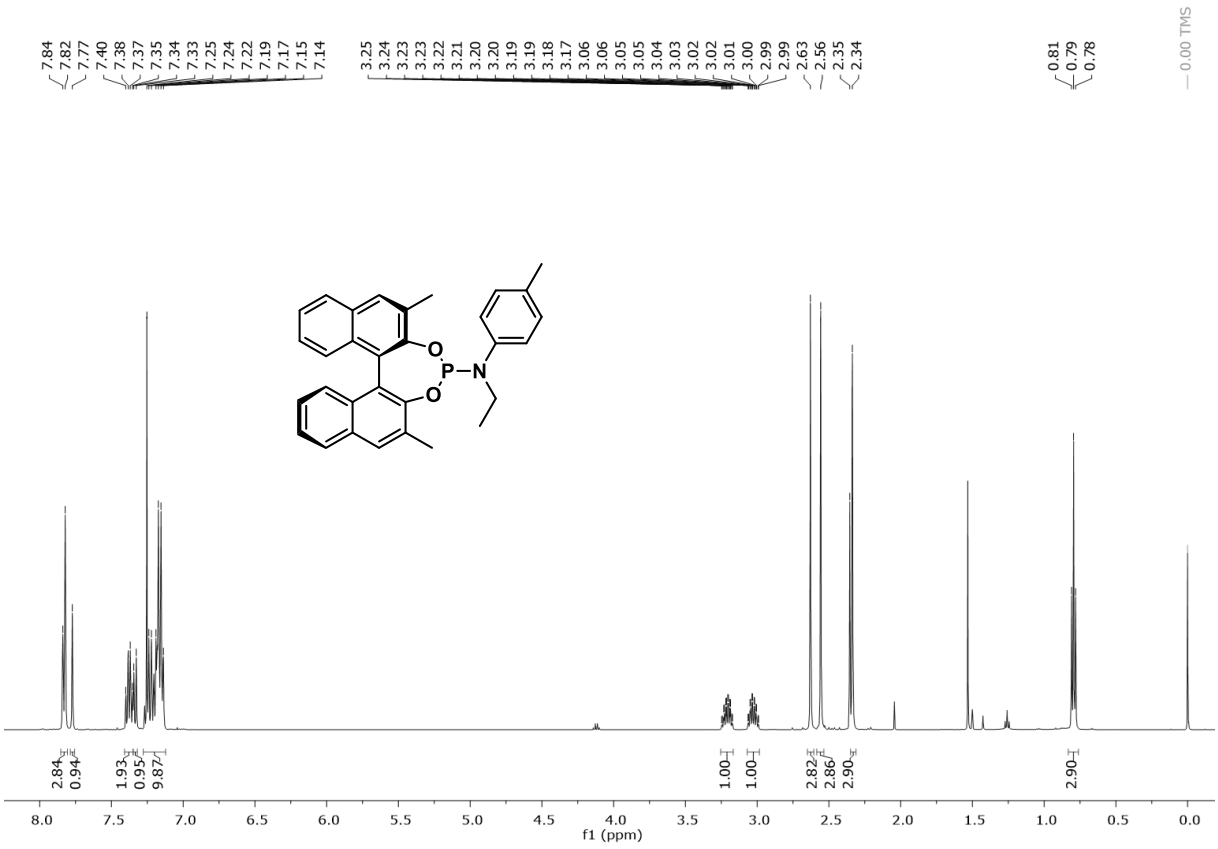


*Figure 22: ^{1}H NMR (500 MHz, $CDCl_3$) of O,O‘-(3,3‘-Dimethyl-(1,1‘-dinaphthyl)-2,2‘-diyl)-N,N-ethyl-3-methylphenylphosphoramidite (**L7d**).*

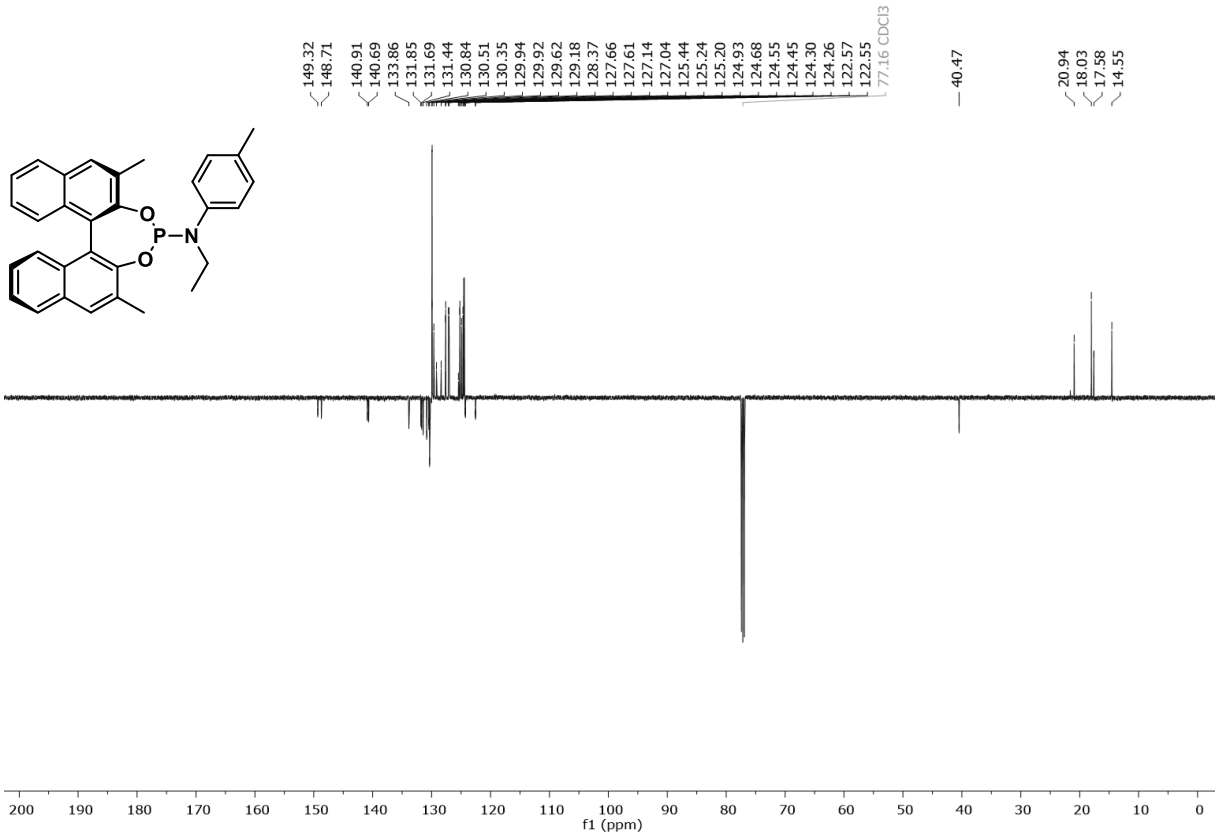


*Figure 23: ^{13}C NMR (126 MHz, $CDCl_3$) of O,O'-(3,3'-Dimethyl-(1,1'-dinaphthyl)-2,2'-diyl)-N,N-ethyl-3-methylphenylphosphoramidite (**L7d**).*

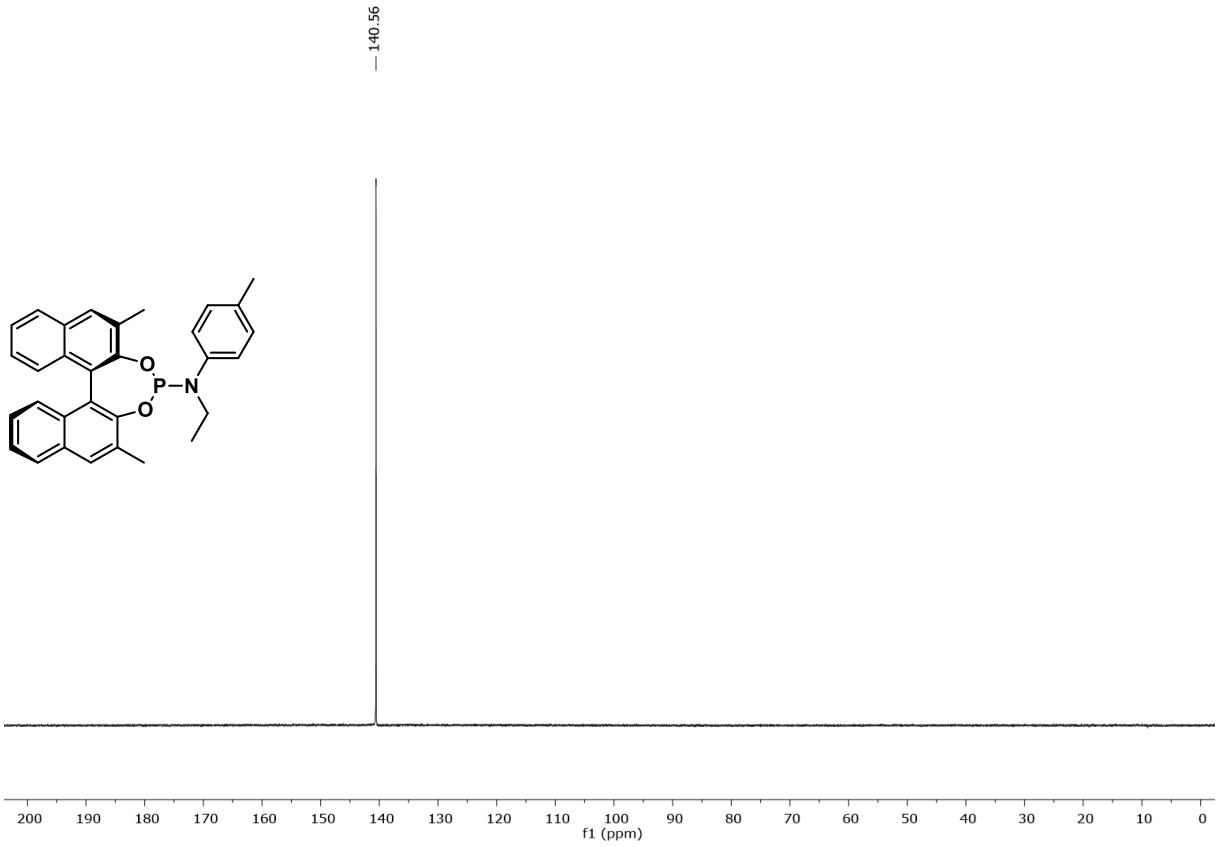


*Figure 24: ^{31}P NMR (202 MHz, $CDCl_3$) of O,O'-(3,3'-Dimethyl-(1,1'-dinaphthyl)-2,2'-diyl)-N,N-ethyl-3-methylphenylphosphoramidite (**L7d**).*

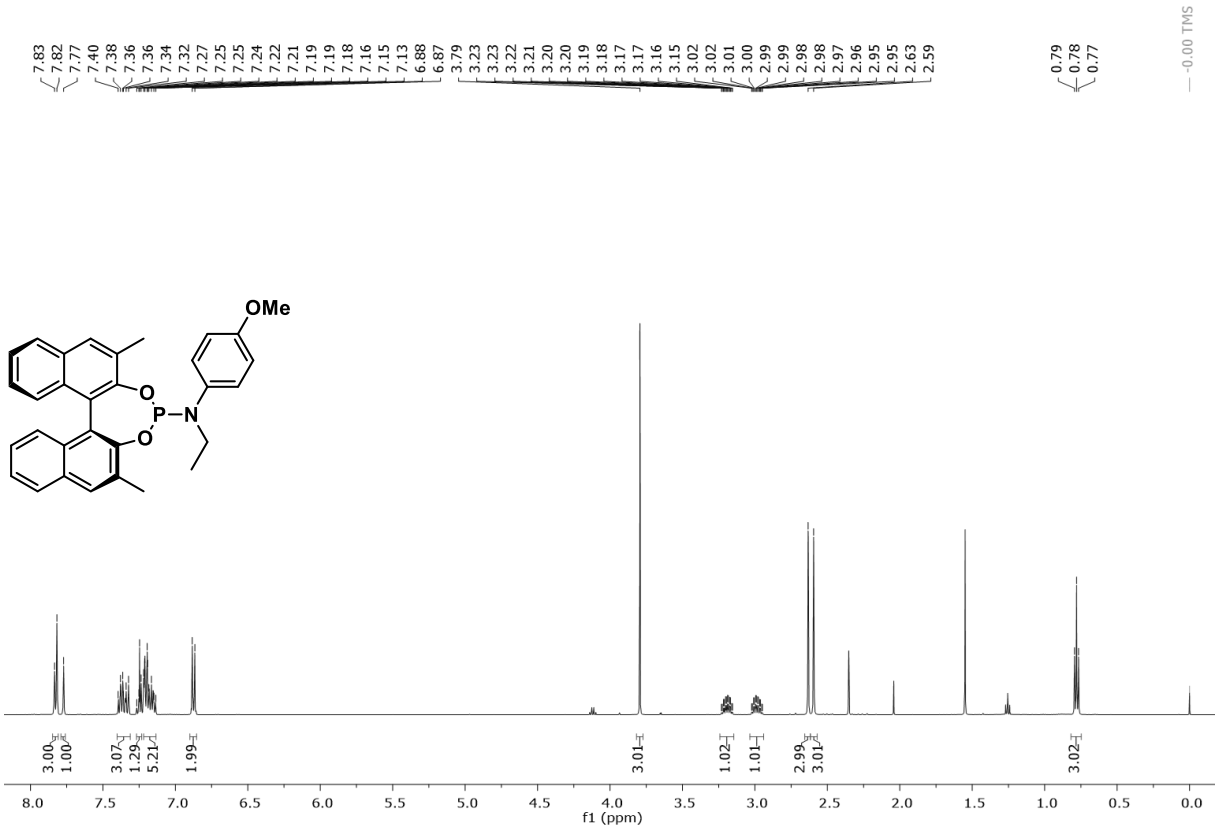


*Figure 25: [1]H NMR (500 MHz, $CDCl_3$) of O,O‘-(3,3‘-Dimethyl-(1,1‘-dinaphthyl)-2,2‘-diyl)-N,N-ethyl-3-methoxyphenylphosphoramidite (**L7e**).*

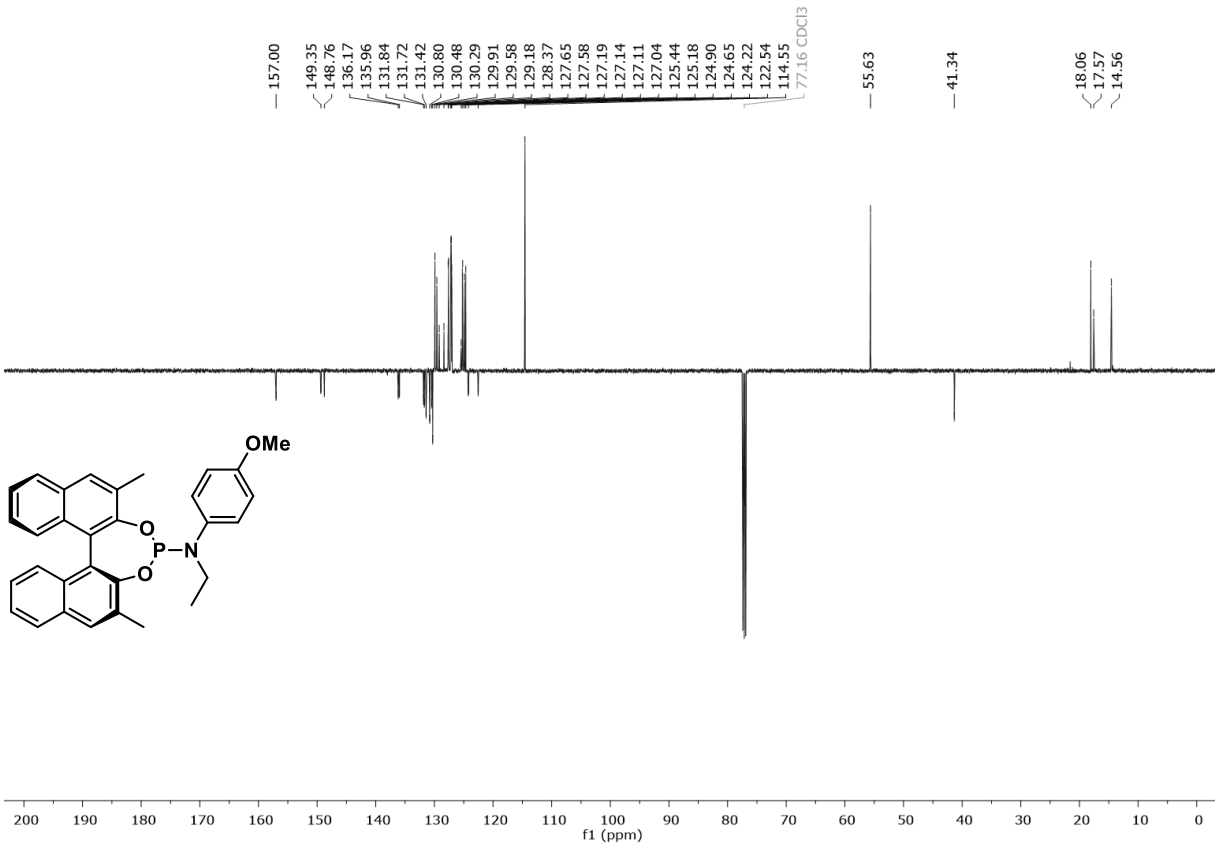


*Figure 26: [13]C NMR (126 MHz, $CDCl_3$) of O,O‘-(3,3‘-Dimethyl-(1,1‘-dinaphthyl)-2,2‘-diyl)-N,N-ethyl-3-methoxyphenylphosphoramidite (**L7e**).*

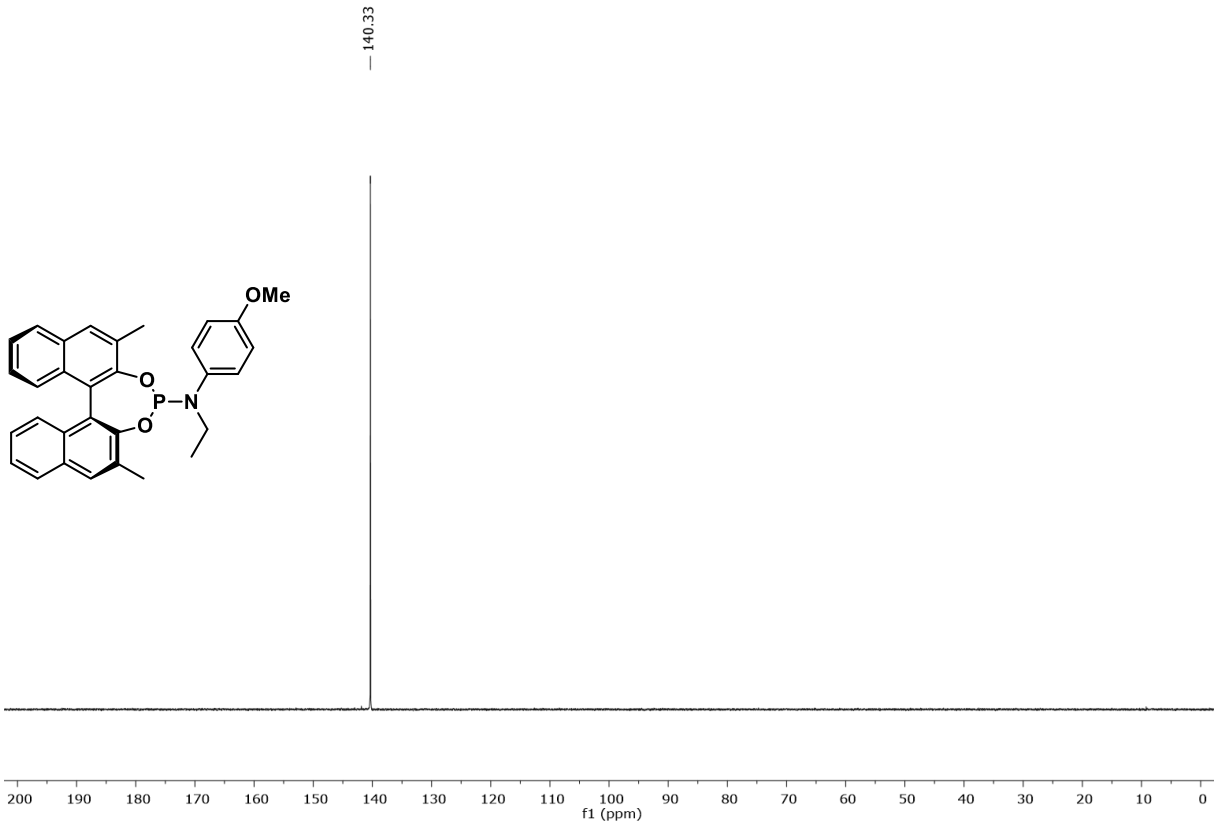


*Figure 27: ^{31}P NMR (202 MHz, $CDCl_3$) of O,O‘-(3,3‘-Dimethyl-(1,1‘-dinaphthyl)-2,2‘-diyl)-N,N-ethyl-3-methoxyphenylphosphoramidite (**L7e**).*

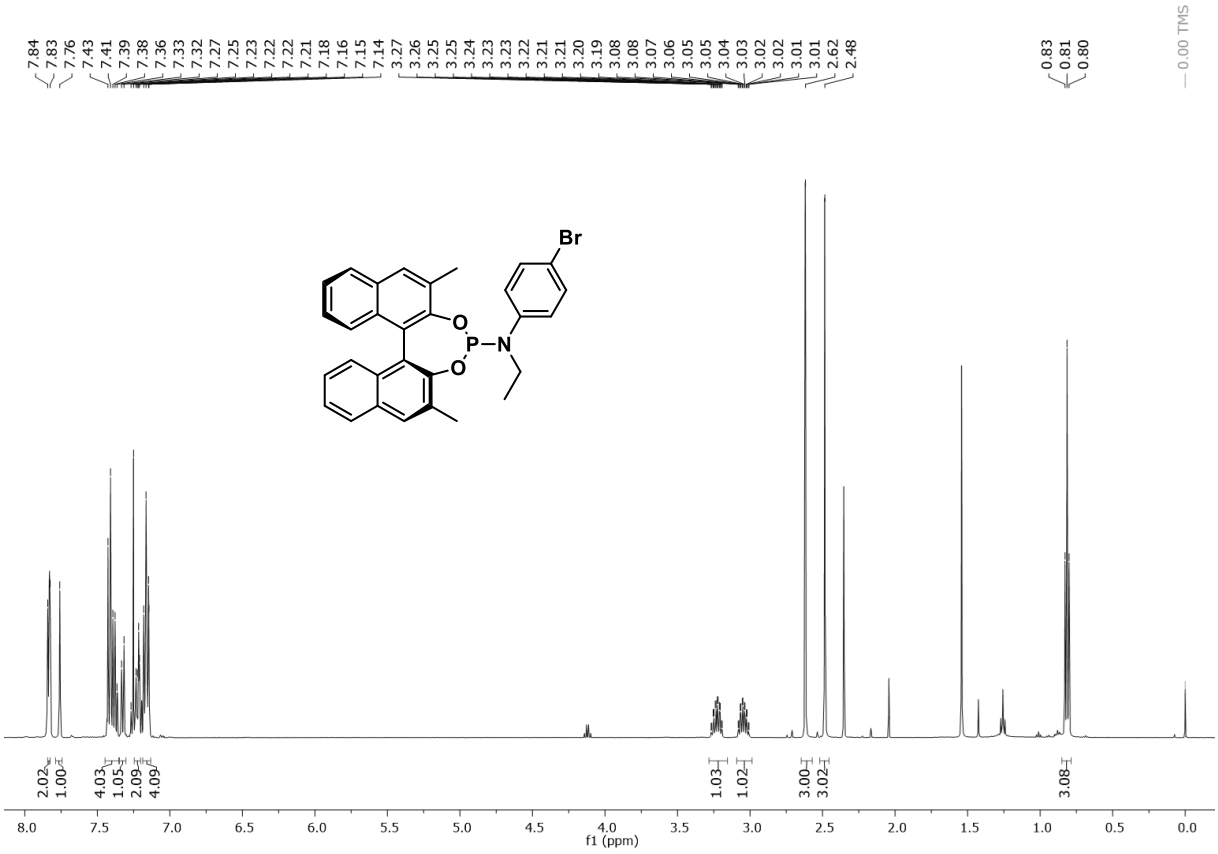


*Figure 28: ^{1}H NMR (500 MHz, $CDCl_3$) of O,O‘-(3,3‘-Dimethyl-(1,1‘-dinaphthyl)-2,2‘-diyl)-N,N-ethyl-3-bromophenylphosphoramidite (**L7f**).*

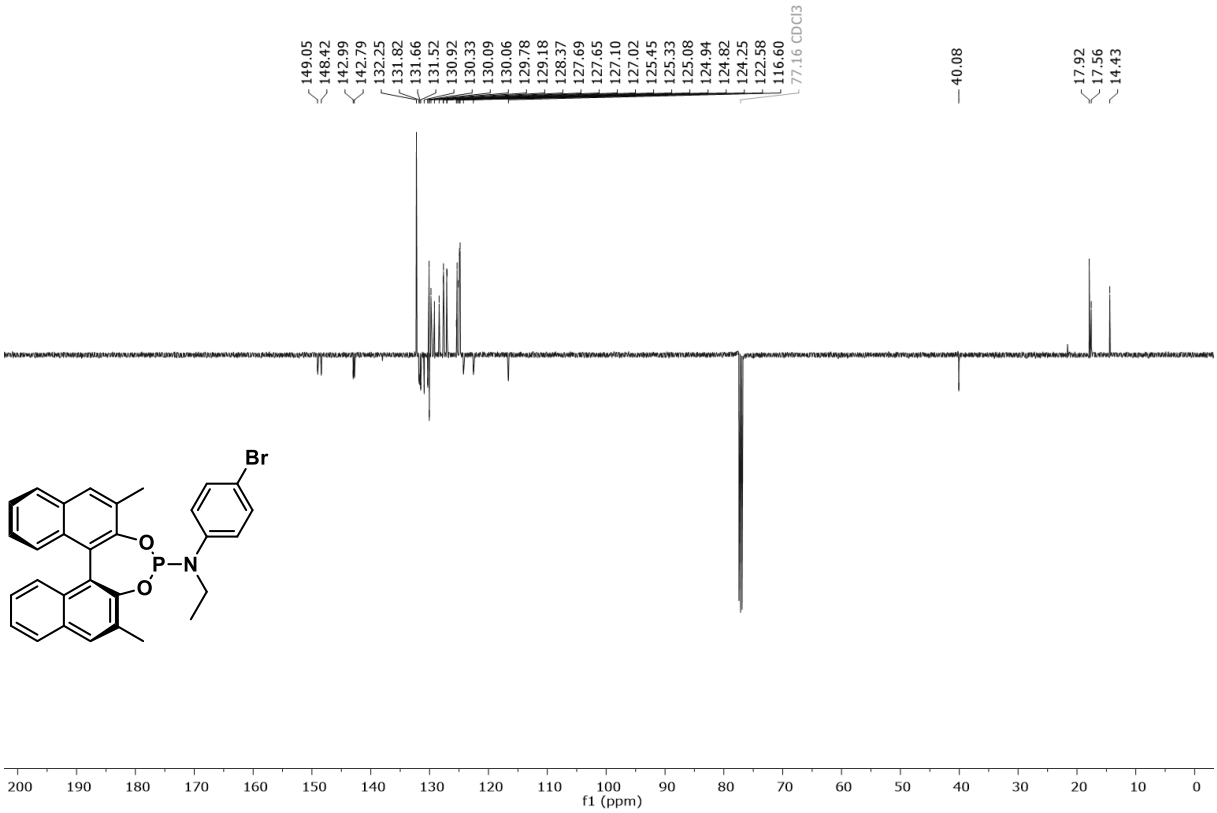


*Figure 29: ^{13}C NMR (126 MHz, $CDCl_3$) of O,O'-(3,3'-Dimethyl-(1,1'-dinaphthyl)-2,2'-diyl)-N,N-ethyl-3-bromophenylphosphoramidite (**L7f**).*

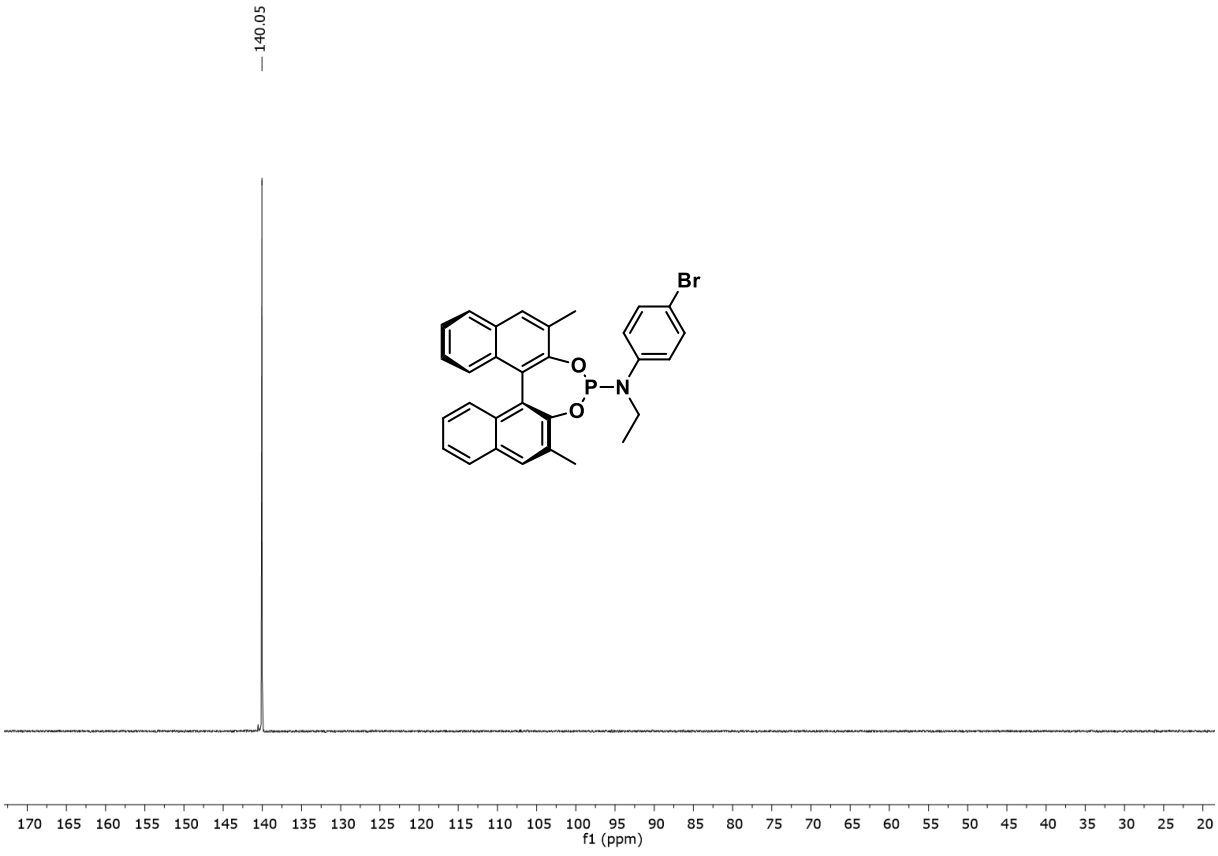


*Figure 30: ^{31}P NMR (202 MHz, $CDCl_3$) of O,O'-(3,3'-Dimethyl-(1,1'-dinaphthyl)-2,2'-diyl)-N,N-ethyl-3-bromophenylphosphoramidite (**L7f**).*

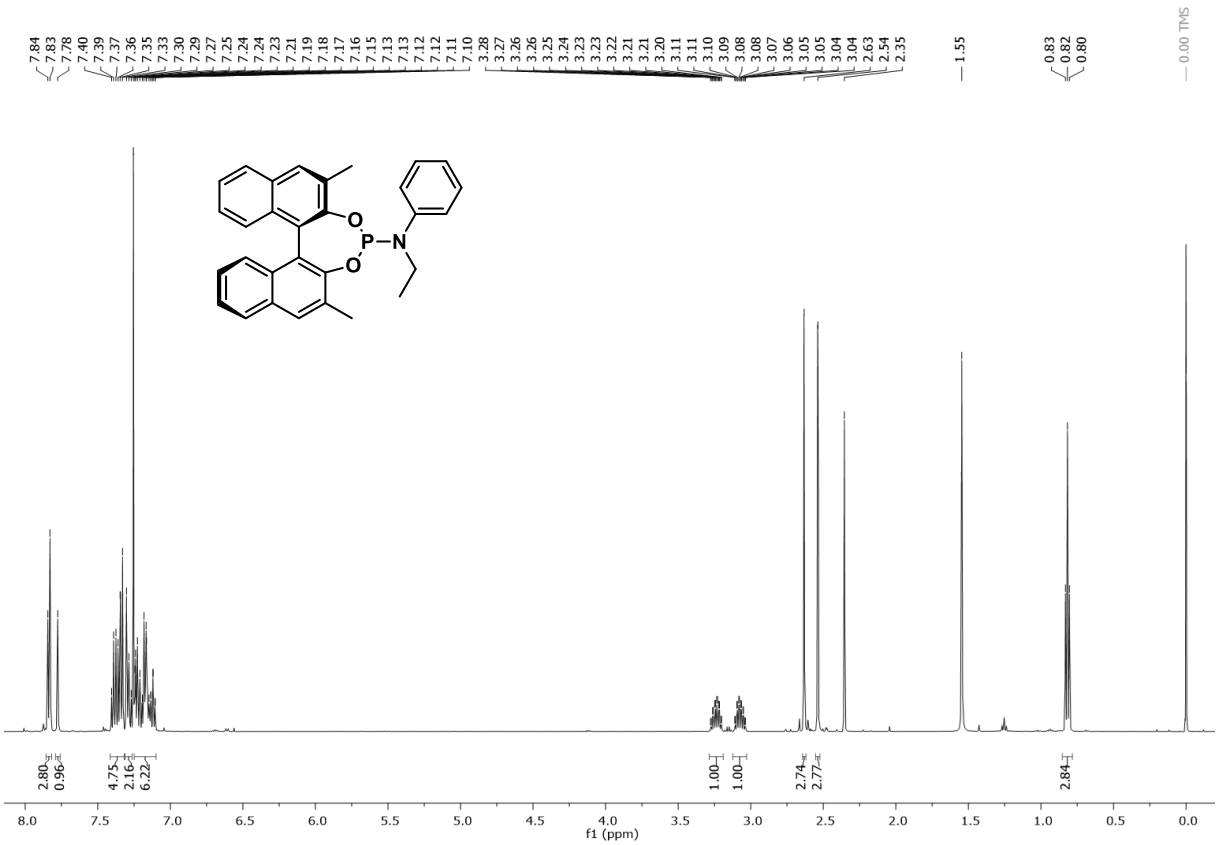


*Figure 31: [1]H NMR (500 MHz. $CDCl_3$) of O,O‘-(3,3‘-Dimethyl-(1,1‘-dinaphthyl)-2,2‘-diyl)-N,N-ethyl-phenylphosphoramidite (**L7g**).*

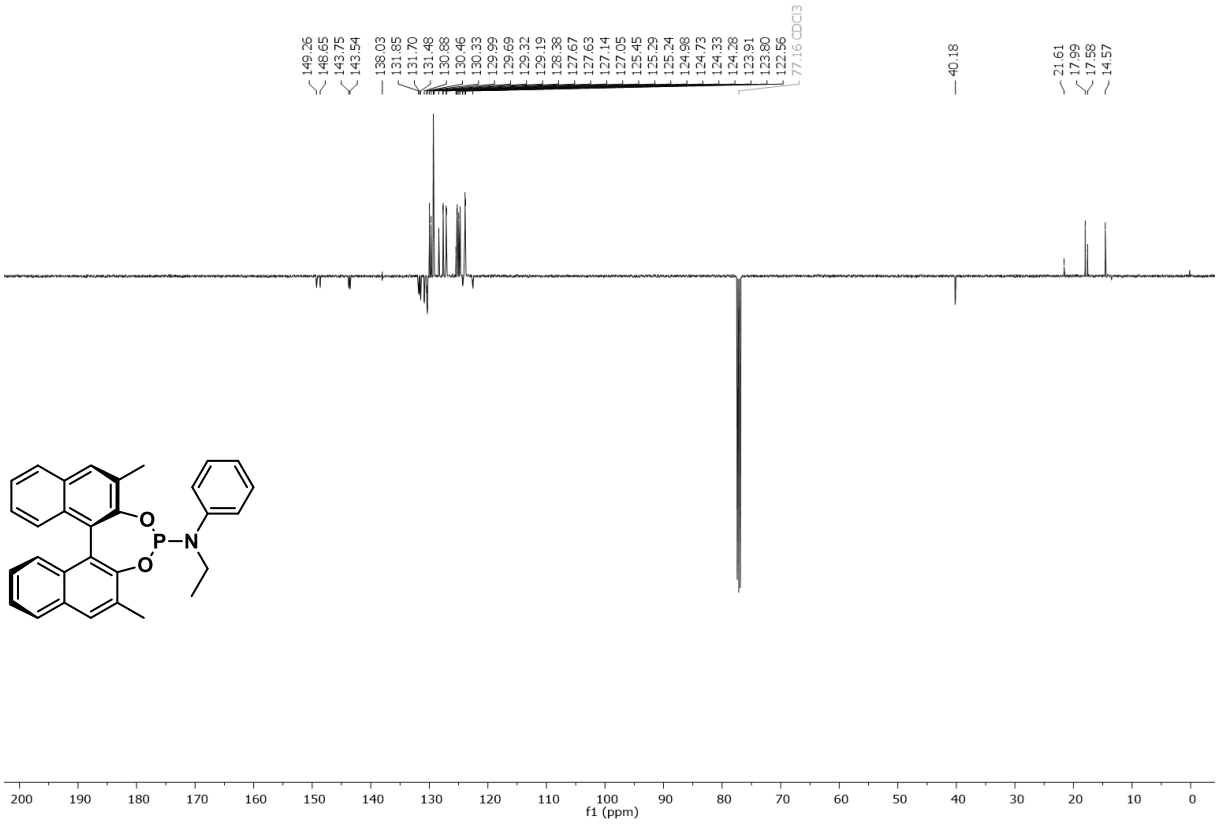


*Figure 32: [13]C NMR (126 MHz. $CDCl_3$) of O,O‘-(3,3‘-Dimethyl-(1,1‘-dinaphthyl)-2,2‘-diyl)-N,N-ethyl-phenylphosphoramidite (**L7g**).*

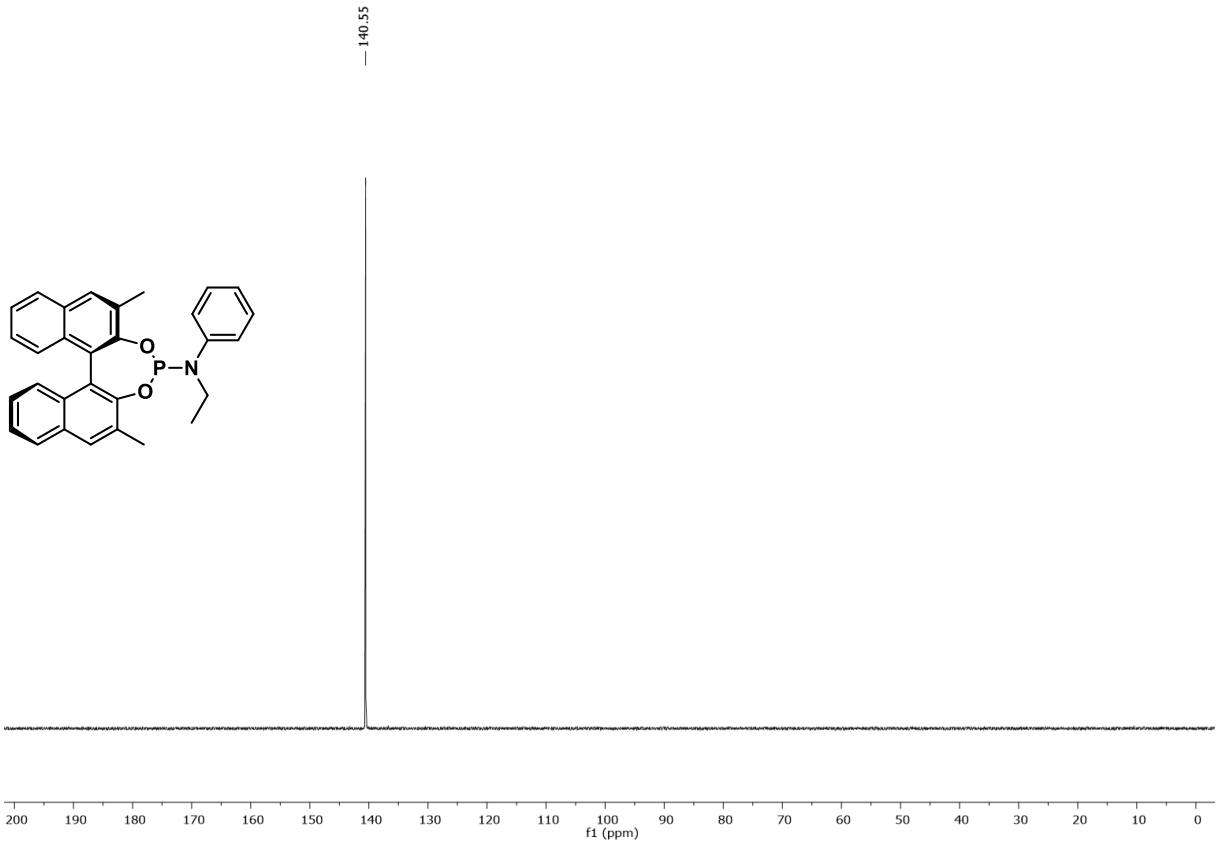


*Figure 33: ^{31}P NMR (202 MHz. $CDCl_3$) of O,O‘-(3,3‘-Dimethyl-(1,1‘-dinaphthyl)-2,2‘-diyl)-N,N-ethyl-phenylphosphoramidite (**L7g**).*

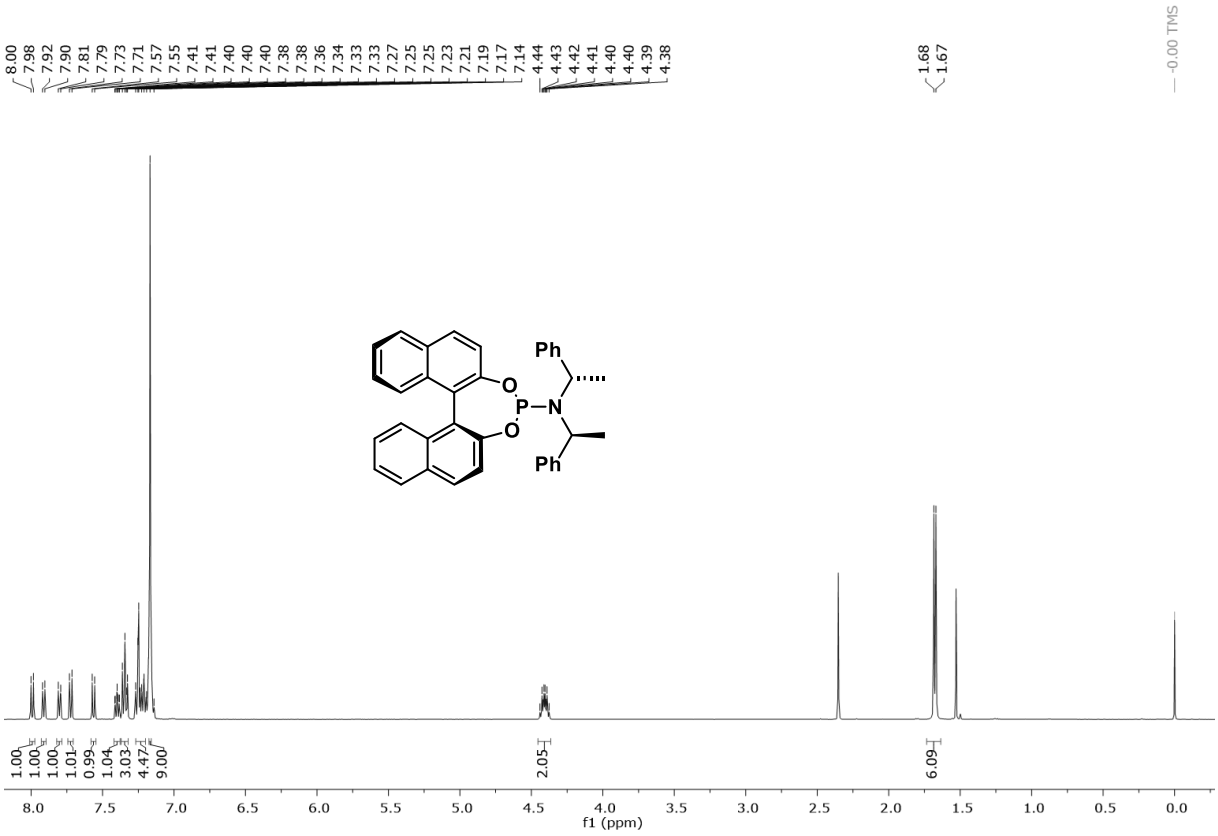


*Figure 34: ^{1}H NMR (500 MHz, $CDCl_3$) of O,O‘-(1,1‘-Dinaphthyl-2,2‘-diyl)-N,N-di-1-phenylethyl-phosphoramidite (**L2**).*

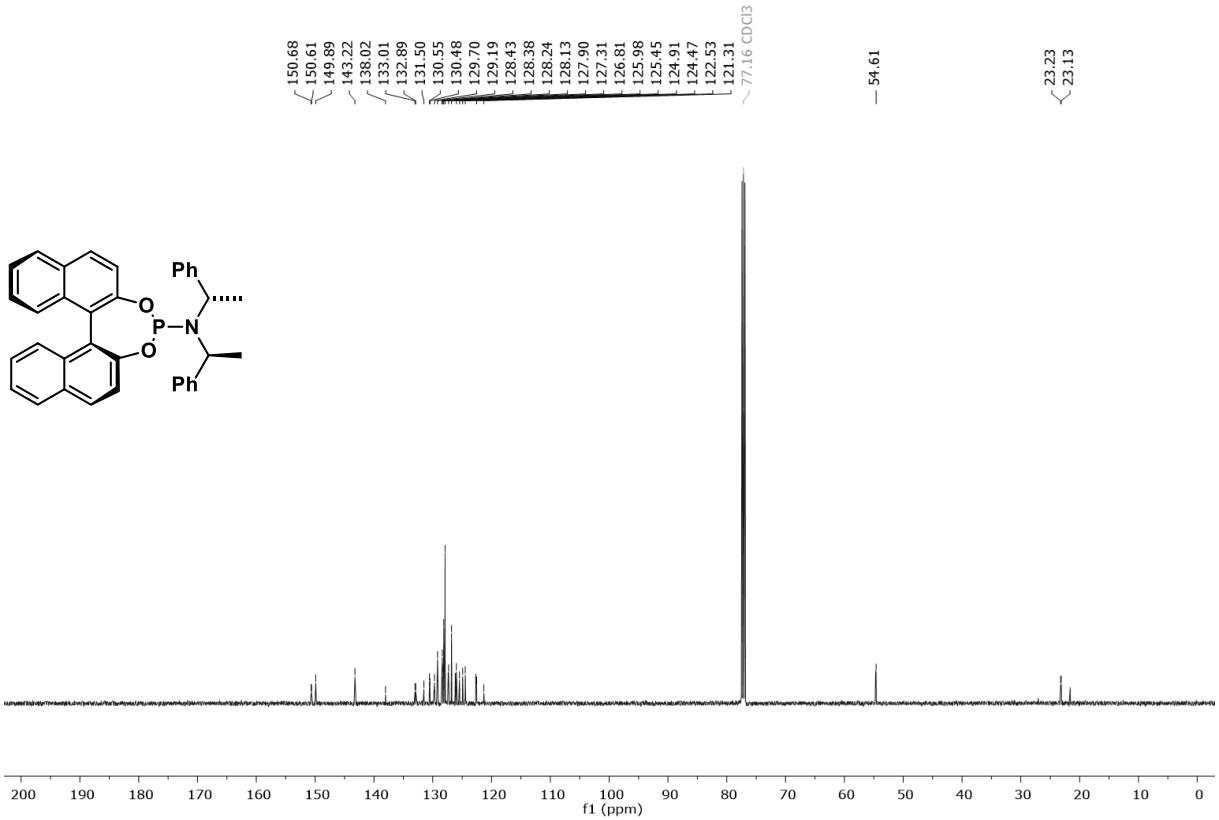


*Figure 35: ^{13}C NMR (126 MHz, $CDCl_3$) of O,O'-(1,1'-Dinaphthyl-2,2'-diyl)-N,N-di-1-phenylethyl-phosphoramidite (**L2**).*

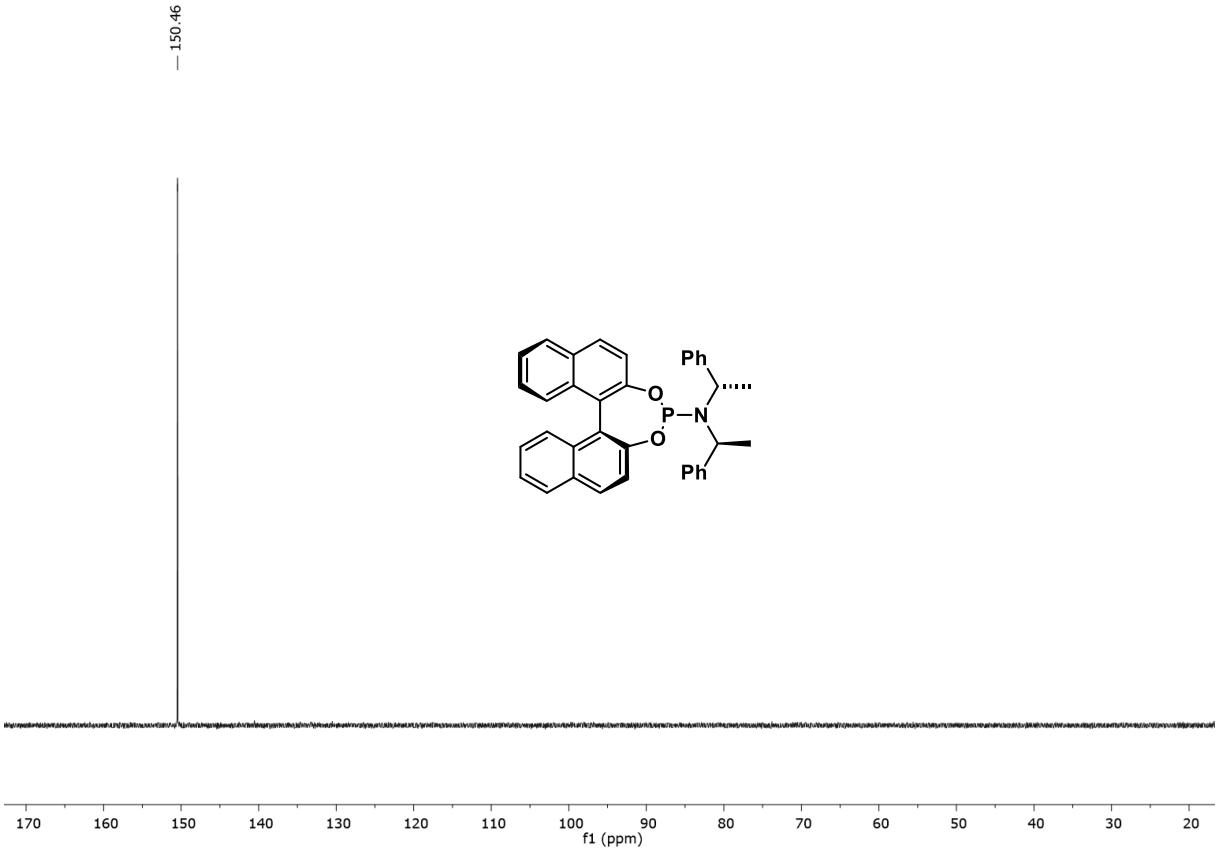


*Figure 36: ^{31}P NMR (500 MHz, $CDCl_3$) of O,O'-(1,1'-Dinaphthyl-2,2'-diyl)-N,N-di-1-phenylethyl-phosphoramidite (**L2**).*

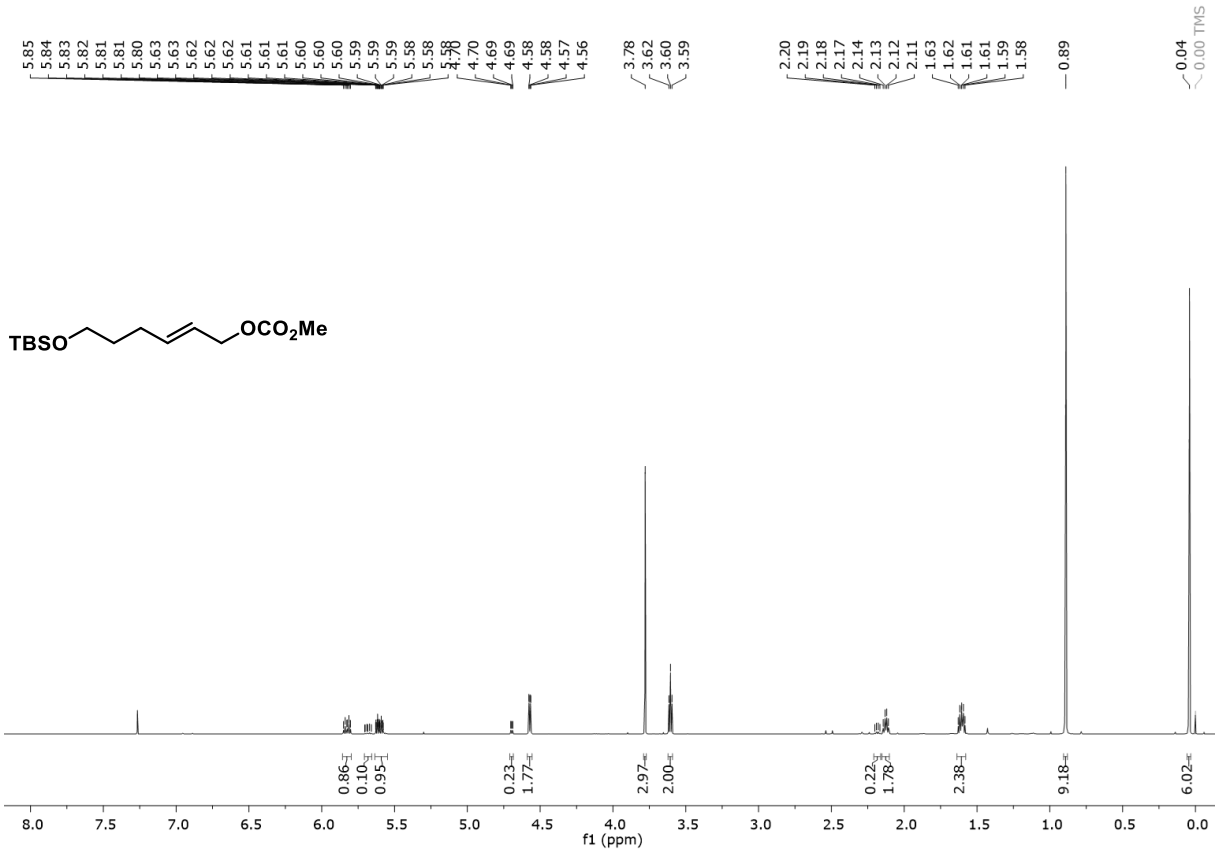


*Figure 37: ^{1}H NMR (600 MHz, $CDCl_3$) of (E)-6-((tert-butyldimethylsilyl)oxy)hex-2-en-1-yl methyl carbonate (**144**).*

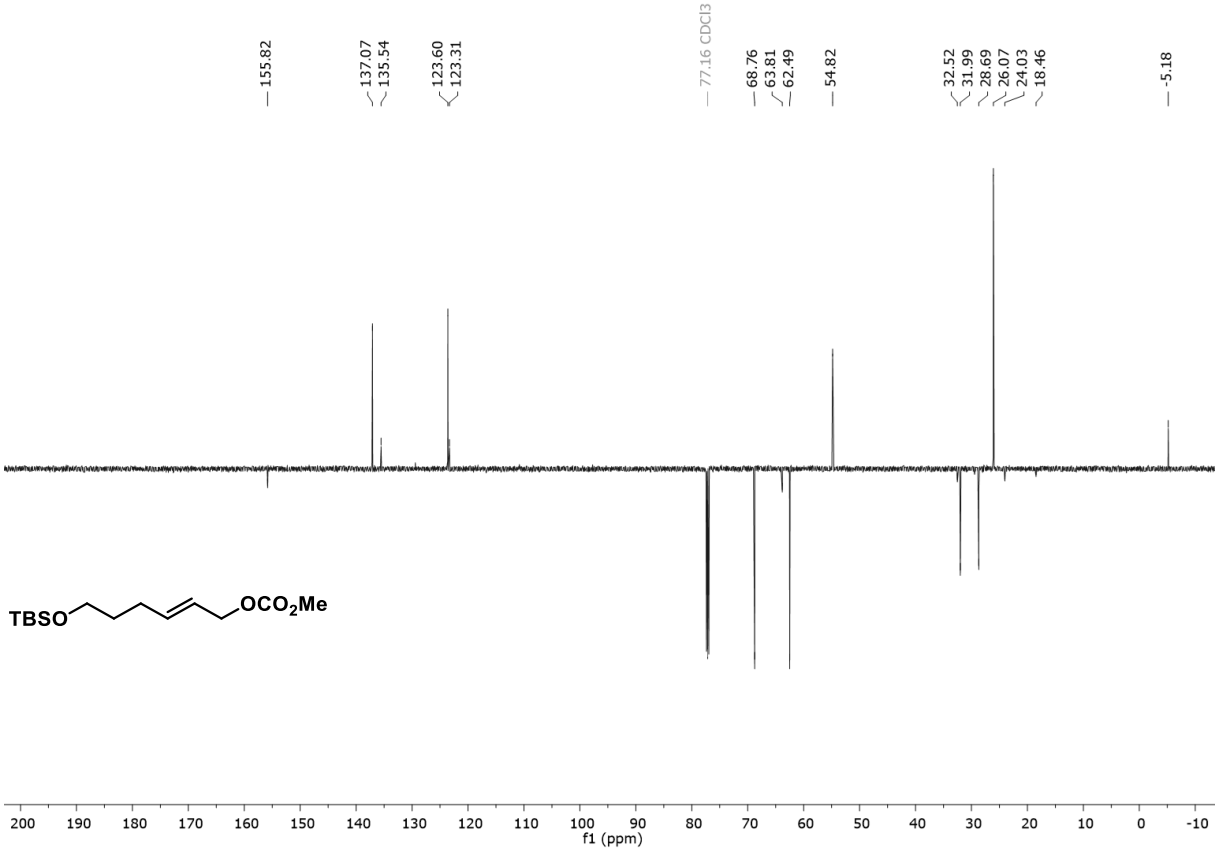


*Figure 38: ^{13}C NMR (151 MHz, $CDCl_3$) of (E)-6-((tert-butyldimethylsilyl)oxy)hex-2-en-1-yl methyl carbonate (**144**).*

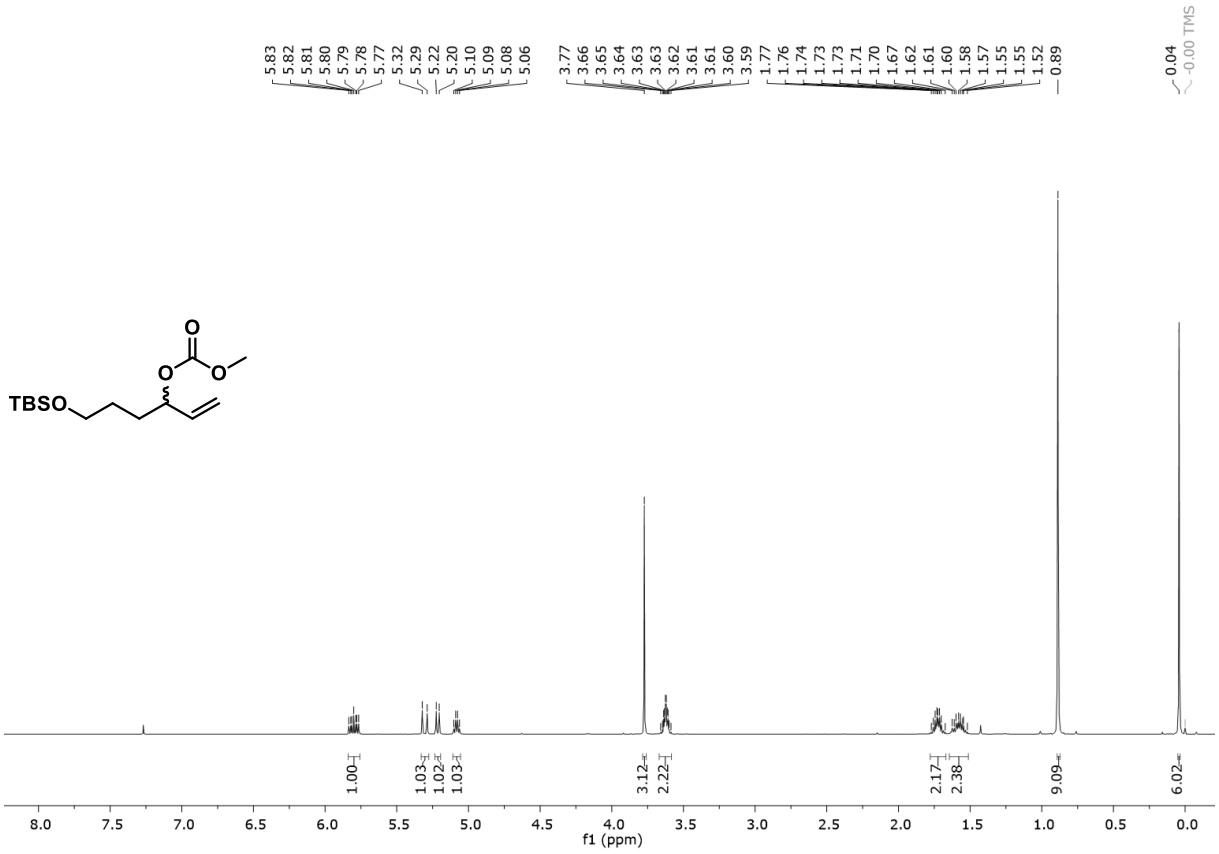


*Figure 39: ^{1}H NMR (500 MHz, $CDCl_3$) of 6-((tert-butyldimethylsilyl)oxy)hex-1-en-3-yl methyl carbonate (**121**).*

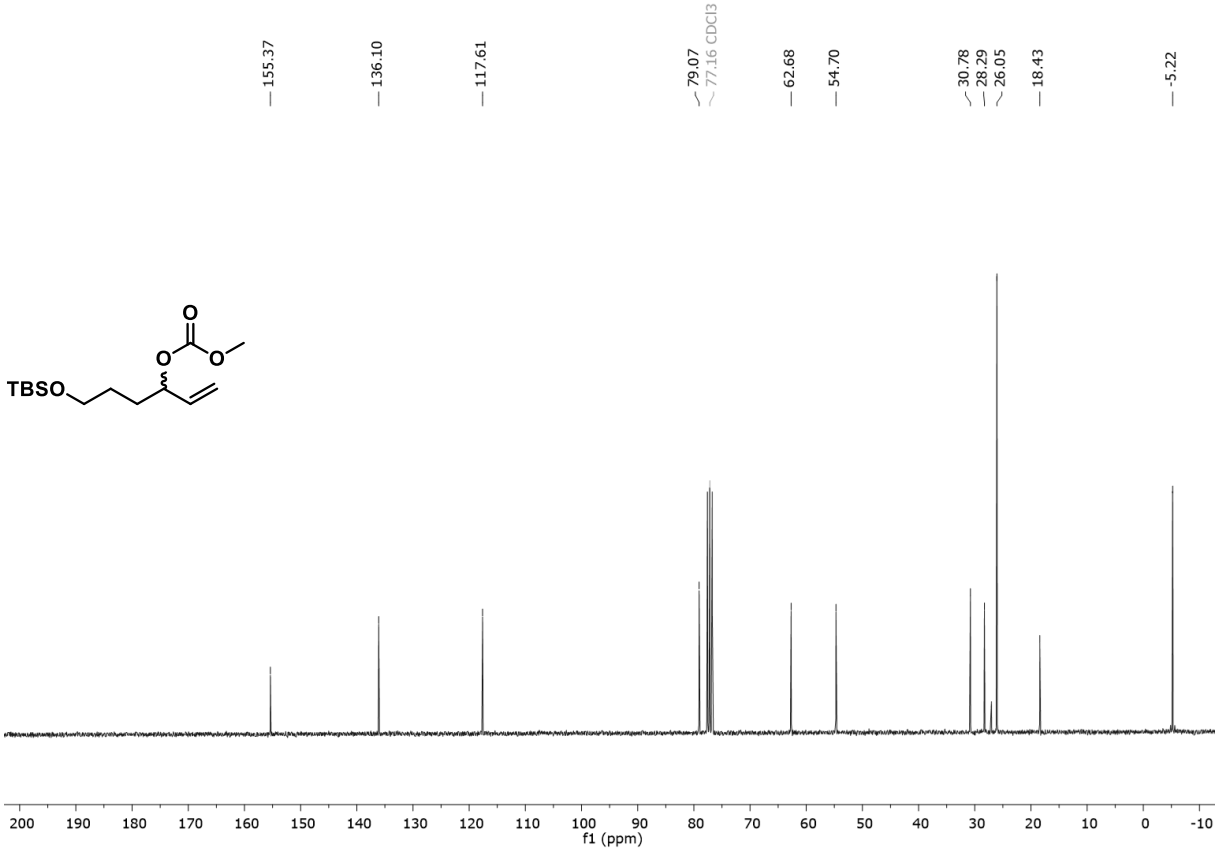


*Figure 40: ^{13}C NMR (126 MHz, $CDCl_3$) of 6-((tert-butyldimethylsilyl)oxy)hex-1-en-3-yl methyl carbonate (**121**).*

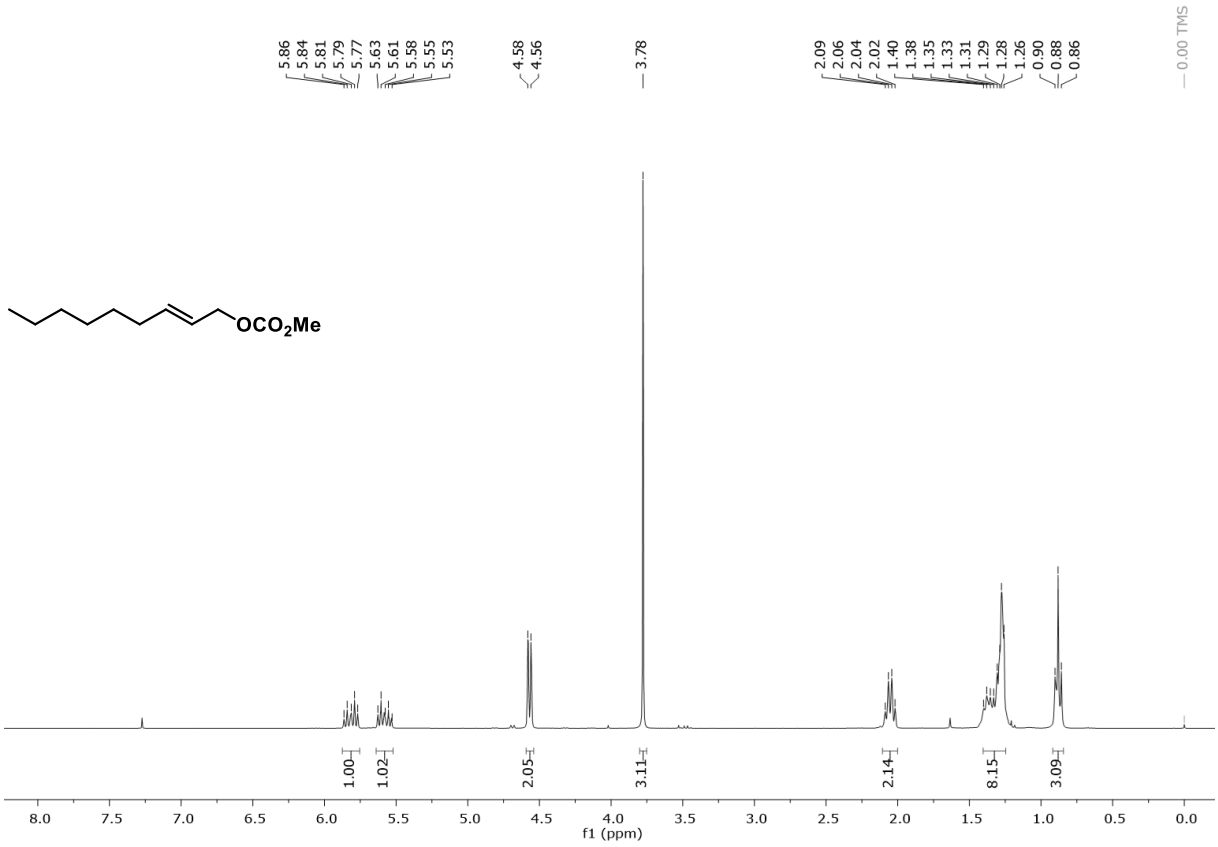


*Figure 41: ^{1}H NMR (300 MHz, $CDCl_3$) of (E)-methyl non-2-en-1-yl carbonate (**124**).*

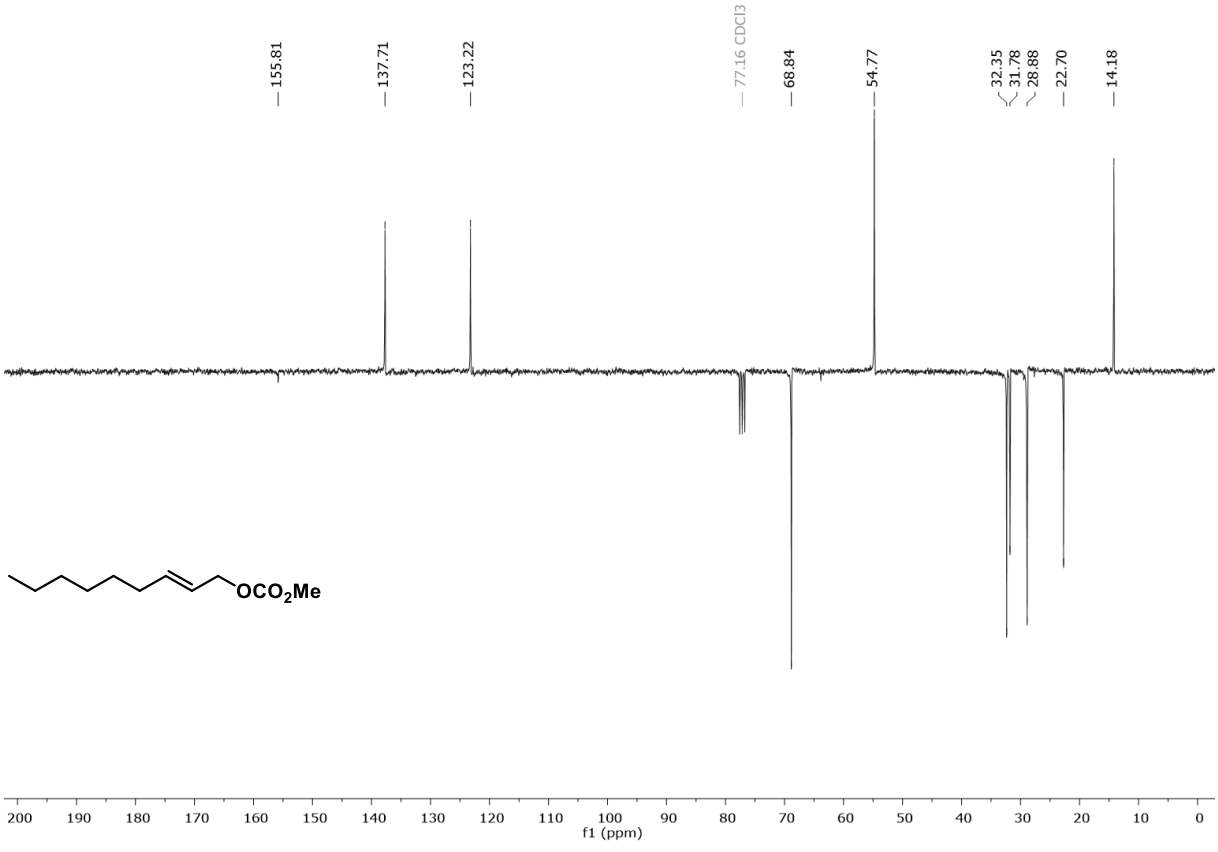


*Figure 42: ^{13}C NMR (75 MHz, $CDCl_3$) of (E)-methyl non-2-en-1-yl carbonate (**124**).*

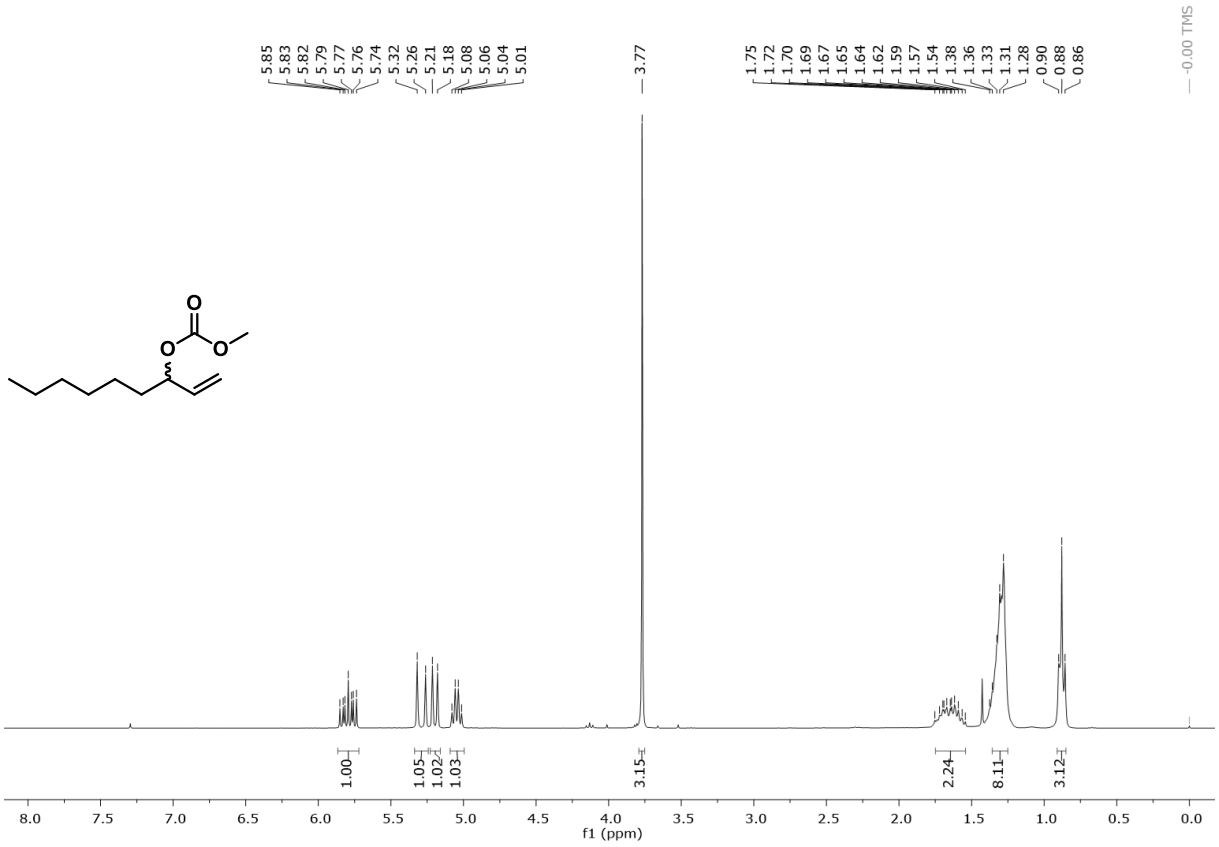


*Figure 43: ^{1}H NMR (300 MHz, $CDCl_3$) of methyl non-1-en-3-yl carbonate (rac-**190**).*

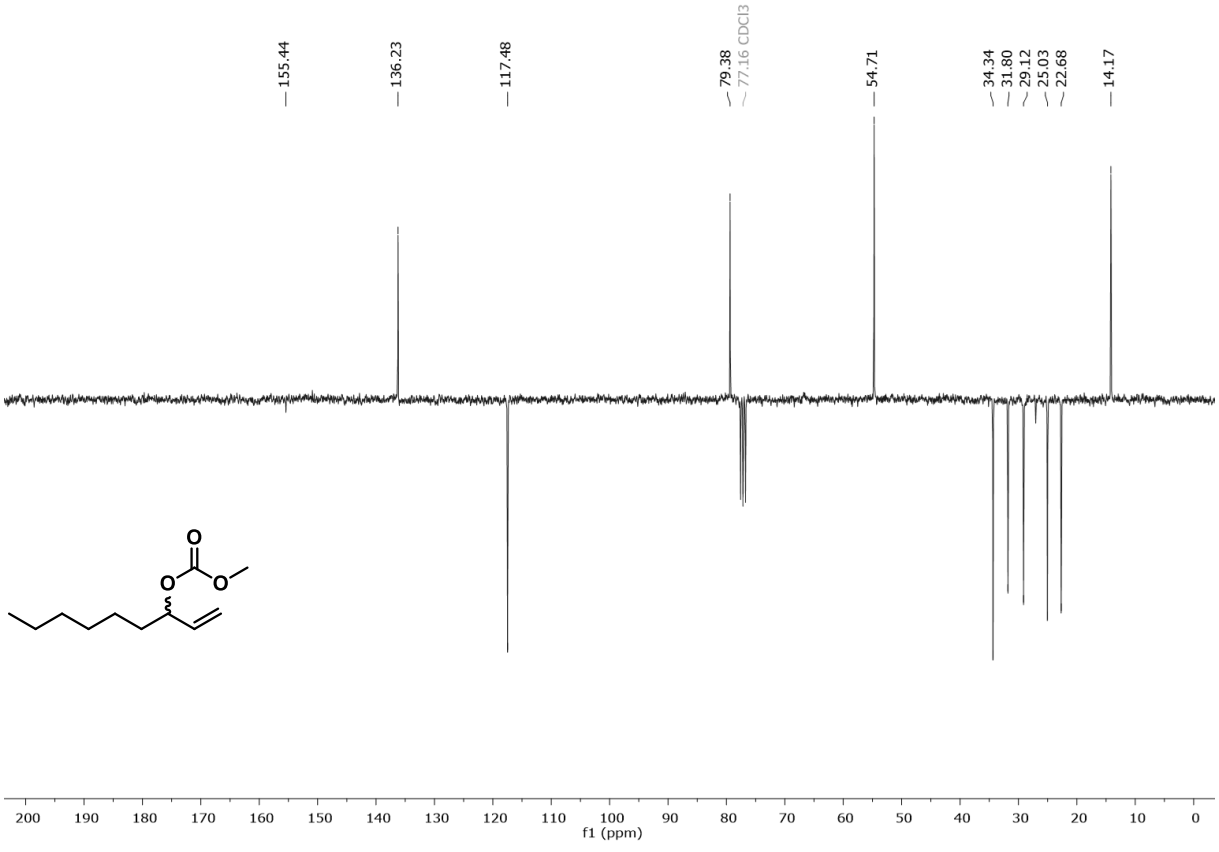


*Figure 44: ^{13}C NMR (75 MHz, $CDCl_3$) of methyl non-1-en-3-yl carbonate (rac-**190**).*

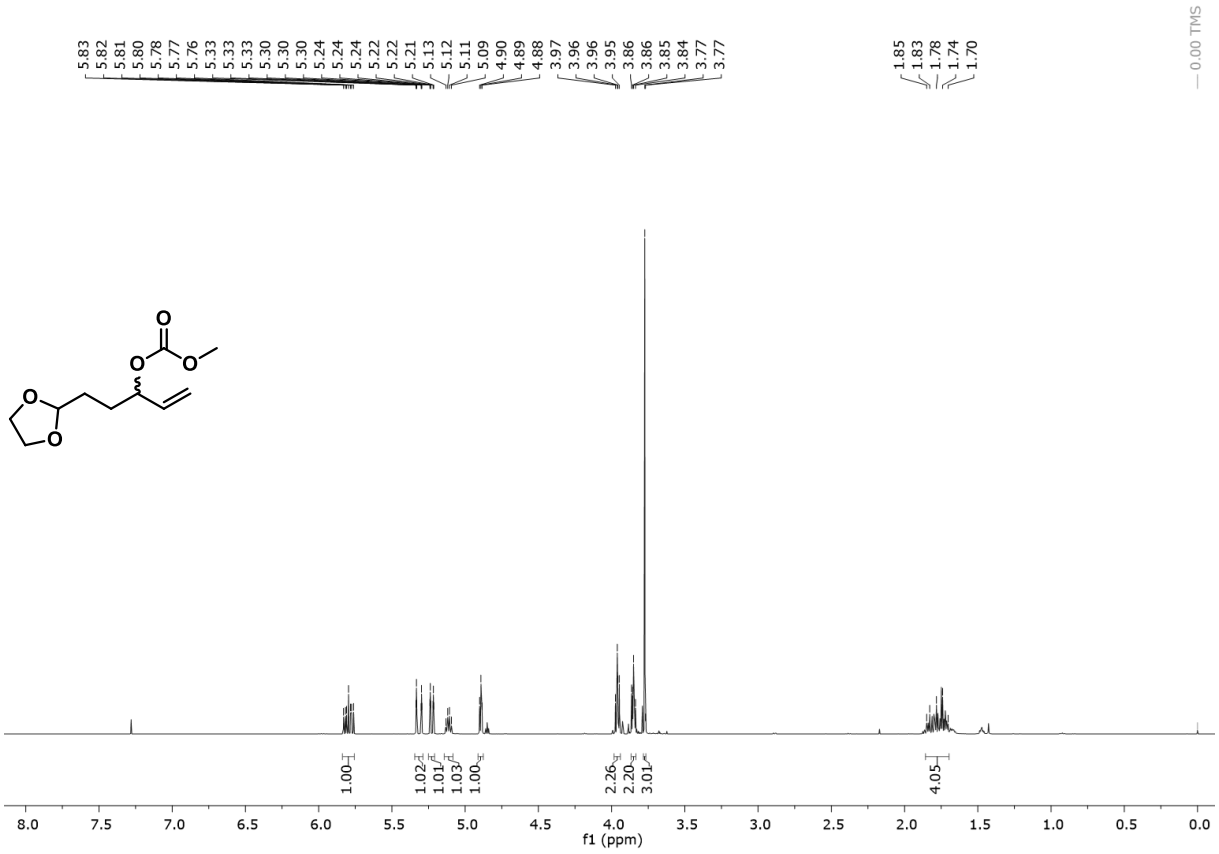


*Figure 45: ^{1}H NMR (500 MHz, $CDCl_3$) of 5-(1,3-dioxolan-2-yl)pent-1-en-3-yl methyl carbonate (rac-**160**).*

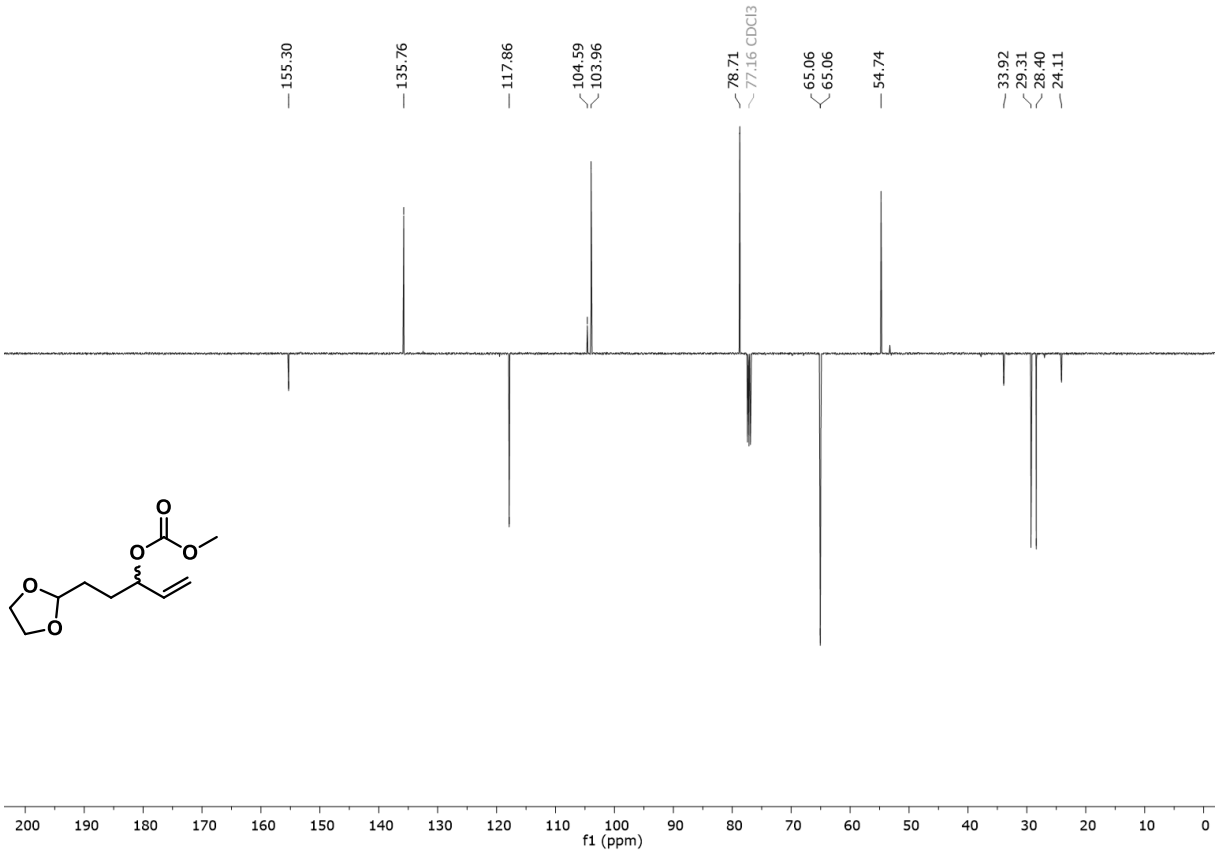


*Figure 46: ^{13}C NMR (121 MHz, $CDCl_3$) of 5-(1,3-dioxolan-2-yl)pent-1-en-3-yl methyl carbonate (rac-**160**).*

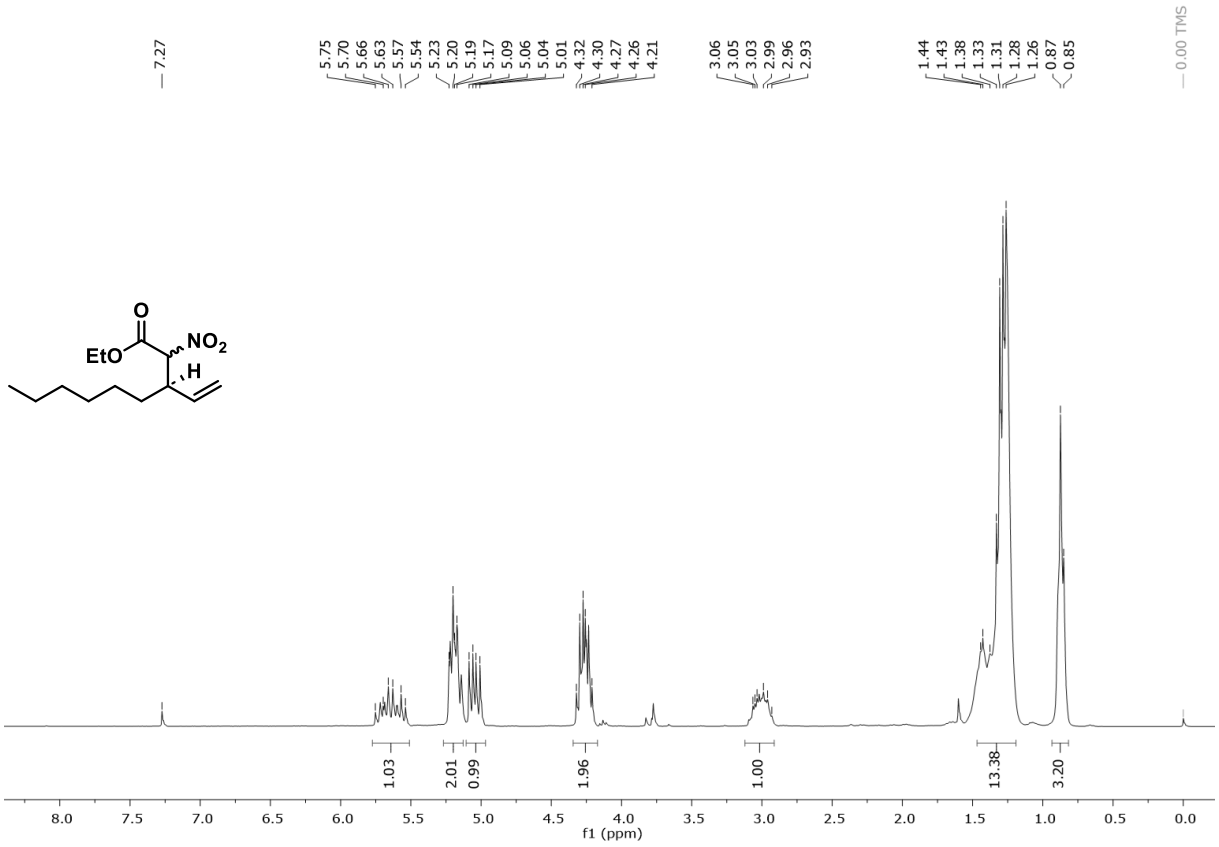


*Figure 47: ^{1}H NMR (500 MHz, $CDCl_3$) of ethyl (3R)-2-nitro-3-vinylnonanoate (**189**).*

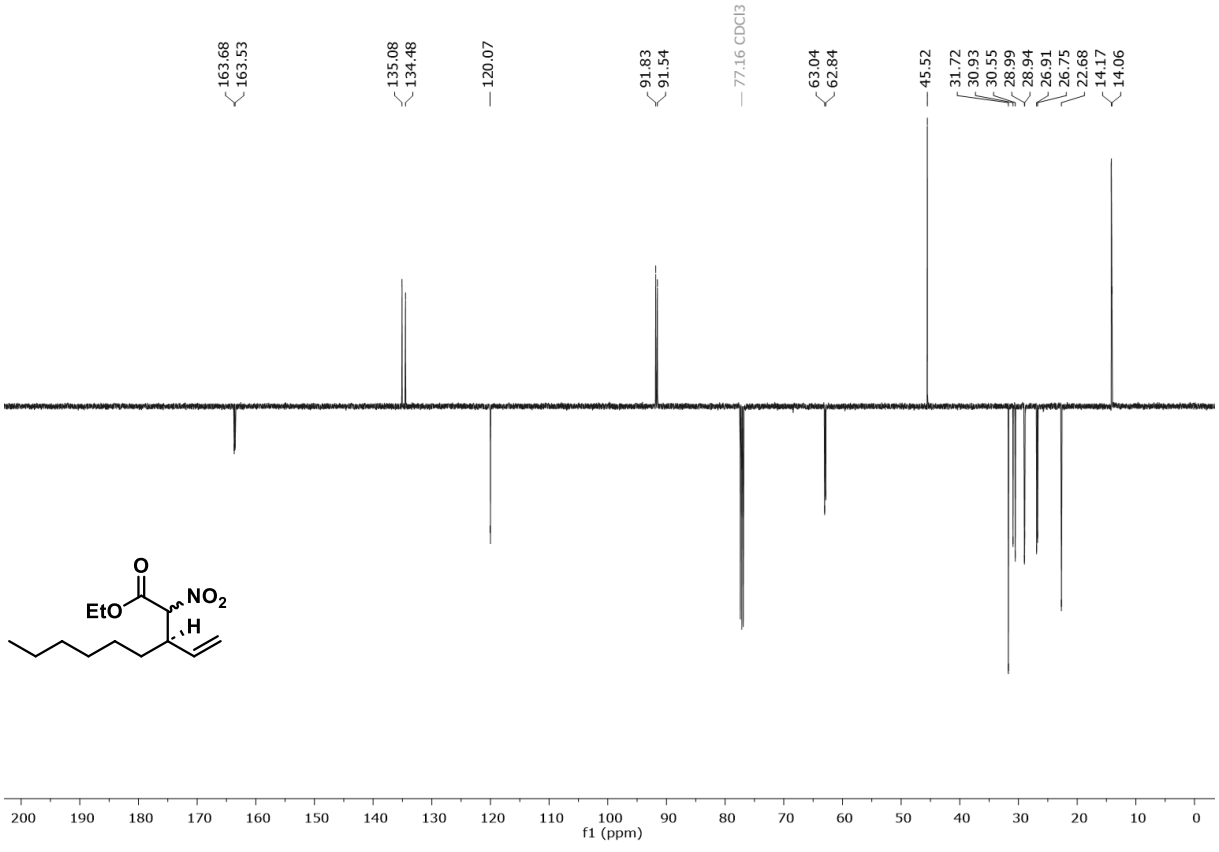


*Figure 48: ^{13}C NMR (126 MHz, $CDCl_3$) of ethyl (3R)-2-nitro-3-vinylnonanoate (**189**).*

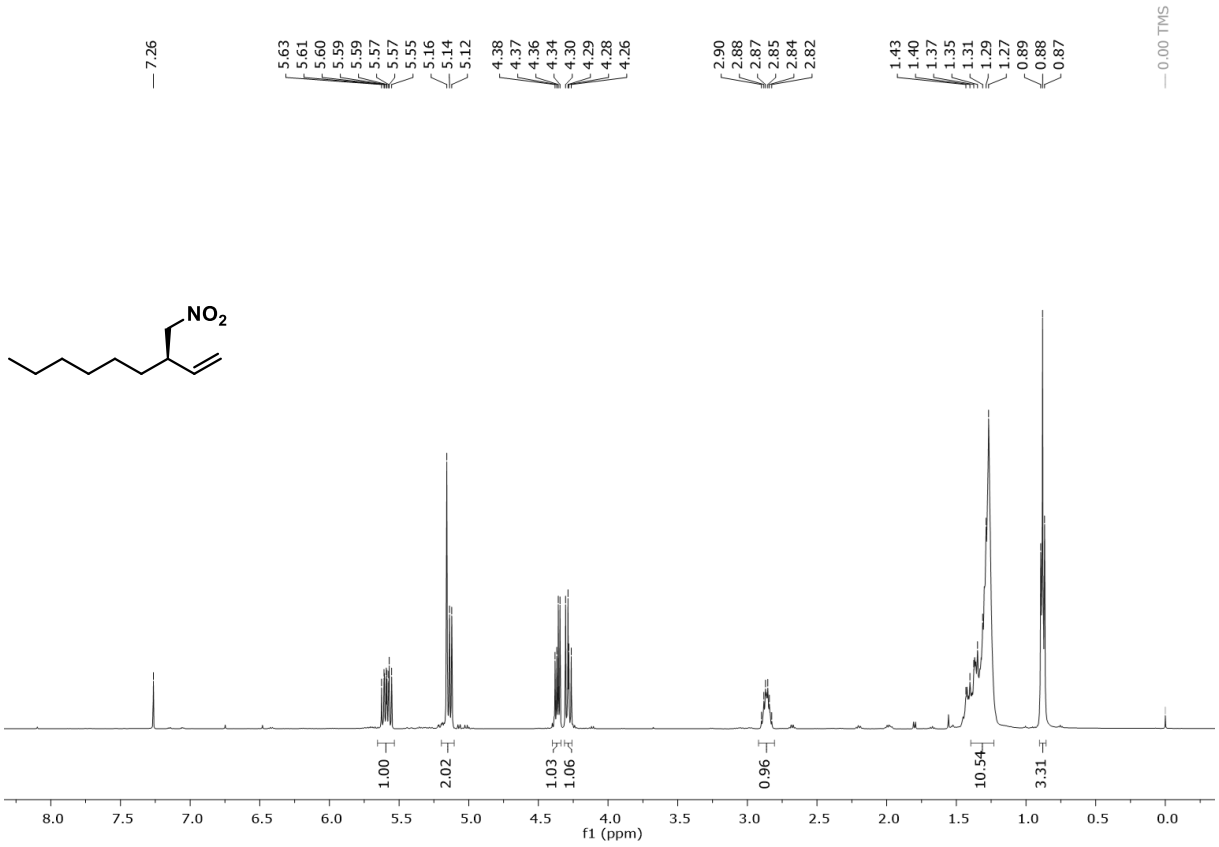


*Figure 49: ^{1}H NMR (500 MHz, $CDCl_3$) of (R)-3-(nitromethyl)non-1-ene (**123**).*

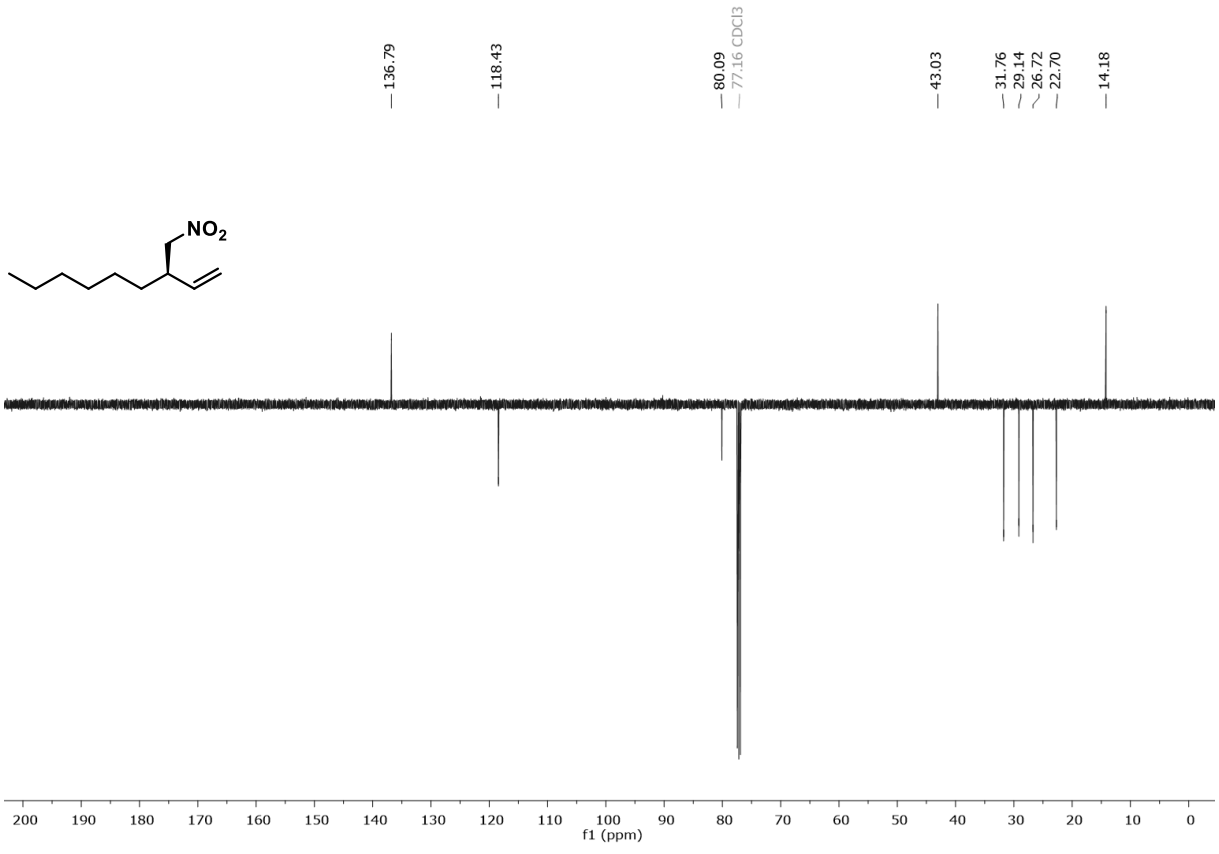


*Figure 50: ^{13}C NMR (126 MHz, $CDCl_3$) of (R)-3-(nitromethyl)non-1-ene (**123**).*

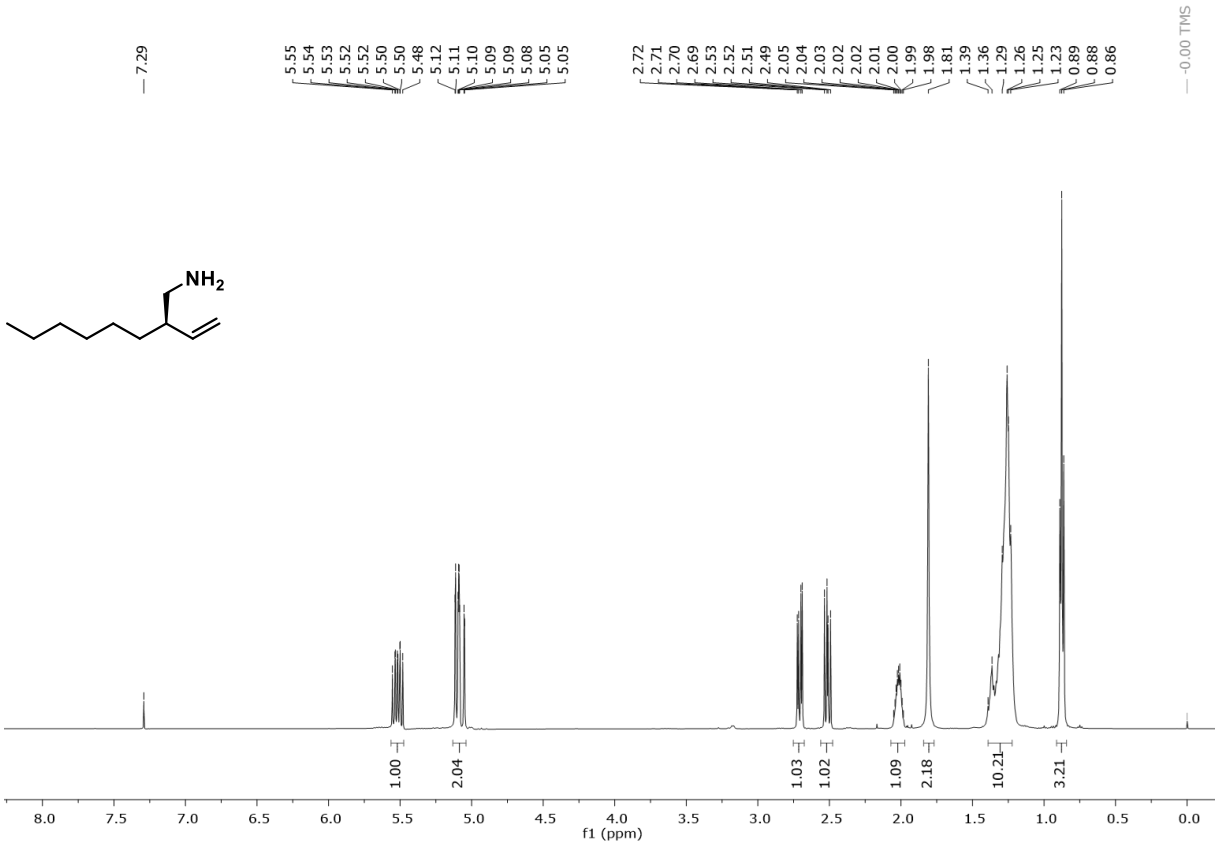


*Figure 51: ^{1}H NMR (500 MHz, $CDCl_3$) of (R)-2-vinyloctan-1-amine (**122**).*

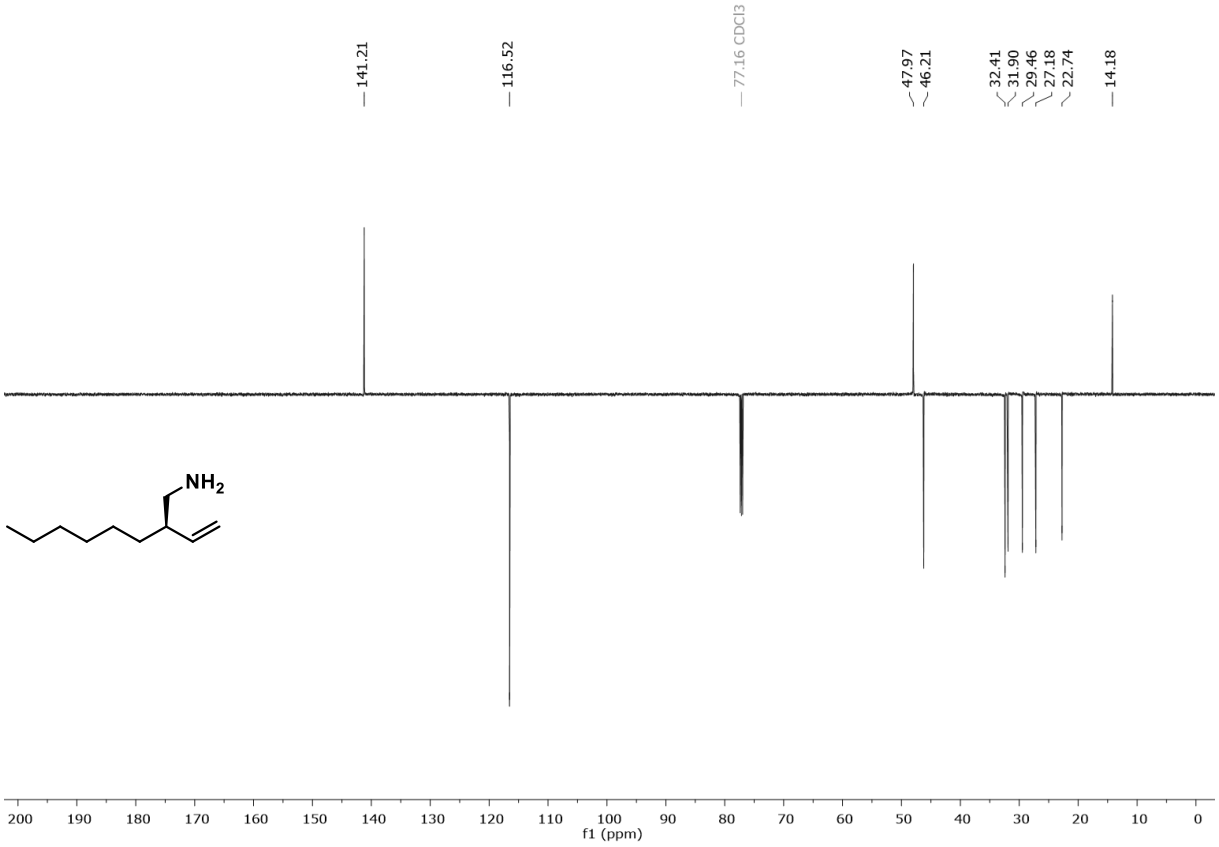


*Figure 52: ^{13}C NMR (500 MHz, $CDCl_3$) of (R)-2-vinyloctan-1-amine (**122**).*

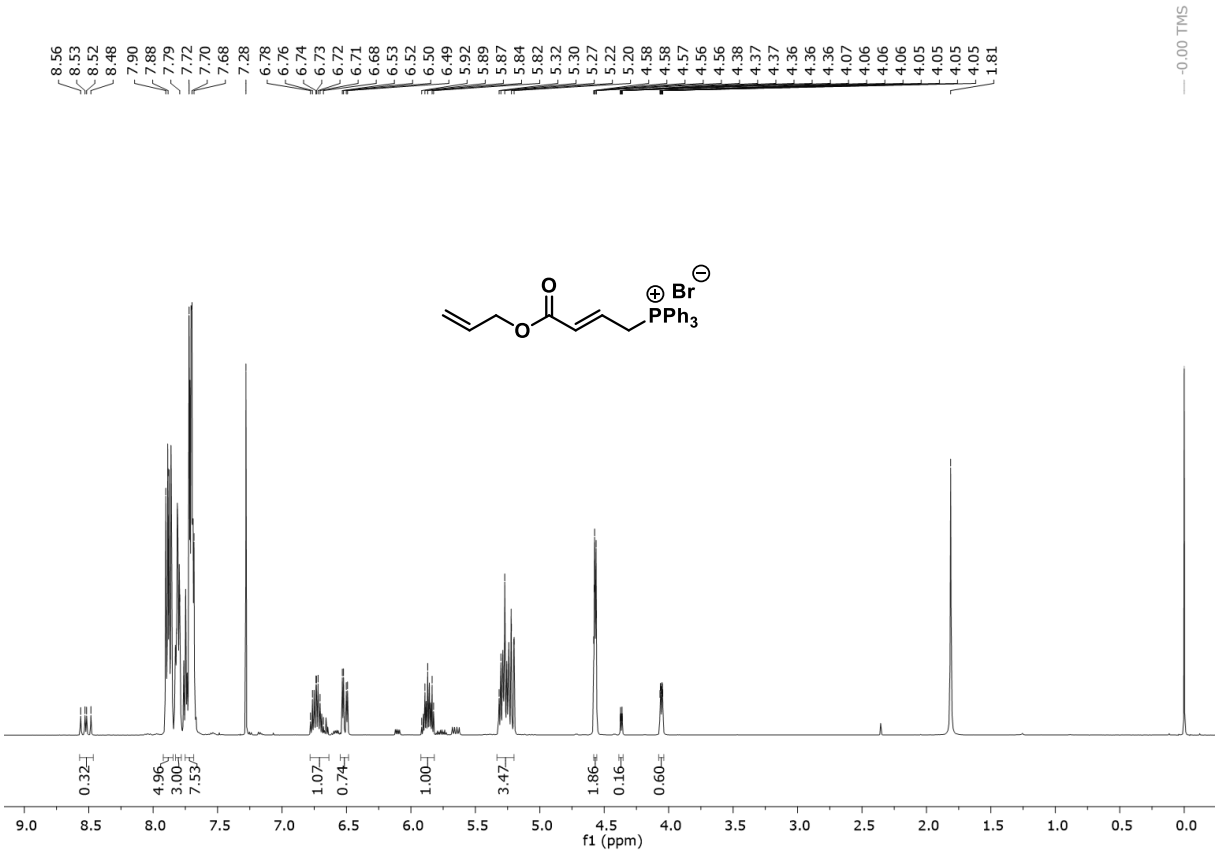


*Figure 53: ^{1}H NMR (500 MHz, $CDCl_3$) of (E)-(4-(allyloxy)-4-oxobut-2-en-1-yl)triphenylphosphonium bromide (**181**).*

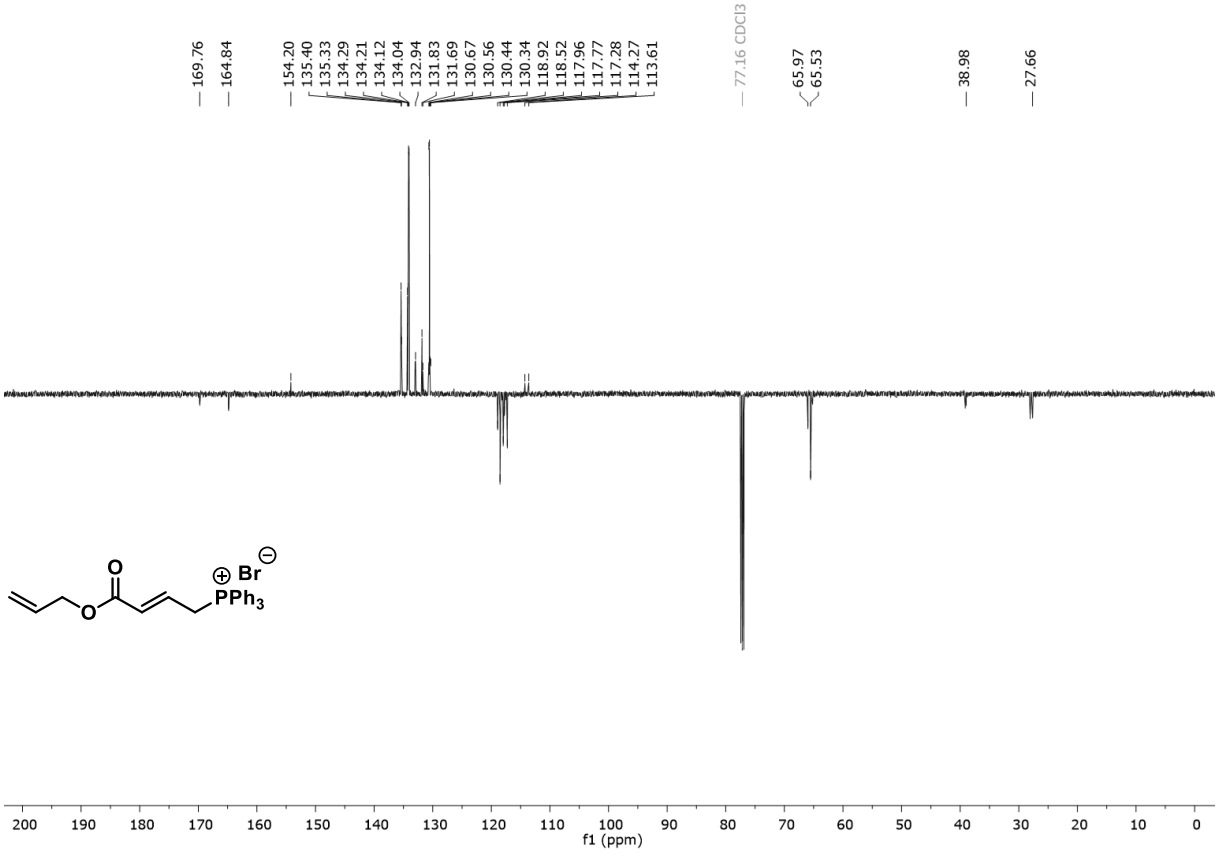


*Figure 54: ^{13}C NMR (126 MHz, $CDCl_3$) of (E)-(4-(allyloxy)-4-oxobut-2-en-1-yl)triphenylphosphonium bromide (**181**).*

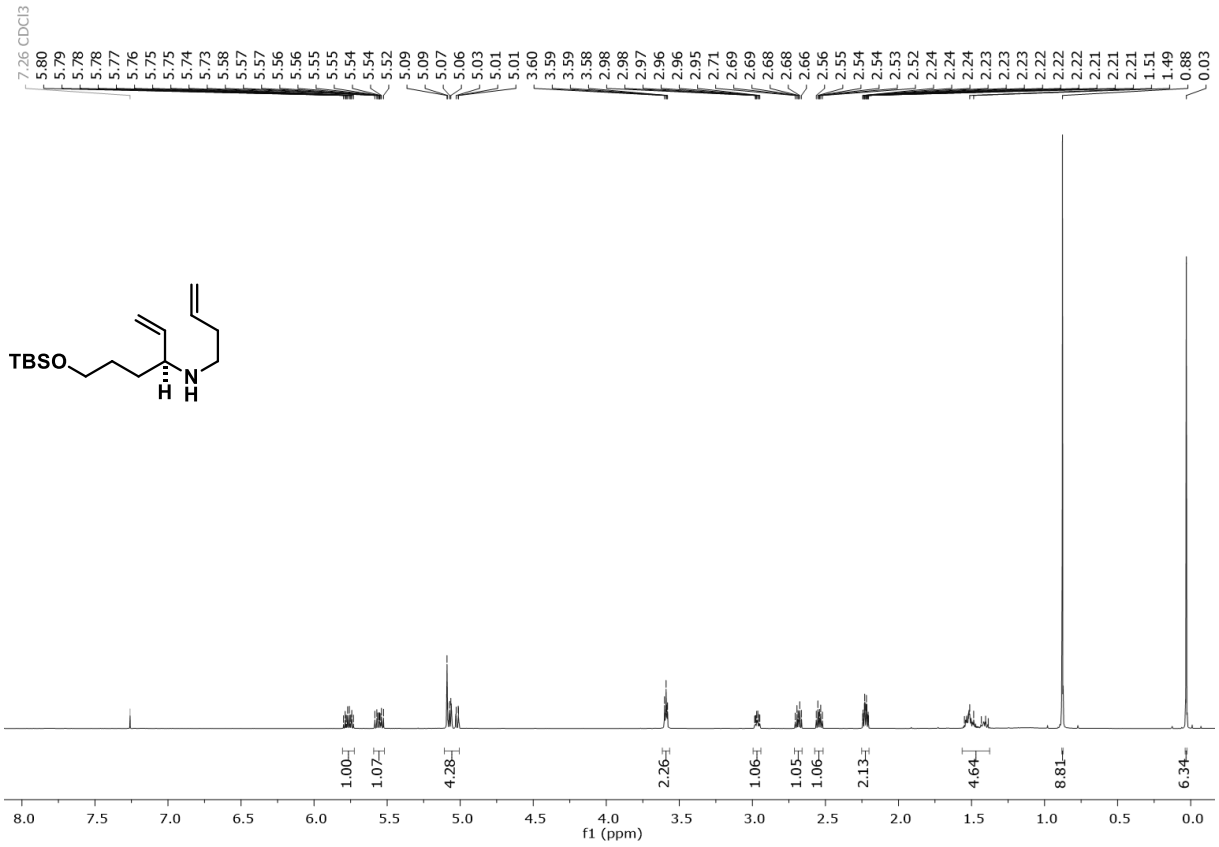


*Figure 55: [1]H NMR (600 MHz, $CDCl_3$) of (S)-N-(but-3-en-1-yl)-6-((tert-butyldimethylsilyl)oxy)hex-1-en-3- amine (**149**).*

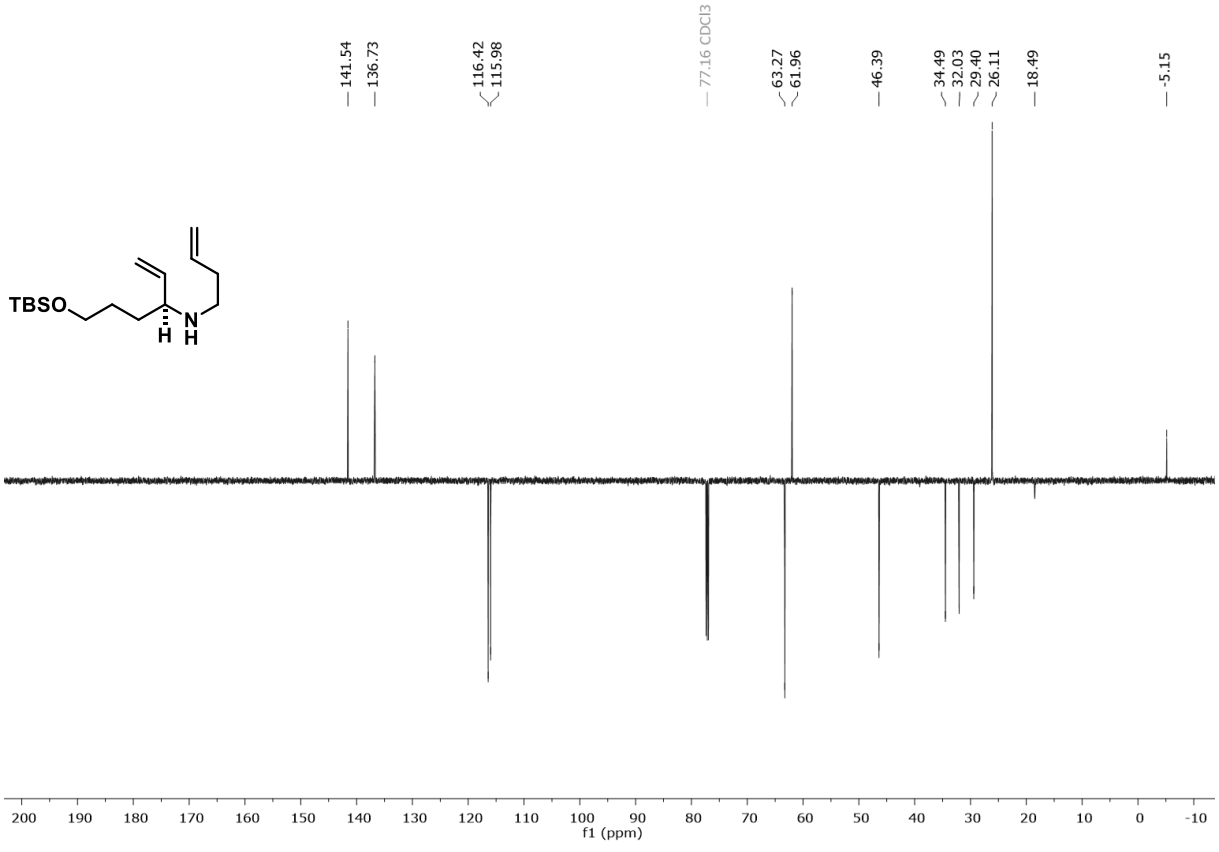


*Figure 56: [13]C NMR (151 MHz, $CDCl_3$) of (S)-N-(but-3-en-1-yl)-6-((tert-butyldimethylsilyl)oxy)hex-1-en-3- amine (**149**).*

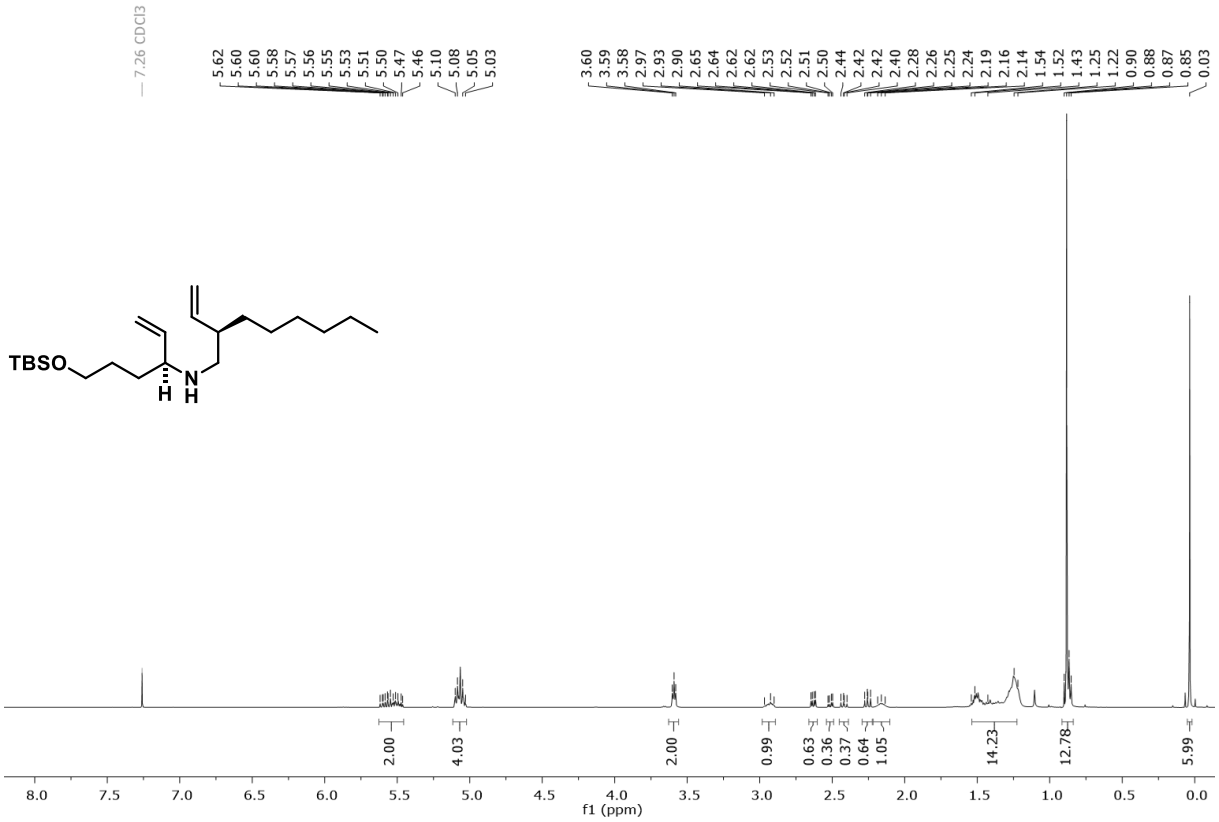


*Figure 57: [1]H NMR (500 MHz, $CDCl_3$) of (R)-N-((S)-6-((tert-butyldimethylsilyl)oxy)hex-1-en-3-yl)-2- vinyloctan-1-amine (**150**).*

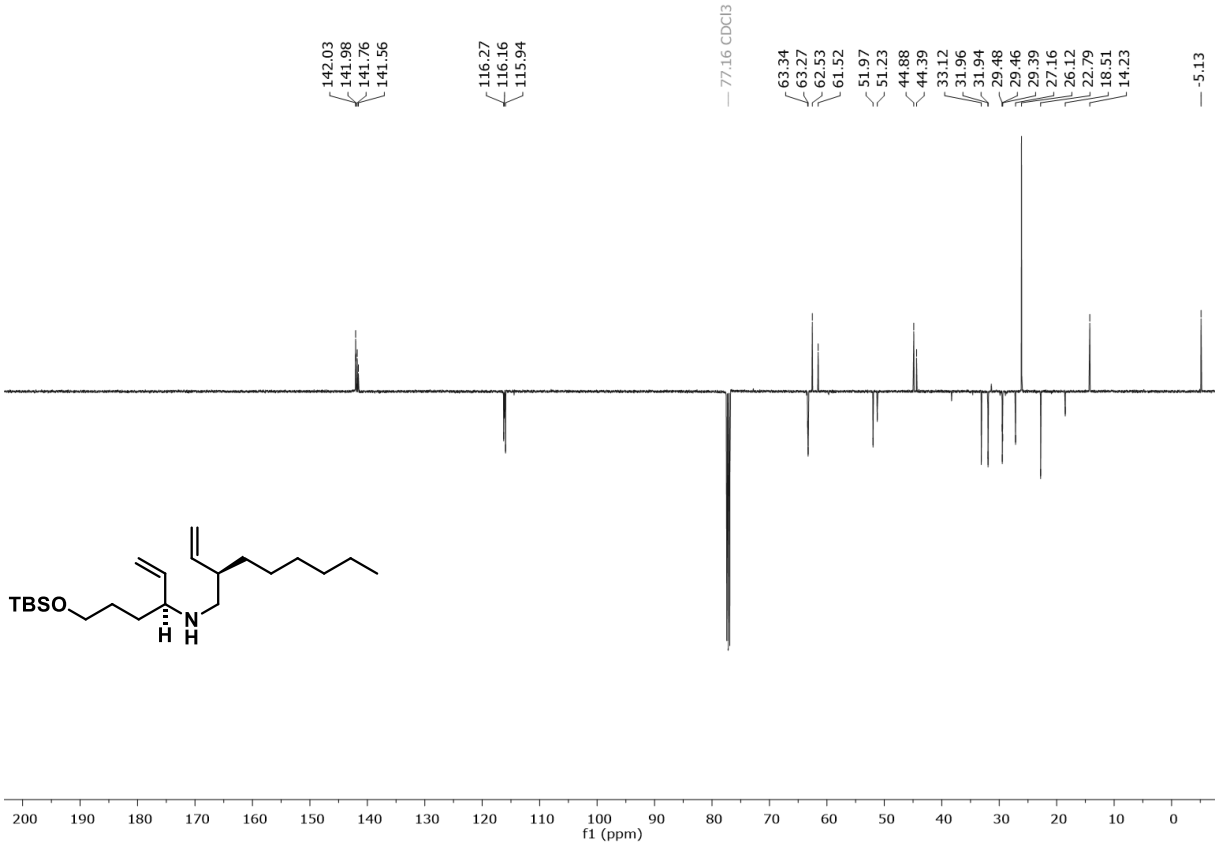


*Figure 58: [13]C NMR (126 MHz, $CDCl_3$) of (R)-N-((S)-6-((tert-butyldimethylsilyl)oxy)hex-1-en-3-yl)-2- vinyloctan-1-amine (**150**).*

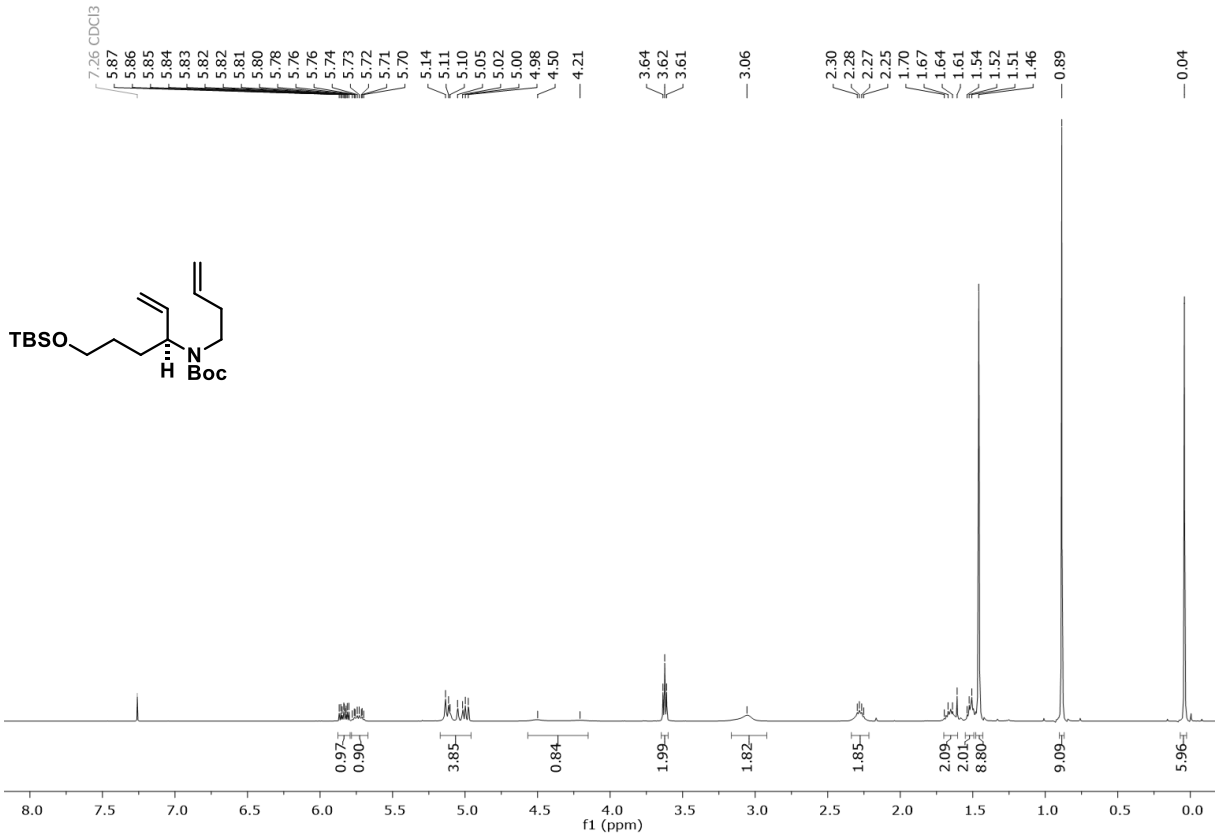


*Figure 59: ^{1}H NMR (500 MHz, $CDCl_3$) of tert-butyl (S)-but-3-en-1-yl(6-((tert-butyldimethylsilyl)oxy)hex-1- en-3-yl)carbamate (**133a**).*

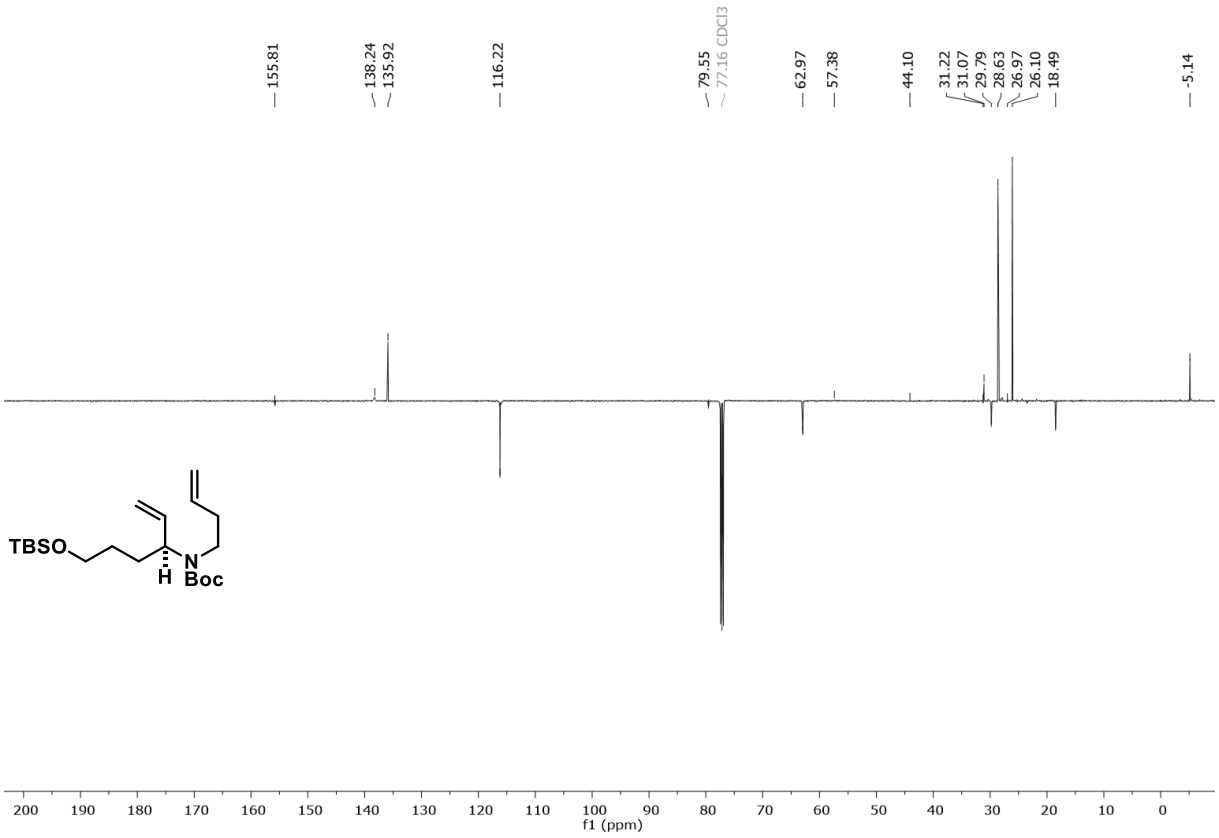


*Figure 60: ^{13}C NMR (126 MHz, $CDCl_3$) of tert-butyl (S)-but-3-en-1-yl(6-((tert-butyldimethylsilyl)oxy)hex-1- en-3-yl)carbamate (**133a**).*

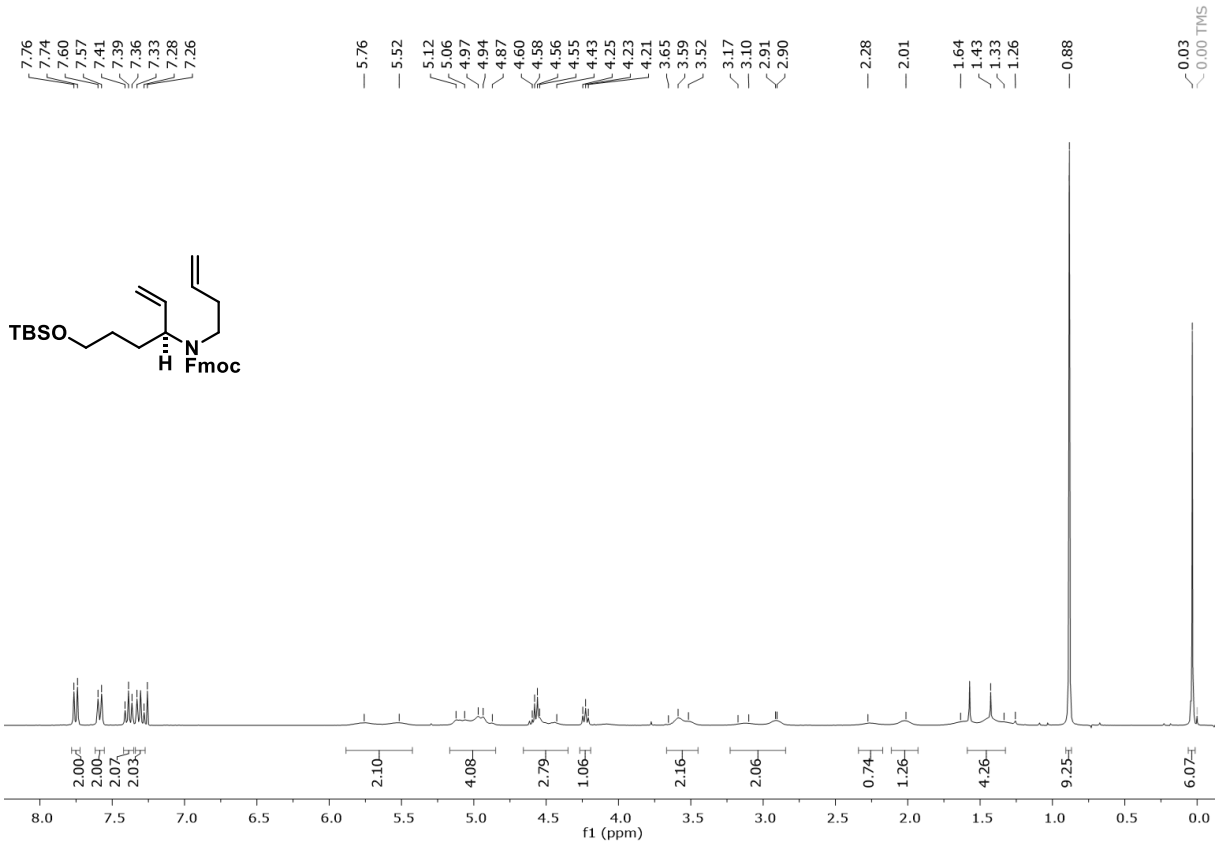


*Figure 61: [1]H NMR (500 MHz, $CDCl_3$) of 9H-fluoren-9-yl)methyl (S)-but-3-en-1-yl(6-((tert-butyldimethylsilyl)oxy)hex-1-en-3-yl)carbamate (**133b**).*

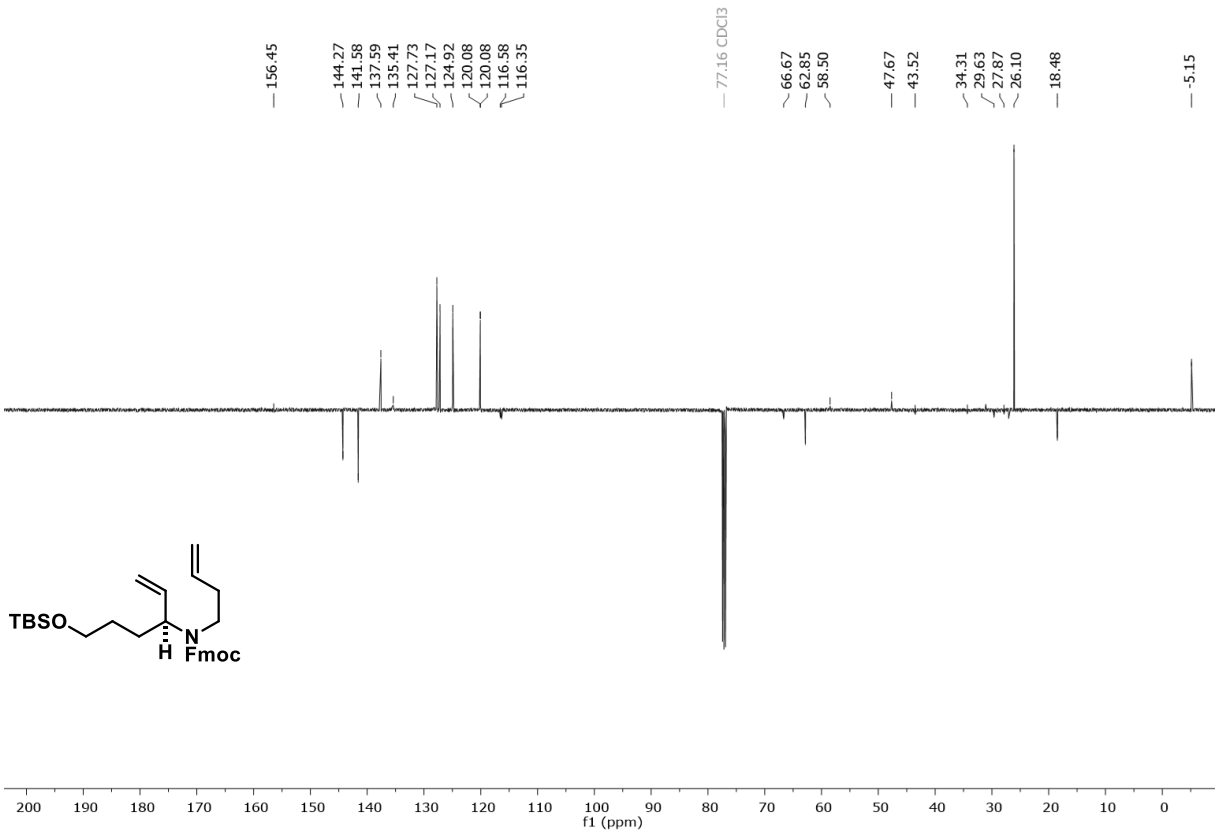


*Figure 62: [13]C NMR (126 MHz, $CDCl_3$) of 9H-fluoren-9-yl)methyl (S)-but-3-en-1-yl(6-((tert-butyldimethylsilyl)oxy)hex-1-en-3-yl)carbamate (**133b**).*

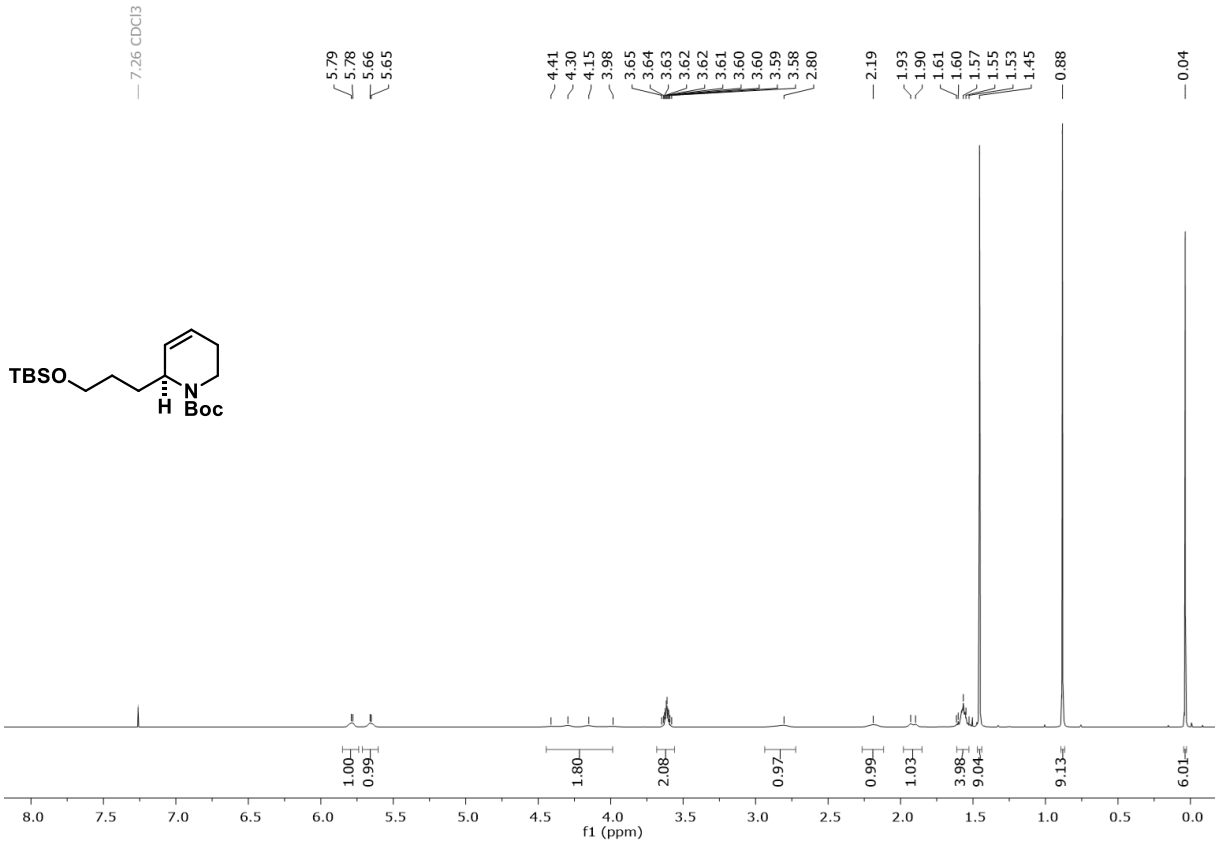


*Figure 63: ^{1}H NMR (500 MHz, $CDCl_3$) of tert-butyl (S)-6-(3-((tert-butyldimethylsilyl)oxy)propyl)-3,6- dihydropyridine-1(2H)-carboxylate (**132a**).*

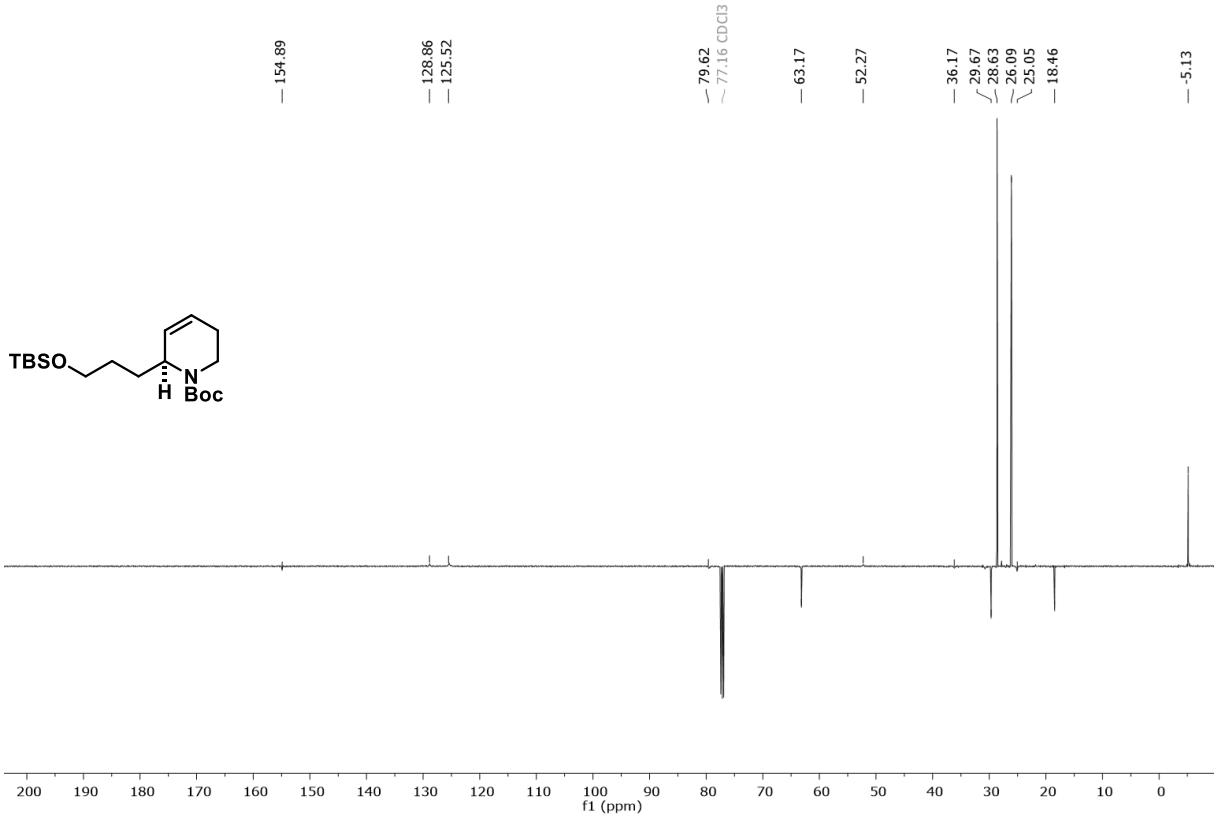


*Figure 64: ^{13}C NMR (126 MHz, $CDCl_3$) of tert-butyl (S)-6-(3-((tert-butyldimethylsilyl)oxy)propyl)-3,6- dihydropyridine-1(2H)-carboxylate (**132a**).*

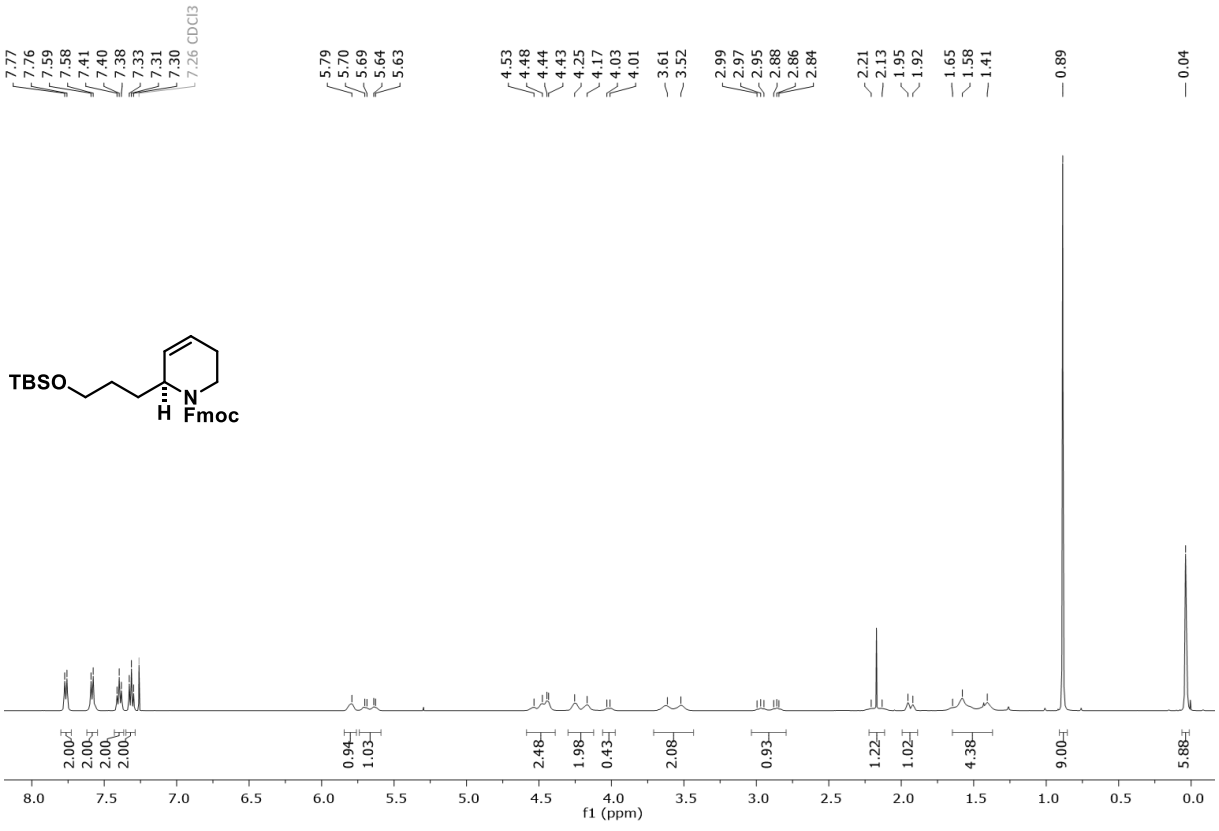


*Figure 65: ^{1}H NMR (500 MHz, $CDCl_3$) of (9H-fluoren-9-yl)methyl (S)-6-(3-((tert-butyldimethylsilyl)oxy)propyl)-3,6-dihydropyridine-1(2H)-carboxylate (**132b**).*

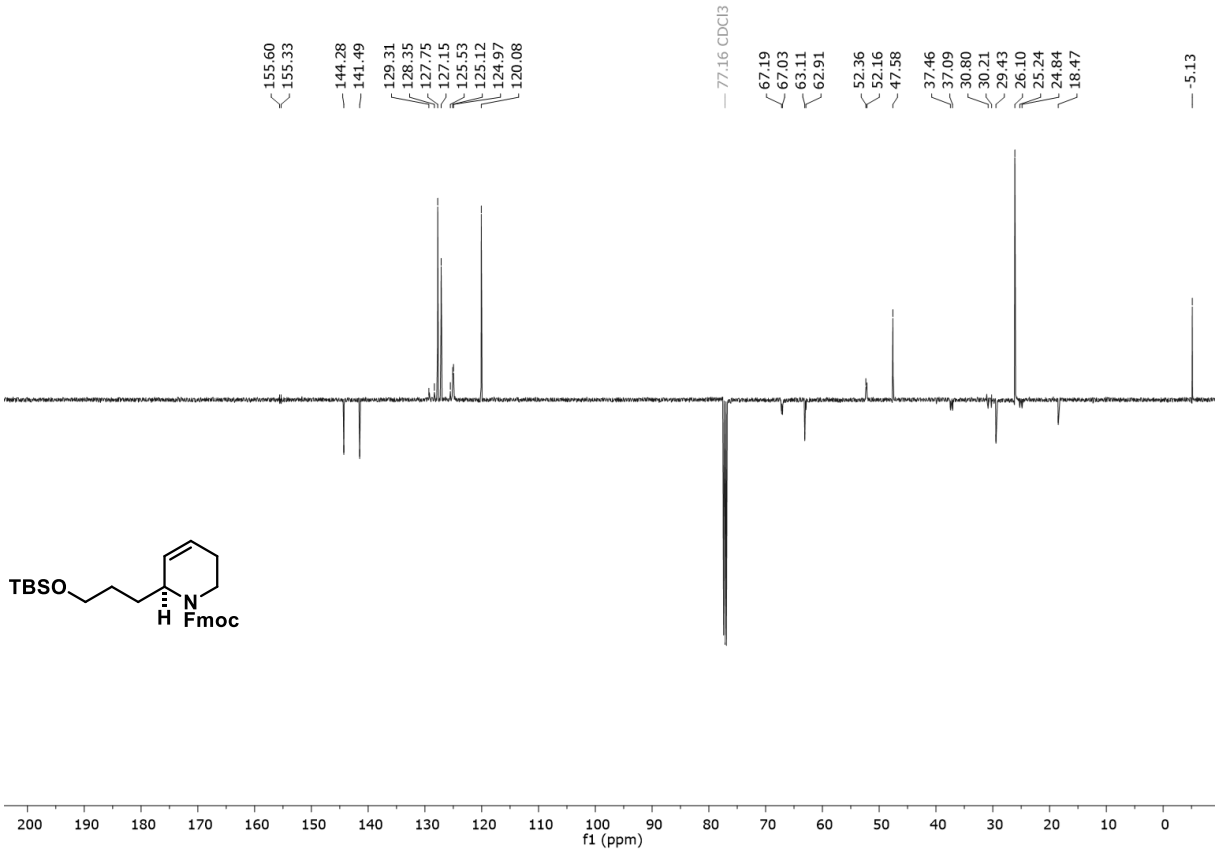


*Figure 66: ^{13}C NMR (126 MHz, $CDCl_3$) of (9H-fluoren-9-yl)methyl (S)-6-(3-((tert-butyldimethylsilyl)oxy)propyl)-3,6-dihydropyridine-1(2H)-carboxylate (**132b**).*

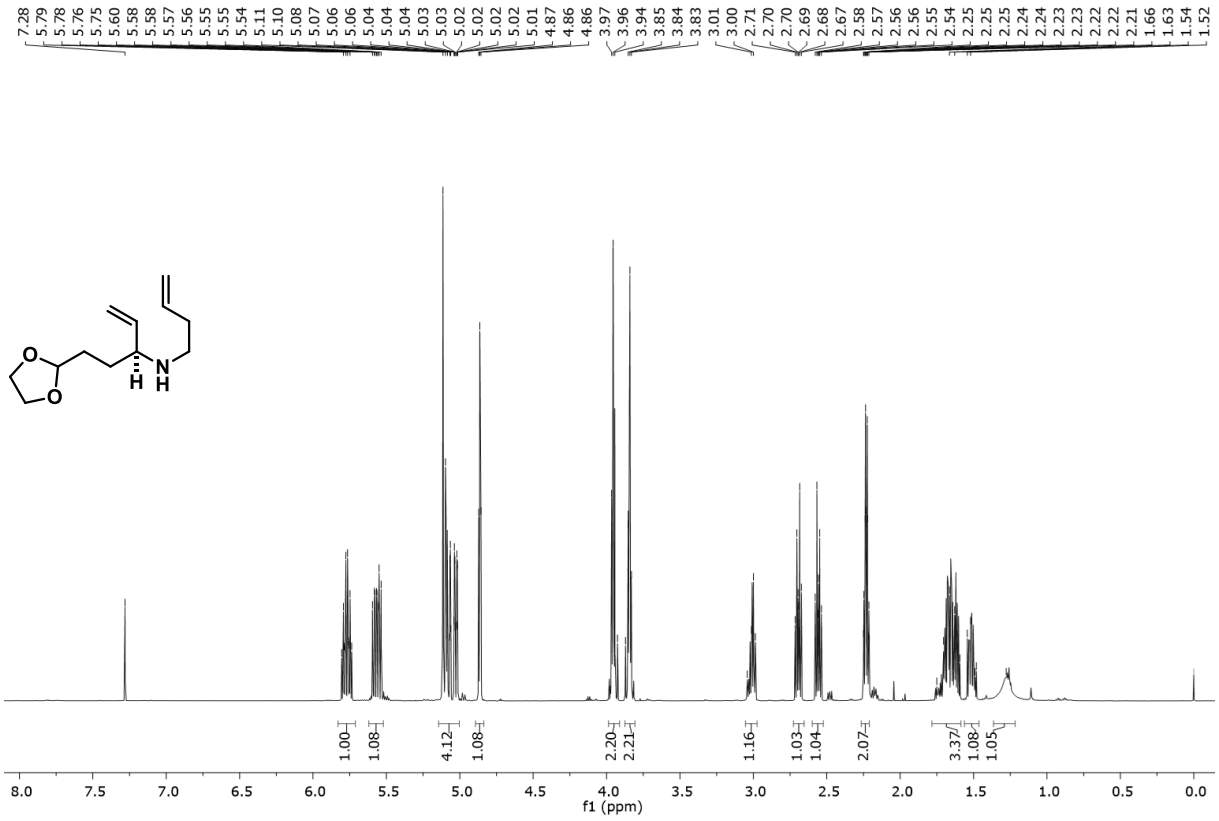


*Figure 67: ^{1}H NMR (600 MHz, $CDCl_3$) of (S)-N-(but-3-en-1-yl)-5-(1,3-dioxolan-2-yl)pent-1-en-3-amine (**164**).*

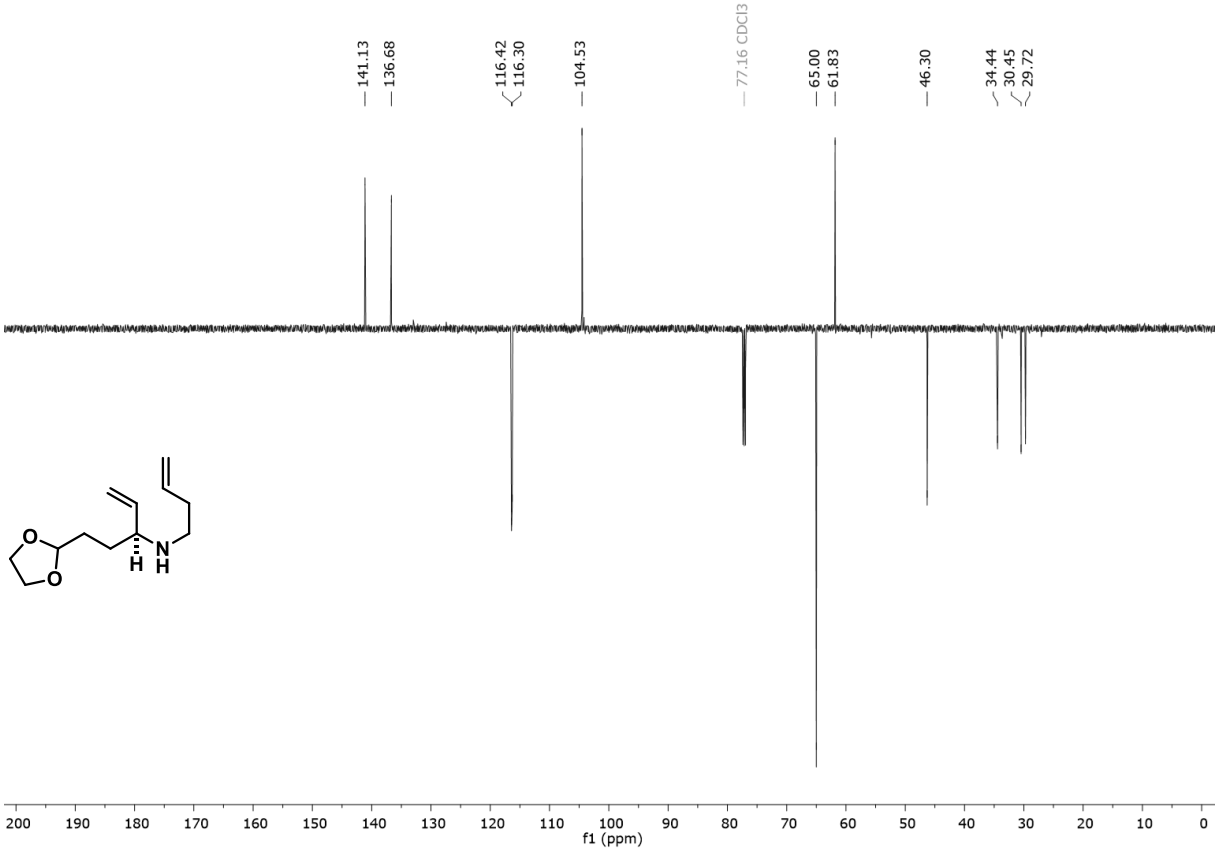


*Figure 68: ^{13}C NMR (151 MHz, $CDCl_3$) of (S)-N-(but-3-en-1-yl)-5-(1,3-dioxolan-2-yl)pent-1-en-3-amine (**164**).*

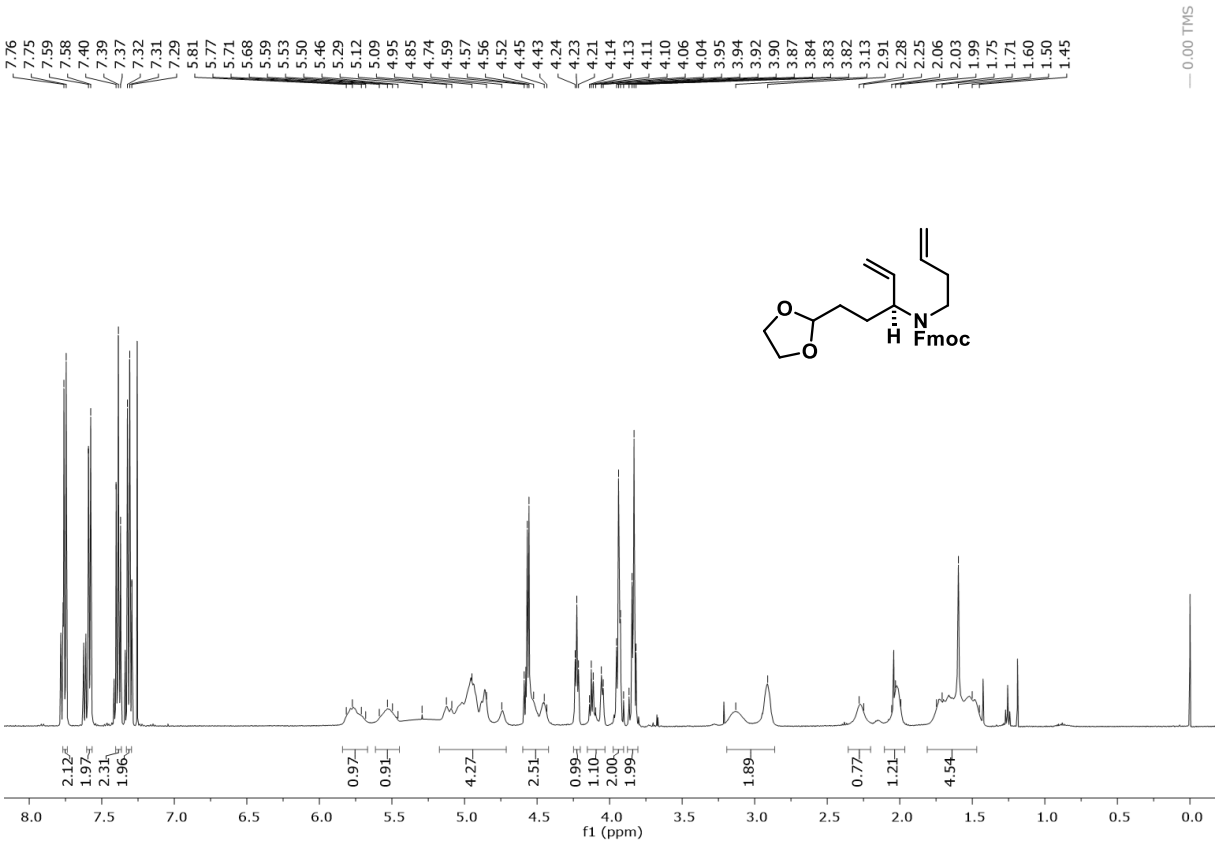


*Figure 69: [1]H NMR (500 MHz, $CDCl_3$) of (9H-fluoren-9-yl)methyl (S)-(5-(1,3-dioxolan-2-yl)pent-1-en-3- yl)(but-3-en-1-yl)carbamate (**159a**).*

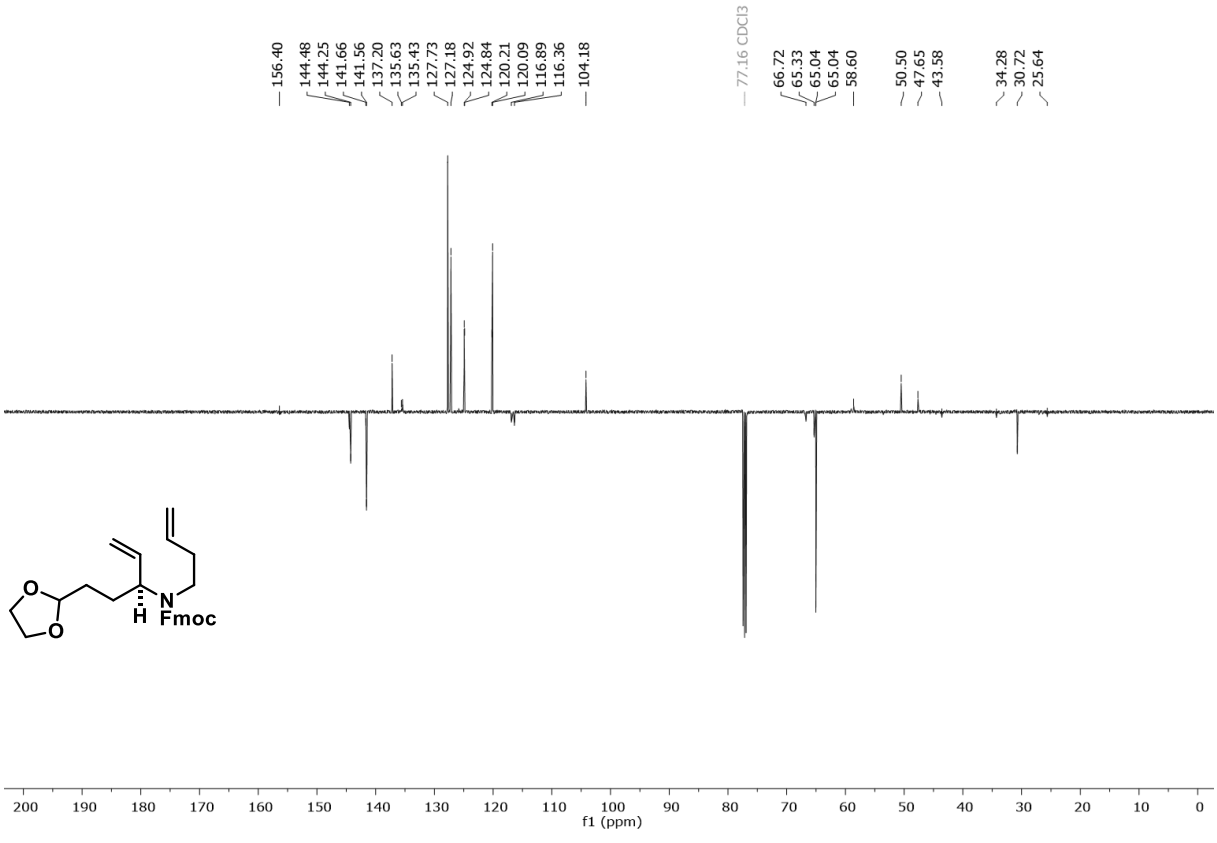


*Figure 70: [13]C NMR (126 MHz, $CDCl_3$) of (9H-fluoren-9-yl)methyl (S)-(5-(1,3-dioxolan-2-yl)pent-1-en-3- yl)(but-3-en-1-yl)carbamate (**159a**).*

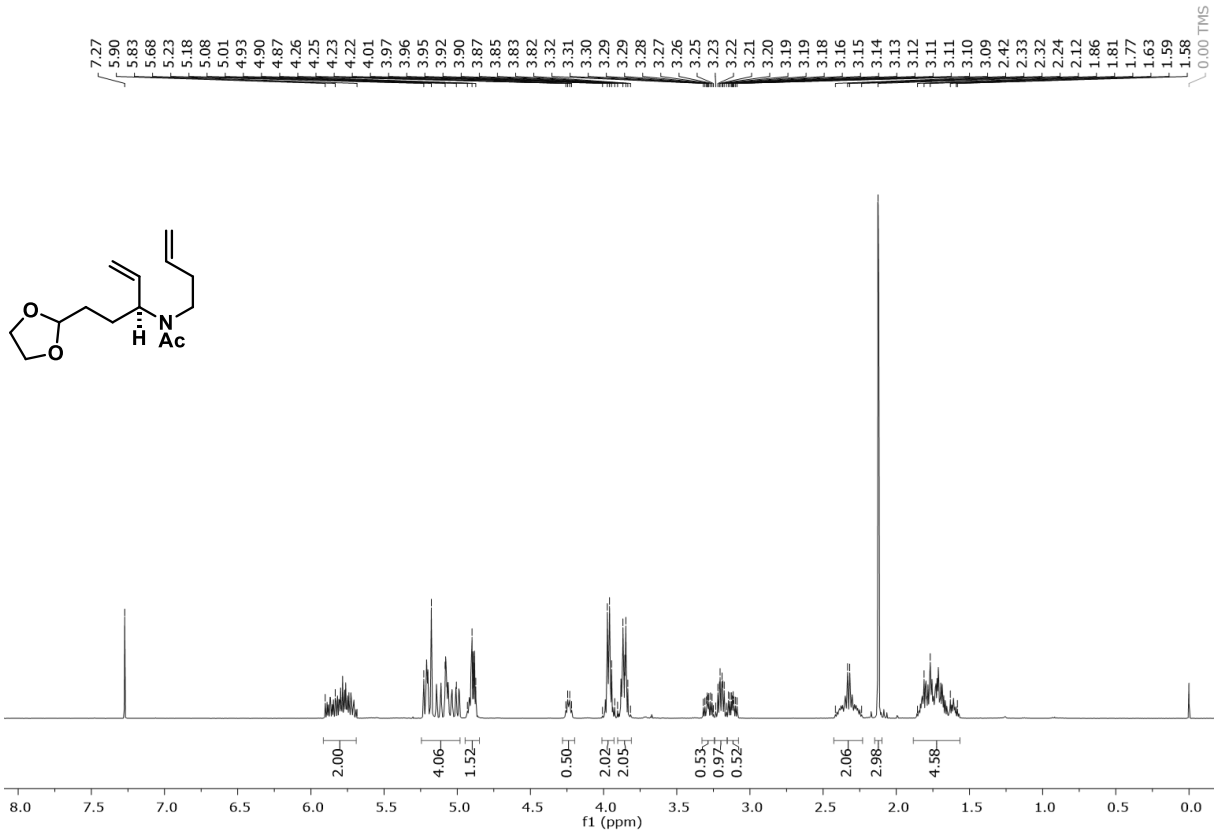


*Figure 71: ^{1}H NMR (500 MHz, $CDCl_3$) of (S)-N-(5-(1,3-dioxolan-2-yl)pent-1-en-3-yl)-N-(but-3-en-1- yl)acetamide (**159b**).*

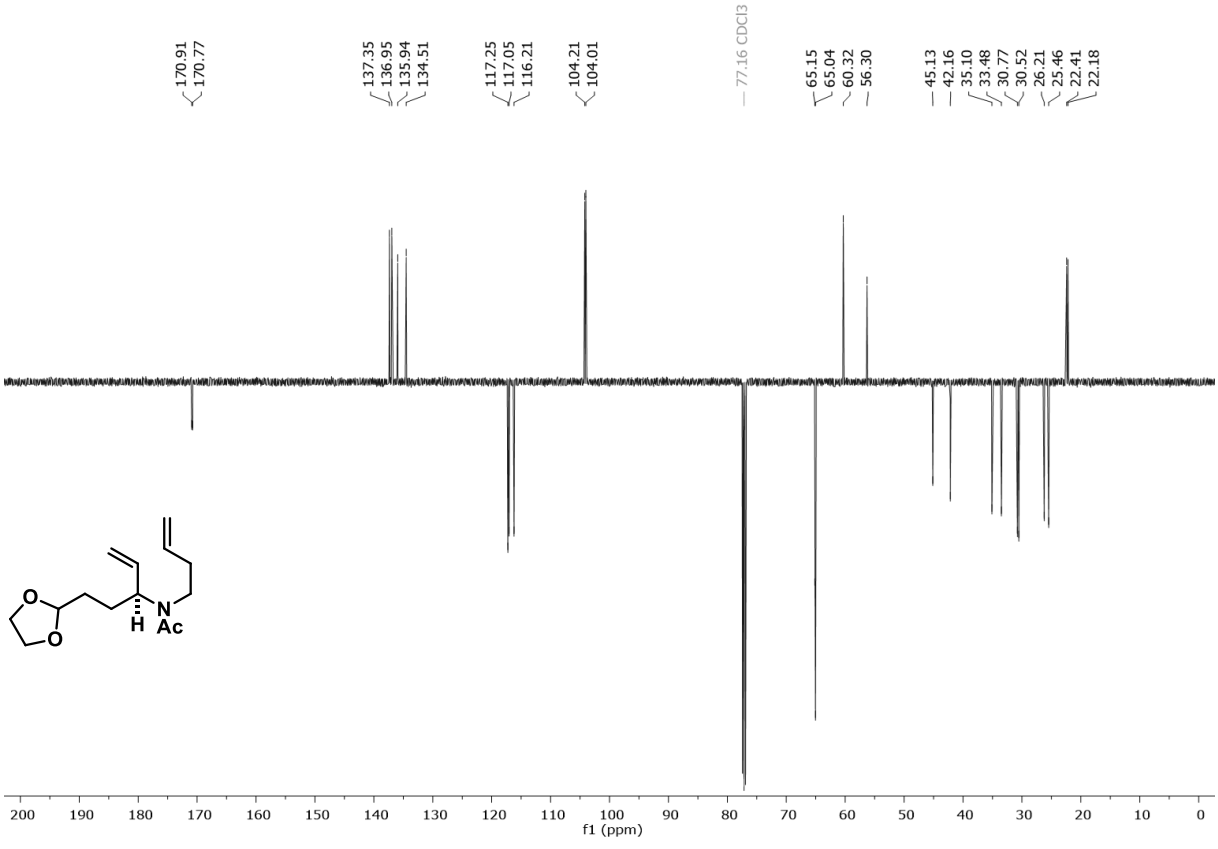


*Figure 72: ^{13}C NMR (126 MHz, $CDCl_3$) of (S)-N-(5-(1,3-dioxolan-2-yl)pent-1-en-3-yl)-N-(but-3-en-1-yl)acetamide (**159b**).*

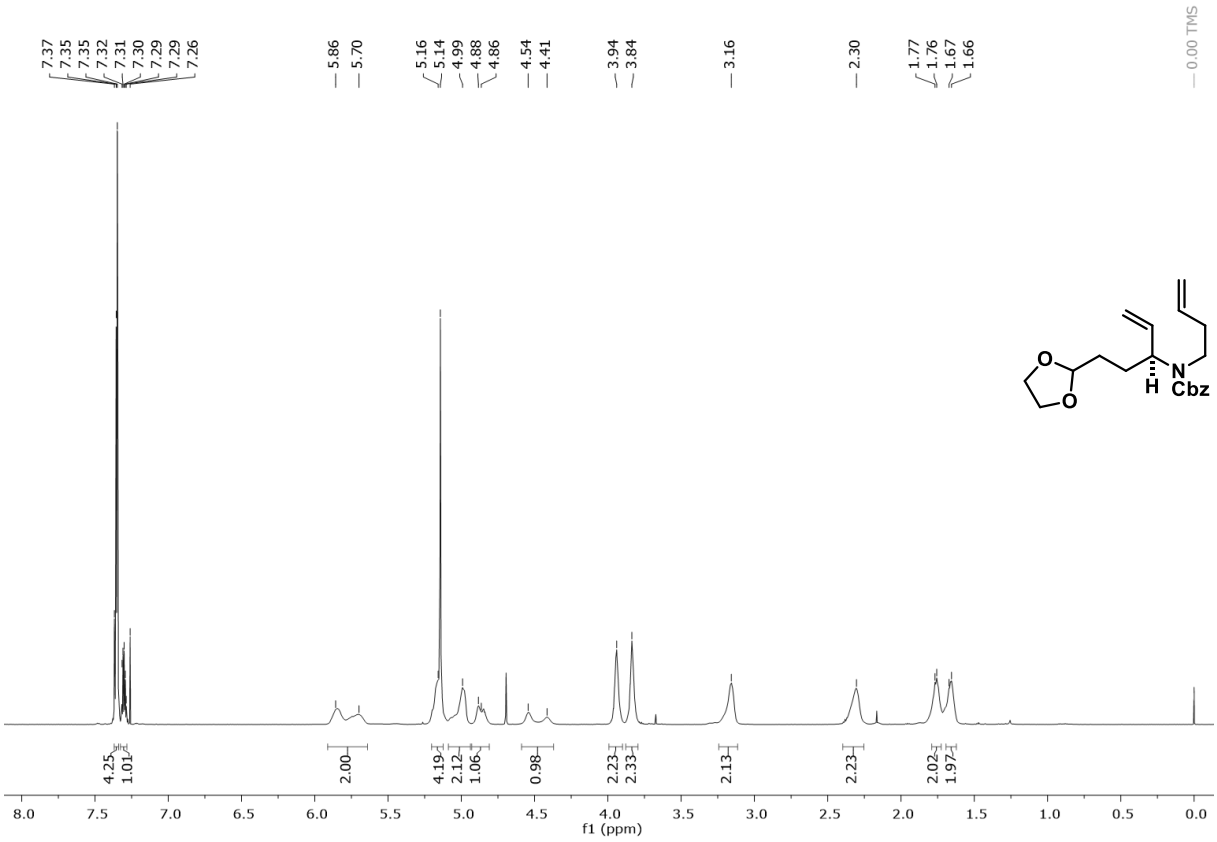


*Figure 73: ^{1}H NMR (600 MHz, $CDCl_3$) of benzyl (S)-(5-(1,3-dioxolan-2-yl)pent-1-en-3-yl)(but-3-en-1- yl)carbamate (**159c**).*

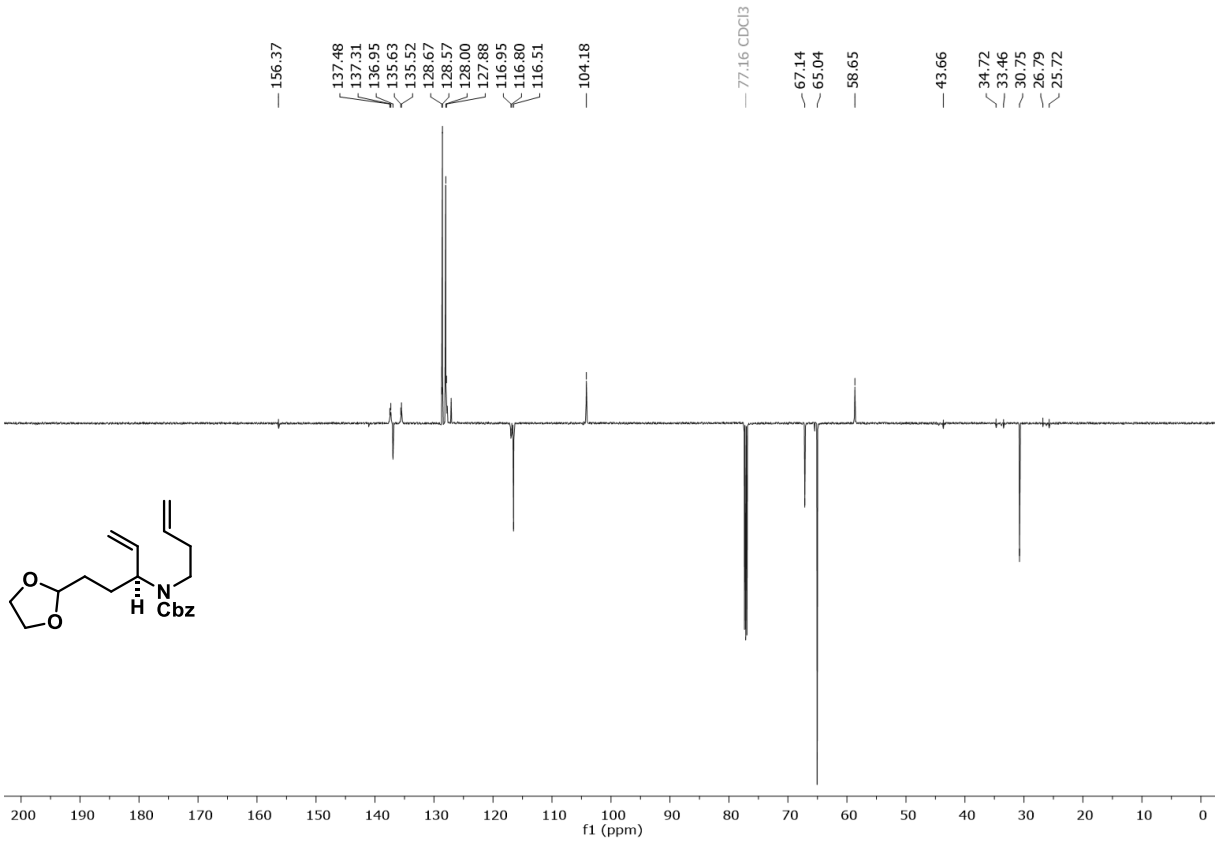


*Figure 74: ^{13}C NMR (151 MHz, $CDCl_3$) of benzyl (S)-(5-(1,3-dioxolan-2-yl)pent-1-en-3-yl)(but-3-en-1- yl)carbamate (**159c**).*

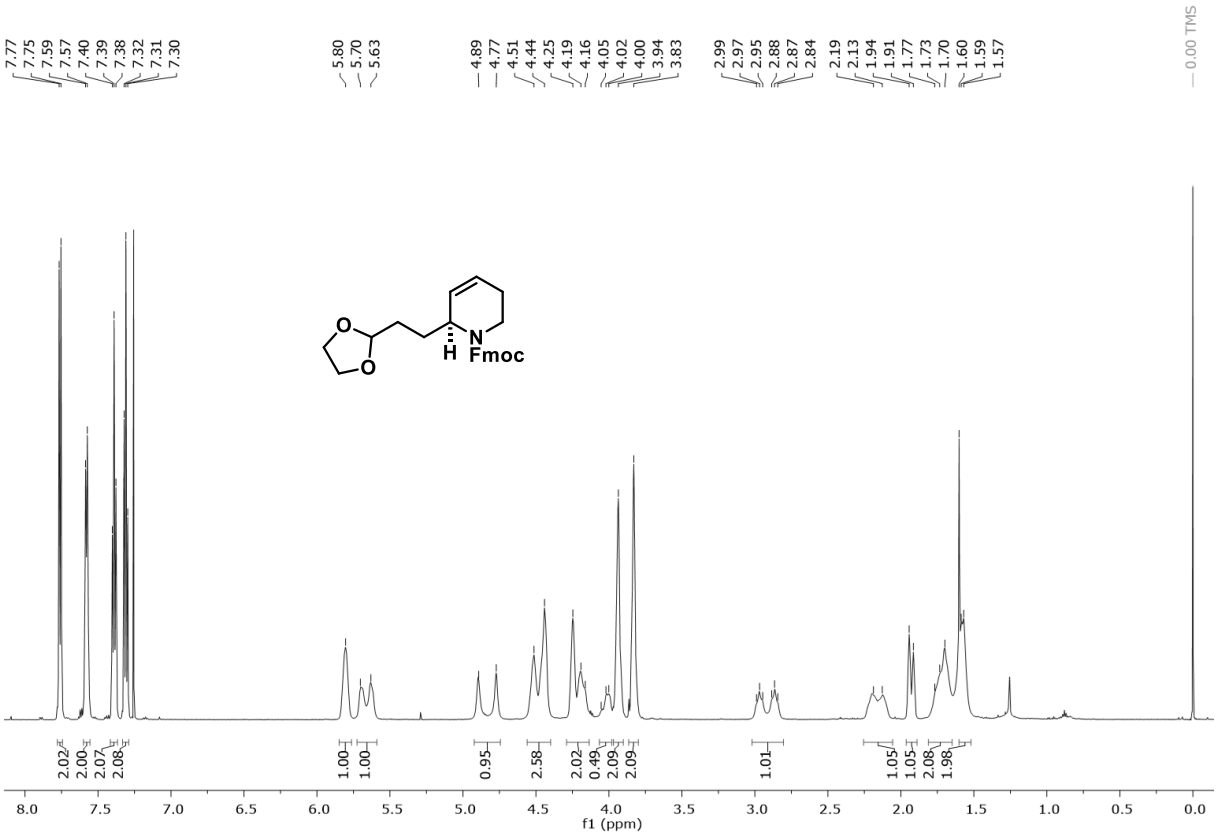


*Figure 75: ^{1}H NMR (600 MHz, $CDCl_3$) of (9H-fluoren-9-yl)methyl (S)-6-(2-(1,3-dioxolan-2-yl)ethyl)-3,6- dihydropyridine-1(2H)-carboxylate (**158a**).*

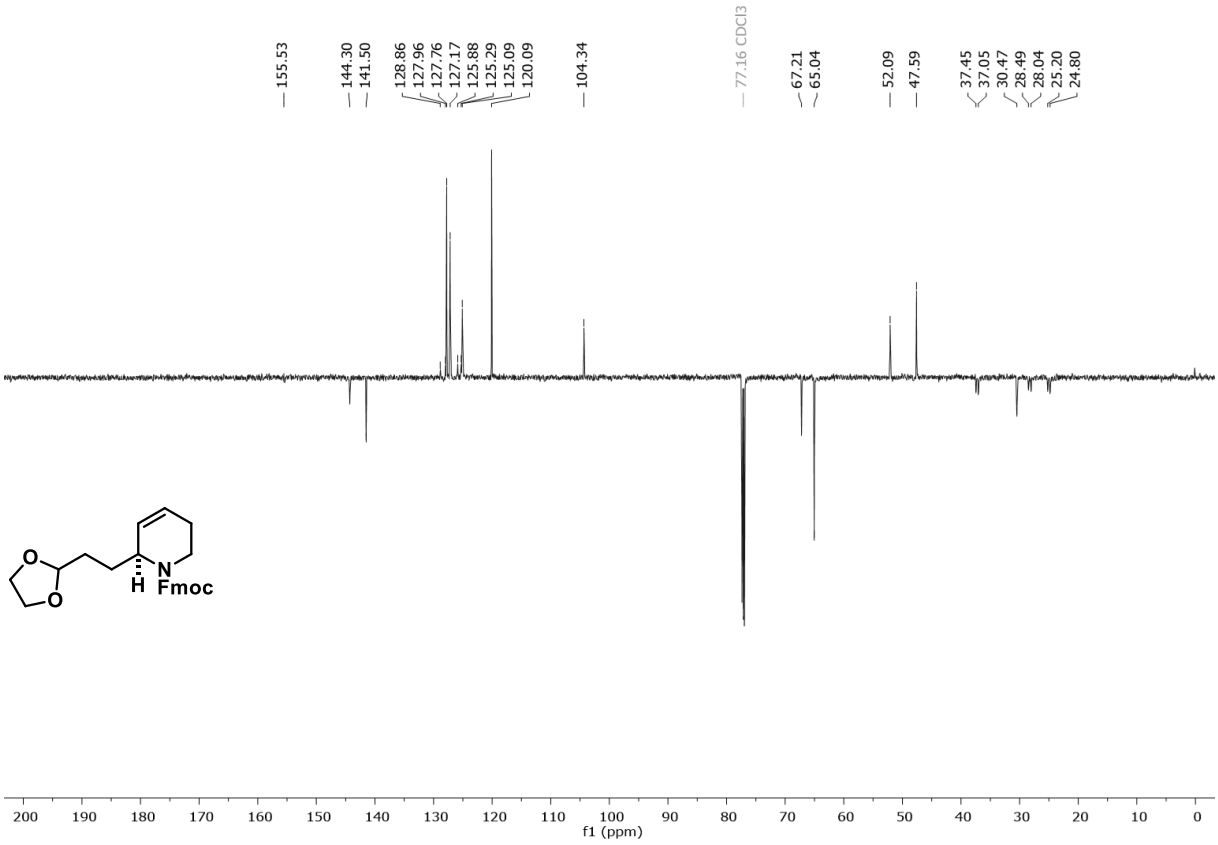


*Figure 76: ^{13}C NMR (151 MHz, $CDCl_3$) of (9H-fluoren-9-yl)methyl (S)-6-(2-(1,3-dioxolan-2-yl)ethyl)-3,6- dihydropyridine-1(2H)-carboxylate (**158a**).*

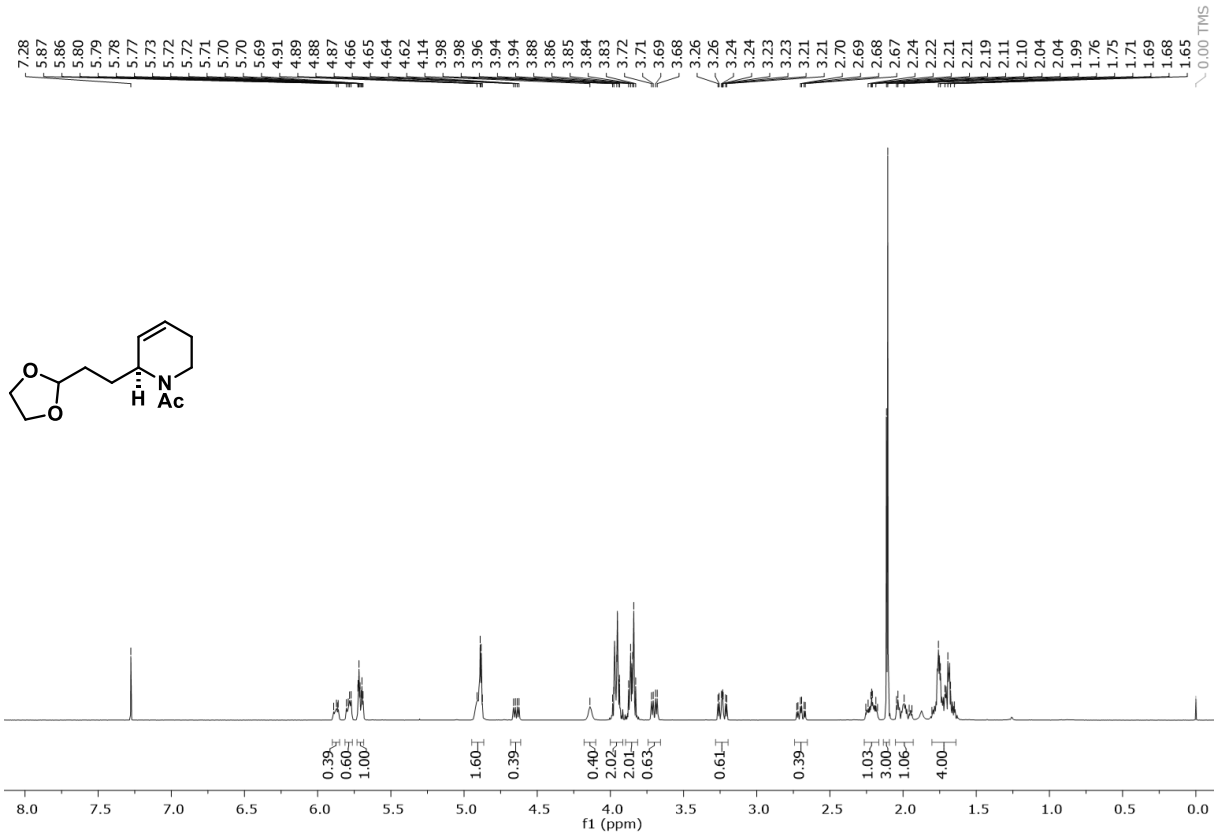


*Figure 77: ^{1}H NMR (500 MHz, $CDCl_3$) of (S)-1-(6-(2-(1,3-dioxolan-2-yl)ethyl)-3,6-dihydropyridin-1(2H)- yl)ethan-1-one (**158b**).*

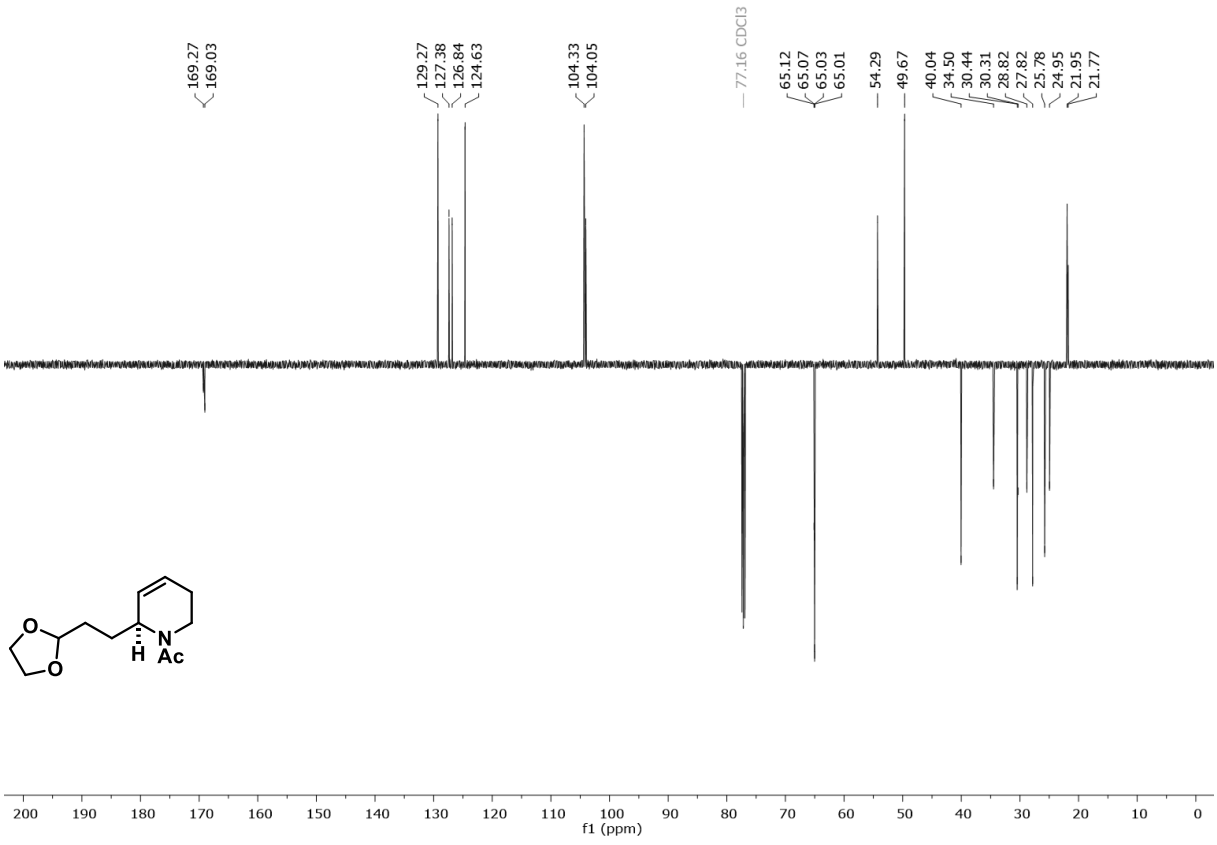


*Figure 78: ^{13}C NMR (126 MHz, $CDCl_3$) of (S)-1-(6-(2-(1,3-dioxolan-2-yl)ethyl)-3,6-dihydropyridin-1(2H)- yl)ethan-1-one (**158b**).*

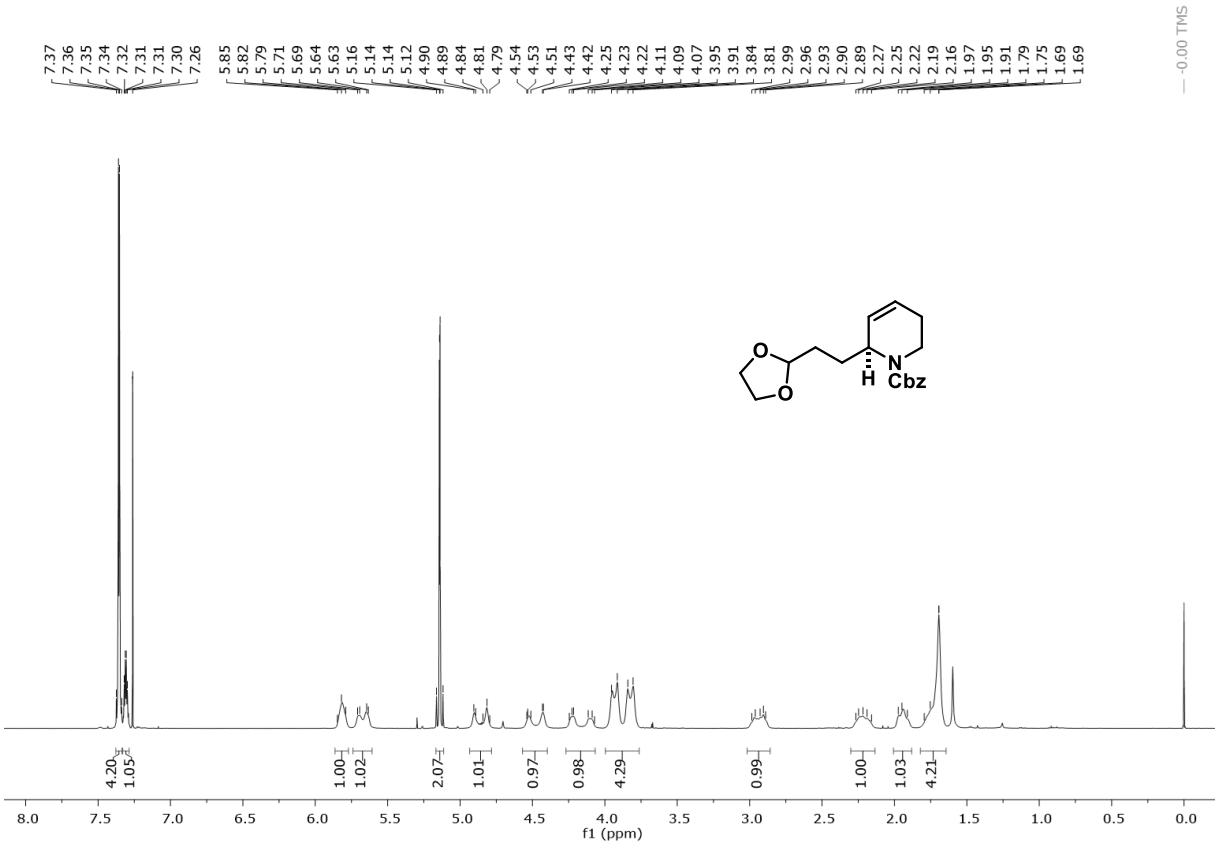


*Figure 79: ^{1}H NMR (600 MHz, $CDCl_3$) of benzyl (S)-6-(2-(1,3-dioxolan-2-yl)ethyl)-3,6-dihydropyridine- 1(2H)-carboxylate (**158c**).*

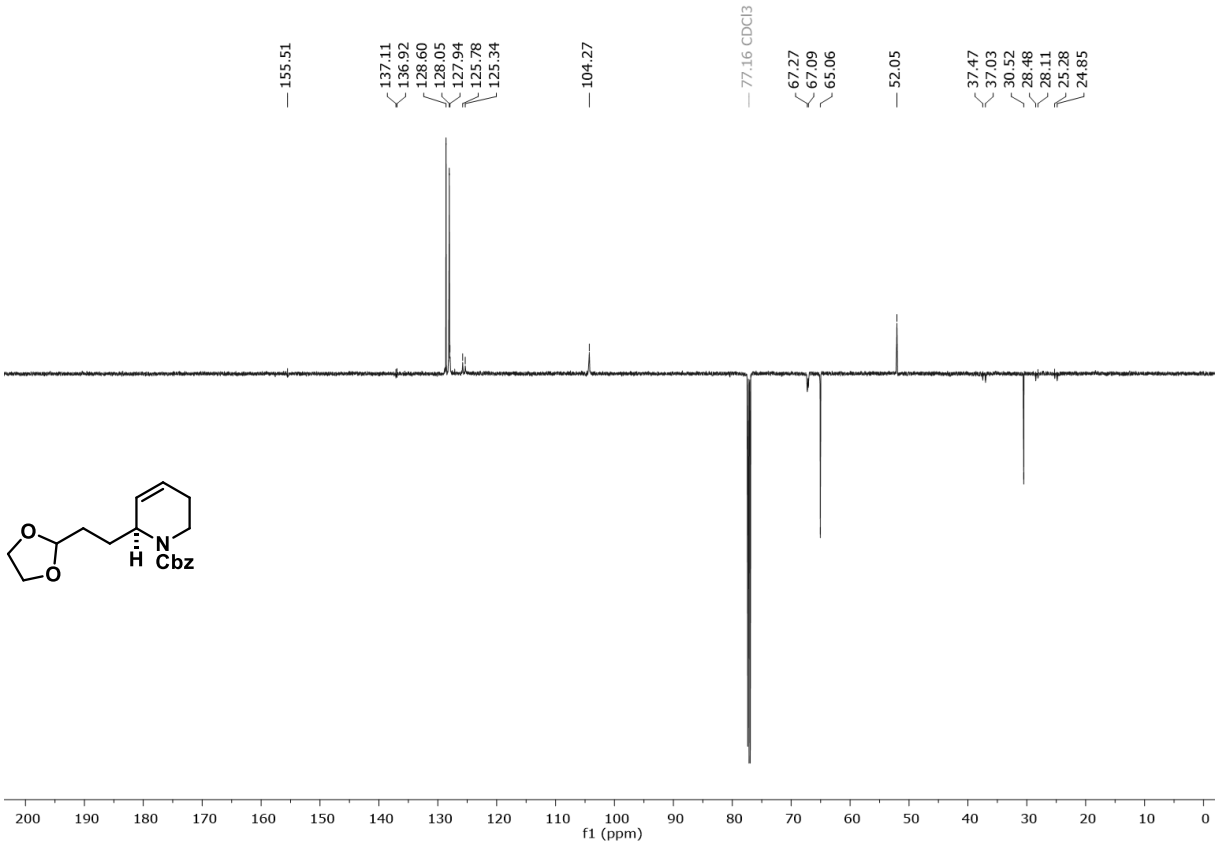


*Figure 80: ^{13}C NMR (151 MHz, $CDCl_3$) of benzyl (S)-6-(2-(1,3-dioxolan-2-yl)ethyl)-3,6-dihydropyridine- 1(2H)-carboxylate (**158c**).*

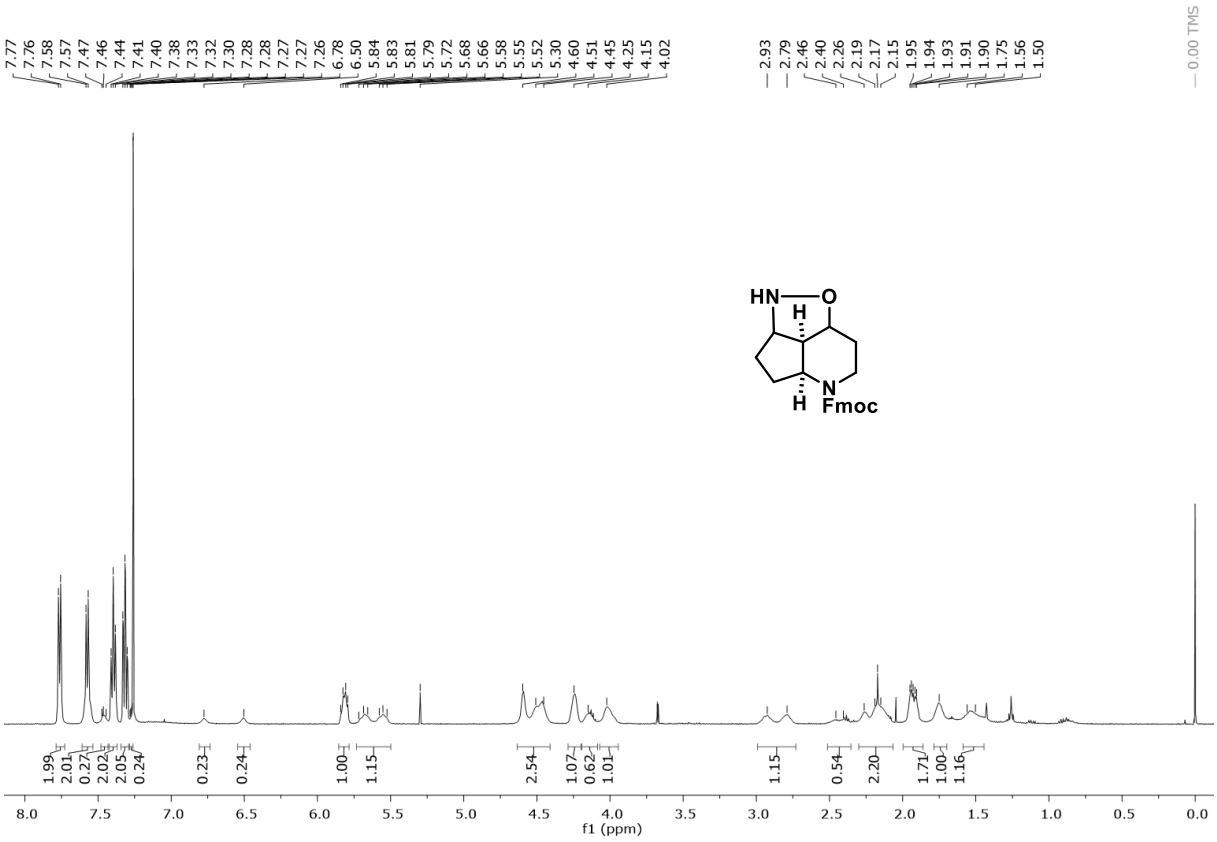


*Figure 81: [1]H NMR (500 MHz, $CDCl_3$) of (9H-fluoren-9-yl)methyl (2a[1]S,7aS)-octahydro-4-oxa- 3,7-diazacyclopenta[cd]indene-7(2H)-carboxylate (**157a**).*

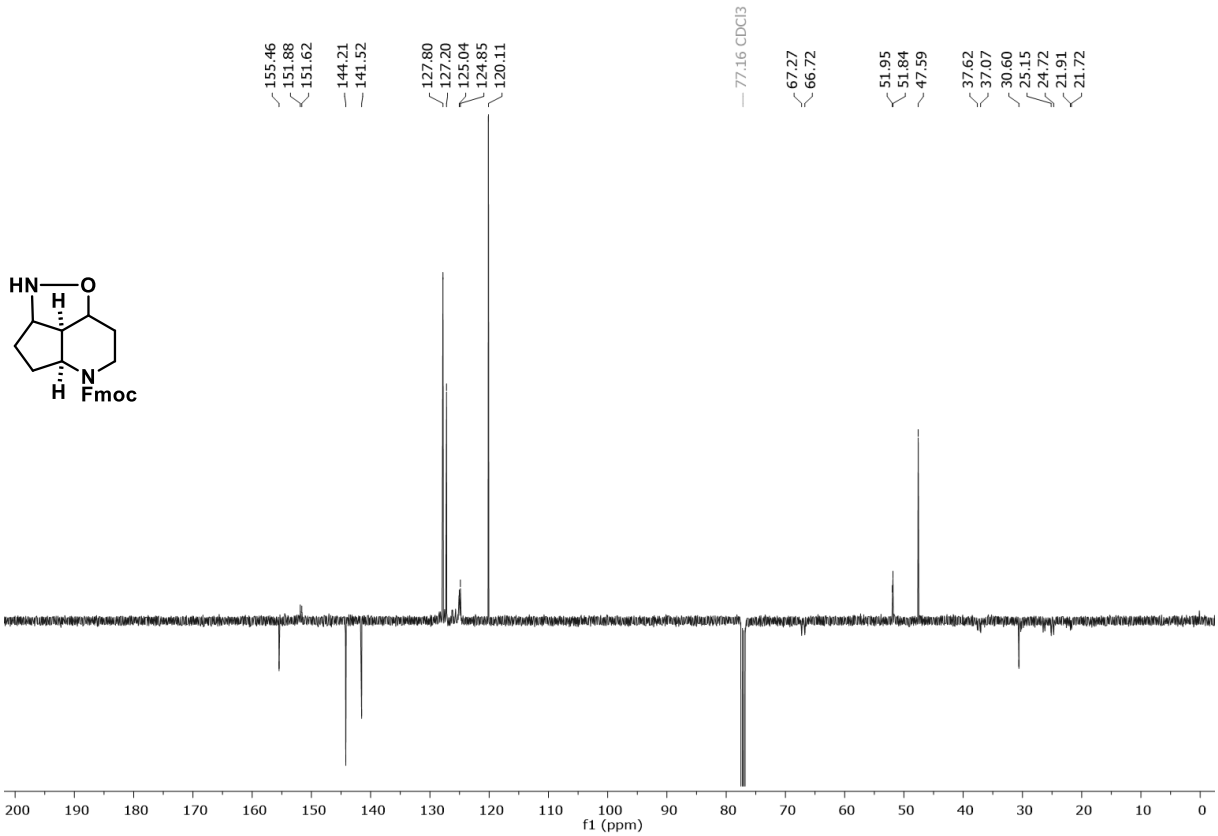


*Figure 82: [13]C NMR (126 MHz, $CDCl_3$) of (9H-fluoren-9-yl)methyl (2a[1]S,7aS)-octahydro-4-oxa- 3,7-diazacyclopenta[cd]indene-7(2H)-carboxylate (**157a**).*

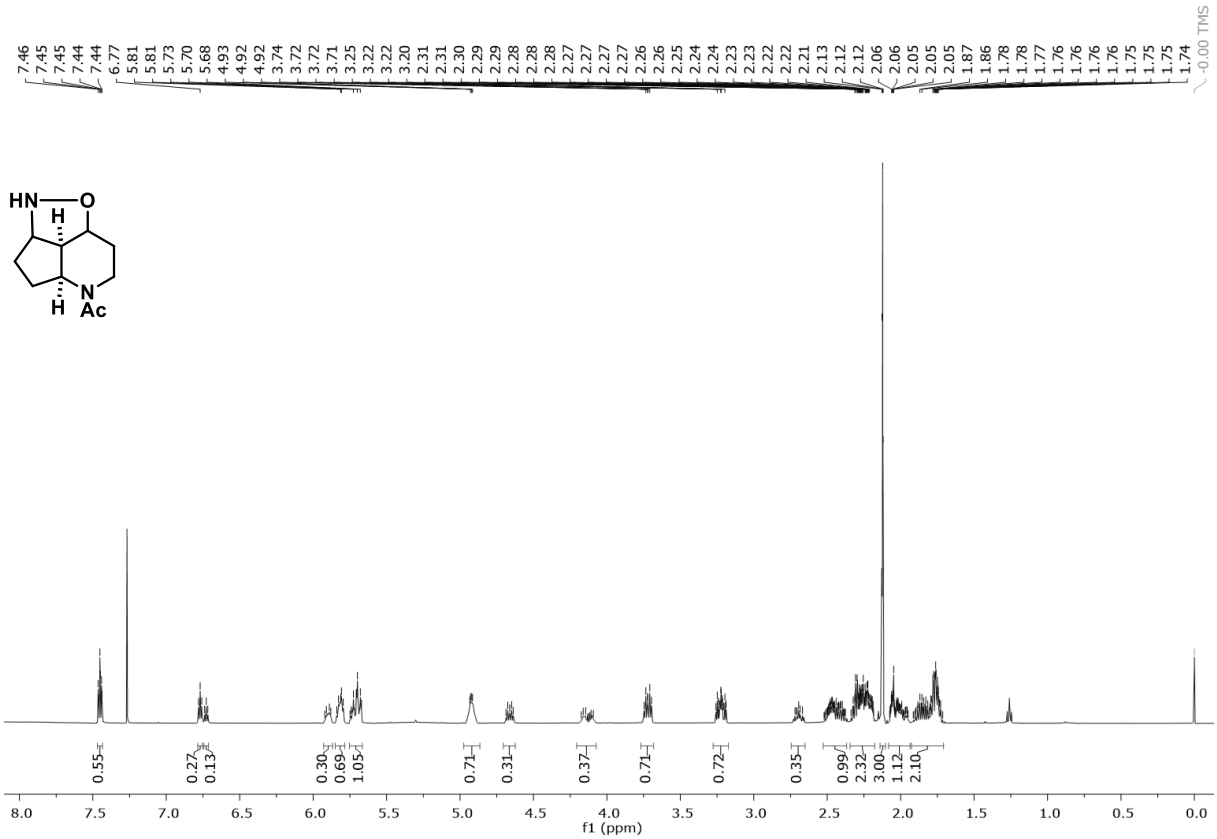


*Figure 83: ^{1}H NMR (500 MHz, $CDCl_3$) of 1-((2a^{1}S,7aS)-octahydro-4-oxa-3,7- diazacyclopenta[cd]inden-7(2H)-yl)ethan-1-one (**157b**).*

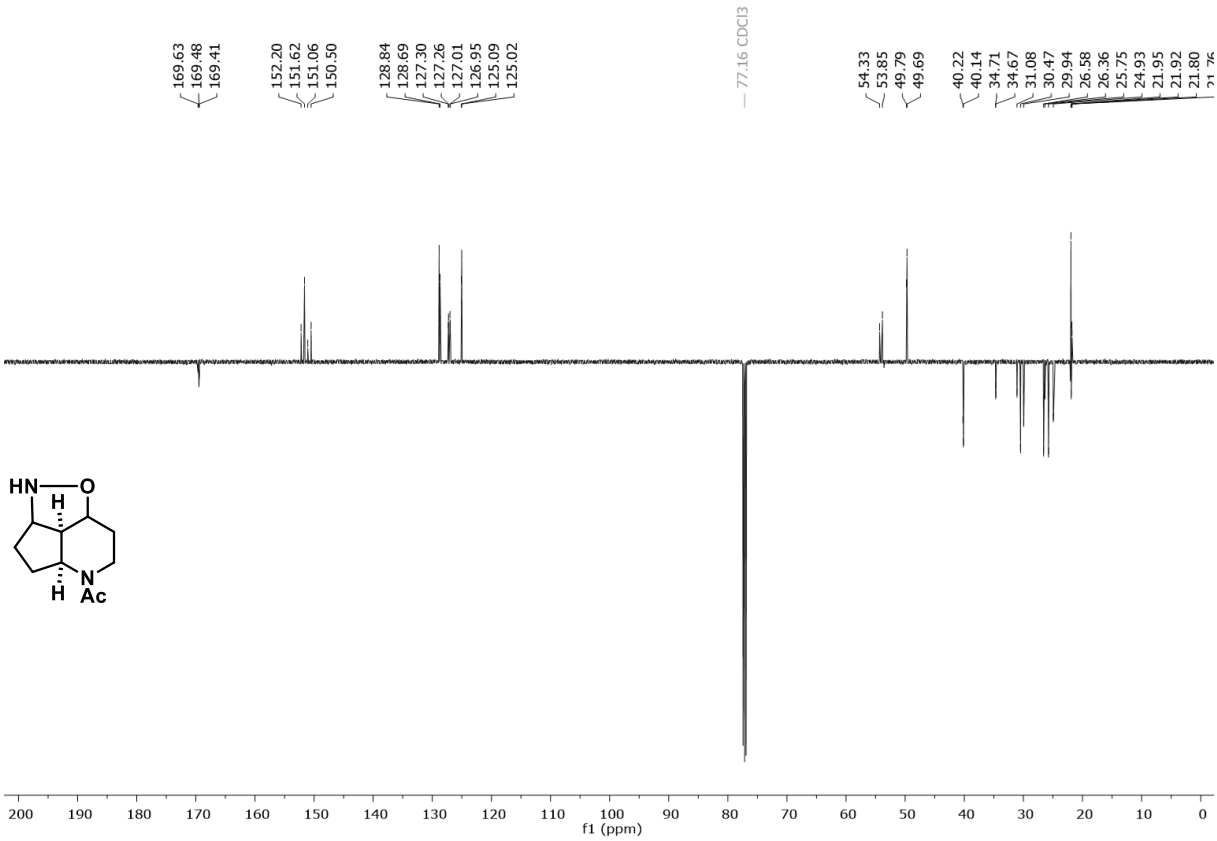


*Figure 84: ^{13}C NMR (126 MHz, $CDCl_3$) of 1-((2a^{1}S,7aS)-octahydro-4-oxa-3,7- diazacyclopenta[cd]inden-7(2H)-yl)ethan-1-one (**157b**).*

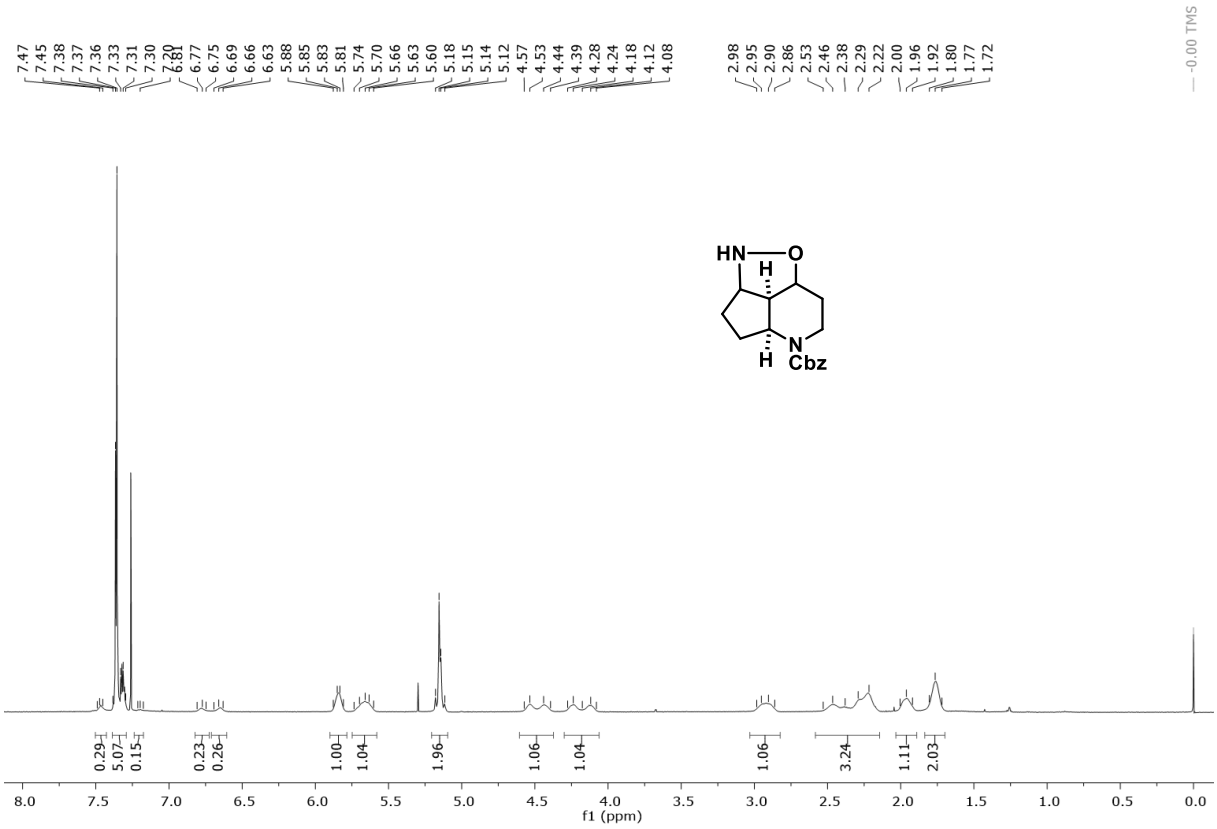


*Figure 85: [1]H NMR (500 MHz, $CDCl_3$) of benzyl (2a[1]S,7aS)-octahydro-4-oxa-3,7- diazacyclopenta[cd]indene-7(2H)-carboxylate (**157c**).*

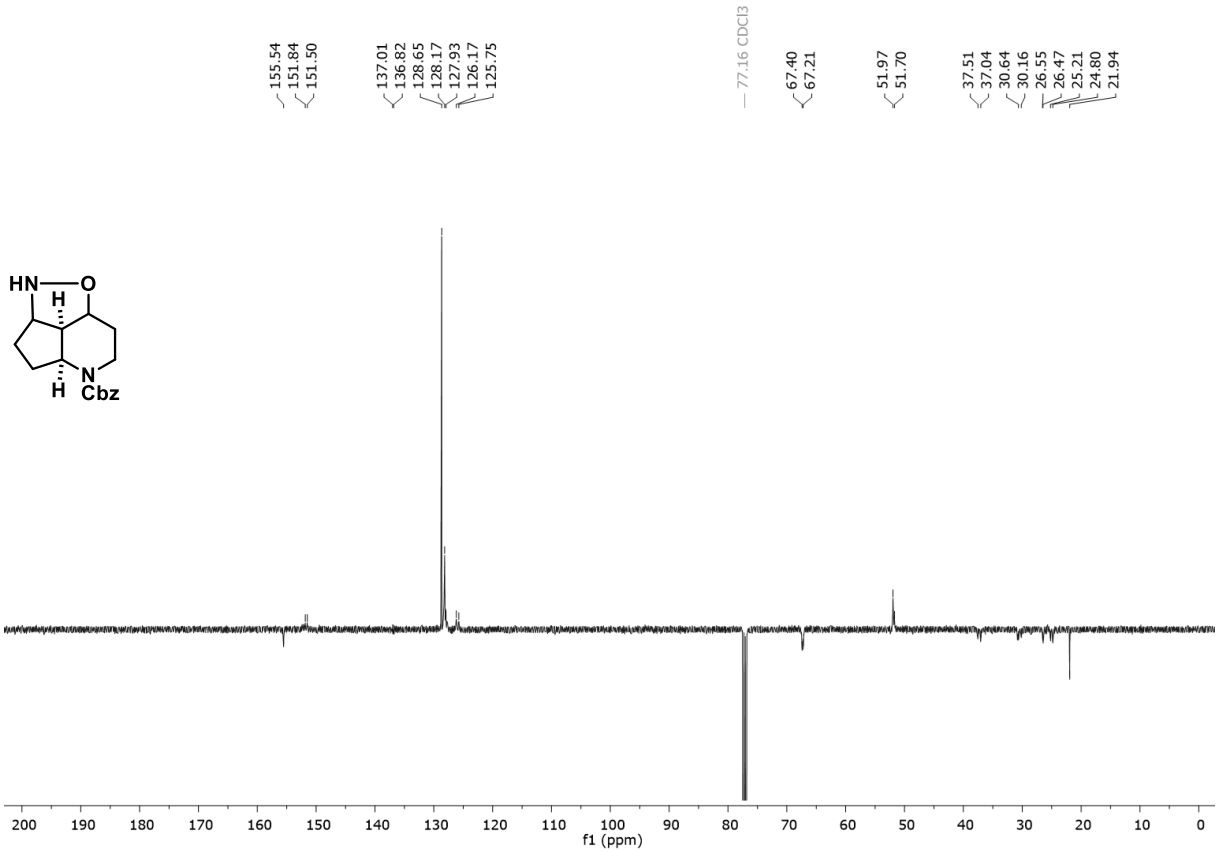


*Figure 86: [13]C NMR (126 MHz, $CDCl_3$) of benzyl (2a[1]S,7aS)-octahydro-4-oxa-3,7- diazacyclopenta[cd]indene-7(2H)-carboxylate (**157c**).*

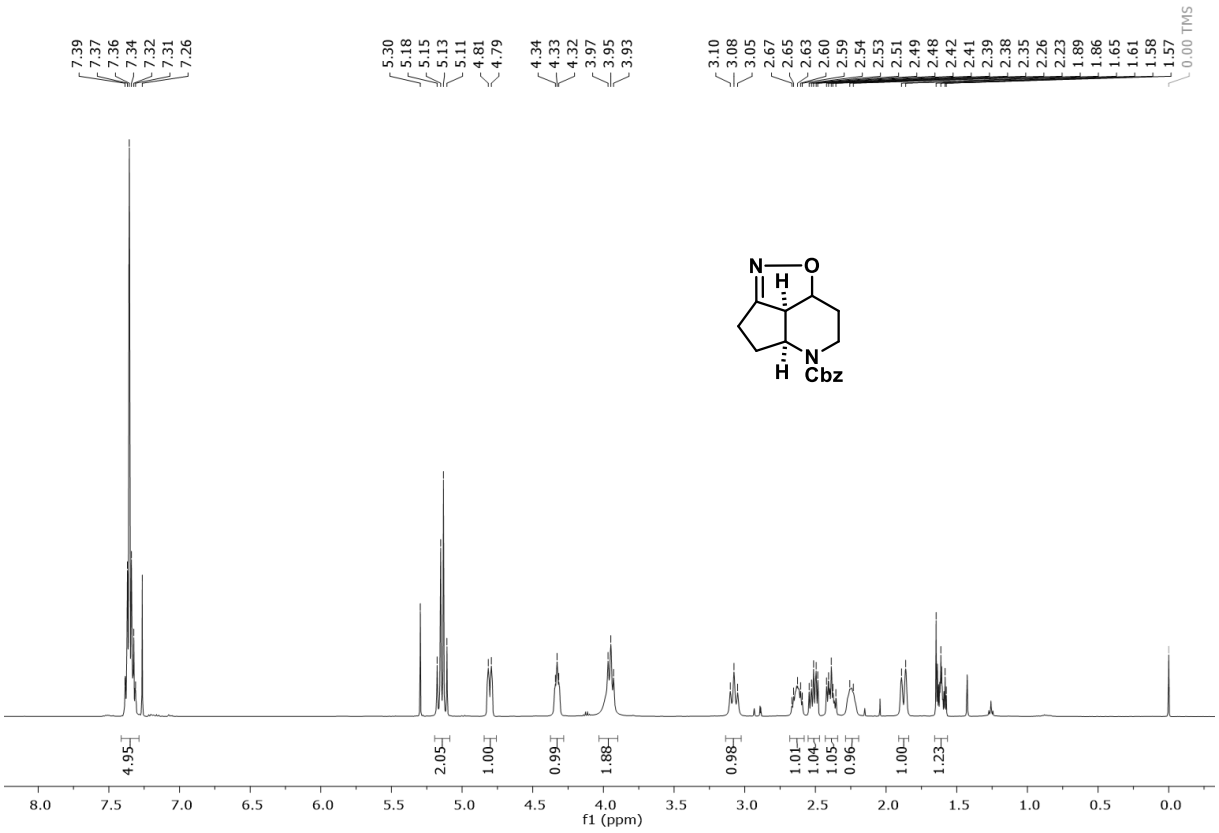


*Figure 87: ^{1}H NMR (600 MHz, $CDCl_3$) of benzyl (2a^{1}S,7aS)-1,2a^{1},4a,5,6,7a-hexahydro-4-oxa- 3,7-diazacyclopenta[cd]indene-7(2H)-carboxylate (**130**).*

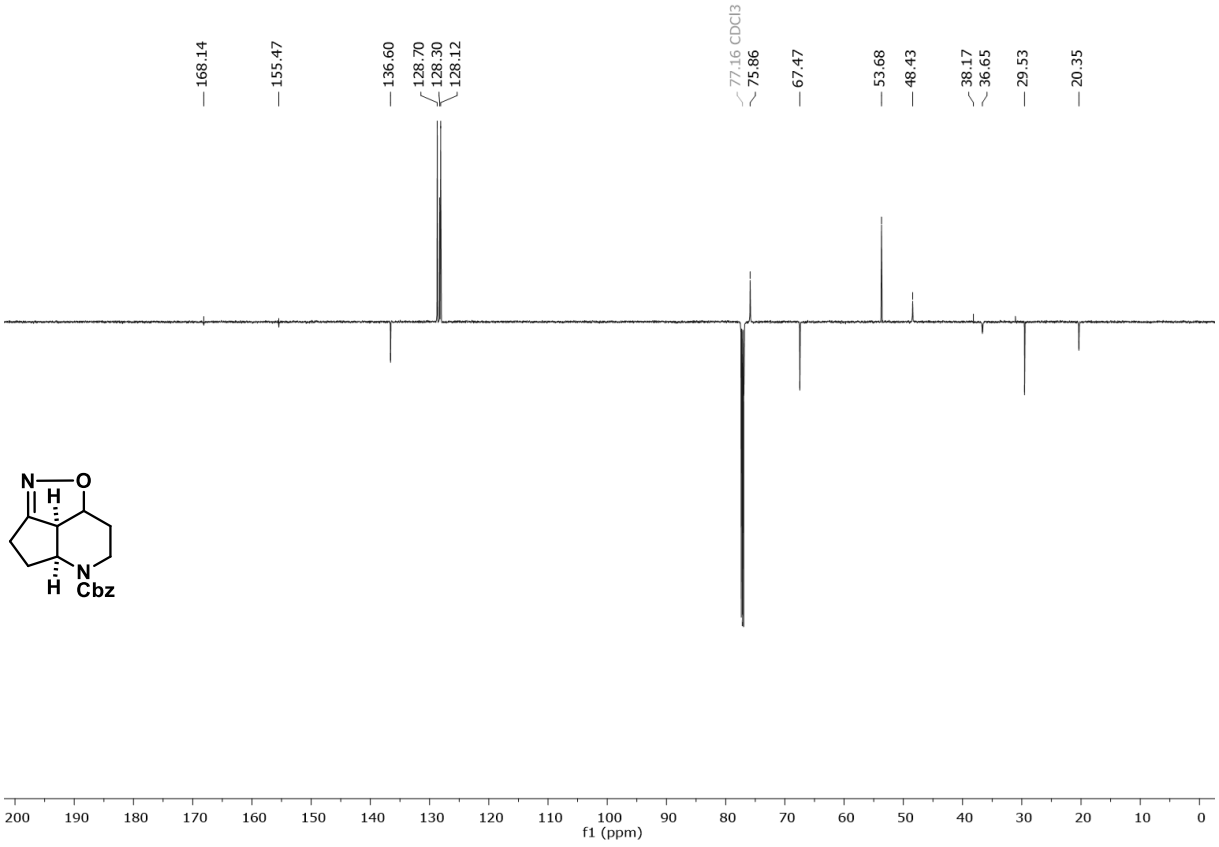


*Figure 88: ^{13}C NMR (151 MHz, $CDCl_3$) of benzyl (2a^{1}S,7aS)-1,2a^{1},4a,5,6,7a-hexahydro-4-oxa- 3,7-diazacyclopenta[cd]indene-7(2H)-carboxylate (**130**).*

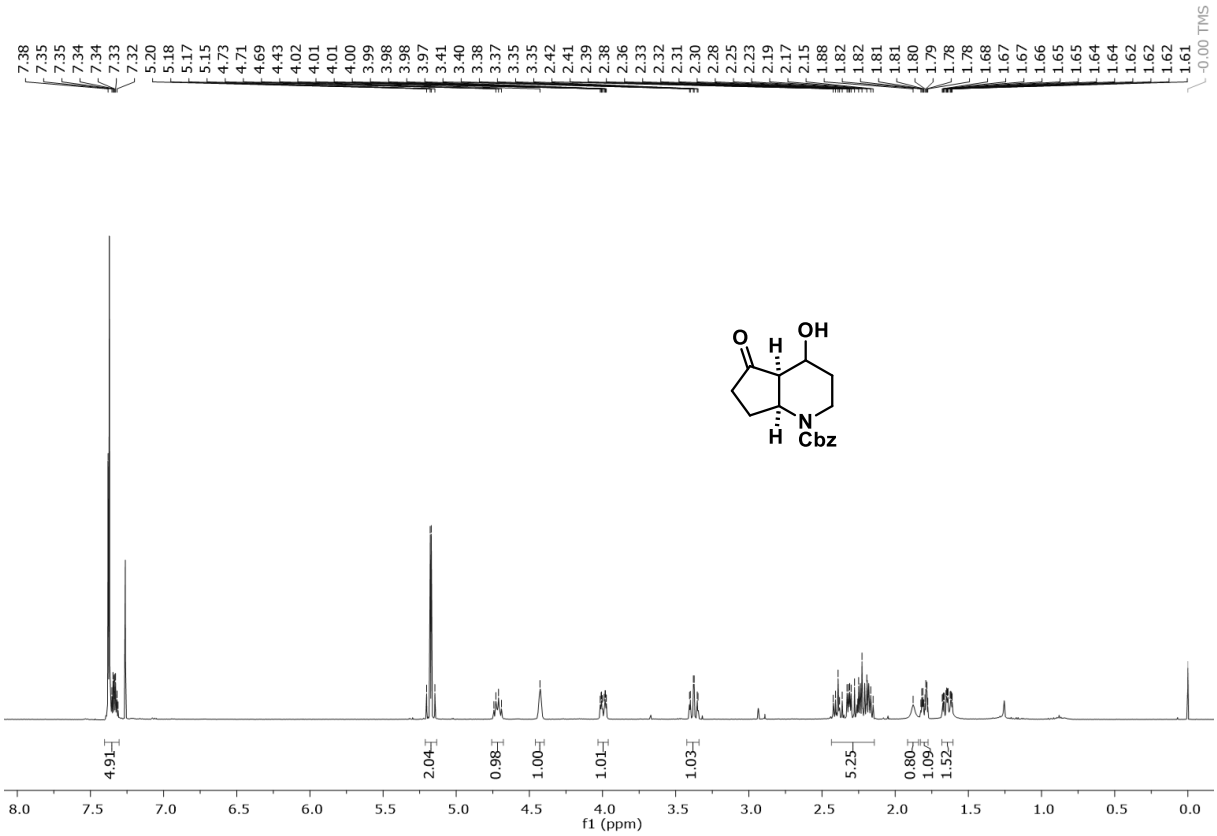


*Figure 89: ^{1}H NMR (500 MHz, $CDCl_3$) of benzyl (4aR,7aS)-4-hydroxy-5-oxooctahydro-1H-cyclopenta[b]pyridine-1-carboxylate (**167**).*

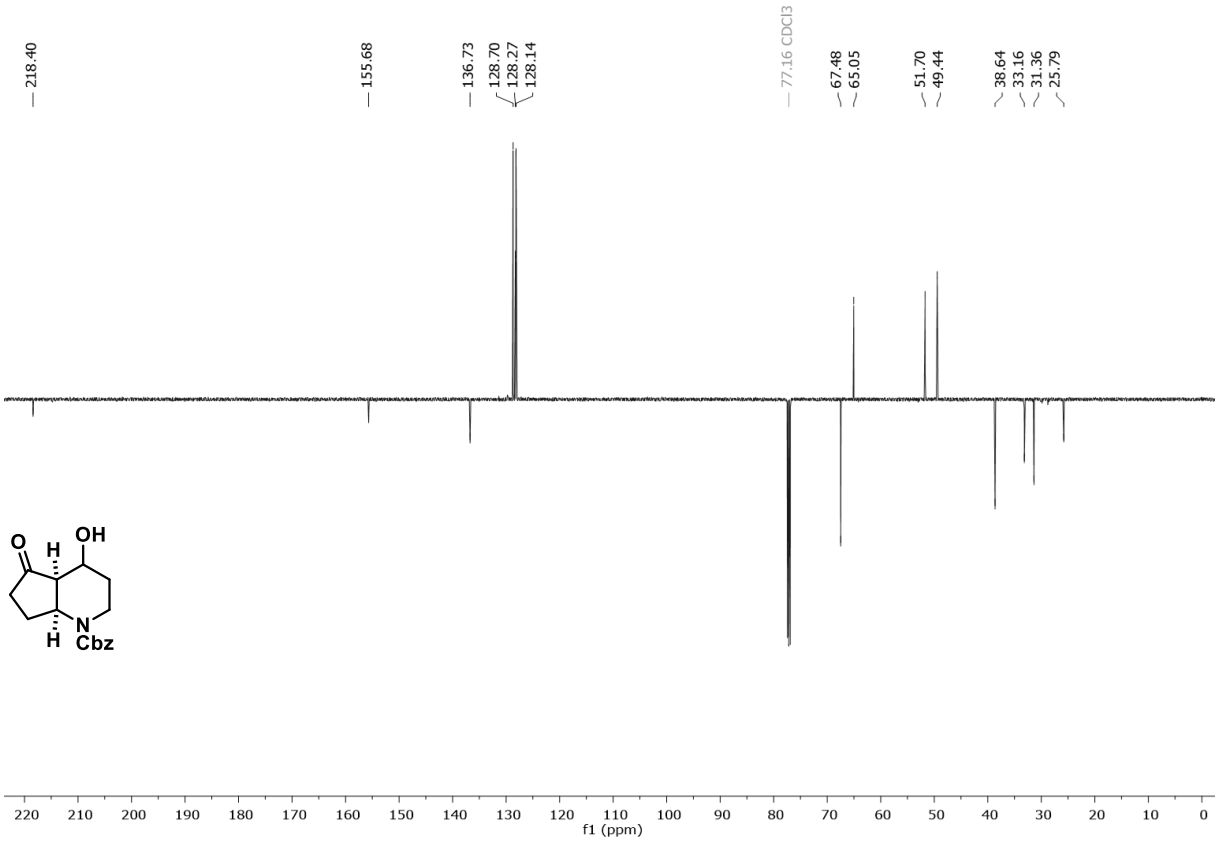


*Figure 90: ^{13}C NMR (126 MHz, $CDCl_3$) of benzyl (4aR,7aS)-4-hydroxy-5-oxooctahydro-1H-cyclopenta[b]pyridine-1-carboxylate (**167**).*

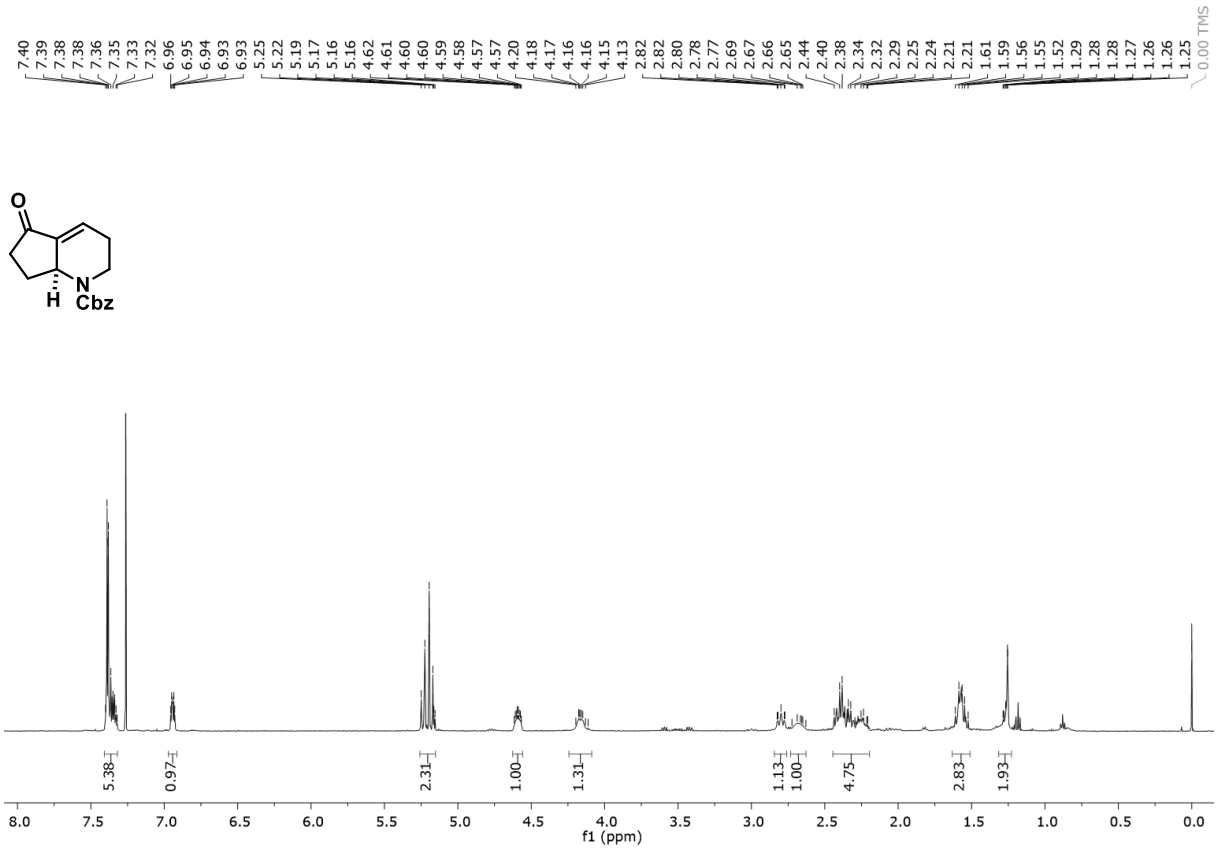


*Figure 91: ^{1}H NMR (500 MHz, $CDCl_3$) of benzyl (S)-5-oxo-2,3,5,6,7,7a-hexahydro-1H-cyclopenta[b]pyridine-1-carboxylate (**168**).*

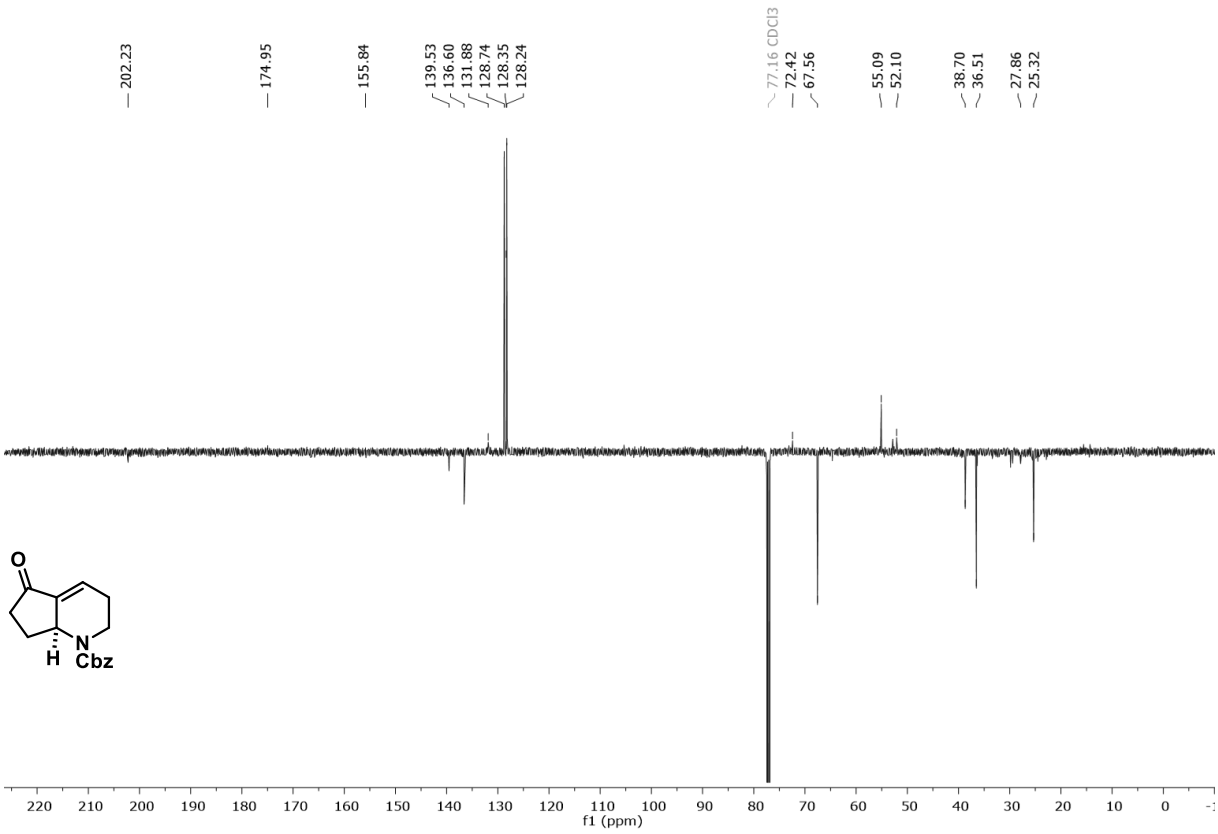


*Figure 92: ^{13}C NMR (126 MHz, $CDCl_3$) of benzyl (S)-5-oxo-2,3,5,6,7,7a-hexahydro-1H-cyclopenta[b]pyridine-1-carboxylate (**168**).*

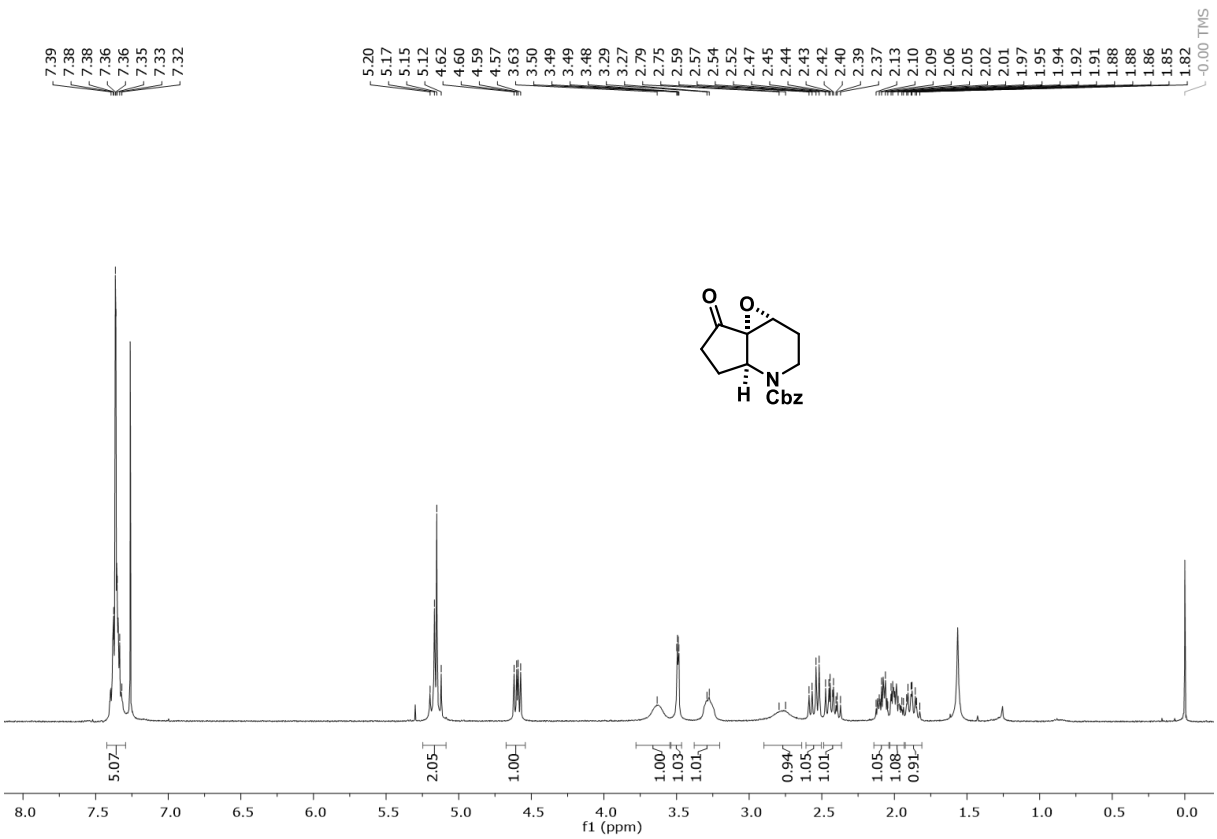


*Figure 93: ^{1}H NMR (400 MHz, $CDCl_3$) of benzyl (1aR,4aS,7aS)-7- oxohexahydrocyclopenta[b]oxireno[2,3-c]pyridine-4(1aH)-carboxylate (**169**).*

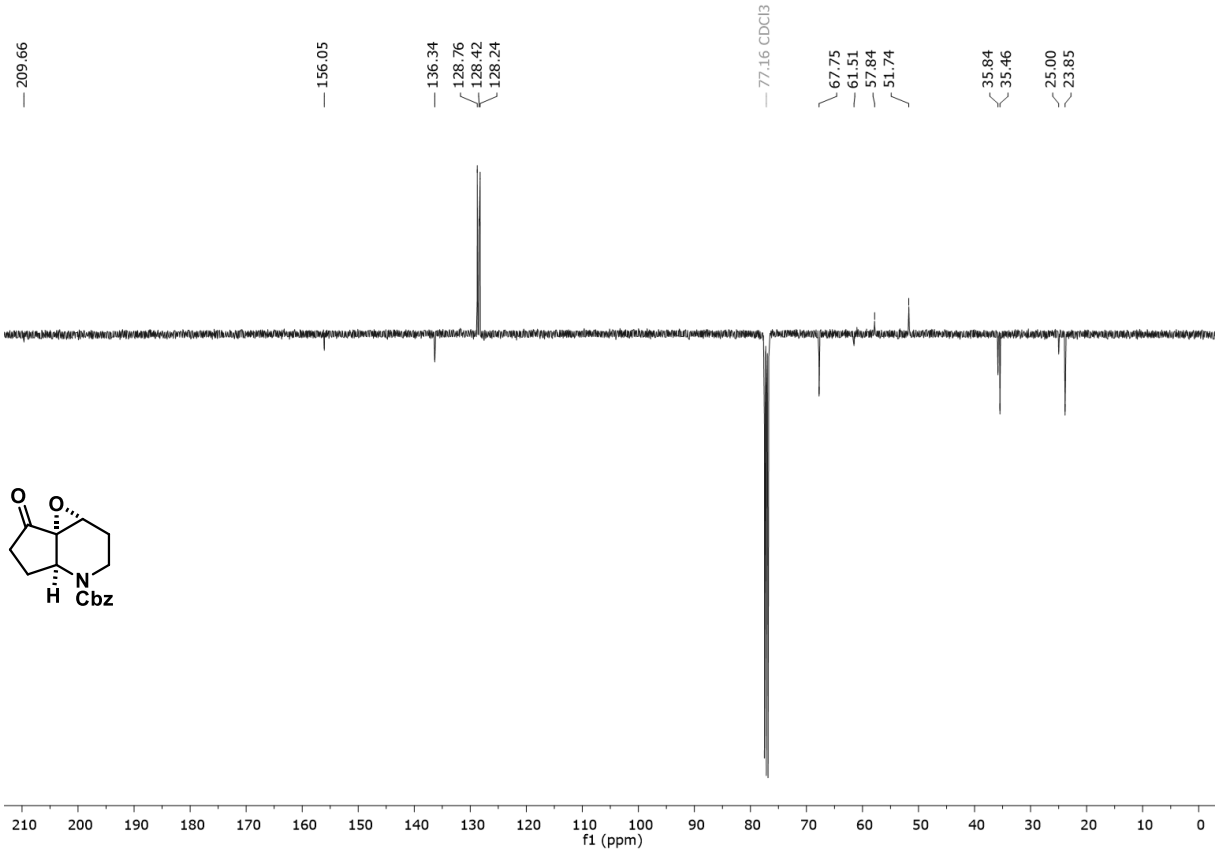


*Figure 94: ^{13}C NMR (101 MHz, $CDCl_3$) of benzyl (1aR,4aS,7aS)-7- oxohexahydrocyclopenta[b]oxireno[2,3-c]pyridine-4(1aH)-carboxylate (**169**).*

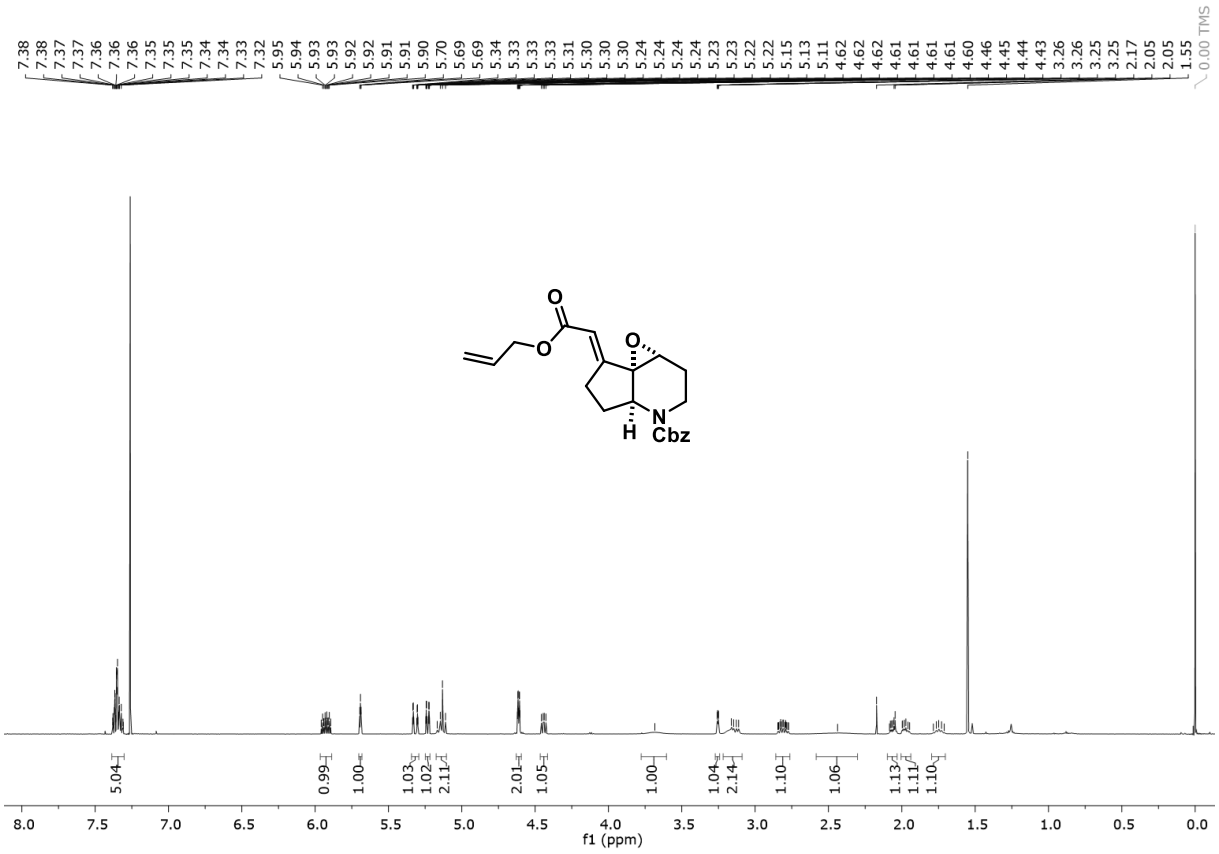


*Figure 95: ^{1}H NMR (600 MHz, $CDCl_3$) of benzyl (1aR,4aS,7aS,E)-7-(2-(allyloxy)-2-oxoethylidene)hexahydrocyclopenta[b]oxireno[2,3-c]pyridine-4(1aH)-carboxylate (**175b**).*

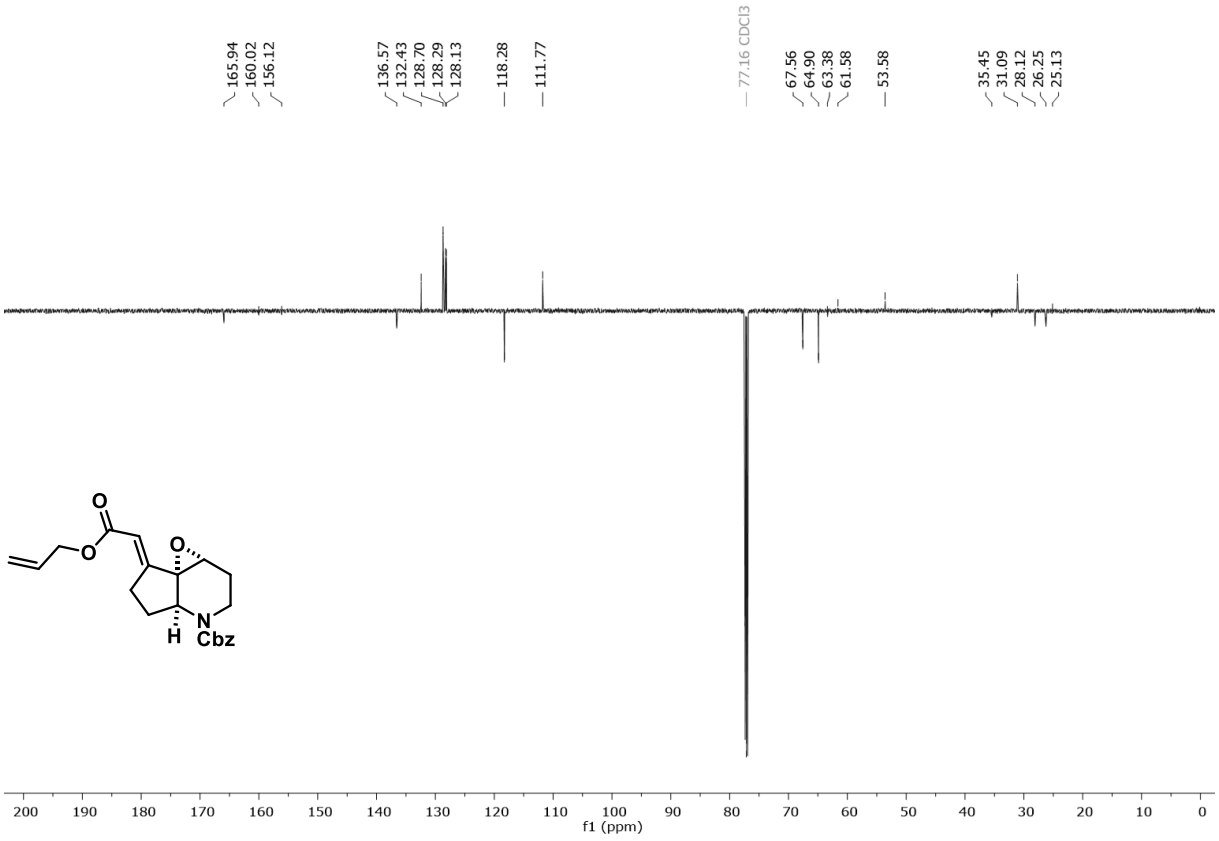


*Figure 96: ^{13}C NMR (151 MHz, $CDCl_3$) of benzyl (1aR,4aS,7aS,E)-7-(2-(allyloxy)-2-oxoethylidene)hexahydrocyclopenta[b]oxireno[2,3-c]pyridine-4(1aH)-carboxylate (**175b**).*

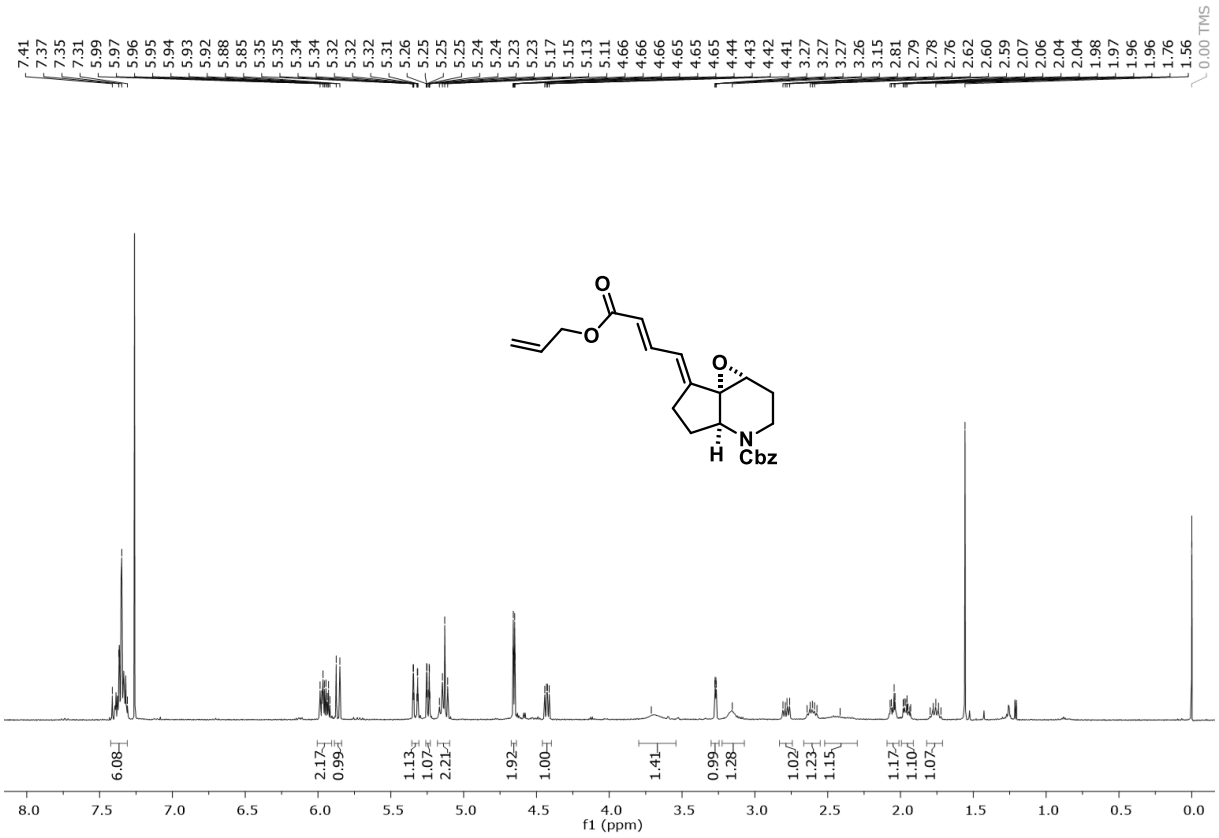


*Figure 97: ^{1}H NMR (600 MHz, $CDCl_3$) of benzyl (1aR,4aS,7aS,E)-7-((E)-4-(allyloxy)-4-oxobut-2-en-1-ylidene)hexahydrocyclopenta[b]oxireno[2,3-c]pyridine-4(1aH)-carboxylate (**182a**).*

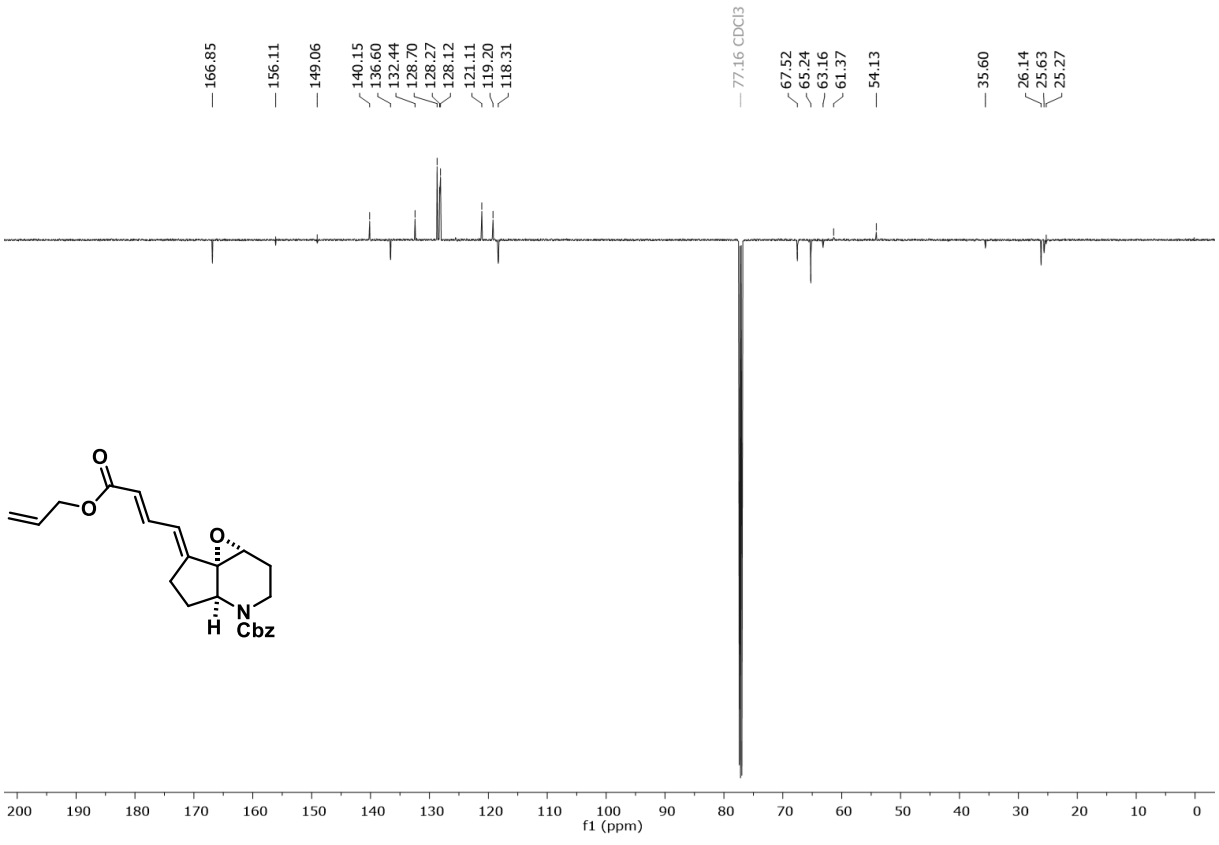


*Figure 98: ^{13}C NMR (151 MHz, $CDCl_3$) of benzyl (1aR,4aS,7aS,E)-7-((E)-4-(allyloxy)-4-oxobut-2-en-1-ylidene)hexahydrocyclopenta[b]oxireno[2,3-c]pyridine-4(1aH)-carboxylate (**182a**).*

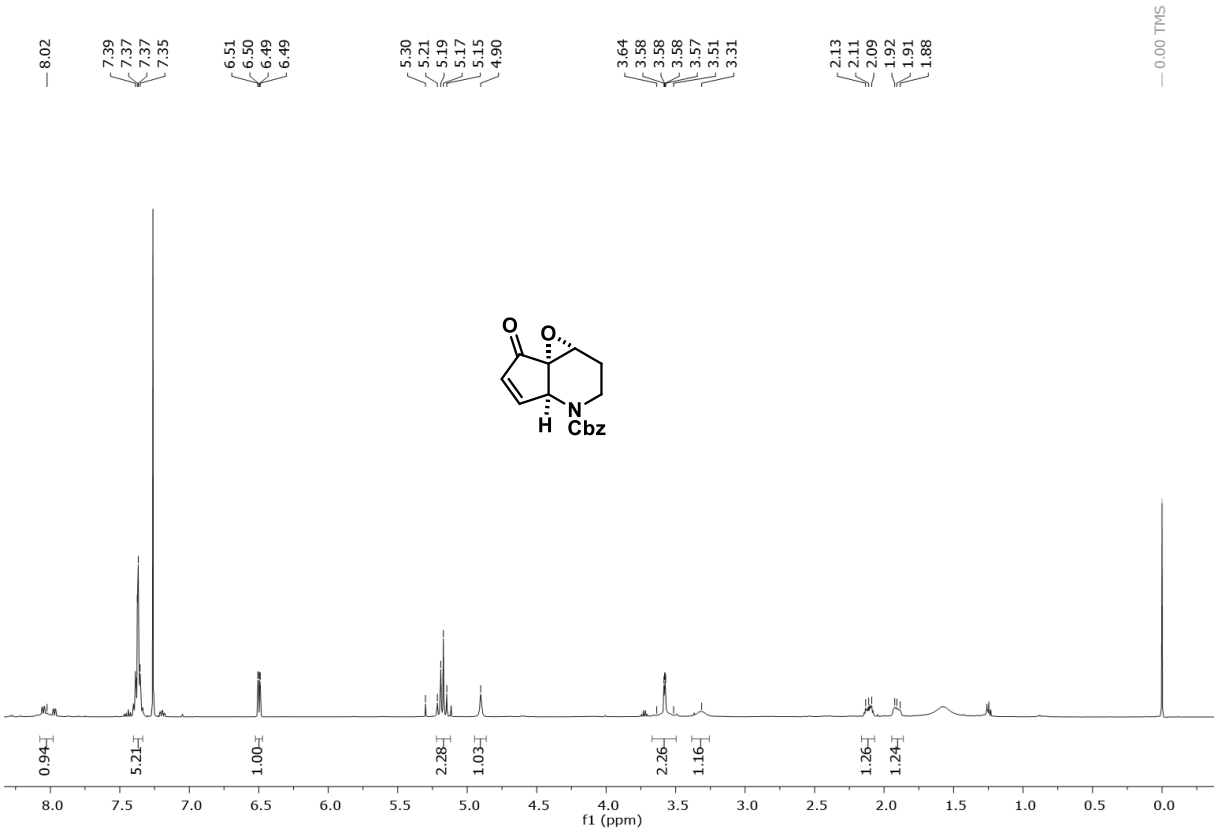


*Figure 99: ^{1}H NMR (500 MHz, $CDCl_3$) of benzyl (1aR,4aS,7aS)-7-oxo-2,3,4a,7- tetrahydrocyclopenta[b]oxireno[2,3-c]pyridine-4(1aH)-carboxylate (**170**).*

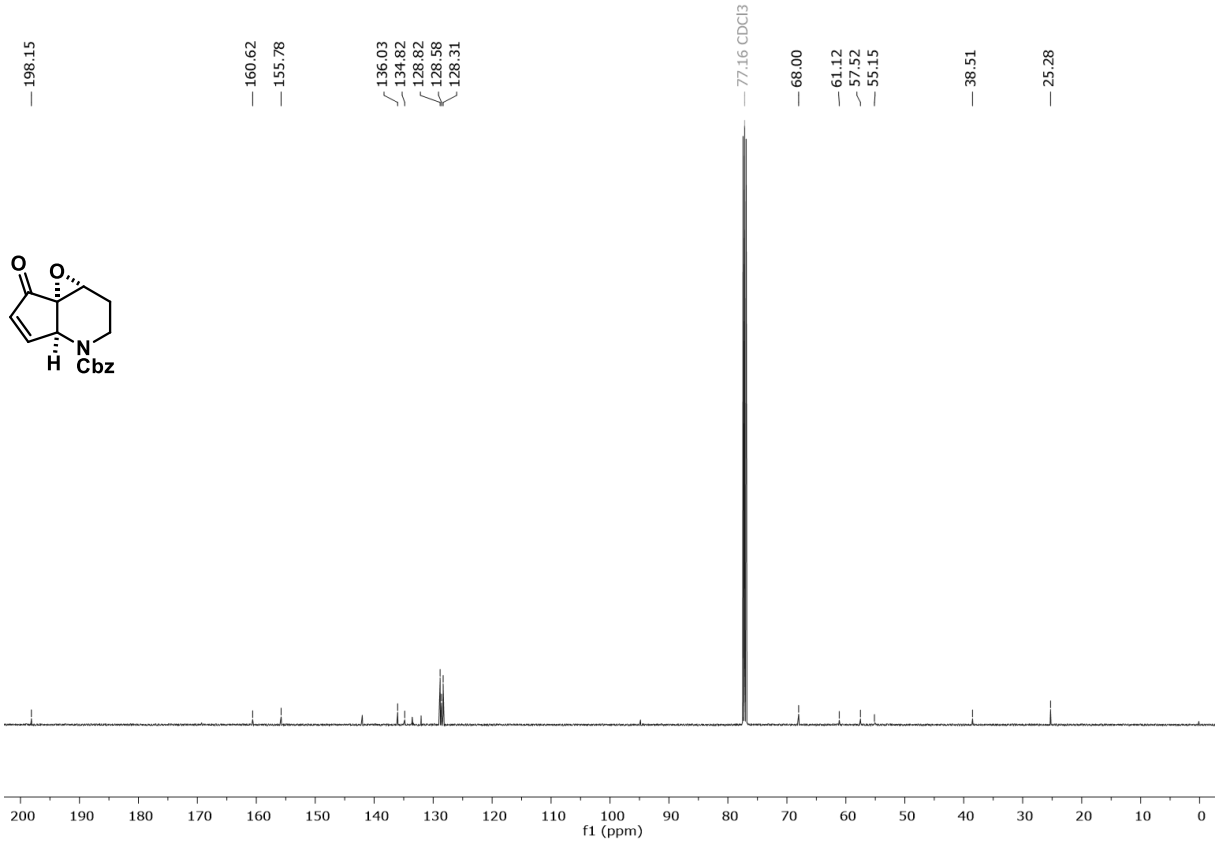


*Figure 100: ^{13}C NMR (126 MHz, $CDCl_3$) of benzyl (1aR,4aS,7aS)-7-oxo-2,3,4a,7- tetrahydrocyclopenta[b]oxireno[2,3-c]pyridine-4(1aH)-carboxylate (**170**).*

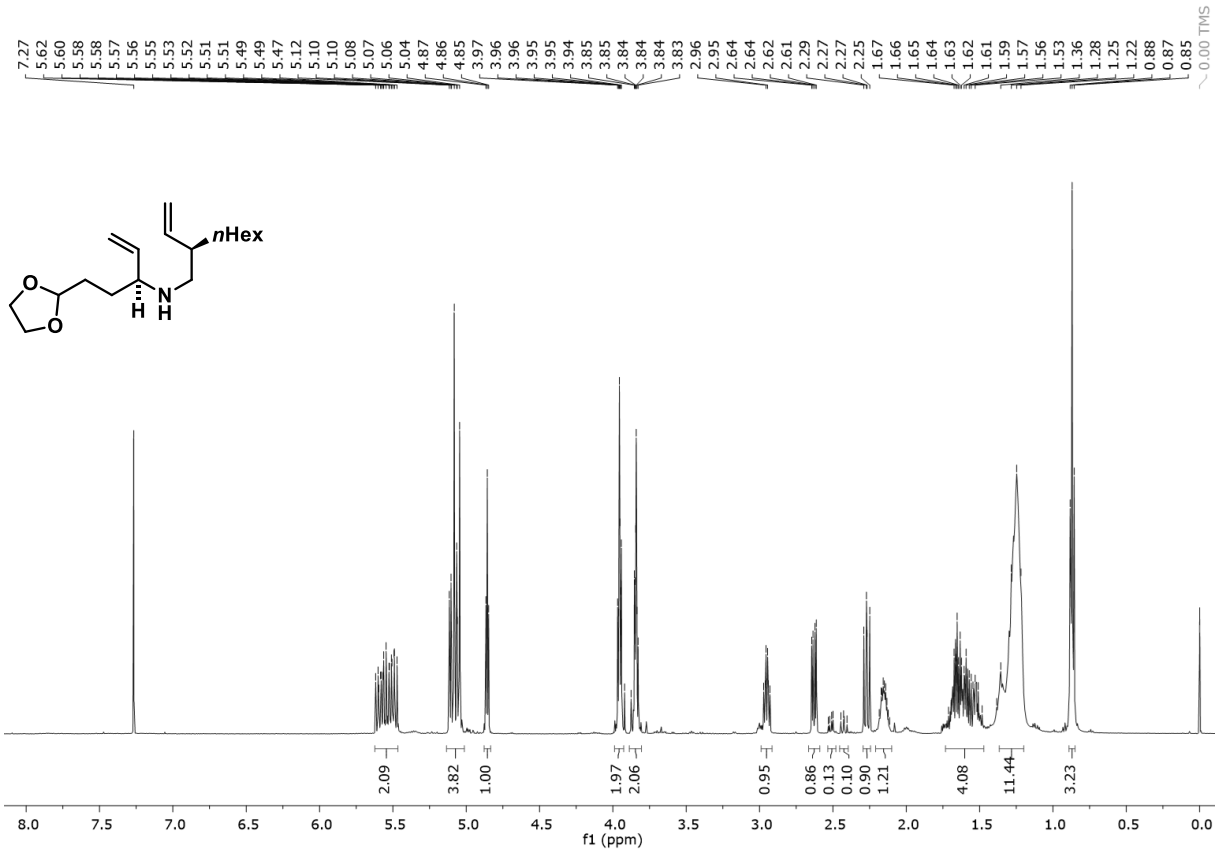


*Figure 101: ^{1}H NMR (500 MHz, $CDCl_3$) of (R)-N-((S)-5-(1,3-dioxolan-2-yl)pent-1-en-3-yl)-2-vinyloctan-1- amine (**205**).*

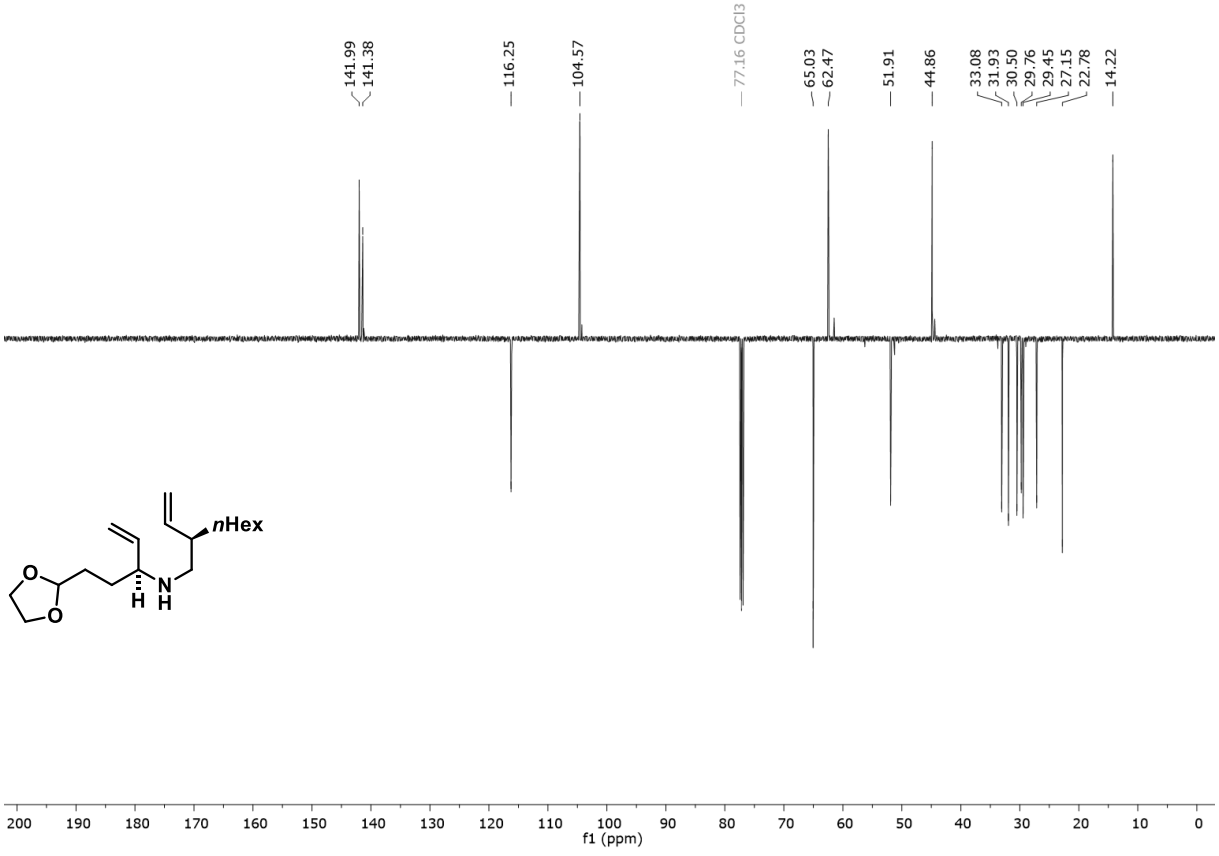


*Figure 102: ^{13}C NMR (126 MHz, $CDCl_3$) of (R)-N-((S)-5-(1,3-dioxolan-2-yl)pent-1-en-3-yl)-2-vinyloctan-1- amine (**205**).*

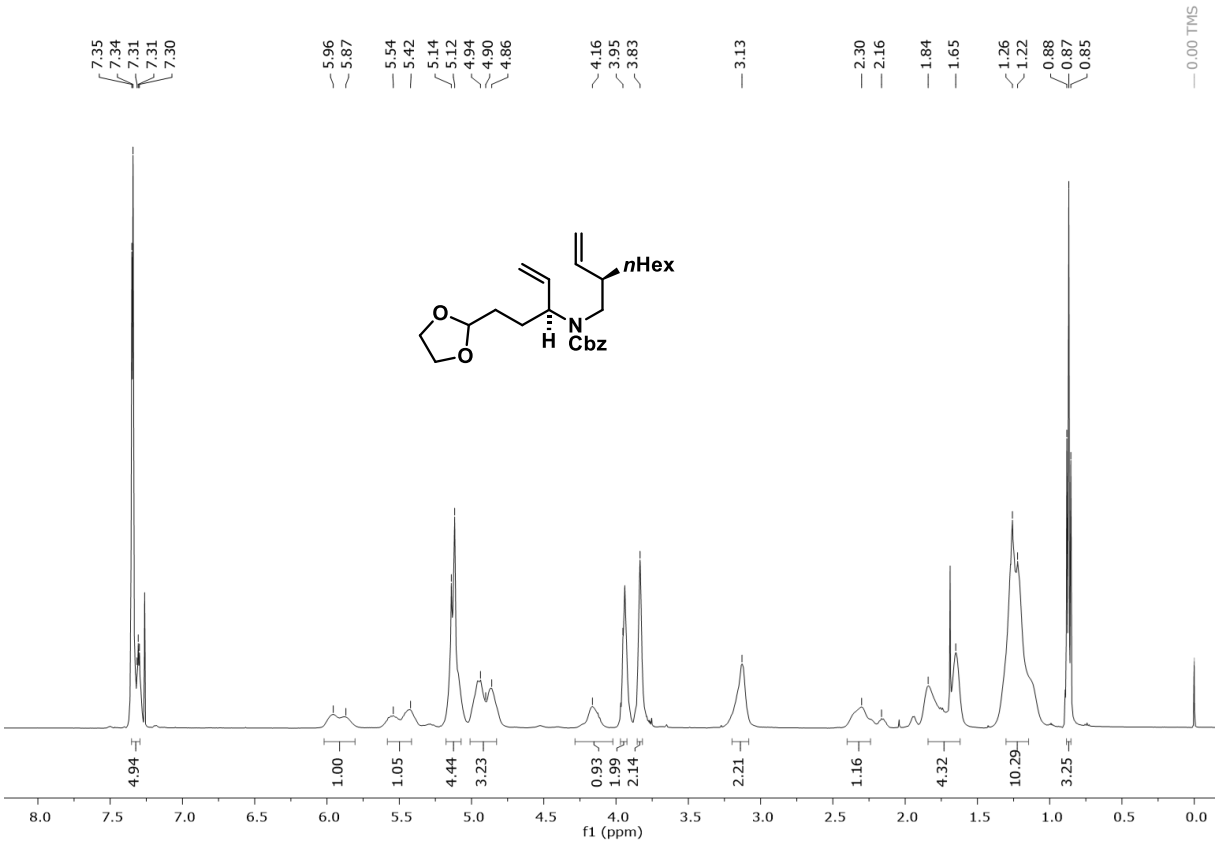


*Figure 103: ^{1}H NMR (500 MHz, $CDCl_3$) of benzyl ((S)-5-(1,3-dioxolan-2-yl)pent-1-en-3-yl)((R)-2- vinyloctyl)carbamate (**120**).*

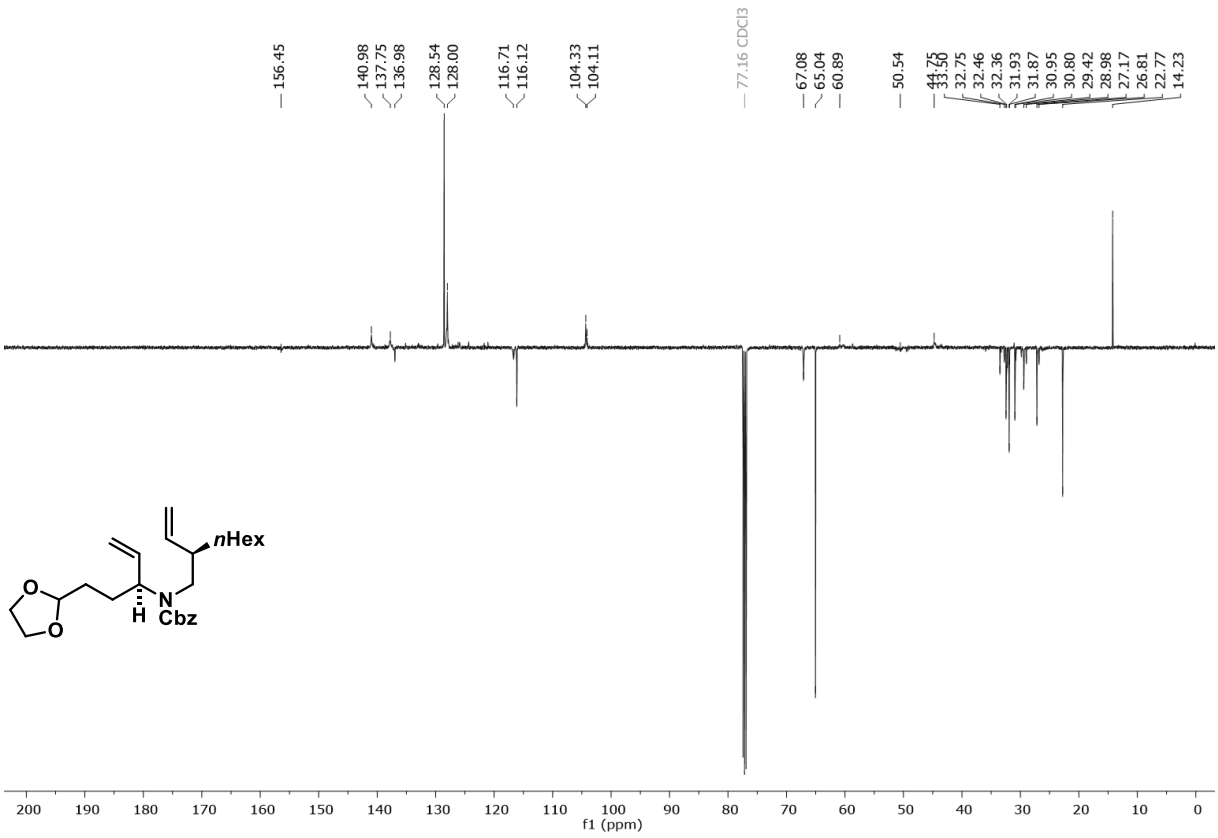


*Figure 104: ^{13}C NMR (126 MHz, $CDCl_3$) of benzyl ((S)-5-(1,3-dioxolan-2-yl)pent-1-en-3-yl)((R)-2- vinyloctyl)carbamate (**120**).*

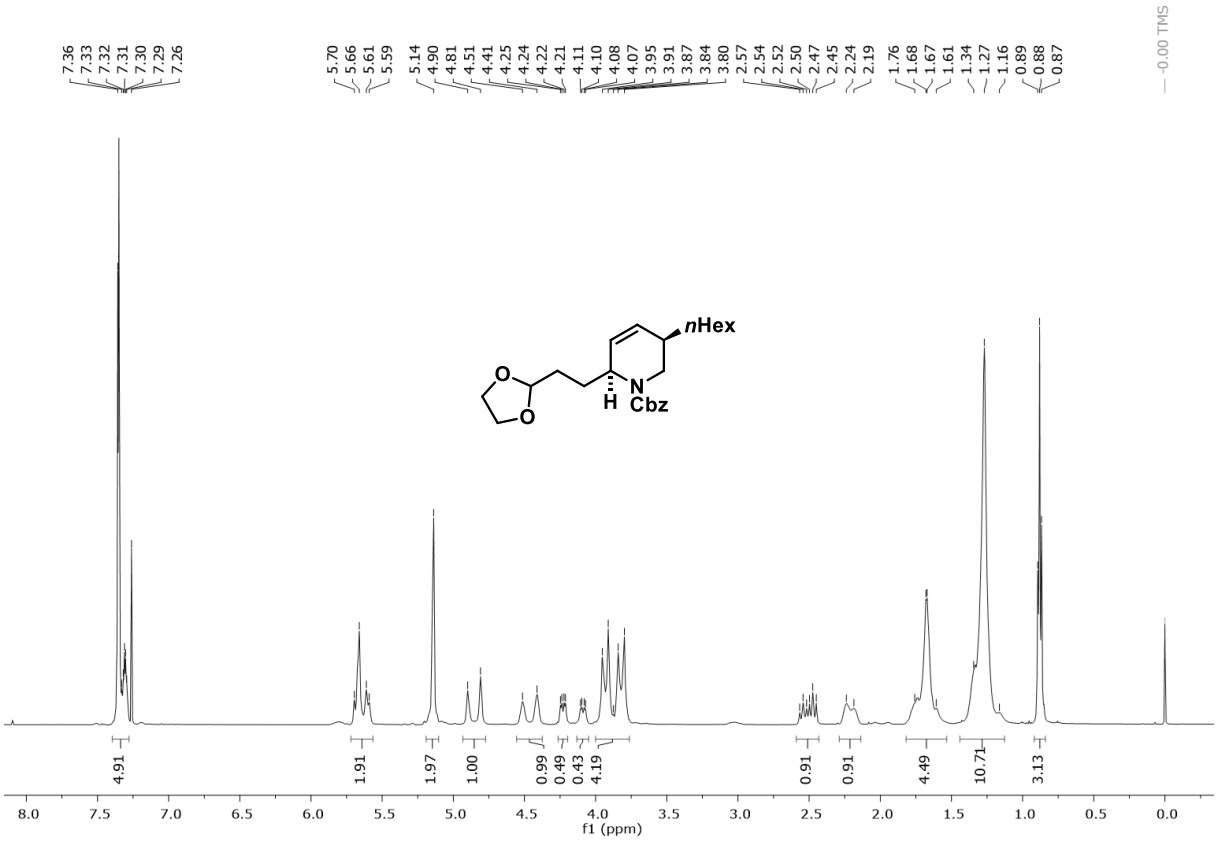


*Figure 105: ^{1}H NMR (500 MHz, $CDCl_3$) of benzyl (3R,6S)-6-(2-(1,3-dioxolan-2-yl)ethyl)-3-hexyl-3,6- dihydropyridine-1(2H)-carboxylate (**119**).*

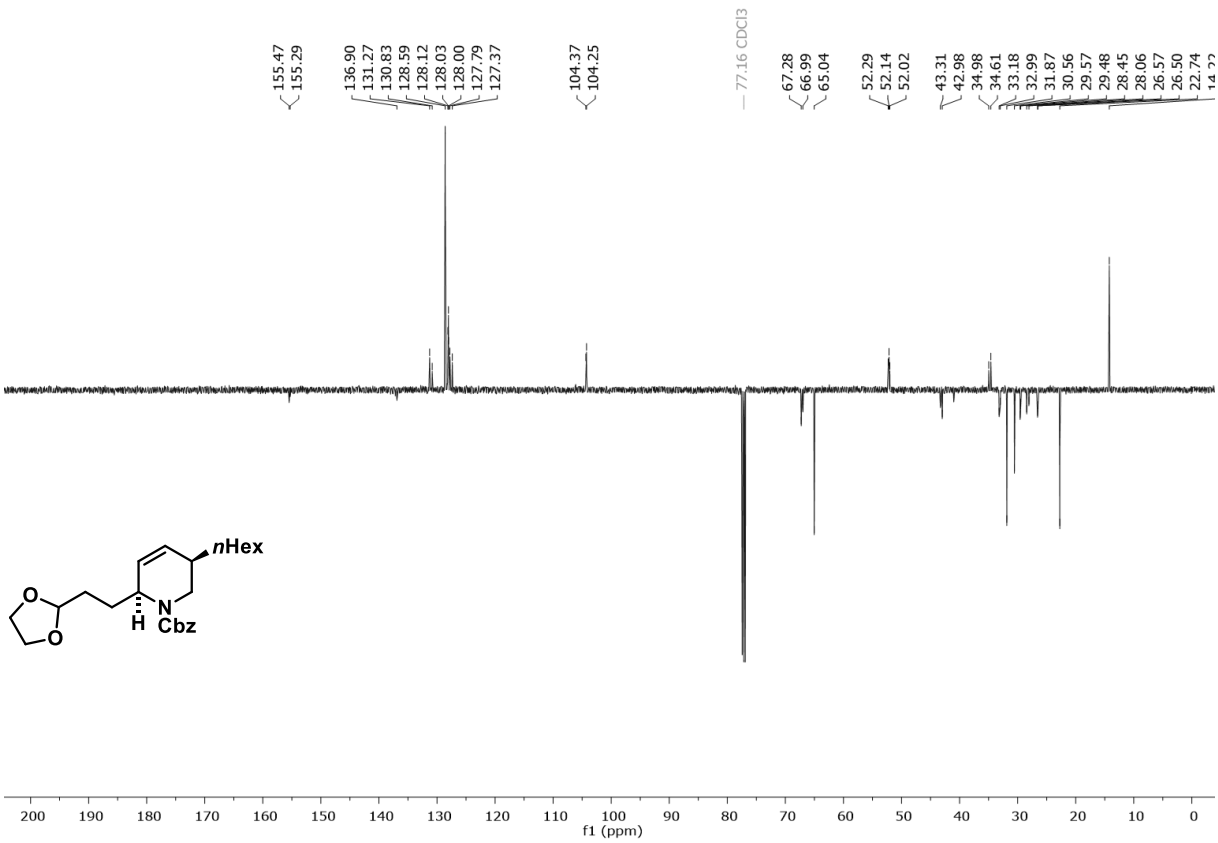


*Figure 106: ^{13}C NMR (126 MHz, $CDCl_3$) of benzyl (3R,6S)-6-(2-(1,3-dioxolan-2-yl)ethyl)-3-hexyl-3,6- dihydropyridine-1(2H)-carboxylate (**119**).*

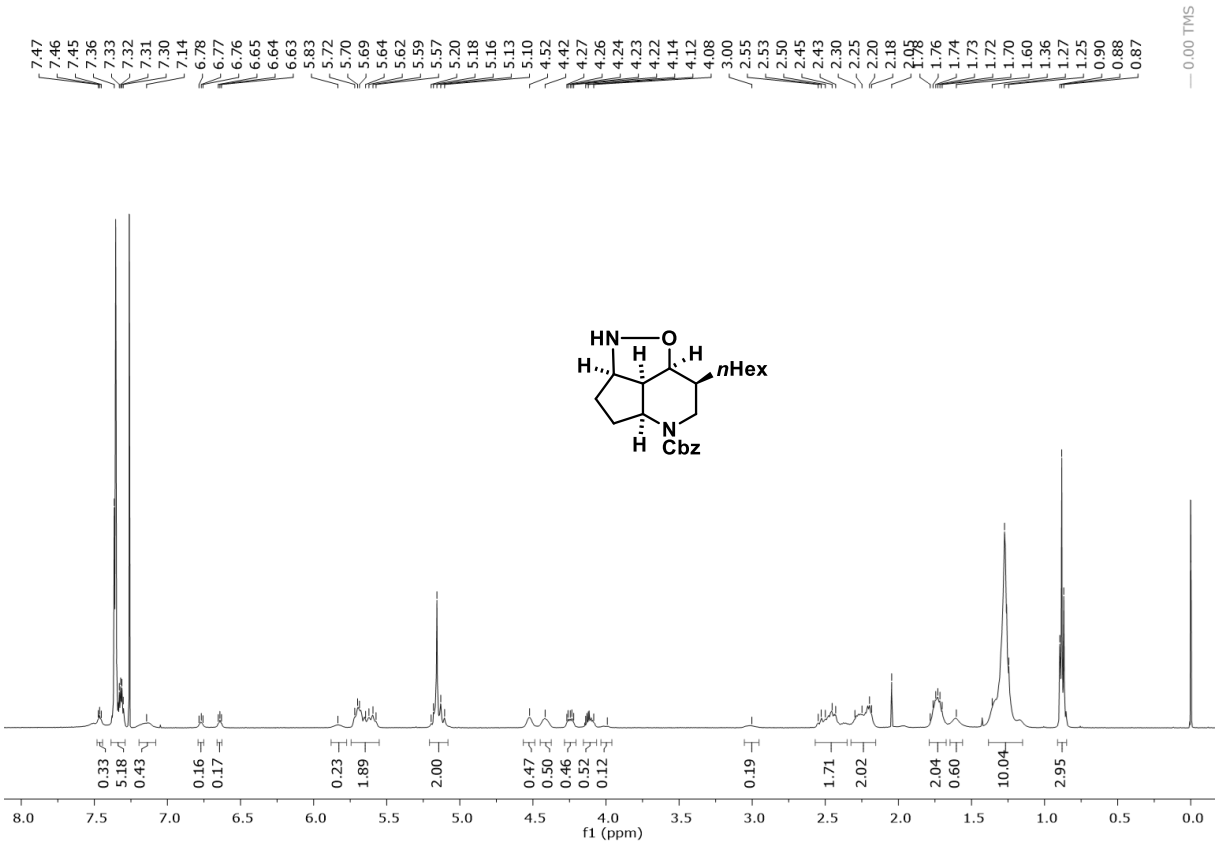


*Figure 107: ^{1}H NMR (500 MHz, $CDCl_3$) of benzyl (2aR,2a^{1}S,4aS,5S,7aS)-5-hexyloctahydro-4-oxa-3,7-diazacyclopenta[cd]indene-7(2H)-carboxylate (**206**).*

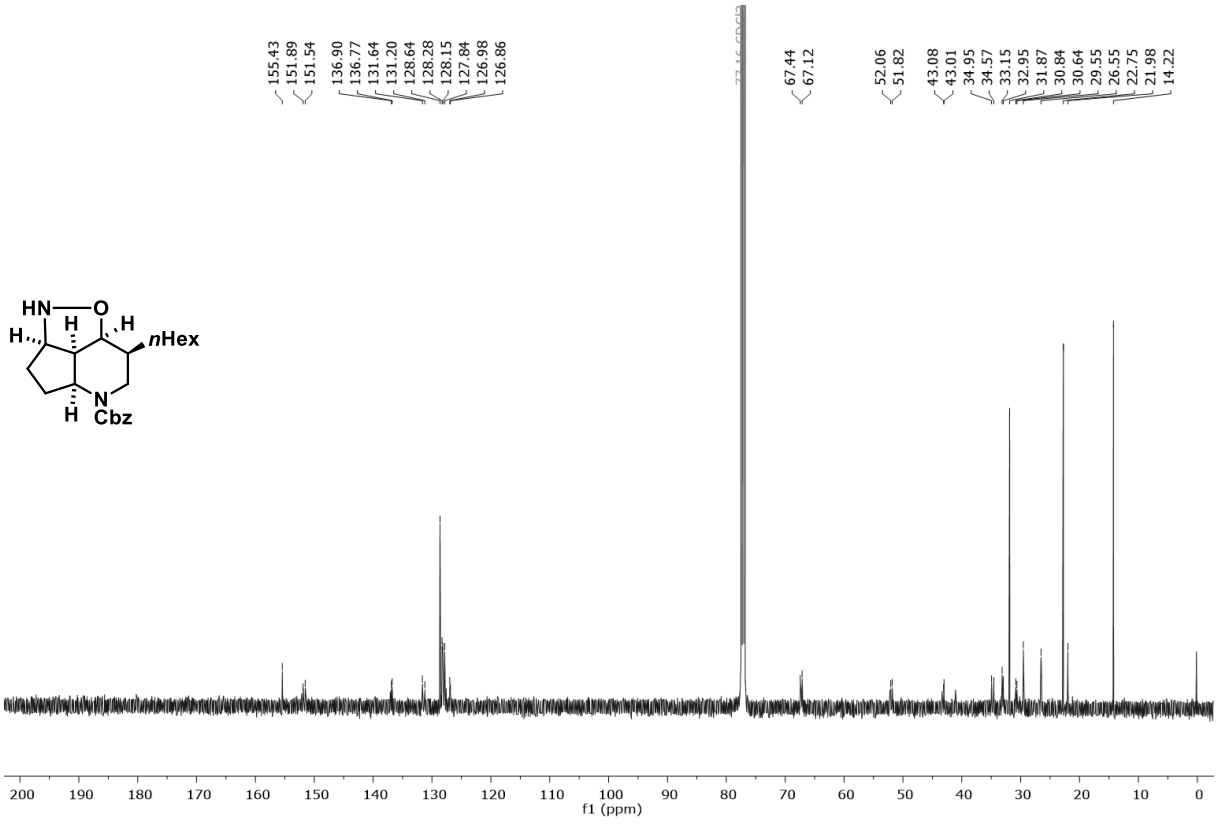


*Figure 108: ^{13}C NMR (121 MHz, $CDCl_3$) of benzyl (2aR,2a^{1}S,4aS,5S,7aS)-5-hexyloctahydro-4-oxa-3,7-diazacyclopenta[cd]indene-7(2H)-carboxylate (**206**).*

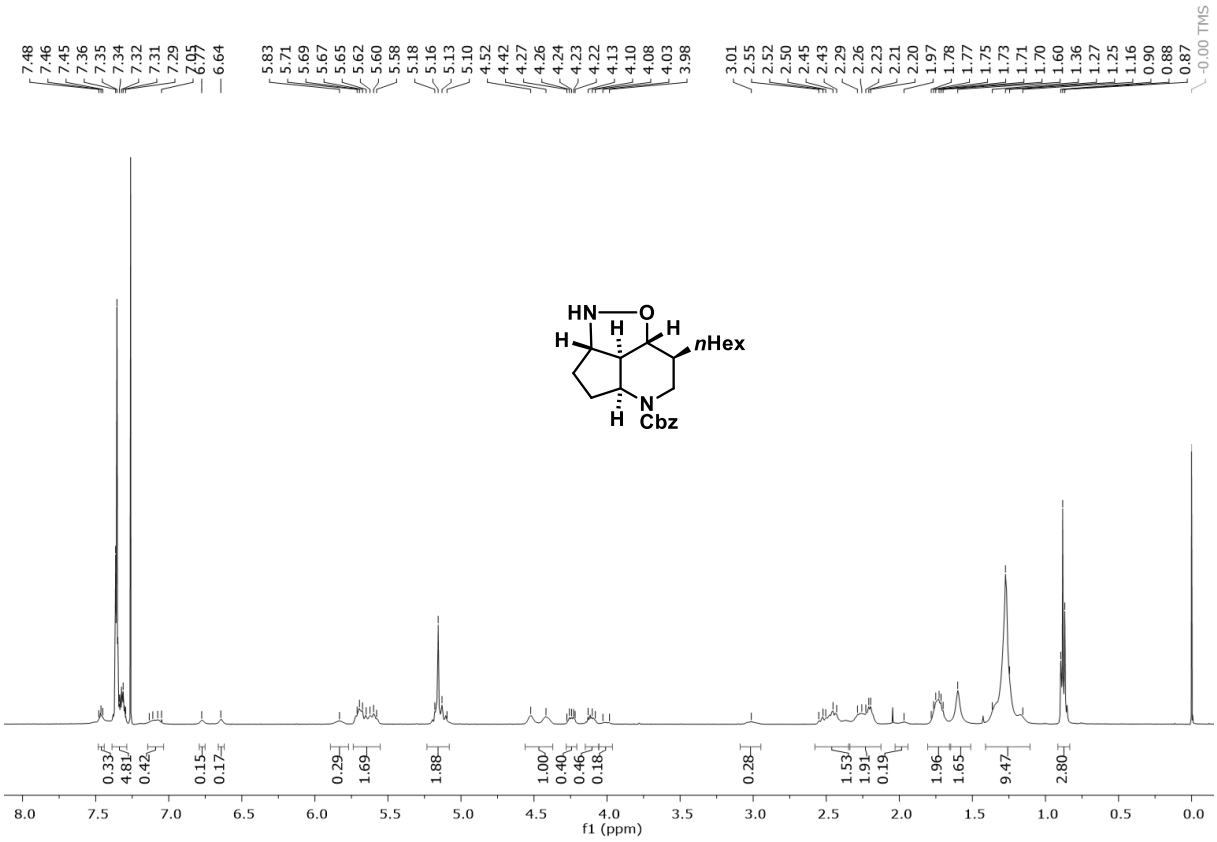


*Figure 109: ^{1}H NMR (500 MHz, $CDCl_3$) of benzyl (2aS,2a^{1}S,4aR,5S,7aS)-5-hexyloctahydro-4-oxa-3,7-diazacyclopenta[cd]indene-7(2H)-carboxylate (**206**).*

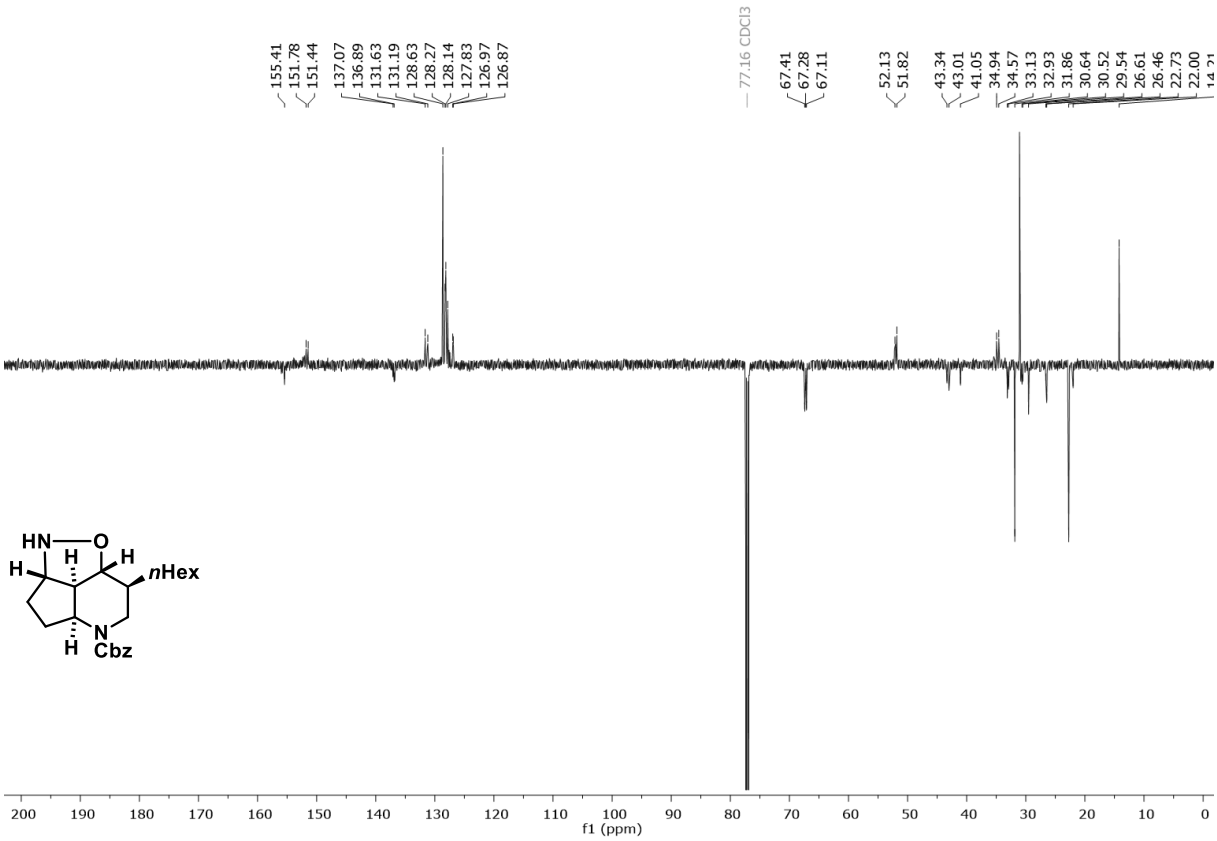


*Figure 110: ^{13}C NMR (126 MHz, $CDCl_3$) of benzyl (2aR,2a^{1}S,4aS,5S,7aS)-5-hexyloctahydro-4-oxa-3,7-diazacyclopenta[cd]indene-7(2H)-carboxylate (**206**).*

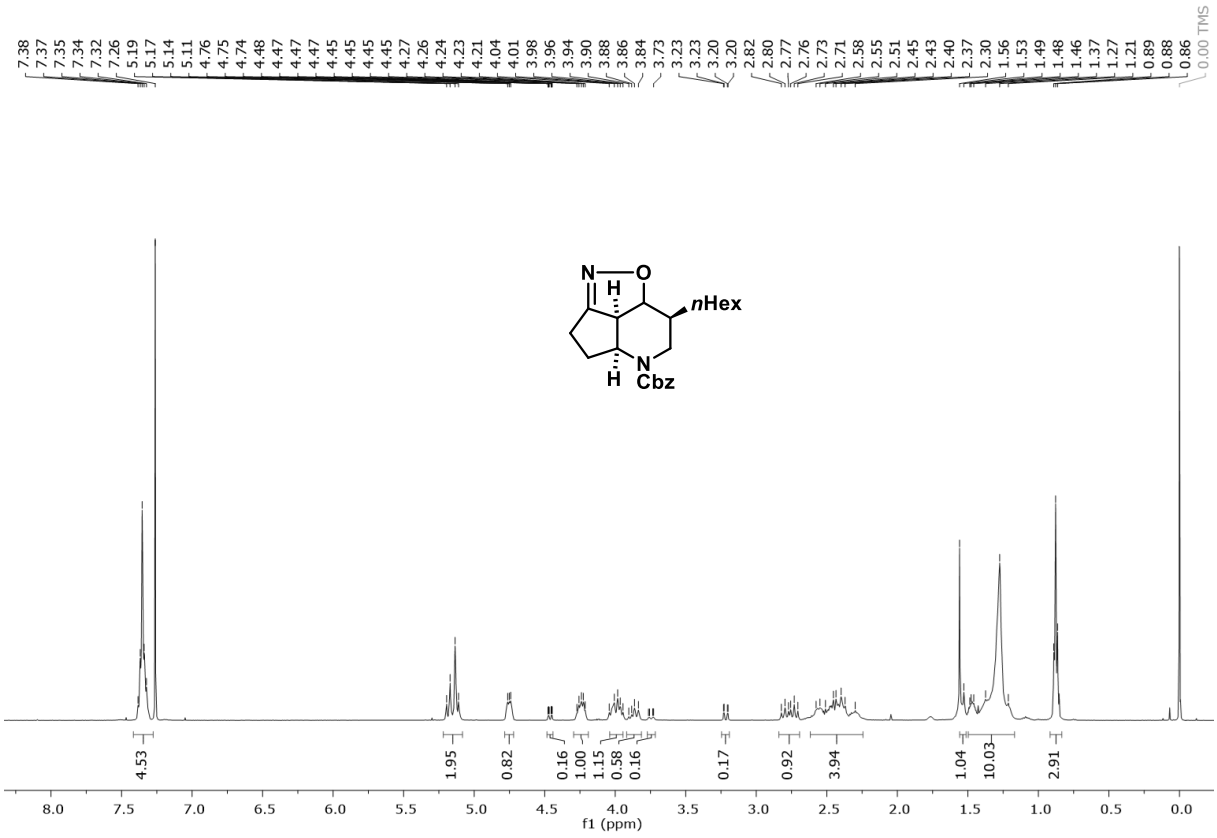


*Figure 111: [1]H NMR (500 MHz, $CDCl_3$) of benzyl (2a[1]S,5S,7aS)-5-hexyl-1,2a[1],4a,5,6,7a-hexahydro-4- oxa-3,7-diazacyclopenta[cd]indene-7(2H)-carboxylate (**117**).*

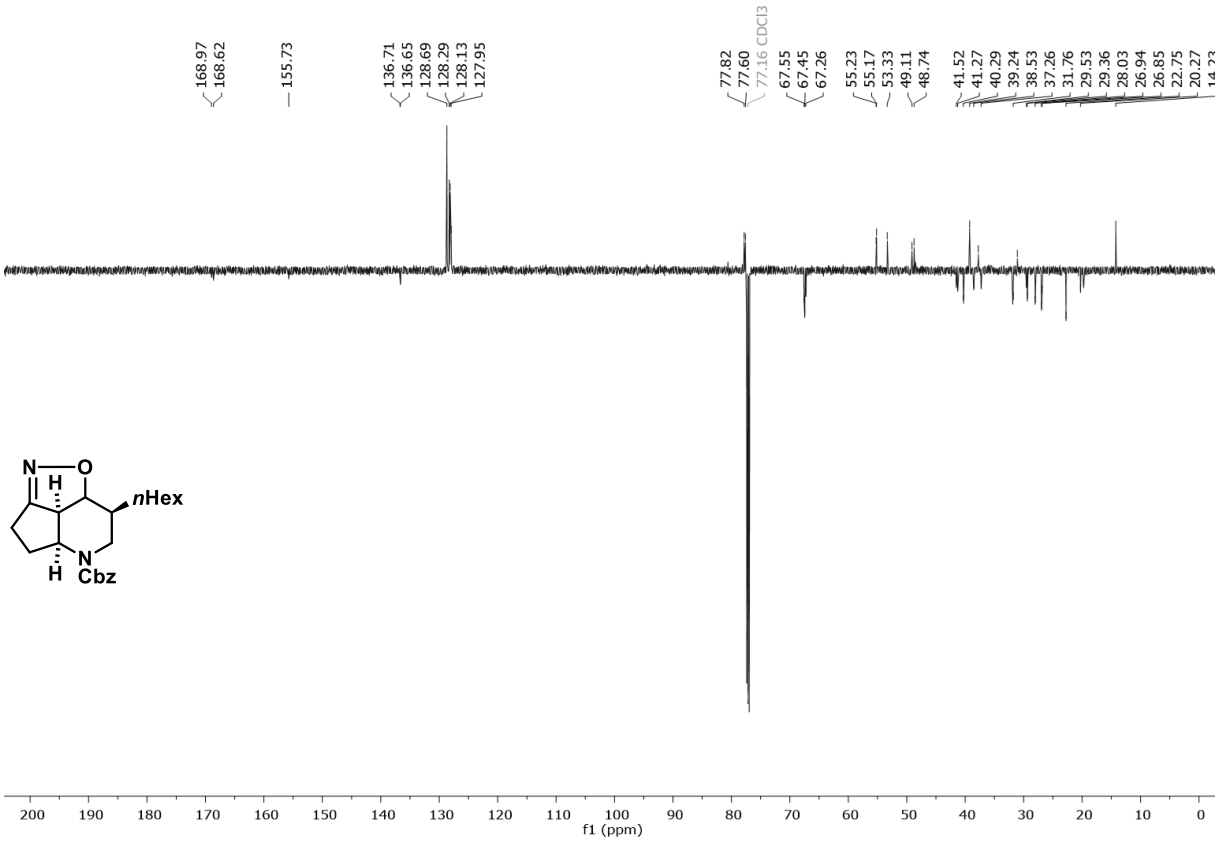


*Figure 112: [13]C NMR (126 MHz, $CDCl_3$) of benzyl (2a[1]S,5S,7aS)-5-hexyl-1,2a[1],4a,5,6,7a-hexahydro-4- oxa-3,7-diazacyclopenta[cd]indene-7(2H)-carboxylate (**117**).*

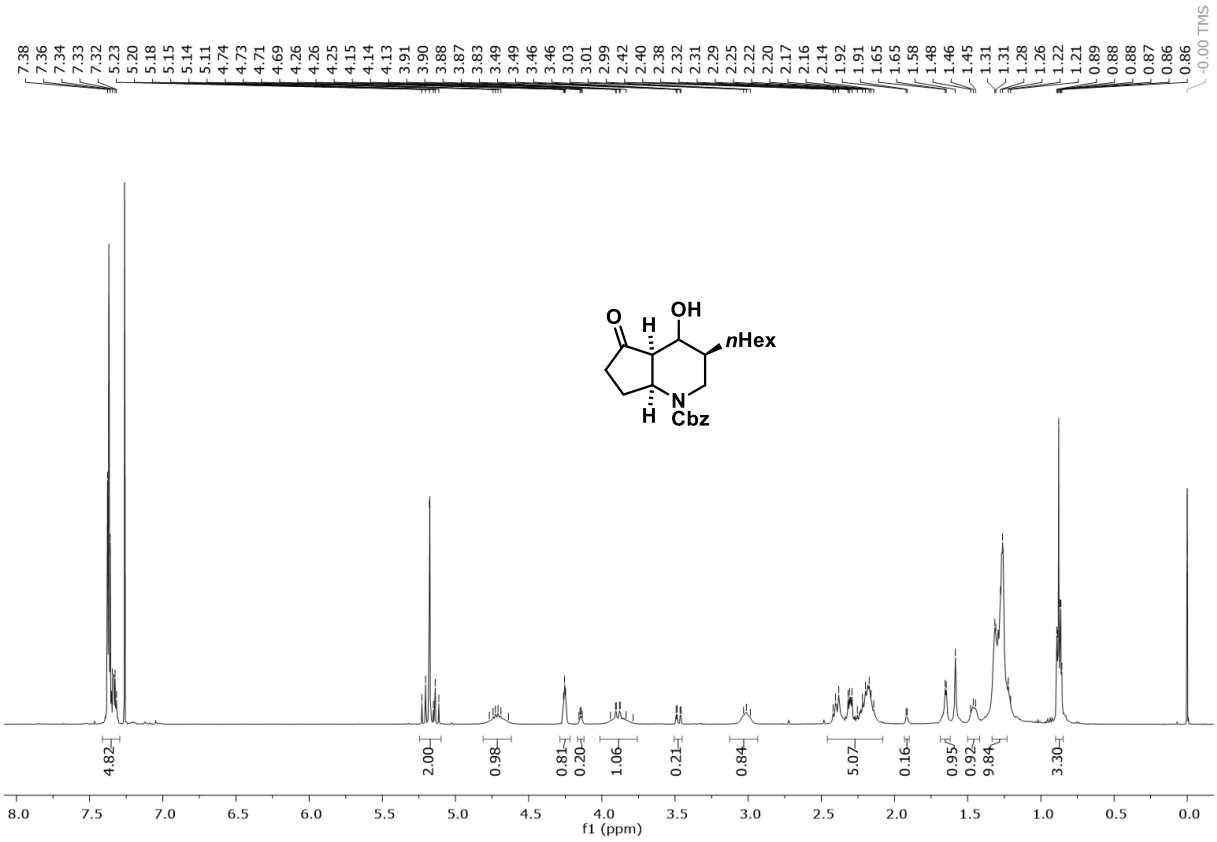


*Figure 113: ^{1}H NMR (500 MHz, $CDCl_3$) of benzyl (3S,4aR,7aS)-3-hexyl-4-hydroxy-5-oxooctahydro-1H-cyclopenta[b]pyridine-1-carboxylate (**207**).*

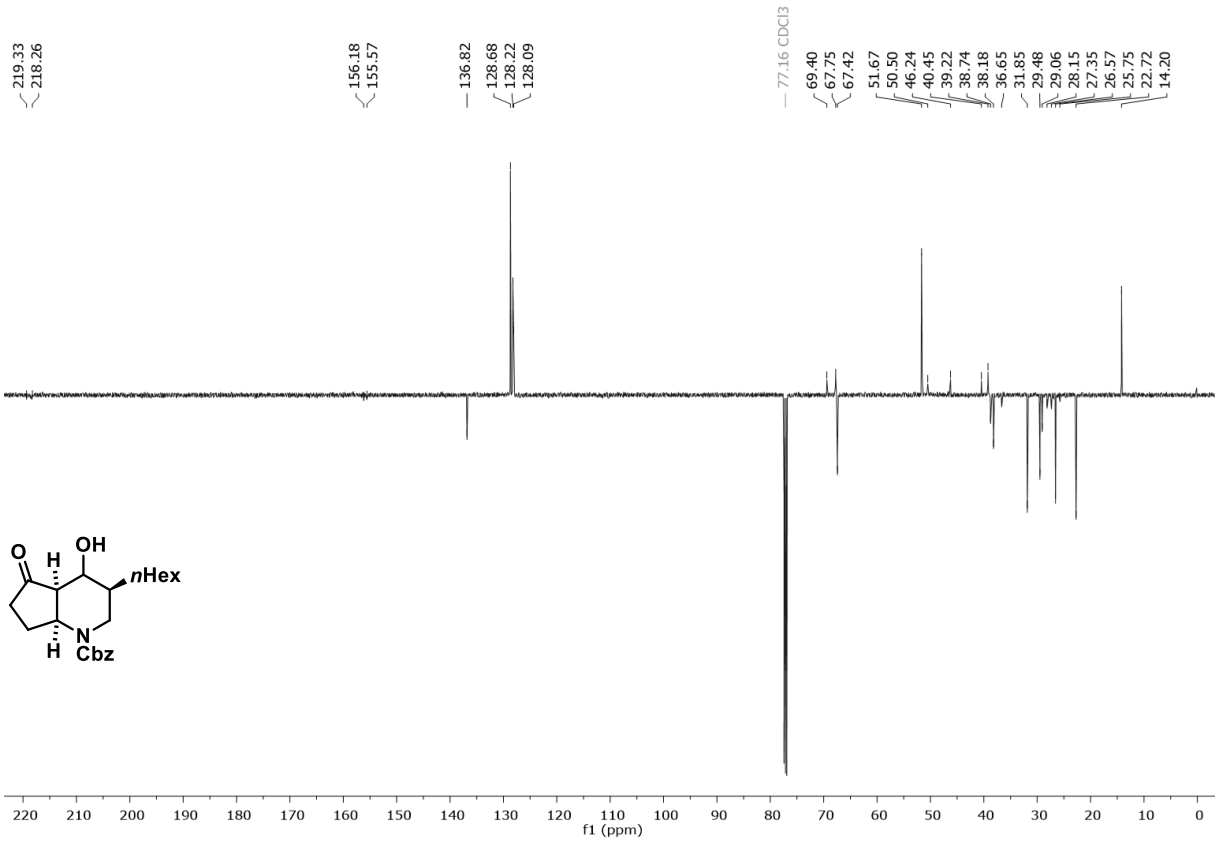


*Figure 114: ^{13}C NMR (126 MHz, $CDCl_3$) of benzyl (3S,4aR,7aS)-3-hexyl-4-hydroxy-5-oxooctahydro-1H-cyclopenta[b]pyridine-1-carboxylate (**207**).*

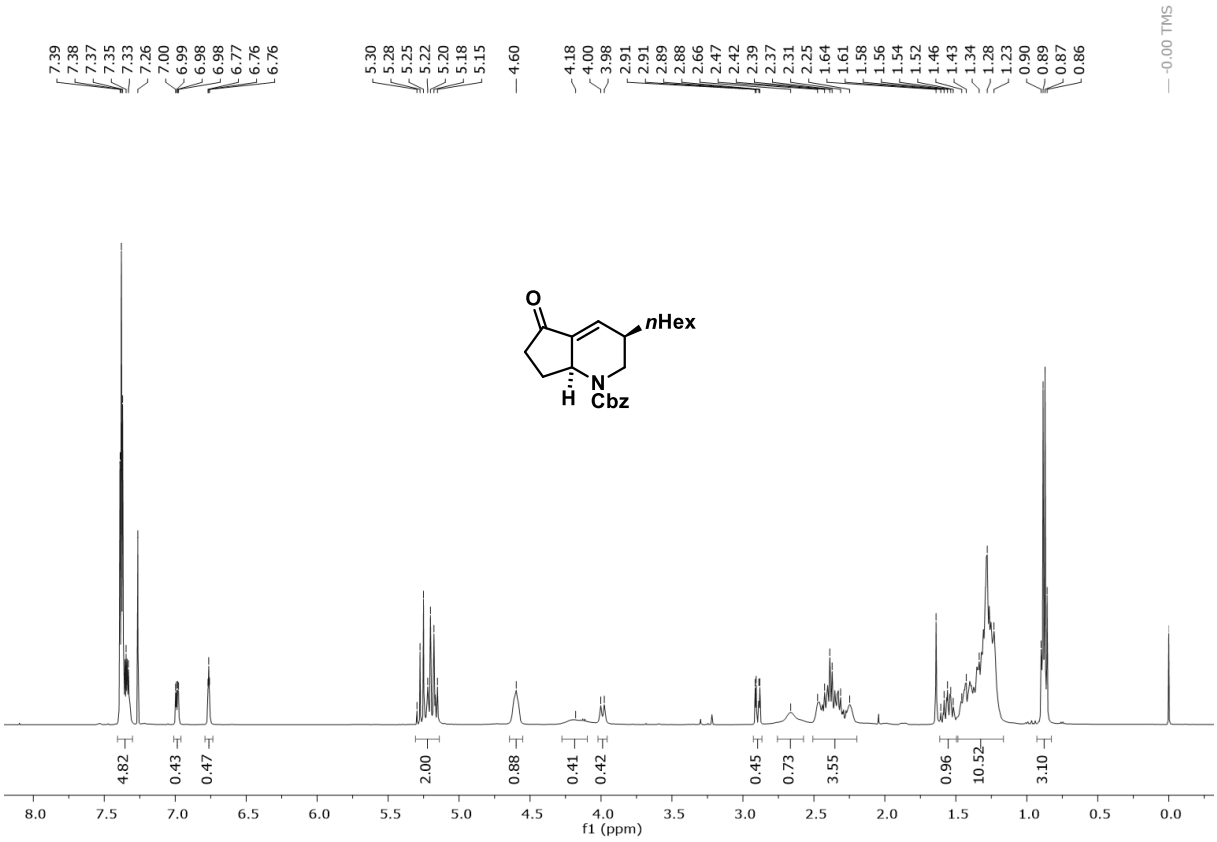


*Figure 115: [1]H NMR (500 MHz, $CDCl_3$) of benzyl (3R,7aS)-3-hexyl-5-oxo-2,3,5,6,7,7a-hexahydro-1H-cyclopenta[b]pyridine-1-carboxylate (**116**).*

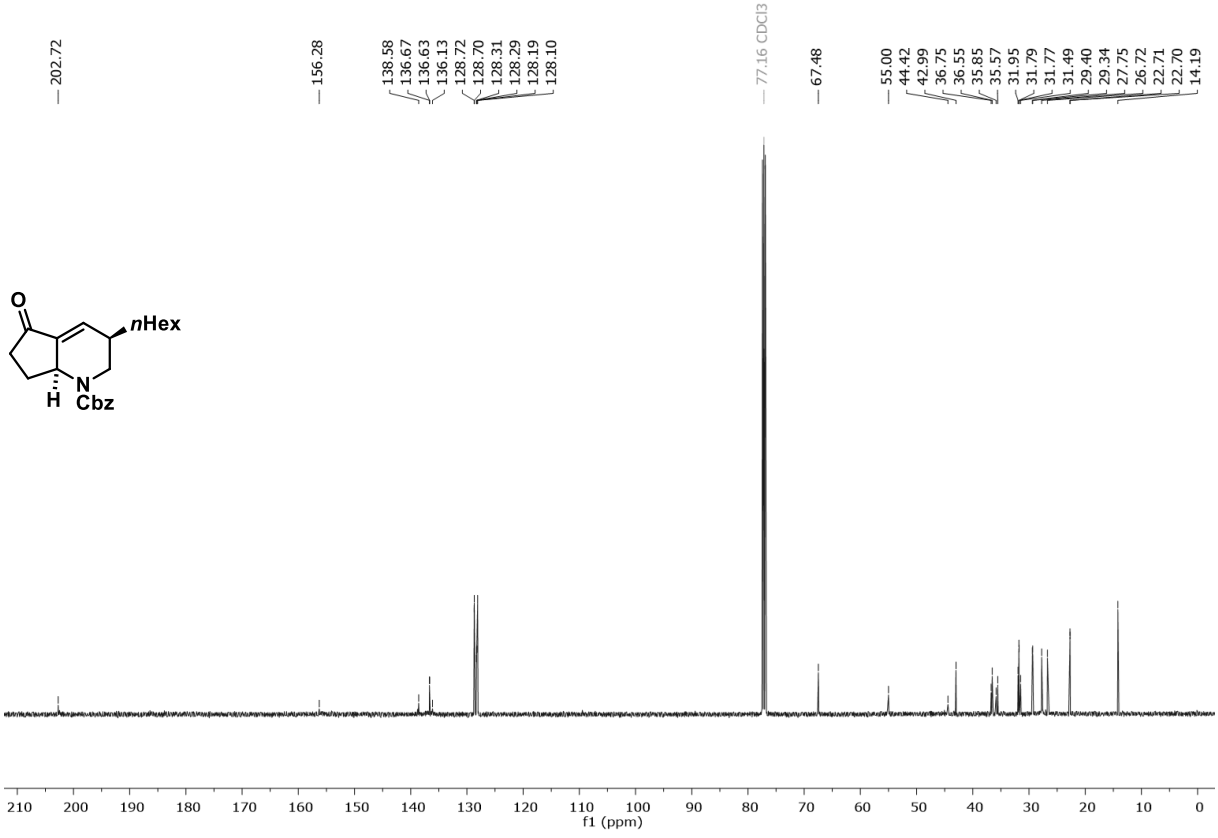


*Figure 116: [13]C NMR (126 MHz, $CDCl_3$) of benzyl (3R,7aS)-3-hexyl-5-oxo-2,3,5,6,7,7a-hexahydro-1H-cyclopenta[b]pyridine-1-carboxylate (**116**).*

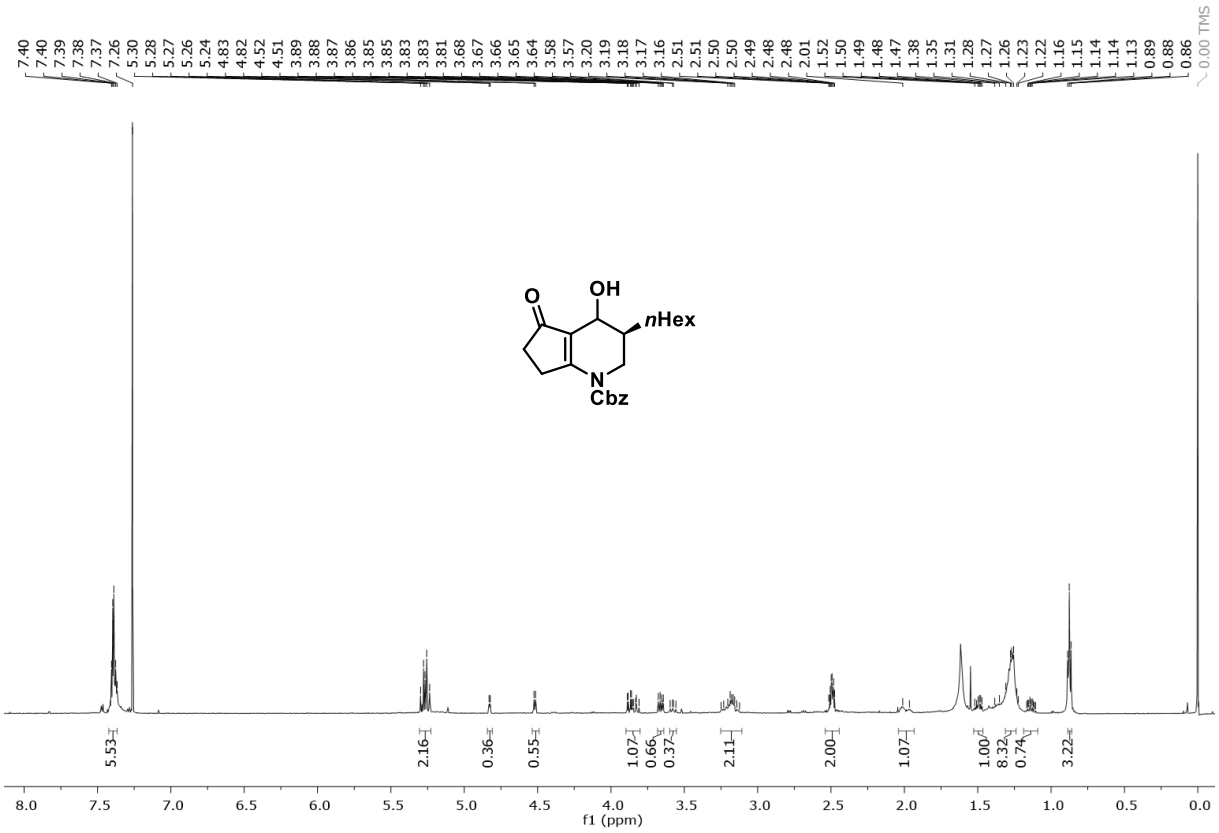


*Figure 117: ^{1}H NMR (600 MHz, $CDCl_3$) of benzyl (3S)-3-hexyl-4-hydroxy-5-oxo-2,3,4,5,6,7-hexahydro-1H-cyclopenta[b]pyridine-1-carboxylate (**208**).*

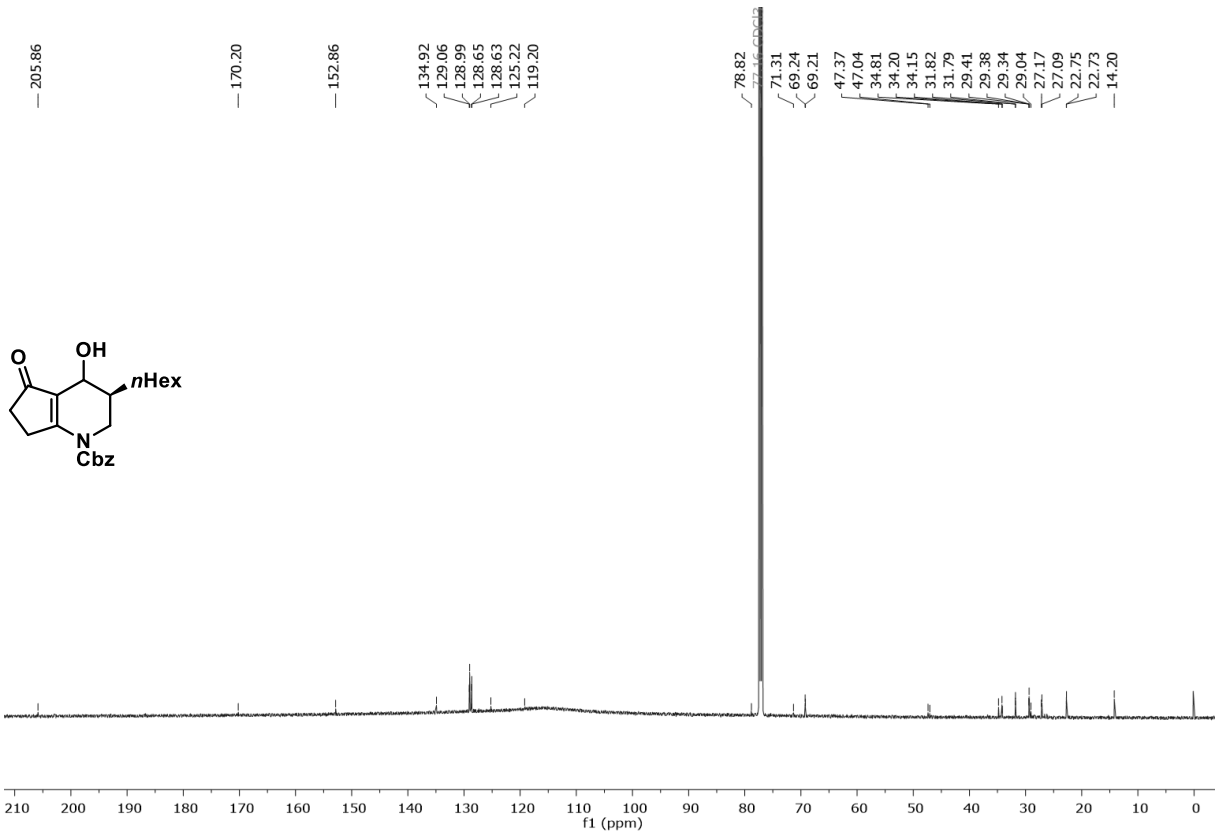


*Figure 118: ^{13}C NMR (151 MHz, $CDCl_3$) of benzyl (3S)-3-hexyl-4-hydroxy-5-oxo-2,3,4,5,6,7-hexahydro-1H-cyclopenta[b]pyridine-1-carboxylate (**208**).*

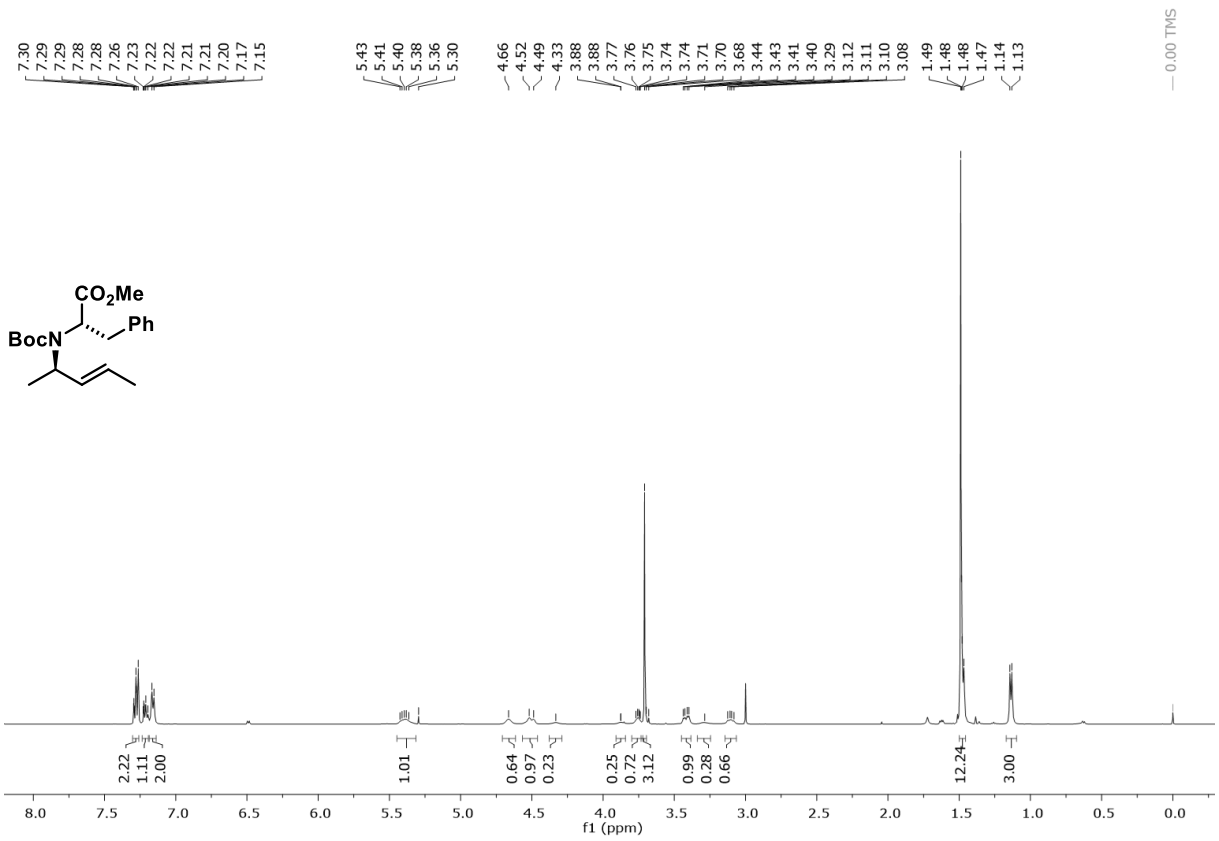


*Figure 119: ^{1}H NMR (500 MHz, $CDCl_3$) of N-(tert-butoxycarbonyl)-N-((E)-pent-3-en-2-yl)-L-phenylalaninate ((R,S)-**256**).*

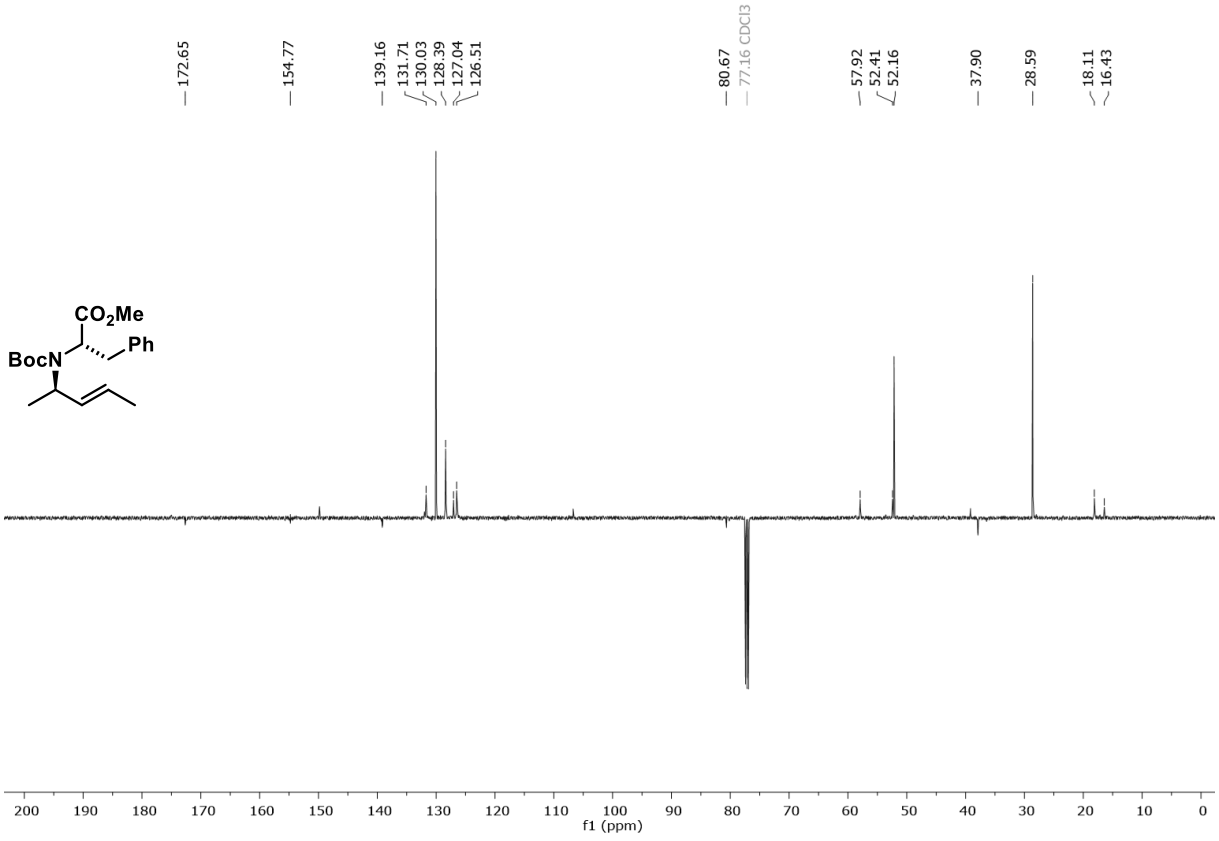


*Figure 120: ^{13}C NMR (126 MHz, $CDCl_3$) of N-(tert-butoxycarbonyl)-N-((E)-pent-3-en-2-yl)-L-phenylalaninate ((R,S)-**256**).*

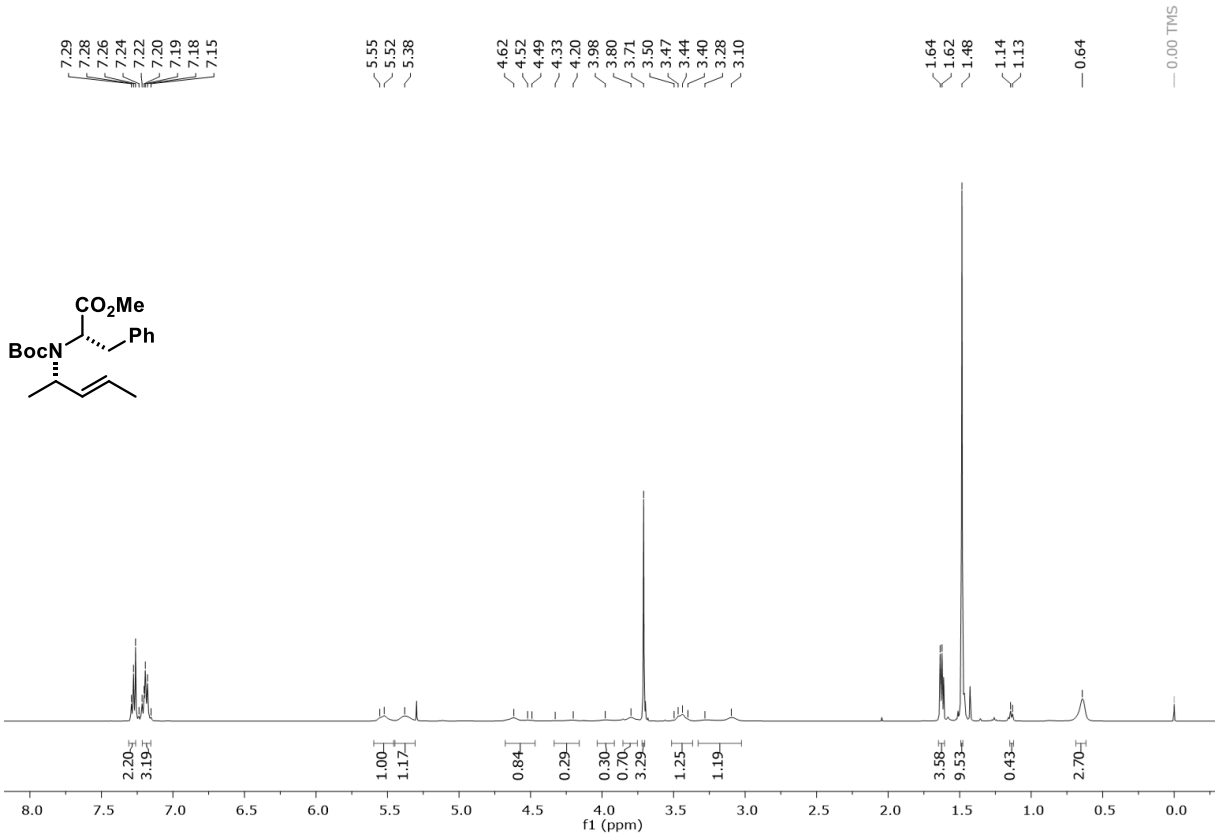


*Figure 121: ^{1}H NMR (500 MHz, $CDCl_3$) of N-(tert-butoxycarbonyl)-N-((E)-pent-3-en-2-yl)-L-phenylalaninate ((S,S)-**256**).*

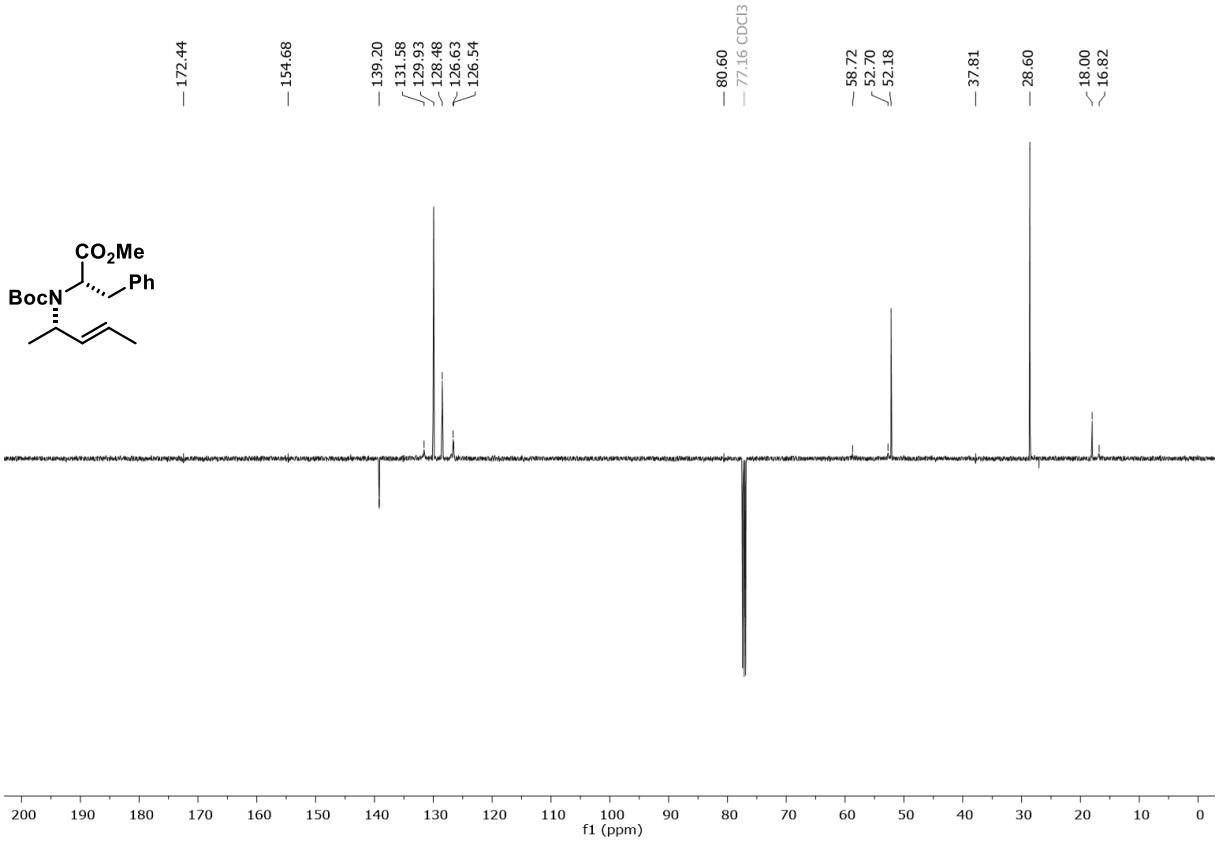


*Figure 122: ^{13}C NMR (126 MHz, $CDCl_3$) of N-(tert-butoxycarbonyl)-N-((E)-pent-3-en-2-yl)-L-phenylalaninate ((S,S)-**256**).*

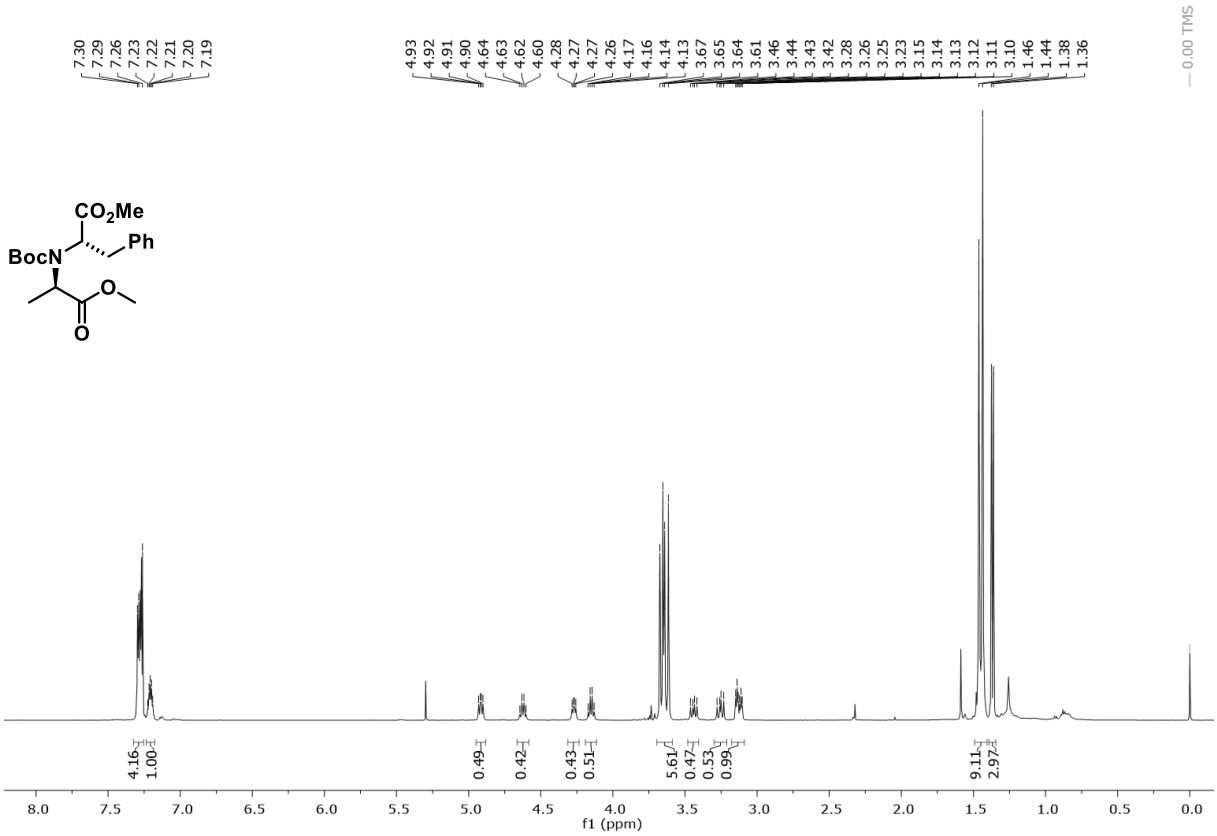


*Figure 123: [1]H NMR (500 MHz, $CDCl_3$) of methyl N-(tert-butoxycarbonyl)-N-(-1-methoxy-1- oxopropan-2-yl)-L-phenylalaninate ((R,S)-**251**).*

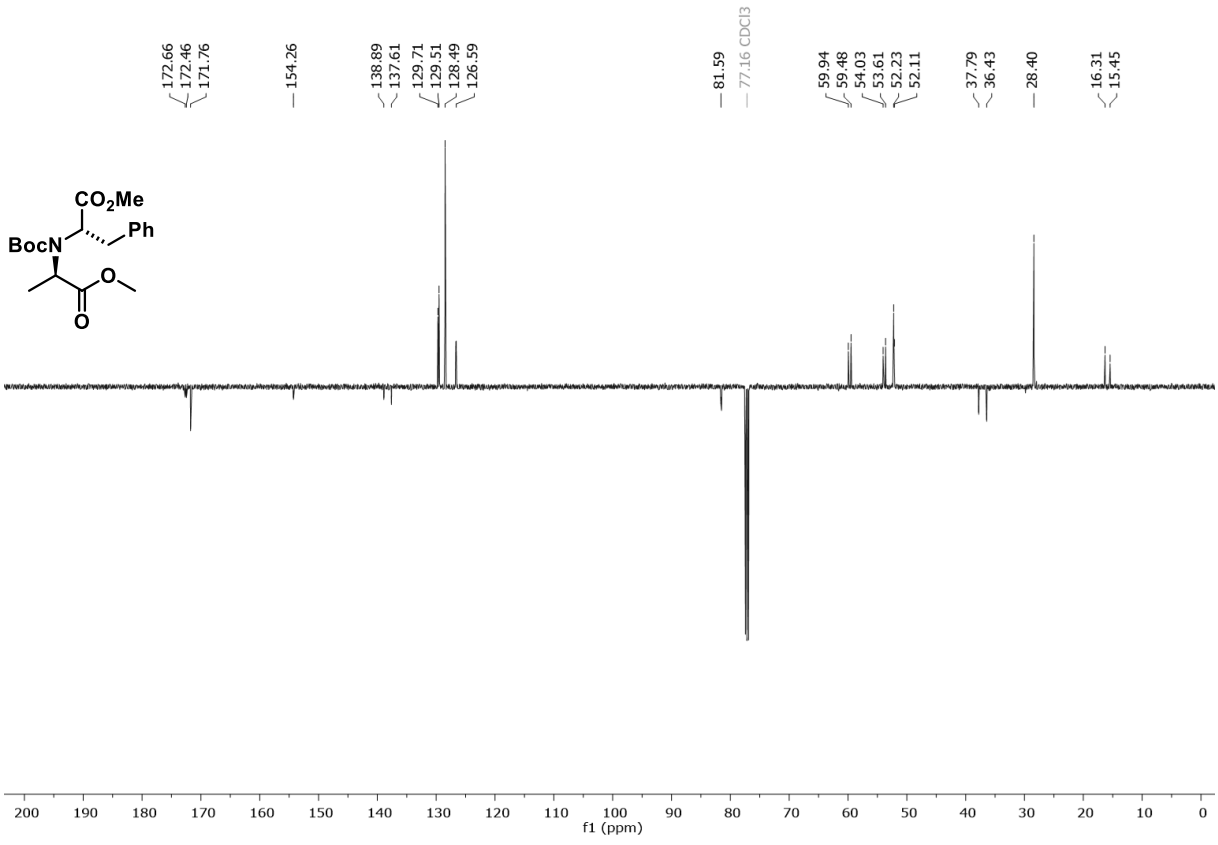


*Figure 124: [13]C NMR (126 MHz, $CDCl_3$) of methyl N-(tert-butoxycarbonyl)-N-(-1-methoxy-1- oxopropan-2-yl)-L-phenylalaninate ((R,S)-**251**).*

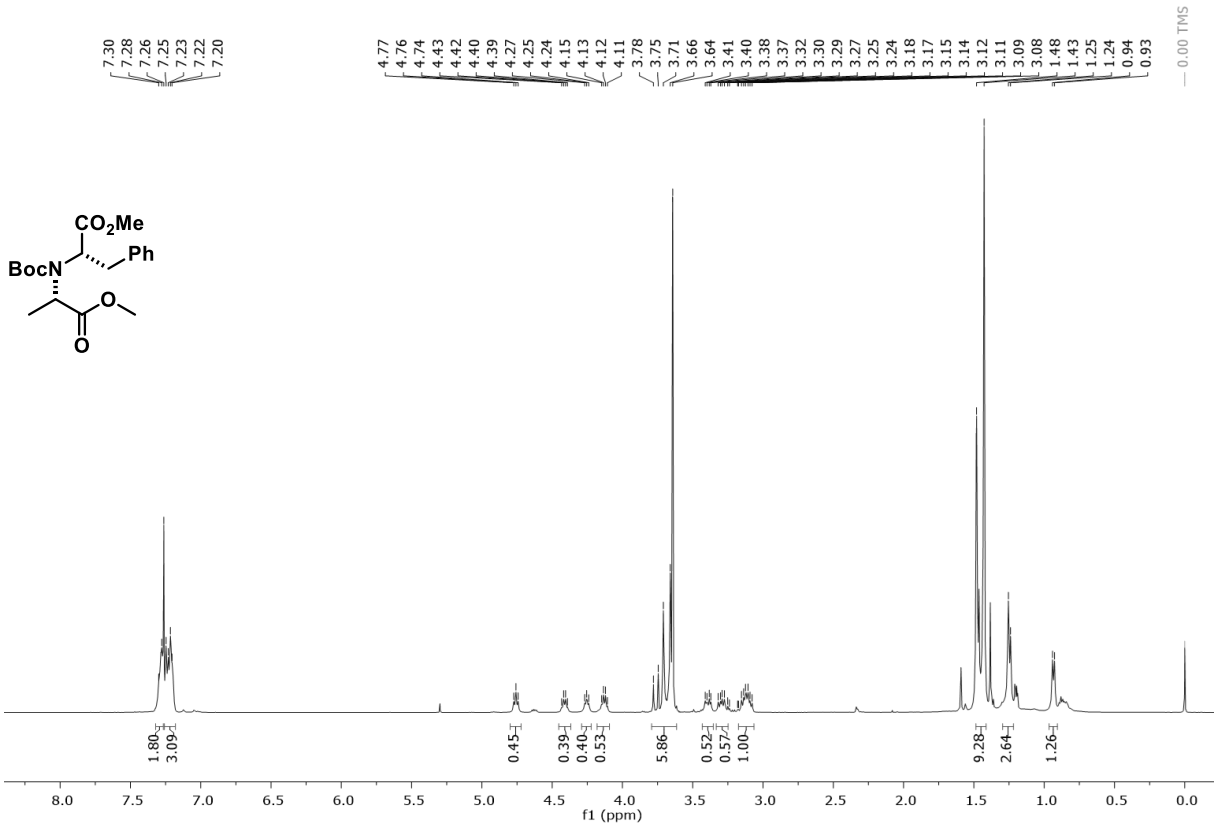


*Figure 125: ^{1}H NMR (500 MHz, $CDCl_3$) of methyl N-(tert-butoxycarbonyl)-N-(-1-methoxy-1- oxopropan-2-yl)-L-phenylalaninate ((S,S)-**251**).*

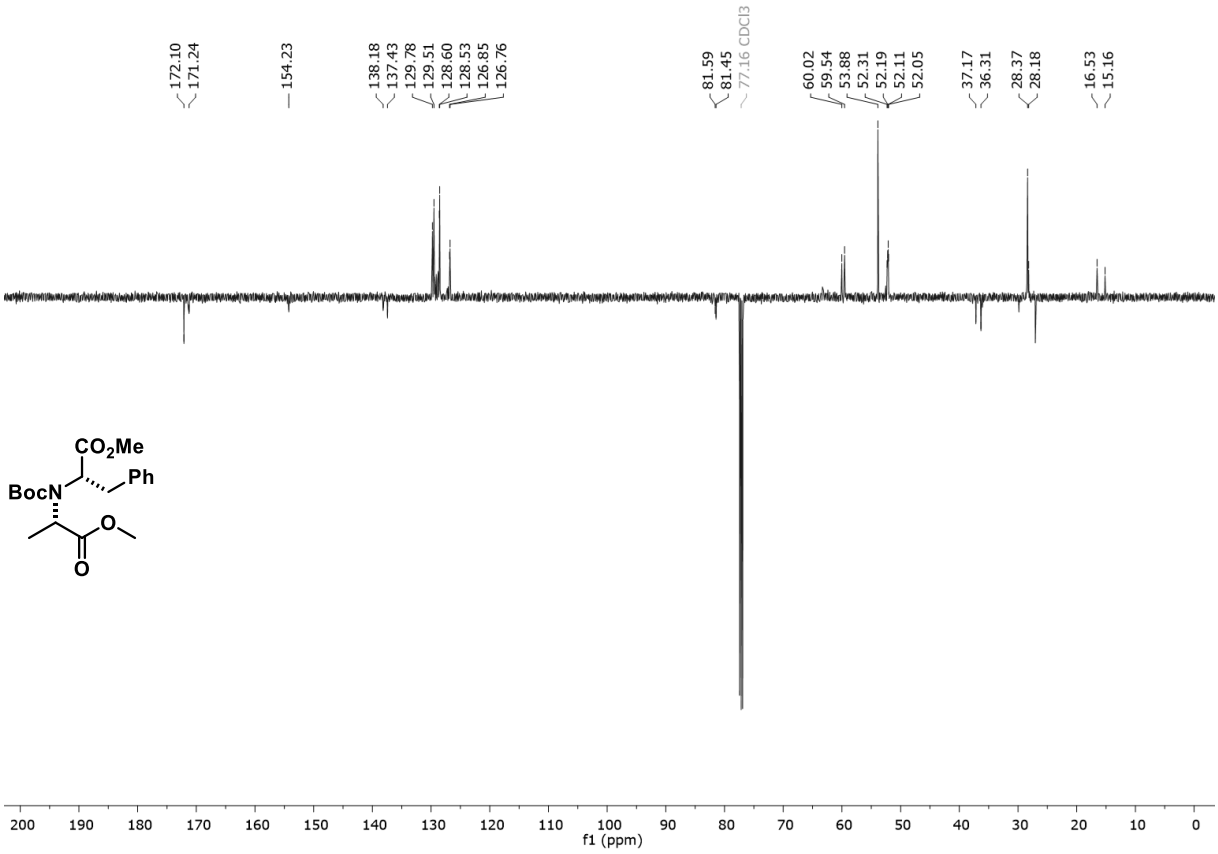


*Figure 126: ^{13}C NMR (126 MHz, $CDCl_3$) of methyl N-(tert-butoxycarbonyl)-N-(-1-methoxy-1- oxopropan-2-yl)-L-phenylalaninate ((S,S)-**251**).*

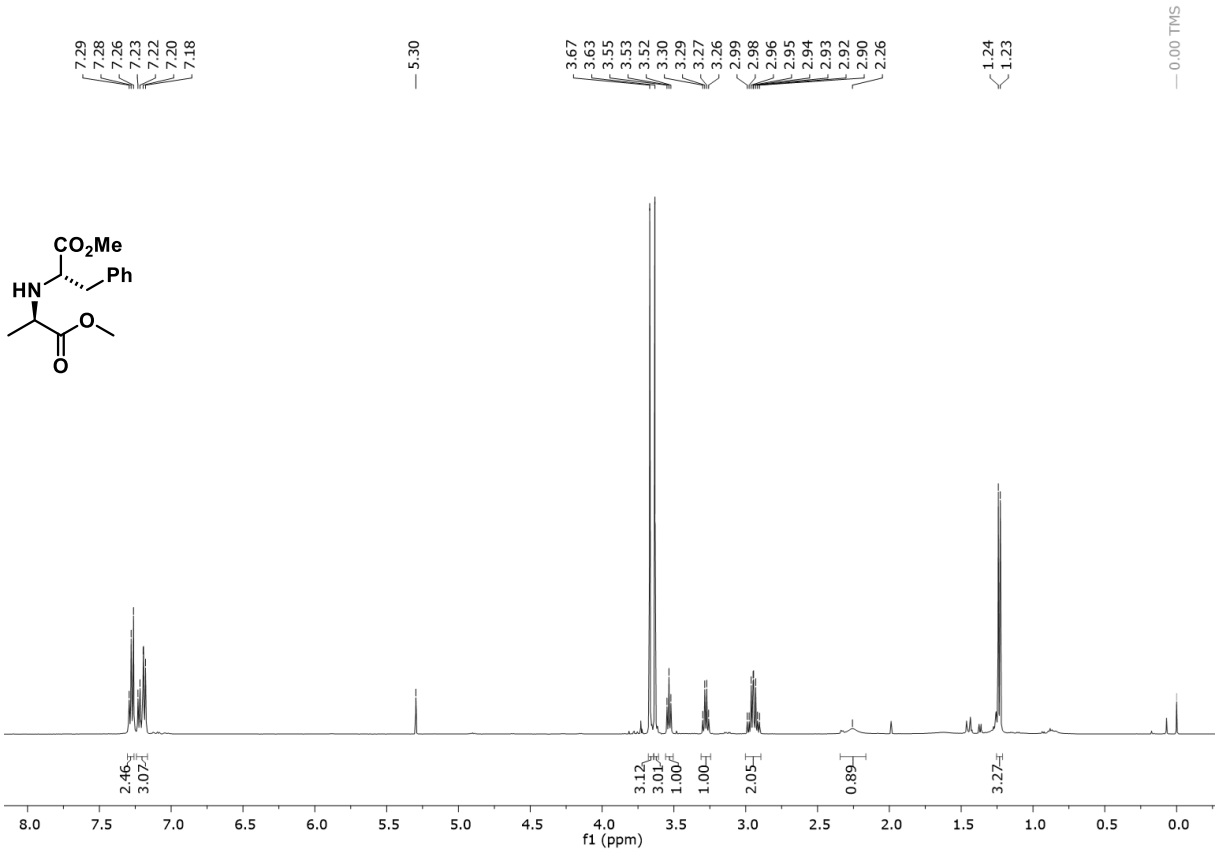


*Figure 127: ^{1}H NMR (500 MHz, $CDCl_3$) of methyl (1-methoxy-1-oxopropan-2-yl)-L-phenylalaninate ((R,S)-**258**).*

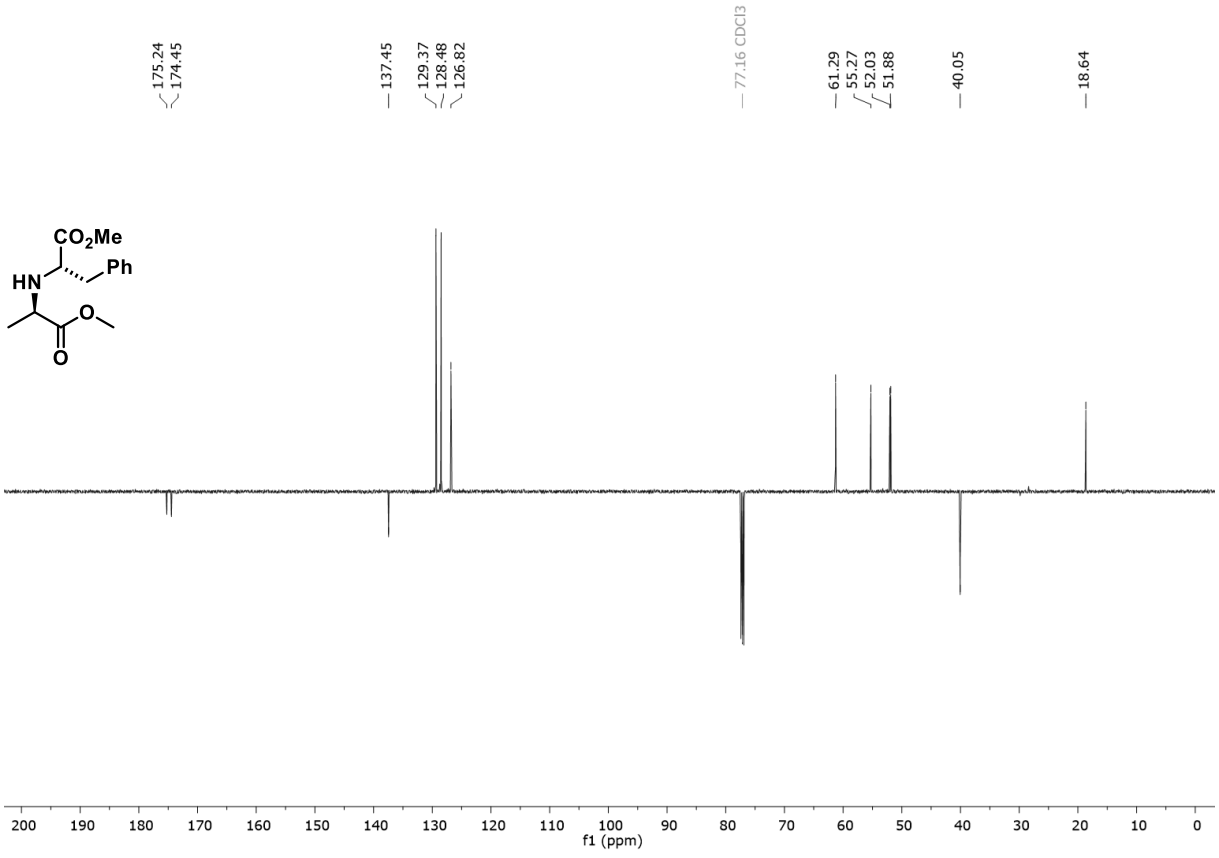


*Figure 128: ^{13}C NMR (126 MHz, $CDCl_3$) of methyl (1-methoxy-1-oxopropan-2-yl)-L-phenylalaninate ((R,S)-**258**).*

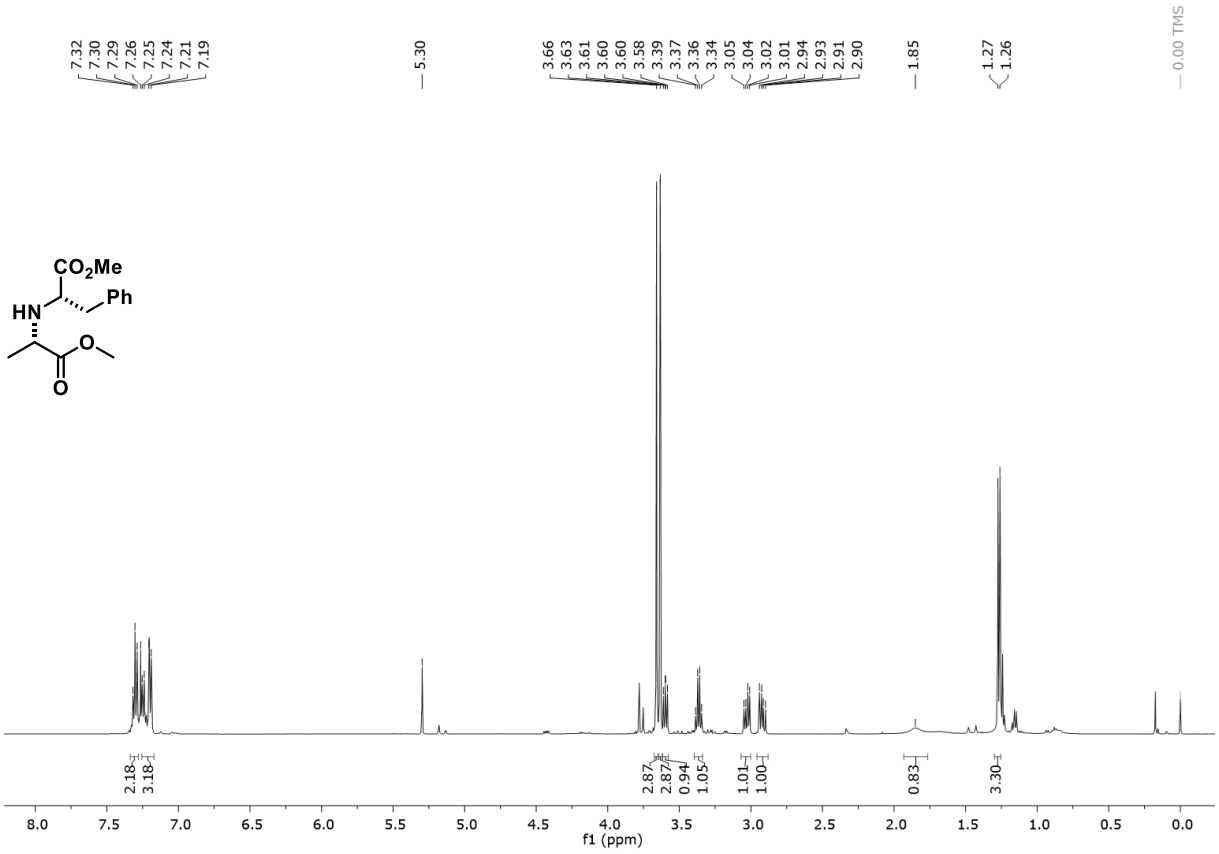


*Figure 129: ^{1}H NMR (500 MHz, $CDCl_3$) of methyl (1-methoxy-1-oxopropan-2-yl)-L-phenylalaninate ((S,S)-**258**).*

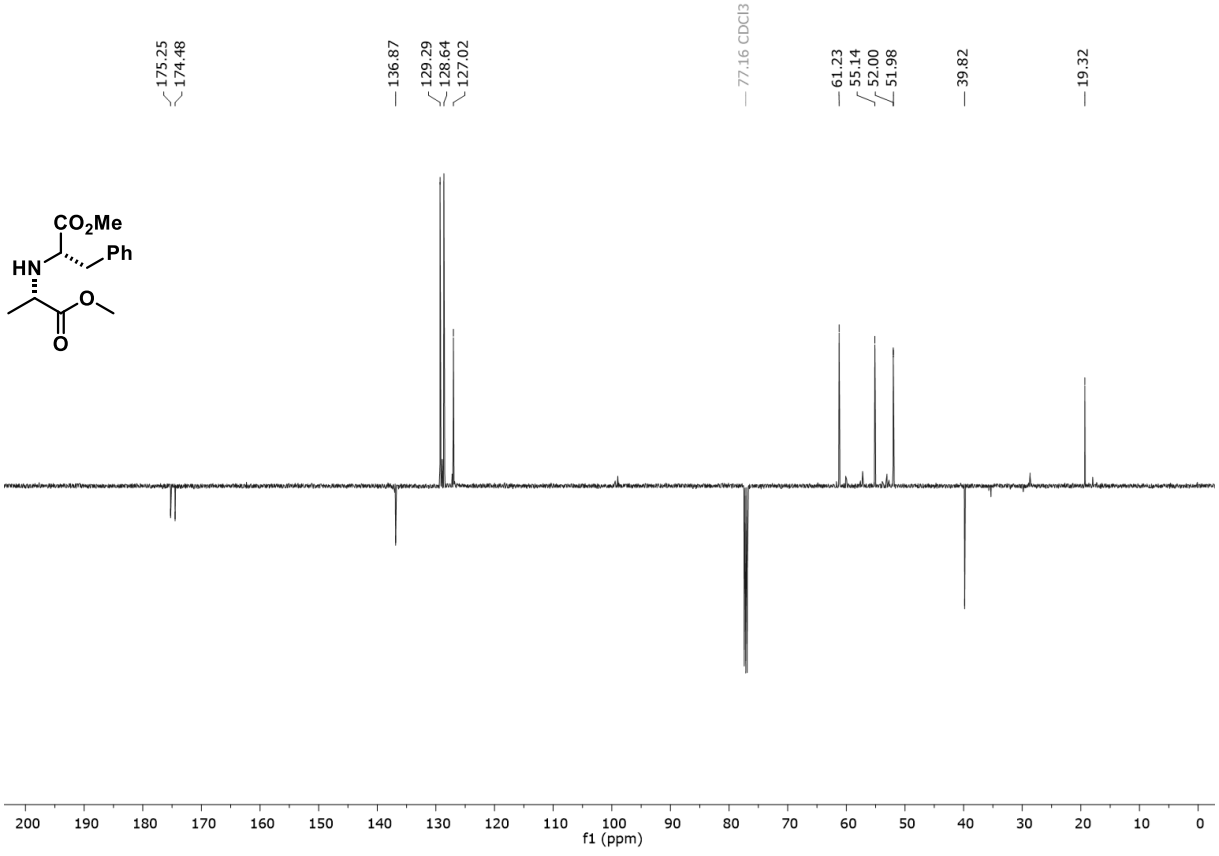


*Figure 130: ^{13}C NMR (126 MHz, $CDCl_3$) of methyl (1-methoxy-1-oxopropan-2-yl)-L-phenylalaninate ((S,S)-**258**).*

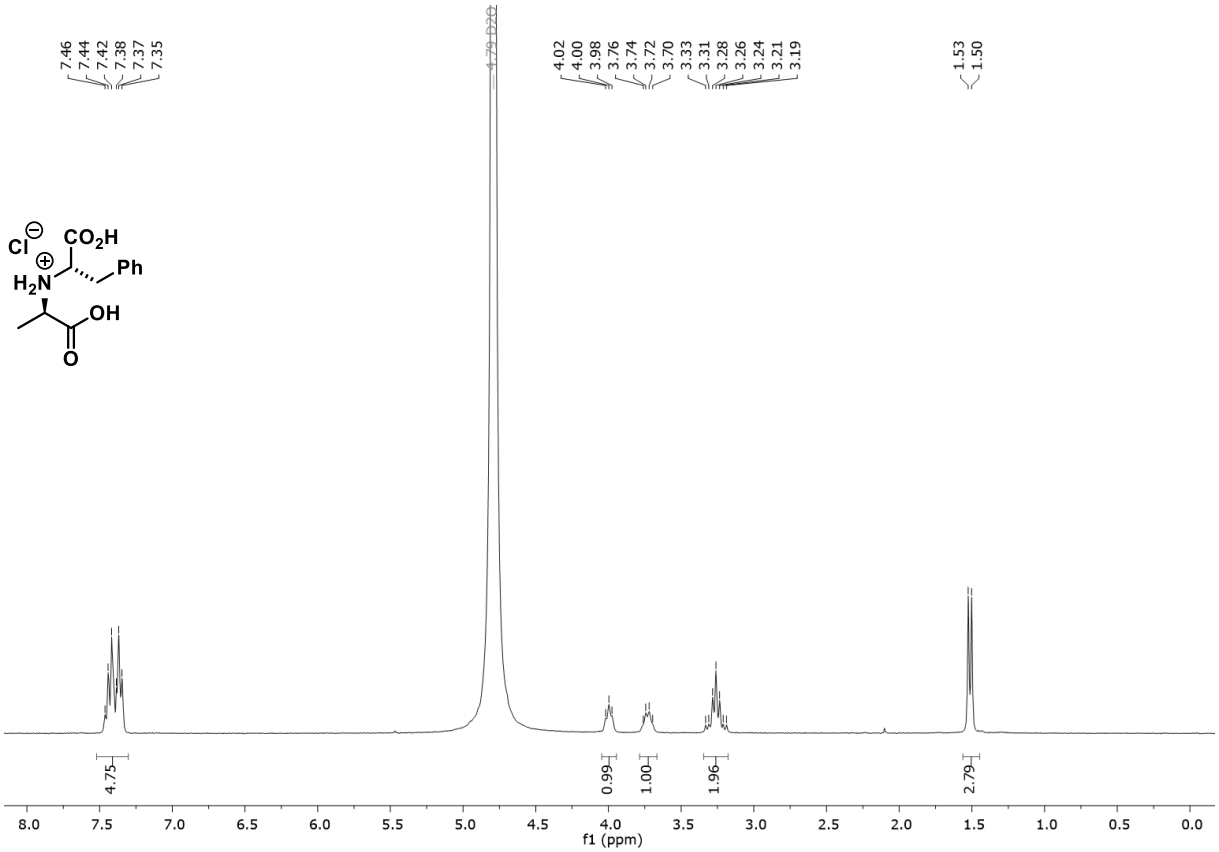


*Figure 131: [1]H NMR (500 MHz, D_2O) of (S)-1-carboxy-N-(1-carboxyethyl)-2-phenylethan-1- aminium chloride ((R,S)-**249·HCl**).*

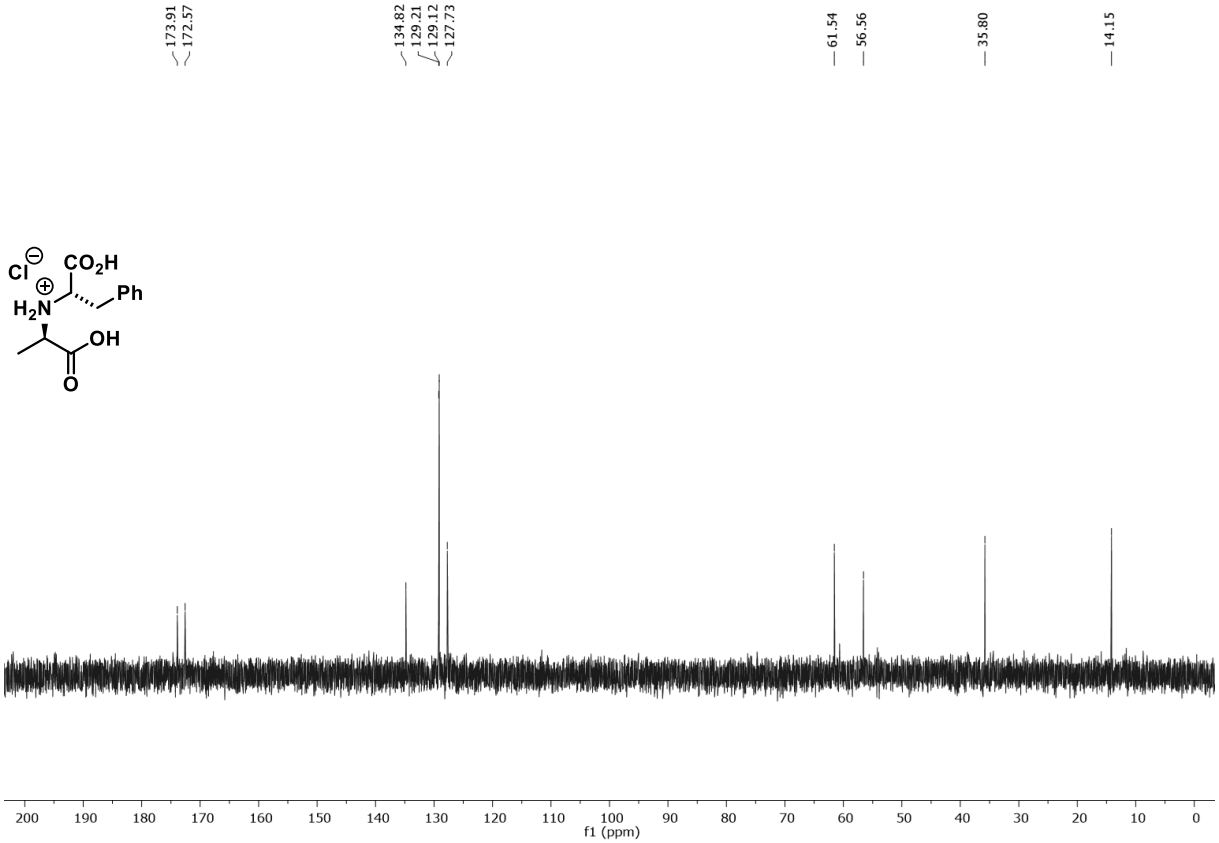


*Figure 132: [13]C NMR (126 MHz, D_2O) of (S)-1-carboxy-N-(1-carboxyethyl)-2-phenylethan-1- aminium chloride ((R,S)-**249·HCl**).*

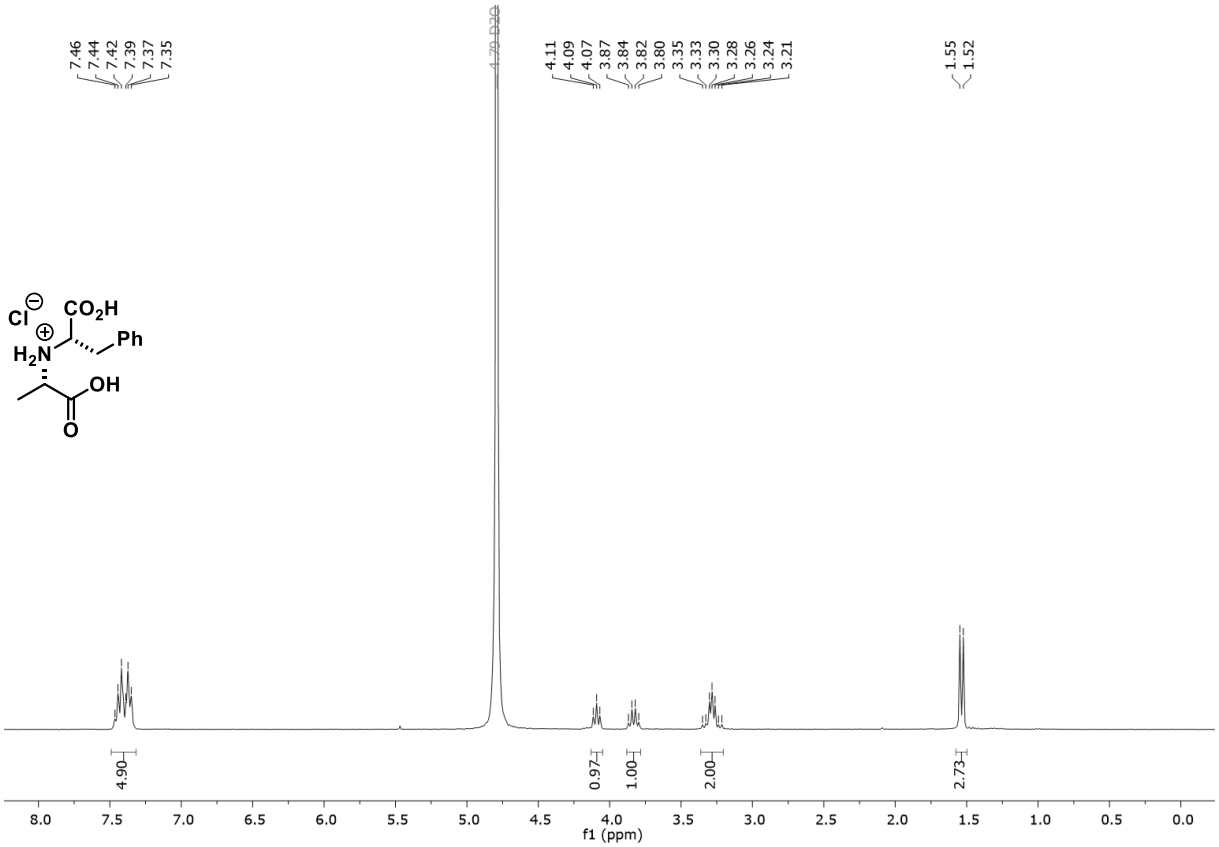


*Figure 133: ^{1}H NMR (500 MHz, D_2O) of (S)-1-carboxy-N-(1-carboxyethyl)-2-phenylethan-1- aminium chloride ((S,S)-**249·HCl**).*

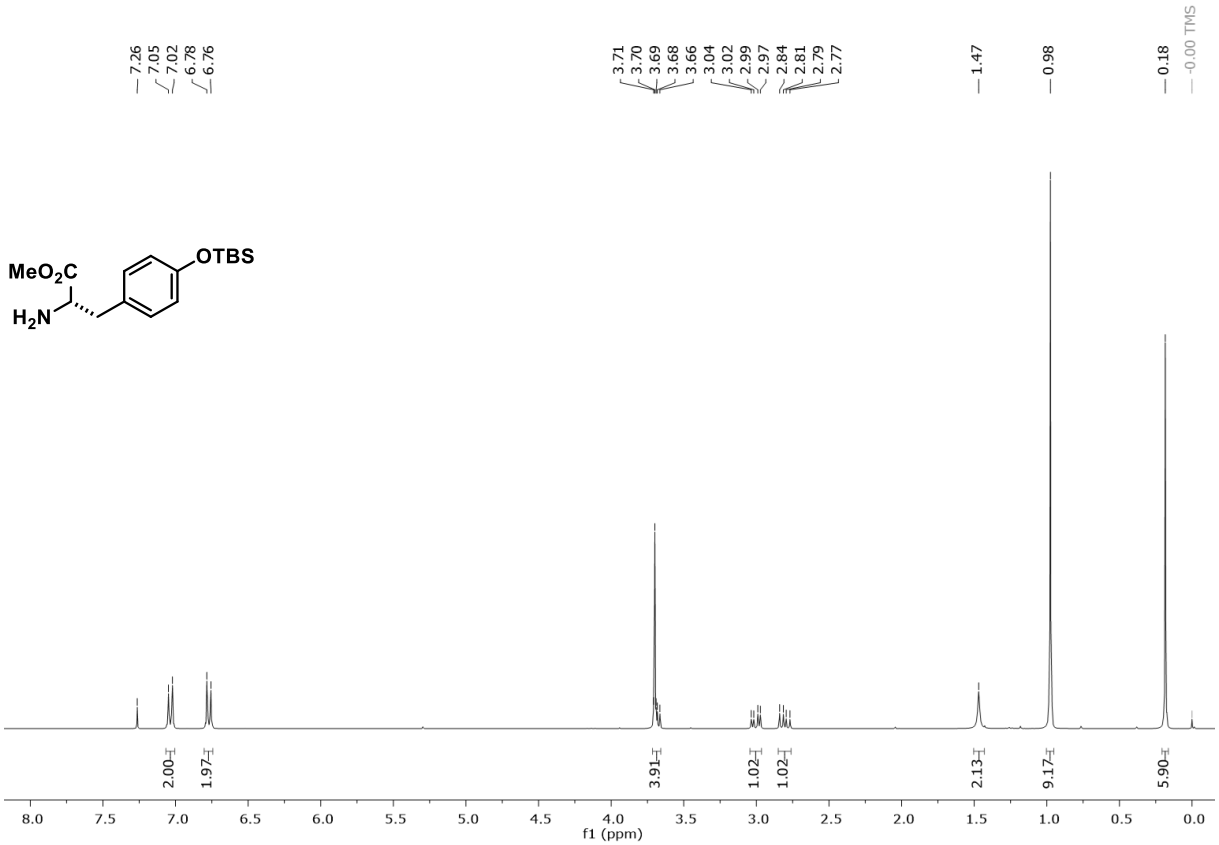


*Figure 134: ^{1}H NMR (500 MHz, $CDCl_3$) of methyl (S)-2-amino-3-(4-((tert-butyldimethylsilyl)oxy)phenyl)propanoate (**254e**).*

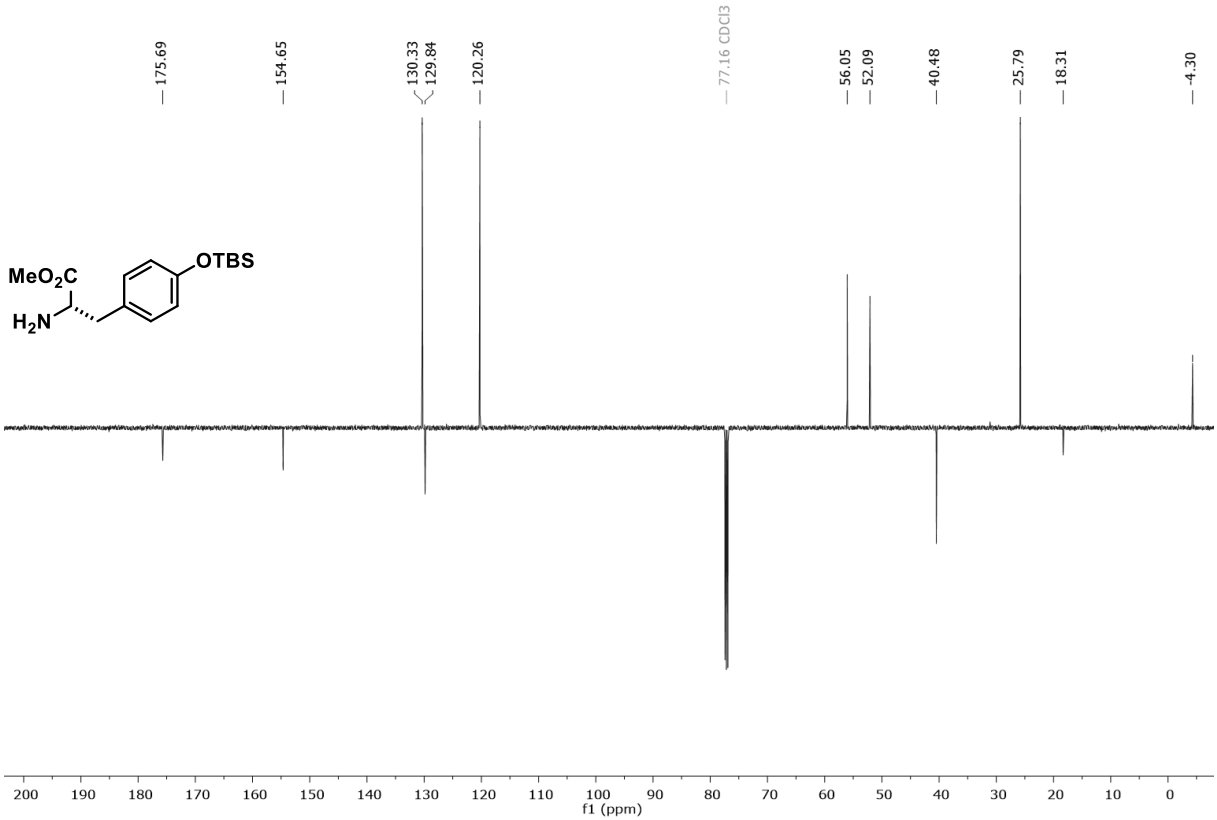


*Figure 135: ^{13}C NMR (126 MHz, $CDCl_3$) of methyl (S)-2-amino-3-(4-((tert-butyldimethylsilyl)oxy)phenyl)propanoate (**254e**).*

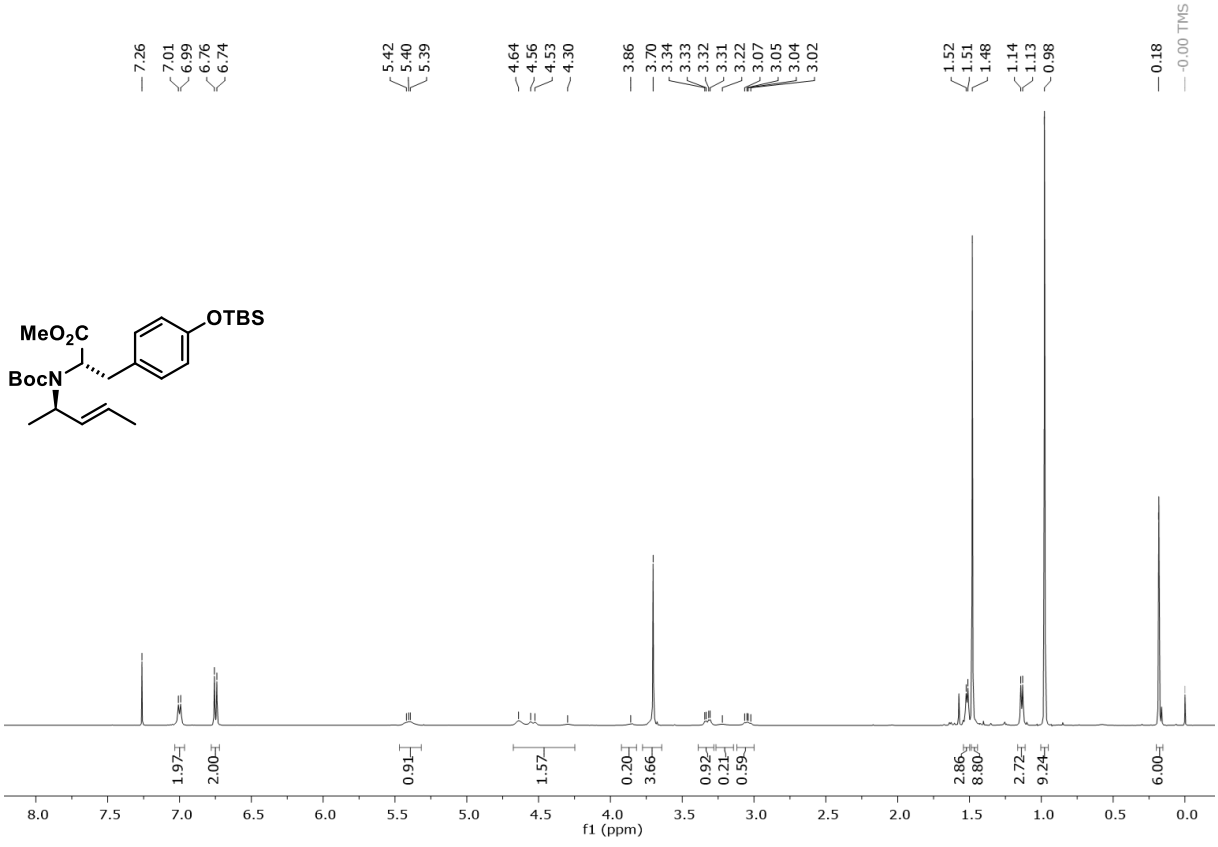


*Figure 136: ^{1}H NMR (500 MHz, $CDCl_3$) of methyl (S)-2-((tert-butoxycarbonyl)((E)-pent-3-en-2- yl)amino)-3-(4-((tert-butyldimethylsilyl)oxy)phenyl)propanoate ((R,S)-**257**).*

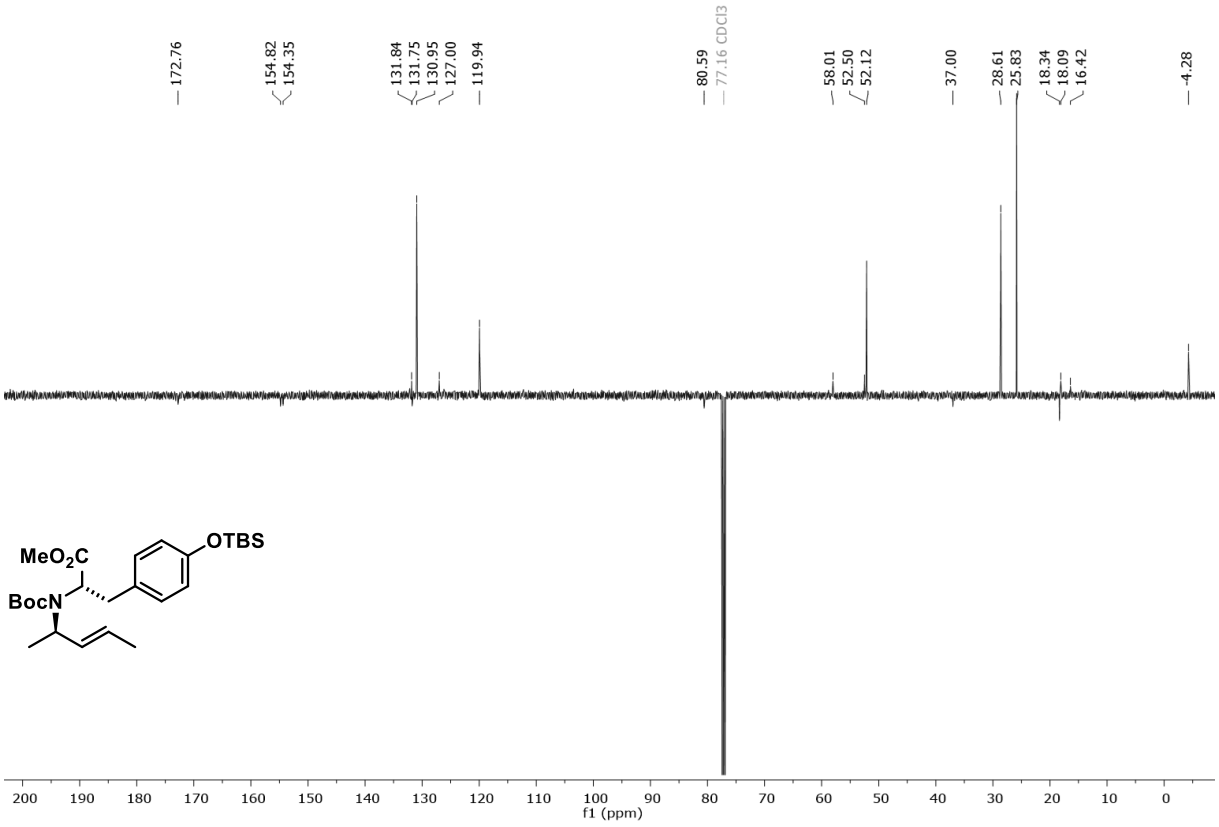


*Figure 137: ^{13}C NMR (126 MHz, $CDCl_3$) of methyl (S)-2-((tert-butoxycarbonyl)((E)-pent-3-en-2- yl)amino)-3-(4-((tert-butyldimethylsilyl)oxy)phenyl)propanoate ((R,S)-**257**).*

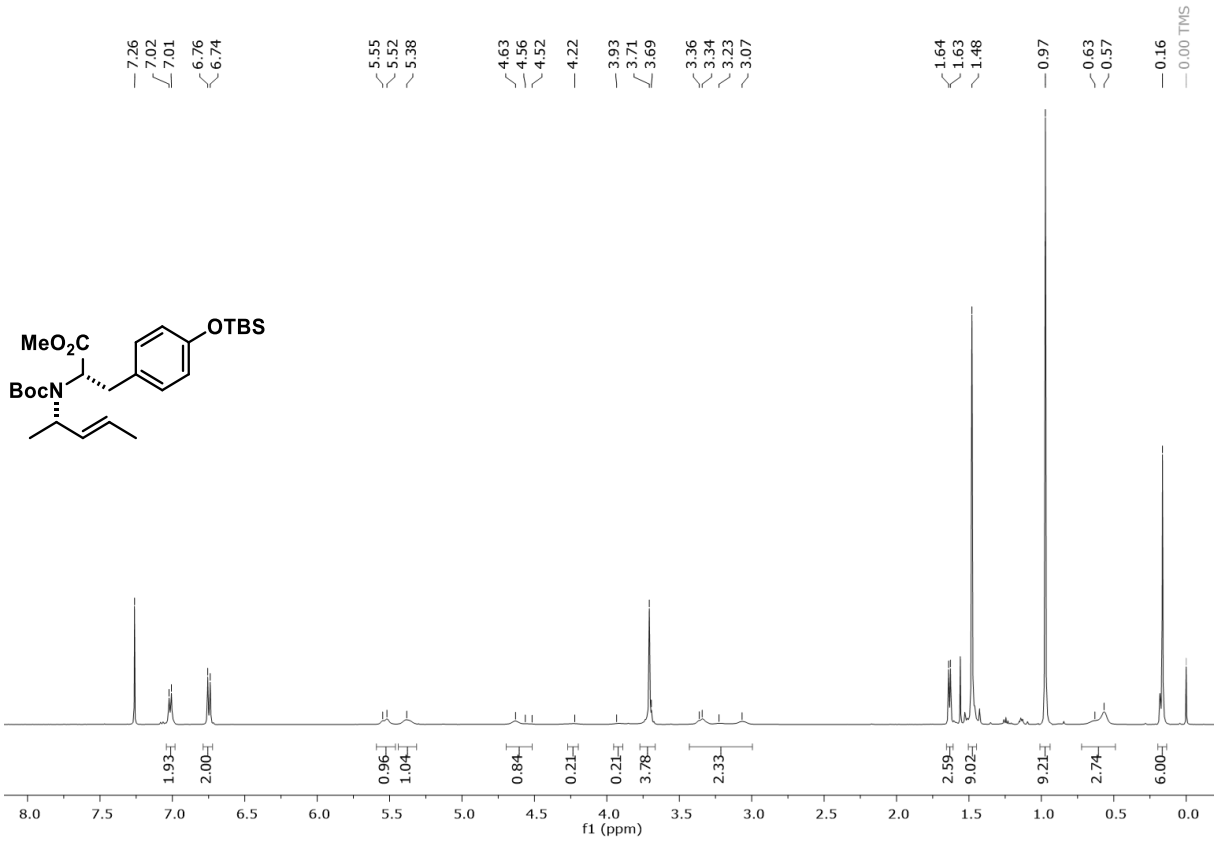


*Figure 138: ^{1}H NMR (500 MHz, $CDCl_3$) of methyl (S)-2-((tert-butoxycarbonyl)((E)-pent-3-en-2- yl)amino)-3-(4-((tert-butyldimethylsilyl)oxy)phenyl)propanoate ((S,S)-**257**).*

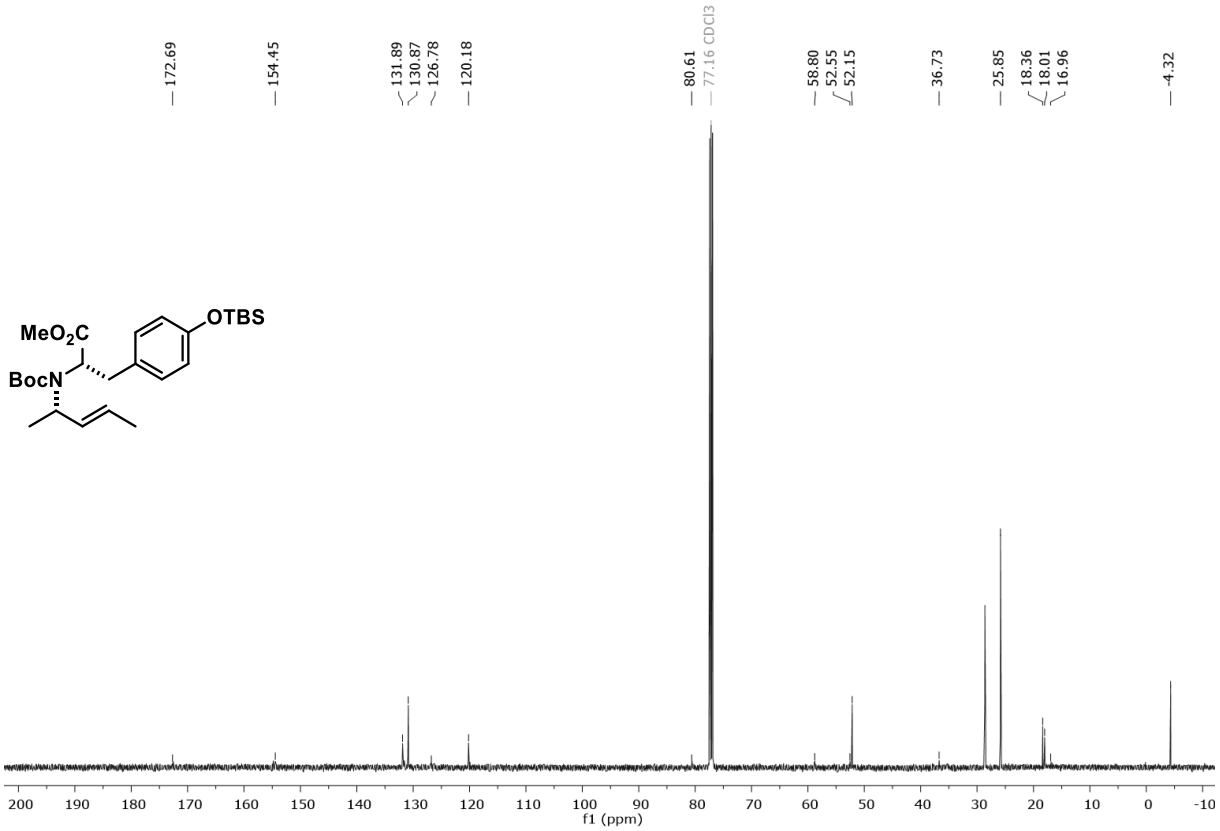


*Figure 139: ^{13}C NMR (121 MHz, $CDCl_3$) of methyl (S)-2-((tert-butoxycarbonyl)((E)-pent-3-en-2- yl)amino)-3-(4-((tert-butyldimethylsilyl)oxy)phenyl)propanoate ((S,S)-**257**).*

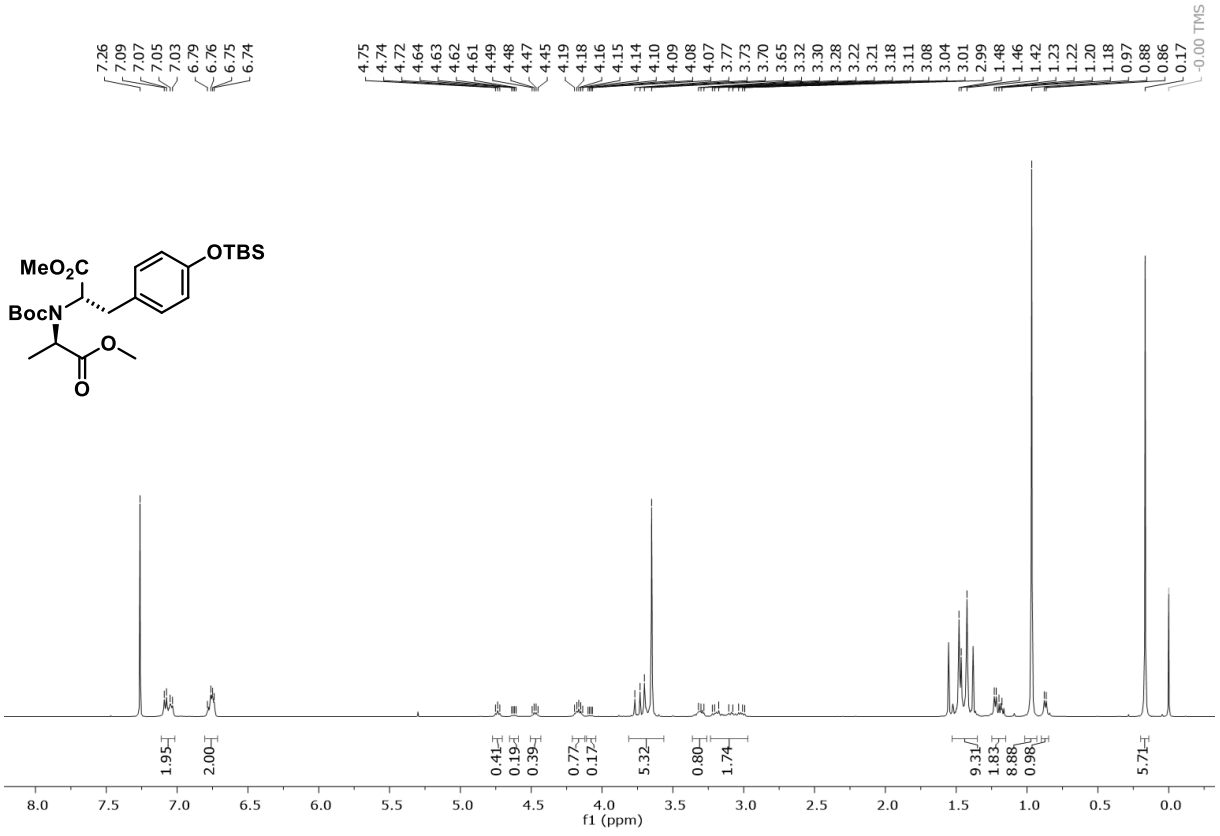


*Figure 140: ^{1}H NMR (500 MHz, $CDCl_3$) of methyl (S)-2-((tert-butoxycarbonyl)(-1-methoxy-1- oxopropan-2-yl)amino)-3-(4-((tert-butyldimethylsilyl)oxy)phenyl)propanoate ((R,S)-**259**).*

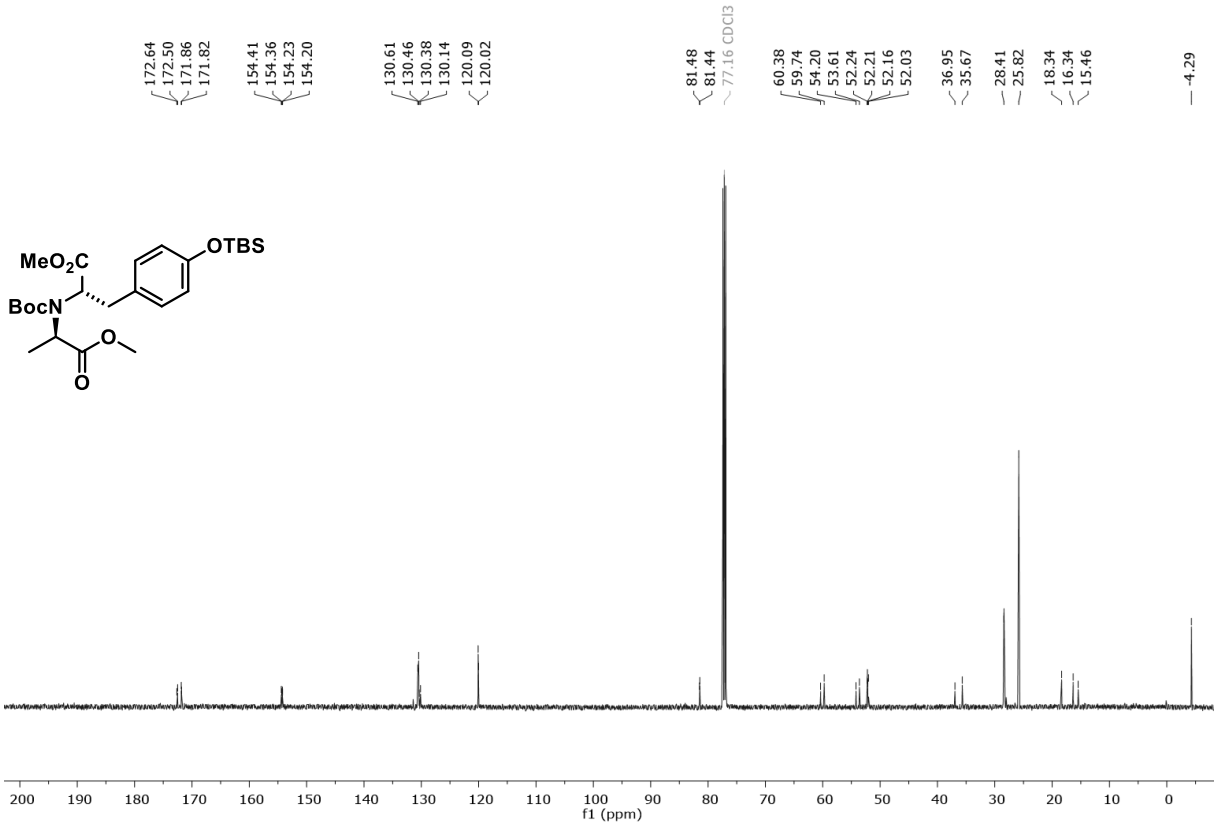


*Figure 141: ^{13}C NMR (126 MHz, $CDCl_3$) of methyl (S)-2-((tert-butoxycarbonyl)(-1-methoxy-1- oxopropan-2-yl)amino)-3-(4-((tert-butyldimethylsilyl)oxy)phenyl)propanoate ((R,S)-**259**).*

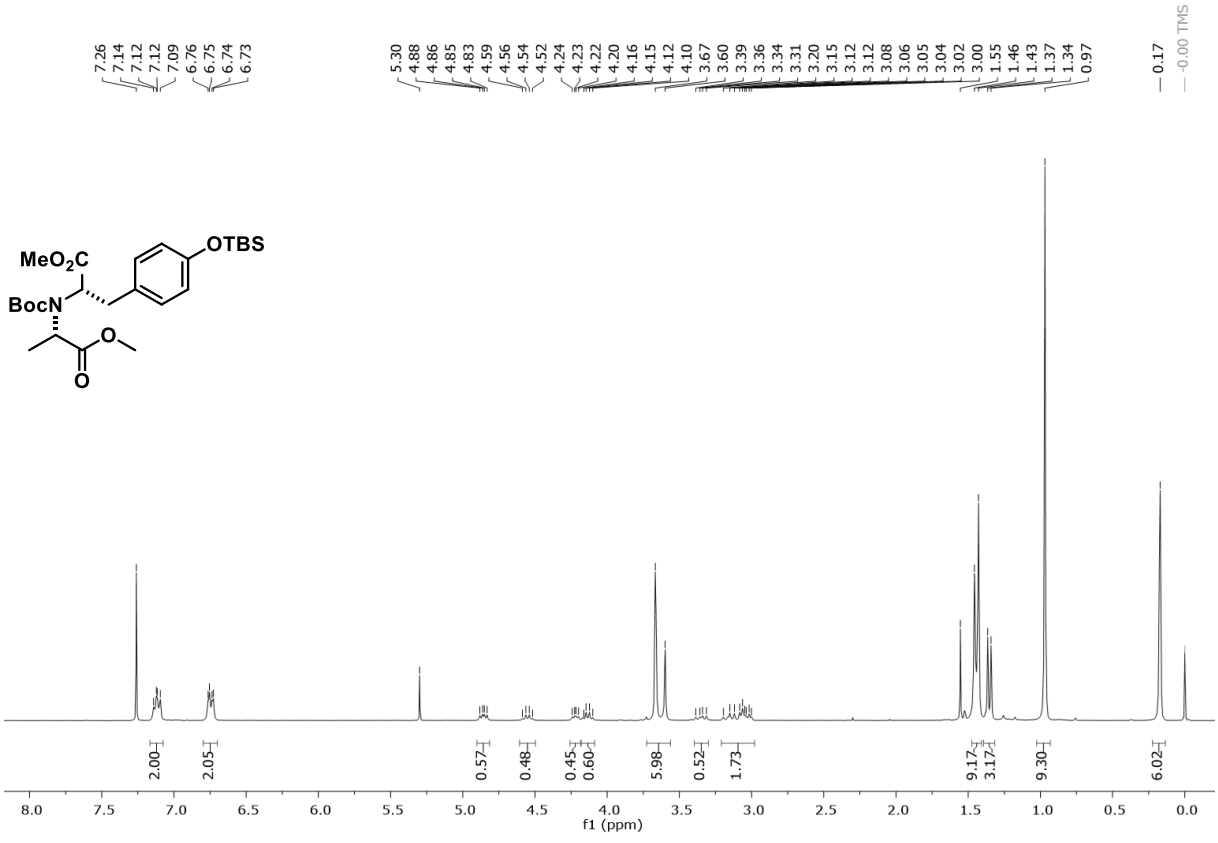


*Figure 142: ^{1}H NMR (500 MHz, $CDCl_3$) of methyl (S)-2-((tert-butoxycarbonyl)(-1-methoxy-1- oxopropan-2-yl)amino)-3-(4-((tert-butyldimethylsilyl)oxy)phenyl)propanoate ((S,S)-**259**).*

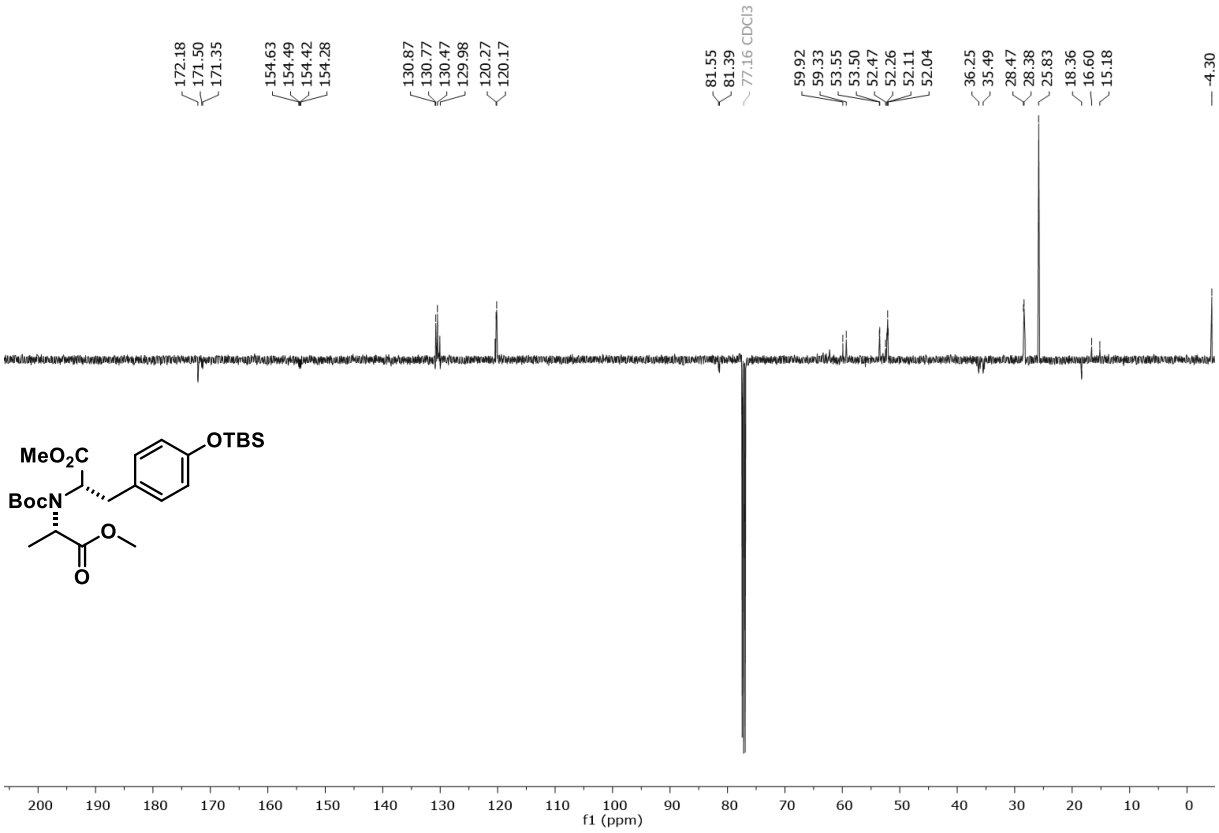


*Figure 143: [13]C NMR (126 MHz, $CDCl_3$) of methyl (S)-2-((tert-butoxycarbonyl)(-1-methoxy-1- oxopropan-2-yl)amino)-3-(4-((tert-butyldimethylsilyl)oxy)phenyl)propanoate ((S,S)-**259**).*

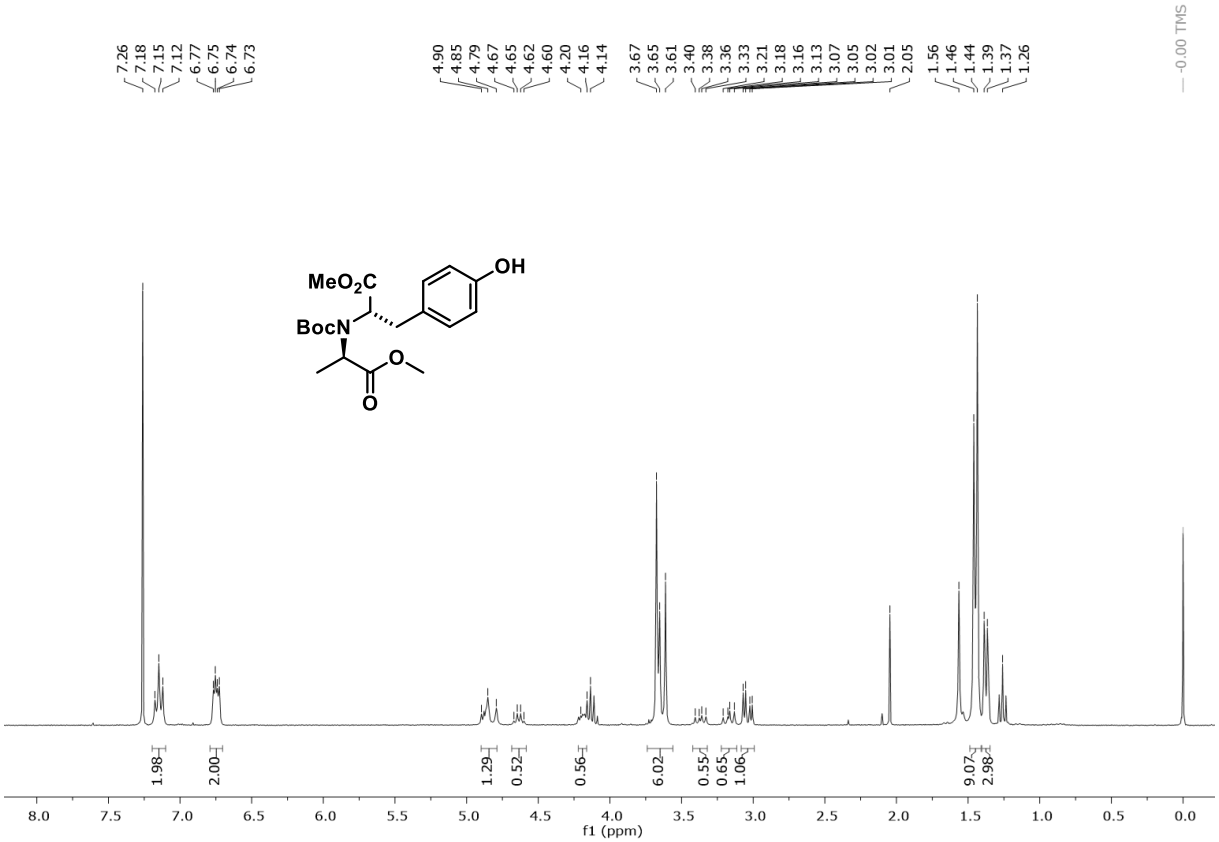


*Figure 144: [1]H NMR (500 MHz, $CDCl_3$) of methyl N-(tert-butoxycarbonyl)-N-(1-methoxy-1- oxopropan-2-yl)-L-tyrosinate ((R,S)-**252**).*

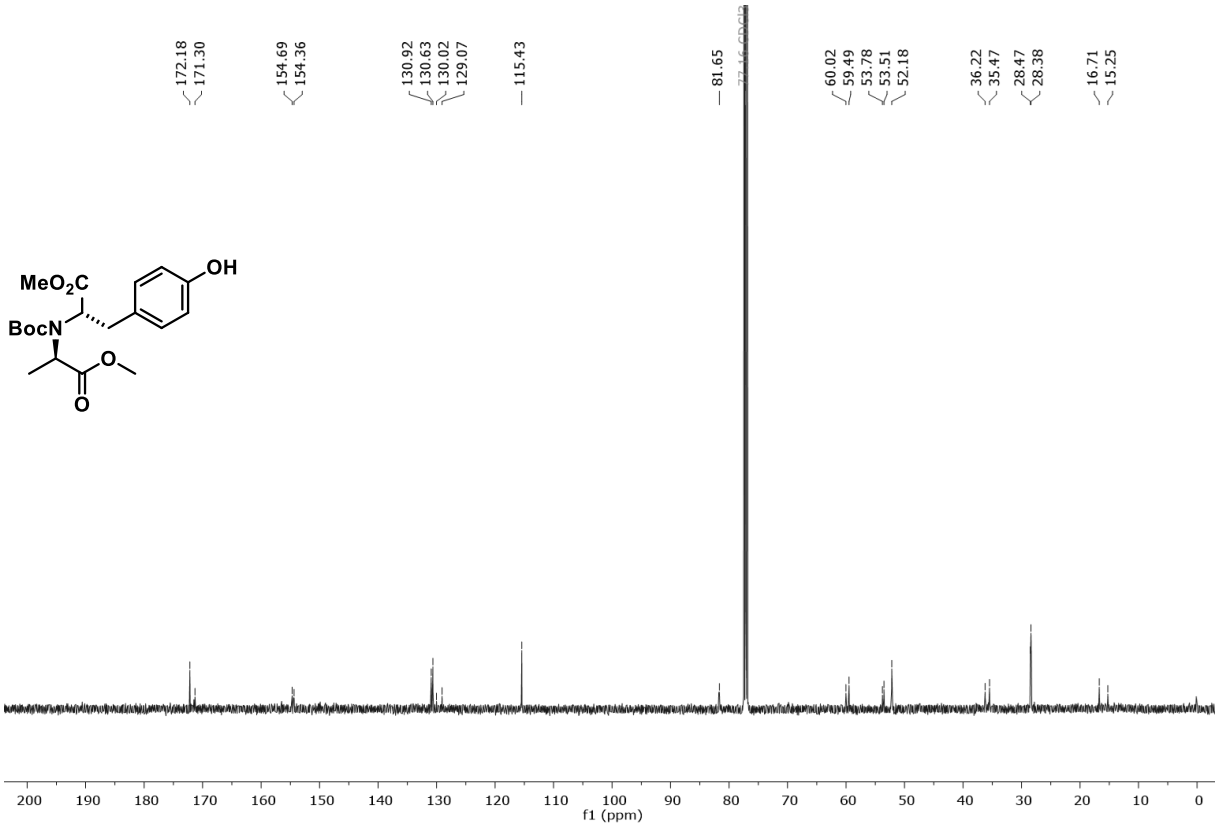


*Figure 145: [13]C NMR (126 MHz, $CDCl_3$) of methyl N-(tert-butoxycarbonyl)-N-(1-methoxy-1- oxopropan-2-yl)-L-tyrosinate ((R,S)-**252**).*

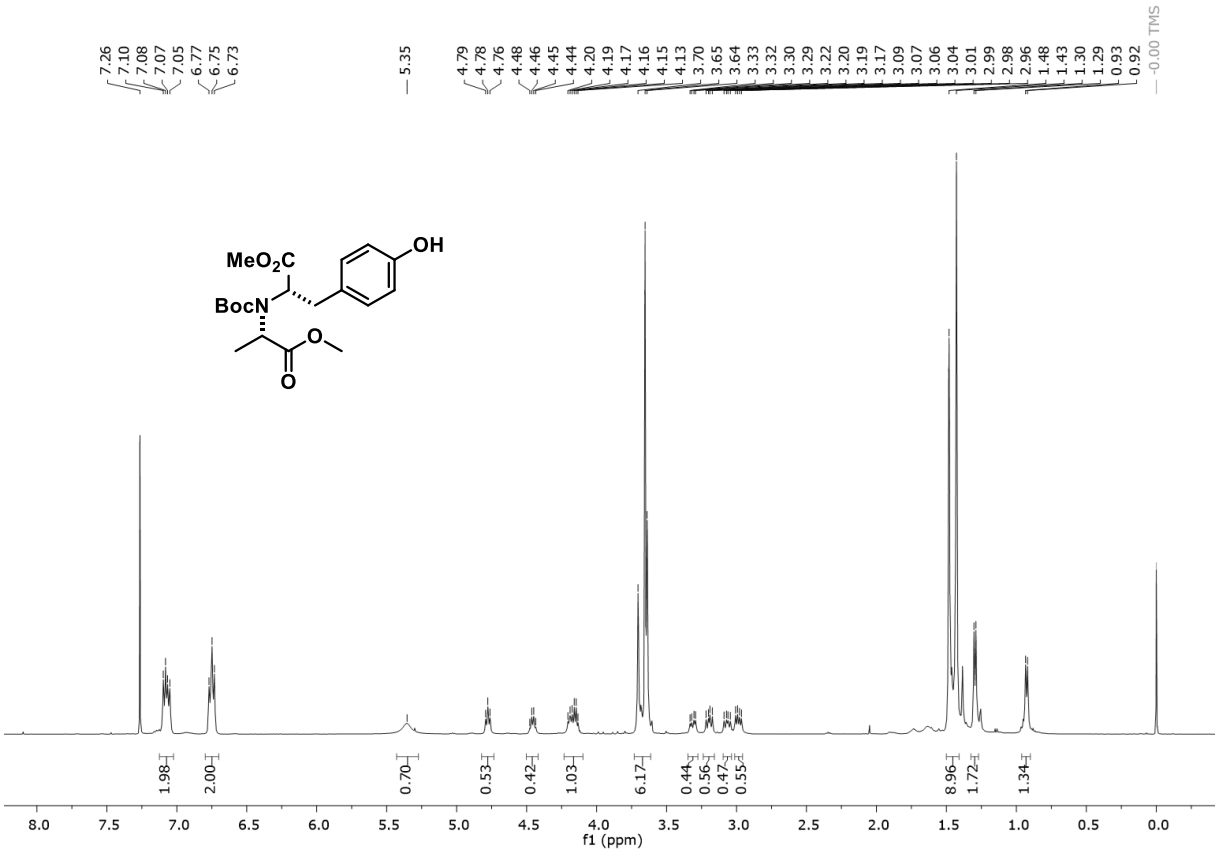


*Figure 146: [1]H NMR (500 MHz, $CDCl_3$) of methyl N-(tert-butoxycarbonyl)-N-(1-methoxy-1- oxopropan-2-yl)-L-tyrosinate ((S,S)-**252**).*

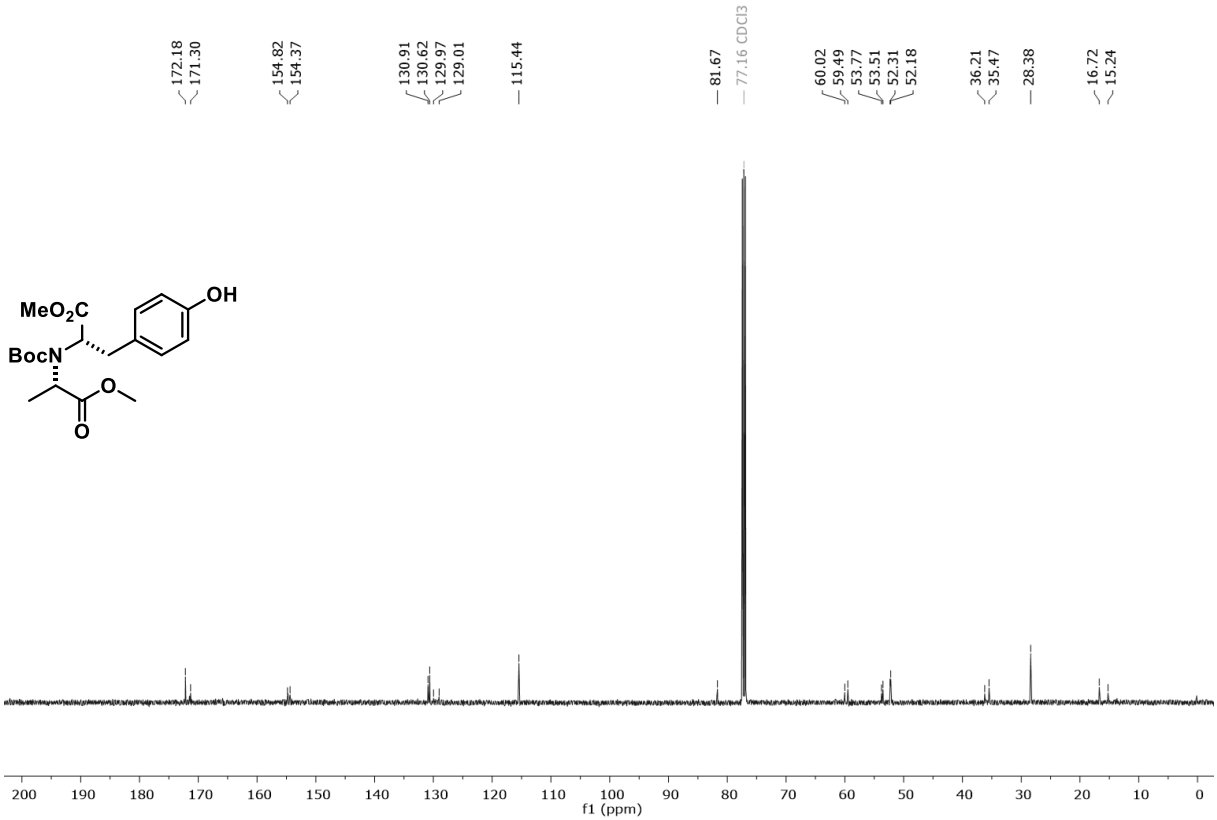


*Figure 147: ^{13}C NMR (126 MHz, $CDCl_3$) of methyl N-(tert-butoxycarbonyl)-N-(1-methoxy-1- oxopropan-2-yl)-L-tyrosinate ((S,S)-**252**).*

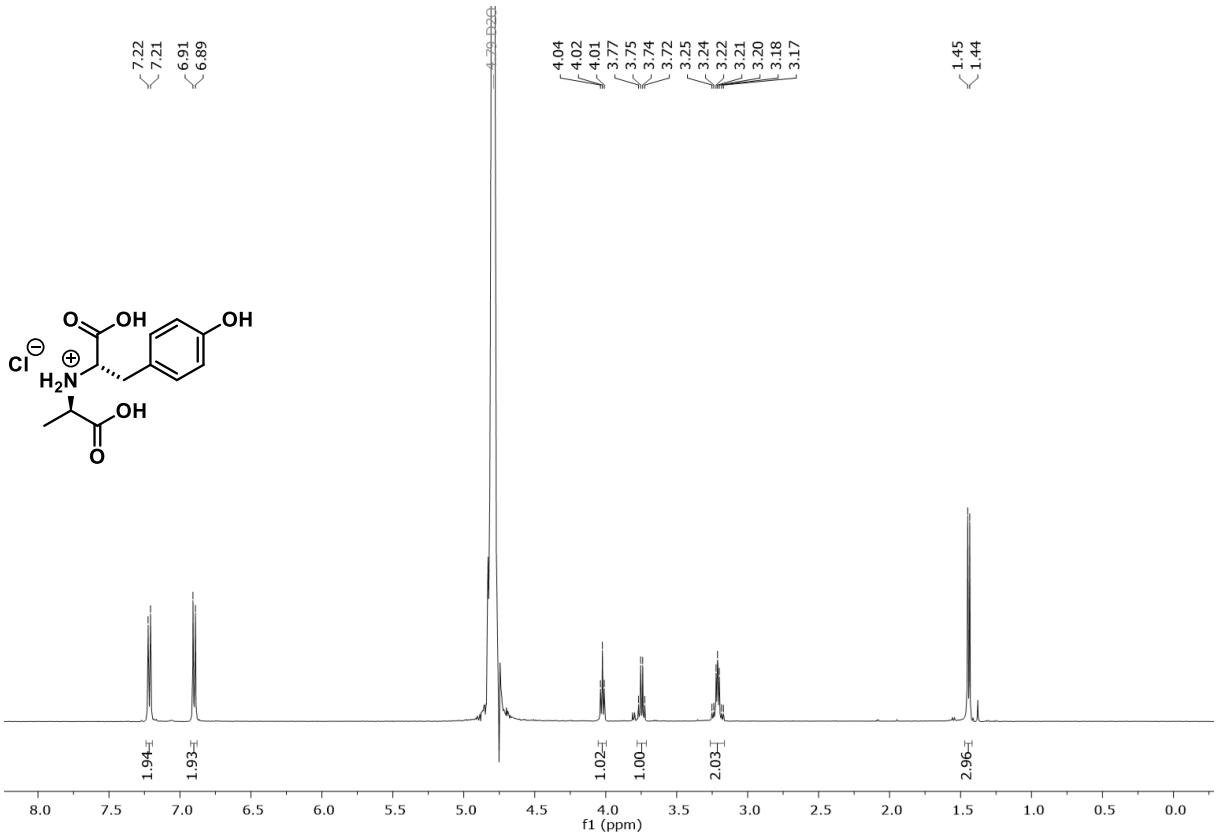


*Figure 148: ^{1}H NMR (500 MHz, D_2O) of (S)-1-carboxy-N-(1-carboxyethyl)-2-(4- hydroxyphenyl)ethan-1-aminium chloride ((R,S)-**250·HCl**).*

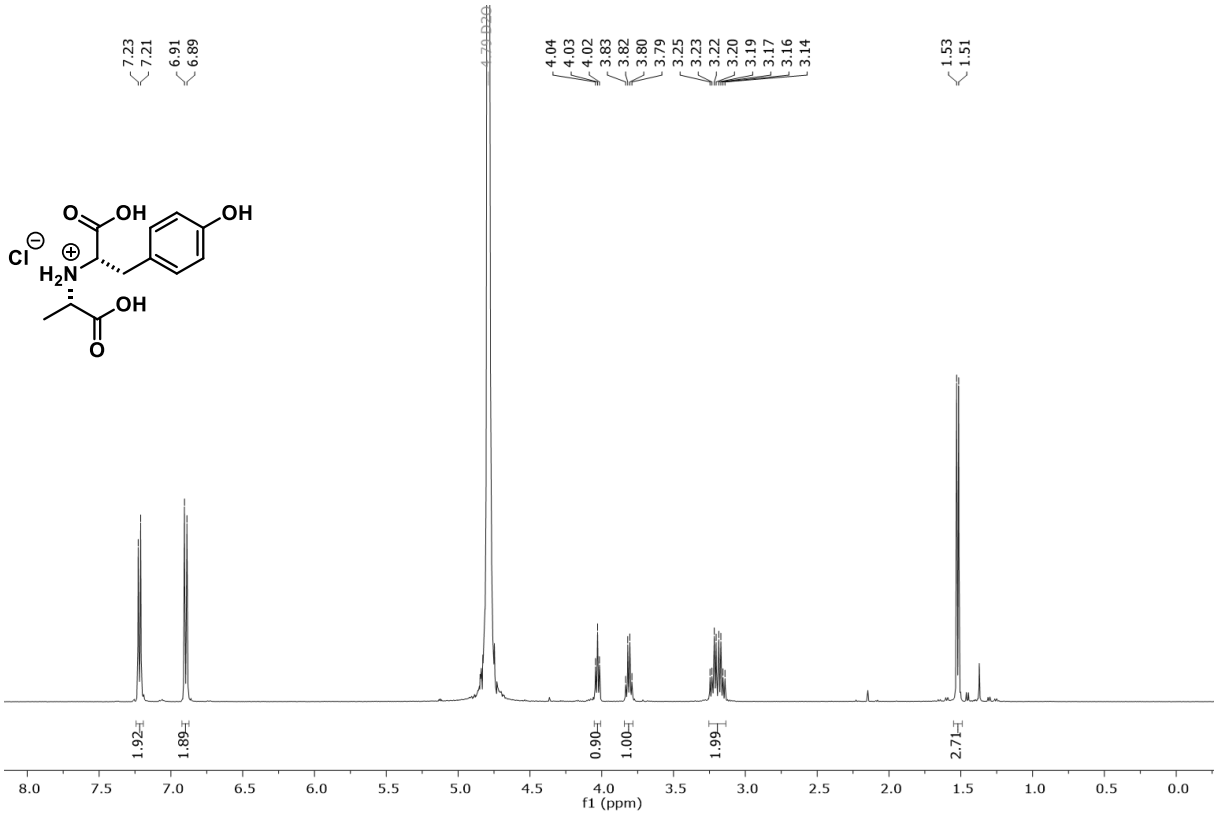


*Figure 149: [1]H NMR (500 MHz, D_2O) of (S)-1-carboxy-N-(1-carboxyethyl)-2-(4- hydroxyphenyl)ethan-1-aminium chloride ((S,S)-**250·HCl**).*

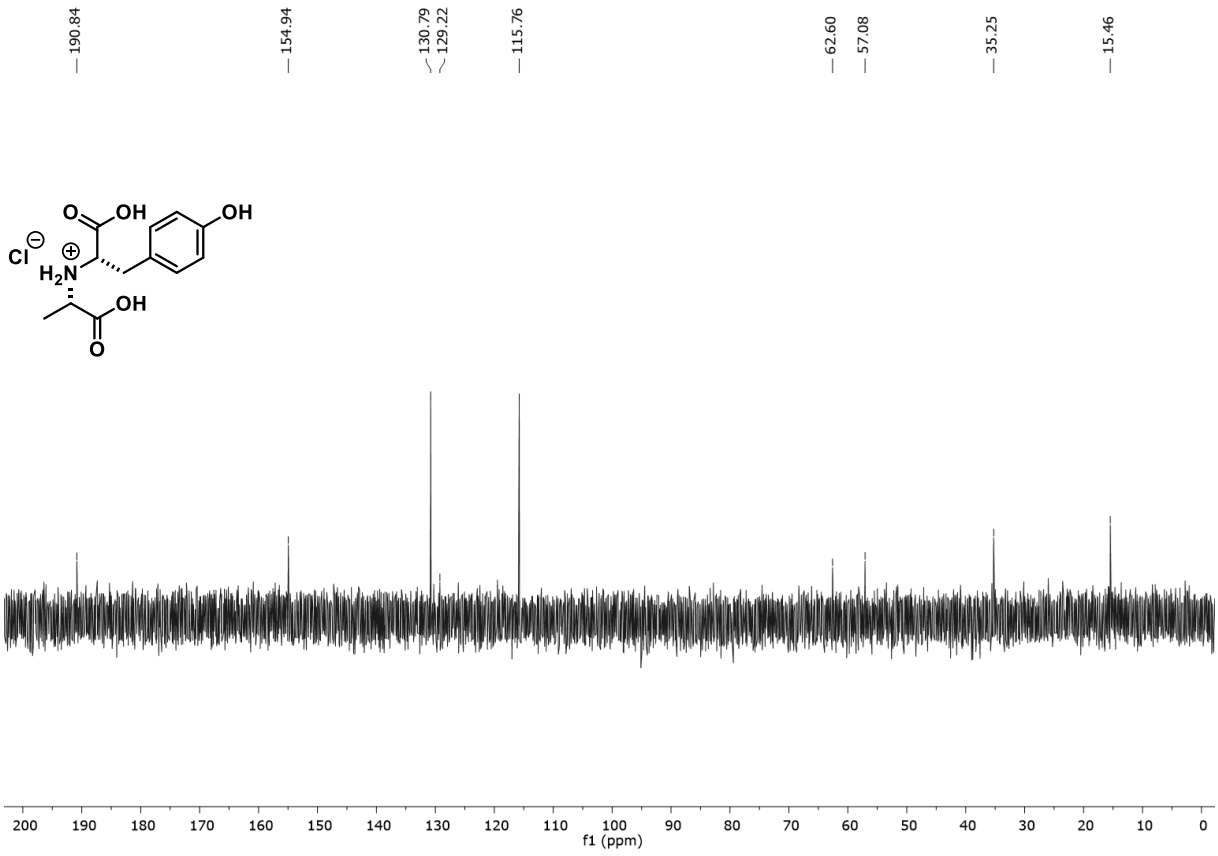


*Figure 150: [13]C NMR (126 MHz, D_2O) of (S)-1-carboxy-N-(1-carboxyethyl)-2-(4- hydroxyphenyl)ethan-1-aminium chloride ((S,S)-**250·HCl**).*

13.3 Chiral GC-MS and HPLC measurements

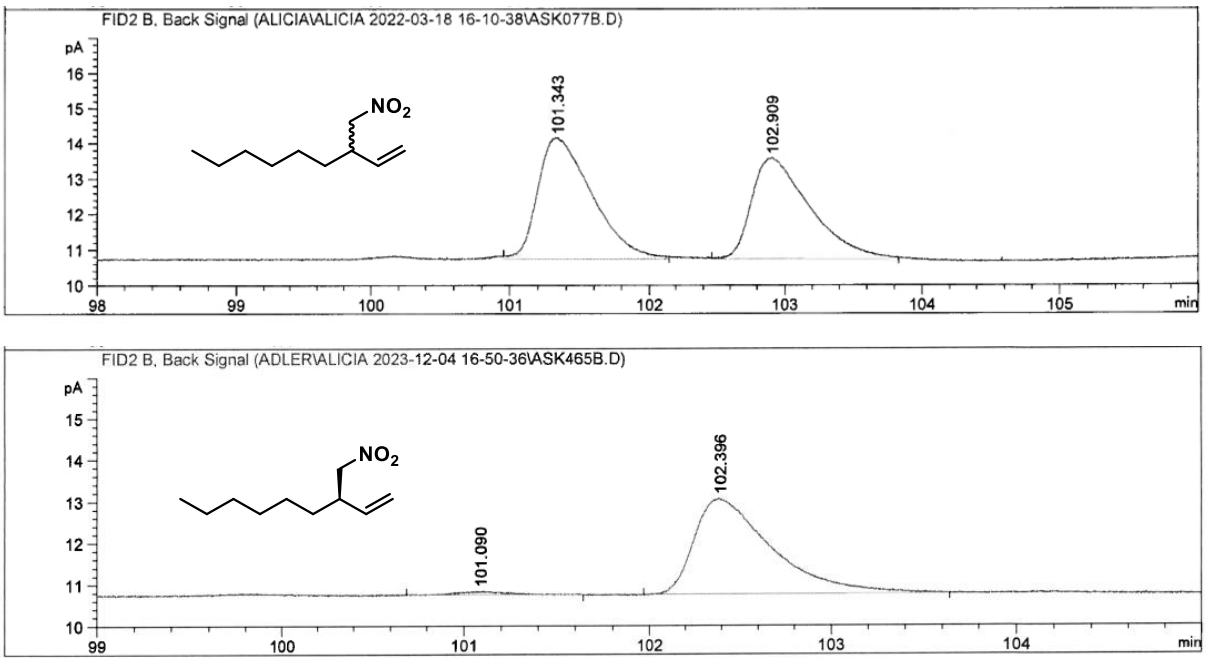


*Figure 151: Separation of the two enantiomers (R)- and (S)-**123** by GC-FID on chiral stationary phase (capillary column: Mega-Dex B-SE 12582, temperature program: start at 50 °C, then 0.5 °C/min to 170 °C, retention times: (S)-**123**: 101 min; (R)-**123**: 102 min).*

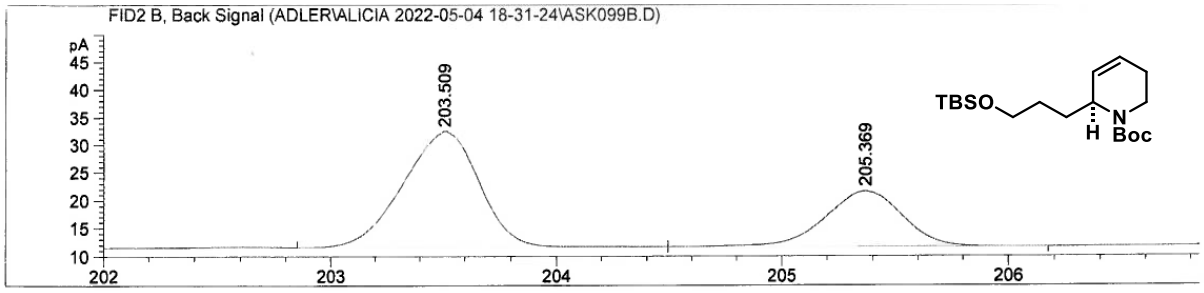


*Figure 152: Separation of the two enantiomers (R)- and (S)-**132a** by GC-FID on chiral stationary phase (capillary column: Mega-Dex B-SE 12582, temperature program: start at 50 °C, then 0.5 °C/min to 170 °C, retention times: (S)-**132a**: 204 min; (R)-**132a**: 205 min).*

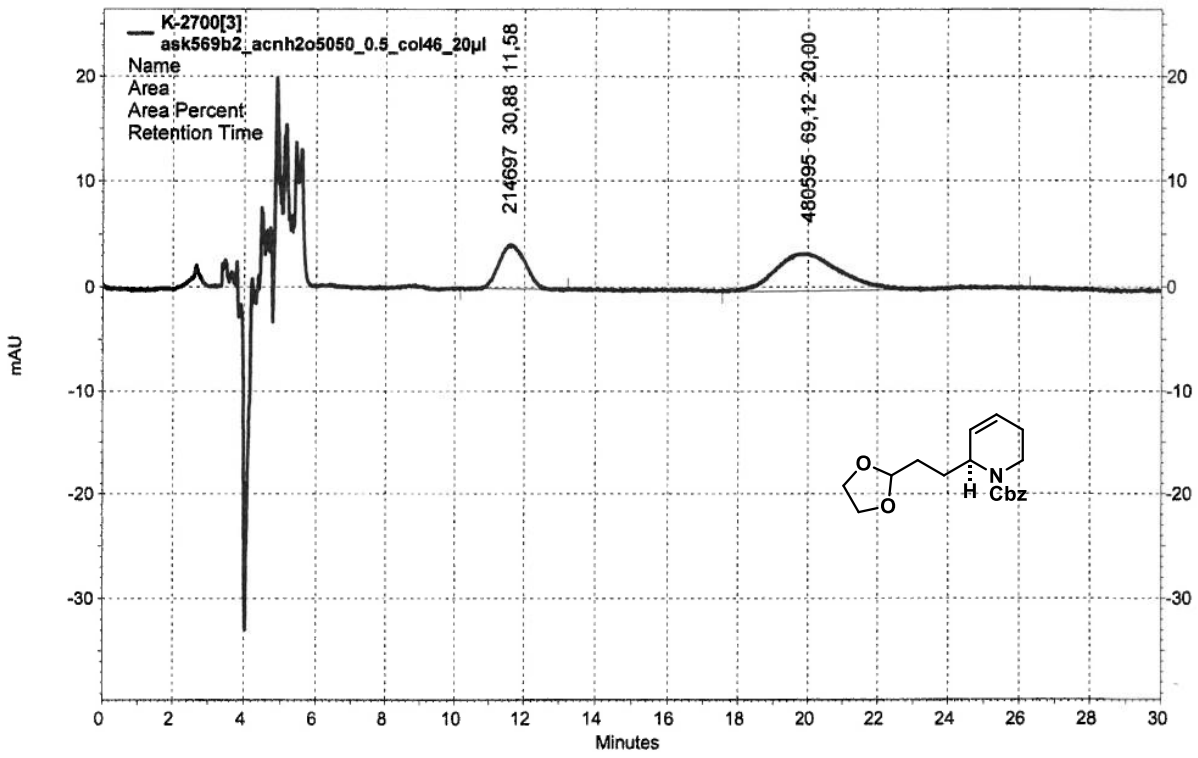


*Figure 153: Separation of the two enantiomers (R)- and (S)-**158c** by HPLC on chiral stationary phase (column: Diacel Chiralpak AD-RH, flow rate: 0.5 mL/min, temperature: 25 °C, solvent: H_2O/MeCN, gradient: H_2O/MeCN 50:50).*

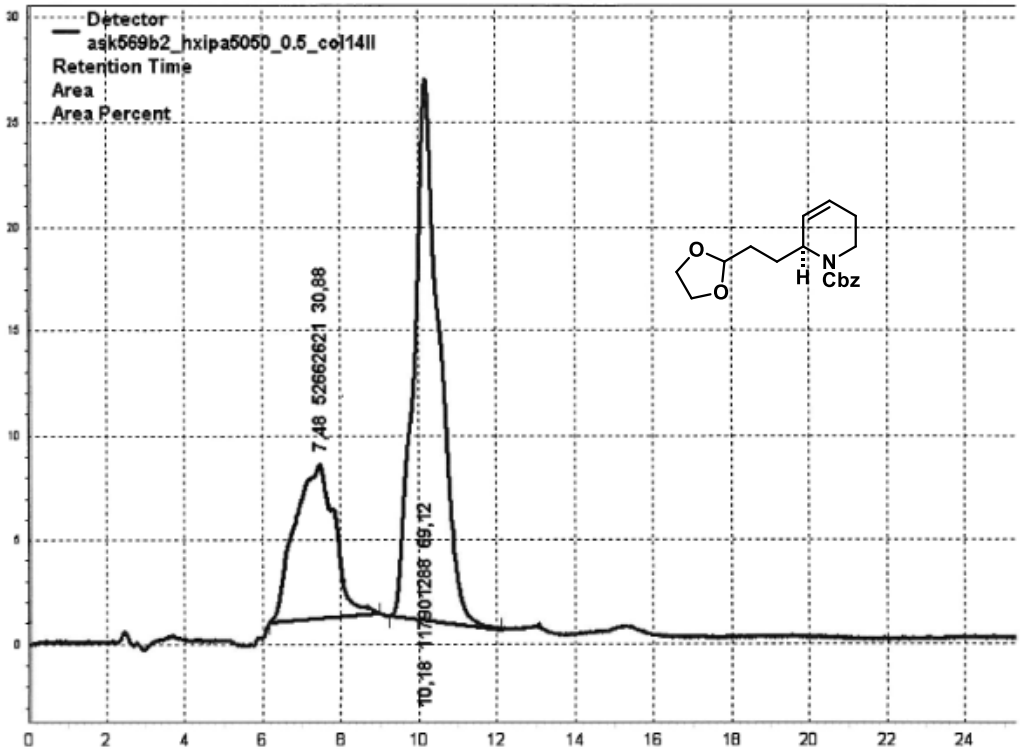


*Figure 154: Separation of the two enantiomers (R)- and (S)-**158c** by HPLC on chiral stationary phase (column: Diacel Chiralpak AD-H, flow rate: 0.5 mL/min, temperature: rt, solvent: hexane/iPrOH 50:50).*

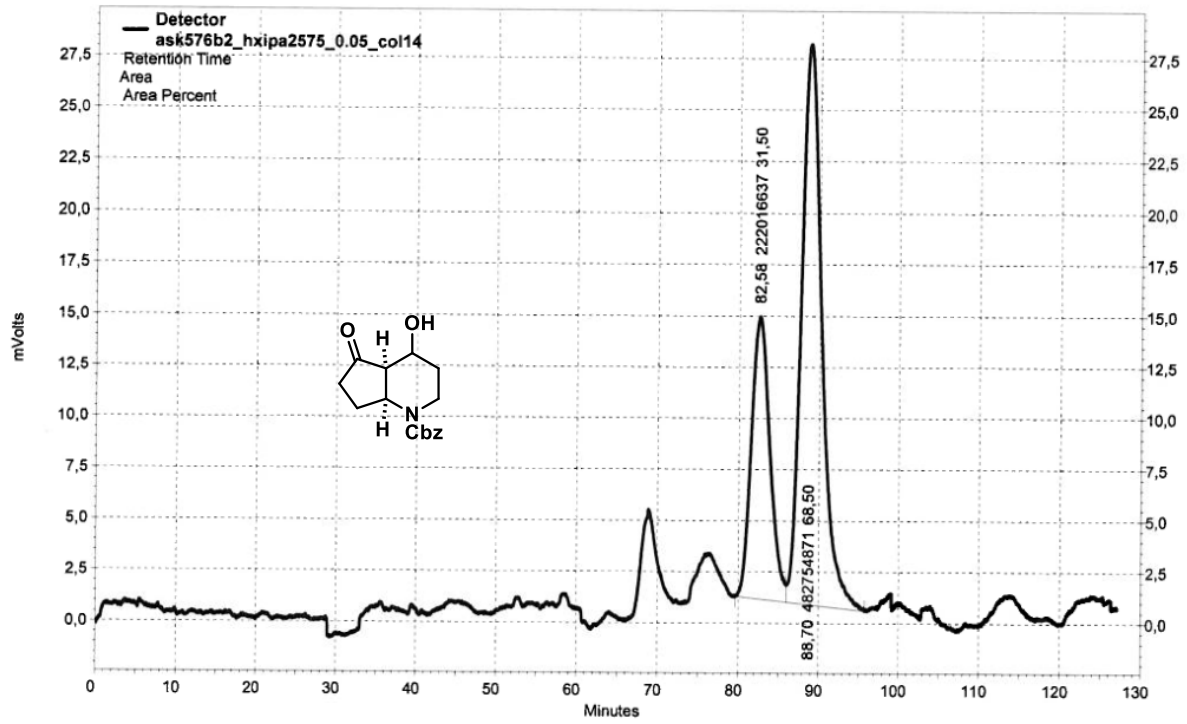


*Figure 155: HPLC-chromatogram of **168** (column: Diacel Chiralpak AD-H, flow rate: 0.05 mL/min, temperature: rt, solvent: hexane/iPrOH 25:75).*

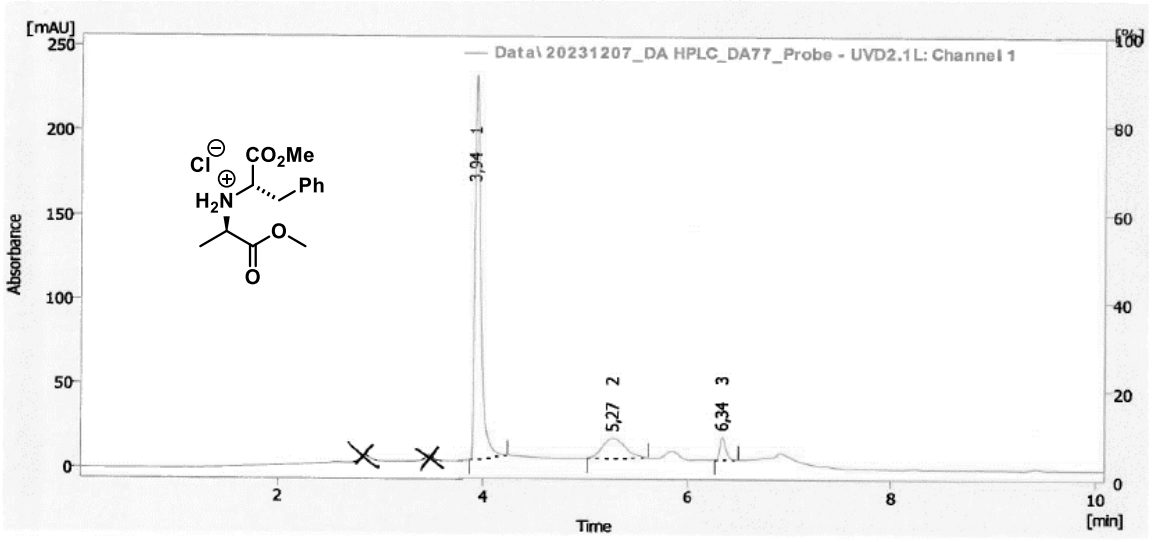


*Figure 156: HPLC-chromatogram of (R,S)-**249·HCl** (column: XSelect CSH C18, flow rate: 0.5 mL/min, temperature: 30 °C, solvent: H_2O/MeCN, gradient: H_2O/MeCN 95:5 to 10:90 over 15 minutes, 10:90 for 10 minutes, back to start gradient over 5 minutes).*

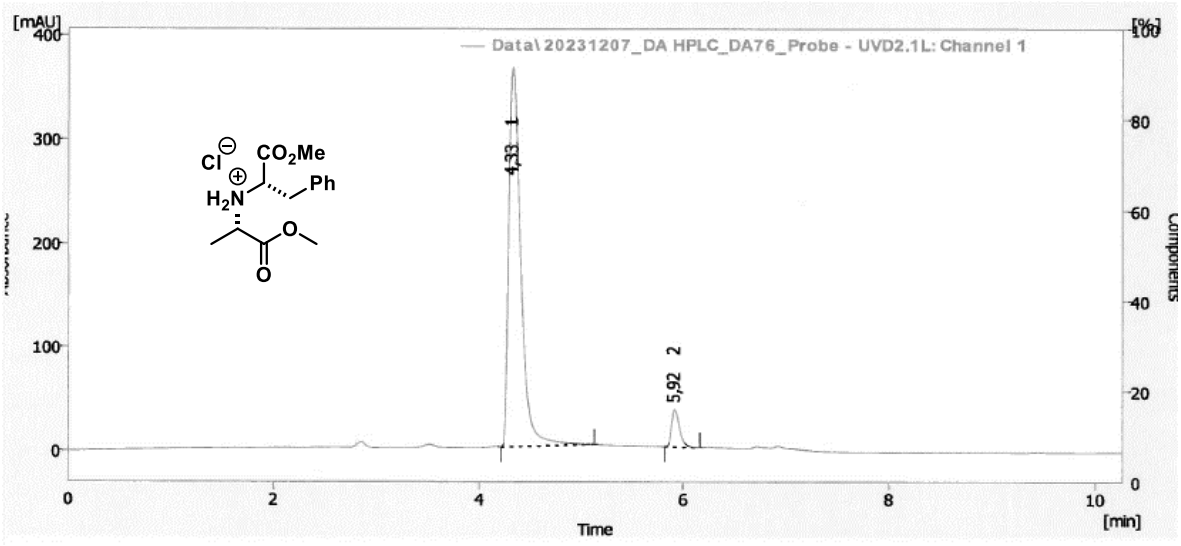


*Figure 157: HPLC-chromatogram of (S,S)-**249·HCl** (column: XSelect CSH C18, flow rate: 0.5 mL/min, temperature: 30 °C, solvent: H_2O/MeCN, gradient: H_2O/MeCN 95:5 to 10:90 over 15 minutes, 10:90 for 10 minutes, back to start gradient over 5 minutes).*

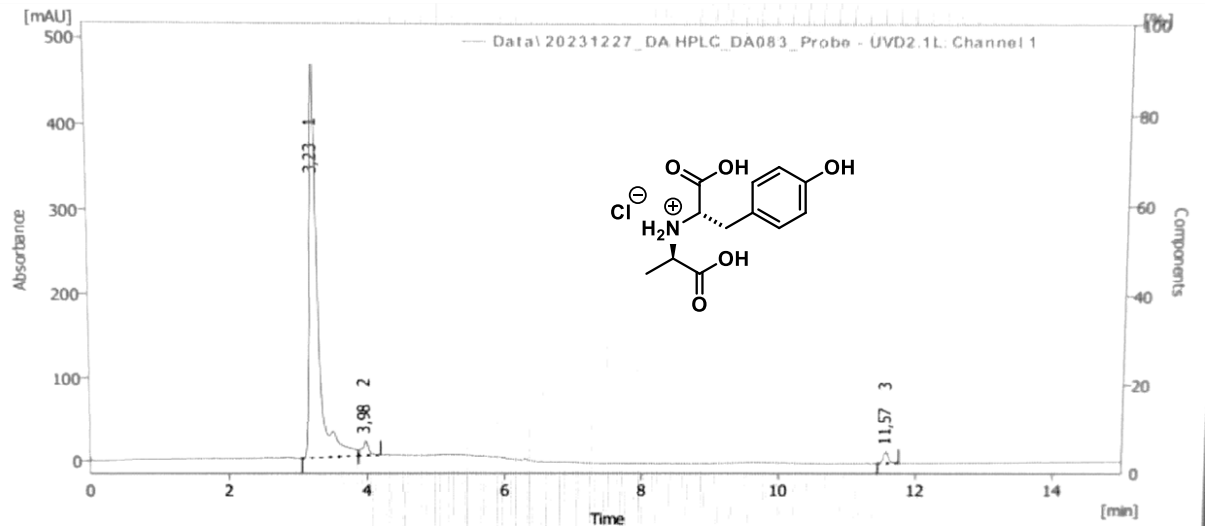


*Figure 158: HPLC-chromatogram of (R,S)-**250·HCl** (column: XSelect CSH C18, flow rate: 0.5 mL/min, temperature: 30 °C, solvent: H_2O/MeCN, gradient: H_2O/MeCN 95:5 to 10:90 over 15 minutes, 10:90 for 10 minutes, back to start gradient over 5 minutes).*

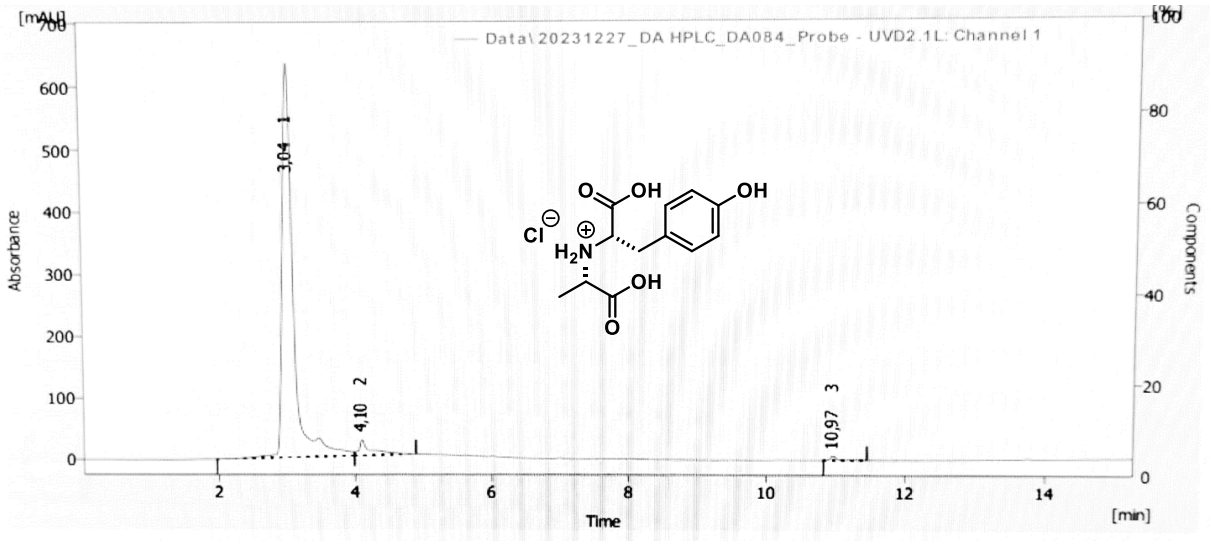


*Figure 159: HPLC-chromatogram of (S,S)-**250·HCl** (column: XSelect CSH C18, flow rate: 0.5 mL/min, temperature: 30 °C, solvent: H_2O/MeCN, gradient: H_2O/MeCN 95:5 to 10:90 over 15 minutes, 10:90 for 10 minutes, back to start gradient over 5 minutes).*

13.4 Curriculum vitae

Name	Alicia Sabrina Köcher
Date of birth	11.02.1997
Place of birth	Bergisch Gladbach (Germany)
Nationality	German

Education

11/2021 – 02/2025	PhD studies in organic chemistry in the research group of Prof. Dr. Hans-Günther Schmalz, University of Cologne
04/2019 – 10/2021	Master studies, University of Cologne Master thesis: “Investigations on the total synthesis of camporidine A – a potential anti-metastatic compound”
10/2015 – 12/2018	Bachelor studies, University of Cologne Bachelor thesis: “Untersuchungen zur Synthese von Derivaten des Naturstoffes Colchicin“
08/2007 – 06/2015	Abitur, Gymnasium Odenthal

13.5 Declaration

Erklärung zur Dissertation gemäß der Promotionsordnung vom 12. März 2020

„Hiermit versichere ich an Eides statt, dass ich die vorliegende Dissertation selbstständig und ohne die Benutzung anderer als der angegebenen Hilfsmittel und Literatur angefertigt habe. Alle Stellen, die wörtlich oder sinngemäß aus veröffentlichten und nicht veröffentlichten Werken dem Wortlaut oder dem Sinn nach entnommen wurden, sind als solche kenntlich gemacht. Ich versichere an Eides statt, dass diese Dissertation noch keiner anderen Fakultät oder Universität zur Prüfung vorgelegen hat; dass sie - abgesehen von unten angegebenen Teilpublikationen und eingebundenen Artikeln und Manuskripten - noch nicht veröffentlicht worden ist sowie, dass ich eine Veröffentlichung der Dissertation vor Abschluss der Promotion nicht ohne Genehmigung des Promotionsausschusses vornehmen werde. Die Bestimmungen dieser Ordnung sind mir bekannt. Darüber hinaus erkläre ich hiermit, dass ich die Ordnung zur Sicherung guter wissenschaftlicher Praxis und zum Umgang mit wissenschaftlichem Fehlverhalten der Universität zu Köln gelesen und sie bei der Durchführung der Dissertation zugrundeliegenden Arbeiten und der schriftlich verfassten Dissertation beachtet habe und verpflichte mich hiermit, die dort genannten Vorgaben bei allen wissenschaftlichen Tätigkeiten zu beachten und umzusetzen. Ich versichere, dass die eingereichte elektronische Fassung der eingereichten Druckfassung vollständig entspricht."

Poster

A. Köcher, H.-G. Schmalz, *Studies Towards the Total Synthesis of Camporidine A – A Challenging Application for the Ir-Catalyzed Allylic Substitution*, GDCh Wissenschaftsforum Chemie (WiFo) 2023, September 2023, Leipzig (Germany).

Köln, 02.12.2024_____

Alicia Sabrina Köcher