Bachelor Thesis

Studies towards construction of the

[4.3.0]-*N*-heterocyclic framework of Camporidine A

via an intramolecular *imino-Diels-Alder*-reaction

University of Cologne

Faculty of Mathematics and Natural Sciences

Bachelor of Science Chemistry

Submitted by

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Contents

1 Introduction

The modern scientific development has been strongly influenced by the profound impact of the rapidly growing, so-called life sciences.[1] It is the utilization of nature through biotechnological methods, due to which humans have access to antibiotics like penicillin G or other β-lactams[2], vaccines against Hepatitis B[3] or COVID-19[4], or the peptide hormone insulin[3]. The power of enzymatic, perfectly enantioselective catalysis in living cells makes nature capable of synthesizing complex molecules. The synthetic organic chemist comes into play when nature alone cannot accomplish a synthetic demand. When the bacteria *S. aureus* developed a resistance against penicillin by the biosynthesis of a β-lactamase, it was in the hand of organic chemists to find and prepare a suitable penicillin derivative via semi-synthesis.[2] Furthermore, if humans are not able to gain access to certain natural products on a bigger scale, because of economical or ethic reasons, a deep understanding of organic chemistry can be used to develop for a total synthesis of these compounds.

Pioneers like *E. J. Corey, A. Eschenmoser* or *R. Woodward* have driven the field of total synthesis to excellence. The latter two have impressively demonstrated what organic chemistry is capable of, through the synthesis of the extremely complex molecule vitamin B_{12}, only by utilizing (*S*)-2-phenyl-ethylisocyanate and (–)-camphor for the needed stereochemical information.[5] *B. Sharpless* showed that the chiral pool could not only be used as a source for enantiomerically pure starting materials or chiral resolution, but also for the asymmetric metal catalyzed epoxidation of allylic alcohols.[6] This field has been expanded, for example, by *W. Knowles*, who was honored with the Nobel-prize together with *R. Noyori* and *B. Sharpless*, for his work on asymmetric metal catalyzed hydrogenation using the chiral, non-natural ligand DIPAMP for the synthesis of L-DOPA; an important prodrug in the treatment of the *Alzheimer*-disease.[7] Lastly, *B. List* and *D. MacMillan* showed that natural compounds, or their derivatives, alone can be used for asymmetric catalysis[8], which is today known as organocatalysis and is being applied, inter alia, in the synthesis of steroid building blocks.[9] The investigation of such catalytical methods, and especially metal-free methods, is an important step towards the establishment of sustainable (“green”) chemistry.

The importance of organic chemistry for modern research and their application is indisputable – and the purpose is not to perceive it as a rival, but as a complement, to what nature already provides.

2 State of the art

2.1 Camporidine A and other members of the [4.3.0]-bicyclo-alkaloid family

It is well established in natural product research that bacterial symbionts are a valuable source for novel bioactive compounds, which cover a broad range of structural complexity and can sometimes lead to commercial interest.[10]

Camporidine A (**1**) is an example for a rather small natural compound with a high density of structural motifs, which was discovered in 2019 by *Hong et al.*, together with its derivative Camporidine B (**2**), during their chemical investigation of the gut bacteria *Streptomyces* sp. STA1. from the carpenter ant *Camponotus kiusiuensis* (figure 1).[11]

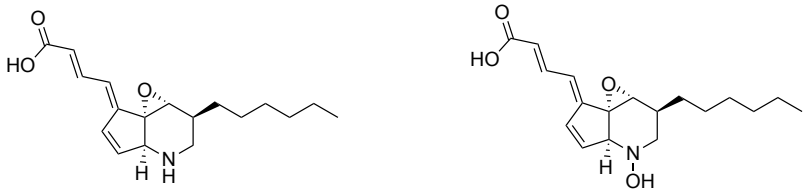


*Figure 1 - Structural formula of Camporidine A and B (**1** and **2**), as determined by Hong et al. in 2019.[11]*

Studies towards the bioactivity of the polyketide alkaloids **1** and **2** have revealed that both compounds do not show antibacterial, antifungal, or cytotoxic activities in general. Camporidine A (**1**) has however shown to suppress the migration (50 % decrease at 20 µM and 73 % at 40 µM) and cell invasion (20 % decrease at 20 µM and 36 % at 40 µM) of metastatic cancer cells. A cytotoxicity unrelated, anti-inflammatory activity could furthermore be measured with a half maximal inhibitory concentration of IC_{50} = 16.9 µM. Camporidine B (**2**) on the other hand, did not show any of those effects significantly.[11] A central role of the NH-moiety for the bioactivity of this alkaloid, due to the structural motif of an oligovinylogous α-amino acid, can thus be suggested. The potential medical application and its density of functional groups makes Camporidine A (**1**) interesting for further research, especially from a chemical standpoint, since no synthetic access has been reported yet.[12]

Not only have numerous other bioactive compounds originating from bacteria symbionts of insects been reported[10a], like the pseudonocardones A-C[13], nicrophorusamide A and B[14], or the deinococcucins A-D[15]; but also many structural analogous to Camporidine A (**1**) have already been discovered and characterized (figure 2).[16]

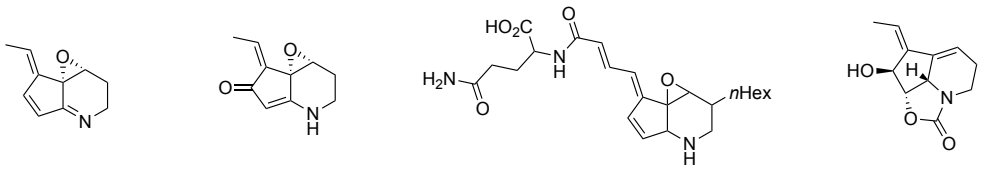
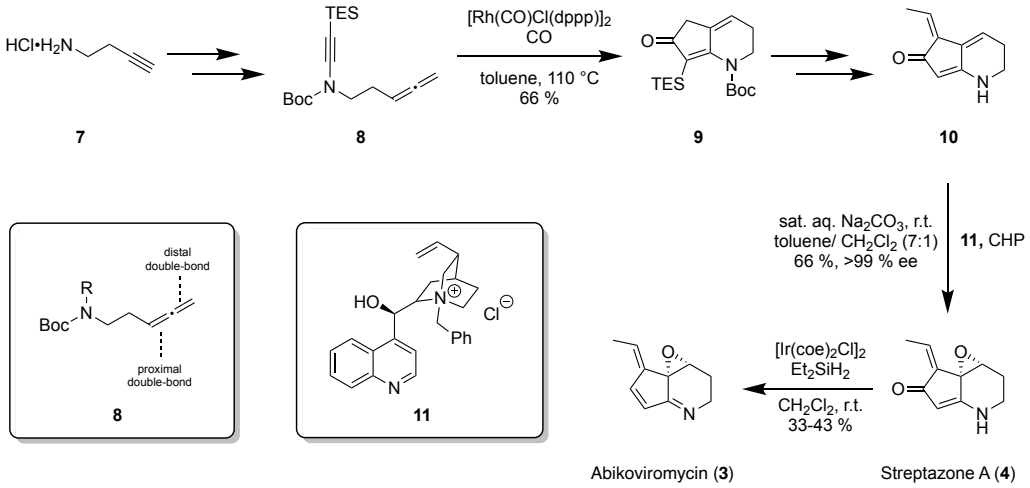


*Figure 2 – Structurally related compounds to Camporidine A (**1**) with [4.3.0] cores and diverse biological activity.[16]*

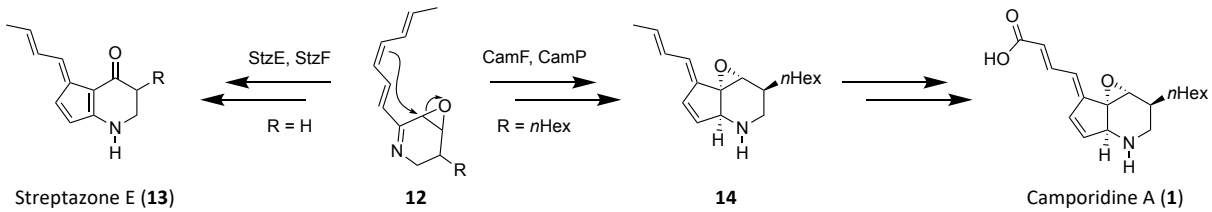
Particularly interesting to the organic chemist is α-β-unsaturated imine Abikoviromycin (3) and enaminone streptazone A (**4**), which have both been synthesized by *Wørmer et al.* in 2021 (scheme 1).[16]



*Scheme 1 - Abbreviated total synthesis of streptazone A (**4**) and abikoviromycin (**3**) by Wørmer et al.[16]*

The cyclopentenone motif was concisely constructed by a distal-selective *Pauson-Khand*-reaction, followed by further modifications, to perform a late-stage, enantioselective epoxidation on enaminone **10** with chiral catalyst **11** to yield streptazone A (**4**). Reduction of the vinylogue amide leads to abikoviromycin (**3**).[16]

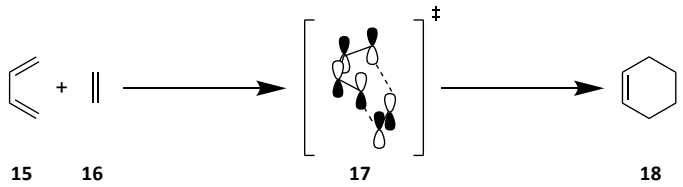
It is clear to see that the *Pauson-Khand*-reaction could also be applied to form the [4.3.0] core of other relative structures, such as Camporidine A (**1**) itself. Nature probably performs the cyclization of intermediate **12** via ring-opening and subsequent closure of the epoxide (scheme 2).[16]



*Scheme 2 – Postulated construction of the [4.3.0] core structure in the not fully resolved biosynthetic pathway of Camporidine A (**1**) and Streptazone E (**13**).[16]*

2.2 [4+2]-Cycloaddition - The *Diels-Alder*-reaction and its applications

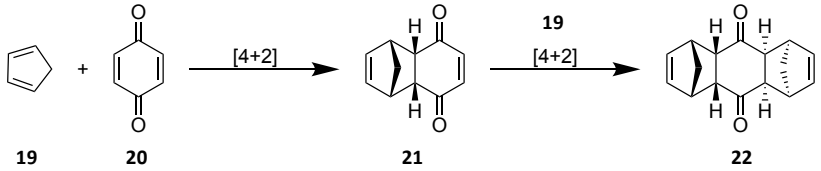
The formation of carbon-carbon-bonds is the heart of organic chemistry, enabling the construction of molecules with astonishing complexity. The variety of tools for organic synthesis has grown continuously in the last century, but some reactions have proven to be of such ubiquitous use and importance, that their discovery was honored with the Nobel Prize. One of which being the *Diels-Alder*-reaction, which was published by *Otto Diels* and *Kurt Alder* in 1928.[17]



*Scheme 3 - Abstract scheme of the Diels-Alder-reaction and the corresponding frontier-molecular-orbital-interaction (FMO-interaction) in the transition state **17**.[18]*

The *Diels-Alder*-reaction is, from an abstract point of view, a [4+2]-cycloaddition of a diene **15** and a dienophile **16** to a cyclohexene **18** (scheme 3).[18] It is arguably one of the most powerful reactions in organic chemistry, with an exponentially growing rate of citations per decade, in relation to the total number of publications, since 1970.[19]

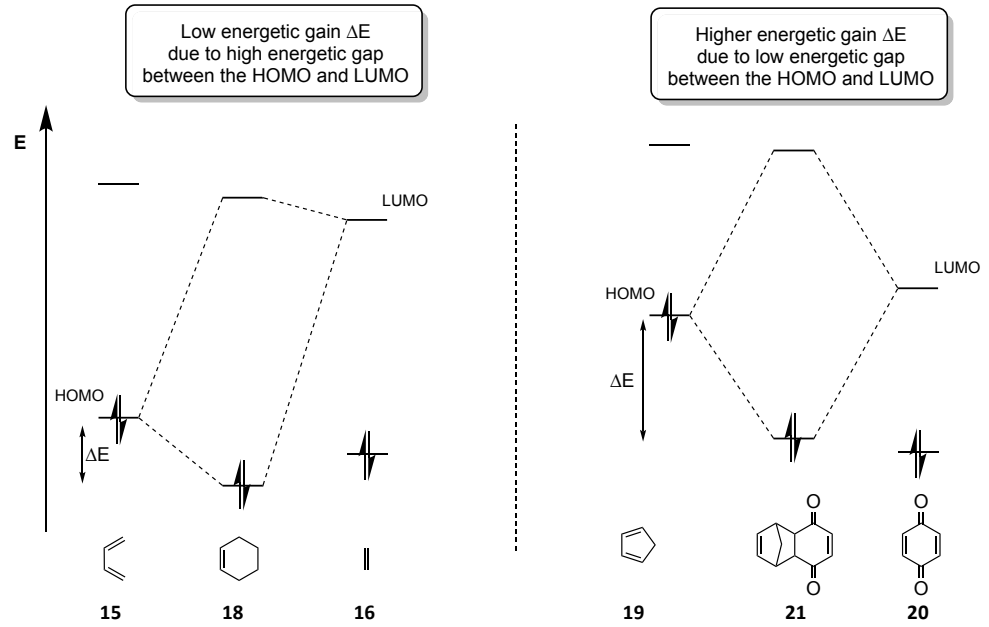
Its potential was already recognized in the original paper from *Diels* and *Alder*, who foretold an useful application in the field of natural product synthesis, especially regarding terpenes and alkaloids.[17b]



*Scheme 4 – Twofold cycloaddition of cyclopentadiene (**19**) with quinone (**20**) to the unsaturated polycyclic compound **22**.[17b]*

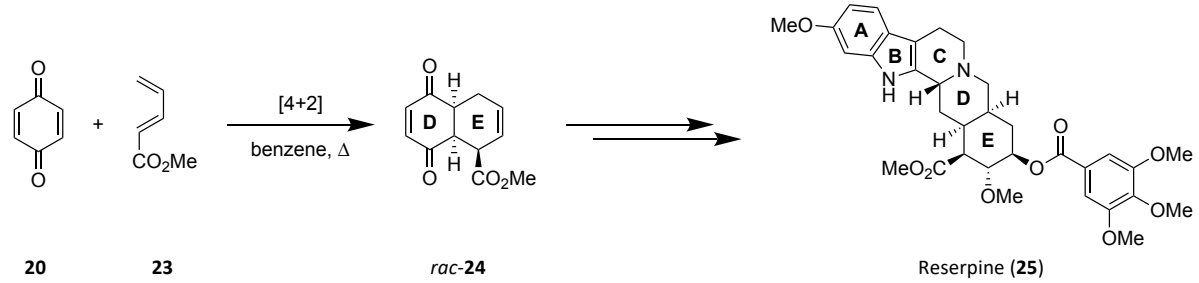
Diels and *Alder* observed the endo-selective, twofold [4+2]-cycloaddition of the s-*cis* diene cyclopentadiene (**19**) with the electron deficient dienophile quinone (**20**, scheme 4).

Both properties are important for the *Diels-Alder*-reaction to take place with good yields and under moderate reaction temperatures, due to the more favorable relative energetic level of the FMO´s, as qualitatively shown in scheme 5.[18]



Scheme 5 - Qualitative diagram for the interaction of the highest occupied molecular orbital (HOMO) of the diene with the lowest unoccupied molecular orbital (LUMO) of the dienophile of different dienes and dienophiles during the Diels-Alder-reaction.[18, 20]

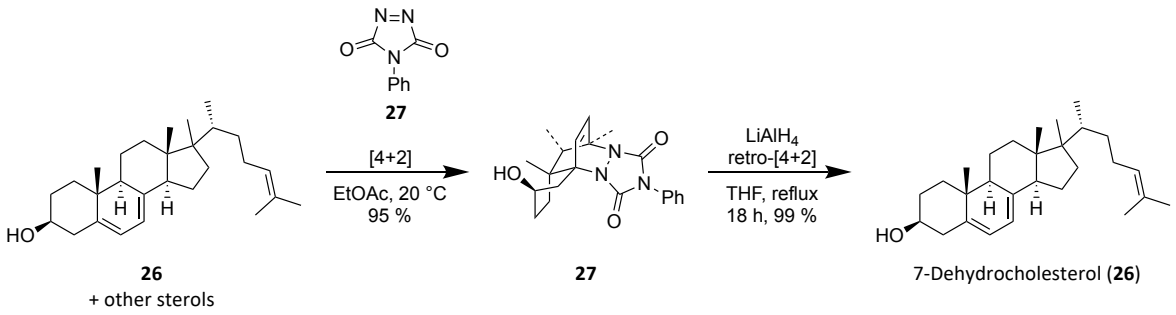
The *Diels-Alder*-reaction has been utilized in many prominent syntheses, as, for example, in the total synthesis of the **E**-ring of Reserpine (**25**) by *Woodward et al.* in 1956 (scheme 6).[21]



*Scheme 6 -Diels-Alder-reaction in the total synthesis of Reserpine (**25**) by Woodward et al.[21]*

Likewise, the *Diels-Alder*-reaction was one of the key reactions for the construction of the frameworks of morphine[22], cholesterol and cholesterine[23], estrone[24], prostaglandine $F_{2\alpha}$[25] and many more[17a], which impressively shows that this type of C-C-bonding is essential for the field of total synthesis.

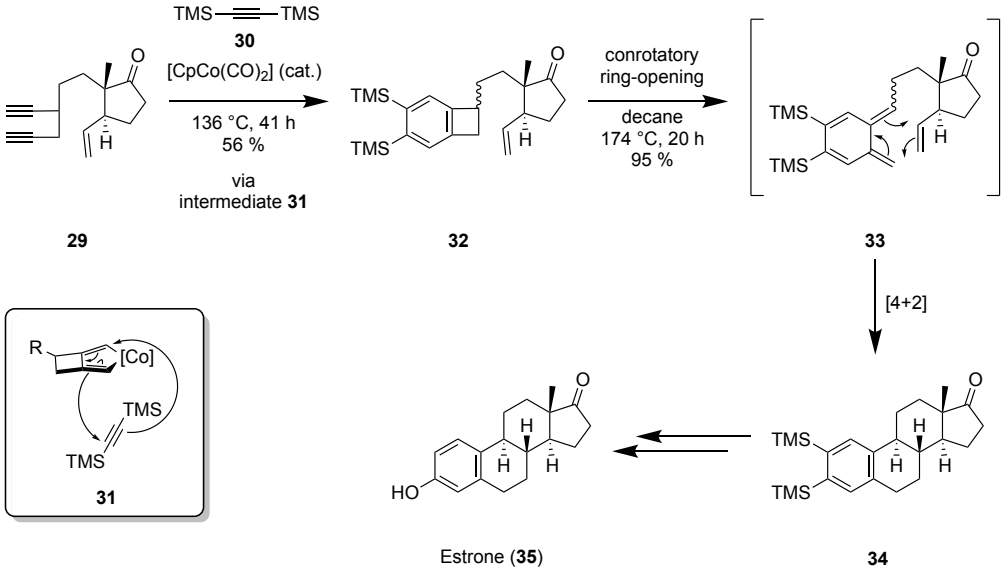
It goes without saying, that the *Diels-Alder*-reaction is also widely used in industrial syntheses, for example for the preparation of Vitamin B_6[26] by DSM or Lonapalene[27], a drug for the treatment of psoriasis, by Roche.[19] One remarkable industrial application is however the purification of sterol extracts, which are obtained by yeast fermentation, for the preparation of Vitamin D precursors on industrial scale (scheme 5).[19]



*Scheme 7 - Industrial extraction of 7-dehydrocholesterol (**26**) by the Diels-Alder-reaction with the triazolindione **27** and subsequent retro-Diels-Alder-reaction under reductive conditions.[19, 28]*

The mixture of sterols is brought to reaction with 4-phenyl-1,2,4-triazolin-3,5-dione (**27**). Only those sterols with a diene moiety form cycloadducts, which can then be purified by column chromatography, leading to 7-dehydrocholesterol-cycloadduct **28**. After undergoing a retro-*Diels-Alder*-reaction under reductive conditions, the pure sterol **26** is obtained.[28] Thus, the *Diels-Alder*-reaction can also be utilized for the purification or protection of dienes.

Regarding further applications of the *Diels-Alder*-reactions, the clever use of different kinds of dienes or dienophiles can make substituted aromatic system easily amenable, either by formation of an aromatic system (or a precursor), or by conversion of an arene into a diene beforehand.

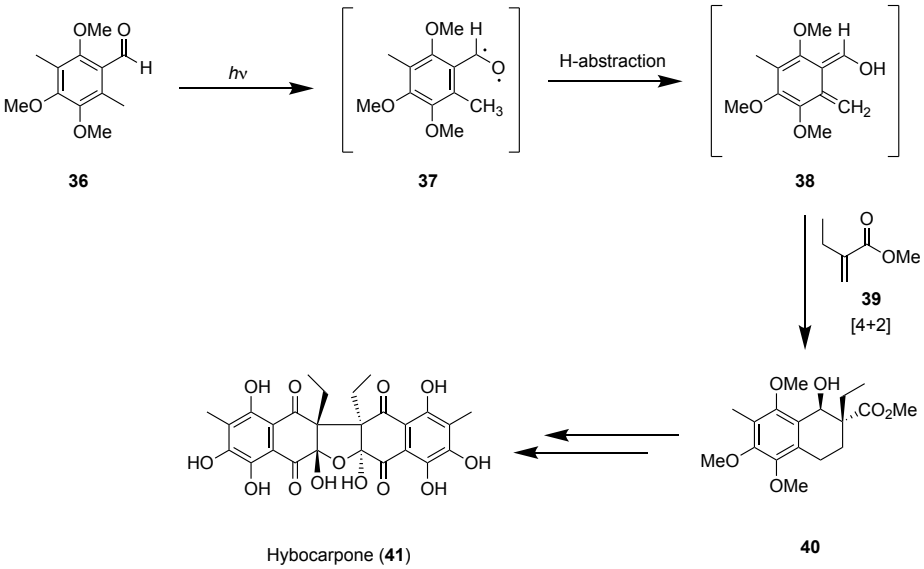


*Scheme 8 - Total synthesis of Estrone (**35**) by Vollhardt and Funk and utilization of the Diels-Alder-reaction.[24]*

The already mentioned synthesis of Estrone (**35**) is an excellent example for the symbiosis of the *Diels-Alder*-reaction and aromaticity (scheme 8). The formation of arene **32** is performed by a *Vollhardt*-Alkin-trimerization from 1,5-diyne **29** with bis(trimethylsilyl)acetylene (BTMSA,

30).[24] The cyclization can be assumed to take place by a *Diels-Alder*-like reaction of BTMSA (**30**) with the cobalto-cyclopentadiene-complex, as shown in the framed section of scheme 6 by intermediate **31**. However, the exact mechanism is still in debate, as other mechanisms and intermediates are also conceivable.[29] In the next step, the benzocyclobutene **32** undergoes conrotatory ring opening, leading to the diene intermediate **33**, which readily proceeds via an intramolecular *Diels-Alder*-reaction to cycloadduct **34**. The regained aromaticity by the [4+2]-cycloaddition of **33** to **34**, and the released strain-tension from **32** to **33**, create a strong thermodynamic force for this reaction, leading to an overall high yield of 95 %. Further transformations lead to the steroid Estrone (**35**).[24]

As an alternative to the formation of the σ-xylylene motif by the synthesis of a benzocyclobutane via *Vollhardt*-alkyne-trimerization and following ring-opening (see scheme 8), or by the cheletropic elimination of SO_2 from 1,3-dihydrobenzothiophene-2,2-dioxides[30], photoechemical methods can be utilized for the *in situ* generation of σ-xylylenes (scheme 9).



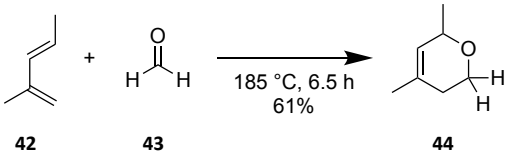
*Scheme 9 - Photochemically enabled Diels-Alder-reaction in the total synthesis of Hybocarpone (**41**) by Nicolaou and Gray.[31]*

By the excitement of the carbonyl group into an energetically higher triplet state, a biradical **37** is formed, which stabilizes by δ-H-abstraction. The so formed hydroxy-σ-xylylene **38** is trapped by methyl 2-ethylacrylate (**39**) to form the annulated product **40**. Further steps lead to cytotoxin Hybocarpone (**41**), as shown by *Nicolaou and Gray*.[31]

2.3 Hetero-*Diels-Alder*-Reactions

2.3.1 The *oxo-Diels-Alder*-reaction and its use for asymmetric dihydropyrone synthesis

As shown in section 2.2, the *Diels-Alder*-reaction is the most important reaction for the formation of unsaturated six-membered rings, albeit only the formation of solely carbogenic structural motifs was discussed. However, the *Diels-Alder*-reaction also allows the formation of unsaturated heterocyclic compounds, as shown by *Gresham* and *Steadman* in 1948 for the first time (scheme 10).[32]

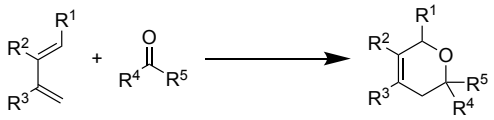


42 **43** **44**

*Scheme 10 - Oxo-Diels-Alder reaction of formaldehyde (**43**) and diene **44**, reported by Gresham and Steadman.[32]*

[4+2]-Cycloadditions of carbonyl-compounds with dienes enable the synthesis of 2-dihydropyranes and are called *oxo-Diels-Alder*-reactions. However, these reactions require highly electron-deficient dienophiles such as formaldehyde (see scheme 10), trichloracetaldehyde[33] or methylglyoxal[34], if no catalyst or reactive diene, as shown later, is involved. An overview over said reactions is given in Table 1.

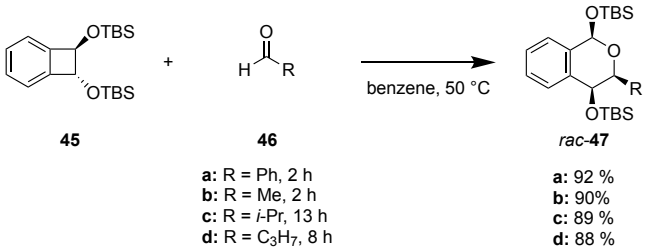
Table 1 - Overview over different oxo-Diels-Alder-reactions, involving (highly) reactive aldehydes.



Entry	R^1	R^2	R^3	R^4	R^5	Reaction conditions	Yield
1[32]	Me	H	Me	H	H	185 °C, 6.5 h	61 %
2[33]	H	Me	Me	H	CCl_3	150 °C, 24 h	92 %
3[34]	OMe	H	H	Me	CO_2Me	50 °C, 19.5 kbar, 15 h	85 %
4[34]	OMe	H	H	CF_3	Ph	50 °C, 19.5 kbar, 15 h	81 %
5[34]	OMe	H	H	H	Me	50 °C, 19.5 kbar, 15 h	62 %

Evidently, the required harsh reaction conditions and limited scope of utilizable dienophiles limit the applicability of the uncatalyzed *oxo-Diels-Alder*-Reaction to simple dienes.

A wider range of application can be covered, if extremely activated dienes are used, such as tributylsilyloxy-σ-xylylenes (OTBS-σ-xylylenes, **45**, scheme 11).

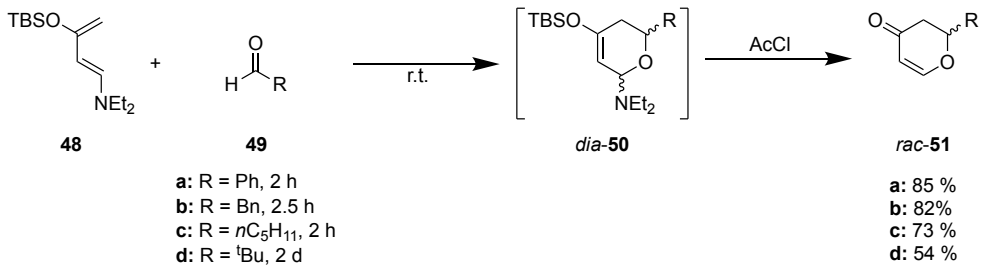


*Scheme 11 – Oxo-Diels-Alder-Reaction of different aldehydes **46** with disilyloxy-benzocyclobutene **45** under conrotatory ring opening, as reported by Hentemann et al. in 2000.[35]*

Hentemann et al. reported that the *in situ* generation of disilyloxy σ-xylylenes, from the benzocyclobutane precursor **45**, leads to the *oxo-Diels-Alder*-reaction of non-activated aldehydes **46** to the cycloadduct *rac*-**47**. Full *endo*-selectivity and *regio*-selectivity, if substituted benzocyclobutanes are used, could be observed.[35] In this way, 3-substituted isochromanes can easily be obtained in high yields.

The origin of the *endo*-selectivity cannot be explained with secondary orbital interactions by the carbonyl function, as usually done for *Diels-Alder*-reactions, and is thus non-trivial. The *endo*-directing interactions between the σ-xylylene and the dienophile are strongly dependent of the substituent R of aldehyde **46**, as shown by *Ujaque et al.* in theoretical studies with benzaldehyde (**46a**) and acetaldehyde (**46b**).[36]

An alternative application for the *oxo-Diels-Alder*-reaction was published in 2000 by *Huang* and *Rawai*, regarding their investigation of the reaction of non-activated aldehydes under strictly thermal, uncatalyzed reaction conditions with the monosilyloxy diene **48**. Subsequent reaction with acetyl chloride (AcCl) lead to dihydropyrones in high yields at room temperature (Scheme 12).[37]



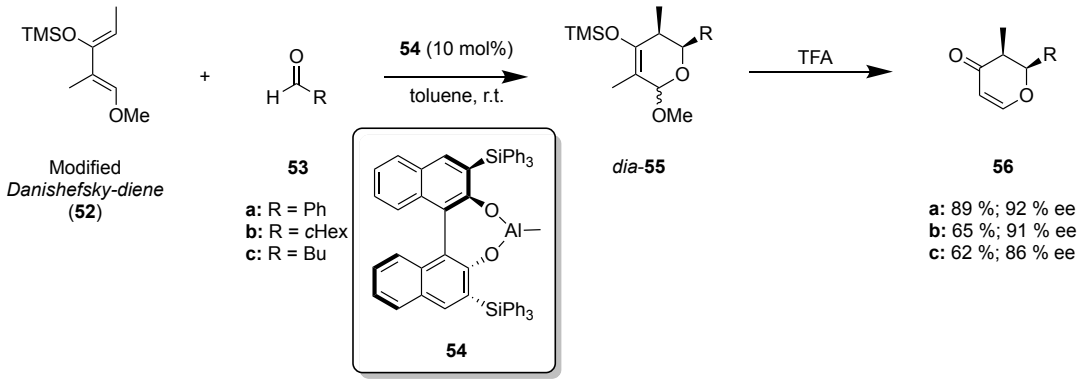
*Scheme 12 - Overview over the oxo-Diels-Alder-reaction with silyloxy diene **48** and subsequent quenching with acetyl chloride by Huang and Rawai.[37]*

The use of monosilyloxy dienes for *Diels-Alder*-reactions was already known, as they offer high reactivity towards dienophiles, can easily be prepared from the corresponding enone by

well-known silyl etherification protocols and allow the conversion of the cycloadduct into the respective dihydropyrones.[37-38]

A related class of silyloxy diene are the so-called *Danishefsky*-dienes (derived from 1-methoxy-3-(trimethylsilyl)-butadiene (**57**))[39], which were first described in 1974 for the preparation of cyclohexenones after [4+2]-cycloaddition.[40]

The asymmetric catalysis of the *oxo-Diels-Alder*-reaction of *Danishefsky*-dienes by chiral *Lewis*-acid **54**, followed by the formation of the enone by reaction with trifluoroacetic acid (TFA), is well investigated. This method makes enantiomerically pure dihydropyrones **56** amenable (scheme 13), which are broadly prominent in natural product synthesis.[39, 41]



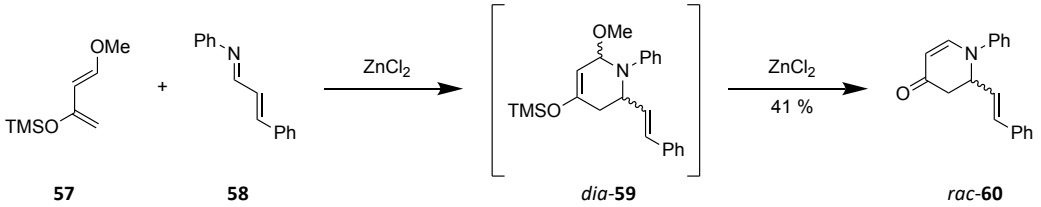
*Scheme 13 - Asymmetric synthesis of dihydropyrones **56** by Maruoka et al. via an oxo-Diels-Alder reaction.[41]*

The reaction sequence proceeds highly regioselective, as the electron-poor carbonyl carbon is attracted to the very electron-rich C1 in β-position to the trimethylsilyl-group (TMS-group).[39]

In conclusion, the most useful application for *oxo-Diels-Alder*-reactions is the cycloaddition of aldehydes to disilyloxy σ-xylylenes or mono-silyloxydienes via asymmetric *Lewis*-acid catalysis for the synthesis of dihydropyrones. *Bednarski* and *Danishefsky* utilized the latter method for the synthesis of unnatural L-glycolipids and L-glucose.[42]

2.3.2 The intermolecular *imino-Diels-Alder*-reaction

Analogue to the *oxo-Diels-Alder*-reaction, the use of compounds with *N-C*-double bonds as dienophiles are well known, leading to unsaturated six-membered *N*-heterocycles.[43]



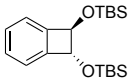
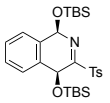
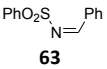
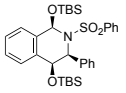
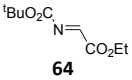
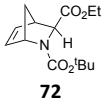
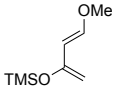
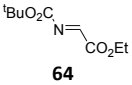
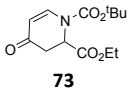
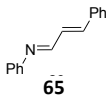
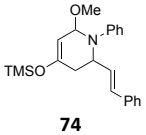
57 **58** *dia*-**59** *rac*-**60**

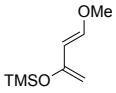
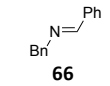
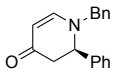
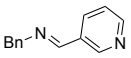
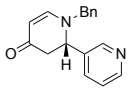
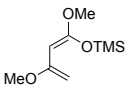
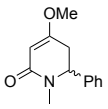
Scheme 14 - First ever reported imino-Diels-Alder-reaction by Danishefsky and Kerwin.[44]

The first *imino-Diels-Alder*-reaction was reported by *Danishefsky* and *Kerwin* in 1981 by the reaction of the *Danishefsky*-diene (**57**) with imine **58** under *Lewis*-acid catalysis with $ZnCl_2$ (scheme 14).[44] The cycloadduct *dia*-**59** reacts to the dihydropyridinone *rac*-**60** in the same manner as shown in section 2.3.1.

Intermolecular *imino-Diels-Alder*-reactions are known to proceed rather sluggish in comparison to the regular *Diels-Alder*-reaction.[45] In general, these reactions are only feasible if 1) a highly activated diene (silyloxy-dienes[43-44, 46] or silyloxy-σ-xylylenes[35]), 2) an activated dienophile[43] (as confirmed in theoretical studies by *Whiting* and *Windsor*[47]), 3) additional *Lewis-acid*[44, 46, 48], or 4) additional *Brønstedt*-acid[49] is used. A related option is the use of a keteneimmonium ion[50] or *in situ* generation[51] of an *N*-disubstitued-iminium ion.

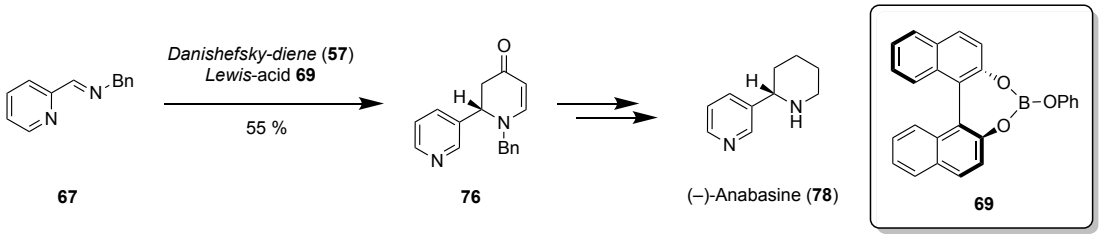
Table 2 - Overview over the scope of intermolecular imino-Diels-Alder-reactions with and without Lewis-acid-catalysis.

Entry	Diene	Dienophile	Additive	Product	Yield
1[35]	 **45**	 **62**	---	 **70**	73 %
2[35]		 **63**	---	 **71**	68 %
3[43]	 **19**	 **64**	---	 **72**	55 %
4[43]	 **57**	 **64**	---	 **73**	84 %[a]
5[44a]		 **65**	$ZnCl_2$	 **74**	41 %

Entry	Diene	Dienophile	Additive	Product	Yield
6[52]	 **57**	 **66**	Chiral *Lewis*-acid **69**	 **75**	75 %
7[52]		 **67**	Chiral *Lewis*-acid **69**	 **76**	55%
8[53]	 **61**	 **68**	Et_2AlCl	 **77**	82 %

[a] The cycloadduct was directly converted into the corresponding dihydropyridone **73** by addition of aqueous acid.

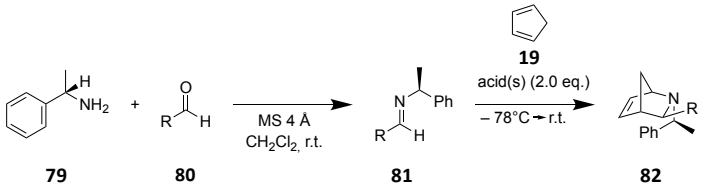
Table 2 shows a selection of reported *imino-Diels-Alder*-reactions with and without *Lewis*-acid catalysis. The scope of possibilities is clearly rather small; however, a useful strategy is the asymmetric *Lewis*-acid catalysis of the cycloaddition (entry 6 and 7), enabling access to enantiomerically pure dihydropyridones - analogue to the asymmetric synthesis of dihydropyrones - as shown in scheme 15.



*Scheme 15 – Synthesis of the alkaloid (–)-Anabasine (**78**) by a chiral imino-Diels-Alder-reaction by Hattori and Yamamoto.[52]*

This was applied by *Hattori* and *Yamoto* in 1993 in the synthesis of the alkaloid (–)-Anabasine (**78**). The aldimine **67**, prepared from benzylamine and nicotinaldehyde, was converted to dihydropyridone **76** with the *Danishefsky*-diene (**57**) and the chiral *Lewis*-acid (*S*)-1,1'-bi-2-napthol-phenoxyborane ((*S*)-BINOL-phenoxyborane, **69**). Further reduction and removal of the benzyl-substituent lead to the desired alkaloid **78**.[52] The *Lewis*-acid **69** had to be used in stochiometric amounts, due to the high *Lewis*-basicity of the involved amine, which is well-known for the catalyzed *imino-Diels-Alder*-reaction and thus contrasts it from the *oxo-Diels-Alder*-reaction (section 2.3.1).[44b]

*Table 3 – Overview of the imino-Diels-Alder-reaction of different aldimines **81** with cyclopentadiene (**19**) stochiometric amounts of Brønstedt-acid by Hedberg et al.[49]*

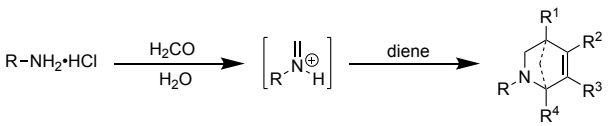


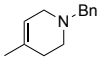
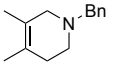
Entry	Aldehyde	Acid(s)	Yield
1	 **83**	CH_3SO_3H/ TFA	80 %
2	 **84**	CH_3SO_3H	80 %
3	 **85**	CH_3SO_3H	60 %
4	 **86**	CH_3SO_3H/ TFA or CH_3SO_3H	---

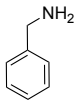
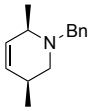
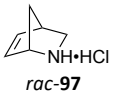
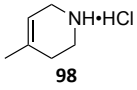
A more convenient method was published by *Hedberg et al.*, who showed that aldimines **22** react readily with cyclopentadiene (**19**) via *endo*-selective [4+2]-cycloaddition at mild conditions, if stochiometric amounts of *Brønstedt*-acid are added (Table 3). Furthermore, it was shown that aldimines **80**, which do not contain a second nitrogen in conjugation, do not undergo cycloaddition. For this reason, aldehydes like **86** (entry 4) cannot be utilized for this protocol.[49]

In addition to the procedure by *Hedberg et al.*[49], *Larsen* and *Grieco* have shown that *Mannich*-salts of benzyl-amine, methylamine or ammonia undergo [4+2]-cycloaddition with simple dienes (Table 4).[54]

Table 4 – Overview of different imino-Diels-Alder-reactions under Mannich-conditions, according to Larsen and Grieco.[54]



Entry	Amine	Diene	Product	Reaction conditions[a]	Yield
1	 **87**	 **90**	 **93**	35 °C, 70 h	59 %
2		 **91**	 **94**	35°C, 48 h	64 %

Entry	Amine	Diene	Product	Reaction conditions[a]	Yield
3	 **87**	 **92**	 *rac*-**95**	55 °C, 96 h	62 %
4	H_3C-NH_2 **88**	 **19**	 *rac*-**96**	25 °C, 3 h	82 %
5	NH_3 **89**	 **19**	 *rac*-**97**	25 °C, 6 h	44 %
6		 **91**	 **98**	35 °C, 96 h	40 %

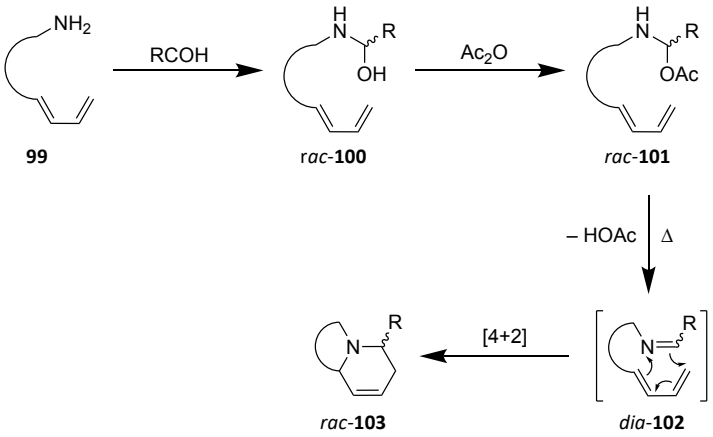
[a] All reactions were carried out in aqueous solution.

The mild reaction conditions and use of an aqueous reaction medium makes this strategy environmentally friendly and the moderate to good yield, as well as the utilization of simple starting materials and the good regioselectivity, provide potential for wide-spread use in synthetic organic chemistry for the synthesis of different kinds of dihydropyridine-frameworks.[54] On the other hand, full stereochemical control would be desirable for the use in modern total synthesis, which would be rather difficult to achieve with this method.

Thus, the intermolecular *imino-Diels-Alder*-reaction bears indeed potential for the synthesis of alkaloids and other compounds with *N*-heterocycles, but its limited scope hinders it from becoming a standard method. Still, the possibility for asymmetric synthesis of dihydropyridones and the *Brønstedt*-acid mediated cycloaddition to cyclopentadiene (**19**) or other simple butadiene derivatives should be kept in mind.

2.3.3 The intramolecular *imino-Diels-Alder*-reaction and tandem reactions

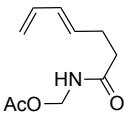
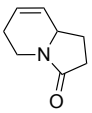
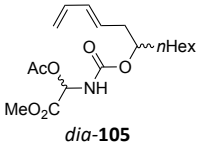
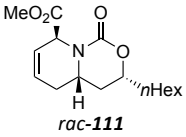
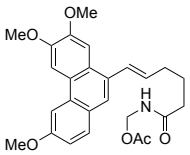
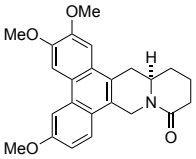
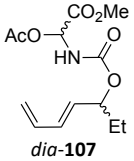
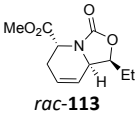
In contrast to its intermolecular counterpart, the intramolecular *imino-Diels-Alder*-reaction is known to cover a wider range of possible reactions, whereby activated dienes are not required (scheme 16).

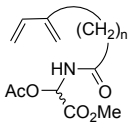
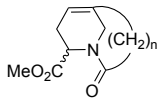
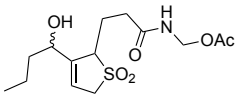
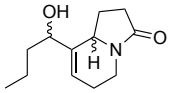


*Scheme 16 - Well-known synthetic strategy for the in situ generation of imines dia-**102** via ester-pyrolysis for a subsequent, intramolecular imino-Diels-Alder-reaction.*

A common strategy for the execution of intramolecular *imino-Diels-Alder*-reactions, is the *in situ* generation of the imine via ester pyrolysis of *O*-acyl aminals. This sequence enables access to labile imines, which could not been isolated due to their high reactivity towards hydrolysis, such as formaldimines (scheme 16, *dia*-**102**, R = H).

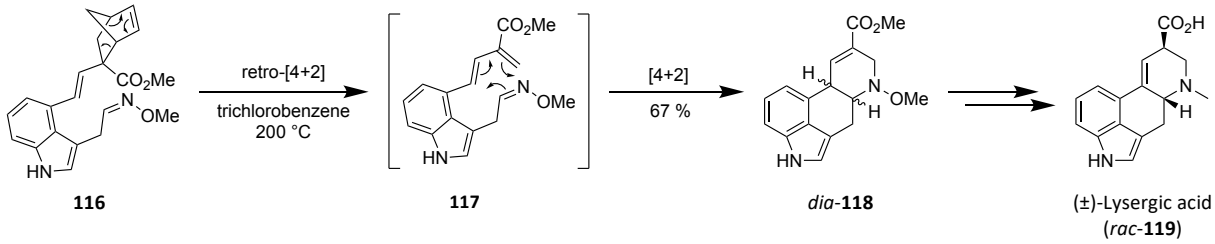
Table 5 - Overview of different imino-Diels-Alder-reactions performed via ester pyrolysis of O-acyl aminals.

Entry	***O*-Acyl aminal**	**Product**	**Reaction conditions**	**Yield**
1[55]	 **104**	 **110**	Hot tube of glass helices	73 %
2[55]	 *dia*-**105**	 *rac*-***111***	215 °C[a]	83 %
3[55]	 **106**	 *rac*-**112**	220°C, sealed tube	50 %
4[56]	 *dia*-**107**	 *rac*-**113**	230-240 °C, 2.5 h, sealed tube	46 %

Entry	*O*-Acyl aminal	Product	Reaction conditions	Yield
5[57]	 n = 2, 3, 4 **108**	 n = 2, 3, 4 **114**	2.5 min, 252 °C; 2 h, 200 °C; 2 h, 215 °C;	29 %, 82 %, 76 %
6[55]	 *rac*-**109**	 *dia*-**115**	Hot tube of glass helices, 370 °C	68 %

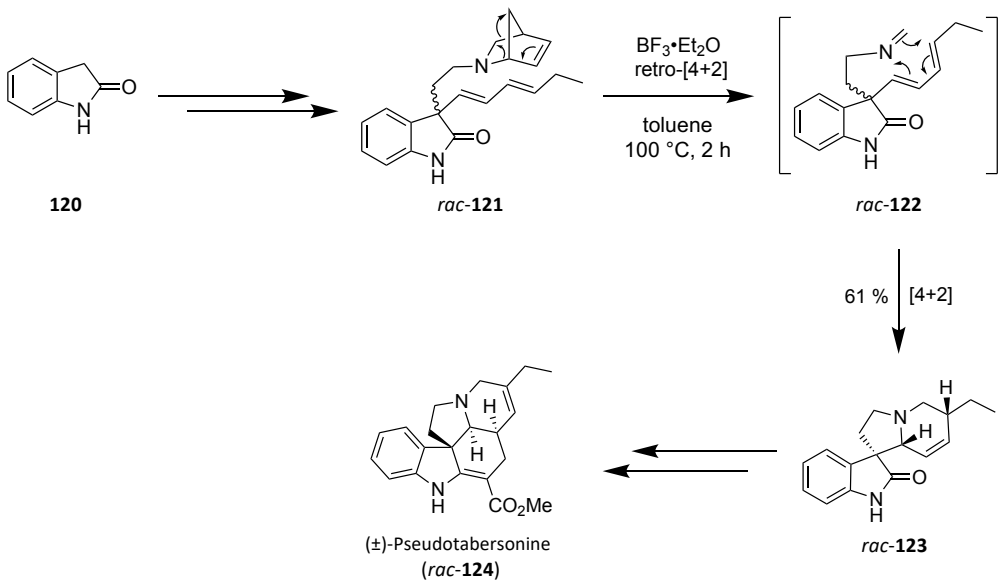
[a] Probably also in a hot tube, as toluene was used as a solvent.

It can be concluded that harsh reaction conditions are needed to perform these reactions, but moderate to good yields of different kind of *N*-heterocycles can be obtained (Table 5). Entry 5 proves, that different kind of bridgehead lactames are feasible through this strategy, which is very remarkable, as they do not obey *Bredt´s* rule.[57-58] Also, entry 6 demonstrates that the *imino-Diels-Alder*-reaction can be performed via a reaction cascade of cheletropic SO_2-elimination, ester-pyrolysis and subsequent [4+2]-cycloaddition.[55]



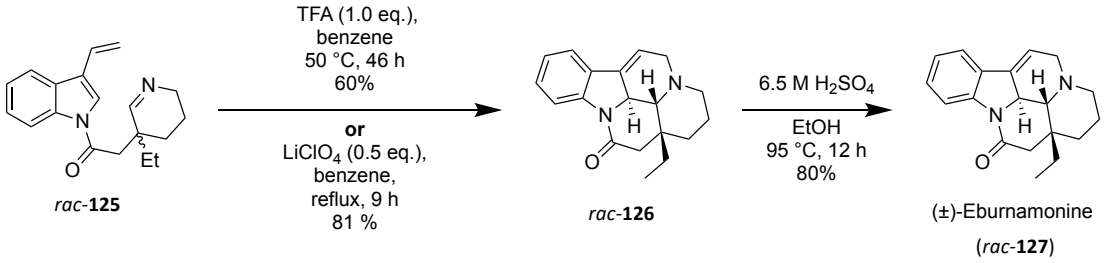
*Scheme 17 - Imino-Diels-Alder-reaction in the synthesis of (±)-lysergic acid (rac-**119**) by Oppolzer.[59]*

Another class of imines, which are known to undergo *imino-Diels-Alder*-reactions, are oxime-methyl ethers, as shown by *Oppolzer* in the synthesis of the lysergic-acid-diethylamide-precursor (LSD-precursor) (±)-Lysergic acid (rac-**119**, scheme 17). The dihydropyridine-ring is formed after retro-*Diels-Alder*-reaction of precursor **116**, under elimination of cyclopentadiene (**19**), and subsequent *imino-Diels-Alder*-reaction with the oxime-methyl-ether of diene **117**. Further reaction steps lead to (±)-Lysergic acid (rac-**119**). Oxime-methyl-ethers have also been reported to add to σ-xylylenes in low yields, forming isoquinolines.[60]



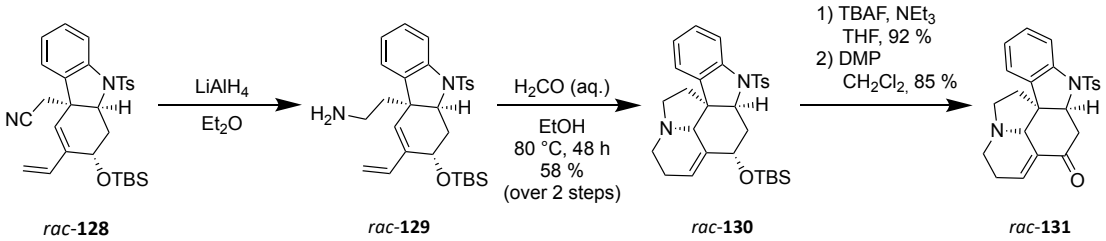
*Scheme 18 - Tandem retro-Diels-Alder/ imino-Diels-Alder reaction in the synthesis of (±)-Pseudotabersonine (rac-**124**) by Carrol and Grieco.*[61]

Similar to the tandem reaction by *Oppolzer* (scheme 17), a reaction sequence of retro-[4+2]-cycloaddition and following intramolecular [4+2]-cycloaddition can be utilized for the *in situ* formation of imines and its further applications for *imino-Diels-Alder*-reactions. *Carrol* and *Grieco* applied this tandem reaction for their racemic synthesis of Pseudotabersonine (*rac*-**124**, scheme 18).[61]



*Scheme 19 -Lewis- and Brønstedt-acid catalyzed imino-Diels-Alder-reaction in the syntheses of (±)-Eburnamonine (rac-**127**) by Grieco and Kaufman in 1999.*[62]

The *imino-Diels-Alder* reaction can also be catalyzed by *Brønstedt*- or *Lewis*-acids, thus activating simple imines, allowing their cycloaddition (scheme 19), as shown by *Grieco* and *Kaufman* in their synthesis of the pentacyclic alkaloid (±)-Eburnamonine (*rac*-**127**).[62]



rac-**128** *rac*-**129** *rac*-**130** *rac*-**131**

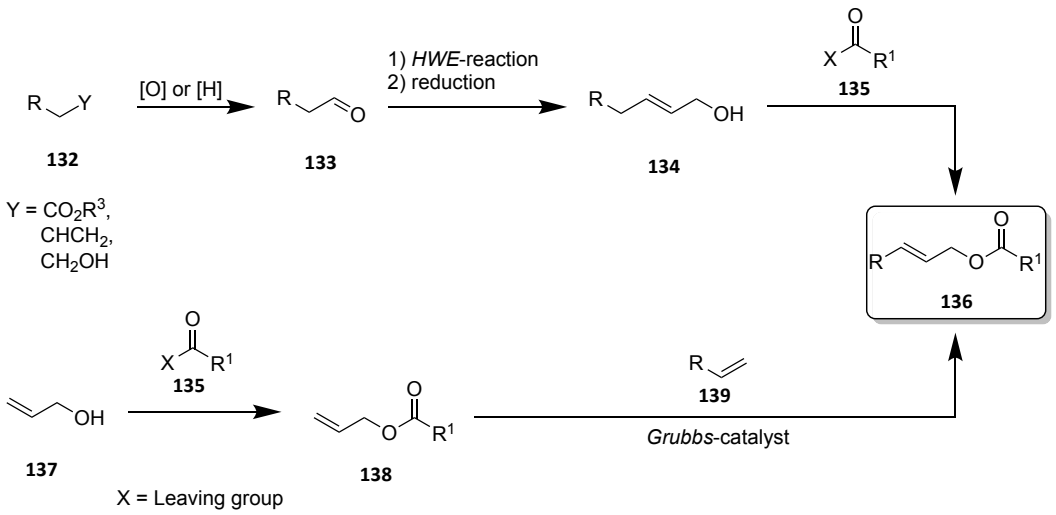
Scheme 20 -Imino-Diels-Alder reaction by Thanh et al. with relatively mild reaction conditions for the framework-synthesis of aspidosperma alkaloids.[63]

Lastly, the reaction of imines without strong *Brønstedt*- or *Lewis*-acid catalysis and/ or temperatures below 100 °C is rather exceptional but has been executed in the framework-synthesis of the aspidosperma alkaloids by *Thanh et al.* in 2010 (scheme 20).[63] The low acidity of ethanol[18] therefore seems sufficient for the generation of reactive iminium-dienophiles if long reaction times are used.

In conclusion, albeit it is possible to perform the intramolecular *imino-Diels-Alder-reaction* with weak *Brønstedt*-acids and relatively low reaction temperatures (scheme 19), its main application lies in the tandem elimination/ cycloaddition reaction sequence. The possibility to use simple dienes as reactive centers, in contrast to the highly activated silyloxy dienes (see section 2.3.2 and 2.3.1), makes the intramolecular *imino-Diels-Alder*-reaction attractive for alkaloid-synthesis and superior against its intermolecular variant, due to its more generic range of application. Its scope is, however, limited due to the rather harsh reaction conditions, which are often required (table 4). Thus, the framework of the starting material requires stability towards high reaction temperatures and/ or *Lewis*-/ *Brønstedt*-acids.

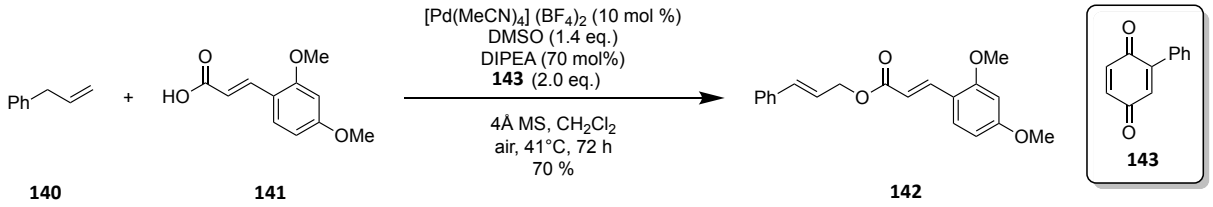
2.4 Novel methods for the synthesis of (chiral) allylic esters

The esterification is arguably one of the most important reactions in organic synthesis, and since today, many methods for the synthesis of esters have been reported, such as the well-known *Fischer*-, *Steglich*- or *Mitsonobu*-esterification.[18, 64] Allylic esters in particular are feasible through a variety of methods, which either act via *C*-*O*- or *C*-*C*-bonding (scheme 21).



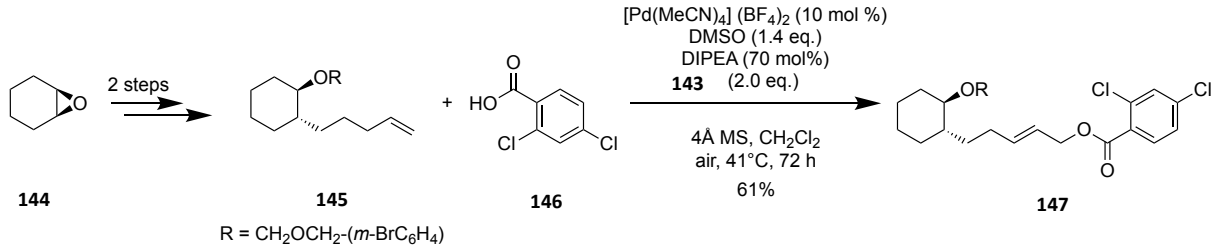
Scheme 21 - Generic route to allylic esters, either by C-O-bonding (upper path) or C-C-bonding (lower path).[18, 64]

In the following, two novel methods for the synthesis of allylic esters will be discussed, the first one being a Pd(II)-catalyzed procedure for selective C-H-oxidation by *Vermeulen et al.*[64]



*Scheme 22 - General procedure for the synthesis of allylic esters **142** via C-H-oxidation by Vermeulen et al.[64]*

This method allows the synthesis of complex allylic esters with only catalytic amounts of the Pd(II)-catalyst and cheap starting materials in moderate to good yields (scheme 22). Furthermore, its biggest advantage lies in the possibility of creating alternative routes to the methods shown above, which may reduce the required steps for the synthesis of certain compounds drastically.



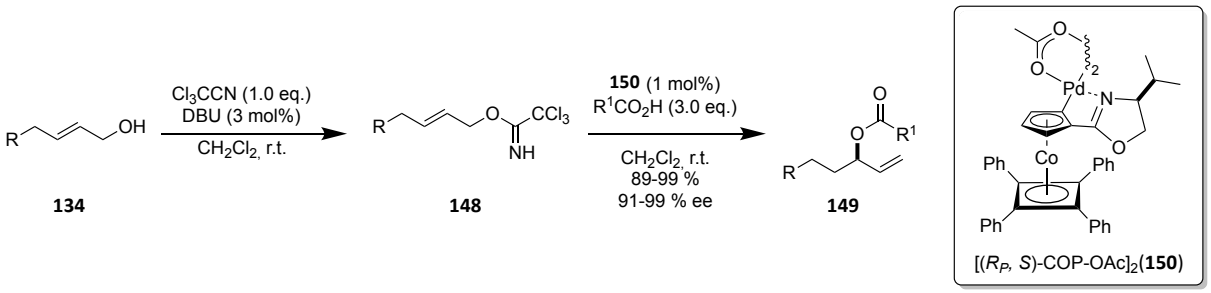
*Scheme 23 - Synthesis of allylic ester **147** by Vermeulen et al. via Pd(II)-catalyzed C-H-oxidation.[64]*

Scheme 23 shows the synthesis of the Brevetoxin precursor **147**, which applied this C-H-oxidation method. This sequence enables access to **147** in only three steps, with an overall

yield of 47%, whereas the original procedure by *Barlett* and *Ting*[65] required six reaction steps, with an overall yield of only 19 %.[64]

However, some disadvantages of this reaction are the necessity of ≥ 3.0 eq. of the carboxylic acid, the long reaction times, and a lack of enantioselectivity.[64]

In 2005, *Kirsch* and *Overman* reported the first asymmetric catalyzed synthesis for chiral allylic esters, involving the chiral cobalt-palladium-complex [(R_P, *S*)-COP-OAc]$_2$ (**150**, framed section, scheme 24).[66]

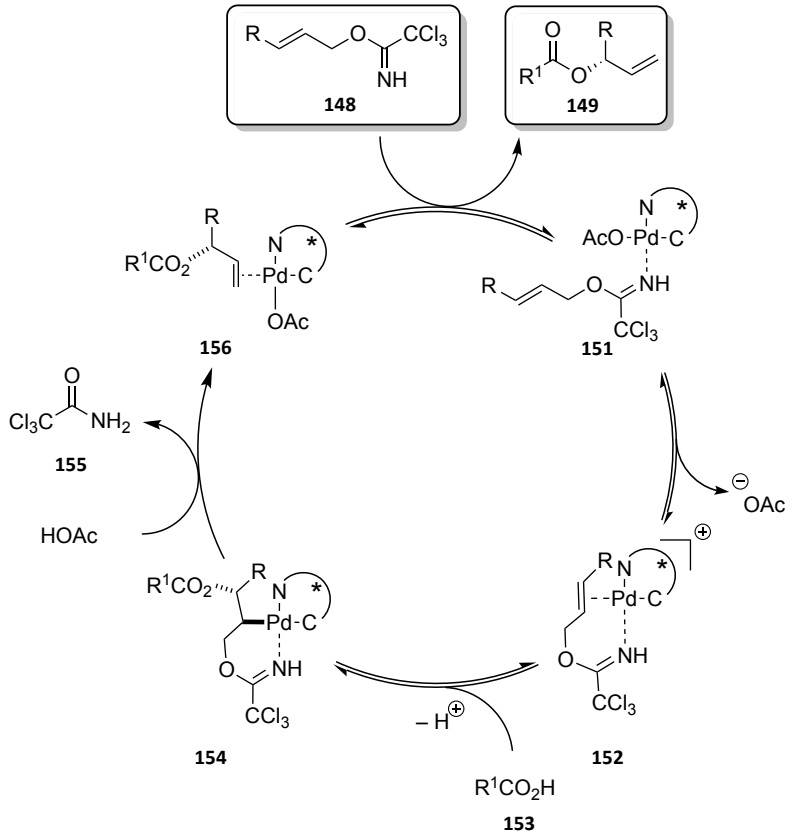


*Scheme 24 -Reaction sequence for the synthesis of chiral allylic esters **134** with the catalyst **150** by Cannon et al.*[66]

The chiral allylic ester is formed by the synthesis of the trichloroacetimidate **148** from the respective allylic alcohol **134** (*in situ* or isolated) and subsequent reaction with the carboxylic acid and the chiral catalyst [(R_P, *S*)-COP-OAc]$_2$ (**150**, scheme 24).[66]

This reaction enables the access to enantiomerically pure allylic esters with high to excellent yields, high enantiomeric excess and under mild reaction conditions. Thus, this procedure is certainly applicable for a broad application in modern synthesis, albeit the chiral catalyst **150** must be synthesized initially, as it only has to be used in very small amounts per reaction and can be synthesized in five reaction steps with an good overall yield of 47 %.[67]

The postulated mechanism for this esterification is shown in scheme 25.[66]

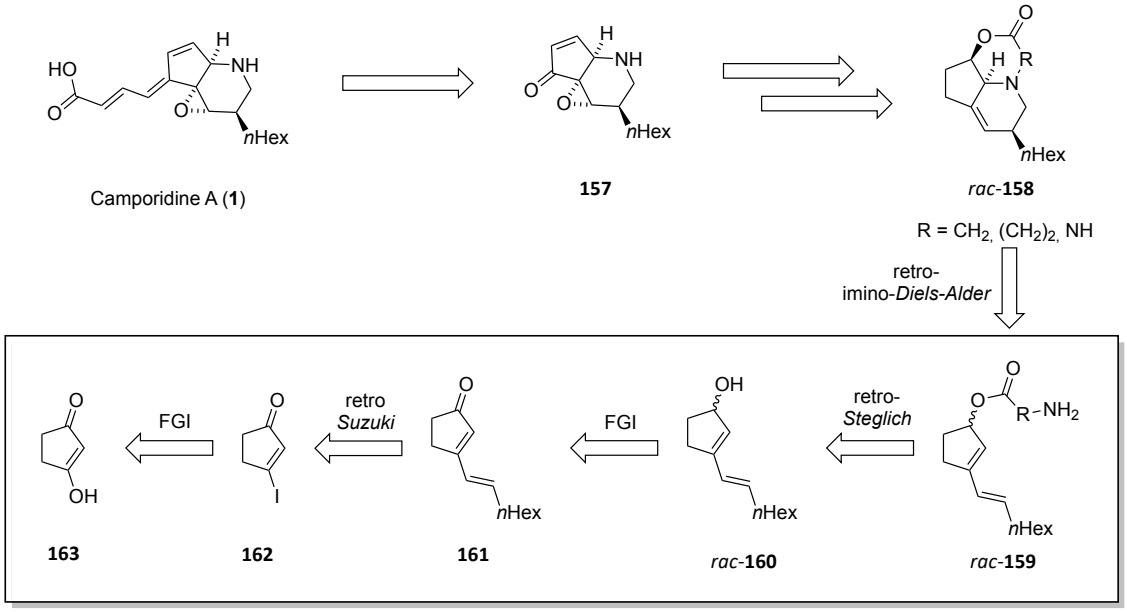


Scheme 25 - Postulated mechanism for the asymmetric catalyzed allyl ester synthesis by Kirsch and Overman.[66]

Trichloroacetimidate **148** forms complex **151** with the monomer of the [(*R*$_P$, *S*)-COP-OAc]$_2$-catalyst (**150**). A reversible ligand exchange takes place by the dissociation of an acetate-ion and subsequent π-bonding to the prochiral double bond from the trichloroacetimidate ligand **148**. The so activated C-C-double bond undergoes nucleophilic addition with carboxylic acid **153**, leading to complex **154**, which reacts via irreversible *β*-elimination of 2,2,2-trichloroacetamide (**155**) and consequent ligand exchange with an acetate-ion after proton exchange. Ligand exchange at π-complex **156** achieves catalytic turnover by dissociation of the desired allylic ester **149** and association of starting material **148**.[66]

3 Motivation

This work aims to the construction of the bicyclic core structure of Camporidine A (**1**) by the synthesis of the tricyclic compound *rac*-**158** via an intramolecular *imino-Diels-Alder*-reaction.



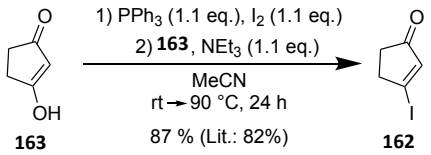
*Scheme 26 - Retrosynthesis of Camporidine A (**1**) through different functional group interconversions (FGI) and disconnections leads to the tricyclic compound rac-**158**, which is supposed to be prepared out of 3-hydroxy-cyclopent-2-enon (**163**) via Suzuki-coupling, Steglich-esterification and an imino-Diels-Alder-reaction.*

An access to the free amine *rac*-**159** is crucial for testing of the [4+2]-cycloaddition, which should be synthesized from 3-hydroxy-cyclopent-2-enon (**163**) as shown in the framed section of scheme 26. The diene system will be formed by the *Suzuki*-coupling of 3-iodo-cyclopent-2-enon (**162**) with (*E*)-1-(oct-1-enyl)-pinacolboronate (**172**). Subsequent reduction of the ketone **161** to dienylic alcohol *rac*-**160** will create a precursor for the attachment of different linkers, which will be attached through carbazate synthesis or a *Steglich*-esterification. For the latter, *N*-protected glycine and β-alanine will be used, whereby different protecting group will be tested. After successful deprotection, the *imino-Diels-Alder*-reaction will be tested under different reaction conditions and with different additives. This cycloaddition will be one of the key-steps towards the synthesis of Camporidine A (**1**) and will provide the correct relative configuration in compound *rac*-**158** of the stereocenters of the six-membered ring, due to the stereospecificity of the *imino-Diels-Alder*-reaction.

Thus, this work will provide important information regarding the synthetic strategy towards the bicyclic framework and shall contribute to the total synthesis of Camporidine A (**1**) overall.

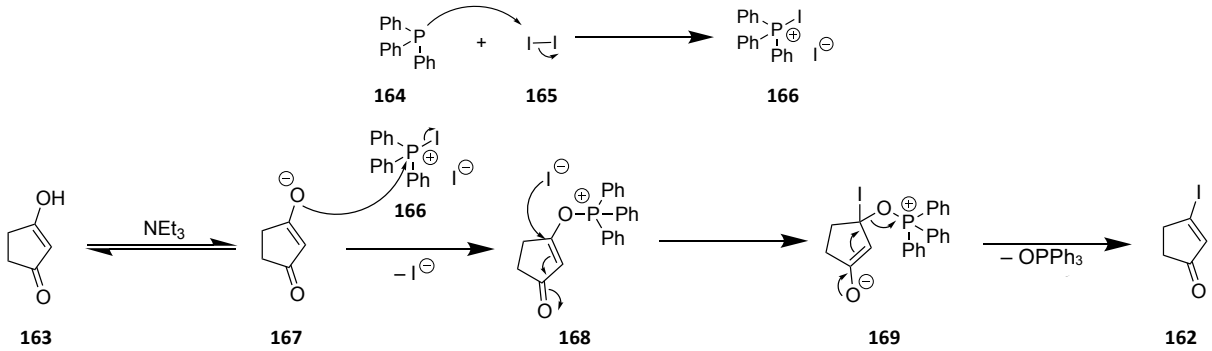
4 Results and discussion

4.1 Synthesis of the dienyl alcohol 3-[(*E*)-Oct-1-enyl]-cyclopent-2-enol



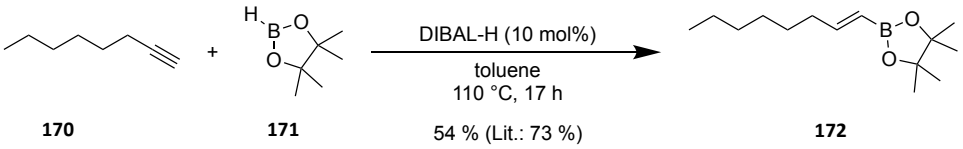
*Scheme 27 – Synthesis of 3-iodo-cyclopent-2-enon (**162**) by Iodination of 3-hydroxy-cyclopent-2-enon (**163**), adapted from Lemiére et al.[68]*

The first step towards the construction of Camporidine A´s bicyclic framework is the iodination of 3-hydroxy-cyclopent-2-enon (**163**) with triphenylphosphine, iodine and triethylamine in acetonitrile; following a procedure from *Lemiére et al.*[68]. To have access to large amounts of the dienylic alcohol *rac*-**160** after three reactions steps, this reaction was performed on a 29 g scale, which did not have a noticeable influence on the yield of this reaction. The good yield of 87 % slightly exceeded the yield of *Lemiére et al.* (82 %)[68].



*Scheme 28 - Mechanism of the iodination of 3-hydroxy-cyclopent-2-enon (**163**) according to Piers et al.[69]*

The nucleophilic attack of triphenylphosphine **164** at iodine **165** leads to iodo-triphenylphosphonium iodide (**166**). 3-Hydroxy-cyclopent-2-enon (**163**) is deprotonated by NEt_3. The acidity of **163** is relatively high due to its structural motif of a vinylogue carboxylic acid, with a pK_a value of 4.5[70]. After the nucleophilic attack of the vinylogue carboxylate **167** at the iodo triphenylphosphonium ion **166**, a conjugated addition of an iodide ion takes place at **168**. The final product **162** is formed after elimination of triphenylphosphine oxide, which creates a thermodynamic driving force for this reaction.[69]



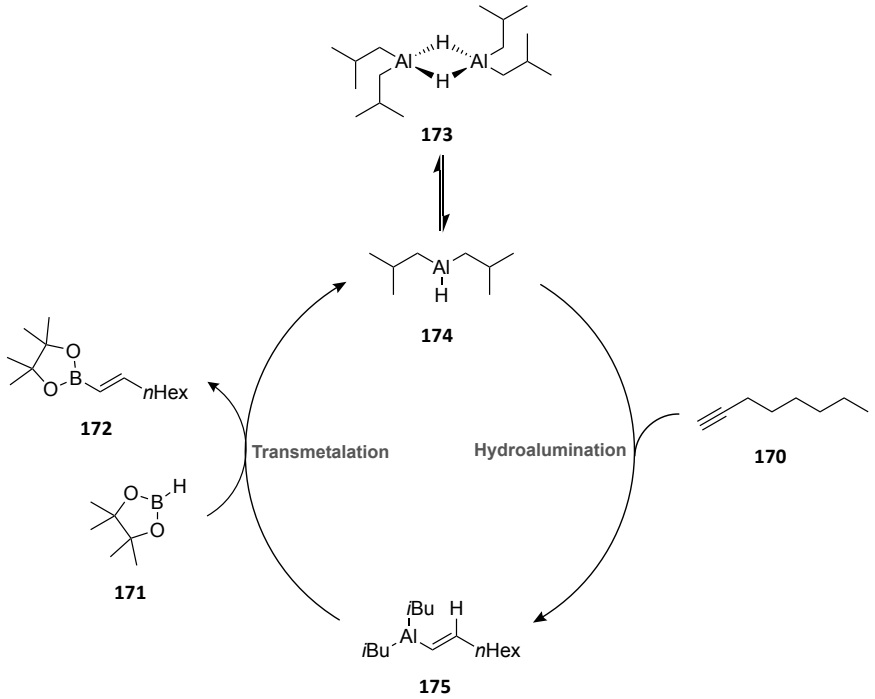
170 **171** **172**

*Scheme 29 – Diisobutylaluminium hydride (DIBAL-H, **173**) catalyzed hydroboration of 1-octyne (**170**) with pinacolborane, adapted from Bismuto et al.[71]*

The preparation of the boronate for the *Suzuki*-coupling was realized by the hydroboration of 1-octyne (**170**) with pinacolborane (**171**) via DIBAL-H-catalysis (scheme 29), following a procedure from *Bismuto et al.*[71]

The moderate yield (54 %) of this reaction, in comparison to the literature (71 %)[71], has to be due to problems at the work up or column chromatography, as full conversion was observed by GC-MS.

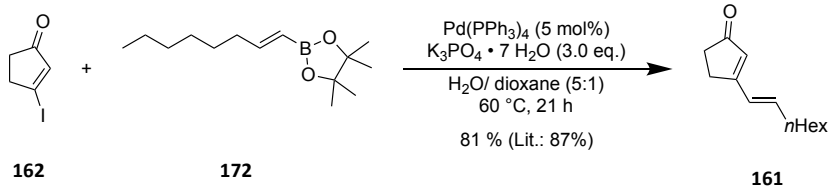
Bismuto et al.[71] showed that this reaction is catalyzed through hydroalumination, whereby DIBAL-H catalysis lead to the best yield for the hydroboration of 1-octyne (**170**), out of five different alkylalanes tested.



*Scheme 30 - Mechanism of the hydroboration of 1-octyne (**170**) by DIBAL-H (**173**) catalysis via hydroalumination.[71]*

Monomeric DIBAL-H (**174**) undergoes hydroalumination at the C-C-triplebond of 1-octyne (**170**) to form (*E*)-dialkylaluminium-octen **175**. Subsequent transmetalation with pinacolborane (**171**) forms the hydroborylated product **172** and regenerates DIBAL-H (**174**) to achieve catalytic turnover. The well-known transmetalation from aluminum to boron is a

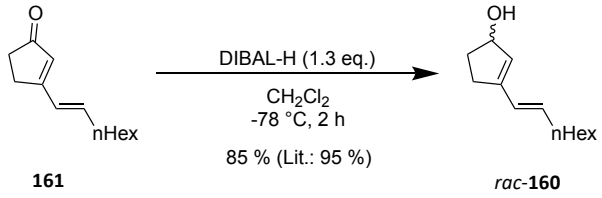
result of the higher affinity of carbon to the less electropositive metal during the transmetalation.[18]



162 **172** **161**

*Scheme 31 - Suzuki-coupling of 3-iodo-cyclopent-2-enon (**162**) with pinacol boronate **172**.*

The C-C-bonding was performed by a *Suzuki*-coupling of the iodide **162** and the alkenyl pinacolboronate **172** with Pd(0)-catalyst $Pd(PPh_3)_4$ and base $K_3PO_4 \bullet 7\ H_2O$ to form ketone **161** in a yield of 81 %, through an unpublished procedure by *T. Wilczek* (scheme 31).[72] Prior to use, the solvent mixture was degassed, to limit the oxidation of the Pd^0-catalyst by oxygen in the solvent. Monitoring of the reaction process via GC-MS showed that no full conversion has taken place after 16 h. Further 1 mol% of the catalyst was added to the mixture, which lead to further conversion of the starting material after further heating for 3 h. However, full conversion could still not be observed. One must assume that the catalyst was oxidized by residual oxygen during this reaction, due to insufficient degassing of the rather large amount of solvent (150 mL). Thus, this degassing method should be replaced by degassing of the solvent by repeated evacuation and venting of the solvent while stirring[73] or freeze-pump-thaw degassing.



161 *rac*-**160**

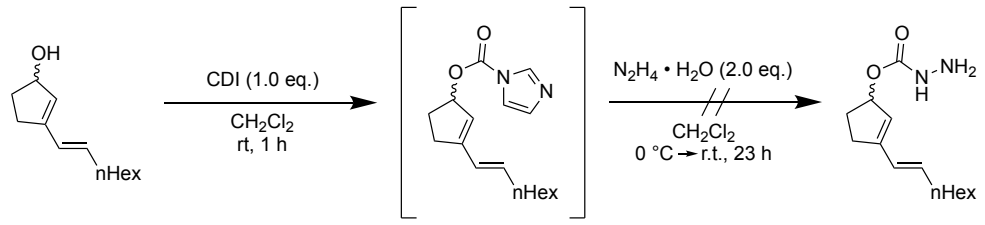
*Scheme 32 - Reduction of ketone **161** with DIBAL-H (**173**) to dienylic alcohol rac-**160**.*

With 6.5 g of dieneone **161** in hand, the next step was the reduction to the dienylic alcohol *rac*-**160**, according to the unpublished literature by *T.Wilczek* (scheme 32).[72] Only 2.9 g of ketone **161** was used, as the dienylic alcohol *rac*-**160** has shown tendency to decompose over time.

A yield of 85 % (2.5 g) could be achieved by the reaction of ketone **161** with DIBAL-H (**173**), which was 10 % less than expected, due to the occurrence of mixed fractions during the

column chromatography because of the very similar R_f values of both compounds (R_f (**161**) = 0.53, R_f (*rac*-**160**) = 0.55, SiO_2, *c*Hex/ EtOAc = 1:1), which were not purified further.

4.2 Synthesis of the *O*-[3-[(*E*)-Oct-1-enyl]-cyclopent-2-enyl]-oxycarbonylhydrazine



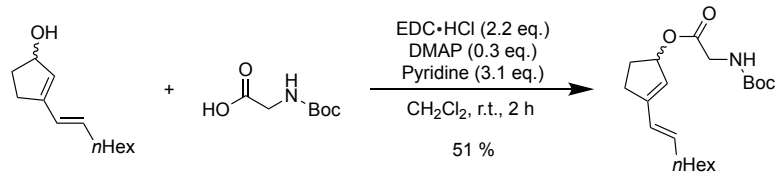
rac-**160** *rac*-**176** *rac*-**177**

*Scheme 33 – Carbonyldiimidazole (CDI) mediated carbazate synthesis from dienylic alcohol rac-***160***, adapted from Kumar et al.*[74]

The synthesis of carbazate *rac*-**177** was tested, adapting a literature known procedure[74], as this hydrazine derivative could be converted into an electron deficient dienophile for the *imino-Diels-Alder*-reaction. Furthermore, this reaction would yield the free amine for the imine synthesis, without the need of a protection group.

The first step was the *in situ* formation of imidazole carbamate *rac*-**176** by the reaction of dienylic alcohol *rac*-**160** with CDI. The formation of the imidazole-carboxylate *rac*-**176** could be observed via thin-layer chromatography (TLC). Subsequent addition of N_2H_4•H_2O should yield carbazate *rac*-**177** after nucleophilic addition/ elimination on *rac*-**176**. Conversion could be observed to a moderate extend on TLC, but no conversion to carbazate *rac*-**177** took place, as NMR-spectroscopy of the isolated product showed.

4.3 Synthesis of the free amine via *N*-Boc-protected amino acids

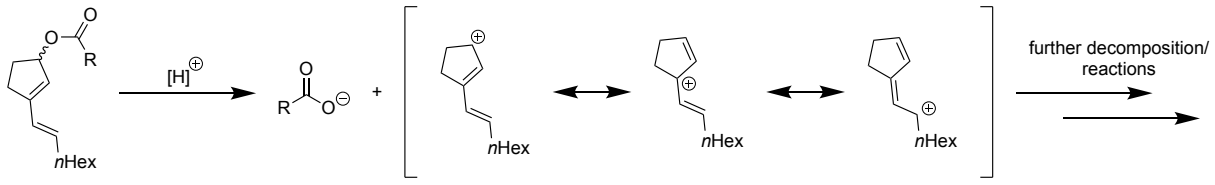


rac-**160** **178** *rac*-**179**

*Scheme 34 - Steglich-esterification of dienylic alcohol rac-***160** *with N-Boc-glycine (**178**).*

The *Steglich*-esterification with *N*-Boc-glycine (*N*-Boc-Gly, **178**) was performed using *N*-Boc-glycine (**178**), EDC•HCl, nucleophilic catalyst DMAP and pyridine to form dienylic ester *rac*-**160** in a moderate yield of 51 % (scheme 34).

TLC monitoring of the reaction process was not possible, as the reaction product *rac*-**179** decomposed on the silica plate, which was later confirmed by 2D-TLC of the isolated reaction product *rac*-**179**. As the same decomposition pattern on the silica plate could be observed with every other ester that was synthesized for this study, one can assume that the instability is due to the highly stabilized carbocation, which results after dissociation of the carboxylate or the respective carboxylic acid as a moderate leaving group (scheme 35).



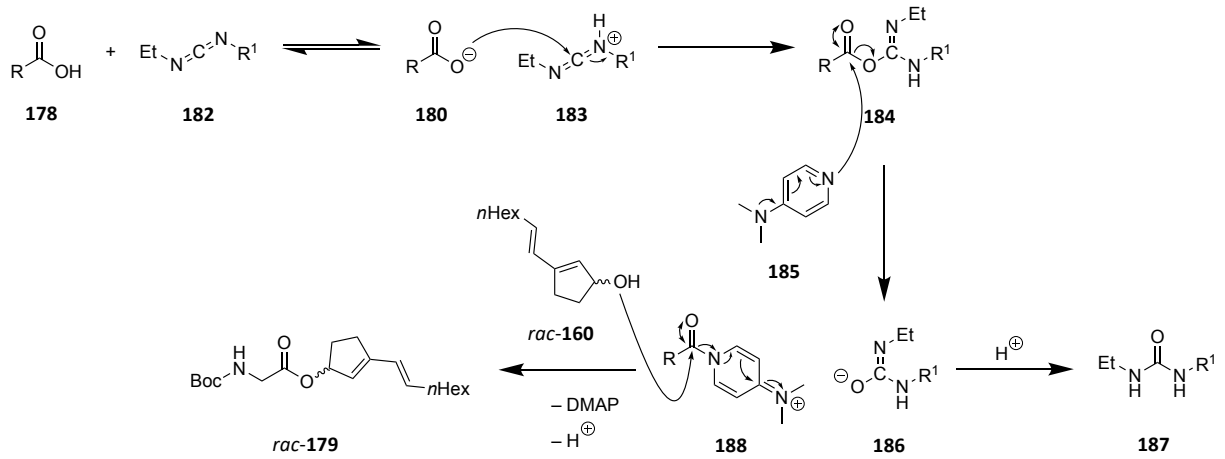
rac-**179** **180** **181** **181** **181**

Scheme 35 - Postulated decomposition sequence of a dienylic ester rac-***179*** *by contact with SiO_2.*

This postulated sequence is supported by the observation, that the dienylic alcohol *rac*-**160** and the dienylic ester *rac*-**179** show the same m/z-value in GC-MS, albeit the corresponding molecule could not be identified from its m/z-value.

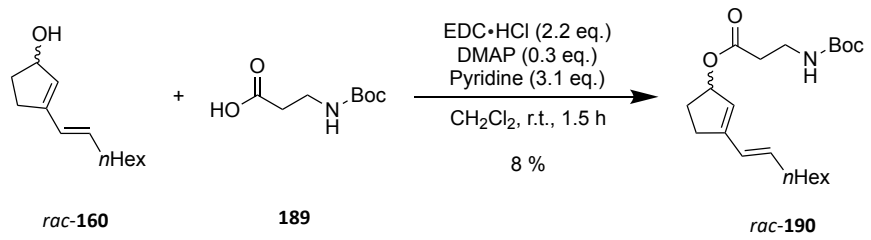
It is reasonable to assume that this decomposition sequence is catalyzed due to the *Lewis*-acidity of SiO_2 and/ or through residual silicic acid in the stationary phase. Addition of 3 % NEt_3 to the mobile phase did not influence the stability of the ester *rac*-**179** on the silica plate. It is remarkable that, however, ester *rac*-**179** could be purified via flash column chromatography on SiO_2.

Thus, monitoring of the reaction process for this and all further *Steglich*-esterifications was only possible through crude NMR-spectroscopy, but purification via column chromatography was still feasible. Some decomposition could also have taken place during the column chromatography, which is indicated by the moderate yield of about 50 %, even though crude NMR-spectroscopy of the reaction mixture showed full conversion of the dienylic alcohol *rac*-**160** after 1 h. *Steglich*-Esterifications are usually known to provide high yields of >90 %, if the alcohol is not sterically demanding[75], but many examples for *Steglich*-esterifications of secondary alcohols with moderate yields of 38-72 % are also known.[76]



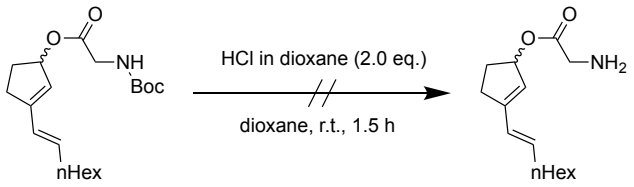
Scheme 36 - Reaction mechanism of the Steglich-esterification (R=BocNHCH₂, R¹=C₃H₆NMe₂.).[77]

The *Steglich*-esterification enables the esterification of sterically demanding alcohols under full retention of their stereochemistry and under mild reaction conditions. Water is formally bound by 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDC, **182**), which forms the corresponding urea **187** and therefore acts as a dehydrating reagent while creating a thermodynamic driving force. *N*,*N*-Dimethylaminopyridine (DMAP, **185**) acts as a nucleophilic catalyst and is needed to suppress the [1,3]-rearrangement of the *O*-isoacyl-urea **184** to the corresponding *N*-acyl urea. The active ester **188** undergoes nucleophilic addition and subsequent elimination of DMAP (**185**) with the alcohol *rac*-**160**, resulting in the desired ester *rac*-**179**.[77-78]



*Scheme 37 - Steglich-esterification of dienylic alcohol rac-**160** with N-Boc-β-alanine (**189**).*

To vary the tether length, a *Steglich*-esterification of dienylic alcohol *rac*-**160** with *N*-Boc-*β*-alanine (*N*-Boc-*β*-Ala, **189**) was performed, using EDC•HCl, DMAP and pyridine (scheme 37). The mobile phase for the flash column chromatography only contained 1 % NEt_3, which is most likely the reason for the low yield of 8 % despite full conversion of the starting material was indicated by crude NMR-spectroscopy. This observation supports the assumption that decomposition of the dienylic esters also takes place on the stationary phase during flash column chromatography.



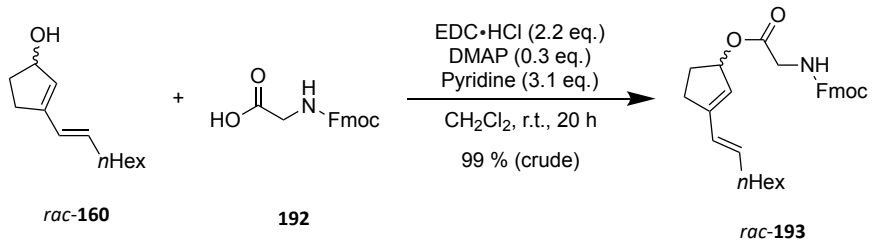
rac-**179** *rac*-**191**

*Scheme 35 - Boc-deprotection of dienylic ester rac-**179** with HCl in dioxane.*

To obtain the free amine for the *imino-Diels-Alder*-reaction, the cleavage of the Boc protecting group was attempted by the reaction of HCl in dioxane with dienylic-β-alanine ester rac-**179** (scheme 38). It was to be expected that decomposition might take place due to the acidic reaction conditions, in a similar fashion as shown in scheme 35. 2D-NMR of the crude product confirmed that the desired amine *rac*-**191** was indeed not obtained, and decomposition took place instead.

Thus, *N*-Boc-protected amino acids can be used for *Steglich*-esterification with the dienylic alcohlol *rac*-**160**, but the lability of the framework towards *Brønstedt*- and *Lewis*-acids makes acidic deprotection impossible. The free amine *rac*-**159** is therefore not amenable through this synthetic strategy.

4.4 Synthesis of the free amine via *N*-Fmoc-protected glycine

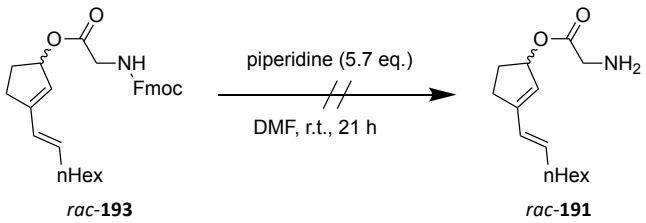


rac-**160** **192** *rac*-**193**

*Scheme 36 - Steglich-esterification of dienylic alcohol rac-**160** with N-Fmoc-glycin (**192**).*

As shown in section 4.3, the *Lewis*- and *Brønstedt*-acid lability of the dienylic system demands the use of a protection group for the amine moiety of the amino acid, which does not require acidic conditions for its cleavage. Therefore, *Steglich*-esterification of the dienylic alcohol *rac*-**160** with Fmoc-protected glycine (**192**) was performed, using EDC•HCl, nucleophilic catalyst DMAP and pyridine (scheme 39).

The crude product was not purified via column chromatography, as the required use of a base in the eluent might lead to deprotection of dienylic ester *rac*-**193** inside the column. The crude product was thus obtained in a yield of 99 %.



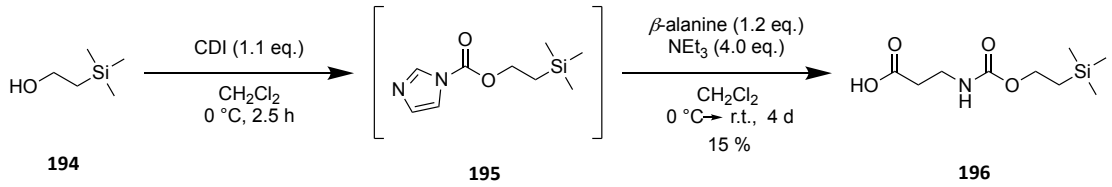
rac-**193** *rac*-**191**

*Scheme 37 – Fmoc deprotection of dienylic ester rac-***193** *with piperidine.*

The deprotection of Fmoc-protected dienylic ester *rac*-**193** with piperidine in dimethylformamide (DMF) was attempted with reaction conditions applied from *Chi et al.*[79], but did not lead to the desired amine *rac*-**191** (scheme 40). Flash column chromatography of the crude product gave the dienylic alcohol *rac*-**160** - probably due to unconverted starting material from the *Steglich*-esterification- and fractions with 2 mg of decomposition products.

4.5 Synthesis of the free amine via *N*-Teoc-protected amino acids

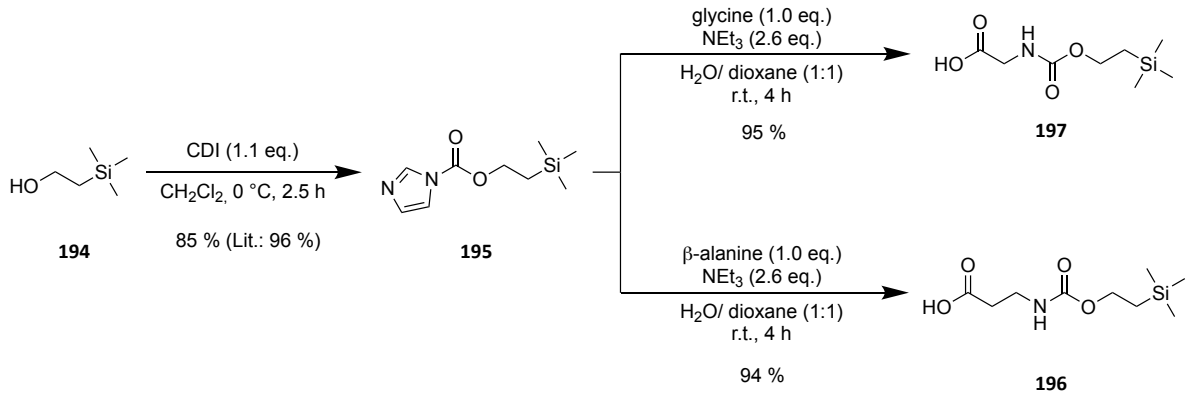
As the Boc- and Fmoc-protecting groups both did not give access to the free amine, the Teoc-protecting group (2-(Trimethylsilyl)ethoxycarbonyl-protecting group) was tested as a fluoride-labile alternative. Deprotection during the basic column chromatography and decomposition of the ester through acidic reaction conditions could thus be avoided.



194 **195** **196**

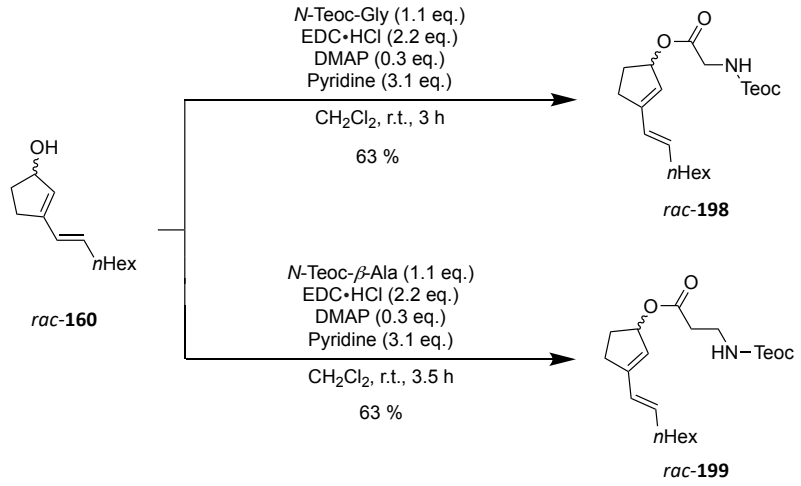
Scheme 38 – Teoc protection of β-alanine by in situ formation of the protection compound ***195****.*

The first attempt to obtain the Teoc-protected amino acids was the reaction of 2-(Trimethylsilyl)-ethanol (**194**) with CDI to form the protection reagent **195** *in situ*, followed by addition of β-Ala to the reaction mixture to form *N*-Teoc-β-alanine (**196**, scheme 41). Monitoring of the reaction process via TLC showed full conversion of the TMS-Ethanol **194**, but the subsequent reaction with β-alanine only gave a low yield of 15 %, despite the addition of NEt_3 and the long reaction time of 4 d.



*Scheme 39 - Preparation of the Teoc-protecting reagent **195** and subsequent Teoc-protection of glycine (**217**) and β-alanine (**218**), following a procedure from Economou et al. [80] for the first step, and by following an modified procedure by Shute and Rich[81] for the protection steps.*

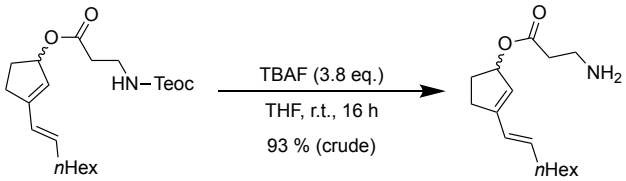
As the *in situ* protection of β-alanine only lead to a poor yield, a stepwise Teoc-protection was performed (scheme 42), adapted from *Economou et al*.[80] for the synthesis of protecting reagent **195** and modified from *Shute and Rich[81]* for the protecting reactions. The reaction of TMS-Ethanol **194** with CDI lead to the Teoc-protecting agent **195** in a yield of 85 %. *N*-Teoc-glycine (**197**, 95 %) and N-Teoc-β-alanine (**196**, 97 %) could be obtained in high yields through the ensuing protecting reactions.



*Scheme 40 - Steglich-esterifications of N-Teoc-glycine (**197**) and N-Teoc-β-alanine (**198**) with dienylic alcohol rac-**160**.*

With the Teoc-protected amino acids amenable, both dienylic esters *rac*-**198** and *rac*-**199** could be synthesized by the *Steglich*-esterification of dienylic alcohol *rac*-**160** with the corresponding Teoc-protected amino acids **196** and **197** (scheme 43). The crude products could successfully be purified by basic flash column chromatography. *N*-Teoc-Gly-ester *rac*-**198** and *N*-β-Ala-ester *rac*-**199** were both obtained in a yield of 63 %.

However, the moderate yield and the occurrence of fractions with starting material *rac*-**160** indicate that no full conversion took place, even though monitoring of the reaction process via 2D-NMR-spectroscopy always implied full conversion of the starting material after 1 h. Thus, either longer reaction times are needed to convert the residual starting material, as seen in literature[76b, 76c, 82], or a part of the desired ester is cleaved during the basic extraction of the crude product. If the latter is the case, extraction with only water and brine could lead to higher yields for this reaction, as generally done for *Steglich*-esterifications of other systems.[75] Furthermore, the work up method for *Steglich*-esterifications does usually not involve the extraction with saturated aqueous $NaHCO_3$-solution[76, 82], making this extraction step thus avoidable.



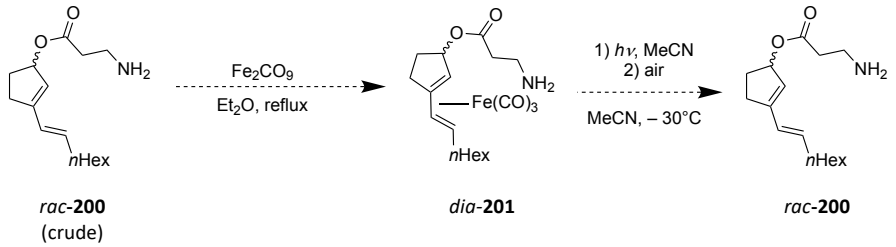
rac-**199** *rac*-**200**

*Scheme 41 - Teoc-deprotection of dienylic ester rac-**199** with TBAF to the free amine rac-**200**.*

The free amine *rac*-**200** was prepared by the deprotection of dienylic ester *rac*-**199** using tetrabutylammonium fluoride (TBAF, scheme 44). The crude product contained larger amounts of TBAF, which could not be removed through the extraction of the reaction mixture. Flash column chromatography on silica (regular and ultrapure) under basic conditions lead to decomposition of the amine *rac*-**200** but showed that TBAF was not able to pass through the column. Therefore, a short filtration of the crude product through a pad of silica was attempted, which lead to the separation of TBAF from the crude product, but also to decomposition of the amine. An acid-base-extraction was essayed, but the amine decomposed during the extraction with 1 M hydrochloric acid, as well as with 0.1 M hydrochloric acid. Lastly, recrystallization of *rac*-**200** as the corresponding hydrochloride was attempted. 1.0 equivalent of HCl in dioxane was added to a solution of the crude product in diethyl ether. The solution turned slightly cloudy, but no precipitation took place when the solution was cooled in the freezer. This work up method was therefore not investigated further.

An access to the pure amine *rac*-**200** could thus not be found and the following testing of the *imino-Diels-Alder*-reaction was performed with the crude product.

One last alternative approach could be the formation of a η^4-dienyl-tricarbonyliron(0) complex, as done for comparable systems by *Romanski et al.*[83] The *s-cis*-diene moiety of amine *rac*-**200** could potentially form a stable 18-electron-complex with the Fe(0)-center, which might allow purification via column chromatography, and subsequent demetallation, adapted from *Knöler et al.*[84], to obtain the pure amine *rac*-**200** (scheme 45).



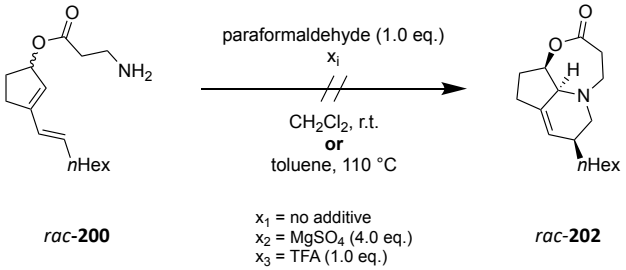
*Scheme 42 -Conceivable reaction sequence for the purification of amine rac-**201** via complexation of the diene system.*[83-84]

The viability of this route is strongly dependent on the decomposition mechanism of the amine on silica. If the diene system is involved in this progress, one can expect this method to work, as the diene system will not be available for those reactions anymore in complex *dia*-**201**. If decomposition takes place on the side chain, for example by elimination of ammonia, then this strategy will probably be of no use. It is also questionable if complex *dia*-**201** will be less reactive towards dissociation of the allylic C-O-sigma bond (see scheme 35), as the p-Orbital will be less available to negative hyperconjugation with the σ^*_{C-O}-bond on the one hand; but on the other hand, the diene system might stabilize the resulting carbocation even more, due to the π-backbonding from the Fe-center to the cationic dienyl ligand. The latter is similar to the reactions investigated by *Tsuji*[85] and *Trost*[86] and have already been utilized by *Noyori*[87] and *El-Wareth*[88] in [4+3]-cycloaddition reactions. Albeit this purification method is also rather less promising, it is still worth examination, considering that every other method for purification has failed yet.

4.6 Testing of the *imino-Diels-Alder*-reaction

To investigate the intramolecular *imino-Diels-Alder*-reaction with the crude amine *rac*-**200** as starting material, different additives and reaction conditions were tested (table 6).

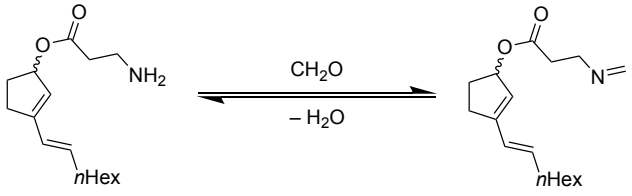
*Table 6 - Overview over the test reactions for the imino-Diels-Alder reaction of amine rac-**200**.*



rac-**200** *rac*-**202**

Entry	Additive	Solvent	Reaction conditions	Reaction time	Conversion
1	-	CH_2Cl_2	r.t.	22 h	Decomposition
2	-	toluene	110 °C, *Dean-Stark*-apparatus	3.5 h	Decomposition
3	$MgSO_4$ (4.0 eq.)	CH_2Cl_2	r.t.	22 h	Decomposition
4	TFA (1.0 eq.)	CH_2Cl_2	r.t.	4 h	Decomposition

For the cycloaddition to take place, the corresponding imine *rac*-**203** has to form through the reaction of the amine *rac*-**200** with (para-)formaldehyde under elimination of water (scheme 47).



rac-**200** *rac*-**203**

*Scheme 43 - Imine formation through the reaction of amine rac-**200** with formaldehyde.*

To shift this equilibrium to the side of the imine *rac*-**203**, water must be removed out of the reaction mixture. This was essayed by the addition of $MgSO_4$ to the reaction mixture on entry 3, and by using toluene as a solvent and heating the mixture to reflux under *Dean-Stark*-conditions[73] (entry 4).

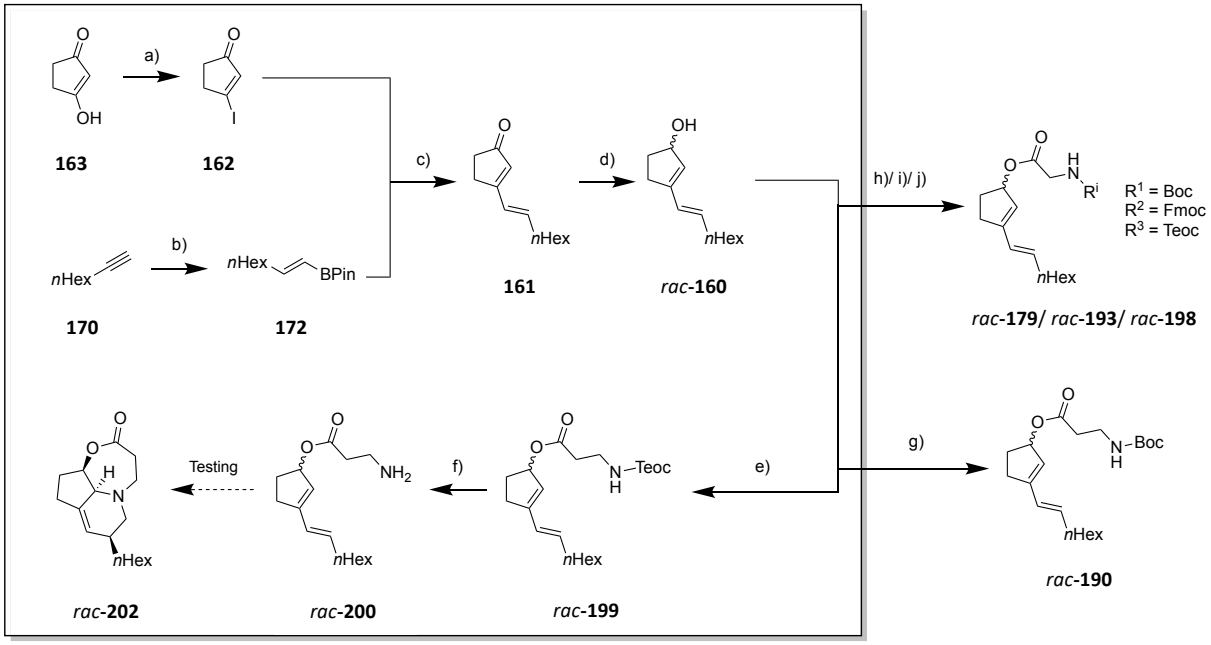
Furthermore, 1.0 equivalent of TFA was added on entry 3 to convert the imine *rac*-**203** into the corresponding iminium ion and therefore lowering the activation barrier of the cycloaddition by making the dienophile more electron deficient.

Entry 1 and entry 2 were both performed without additives and only the crude amine *rac*-**200** and paraformaldehyde were added to the respective solvent (entry 1: $CHCl_2$, entry 2: toluene). Entry 1 was stirred at room temperature, whereas entry 2 was heated to reflux in a *Dean-Stark*-apparatus. Both entries did not lead to the desired product, and the formed side products could not be characterized. Entry 3 used $MgSO_4$ as an additive in $CHCl_2$ at room temperature. Only uncharacterized side products were obtained instead of the desired cycloadduct *rac*-**202**. TFA was added on entry 4 in CH_2Cl_2 and a rapid change in color could be observed, which however was due to decomposition, as already expected. The side products were also not characterized.

Regarding the literature known intramolecular *imino-Diels-Alder*-reactions (see section 2.3.3), one has to assess the further optimization of these entries as less promising. As stated, intramolecular *imino-Diels-Alder*-reactions without the use of a *Lewis*/ *Brønstedt*-acid or an elimination/ cycloaddition reaction sequence are rather exceptional. A *Brønstedt*-acid was used in entry 4, but the labile framework makes this strategy impossible. Thus, different methods should be examined for further testing.

Density-functional-theroy-calculations (DFT-calculations)[89] with the functionals B3LYP, or BP86,[90] and by using the def2-TZVP-base[91] estimated an activation energy for the *imino-Diels-Alder*-reaction of imine *rac*-**203** of ΔE = 125± 25 kJ/mol, in unpublished work by *D. Weßling*.[92] Further calculations with different electron withdrawing groups, tether lengths or frameworks could thus provide valuable information, whether these changes will increase or decrease the activation barrier for the cycloaddition, and to which extend.

5 Summary and outlook

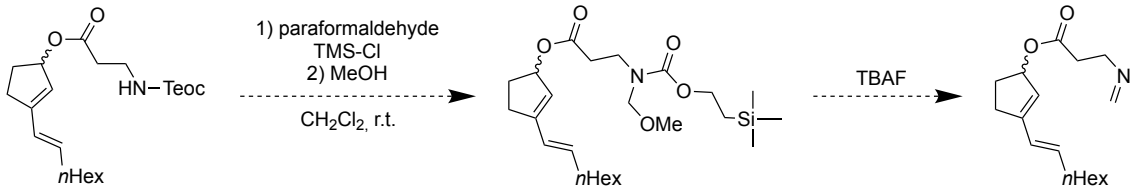


*Scheme 44 -Overview over the most important performed reactions: a) 1) PPh_3, I_2 2) **163**, NEt_3, MeCN, r.t.→90 °C, 87 %; b) HBPin, DIBAL-H, toluene, 110 °C, 55 %; c) $Pd(PPh_3)_4$, K_3PO_4•7 H_2O, H_2O/ dioxane (5:1), 60 °C, 81 %; d) DIBAL-H, CH_2Cl_2, -78°C, 85 %; e) N-Teoc-β-Ala, EDC•HCl, DMAP, pyridine, CH_2Cl_2, r.t., 63 %; f) TBAF, tetrahydrofuran (THF), r.t., 93 % (crude); g) N-Boc-β-Ala, EDC•HCl, DMAP, pyridine, CH_2Cl_2, r.t., 8 %; h) N-Boc-Gly, EDC•HCl, DMAP, pyridine, CH_2Cl_2, r.t., 51 %; i) N-Fmoc-Gly, EDC•HCl, DMAP, pyridine, CH_2Cl_2, r.t., 99 % (crude); j) N-Teoc-Gly, EDC•HCl, DMAP, pyridine, CH_2Cl_2, r.t., 63 %.*

The dienylic alcohol *rac*-**160** was synthesized on a big scale, to enable testing of the *Steglich*-esterification of the differently *N*-protected amino acids Gly and β-Ala. Every thus prepared ester showed great lability towards *Lewis*- and *Brønstedt*-acids. Therefore, the Boc-protected dienylic esters *rac*-**179** and *rac*-**190** could be synthesized, but the reaction of *rac*-**179** with HCl in dioxane lead to decomposition. The Fmoc-protected ester *rac*-**193** could not be purified, and subsequent deprotection with piperidine was not successful. *N*-Teoc-Gly **197** and *N*-Teoc-β-Ala **196** were synthesized, from which the respective dienylic esters *rac*-**198** and *rac*-**199** could be prepared. Deprotection of the *N*-Teoc-β-Ala ester *rac*-**199** with TBAF was possible, but the crude product could not be purified. The desired cycloadduct *rac*-**202** was not formed from the reaction of the crude amine *rac*-**200** with paraformaldehyde, different additives, and reaction conditions, but conversion to side products could be observed.

A key step for the *imino-Diels-Alder* reaction to succeed, is the full conversion of the free amine *rac*-**200** to the corresponding imine *rac*-**203**, which must be formed *in situ*. Reaction

monitoring via 2D-NMR-spectroscopy, as done by *Hedberg et al*.[49], is needed to investigate the best conditions for the imine formation. Once the imine is formed completely, and water is ideally removed from the system, the best conditions for the actual cycloaddition can be tested. Here, one can expect that high reaction temperatures are necessary, and/ or an electron withdrawing group needs to be in conjugation with the imine (see section 2.3.3).
Another problem could be that the imine does not form in the first place, in which case a reaction sequence via the conversion of *N*-Teoc-protected ester *rac*-**199** to a *N,N*-MOM-Teoc-carbamate, can be tested, adapted from *Barnes et al.*[93] (scheme 50).

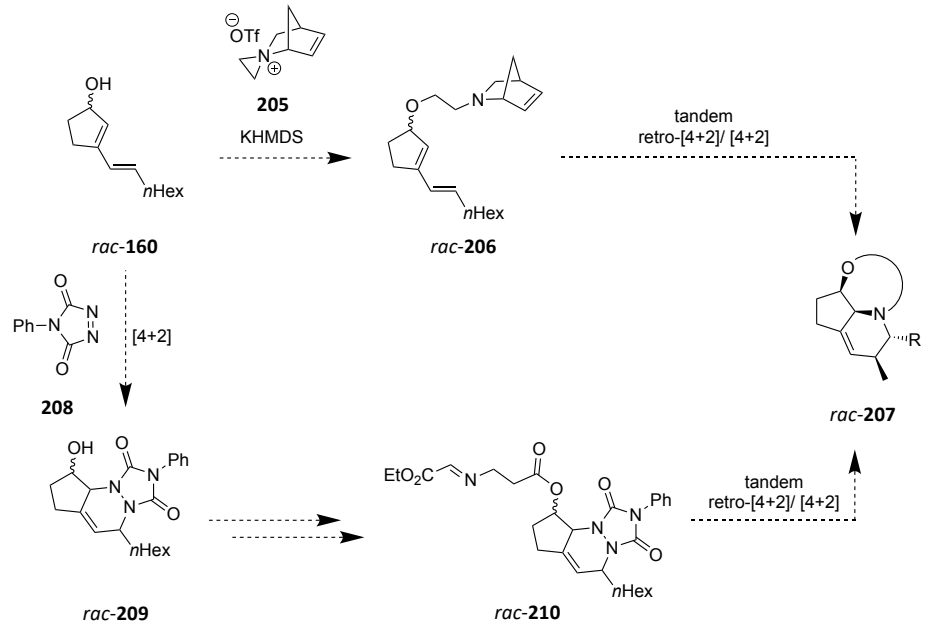


rac-**199** *rac*-**204** *rac*-**203**

*Scheme 45 - Synthesis of the Teoc-MOM-Carbamate rac-***204***, adapted from Barnes et al.[93], and conceivable imine formation by subsequent reaction with TBAF.*

The reaction with TBAF could lead to Teoc-deprotection and simultaneous elimination of methanolate, leading to the *in situ* formation of the desired imine (scheme 50). This sequence is especially useful if no access to the pure amine *rac*-**200** can be found.

Alternatively, as already shown in section 2.3.3, a tandem retro-[4+2]-cycloaddition/ *imino-Diels-Alder* reaction sequence could be tested in two different ways.



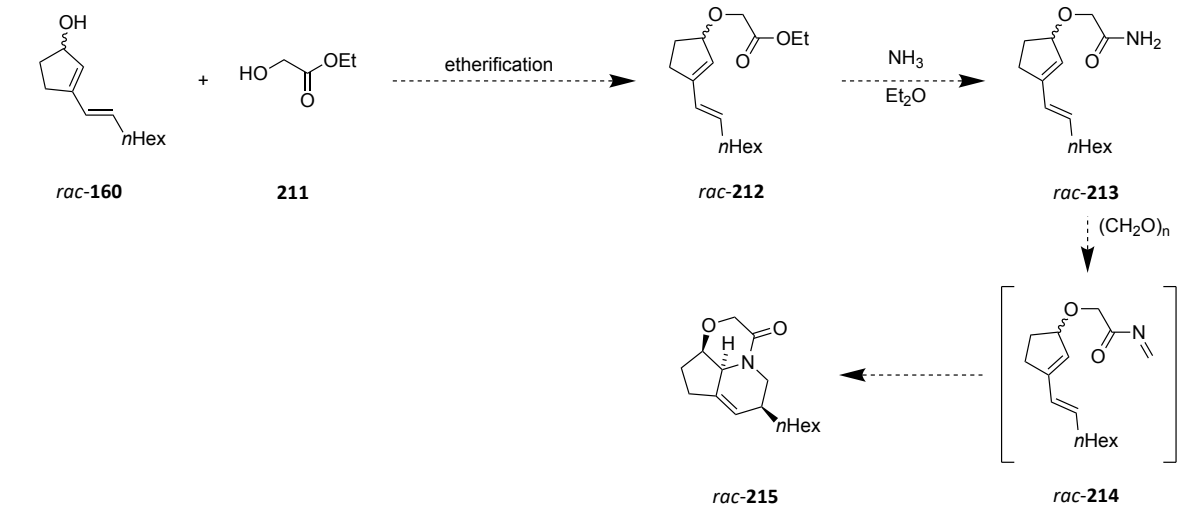
rac-**160** *rac*-**206** *rac*-**207**

rac-**209** *rac*-**210**

Scheme 46 - Conceivable routes for the execution of a tandem-Diels-Alder-reaction.

The path via tertiary amine *rac*-**206**, adapted from *Carrol* and *Grieco*[61], would be an alternative access to the dienophile; whereas the lower path, by *Barton et al.*[28] would probably increase the overall stability of the system, enabling different methods, that could be tested.

If the instability of the basic framework, due to the dienylic position of the ester, makes the pathways stated above impossible, etherification with ethyl glycolate (**211**) to the dienylic alcohol *rac*-**160** can be tested, lowering the stability of the leaving group in dienylic position (scheme 52).



Scheme 47 - Alternative approach for the synthesis of an amine for the imino-Diels-Alder-reaction by etherification.

The *Mitsonobu*-etherification with ethyl glycolate (**211**) is already known with good yields for similar systems.[94] Etherification can alternatively be achieved by using pentaflourophenylboronic acid and oxalic acid, as published by *Estopiñá-Durán et al.*[95]. Then, the corresponding amine *rac*-**213** could be obtained by the reaction with ammonia.[96] The stability of the framework is not only increased by this route, but the potentially formed imine *rac*-**214** is expected to be more reactive towards the diene than imine *rac*-**203** due to the –M-effect of the carbonyl moiety, making this pathway thus more promising than those stated above. Its tether-moiety is similar to the tether of tertiary amine *rac*-**206** (scheme 51); therefore, a combination of both methods is also plausible.

Thus, a variety of interesting strategies for the successful execution of the *imino-Diels-Alder*-reaction are amenable for further research.

6 Experimentals

6.1 General methods

Working under argon atmosphere

Prior to use, the reaction vessels were flame dried under an oil pump vacuum and flushed with argon (99.996 %) from *Linde* at a *Schlenk* apparatus. Liquids were added through a septum via plastic syringes or, for solvents, metal cannulas.

Reagents and solvents

Reagents and solvents were purchased with purities of ≥95 % from *Acros, Carbolution, Merck* or *Sigma-Aldrich.* Cyclohexane, dichloromethane, ethyl acetate and tetrahydrofuran were purchased in technical quality and freshly distilled before use.

Removal of solvents

Concentration of samples were performed at 40°C and under reduced pressure. For full removal of solvents, the sample was subsequently dried under an oil pump vacuum at a *Schlenk* apparatus at room temperature.

Column and thin-layer chromatography

Column chromatography was performed with silica gel 60 (0.035-0.070 mm) from *Acros Organics*. If possible and not stated differently, all reactions were monitored by TLC over silica-gel-coated aluminium sheets 60 F_{254} (0.20 mm silica gel, fluorescence indicator) from *Merck*. The plates were analyzed by visualization with UV-light (254 nm) and/ or staining using an aqueous $KMnO_4$- or vanillin-solution in ethanol.

Gas chromatography with a mass selective detector

GC-MS spectra were measured on an *Agilent* HP6890N with the mass detector 5937N and the measurement option 50-300MXtralong.

High-resolution mass spectroscopy (HR-MS)

High-resolution mass spectroscopy was carried out at a *Thermo Scientific LTQ Orbitrap XL* via electrospray ionization (ESI), if not stated differently.

Fourier transform infrared spectroscopy (FT-IR)

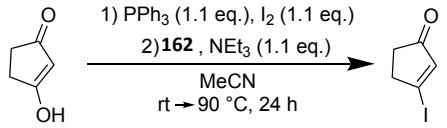
IR-spectra were measured on a *Perkin-Elmer* UATR Two FT-IR-Spectrometer at room temperature. The intensities of the bands were marked as “s” (strong), “m” (medium) or “w” (weak).

Nuclear-magnetic-resonance spectroscopy (NMR)

300 MHz NMR spectra were measured on a *Bruker Avance II 300* spectrometer, whereas 500 MHz spectra and high-field measurements were obtained on a *Bruker Avance III 500* spectrometer. $CDCl_3$ + 0.03 % Tetramethylsilan was used as a solvent for all NMR-analytics. ^{1}H-NMR-spectra were referenced to tetramethylsilan at 0.00 ppm, if no silicon was present in the measured compound. Otherwise, ^{1}H-NMR-spectra were referenced to $CDCl_3$ at 7.26 ppm. ^{13}C-NMR-spectra were referenced to $CDCl_3$ at 77.16 ppm. The multiplets in ^{1}H-NMR-spectra were labeled as “s” (singlets), “d” (doublets), “t” (triplets), “q” (quadruplets) or “m”, if the signals contained unclear splitting.

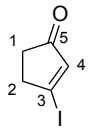
6.2 Experimental procedures

6.2.1 Synthesis of 3-Iodo-cyclopent-2-enone (161)



162 **161**

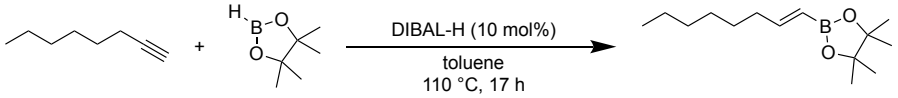
Following a literature known procedure[68], triphenylphosphine (28.9 g, 110 mmol, 1.1 eq.) and iodine (27.9 g, 110 mmol, 1.1 eq.) were dissolved in acetonitrile (1.0 L). After stirring at room temperature for 2 h, 1,3-cyclopentadinone (**162**, 9.80 g, 100 mmol, 1.0 eq.) and NEt_3 (15.5 mL, 11.2 g, 111 mmol, 1.1 eq.) were added and the mixture was first heated to 80 °C for 1 h and then stirred at room temperature for 17 h. The mixture was heated again at 90 °C for 45 min. The progress of the reaction was monitored via TLC (SiO_2, *c*Hex/EtOAc = 3:1). The solution was cooled to room temperature and concentrated under reduced pressure. The residue was dissolved in few DCM and diluted with diethyl ether until precipitation. The solid was filtered off and the solvent of the filtrate was removed under reduced pressure, yielding the crude product which was purified by flash column chromatography (SiO_2, *c*Hex/ EtOAc = 15:1) and the product **161** was obtained as pale yellow crystals in a yield of 87 % (18.0 g, 86.5 mmol, Lit.: 82 %).



Yield:	87 % (18.0 g, 86.5 mmol, Lit.[68]: 82 %).
Habitus:	Pale yellow crystals.
R_f:	0.39 (*c*Hex/ EtOAc = 3:1).
^{1}H-NMR:	(300 MHz, $CDCl_3$): δ [ppm] = 6.69 (t, ^4J = 1.9 Hz, 1H, H-4), 3.07 (dt, ^3J = 7.1 Hz, ^4J = 2.0 Hz, 2H, H-1), 2.52-2.47 (m, 2H, H-2).
^{13}C-NMR:	(126 MHz, $CDCl_3$): δ [ppm] = 205.3 (C-5), 197.6 (C-3), 143.7 (C-4), 41.8 (C-1), 37.6 (C-2).

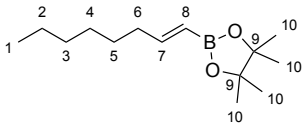
The analytical data is in accordance with reported literature[68].

6.2.2 Synthesis of (*E*)-Oct-1-enylboronic acid pinacol ester (**172**)



170 **171** **172**

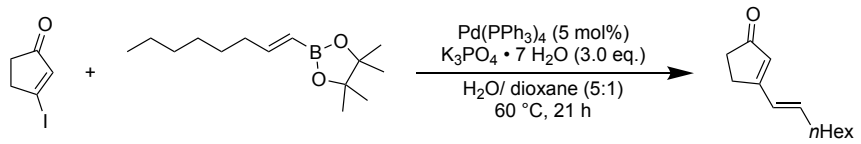
Following a literature known procedure[71], 1-octyne (**170**, 15.0 mL, 11.2 g, 102 mmol, 1.0 eq.), 1 M DIBAL-H in hexane (10.0 mL, 10.0 mmol, 10 mol%) and pinacolborane (17.5 mL, 120 mmol, 1.2 eq.) were dissolved in toluene (400 mL) under argon atmosphere and heated to 110°C for 17 h. The reaction was monitored via GC-MS. After full conversion of the starting material silica was added followed by further stirring at room temperature, the mixture was filtered through SiO_2, and the solvent was removed under reduced pressure. The crude product was purified by flash column chromatography (SiO_2, *c*Hex/ EtOAc = 49:1) and the boronate **172** was obtained as a colorless liquid in a yield of 55 % (13.1 g, 55.0 mmol, Lit.: 73 %).



Yield:	54 % (13.1 g, 55.0 mmol, Lit.[71]: 73 %).
Habitus:	Colorless liquid.
R_f:	0.71 (*c*Hex/ EtOAc = 2:1).
^{1}H-NMR:	(500 MHz, $CDCl_3$): δ [ppm] = 6.63 (dt, ^3J = 18.0 Hz, ^3J = 6.4 Hz, 1H, H-7), 5.42 (dt, ^3J = 17.9 Hz, ^4J = 1.6 Hz, 1H, H-8), 2.18-2.12 (m, 2H, H-6), 1.42-1.37 (m, 2H, H-5), 1.31-1.25 (m, 18H, H-2, H-3, H-4, H-10), 0.86 (t, ^3J = 7.0 Hz, 3H, H-1).
^{13}C-NMR:	(126 MHz, $CDCl_3$): δ [ppm] = 155.0 (C-7), 83.1 (C-9), 36.0 (C-6), 31.9 (C-5), 29.1 (C-4), 28.3 (C-3), 24.9 (C-10), 22.8 (C-2), 14.2 (C-1).

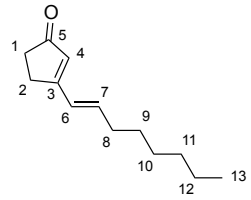
The analytical data is in accordance with reported literature[71].

6.2.3 Synthesis of 3-[(*E*)-Oct-1-enyl]-cyclopent-2-enon (**161**)



162 **172** **161**

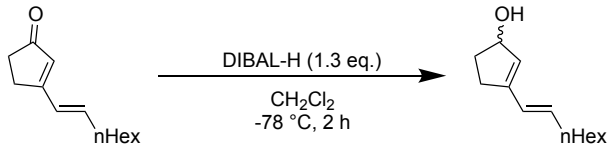
Following an unpublished procedure[72], 3-Iodo-cyclopent-2-enon (**162**, 8.66 g, 41.6 mmol, 1.0 eq.), boronic acid pinacol ester **172** (12.0 g, 50.4 mmol, 1.2 eq.), K_3PO_4 • 7 H_2O (42.3 g, 125 mmol, 3.0 eq.) and $Pd(PPh_3)_4$ (1.93 g, 1.67 mmol, 4 mol%) were dissolved in degassed H_2O/ dioxane (5:1, 110 mL) under an atmosphere of argon. The mixture was heated to 60 °C and the progress of the reaction was monitored by GC-MS. After 16 h, $Pd(PPh_3)_4$ (0.481 g, 0.416 mmol, 1 mol%) was added to the reaction mixture, followed by further stirring at 60°C for 5 h. The solution was filtered through celite, diluted with H_2O and extracted with EtOAc (3x). The combined organic phases were washed with brine (3x) and dried over $MgSO_4$. The solvent was removed under reduced pressure and the crude product was purified by flash column chromatography (SiO_2, *c*Hex/ EtOAc = 7:1). The final product **161** was obtained in a yield of 81 % as a colorless oil (6.50 g, 33.7 mmol, Lit.: 87 %).



Yield:	81 % (6.499 g, 33.7 mmol, Lit.[72]: 87 %).
Habitus:	Colorless oil.
R_f:	0.49 (*c*Hex/ EtOAc = 1:1).
^{1}H-NMR:	(500 MHz, $CDCl_3$): δ [ppm] = 6.53 (d, ^{3}J = 15.7 Hz, 1H, H-6), 6.33 (dt, ^3J = 15.7 Hz, ^3J = 7.0 Hz, 1H, H-7), 5.96 (s, 1H, H-4), 2.76-2.71 (m, 2H, H-1), 2.47-2.43 (m, 2H, H-2), 2.27-2.20 (m, 2H, H-8), 1.50-1.43 (m, 2H, H-9), 1.37-1.25 (m, 6H, H-10, H-11, H-12), 0.89 (t, ^3J = 7.0 Hz, 3H, H-13).
^{13}C-NMR:	(126 MHz, $CDCl_3$): δ [ppm] = 209.8 (C-5), 172.9 (C-3), 141.4 (C-7), 129.2 (C-4), 126.7 (C-6), 34.9 (C-2), 33.3 (C-8), 31.8 (C-10), 29.0 (C-11), 28.8 (C-9), 27.2 (C-1), 22.7 (C-12), 14.2 (C-13).

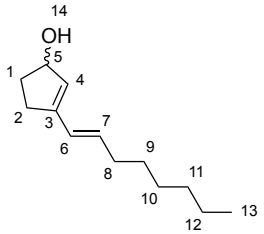
The analytical data is in accordance with unpublished literature[72].

6.2.4 Synthesis of *rac*-3-[(*E*)-Oct-1-enyl]-cyclopent-2-enol (*rac*-**160**)



161 *rac-**160***

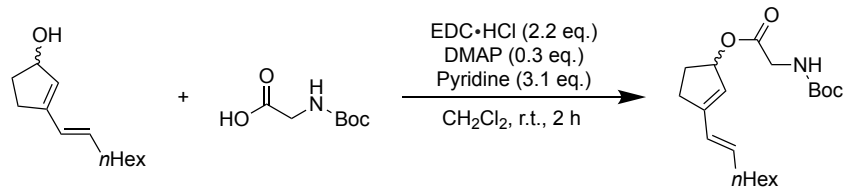
Following an unpublished procedure[72], cyclopentenon **161** (2.89 g, 15.0 mmol, 1.0 eq.) was dissolved in CH_2Cl_2 (75 mL), cooled to –78 °C and 1 M DIBAL-H in hexanes (19.0 mL, 19 mmol, 1.3 eq.) was slowly added. The mixture was stirred at –78 °C for 2 h and the progress of the reaction was monitored via GC-MS. After quenching with MeOH, the solution was warmed to room temperature and a saturated aqueous solution of NaK-tartrate was added, followed by stirring at room temperature for 45 min. H_2O was added and the aqueous phase was extracted with CH_2Cl_2 (5x). The joined organic phases were dried over $MgSO_4$ and the solvent was removed under reduced pressure. The crude product was purified by flash column chromatography (SiO_2, *c*Hex/ EtOAc = 9:1). The alcohol *rac*-**160** was obtained in a yield of 85 % as a slightly orange oil (2.49 g, 12.8 mmol, Lit.: 95 %).



Yield:	85 % (2.49 g, 12.8 mmol, Lit.[72]: 95 %).
Habitus:	Slightly orange oil.
R_f:	0.6 (*c*Hex/ EtOAc = 1:1).
^{1}H-NMR:	(500 MHz, $CDCl_3$): δ [ppm] = 6.25 (d, ^{3}J = 15.7 Hz, 1H, H-6), 5.75 (dt, ^3J = 15.6 Hz, ^3J = 7.0 Hz, 1H, H-7), 5.66 (d, ^3J = 2.1 Hz, 1H, H-4), 4.87 (s, 1H, H-5), 2.68-2.58 (m, 1H, H-2), 2.38-2.31 (m, 2H, H-1, H-2´), 2.14 (q, ^3J = 6.9 Hz, 2H, H-8), 1.82-1.73 (m, 1H, H-1'), 1.46-1.34 (m, 3H, H-9, H-14), 1.34-1.27 (m, 6H, H-10, H-11, H-12), 0.91 (t, ^3J = 7.0 Hz, 3H, H-13).
^{13}C-NMR:	(126 MHz, $CDCl_3$): δ [ppm] = 146.2 (C-3), 134.8 (C-7), 129.3 (C-4), 126.5 (C-6), 77.7 (C-5), 33.8 (C-1), 33.0 (C-8), 31.9 (C-10), 29.8 (C-11), 29.4 (C-9), 29.0 (C-1), 22.8(C-12), 14.2 (C-13).

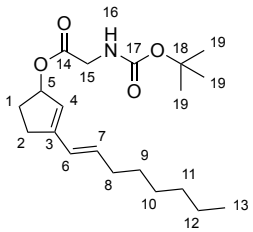
The analytical data is in accordance with unpublished literature[72].

6.2.5 Synthesis of *rac*-*N*-Boc-*O*-(3-(Oct-1-enyl)-cyclopent-2-enyl)-glycine (*rac*-**179**)



rac-***160*** **178** *rac*-**179**

Under an atmosphere of argon, EDC•HCl (218 mg, 1.14 mmol, 2.2 eq.), DMAP (19 mg, 0.156 mmol, 0.3 eq.), pyridine (0.13 mL, 0.13 g, 1.6 mmol, 3.1 eq.), dienylic alcohol *rac*-**160** (0.100 g, 0.516 mmol, 1.0 eq.) and *N*-Boc-glycine (**179**) (0.100 g, 0.571 mmol, 1.1 eq.) were dissolved in CH_2Cl_2 (5 mL) and stirred at room temperature for 2 h. The progress of the reaction was monitored by crude ^{1}H-NMR spectroscopy. The mixture was diluted with EtOAc and washed with saturated aqueous $NaHCO_3$ solution, water and brine. The organic phase was dried over $MgSO_4$, followed by removal of the solvent under reduced pressure. The crude product was purified by flash column chromatography (SiO_2, *c*Hex/EtOAc = 6:1, 3 % NEt_3) to yield the dienylic ester *rac*-**179** as a pale-yellow oil (103 mg, 0.293 mmol, 51 %).



Yield: 51 % (103 mg, 0.293 mmol).

Habitus: Pale-yellow oil.

R_f: 0.14 (SiO_2, *c*Hex/ EtOAc = 6:1, 3 % NEt_3, decomposition on TLC).

^{1}H-NMR: (500 MHz, $CDCl_3$): δ [ppm] = 6.26 (d, ^3J = 15.8 Hz, 1H, H-4), 5.81-5.73 (m, 2H, H-5, H-7), 5.61 (s, 1H, H-6), 4.99 (s, 1H, H-16), 3.92-3.77 (m, 2H, H-15), 2.66-2.56 (m, 1H, H-2), 2.44-2.31 (m, 2H, H-1, H-2´), 2.12 (q, ^3J = 6.9 Hz, 2H, H-8), 1.96-1.88 (m, 1H, H-1´), 1.45 (s, 9H, H-19), 1.43-1.36 (m, 2H, H-9), 1.32-1.26 (m, 6H, H-12, H-11, H-10), 0.88 (t, ^3J = 7.1 Hz, 3H, H-13).

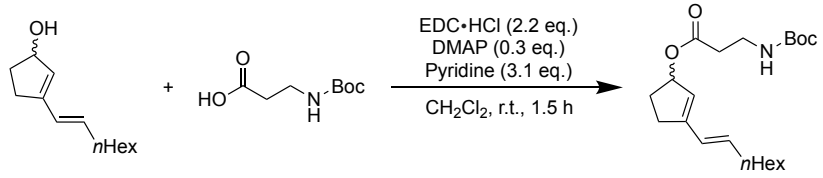
^{13}C-NMR: (126 MHz, $CDCl_3$): δ [ppm] = 170.3 (C-17), 155.7 (C-14), 149.0 (C-3), 135.9 (C-7), 126.1 and 125.9 (C-4*), 124.9 (C-6), 124.2 (C-7), 81.9 (C-5), 80.0 (C-18), 42.7 (C-15), 33.0 and 32.9 (C-8*), 31.8 and 31.7 (C-10*), 30.0 (C-1), 29.7 (C-2), 29.5 and 29.4 (C-9*), 29.1 (C-11), 28.3 (C-19*), 22.6 (C-12*), 14.1 (C-13).

HR-GC-MS: (m/z $[M\text{-}C_7H_{13}NO_3]^+$) = 193.15863 (calc. for $[C_{13}H_{21}O]^+$: m/z = 193.15924).

IR: $\tilde{\nu}$ [cm^{-1}]: 3364 (b), 2954 (m), 2930 (s), 2858 (m), 1718 (s), 1518 (m), 1454 (w), 1393 (m), 1368 (m), 1288 (w), 1252 (m), 1164 (s), 1055 (m), 1030 (w), 953 (w), 860 (w), 782 (w).

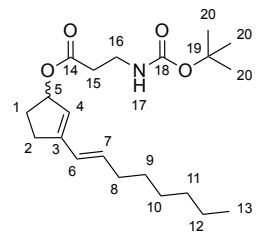
*Pair of signals due to rotamers

6.2.4 Synthesis of *rac*-*N*-Boc-*O*-(3-(Oct-1-enyl)-cyclopent-2-enyl)-β-alanine (*rac*-**190**)



rac-***160*** **189** *rac*-**190**

Under an atmosphere of argon, EDC•HCl (218 mg, 1.14 mmol, 2.2 eq.), DMAP (19 mg, 0.156 mmol, 0.3 eq.), pyridine (0.13 mL, 0.13 g, 1.6 mmol, 3.1 eq.), dienylic alcohol *rac*-**160** (99 mg, 0.510 mmol, 1.0 eq.) and *N*-Boc-β-alanine (**189**) (0.106 g, 0.571 mmol, 1.1 eq.) were dissolved in CH_2Cl_2 (5 mL) and stirred at room temperature for 1.5 h. The progress of the reaction was monitored via crude ^{1}H-NMR spectroscopy. The mixture was diluted with EtOAc and washed with saturated aqueous $NaHCO_3$ solution, water and brine. The organic phase was dried over $MgSO_4$, followed by removal of the solvent under reduced pressure. The crude product was purified by flash column chromatography (SiO_2, *c*Hex/EtOAc = 6:1, 1 % NEt_3), followed by another flash column chromatography (SiO_2, *c*Hex/EtOAc = 20:1, 1 % NEt_3) to yield the dienylic ester *rac*-**190** as a pale-yellow oil (16 mg, 0.042 mmol, 8 %).



Yield: 8 % (16 mg, 0.042 mmol).

Habitus: Pale-yellow oil.

R_f: 0.11 (SiO_2, *c*Hex/ EtOAc = 6:1, 1 % NEt_3, decomposition on TLC).

^{1}H-NMR: (500 MHz, $CDCl_3$): δ [ppm] = 6.26 (d, ^3J = 15.7 Hz, 1H, H-4), 5.81-5.69 (m, 2H, H-5, H-7), 5.62 (d, ^3J = 16.4 Hz, 1H, H-6), 5.03 (s, 1H, H-17), 3.44-3.32 (m, 2H, H-16), 2.64-2.58 (m, 1H, H-2'), 2.48 (t, ^3J = 6.1 Hz, 2H, H-15) 2.43-2.29 (m, 2H, H-1´, H-2´), 2.15-2.07 (m,

^{1}H-NMR: 2H, H-8), 1.92-1.86 (m, 1H, H-1´), 1.49-1.37 (m, 11H, H-9, H-20), 1.32-1.25 (m, 6H, H-10, H-11, H-12), 0.88 (t, ^{3}J = 7.1 Hz, 3H, H-13).

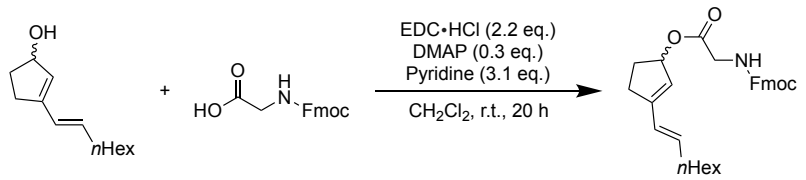
^{13}C-NMR: (126 MHz, $CDCl_3$): δ [ppm] = 172.6 (C-14), 155.9 (C-18), 148.7 (C-3), 135.8 and 134.8 (C-7*), 126.4 and 126.0 (C-4*), 124.7 (C-6), 81.1 (C-5), 79.4 (C-19), 36.2 (C-16), 34.9 (C-15), 33.8 (C-2) 33.0 (C-8), 31.8 (C-10), 29.9 and 29.8 (C-1*), 29.3 (C-20*) 29.0 (C-11), 28.5 (C-9), 22.7 (C-12), 14.2 (C-13).

HR-GC-MS: (m/z $[M\text{-}C_{16}H_{26}O_2]^+$) = 116.03426 (calc. for $[C_5H_{10}NO_2]^+$: m/z = 116.07115).

IR: $\tilde{\nu}$ [cm^{-1}]: 3457 (w), 3384 (b), 3025 (w), 2956 (m), 2955 (m), 1717 (s), 1605 (w), 1505 (m), 1456 (m), 1391 (w), 1366 (m), 1278 (m), 1248 (m), 1169 (s), 1064 (m), 1023 (m), 963 (s), 886 (w), 871 (w), 781 (w), 725 (w).

*Pair of signals due to rotamers

6.2.8 Synthesis of *rac*-*N*-Fmoc-*O*-(3-(Oct-1-enyl)-cyclopent-2-enyl)-glycine (*rac*-**193**)

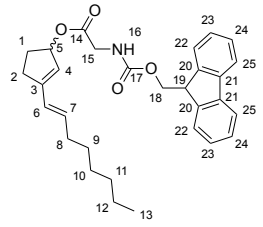


rac-***160*** **192** *rac*-**193**

Under an argon atmosphere, EDC•HCl (218 mg, 1.14 mmol, 2.2 eq.), DMAP (20 mg, 0.16 mmol, 0.3 eq.), pyridine (0.13 mL, 0.13 g, 1.6 mmol, 3.1 eq.), dienylic alcohol *rac*-**160** (99 mg, 0.510 mmol, 1.0 eq.) and *N*-Fmoc-glycine (**192**, 168 mg, 0.565 mmol, 1.1 eq.) were dissolved in CH_2Cl_2 (5 mL) and stirred at room temperature for 20 h. The progress of the reaction was monitored via ^{1}H-NMR spectroscopy. The mixture was diluted with EtOAc and washed with saturated aqueous $NaHCO_3$ solution, water and brine. The organic phase was dried over $MgSO_4$, followed by removal of the solvent under reduced pressure to yield the crude product, which was directly used in further experiments (239 mg, 0.505 mmol, 99 %).

Yield (crude): 99 % (239 mg, 0.505 mmol).

Habitus: Orange solid.



R_f: 0.14 (SiO_2, *c*Hex/ EtOAc = 6:1, decomposition on TLC).

^{1}H-NMR: (500 MHz, $CDCl_3$): δ [ppm] = 7.79 (d, ^3J = 7.5 Hz, 2H, H-22), 7.63 (d, ^3J = 7.5 Hz, 2H, H-25), 7.40 (t, ^3J = 7.4 Hz, 2H, H-23), 7.31 (td,

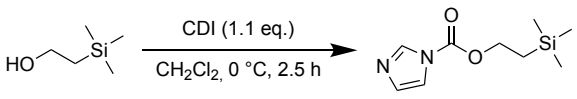
^{1}H-NMR: ^3J = 7.4 Hz, ^4J = 1.2 Hz, 2H, H-24), 6.25 (d, ^3J = 15.7 Hz, 1H, H-4), 5.84-5.73 (m, 2H, H-7, H-5), 5.61 (s, 1H, H-6), 5.28 (s, 1H, H-16), 4.42-4.34 (m, 2H, H-18), 4.27-4.19 (m, 1H, H-19), 3.98-3.87 (m, 2H, H-15), 2.65-2.58 (m, 1H, H-2), 2.44-2.29 (m, 2H, H-1, H-2´), 2.18-2.07 (m, 2H, H-8), 1.98-1.89 (m, 1H, H-1´), 1.43-1.36 (m, 2H, H-9), 1.35-1.21 (m, 6H, H-10, H-11, H-12), 0.92-0.79 (m, H-13).

^{13}C-NMR: (126 MHz, $CDCl_3$): δ [ppm] = 170.1 (C-14), 156.4 (C-17), 149.3 (C-3), 144.0 (C-20), 141.4 (C-21), 136.1 (C-7), 127.8 (C-23), 127.0 (C-24), 126.2 (C-4), 125.1 (C-25), 124.2 (C-6), 120.1 (C-22), 82.3 (C-5), 67.3 (C-18), 47.3 (C-19), 43.1 (C-15), 33.0 (C-8), 31.9 (C-10), 30.1 (C-1), 29.9 (C-2), 29.3 (C-9), 29.0 (C-11), 22.7 (C-12), 14.2 (C-13).

HR-GC-MS: (m/z $[M\text{-}C_{17}H_{26}NO_4]^+$) = 165.06953 (calc. for $[C_{13}H_9]^+$: m/z = 165.07043).

IR: $\tilde{\nu}$ [cm^{-1}]: 3413 (w), 3333 (w), 3065 (w), 3041 (w), 3015 (w), 2954 (m), 2927 (s), 2855 (m), 1715 (s), 1611 (w), 1524 (m), 1450 (s), 1407 (m), 1347 (m), 1245 (m), 1204 (s), 1104 (m), 1051 (s), 1007 (m), 966 (m), 876 (w), 759 (m), 740 (s), 621 (m), 539 (w), 427 (w).

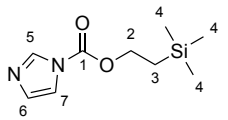
6.2.9 Synthesis of 1-[O-[2-(Trimethylsilyl)ethyl]-oxycarbonyl]imidazole (**195**)



194 **195**

Adapting a literature known procedure[80], CDI (1.66 g, 10.24 mmol, 1.1 eq.) was dissolved in CH_2Cl_2 (13.5 mL) under argon atmosphere and cooled to 0°C. 2-Trimethylsilylethanol (**194**, 1.14 g, 9.61 mmol, 1.0 eq.) was added and the mixture was stirred at 0 °C for 2.5 h. The progress of the reaction was monitored via TLC (SiO_2, *c*Hex/ EtOAc = 1:1). H_2O (6 mL) was added, followed by vigorous stirring at room temperature for 15 min. The two phases were separated, and the organic phase was washed with H_2O (3x) and brine (1x) and dried over

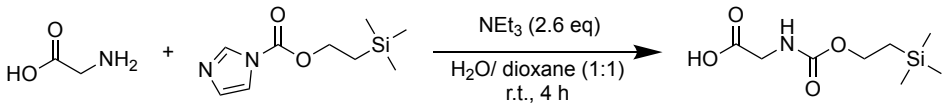
Na_2SO_4. The solvent was removed under reduced pressure to yield *O*-[2-(trimethylsilyl)ethyl)carbamate **195** as a white crystalline solid (1.73 g, 8.15 mmol, 85%, Lit.: 96%).



Yield:	85 % (1.73 g, 8.15 mmol, Lit.[80]: 96%).
Habitus:	White crystalline solid.
R_f:	0.81 (SiO_2, *c*Hex/ EtOAc = 1:1).
^{1}H-NMR:	(500 MHz, $CDCl_3$): δ [ppm] = 8.13 (s, 1H, H-5), 7.43-7.41 (m, 1H, H-6), 7.06 (dd, ^3J = 1.7 Hz, ^4J = 0.8 Hz, 1H, H-7), 4.53-4.48 (m, 2H, H-2), 1.21-1.14 (m, 2H, H-3), 0.09 (s, 9H, H-4).
^{13}C-NMR:	(126 MHz, $CDCl_3$): δ [ppm] = 148.9 (C-1), 137.2 (C-5), 130.7 (C-7), 117.2 (C-6), 67.3 (C-2), 17.7 (C-3), –1.4 (C-4).

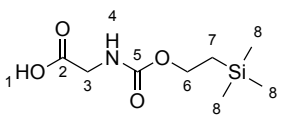
The analytical data is in accordance with reported literature[80].

6.2.10 Synthesis of *N*-Teoc-glycine (197)



217 **195** **197**

Modifying a known procedure[81], glycine (**219**, 242 mg, 3.22 mmol, 1.0 eq.) was dissolved in H_2O (3.2 mL) and a 2.6 M solution of NEt_3 in dioxane (3.2 mL, 840 mg, 8.3 mmol, 2.6 eq.) was added. *O*-[2-(trimethylsilyl)ethyl)carbamate **195** (747 mg, 3.52 mmol, 1.1 eq.) was added and the mixture was stirred at room temperature for 4 h. The progress of the reaction was monitored by TLC (SiO_2, *c*Hex/ EtOAc = 1:1). The solution was diluted with H_2O, acidified with saturated aqueous $KHSO_4$-solution and extracted with MTBE (3x). The joined organic phases were washed with H_2O (2x) and brine (1x), and dried over $MgSO_4$. The solvent was removed under reduced pressure to yield *N*-Teoc-glycine (**197**) as a colorless oil (672 mg, 3.06 mmol, 95%).



Yield:	95 % (1.730 g, 8.15 mmol).
Habitus:	Colorless oil.

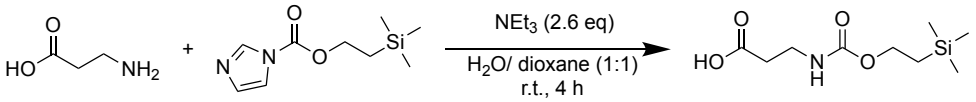
^{1}H-NMR: (500 MHz, $CDCl_3$): δ [ppm] = 9.50 (s, 1H, H-1), 7.03 and 5.29 (s, 1H, H-4*), 4.27-4.11 (2H, H-6), 4.01 (d, ^3J = 5.6 Hz, 2H, H-3), 1.03-0.95 (m, 2H, H-7), 0.03 (s, 9H, H-8).

^{13}C-NMR: (126 MHz, $CDCl_3$): δ [ppm] = 174.6 and 173.6 (C-2*), 157.1 (C-5), 64.8 and 64.0 (C-3*), 43.2 and 42.6 (C-6*), 17.8 (C-7), –1.4 (C-8).

*Pair of signals due to rotamers

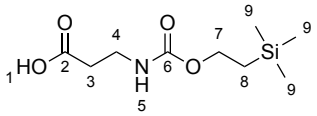
The analytical data is in accordance with reported literature[97].

6.2.11 Synthesis of *N*-Teoc-β-alanine (196)



218 **195** **196**

Modifying a known procedure[81], β-alanine (**220**, 287 mg, 3.22 mmol, 1.0 eq.) was dissolved in H_2O (3.2 mL) and a 2.6 M solution of NEt_3 in dioxane (3.2 mL, 840 mg, 8.3 mmol, 2.6 eq.) was added. *O*-[2-(trimethylsilyl)]ethyl)carbamate **195** (759 mg, 3.57 mmol, 1.1 eq.) was added and the mixture was stirred at room temperature for 4 h. The progress of the reaction was monitored by TLC (SiO_2, *c*Hex/ EtOAc = 1:1). The solution was diluted with H_2O, acidified with saturated aqueous $KHSO_4$-solution, and extracted with methyl *tert*-butylether (MTBE) (3x). The joined organic phases were washed with H_2O (2x) and brine (1x) and dried over $MgSO_4$. The solvent was removed under reduced pressure to yield *N*-Teoc-β-alanine (**196**) as a colorless oil (706 mg, 3.03 mmol, 94 %).



Yield: 94 % (1.730 g, 8.15 mmol).

Habitus: Colorless oil.

^{1}H-NMR: (500 MHz, $CDCl_3$): δ [ppm] = 10.41 (s, 1H, H-1), 6.42 and 5.24 (s, 1H, H-5*), 4.24-4.09 (m, 2H, H-7), 3.47-3.37 (m, 2H, H-4), 2.61-2.50 (m, 2H, H-3) 1.04-0.91 (m, 2H, H-8), 0.02 (s, 9H, H-9).

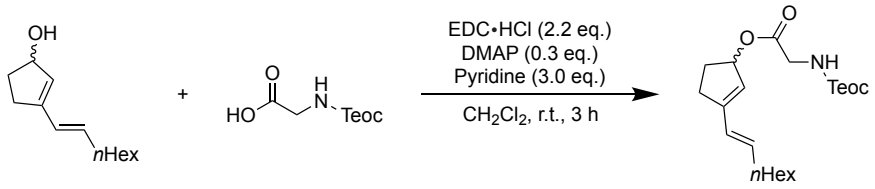
^{13}C-NMR: (126 MHz, $CDCl_3$): δ [ppm] = 177.5 (C-2), 157.0 (C-6), 63.4 (C-7), 36.3 (C-4), 34.4 (C-3) 17.8 (C-8), –1.4 (C-9).

HR-GC-MS: (m/z $[M\text{-}C_4H_6NO_3]^+$) = 117.03663 (calc. for $[C_5H_{13}OSi]^+$: m/z = 117.07357).

IR: $\tilde{\nu}$ [cm^{-1}]: 3456 (w), 3334 (w), 2954 (m), 2899 (w), 1707 (s), 1523 (m), 1478 (w), 1412 (m), 1340 (m), 1249 (s), 1178 (m), 1064 (m), 984 (w), 858 (s), 835 (s), 770 (m), 694 (m), 663 (w), 609 (w), 587 (w).

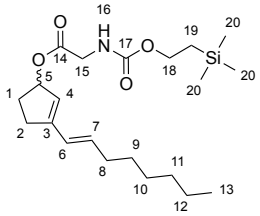
*Pair of signals due to rotamers

6.2.12 Synthesis of *rac*-*N*-Teoc-*O*-(3-(Oct-1-enyl)-cyclopent-2-enyl)-glycine (*rac*-198)



rac-***160*** **197** *rac*-**198**

Under an argon atmosphere, EDC•HCl (977 mg, 5.10 mmol, 2.2 eq.), DMAP (91 mg, 0.74 mmol, 0.3 eq.), pyridine (0.56 mL, 0.55 g, 6.95 mmol, 3.0 eq.), dienylic alcohol *rac*-**160** (444 mg, 2.29 mmol, 1.0 eq.) and *N*-Teoc-glycine (**197**, 548 mg, 2.50 mmol, 1.1 eq.) were dissolved in CH_2Cl_2 (23 mL) and stirred at room temperature for 3 h. The mixture was diluted with EtOAc and washed with saturated aqueous $NaHCO_3$ solution, water and brine. The organic phase was dried over $MgSO_4$, followed by removal of the solvent under reduced pressure. The crude product was purified by flash column chromatography (SiO_2, *c*Hex/EtOAc =9:1, 3 % NEt_3) to yield dienylic ester *rac*-**198** as a pale-yellow oil (574 mg, 1.45 mmol, 63 %).



Yield: 63 % (574 mg, 1.45 mmol).

Habitus: Pale-yellow oil.

R_f: 0.72 (SiO_2, *c*Hex/ EtOAc = 1:1, 3 % NEt_3, decomposition on TLC).

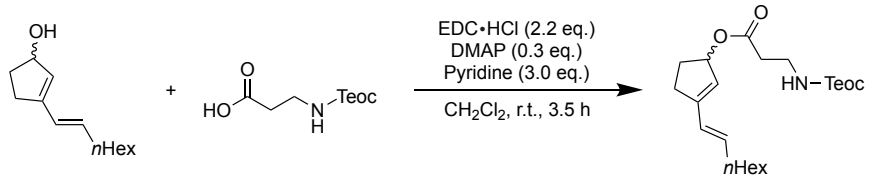
^{1}H-NMR: (500 MHz, $CDCl_3$): δ [ppm] = 6.26 (d, ^3J = 15.7 Hz, 1H, H-4), 5.82-5.73 (m, 2H, H-5, H-7), 5.61 (s, 1H, H-6), 5.08 (s, 1H, H-16), 4.17 (t, ^3J = 8.4 Hz, 2H, H-18), 3.91 (d, ^3J = 4.8 Hz, 2H, H-15), 2.66-2.57 (m, 1H, H-2), 2.44-2.30 (m, 2H, H-1, H-2´), 2.12 (q, ^3J = 7.2 Hz, 2H, H-8), 1.96-1.88 (m, 1H, H-1´), 1.43-1.36 (m, 2H, H-9), 1.32-1.23 (m, 6H, H-12, H-11, H-10), 1.02-0.96 (m, 2H, H-19), 0.88 (t, ^3J = 7.0 Hz, 3H, H-13), 0.03 (s, 9H, H-20).

^{13}C-NMR: (126 MHz, $CDCl_3$): δ [ppm] = 170.3 (C-14), 156.8 (C-17), 149.2 (C-3), 136.1 (C-7), 126.0 and 125.1 (C-4*), 124.3 (C-6), 82.2 (C-5), 64.0 and 63.7 (C-18*), 43.0 (C-15), 33.1 (C-8), 31.9 (C-10), 30.1 (C-2), 29.9 (C-1), 29.3 (C-9), 29.0 (C-11), 22.8 (C-12), 17.9 (C-19), 14.2 (C-13), –1.3 (C-20).

IR: $\tilde{\nu}$ [cm^{-1}]: 3364 (b), 3029 (w), 2954 (m), 2926 (m), 2954 (m), 2855 (w), 1723 (s), 1604 (w) 1517 (m), 1454 (w), 1381 (w), 1357 (m), 1249 (s), 1192 (s), 1160 (m), 1050 (m), 1023 (w), 964 (m), 859 (s), 835 (s), 769 (m), 694 (m), 608 (w), 486 (w).

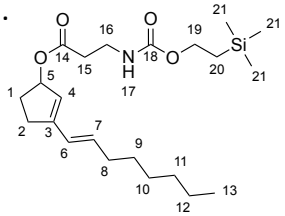
*Pair of signals due to rotamers

6.2.13 Synthesis of *rac*-*N*-Teoc-*O*-(3-(Oct-1-enyl)-cyclopent-2-enyl)-β-alanine (*rac*-**199**)



rac-***160*** **196** *rac*-**199**

Under an atmosphere of argon, EDC•HCl (986 mg, 5.14 mmol, 2.2 eq.), DMAP (90 mg, 0.74 mmol, 0.3 eq.), pyridine (0.57 mL, 0.56 g, 7.1 mmol, 3.0 eq.), dienylic alcohol *rac*-**160** (456 mg, 2.35 mmol, 1.0 eq.) and *N*-Teoc-β-alanine (**196**, 600 mg, 2.57 mmol, 1.1 eq.) were dissolved in CH_2Cl_2 (23 mL) and stirred at room temperature for 3.5 h. The progress of the reaction was monitored via ^{1}H-NMR spectroscopy. The mixture was diluted with EtOAc and washed with saturated aqueous $NaHCO_3$ solution, water and brine. The organic phase was dried over $MgSO_4$, followed by removal of the solvent under reduced pressure. The crude product was purified by flash column chromatography (SiO_2, *c*Hex/EtOAc = 6:1, 3 % NEt_3) to yield dienylic ester *rac*-**199** as a colorless oil (607 mg, 1.48 mmol, 63 %).



Yield: 63 % (607 mg, 1.48 mmol).

Habitus: Colorless oil.

R_f: 0.23 (SiO_2, *c*Hex/ EtOAc = 6:1, 3 % NEt_3, decomposition on TLC).

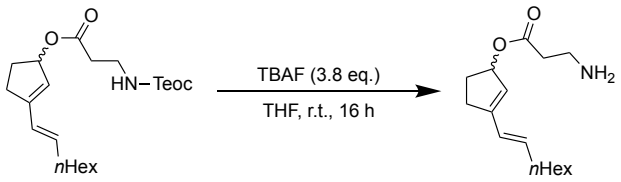
^{1}H-NMR: (500 MHz, $CDCl_3$): δ [ppm] = 6.26 (d, ^3J = 15.6 Hz, 1H, H-4), 5.77 (dt, ^3J = 15.6 Hz, ^3J = 7.0 Hz, 1H, H-7), 5.74-5.71 (m, 1H, H-5),

^{1}H-NMR: 5.61(s, 1H, H-6), 5.11 (s, 1H, H-17), 4.16-4.10 (m, 2H, H-19), 3.46-3.38 (m, 2H, H-16), 2.65-2.58 (m, 1H, H-2), 2.49 (t, ^{3}J = 6.0 Hz, 2H, H-15), 2.42-2.31 (m, 2H, H-1, H-2´), 2.12 (q, ^{3}J = 7.34 Hz, 2H, H-8), 1.91-1.85 (m, 1H, H-1´), 1.42-1.36 (m, 2H, H-9), 1.31-1.24 (m, 6H, H-12, H-11, H-10), 0.97 (t, ^{3}J = 8.5 Hz, 2H, H-20), 0.88 (t, ^{3}J = 7.1 Hz, 3H, H-13), 0.03 (s, 9H, H-21).

^{13}C-NMR: (126 MHz, $CDCl_3$): δ [ppm] = 172.8 (C-14), 157.0 (C-18), 149.0 (C-3), 136.0 (C-7), 126.3 (C-4), 124.9 (C-6), 81.4 (C-5), 63.4 (C-19), 36.8 (C-16), 35.1 (C-15), 33.3 (C-8), 32.1 (C-10), 30.4 (C-1), 30.1 (C-2), 29.5 (C-9), 29.3 (C-11), 23.0 (C-12), 18.1 (C-20), 14.5 (C-13), –1.1 (C-21).

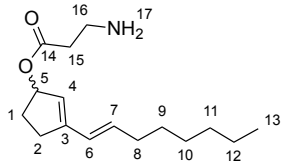
IR: $\tilde{\nu}$ [cm^{-1}]: 3451 (w), 3359 (b), 3056 (w), 3025 (w), 2954 (m), 2927 (m), 2856 (s), 1725 (s), 1513 (m), 1468 (w), 1454 (w), 1378 (w), 1358 (w), 1250 (s), 1181 (s), 1140 (m), 1062 (w), 1023 (w), 964 (m), 895 (w), 860 (m), 834 (m), 778 (w), 695 (w).

6.2.14 Synthesis of *O*-(3-(Oct-1-enyl)-cyclopent-2-enyl)-β-alanine (*rac*-200)



rac-**199** *rac*-**200**

Dienylic ester *rac*-**199** (53 mg, 0.13 mmol, 1.0 eq.) was dissolved in THF (0.6 mL) under an atmosphere of argon. 1 M TBAF in THF (0.50 mL, 0.50 mmol, 3.8 eq.) was added and the solution was stirred at room temperature for 16 h. The progress of the reaction was monitored by TLC (SiO_2, *c*Hex/ EtOAc = 1:1, 3 % NEt_3). The mixture was diluted with EtOAc, washed with saturated aqueous $NaHCO_3$-solution (3x) and the aqueous phase was extracted with EtOAc (3x). The combined organic phases were washed with brine (1x) and dried over $MgSO_4$. The solvent was removed under reduced pressure to yield the crude product as a dark brown oil, which was directly used in further experiments (32 mg, 0.12 mmol, 93%).



Yield (crude): 93 % (32 mg, 0.12 mmol).

Habitus: Dark brown oil.

R_f: 0.11 (SiO_2, *c*Hex/ EtOAc = 1:1, 3 % NEt_3, decomposition on TLC).

^{1}H-NMR: (500 MHz, $CDCl_3$): δ [ppm] = 6.25 (d, ^3J = 15.6 Hz, 1H, H-4), 5.79-5.66 (m, 2H, H-5, H-7), 5.60 (s, 1H, H-6), 2.95 (t, 2H, ^3J = 6.3 Hz, H-16), 2.67-2.55 (m, 1H, H-2), 2.42 (t, ^3J = 6.3 Hz, 2H, H-15), 2.39-2.26 (m, 2H, H-1, H-2´), 2.10 (q, ^3J = 6.0 Hz, 2H, H-8), 1.90-1.83 (m, 1H, H-1´), 1.40-1.34 (m, 2H, H-9), 1.30-1.22 (m, 6H, H-12, H-11, H-10), 0.86 (t, ^3J = 7.1 Hz, 3H, H-13).

^{13}C-NMR: (126 MHz, $CDCl_3$): δ [ppm] = 172.7 (C-14), 148.8 (C-3), 135.8 (C-7), 126.2 (C-4), 125.0 (C-6), 83.0 (C-5*), 41.6 (C-15), 39.9 (C-16), 33.1 and 33.0 (C-8*), 31.9 (C-10*), 29.9 (C-2), 29.8 (C-1), 29.4 (C-9*), 29.1 and 29.0 (C-11*), 22.8 and 22.7 (C-12*), 14.3 and 14.2 (C-13*).

ESI-HR-MS: (m/z $[M+H]^+$) = 266.21179 (calc. for $C_{16}H_{27}NO_2$: m/z = 266.21146).

IR: $\tilde{\nu}$ [cm^{-1}]: 3378 (b), 2957 (m), 2925 (s), 2871 (m), 2855 (m), 1726 (s), 1650 (m), 1572 (m), 1457 (m), 1378 (m), 1355 (s), 1206 (s), 1181 (s), 1159 (s), 1066 (m), 1024 (s), 963 (s), 891 (m), 800 (s), 725 (m), 662 (s), 592 (m), 471 (m).

*Pair of signals due to rotamers

7 Appendix

7.1 List of abbreviations

β-Ala	β-Alanine
4 Å MS	4 Å Molecular sieve
Ac_2O	Acetic anhydride
AcCl	Acetyl chloride
BINOL	1,1'-Bi-2-naphtol
Boc	*tert*-Butyloxycarbonyl
BTMSA	Bis-(trimethylsilyl)acetylene
CDI	Carbonyldiimidazole
CHP	Cumolhydroperoxide
coe	Cyclooctene
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DEAD	Diethyl azodicarboxylate
DFT	Density functional theory
DIBAL-H	Diisobutylaluminium hydride
DIPEA	*N,N*-Diisopropylethylamine
DMAP	*N*,*N*-Dimethylaminopyridine
DMF	Dimethylformamide
DMP	*Dess-Martin* periodinane
DMSO	Dimethylsulfoxide
dppp	1,3-Bis(diphenylphosphino)propane
EDC	1-Ethyl-3-(3-dimethylaminopropyl)-carbodiimide
EI-MS	Electron ionization mass spectrometry
ESI-MS	Electrospray ionization mass spectrometry
FGI	Functional group interconversion
FMO	Frontier molecular orbital
Fmoc	Fluorenylmethyloxycarbonyl
FT-IR	Fourier transform infrared spectroscopy

List of abbreviations

GC-MS	Gas chromatography mass spectrometry
Gly	Glycine
HOMO	Highest occupied molecular orbital
HR-MS	High resolution mass spectrometry
HWE	*Horner-Wadsworth-Emmons*
KHMDS	Potassium hexamethyldisilazide
LSD	Lysergic acid dimethylamide
LUMO	Lowest unoccupied molecular orbital
MeCN	Acetonitrile
MTBE	Methyl *tert*-butylether
NMR	Nuclear magnetic resonance
r.t.	Room temperature
TBAF	Tetrabutylammoniumflouride
Teoc	2-(Trimethylsilyl)ethoxycarbonyl
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
TLC	Thin layer chromatography

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7.3 NMR spectra

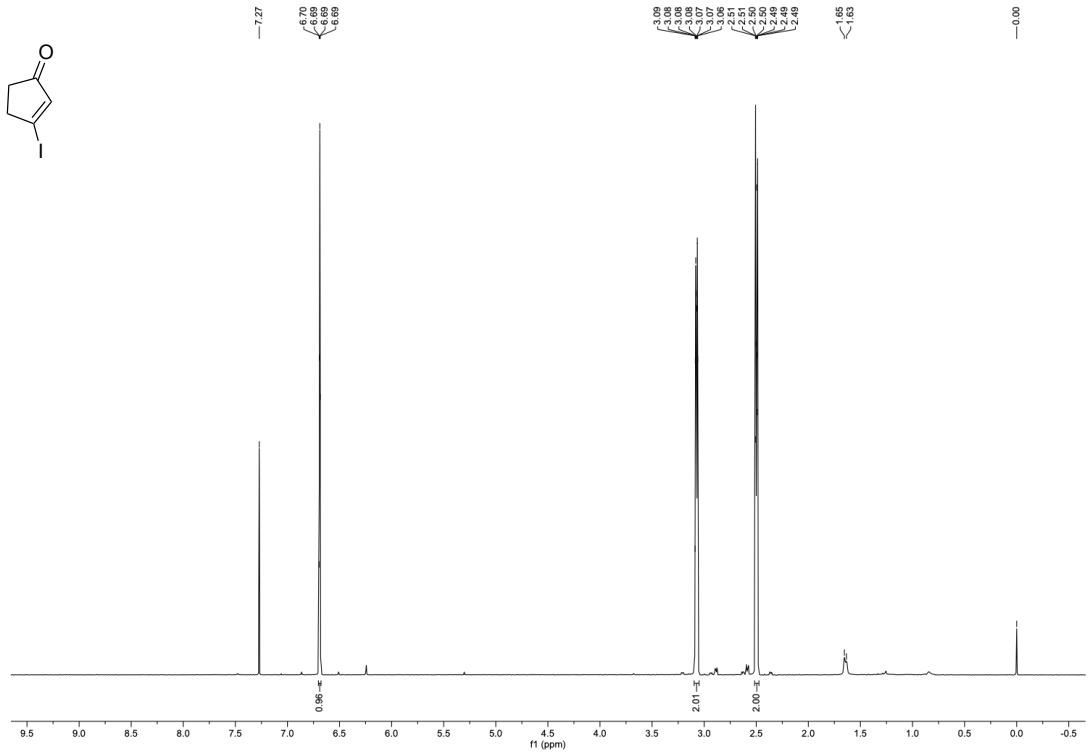

*Figure 3 – ^{1}H-NMR (300 MHz, $CDCl_3$) of 3-Iodo-cyclopent-2-enone (**162**).*

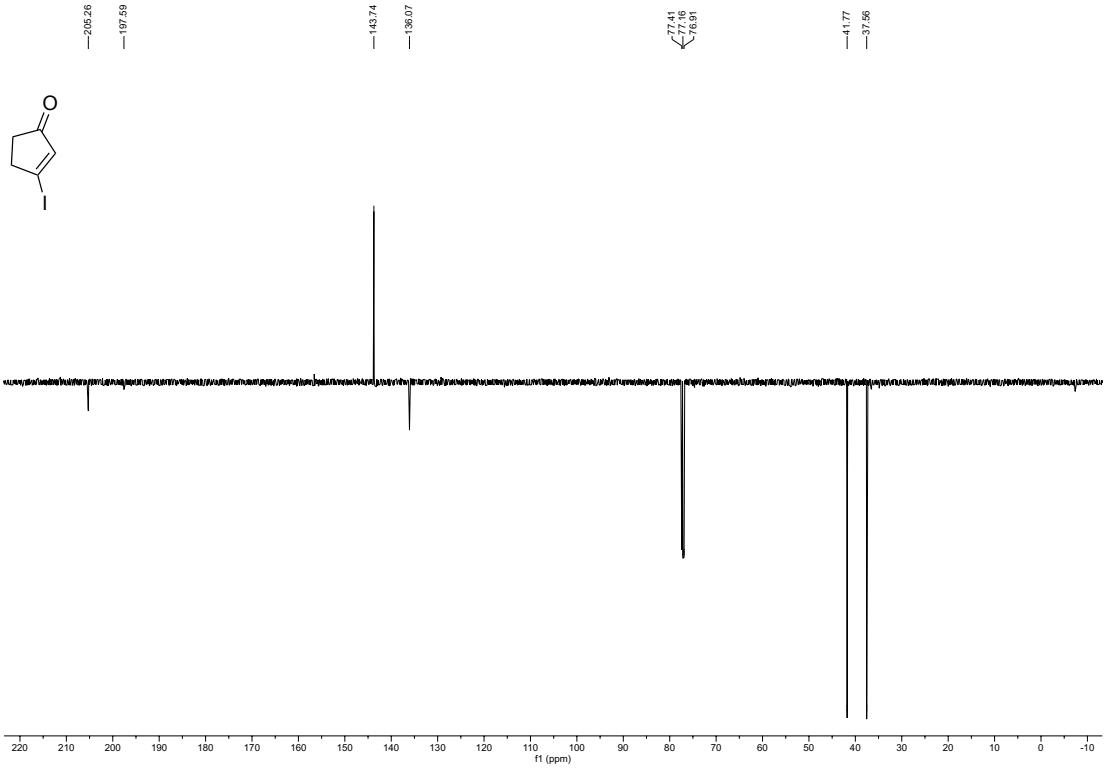

*Figure 4 – ^{13}C-NMR (126 MHz, $CDCl_3$) of 3-Iodo-cyclopent-2-enone (**162**).*

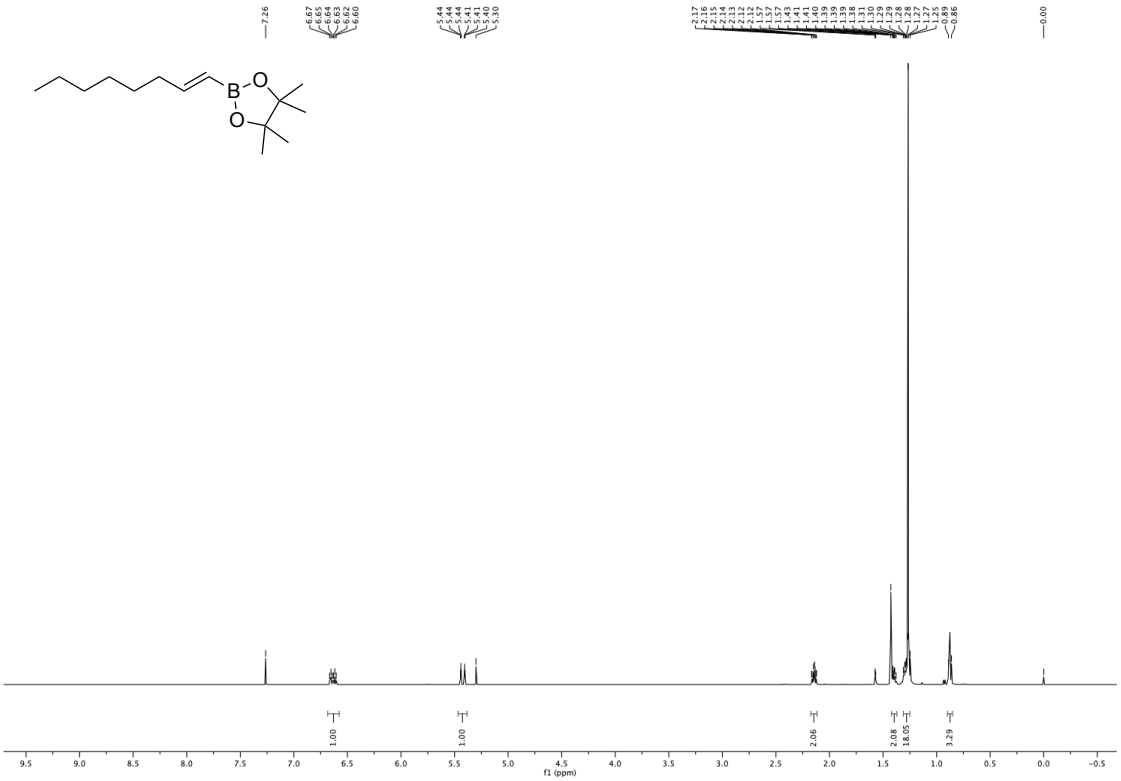

*Figure 5 - 1H-NMR (500 MHz, CDCl3) of E-Oct-1-enylboronic acid pinacol ester (**172**).*

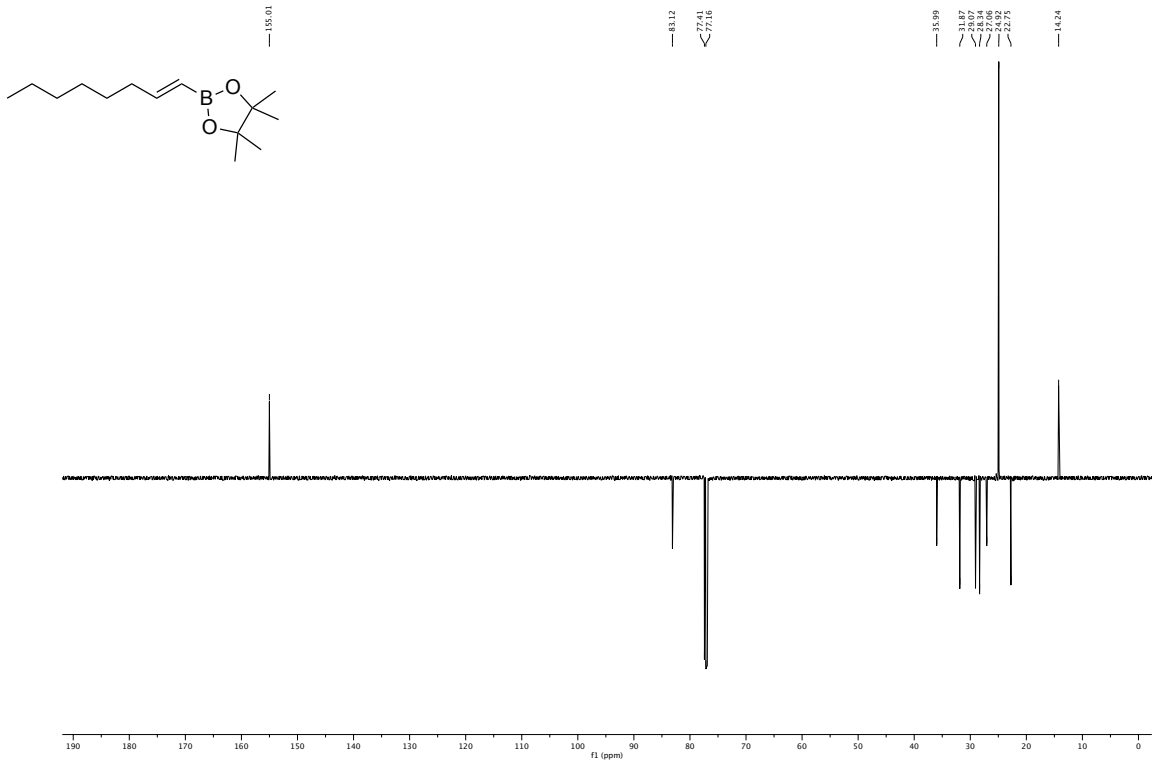

*Figure 6 - 13C-NMR (126 MHz, CDCl3) of E-Oct-1-enylboronic acid pinacol ester (**172**).*

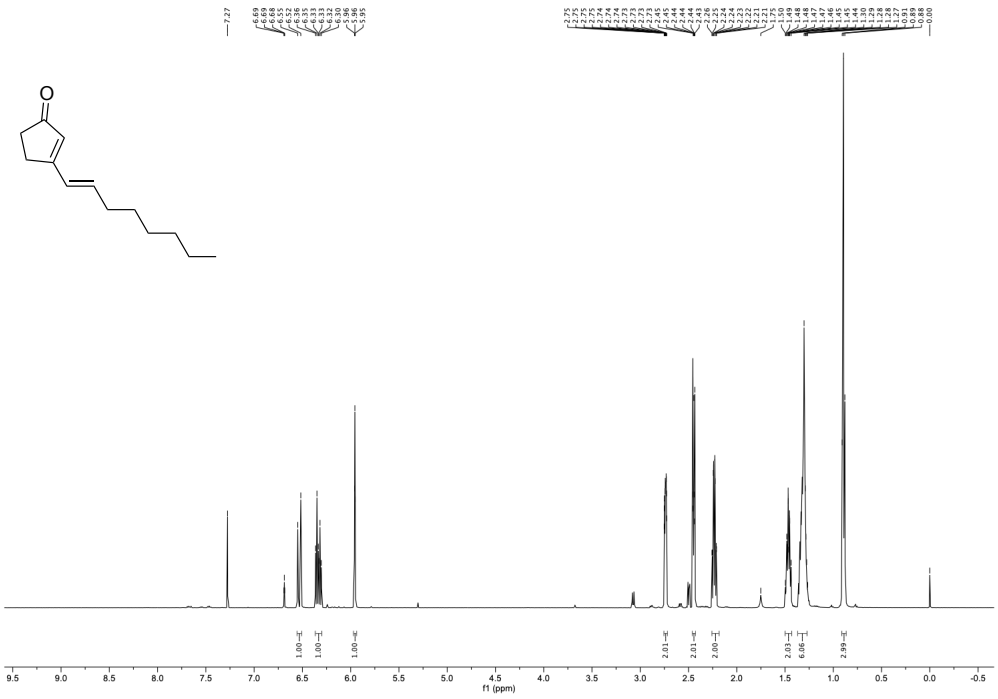

*Figure 7 – ^{1}H-NMR (500 MHz, $CDCl_3$) of 3-[(E)-Oct-1-enyl]-cyclopent-2-enon (**161**).*

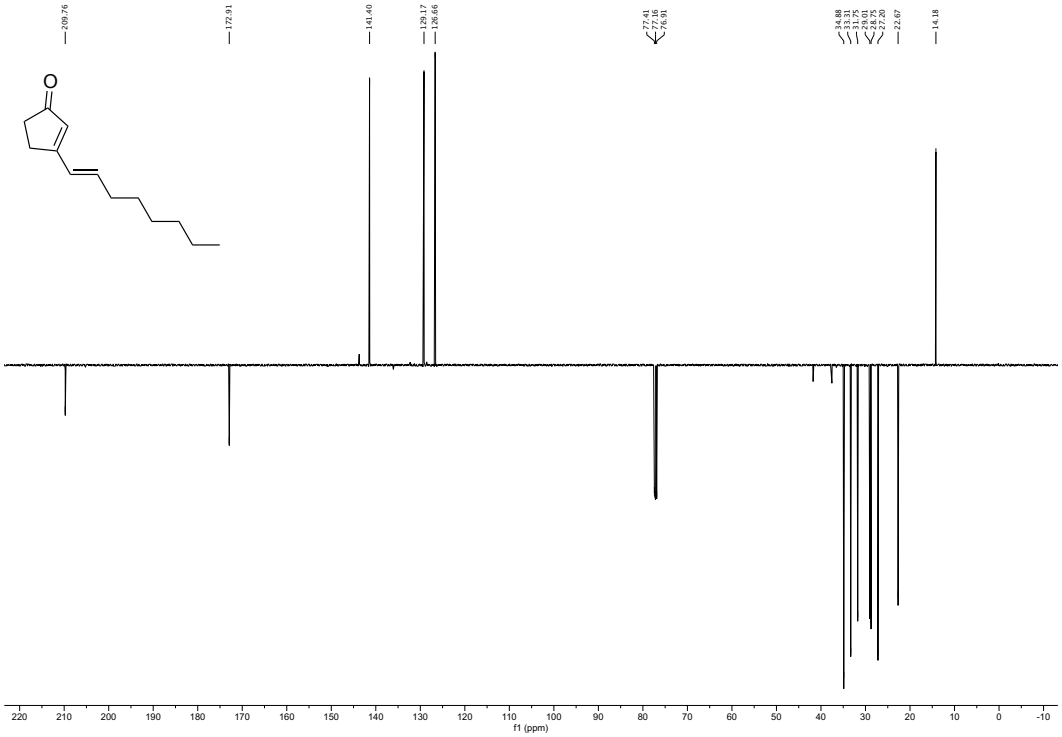

*Figure 8 – ^{13}C-NMR (126 MHz, $CDCl_3$) of 3-[(E)-Oct-1-enyl]-cyclopent-2-enon (**161**).*

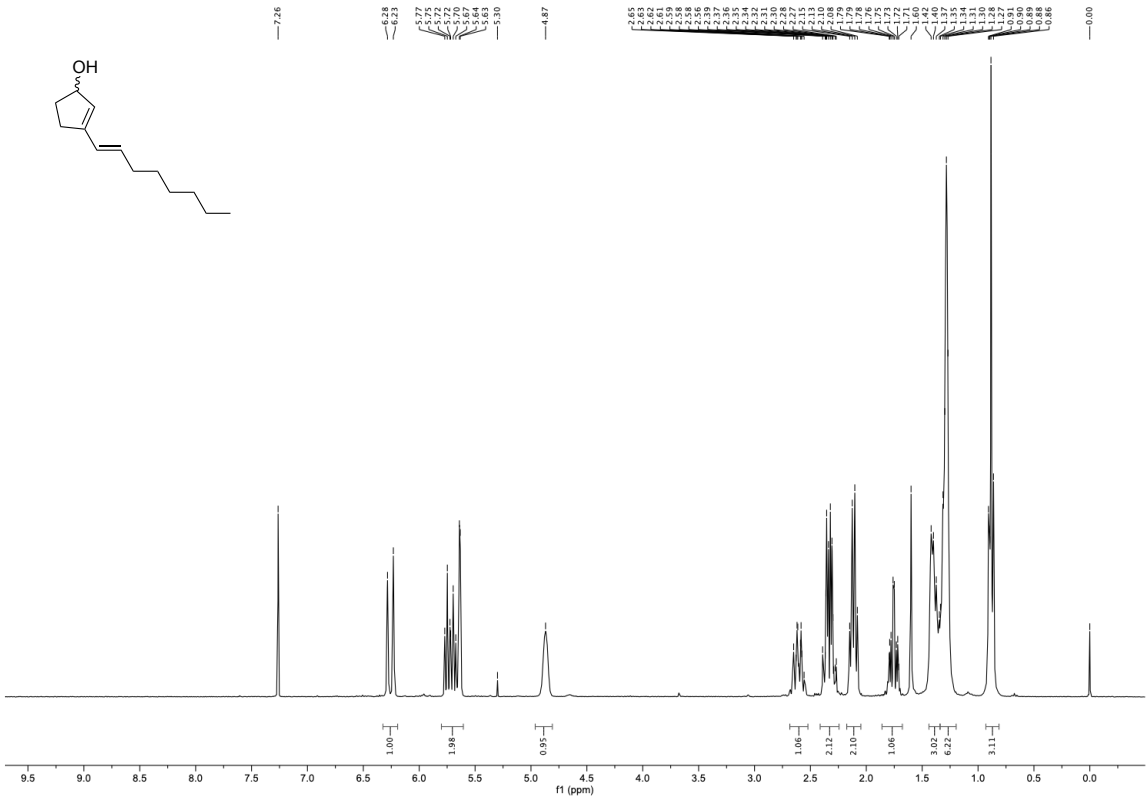

*Figure 9 – ^{1}H-NMR (500 MHz, $CDCl_3$) of rac-3-[(E)-Oct-1-enyl]-cyclopent-2-enol (rac-**160**).*

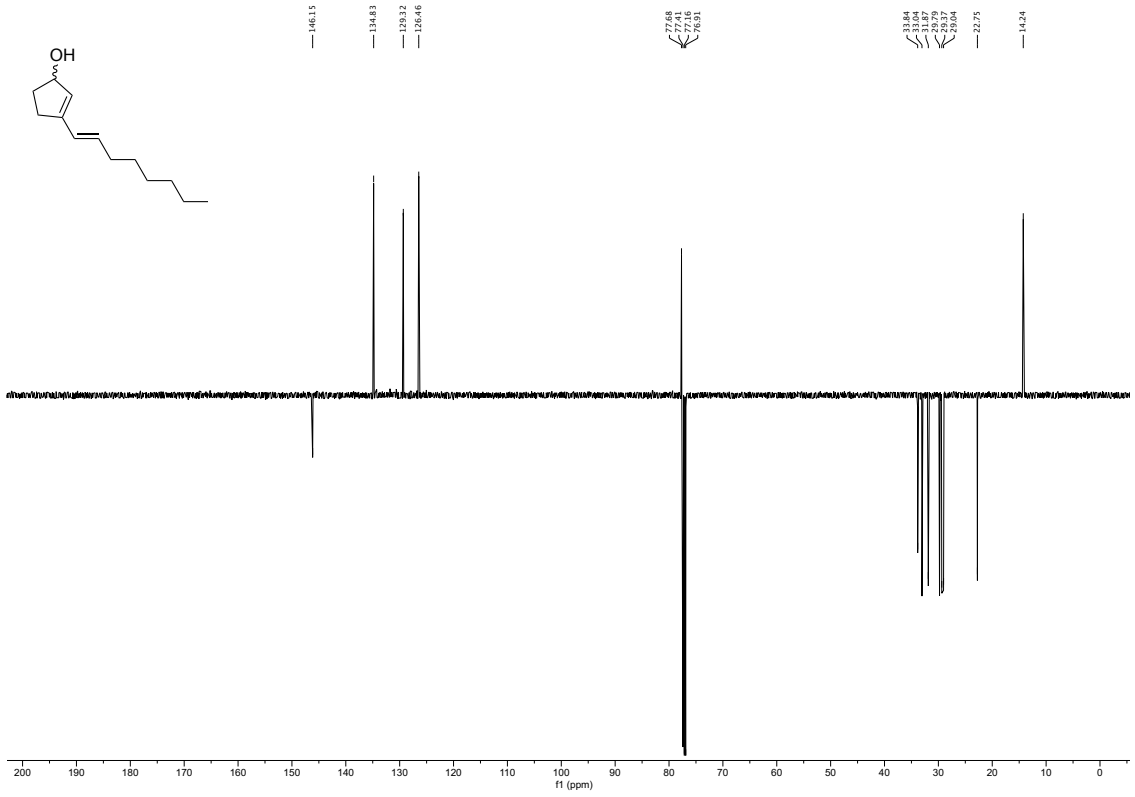

*Figure 10 – ^{13}C-NMR (126 MHz, $CDCl_3$) of rac-3-[(E)-Oct-1-enyl]-cyclopent-2-enol (rac-**160**).*

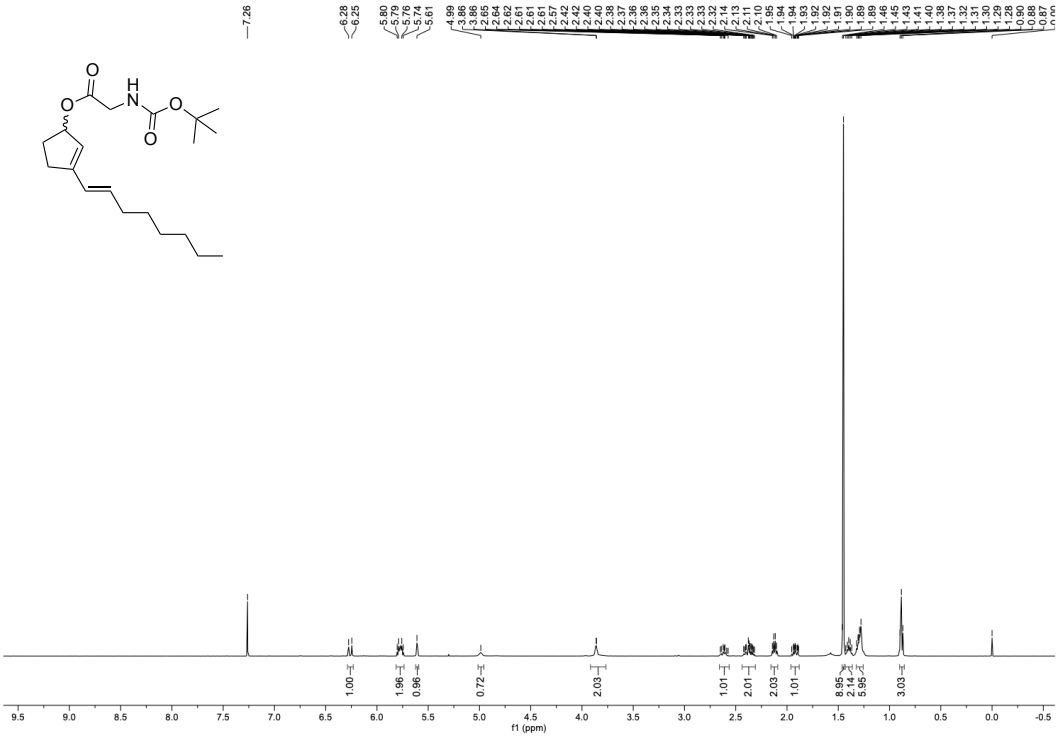

*Figure 11 – ^{1}H-NMR (500 MHz, $CDCl_3$) of N-Boc-O-(3-(Oct-1-enyl)-cyclopent-2-enyl)-glycine (rac-**179**).*

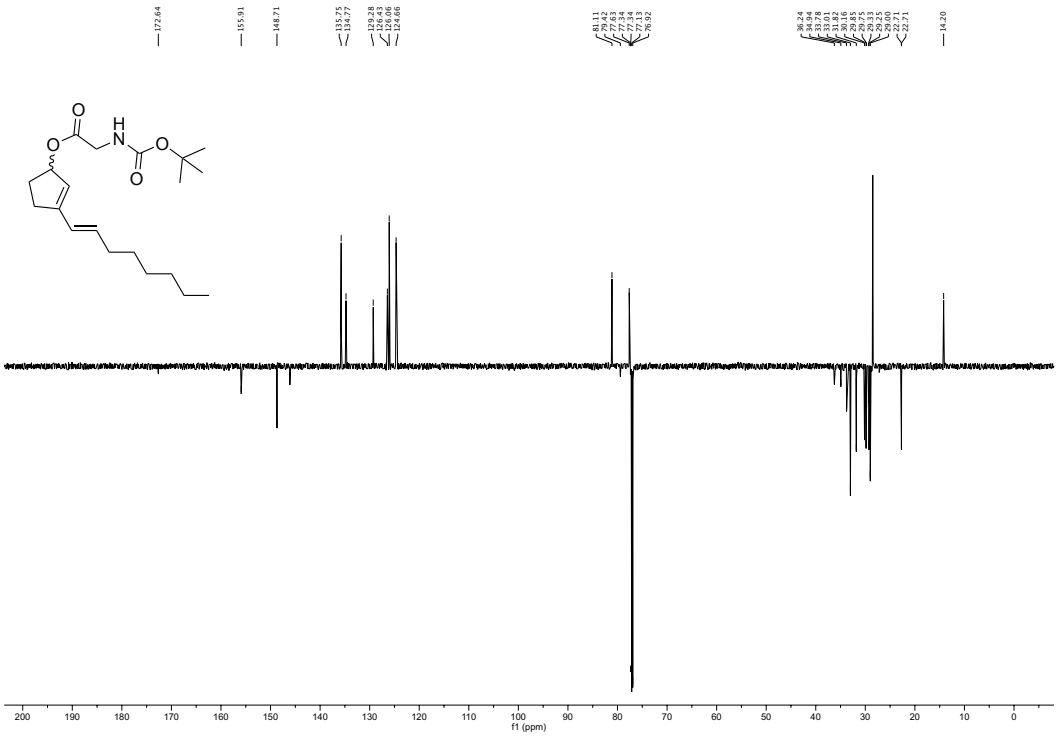

*Figure 12 – ^{13}C-NMR (126 MHz, $CDCl_3$) of N-Boc-O-(3-(Oct-1-enyl)-cyclopent-2-enyl)-glycine (rac-**179**).*

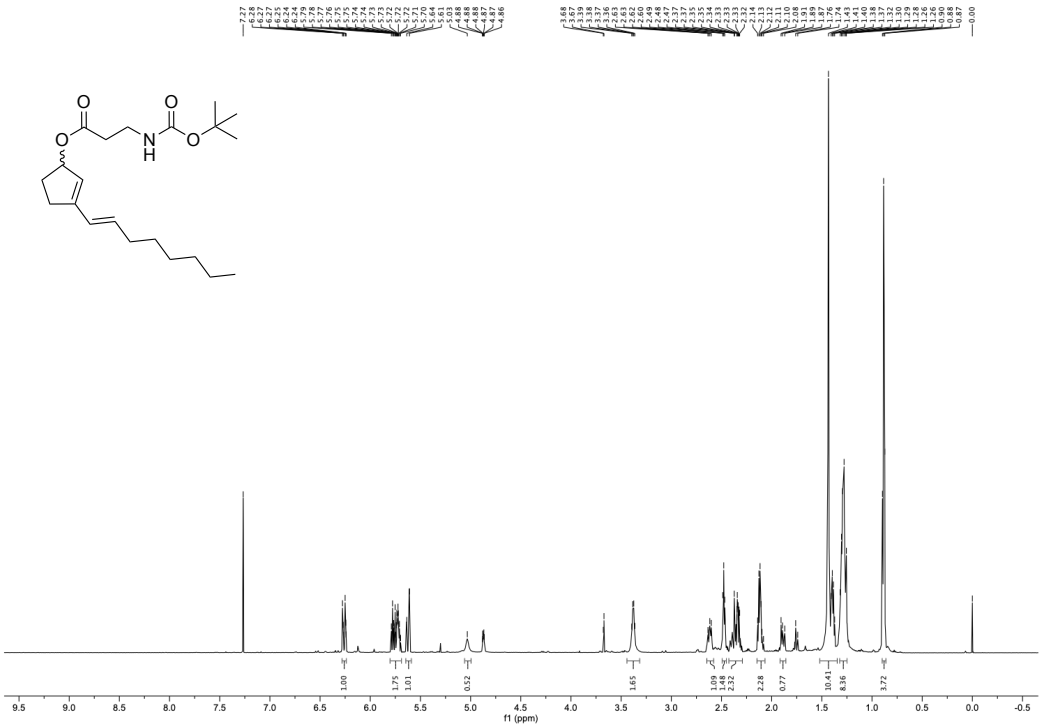

*Figure 13 – ^{1}H-NMR (500 MHz, $CDCl_3$) of N-Boc-O-(3-(Oct-1-enyl)-cyclopent-2-enyl)- β-alanine (rac-**190**).*

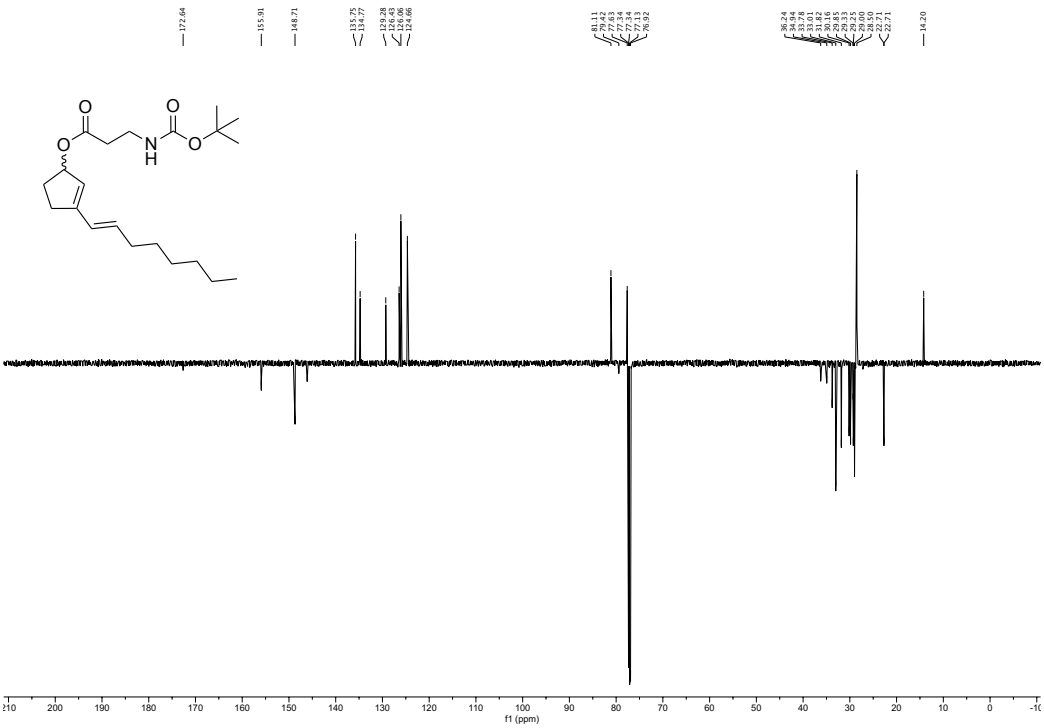

*Figure 14 – ^{13}C-NMR (126 MHz, $CDCl_3$) of N-Boc-O-(3-(Oct-1-enyl)-cyclopent-2-enyl)-β-alanine (rac-**190**).*

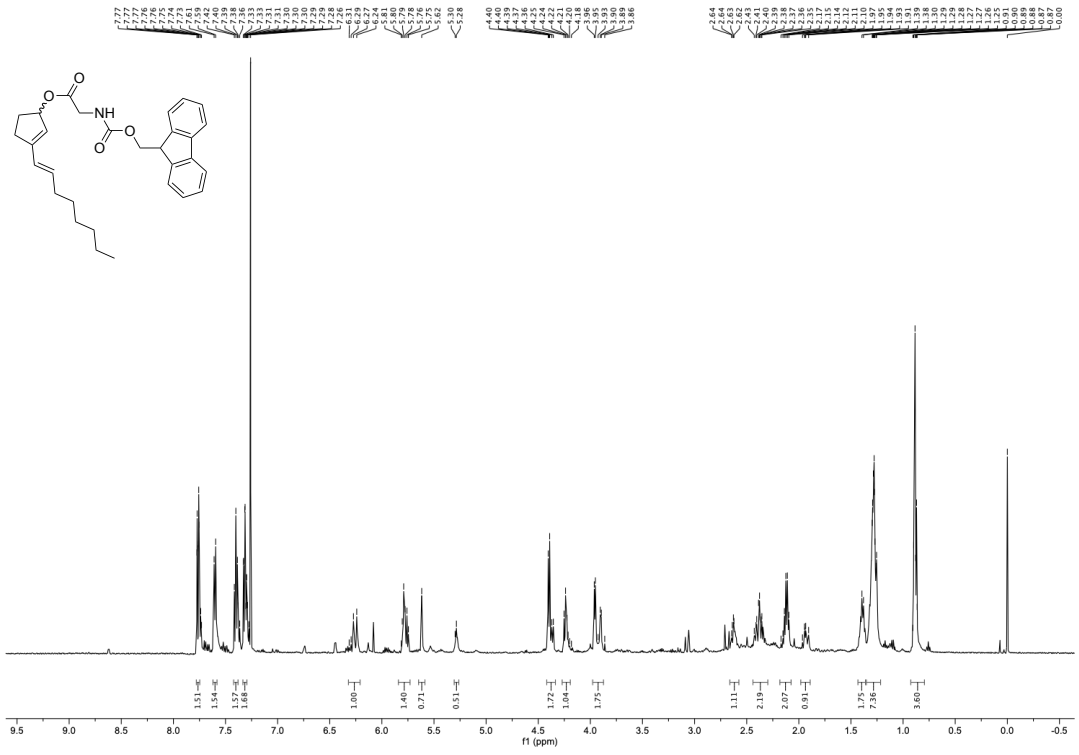

*Figure 15 – ^{1}H-NMR (500 MHz, $CDCl_3$) of N-Fmoc-O-(3-(Oct-1-enyl)-cyclopent-2-enyl)-glycine (rac-**193**).*

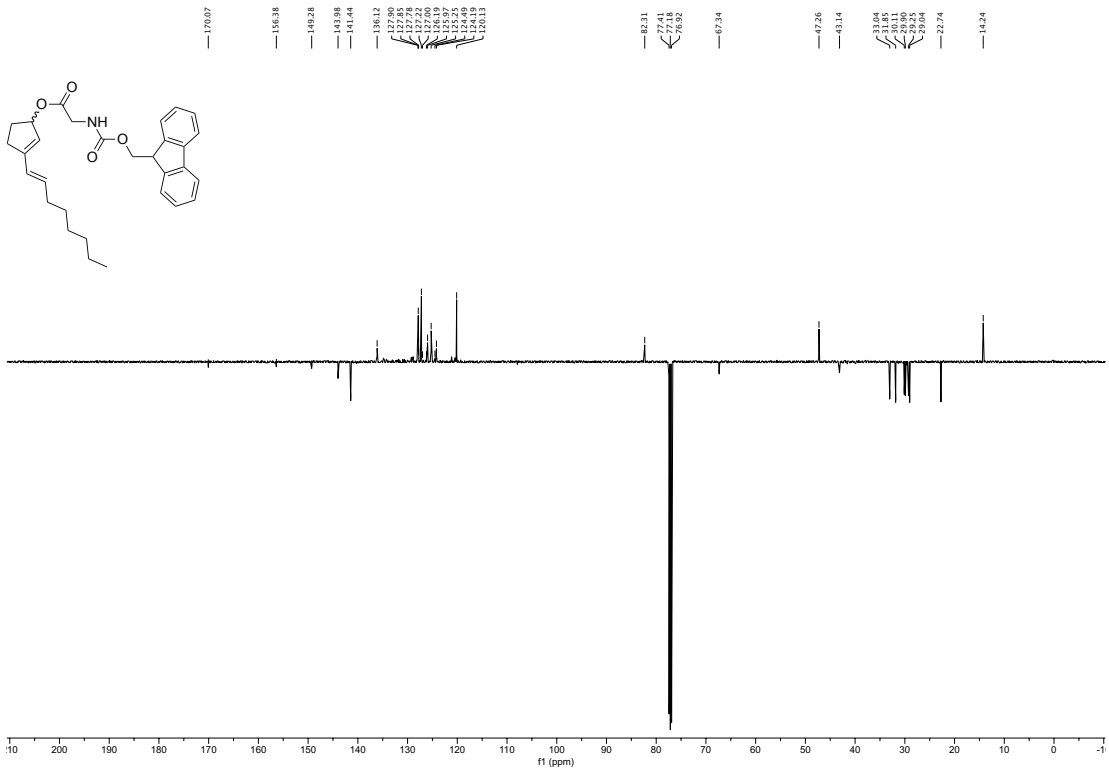

*Figure 16 – ^{13}C-NMR (126 MHz, $CDCl_3$) of N-Fmoc-O-(3-(Oct-1-enyl)-cyclopent-2-enyl)-glycine (rac-**193**).*

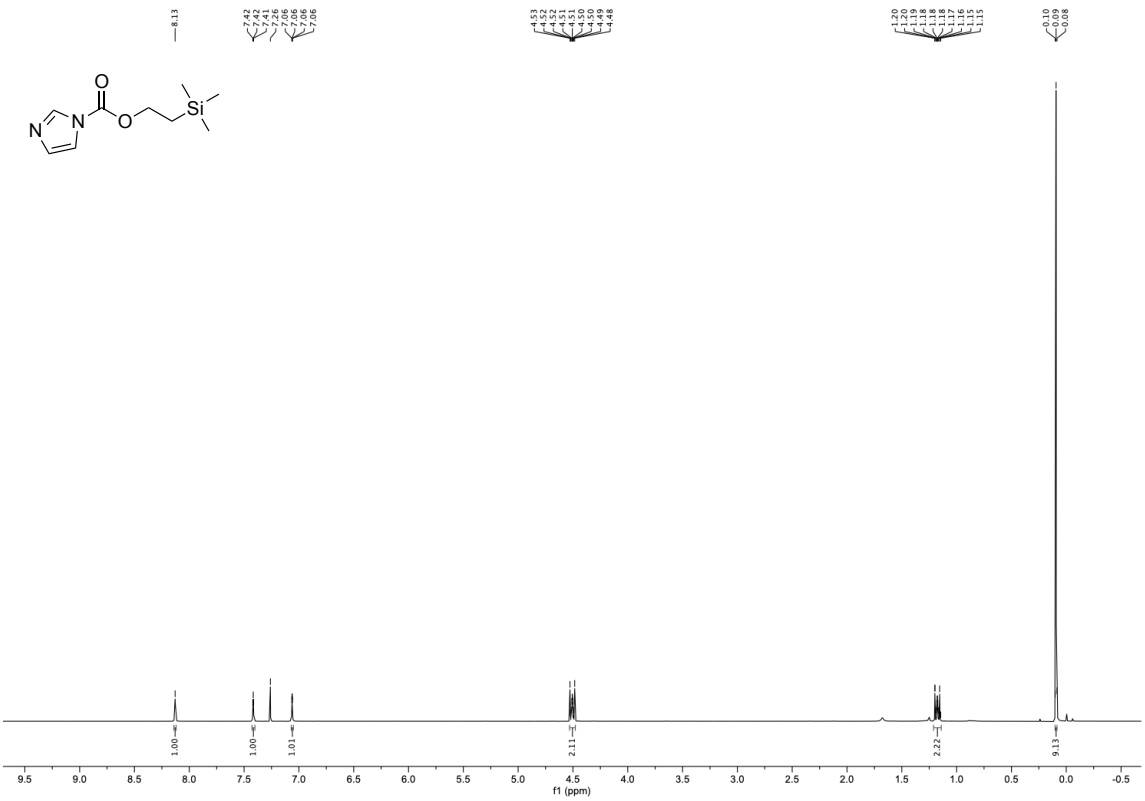

*Figure 17 – ^{1}H-NMR (500 MHz, $CDCl_3$) of 1-[O-[2-(Trimethylsilyl)ethyl]-oxycarbonyl]imidazole (**195**).*

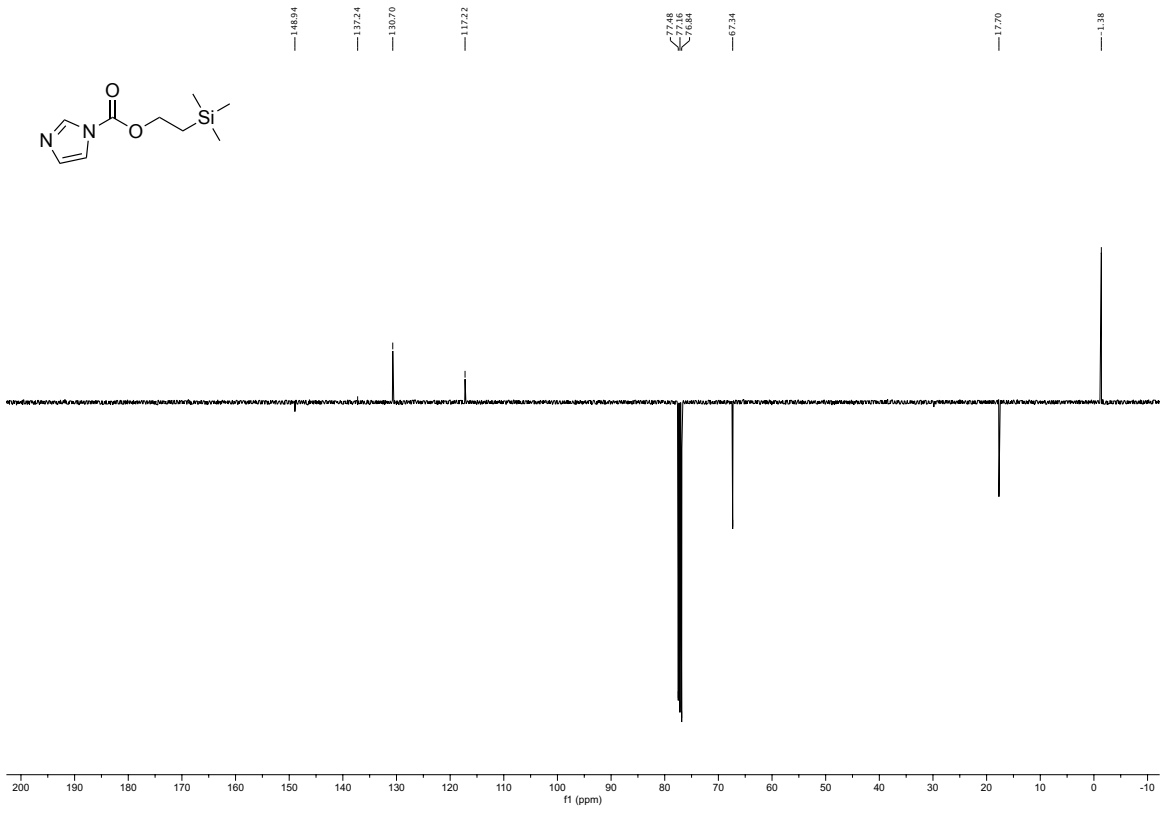

*Figure 18 – ^{13}C-NMR (126 MHz, $CDCl_3$) of 1-[O-[2-(Trimethylsilyl)ethyl]-oxycarbonyl]imidazole (**195**).*

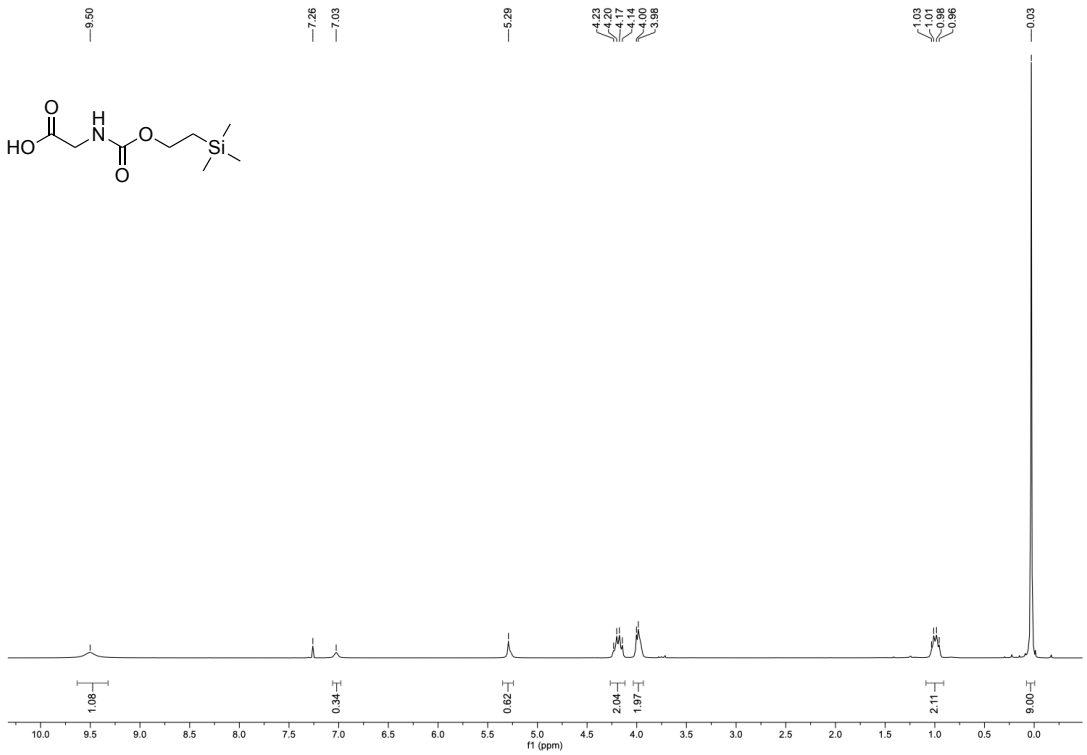

*Figure 19 – ^{1}H-NMR (500 MHz, $CDCl_3$) of N-Teoc-glycine (**197**).*

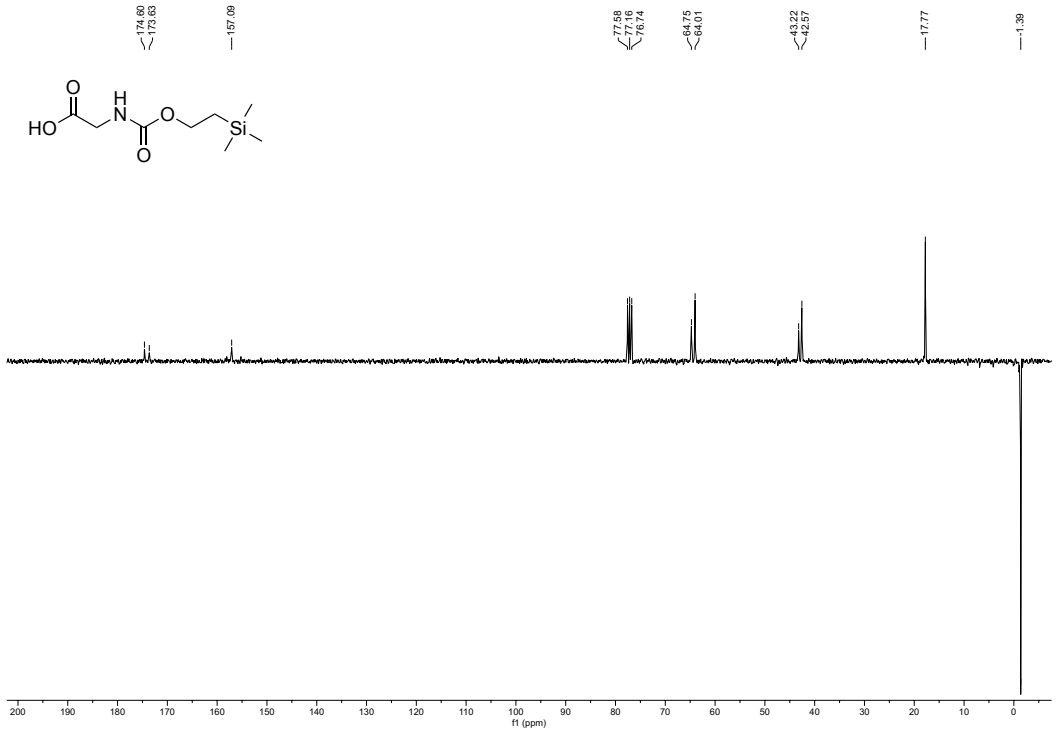

*Figure 20 – ^{13}C-NMR (126 MHz, $CDCl_3$) of N-Teoc-glycine (**197**).*

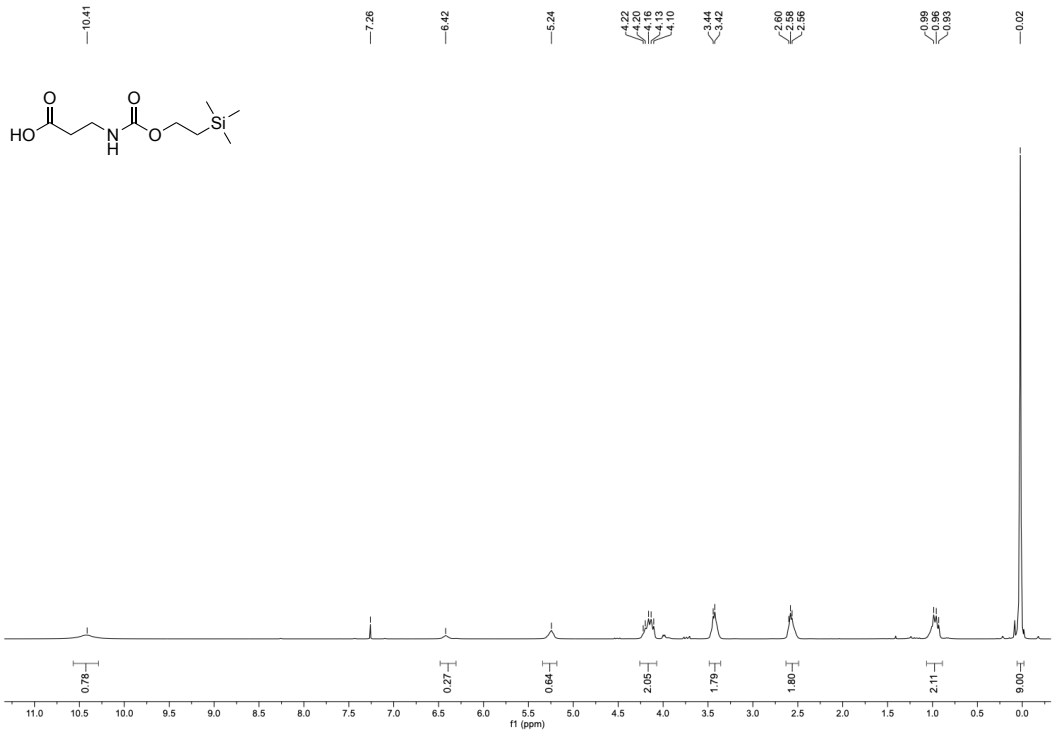

*Figure 21 – ^{1}H-NMR (500 MHz, $CDCl_3$) of N-Teoc-β-alanine (**196**).*

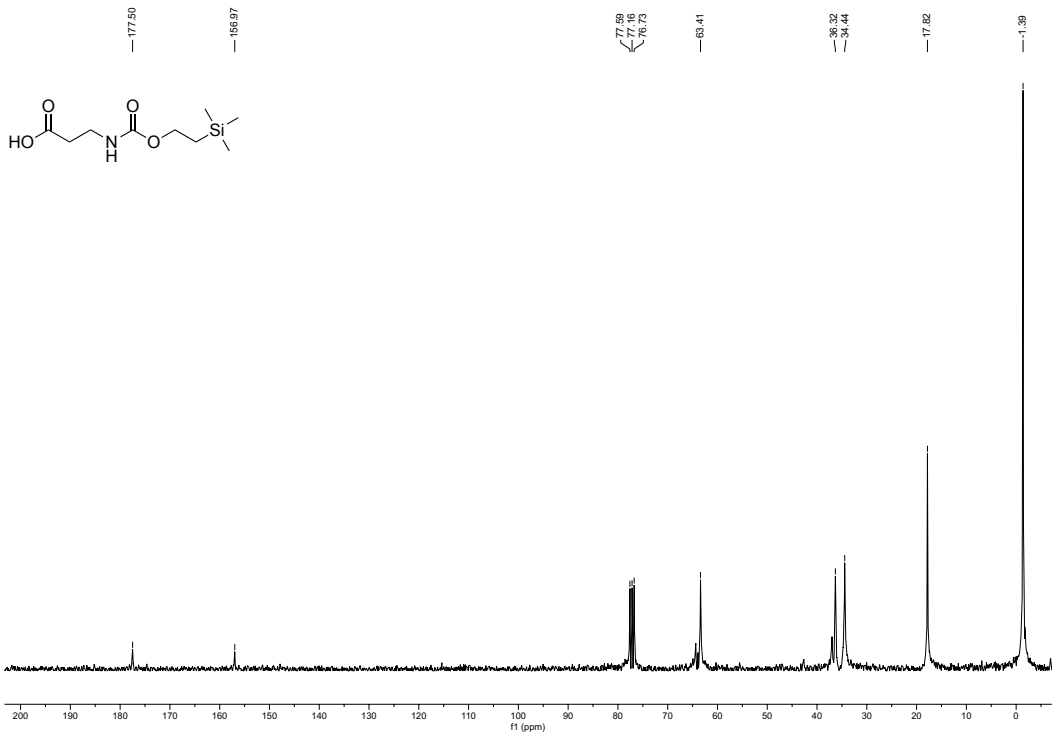

*Figure 22 – ^{13}C-NMR (126 MHz, $CDCl_3$) of N-Teoc-β-alanine (**196**).*

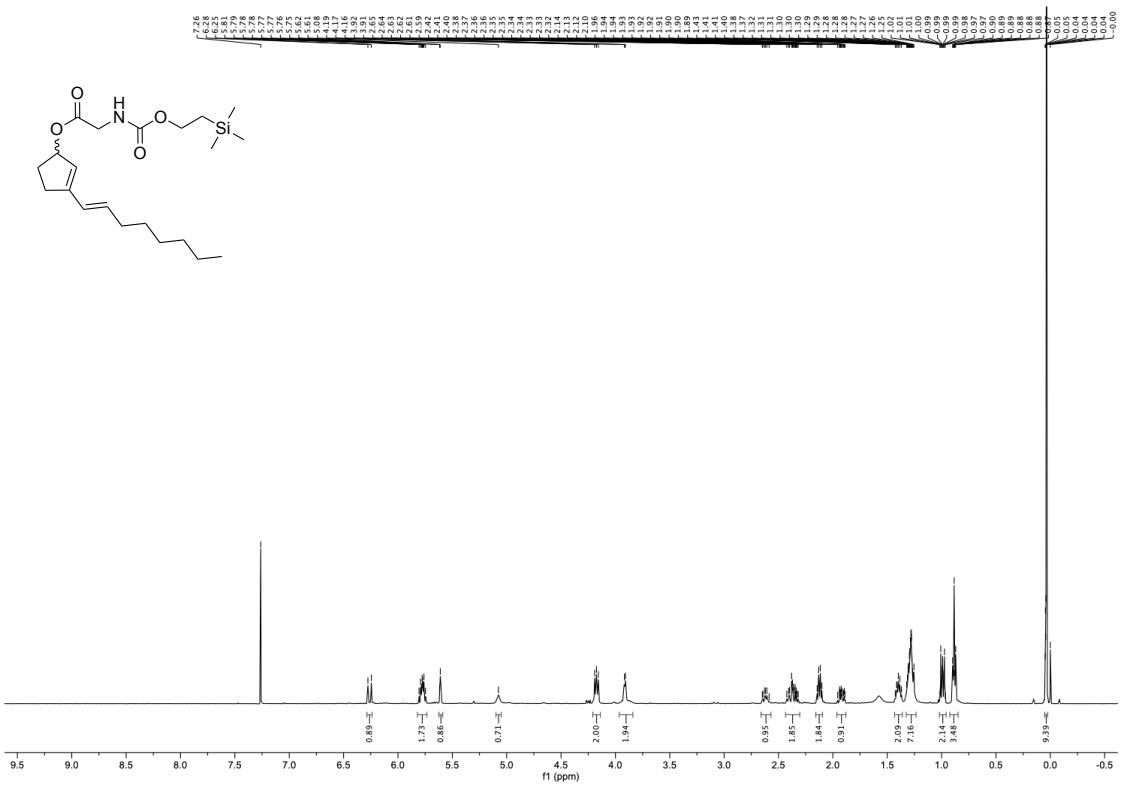

*Figure 23 – ^{1}H-NMR (500 MHz, $CDCl_3$) of N-Teoc-O-(3-(Oct-1-enyl)-cyclopent-2-enyl)-glycine (rac-**198**).*

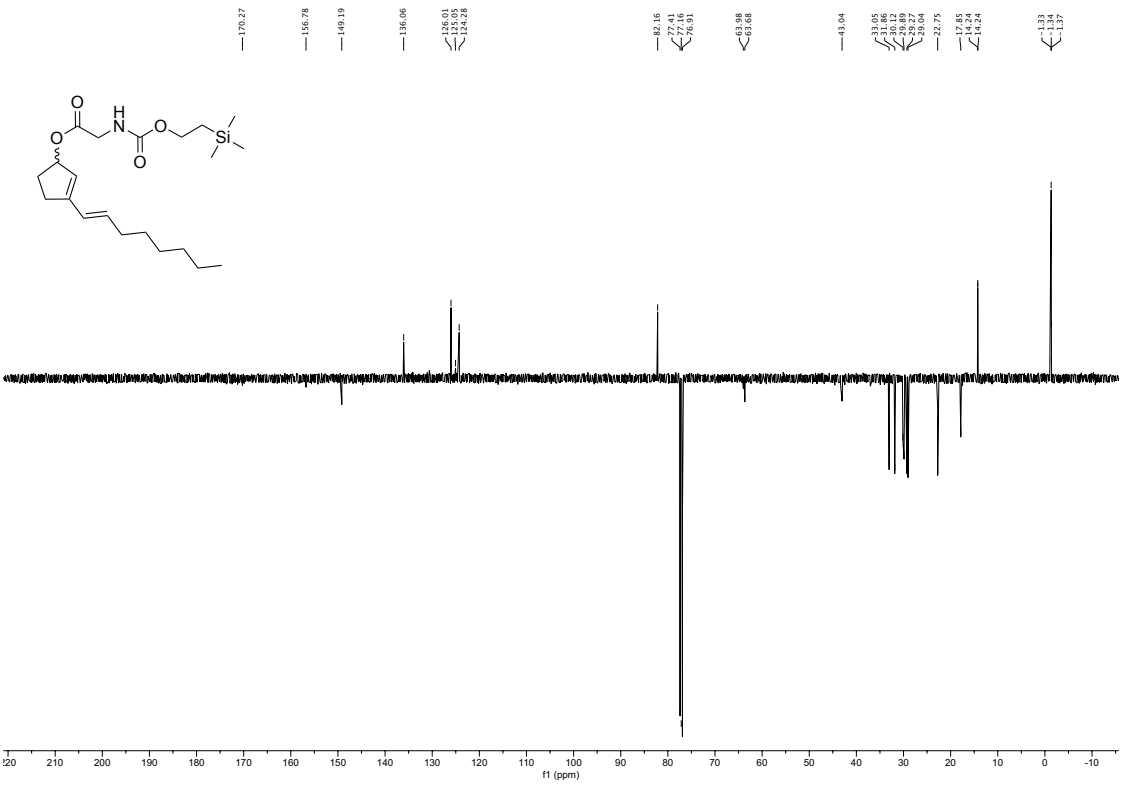

*Figure 24 – ^{13}C-NMR (126 MHz, $CDCl_3$) of N-Teoc-O-(3-(Oct-1-enyl)-cyclopent-2-enyl)-glycine (rac-**198**).*

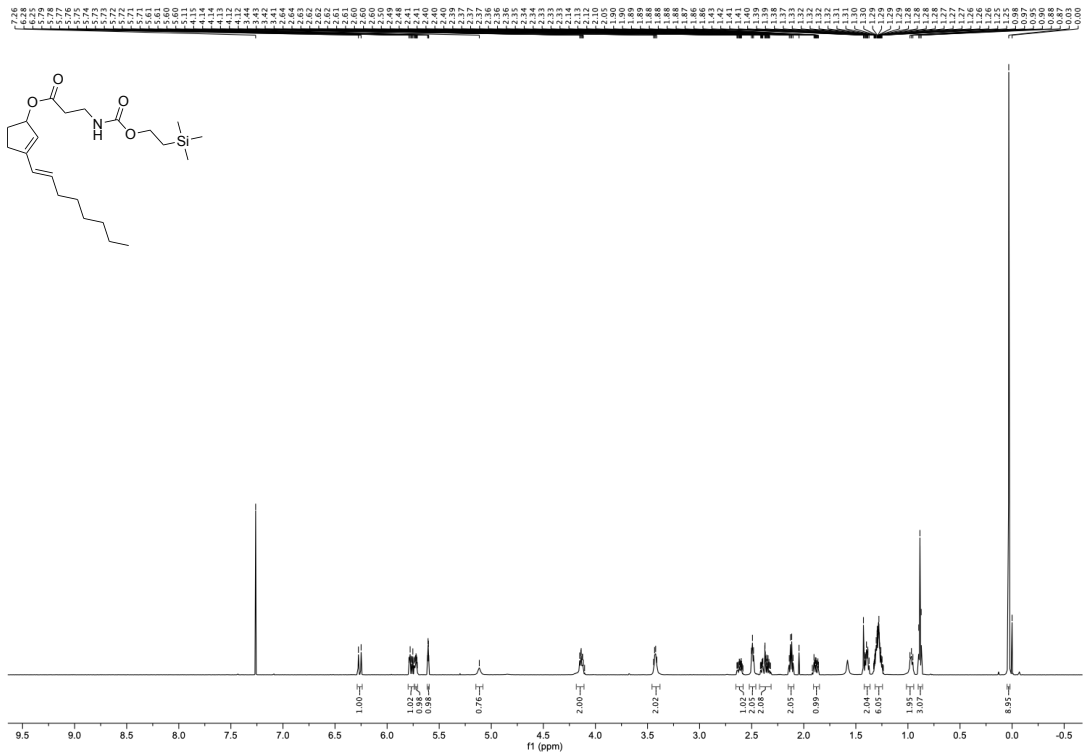

*Figure 25 – ^{1}H-NMR (500 MHz, $CDCl_3$) of N-Teoc-O-(3-(Oct-1-enyl)-cyclopent-2-enyl)-β-alanine (rac-**199**).*

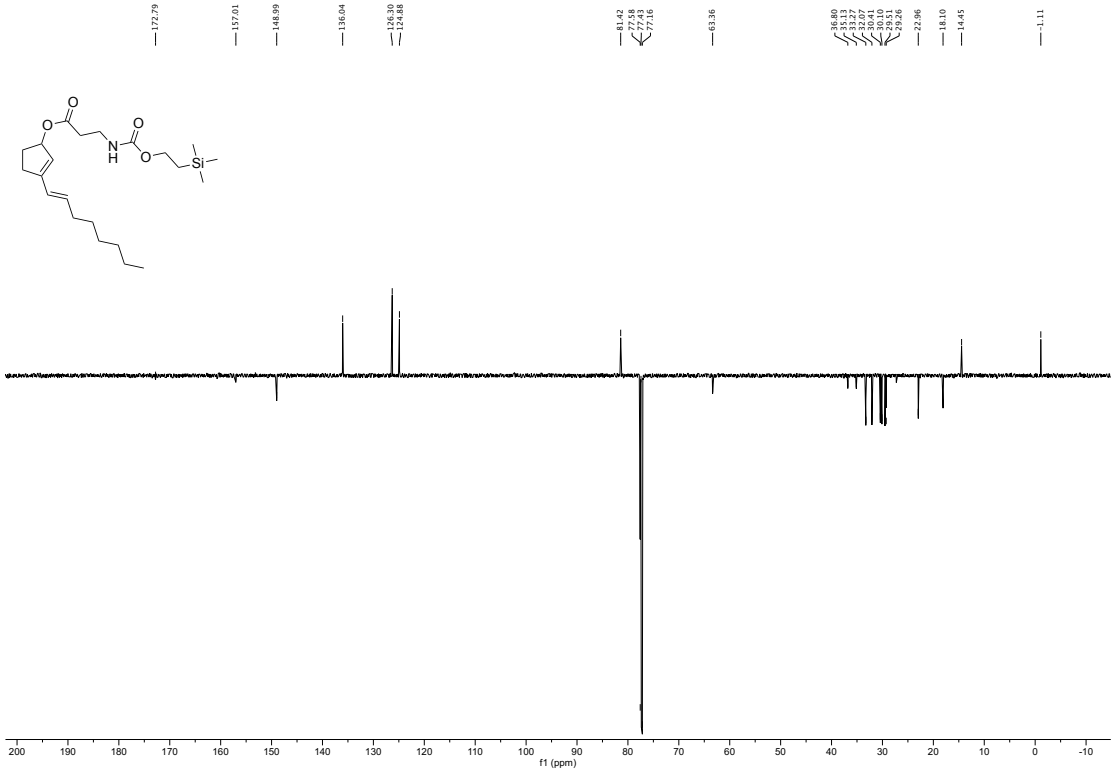

*Figure 26 – ^{13}C-NMR (126 MHz, $CDCl_3$) of N-Teoc-O-(3-(Oct-1-enyl)-cyclopent-2-enyl)-β-alanine (rac-**199**).*

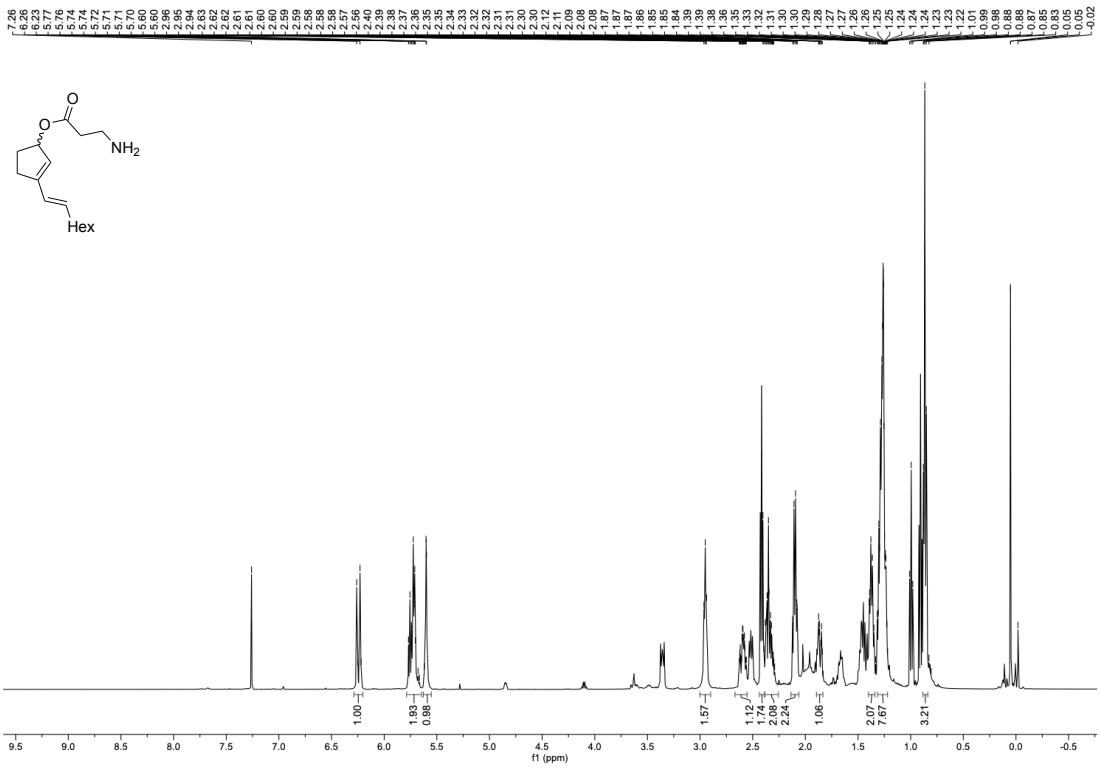

*Figure 27 – ^{1}H-NMR (500 MHz, $CDCl_3$) of O-(3-(Oct-1-enyl)-cyclopent-2-enyl)-β-alanine (rac-**200**).*

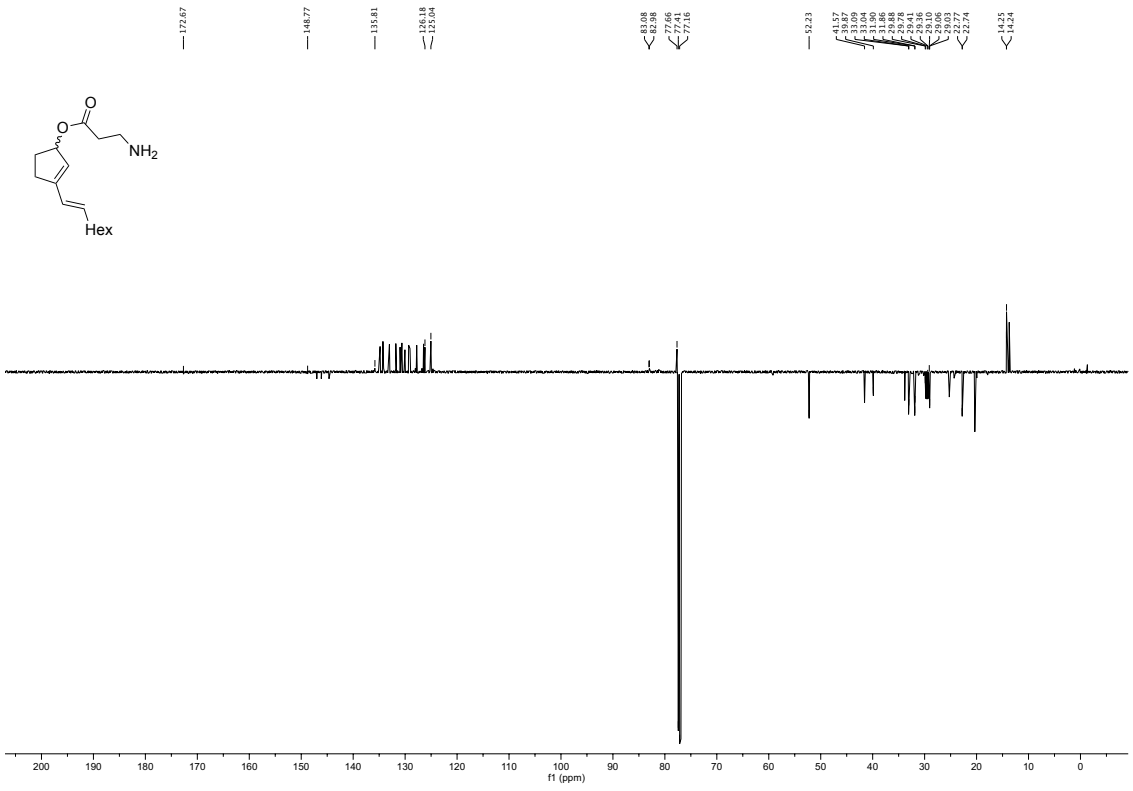

*Figure 28 – ^{13}C-NMR (126 MHz, $CDCl_3$) of O-(3-(Oct-1-enyl)-cyclopent-2-enyl)-β-alanine (rac-**200**).*

7.4 Statutory declaration

Hiermit versichere ich, André-Marcel Weßeling, an Eides statt, dass ich die vorliegende Arbeit mit dem Thema

“Studies towards construction of the
[4.3.0]-*N*-heterocyclic framework of Camporidine A
via an intramolecular *Diels-Alder*-reaction”

selbstständig und ohne die Benutzung anderer als der angegebenen Hilfsmittel angefertigt habe.
Alle Stellen, die wörtlich oder sinngemäß aus veröffentlichten oder nicht veröffentlichten Schriften entnommen wurden, sind als solche kenntlich gemacht.
Die Arbeit ist in gleicher oder ähnlicher Form oder auszugsweise im Rahmen einer anderen Prüfung noch nicht vorgelegt worden.
Ich versichere, dass die eingereichte elektronische Fassung der eingereichten Druckfassung vollständig entspricht.

Köln, der 31.08.2022
Place and date


Signature