“Photocatalytic and Lewis Acid-Mediated Transformations of Cyclopropanes: Towards Bicyclic Endoperoxides and Lactams”

Dissertation

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Für meine Familie

„Nur ein Narr macht keine Experimente.“ -

(Charles Darwin)

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Abbreviations

°C	degrees Celcius
^{13}C NMR	carbon NMR
^{1}H NMR	proton NMR
A	Acceptor
APCI	Atmospheric pressure chemical ionization
Ar	Aryl
aq.	aqueous
Boc	*tert*-butyloxycarbonyl
BP	Biphenyl
brine	saturated NaCl-solution
cat.	catalytic
cm^{-1}	wavenumbers
DAA	direct-acting antiviral drugs
DAC	donor-acceptor cyclopropane
DBTP	benzo[*b*]triphenylene-9,14-dicarbonitrile
DBU	1,8-diazabicyclo-[5.4.0]undec-7-en
DCA	9,10-dicyanoanthracene
DCE	1,2-dichloroethane
DCM	dichloromethane
DEPT	distortionless enhancement by polarization transfer
DMF	dimethylformamide
DMSO	dimethylsulfoxide
DNA	Deoxyribonucleic acid
dr	diastereomeric ratio
e.g.	for example
EA	ethyl acetate
EDG	electron donating group
ee	enantiomeric eccess
EI	electron impact
equiv	equivalents
ESI	electrospray ionization
et al.	and others (co-authors)
Et	ethyl
Et$_2$O	diethyl ether
EtOH	ethanol
EWG	electron withdrawing group
FDA	Food and Drug Administration
h	hour(s)
HIV	Human immunodeficiency virus
HPLC	high-performance liquid chromatography
HRMS	high-resolution mass
i-Pr	isopropyl
IR	infrared
J	coupling constant

kJ	kilojoule
LA	Lewis acid
LED	light-emitting diode
M	Metal
Me	methyl
MeCN	acetonitrile
MeOH	methanol
MesAcr	9-mesityl-10-methylacridinium
MHz	megahertz
mp	melting point
NBS	*N*-Bromosuccinimide
nm	nanometer(s)
NMO	*N*-methyl morpholine *N*-oxide
NMR	nuclear magnetic resonance
NNRTI	non-nucleoside reverse transcriptase inhibitor
OAc	acetate
PCC	pyridinium chlorochromate
PE	petroleum ether
PET	photoinduced electron Transfer
PFT	Perfluorotoluene
Pg	protecting group
Ph	phenyl
PMP	*para*-methoxyphenol
ppm	parts per million
R	arbitrary residue
rac	racemic
R_f	retention factor
rt	room temperature
SCE	standard calomel electrode
SET	single-electron-transfer
T	temperature
t	time
TBA	tetrabutylammonium
TBAF	tetra-n-butylammonium fluoride
TBS	*tert*-butyldimethylsilyl
TBDPS	*tert*-butyldiphenylsilyl
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TLC	thin-layer chromatography
Ts	tosyl
UV	ultraviolet
WHO	World health organization
X	heteroatom
λ_{max}	max. UV-VIS wavelength

A. Synthesis of Endoperoxides from Cyclopropanated Alkylated Indenes[1]

1. Introduction

1.1. Endoperoxides as Important Compounds in the Treatment of Malaria

Malaria is a disease that has affected humanity for thousands of years, leaving its mark on historical records and medical literature. The earliest documented mention of malaria can be traced back to the ancient Chinese medical text, the *Nei Ching*, believed to have been written around 2600 BCE. Although it was more likely written around 300 BCE,[2,3] this text describes malaria as a flu-like illness, noting its seasonal variations and manifestations such as splenomegaly.[4] For centuries, malaria has persisted in human history, leading to the exploration of various traditional remedies. The first available drug against malaria was Quinine, but it showed many side effects, which is why Bayer developed Chloroquine, a structurally related compound of quinine, which was taken over by the Americans after the war.[5] Over the years, 1200 plant species have been identified for their potential in malaria treatment, including the use of *Artemisia annua*, commonly known as sweet wormwood.[6] The significant impact of malaria, especially during the Vietnam War, has catalyzed concerted efforts to combat the disease. Project 523, initiated by the People's Republic of China, aimed to utilize traditional Chinese herbal knowledge to develop effective antimalarial treatments.[7] Tu Youyou's work stands out among these endeavors, culminating in the discovery of Artemisinin (**2**), a breakthrough endoperoxide compound that revolutionized malaria treatment.[8] Isolated from *Artemisia annua*, **2** proved to be highly effective against malaria parasites, earning Tu Youyou the Nobel Prize in Medicine in 2015.[9]

Artemisinin (**2**) is just one example of important endoperoxides in both chemical and biological fields. Many different kinds of natural endoperoxides are known, with Prostaglandin H_2 (**1**)[10] and plakinic acids **3-4** being famous representatives among this particular class of natural products (Figure 1). Prostaglandins were first isolated by Euler[11] and Goldblatt[12] from human sperm. These compounds are synthesized from arachidonic acid *via* Prostaglandin H_2 (**1**) and have widespread use in pharmacology due to their ubiquitous mechanisms in the body.[13] Plakinic acids **3-4** are isolated from marine *plaktortis* sponges and show antimalarial as well as

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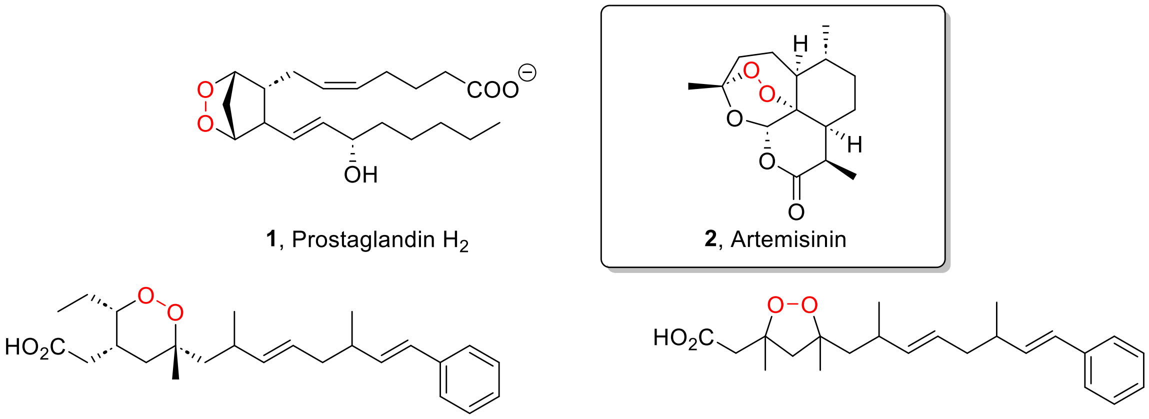
[1] This chapter is partially based on my masterthesis: A. Ratzenboeck, *Visible-light mediated synthesis of endoperoxides from carbocyclic anellated cyclopropanes.* Masterthesis, University of Regensburg, Regensburg, **2020**[1].

anti-cancer properties.[14] Nevertheless, Artemisinin (**2**) is the most famous endoperoxide, as it plays a crucial role in the treatment of malaria.

Overview of naturally occurring endoperoxides



1, Prostaglandin H_2

2, Artemisinin

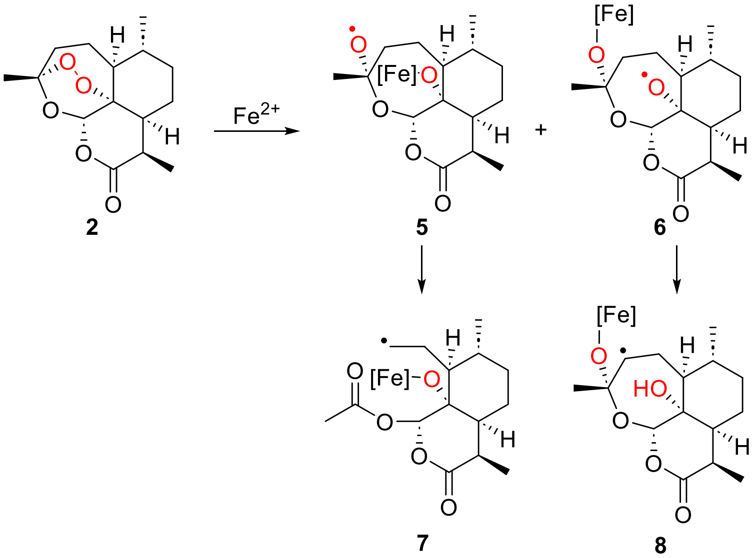
3, Plakinic acid A

4, Plakinic acid B

Figure 1. Endoperoxide natural products.

In the 1950s and 1960s, resistance against **2** became widespread, reversing many gains in the fight against Malaria.[15] Today, Artemisinin (**2**) is used in a combination therapy, the use as a monotherapy is strongly discouraged by the WHO to prevent resistance.[16] The mode of action is still under debate. A possible option describing the antimalarial activity of Artemisinin (**2**) is based on the reductive scission model. The endoperoxide seems to play a crucial role, as it is activated by Fe^{2+}, which cleaves the O–O bond, producing free radicals that attack the parasite and destroy it, independent from its stage of development (Scheme 1).[17]

Artemisinin: Mode of action



Scheme 1. Bioactivation of Artemisinin *via* reductive scission model.[17]

However, Artemisinin (**2**) has to be extracted from *Artemisia annua*, from which new problems arise: the varying supply of the plant and the inconsistent amounts of **2** obtained from extraction.[18] The total synthesis has therefore been of great interest to scientists across the world. At the same time, new endoperoxides are being developed and being tested against Malaria pathogens in search of higher activities.[19,20]

1.2. The Endoperoxide Moiety

Life on Earth, with the exception of certain deep-sea organisms, is heavily influenced by an oxidizing atmosphere, as it revolves around the dynamic process of cleaving and forming carbon-oxygen bonds, thereby altering the oxidation state of oxygen from 0 to –II or *vice versa*.[21] In its –I state, oxygen is rarely found in isolable molecules, primarily manifesting in reactive intermediates. These highly reactive intermediates hold significant interest for chemistry, garnering attention even in popular science. Among these compounds, hydrogen peroxide (H_2O_2, **9**) stands out as the simplest peroxide, finding various applications such as disinfection, bleaching, and serving as a component in rocket fuel, owing to its potent oxidizing properties.[22]

The inherent instability of hydrogen peroxide (**9**) is diminished by substituting hydrogen with suitable carbon residues, thereby modulating reactivity through electronic and steric effects (Figure 2a). While these organic peroxides **10** exhibit enhanced stability, they are seldom found in nature. Nevertheless, many display pharmaceutical properties, as exemplified by the first isolated organic peroxide, ascaridole (**11**)[23] (Figure 2b), which was purified from goosefoot oil in 1908 and synthesized in 1944 by Karl Ziegler and Günther Schenck.[24] Ascaridole (**11**), like most naturally occurring peroxides, is a cyclic molecule where the peroxide is part of at least one cycle. In its pure form it was found to explode only when heated above 130 °C and was used as a pharmaceutical for its anthelmintic properties.[25]

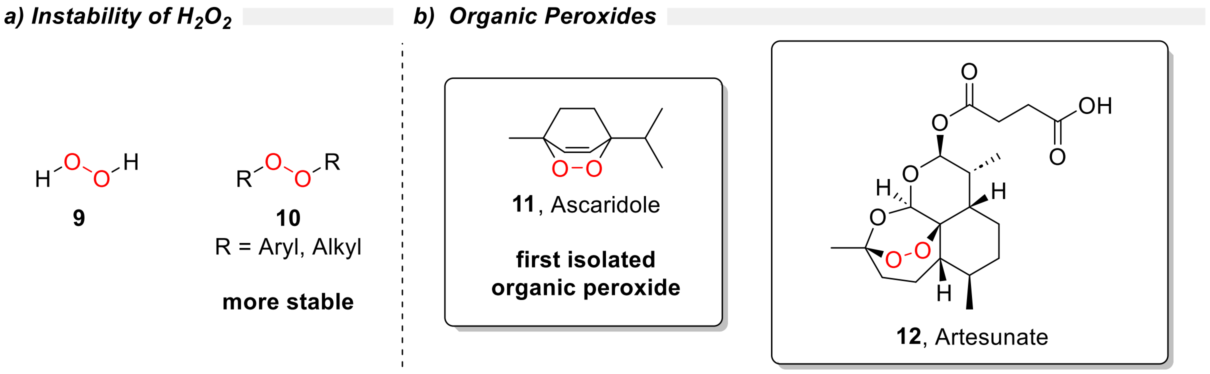
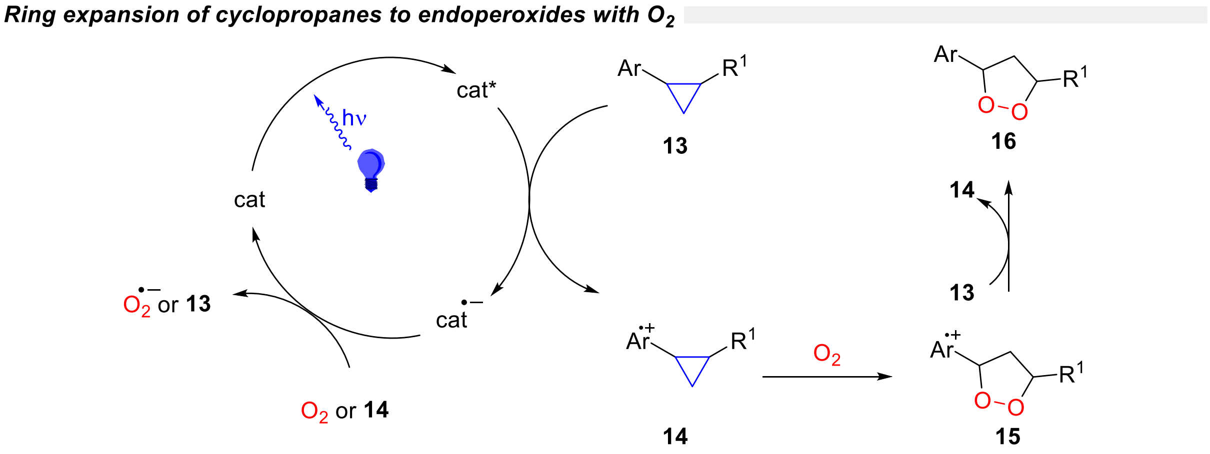


Figure 2. a) Hydrogen peroxide stabilization with organic residues. b) Endoperoxides in Nature.

More complex organic peroxides, such as Artesunate (**12**) (Figure 2b), demonstrate remarkable selectivity in a pharmaceutical context, delivering oxidative power exclusively to specific sites in the body. This unique combination of selectivity and reactivity renders **12** as an effective treatment for malaria.[16]

Despite their pharmaceutical promise, the synthesis of cyclic peroxides like Artesunate (**12**) from scratch possess significant challenges. While utilizing natural precursors proves effective for large-scale synthesis, [26,27] the diversity of achievable derivatives is somewhat limited by the structural diversity of these natural sources.[28] Various synthetic methods exist for introducing peroxide bridges akin to those found in artesunate,[29–31] although they often necessitate harsh conditions such as highly reactive reagents or UV-light, making them unsuitable for synthesizing complex molecules due to functional group incompatibility.

The structural uniqueness of the diatomic oxygen molecule existing as a diradical with two unpaired electrons guides the most commonly employed synthetic routes to organic peroxides, wherein latent or manifest diradicals serve as precursors. Cyclopropanes play a crucial role in this context. The distortion in bond angles within the cyclopropane molecule, storing approximately 27 kcal/mol of energy, facilitates energetically favorable processes like ring-opening,[32] generating a radical center in α-position of the three-membered ring.[33] This behavior is exploited in utilizing cyclopropylmethyl substituents as radical clocks for elucidating mechanisms, providing insights into both the type and rate constant of the reactions involved. The relative ease of synthesizing cyclopropanes *via* numerous routes, including chiral ones, underscores their utility as synthetic precursors, establishing a foundation for broad application.[34–36] Cyclopropane's latent diradical nature establishes it as a well-matched reaction partner for oxygen molecules, making it a favored precursor for peroxide-containing molecules.



Scheme 2. General catalytic cycle for photoinduced SET.[37]

Mechanistically, such reactions usually proceed *via* a single-electron-transfer (SET) from the aryl cyclopropane **13** to the excited catalyst, to give the corresponding radical cation **14** as a key intermediate. Ring opening and trapping of the radical by molecular oxygen leads to the radical cation of the dioxolane **15**, which is subsequently reduced by another equivalent of **13** to give the final product **16**. Regeneration of the catalyst requires a one-electron oxidation, which could be achieved either by chain-terminating reaction with the radical cation of the aryl cyclopropane **14** or by reaction with molecular oxygen (Scheme 2).[37]

1.3. Conclusion

In conclusion, endoperoxides are a fascinating class of compounds with diverse chemical, physical, and biological properties. They are found in natural sources such as Prostaglandin H_2, plakinic acids, and Artemisinin, as well as in synthetic variants. Their significance spans across various fields, including pharmacology and organic synthesis. Artemisinin's crucial role in combating malaria stands out prominently, exemplifying the profound impact of endoperoxides in medicine. However, challenges persist, such as the variability in Artemisinin supply and extraction issues, driving ongoing efforts in total synthesis and the development of new endoperoxides.

Therefore, understanding the fundamental nature of the endoperoxide moiety is essential. Organic peroxides exhibit strong oxidizing properties and hold great pharmaceutical promise. Although the synthesis of complex cyclic peroxides such as artesunate poses significant challenges, it offers tremendous potential for targeted pharmaceutical applications.

Exploring synthetic routes, such as using cyclopropanes as precursors, provides insights into the mechanism of peroxide formation. This pathway expands our synthetic toolbox and sets the stage for numerous syntheses of endoperoxides.

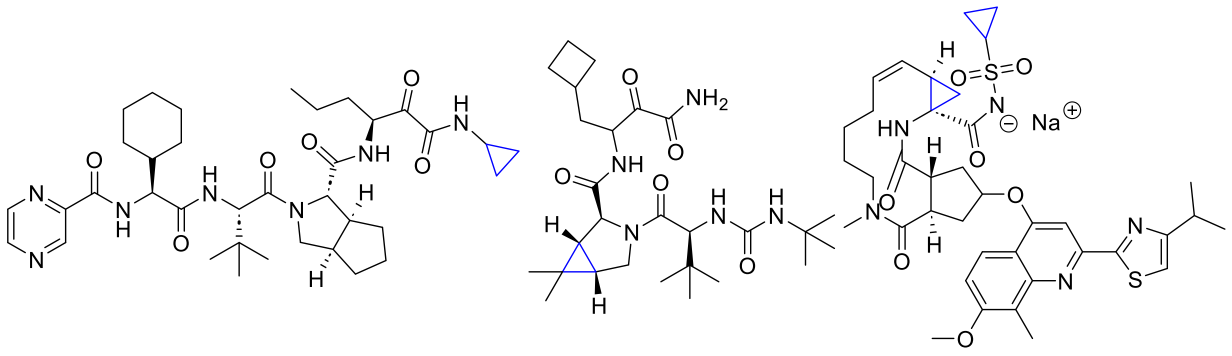
2. Main Part

2.1. Introduction

2.1.1 The Cyclopropane Moiety – A widespread Motif in Nature and Drug Discovery

Cyclopropanes hold significant importance in pharmaceutical and organic chemistry since the cyclopropane skeleton is widely distributed in various natural products with biological activity. Derived from plants, fungi, and microorganisms, this structural motif is predominantly present in terpenoids, fatty acid metabolites, pheromones, and unusual amino acids.[38] This chapter presents a selection of bioactive cyclopropanes employed in the treatment of major diseases (e.g. HIV), outlining their importance in drug discovery.

a) HCV Protease Inhibitors

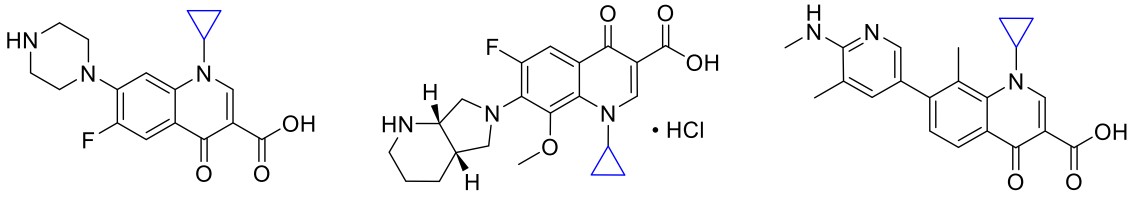


17, Telaprevir

18, Boceprevir

19, Simeprevir Sodium

b) Quinolone Antibacterials

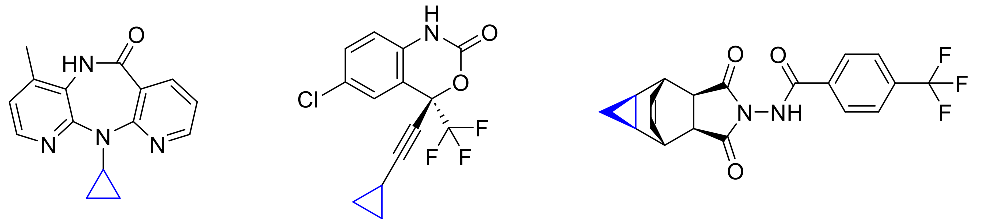


20, Ciprofloxacin

21, Moxifloxacin Hydrochloride

22, Ozenoxacin

c) Anti HIV-Drugs



23, Nevirapine

24, Efavirenz

25, Tecovirimat

Figure 3. Selected examples of cyclopropane containing a) HCV Protease Inhibitors. b) Quinolone Antibacterials. C) Anti HIV-Drugs.[39]

A number of biologically significant cyclopropanes are known as HCV Protease Inhibitors (Scheme 1a). For instance, Telaprevir (**17**) and Boceprevir (**18**) stand as first-generation direct-acting antiviral drugs (DAAs) employed in treating chronic hepatitis C genotype 1 infection. Subsequent advancements have revealed second-generation DAAs like Simeprevir Sodium (**19**). Notable advantages of this marketed drug include elevated cure rates, improved tolerance, enhanced safety profile, and abbreviated treatment duration.[39] Furthermore, the cyclopropane moiety plays an important role in Quinolone Antibacterials (Scheme 1b). Ciprofloxacin Hydrochloride (**20**), a member of this compound class, was developed by Bayer and received approval in 1987. It disrupts DNA replication and transcription by inhibiting bacterial topoisomerase II, IV and DNA gyrase activity. Additionally, Moxiflocacin Hydrochloride (**21**) and Ozenoxacin (**22**) serve as marketed drugs for treatment of Gram-negative and Gram-positive bacterial infections. Cyclopropyl units can also be found in a variety of Anti HIV-Drugs (Scheme 1c). The first-generation non-nucleoside reverse transcriptase inhibitor (NNRTI) Nevirapine (**23**), developed by Boehringer-Ingelheim, was FDA-approved in 1996 for HIV treatment. To combat drug resistance, a second-generation NNRTI, Efavirenz (**24**), was developed by Bristol-Myers Squibb and FDA-approved in 1998. Efavirenz incorporates a small propynyl-cyclopropyl group in place of the bulky aromatic pyridine ring, enhancing its resistance against non-aromatic mutations in the side chain of Tyrosine. Another notable drug, Tecovirimat (**25**), developed by SIGA Technologies and approved in 2018, targets human smallpox disease caused by the smallpox virus.

Given that Cyclopropyl is regarded as a privileged scaffold due to its distinct physical and pharmacological properties, as evidenced by nine marketed drugs, continued research in this are remains a significant challenge for the future.[39]

2.1.2 Cyclopropanation Methods

The process of cyclopropanation plays a crucial role in modern organic chemistry, given the abundance of valuable compounds characterized by this particular motif (refer to Figure 3).[40] Numerous techniques for synthesizing cyclopropane or its derivatives have been documented, with the earliest dating back to 1882 by August Freund.[41] Among these methods, two transformations have proven to be very important in synthetic organic chemistry. On the one hand, the Simmons-Smith reaction,[42] which uses zinc to form a carbenoid for cyclopropanation of olefins and on the other hand the Johnson-Corey-Chaykovsky reaction,[43] in which a sulfur ylide reacts with an α,β-unsaturated carbonyl. Besides the classical approaches, a large number of different cyclopropanation reactions have been developed over the last decades with significant impact on organic chemistry.[44,34,45,46,35] Among all the methods described in the literature, the cyclopropanation of alkenes under transition metal catalysis is one of the most studied and efficient strategies, especially concerning asymmetric cyclopropanations,[47] given the chirality of nearly all biological compounds and, consequently, medicinal drugs.[40] It turned out that transition metal catalysts, such as Rh(II)[48] or Cu(I),[49] are essential for cyclopropanations of alkenes, especially with diazo compounds forming a carbenoid during the reaction.

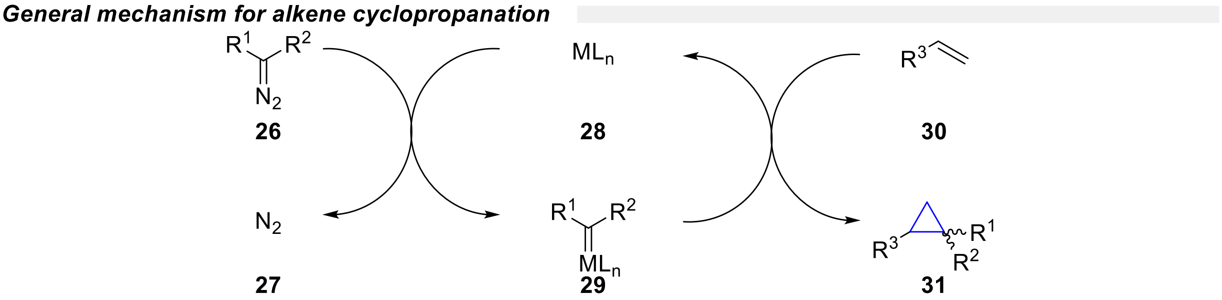


Figure 4. Proposed mechanism for transition-metal catalyzed cyclopropanation of olefins **30**.

Mechanistically, the process involves the formation of a metal carbenoid **29** through the extrusion of N_2 from diazo compound **26** in the presence of a transition metal catalyst **28** (Figure 4).

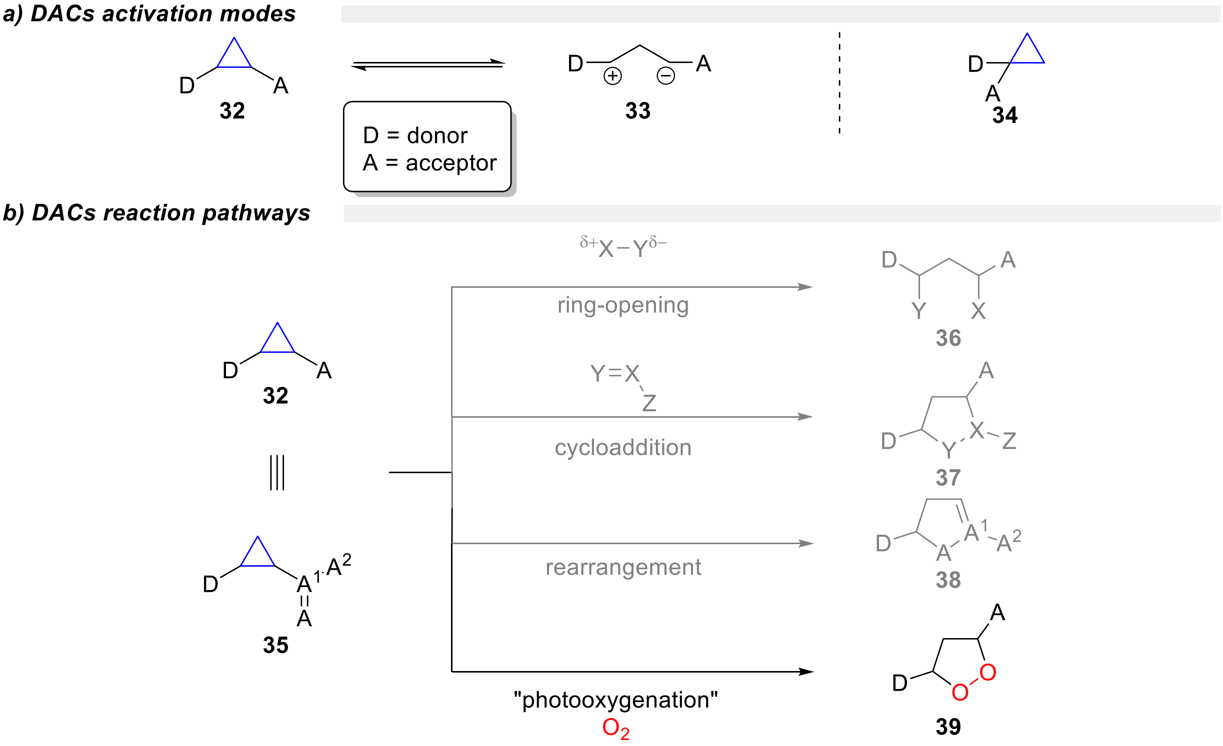


Figure 5. a) Zwitterionic relationship in vicinally substituted DACs **32** as well as geminal substitution in **34**. b) Different reaction types of DACs **32/35**.

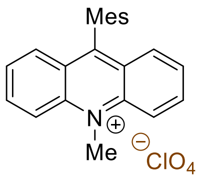
Subsequently, carbenoid **29** reacts with an olefin **30** to yield cyclopropane compound **31**, while simultaneously regenerating the catalyst **28**.[50] This way, donor-acceptor cyclopropanes (DACs)[51] **32** and **34** became accessible (Figure 5a), being famous building blocks for subsequent ring opening[52,53], cycloaddition,[54] rearrangement reactions or photooxygenations[55] to endoperoxides **39**[56] (Figure 5b).

2.1.3 Acridinium Photocatalysts: A Sustainable Alternative for Advanced Photoredox Transformations

In recent years, photoredox catalysis has emerged as a powerful and sustainable tool in the field of synthetic organic chemistry, as it enables the generation of complex molecular structures through single-electron transfer (SET) reactions under mild conditions. Iridium and ruthenium-based polypyridyl complexes have historically been the most widely used photoredox catalysts due to their long excited-state lifetimes and broad redox windows, which make them ideal for various oxidative and reductive transformations. However, the high cost and scarcity of these metals pose significant sustainability challenges, particularly for large-scale industrial applications.[57] The use of acridinium-based photocatalysts, initially developed by Fukuzumi[58,59] and subsequently refined by Nicewicz,[60,61] represents a novel and environmentally friendly alternative to traditional metal-based systems. Acridinium salts are of significant value due to their photophysical robustness, high excited-state oxidation potentials, and solubility in organic solvents, which render them highly versatile across a range of reaction media. Of particular importance is the fact that these organic dyes can drive challenging oxidative transformations without the necessity for the use of precious metals, thus positioning them as a highly promising solution for the advancement of catalysis.[62,63]

One of the main limitations of acridinium photocatalysts is their susceptibility to degradation, particularly through nucleophilic attack and photobleaching. Researchers have introduced structural modifications to the acridinium core, including N-arylation and the addition of bulky mesityl or tert-butyl groups at different positions. These groups act as steric shields, protecting the core from degradation pathways such as demethylation. These modifications enhance both the photostability and longevity of the catalyst, allowing for a broader range of applications in photoredox reactions where high oxidative power is required (see Table 1).[60]

Table 1. Photophysical Properties and Structures of Photocatalysts **40-45**.[60] [a] Excited state reduction potentials were estimated from ground state redox potentials and the intersection of the absorption and emission bands. [b] Determined by cyclic voltammetry in acetonitrile versus SCE.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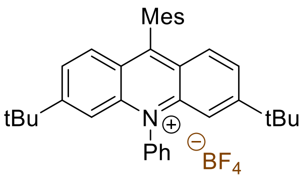
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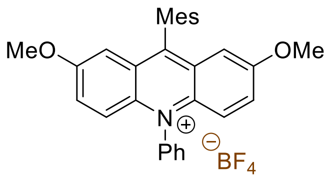
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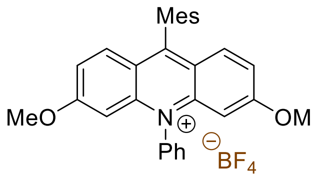
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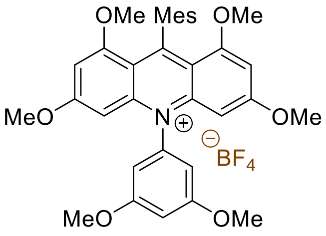
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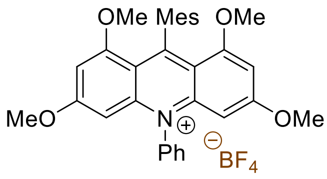
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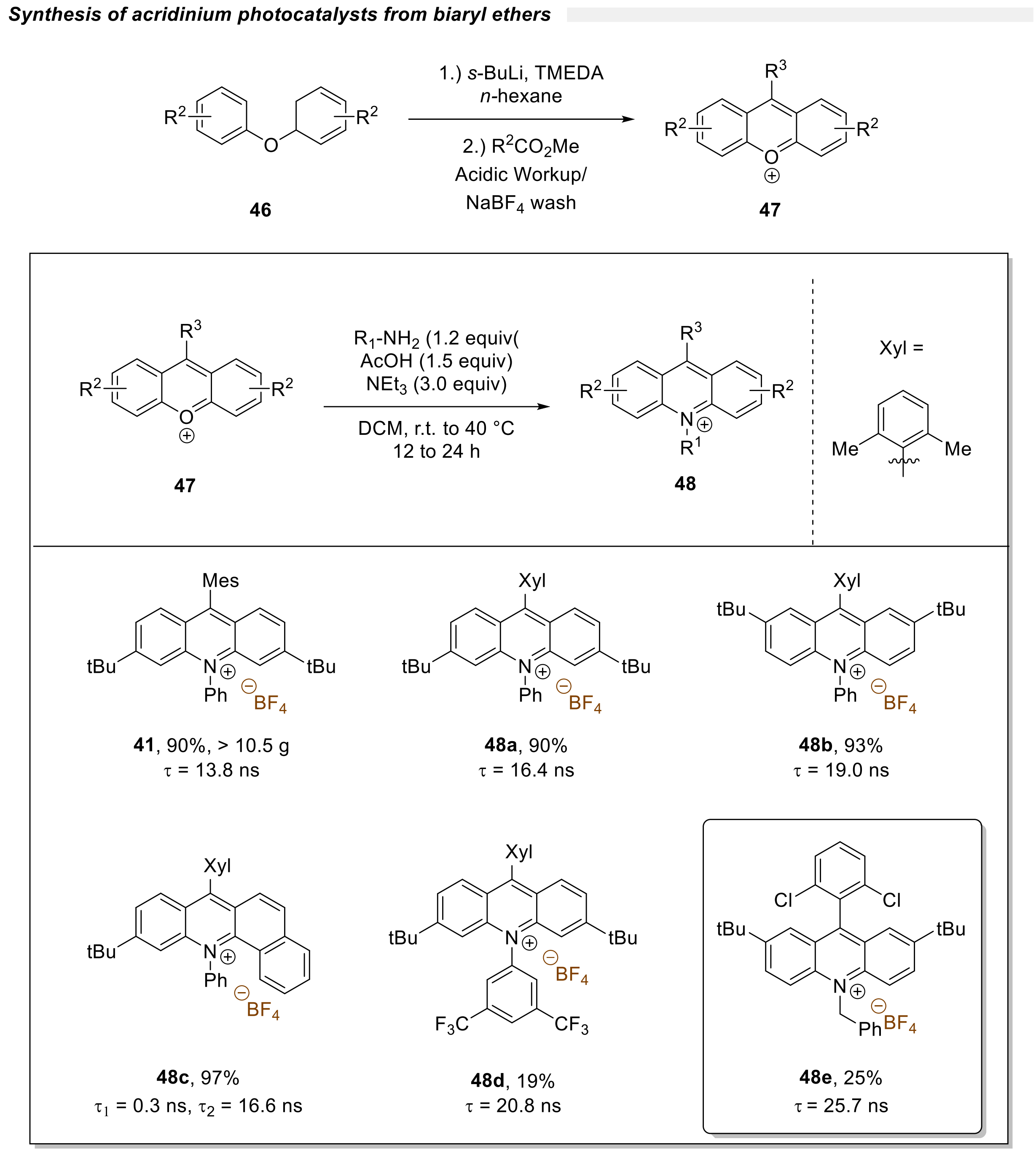
Entry	Catalyst	$E_{1/2}(C^*/C^-)$[a] (V)	$E_{1/2}(C/C^-)$[b] (V)	Excited state Lifetime τ (ns)	Excitation λ_{max} (nm)	Emission λ_{max} (nm)
1	**40**	+2.06	-0.57	$t_F = 6.4$	430	570
2	**41**	+2.08	-0.59	$t_F = 14.4$	420	517
3	**42**	+1.90	-0.57	$t_F = 18.7$	466	545
4	**43**	+2.01	-0.71	$t_{F1} = 3.0$ $t_{F2} = 10.1$	407	525
5	**44**	+1.65	-0.82	$t_{F1} = 1.3$ $t_{F2} = 12.3$	414	550
6	**45**	+1.62	-0.84	$t_{F1} = 1.3$ $t_{F2} = 8.9$	412	550

Traditionally, the synthesis of acridinium salts has involved the addition of an organometallic nucleophile to acridone, followed by protonation and dehydration to form the aromatic acridinium core.[64] However, challenges such as low yields, long reaction times, and difficult purifications have limited the efficiency of this approach. In particular, the preparation of di-tert-butyl acridone precursors often requires complex procedures with variable yields due to the sensitive nature of the starting materials and demanding reaction conditions.[62]

In search of a more streamlined approach, recent studies from Nicewicz[60] have developed new electron-rich acridinium photocatalysts (ref. to Table 1). These catalysts are synthesized using a modified strategy based on a triarylamine precursor and a Friedel-Crafts reaction with a benzoyl chloride derivative, which facilitates efficient formation of the acridinium core. This modified route has greatly simplified the synthesis, allowing for more stable, highly oxidizing catalysts with attenuated excited state reduction potentials.

Building on the modularity of this synthetic approach, Sparr *et al.* proposed the use of 1,5-bifunctional nucleophiles added to aromatic esters for creating acridinium salts.[65,66] However, this method is not universally applicable due to specific limitations in precursor preparation. Afterward, Nicewicz employed biaryl ether **46** as a starting material to prepare a xanthylium intermediate **47**, which could then be efficiently converted into the target acridinium catalyst **48** via condensation with aniline. By optimizing the conditions based on the sequential addition of triethylamine and acetic acid, high conversions with excellent yields were achieved, thus overcoming the previous challenges associated with product isolation and scalability. This optimized route facilitated the gram-scale synthesis of highly pure acridinium salt **41** within a significantly reduced timeframe, representing a substantial improvement over prior methodologies (Scheme 3).[62]

To further examine the structural adaptability of acridinium salts, a library of derivatives was synthesized, varying structural components such as the aryl group at the 9-position, the acridinium core structure, and the substitution on the nitrogen atom. Through a systematic evaluation, it was observed that specific modifications could significantly enhance the excited-state lifetime and fluorescence properties (Scheme 3). As an example, the substitution of mesityl with xylyl (Scheme 3, Compound **48b**) at the 9-position resulted in an extension of the catalyst's fluorescence lifetime, which is likely due to a reduction in charge-transfer (CT) interactions, which are often associated with rapid nonradiative decay.[67] Furthermore, the incorporation of trifluoromethyl groups at the nitrogen atom led to an increase in fluorescence lifetime (Scheme 3, Compound **48d**), which can be attributed to the restriction of bond rotation and the enhancement of electronic stabilization. The collective findings of these modifications led to the synthesis of a "best-in-class" acridinium salt **48e**, which features a 2,6-dichlorophenyl group at the 9-position, a 2,7-di-tert-butyl-substituted acridinium core, and a benzyl-substituted nitrogen atom. This tailored structure exhibited the longest excited-state lifetime among the tested salts, exceeding 25 nanoseconds, which makes it particularly promising for applications in photoredox catalysis.

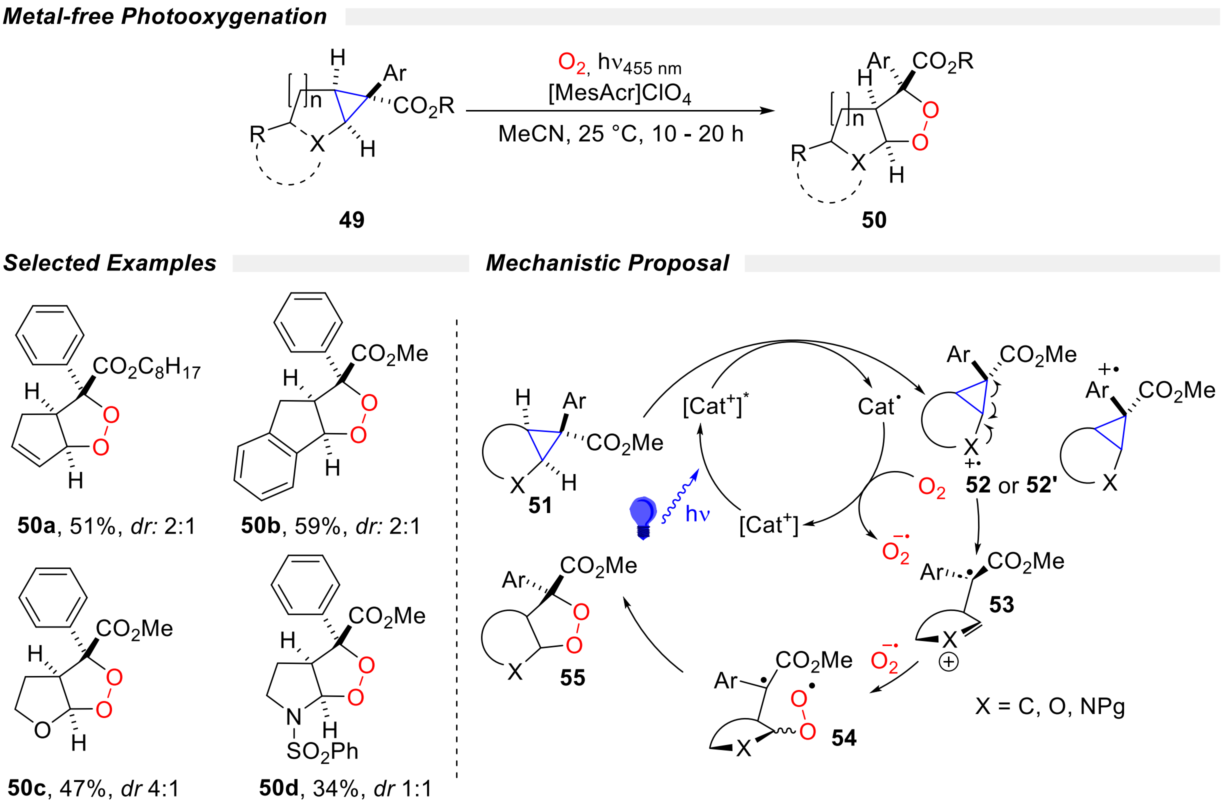


Scheme 3. Synthetic approach to different acridinium photocatalysts and their corresponding fluorescence lifetimes.[62]

In conclusion, acridinium-based photocatalysts present a sustainable and versatile alternative to traditional iridium and ruthenium complexes in photoredox catalysis. Their elevated oxidation potentials, stability, and compatibility with organic solvents facilitate the execution of efficient single-electron transfer (SET) reactions under conditions that are mild. Further enhancements to the longevity and photophysical properties of acridinium catalysts have been achieved through structural modifications, including core substitutions and tailored synthesis methods. As a result, these catalysts are now suitable for a wide range of applications. These developments facilitate the creation of stable, scalable, and environmentally friendly photocatalysts, thereby paving the way for their broader implementation in sustainable organic synthesis.

2.2. Aim of this Chapter

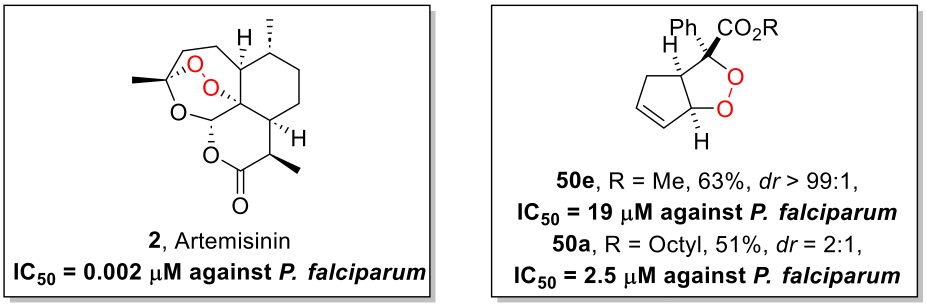
Recently, Reiser *et al.* published a visible light mediated ring expansion of carbo- and heterocyclically anellated cyclopropanes **49** by molecular oxygen using the highly oxidizing Fukuzumi catalyst.[68] The reaction tolerated a wide range of functional groups and afforded fused endoperoxides **50a-d** in good yields (34-59%) with moderate diastereoselectivities (Scheme 4, Selected Examples). The mechanism follows a photooxidative pathway (SET), from which **53** is trapped by superoxide radical anion, leading to diradical **54**, which then recombines productively to product **55** (Scheme 4, Mechanistic Proposal). It should be noted that the donor-acceptor substitution pattern on the three-membered ring was essential for the desired transformation.



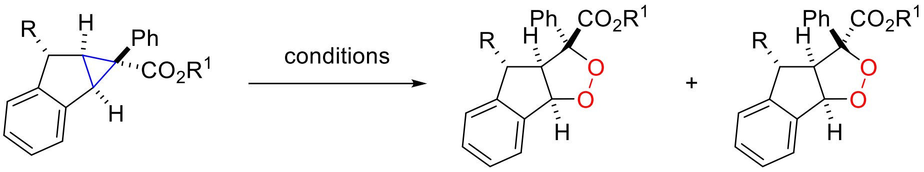
Scheme 4. Visible light mediated synthesis of endoperoxides from anellated cyclopropanes.[68]

The synthesis of endoperoxides is one of the most interesting areas of modern organic chemistry, as the supply of natural drugs for the treatment of malaria is limited. Artemisinin (**2**), the state-of-the-art treatment, is conventionally obtained by extraction from the leaves of *Artemisia annua*, although other methods, such as Seeberger's flow[69] semi-synthesis, now also represent an alternative. Unfortunately, Artemisinin is only produced in small quantities in the plant and is therefore very expensive.[28] Therefore, other synthetically accessible endoperoxides, especially *via* SET reactions of cyclopropanes, are becoming increasingly important. It was decided to continue an ongoing research project based on the visible light mediated synthesis of endoperoxides from anellated cyclopropanes recently published by Reiser and co-workers.[68] In this work it was shown that the antimalarial activity of the synthesized endoperoxides increased with increasing lipophilicty, whereby activities of 2.5 µM (IC_{50} against *P. falciparum*) were possible (Scheme 5a, Compound **50a**; For Comparison: Artemisinin (**2**): IC_{50} = 0.002 µM against *P. falciparum*). Therefore, cyclopropanated indene derivatives **56** were chosen as suitable precursors for subsequent endoperoxide synthesis, considering their strong lipophilic character and easy accessibility *via* rhodium-catalyzed cyclopropanation (Scheme 5b).

a) Antimalarial activity of Artemisinin and compounds 50e and 50a



b) Aim of this work: Synthesis of indene endoperoxides



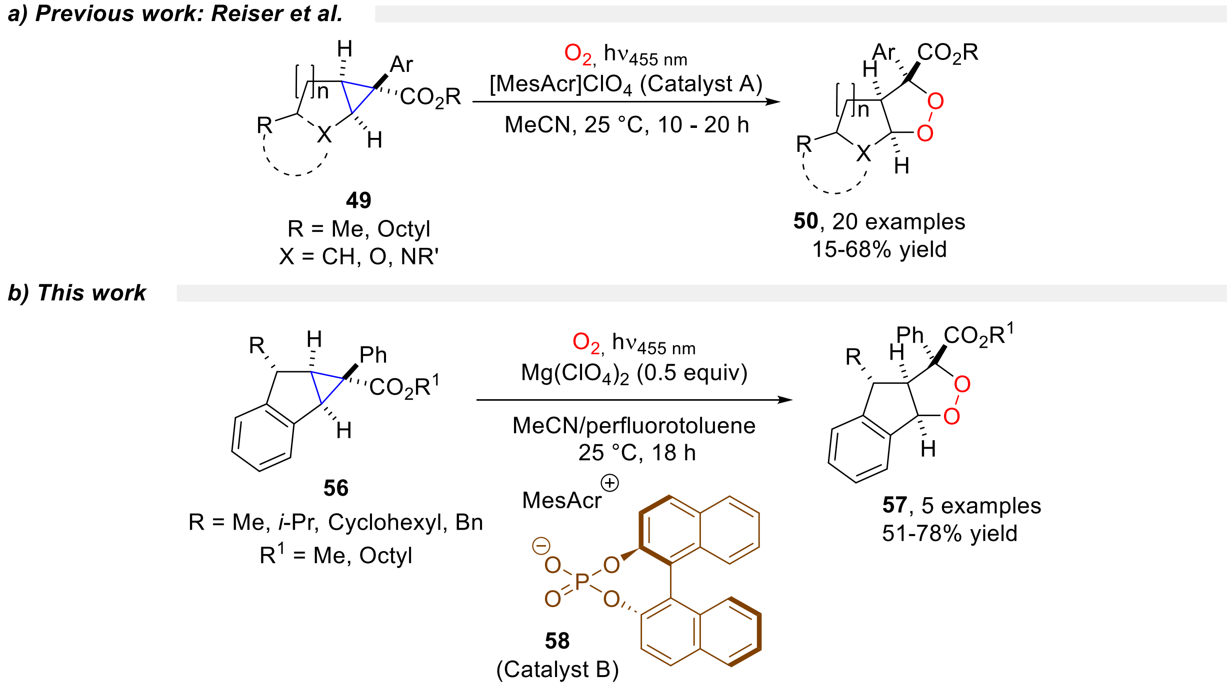
56 **57** **57'**

Scheme 5. a) Comparison of antimalarial activities of Artemisinin and synthesized compounds from Reiser *et al.*[68] b) Aim of this work.

2.3. Photo-Ring Expansion of Cyclopropanated Indenes to Endoperoxides

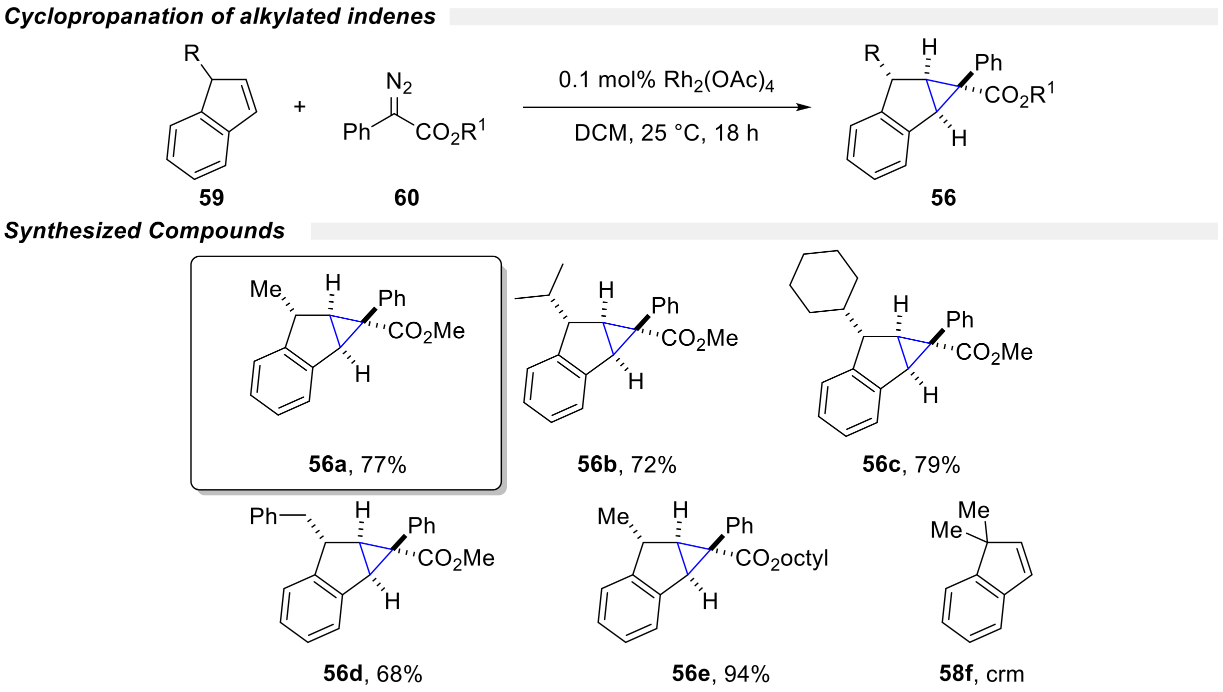
Over the past decade, photo(redox) catalysis has emerged as one of the most attractive fields for increasing molecular complexity in synthetic organic chemistry *via* radical pathways.[61] Especially aminoacridinium-based organic dyes, pioneered by Shunichi Fukuzumi[59], showed a broad range of redox properties and are subsequently good candidates as green photoredox-catalysts. Furthermore, they also possess the potential for a sustainable application in large-scale synthesis.[63,70] Particularly the group of Nicewicz has introduced and popularized those compounds as an attractive alternative for photoredox catalysis (cf. Chapter 2.1.3).[60] Over the years, the 9-Mesityl-10-methylacridinium perchlorate has adapted as a commonly used photocatalyst in the greater synthetic community by means of commercial availability and uncomplicated synthesis process.[58]

As highlighted before (cf. Chapter 2.2, Scheme 4), a visible-light mediated synthesis of endoperoxides from anellated cyclopropanes in presence of 9-Mesityl-10-methylacridinium perchlorate (Catalyst A) was reported by our group (Scheme 6a).[68] This approach should be applied to indene derivatives **56** using 9-mesityl-10-methylacridinium ion with a novel phosphoric-acid-counteranion (Scheme 6b).



Scheme 6. a) Previous work by our group. b) This work: Synthesis of indene endoperoxides.

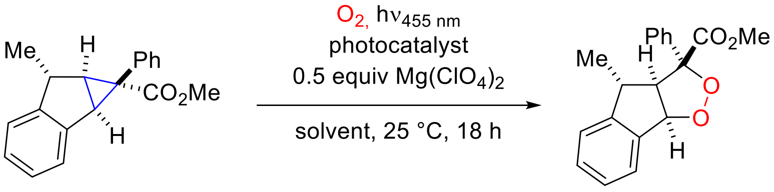
Reaction elaboration began with the synthesis of appropriate cyclopropane precursors **56**. To achieve this, a modified literature procedure[48] was used, resulting in the diastereoselective production of **56** in good yields (68-79%) *via* rhodium-catalyzed conditions. The cyclopropanation occurred opposite to the alkyl group R, and the ester group was oriented on the convex phase of the bicycle (Scheme 7). Compound **56e** allowed for variation on the ester group, while compound **58f** did not successfully undergo cyclopropanation due to double functionalization on the indene.



Scheme 7. Cyclopropanation of **58**. Reaction conditions: 5.0 mmol scale, **58** (1.0 equiv), **59** (1.5 equiv), 1.0 mL DCM per mmol **58**.

For reaction optimization, methyl-substituted cyclopropanated indene **56a** was chosen and subjected to photocatalytic conditions using $[MesAcr]BF_4$. Unfortunately, the reaction yielded only 14% with a diastereomeric ratio of 1:1, prompting us to explore alternative counterions for further optimization of the reaction conditions (Table 2, Entry 1). Subsequently, Catalyst A, which was previously described in our recent publication on endoperoxide synthesis, [68] was utilized, resulting in a slightly better yield (19%) of **57a**, but delivering high amounts of endoperoxide decomposition product (Table 2, Entry 2). Under identical conditions, Catalyst B delivered the same reaction outcome (Table 2, Entry 3). The issue of endoperoxide decomposition, including (photo)decomposition, was previously reported by Otsuji in 1992[71]. Addition of $Mg(ClO_4)_2$ as a Lewis acid and photodecomposition inhibitor prevented this problem. Additionally, Lewis acids are known to enhance the overall photocatalytic activity of organic photocatalysts by prohibiting back electron transfer from radical ions to the photocatalyst.[72] Nevertheless, magnesium perchlorate negatively effected the reaction outcome, resulting in a yield of only 10% of **57a** and a diastereomeric ratio of 1.5:1 using Catalyst A (Table 2, Entry 4). In contrast, Catalyst B furnished **57a** with a significantly higher yield (56%) and a diastereomeric ratio of 1.7:1 (Table 2, Entry 5). Further attempts to improve the yield were made by adding equal amounts of perfluorotoluene (PFT), a potent gas-dissolving solvent, leading to a significant increase to 80% (Table 2, Entry 6). For comparison, the optimized system was tested with Catalyst A. As anticipated, reverting to perchlorate anion had a negative impact, resulting in only 25% yield of **57a** (Table 2, Entry 7). Further optimization revealed that the catalyst loading could be reduced to 1 mol% (Table 2, Entry 8). Scale-up to 1.5 mmol was possible without any adverse effects on the yield and diastereomeric ratio (Table 2, Entry 9).

Table 2. Reaction Optimization. Reaction conditions: 8 mol% photocatalyst, 0.2 mmol **56a**, 2.0 mL solvent, blue LED, O_2-balloon. Only the major diastereomer **57a** is shown. [a] Reaction without $Mg(ClO_4)_2$. [b] Catalyst loading 1 mol%. [c] 1.5 mmol scale.

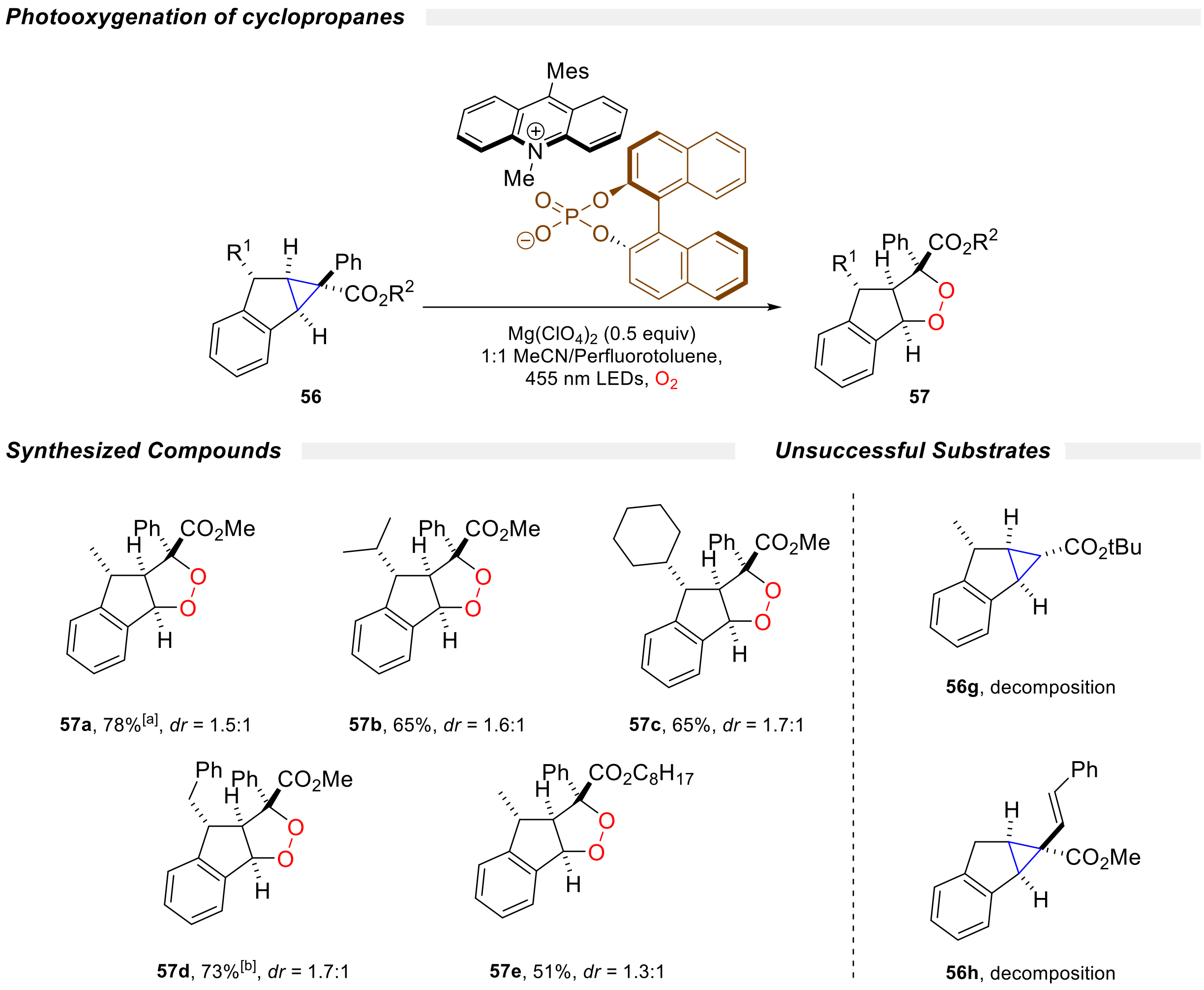


56a

57a, major

Entry	Solvent	Photocatalyst	NMR-yield [%]	*Dr*
1[a]	MeCN	[MesAcr]BF_4	14	1.0:1
2[a]	MeCN	Catalyst A	19	1.5:1
3[a]	MeCN	Catalyst B	20	1.0:1
4	MeCN	Catalyst A	10	1.5:1
5	MeCN	Catalyst B	56	1.7:1
6	MeCN/PFT 1:1	Catalyst B	80	1.5:1
7	MeCN/PFT 1:1	Catalyst A	25	1.5:1
8	MeCN/PFT 1:1	Catalyst B	80	1.5:1
9[c]	MeCN/PFT 1:1	Catalyst B	78	1.5:1

Under the optimized conditions, the scope of the reaction was explored (Scheme 8). Variations on the *3*-position of the indene were tolerated, delivering compounds **57a-d** in good yields within the same range (65-78%). Furthermore, apolar octyl ester was applied to the optimized conditions, leading to endoperoxide **57e** in a moderate yield of 51% (dr 1.3:1) Less-electron rich compound **56g** and vinyl-substituted cyclopropane **56h** were unsuccessful in the reaction and only led to decomposition (Scheme 8, unsuccessful substrates).

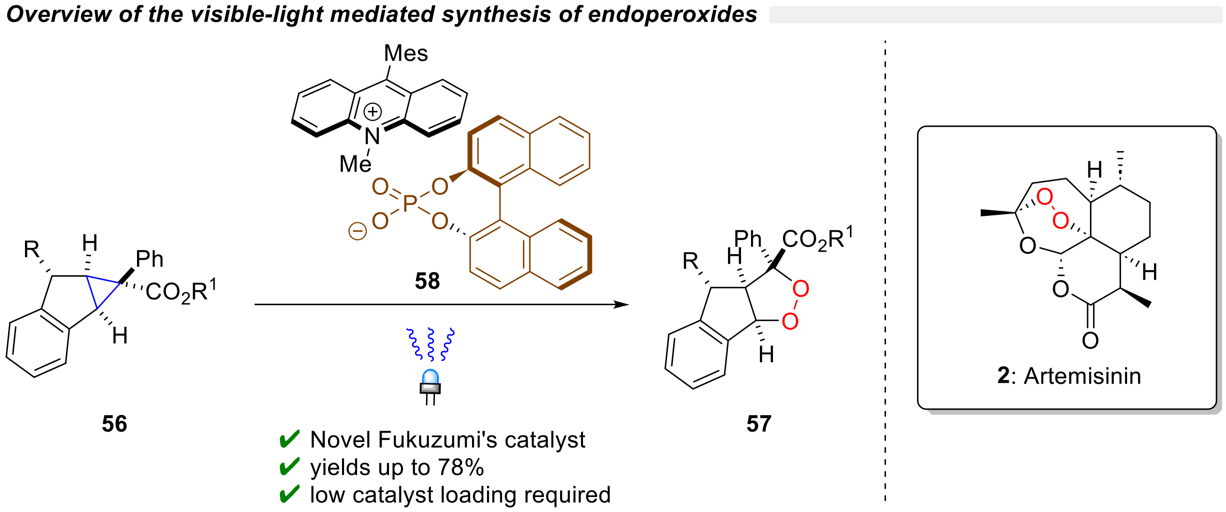


Scheme 8. Scope of the reaction. Reaction conditions: 1 mol% photocatalyst, 0.5-1.5 mmol **56**, 1.0 mL solvent per mmol **56**, blue LED, O_2-balloon, 25 °C, 18 h. Only the major diastereomer **57** is shown. [a] 1.5 mmol scale. [b] NMR-yield given due to fast decomposition of endoperoxide at 25 °C.

In conclusion, the specific dependence of the reaction on the counteranion of the 9-mesityl-10-methylacridinium ion in the visible-light mediated synthesis of complex tricyclic endoperoxides from cyclopropanated alkylated indenes was shown. The exchange of perchlorate counteranion to chiral phosphoric acid resulted in great yield-improvements, whereas the diastereomeric ratio stayed unaffected. Considering the possibility of constructing enantiomerically pure endoperoxides using chiral phosphoric acid compounds, this method could be further explored towards novel antimalarial drugs.

3. Summary

In summary, the first project of the present thesis aimed to address the pressing need for novel and accessible antimalarial drugs, particularly in light of the limited supply and high cost of natural drugs like Artemisinin (**2**). Through the synthesis of antimalarial endoperoxides *via* SET reactions of cyclopropanes, the focus shifted towards developing synthetically accessible alternatives to **2**. Building upon previous research on visible light-mediated synthesis of endoperoxides in our group, this project explored the application of this methodology to cyclopropanated indenes **56**. The journey began with the synthesis of suitable cyclopropane precursors **56**, followed by optimization of the photocatalytic ring expansion process using various catalysts and additives. Despite challenges such as endoperoxide decomposition, the addition of a Lewis acid proved crucial in enhancing yield, albeit with varying effectiveness depending on the choice of catalyst. Further optimizations, including the use of perfluorotoluene as a co-solvent and reduction of catalyst loading, resulted in significant improvements in yield without changing the diastereomeric ratio.

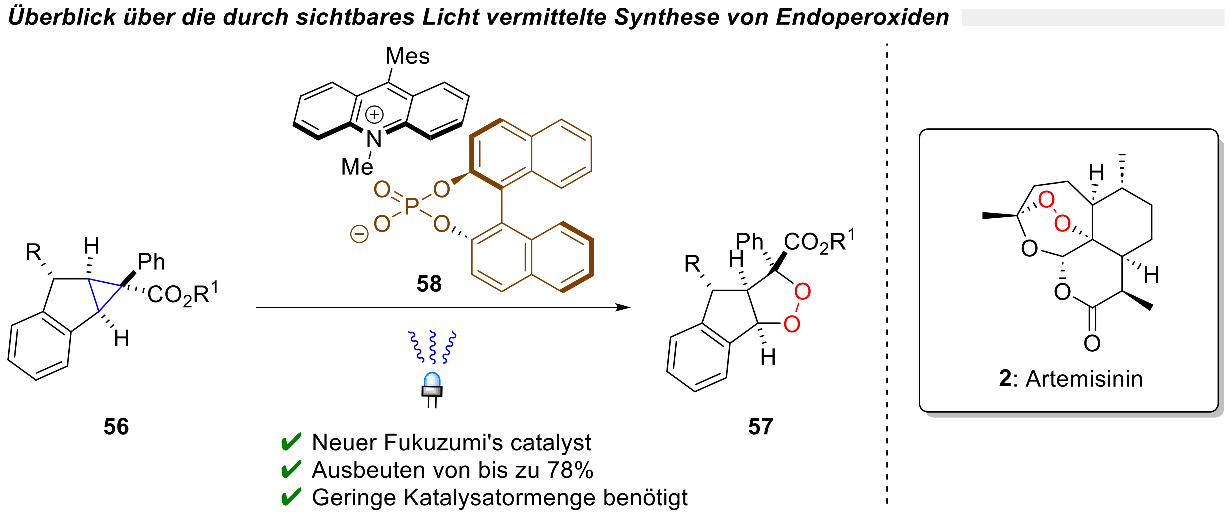


Scheme 9. Schematical summary of the first project.

Furthermore, the study revealed the critical role of the counteranion of the photoredox catalyst in dictating reaction outcomes. The replacement of the perchlorate counteranion (Fukuzumi’s catalyst) with chiral phosphoric acid (compound **58**) led to a notable enhancement in yield, indicating the potential for further investigation into the synthesis of enantiomerically pure endoperoxides (Scheme 9).

4. Zusammenfassung

In der vorliegenden Arbeit wurde im Rahmen des ersten Projekts der dringende Bedarf an neuartigen und zugänglichen Malariamedikamenten untersucht. Dies erfolgte insbesondere vor dem Hintergrund des begrenzten Angebots und der hohen Kosten natürlicher Wirkstoffe wie Artemisinin (**2**). Im Rahmen des Projekts wurde die Synthese von Antimalaria-Endoperoxiden über SET-Reaktionen von Cyclopropanen vorangetrieben, um synthetisch zugängliche Alternativen zu **2** zu entwickeln. Aufbauend auf früheren Forschungen zur mit sichtbarem Licht vermittelten Synthese von Endoperoxiden in unserer Gruppe, wurde in diesem Projekt die Anwendung dieser Methode auf cyclopropanierte Indene **56** untersucht. Das Projekt begann mit der Synthese geeigneter Cyclopropan-Vorläufer **56**, gefolgt von der Optimierung des photokatalytischen Ringerweiterungsprozesses mithilfe verschiedener Katalysatoren und Additive. Obgleich die Endoperoxidzersetzung als Herausforderung zu betrachten war, konnte die Zugabe einer Lewis-Säure als entscheidend für die Steigerung der Ausbeute identifiziert werden. Dabei zeigte sich jedoch eine unterschiedliche Wirksamkeit in Abhängigkeit von der Wahl des Katalysators. Weitere Optimierungen, einschließlich der Verwendung von Perfluortoluol als Co-Lösungsmittel und der Reduzierung der Katalysatorbeladung, führten zu signifikanten Verbesserungen der Ausbeute, ohne das Diastereomerenverhältnis zu verändern.


Überblick über die durch sichtbares Licht vermittelte Synthese von Endoperoxiden

✔ Neuer Fukuzumi's catalyst
✔ Ausbeuten von bis zu 78%
✔ Geringe Katalysatormenge benötigt

Schema 9. Schematische Zusammenfassung des ersten Projekts.

Des Weiteren verdeutlichte die Studie die entscheidende Rolle des Gegenanions des Photoredoxkatalysators bei der Bestimmung des Reaktionsergebnisses. Der Austausch des Perchlorat-Gegenions (Fukuzumis Katalysator) durch eine chirale Phosphorsäure (Verbindung

58) resultierte in einer signifikanten Steigerung der Ausbeute, was auf das Potenzial für weitere Synthesen enantiomerenreiner Endoperoxide hinweist (Schema 9).

5. Experimental procedures

General Information

Solvents and Chemicals

All commercially available compounds were used as received. Anhydrous solvents were prepared by established laboratory procedures.[2] Ethyl acetate and hexanes (40/60) were distilled prior to use in chromatography. [MesAcr]ClO_4 was prepared according to the literature.[59] Methyl 2-diazo-2-phenylacetate[75] and Octyl 2-diazo-2-phenylacetate[76] were prepared according to literature.

Light source in photoreactions

For irradiation, CREE XLamp XP-E D5-15 or OSLON SSL 80 LED ($\lambda = 450\text{-}465$ nm, maximum at 455 nm) light emitting diodes were employed.

NMR spectroscopy

^{1}H, ^{13}C, and ^{31}P spectra were recorded on BRUKER Avance 300 or BRUKER Avance III 400 "Nanobay" spectrometers. The spectra were recorded in $CDCl_3$ unless otherwise specified. The ^{1}H-NMR chemical shifts are reported as δ in parts per million (ppm) relative to the signal of $CHCl_3$ at 7.26 ppm. Coupling constants *J* are given in Hertz (Hz), with following indications for the multiplicity of the signals: s = singlet, d = doublet, t = triplet, q = quartet, quint = quintet, sept = septet, m = multiplet;

The chemical shifts for ^{13}C-NMR are reported as δ in parts per million (ppm) relative to the center line of $CDCl_3$ at 77.0 ppm.

Chromatography

For column chromatography silica gel 60 (Merck, 0.040-0.063 mm particle size) was used. Thin layer chromatography (TLC) was performed on silica gel 60 F254 coated aluminum sheets (Merck) and visualized with UV and vanillin (2.5 g vanillin, 425 mL EtOH, 50 mL conc. AcOH, 25 mL conc. H_2SO_4).

Further analytics

Melting points were determined on an OptiMelt MPA 100.

FT-IR spectroscopy was carried out on an Agilent Technologies Cary 680 FTIR machine with diamond single reflection accessory.

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[2] a) Armarego, W. L. F.; Chai, C. L. L., Purification of Laboratory Chemicals. 6 ed.; Butterworth-Heinemann Oxford, 2009.[73]
b) Hünig, S.; Felderhoff, M.; Kemmerer, M.; Kreitmeier, P.; Märkl, G.; Sauer, J.; Seifert, M.; Sustmann, R.; Troll, Integriertes Organisch-Chemisches Praktikum (I.O.C.-Praktikum); 1. ed.; Lehmanns, 2007.[74].

Mass spectroscopy was carried out by the Central Analytical Laboratory of the University of Regensburg on Jeol AccuTOF GCX or Agilent Q-TOF 6540 UHD systems.

Cyclovoltammetry

Cyclic voltammetry was used to determine the oxidation potential of photocatalyst. Ferrocene was used as internal standard (peaks are marked in *italics*), the potential vs. SCE is then calculated as follows[77]:

$$E_{1/2}[V]=E_{\mathrm{S}}[V]-E_{\mathrm{F}}[V]+C$$

($E_{1/2}[V]$: Redox potential vs. SCE; $E_{\mathrm{S}}[V]$: Measured redox potential of the analyte; $E_{\mathrm{F}}[V]$: Measured redox potential of ferrocene; Correction factor $C \coloneqq +\ 0.38$ V).

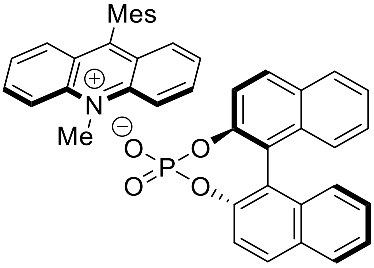
UV/Vis

Absorption spectra were measured on an Agilent Cary 100 UV/Vis spectrometer in a 0.10 mm thick 10 mm × 10 mm quartz cuvette at 25.0 °C.

Emission spectra were recorded with a Horiba® Scientific FluoroMax-4 instrument.

5.1. Catalyst and Substrate Synthesis

9-Mesityl-10-methylacridin-10-ium dinaphtho[2,1-d:1',2'-f][1,3,2]dioxaphosphepin-4-olate 4-oxide (58)



A solution of 9-Mesityl-10-methylacridin-10-ium perchlorate (1.1 g, 2.6 mmol, 1.0 equiv) and sodium dinaphtho[2,1-d:1',2'-f][1,3,2]dioxaphosphepin-4-olate 4-oxide (0.9 g, 2.6 mmol, 1.0 equiv) were suspended together in $CHCl_3$ (5 mL) and refluxed for 1 h. Afterwards, the precipitated solid ($NaClO_4$) was filtered off and the solvent was evaporated under reduced pressure yielding **58** as a pale yellow solid (1.7 g, 2.6 mmol, quant.)

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.47 (d, *J* = 9.3 Hz, 2H), 7.95 (t, *J* = 8.0 Hz, 2H), 7.74 (dd, *J* = 19.5, 8.4 Hz, 4H), 7.55 (d, *J* = 9.1 Hz, 4H), 7.41 (t, *J* = 7.7 Hz, 2H), 7.26 (t, *J* = 10.4 Hz, 4H), 7.13 – 7.02 (m, 4H), 4.62 (s, 3H), 2.40 (s, 3H), 1.54 (s, 6H).

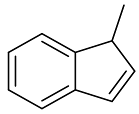
^{13}C-NMR (101 MHz, $CDCl_3$): δ 161.5, 150.3, 150.2, 141.1, 140.1, 139.2, 135.6, 132.6, 130.9, 129.9, 129.4, 129.0, 128.2, 128.1, 128.0, 127.0, 125.6, 125.4, 124.2, 122.8, 122.8, 122.4, 122.4, 119.6, 39.2, 21.2, 20.0.

^{31}P-NMR (162 MHz, $CDCl_3$): δ 6.8.

General Procedure A: Synthesis of Alkylated Indenes:

In a procedure modified from the literature,[78] a flame-dried Schlenk flask containing a solution of indene (1.0 equiv) in anhydrous Et_2O (1 mL per mmol of indene) was prepared. n-Butyllithium (1.1 equiv) was then added dropwise at 0 °C. The mixture was allowed to warm to room temperature and stirred for 3 hours. Afterwards, the indene solution was added dropwise to the corresponding alkylhalogenide (4.0 equiv) dissolved in Et_2O (approx. 0.25 mL per mmol alkyhalogenide) at 0 °C. The mixture was allowed to reach room temperature and stirred overnight. $NH_4Cl_{aq.}$ was added and the mixture was extracted with Et_2O. The combined organic layers were dried over anhydrous Na_2SO_4 and the volatiles were removed under reduced pressure. The residue was purified by flash chromatography with hexanes and used in the next step without further purification.

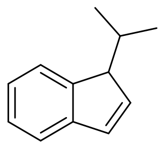
1-Methyl-1H-indene (59a)



Following general procedure A, compound was prepared from indene (4.7 mL, 40.0 mmol, 1.0 equiv) and methyl iodide (10.0 mL, 160.0 mmol, 4.0 equiv). Flash colum chromatography with hexanes yielded title compound **59a** as a colorless oil (3.5 g, 27.0 mmol, 68%).

^{1}H-NMR (300 MHz, CDCl3): δ 7.48 – 7.15 (m, 4H), 6.82 – 6.75 (m, 1H), 6.49 (dd, *J* = 5.5, 1.9 Hz, 1H), 3.55 – 3.46 (m, 1H), 1.33 (d, *J* = 7.6 Hz, 3H).
^{13}C-NMR (101 MHz, CDCl3): δ 149.3, 144.0, 141.4, 130.3, 126.50, 124.9, 122.7, 121.1, 45.2, 16.1.
Analytical data is in accordance with the literature.[78]

1-Isopropyl-1*H*-indene (59b)



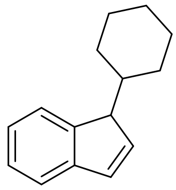
Following general procedure A, compound was prepared from indene (1.2 mL, 10 mmol, 1.0 equiv) and isopropyliodide (1.0 mL, 40 mmol, 4.0 equiv). Flash column chromatography with hexanes yielded title compound **59** as a colorless oil (1.3 g, 8.1 mmol, 81%).

^{1}H-NMR (400 MHz, CDCl$_3$): δ 7.37 – 7.32 (m, 1H), 7.27 (dt, *J* = 7.4, 1.0 Hz, 1H), 7.21 – 7.07 (m, 2H), 6.77 (dd, *J* = 5.7, 2.0 Hz, 1H), 6.43 (dd, *J* = 5.7, 1.9 Hz, 1H), 3.38 – 3.33 (m, 1H), 2.28 (m, 1H), 1.07 (d, *J* = 6.9 Hz, 3H), 0.56 (d, *J* = 6.8 Hz, 3H).

^{13}C-NMR (101 MHz, CDCl$_3$): δ 147.0, 145.1, 137.0, 131.9, 126.5, 124.7, 123.1, 121.0, 57.1, 30.1, 21.7, 17.8.

Analytical data is in accordance with the literature.[78]

1-Cyclohexyl-1*H*-indene (59c)



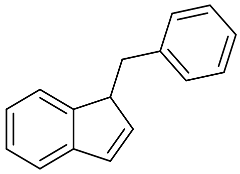
Following general procedure A, compound was prepared from indene (1.8 mL, 15 mmol, 1.0 equiv) and cyclohexylbromide (7.4 mL, 60 mmol, 4.0 equiv). Flash column chromatography with hexanes yielded title compound **59c** as a colorless oil (1.3 g, 6.5 mmol, 43%).

^{1}H-NMR (400 MHz, CDCl$_3$): δ 7.39 – 7.31 (m, 1H), 7.27 (dd, *J* = 7.0, 1.1 Hz, 1H), 7.20 – 7.15 (m, 1H), 7.11 (dt, *J* = 7.4, 1.3 Hz, 1H), 6.75 (dd, *J* = 5.6, 2.0 Hz, 1H), 6.46 (dd, *J* = 5.6, 1.9 Hz, 1H), 3.34 (q, *J* = 2.1 Hz, 1H), 1.92 (ddt, *J* = 11.6, 7.8, 3.8 Hz, 1H), 1.88 – 1.79 (m, 1H), 1.77 – 1.68 (m, 1H), 1.63 – 1.49 (m, 2H), 1.33 – 1.12 (m, 3H), 1.12 – 0.98 (m, 2H), 0.85 (m, 1H).

^{13}C-NMR (101 MHz, CDCl$_3$): δ 146.8, 145.1, 137.7, 131.5, 126.4, 124.6, 123.2, 120.9, 56.7, 40.5, 32.4, 28.4, 27.1, 26.7.

Analytical data is in accordance with the literature.[78]

1-Benzyl-1*H*-indene (59d)



Following general procedure A, compound was prepared from indene (1.8 mL, 15 mmol, 1.0 equiv) and benzylbromide (7.1 mL, 60 mmol, 4.0 equiv). Flash column chromatography with hexanes yielded title **59d** compound as a colorless oil (1.6 g, 7.9 mmol, 53%).

^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.38 – 7.23 (m, 8H), 7.20 – 7.13 (m, 1H), 6.84 – 6.77 (m, 1H), 6.44 (dd, *J* = 5.6, 1.9 Hz, 1H), 3.78 – 3.67 (m, 1H), 3.12 (dd, *J* = 13.4, 6.8 Hz, 1H).

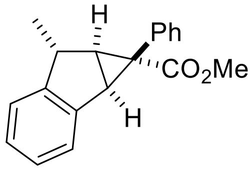
^{13}C-NMR (75 MHz, $CDCl_3$): δ 266.0, 206.6, 147.2, 144.5, 140.5, 139.1, 131.1, 129.2, 128.5, 126.8, 126.4, 124.8, 123.3, 121.3, 52.0, 38.2.

Analytical data is in accordance with the literature.[78]

General Procedure B: Cyclopropanation of Alkylated Indenes with $Rh_2(OAc)_4$:

In a modified literature procedure[48], a 100 mL round bottom flask was charged with a solution of alkylated indene (1.0 equiv) and $Rh_2(OAc)_4$ (0.1 mol%) in DCM (anh., approx. 2 mL per mmol Indene). The flask was then equipped with a rubber septum. In a separate flask, diazoacetate (1.5 equiv) was dissolved in DCM (anh., approx. 0.3 mL per mmol diazoacetate). This solution was then drawn up into a syringe and added to the solution of substrate and catalyst via a syringe pump over the course of 3 h. The resulting solution was stirred overnight, then the solvent was removed under reduced pressure and the resulting crude product purified by recrystallization from ethanol.

Methyl (1*S*,1a*R*,6*R*,6a*R*)-6-methyl-1-phenyl-1,1a,6,6a-tetrahydrocyclopropa[*a*]indene-1-carboxylate (56a)



Following general procedure B, compound **59a** (2.4 g, 18.1 mmol, 1.0 equiv) and methyl 2-phenyl-2-diazoacetate (4.8 g, 27.1 mmol, 1.5 equiv) were reacted. Recrystallization from ethanol yielded title compound **56a** as a white crystalline solid (3.9 g, 13.8 mmol, 77%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.44 – 7.40 (m, 1H), 7.14 – 7.09 (m, 1H), 7.06 (dd, *J* = 5.1, 1.9 Hz, 3H), 6.99 – 6.92 (m, 3H), 6.78 – 6.73 (m, 1H), 3.64 (s, 3H), 3.51 (dd, *J* = 6.6, 1.3 Hz, 1H), 2.99 – 2.91 (m, 1H), 2.68 (dd, *J* = 6.6, 0.6 Hz, 1H), 1.32 (d, *J* = 7.3 Hz, 3H).

^{13}C-NMR (101 MHz, $CDCl_3$): δ 173.9, 148.7, 140.6, 132.7, 132.3, 127.4, 126.6, 126.5, 125.0, 123.5, 52.6, 39.9, 39.7, 39.7, 39.5, 21.9.

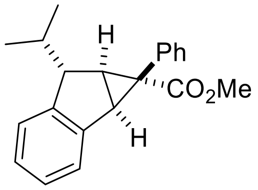
R_f = 0.41 (hexanes/EtOAc : 5/1), Staining: dark brown with vanillin.

IR (neat) ν [cm^{-1}]: 3030, 2960, 2930, 2889, 1707, 1495, 1435, 1372, 1320, 1286, 1241, 1126, 1059, 936, 872, 768, 705, 667.

mp: 89 °C

HRMS (EI-MS): m/z calculated for $C_{19}H_{18}O_2$ [$M^{+\cdot}$] 278.13013, found 278.12910.

Methyl (1*S*,1a*R*,6*R*,6a*R*)-6-isopropyl-1-phenyl-1,1a,6,6a-tetrahydrocyclopropa[*a*]indene-1-carboxylate (56b)



Following general procedure B, compound **59b** (791.0 mg, 5.0 mmol, 1.0 equiv) and methyl 2-phenyl-2-diazoacetate (1.3 g, 7.5 mmol, 1.5 equiv) were reacted. Recrystallization from ethanol yielded title compound **56b** as a white crystalline solid (1.1 g, 3.6 mmol, 72%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.40 (d, *J* = 7.5 Hz, 1H), 7.10 (tt, *J* = 7.4, 0.8 Hz, 1H), 7.07 – 7.00 (m, 3H), 6.96 – 6.86 (m, 3H), 6.73 (d, *J* = 7.5 Hz, 1H), 3.64 (s, 3H), 3.45 (dd, *J* = 6.7, 1.2 Hz, 1H), 2.81 (d, *J* = 3.9 Hz, 1H), 2.72 (d, *J* = 6.7 Hz, 1H), 2.06 (pd, *J* = 6.9, 3.9 Hz, 1H), 1.07 (d, *J* = 6.9 Hz, 3H), 0.79 (d, *J* = 6.9 Hz, 3H).

^{13}C-NMR (101 MHz, $CDCl_3$): δ 174.1, 145.5, 141.8, 132.8, 132.2, 127.3, 126.5, 126.4, 126.2, 124.9, 124.0, 52.6, 51.4, 40.1, 39.1, 34.9, 32.9, 20.2, 18.1.

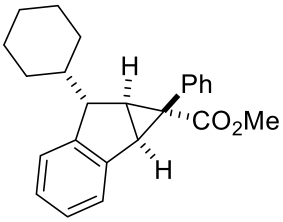
R_f = 0.63 (hexanes/EtOAc : 5/1), Staining: dark brown with vanillin.

IR (neat) ν [cm^{-1}]: 3027, 2956, 2874, 1703, 1435, 1238, 943, 787, 701, 667.

mp: 110 °C

HRMS (EI-MS): m/z calculated for $C_{21}H_{22}O_2$ [$M^{+\cdot}$] 306.16143, found 306.16223.

Methyl (1*S*,1a*R*,6*R*,6a*R*)-6-cyclohexyl-1-phenyl-1,1a,6,6a-tetrahydrocyclopropa[*a*]indene-1-carboxylate (56c)



Following general procedure B, compound **59c** (991.6 mg, 5.0 mmol, 1.0 equiv) and methyl 2-phenyl-2-diazoacetate (1.3 g, 7.5 mmol, 1.5 equiv) were reacted. Recrystallization from ethanol yielded title compound **56c** as a white crystalline solid (1.4 g, 4.0 mmol, 79%).

^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.38 (dd, *J* = 7.5, 1.0 Hz, 1H), 7.12 – 7.01 (m, 4H), 6.97 – 6.84 (m, 3H), 6.72 (ddd, *J* = 7.6, 1.2, 0.6 Hz, 1H), 3.63 (s, 3H), 3.43 (dd, *J* = 6.7, 1.2 Hz, 1H), 2.82 – 2.69 (m, 2H), 1.84 – 1.60 (m, 5H), 1.34 – 1.08 (m, 6H).

^{13}C-NMR (101 MHz, $CDCl_3$): δ 174.2, 145.3, 141.9, 132.8, 132.3, 127.3, 126.5, 126.4, 126.3, 124.9, 124.2, 52.6, 51.2, 43.5, 40.2, 39.4, 35.7, 30.9, 28.7, 26.8, 26.7, 26.7.

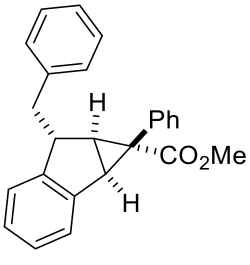
R_f = 0.65 (hexanes/EtOAc : 5/1), Staining: light brown with vanillin.

IR (neat) ν [cm^{-1}]: 3019, 2919, 2848, 1711, 1498, 1435, 1301, 1249, 1126, 1077, 1029, 951, 872, 738, 701, 667.

mp: 130 °C

HRMS (ESI-MS): m/z calculated for $C_{24}H_{27}O_2$ ($[M+H]^+$) 347.2006, found 347.2011.

Methyl (1*S*,1a*R*,6*R*,6a*R*)-6-benzyl-1-phenyl-1,1a,6,6a-tetrahydrocyclopropa[*a*]indene-1-carboxylate (56d)



Following general procedure B, compound **59d** (1.0 g, 5.0 mmol, 1.0 equiv) and methyl 2-phenyl-2-diazoacetate (1.3 g, 7.5 mmol, 1.5 equiv) were reacted. Recrystallization from ethanol yielded title compound **56d** as a white crystalline solid (1.2 g, 3.2 mmol, 68%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.64 (d, *J* = 7.5 Hz, 1H), 7.57 (dd, *J* = 8.0, 6.7 Hz, 2H), 7.51 – 7.45 (m, 3H), 7.38 – 7.32 (m, 1H), 7.27 (dd, *J* = 5.0, 1.9 Hz, 3H), 7.13 (dt, *J* = 7.5, 2.1 Hz, 3H), 6.81 (d, *J* = 7.4 Hz, 1H), 3.81 (s, 3H), 3.70 (dd, *J* = 6.6, 1.2 Hz, 1H), 3.41 (dd, *J* = 9.5, 5.9 Hz, 1H), 3.24 (dd, *J* = 13.8, 5.9 Hz, 1H), 3.02 (dd, *J* = 13.8, 9.5 Hz, 1H), 2.95 (d, *J* = 6.6 Hz, 1H).

^{13}C-NMR (101 MHz, $CDCl_3$): δ 173.8, 146.2, 141.1, 139.6, 132.7, 132.2, 129.4, 128.6, 127.5, 126.9, 126.6, 126.4, 126.4, 125.2, 124.1, 52.6, 46.9, 42.5, 39.7, 39.6, 37.1.

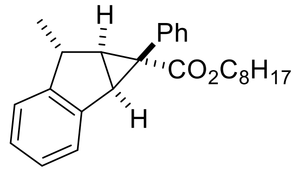
R_f = 0.58 (hexanes/EtOAc : 5/1), Staining: light brown with vanillin.

IR (neat) ν [cm^{-1}]: 3060, 3027, 2952, 2904, 2851, 1715, 1603, 1495, 1435, 1338, 1238, 1211, 1185, 1077, 1025, 969, 872, 835, 738, 701.

mp: 137 °C

HRMS (ESI-MS): m/z calculated for $C_{25}H_{23}O_2$ ($[M+H]^+$) 355.1693, found 355.1700.

Octyl (1S,1aR,6R,6aR)-6-methyl-1-phenyl-1,1a,6,6a-tetrahydrocyclopropa[a]indene-1-carboxylate (56e)



Following general procedure compound **59e** (651.0 mg, 5.0 mmol, 1.0 equiv) and octyl 2-phenyl-2-diazoacetate (2.1 g, 7.5 mmol, 1.5 equiv) were reacted. Column chromatography (hexanes/ethyl acetate 9:1) yielded title compound **56e** as a colorless oil (1.8 g, 4.7 mmol, 93%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.40 (d, *J* = 7.5 Hz, 1H), 7.10 (td, *J* = 7.5, 1.0 Hz, 1H), 7.02 (dd, *J* = 5.2, 1.9 Hz, 3H), 6.94 (td, *J* = 7.5, 2.5 Hz, 3H), 6.74 (d, *J* = 7.5 Hz, 1H), 4.10 – 3.96 (m, 2H), 3.46 (dd, *J* = 6.7, 1.2 Hz, 1H), 2.93 (q, *J* = 7.3 Hz, 1H), 2.62 (d, *J* = 6.6 Hz, 1H), 1.50 (p, *J* = 6.7 Hz, 2H), 1.30 (d, *J* = 7.3 Hz, 4H), 1.22 (dt, *J* = 7.9, 3.9 Hz, 8H), 0.89 (t, *J* = 7.0 Hz, 3H).

^{13}C-NMR (101 MHz, $CDCl_3$): δ 173.4, 148.8, 140.8, 132.3, 127.3, 126.5, 126.5, 125.0, 123.6, 65.4, 40.0, 39.9, 39.4, 39.3, 31.8, 29.3, 29.2, 28.6, 25.8, 22.8, 21.9, 14.2.

R_f = 0.55 (hexanes/EtOAc : 19/1), Staining: dark brown with vanillin

IR (neat) ν [cm^{-1}]: 3027, 2956, 2926, 2855, 1715, 1450, 1379, 1286, 1241, 1170, 1129, 936, 746,

mp: 89 °C

HRMS (EI-MS): m/z calculated for $C_{26}H_{32}O_2$ [$M^{+\cdot}$] 367.23968, found 367.23940.

General procedure C: Photooxygenation of Cyclopropanes

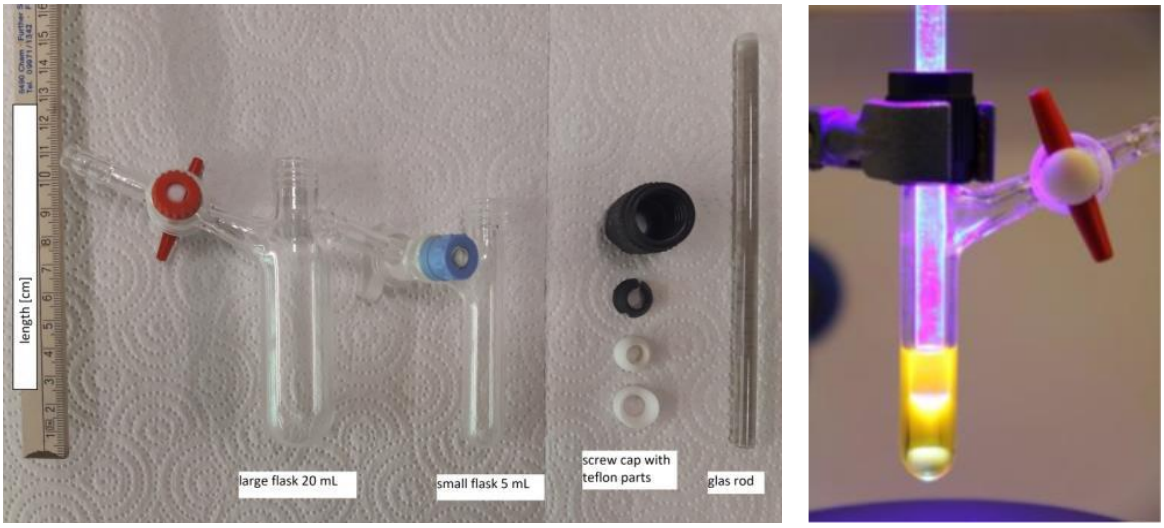
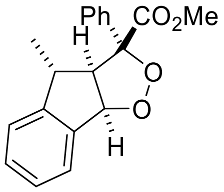
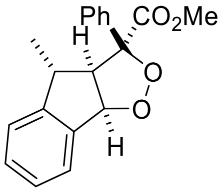


Figure 6. Irradiation setup for photochemical reactions.[68]

In a modified literature procedure[68], a schlenk tube equipped with a magnetic stirring bar, was charged with cyclopropane (1.0 equiv), catalyst B (1 mol%) and $Mg(ClO_4)_2$ (0.5 equiv) and dissolved in a 1:1 mixture of acetonitrile (MeCN) and perfluorotoluene (PFT) (approx. 10 mL per mmol cyclopropane). After oxygen bubbling for 5 minutes, an O_2 filled rubber balloon was attached to the schlenk, while the screw-cap was replaced with a Teflon sealed inlet for a glass rod, through which irradiation with a 455 nm high power LED took place from above while the reaction mixture was magnetically stirred at room temperature (25 °C) until complete conversion of starting material was observed as judged by TLC (4–10 h). Then the solvent was evaporated under reduced pressure and the diastereomeric ratio was determined from the crude reaction mixture via NMR. Column chromatography on silica gel was used for purification.

Methyl (3*R*,3a*R*,4*R*,8b*R*)-4-methyl-3-phenyl-3,3a,4,8b-tetrahydroindeno[1,2-*c*][1,2]dioxole-3-carboxylate (57a) and Methyl (3*S*,3a*R*,4*R*,8b*R*)-4-methyl-3-phenyl-3,3a,4,8b-tetrahydroindeno[1,2-*c*][1,2]dioxole-3-carboxylate (57aa)





Following general procedure C, cyclopropane **56a** (417.5 mg, 1.5 mmol, 1.0 equiv) and $Mg(ClO_4)_2$ (167.4 mg, 0.75 mmol, 0.5 equiv) were dissolved in a 1:1 mixture of MeCN/PFT (15 mL) and irradiated with blue light for 8 h in the presence of **catalyst B** (9.9 mg, 0.015 mmol, 1 mol%). Crude NMR revealed a diastereomeric ratio of 1.5:1. Column chromatography (hexanes:acetone 19:1) yielded the major diastereomer **57a** as a white crystalline solid (219.8 mg, 0.71 mmol, 47%); The minor diastereomer **57aa** could not be purified, the total yield was calculated based on the diastereomeric ratio determined from the crude NMR as 78%.

^{1}H-NMR (**57a**, 400 MHz, $CDCl_3$): δ 7.79 – 7.73 (m, 2H), 7.47 – 7.41 (m, 2H), 7.38 (dt, *J* = 6.6, 1.3 Hz, 2H), 7.35 – 7.30 (m, 1H), 7.30 – 7.21 (m, 2H), 5.57 (d, *J* = 6.9 Hz, 1H), 3.91 (dd, *J* = 7.0, 4.9 Hz, 1H), 3.74 (s, 3H), 3.49 – 3.41 (m, 1H), 1.51 (d, *J* = 7.1 Hz, 3H).

^{13}C-NMR (**57a**, 101 MHz, $CDCl_3$): δ 168.6, 148.5, 138.6, 138.4, 130.2, 128.7, 128.6, 127.8, 126.4, 126.0, 123.8, 93.1, 88.8, 69.1, 52.8, 42.9, 21.8.

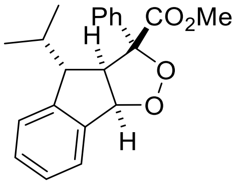
R_f (**57a**) = 0.46 (hexanes/EtOAc : 5/1), dark brown with vanillin.

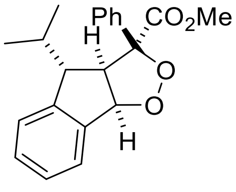
IR (**57a**, neat) ν [cm^{-1}]: 2960, 2926, 2855, 1733, 1450, 1241, 1066, 1021, 753, 716.

mp (**57a**): 148 °C

HRMS (EI-MS): m/z calculated for **57a** $C_{19}H_{18}O_4Na$ $[(M+Na)]^+$ 333.1101, found 333.1097.

Methyl (3*R*,3a*R*,4*R*,8b*R*)-4-isopropyl-3-phenyl-3,3a,4,8b-tetrahydroindeno[1,2-*c*][1,2]dioxole-3-carboxylate (57b) and Methyl (3*S*,3a*R*,4*R*,8b*R*)-4-isopropyl-3-phenyl-3,3a,4,8b-tetrahydroindeno[1,2-*c*][1,2]dioxole-3-carboxylate (57bb)





Following general procedure C, cyclopropane **56b** (153.2 mg, 0.5 mmol, 1.0 equiv) and $Mg(ClO_4)_2$ (55.8 mg, 0.25 mmol, 0.5 equiv) were dissolved in a 1:1 mixture of MeCN/PFT (5 mL) and irradiated with blue light for 10 h in the presence of **catalyst B** (3.3 mg, 0.005 mmol, 1 mol%). Crude NMR revealed a diastereomeric ratio of 1.6:1. Column chromatography (hexanes:acetone 19:1) yielded the major diastereomer **57b** as a white crystalline solid (67.8 mg, 0.20 mmol, 40%); The minor diastereomer **57bb** could not be purified, the total yield was calculated based on the diastereomeric ratio determined from the crude NMR as 65%.

^{1}H-NMR (**57b**, 400 MHz, $CDCl_3$): δ 7.64 – 7.52 (m, 2H), 7.30 – 7.03 (m, 7H), 5.56 (d, *J* = 7.1 Hz, 1H), 3.78 (dd, *J* = 7.1, 2.3 Hz, 1H), 3.49 (s, 3H), 3.29 (dd, *J* = 4.0, 2.3 Hz, 1H), 1.97 (pd, *J* = 6.9, 3.9 Hz, 1H), 0.88 (d, *J* = 6.8 Hz, 3H), 0.63 (d, *J* = 6.9 Hz, 3H).

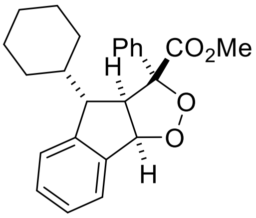
^{13}C-NMR (**57b**, 101 MHz, $CDCl_3$): δ 168.9, 145.4, 140.2, 139.9, 129.6, 128.4, 128.4, 128.0, 126.5, 125.4, 124.5, 92.8, 89.6, 64.2, 53.5, 52.7, 33.9, 20.3, 18.6.

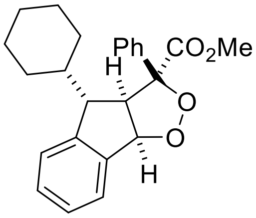
R_f (**57b**) = 0.5 (hexanes/EtOAc : 5/1), Staining: brown with vanillin.

IR (**57b**, neat) ν [cm^{-1}]: 3068, 3030, 2960, 2874, 1711, 1601, 1461, 1267, 1238, 1178, 1166, 1096, 1044, 760, 712.

HRMS (ESI-MS): m/z calculated for **57b** $C_{21}H_{23}O_4$ $[(M+H)]^+$ 339.1591, found 339.1587.

Methyl (3*R*,3a*R*,4*R*,8b*R*)-4-cyclohexyl-3-phenyl-3,3a,4,8b-tetrahydroindeno[1,2-*c*][1,2]dioxole-3-carboxylate (57c) and Methyl (3*S*,3a*R*,4*R*,8b*R*)-4-cyclohexyl-3-phenyl-3,3a,4,8b-tetrahydroindeno[1,2-*c*][1,2]dioxole-3-carboxylate (57cc)





Following general procedure C, cyclopropane **56c** (173.2 mg, 0.5 mmol, 1.0 equiv) and $Mg(ClO_4)_2$ (55.8 mg, 0.25 mmol, 0.5 equiv) were dissolved in a 1:1 mixture of MeCN/PFT (5 mL) and irradiated with blue light for 4 h in the presence of **catalyst B** (3.3 mg, 0.005 mmol, 1 mol%). Crude NMR revealed a diastereomeric ratio of 1.7:1. Column chromatography (hexanes:acetone 19:1) yielded the major diastereomer **57c** as a white crystalline solid (78.3 mg, 0.21 mmol, 41%); The minor diastereomer **57cc** could not be purified, the total yield was calculated based on the diastereomeric ratio determined from the crude NMR as 65%.

^{1}H-NMR (**57c**, 400 MHz, $CDCl_3$): δ 7.62 – 7.51 (m, 2H), 7.31 – 7.00 (m, 7H), 5.55 (d, *J* = 7.0 Hz, 1H), 3.82 (dd, *J* = 7.1, 2.2 Hz, 1H), 3.46 (s, 3H), 3.24 (t, *J* = 2.9 Hz, 1H), 1.67 – 1.48 (m, 5H), 1.19 – 0.85 (m, 6H).

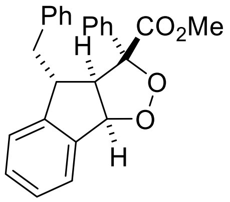
^{13}C-NMR (**57c**, 101 MHz, $CDCl_3$): δ 168.9, 145.2, 140.3, 140.0, 129.5, 128.4, 128.4, 127.9, 126.5, 125.3, 124.6, 92.7, 89.6, 64.9, 53.2, 52.6, 44.4, 31.1, 29.2, 26.7, 26.7, 26.6.

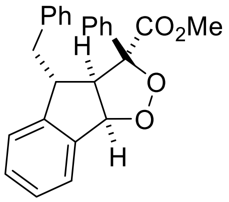
R_f (**57c**) = 0.5 (hexanes/EtOAc : 5/1), Staining: light brown with vanillin.

IR (**57c**, neat) ν [cm^{-1}]: 3068, 3030, 2922, 2851, 1711, 1603, 1495, 1450, 1267, 1241, 1036, 999, 757.

HRMS (EI-MS): m/z calculated for **57c** $C_{24}H_{26}O_4Na$ [(M+Na)]$^+$ 401.1723, found 401.1727.

Methyl (3*R*,3a*R*,4*R*,8b*R*)-4-benzyl-3-phenyl-3,3a,4,8b-tetrahydroindeno[1,2-*c*][1,2]dioxole-3-carboxylate (57d) and Methyl (3*S*,3a*R*,4*R*,8b*R*)-4-benzyl-3-phenyl-3,3a,4,8b-tetrahydroindeno[1,2-*c*][1,2]dioxole-3-carboxylate (57dd)





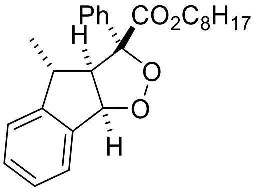
Following general procedure C, cyclopropane **56d** (531.7 mg, 1.5 mmol, 1.0 equiv) and $Mg(ClO_4)_2$ (167.4 mg, 0.75 mmol, 0.5 equiv) were dissolved in a 1:1 mixture of MeCN/PFT (15 mL) and irradiated with blue light for 8 h in the presence of **catalyst B** (9.9 mg, 0.015 mmol, 1 mol%). Crude NMR revealed a diastereomeric ratio of 1.7:1. Column chromatography (hexanes:acetone 19:1) yielded the major diastereomer **57d** as a white crystalline solid (242.4 mg, 0.63 mmol, 42%), which quickly decomposed to a yellow oil after isolation; The minor diastereomer **57dd** could not be purified, the total yield was calculated based on the diastereomeric ratio determined from the crude NMR as 66%.

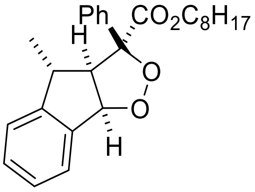
^{1}H-NMR and **^{13}C-NMR**: no pure spectra could be recorded due to fast decomposition of endoperoxide.

R_f (**57d**) = 0.41 (hexanes/EtOAc : 5/1), Staining: brown with vanillin.

HRMS (ESI-MS): m/z calculated for **57d** $C_{25}H_{23}O_4$ [(M+H)]$^+$ 387.1590, found 387.1591.

Octyl (3R,3aR,4R,8bR)-4-methyl-3-phenyl-3,3a,4,8b-tetrahydroindeno[1,2-c][1,2]dioxole-3-carboxylate (57e) and Octyl (3S,3aR,4R,8bR)-4-methyl-3-phenyl-3,3a,4,8b-tetrahydroindeno[1,2-c][1,2]dioxole-3-carboxylate (57ee)





Following general procedure C, cyclopropane **56e** (188.3 mg, 0.5 mmol, 1.0 equiv) and $Mg(ClO_4)_2$ (55.8 mg, 0.25 mmol, 0.5 equiv) were dissolved in a 1:1 mixture of MeCN/PFT (5 mL) and irradiated with blue light for 5 h in the presence of **catalyst B** (3.3 mg, 0.005 mmol, 1 mol%). Crude NMR revealed a diastereomeric ratio of 1.3:1. Column chromatography (hexanes:acetone 19:1) yielded the major diastereomer **57e** as a colorless oil (59.6 mg, 0.15 mmol, 29%); The minor diastereomer **57ee** could not be purified, the total yield was calculated based on the diastereomeric ratio determined from the crude NMR as 51%.

^{1}H-NMR (**57e**, 400 MHz, $CDCl_3$) δ 7.65 – 7.54 (m, 2H), 7.27 – 7.06 (m, 7H), 5.39 (d, *J* = 6.9 Hz, 1H), 4.02 – 3.90 (m, 2H), 3.74 (dd, *J* = 7.0, 4.8 Hz, 1H), 3.36 – 3.27 (m, 1H), 1.44 – 1.38 (m, 2H), 1.35 (d, *J* = 7.1 Hz, 3H), 1.04 (s, 10H), 0.71 (t, *J* = 7.0 Hz, 3H).

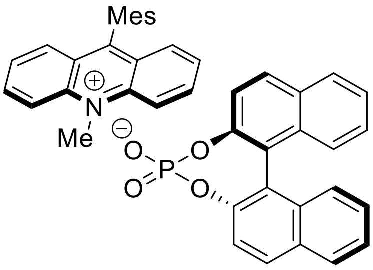
^{13}C-NMR (**57e**, 101 MHz, $CDCl_3$) δ 168.1, 148.5, 138.8, 138.6, 130.1, 128.5, 128.5, 127.7, 126.3, 126.0, 123.7, 93.0, 88.7, 68.7, 66.1, 42.8, 31.8, 29.2, 29.2, 28.5, 25.8, 22.7, 21.8, 14.2.

R_f (**57e**) = 0.40 (hexanes/EtOAc : 19/1), Staining: brown with vanillin

HRMS (ESI-MS): m/z calculated for **57e** $C_{26}H_{33}O_4$ $[(M+H)]_+$ 409.2373, found 409.2373.

5.2. Spectrophotometric and Electrochemical Data

9-Mesityl-10-methylacridin-10-ium dinaphtho[2,1-d:1',2'-f][1,3,2]dioxaphosphepin-4-olate 4-oxide (58, Catalyst B)



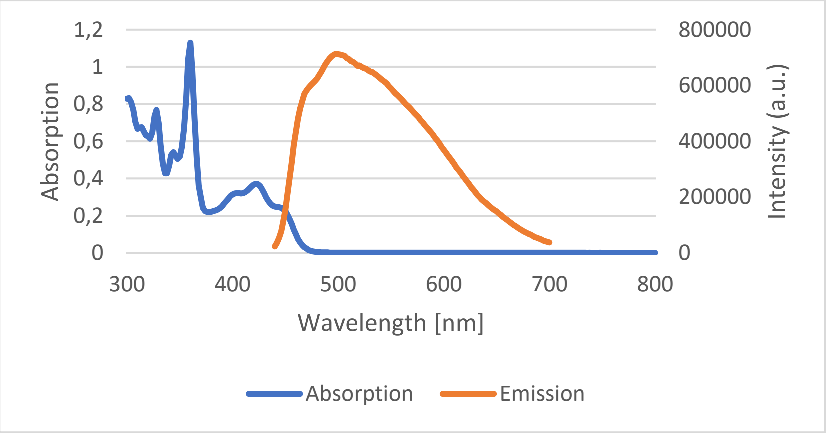


Figure 6. UV-vis absorption and emission spectra of **catalyst B** in MeCN. Intersection at 455 nm.

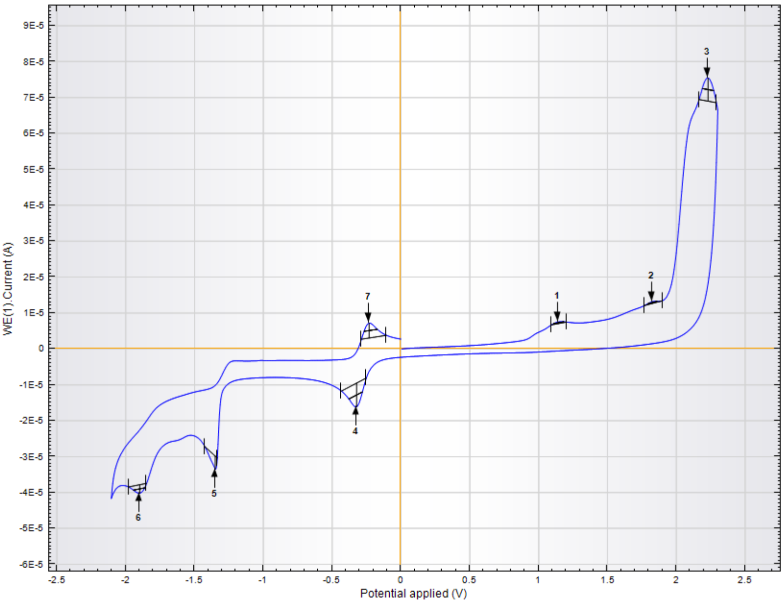


Figure 7. Cyclic voltammetry of **catalyst B** in MeCN. Peaks marked in bold were used to calculate electrochemical potentials against an internal standard ferrocene.

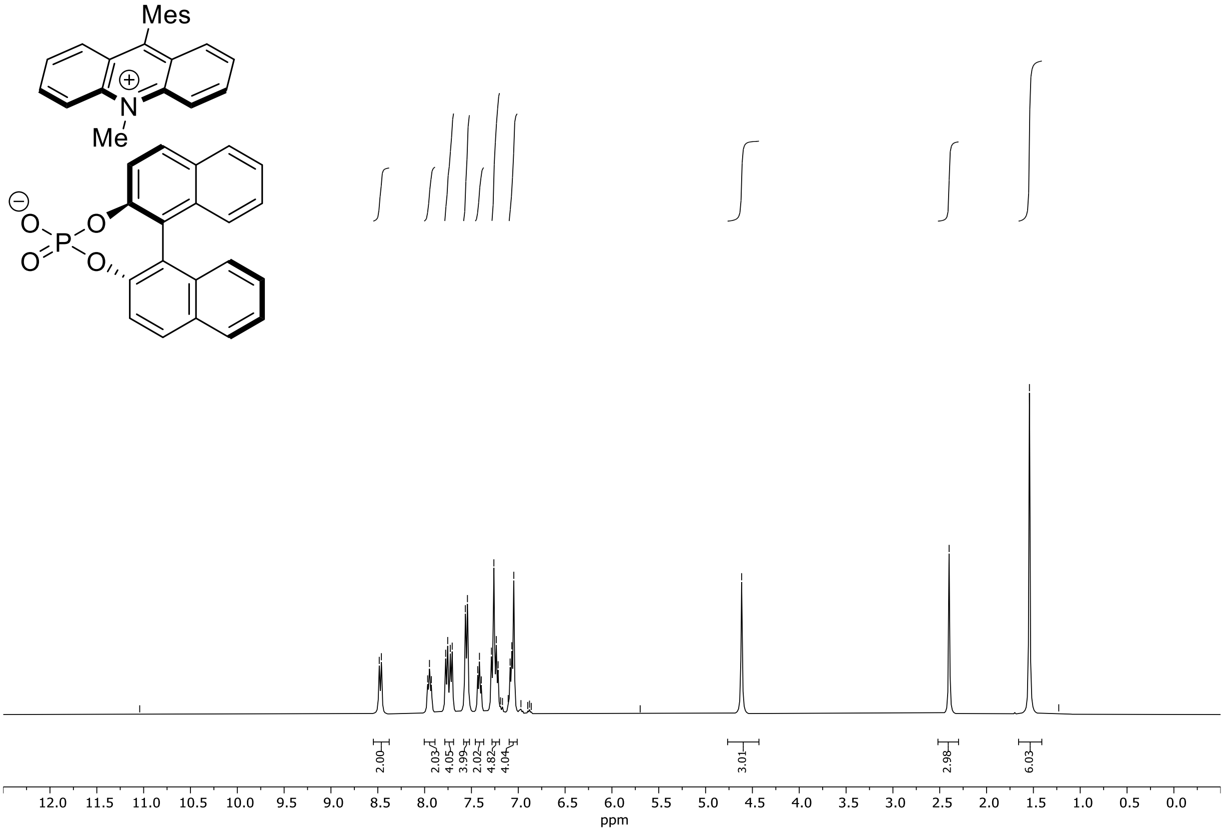
Index	**Peak position**
1	1.143
2	1.8279
3	2.2307
4	**-0.32227**
5	-1.3495
6	-1.8983
7	-0.23163

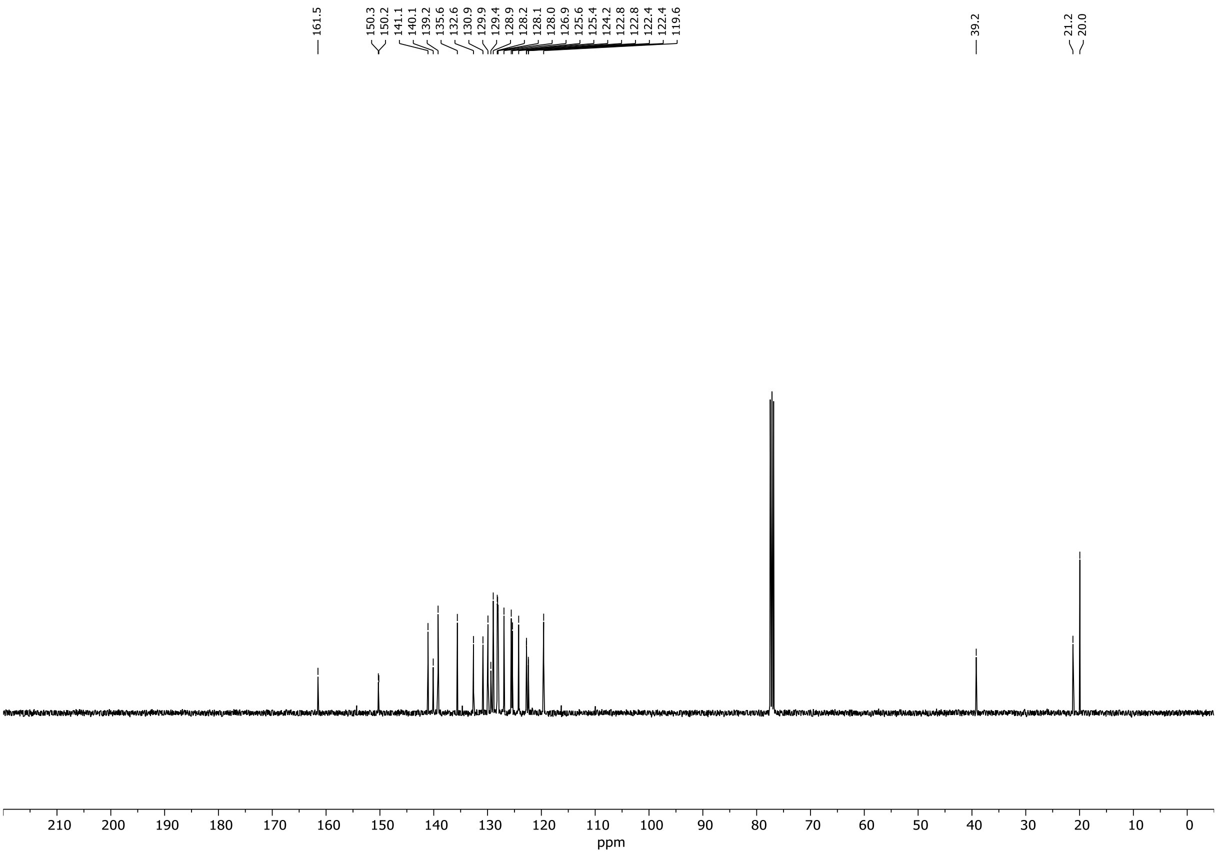
$E_{1/2}[C/C^{-}]$ = **-0.59 V** vs. SCE

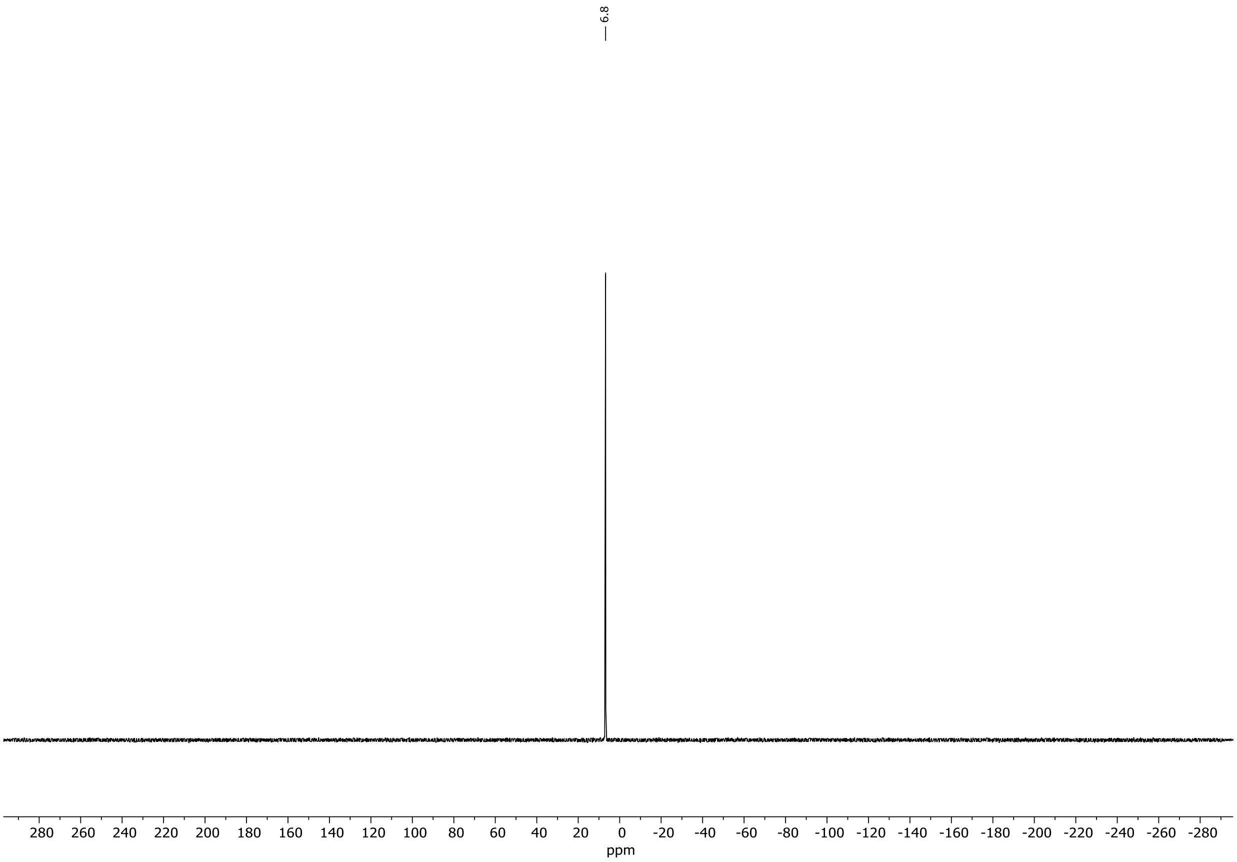
$E_{1/2}[C^{*}/C^{-}]$ = 2.74 + (-0.59) = **2.14** vs. SCE

5.3. NMR-spectra

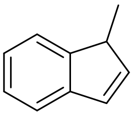
Compound 58: ^{1}H NMR (400 MHz, CDCl$_3$), ^{13}C NMR (101 MHz, CDCl$_3$) and ^{31}P NMR (162 MHz, CDCl$_3$):

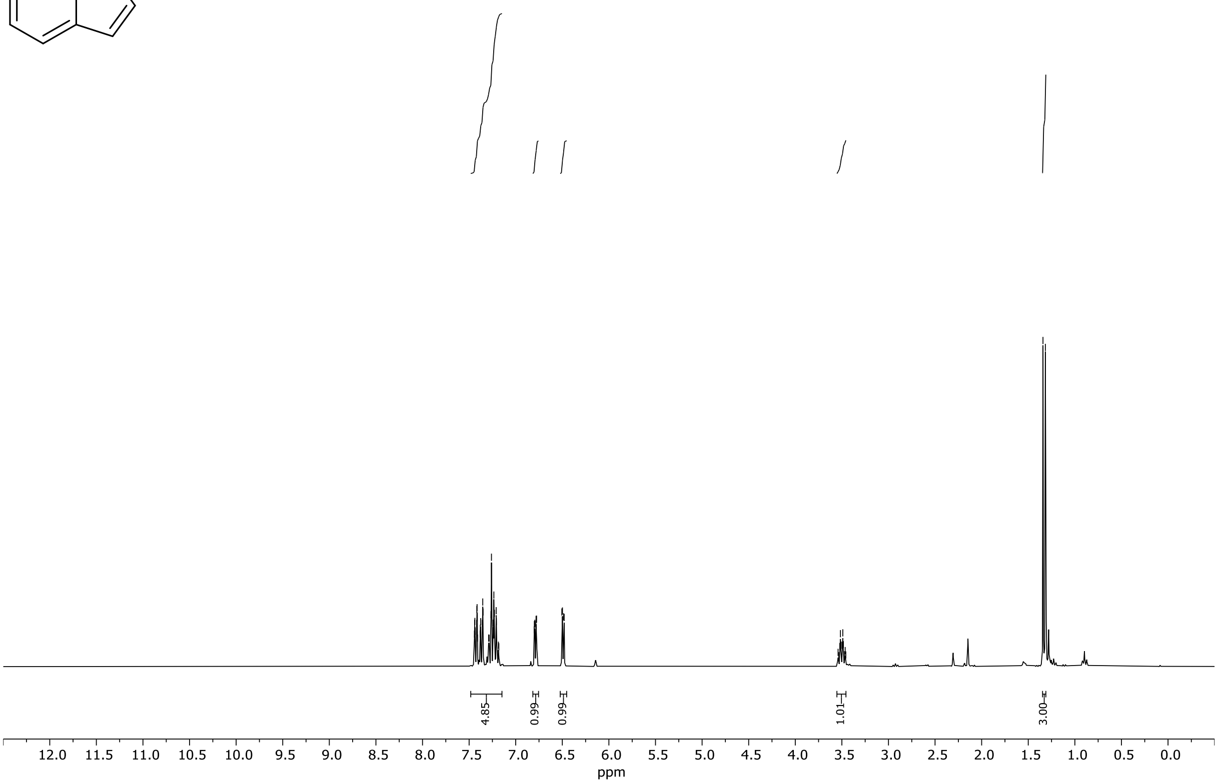


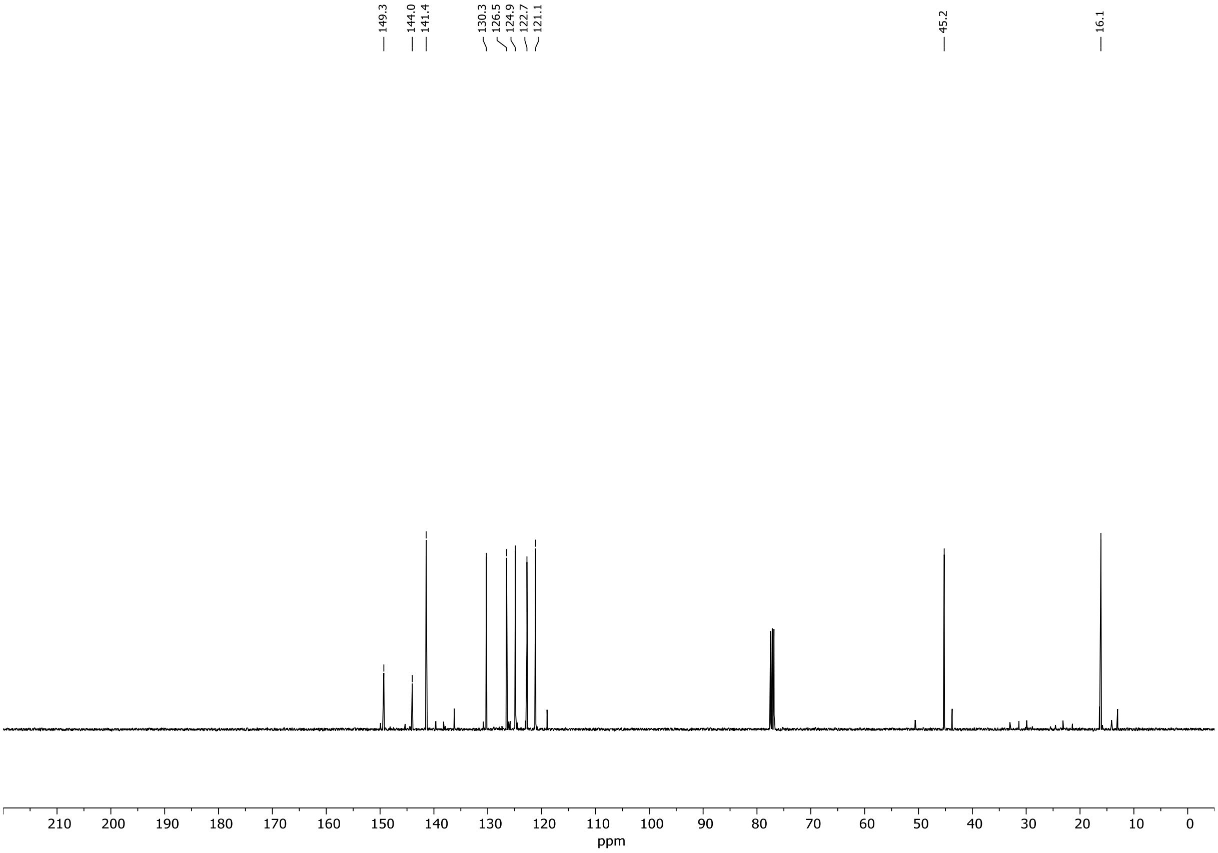



6.8
280
260
240
220
200
180
160
140
120
100
80
60
40
20
0
-20
-40
-60
-80
-100
-120
-140
-160
-180
-200
-220
-240
-260
-280
ppm

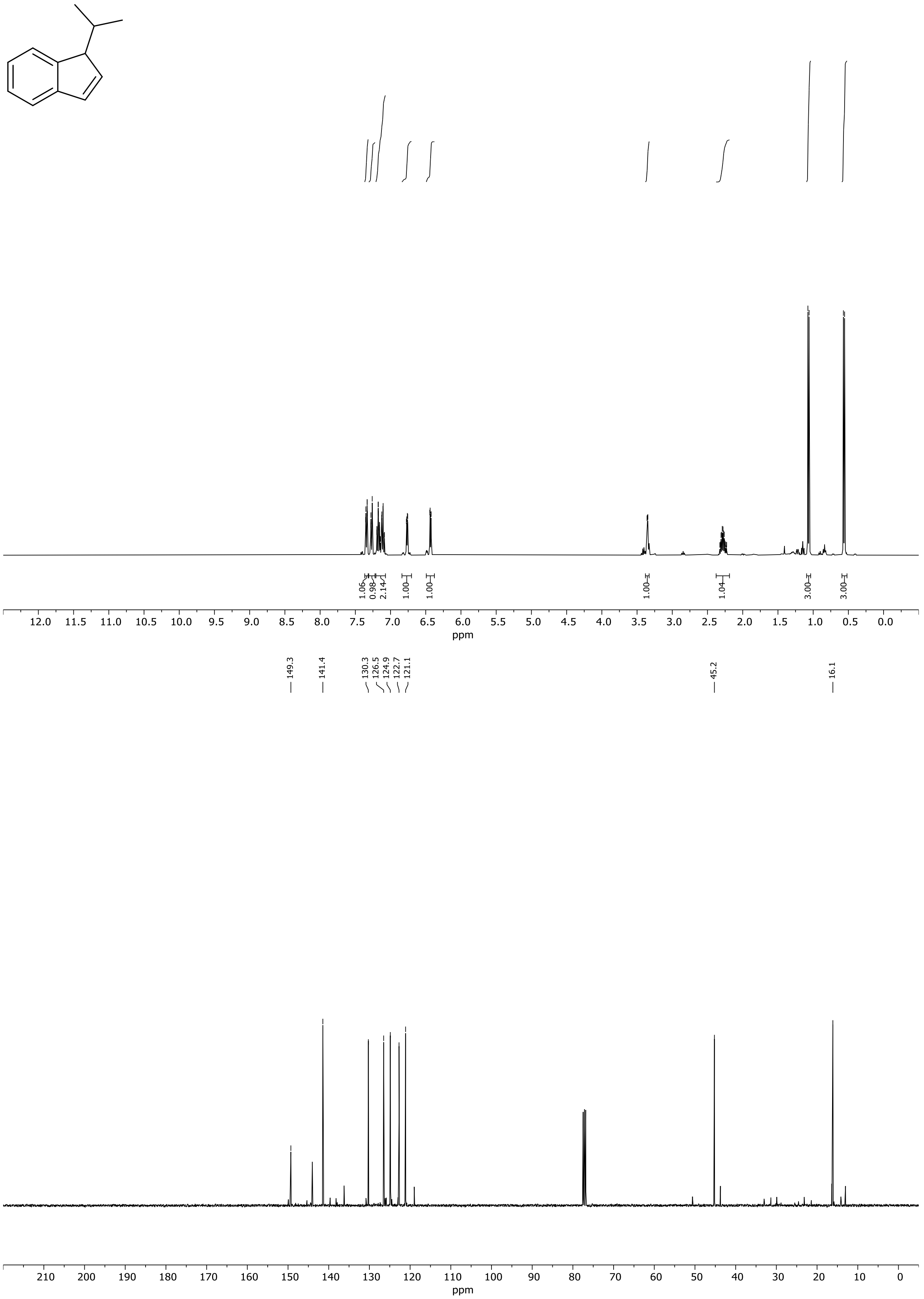
Compound 59a: ^{1}H NMR (400 MHz, $CDCl_3$), ^{13}C NMR (101 MHz, $CDCl_3$)



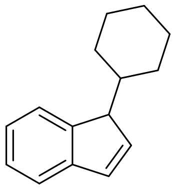


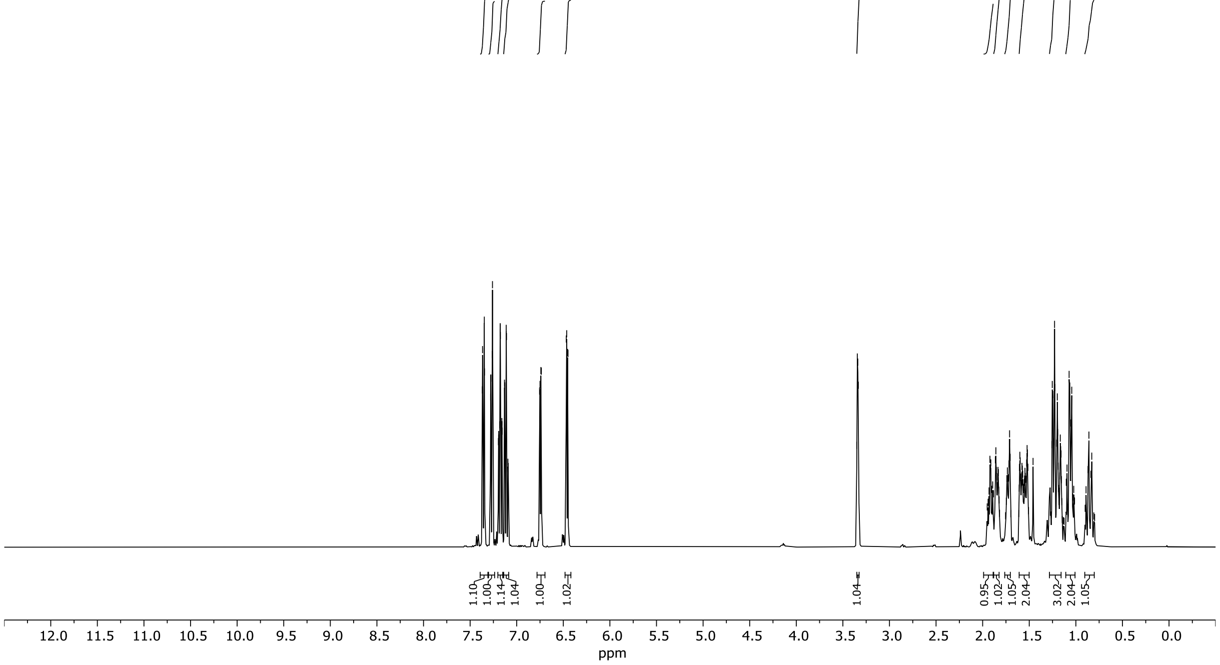


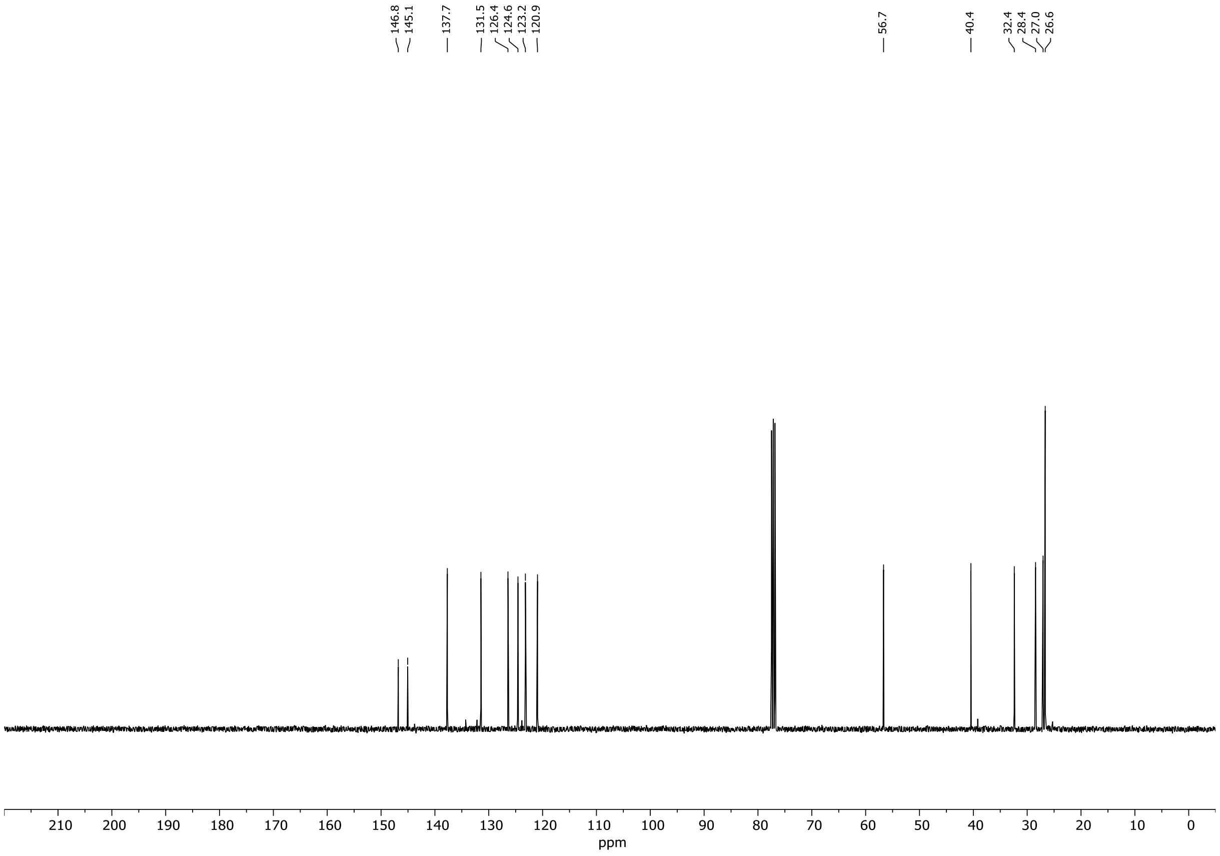
Compound 59b: ^{1}H NMR (400 MHz, CDCl$_3$), ^{13}C NMR (101 MHz, CDCl$_3$)



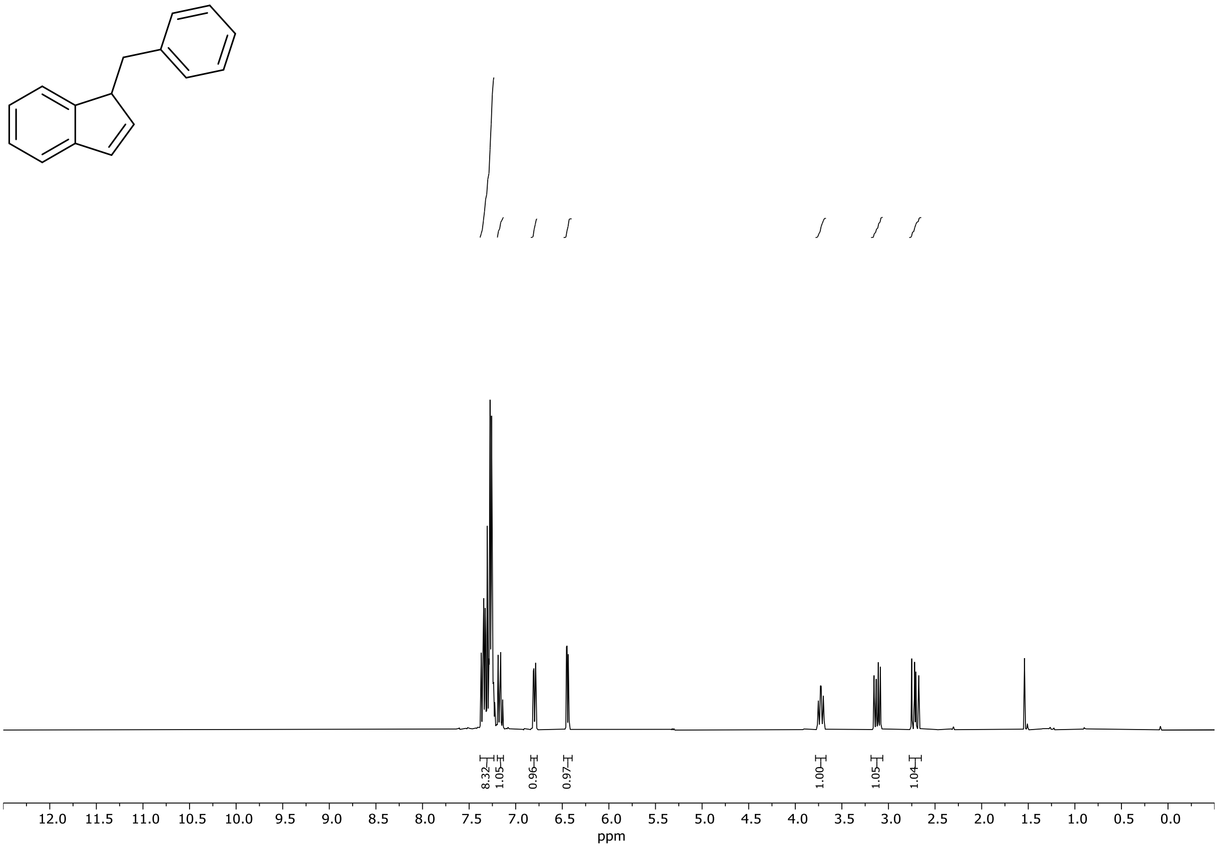
Compound 59c: ^{1}H NMR (400 MHz, CDCl$_3$), ^{13}C NMR (101 MHz., CDCl$_3$)

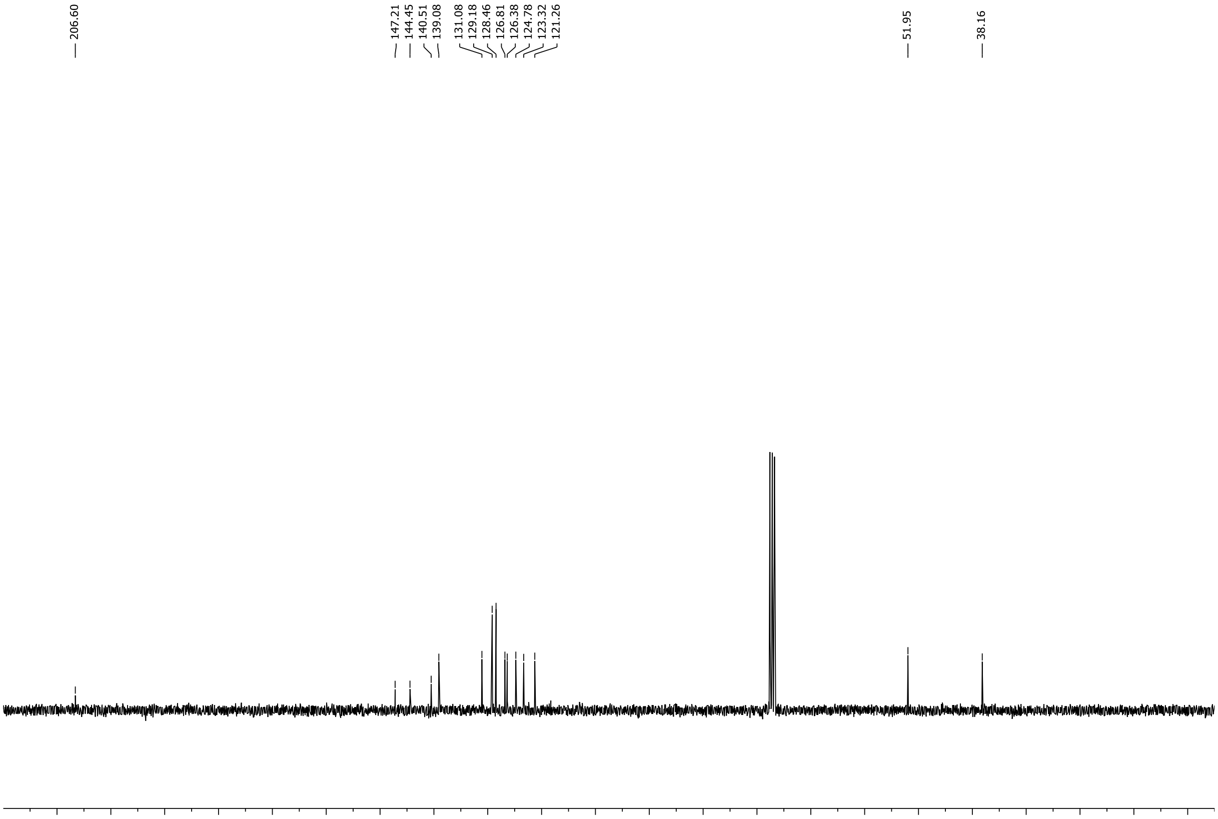




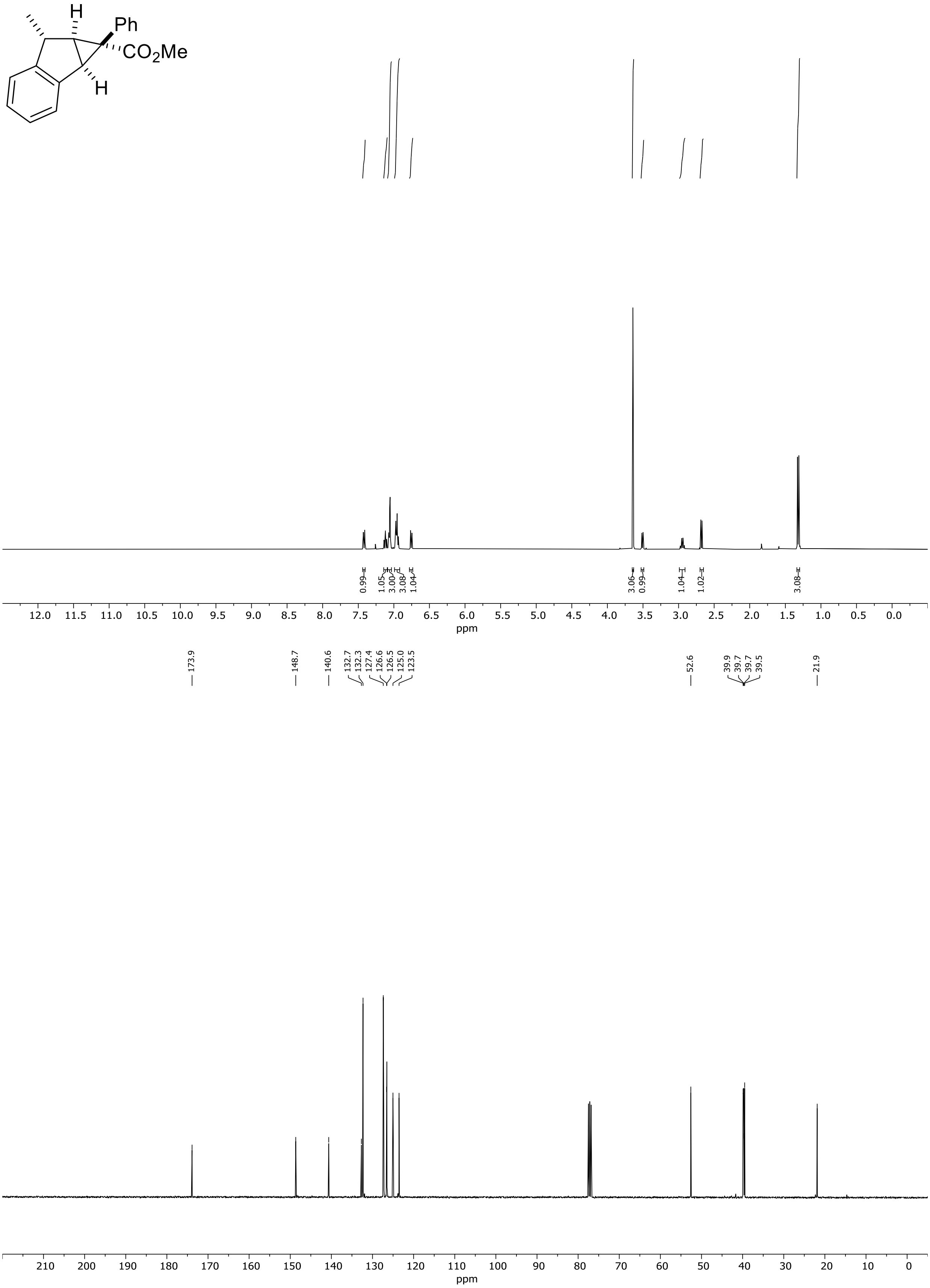


Compound 59d: ^{1}H NMR (400 MHz, CDCl$_3$), ^{13}C NMR (101 MHz, CDCl$_3$)

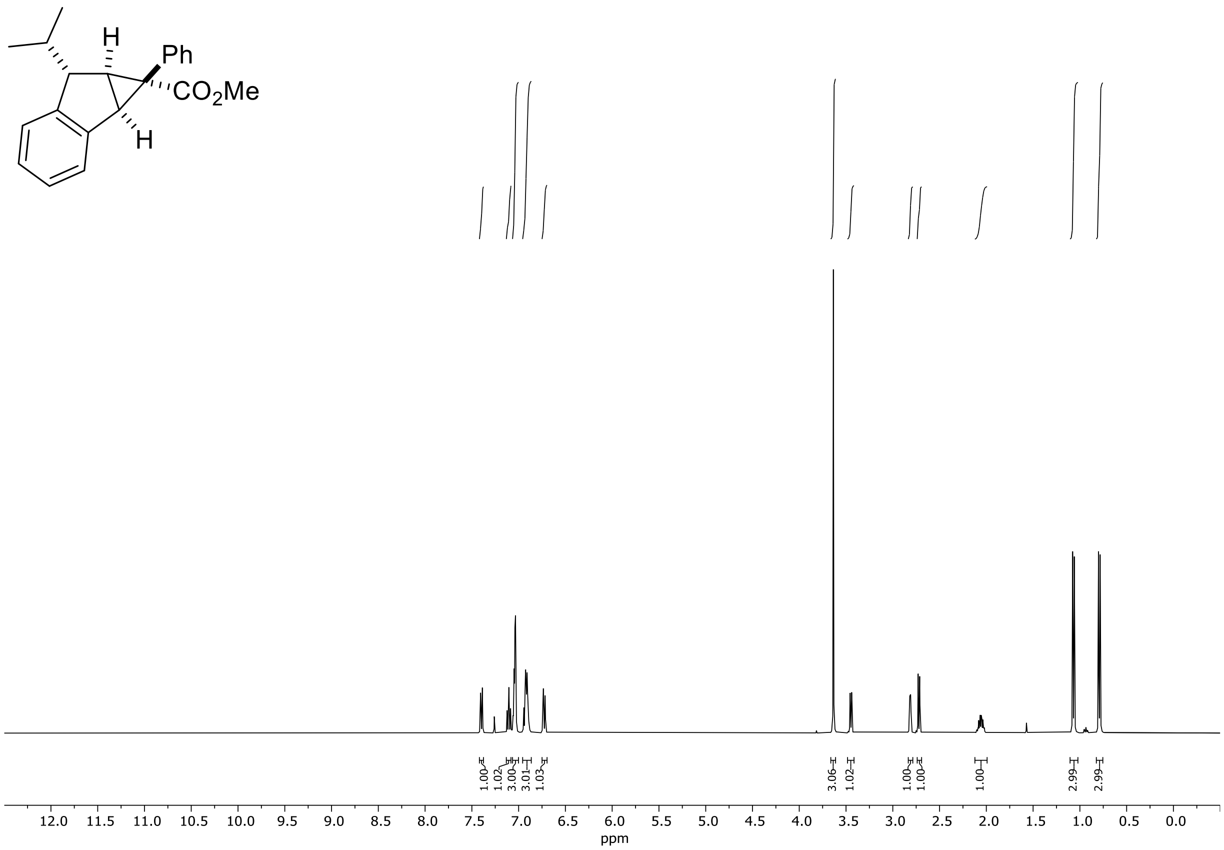


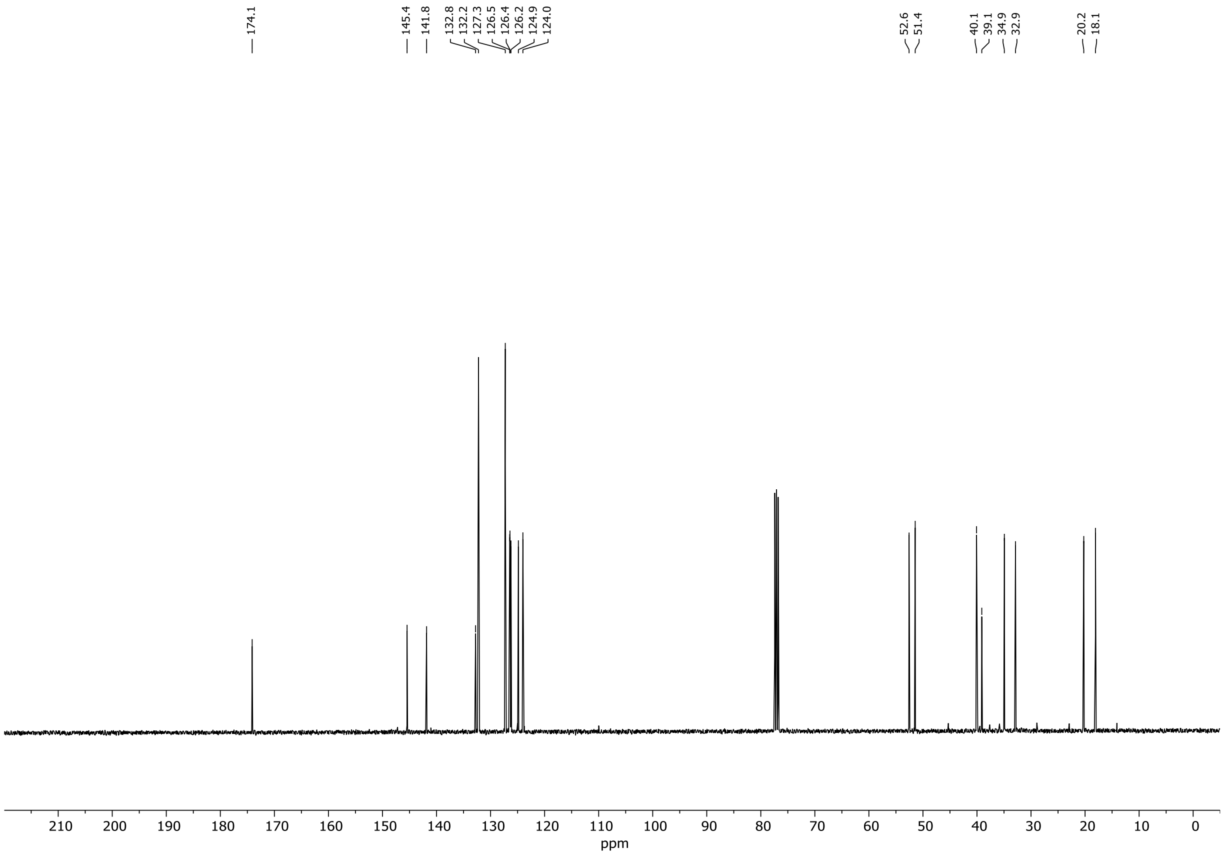


Compound 56a: ^{1}H NMR (400 MHz, $CDCl_3$) and ^{13}C NMR (101 MHz, $CDCl_3$):

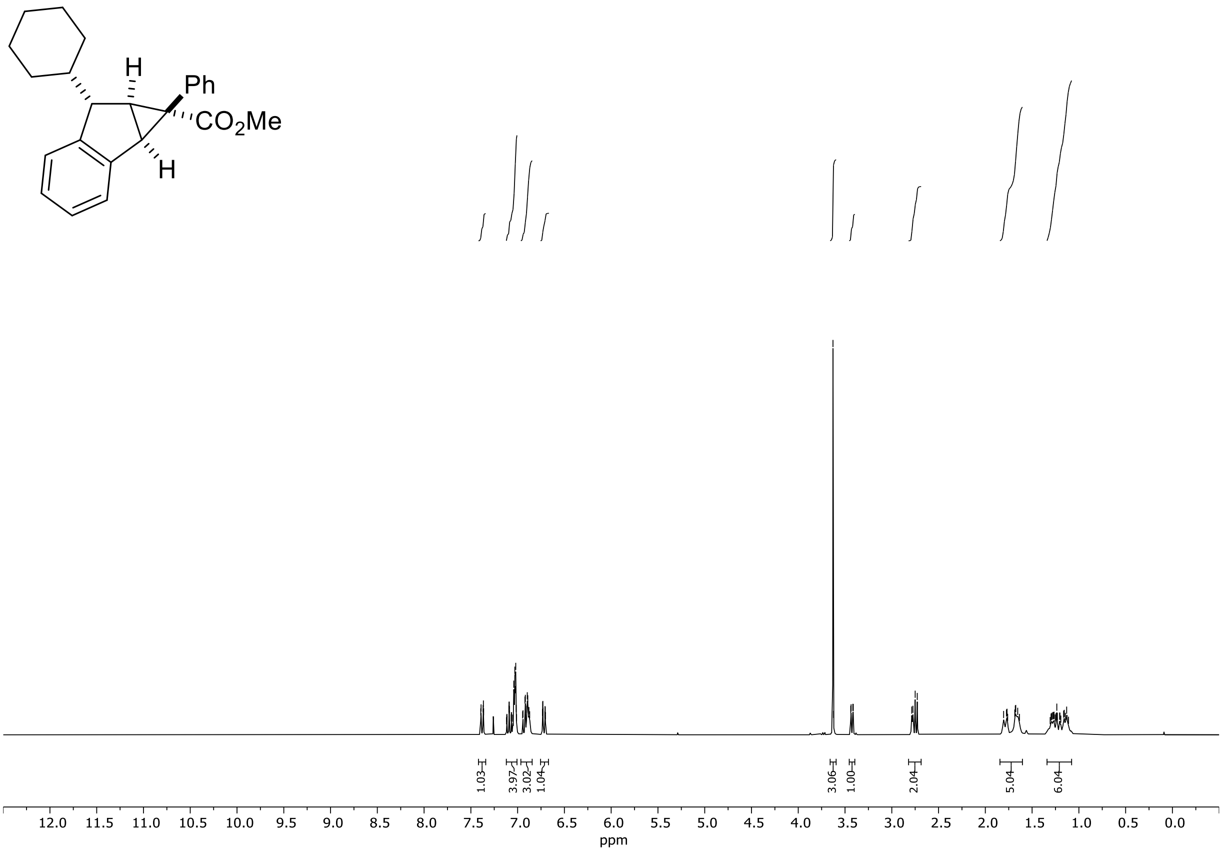


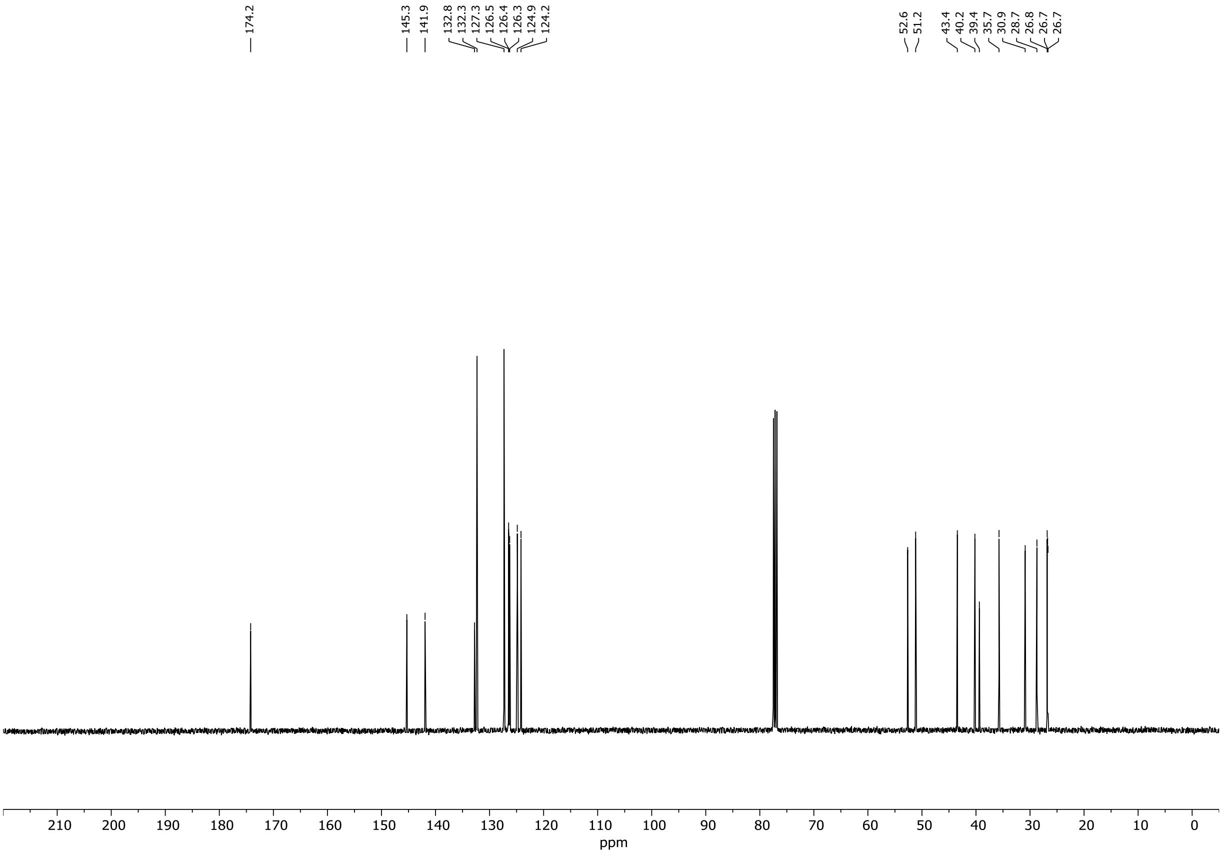
Compound 56b: ^{1}H NMR (400 MHz, $CDCl_3$) and ^{13}C NMR (101 MHz, $CDCl_3$):


H
Ph
CO2Me
H
1.00
1.02
3.00
3.01
1.03
3.06
1.02
1.00
1.00
1.00
2.99
2.99
12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
ppm

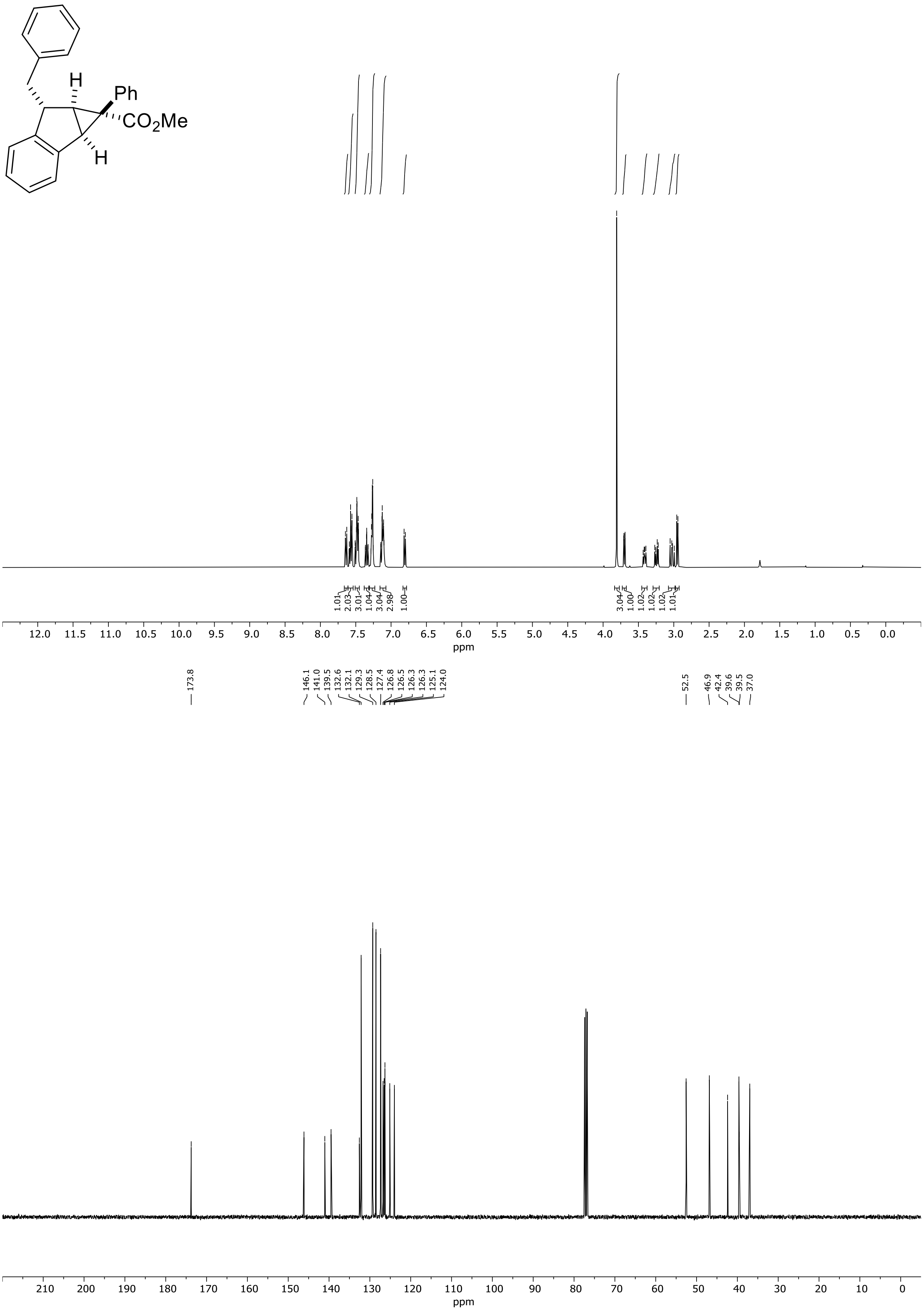

174.1
145.4
141.8
132.8
132.2
127.3
126.5
126.4
126.2
124.9
124.0
52.6
51.4
40.1
39.1
34.9
32.9
20.2
18.1
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
ppm

Compound 56c: ^{1}H NMR (400 MHz, CDCl$_3$) and ^{13}C NMR (101 MHz, CDCl$_3$):

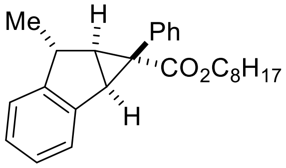




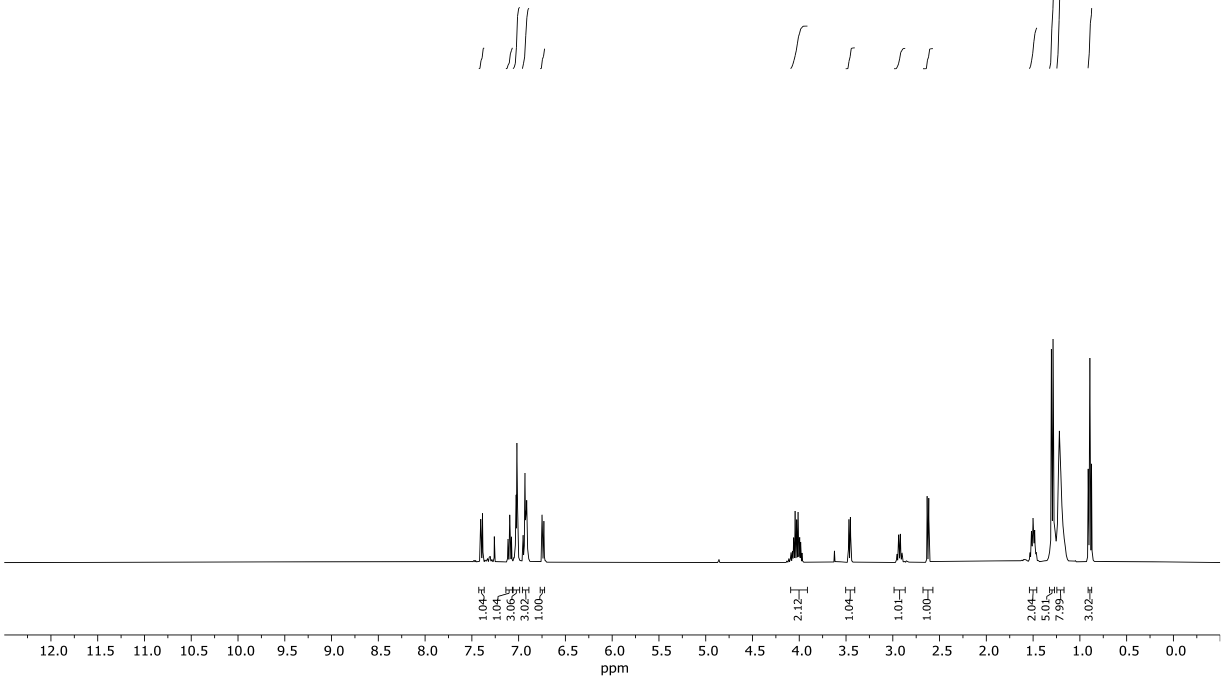
Compound 56d: ^{1}H NMR (400 MHz, CDCl$_3$) and ^{13}C NMR (101 MHz, CDCl$_3$):

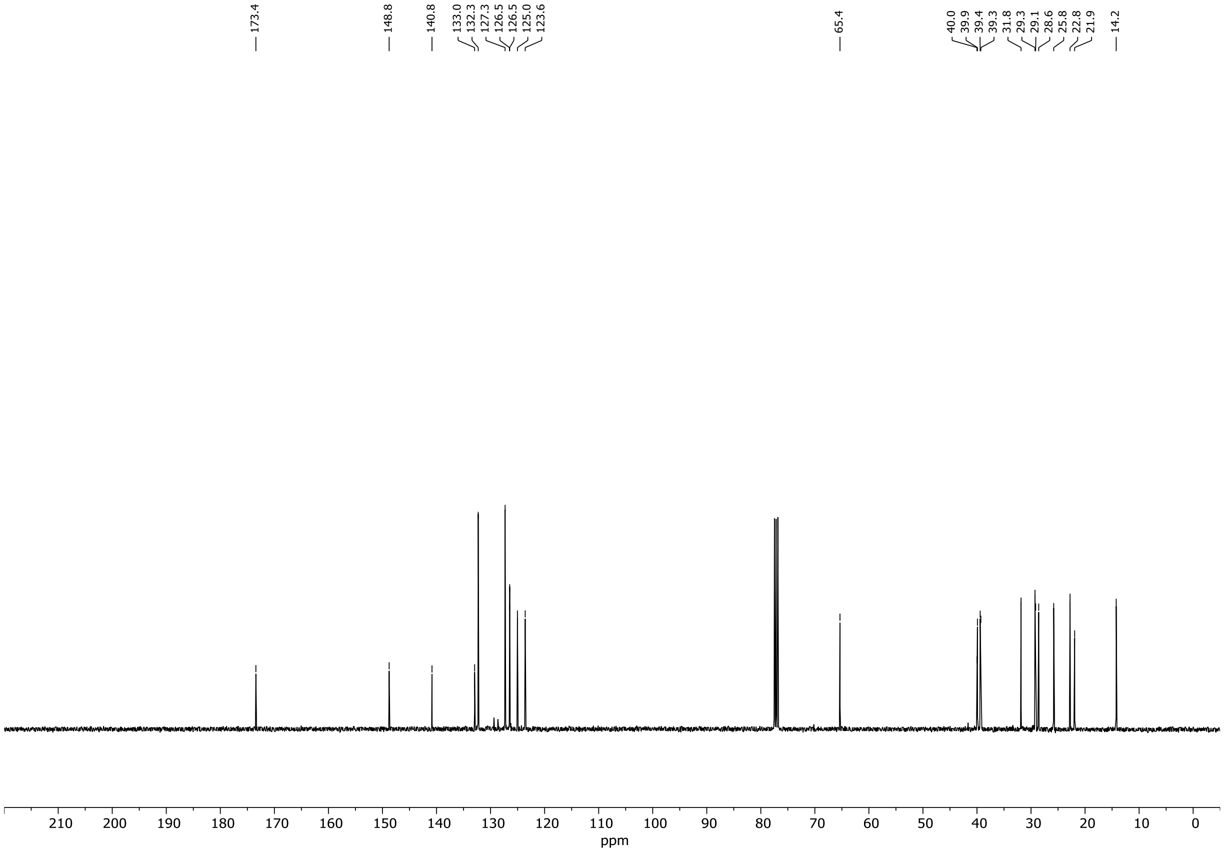


Compound 56e: ^{1}H NMR (400 MHz, CDCl$_3$) and ^{13}C NMR (101 MHz, CDCl$_3$):

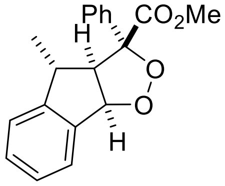


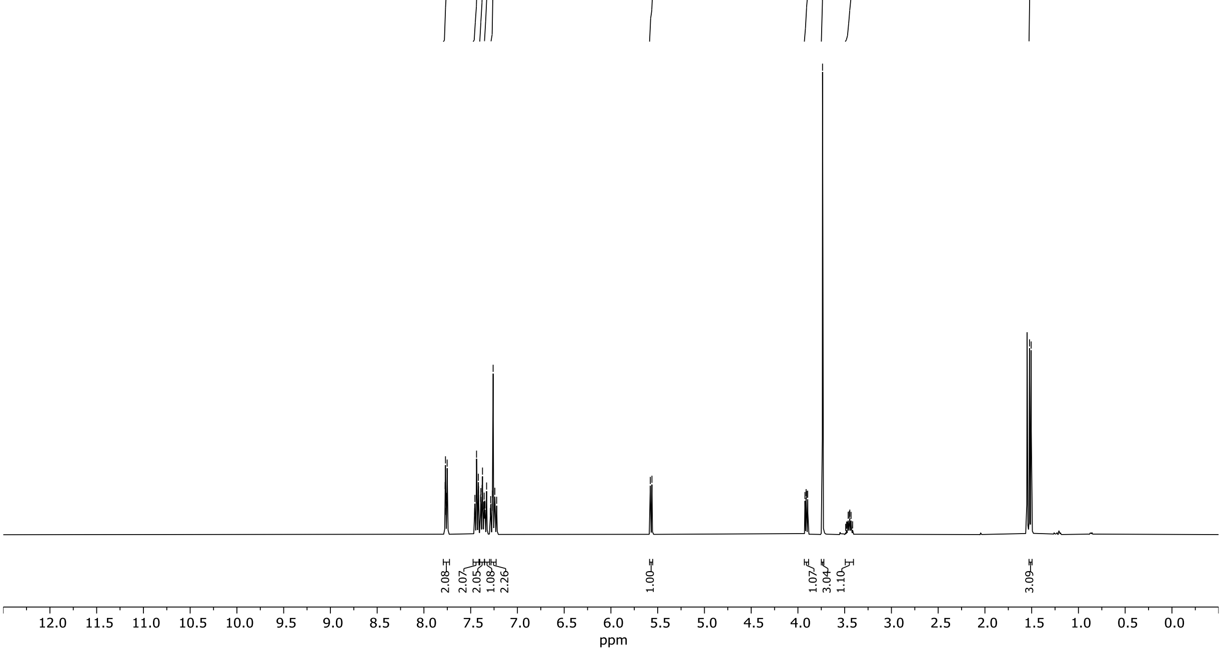
contains $PhCH_2CO_2C_8H_{17}$

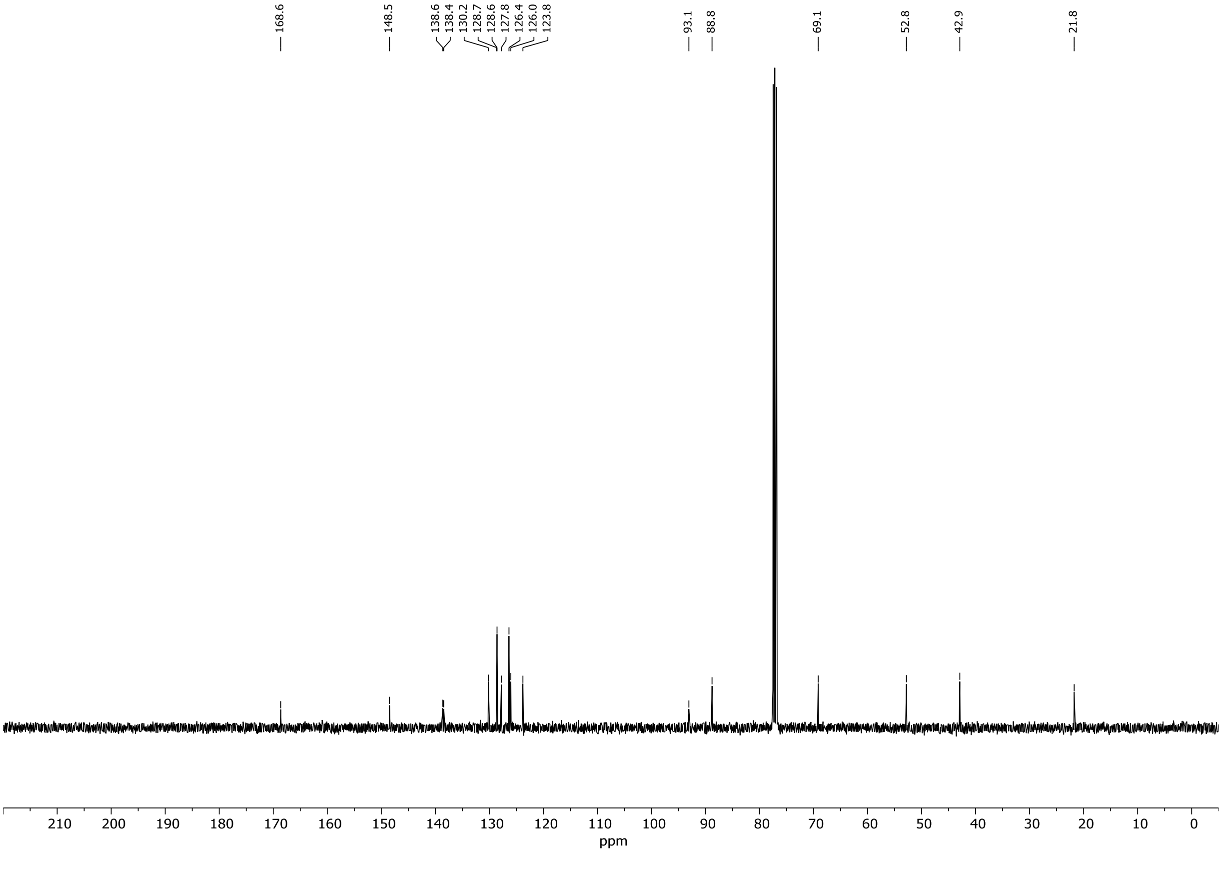




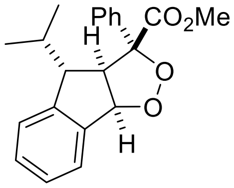
Compound 57a: ^1H NMR (400 MHz, $CDCl_3$) and ^{13}C NMR (101 MHz, $CDCl_3$):

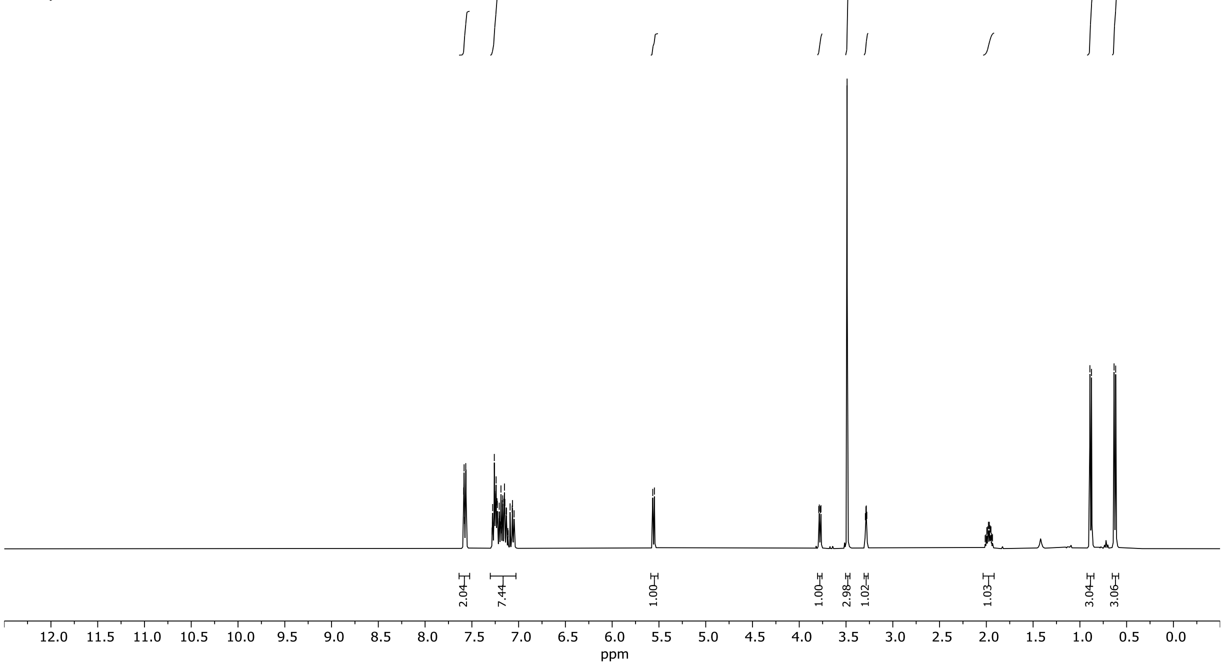


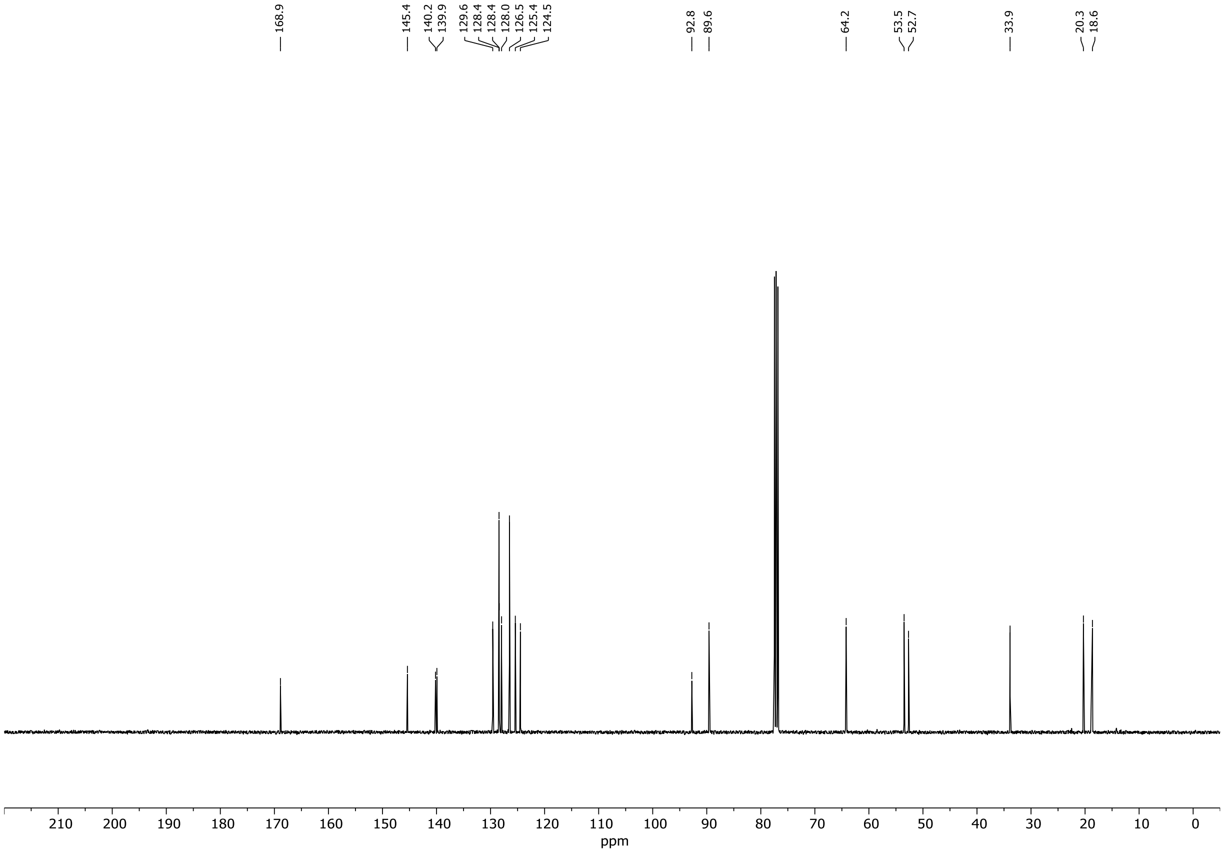




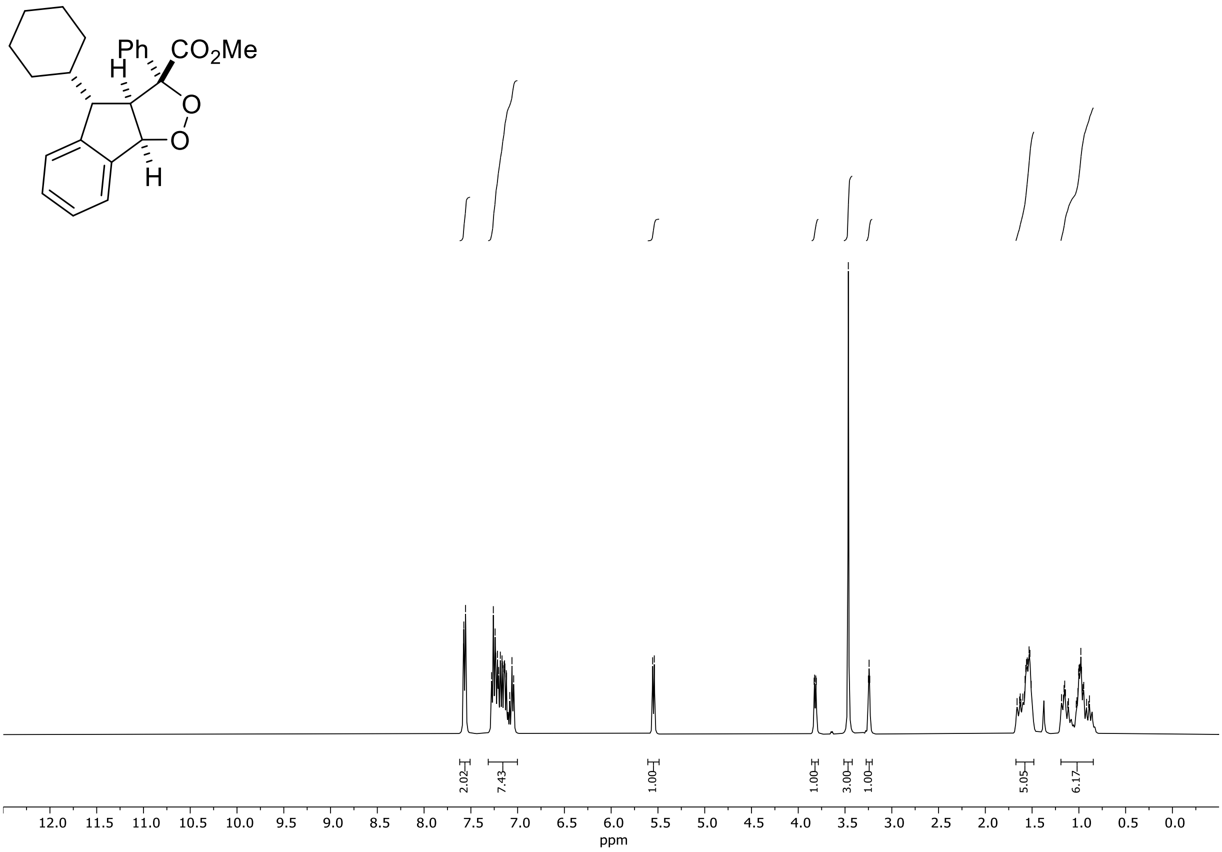
Compound 57b: ^{1}H NMR (400 MHz, CDCl$_3$) and ^{13}C NMR (101 MHz, CDCl$_3$):

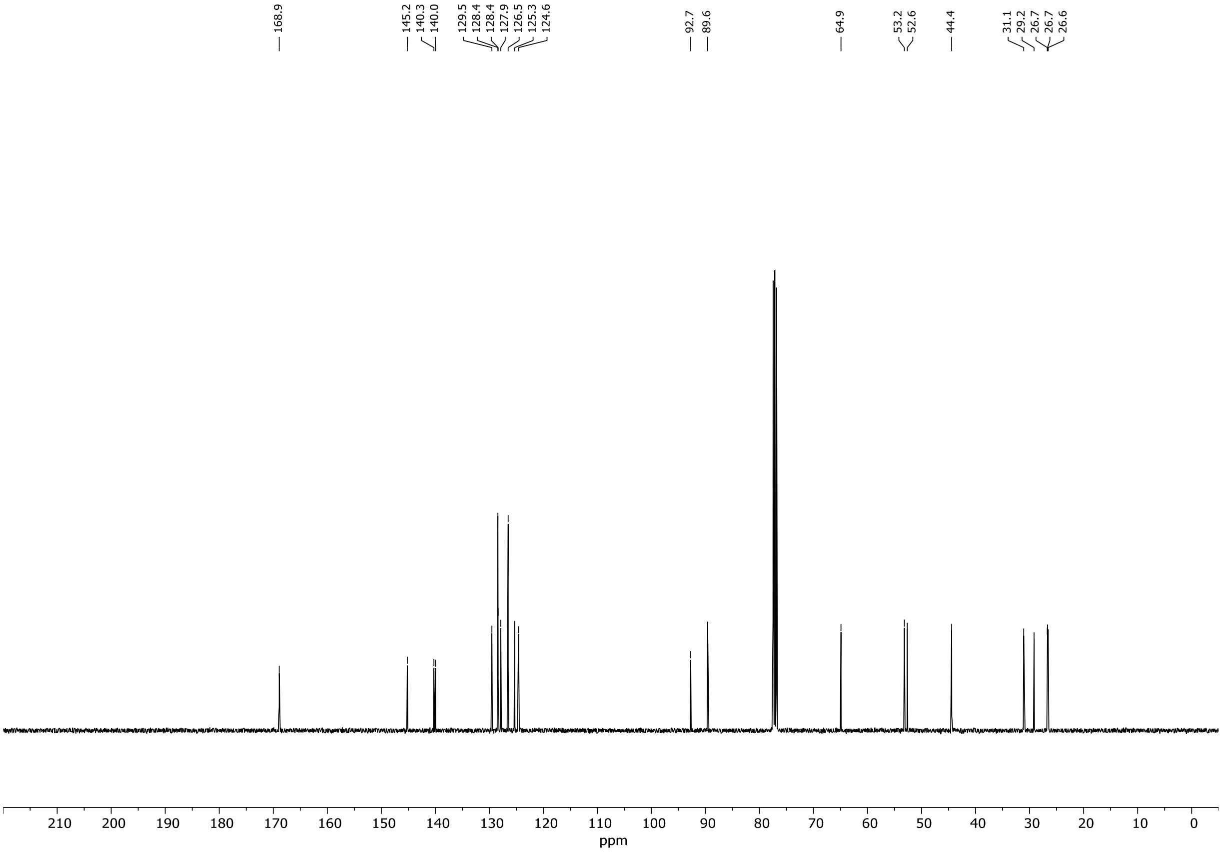




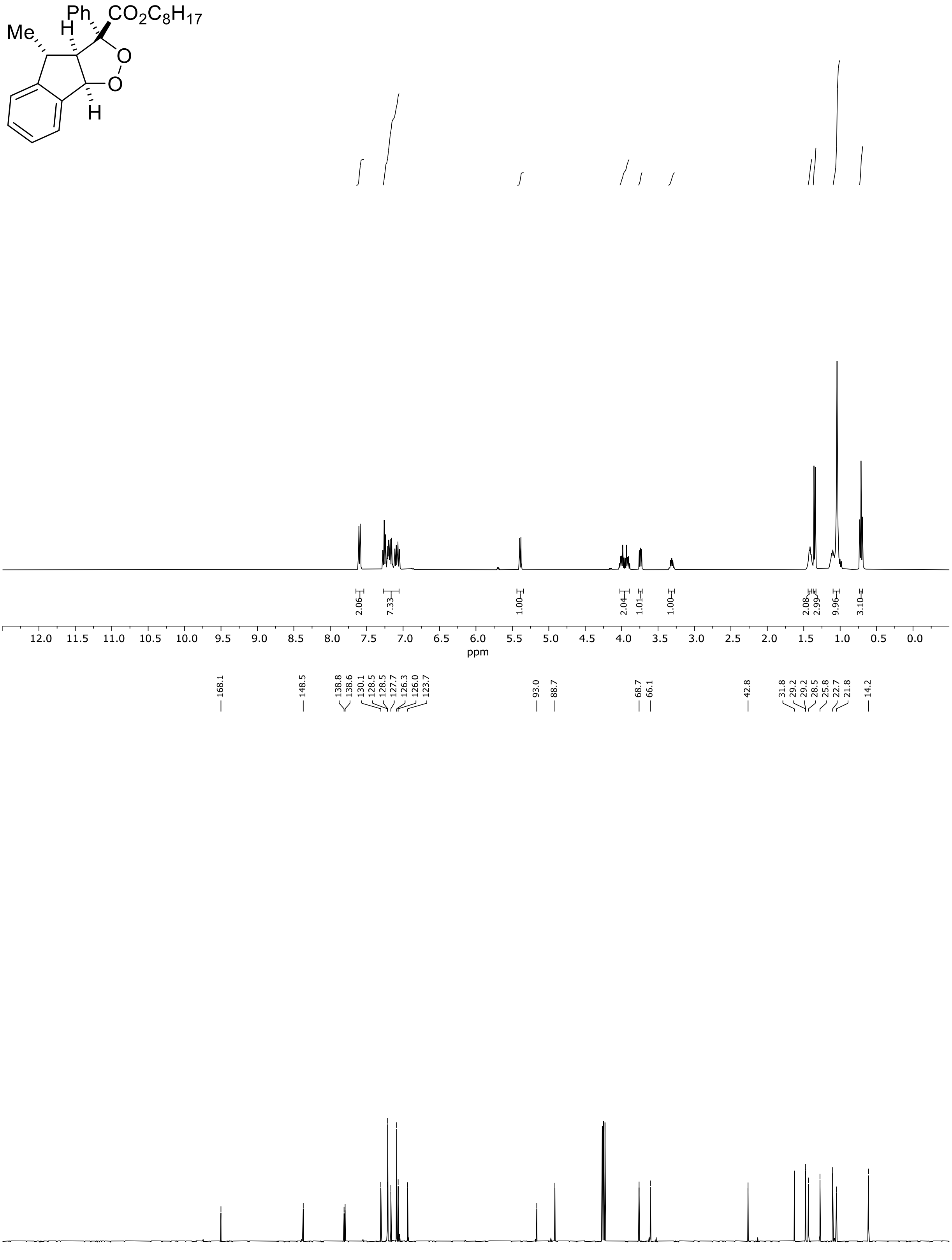


Compound 57c: ^{1}H NMR (400 MHz, CDCl$_3$) and ^{13}C NMR (101 MHz, CDCl$_3$):





Compound 57e: ^{1}H NMR (400 MHz, $CDCl_3$) and ^{13}C NMR (101 MHz, $CDCl_3$):



B. Lewis Acid Catalyzed Cyclopropane Ring Opening and Cyclization Cascade Using Thioureas: Synthesis of Novel Fused Bicyclic Furo-, Pyrano-, and Pyrrololactams via a Formal [4+1]-Addition[3]

1. Introduction

1.1. The Furofuranone Ring System in Natural Products

Furofuranones, characterized by the dioxabicyclo[3.3.0]octane framework, are a prominent class in natural product chemistry,**[80–85]** found in diverse ecosystems such as terrestrial plants, marine organisms, fungi, bacteria, sponges, and insects. They have been extensively studied and documented in scientific literature, particularly as pharmacophore-bearing compounds with fused γ-lactam-furan-ring structures. These compounds exhibit intriguing synergies and are widely distributed in biological systems, historically used as remedies for various diseases.**[86,87]** Synthesis efforts have yielded numerous compounds and drug-like molecules incorporating furofuranone motifs, drawing inspiration from nature.**[88]** There are six different types of furofuranones, which are classified based on the position of the oxygen functionalities (Figure 9): the furo[3,2-*b*]furanone **61**, the furo[3,4-*c*]furanone **62**, the furo[2,3-*b*]furanone **63**, the furo[3,4-*b*]furan-2(3*H*)-one **64**, the furo[3,4-*b*]furan-4(2*H*)-one **65** and the furo[3,4-*b*]furan-6(4*H*)-one **66** (Figure 9).**[85]** Among these structure types, the furo[2,3-*b*]furanone motif **63** is present in more than 100 natural products.**[89]** One prominent example is (+)-Norrisolide (**67**) (Figure 9), which was isolated in 1983 by Faulkner *et al.* from the skin extracts of the dorid nudibranch *Chromodoris norrisi*.**[90]** Interest in **67** arose because of its ability to induce irreversible vesiculation of the Golgi complex in intact cells, which is very useful in order to investigate the function and the dynamics of the Golgi apparatus.**[87]** Another interesting compound known as (+)-paeonilide (**68**) was isolated by Liu *et al.* in 2000 from the roots of *Paeonia delavayi*, an endemic peony species in China.**[91]** Its unique molecular scaffold was elucidated through spectroscopic and single-crystal X-ray analysis (Figure 8).

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[3] This chapter is partially based on: A. Ratzenböck, M. Kobras, A. Rustler, O. Reiser, *Chem. Eur. J.* **2024**, e202401332.[79]

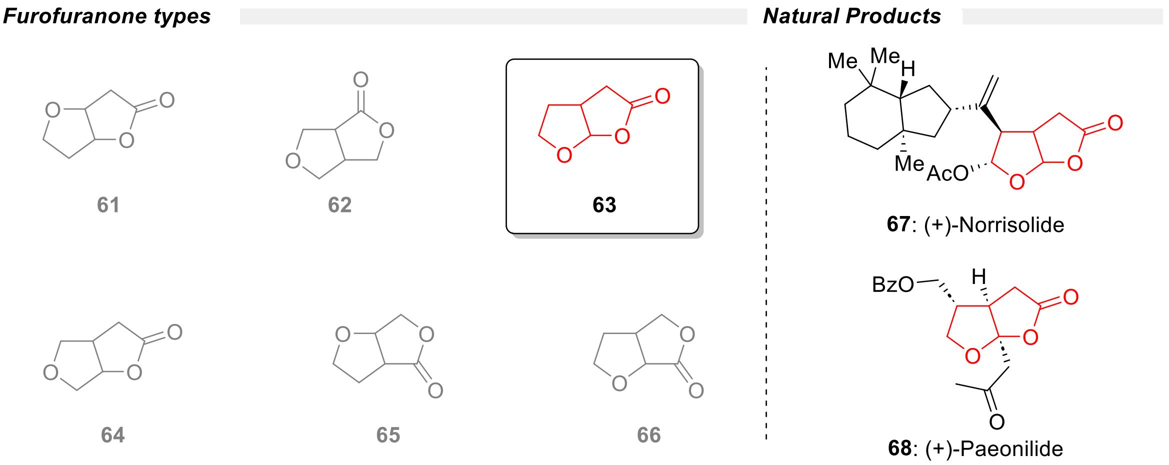
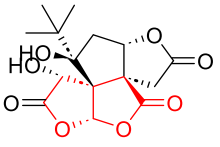


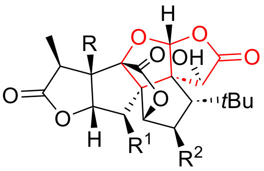
Figure 8. Different types of furofuranones **61-66** present in natural products **67-68**.

The ring structure of (+)-paeonilide (**68**) is similar to the partial ring system found in bilobalide (**69**) and the class of ginkgolides **70** (Figure 9). Bilobalide (**69**) and the ginkgolides **70** are bioactive compounds exclusively obtained from the *Ginkgo biloba* tree, the only surviving member of the *Ginkgoaceae* family that dates back over 200 million years to the Permian period.[92,93] *Ginkgo biloba* extracts are a highly significant herbal medicine today, with annual production exceeding 8000 tons of dried leaves and global sales of finished products reaching over US $1.2 billion in 2012.[94,95] These extracts have a diverse range of pharmacological effects and are utilized in the treatment of various conditions, such as memory impairment,[96] Alzheimer's disease and dementia,[97] and cerebrovascular insufficiency.[98]

Bilobalide and Gingkolides from Ginkgo biloba



69, Bilobalide



70, Gingkolides

Gingkolide	R	R^1	R^2
A	OH	H	H
B	OH	OH	H
C	OH	OH	OH
J	OH	H	OH
M	H	OH	OH

Figure 9. Structure of Bilobalide (**69**) and Ginkgolides **70** from *Gingko biloba* (leaves shown).[99]

In summary, furofuranones, characterized by the dioxabicyclo[3.3.0]octane framework, represent a diverse and increasingly studied group in natural product chemistry. These compounds are found in various ecosystems and exhibit significant pharmacophore-bearing properties. They are prevalent in traditional remedies and modern research confirms their bioactivity, leading to interest in total synthesis and structural diversification. The discovery of compounds such as (+)-paeonilide (**68**) from *Paeonia delavayi* roots highlights their potential therapeutic relevance, particularly in conditions such as memory impairment and Alzheimer's disease.

1.2. Synthesis of Furo[2,3-*b*]-furanone-containing Natural Products

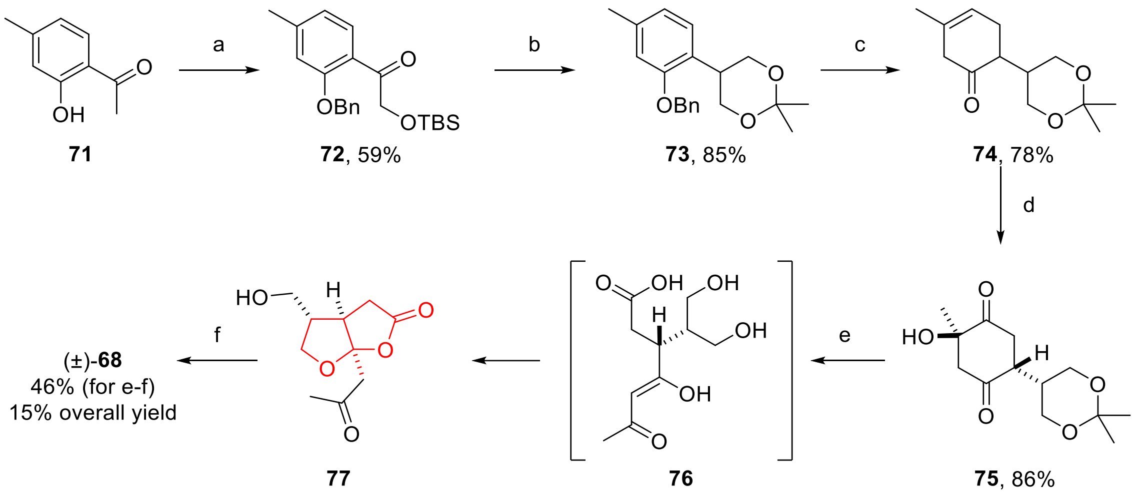
Furo[2,3-*b*]furanone-derived natural compounds exhibit a range of biological activities, particularly within the spongian diterpene class. These compounds, which include simple monoterpenoids such as (+)-paeonilide (**68**) and complex structures such as bilobalide (**69**) and ginkgolides **70**, feature multiple hetero- and carbocyclic ring systems and chiral centers, presenting challenges for total synthesis. While some of these compounds show promising bioactivities, their limited availability hampers comprehensive studies, and no drug candidate has emerged. Efforts to synthesize them aim for scalability. This chapter shows the progress in their total synthesis by focusing on three examples: Paeonilide (**68**), Norrisolide (**67**) and Macfarlandin C (**142**).[100]

1.2.1 Paeonilide

Paeonilide (**68**), which is distinguished by its distinctive monoterpenoid structure comprising a furo[2,3-*b*]furanone core, is a constituent of the Chinese herbal medicine *mu-dan-pi* or *dan-pi*, which has been traditionally employed for addressing a range of illnesses, including abdominal pain and muscular stiffness.[100] Over the years, five syntheses of **68** have been reported, three of which were diastereoselective and two of which were enantioselective.[101–104,49]

In 2006, Zhang *et al.* achieved the first racemic total synthesis of **68**, yielding 15% of compound (±)-**68** in 16 steps.[101] This synthesis commenced from commercially available 2-hydroxy-4-methylacetophenone (**71**). Initial benzyl protection of **71**, which then underwent Rubottom oxidation followed by silyl protection and Wittig olefination afforded compound **72**. Subsequent hydroboration-oxidation and deprotection-protection approaches led to the formation of intermediate **73**. Birch reduction and desilylation then provided a non-conjugated enone **74**. *Syn*-dihydroxylation of **74**, followed by hydroxyl group oxidation, yielded a pivotal 1,4-diketone intermediate **75**. The deprotection of the acetonide and the oxidative cleavage of **75**, mediated by periodic acid, resulted in the formation of intermediate **76**. This underwent intramolecular cyclization, producing the furo[2,3-*b*]furanone compound **77**. The synthesis was completed through the benzoylation of **77**, generating (±)-**68** in 15% overall yield (Scheme 10).

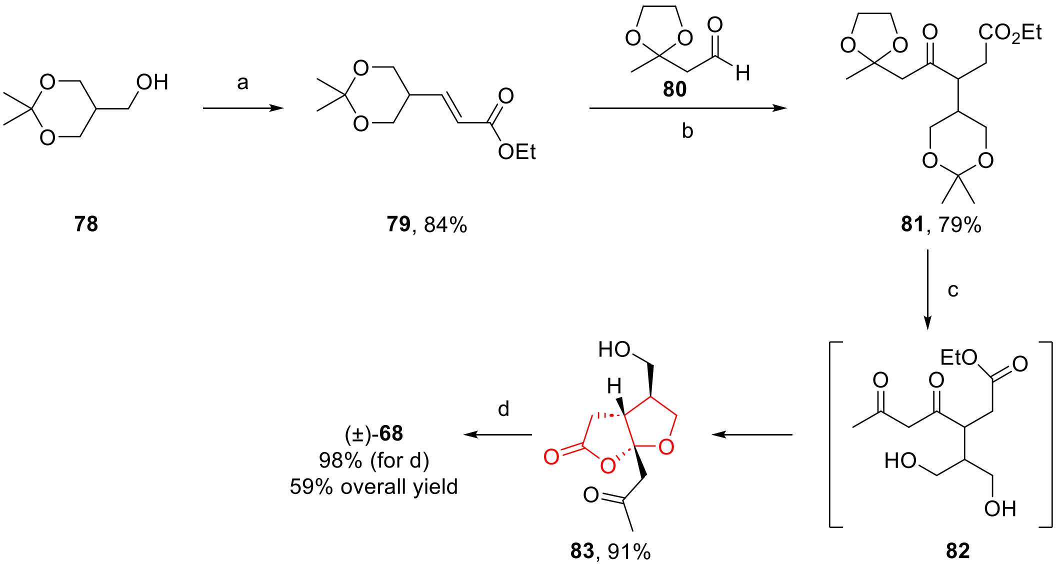
Synthesis of rac. paeonilide by Zhang et al.



Scheme 10. Racemic synthesis of (±)-**68** by Zhang *et al.*[101] Reagents: (a) (i) K_2CO_3, KI, BnCl; (ii) LDA then Me_3SiCl, m-CPBA; (iii) TBSCl, imidazole; (iv) Ph_3PCH_3I, t-BuOK; (b) (i) B_2H_6 then H_2O_2, 6N NaOH; (ii) Pd/C, H_2; (iii) DMP, PPTS, (iv) TBSCl, Et_3N; (c) (i) Li, NH_3 (l); (ii) TBAF, H_3BO_3; (d) (i) OsO_4, NMO; (ii) IBX; (e) H_5IO_6; (f) BzCl, pyr.

One year later, Du initiated the shortest reported synthesis of paeonilide (±)-**68** using acetonide-protected glycerol **78** as the starting material.[102] The synthesis began with Swern oxidation and Horner-Wittig olefination of **78**, which resulted in the formation of *trans*-ester **79**. After the radical-mediated 1,4-addition of aldehyde **80** to unsaturated ester **79**, the γ-ketoester intermediate **81** was formed.

Synthesis of (±)-paeonilide by Du et al.

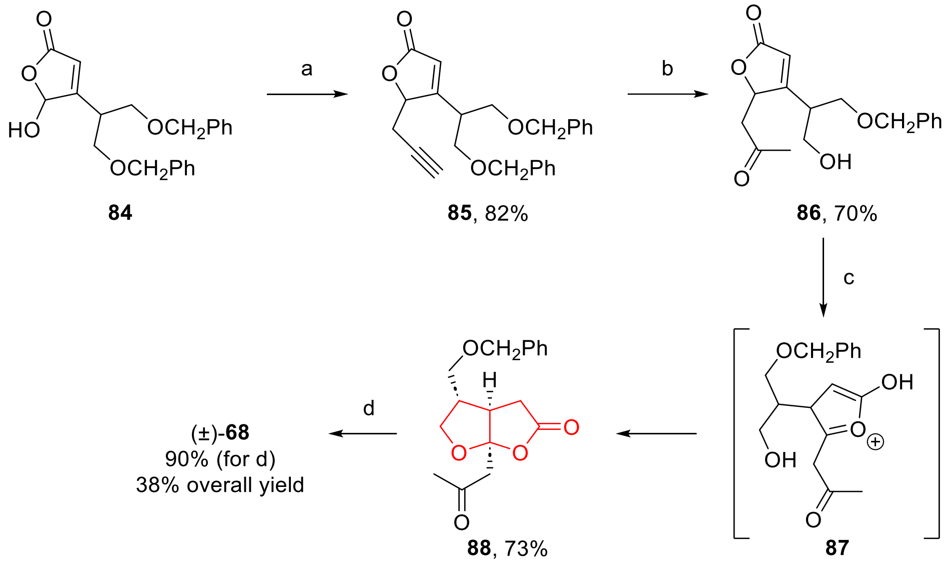


Scheme 11. Shortest racemic synthesis of (±)-**68** by Du *et al.*[102] Reagents: (a) (i) $(COCl)_2$, DMSO, Et_3N; (ii) $Ph_3P{=}CHCO_2Et$; (b) $(C_6H_5COO)_2$; (c) 1N HCl; (d) BzCl, pyr.

Acid-mediated deprotection of **81** facilitated the cyclization/lactonization of the intermediate **82**, resulting in the bicyclic lactone **83**. The synthesis was completed through the benzoylation of compound **83**, resulting in the succinct synthesis of (±)-**68** in 59% overall yield (Scheme 11).

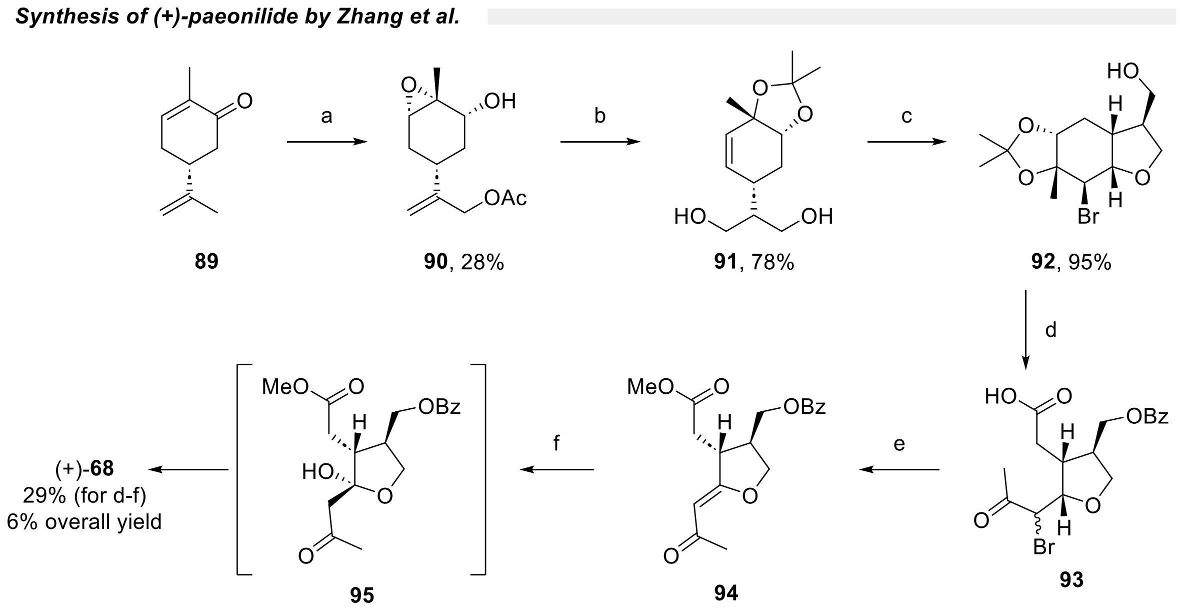
Another diastereoselective synthesis of compound (±)-**68** was initiated by Argade *et al.* using a readily available maleic anhydride derivative **84**.[103,105] The zinc-mediated Barbier-type addition of propargyl bromide to the masked aldehyde in **84** resulted in the formation of propargylated compound **85**, which upon hydrolysis of the alkyne group and selective debenzylation yielded the desired butenolide **86**. The acid-mediated cyclization of **86** facilitated the formation of the desired bicyclic lactone **88** in a chemo- and diastereoselective manner *via* an intramolecular cyclization pathway. Subsequent benzyl group deprotection-re-derivatisation manoeuvre on **88** led to the synthesis of racemic compound (±)-**68** in 38% overall yield (Scheme 12).

Synthesis of (±)-paeonilide by Argade et al.



Scheme 12. Diastereomeric synthesis of (±)-**68** by Argade *et al.*[103] Reagents: (a) propargyl bromide, Zn powder; (b) (i) $Hg(OAc)_2$, H_2SO_4 on silica; (ii) $AlCl_3$; (c) p-TSA; (d) (i) H_2, Pd/C; (ii) BzCl, pyr.

Zhang's research group also documented the first enantioselective synthesis of (+)-**68**, concurrently establishing its absolute stereochemistry.[104] The synthesis began with (*R*)-(−)-carvone (**89**), undergoing allylic bromination, followed by sequential S_N2 substitution reaction with AgOAc, Luche reduction, and regioselective epoxidation to yield epoxy alcohol **90**.

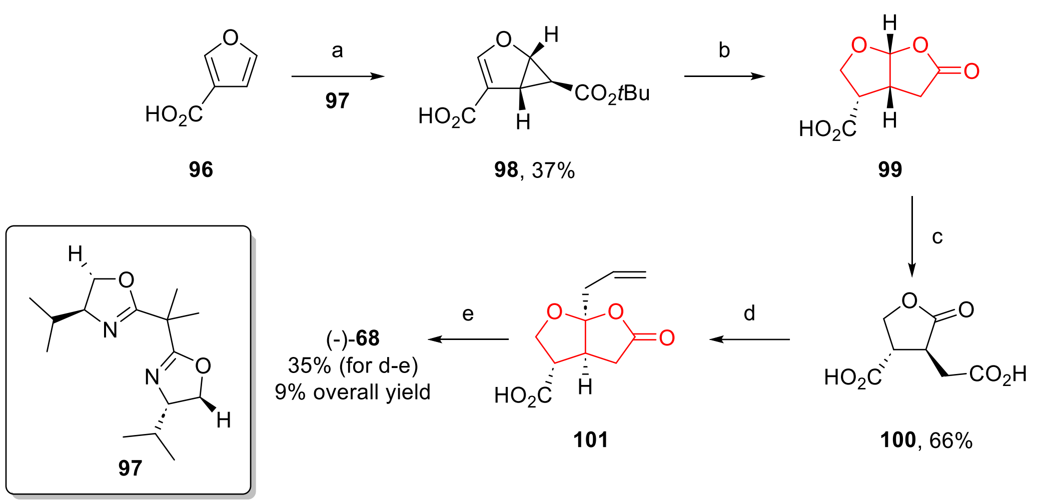

Synthesis of (+)-paeonilide by Zhang et al.

Scheme 13. Enantioselective synthesis of (+)-**68** by Zhang *et al.*[104] Reagents: (a) (i) NBS, NaOAc; (ii) AgOAc; (iii) $NaBH_4$, $CeCl_3$; (iv) m-CPBA; (b) (i) LiBr; (ii) DMP; (iii) $BH_3 \cdot SMe_2$, H_2O_2, 6N NaOH; (iv) t-BuOK; (c) NBS; (d) (i) BzCl, pyr.; (ii) 6N HCl; (iii) IBX; (iv) H_5IO_6; (e) (i) diazomethane; (ii) DBU; (f) 6N HCl.

Subsequent steps involved the regioselective opening of the epoxide, the acetonide protection of the 1,2-diol moiety, the hydroboration of the exomethylene group, and the dehydrobromination, resulting in the formation of the cyclohexene intermediate **91**. The NBS-mediated diastereoselective bromoetherification of **91** yielded the tetrahydrofuran compound **92**. The introduction of a benzoyl group to **92**, followed by acetonide deprotection, oxidation of the secondary hydroxyl group, and oxidative cleavage, produced intermediate **93**. Further transformations led to the synthesis of *α,β*-unsaturated ketone **94**. Cyclization of compound **94** was triggered by exposure to aqueous acid, ultimately furnishing the desired product (+)-**68** in 6% overall yield (Scheme 13).

Our group reported the enantioselective synthesis of the other enantiomer (−)-**68**, using commercially available furan-3-carboxylic acid (**96**).[49] Initially, esterification of **96** was followed by copper-catalyzed enantioselective cyclopropanation in the presence of (*S*,*S*)-*i*-Pr-box **97**. Subsequent selective hydrolysis of the methyl ester and double bond reduction led to the formation of a carboxylic acid derivative **98**. Acid-mediated cyclopropane ring-opening/lactonization then afforded the key bicyclic lactone **99**. Epimerization in compound **99**, followed by Jones oxidation, resulted in simultaneous lactone opening and oxidation to yield γ-lactone **100**. The stereoselective addition of allyl magnesium bromide to **100**, followed by exposure to acid, furnished the bicyclic lactone **101**.

Enantioselective synthesis of (-)-paeonilide by Reiser et al.



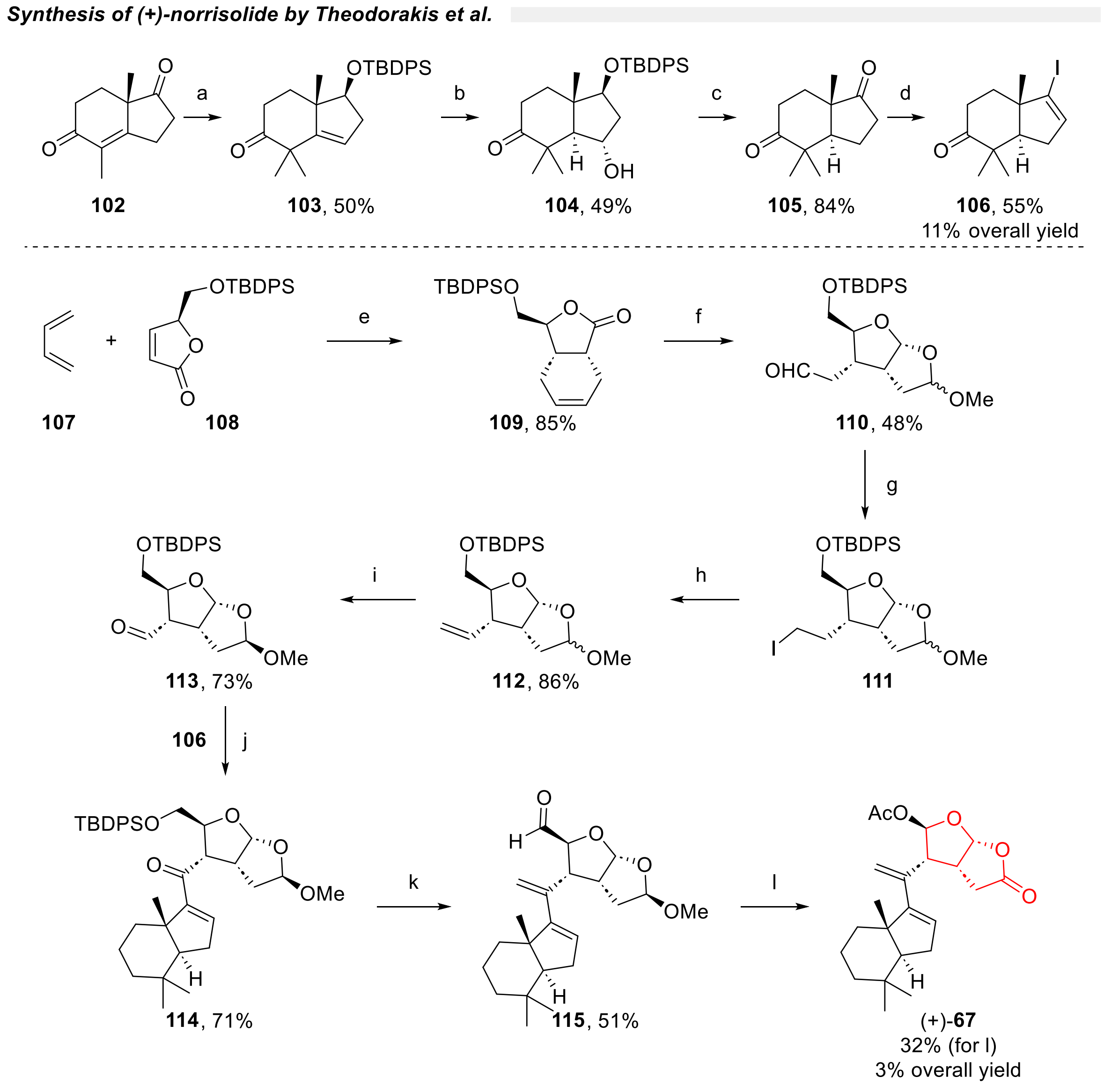
Scheme 14. Enantioselective synthesis of (–)-**68** by Reiser *et al.*[49] Reagents: (a) (i) H_2SO_4, MeOH; (ii) $Cu(OTf)_2$, $PhNHNH_2$, N_2CHCO_2t-Bu, 83% ee; (iii) LiOH; (iv) Pd/C, H_2; (b) HCl; (c) (i) pyr.; (ii) Jones reagent; (d) allyl-MgBr; (e) (i) $Hg(OAc)_2$, Jones reagent; (ii) BH_3; (iii) BzCl, NEt_3, DMP.

The synthesis was completed through oxymercuration-Jones oxidation, reduction of the carboxylic acid group, and benzoylation of the resulting hydroxyl group, ultimately delivering (−)-**68** in 9% overall yield (Scheme 14).

1.2.2 Norrisolide

While early reports primarily focused on norrisolide's (**67**) antimicrobial activity, recent investigations have revealed that it can also induce irreversible vesiculation of the Golgi apparatus, as validated through fluorescence microscopy. The observed biological activity of compound **67** is attributed to its ability to form covalent interactions with its biological receptors, with the furo[2,3-*b*]furanone segment playing a key role in these covalent interactions, making it an interesting compound for total synthesis.[87,86] So far, two groups contributed enantioselective syntheses of **67**.[106–108]

The first synthesis started from readily available enantiopure enone **102**.[106,107] Selective reduction of the saturated carbonyl group in **102**, followed by TBDPS protection and regioselective methylation of the enolate, facilitated the incorporation of the gem-dimethyl group and yielded β-γ-unsaturated ketone **103**. Further transformations included reduction of the carbonyl group, Barton-McCombie radical deoxygenation, and stereoselective hydroboration-oxidation, resulting in the formation of bicyclic alcohol **104**. Successive Barton-McCombie radical deoxygenation of the trans-fused bicyclic compound, along with silyl deprotection and PCC oxidation of the secondary hydroxyl group, furnished cyclopentanone **105**. The hydrazone derived from **105** underwent iodination mediated by I_2/Et_3N, resulting in the desired carbocyclic segment with a vinyl iodide functionality, **106**. Concurrently, the furofuranoid aldehyde partner **113** was synthesized through a diastereoselective Diels-Alder reaction between butenolide **108** and 1,3-butadiene (**107**), resulting in the formation of bicyclic lactone **109** as a single isomer.

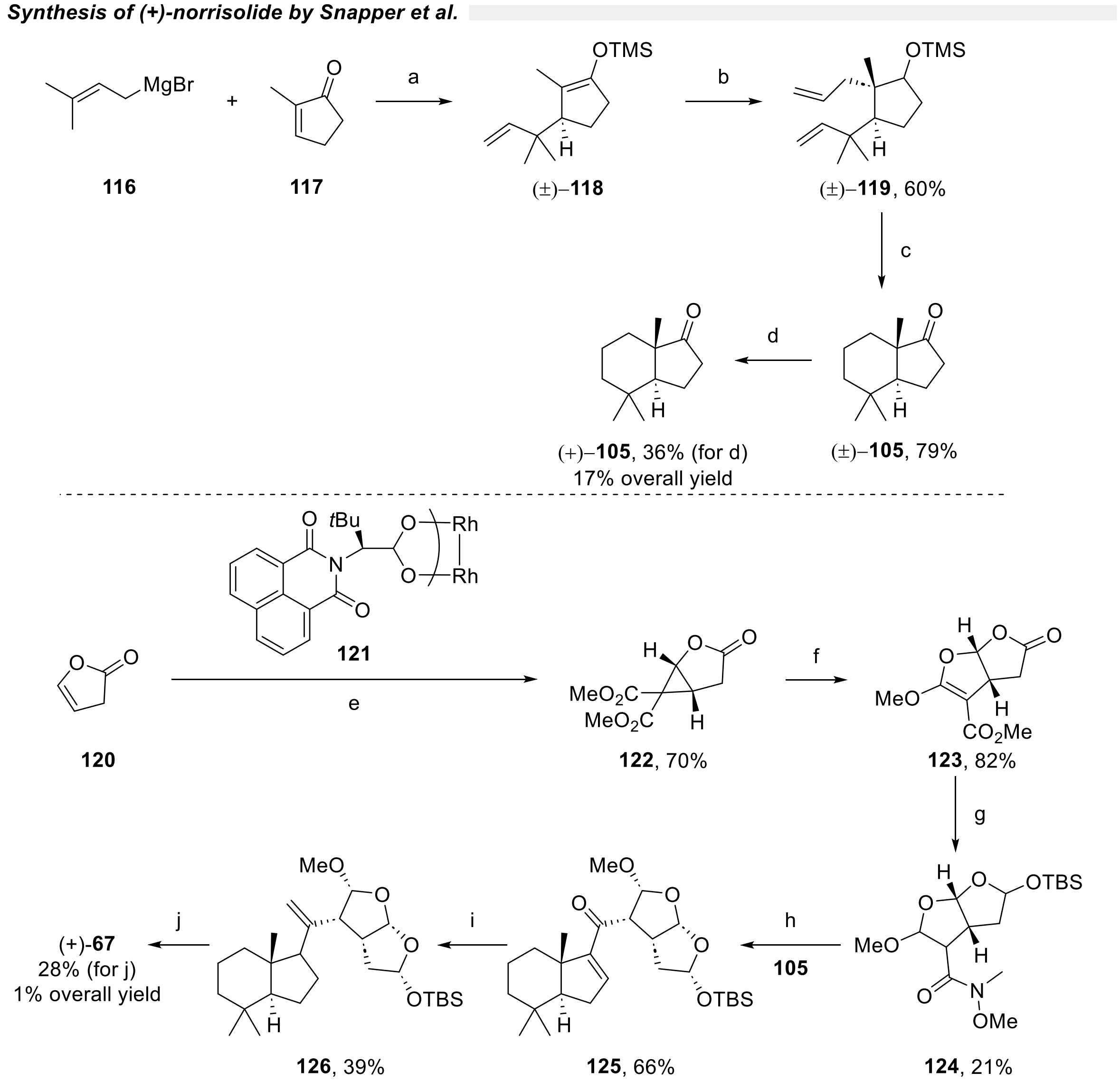


Scheme 15. Enantioselective synthesis of (+)-**67** by Theodorakis *et al.*[106,107] Reagents: (a) (i) $NaBH_4$; (ii) TBDPSCl, imidazole, DMAP; (iii) t-BuOK, MeI; (b) (i) $NaBH_4$; (ii) n-BuLi, CS_2, MeI; (iii) *n*-Bu_3SnH, AIBN; (iv) BH_3, NaOH, H_2O_2; (c) (i) *n*-BuLi, CS_2, MeI; (ii) *n*-Bu_3SnH, AIBN; (iii) TBAF; (iv) PCC; (d) (i) $N_2H_4 \cdot H_2O$, Et_3N; (ii) I_2, Et_3N; (e) $AlCl_3$; (f) (i) DIBAL-H; (ii) OsO_4, NMO; (iii) $Pb(OAc)_4$; (iv) MeOH, amberlyst 15, molecular sieves, ($\alpha{:}\beta = 1{:}1$); (g) (i) $NaBH_4$; (ii) imidazole, PPh_3, I_2; (h) (i) $(PhSe)_2$, $NaBH_4$; (ii) $NaIO_4$; (i) (i) OsO_4, NMO, pyr.; (ii) $Pb(OAc)_4$; (j) (i) *t*-BuLi; (ii) Dess-Martin periodane; (k) (i) 10% Pd/C, H_2; (ii) MeLi; (iii) $SOCl_2$, pyr.; (iv) TBAF; (v) IBX; (l) (i) MeMgBr; (ii) Dess-Martin periodinane; (iii) CrO_3; (iv) m-CPBA, $NaHCO_3$.

The lactone group in **109** was reduced, and the alkene was then cleaved by oxidation, resulting in a 1:1 diastereomeric mixture of fused lactols **110**. These were subsequently separated after conversion to their corresponding methyl ethers. Compound **110** underwent sequential aldehyde reduction and iodination of the resulting alcohol, leading to the formation of **111**. Phenylselenylation followed by selenoxide elimination resulted in the formation of alkene **112**, which upon oxidative cleavage afforded the requisite aldehyde partner **113**.

The coupling of segments **106** and **113** involved the lithiation of vinyl iodide **106**, followed by the addition of aldehyde **113** to generate an alcohol intermediate. This intermediate was oxidized to yield coupled enone **114**. Sequential transformations including double bond reduction, methyl lithium addition, elimination, silyl deprotection, and oxidation produced an advanced compound **115**. The homologation of the aldehyde group to the methyl ketone moiety was achieved through a Grignard addition-oxidation, followed by a final Baeyer-Villiger oxidation. This process culminated in the synthesis of compound (+)-norrisolide (**67**) in 3% overall yield (Scheme 15).

An alternative synthesis of the compound (+)-**67** commenced with the preparation of the hydrindane core, denoted as (+)-**105**.[108] This was achieved through the Gilman addition of the isoprenyl Grignard reagent **116** to enone **117**, resulting in the formation of the silyl enol ether **118**. Subsequent metallation of **118** and allylation led to the formation of compound **119**. Subsequently, ring-closing metathesis was performed on **119**, followed by double bond hydrogenation, which ultimately yielded compound **105**. To achieve enantiomerically enriched furofuranoid fragment **123**, cyclopropanation of butenolide **120** in the presence of Müller’s catalyst (**121**) was conducted, followed by thermolysis of the resulting cyclopropane adduct **122**, leading to the formation of **123**. The sequential hydrogenation, lactone reduction, OTBS protection, and amide formation of the starting material afforded the bicyclic Weinreb amide **124**. Subsequent to this, a Shapiro reaction was carried out between the 2,4,6-triisopropylphenylsulfonyl hydrazone of ketone **105** and **124**, resulting in the formation of **125** as an inseparable mixture of diastereomers. The hydrogenation of the enone in **125**, followed by the Peterson olefination, led to the formation of **126**. The sequential deprotection of the –OTBS, PCC oxidation, TFA-mediated methylacetal hydrolysis, and acetylation in **126** completed the synthesis of the natural product (+)-**67** in 1% overall yield (Scheme 16).



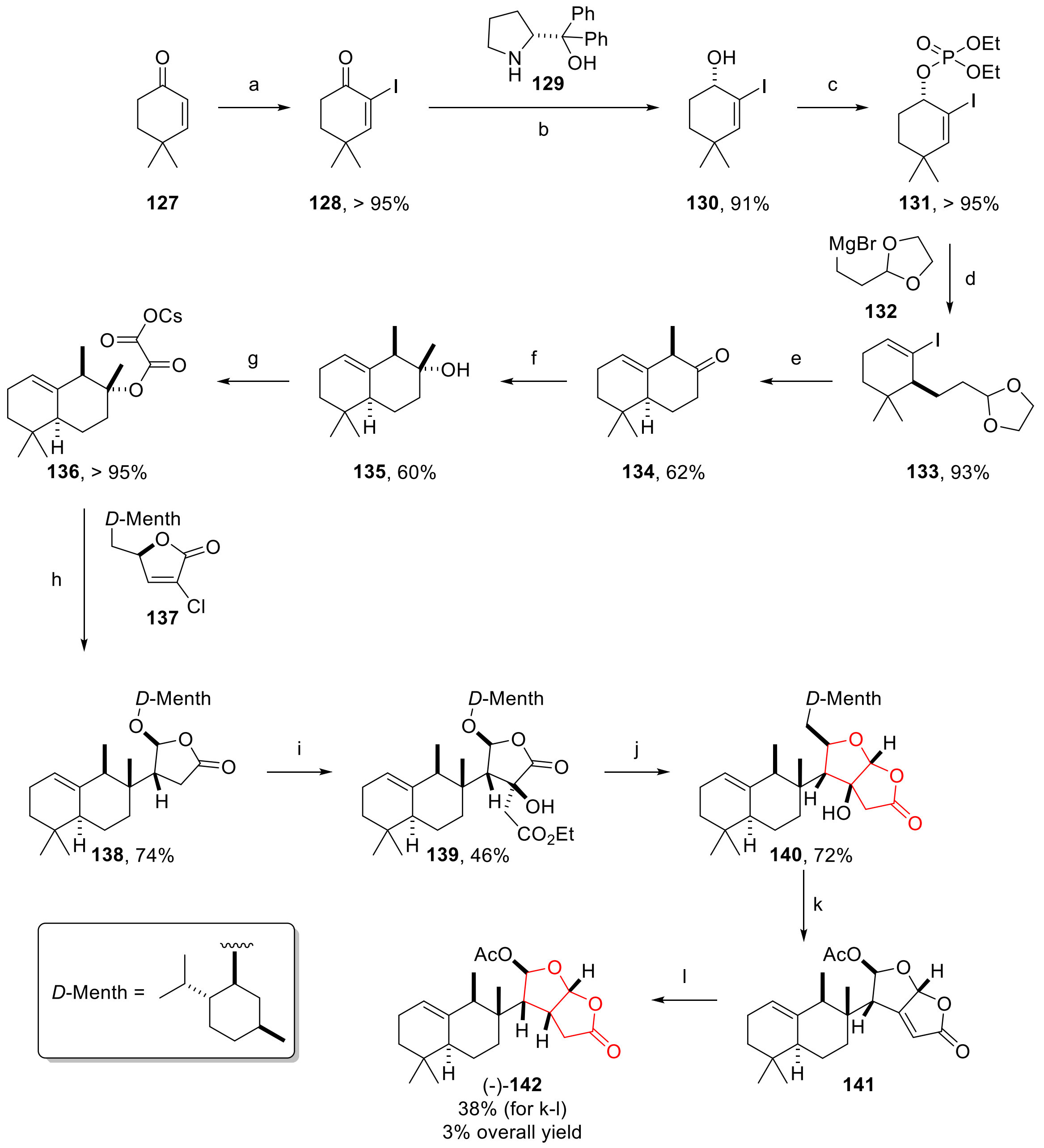
Scheme 16. Enantioselective synthesis of (+)-**67** by Snapper *et al.*[108] Reagents: (a) CuBr-DMS, TMSCl, HMPA, Et$_3$N; (b) (i) MeLi, HMPA, allylbromide; (c) (i) Grubbs-II; (ii) Pd/C, H$_2$; (d) (*S*)-(_)-2-methyl-CBS-oxazaborolidine, BH$_3$_DMS, (95% ee); (e) Mueller's catalyst, dimethyl-2-diazomalonate, (60–70% ee); (f) Benzene, 185 °C; (g) (i) H$_2$, Pd/C; (ii) DIBALH; (iii) TBSCl, imidazole; (iv) MeN(-OMe)·HCl, i-PrMgCl; (h) (i) 2,4,6- triisopropylphenylsulfonylhydrazide, HBF$_4$; (ii) n-BuLi; (i) (i) H$_2$, Rh/Al$_2$O$_3$; (ii) TMSCH$_2$MgCl; (iii) KHMDS, Tf$_2$O, pyr.; (j) (i) TBAF; (ii) PCC, NaOAc, 4 A° MS; (iii) TFA/H$_2$O; (iv) Ac$_2$O, DMAP, Et$_3$N.

1.2.3 Macfarlandin C

Macfarlandin C (**142**) represents a spongian norditerpene natural product initially isolated by Faulkner *et al*. from *Chromodoris macfarlandi*, a dorid nudibranch which inhabits the coastal waters of California.[109] The class of Macfarlandins usually possess unique Golgi-altering activity and therefore their synthesis is highly desirable.

In 2020, Overman *et al.*[110] reported the only currently known example for the synthesis of Macfarlandin C. The synthesis starts with the enantioselective transformation to octahydronapthalene tertiary alcohol **135**, which is achieved in nine steps from 4,4-dimethylcyclohexen-1-one (**127**). At first, catalytic enantioselective reduction of α-iodocyclohexenone **128** yields (*S*)-cyclohexenol **130** with a high yield and 98% ee. Subsequent transformations, including conversion to allylic phosphate **131** and anti-S_N2' allylic displacement, generate vinyl iodide **133**. The preparation of the (*E*)-ethylidene side chain, which is a pivotal intermediate in the intramolecular *ene* cyclization, involves a Negishi vinylation, followed by a selective hydrogenation to afford exclusively the (*E*)-ethylidene product.

The stereoselective intramolecular carbonyl–*ene* cyclization then leads to the formation of alcohol, which harbours the octahydronapthalene core. The oxidation of the secondary alcohol leads to the ketone, which upon treatment with Yamamoto's MAD reagent is transformed to equatorial tertiary alcohol **135**. Alcohol **135** is then converted to the oxalate radical precursor **136**, which, upon irradiation with high-intensity blue LEDs, undergoes coupling with *D*-menthol-derived chlorobutenolide **137** to yield the coupled product **138**. Subsequent transformations yield the vinylogous b-alkoxyacyl ester, which upon Mukaiyama hydration delivers the alcohol intermediate **139**. A series of transformations, including silane reduction mediated by an N-heterocyclic carbene copper complex finally affords (–)-Macfarlandin C (**142**) in 3% overall yield. Spectroscopic analysis and optical rotation confirmed the synthetic product's resemblance to the natural isolate (Scheme 17).

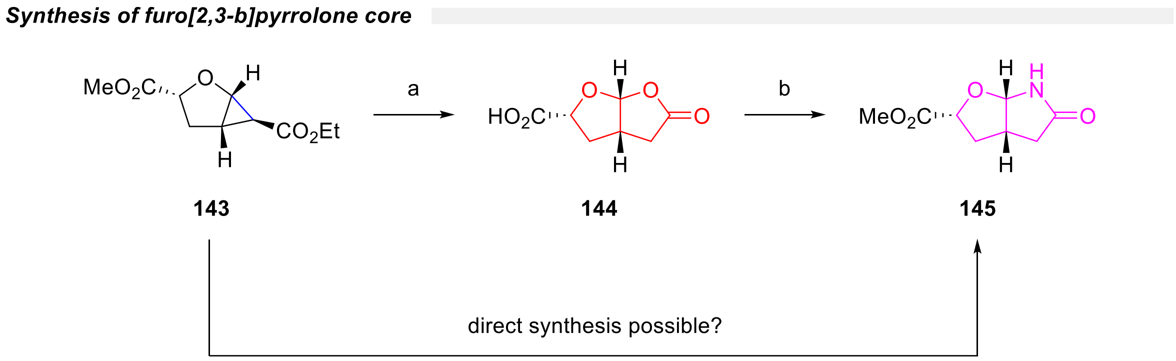

Synthesis of (-)-macfarlandin C by Overman et al.

Scheme 17. Enantioselective synthesis of (-)-**142** by Overman *et al.*[110] Reagents: (a) I_2, K_2CO_3, cat. DMAP, 1:1 THF/H_2O; (b) 5 mol% $B(OME)_3$, $BH_3{\cdot}Et_2NPh$, THF, 98% *ee*; (c) $POCl(OEt)_2$, *N*-methylimidazole, DCM, 0 °C to rt, 18 h; (d) CuCN, LiCl, THF, -78 °C, 30 min; 0 °C, 30 min; (e) (i) $ZnCl_2$, *vinyl*-MgBr, cat. $Pd(PPh_3)_4$, 3:1 THF/DMF, rt, 36 h; (ii) cat. (η-6 nap)$Cr(CO)_3$, H_2 (75 atm), acetone, 55 °C, 18 h; (iii) cat. PPTS, acetone/H_2O, 70 °C, 20 h; (f) (i) DMP, DCM, 0 °C, 4 h; (ii) $MeAl(BHT)_2$, MeMgBr, toluene, -78 °C, 3 h; (g) (i) $ClCOCO_2Me$, cat. DMAP, Et_3N, DCM; (ii) CsOH, THF/H_2O; (h) 2 mol% $Ir[dF(CF_3)ppy]_2(dtbbpy)PF_6$, H_2O, THF, 60 °C, 34 W blue LEDs, Bu_3N, > 20:1 *dr*; (i) (i) $CHOCO_2Et$, LHMDS, toluene, - 78 °C, 2 h, 4:1 *dr*; (ii) cat. DMAP, TFAA, pyridine, DCM, 40 °C, 2 h; DBU, rt, 1 h, 2:1 *E/Z*; (iii) cat. $Mn(dpm)_3$, Ph(O*i*-Pr)SiH_2, O_2, DCM, *i*-PrOH, 0 °C, 16 h, > 20:1 *dr*; (j) (i) $LiAlH_4$, Et_2O, 0 °C, 30 min; (ii) PCC, DCM, rt, 16 h, 72%; (k) (i) HCl, H_2O, THF, 35 °C, 5 days; (ii) DMAP, Ac_2O, Et_3N, DCM, rt, 16 h; (l) cat. (IPr)CuCl, cat. NaO*t*Bu, *t*BuOH, PMHS, toluene, rt, 16 h.

1.2.4 Derivatization of the Furo[2,3-*b*]furanone Core towards Furo[2,3-*b*]pyrrolone Moietys

In some cases, the biological activity of naturally occurring substances can be improved through chemical derivatizations. Therefore, the transformation of furofuranones to their corresponding furo[2,3-*b*]pyrrolones could create highly attractive unexplored analogs, given the relevance of furolactones and furofuranones in drug development.[85]

To date, only one example for the synthesis of furolactam from furolactone is known. In 2006, Roland Weisser reported a three-step process from cyclopropane **143** involving acid-mediated ring expansion to **144**. Subsequent lactone ring opening with ammonia and acid-mediated ring closure furnished furolactam **145** in an overall moderate yield of 42% (Scheme 18).[111]

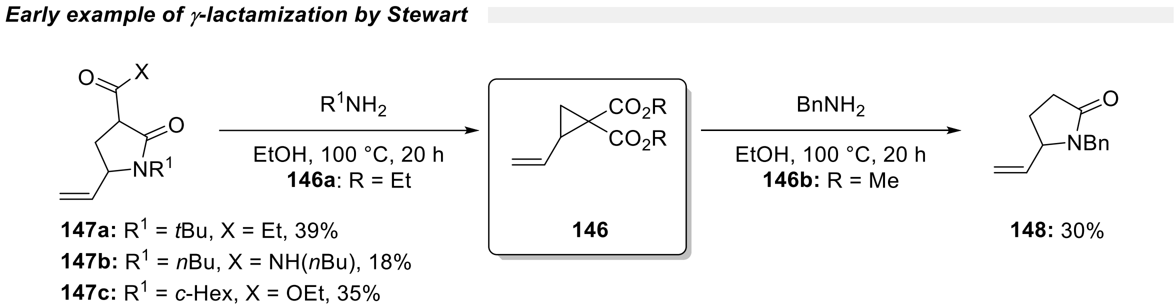


Scheme 18. Synthesis of furo[2,3-*b*]pyrrolone **145** from cyclopropane **143** by Weisser.[111] Reagents: (a) 2M HCl/1,4-Dioxan 1:1, rt, 20 h, 75%; (b) (i) konz. NH_3, rt, 30 min; (ii) kat. H_2SO_4, MeOH, 60 °C, 1 h, 56% (for i-ii).

Given the lack of effective synthesis strategies for furo[2,3-*b*]pyrrolones from furo[2,3-*b*]furanones, direct transformations *via* DAC ring opening with *N*-nucleophiles, especially amines, could be used as an alternative approach.

1.3. Synthesis of γ-lactams with Amines from DACs

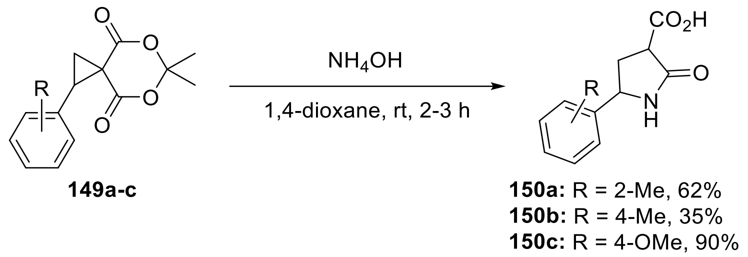
The nucleophilic ring opening of activated cyclopropanes with amines emerged as a distinct field within three-membered carbocycle chemistry during the mid-20th century, largely due to the seminal contributions of Stewart and Danishefsky *et al.*[112–115] The involvement of secondary processes in such reactions is often facilitated by the presence of at least one additional electrophilic centre, typically localized within the activating electron-withdrawing group (EWG) of the initial cyclopropane substrate. Consequently, in cases where primary amines participate as reactants, the nucleophilic ring-opening reactions of cyclopropanes activated by ester groups can be accompanied by *γ*-lactamization of intermediate *γ*-amino esters, leading to the formation of derivatives of 2-pyrrolidone. An illustrative example of such a domino process, as documented by Stewart and Pagenkopf in 1969, involved vinylcyclopropane-1,1-diesters **146** and aliphatic amines (Scheme 19).[114]



Scheme 19. Ring opening of vinylcyclopropane **146** to γ-lactams by Stewart *et al.*[114]

Subsequent investigations predominantly focused on analogous processes employing spiro-activated cyclopropanes, which were synthetically derived from Meldrum’s acid. The synthesis of 2-oxopyrrolidinecarboxylic acids **150a-c** was achieved by the Bernabé group through the reaction of spiro-activated cyclopropanes **149a-c** with NH_4OH in dioxane (Scheme 20).[116] It was demonstrated that the electronic properties of the R substituent in the phenyl ring exerted discernible effects on the reaction pathway. Specifically, the formation of lactams **150a-c** was observed exclusively when R represented a donor group. Conversely, electron-neutral or -acceptor aryl groups in compound **149a-c** impeded the ring opening of the cyclopropane, resulting in the formation of the corresponding 2-aryl-1-carbamoylcyclopropanecarboxylic acids.

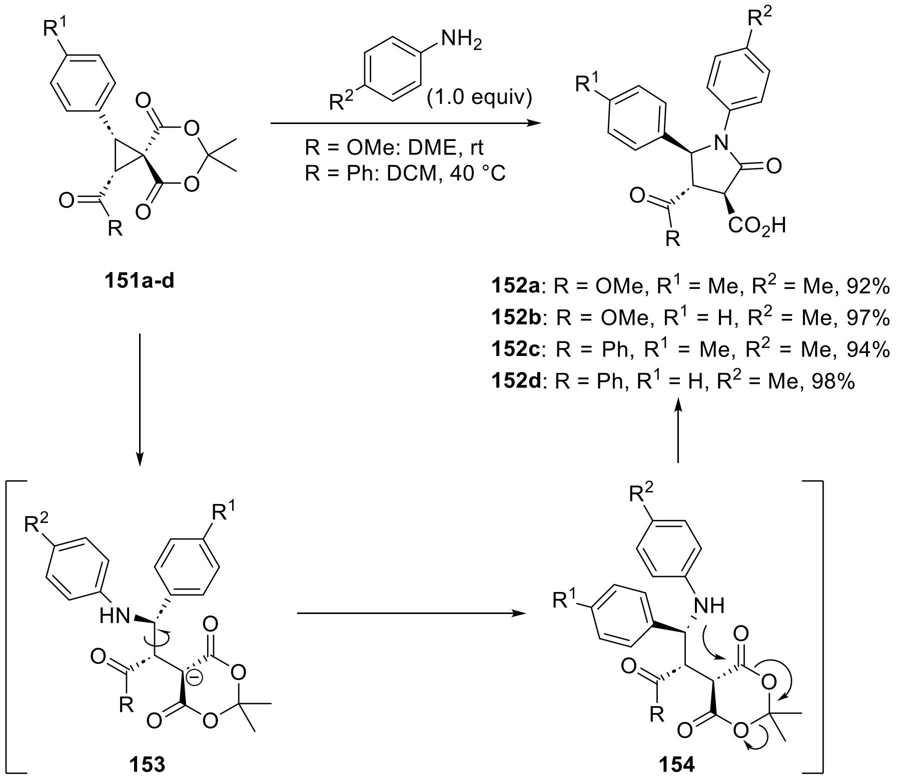
Ring opening/γ-lactamization with Danishefsky cyclopropane



Scheme 20. Ring opening of Danishefsky cyclopropane **149** to γ-lactams **150** by Bernabé *et al.*[116]

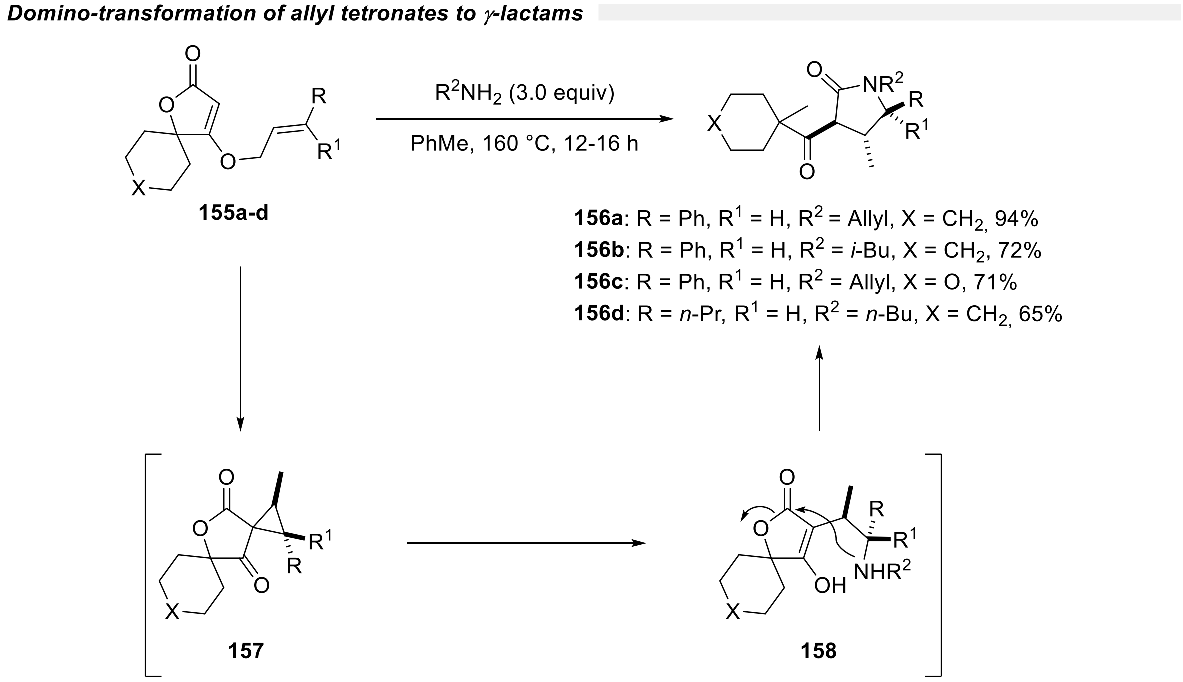
Later, Chen et al. developed a stereoselective methodology for the synthesis of substituted *γ*-butyrolactams **152** through the nucleophilic ring opening of tetrasubstituted DACs **151** with anilines (Scheme 21).[117,118] It is postulated that the formation of compound **152** proceeds *via* a mechanism analogous to that proposed by Danishefsky,[119] involving the cyclization of intermediate amine **154** to yield lactam **152** concomitant with the elimination of acetone. The stereochemical outcome of the reaction is consistent with an S_N2-like mechanism for the nucleophilic ring opening of cyclopropane **151** by an amine.

Ring opening of tetrasubstituted DACs with aniline



Scheme 21. Ring opening of tetrasubstituted DACs **151** to γ-lactams **152** by Chen *et al.*[117,118]

The Schobert group elucidated an intriguing reaction mechanism involving allyl tetronates **155a-d** and primary amines under stringent conditions (Scheme 22).[120] The resultant lactams **156a-d** are observed to originate from a complex domino process. Initially, the esters **155** undergo Claisen rearrangement coupled with Conia-*ene* cyclization, yielding spirocyclopropanes **157**. Subsequent to the nucleophilic ring opening of the three-membered ring in **157** by amines, the intermediate **158** is formed. This undergoes lactamization, which initiates cleavage in the furanone moiety, culminating in the formation of **156a-d**.

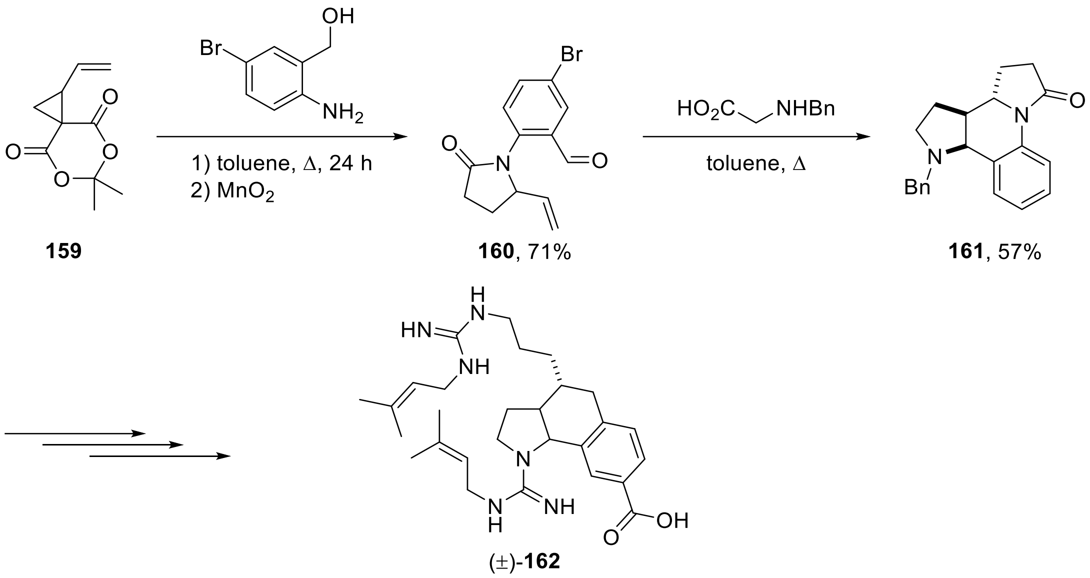


Scheme 22. Ring opening of *in situ* formed cyclopropanes **157** to γ-lactams **156** by Schober *et al.*[120]

The integration of nucleophilic ring opening with amines in conjunction with *γ*-lactamization has also been effectively harnessed in the synthesis of bioactive compounds with physiological relevance. Notably, the Snider research team orchestrated a total synthesis strategy for (±)-martinellic acid, which derivatives are known for their antagonistic activity towards bradykinin receptors B_1, B_2.[121,122]

The synthesis strategy involved the ring opening of vinylcyclopropane **159** by aniline, followed by lactamization to **160**. Subsequently, the latter compound underwent a reaction with *N*-benzylglycine, resulting in an intramolecular (3+2)-cycloaddition reaction. This ultimately furnished tetracyclic diamine **161**, a pivotal intermediate in the synthesis pathway of (±)-martinellic acid (**162**) (Scheme 23).

Total synthesis of (±)-martinellic acid



Scheme 23. Ring opening of spyrocyclopropane **159** to active compound (±)-**162** by Snider *et al.*[121,122]

1.4. Conclusion

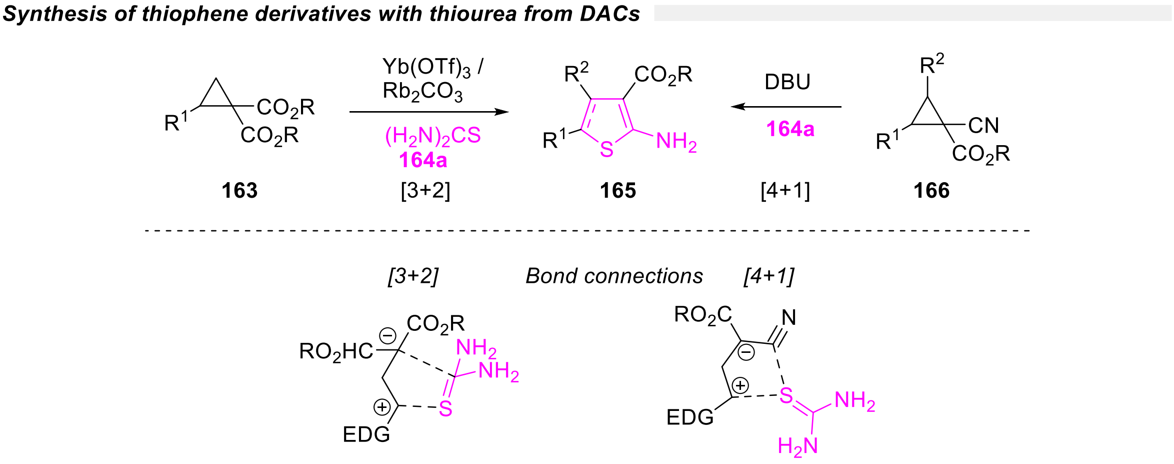
In conclusion, within natural product chemistry, the study of furofuranones has highlighted compounds with pharmacophore-bearing properties of significant interest. While challenges persist in their synthesis, detailed syntheses of compounds such as paeonilide, Norrisolide, and Macfarlandin C underline advancements in synthetic methodologies. Meanwhile, the synthesis of *γ*-lactams with amines from DACs represents a significant advancement in the field of three-membered carbocycle chemistry. This has led to the synthesis of diverse bioactive compounds. From the formation of *2*-oxopyrrolidinecarboxylic acids to the development of stereoselective methodologies for substituted *γ*-butyrolactams, researchers have demonstrated the versatility and utility of this synthetic approach. Furthermore, the total synthesis of (±)-martinellic acid by the Snider group exemplifies its potential in accessing pharmacologically relevant molecules. Combining both fields, further exploration of derivatization towards furo[2,3-*b*]pyrrolones starting from furofuranones offers avenues for diversification and potential therapeutic applications, suggesting exciting directions for future research in this field.

2. Main Part

2.1. Introduction

DACs offer great value as versatile and readily prepared three-carbon building blocks in organic synthesis.[123–125,51,126–130] When activated by Lewis acids, these cyclopropanes easily undergo ring-opening followed by [3+2]-cycloaddition reactions with a wide array of dipolarophiles,[131,54,132–135] enabling the generation of 5-membered ring systems that are valuable from a synthetic and biological point of view. Alternatively, but less explored are formal [4+1]-cycloadditions, in which a bis-nucleophile interacts both with the electrophilic center adjacent to the donor and the acceptor group of the DAC.[52]

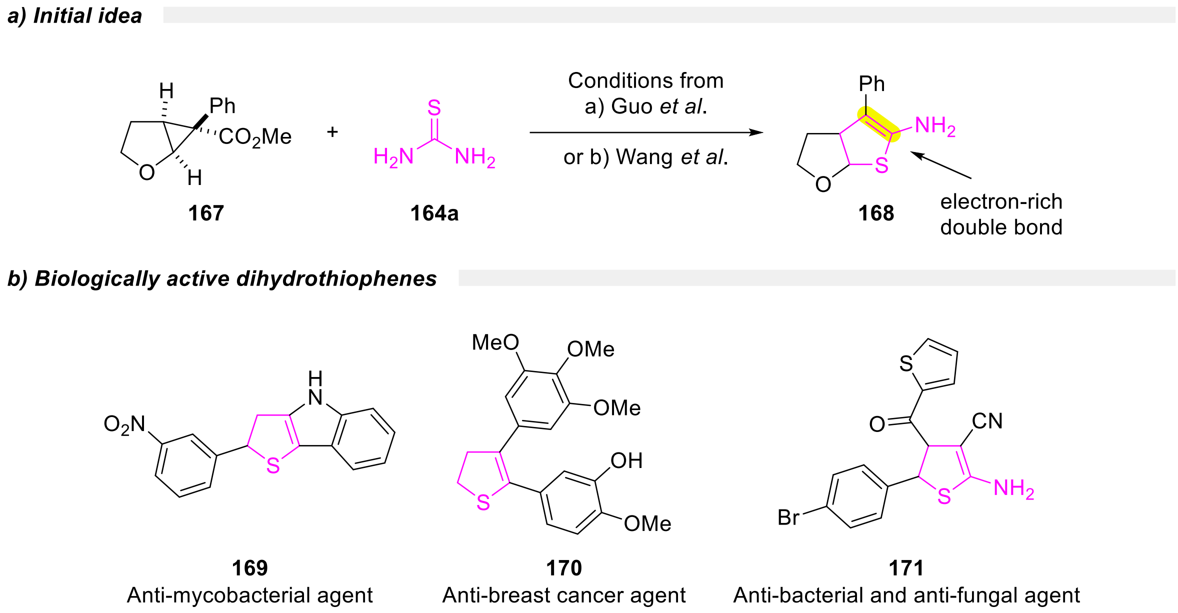
The functionalization of thiocarbonyl compounds in combination with DACs has been scarcely explored.[136–139] Notably, thiourea (**164a**), an odorless, cost-effective, and manageable sulfur source,[140,141] has been employed in only two examples for this purpose (Scheme 24): Guo *et al.* reported in 2019 the $Yb(OTf)_3$-catalyzed [3+2]-cycloaddition of cyclopropane-1,1-dicarboxylic acid esters **163**,[142] which resulted in the formation of 2-amino-4,5-dihydrothiophene derivatives **165**. Wang *et al.* disclosed a DBU-mediated [4+1]-annulation of DACs **166** with thiourea (**164a**) for the synthesis of 2-aminothiophene-3-carboxylates **165**.[143] Both reactions proceeded *via* an S-nucleophilic attack of thiourea, producing similar 2-aminothiophene products, albeit through different reaction pathways (Scheme 24, bond connections).



Scheme 24. Ring expansion of DACs with thiourea via [3+2]- or [4+1]-additions.

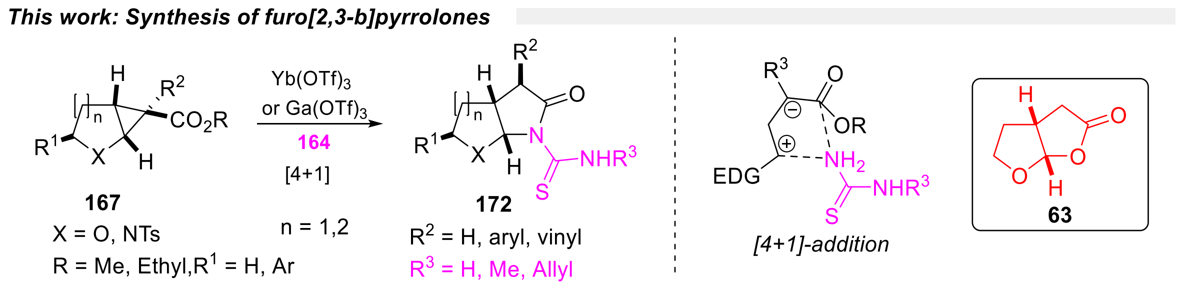
2.2. Aim of this Work

Inspired by these results from Guo[142] and Wang[143] and building upon our ongoing interest in ring opening chemistry of cyclopropanated furans and pyrroles,[68,144–148] we sought to explore the potential of this reaction with bicyclic system **167**, assuming an analogous reaction outcome (Scheme 25a). This way, bicyclic dihydrothiophene compounds such as **168** would become accessible, being an attractive scaffold considering the relevance of dihydrothiophene moieties in biologically active compounds (Scheme 25b).[149]



Scheme 25. a) Initial idea of this work. b) Dihydrothiophenes **169-171** in drug development.

In contrast to our expectations, this combination led to a formal [4+1]-cycloaddition through a cascade ring opening/cyclization reaction (Scheme 26), representing to the best of our knowledge the first example of thioureas **164** acting as *N*,*N*-bisnucleophiles in DAC ring openings.



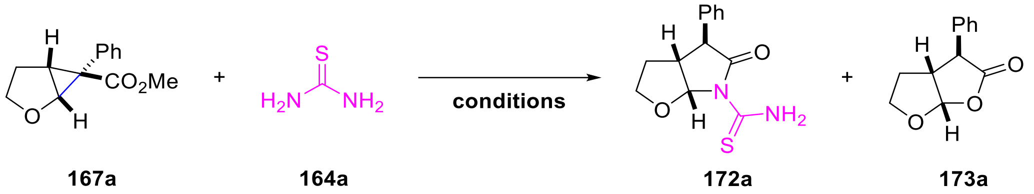
Scheme 26. This work: Ring expansion of DACs **172** with thioureas **164** to furolactams **172**.

This way, bicyclic furo[2,3-*b*]pyrrolones **172** became accessible being attractive scaffolds given the relevance of furo[2,3-*b*]furanones **63** in drug development.[85]

2.3. Preliminary Studies

Reaction development was initiated by subjecting fused cyclopropane **167a** and thiourea (**164a**) to the conditions reported by Guo *et al.*[142] and Wang *et al.*[143] (Table 3, Entries 1-2). These protocols resulted in the complete conversion of starting materials; however, in both cases, it yielded a complex product mixture that was not subjected to further investigation. Subsequent attempts to improve the reaction outcome by reducing the temperature led to the formation of a complex mixture at 50 °C or no conversion of the starting materials at 25 °C (Table 3, Entries 3-4). Notably, a solvent switch to toluene facilitated the formation of furolactam **172a** (32%, *dr* 7:1), accompanied by the known lactonization to furolactone **173a** (18%, *dr* 3:1).[49] Furthermore, among the various Lewis acids that were investigated, $Yb(OTf)_3$ exhibited superior catalytic activity in comparison to $Sc(OTf)_3$, $Zn(OTf)_2$, or $Cu(OTf)_2$ (Table 3, Entries 5-8).

Table 3. Initial screening experiments. Reaction conditions: 0.2 mmol **167a**, 0.4 mmol **164a**, 3.0 mL solvent, 20 mol% Rb_2CO_3, 18 h. Reaction was done in a closed vessel. Oil bath temperature 90-120 °C. NMR-yields determined using ethylene carbonate or 1,1,2,2-tetrachloroethane as internal standard. [a] 0.16 mmol DBU instead of LA. 2.0 mL DMF [b] Reaction at 50 °C. [c] Reaction at 25 °C.

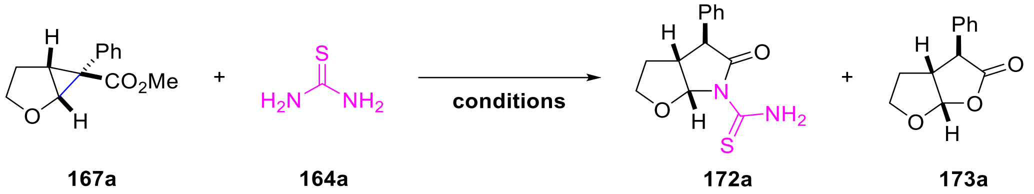


Entry	Solvent	Lewis acid [20 mol%]	Result
1	DCE	$Yb(OTf)_3$	Complex mixture
2[a]	DMF	-	Complex mixture
3[b]	DCE	$Yb(OTf)_3$	Complex mixture
4[c]	DCE	$Yb(OTf)_3$	No conversion
5	Toluene	$Yb(OTf)_3$	**172a:** 32%, *dr* 7:1 **173a**: 18%, *dr* 3:1
6	Toluene	$Sc(OTf)_3$	Complex mixture
7	Toluene	$Zn(OTf)_2$	Traces of **172a** and **173a**
8	Toluene	$Cu(OTf)_2$	Traces of **172a** and **173a**

2.4. Reaction Optimization

Following the identification of product **172a**, further investigation was conducted into the reaction parameters to enhance the yield, suppressing the formation of byproduct **173a**, and optimizing atom economy. A solvent screening revealed a profound influence on the reaction outcome, with polar aprotic solvents such as MeCN, THF and 1,4-dioxane yielding significant amounts of product **172a** (Table 4, Entries 3-5).

Table 4. Solvent screening. Reaction conditions: 0.2 mmol **167a**, 0.4 mmol **164a**, 3.0 mL solvent, 20 mol% Yb(OTf)$_3$, 20 mol% Rb_2CO_3. Reaction was done in a closed vessel and stopped after complete conversion of **167a** (TLC-analysis). Oil bath temperature 90-120 °C. NMR-yields determined using ethylene carbonate or 1,1,2,2-tetrachloroethane as internal standard.

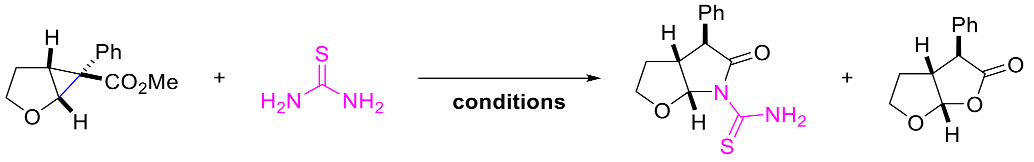


Entry	Solvent	Reaction time	Result	
1	*i*-Propanol	18 h	**172a:** 7%, *dr* 7:1	**173a:** 11%, *dr* 1:1
2	DMF	18 h	**172a:** traces	**173a:** 34%, *dr* 4:1
3	MeCN	18 h	**172a:** 62%, *dr* 7:1	**173a:** 12%, *dr* 3:1
4	THF	30 min	**172a:** 56%, *dr* 11:1	**173a:** 11%, *dr* 2:1
5	1,4-dioxane	15 min	**172a:** 72%, *dr* 8:1	**173a:** 5%, *dr* 1:1

Conversely, other solvents (*i*-Propanol, DMF) were found to have no beneficial effect on the reaction (Table 4, Entries 1-2). Therefore, 1,4-dioxane/Yb(OTf)$_3$ was chosen as the optimal solvent/catalyst system.

With the established conditions, a base-screening was conducted to investigate the influence of different carbonate bases on the reaction. It was observed that the use of other bases had no observable effect on the reaction, yielding **172a** within similar ranges and diastereomeric ratios (Table 5, Entries 1-4). Furthermore, the utilization of a base was considered disadvantageous, as it was hypothesized that this would promote the hydrolysis of the methyl ester moiety, thereby leading to the formation of byproduct **173a**. Consequently, performing the reaction without additional base furnished furolactam **172a** in quantitative yield (10:1 *dr*), with the exclusion of byproduct **173a**.

Table 5. Base screening. Reaction conditions: 0.2 mmol **167a**, 0.4 mmol **164a**, 3.0 mL 1,4-dioxane, 20 mol% Yb(OTf)$_3$. Reaction was done in a closed vessel and stopped after complete conversion of **167a** (TLC-analysis). Oil bath temperature 90-120 °C. NMR-yields determined using ethylene carbonate or 1,1,2,2-tetrachloroethane as internal standard.

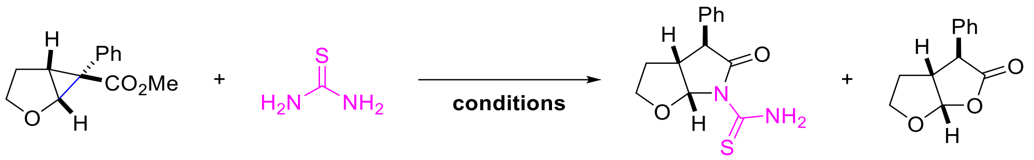


167a **164a** **172a** **173a**

Entry	Base [20 mol%]	Reaction time	Result	
1	Li$_2$CO$_3$	30 min	**172a:** 77%, *dr* 7:1	**173a:** traces
2	Na$_2$CO$_3$	30 min	**172a:** 82%, *dr* 8:1	**173a:** traces
3	Cs$_2$CO$_3$	30 min	**172a:** 66%, *dr* 8:1	**173a:** traces
4	K$_2$CO$_3$	2 h	**172a:** 69%, *dr* 14:1	**173a:** 7%, *dr* 1:1
5	-	3 h	**172a:** 99%, *dr* 10:1	**173a:** -

Afterwards, the reaction conditions were optimized. First, the amount of solvent was reduced, resulting in diminished yields of **172a** (Table 6, Entries 1-2). Following this, a reduction of thiourea equivalents was carried out. This hindered the reaction, yielding decreased amounts of product **172a** along with 13% of byproduct **173a** (Table 6, Entry 3). Furthermore, the catalyst loading was reduced to 10 mol% and 5 mol%, which did not affect the yield or the diastereomeric ratio (Table 6, Entries 4-5). Thus, optimal conditions were identified with the combination of Yb(OTf)$_3$ (5 mol%) in dioxane at 90 °C, which gave **172a** in quantitative yield and high (10:1) diastereoselectivity, with the phenyl group oriented on the convex face of the bicycle (Table 6, Entry 5). Further reduction of the catalyst loading (1 mol%, Table 6, Entry 6) decreased the yield. In addition, no conversion of the starting materials was observed without Lewis acid, excluding a thermal-driven reaction (Table 6, Entry 7).

Table 6. Reaction optimization. Reaction conditions: 0.2 mmol **167a**, 0.4 mmol **164a**, 3.0 mL 1,4-dioxane,. Reaction was done in a closed vessel. Oil bath temperature 90-120 °C. NMR-yields determined using ethylene carbonate or 1,1,2,2-tetrachloroethane as internal standard. [a] 2.0 mL 1,4-dioxane. [b] 1.0 mL 1,4-dioxane. [C] 1.5 equiv of **164a**.



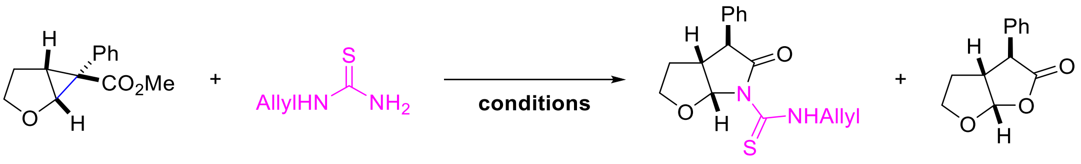
167a **164a** **172a** **173a**

Entry	Yb(OTf)$_3$ [mol%]	Time	Result	
1[a]	20	3 h	**172a:** 86%, *dr* 10:1	**173a:** -
2[b]	20	3 h	**172a:** 87%, *dr* 9:1	**173a:** -
3[c]	20	5 h	**172a:** 77%, *dr* 8:1	**173a:** 13%, *dr* 4:1
4	10	5 h	**172a:** 99%, *dr* 10:1	**173a:** -
5	5	8 h	**172a:** 99%, *dr* 10:1	**173a:** -
6	1	10 h	**172a:** 99%, *dr* 10:1	**173a:** -
7	-	18 h	no conversion	

Following the reaction optimization for thiourea (**164a**), the feasibility of using monosubstituted thioureas under the optimized conditions was investigated. Unfortunately, the monosubstituted allylthiourea **164c** could not be catalyzed by Yb(OTf)$_3$, resulting in a complex product mixture (Table 7, Entry 1). A brief screening of Lewis acids revealed that

$Ga(OTf)_3$ outperformed other Lewis acids, including $Yb(OTf)_3$, $La(OTf)_3$, and $Sc(OTf)_3$ (Table 7, Entries 1-4). In addition, the effectiveness of the transformation was significantly influenced by the choice of solvent, with MeCN being the most efficient (Table 7, Entry 7). However, other polar aprotic solvent (THF), as well as apolar aprotic (DCE, toluene) and protic solvents (MeOH), failed to yield any product and resulted in complex product mixtures or incomplete conversions (Table 7, Entries 5-9).

Table 7. Reaction optimization with **164c**. Reaction conditions: 0.2 mmol **167a**, 0.4 mmol **164c**, 3.0 mL solvent. Reaction was done in a closed vessel. Oil bath temperature 90-120 °C. NMR-yields determined using ethylene carbonate as internal standard.



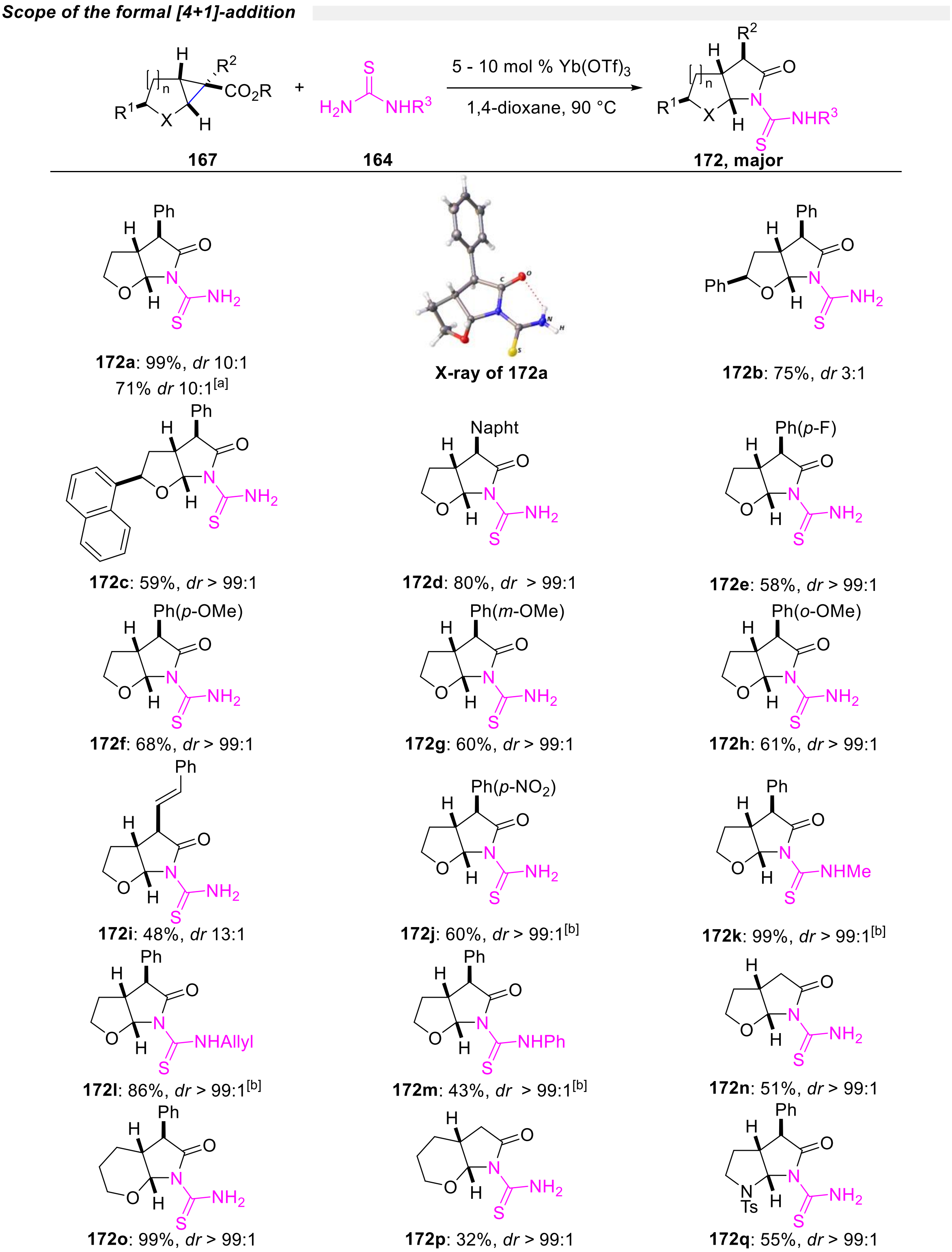
167a **164c** **172l** **173a**

Entry	Solvent	Lewis acid [10 mol%]	Result
1	1,4-dioxane	$Yb(OTf)_3$	Complex mixture
2	1,4-dioxane	$Ga(OTf)_3$	**172l:** 31%, *dr* 4:1 **173a:** 32%, *dr* 6:1
3	1,4-dioxane	$La(OTf)_3$	Complex mixture
4	1,4-dioxane	$Sc(OTf)_3$	Complex mixture
5	DCE	$Ga(OTf)_3$	No conversion
6	Toluene	$Ga(OTf)_3$	No conversion
7	MeCN	$Ga(OTf)_3$	**172l:** 91%, *dr* > 99:1 **173a: -**
8	THF	$Ga(OTf)_3$	No conversion
9	MeOH	$Ga(OTf)_3$	Complex mixture

In summary, our exploration of the reaction with bicyclic DACs **167** yielded promising results. Despite initial challenges, optimization efforts including temperature adjustments, solvent screening, and catalyst selection were successful. The exclusive formation of furolactam **172a** under optimal conditions highlights the potential of this reaction to access important scaffolds. Further investigation revealed that the reaction could be applied to monosubstituted thioureas by slightly modifying the conditions. This sets the stage for the synthesis of numerous bicyclic compounds **172** and provides first insights into the reaction mechanism, which will be discussed later.

2.5. Scope of the Reaction and Limitations

After establishing the optimized conditions, we investigated the scope of this formal [4+1]-cycloaddition (Scheme 27).



Scope of the formal [4+1]-addition

167 **164** **172, major**

172a: 99%, *dr* 10:1
71% *dr* 10:1[a]

X-ray of 172a

172b: 75%, *dr* 3:1

172c: 59%, *dr* > 99:1

172d: 80%, *dr* > 99:1

172e: 58%, *dr* > 99:1

172f: 68%, *dr* > 99:1

172g: 60%, *dr* > 99:1

172h: 61%, *dr* > 99:1

172i: 48%, *dr* 13:1

172j: 60%, *dr* > 99:1[b]

172k: 99%, *dr* > 99:1[b]

172l: 86%, *dr* > 99:1[b]

172m: 43%, *dr* > 99:1[b]

172n: 51%, *dr* > 99:1

172o: 99%, *dr* > 99:1

172p: 32%, *dr* > 99:1

172q: 55%, *dr* > 99:1

Scheme 27. Scope of the reaction. Reaction conditions: **167** (0.4-0.5 mmol), **164** (2.0 equiv), 1,4-dioxane (3.0

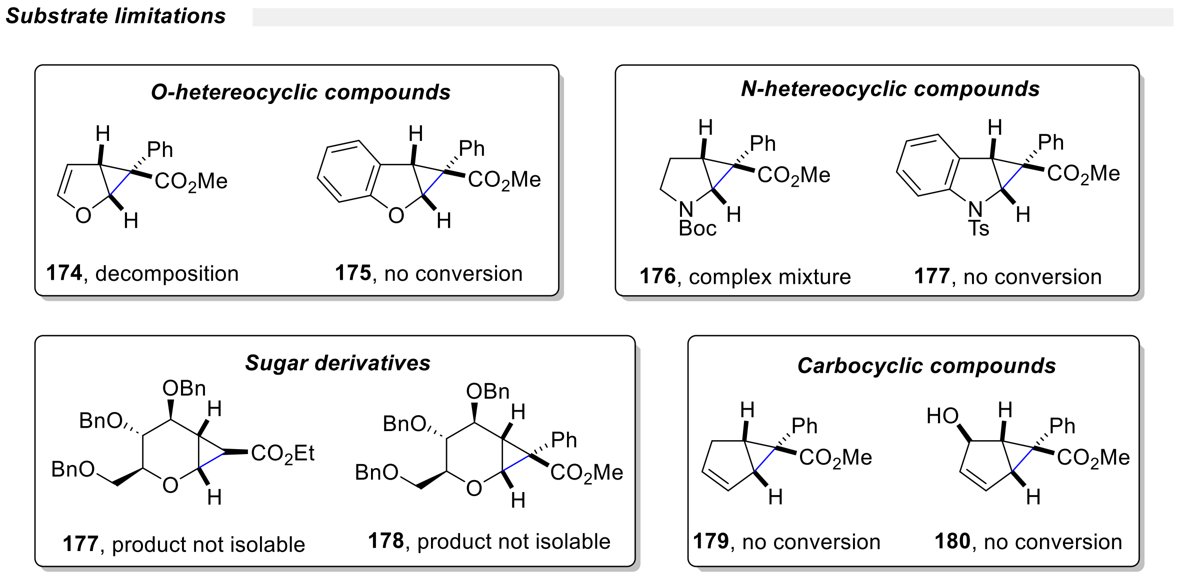
mL), $Yb(OTf)_3$ (5 mol%; 10 mol% for **172q**), 24 h; the major diastereomer is shown. Reactions were carried out in closed vessels. Oil bath temperature 90-120 °C. [a] 7.0 mmol scale. [b] Reaction conditions: $Ga(OTf)_3$ (10 mol%) instead of $Yb(OTf)_3$, MeCN (3.0 mL), 18 h

Cyclopropanated dihydrofurans **167a-h** afforded the desired bicyclic products **172a-h** in favorable yields and diastereoselectivities, demonstrating tolerance to aryl substitution at the *3*-position of the dihydrofuran ring as well as various electronically differentiated aryl substituents in the arene moiety. Styryl substitution on the cyclopropane was also viable, albeit resulting in compound **172i** with a moderate yield of 48%.

Monosubstituted thioureas did not react under catalysis with $Yb(OTf)_3$. A short screening with $Ga(OTf)_3$ (10 mol%) in MeCN proved to be effective (see chapter 2.5), allowing the synthesis of methyl-, allyl- and phenyl-substituted thioureas **172k-m** (43-99%, > 99:1 d.r.). Notably, compound **172j** with a highly electron-deficient aryl group was successfully synthesized using this method, whereas the protocol using $Yb(OTf)_3$ as a Lewis acid catalyst failed. Furthermore, the reaction proceeded even in the absence of an aryl group on the cyclopropane ring, even though in a comparatively lower yield of 51% to give compound **172n**. In addition, other heterocyclic ring systems were also compatible, yielding compounds **172o-q** (32-99% yield). Successful scale-up for lactam annulation was demonstrated at a 7 mmol scale, yielding compound **172a** in 71% yield (1.3 g) and a 10:1 diastereomeric ratio.

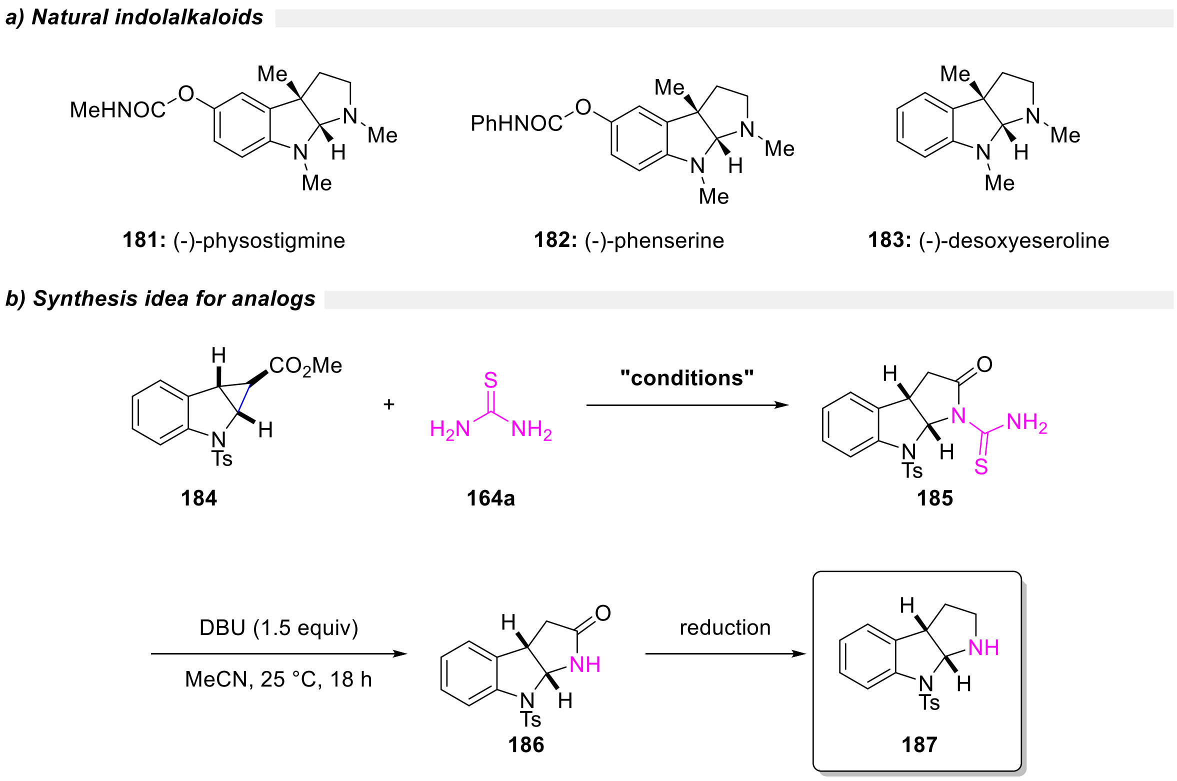
Despite its efficacy, the reaction had certain limitations. *O*-heterocyclic compounds containing a double bond or a fused phenyl ring (**174-175**) were unsuitable for the desired conversion to furolactams. In addition, attempts with the *Boc*-protected compound **176** resulted in decomposition, while the indol compound **177** showed no reactivity towards the optimized conditions. Although Chandrasekaran's sugar derivatives[150] **177-178** could be converted to the desired compounds, their isolation using standard purification methods proved to be impractical. Carbocyclic compounds **179-180** were not converted to the corresponding lactams, possibly due to the more challenging cyclopropane activation in the absence of a heteroatom (Scheme 28).

Regarding carbocyclic compounds **179-180**, as well as compounds **175** and **177**, harsher reaction conditions may be necessary. Therefore, future investigations should include screening for optimal reaction conditions to increase the versatility of the method and facilitate the synthesis of diverse and interesting compounds. In particular, the synthesis of pyrrolo[2,3-*b*]indole **187** seems promising given the prevalence of this moiety in various indole alkaloids such as (–)-physostigmine (**181**), (–)-phenserine (**182**), and (–)-desoxyeseroline (**183**) (Scheme 29a).[151]



Scheme 28. Unsuccessful substrates under the optimized conditions. Reaction conditions: 0.2 mmol substrate, 0.4 mmol thiourea (**164a**), 10 mol% Yb(OTf)$_3$, 3.0 mL 1,4-dioxane. 90 °C, 18 h.

The synthetic route could start from cyclopropane **184**, which upon treatment with thiourea (**164a**) under optimized conditions would yield the intermediate **185**.



Scheme 29. a) Selection of natural indole alkaloids. b) Possible pathway for synthesis of natural product analog **187**.

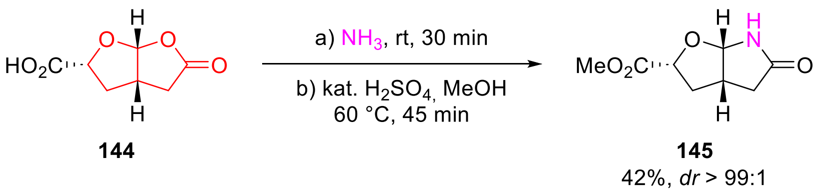
Subsequent cleavage of the pyrrolidine moiety yields compound **186**, followed by reduction using standard methods such as LAH reduction, which ultimately leads to the desired natural product analog **187** (Scheme 29b).

2.6. Mechanism of the Reaction

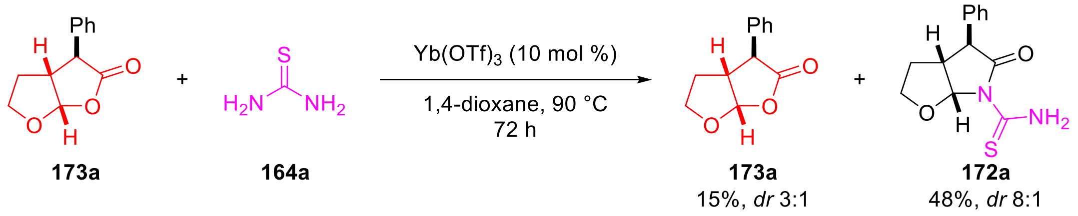
In 2007, Roland Weisser described a three-step synthetic route starting with cyclopropane **143**, which involved acid-mediated ring expansion to give compound **144** (see chapter 1.2.4). Subsequent ring opening of the lactone moiety with ammonia, followed by acid-mediated ring closure, resulted in the formation of furolactam **145** with an overall yield of 42% (Scheme 30a).[111]

Based on this synthetic pathway, it was hypothesized that thiourea might act analogously to ammonia to produce compound **172a**. To elucidate the underlying mechanism, compound **173a**, which was identified as a byproduct in some cases (see Table 3-7), was subjected to the reaction conditions (Scheme 30b). Notably, product **172a** was obtained after a prolonged reaction period (72 h) with a moderate yield of 48% and a diastereomeric ratio of 8:1. Therefore, while the conversion of bicyclic furolactone **173a** to **172a** is theoretically plausible, the reaction kinetics, conversion rates, and overall yield make this proposed pathway unlikely.

a) Synthesis of furo[2,3-b]pyrrolone core

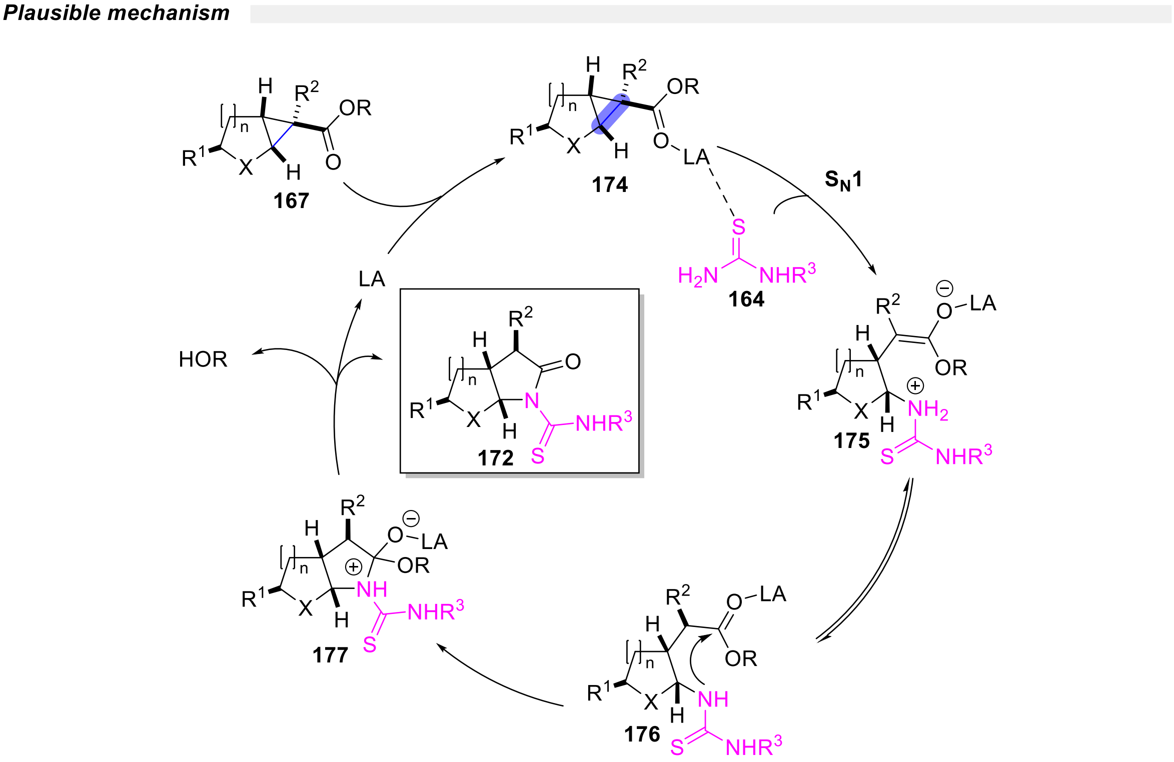


b) Control experiment



Scheme 30. a) Synthesis of furo[2,3-*b*]pyrrolone **145** from furo[2,3-*b*]furanone **144** by Weisser.[111] b) Control experiment with **173a** using optimized conditions.

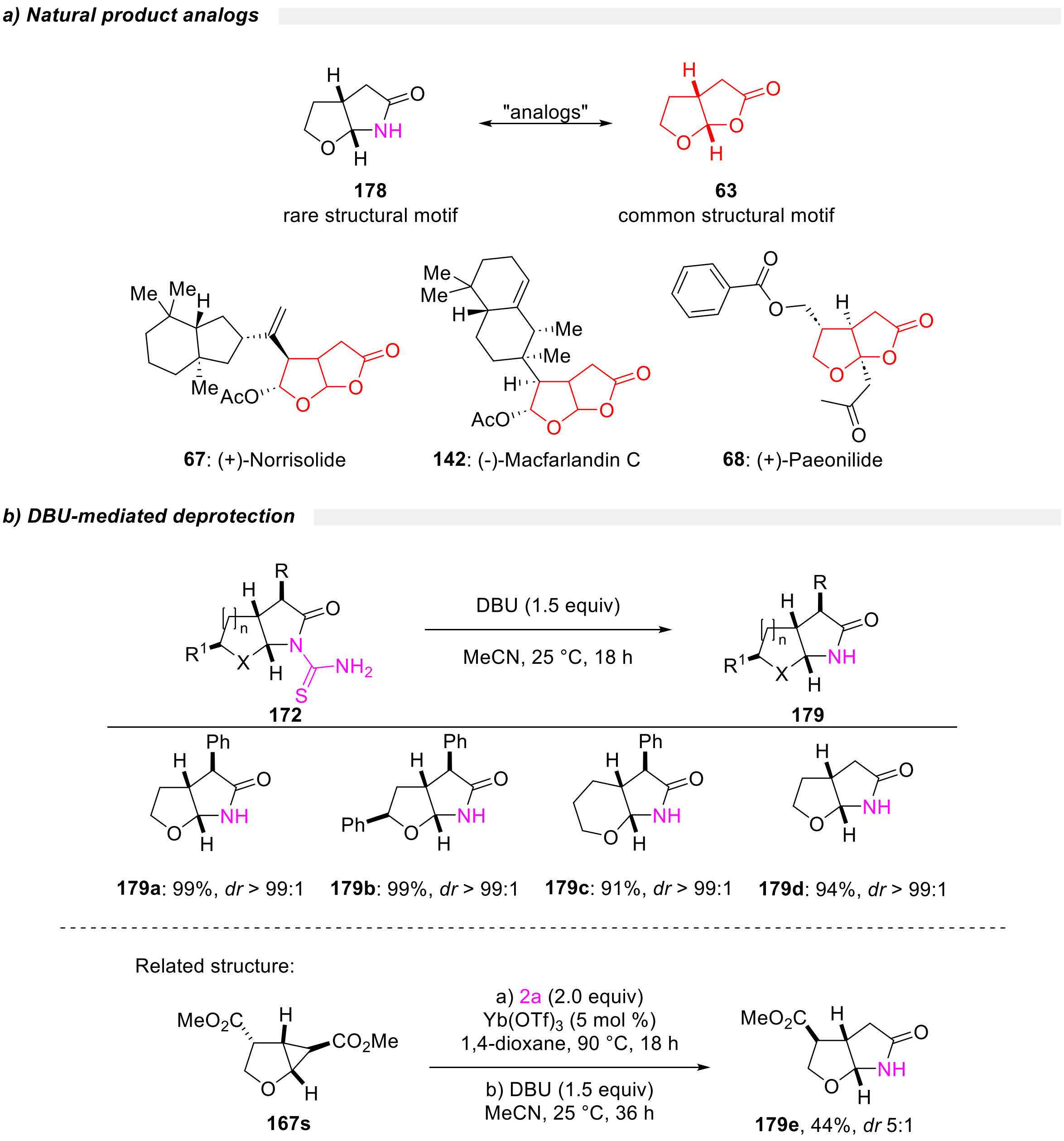
Hence, we propose (Scheme 31) the Lewis acid activation of the ester moiety in **167**, leading to the S_N1-type ring opening along the DAC bond in **174** (highlighted in blue) to give **175**. Protonation of the enolate to **176** sets the stage for a second *N*-nucleophilic attack of the thiourea moiety **164**, favoring a 5-*exo* over a 7-*exo* cyclization in which the substituent R^2 is oriented on the convex face of the bicyclic system (Intermediate **177**). Final product **172** is obtained by extrusion of the alcohol and the Lewis acid, which can initiate a new catalytic cycle.



Scheme 31. Proposed mechanism for the synthesis of furo[2,3-*b*]pyrrolones **172**.

2.7. Chemical Transformation towards useful Natural Product Analogs

A notable goal in synthetic organic chemistry is the development of novel or improved routes to complex chemical structures, particularly those that are prevalent in biologically active compounds or pharmaceutical agents. Within this framework, bicyclic structures containing nitrogen have received considerable attention due to their fundamental role as scaffolds for a wide variety of bioactive molecules.[152,153]

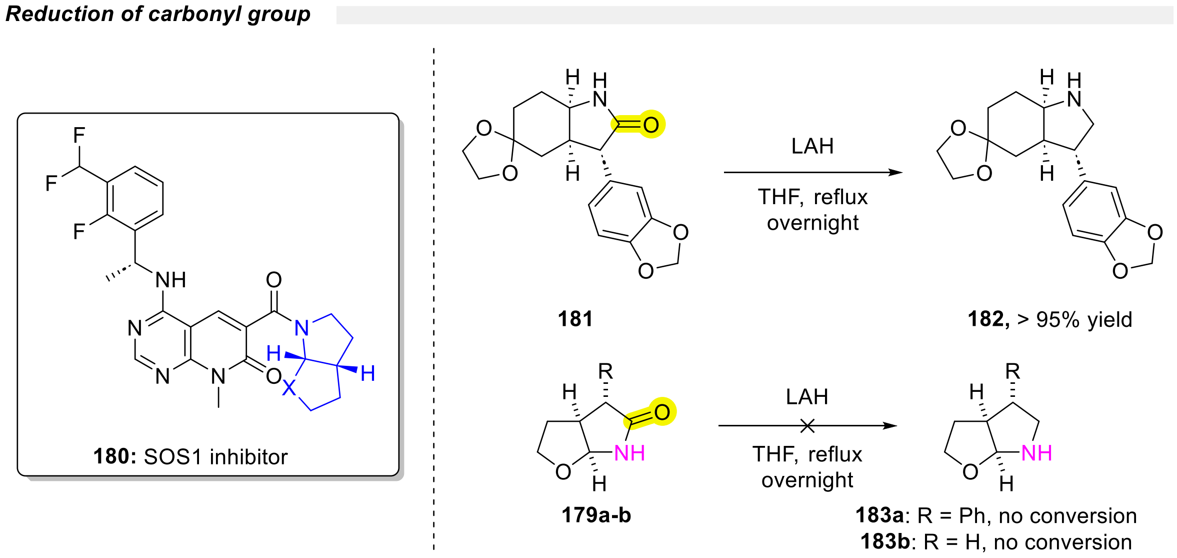


Scheme 32. a) Furolactone natural products. b) Scope of the DBU-mediated elimination.

The bicyclic furo[2,3-*b*]pyrrolone nucleus **178** is structurally similar to the widely used furo-γ-lactone ring system **63**. However, it represents a relatively underexplored analog that may be of significance to the pharmaceutical industry, given the importance of furolactones such as **67**, **68**, and **142** in drug discovery efforts (Scheme 32a).[85] Consequently, unmasking of the pyrrolidine moiety in **172** was chosen as a suitable follow-up reaction. This transformation was readily achieved by treating **172** with DBU in acetonitrile, yielding compounds **179** in high yields (> 90%). Moreover, this deprotection protocol offers the additional advantage of enhancing the selectivity towards the sterically favored *exo*-diastereomer *via* a deprotonation/protonation sequence (Scheme 32b).

Furthermore, it is noteworthy that furo[2,3-*b*]furanones often contain substitution at the 3-position of the dihydrofuran ring. Therefore, compound **179e** was synthesized from **167s** with good overall yield (44%, dr 5:1), having a versatile methyl ester in this position, which should allow for further modification towards analogs of natural products, such as Norrisolide (**67**),[107] Macfarlandin C (**142**),[110] and Paeonilide (**67**),[49] that display significant bioactive properties (Scheme 32c).[85]

Following the synthesis of compounds **179**, efforts were made to reduce the carbonyl group (highlighted in yellow). The primary objective was the synthesis of bicyclic fragments **183a-b**, which constitutes a component of a SOS1 (Son of sevenless homolog 1) inhibitor **180** which is utilized as an indirect means to impede RAS signaling, thereby holding promise for cancer therapy. In this context, the reduction of the carbonyl group could yield a spectrum of compounds that could serve as potential precursors for the synthesis of drugs analogous to **180**.

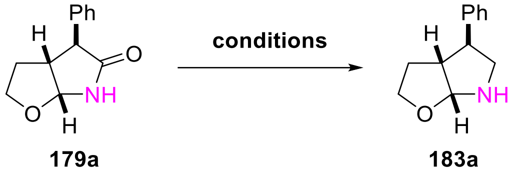


Scheme 33. Furo[2,3-*b*]-pyrroles **183a-b** as potential building blocks for SOS1 inhibitors.

The reduction method by Cossío *et al.*[154] was employed as a basis for reaction optimization, using a comparable starting compound **181** and following the standard $LiAlH_4$ reduction protocol. However, the reaction yielded no conversion of the starting materials **179a-b** (Scheme 33).

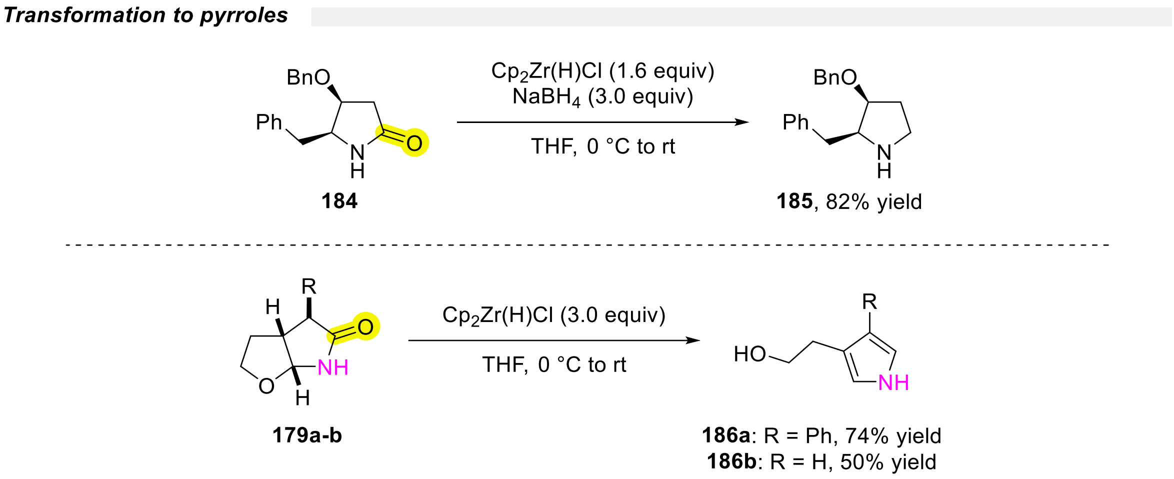
Consequently, a screening involving model substrate **179a** was conducted. Lithium-based reduction protocols applied to **179a** were found to be ineffective, resulting in either no conversion or the formation of complex product mixtures (Table 8, Entries 1-3). The use of a milder reducing agent, $BH_3{\cdot}SMe_2$, across various temperature regimes and stoichiometric ratios similarly failed to yield the targeted product **183a**. Moreover, attempts were made to generate BH_3 *in situ* through the $NaBH_4/I_2$ system, but this only led to a complex product mixture (Table 8, Entries 4-9)

Table 8. Reduction of γ-lactam moiety. Reaction conditions: 0.1 mmol **179a**, 1.0 mL dry THF, 18 h.



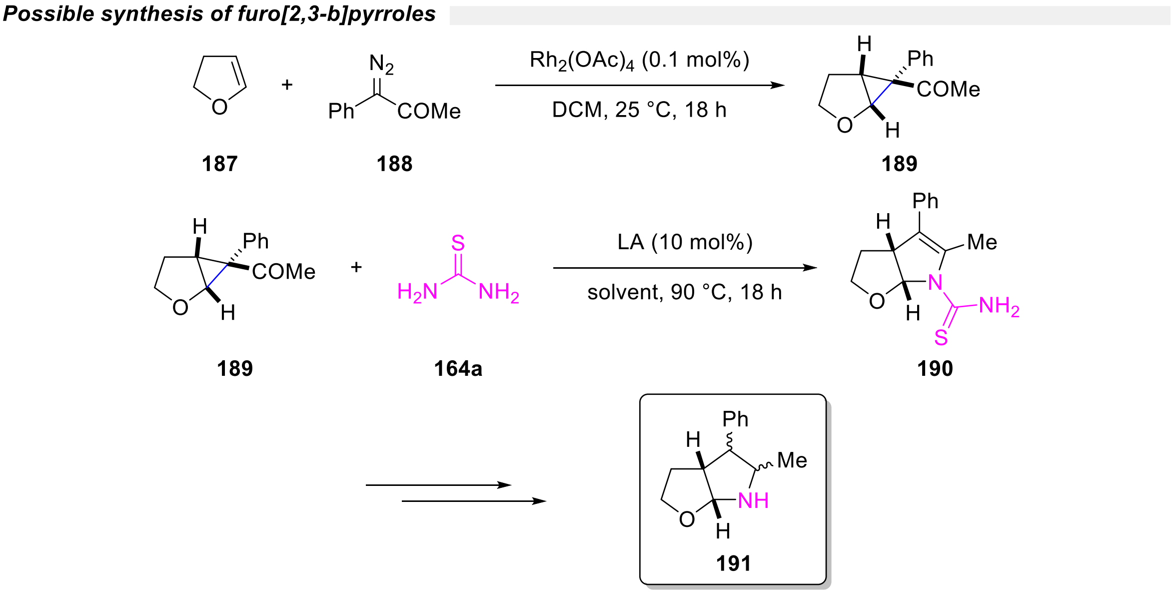
Entry	Reducing agent	Temperature	Result
1	LAH (2.0 equiv)	Reflux	No conversion
2	LAH (2.0 equiv)	Reflux	Complex mixture
3	LAH (10.0 equiv)	25 °C	Complex mixture
4	$BH_3 \cdot SMe_2$ (10.0 equiv)	Reflux	Complex mixture
5	$BH_3 \cdot SMe_2$ (10.0 equiv)	25 °C	Complex mixture
6	$BH_3 \cdot SMe_2$ (2.0 equiv)	25 °C	No conversion
7	$BH_3 \cdot SMe_2$ (10.0 equiv)	- 78 °C	No conversion
8	$BH_3 \cdot SMe_2$ (10.0 equiv)	- 15 °C	Complex mixture
9	$NaBH_4/I_2$ (2.5 equiv/1.0 equiv)	Reflux	Complex mixture

Given the inadequacy of standard reduction methodologies for this transformation, alternative protocols sourced from the literature were explored to obtain the reduced compound **183a**. Among these, a zirconium-catalyzed reduction (Schwartz salt) of lactams as proposed by Geng *et al.*[155] *via* an assumed imine-zirconium complex, subsequently reduced by $NaBH_4$, emerged as a viable route for bicyclic compounds **183a-b**. Indeed, reduction of the carbonyl group occurred; however *in-situ* follow-up reaction furnished pyrrole compounds **186a-b**, likely due to the instability of the semiaminal structure, which undergoes ring-opening under slightly acidic conditions facilitated by $Cp_2Zr(H)Cl$ (Scheme 34).



Scheme 34. Reductive synthesis of pyrroles **186a-b** *via* Schwartz reagent.

Due to the inherent instability of the semiaminal structure, it seems unlikely that reduction will occur under the tested conditions. Consequently, it is advisable to implement preemptive measures during the synthesis of the bicyclic structure to circumvent this issue.

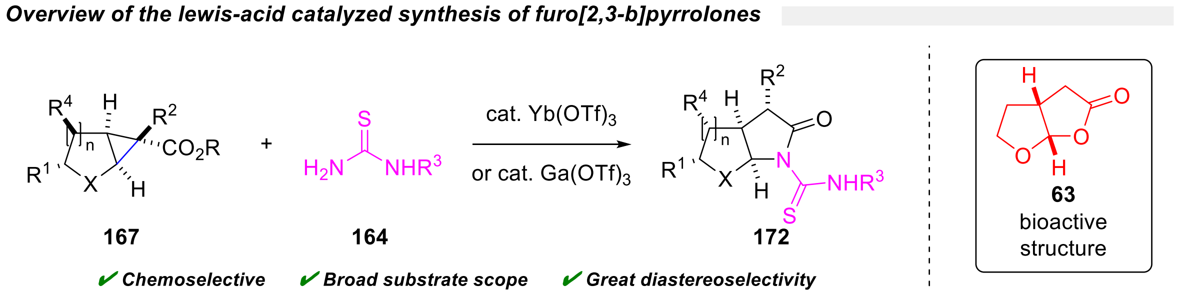


Scheme 35. Possible pathway for the synthesis of carbonyl-free compound **191**.

One potential strategy involves the utilization of alternative starting materials, such as diazo ketones **188**, to obviate the necessity for subsequent reduction steps. This approach could result in the synthesis of bicyclic compounds **191**, which could be of interest for pharmaceutical and medicinal chemistry applications (Scheme 35).

3. Summary

In summary, the second project of the present work investigated the reaction of fused cyclopropanes **167** and thioureas **164** with the aim of making valuable bicyclic compounds, in particular furolactams **172**, accessible (Scheme 36).



Scheme 36. Schematical summary of the second project.

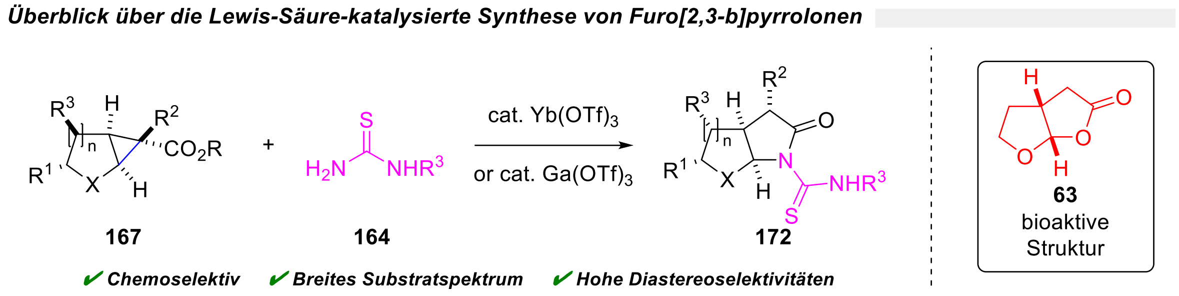
Initial experiments performed under the conditionds described by Guo *et al.* and Wang *et al.* resulted in complete conversion of the starting materials, but the resulting product mixtures were complex, so further exploration of these conditions was not pursued. Subsequent efforts have focused on temperature adjustments, solvent selection, and catalyst screening to improve product yield and selectivity. It is noteworthy that switching to toluene as the solvent resulted in the formation of furolactams **172a**, albeit with the known lactonization to furolactone **173a**. The crucial role of Lewis acids in catalyzing the reaction was highlighted by extensive screening, with $Yb(OTf)_3$ proving to be a superior catalyst compared to other Lewis acids tested. Further optimization, including solvent screening and base studies, shed light on key reaction parameters and revealed 1,4-dioxane as the optimal solvent. In addition, the exclusion of base was found to promote product formation and minimize undesired side reactions.

After identifying the optimal conditions for the synthesis of furolactams **172**, our investigations were extended to the applicability of monosubstituted thioureas and yielded promising results using $Ga(OTf)_3$ as a catalyst in MeCN. This expansion of the substrate spectrum highlights the versatility of the reaction and opens up possibilities for the synthesis of various bicyclic compounds with different functionalities. The scalability of the reaction has been demonstrated, although with certain limitations regarding its applicability to certain substrates. Consequently, furopyrrolones have been synthesized as natural product analogues of the widely used and studied bioactive furofuranones.

In parallel with our product synthesis efforts, we also investigated the reduction of the carbonyl group in the synthesized bicyclic compounds to explore potential precursors for drug synthesis. However, standard reduction methods proved to be ineffective and alternative routes need to be explored in the future.

4. Zusammenfassung

Zusammenfassend untersuchte das zweite Projekt der vorliegenden Arbeit die Reaktion von kondensierten Cyclopropanen **167** und Thioharnstoffen **164** mit dem Ziel, wertvolle bicyclische Verbindungen, insbesondere Furolactame **172**, zugänglich zu machen (Schema 36).



Schema 36. Schematische Zusammenfassung des zweiten Projekts.

Erste Experimente, die unter zuvor von Guo *et al.* und Wang *et al.* beschriebenen Bedingungen durchgeführt wurden, führten zu einer vollständigen Umwandlung der Ausgangsmaterialien, die resultierenden Produktmischungen waren jedoch komplex, sodass eine weitere Erforschung dieser Bedingungen nicht weiterverfolgt wurde. Nachfolgende Bemühungen konzentrierten sich auf Temperaturanpassungen, Lösungsmittelauswahl und Katalysator-Screening, um die Produktausbeute und -selektivität zu verbessern. Bemerkenswert ist, dass die Umstellung auf Toluol als Lösungsmittel zur Bildung der Furolactame **172a** führte, wenn auch mit der bekannten Lactonisierung zum Furolacton **173a**. Die entscheidende Rolle von Lewis-Säuren bei der Katalyse der Reaktion wurde durch ein umfangreiches Screening unterstrichen, wobei sich Yb(OTf)$_3$ im Vergleich zu anderen getesteten Lewis-Säuren als überlegener Katalysator erwies. Weitere Optimierungen, einschließlich Lösungsmittelscreening und Basenuntersuchungen, haben Aufschluss über entscheidende Reaktionsparameter gegeben und 1,4-Dioxan als optimales Lösungsmittel aufgezeigt. Darüber hinaus wurde festgestellt, dass der Ausschluss von Base die Produktbildung begünstigt und unerwünschte Nebenreaktionen minimiert.

Nachdem wir optimale Bedingungen für die Synthese der Furolactame **172** ermittelt hatten, weiteten sich unsere Untersuchungen auf die Anwendbarkeit monosubstituierter Thioharnstoffe aus und brachten vielversprechende Ergebnisse mit Ga(OTf)$_3$ als Katalysator in MeCN. Diese Erweiterung des Substratspektrums unterstreicht die Vielseitigkeit der Reaktion und eröffnet Möglichkeiten für die Synthese verschiedener bicyclischer

Verbindungen mit unterschiedlichen Funktionalitäten. Die Skalierbarkeit der Reaktion wurde nachgewiesen, wenn auch mit gewissen Einschränkungen hinsichtlich der Anwendbarkeit auf bestimmte Substrate. Folglich wurden Furopyrrolone als Naturstoffanaloga zu den weit verbreiteten und untersuchten bioaktiven Furofuranonen synthetisiert.

Parallel zu unseren Bemühungen in der Produktsynthese untersuchten wir auch die Reduktion der Carbonylgruppe in den synthetisierten bicyclischen Verbindungen, um potenzielle Vorläufer für die Arzneimittelsynthese zu erschließen. Standardmethoden zur Reduzierung erwiesen sich jedoch als unwirksam, so dass in Zukunft alternative Routen untersucht werden mussten.

5. Experimental Procedures

General Information

Moisture sensitive reactions were performed in flame-dried glassware and under nitrogen atmosphere. Commercially available chemicals were used without further purification and anhydrous solvents were prepared according to established procedures.[4] Used H_2O is deionized H_2O, unless otherwise stated. Photochemical reactions were carried out in oven-dried glassware. EtOAc and hexanes for chromatography were distilled prior to use. The reported yields are isolated compounds unless otherwise stated.

Chromatography

Thin layer chromatography (TLC) was performed with precoated aluminum sheets (ALUGRAM® Xtra SIL G/UV_{254} from MACHEREY-NAGEL GmbH & Co. KG, thickness 0.2 mm). Visualization was done by UV light (λ = 254 nm) and/or staining with vanillin (6.0 g vanillin, 100 mL ethanol (95%), 1 mL conc. sulfuric acid) or potassium permanganate (2.0 g Na_2CO_3, 1.0 g $KMnO_4$, 100 mL DI H_2O (deionized H_2O) or/and followed by heating. Column chromatography was performed with silica gel (Merck Geduran Si 60, 0.063-0.200 mm particle size) and flash silica gel 60 (Merck Geduran Si 60, 0.040-0.063 mm particle size).

NMR-Spectroscopy

^1H NMR- and ^{13}C NMR-spectra were recorded on Bruker Avance 300 (300 MHz for ^1H, 75 MHz for ^{13}C) NMR spectrometer, or on Bruker Avance III 400 (400 MHz for ^1H, 101 MHz for ^{13}C) NMR spectrometer, or Varian/Bruker 400 (400 MHz for ^1H, 101 MHz for ^{13}C) NMR spectrometer, or on INOVA/Bruker 500 (500 MHz for ^1H) NMR spectrometer, or on INOVA/Bruker 600 (600 MHz for ^1H, 151 MHz for ^{13}C) NMR spectrometer. The spectra were recorded in $CDCl_3$ (δ 7.26 ppm) and chemical shifts for ^1H NMR were reported as δ, parts per million (ppm), relative to the signal of $CHCl_3$. Spectra were evaluated in 1st order and the coupling constants *J* are reported in Hertz (Hz). Spin multiplicities were reported in abbreviations as: s = singlet, bs = broad-singlet, d = doublet, t = triplet, q = quartet, p = pentet, dd = doublet of doublet, dt = doublet of triplet, dq = doublet of quartet, dp = doublet

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[4] a) Armarego, W. L. F.; Chai, C. L. L., Purification of Laboratory Chemicals. 6 ed.; Butterworth-Heinemann Oxford, 2009.[73]
b) Hünig, S.; Felderhoff, M.; Kemmerer, M.; Kreitmeier, P.; Märkl, G.; Sauer, J.; Seifert, M.; Sustmann, R.; Troll, Integriertes Organisch-Chemisches Praktikum (I.O.C.-Praktikum); 1. ed.; Lehmanns, 2007.[74].

of pentet, qd = quartet of doublet, ddd = doublet of doublet of doublet, ddt = doublet of doublet of triplet, ddq = doublets of doublet of quartet, dtd = doublet of triplet of doublet, dtt = doublet of triplet of triplet, tdd = triplet of doublet of doublet, ttq = triplet of triplet of quartet, dddd = doublet of doublet of doublet of doublet, ddtd = doublet of doublet of triplet of doublet, dtdd = doublet of triplet of doublet of doublet and m = multiplet. Chemical shifts for ^{13}C-NMR were reported as δ, parts per million (ppm), relative to the signal of $CHCl_3$ (δ 77.16 ppm). NMR yields were determined using tetrachloroethane or ethylene carbonate as internal standard.

Mass Spectrometry

High resolution mass spectra (HRMS) were obtained on Jeol AccuTOF GCX or Agilent Technologies 6540 UHD Accurate-Mass Q-TOF LC/MS and are reported in *m/z*. High-resolution mass spectra were measured using atmospheric pressure chemical ionization (APCI), electron ionization (EI), electrospray ionization (ESI) with a quadrupole time-of-flight (Q-TOF) detector. The analysis was done by the Central Analytical Laboratory (University Regensburg).

IR-Spectroscopy

Infrared spectra (IR) were measured on a Biorad Excalibur FTS 3000 spectrophotometer and are reported in unit of cm^{-1}.

X-Ray Analysis

X-ray crystallographic analysis was performed by the Central Analytic Department of the University of Regensburg using an Agilent Technologies SuperNova, Agilent Technologies Gemini R Ultra, Agilent GV 50 or Rigaku GV 50.

Crystallization was done by dissolving small amounts of the desired solid in DCM or diethyl ether or hexanes (if diethyl ether was used, the solution was warmed of up to 50 °C in a water bath) and slowly evaporated within 48 h at ambient temperatures/pressure.

Melting Points

The measurement of melting points was carried out on an SRS MPA100 - Automated melting point system by OptiMelt.

Photochemical Reactions

For all photochemical reactions monochromatic light emitting diodes (LED) were used as irradiation source. All relevant data are taken from the official data sheets provided by Osram, which are available free of charge *via* the internet at the Osram web page:

Blue-light-promoted reactions were performed using a LED-stick OSLON® SSL 80 deep blue (3 W, 700 mA, dominant wavelength λ_{dom} = 455 nm, spectral bandwidth at 50% I_{max} = 20 nm, radiant power at 25 °C and 700 mA ~ 900 mW) as irradiation source. The LED is placed on a glass rod (8 mm diameter; borosilicate glass; Schott Borofloat® 33) as fiber optics, which directly immerses in the reaction mixture. For the detailed reaction setup see Figure 10.

Photochemical Setup[5]

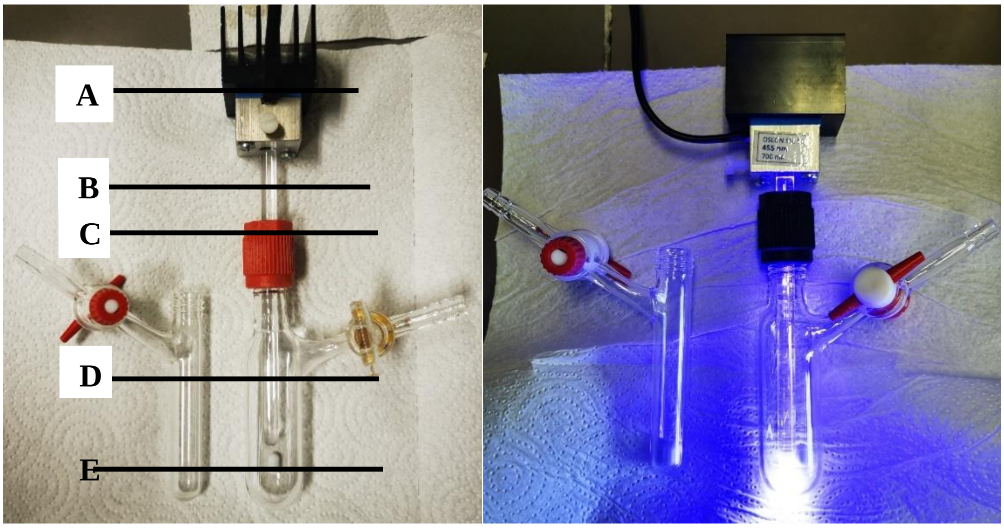

Figure 10. Photochemical setup for cyclopropanation reactions. (A) LED, (B) glass rod, (C) Teflon adapter, (D) Schlenk tube (left: 10 mL, right: 20 mL), (E) Teflon-coated stir-bar.

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[5] Fischer, S.; Nguyen, T.-T. H.; Ratzenboeck, A.; Davies, H. M. L.; Reiser, O. *Org. Lett.* 2023, 25, 24, 4411–4415.[148]

5.1. Literature known Starting Materials

Methyl 2-diazo-2-phenylacetate[75], ethyl 2-diazo-2-(naphtalen-2-yl)acetate[156], methyl 2-diazo-2-(4-nitrophenyl)acetate[157], methyl 2-diazo-2-(4-fluorophenyl)acetate[158], methyl 2-diazo-2-(4-methoxyphenyl)acetate[157], methyl 2-diazo-2-(3-methoxyphenyl)acetate[157], methyl 2-diazo-2-(2-methoxyphenyl)acetate[159], ethyl 2-diazoacetate[160], methyl (E)-2-diazo-4-phenylbut-3-enoate[161] 2-phenyl-2,3-dihydrofuran[68] and 2-(naphthalen-1-yl)-2,3-dihydrofuran[68] were prepared following the reported procedures. Their analytical data were consistent with those published in literature. Additionally, literature known compounds, methyl (E)-6-styryl-2-oxabicyclo[3.1.0]hexane-6-carboxylate[162] (**167i**), ethyl (1R,5R,6R)-2-oxabicyclo[3.1.0]hexane-6-carboxylate[163] (**167n**), methyl (1S,6S,7R)-7-phenyl-2-oxabicyclo[4.1.0]heptane-7-carboxylate[164] (**167o**) and ethyl (1R,6R,7R)-2-oxabicyclo[4.1.0]heptane-7-carboxylate[165] (**167p**), required for ring-opening were already in stock in our laboratories and their analytical data were consistent with those published in literature.

5.2. Synthesis of Cyclopropanes

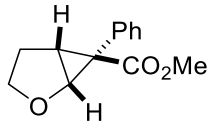
General Procedure GP-I:

After a modified literature procedure,[36] starting material (5.0 equiv) and diazo compound (1.0 equiv) were dissolved in DCM (1.0 M or 0.5 M) in an oven-dried Schlenk-flask equipped with a glass rod (see general information for further experimental details) at 0 °C. The reaction mixture was irradiated with blue light (*hv = 455nm)* for 24 h and allowed to warm to room temperature. Then, the solvent was evaporated under reduced pressure, and the crude product was purified by recrystallization, flash column chromatography, or a washing step with pentane.

General Procedure GP-II:

After a modified literature procedure[166], a flame-dried two-neck round-bottom flask was charged with starting material (1.0 equiv) and $Rh_2(OAc)_4$ (0.1 mol%) dissolved in dry DCM under nitrogen atmosphere. Within 3 h, a solution of diazo compound (1.5 equiv) dissolved in dry DCM (0.2 – 0.5 M) was added dropwise *via* a syringe pump at 0 °C. After addition, the reaction mixture was stirred for another 18 h and allowed to warm up to room temperature. The reaction mixture was filtered through basic Al_2O_3, the solvent was evaporated under reduced pressure, and the crude product was purified by recrystallization, flash column chromatography, or a washing step with pentane.

methyl (1R,5R,6S)-6-phenyl-2-oxabicyclo[3.1.0]hexane-6-carboxylate (167a)



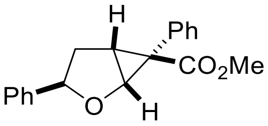
Following the general procedure **GP-I**, 2,3-dihydrofuran (1.1 mL, 14.0 mmol, 5.0 equiv) and methyl-2-diazo-2-phenylacetate (493.3 mg, 2.8 mmol, 1.0 equiv) were dissolved in DCM (14.0 mL) and irradiated for 24 h yielding the title compound (452.6 mg, 2.1 mmol, 74%) as colorless crystals after recrystallization from ethanol.

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.40 – 7.28 (m, 5H), 4.50 (d, *J* = 5.7 Hz, 1H), 3.77 (ddd, *J* = 10.3, 8.5, 3.6 Hz, 1H), 3.57 (s, 3H), 2.65 (t, *J* = 5.9 Hz, 1H), 2.38 (q, *J* = 8.7 Hz, 1H), 2.29 – 2.20 (m, 1H), 1.89 – 1.80 (m, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 172.1, 132.3, 131.6, 128.6, 127.6, 70.2, 70.1, 52.4, 38.2, 32.5, 26.3.

Analytical data is in accordance with literature.[68]

methyl (1R,3R,5R,6S)-3,6-diphenyl-2-oxabicyclo[3.1.0]hexane-6-carboxylate (167b)



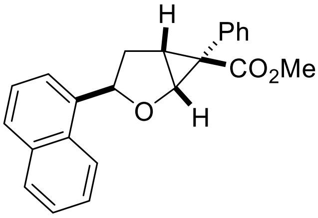
Following the general procedure **GP-I**, 2-phenyl-2,3-dihydrofuran (731.0 mg, 5.0 mmol, 5.0 equiv) and methyl-2-diazo-2-phenylacetate (176.2 mg, 1.0 mmol, 1.0 equiv) were dissolved in DCM (10.0 mL) and irradiated for 24 h yielding the title compound (180.9 mg, 0.6 mmol, 61%) as colorless crystals after column chromatography (PE/EA 19:1).

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.30 – 7.19 (m, 5H), 7.11 – 7.01 (m, 3H), 6.95 – 6.89 (m, 2H), 4.61 (d, *J* = 5.7 Hz, 1H), 3.44 (s, 4H), 2.59 (t, *J* = 5.9 Hz, 1H), 2.20 (dd, *J* = 13.4, 8.3 Hz, 1H), 2.01 (ddd, *J* = 13.4, 8.3, 6.0 Hz, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 172.2, 142.2, 132.5, 131.7, 128.7, 128.4, 127.7, 127.6, 125.5, 83.0, 70.2, 52.4, 37.7, 35.7, 32.2.

Analytical data is in accordance with literature.[68]

methyl (1R,3R,5R,6S)-3-(naphthalen-1-yl)-6-phenyl-2-oxabicyclo[3.1.0]hexane-6-carboxylate (167c)



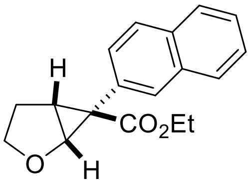
Following the general procedure **GP-I**, 2-(naphthalen-1-yl)-2,3-dihydrofuran (1.1 g, 5.8 mmol, 5.0 equiv) and methyl-2-diazo-2-phenylacetate (205.3 mg, 1.2 mmol, 1.0 equiv) were dissolved in DCM (12.0 mL) and irradiated for 24 h yielding the title compound (253.7 mg, 0.7 mmol, 63%) as colorless crystals after column chromatography (PE/EA 19:1).

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.80 (dd, *J* = 7.6, 1.7 Hz, 1H), 7.71 (d, *J* = 8.1 Hz, 1H), 7.53 – 7.29 (m, 9H), 4.88 (d, *J* = 5.7 Hz, 1H), 4.25 (t, *J* = 8.3 Hz, 1H), 3.63 (s, 3H), 2.81 (t, *J* = 5.9 Hz, 1H), 2.55 (dd, *J* = 13.4, 8.4 Hz, 1H), 2.24 (ddd, *J* = 13.9, 8.4, 6.1 Hz, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 172.2, 137.6, 133.9, 132.6, 131.8, 129.8, 128.9, 128.9, 128.1, 127.9, 126.1, 125.6, 125.5, 123.2, 122.4, 81.1, 70.1, 52.6, 37.8, 34.9, 32.5.

Analytical data is in accordance with literature.[68]

ethyl (1R,5R,6S)-6-(naphthalen-2-yl)-2-oxabicyclo[3.1.0]hexane-6-carboxylate (167d)



Following the general procedure **GP-II**, 2,3-dihydrofuran (0.15 mL, 2.0 mmol, 1.0 equiv) and $Rh_2(OAc)_4$ (0.9 mg, 2.0 µmol, 0.1 mol%) were dissolved in DCM (2.0 mL). Afterwards, ethyl 2-diazo-2-(naphtalen-2-yl)acetate (720.8 mg, 3.0 mmol, 1.5 equiv) dissolved in dry DCM (6.0 mL) was added via syringe pump (3 h) under nitrogen atmosphere yielding the title compound (564.2 mg, 2.0 mmol, 99%) as a yellow oil after washing with pentane.

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.88 – 7.81 (m, 4H), 7.47 (ddd, *J* = 11.7, 7.3, 2.5 Hz, 3H), 4.60 (d, *J* = 5.7 Hz, 1H), 4.04 (q, *J* = 7.1 Hz, 2H), 3.76 (ddd, *J* = 10.3, 8.6, 3.7 Hz, 1H), 2.73 (t, *J* = 5.9 Hz, 1H), 2.41 (q, *J* = 8.6 Hz, 1H), 2.27 (dddd, *J* = 12.9, 10.4, 8.7, 6.1 Hz, 1H), 1.90 (ddd, *J* = 12.7, 8.6, 3.7 Hz, 1H), 1.10 (t, *J* = 7.1 Hz, 3H).

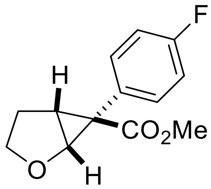
^{13}C NMR (101 MHz, $CDCl_3$) δ 171.5, 133.6, 132.8, 130.6, 130.2, 129.5, 128.1, 128.0, 127.8, 126.0, 125.9, 70.4, 70.2, 61.1, 38.5, 32.5, 26.3, 14.3.

IR: ν[cm^{-1}] = 3053, 2974, 2900, 1703, 1599, 1506, 1450, 1368, 1245, 1115, 1066, 1029, 943, 857, 835, 749.

HRMS: (APCI-MS) m/z calculated for $C_{18}H_{19}O_3$ [M+H]$^+$: 283.1329, found 283.1331.

R$_f$ = 0.32 (hexanes/ethyl acetate = 9/1, stained in vanillin).

methyl (1R,5R,6S)-6-(4-fluorophenyl)-2-oxabicyclo[3.1.0]hexane-6-carboxylate (167e)



Following the general procedure **GP-II**, 2,3-dihydrofuran (0.15 mL, 2.0 mmol, 1.0 equiv) and $Rh_2(OAc)_4$ (0.9 mg, 2.0 µmol, 0.1 mol%) were dissolved in DCM (2.0 mL). Afterwards, methyl 2-diazo-2-(4-fluorophenyl)acetate (582.5 mg, 3.0 mmol, 1.5 equiv) dissolved in dry DCM (6.0 mL) was added via syringe pump (3 h) under nitrogen atmosphere yielding the title compound (472.0 mg, 2.0 mmol, 99%) as a yellow oil after washing with pentane.

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.41 – 7.28 (m, 2H), 7.16 – 7.03 (m, 2H), 4.52 (d, *J* = 5.7 Hz, 1H), 3.84 (ddd, *J* = 10.5, 8.6, 4.2 Hz, 1H), 3.57 (s, 3H), 2.73 (t, *J* = 6.0 Hz, 1H), 2.59 (s, 1H), 2.26 (dq, *J* = 18.0, 8.1, 7.5 Hz, 1H), 1.92 – 1.63 (m, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 171.0, 163.7, 161.3, 133.5, 129.7, 129.6, 124.2, 124.1, 120.0, 119.8, 115.5, 115.3, 70.9, 69.7, 52.3, 33.9, 26.1, 22.3, 14.0. (Signal splitting due to coupling between ^{13}C and ^{19}F)

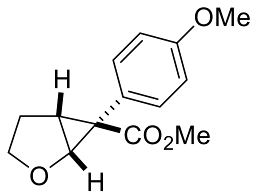
^{19}F NMR (376 MHz, $CDCl_3$) δ -116.1.

IR: ν[cm^{-1}] = 3362, 3258, 3161, 2960, 2878, 2240, 1715, 1580, 1491, 1413, 1357, 1334, 1245, 1189, 1118, 1055, 906, 816, 760, 723.

HRMS: (ESI-MS) m/z calculated for $C_{13}H_{14}FN_2O_2$ [M+H]$^+$: 281.0755, found 281.0756.

R$_f$ = 0.47 (hexanes/ethyl acetate = 9/1, stained in vanillin).

methyl (1R,5R,6S)-6-(4-methoxyphenyl)-2-oxabicyclo[3.1.0]hexane-6-carboxylate (167f)



Following the general procedure **GP-II**, 2,3-dihydrofuran (0.15 mL, 2.0 mmol, 1.0 equiv) and $Rh_2(OAc)_4$ (0.9 mg, 2.0 µmol, 0.1 mol%) were dissolved in DCM (2.0 mL). Afterwards, methyl 2-diazo-2-(4-methoxyphenyl)acetate (618.6 mg, 3.0 mmol, 1.5 equiv) dissolved in dry DCM (6.0 mL) was added via syringe pump (3 h) under nitrogen atmosphere yielding the title compound (495.9 mg, 2.0 mmol, 99%) as a yellow oil after washing with pentane.

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.30 – 7.23 (m, 2H), 6.99 – 6.90 (m, 2H), 4.51 (d, *J* = 5.7 Hz, 1H), 3.87 – 3.78 (m, 4H), 3.60 (s, 3H), 2.65 (t, *J* = 5.9 Hz, 1H), 2.48 (q, *J* = 8.7 Hz, 1H), 2.27 (dddd, *J* = 12.9, 10.4, 8.7, 6.1 Hz, 1H), 1.87 (ddd, *J* = 12.7, 8.7, 3.7 Hz, 1H).

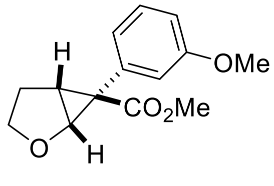
^{13}C NMR (101 MHz, $CDCl_3$) δ 172.2, 158.9, 132.5, 124.1, 113.9, 70.2, 70.1, 55.2, 52.3, 37.3, 32.4, 26.2.

IR: ν[cm^{-1}] = 2952, 2840, 2128, 1774, 1730, 1610, 1513, 1439, 1249, 1163, 1029, 977, 828, 746.

HRMS: (APCI-MS) m/z calculated for $C_{14}H_{17}O_4$ $[M+H]^+$: 249.1121, found 249.1123.

R$_f$ = 0.53 (hexanes/ethyl acetate = 4/1, stained in vanillin).

methyl (1R,5R,6S)-6-(3-methoxyphenyl)-2-oxabicyclo[3.1.0]hexane-6-carboxylate (167g)



Following the general procedure **GP-II**, 2,3-dihydrofuran (0.15 mL, 2.0 mmol, 1.0 equiv) and $Rh_2(OAc)_4$ (0.9 mg, 2.0 µmol, 0.1 mol%) were dissolved in DCM (2.0 mL). Afterwards, methyl 2-diazo-2-(3-methoxyphenyl)acetate (618.6 mg, 3.0 mmol, 1.5 equiv) dissolved in dry DCM (6.0 mL) was added via syringe pump (3 h) under nitrogen atmosphere yielding the title compound (480.7 mg, 1.9 mmol, 97%) as a yellow oil after washing with pentane.

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.26 – 7.20 (m, 1H), 6.90 – 6.81 (m, 3H), 4.44 (d, *J* = 5.7 Hz, 1H), 3.77 (s, 3H), 3.76 – 3.69 (m, 1H), 3.53 (s, 3H), 2.59 (t, *J* = 5.9 Hz, 1H), 2.43 (q, *J* = 8.7 Hz, 1H), 2.24 – 2.15 (m, 1H), 1.85 (ddd, *J* = 12.6, 8.6, 3.5 Hz, 1H).

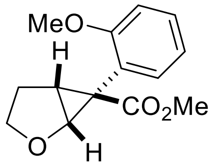
^{13}C NMR (101 MHz, $CDCl_3$) δ 171.9, 159.7, 133.7, 129.4, 123.9, 117.1, 113.2, 70.1, 55.3, 52.4, 38.1, 32.5, 26.4.

IR: ν[cm^{-1}] = 3049, 2952, 2900, 2840, 1707, 1584, 1498, 1457, 1331, 1275, 1238, 1156, 1115, 1070, 1029 969, 943, 902, 865, 798, 753, 701.

HRMS: (APCI-MS) m/z calculated for $C_{14}H_{16}O_4$ $[M+H]^+$: 248.10431, found 248.10407.

R_f = 0.49 (hexanes/ethyl acetate = 4/1, stained in vanillin).

methyl (1R,5R,6S)-6-(2-methoxyphenyl)-2-oxabicyclo[3.1.0]hexane-6-carboxylate (167h)



Following the general procedure **GP-II**, 2,3-dihydrofuran (0.09 mL, 1.2 mmol, 1.0 equiv) and $Rh_2(OAc)_4$ (0.5 mg, 1.2 µmol, 0.1 mol%) were dissolved in DCM (1.2 mL). Afterwards, methyl 2-diazo-2-(2-methoxyphenyl)acetate (200.3 mg, 1.8 mmol, 1.5 equiv) dissolved in dry DCM (3.6 mL) was added via syringe pump (3 h) under nitrogen atmosphere yielding the title compound (129.6 mg, 0.5 mmol, 45%) as a yellow oil after column chromatography (PE/EA 9:1).

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.38 – 7.27 (m, 2H), 6.96 – 6.88 (m, 2H), 4.51 – 4.37 (m, 1H), 3.81 (s, 4H), 3.55 (s, 3H), 2.70 (d, *J* = 16.4 Hz, 1H), 2.16 (s, 1H).

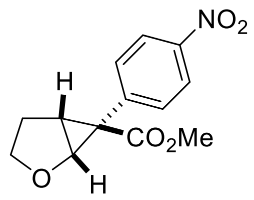
^{13}C NMR (101 MHz, $CDCl_3$) δ 172.0, 159.1, 133.0, 129.1, 121.0, 120.6, 110.5, 71.2, 70.2, 55.5, 52.2, 34.9, 33.2, 25.9.

IR: ν[cm^{-1}] = 2952, 2900, 2837, 1707, 1580, 1491, 1431, 1334, 1222, 1148, 1118, 1070, 1036, 980, 948, 906, 865, 831, 790, 764, 701.

HRMS: (EI-MS) m/z calculated for $C_{14}H_{17}O_4$ [M^+]: 249.1121, found 249.1121.

R$_f$ = 0.30 (hexanes/ethyl acetate = 9/1, stained in vanillin).

methyl (1R,5R,6S)-6-(4-nitrophenyl)-2-oxabicyclo[3.1.0]hexane-6-carboxylate (167j)



Following the general procedure **GP-II**, 2,3-dihydrofuran (0.15 mL, 2.0 mmol, 1.0 equiv) and $Rh_2(OAc)_4$ (0.9 mg, 2.0 µmol, 0.1 mol%) were dissolved in DCM (2.0 mL). Afterwards, methyl 2-diazo-2-(4-nitrophenyl)acetate (342.3 mg, 3.0 mmol, 1.5 equiv) dissolved in dry DCM (6.0 mL) was added via syringe pump (3 h) under nitrogen atmosphere yielding the title compound (449.1 mg, 1.7 mmol, 85%) as a yellow oil after washing with pentane.

^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.26 – 8.20 (m, 2H), 7.54 – 7.46 (m, 2H), 4.55 (d, *J* = 5.7 Hz, 1H), 3.84 (ddd, *J* = 10.1, 8.7, 3.9 Hz, 1H), 3.57 (s, 3H), 2.74 (t, *J* = 5.8 Hz, 1H), 2.40 (p, *J* = 8.6 Hz, 1H), 2.35 – 2.26 (m, 1H), 1.80 (ddd, *J* = 12.9, 8.5, 3.9 Hz, 1H).

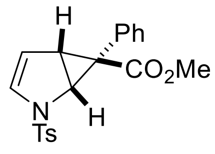
^{13}C NMR (101 MHz, $CDCl_3$) δ 170.6, 147.5, 140.1, 132.7, 123.8, 70.4, 70.1, 52.7, 38.1, 33.1, 26.1.

IR: ν[cm^{-1}] = 2956, 2904, 1715, 1603, 1517, 1435, 1349, 1245, 1118, 1074, 1036, 943, 854, 734, 701.

HRMS: (EI-MS) m/z calculated for $C_{13}H_{13}NO_5$ [M^+]: 263.07882, found 263.07936.

R$_f$ = 0.77 (hexanes/ethyl acetate = 1/1, stained in vanillin).

methyl (1R,5R,6S)-6-phenyl-2-tosyl-2-azabicyclo[3.1.0]hex-3-ene-6-carboxylate (167r)



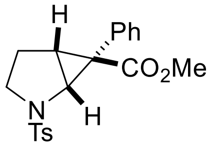
Following the general procedure **GP-I**, 1-tosyl-1*H*-pyrrole (3.5 g, 15.8 mmol, 5.0 equiv) and methyl-2-diazo-2-phenylacetate (556.7 mg, 3.2 mmol, 1.0 equiv) were dissolved in DCM (16.0 mL) and irradiated for 24 h yielding the title compound (1.1 g, 3.0 mmol, 94%) as a yellow oil after column chromatography (PE/EA 9:1 to 3:1).

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.74 – 7.66 (m, 2H), 7.36 – 7.32 (m, 2H), 7.28 – 7.16 (m, 6H), 5.95 (dd, *J* = 3.9, 1.5 Hz, 1H), 5.28 (dd, *J* = 3.9, 2.5 Hz, 1H), 4.53 (dd, *J* = 6.6, 1.5 Hz, 1H), 3.60 (s, 3H), 3.14 (dd, *J* = 6.6, 2.5 Hz, 1H), 2.45 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 173.7, 144.5, 135.0, 132.6, 130.9, 130.5, 130.1, 127.9, 127.5, 127.3, 111.4, 52.9, 52.3, 38.8, 28.1, 21.7.

Analytical data is in accordance with literature.[164]

methyl (1R,5R,6S)-6-phenyl-2-tosyl-2-azabicyclo[3.1.0]hexane-6-carboxylate (167q)



Cyclopropane **1r** (236.7 mg, 0.6 mmol, 1.0 equiv) and Pd/C (6.8 mg, 0.006 mmol, 1 mol%, 10 wt% Pd) were mixed together in MeOH (5.0 mL) in a round bottom flask and stirred under hydrogen pressure (30 bar) until complete conversion of the starting material (24 h). Afterwards, the mixture was filtered over celite, and the solvent was removed. The crude product was purified by recrystallization in ethanol, yielding the title compound (211.0 mg, 0.6 mmol, 89%) as a colorless solid.

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.77 – 7.69 (m, 2H), 7.33 (d, *J* = 6.2 Hz, 7H), 4.25 (d, *J* = 6.7 Hz, 1H), 3.58 (s, 3H), 3.23 – 3.12 (m, 1H), 2.45 (s, 4H), 1.94 – 1.73 (m, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 171.9, 143.7, 136.5, 131.6, 131.3, 130.0, 128.7, 127.9, 127.1, 52.8, 51.9, 48.1, 37.3, 30.7, 25.1, 21.7.

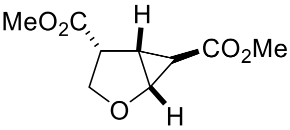
IR: ν[cm^{-1}] = 2952, 1707, 1596, 1435, 1349, 1290, 1249, 1163, 1103, 1055, 865, 816, 708, 664.

HRMS: (ESI-MS) m/z calculated for $C_{20}H_{22}NO_4S$ $[M+H]^+$: 372.1264, found 372.1268.

m.p.: 121 °C

R$_f$ = 0.85 (hexanes/ethyl acetate = 1/1, stained in vanillin).

dimethyl (1R,4R,5R,6R)-2-oxabicyclo[3.1.0]hexane-4,6-dicarboxylate (167s)



a) A flame-dried schlenk flask was charged with $Cu(OTf)_2$ (86.8 mg, 0.24 mmol, 2 mol%), furan-3-carboxylic acid methyl ester (1.5 g, 12.0 mmol, 1.0 equiv) and phenylhydrazine (26.0 mg, 0.24 mmol, 2 mol%) dissolved in DCM (5.0 mL) at 25 °C under nitrogen atmosphere. Methyl 2-diazoacetate (16.6 g, 18.0 mmol, 1.5 equiv, 10.8 wt% in DCM) was added dropwise over days *via* syringe pump (addition rate: 1 drop/10 s). Afterwards, the mixture was filtered through a plug of basic Al_2O_3 and washed with DCM. The solvent was evaporated and purification of the crude product by silica gel column chromatography yielded the title compound (600.0 mg, 3.0 mmol, 25%) as a colorless solid. The product was unstable at ambient temperature and therefore directly subjected to hydrogenation.

b) Cyclopropane (594.5 mg, 3.0 mmol, 1.0 equiv) and Pd/C (16.0 mg, 0.15 mmol, 5 mol%, 10 wt% Pd) were mixed together in MeOH (5.0 mL) in a round bottom flask and stirred under hydrogen pressure (30 bar) until complete conversion of the starting material (24 h). Afterwards, the mixture was filtered over celite, and the solvent was removed. The crude product was purified by column chromatography (PE/EA 3:1), yielding the title compound (500.0 mg, 2.5 mmol, 83%) as a colorless oil.

^{1}H NMR (400 MHz, Chloroform-*d*) δ 4.23 (dd, *J* = 5.4, 1.3 Hz, 1H), 4.14 (t, *J* = 9.4 Hz, 1H), 3.73 (s, 3H), 3.64 (s, 3H), 3.39 (td, *J* = 9.6, 5.4 Hz, 1H), 2.41 (td, *J* = 5.4, 3.7 Hz, 1H), 2.27 (dd, *J* = 3.8, 1.2 Hz, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 171.9, 171.1, 68.1, 66.0, 52.4, 51.9, 44.3, 28.2, 21.7.

IR: ν[cm^{-1}] = 2956, 1718, 1439, 1398, 1320, 1264, 1197, 1118, 984, 932, 861, 693.

HRMS: (EI-MS) m/z calculated for $C_9H_{12}O_5$ [M$^+$]: 200.0679, found 200.0681

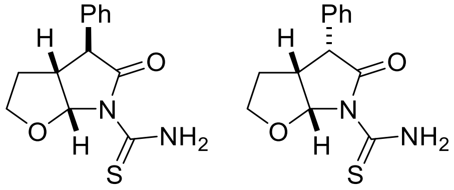
R_f = 0.43 (hexanes/ethyl acetate = 9/1, stained in vanillin).

5.3. Lewis Acid Catalyzed Ring Expansion

General Procedure GP-III:

In a flame-dried pressure tube, cyclopropanated starting material (1.0 equiv), thiourea (2.0 equiv), and Lewis acid (5 mol % or 10 mol %) were dissolved in 1,4-dioxane (0.06 M) or acetonitrile (0.06 M) and the solution stirred at 90 °C for 18 h. Afterwards, the mixture was filtered through a short plug of silica and washed with an excess of ethyl acetate. The solvent was evaporated and chloroform was added to the residue to form insoluble materials, which were filtered off. The solvent evaporated again, and the crude product was purified by recrystallization from ethanol or column chromatography.

(3aR,4S,6aR)-5-oxo-4-phenylhexahydro-6H-furo[2,3-b]pyrrole-6-carbothioamide (172a) and (3aR,4R,6aR)-5-oxo-4-phenylhexahydro-6H-furo[2,3-b]pyrrole-6-carbothioamide (172aa)



Following the general procedure **GP-III**, compound **167a** (109.1 mg, 0.5 mmol, 1.0 equiv), thiourea (76.1 mg, 1.0 mmol, 2.0 equiv) and Yb(OTf)$_3$ (15.5 mg, 0.025 mmol, 5 mol %) were dissolved in 1,4-dioxane (7.5 mL) and stirred at 90 °C for 24 h yielding the title compounds (129.7 mg, 0.4 mmol, 99%, *dr* 10:1) as colorless crystals after recrystallization from ethanol.

^{1}H NMR$_{\text{mixture}}$ (400 MHz, Chloroform-*d*) δ 10.01 (s, 0.10H, **172aa**), 9.94 (s, 1H, **172a**), 7.46 – 7.27 (m, 4.31H, signal overlap), 7.23 – 7.16 (m, 2.18H, signal overlap), 6.67 (d, *J* = 6.3 Hz, 1H, **172a**), 6.62 (d, *J* = 6.7 Hz, 0.10H, minor), 4.19 (ddd, *J* = 9.4, 7.9, 1.7 Hz, 1H, **172a**), 4.04 (ddd, *J* = 11.0, 9.1, 5.2 Hz, 1H, **172a**), 3.89 (ddd, *J* = 9.1, 7.8, 3.8 Hz, 0.12H, **172aa**), 3.76 (d, *J* = 7.4 Hz, 1H, **172a**), 3.64 (td, *J* = 9.1, 6.3 Hz, 0.12H, **172aa**), 3.47 (d, *J* = 5.4 Hz, 0.11H, **172aa**), 3.36 – 3.22 (m, 0.11H, **172aa**), 3.07 (dt, *J* = 8.8, 6.8 Hz, 1H, **172a**), 2.23 (ddt, *J* = 12.9, 11.0, 7.8 Hz, 1H, **172a**), 2.09 – 1.91 (m, 1H, **172a**), 1.81 (dtd, *J* = 13.3, 9.3, 7.8 Hz, 0.12H, **172aa**), 1.50 (ddt, *J* = 13.4, 6.6, 3.6 Hz, 0.11H, **172aa**).

^{13}C NMR$_{\text{mixture}}$ (101 MHz, CDCl$_3$) δ 182.4, 176.0, 137.1, 129.4, 129.3, 129.0, 128.2, 128.1, 128.0, 93.2, 67.4, 67.3, 55.5, 51.9, 43.4, 38.8, 31.7, 28.1.

IR: ν[cm^{-1}] = 3355, 3250, 2960, 2874, 1707, 1580, 1330, 1185, 1051, 869, 749, 697.

HRMS$_{172a}$: (ESI-MS) m/z calculated for $C_{13}H_{15}N_2O_2S$ [M+H]$^+$: 263.0849, found 263.0853.

HRMS$_{172aa}$: (ESI-MS) m/z calculated for $C_{13}H_{15}N_2O_2S$ [M+H]$^+$: 263.0849, found 263.0849.

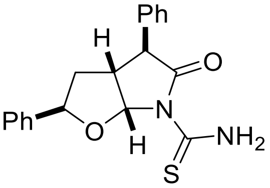
m.p.: 164 °C

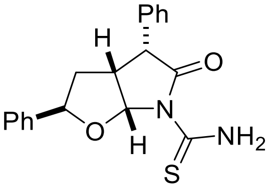
R$_f$ = 0.26 (hexanes/ethyl acetate = 3/1, stained in vanillin).

Big scale synthesis:

In a 250 mL flame-dried Schlenk flask, cyclopropanated starting material (1.5 g, 7.0 mmol, 1.0 equiv), thiourea (1.1 g, 14.0 mmol, 2.0 equiv) and $Yb(OTf)_3$ (217.1 mg, 0.4 mmol, 5 mol %) were dissolved in 1,4-dioxane (105.0 mL) and the solution stirred at 90 °C for 24 h. Afterwards, the solvent was evaporated and the residue was filtered through a short plug of silica with an excess of ethyl acetate. The solvent was evaporated and chloroform was added to the residue to form insoluble materials, which were filtered off. The solvent was again evaporated, and the crude product was purified by column chromatography (PE/EA 2:1) to yield title compounds (1.3 g, 5.0 mmol, 71%, *dr* 10:1) as colorless solids.

(2R,3aR,4S,6aR)-5-oxo-2,4-diphenylhexahydro-6H-furo[2,3-b]pyrrole-6-carbothioamide (172b) and (2R,3aR,4R,6aR)-5-oxo-2,4-diphenylhexahydro-6H-furo[2,3-b]pyrrole-6-carbothioamide (172bb)





Following the general procedure **GP-III**, compound **167b** (147.2 mg, 0.5 mmol, 1.0 equiv), thiourea (76.1 mg, 1.0 mmol, 2.0 equiv) and $Yb(OTf)_3$ (15.5 mg, 0.025 mmol, 5 mol %) were dissolved in 1,4-dioxane (7.5 mL) and stirred at 90 °C for 24 h yielding the title compounds (126.3 mg, 0.4 mmol, 75%, *dr* 3:1) as a yellow oil after column chromatography (PE/acetone 3:1).

^{1}H NMR$_{\textbf{mixture}}$ (400 MHz, Chloroform-*d*) δ 9.95 (d, *J* = 4.4 Hz, 1H, **172b**), 9.89 (d, *J* = 4.4 Hz, 0.29H, **172bb**), 7.45 – 7.21 (m, 14.87H, signal overlap), 7.10 – 7.06 (m, 0.64H, **172bb**), 6.97 (d, *J* = 6.3 Hz, 1H, **172b**), 6.80 (d, *J* = 6.5 Hz, 0.31H, **172bb**), 5.42 (dd, *J* = 7.7, 5.1 Hz, 0.33H, **172bb**), 5.24 (dd, *J* = 10.6, 4.9 Hz, 1H, **172b**), 3.94 (d, *J* = 7.2 Hz, 1H, **172b**), 3.56 (d, *J* = 6.6 Hz, 0.35H, **172bb**), 3.21 (q, *J* = 7.0 Hz, 1H, **172b**), 3.15 – 3.05 (m, 0.31H, **172bb**), 2.77 (dt, *J* = 13.2, 8.0 Hz, 0.34H, **172bb**), 2.39 (dd, *J* = 13.0, 4.9 Hz, 1H, **172b**), 2.24 – 2.09 (m, 1.38H, signal overlap).

^{13}C NMR$_{\textbf{mixture}}$ (101 MHz, $CDCl_3$) δ 182.3, 182.3, 176.0, 175.5, 141.8, 139.8, 137.3, 136.9, 129.4, 129.3, 129.3, 128.8, 128.6, 128.3, 128.1, 128.1, 127.9, 126.2, 125.1, 93.6, 93.3, 81.2, 80.2, 56.4, 56.0, 44.0, 43.5, 40.7, 38.8.

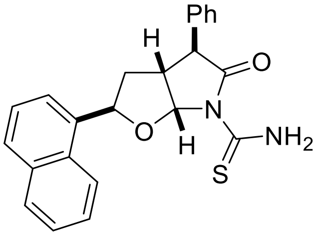
IR: ν[cm^{-1}] = 3355, 3250, 3030, 2922, 1707, 1584, 1331, 1185, 1029, 760, 697.

HRMS$_{172b}$: (ESI-MS) m/z calculated for $C_{19}H_{19}N_2O_2S$ [M+H]$^+$: 339.1162, found 339.1167.

HRMS$_{172bb}$: (ESI-MS) m/z calculated for $C_{19}H_{19}N_2O_2S$ [M+H]$^+$: 339.1162, found 339.1166.

R$_f$ = 0.28 (hexanes/ethyl acetate = 3/1, stained in vanillin).

(2R,3aR,4S,6aR)-2-(naphthalen-1-yl)-5-oxo-4-phenylhexahydro-6H-furo[2,3-b]pyrrole-6-carbothioamide (172c)



Following the general procedure **GP-III**, compound **167c** (172.2 mg, 0.5 mmol, 1.0 equiv), thiourea (76.1 mg, 1.0 mmol, 2.0 equiv) and Yb(OTf)$_3$ (15.5 mg, 0.025 mmol, 5 mol %) were dissolved in 1,4-dioxane (7.5 mL) and stirred at 90 °C for 24 h yielding the title compound (115.2 mg, 0.3 mmol, 59%) as a yellowish solid after column chromatography (PE/acetone 3:1).

^{1}H NMR (400 MHz, Chloroform-*d*) δ 10.00 (d, *J* = 4.1 Hz, 1H), 7.97 – 7.77 (m, 4H), 7.58 – 7.21 (m, 9H), 7.07 (d, *J* = 6.3 Hz, 1H), 6.00 (dd, *J* = 10.0, 5.3 Hz, 1H), 4.05 (d, *J* = 7.1 Hz, 1H), 3.26 (q, *J* = 7.0 Hz, 1H), 2.68 (dd, *J* = 13.2, 5.3 Hz, 1H), 2.26 (ddd, *J* = 13.2, 9.9, 7.6 Hz, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 182.4, 176.0, 137.1, 135.9, 133.8, 130.2, 129.5, 129.1, 128.4, 128.4, 128.1, 126.3, 125.8, 125.7, 122.9, 122.8, 93.1, 77.7, 56.4, 44.1, 39.8.

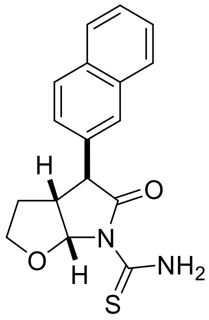
IR: ν[cm^{-1}] = 3276, 3228, 3146, 1711, 1599, 1413, 1338, 1189, 1144, 1047, 779, 693.

HRMS: (ESI-MS) m/z calculated for $C_{23}H_{21}N_2O_2S$ [M+H]$^+$: 389.1318, found 389.1322.

m.p.: 155 °C

R$_f$ = 0.29 (hexanes/ethyl acetate = 3/1, stained in vanillin).

(3aR,4S,6aR)-4-(naphthalen-2-yl)-5-oxohexahydro-6H-furo[2,3-b]pyrrole-6-carbothioamide (172d)



Following the general procedure **GP-III**, compound **167d** (141.2 mg, 0.5 mmol, 1.0 equiv), thiourea (76.1 mg, 1.0 mmol, 2.0 equiv) and Yb(OTf)$_3$ (15.5 mg, 0.025 mmol, 5 mol %) were dissolved in 1,4-dioxane (7.5 mL) and stirred at 90 °C for 24 h yielding the title compound (125.3 mg, 0.4 mmol, 80%) as colorless crystals after recrystallization from ethanol.

^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.98 (s, 1H), 7.92 – 7.80 (m, 3H), 7.72 – 7.68 (m, 1H), 7.56 – 7.46 (m, 2H), 7.33 – 7.23 (m, 2H), 6.74 (d, *J* = 6.3 Hz, 1H), 4.23 (ddd, *J* = 9.3, 7.9, 1.6 Hz, 1H), 4.09 (ddd, *J* = 10.9, 9.1, 5.3 Hz, 1H), 3.93 (d, *J* = 7.4 Hz, 1H), 3.21 – 3.12 (m, 1H), 2.25 (ddt, *J* = 12.8, 11.0, 7.7 Hz, 1H), 2.11 – 2.03 (m, 1H).

^{13}C NMR (101 MHz, CDCl$_3$) δ 182.4, 175.9, 134.3, 133.4, 132.9, 129.4, 127.8, 127.8, 127.5, 126.8, 126.5, 125.2, 93.3, 67.4, 55.7, 43.3, 31.7.

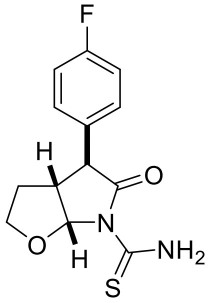
IR: ν[cm^{-1}] = 3437, 3235, 2881, 1707, 1554, 1413, 1334, 1290, 1252, 1185, 1051, 1010, 898, 831, 801, 746, 701.

HRMS: (ESI-MS) m/z calculated for $C_{17}H_{17}N_2O_2S$ [M+H]$^+$: 313.1005, found 313.1009.

m.p.: 185 °C

R$_f$ = 0.13 (hexanes/ethyl acetate = 4/1, stained in vanillin).

(3aR,4S,6aR)-4-(4-fluorophenyl)-5-oxohexahydro-6H-furo[2,3-b]pyrrole-6-carbothioamide (172e)



Following the general procedure **GP-III**, compound **167e** (98.1 mg, 0.4 mmol, 1.0 equiv), thiourea (63.2 mg, 0.8 mmol, 2.0 equiv) and Yb(OTf)$_3$ (12.9 mg, 0.02 mmol, 5 mol %) were dissolved in 1,4-dioxane (6.2 mL) and stirred at 90 °C for 24 h yielding the title compound (67.0 mg, 0.2 mmol, 58%) as a yellow oil after column chromatography (PE/EA 3:1).

^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.94 (s, 1H), 7.38 – 7.28 (m, 2H), 7.20 – 7.08 (m, 3H), 6.65 (d, *J* = 6.3 Hz, 1H), 4.20 (ddd, *J* = 9.2, 7.9, 1.4 Hz, 1H), 4.06 (ddd, *J* = 11.2, 9.1, 5.2 Hz, 1H), 3.91 (d, *J* = 7.9 Hz, 1H), 3.03 (q, *J* = 7.2 Hz, 1H), 2.19 (ddt, *J* = 12.9, 11.2, 7.6 Hz, 1H), 2.04 (dd, *J* = 12.9, 5.1 Hz, 1H).

^{13}C NMR (101 MHz, CDCl$_3$) δ 182.5, 175.3, 161.9, 159.5, 130.4, 130.4, 130.3, 130.2, 125.0, 124.9, 124.7, 124.6, 116.3, 116.1, 93.3, 67.4, 50.6, 42.9, 31.4. (Signal splitting due to coupling between ^{13}C and ^{19}F)

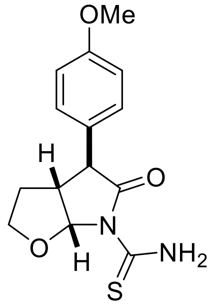
^{19}F NMR (376 MHz, CDCl$_3$) δ -116.8.

IR: ν[cm^{-1}] = 3362, 3258, 3161, 2960, 2878, 2240, 1715, 1580, 1491, 1413, 1357, 1334, 1245, 1189, 1118, 1055, 906, 816, 760, 723.

HRMS: (ESI-MS) m/z calculated for $C_{13}H_{14}FN_2O_2$ [M+H]$^+$: 281.0755, found 281.0756.

R$_f$ = 0.20 (hexanes/ethyl acetate = 3/1, stained in vanillin).

(3aR,4S,6aR)-4-(4-methoxyphenyl)-5-oxohexahydro-6H-furo[2,3-b]pyrrole-6-carbothioamide (172f)



Following the general procedure **GP-III**, compound **167f** (124.1 mg, 0.5 mmol, 1.0 equiv), thiourea (76.1 mg, 1.0 mmol, 2.0 equiv) and Yb(OTf)$_3$ (15.5 mg, 0.025 mmol, 5 mol %) were dissolved in 1,4-dioxane (7.5 mL) and stirred at 90 °C for 24 h yielding the title compound (99.6 mg, 0.3 mmol, 68%) as colorless crystals after recrystallization from ethanol.

^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.97 (s, 1H), 7.20 – 7.08 (m, 3H), 6.95 – 6.90 (m, 2H), 6.67 (d, *J* = 6.3 Hz, 1H), 4.20 (ddd, *J* = 9.4, 7.9, 1.7 Hz, 1H), 4.03 (ddd, *J* = 11.0, 9.1, 5.3 Hz, 1H), 3.81 (s, 3H), 3.70 (d, *J* = 7.5 Hz, 1H), 3.05 (dt, *J* = 7.5, 6.2 Hz, 1H), 2.24 (ddt, *J* = 12.9, 10.9, 7.8 Hz, 1H), 2.01 (ddt, *J* = 12.8, 5.5, 1.5 Hz, 1H).

^{13}C NMR (101 MHz, CDCl$_3$) δ 182.5, 176.2, 159.5, 129.1, 114.7, 93.1, 67.3, 55.4, 54.7, 43.4, 31.6.

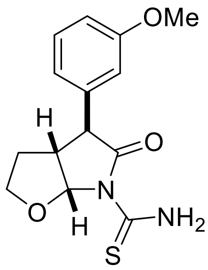
IR: ν[cm^{-1}] = 3448, 3228, 3023, 2963, 2937, 2885, 1715, 1558, 1513, 1245, 1179, 1055, 790, 693.

HRMS: (ESI-MS) m/z calculated for $C_{14}H_{17}N_2O_3S$ [M+H]$^+$: 293.0954, found 293.0957.

m.p.: 170 °C

R$_f$ = 0.10 (hexanes/ethyl acetate = 4/1, stained in vanillin).

(3aR,4S,6aR)-4-(3-methoxyphenyl)-5-oxohexahydro-6H-furo[2,3-b]pyrrole-6-carbothioamide (172g)



Following the general procedure **GP-III**, compound **167g** (124.1 mg, 0.5 mmol, 1.0 equiv), thiourea (76.1 mg, 1.0 mmol, 2.0 equiv) and Yb(OTf)$_3$ (15.5 mg, 0.025 mmol, 5 mol %) were dissolved in 1,4-dioxane (7.5 mL) and stirred at 90 °C for 24 h yielding the title compound (87.7 mg, 0.3 mmol, 60%) as a yellowish solid after recrystallization from ethanol.

^{1}**H NMR** (400 MHz, Chloroform-*d*) δ 9.93 (s, 1H), 7.36 – 7.27 (m, 2H), 6.87 (ddd, *J* = 8.3, 2.6, 0.9 Hz, 1H), 6.78 (dt, *J* = 7.6, 1.2 Hz, 1H), 6.73 (t, *J* = 2.1 Hz, 1H), 6.66 (d, *J* = 6.3 Hz, 1H), 4.18 (ddd, *J* = 9.4, 7.9, 1.7 Hz, 1H), 4.02 (ddd, *J* = 11.0, 9.1, 5.2 Hz, 1H), 3.81 (s, 3H), 3.72 (d, *J* = 7.4 Hz, 1H), 3.10 – 3.03 (m, 1H), 2.22 (ddt, *J* = 12.9, 11.0, 7.7 Hz, 1H), 2.05 – 1.96 (m, 1H).

^{13}**C NMR** (101 MHz, CDCl$_3$) δ 182.4, 175.8, 160.2, 138.5, 130.4, 120.2, 114.2, 113.3, 93.2, 67.4, 55.5, 55.4, 43.3, 31.7.

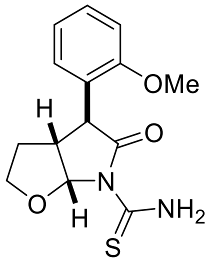
IR: ν[cm^{-1}] = 3362, 3250, 3161, 2960, 2878, 2837, 2236, 1711, 1580, 1491, 1413, 1357, 1331, 1297, 1260, 1185, 1051, 910, 872, 783, 731.

HRMS: (ESI-MS) m/z calculated for $C_{14}H_{17}N_2O_3S$ [M+H]$^+$: 293.0954, found 293.0957.

m.p.: 139 °C

R$_f$ = 0.10 (hexanes/ethyl acetate = 4/1, stained in vanillin).

(3aR,4S,6aR)-4-(2-methoxyphenyl)-5-oxohexahydro-6H-furo[2,3-b]pyrrole-6-carbothioamide (172h)



Following the general procedure **GP-III**, compound **167h** (86.9 mg, 0.4 mmol, 1.0 equiv), thiourea (53.3 mg, 0.7 mmol, 2.0 equiv) and Yb(OTf)$_3$ (10.9 mg, 0.02 mmol, 5 mol %) were dissolved in 1,4-dioxane (5.3 mL) and stirred at 90 °C for 24 h yielding the title compound (62.5 mg, 0.2 mmol, 61%) as colorless crystals after recrystallization from ethanol.

^{1}H NMR (400 MHz, Chloroform-*d*) δ 10.01 (s, 1H), 7.37 – 7.27 (m, 2H), 7.12 (dd, *J* = 7.5, 1.7 Hz, 1H), 6.99 – 6.87 (m, 2H), 6.64 (d, *J* = 6.4 Hz, 1H), 4.16 (ddd, *J* = 9.1, 7.7, 1.3 Hz, 1H), 3.98 (ddd, *J* = 11.4, 9.1, 5.0 Hz, 1H), 3.79 (s, 3H), 3.70 (d, *J* = 7.3 Hz, 1H), 3.02 (q, *J* = 7.1 Hz, 1H), 2.13 (ddt, *J* = 12.7, 11.3, 7.7 Hz, 1H), 1.97 (dd, *J* = 12.8, 5.0 Hz, 1H).

^{13}C NMR (101 MHz, CDCl$_3$) δ 182.8, 176.9, 156.7, 130.7, 129.8, 126.3, 121.1, 111.5, 93.6, 67.1, 55.8, 53.2, 42.1, 32.0.

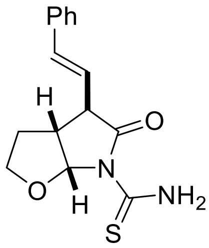
IR: ν[cm^{-1}] = 3362, 3250, 3161, 2967, 2878, 2236, 1715, 1588, 1495, 1461, 1409, 1357, 1252, 1193, 1122, 1055, 1029, 913, 757.

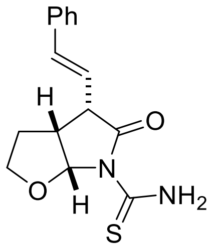
HRMS: (ESI-MS) m/z calculated for C$_{14}$H$_{17}$N$_2$O$_3$S [M+H]$^+$: 293.0954, found 293.0956.

m.p.: 156 °C

R$_f$ = 0.15 (hexanes/ethyl acetate = 3/1, stained in vanillin).

(3aR,4R,6aR)-5-oxo-4-((E)-styryl)hexahydro-6H-furo[2,3-b]pyrrole-6-carbothioamide (172i) and (3aR,4S,6aR)-5-oxo-4-((E)-styryl)hexahydro-6H-furo[2,3-b]pyrrole-6-carbothioamide (172ii)





Following the general procedure **GP-III**, compound **167i** (122.2 mg, 0.5 mmol, 1.0 equiv), thiourea (76.1 mg, 1.0 mmol, 2.0 equiv) and Yb(OTf)$_3$ (15.5 mg, 0.025 mmol, 5 mol %) were dissolved in 1,4-dioxane (7.5 mL) and stirred at 90 °C for 24 h yielding the title compounds (68.6 mg, 0.2 mmol, 48%, *dr* 13:1) as a reddish oil after column chromatography (PE/EA 3:1).

^{1}H NMR$_{\text{mixture}}$ (300 MHz, Chloroform-*d*) δ 10.12 (s, 1.09H, signal overlap), 7.36 – 7.15 (m, 7.17H, signal overlap), 7.02 (td, *J* = 7.8, 2.5 Hz, 1H, **172i**), 6.64 (d, *J* = 6.6 Hz, 1H, **172i**), 6.59 (d, *J* = 6.5 Hz, 0.08H, **172ii**), 6.48 (td, *J* = 7.8, 2.3 Hz, 0.07H, **172ii**), 4.06 (ddd, *J* = 9.1, 7.4, 1.6 Hz, 1.36H, signal overlap), 3.76 – 3.48 (m, 4.54H, signal overlap), 2.40 – 2.25 (m, 1.20H, signal overlap), 2.01 (ddt, *J* = 12.2, 5.1, 1.7 Hz, 1.10H, signal overlap).

^{13}C NMR$_{\text{mixture}}$ (101 MHz, CDCl$_3$) δ 183.0, 168.3, 167.7, 146.0, 141.3, 137.2, 133.7, 129.1, 129.0, 128.7, 128.5, 127.2, 126.8, 91.9, 91.4, 66.4, 66.3, 40.0, 37.3, 35.7, 34.7, 33.9, 33.5.

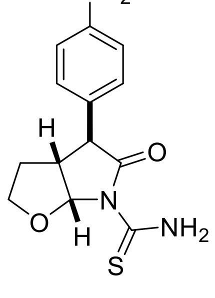
IR: ν[cm^{-1}] = 3358, 3243, 3060, 3027, 2952, 2870, 1700, 1666, 1580, 1495, 1353, 1297, 1230, 1185, 1111, 1055, 917, 842, 731, 697.

HRMS$_{\text{172i}}$: (ESI-MS) m/z calculated for $C_{15}H_{17}N_2O_2S$ [M+H]$^+$: 289.1005, found 289.1006.

HRMS$_{\text{172ii}}$: (ESI-MS) m/z calculated for $C_{15}H_{17}N_2O_2S$ [M+H]$^+$: 289.1005, found 289.1007.

R$_f$ = 0.28 (hexanes/ethyl acetate = 3/1, stained in vanillin).

(3aR,4S,6aR)-4-(4-nitrophenyl)-5-oxohexahydro-6H-furo[2,3-b]pyrrole-6-carbothioamide (172j)



Following the general procedure **GP-III**, compound **167j** (52.7 mg, 0.2 mmol, 1.0 equiv), thiourea (30.5 mg, 0.4 mmol, 2.0 equiv) and Ga(OTf)$_3$ (10.3 mg, 0.02 mmol, 10 mol %) were dissolved in MeCN (3.0 mL) and stirred at 90 °C for 24 h yielding the title compound (37.1 mg, 0.1 mmol, 60%) as a yellow oil after column chromatography (PE/acetone 3:1).

^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.98 – 9.55 (m, 1H), 8.21 (d, *J* = 8.3 Hz, 2H), 7.37 (d, *J* = 8.4 Hz, 2H), 7.18 – 7.03 (m, 1H), 6.64 (d, *J* = 6.2 Hz, 1H), 4.18 (s, 1H), 4.01 (td, *J* = 10.0, 9.6, 5.2 Hz, 1H), 3.84 (d, *J* = 7.6 Hz, 1H), 3.03 (q, *J* = 7.1 Hz, 1H), 2.23 (dq, *J* = 11.0, 7.8 Hz, 1H), 1.98 (dd, *J* = 12.9, 5.1 Hz, 1H).

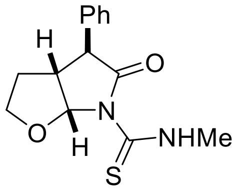
^{13}C NMR (101 MHz, $CDCl_3$) δ 182.0, 174.3, 147.7, 143.8, 129.1, 124.4, 93.1, 67.4, 55.0, 43.0, 31.5.

IR: ν[cm^{-1}] = 3366, 3265, 3157, 2960, 2878, 1718, 1588, 1520, 1416, 1346, 1264, 1189, 1059, 850, 731.

HRMS: (ESI-MS) m/z calculated for $C_{13}H_{14}N_3O_4S$ [M+H]$^+$: 308.0700, found 308.0703.

R$_f$ = 0.23 (hexanes/acetone = 3/1, stained in vanillin).

(3aR,4S,6aR)-N-methyl-5-oxo-4-phenylhexahydro-6H-furo[2,3-b]pyrrole-6-carbothioamide (172k)



Following the general procedure **GP-III**, compound **167a** (109.1 mg, 0.5 mmol, 1.0 equiv), 1-methylthiourea (90.1 mg, 1.0 mmol, 2.0 equiv) and $Ga(OTf)_3$ (25.9 mg, 0.05 mmol, 10 mol %) were dissolved in MeCN (7.5 mL) and stirred at 90 °C for 24 h yielding the title compound (137.9 mg, 0.5 mmol, 99%) as a colorless solid after washing with ethanol.

^{1}H NMR (400 MHz, Chloroform-*d*) δ 10.62 (s, 1H), 7.40 – 7.28 (m, 3H), 7.22 – 7.14 (m, 2H), 6.76 (d, *J* = 6.3 Hz, 1H), 4.14 (ddd, *J* = 9.4, 7.9, 1.7 Hz, 1H), 3.99 (ddd, *J* = 10.9, 9.1, 5.2 Hz, 1H), 3.74 (d, *J* = 7.1 Hz, 1H), 3.12 (d, *J* = 4.7 Hz, 3H), 3.03 (q, *J* = 6.4 Hz, 1H), 2.24 – 2.13 (m, 1H), 2.03 – 1.93 (m, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 180.9, 176.1, 137.4, 129.2, 128.0, 127.9, 93.3, 67.1, 55.9, 43.3, 32.1, 31.7.

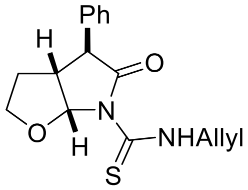
IR: ν[cm^{-1}] = 3217, 3034, 2960, 2878, 2236, 1700, 1539, 1454, 1379, 1297, 1215, 1088, 1040, 906, 764, 723, 697.

HRMS: (ESI-MS) m/z calculated for $C_{14}H_{17}N_2O_2S$ [M+H]$^+$: 277.1005, found 277.1008.

m.p.: 106 °C

R$_f$ = 0.32 (hexanes/ethyl acetate = 3/1, stained in vanillin).

(3aR,4S,6aR)-N-allyl-5-oxo-4-phenylhexahydro-6H-furo[2,3-b]pyrrole-6-carbothioamide (172l)



Following the general procedure **GP-III**, compound **167a** (109.1 mg, 0.5 mmol, 1.0 equiv), 1-allylthiourea (116.2 mg, 1.0 mmol, 2.0 equiv) and Ga(OTf)$_3$ (25.9 mg, 0.05 mmol, 10 mol %) were dissolved in MeCN (7.5 mL) and stirred at 90 °C for 24 h yielding the title compound (129.6 mg, 0.4 mmol, 86%) as a colorless solid after column chromatography (PE/EA 3:1).

^{1}H NMR (400 MHz, Chloroform-*d*) δ 10.74 (t, *J* = 5.2 Hz, 1H), 7.41 – 7.30 (m, 3H), 7.23 – 7.16 (m, 2H), 6.76 (d, *J* = 6.3 Hz, 1H), 5.90 (ddt, *J* = 17.3, 10.3, 5.7 Hz, 1H), 5.31 – 5.09 (m, 2H), 4.28 (tt, *J* = 5.4, 1.6 Hz, 2H), 4.16 (ddd, *J* = 9.4, 7.9, 1.7 Hz, 1H), 4.01 (ddd, *J* = 10.9, 9.1, 5.2 Hz, 1H), 3.76 (d, *J* = 7.3 Hz, 1H), 3.12 – 3.00 (m, 1H), 2.21 (ddt, *J* = 12.8, 10.9, 7.7 Hz, 1H), 2.06 – 1.95 (m, 1H).

^{13}C NMR (101 MHz, CDCl$_3$) δ 179.9, 176.2, 137.2, 131.7, 129.2, 128.1, 127.9, 117.7, 93.3, 67.2, 55.9, 47.9, 43.2, 31.7.

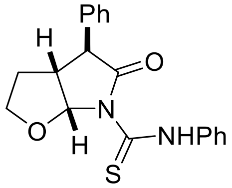
IR: ν[cm^{-1}] = 3254, 3206, 3064, 3030, 2874, 1696, 1528, 1450, 1387, 1327, 1216, 1103, 1055, 910, 764, 723, 693.

HRMS: (ESI-MS) m/z calculated for $C_{16}H_{19}N_2O_2S$ [M+H]$^+$: 303.1162, found 303.1167.

m.p.: 103 °C

R$_f$ = 0.05 (hexanes/ethyl acetate = 3/1, stained in vanillin).

(3aR,4S,6aR)-5-oxo-N,4-diphenylhexahydro-6H-furo[2,3-b]pyrrole-6-carbothioamide (172m)



Following the general procedure **GP-III**, compound **167a** (109.1 mg, 0.5 mmol, 1.0 equiv), 1-phenylthiourea (152.2 mg, 1.0 mmol, 2.0 equiv) and Ga(OTf)$_3$ (25.9 mg, 0.05 mmol, 10 mol %) were dissolved in MeCN (7.5 mL) and stirred at 90 °C for 24 h yielding the title compound (73.3 mg, 0.2 mmol, 43%) as a colorless solid after column chromatography (PE/EA 3:1).

^{1}H NMR (400 MHz, Chloroform-*d*) δ 12.32 (s, 1H), 7.52 – 7.45 (m, 2H), 7.34 – 7.21 (m, 5H), 7.17 – 7.10 (m, 3H), 6.75 (d, *J* = 6.3 Hz, 1H), 4.10 (ddd, *J* = 9.4, 7.9, 1.7 Hz, 1H), 3.96 (ddd, *J* = 11.0, 9.1, 5.2 Hz, 1H), 3.73 (d, *J* = 7.4 Hz, 1H), 2.99 (dt, *J* = 7.5, 6.2 Hz, 1H), 2.14 (ddt, *J* = 12.8, 11.0, 7.7 Hz, 1H), 1.92 (ddt, *J* = 12.9, 5.3, 1.6 Hz, 1H).

^{13}C NMR (101 MHz, CDCl$_3$) δ 178.8, 176.5, 137.8, 137.1, 129.4, 128.9, 128.3, 128.1, 126.9, 124.7, 93.5, 67.4, 56.1, 43.2, 31.8.

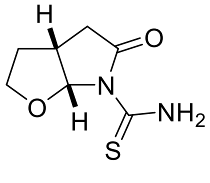
IR: ν[cm^{-1}] = 3168, 3034, 2874, 2240, 1696, 1595, 1528, 1498, 1390, 1293, 1245, 1185, 1100, 1055, 906, 880, 760, 727, 693.

HRMS: (ESI-MS) m/z calculated for $C_{19}H_{19}N_2O_2S$ [M+H]$^+$: 339.1162, found 339.1167.

m.p.: 140 °C

R$_f$ = 0.12 (hexanes/ethyl acetate = 3/1, stained in vanillin).

(3aR,6aR)-5-oxohexahydro-6H-furo[2,3-b]pyrrole-6-carbothioamide (172n)



Following the general procedure **GP-III**, compound **167n** (147.3 mg, 0.9 mmol, 1.0 equiv), thiourea (143.6 mg, 1.9 mmol, 2.0 equiv) and Yb(OTf)$_3$ (29.3 mg, 0.05 mmol, 5 mol%) were dissolved in 1,4-dioxane (15.0 mL) and stirred at 90 °C for 24 h yielding the title compound (90.1 mg, 0.5 mmol, 51 %) as colorless crystals after recrystallization from ethanol.

^{1}H NMR (300 MHz, Chloroform-*d*) δ 9.96 (s, 1H), 7.33 (s, 1H), 6.56 (d, *J* = 5.9 Hz, 1H), 4.09 (ddd, *J* = 9.3, 7.7, 1.7 Hz, 1H), 3.83 (ddd, *J* = 11.1, 9.1, 5.1 Hz, 1H), 3.09 – 2.89 (m, 2H), 2.57 – 2.43 (m, 1H), 2.18 (ddt, *J* = 12.4, 11.0, 7.7 Hz, 1H), 1.92 – 1.69 (m, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 182.5, 175.5, 95.0, 66.6, 38.3, 33.0, 32.7.

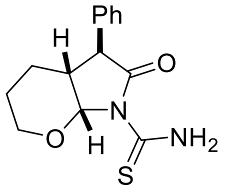
IR: ν[cm^{-1}] = 3332, 3153, 3220, 2986, 2873, 1718, 1588, 1364, 1331, 1301, 1252, 1189, 1040, 805, 664.

HRMS: (ESI-MS) m/z calculated for $C_7H_{11}N_2O_2S$ [M+H]$^+$: 187.0536, found 187.0540.

m.p.: 145 °C

R$_f$ = 0.05 (hexanes/ethyl acetate = 1/1, stained in vanillin).

(4aR,5S,7aR)-6-oxo-5-phenylhexahydropyrano[2,3-b]pyrrole-7(2H)-carbothioamide (172o)



Following the general procedure **GP-III**, compound **167o** (116.1 mg, 0.5 mmol, 1.0 equiv), thiourea (76.1 mg, 1.0 mmol, 2.0 equiv) and $Yb(OTf)_3$ (15.5 mg, 0.03 mmol, 5 mol %) were dissolved in 1,4-dioxane (7.5 mL) and stirred at 90 °C for 24 h yielding the title compound (137.9 mg, 0.5 mmol, 99%) as colorless crystals after recrystallization with ethanol.

^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.88 (s, 1H), 7.54 – 7.06 (m, 6H), 6.20 (d, *J* = 4.3 Hz, 1H), 4.09 (dd, *J* = 19.4, 11.7 Hz, 2H), 3.59 (t, *J* = 11.6 Hz, 1H), 2.47 – 2.30 (m, 1H), 1.82 (m, 3H), 1.52 (d, *J* = 12.2 Hz, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 182.0, 177.1, 135.1, 129.0, 128.9, 128.1, 86.4, 65.7, 51.2, 39.4, 21.6, 19.6.

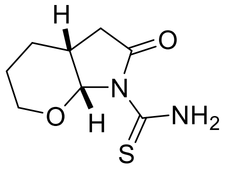
IR: ν[cm^{-1}] = 3351, 3235, 2937, 2870, 1730, 1584, 1346, 1096, 1044, 1010, 887, 842, 760, 712, 678.

HRMS: (ESI-MS) m/z calculated for $C_{14}H_{17}N_2O_2S$ [M+H]$^+$: 277.1005, found 277.1005.

m.p.: 133 °C

R$_f$ = 0.35 (hexanes/ethyl acetate = 3/1, stained in vanillin).

(4aR,7aR)-6-oxohexahydropyrano[2,3-b]pyrrole-7(2H)-carbothioamide (172p)



Following the general procedure **GP-III**, compound **167p** (85.1 mg, 0.5 mmol, 1.0 equiv), thiourea (76.1 mg, 1.0 mmol, 2.0 equiv) and Yb(OTf)$_3$ (15.5 mg, 0.03 mmol, 5 mol %) were dissolved in 1,4-dioxane (7.5 mL) and stirred at 90 °C for 24 h yielding the title compound (31.8 mg, 0.2 mmol, 32%) as colorless crystals after washing with ethanol.

^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.86 (s, 1H), 7.15 (s, 1H), 6.10 (d, *J* = 3.9 Hz, 1H), 3.98 (ddt, *J* = 11.9, 3.6, 1.7 Hz, 1H), 3.52 (td, *J* = 11.9, 2.1 Hz, 1H), 2.92 (dd, *J* = 17.0, 12.3 Hz, 1H), 2.56 – 2.44 (m, 1H), 2.37 (ddq, *J* = 11.8, 7.7, 3.7 Hz, 1H), 1.90 – 1.83 (m, 2H), 1.80 – 1.70 (m, 1H), 1.48 (dtd, *J* = 13.9, 4.9, 4.3, 2.0 Hz, 1H).

^{13}C NMR (101 MHz, CDCl$_3$) δ 182.2, 176.7, 88.3, 65.4, 35.2, 30.7, 23.1, 19.4.

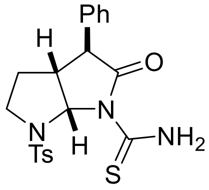
IR: ν[cm^{-1}] = 3340, 3232, 3157, 2937, 2863, 1718, 1592, 1346, 1279, 1182, 1096, 1055, 1025, 992, 902, 842.

HRMS: (ESI-MS) m/z calculated for $C_8H_{13}N_2O_2S$ [M+H]$^+$: 201.0692, found 201.0697.

m.p.: 131 °C

R$_f$ = 0.05 (hexanes/ethyl acetate = 1/1, stained in vanillin).

(3S,3aR,6aR)-2-oxo-3-phenyl-6-tosylhexahydropyrrolo[2,3-b]pyrrole-1(2H)-carbothioamide (172q)



Following the general procedure **GP-III**, compound **167q** (148.6 mg, 0.4 mmol, 1.0 equiv), thiourea (60.9 mg, 0.8 mmol, 2.0 equiv) and Yb(OTf)$_3$ (24.8 mg, 0.04 mmol, 10 mol %)

were dissolved in 1,4-dioxane (6.0 mL) and stirred at 90 °C for 24 h yielding the title compound (91.8 mg, 0.2 mmol, 55%) as a yellow oil after column chromatography (PE/acetone 3:1).

^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.50 – 9.34 (m, 1H), 8.06 – 7.96 (m, 2H), 7.41 – 7.28 (m, 6H), 7.22 – 7.16 (m, 3H), 6.81 (d, *J* = 6.1 Hz, 1H), 3.81 (d, *J* = 8.5 Hz, 1H), 3.78 – 3.70 (m, 2H), 3.09 (dtd, *J* = 8.2, 5.8, 2.3 Hz, 1H), 2.43 (s, 3H), 1.93 – 1.84 (m, 2H).

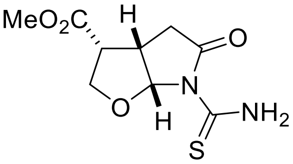
^{13}C NMR (101 MHz, $CDCl_3$) δ 182.1, 175.1, 144.0, 136.3, 135.7, 129.8, 129.4, 128.4, 128.3, 128.2, 77.7, 54.8, 48.0, 46.6, 27.2, 21.7.

IR: ν[cm^{-1}] = 3392, 3280, 3168, 3034, 2960, 2926, 2255, 1722, 1595, 1495, 1454, 1409, 1331, 1156, 1088, 1036, 984, 910, 872, 809, 760, 731, 690.

HRMS: (ESI-MS) m/z calculated for $C_{20}H_{22}N_3O_3S$ [M+H]$^+$: 416.1097, found 416.1105.

R$_f$ = 0.2 (hexanes/acetone = 3/1, stained in vanillin).

methyl (3R,3aS,6aR)-6-carbamothioyl-5-oxohexahydro-2H-furo[2,3-b]pyrrole-3-carboxylate (172s)



Following the general procedure **GP-III**, compound **167s** (144.6 mg, 0.7 mmol, 1.0 equiv), thiourea (110.0 mg, 1.4 mmol, 2.0 equiv) and Yb(OTf)$_3$ (22.4 mg, 0.04 mmol, 5 mol %) were dissolved in 1,4-dioxane (10.8 mL) and stirred at 90 °C for 18 h yielding the title compound (80.1 mg, 0.3 mmol, 45%) as colorless crystals after recrystallization from methanol.

^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.94 (s, 1H), 7.16 (s, 1H), 6.67 (d, *J* = 6.2 Hz, 1H), 4.26 (dd, *J* = 9.3, 7.4 Hz, 1H), 4.00 (dd, *J* = 11.0, 9.3 Hz, 1H), 3.74 (s, 3H), 3.40 (dt, *J* = 11.0, 7.4 Hz, 1H), 3.27 (dtd, *J* = 10.1, 7.4, 6.2 Hz, 1H), 2.91 – 2.69 (m, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 182.2, 174.6, 170.1, 94.8, 67.3, 52.5, 47.2, 35.1, 34.1.

IR: ν[cm^{-1}] = 3384, 3265, 2960, 2896, 1715, 1584, 1435, 1375, 1342, 1290, 1197, 1170, 1085, 1074, 1018, 906, 850, 816, 779, 731, 701.

HRMS: (ESI-MS) m/z calculated for $C_7H_{11}N_2O_2S$ $[M+H]^+$: 245.0591, found 245.0592.

m.p.: 182 °C

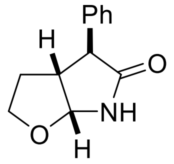
R_f = 0.74 (hexanes/ethyl acetate = 1/3, stained in vanillin).

5.4. DBU mediated Deprotection

General Procedure GP-IV:

In a flame-dried pressure tube, bicyclic starting material (1.0 equiv) and DBU (1.5 equiv) were dissolved in dry acetonitrile (0.1 M), and the solution was stirred at 25 °C for 18 h. Afterwards, the mixture was filtered through a short plug of silica and washed with an excess of ethyl acetate. The solvent was evaporated, and the product was purified by washing with pentane.

(3aR,4S,6aR)-4-phenylhexahydro-5H-furo[2,3-b]pyrrol-5-one (179a)



Following the general procedure **GP-IV**, compounds **172a** and **172aa** (262.3 mg, 1.0 mmol, 1.0 equiv) and DBU (0.2 mL, 1.5 mmol, 1.5 equiv) were dissolved in dry MeCN (10.0 mL) and stirred at 25 °C for 18 h yielding the title compound (201.7 mg, 1.0 mmol, 99%) as a colorless solid after washing with pentane.

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.42 – 7.22 (m, 6H), 5.68 (d, *J* = 6.1 Hz, 1H), 4.05 (ddd, *J* = 9.3, 7.6, 1.8 Hz, 1H), 3.95 (ddd, *J* = 11.0, 9.0, 5.2 Hz, 1H), 3.49 (d, *J* = 5.0 Hz, 1H), 3.17 – 3.06 (m, 1H), 2.22 – 2.10 (m, 1H), 2.00 – 1.93 (m, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 177.8, 139.4, 129.1, 127.7, 127.4, 88.5, 66.0, 54.4, 47.7, 33.2.

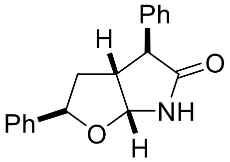
IR: ν[cm^{-1}] = 3228, 2952, 2870, 1656, 1498, 1450, 1260, 1051, 924, 753, 697.

HRMS: (ESI-MS) m/z calculated for $C_{12}H_{14}NO_2$ $[M+H]^+$: 204.1019, found 204.1019.

m.p.: 109 °C

R_f = 0.15 (hexanes/ethyl acetate = 1/1, stained in vanillin).

(2R,3aR,4S,6aR)-2,4-diphenylhexahydro-5H-furo[2,3-b]pyrrol-5-one (179b)



Following the general procedure **GP-IV**, compounds **172b** and **172bb** (58.5 mg, 0.2 mmol, 1.0 equiv) and DBU (0.04 mL, 0.3 mmol, 1.5 equiv) were dissolved in dry MeCN (2.0 mL) and stirred at 25 °C for 18 h yielding the title compound (48.2 mg, 0.2 mmol, 99%) as a yellow oil after washing with pentane.

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.32 – 7.13 (m, 10H), 6.84 (s, 1H), 5.78 (d, *J* = 6.2 Hz, 1H), 5.07 (dd, *J* = 10.9, 4.7 Hz, 1H), 3.52 (d, *J* = 5.1 Hz, 1H), 3.21 – 3.14 (m, 1H), 2.22 (dd, *J* = 12.9, 4.7 Hz, 1H), 1.98 (ddd, *J* = 12.9, 10.9, 8.4 Hz, 1H).

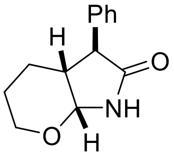
^{13}C NMR (101 MHz, $CDCl_3$) δ 177.6, 139.8, 139.4, 129.2, 128.7, 128.1, 127.8, 127.6, 126.2, 88.4, 78.9, 54.4, 48.5, 42.0.

IR: ν[cm^{-1}] = 3228, 3030, 2967, 2878, 2244, 1700, 1495, 1454, 1379, 1334, 1260, 1029, 980, 910, 872, 753, 697.

HRMS: (ESI-MS) m/z calculated for $C_{18}H_{18}NO_2$ $[M+H]^+$: 280.1332, found 280.1336.

R$_f$ = 0.74 (hexanes/ethyl acetate = 1/3, stained in vanillin).

(4aR,5S,7aR)-5-phenylhexahydropyrano[2,3-b]pyrrol-6(2H)-one (179c)



Following the general procedure **GP-IV**, compound **172p** (55.3 mg, 0.2 mmol, 1.0 equiv) and DBU (0.04 mL, 0.3 mmol, 1.5 equiv) were dissolved in dry MeCN (2.0 mL) and stirred at 25 °C for 18 h yielding the title compound (39.6 mg, 0.2 mmol, 91%) as a colorless solid after washing with pentane.

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.36 (dd, *J* = 8.1, 6.7 Hz, 2H), 7.31 – 7.26 (m, 1H), 7.23 – 7.15 (m, 2H), 6.75 (s, 1H), 4.92 (d, *J* = 3.8 Hz, 1H), 3.93 (ddt, *J* = 11.7, 4.1, 2.3 Hz, 1H), 3.65 (d, *J* = 11.1 Hz, 1H), 3.45 (td, *J* = 11.6, 2.1 Hz, 1H), 2.38 (dt, *J* = 10.3, 4.8 Hz, 1H), 1.81 (td, *J* = 16.3, 14.8, 5.5 Hz, 3H), 1.52 (ddd, *J* = 13.4, 5.3, 2.4 Hz, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 179.4, 137.1, 129.0, 128.9, 127.5, 82.0, 64.7, 48.2, 43.1, 22.5, 20.2.

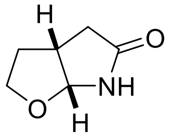
IR: ν[cm^{-1}] = 3261, 2930, 2855, 1711, 1498, 1454, 1297, 1264, 1230, 1103, 1055, 902, 753, 705.

HRMS: (ESI-MS) m/z calculated for $C_{13}H_{16}NO_2$ $[M+H]^+$: 218.1176, found 218.1180.

m.p.: 127 °C

R_f = 0.21 (hexanes/ethyl acetate = 1/3, stained in vanillin).

(3aR,6aR)-hexahydro-5H-furo[2,3-b]pyrrol-5-one (179d)



Following the general procedure **GP-IV**, compound **172** (85.2 mg, 0.5 mmol, 1.0 equiv) and DBU (0.1 mL, 0.7 mmol, 1.5 equiv) were dissolved in dry MeCN (4.6 mL) and stirred at 25 °C for 18 h yielding the title compound (54.6 mg, 0.4 mmol, 94%) as a yellow oil after washing with pentane.

^{1}H NMR (400 MHz, Chloroform-*d*) δ 6.55 (s, 1H), 5.55 (d, *J* = 6.2 Hz, 1H), 3.95 (td, *J* = 8.4, 7.6, 1.7 Hz, 1H), 3.79 (ddd, *J* = 11.1, 9.1, 5.2 Hz, 1H), 3.07 (qd, *J* = 10.0, 9.2, 4.8 Hz, 1H), 2.64 (dd, *J* = 18.0, 10.2 Hz, 1H), 2.17 (dd, *J* = 18.0, 4.3 Hz, 1H), 2.12 – 2.02 (m, 1H), 1.73 (dd, *J* = 12.5, 5.0 Hz, 1H).

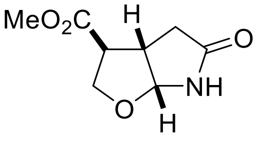
^{13}C NMR (101 MHz, $CDCl_3$) δ 177.2, 89.7, 65.6, 37.4, 36.5, 33.8.

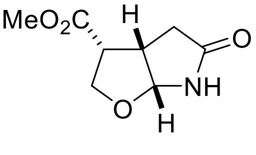
IR: ν[cm^{-1}] = 3250, 2960, 2870, 1674, 1446, 1305, 1264, 1234, 1059, 1029, 924, 857, 790.

HRMS: (EI-MS) m/z calculated for $C_6H_9NO_2$ $[M^+]$: 127.0628, found 127.0631.

R_f = 0.12 (hexanes/ethyl acetate = 1/3, stained in vanillin).

methyl (3S,3aS,6aR)-5-oxohexahydro-2H-furo[2,3-b]pyrrole-3-carboxylate (179e) and methyl (3R,3aS,6aR)-5-oxohexahydro-2H-furo[2,3-b]pyrrole-3-carboxylate (179ee)





Following the general procedure **GP-IV**, compound **172s** (48.9 mg, 0.2 mmol, 1.0 equiv) and DBU (0.04 mL, 0.4 mmol, 1.5 equiv) were dissolved in dry MeCN (2.0 mL) and stirred at 25 °C for 36 h yielding the title compounds (36.0 mg, 0.2 mmol, 97%, *dr* 5:1) as a slightly yellow oil after washing with pentane.

^{1}H NMR$_{\text{mixture}}$ (400 MHz, Chloroform-*d*) δ 6.67 (s, 0.20H, **179ee**), 6.56 (s, 1H, **179e**), 5.64 (d, *J* = 6.4 Hz, 1H, **179e**), 5.59 (dd, *J* = 6.1, 1.2 Hz, 0.20H, **179ee**), 4.21 (ddd, *J* = 9.6, 2.2, 0.8 Hz, 1H, **179e**), 4.09 (ddd, *J* = 9.4, 7.1, 0.6 Hz, 0.22H, **179ee**), 4.02 (dd, *J* = 9.6, 6.0 Hz, 1H, **179e**), 3.93 (dd, *J* = 11.2, 9.4 Hz, 0.24H, **179ee**), 3.73 (s, 3H, **179e**), 3.72 (s, 0.71H, **179ee**), 3.48 (ddtd, *J* = 8.9, 4.5, 3.4, 2.5, 1.4 Hz, 1H, **179e**), 3.36 (ddd, *J* = 10.3, 6.5, 3.8 Hz, 0.24H, **179ee**), 3.22 (ddd, *J* = 11.2, 8.4, 7.1 Hz, 0.22H, **179ee**), 2.86 (dt, *J* = 6.0, 2.2 Hz, 1H, **179e**), 2.71 (dd, *J* = 18.1, 10.5 Hz, 1H, **179e**), 2.48 (dd, *J* = 18.3, 10.3 Hz, 0.24H, **179ee**), 2.30 – 2.19 (m, 1.29H, signal overlap).

^{13}C NMR$_{\text{mixture}}$ (101 MHz, $CDCl_3$) δ 176.5, 176.3, 172.8, 170.5, 89.8, 67.9, 66.0, 52.6, 52.3, 51.6, 47.9, 40.3, 39.6, 35.5, 31.5.

IR: ν[cm^{-1}] = 3254, 2960, 2885, 1700, 1439, 1372, 1301, 1260, 1215, 1092, 1025, 939, 813.

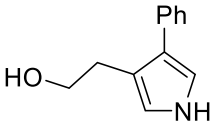
HRMS$_{\text{179e}}$: (ESI-MS) m/z calculated for $C_8H_{12}NO_4$ [M+H]$^+$: 186.0761, found 186.0761.

HRMS$_{\text{179ee}}$: (ESI-MS) m/z calculated for $C_8H_{12}NO_4$ [M+H]$^+$: 186.0761, found 186.0763.

R$_f$ = 0.16 (hexanes/ethyl acetate = 1/3, stained in vanillin).

5.5. Pyrrole Synthesis

2-(4-phenyl-1H-pyrrol-3-yl)ethan-1-ol (186a)



179a (20.3 mg, 0.1 mmol, 1.0 equiv) was dissolved in dry THF (1.0 mL) and Cp_2ZrHCl (103.2 mg, 0.4 mmol, 4.0 equiv) was added portionwise at room temperature under nitrogen atmosphere. The mixture was stirred for 18 h and quenched with H_2O (1.0 mL). Then, the pH of the reaction mixture was adjusted to 11 by the addition of a saturated aqueous sodium carbonate solution at 0 °C. Afterwards, the mixture was filtered through a short plug of silica (washed with Et_2O) and the filtrate was extracted with Et_2O (5 x 2 mL). The combined organic layers were washed with brine (1.0 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by column chromatography (PE/EA 1:3), yielding the title compound (13.8 mg, 0.1 mmol, 74%) as a yellow oil.

^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.19 (s, 1H), 7.42 – 7.34 (m, 4H), 7.26 – 7.22 (m, 1H), 6.87 (t, *J* = 2.5 Hz, 1H), 6.76 – 6.72 (m, 1H), 3.73 (t, *J* = 6.5 Hz, 2H), 2.91 (td, *J* = 6.8, 6.0 Hz, 2H), 1.49 (s, 1H).

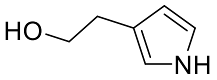
^{13}C NMR (101 MHz, $CDCl_3$) δ 136.1, 128.4, 128.2, 125.9, 124.9, 117.6, 117.1, 116.8, 62.9, 29.0.

IR: ν[cm^{-1}] = 3381, 3056, 2930, 1715, 1603, 1528, 1487, 1446, 1044, 768, 701.

HRMS: (EI-MS) m/z calculated for $C_{12}H_{13}NO$ [M$^+$]: 187.0992, found 187.0986.

R$_f$ = 0.46 (hexanes/ethyl acetate = 1/1, stained in vanillin).

2-(1H-pyrrol-3-yl)ethan-1-ol (186b)



5d (38.1 mg, 0.3 mmol, 1.0 equiv) was dissolved in dry THF (3.0 mL) and Cp_2ZrHCl (232.1 mg, 0.9 mmol, 3.0 equiv) was added portionwise at room temperature under nitrogen atmosphere. The mixture was stirred for 18 h and quenched with H_2O (1.0 mL). Then, the pH of the reaction mixture was adjusted to 11 by the addition of a saturated aqueous sodium carbonate solution at 0 °C. Afterwards, the mixture was filtered through a short plug of silica (washed with Et_2O) and the filtrate was extracted with Et_2O (5 x 2 mL). The combined organic layers were washed with brine (1.0 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by column chromatography (PE/EA 1:3), yielding the title compound (16.6 mg, 0.1 mmol, 50%) as a colorless oil.

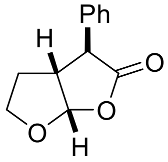
^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.18 (s, 1H), 6.77 (q, *J* = 2.5 Hz, 1H), 6.67 (q, *J* = 2.0 Hz, 1H), 6.13 (q, *J* = 2.4 Hz, 1H), 3.79 (t, *J* = 6.3 Hz, 2H), 2.76 (t, *J* = 6.3 Hz, 2H), 1.60 (s, 1H).

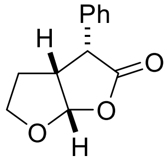
^{13}C NMR (101 MHz, $CDCl_3$) δ 119.8, 118.5, 116.3, 108.8, 63.5, 30.5.

Analytical data is in accordance with literature.[167]

5.6. Other Substrates

(3S,3aR,6aS)-3-phenyltetrahydrofuro[2,3-b]furan-2(3H)-one (173a) and (3R,3aR,6aS)-3-phenyltetrahydrofuro[2,3-b]furan-2(3H)-one (173aa)





In a Schlenk tube, compound **167a** (87.3 mg, 0.4 mmol, 1.0 equiv) was dissolved in MeCN (4 mL). Afterwards, HBr (32.4 mg, 0.4 mmol, 1.0 equiv, 37% aq. solution) was added and the solution was stirred for 18 h. Then water was added to the solution and the resulting mixture was extracted with EA. The organic phases were combined and dried over Na$_2$SO$_4$, yielding title compounds as a yellow oil (77.6 mg, 0.4 mmol, 95%) after evaporation of the solvent.

^{1}H NMR$_{\text{mixture}}$ (400 MHz, Chloroform-*d*) δ 7.35 – 7.16 (m, 6.51H, signal overlap), 6.15 (d, *J* = 5.4 Hz, 1H, **173a**), 6.06 (d, *J* = 5.1 Hz, 0.21H, **173aa**), 4.22 (d, *J* = 9.5 Hz, 0.21H, **173aa**), 4.09 (ddd, *J* = 9.1, 8.1, 2.5 Hz, 1H, **173a**), 4.03 – 3.97 (m, 1H, **173a**), 3.96 – 3.91 (m, 0.22H, **173aa**), 3.86 (td, *J* = 8.7, 7.1 Hz, 0.24H, **173aa**), 3.67 (d, *J* = 4.5 Hz, 1H, **173a**), 3.36 (tt, *J* = 9.8, 5.0 Hz, 0.26H, **173aa**), 3.22 – 3.09 (m, 1H, **173a**), 2.23 (dddd, *J* = 13.0, 10.3, 9.0, 8.1 Hz, 1H, **173a**), 1.93 (ddt, *J* = 13.0, 5.5, 2.6 Hz, 1H, **173a**), 1.72 (ddt, *J* = 13.4, 10.1, 8.3 Hz, 0.24H, **173aa**), 1.50 (ddt, *J* = 13.4, 7.2, 4.6 Hz, 0.24H, **173aa**).

^{13}C NMR$_{\text{mixture}}$ (101 MHz, CDCl$_3$) δ 175.8, 174.4, 137.3, 134.2, 129.3, 129.1, 128.9, 127.9, 127.7, 127.4, 107.2, 106.2, 68.2, 67.6, 53.1, 49.3, 48.1, 45.3, 32.0, 26.4.

IR: ν[cm^{-1}] = 3064, 3030, 1982, 2885, 1767, 1603, 1498, 1454, 1357, 1331, 1297, 1170, 1088, 969, 924, 850, 757, 697.

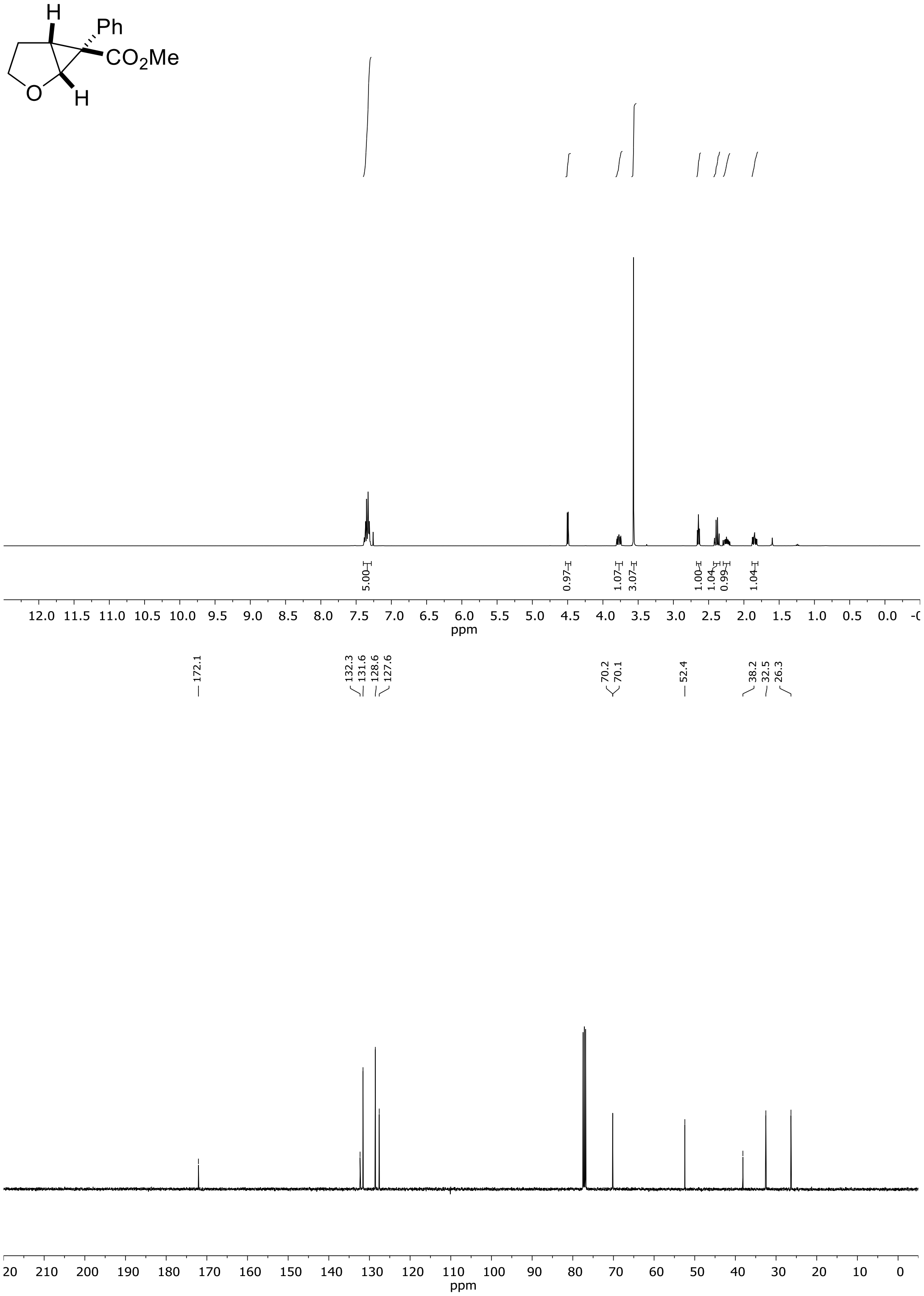
HRMS$_{\text{173a}}$: (EI-MS) m/z calculated for C$_{12}$H$_{13}$O$_3$ [M+H]$^+$: 205.0859, found 205.0861.

HRMS$_{\text{173aa}}$: (EI-MS) m/z calculated for C$_{12}$H$_{13}$O$_3$ [M+H]$^+$: 205.0859, found 205.0864.

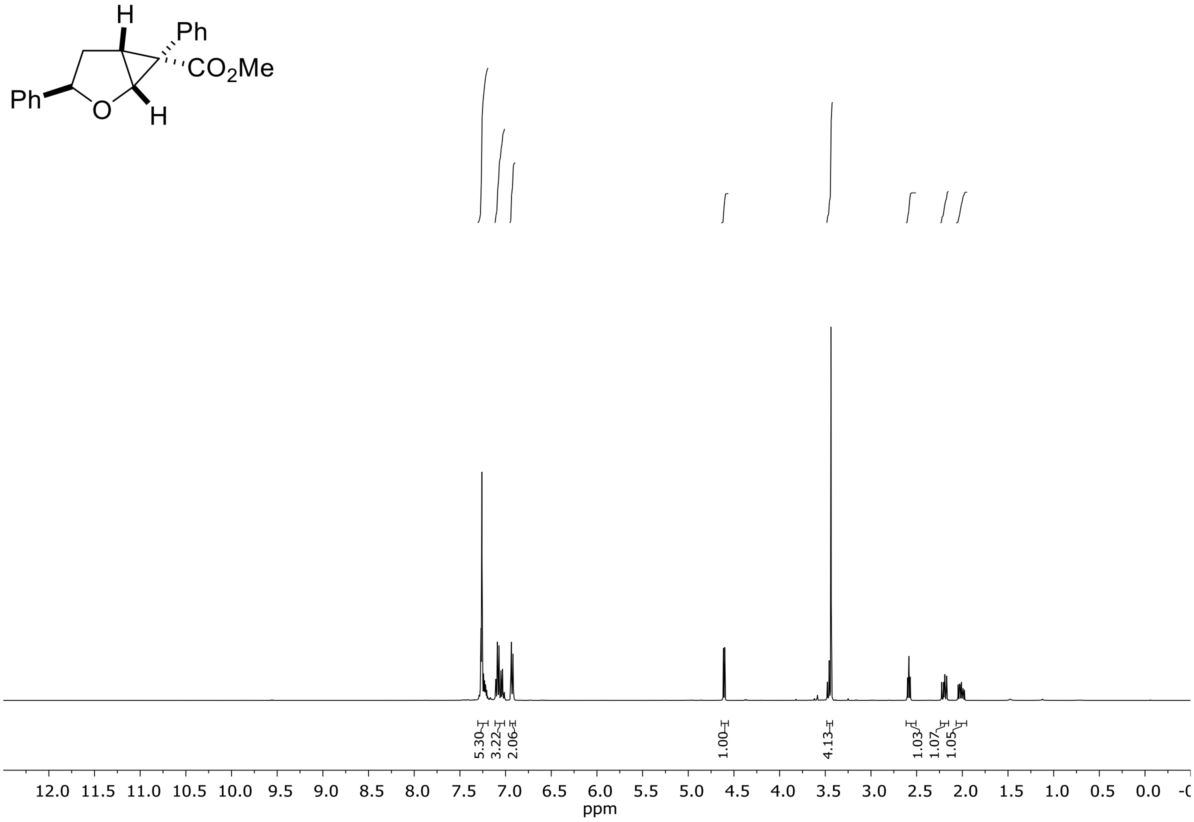
R$_f$ = 0.48 (hexanes/ethyl acetate = 3/1, stained in vanillin).

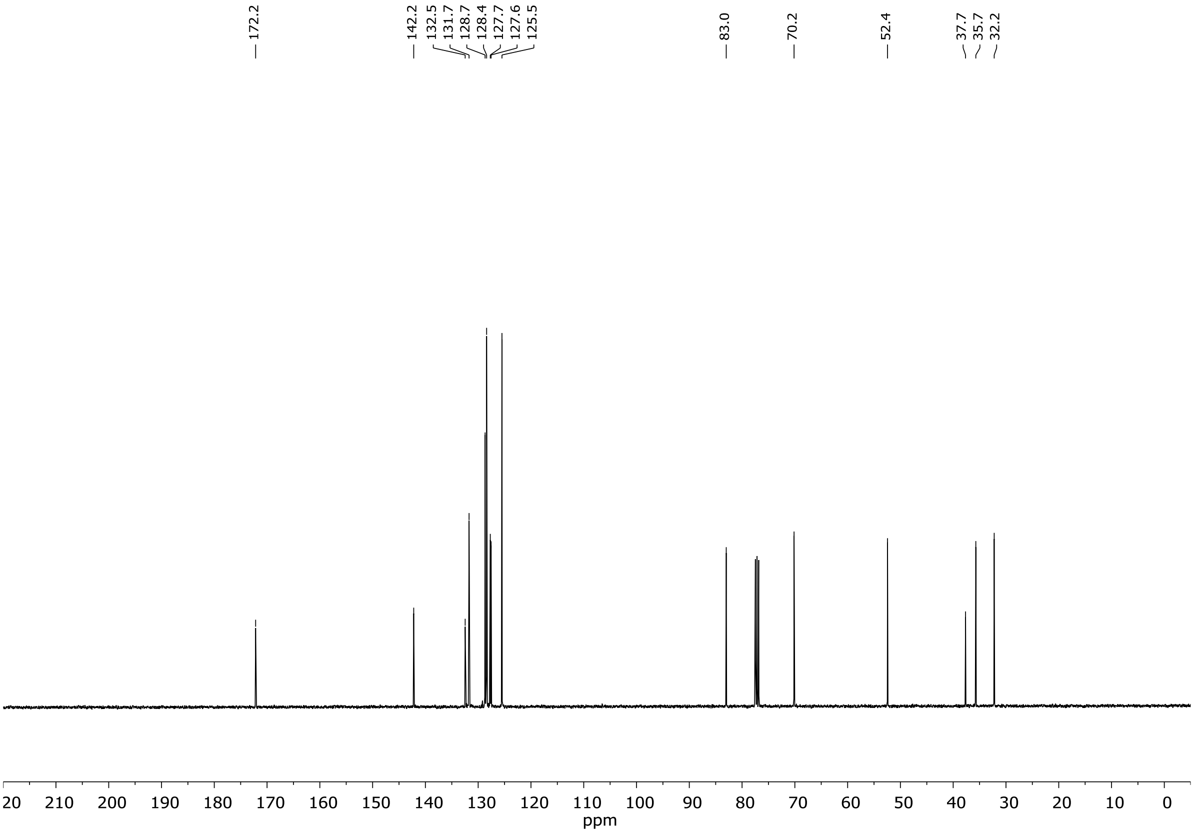
5.7. Copies of NMR Spectra

Compound **167a**: ^{1}H NMR (400 MHz, CDCl$_3$) and ^{13}C NMR (101 MHz, CDCl$_3$):

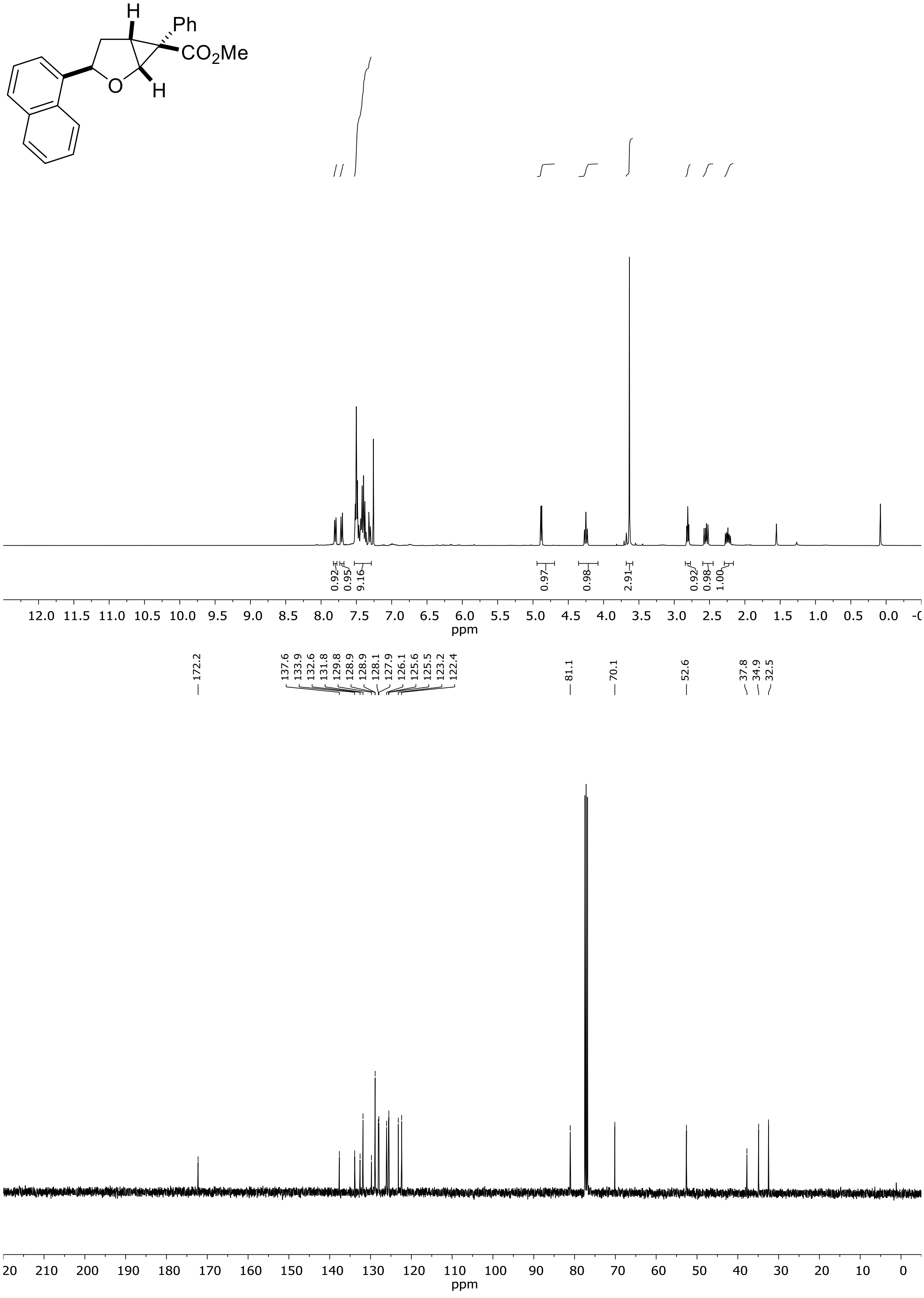


Compound **167b**: ^{1}H NMR (400 MHz, $CDCl_3$) and ^{13}C NMR (101 MHz, $CDCl_3$):

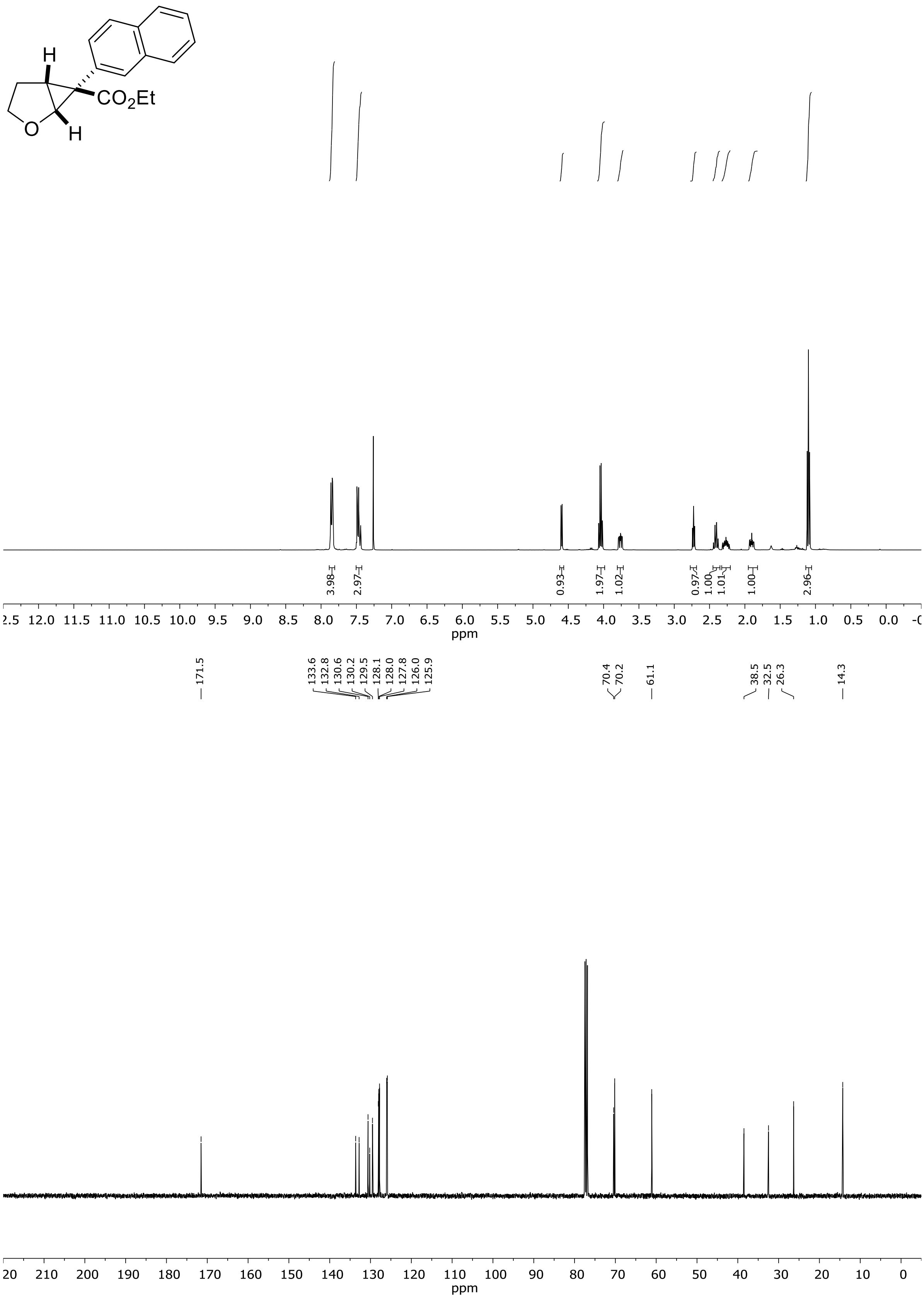




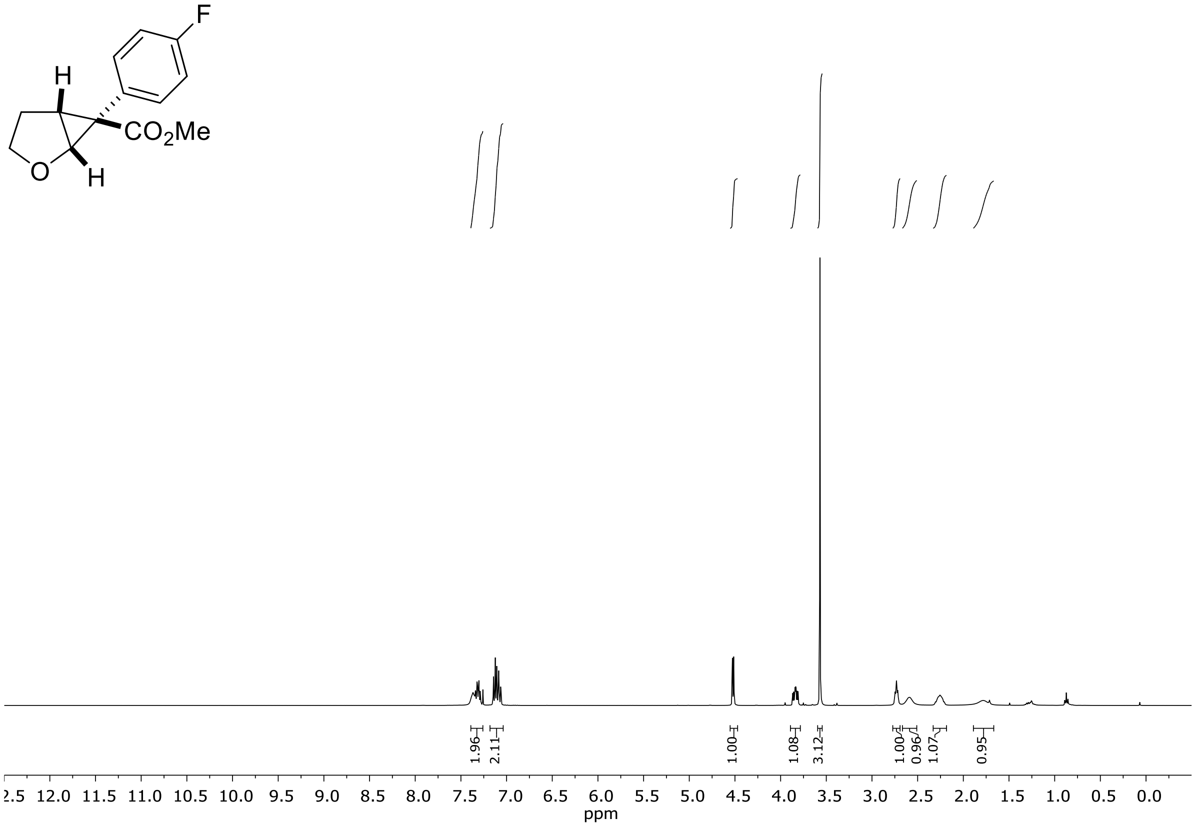
Compound **167c**: ^{1}H NMR (400 MHz, CDCl$_3$) and ^{13}C NMR (101 MHz, CDCl$_3$):

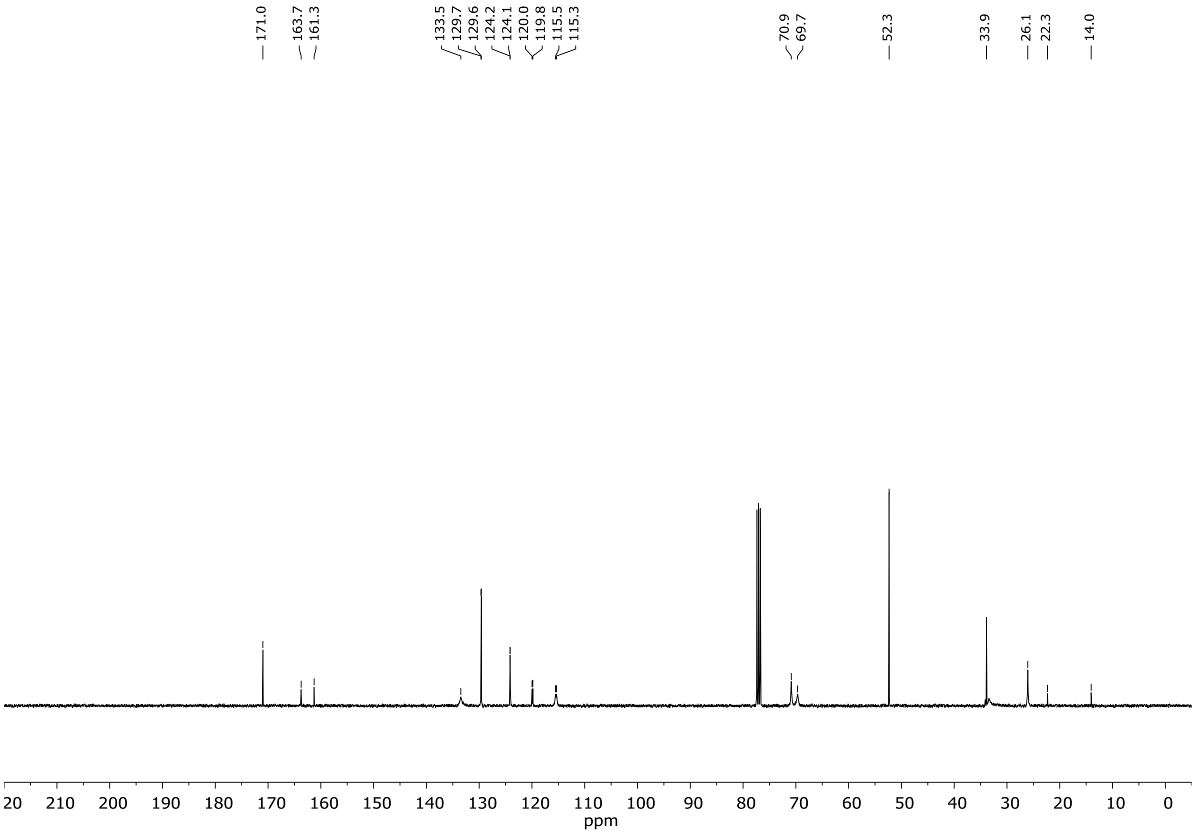


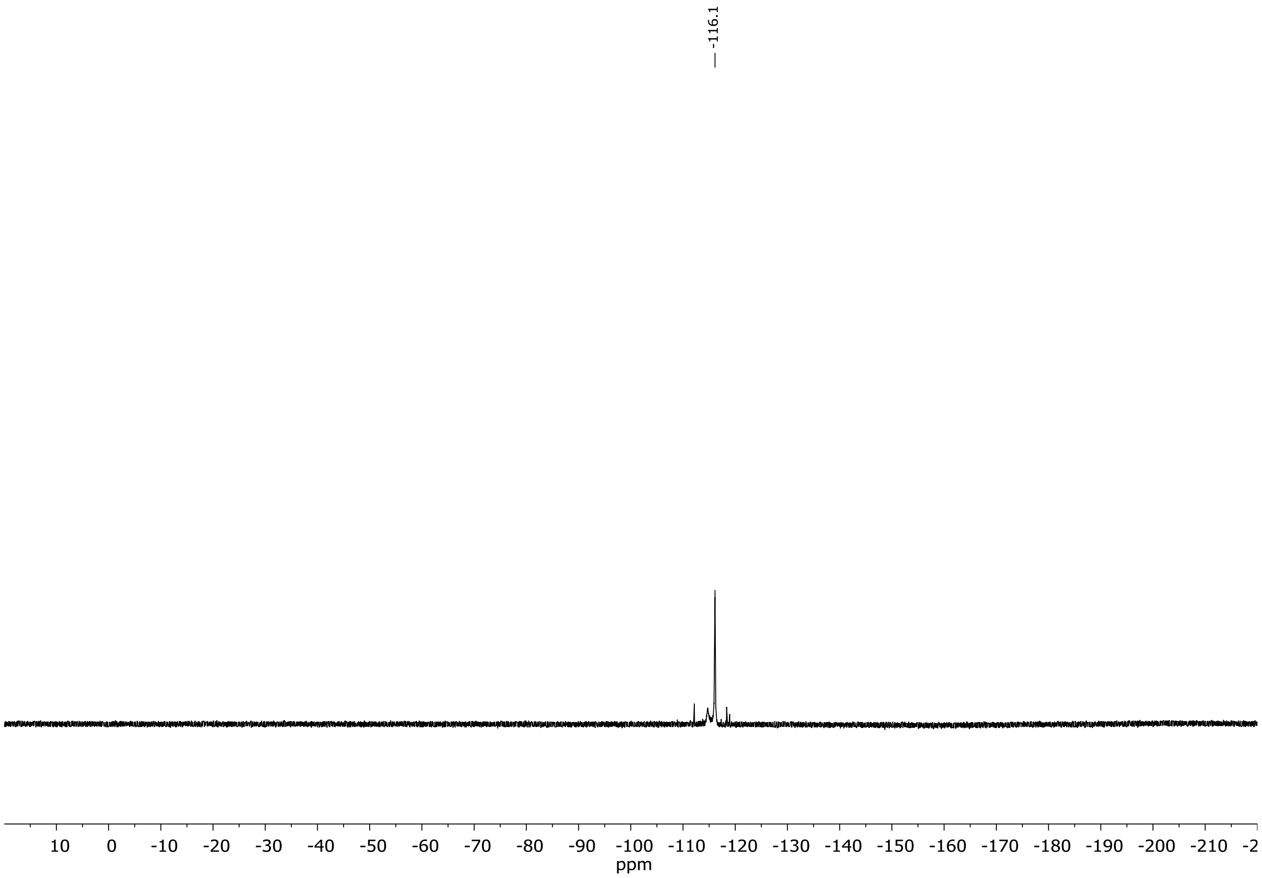
Compound **167d**: ^{1}H NMR (400 MHz, CDCl$_3$) and ^{13}C NMR (101 MHz, CDCl$_3$):



Compound **167e**: ^{1}H NMR (400 MHz, CDCl$_3$), ^{13}C NMR (101 MHz, CDCl$_3$) and ^{19}F NMR (376 MHz, CDCl$_3$):



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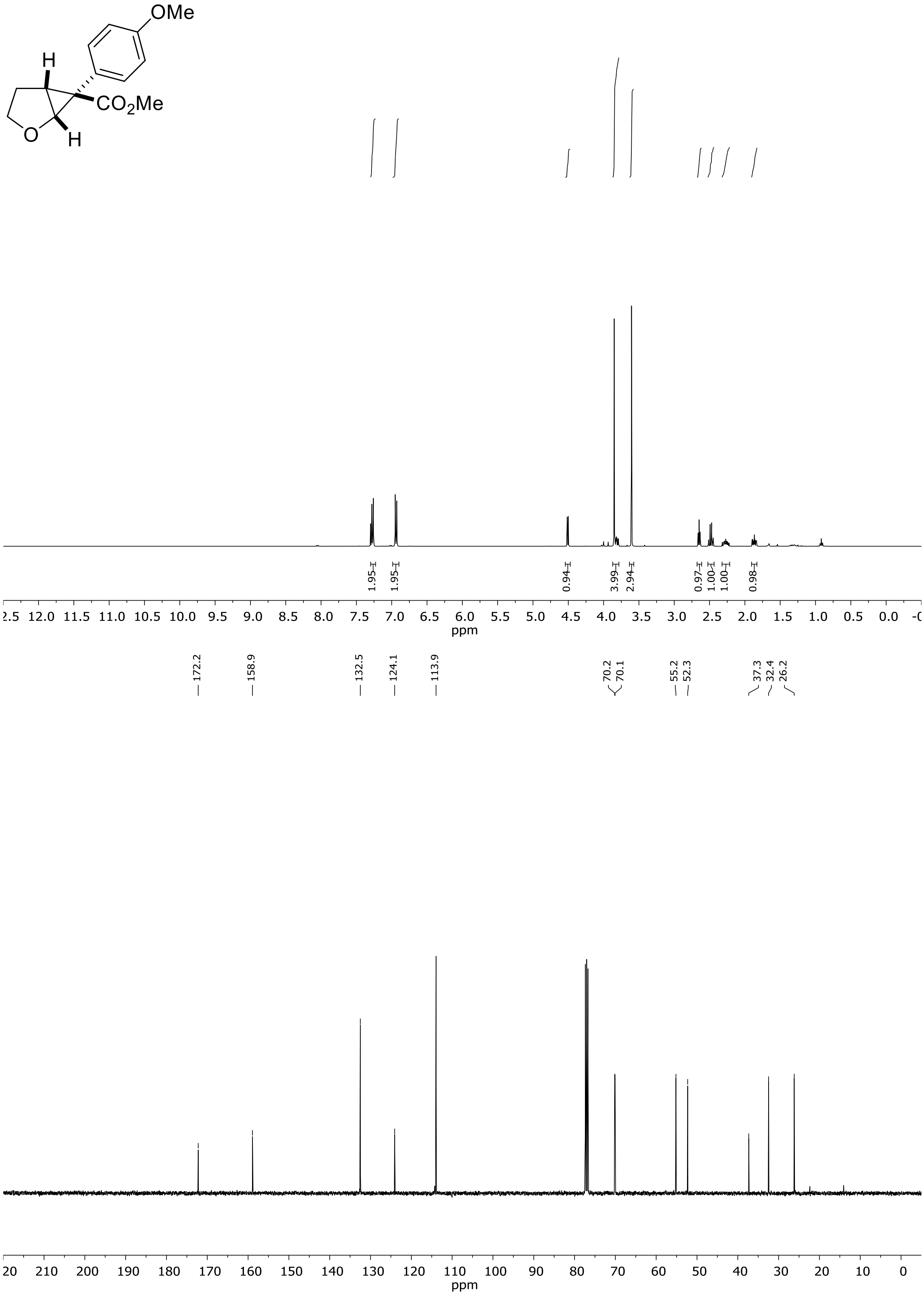
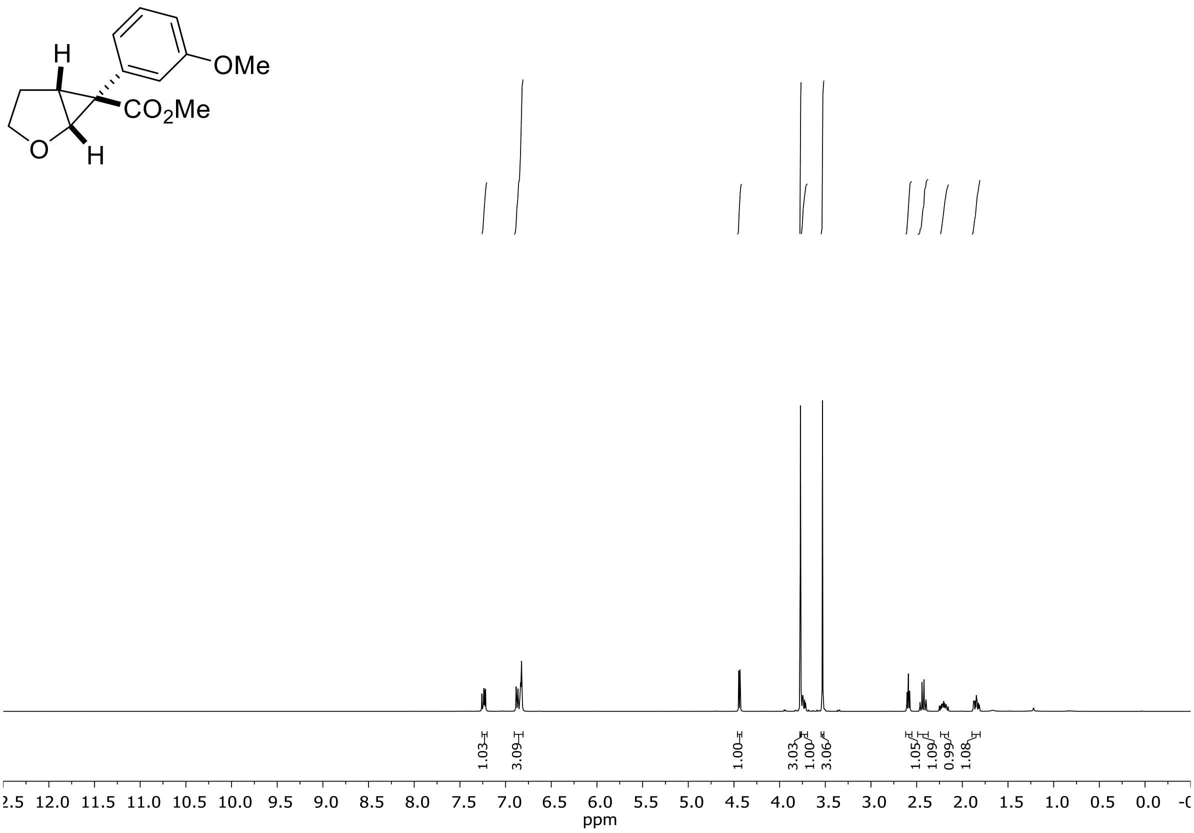
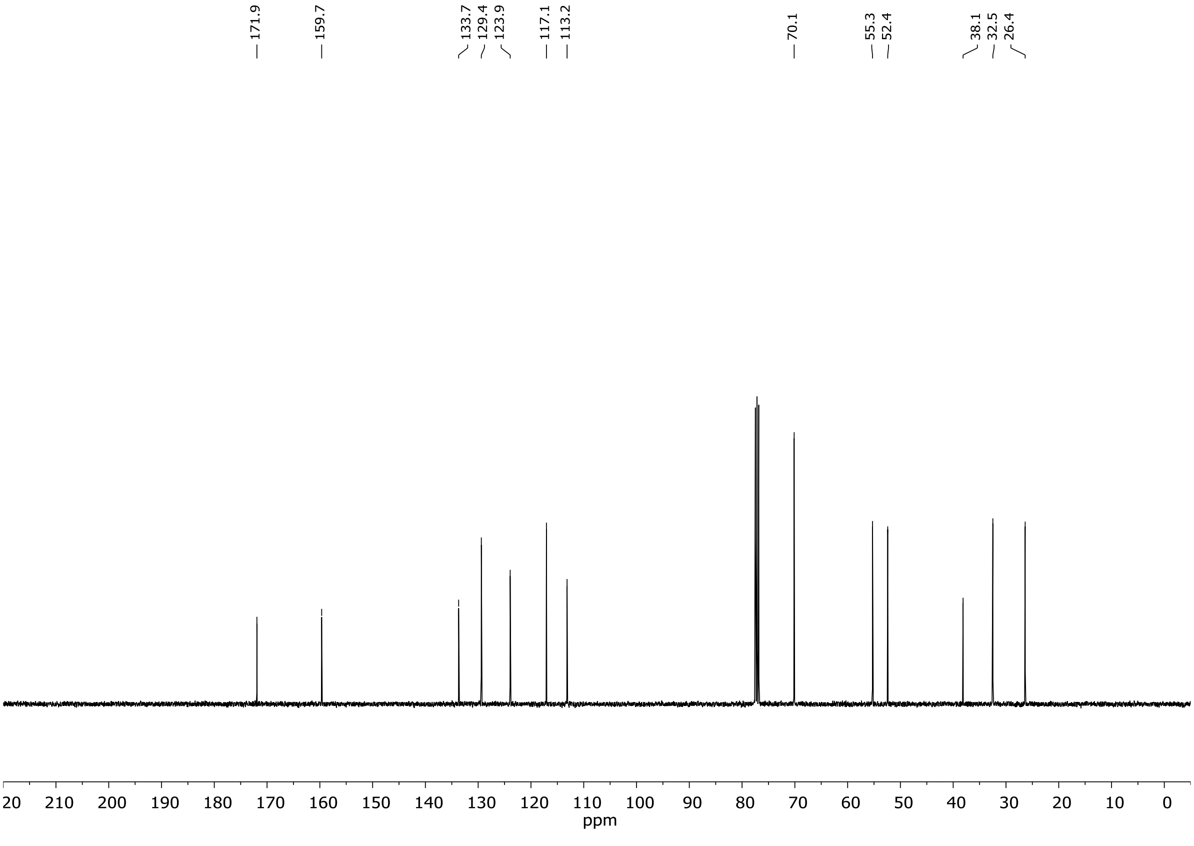
Compound **167f**: ^{1}H NMR (400 MHz, CDCl$_3$) and ^{13}C NMR (101 MHz, CDCl$_3$):

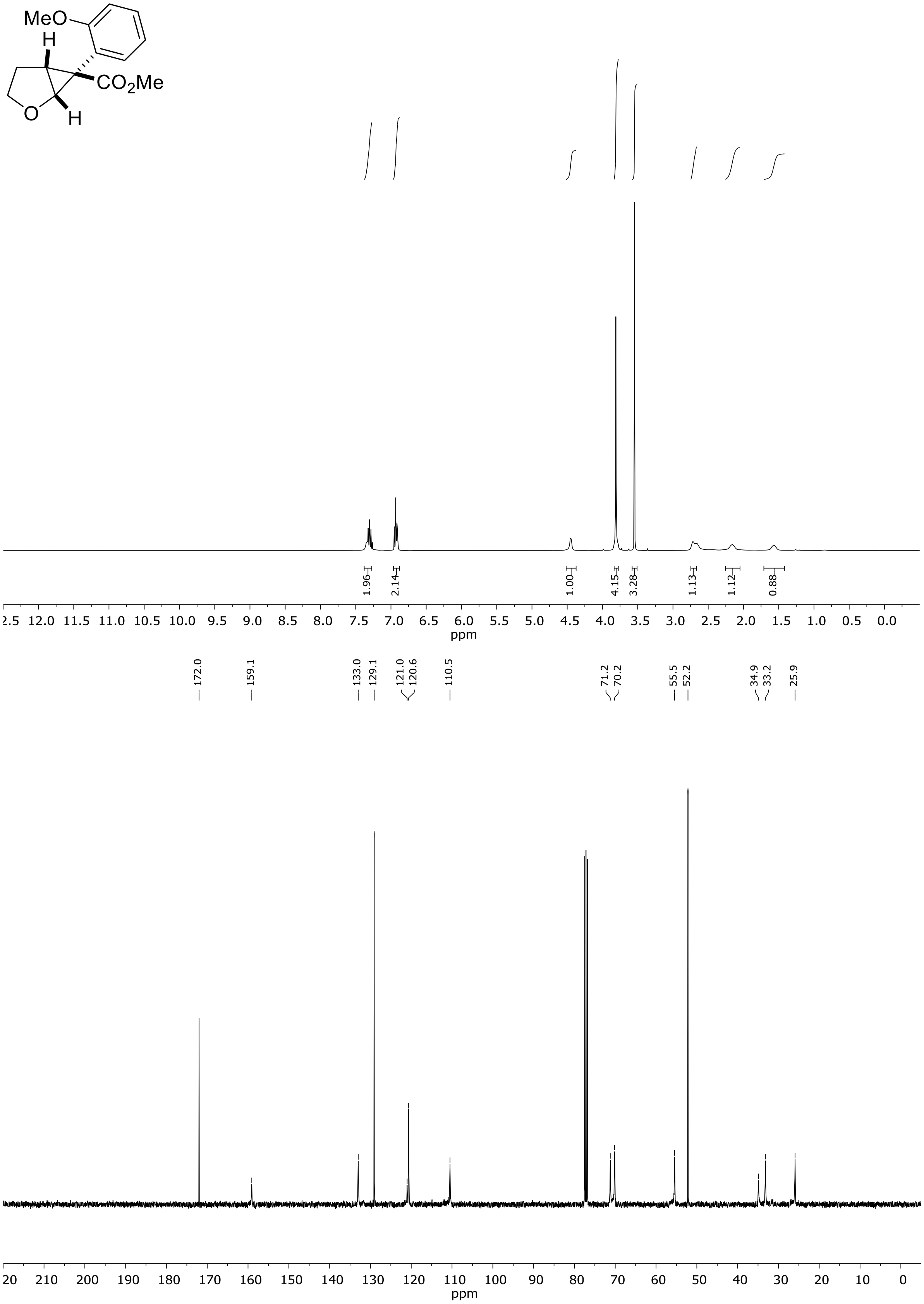


Compound **167g**: ^{1}H NMR (400 MHz, CDCl$_3$) and ^{13}C NMR (101 MHz, CDCl$_3$):

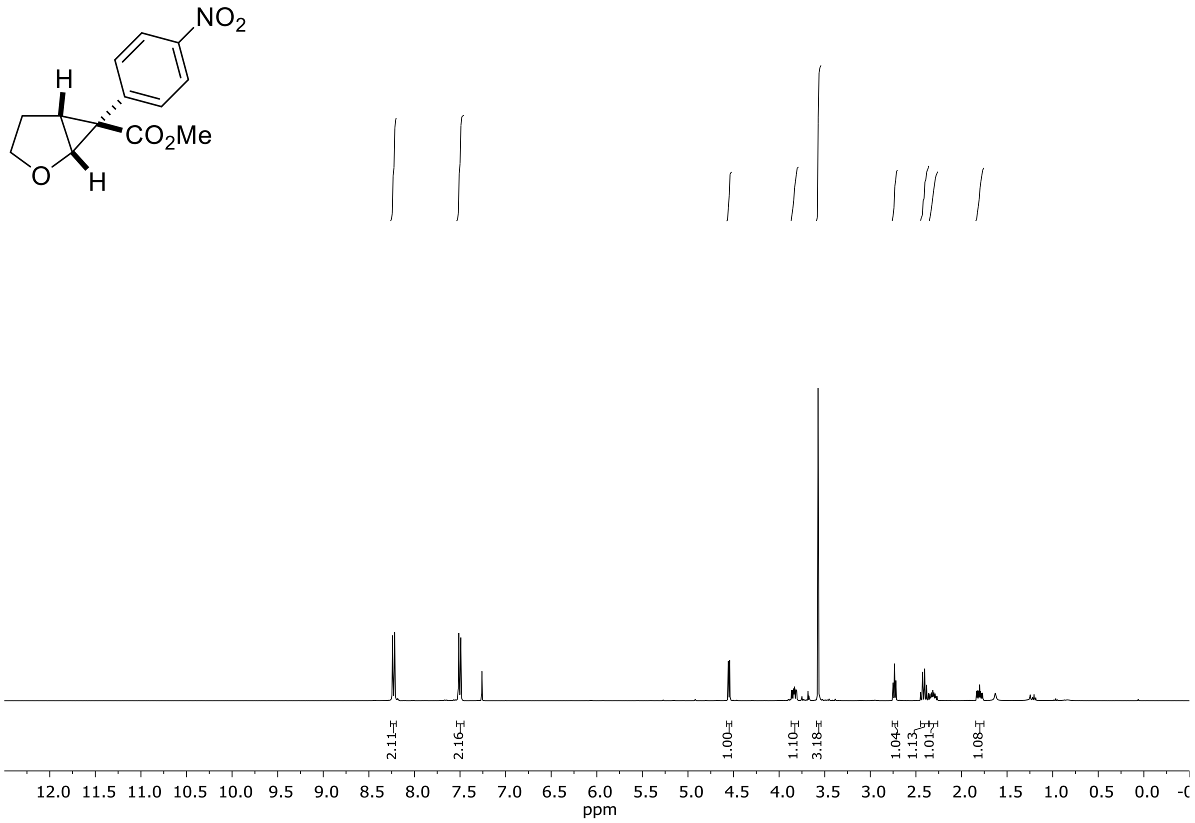


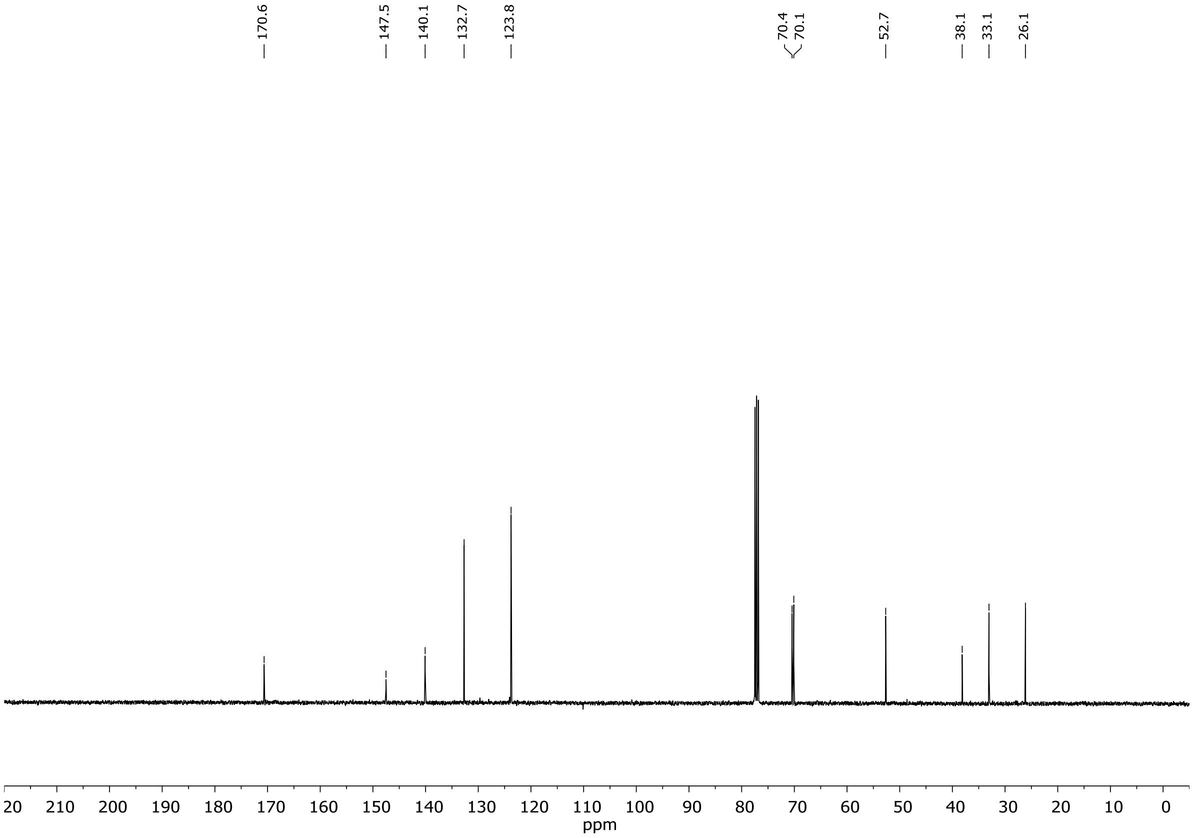


Compound **167h**: ^{1}H NMR (400 MHz, $CDCl_3$) and ^{13}C NMR (101 MHz, $CDCl_3$):

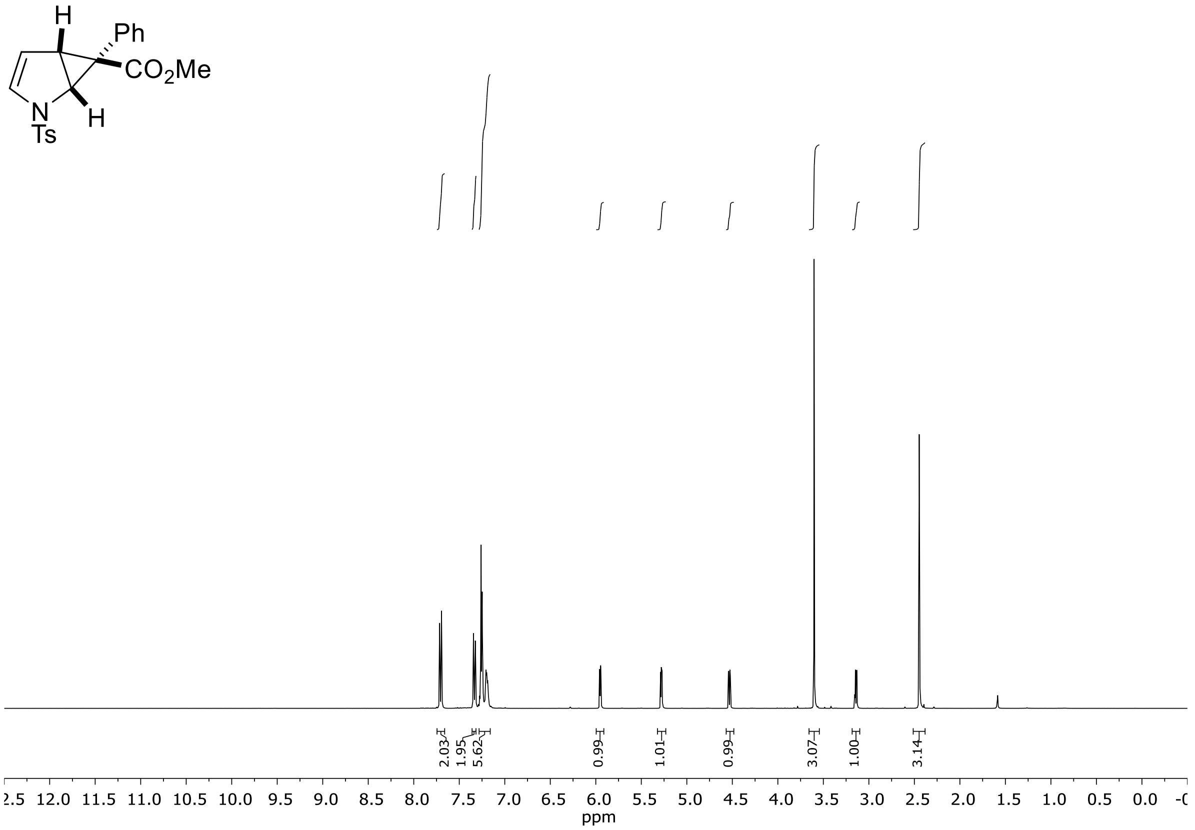


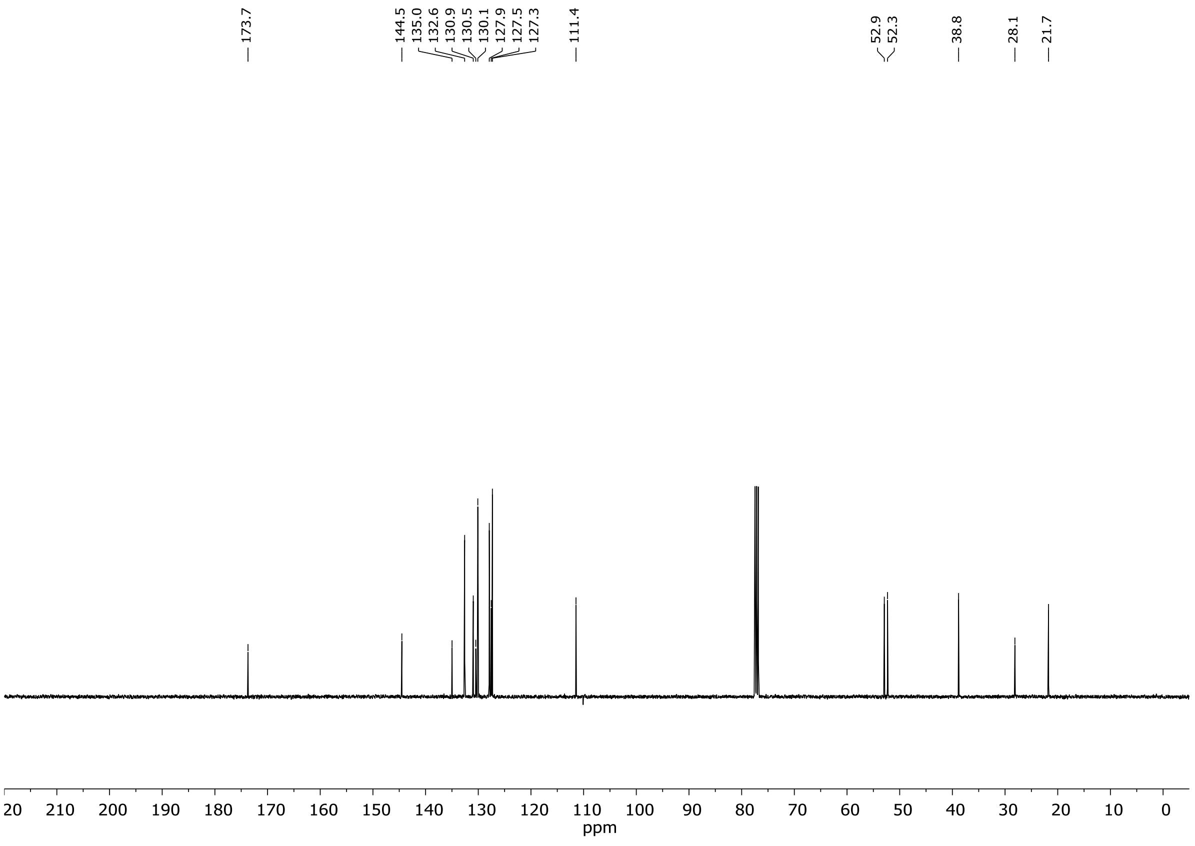
Compound **167j**: ^{1}H NMR (400 MHz, $CDCl_3$) and ^{13}C NMR (101 MHz, $CDCl_3$):



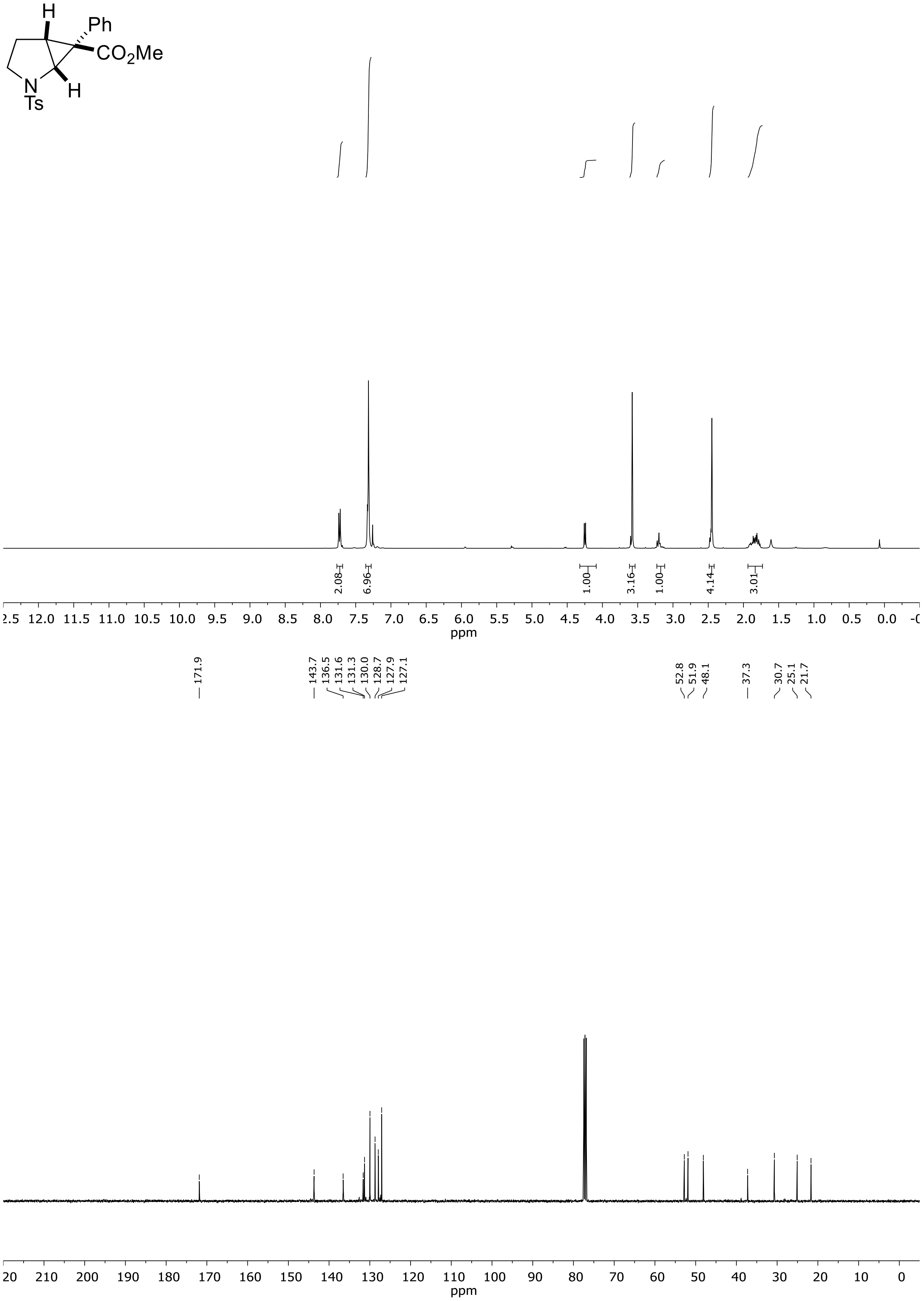


Compound **167r**: ^{1}H NMR (400 MHz, CDCl$_3$) and ^{13}C NMR (101 MHz, CDCl$_3$):

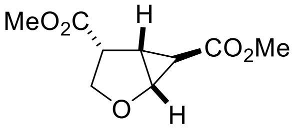


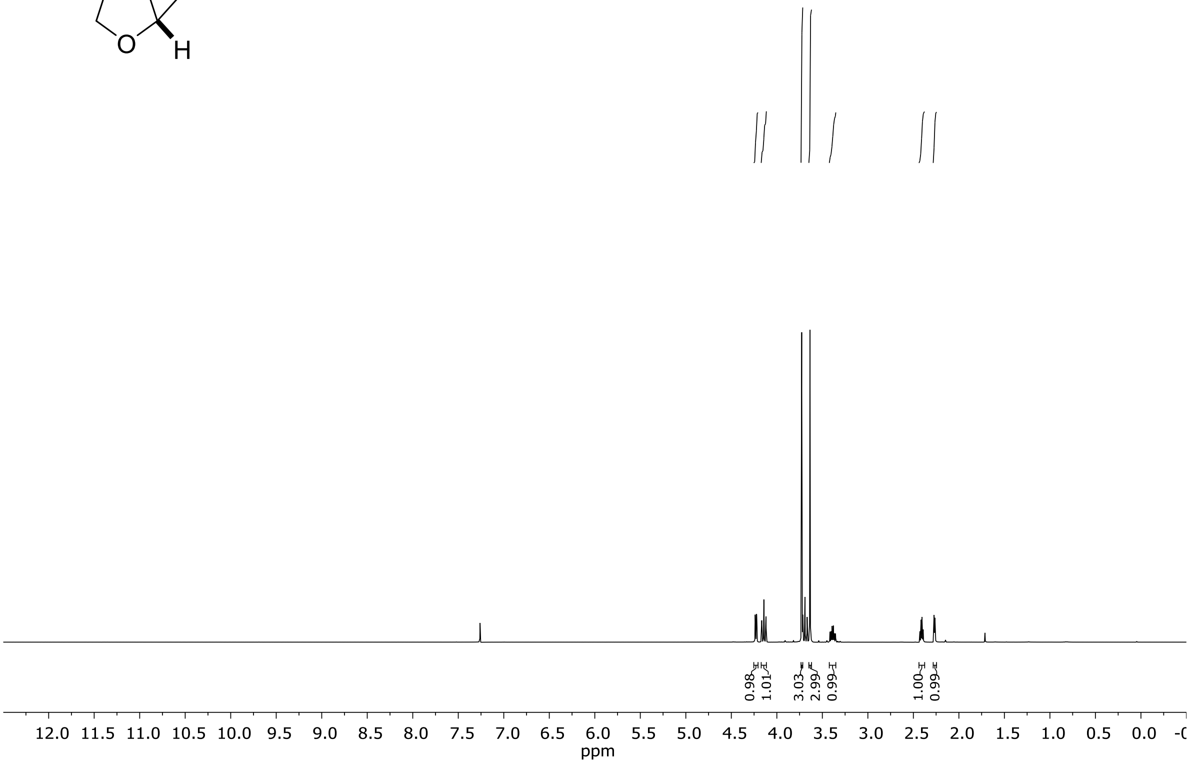


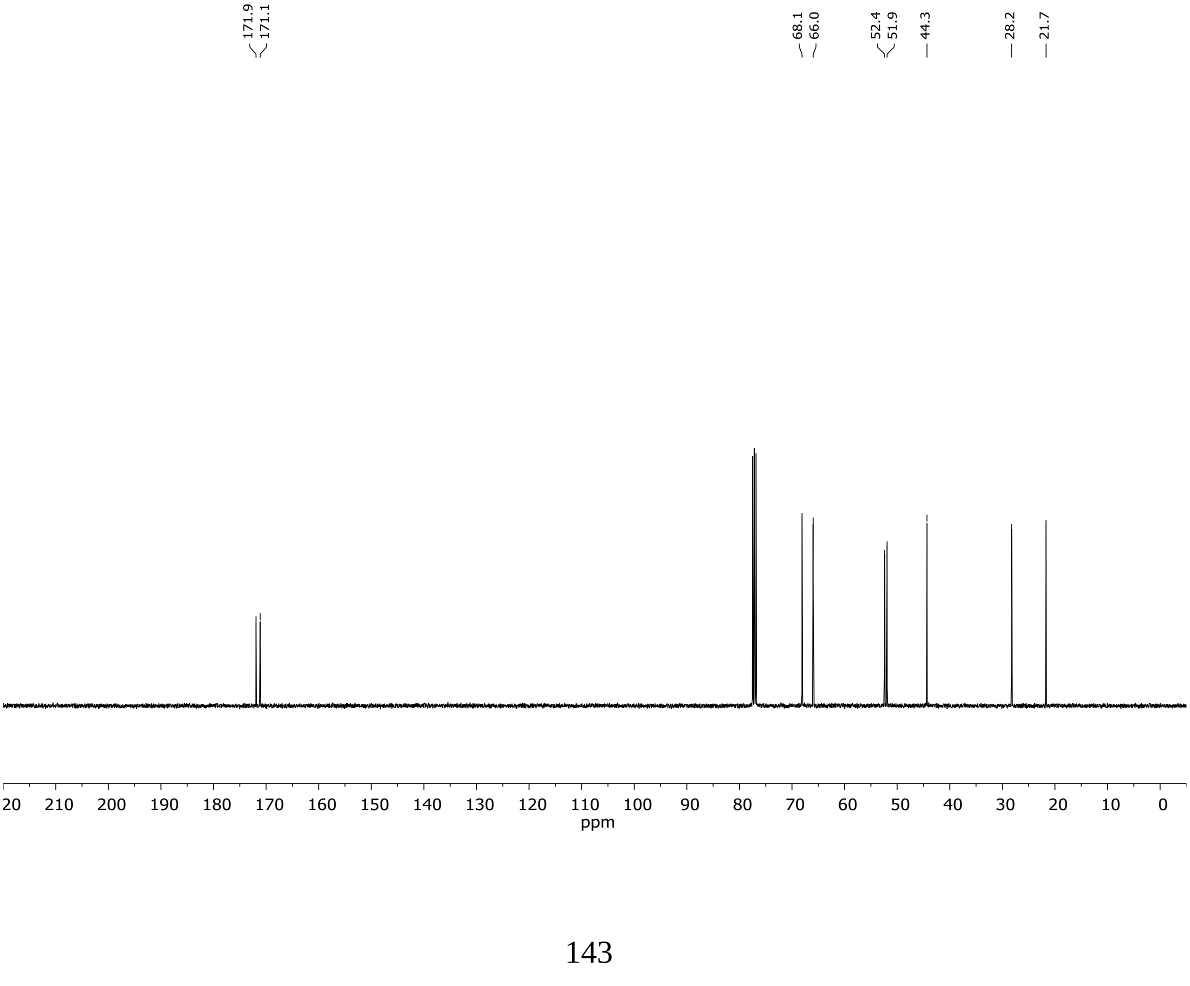
Compound **167q**: ^{1}H NMR (400 MHz, $CDCl_3$) and ^{13}C NMR (101 MHz, $CDCl_3$):



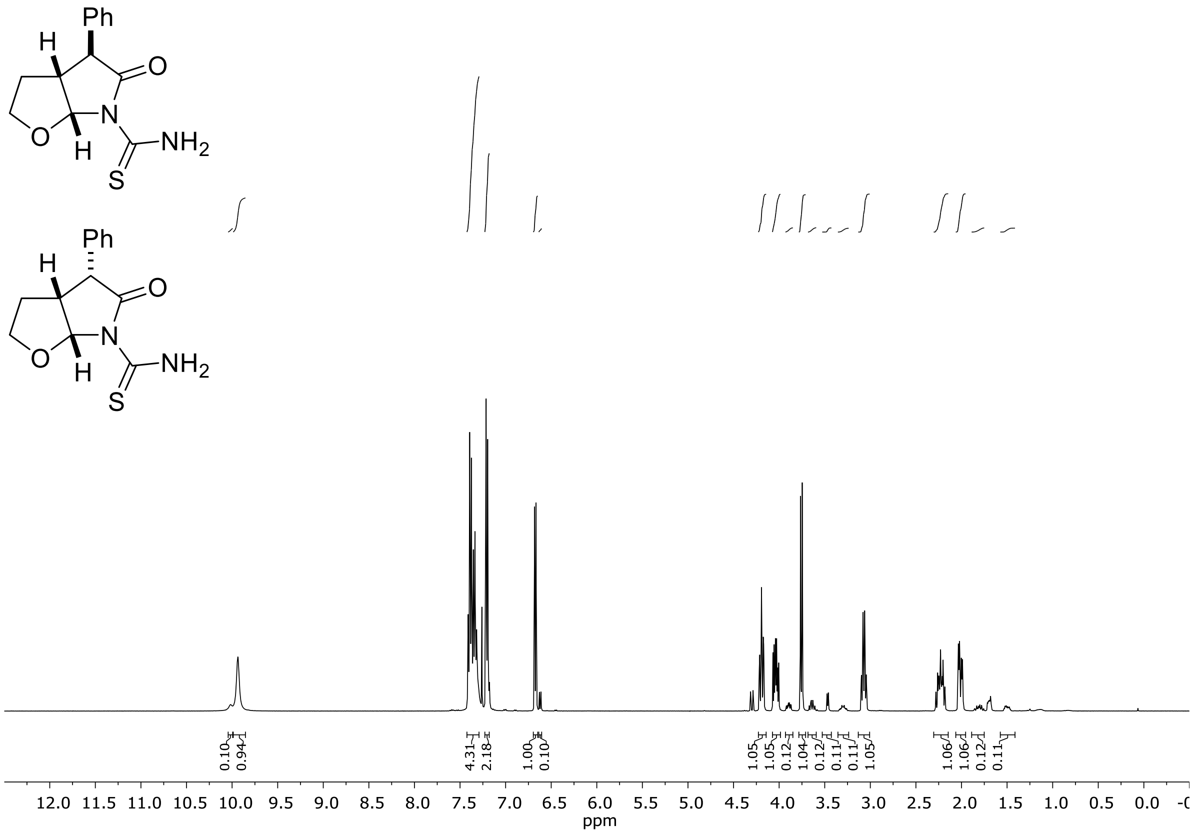
Compound **167s**: ^{1}H NMR (400 MHz, CDCl$_3$) and ^{13}C NMR (101 MHz, CDCl$_3$):

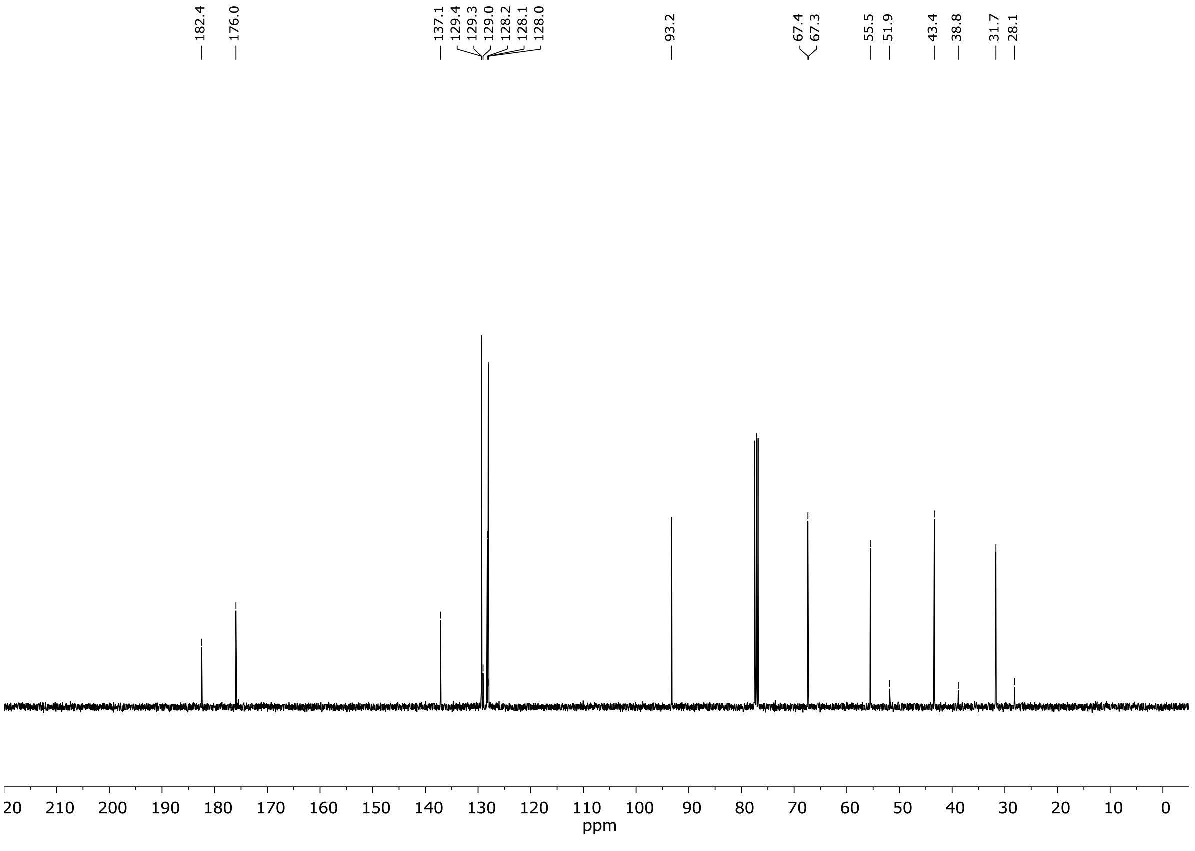




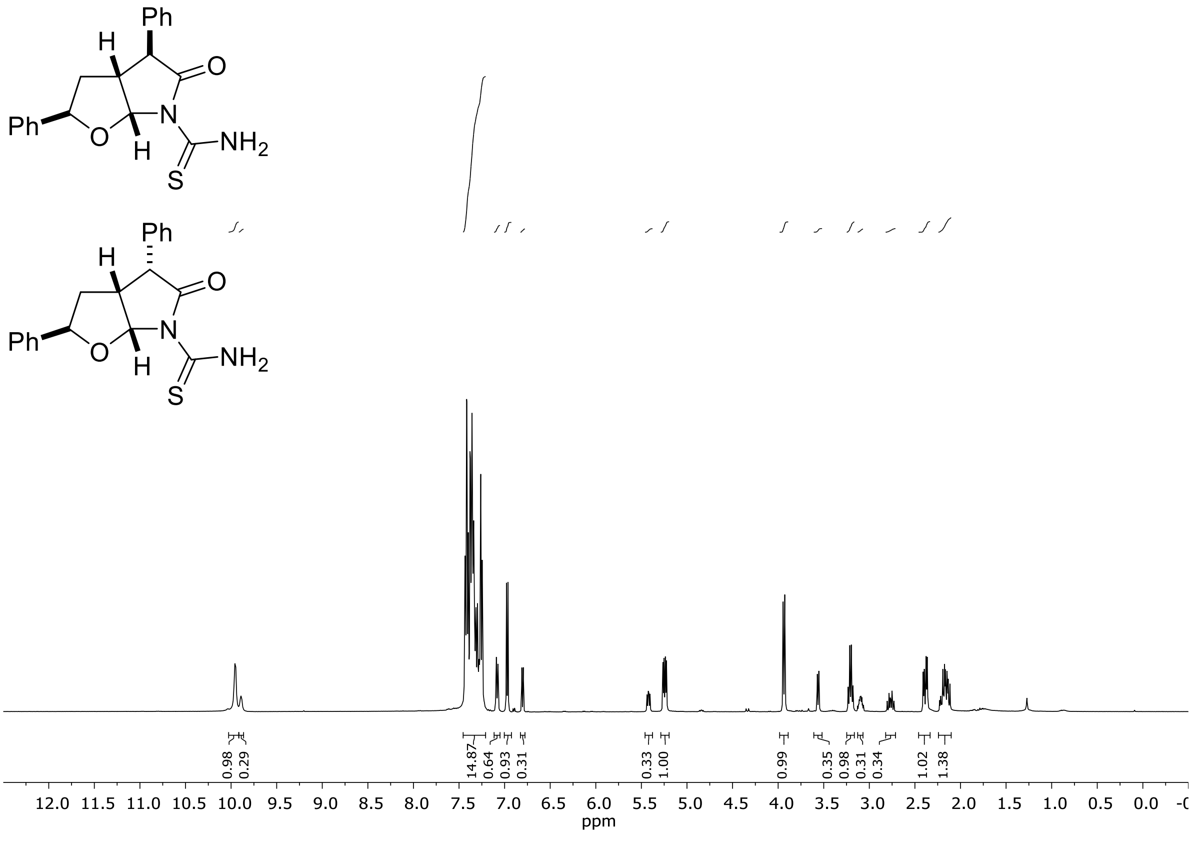


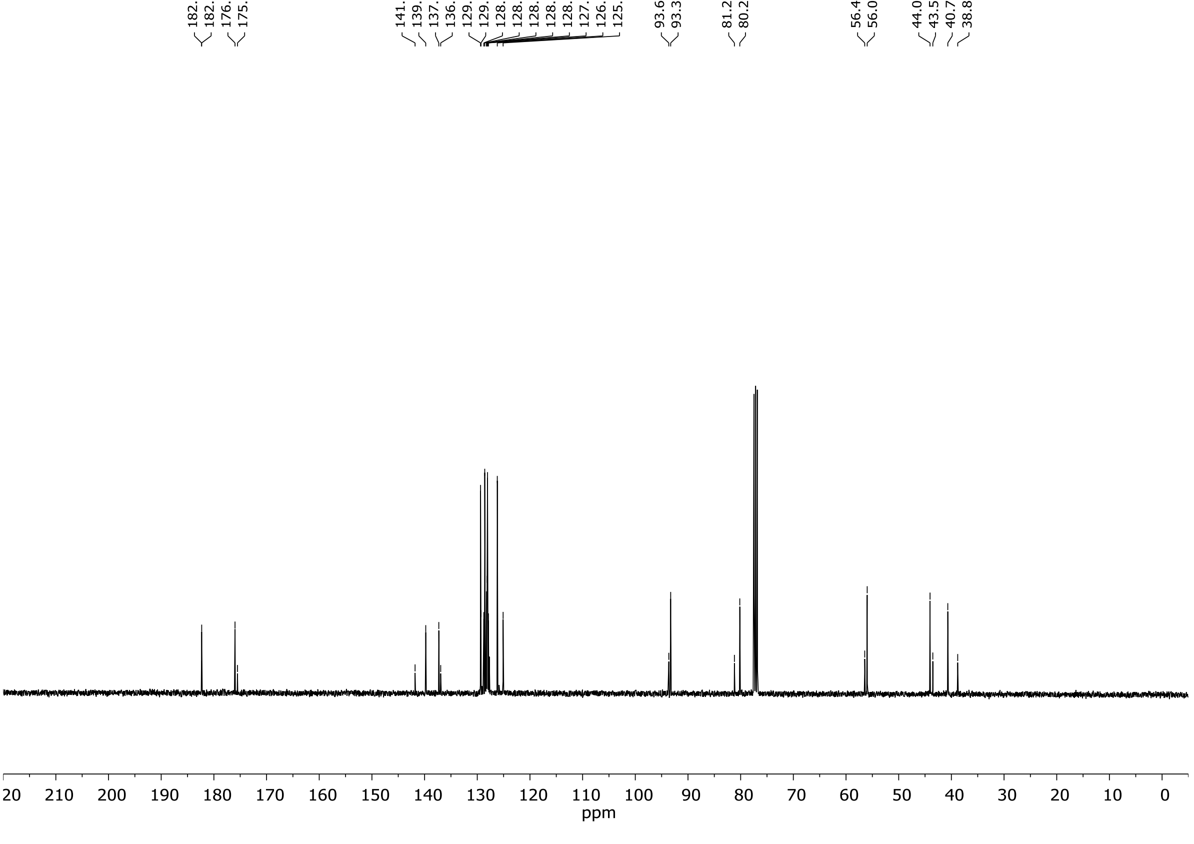
Compounds **172a** and **172aa**: ^{1}H NMR (400 MHz, $CDCl_3$) and ^{13}C NMR (101 MHz, $CDCl_3$):



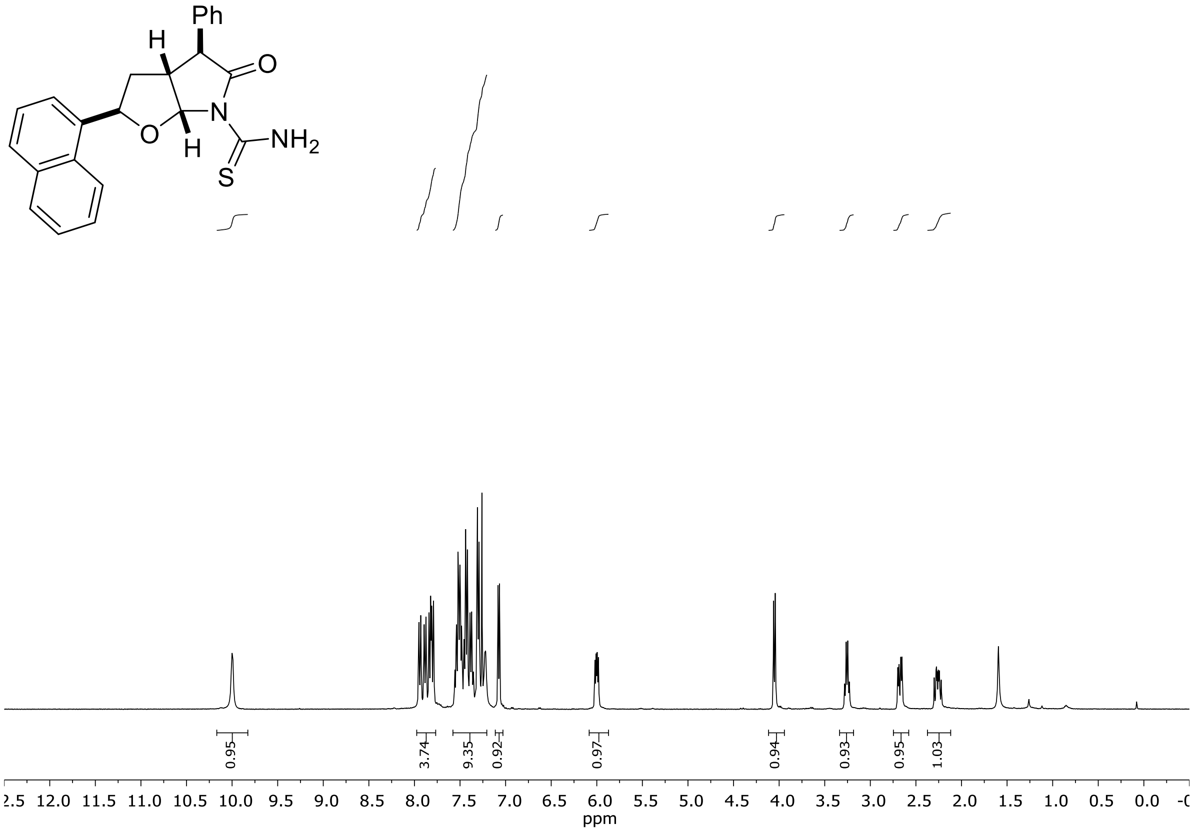


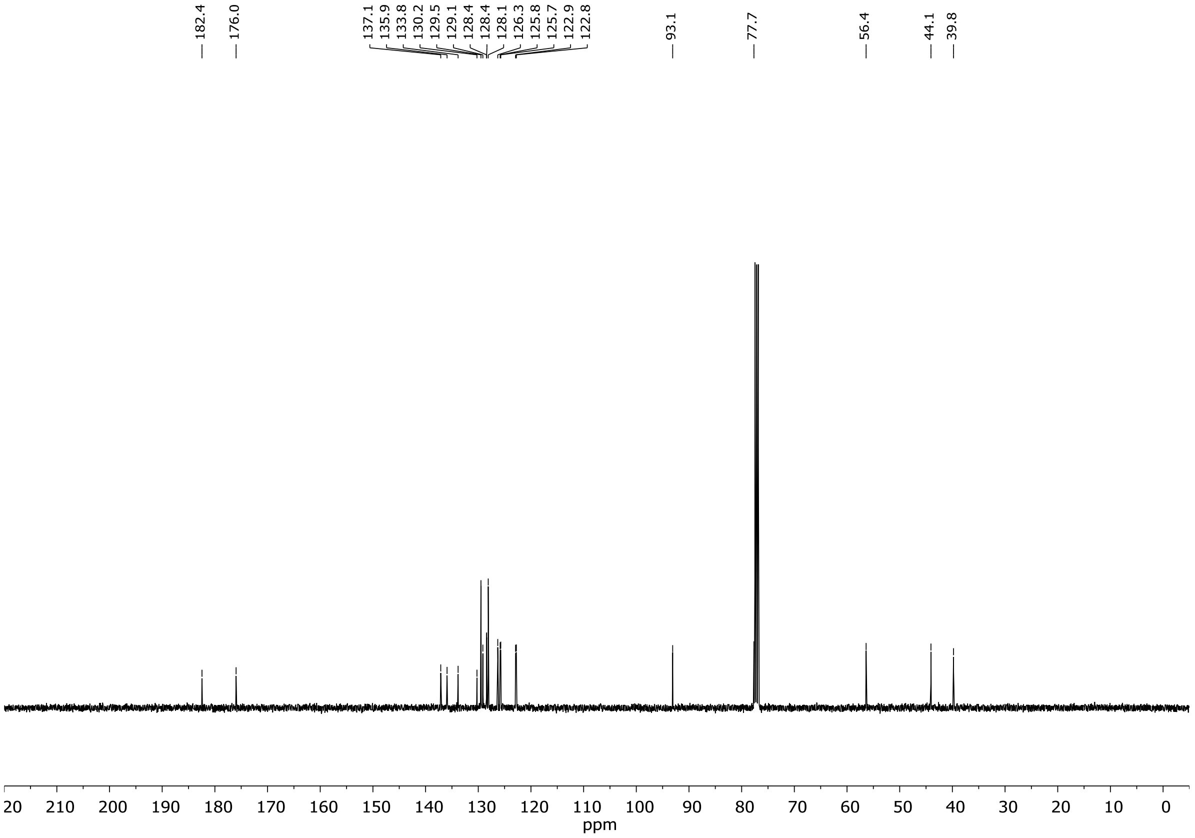
Compounds **172b** and **172bb**: ^{1}H NMR (400 MHz, CDCl$_3$) and ^{13}C NMR (101 MHz, CDCl$_3$):



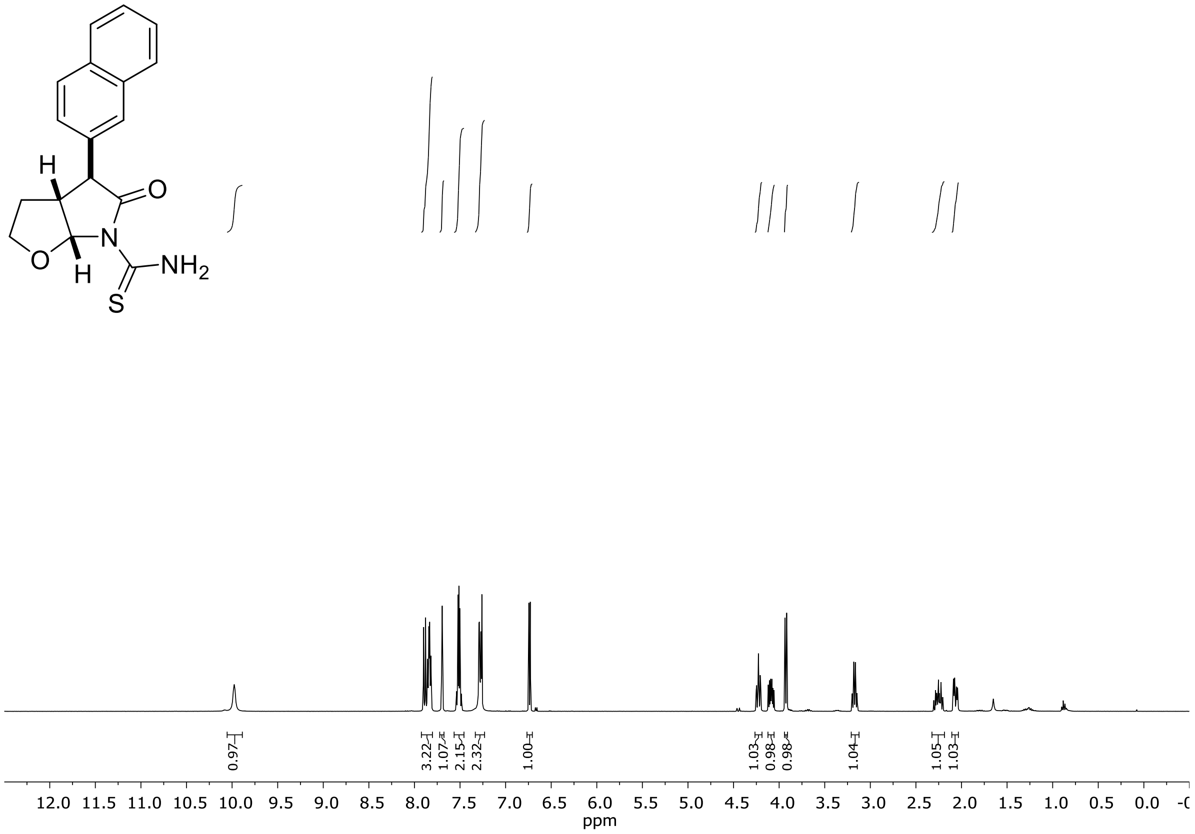


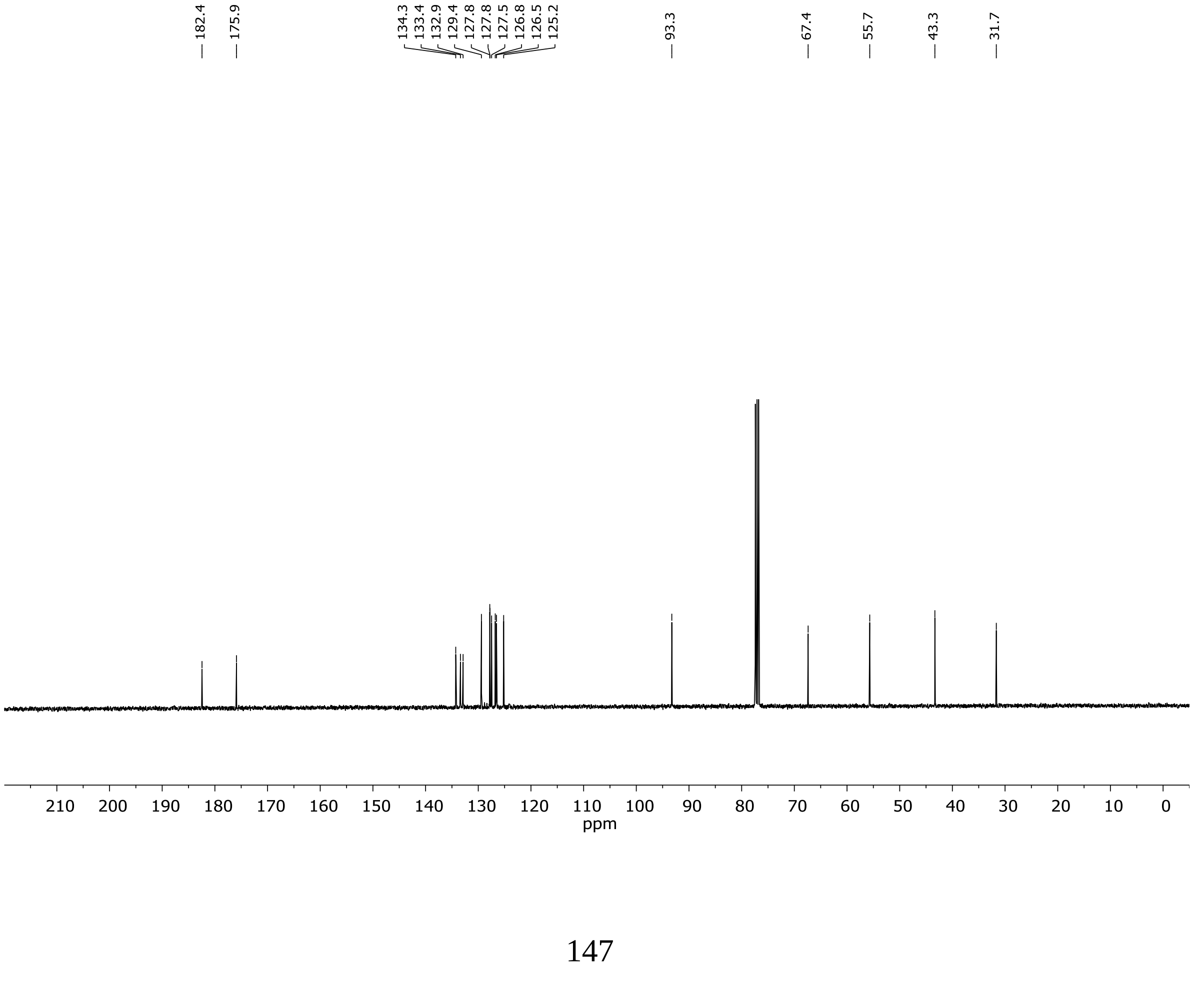
Compound **172c**: ^{1}H NMR (400 MHz, CDCl$_3$) and ^{13}C NMR (101 MHz, CDCl$_3$):



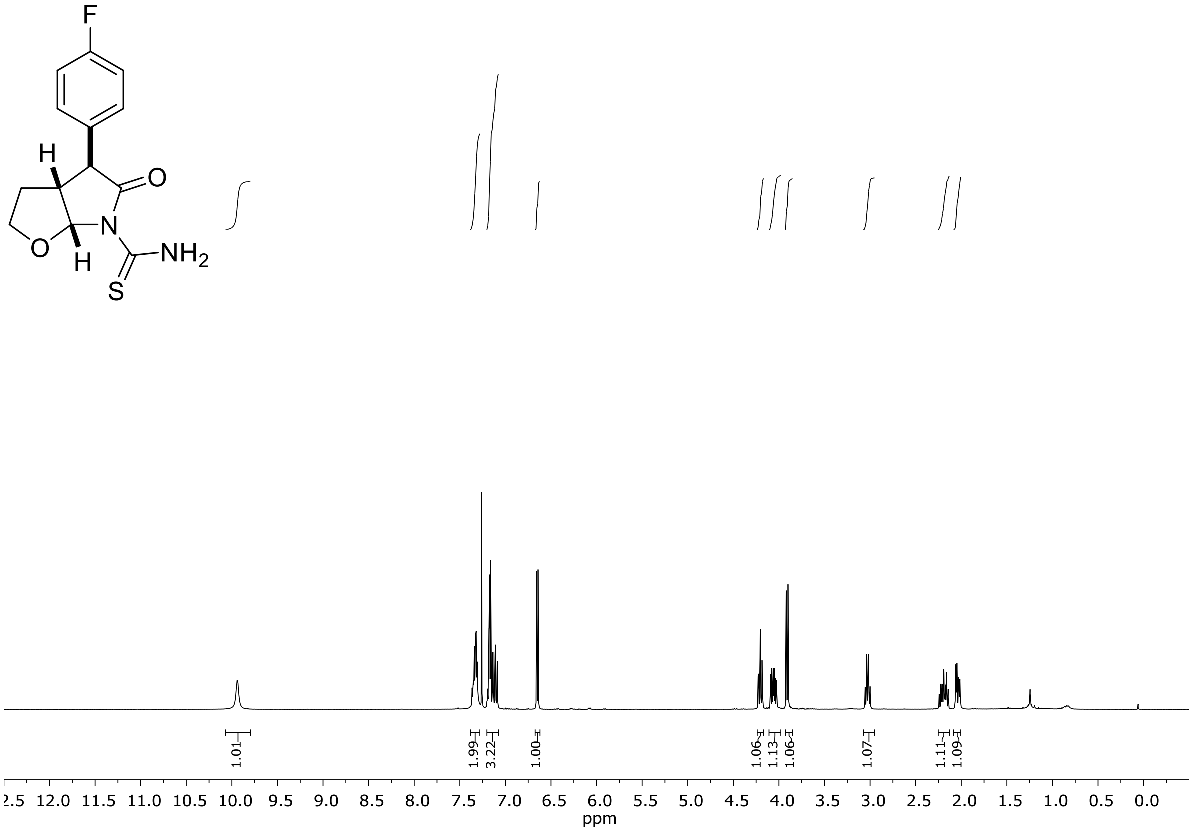


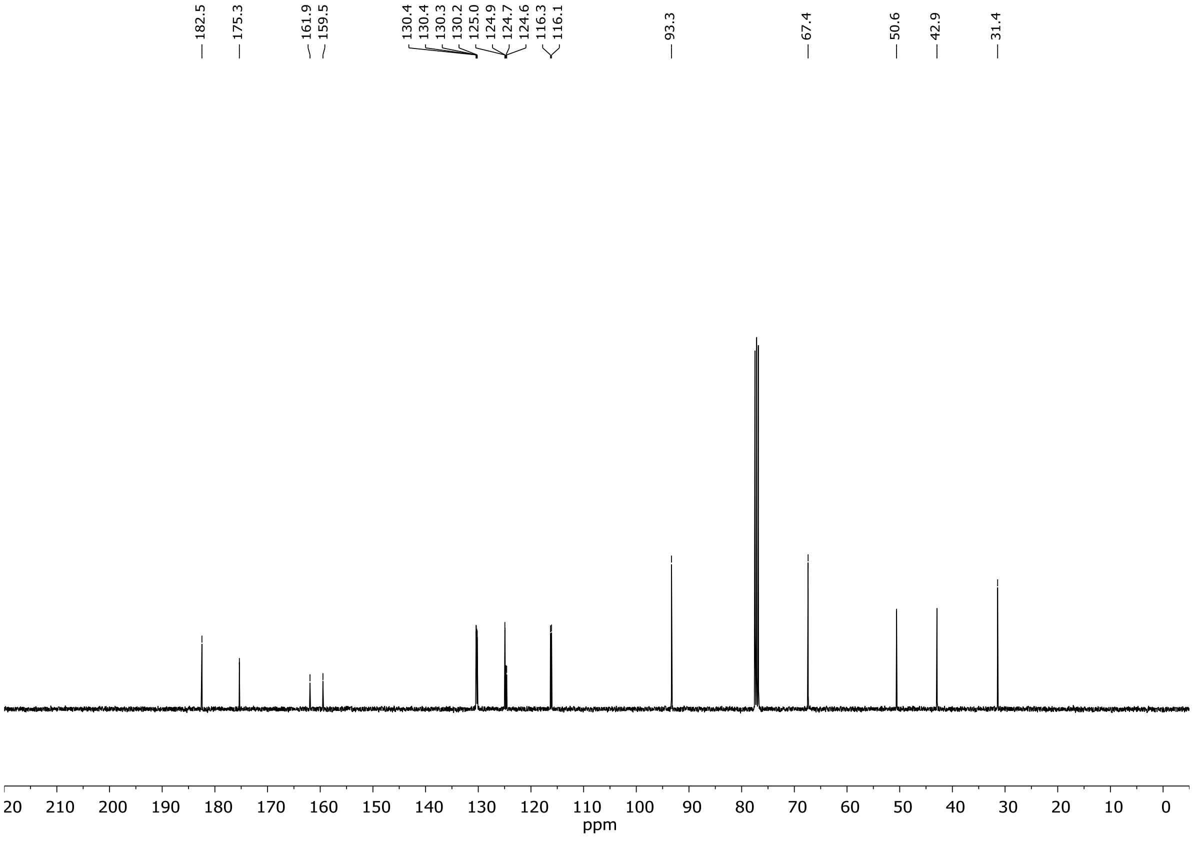
Compound **172d**: ^{1}H NMR (400 MHz, CDCl$_3$) and ^{13}C NMR (101 MHz, CDCl$_3$):

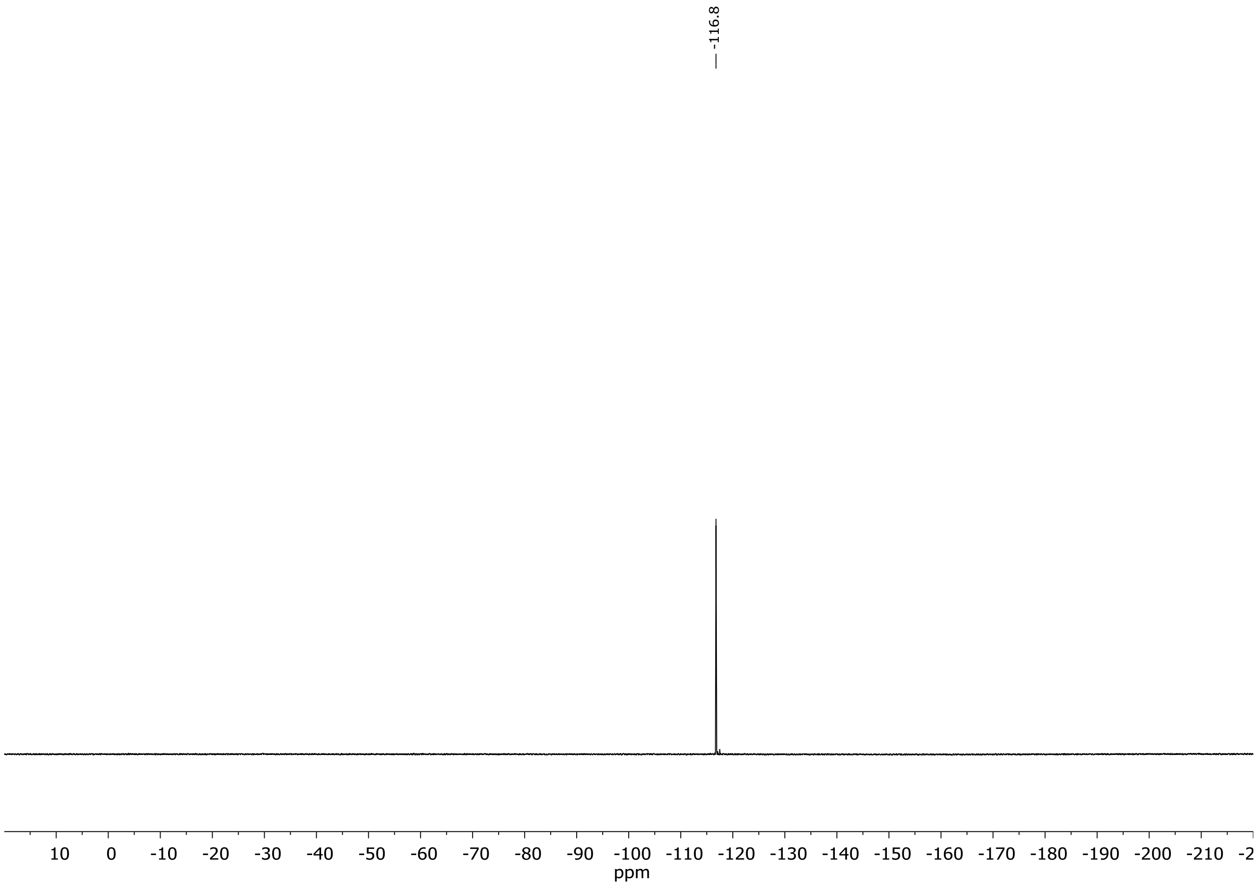




Compound **172e**: ^{1}H NMR (400 MHz, CDCl$_3$), ^{13}C NMR (101 MHz, CDCl$_3$) and ^{19}F NMR (376 MHz, CDCl$_3$):



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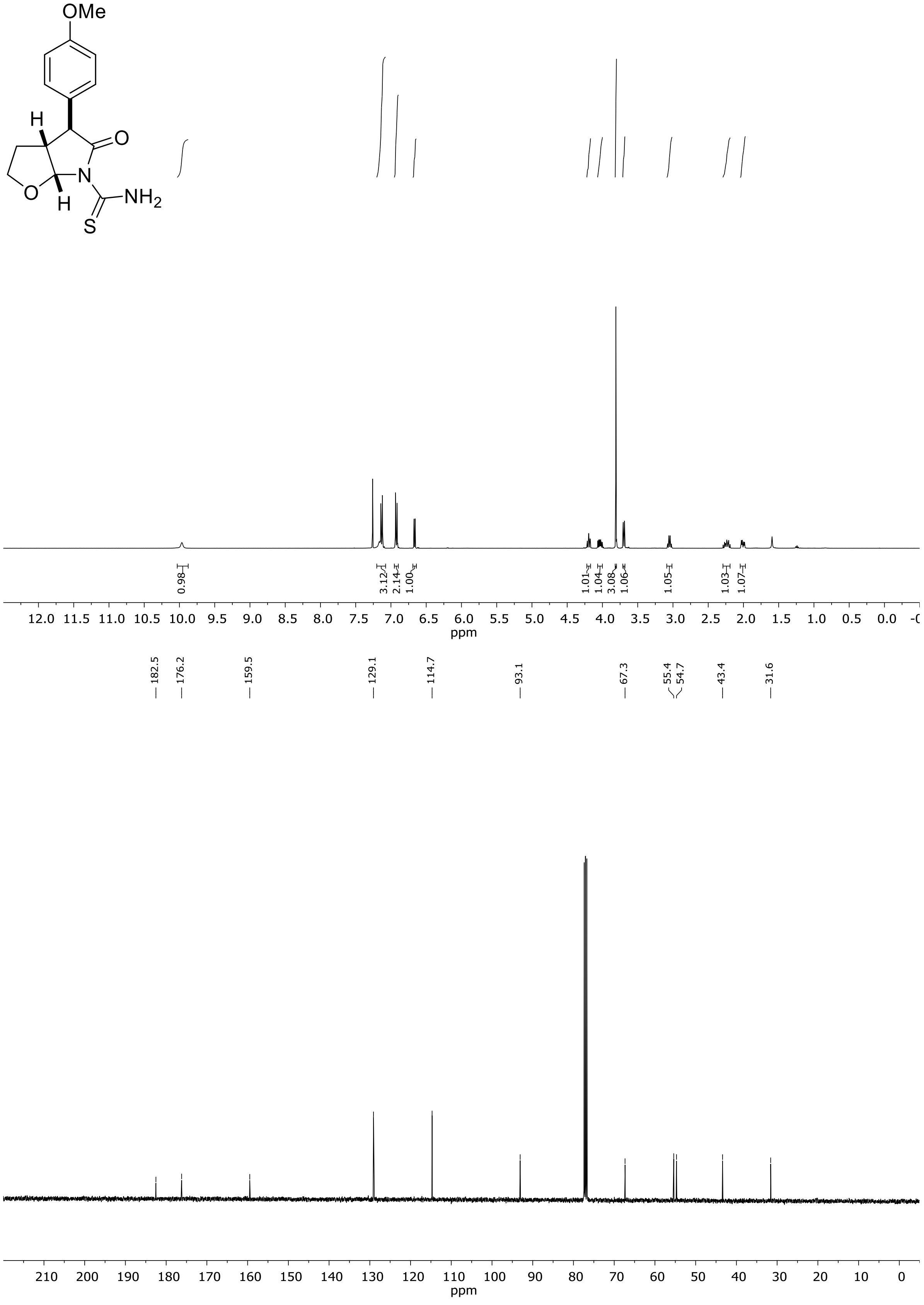
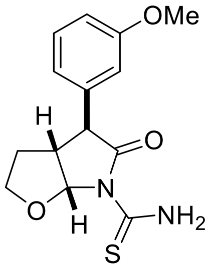
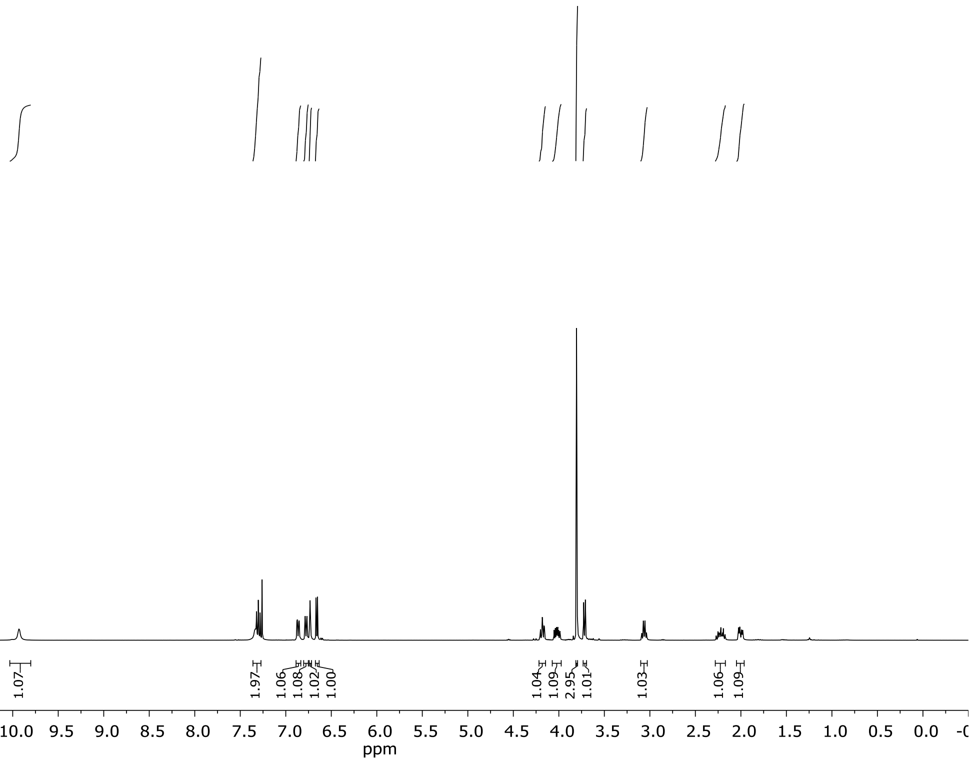
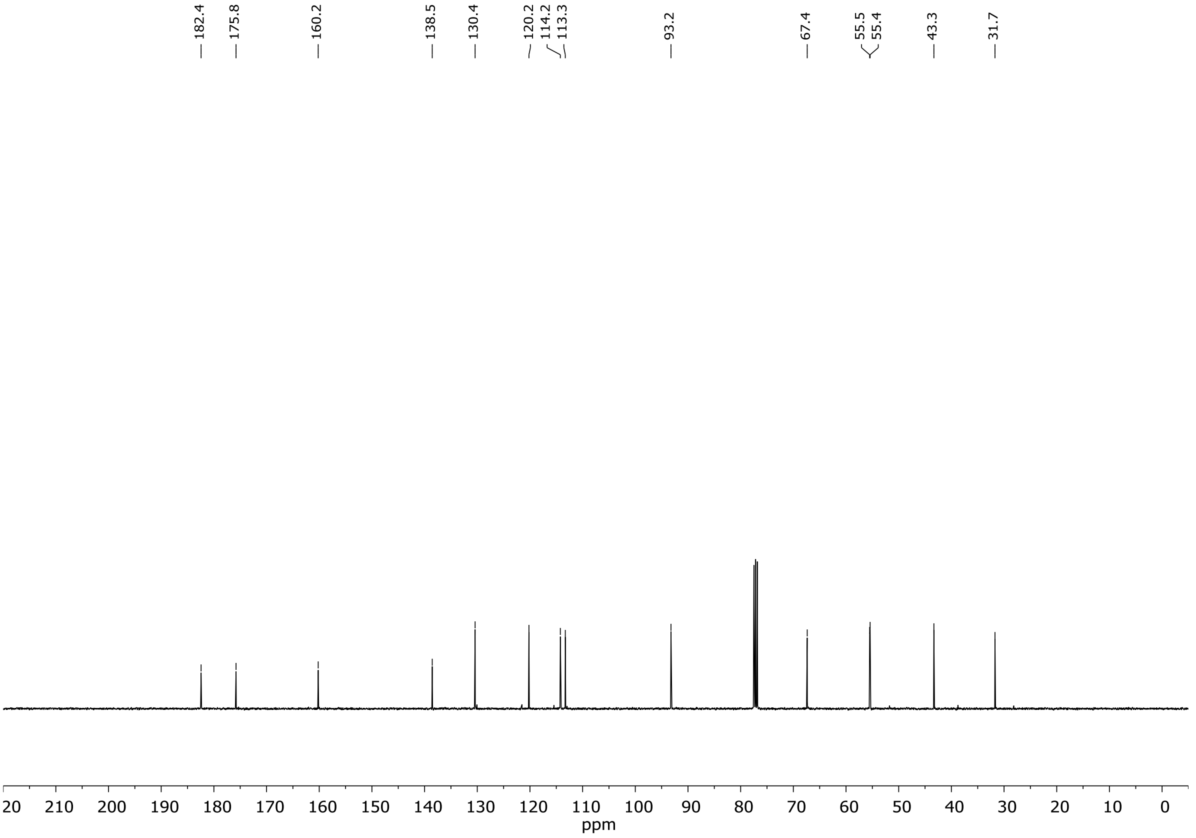
<u>Compound **172f**</u>: ^{1}H NMR (400 MHz, $CDCl_3$) and ^{13}C NMR (101 MHz, $CDCl_3$):



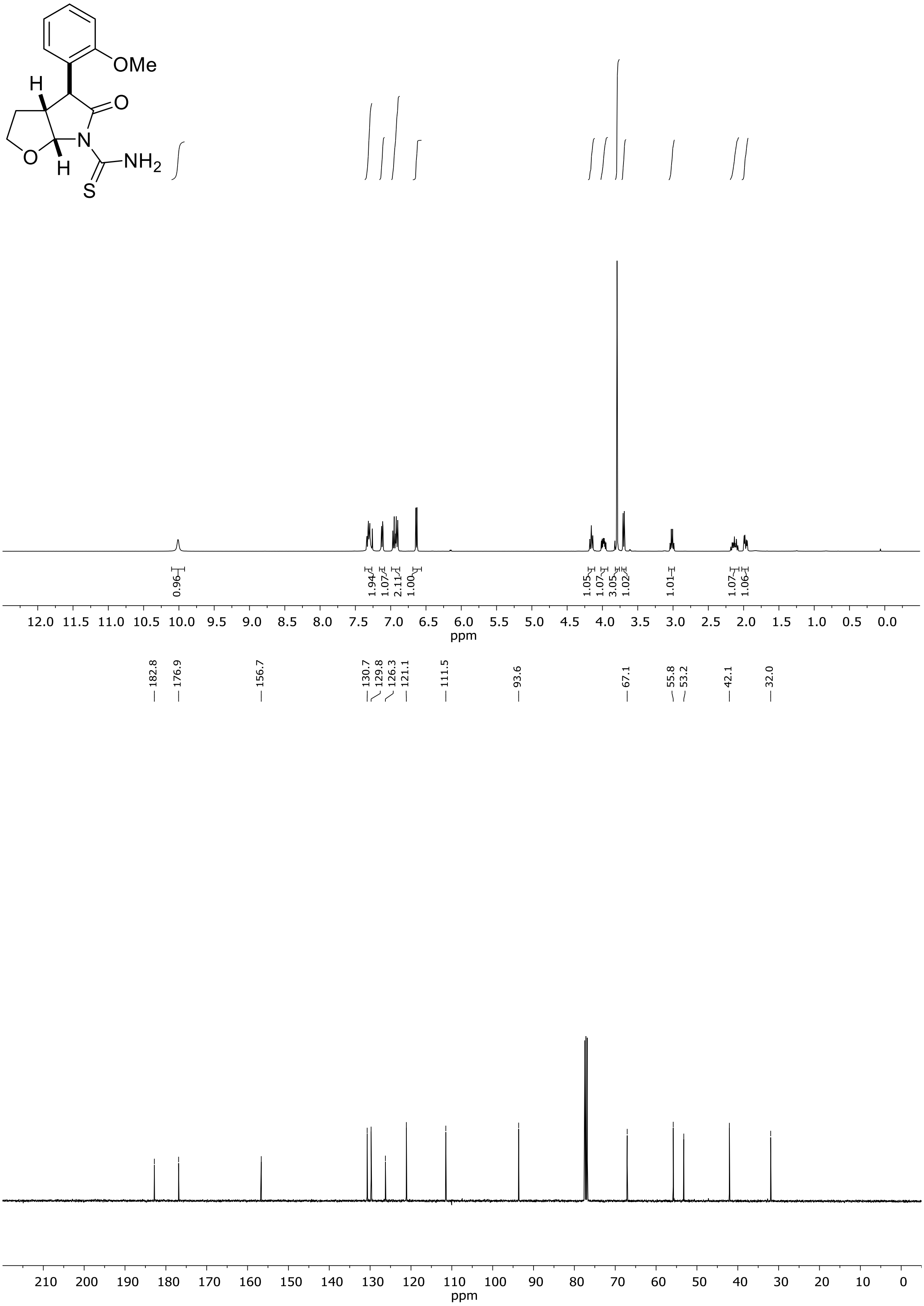
Compound **172g**: ^{1}H NMR (400 MHz, CDCl$_3$) and ^{13}C NMR (101 MHz, CDCl$_3$):



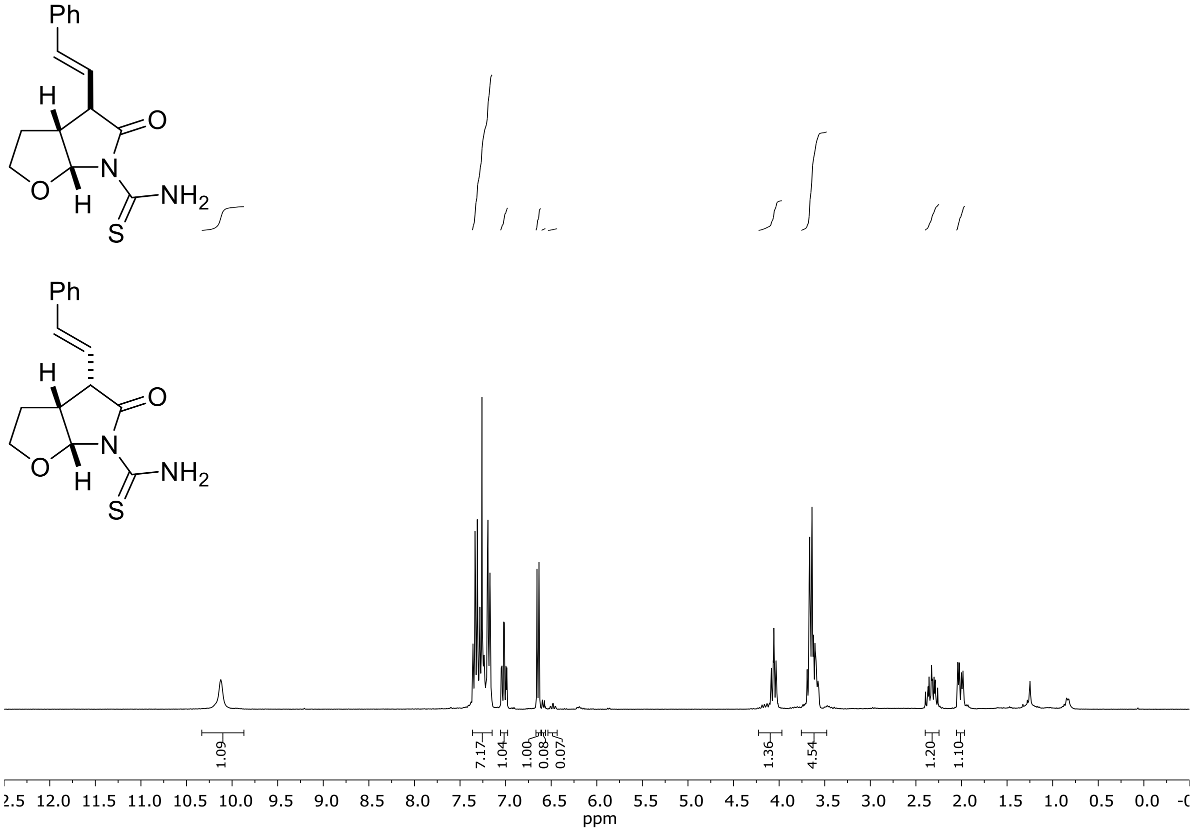


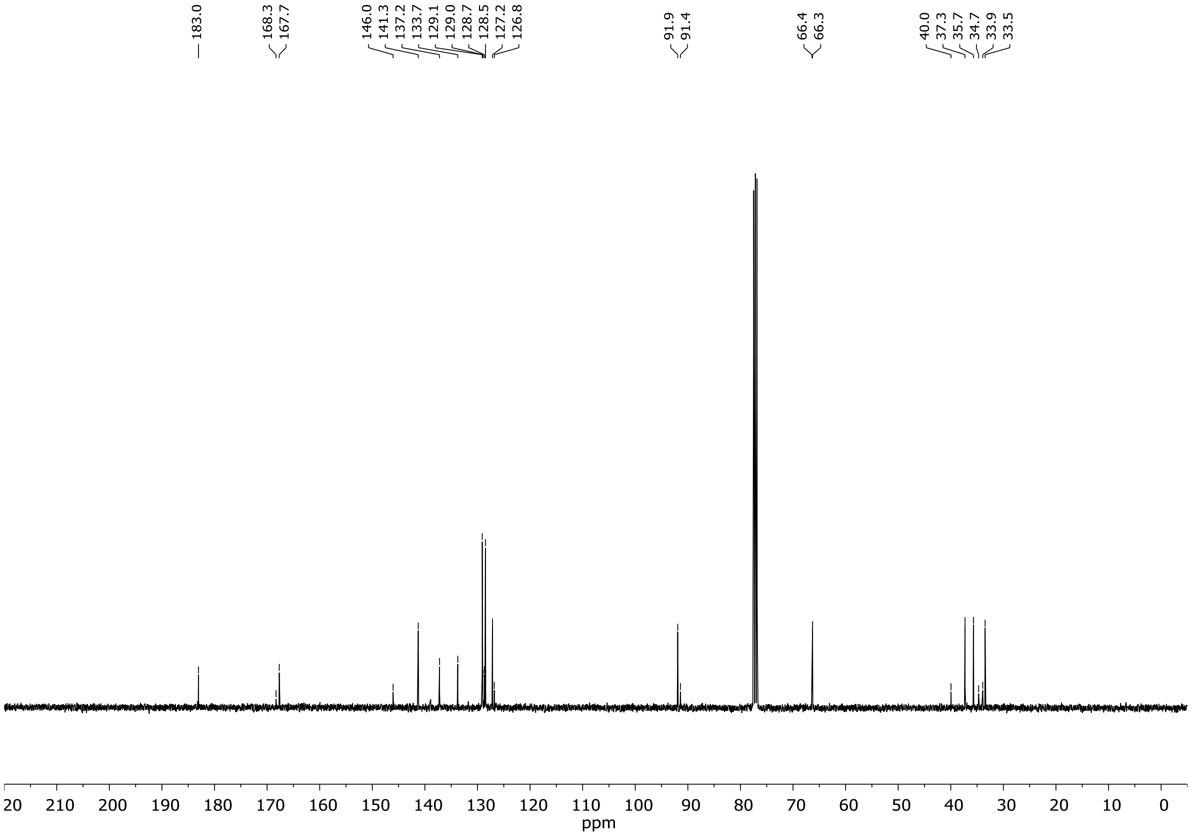


Compound **172h**: ^{1}H NMR (400 MHz, CDCl$_3$) and ^{13}C NMR (101 MHz, CDCl$_3$):

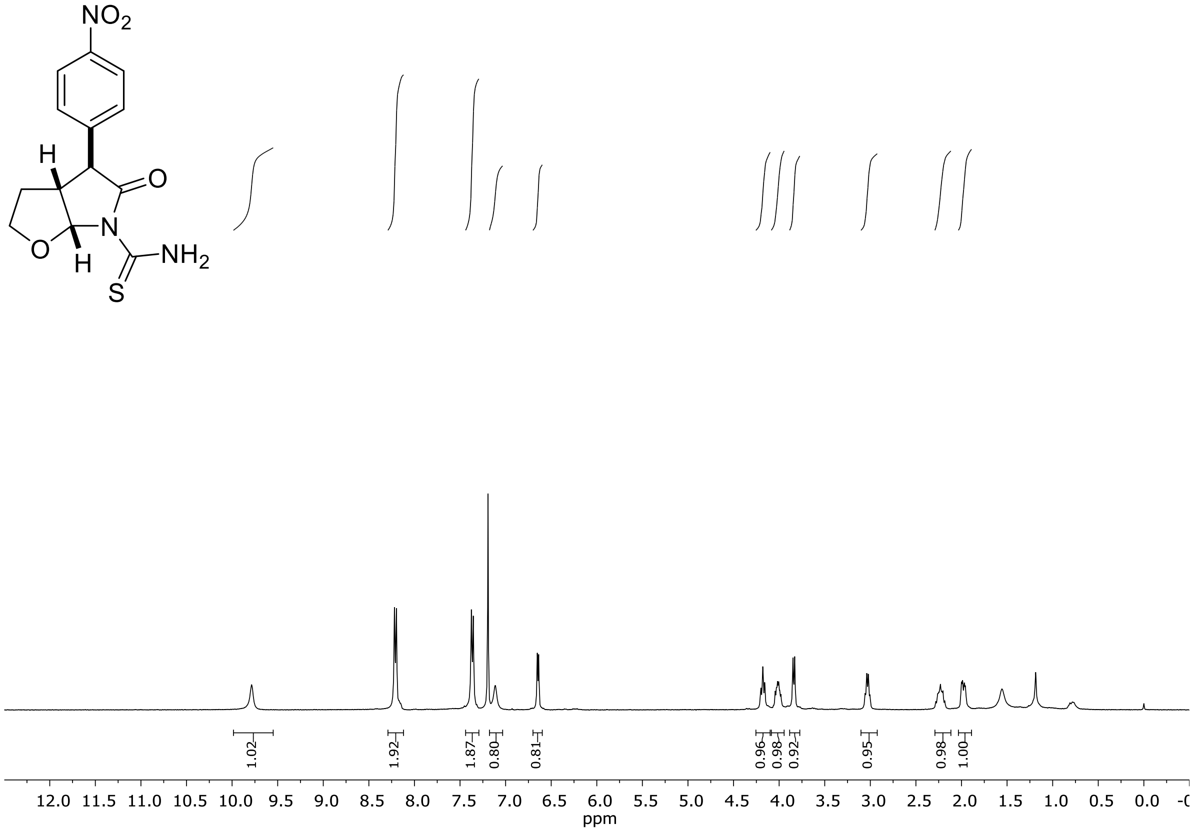


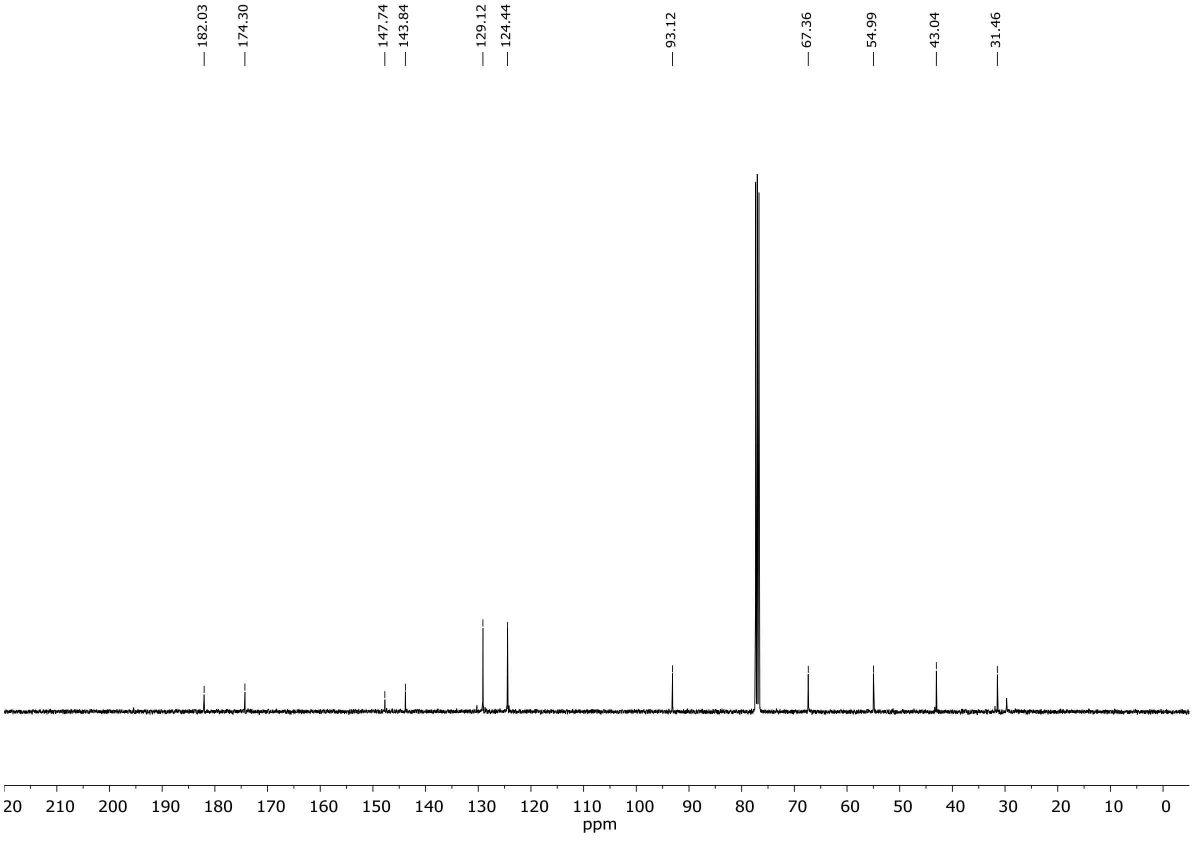
Compounds **172i** and **172ii**: ^{1}H NMR (400 MHz, CDCl$_3$) and ^{13}C NMR (101 MHz, CDCl$_3$):



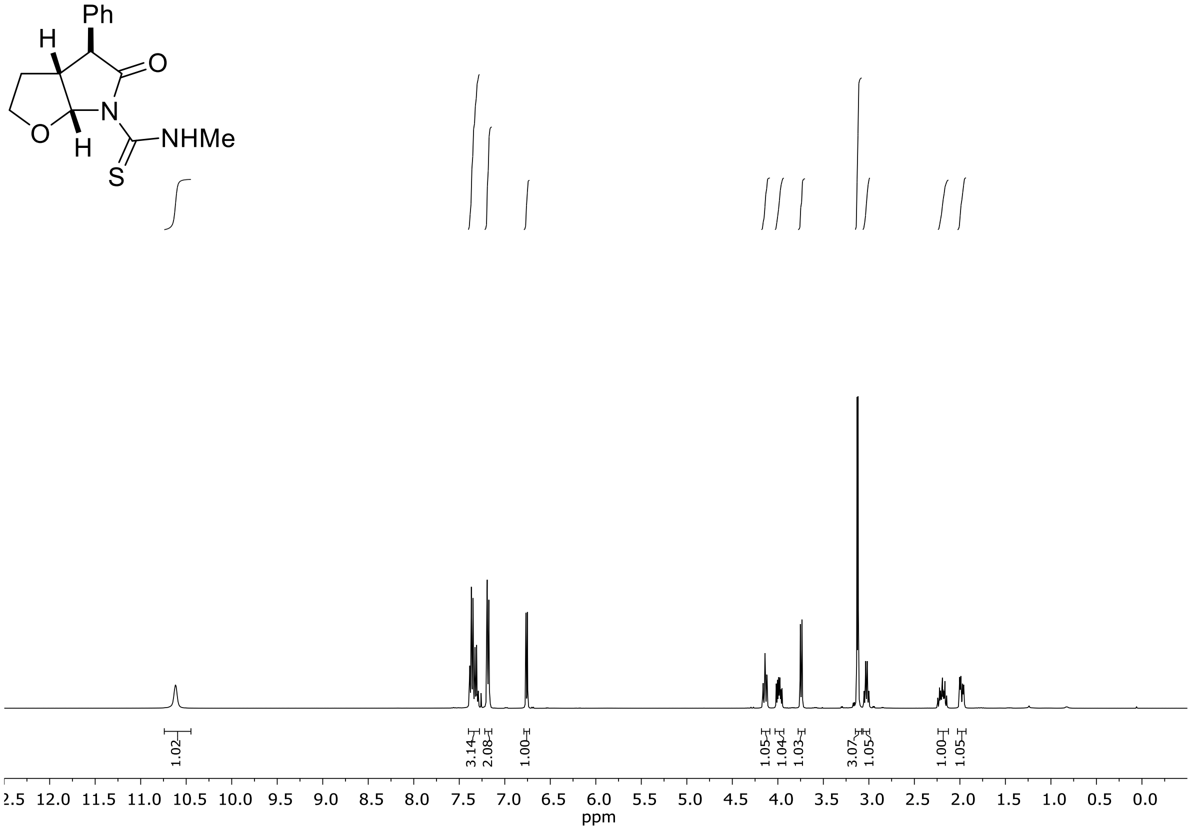


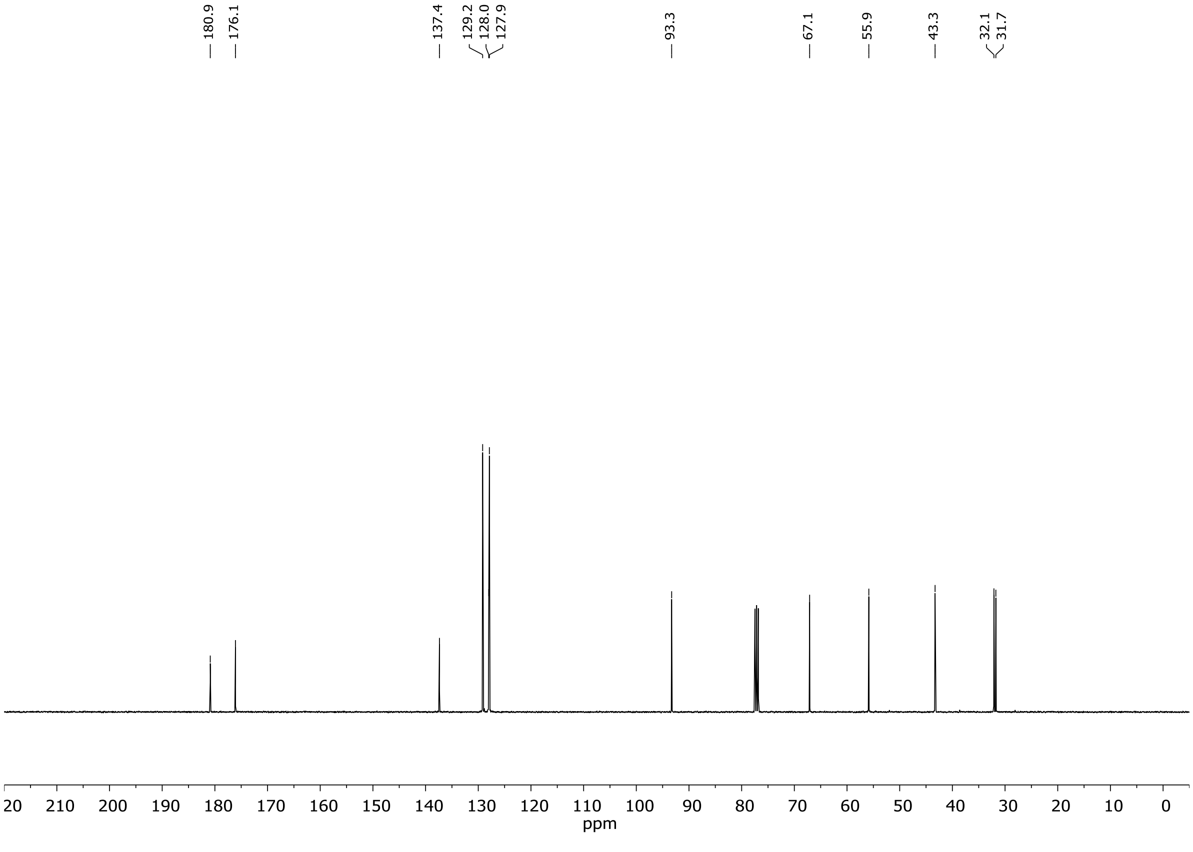
Compound **172j**: ^{1}H NMR (400 MHz, CDCl$_3$) and ^{13}C NMR (101 MHz, CDCl$_3$):



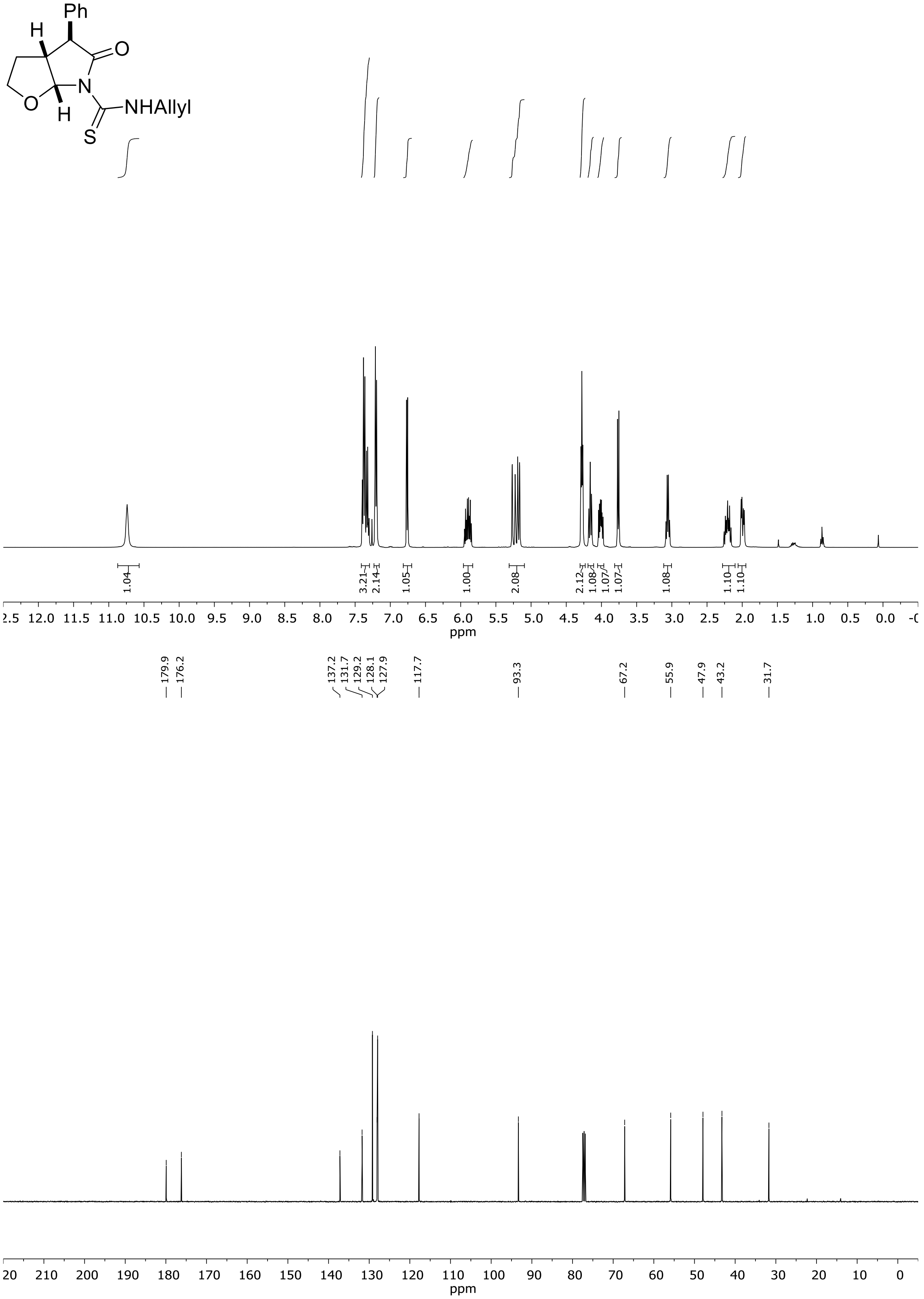


Compound **172k**: ^1H NMR (400 MHz, $CDCl_3$) and ^{13}C NMR (101 MHz, $CDCl_3$):

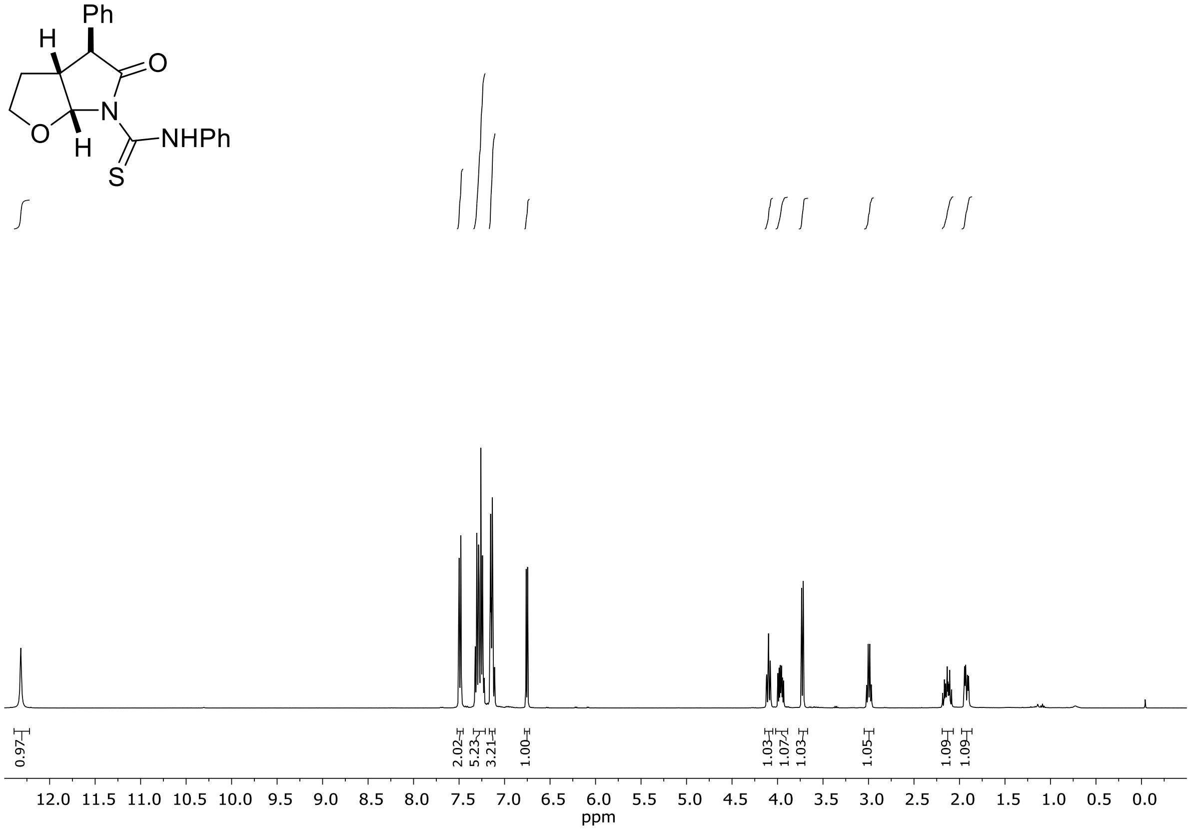


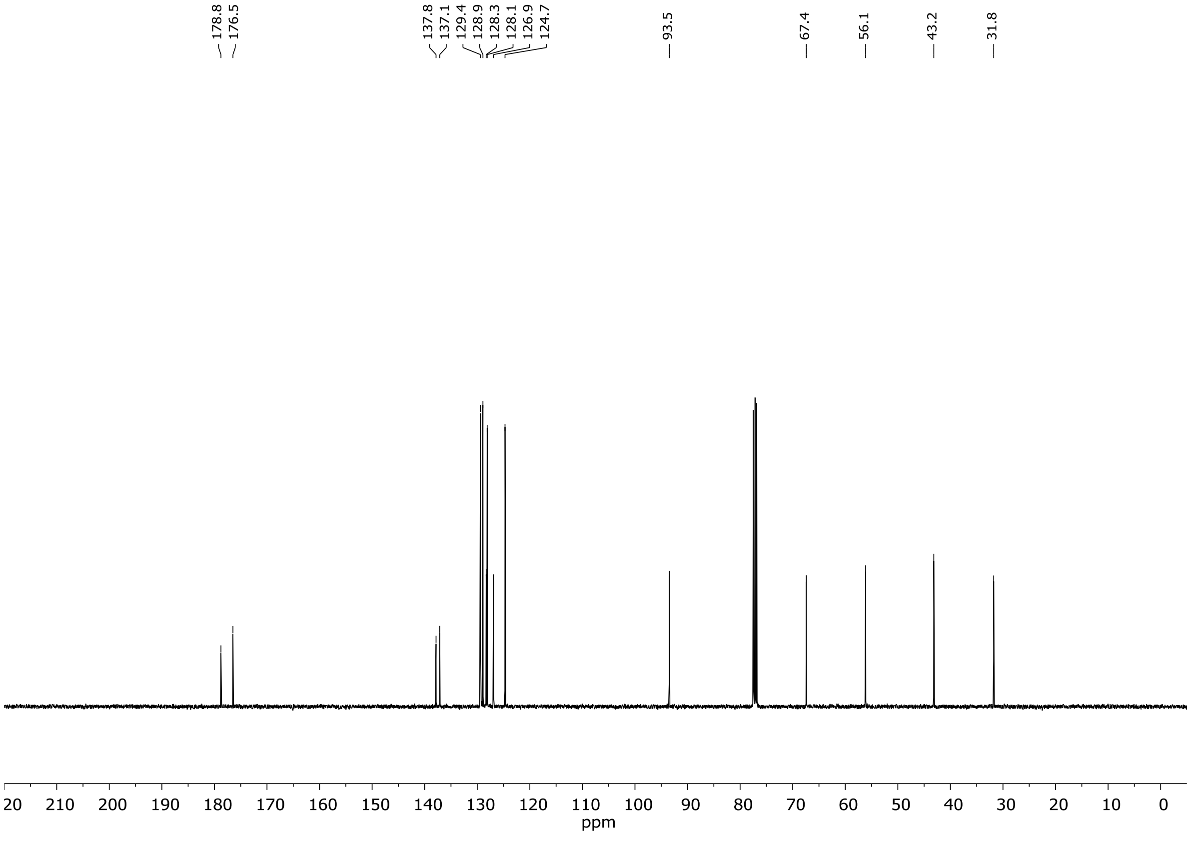


Compound **172l**: ^{1}H NMR (400 MHz, $CDCl_3$) and ^{13}C NMR (101 MHz, $CDCl_3$):

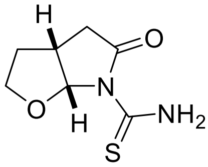


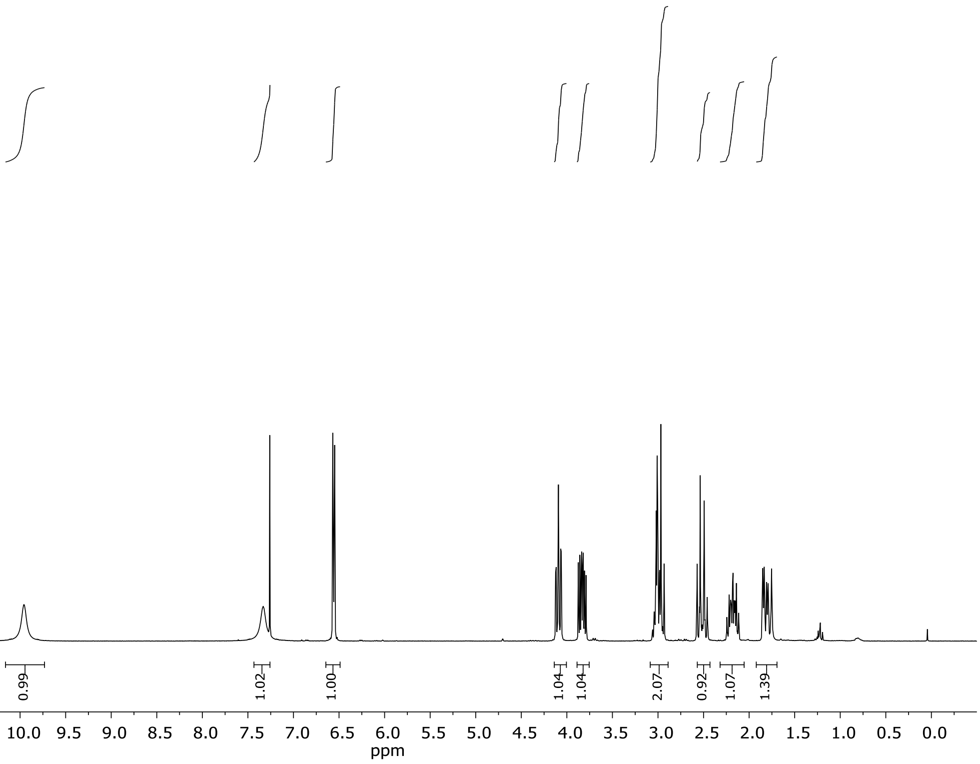
Compound **172m**: ^{1}H NMR (400 MHz, CDCl$_3$) and ^{13}C NMR (101 MHz, CDCl$_3$):

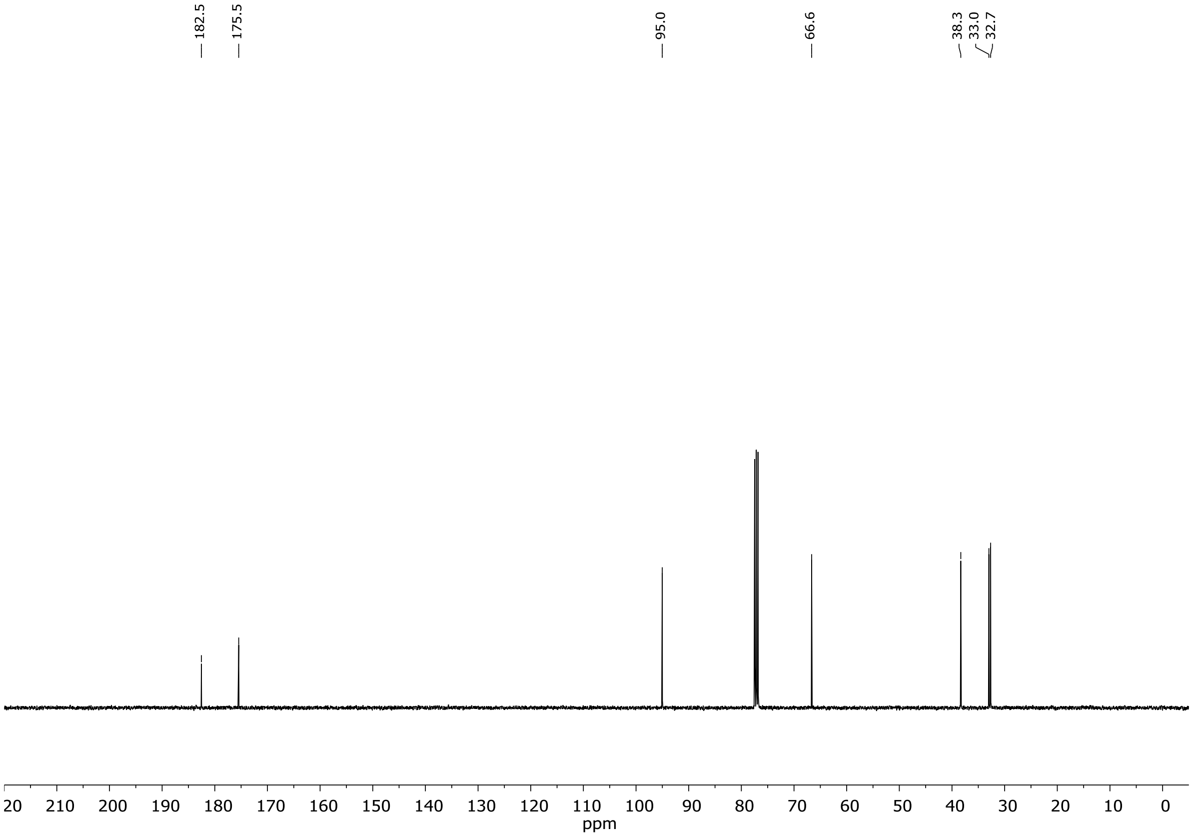




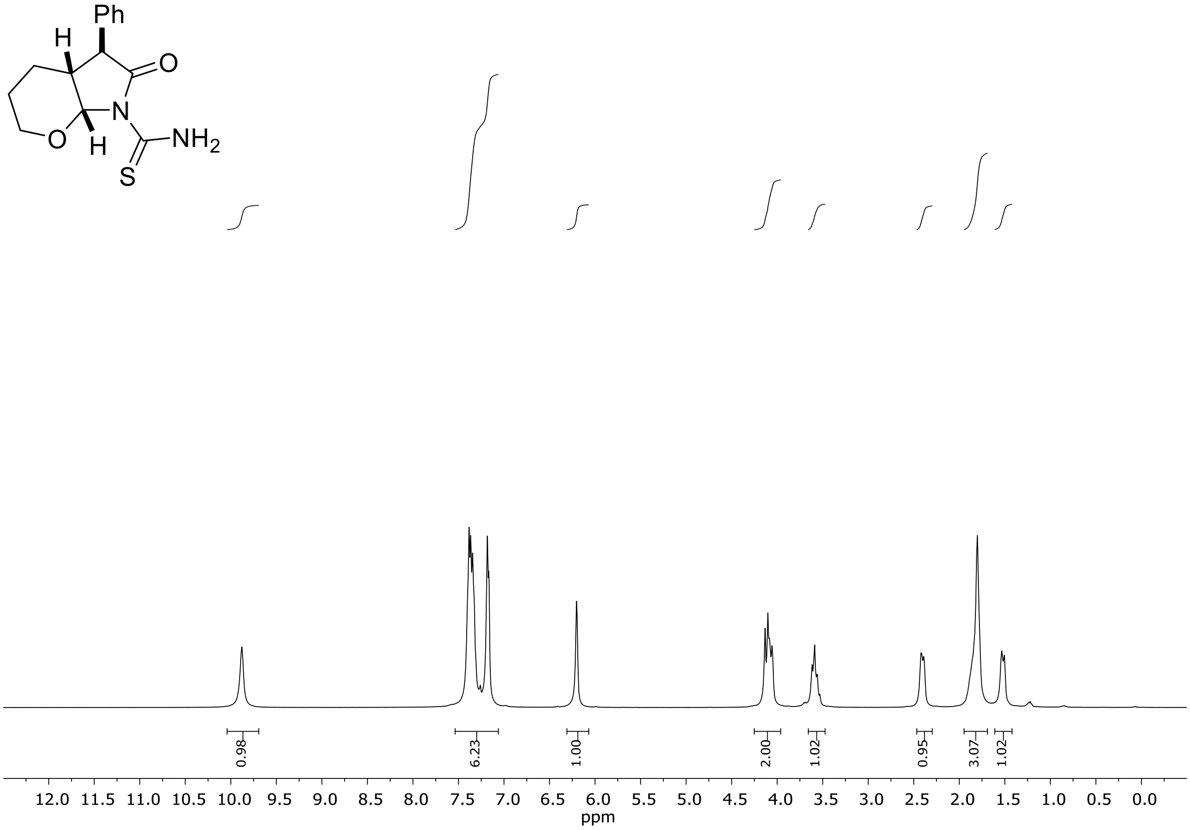
Compound **172n**: ^{1}H NMR (400 MHz, CDCl$_3$) and ^{13}C NMR (101 MHz, CDCl$_3$):

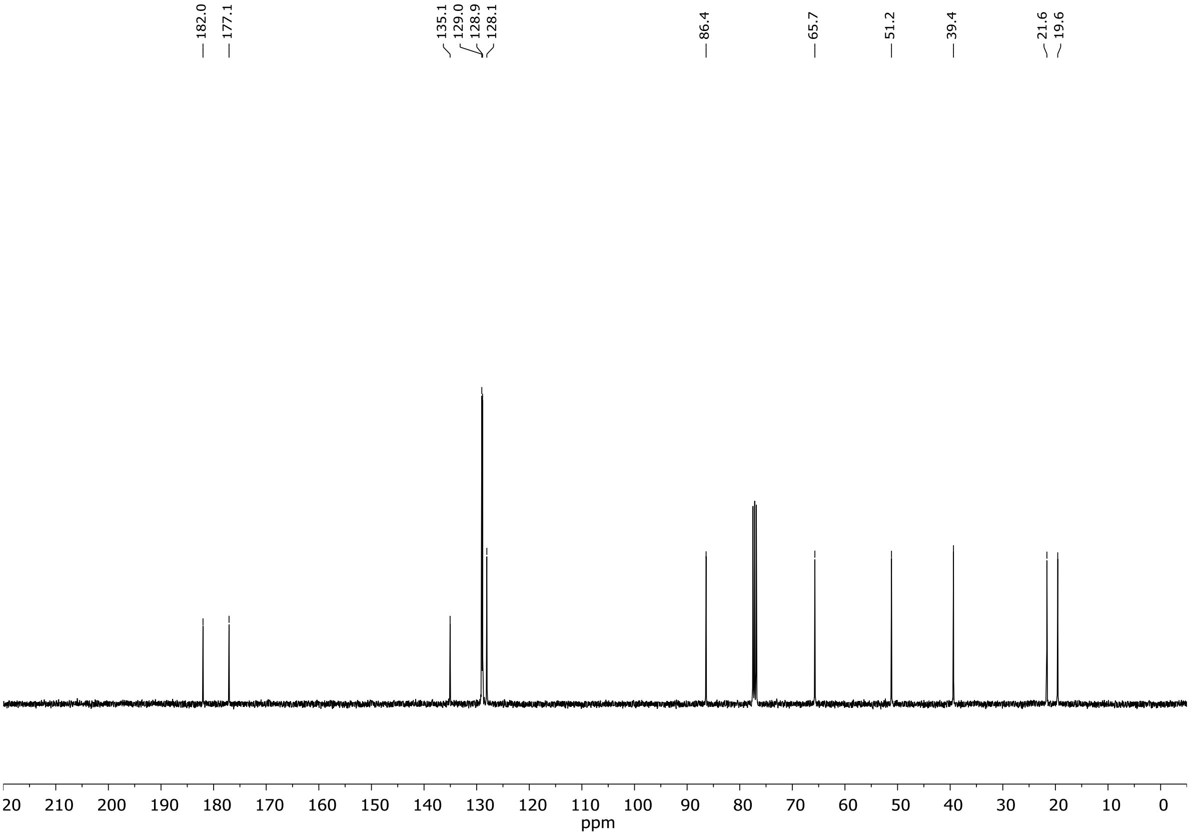




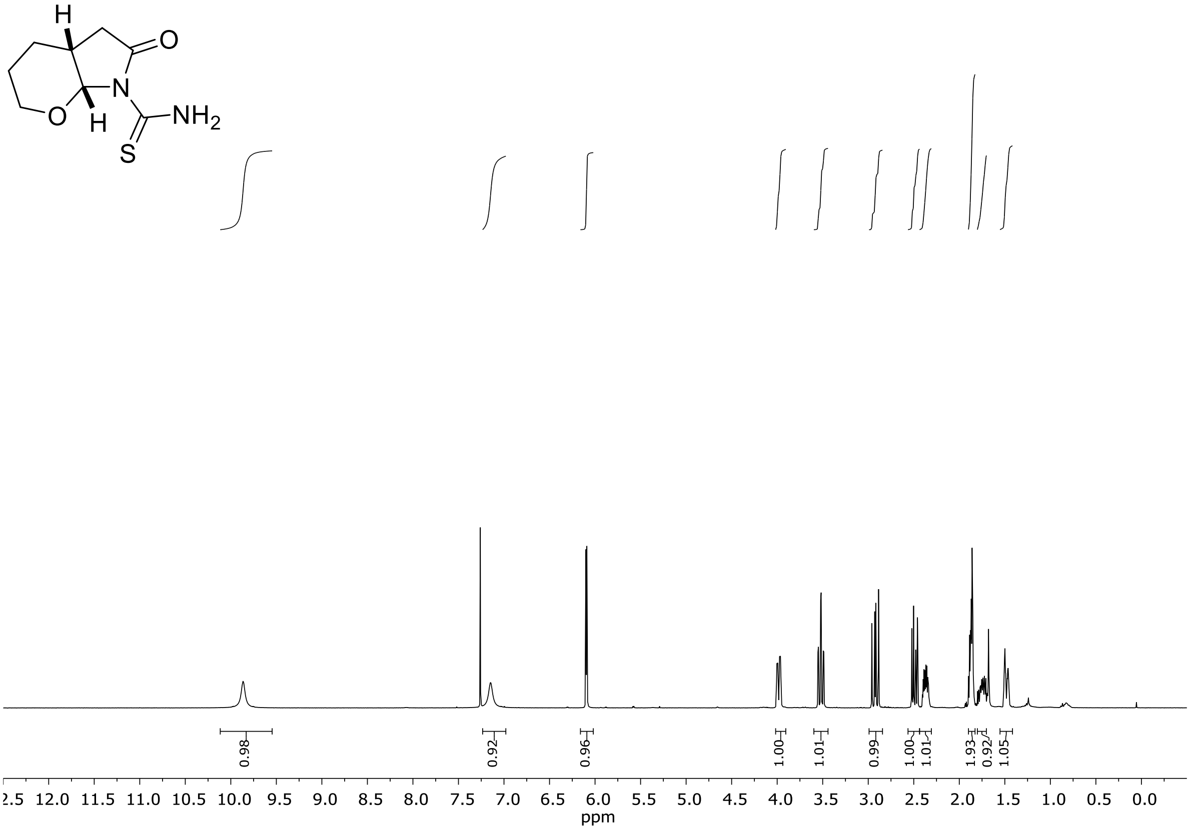


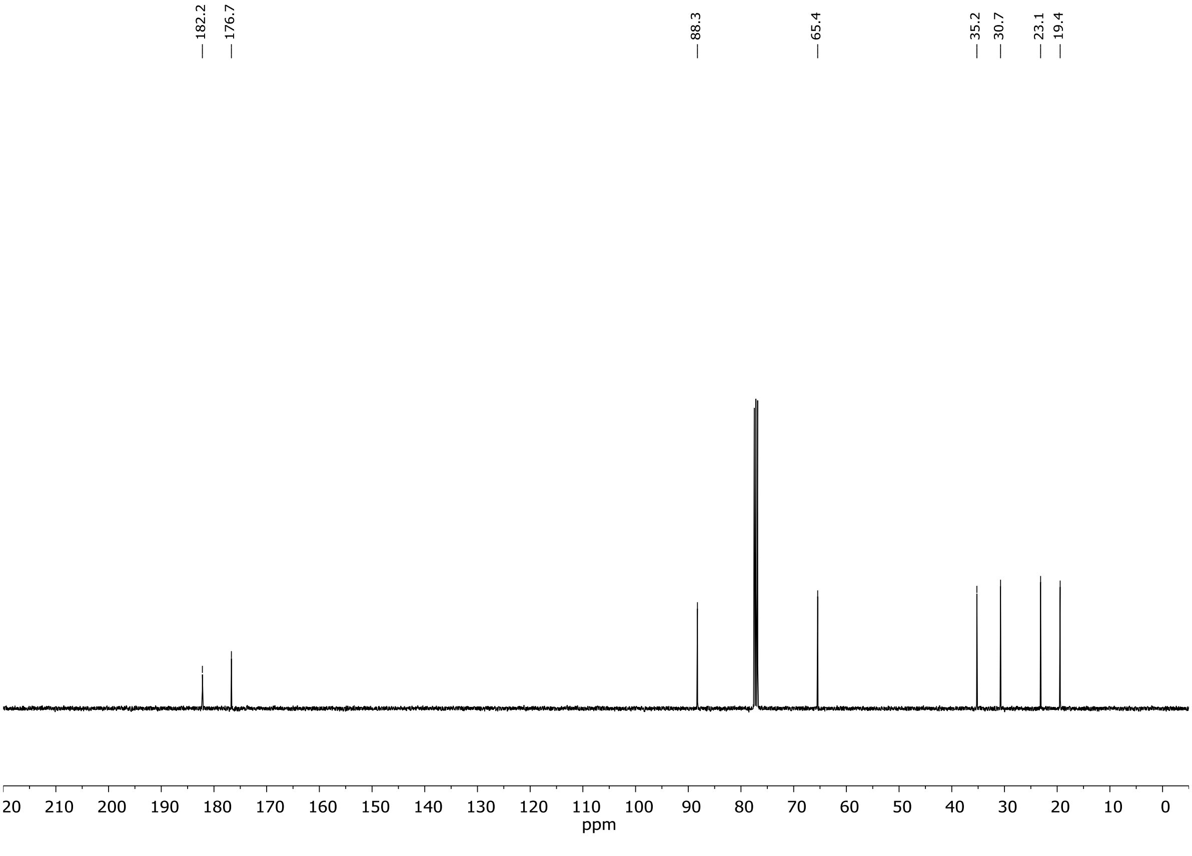
Compound **172o**: ^{1}H NMR (400 MHz, CDCl$_3$) and ^{13}C NMR (101 MHz, CDCl$_3$):



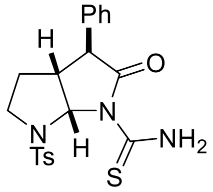


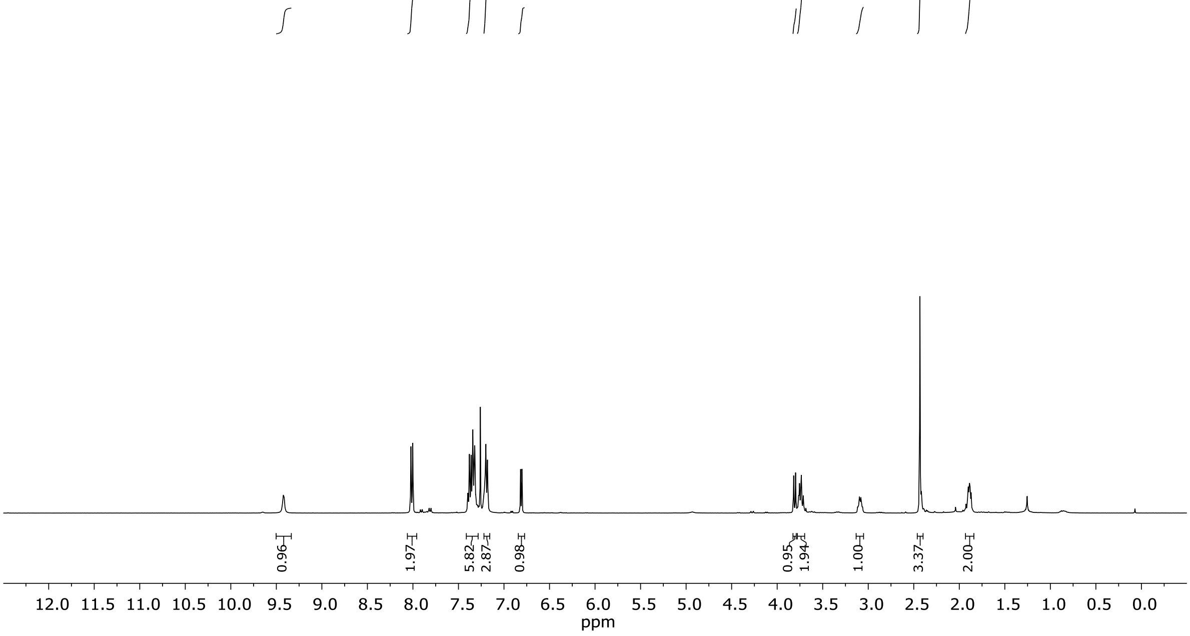
Compound **172p**: ^{1}H NMR (400 MHz, $CDCl_3$) and ^{13}C NMR (101 MHz, $CDCl_3$):

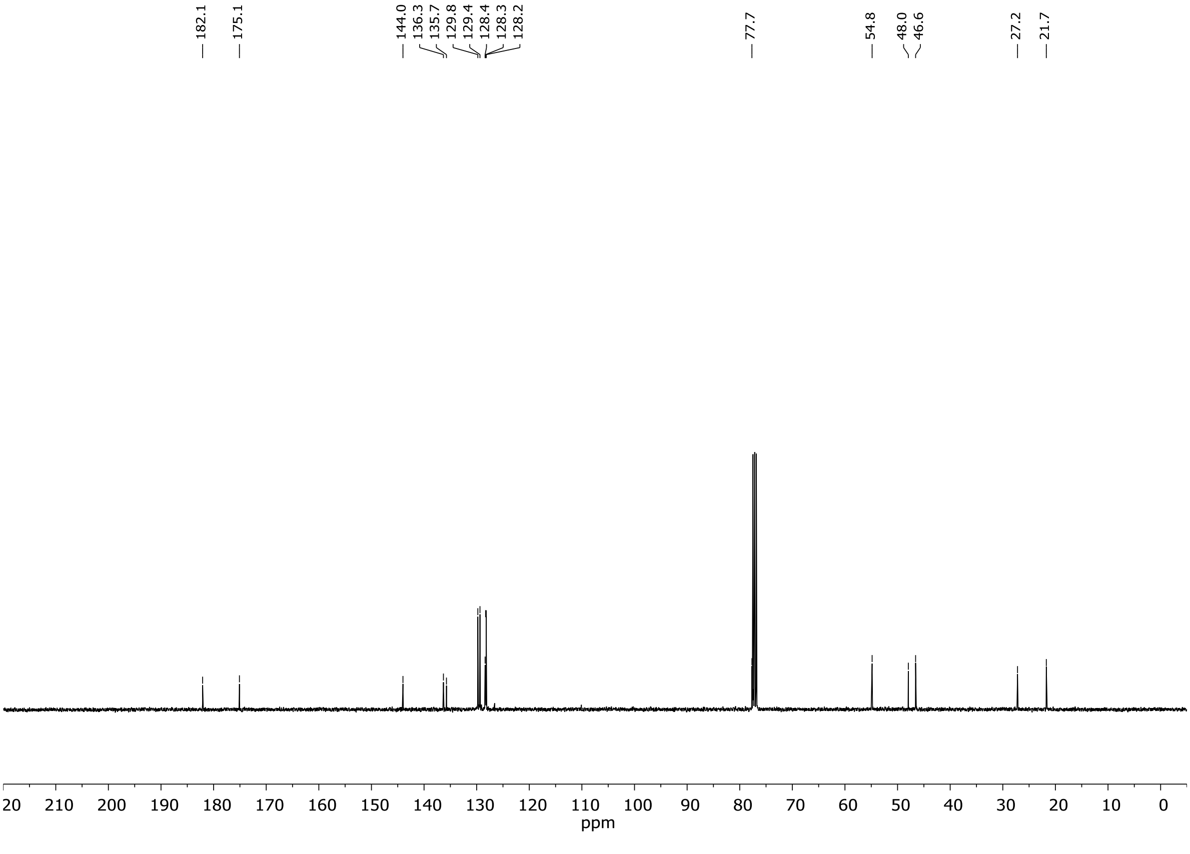




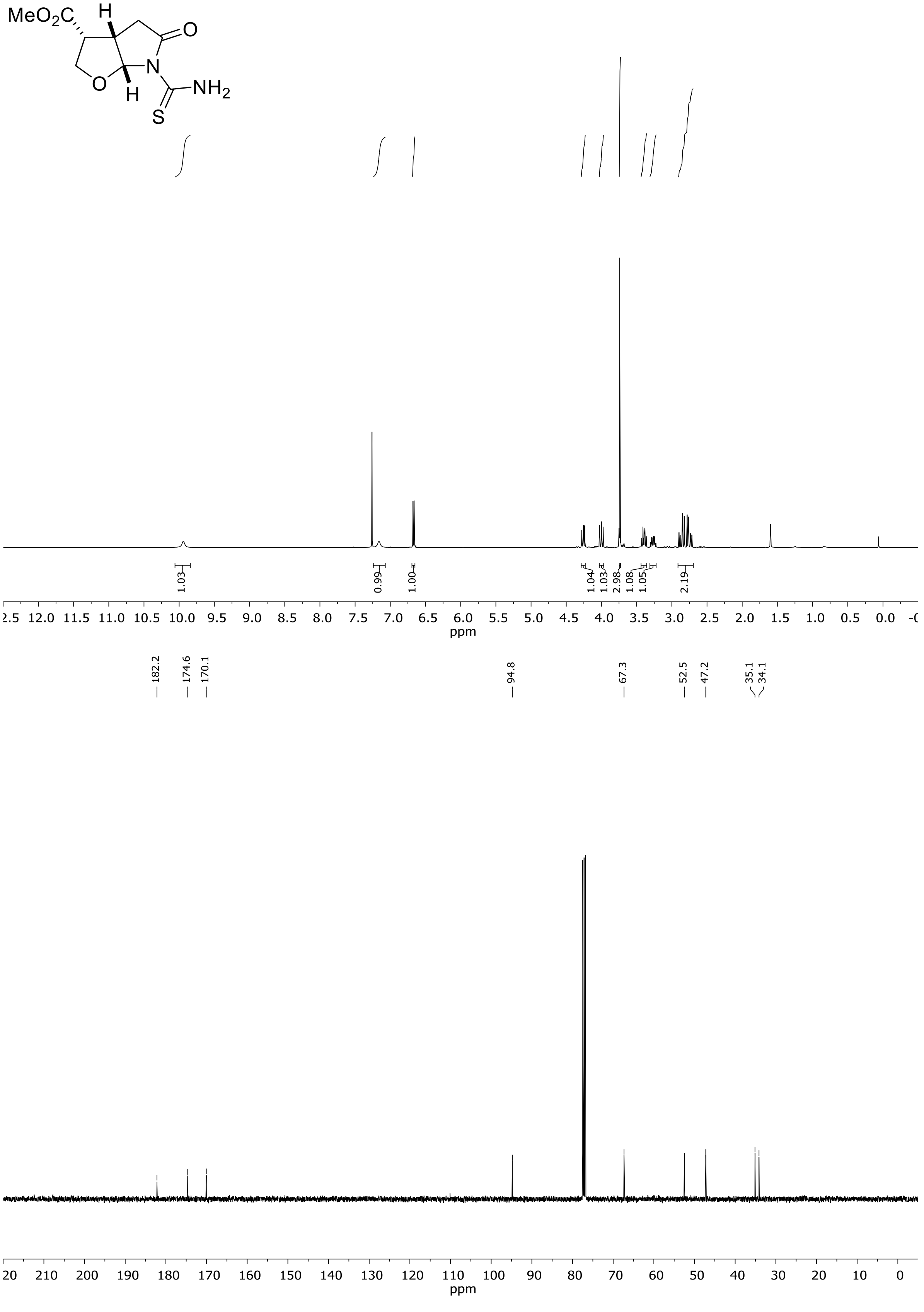
Compound **172q**: ^{1}H NMR (400 MHz, $CDCl_3$) and ^{13}C NMR (101 MHz, $CDCl_3$):



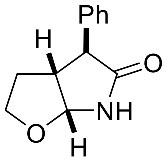


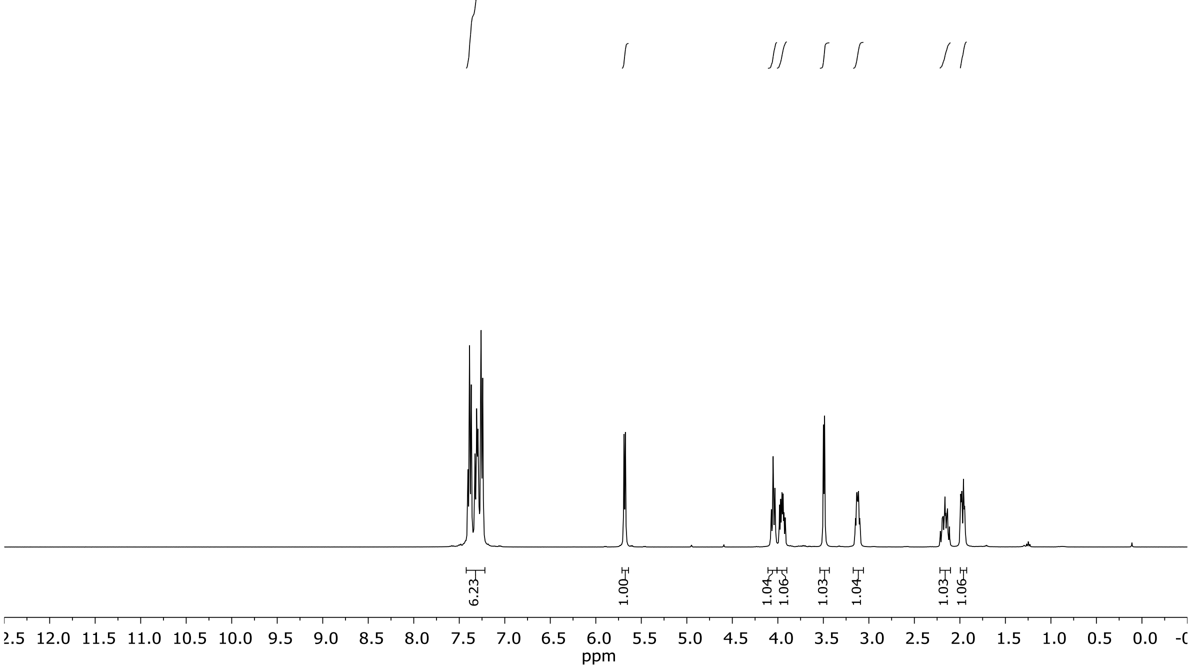


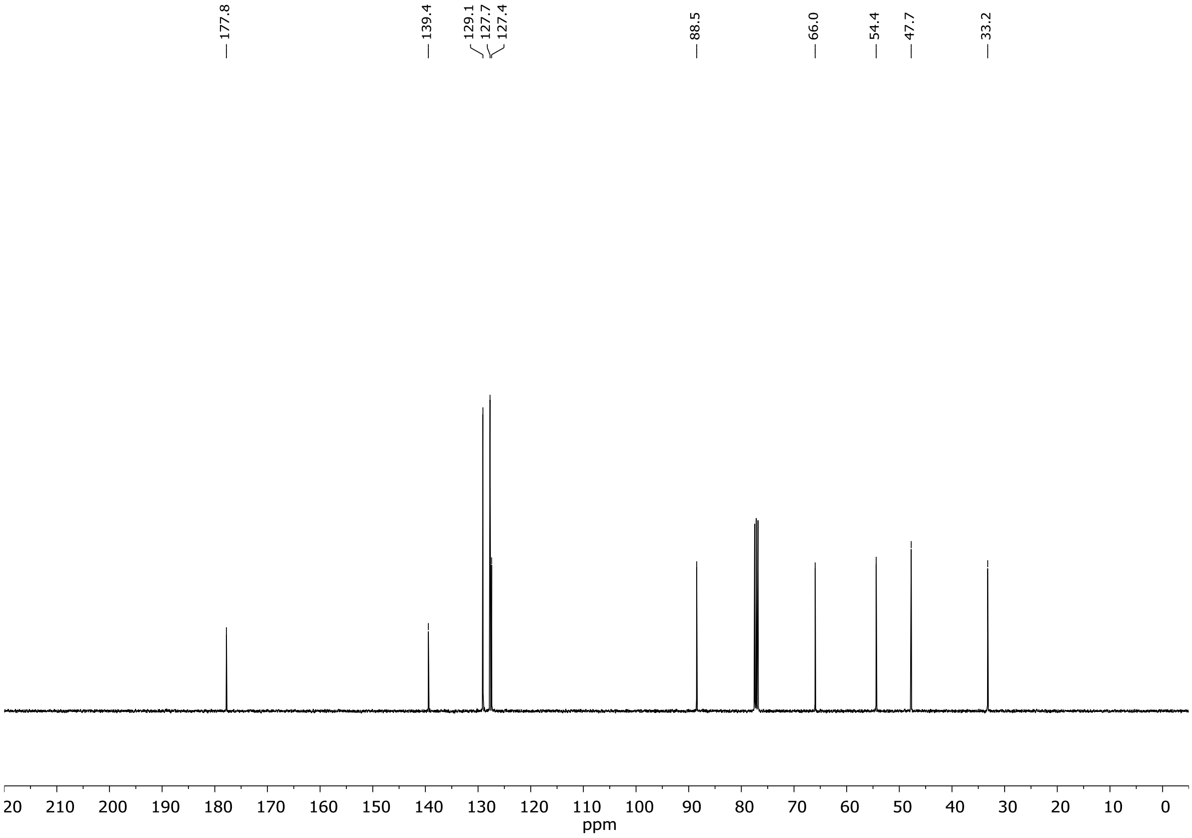
Compound **172s**: ^{1}H NMR (400 MHz, CDCl$_3$) and ^{13}C NMR (101 MHz, CDCl$_3$):



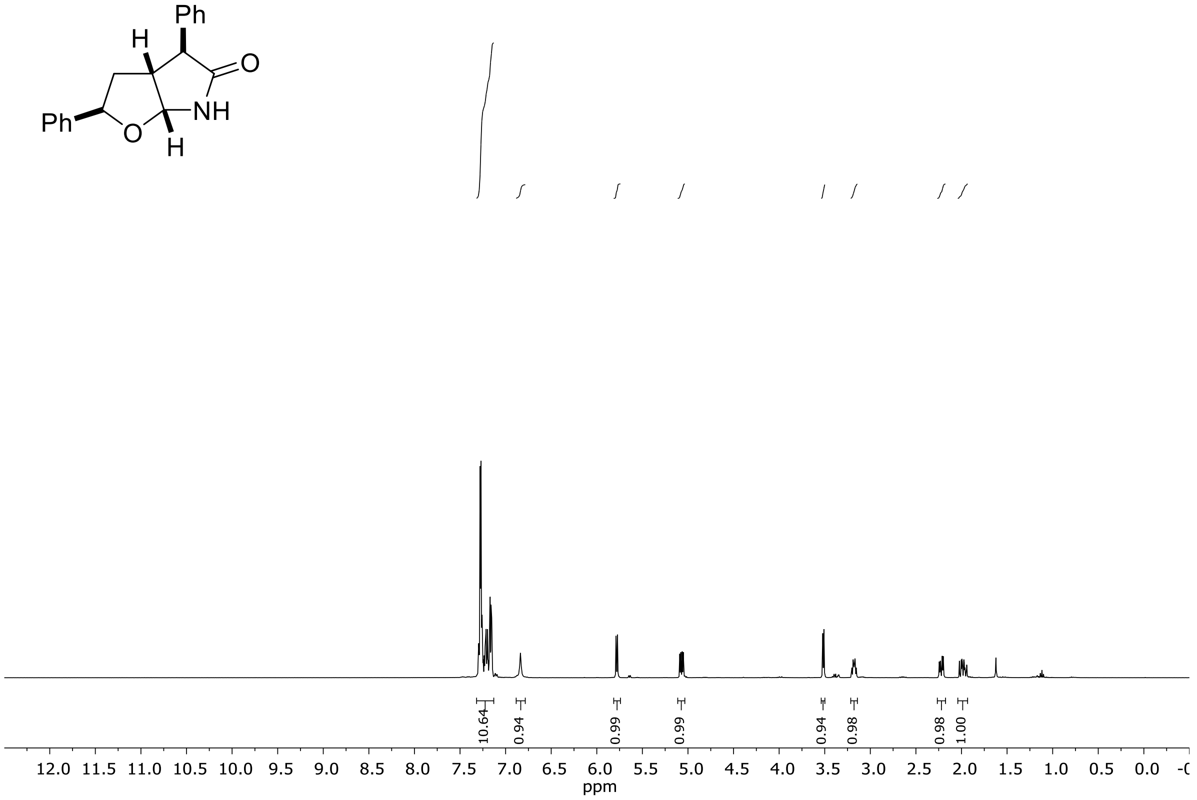
Compound **179a**: ^{1}H NMR (400 MHz, CDCl$_3$) and ^{13}C NMR (101 MHz, CDCl$_3$):

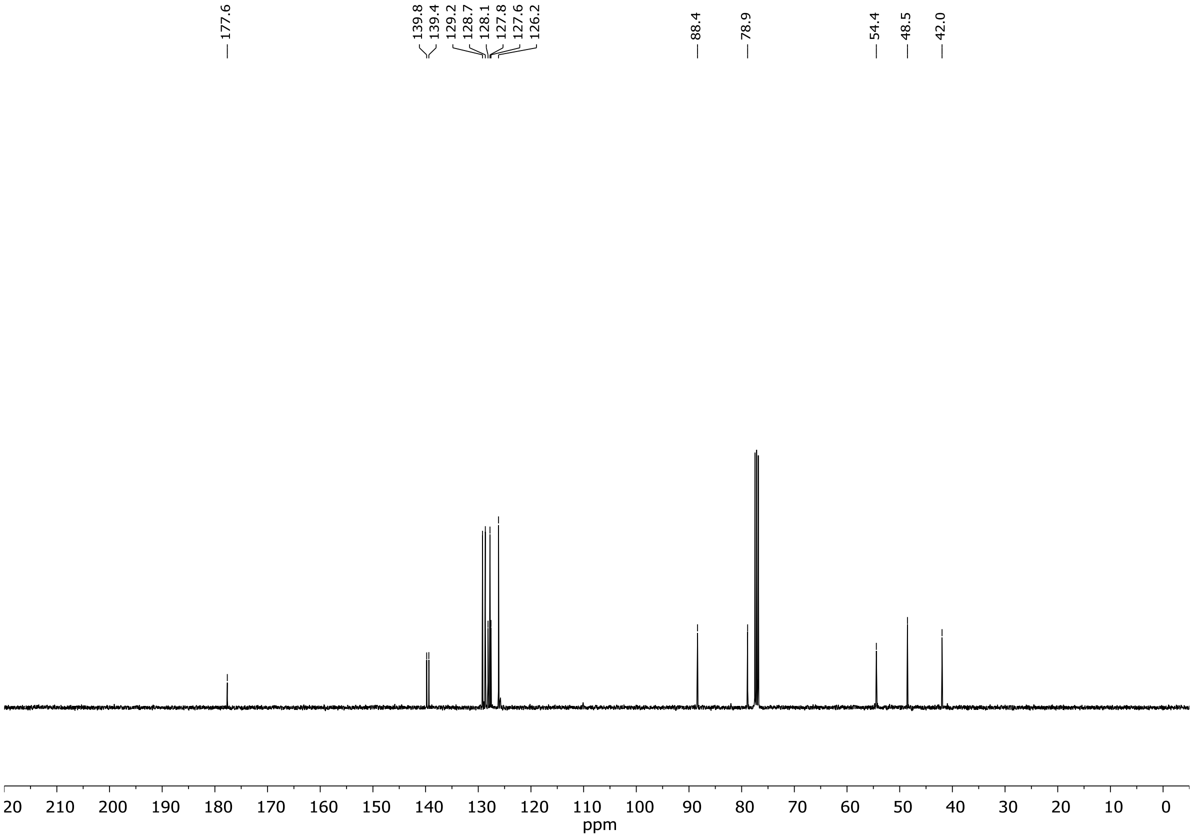




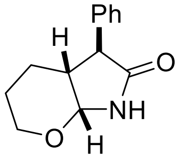


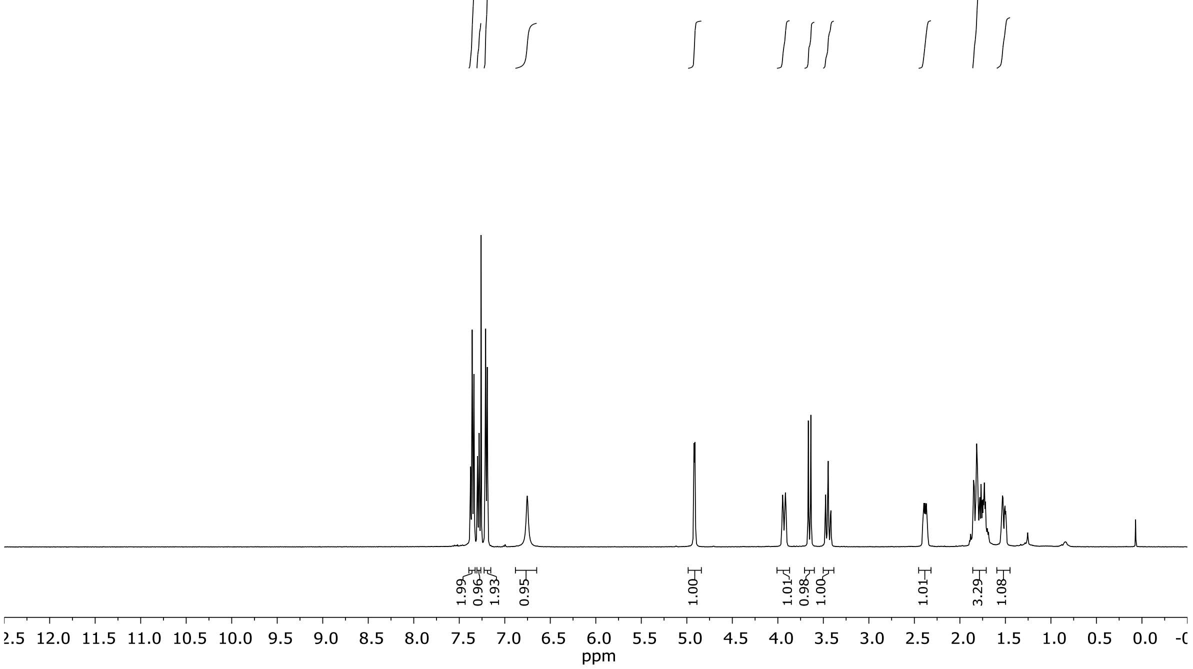
Compound **179b**: ^{1}H NMR (400 MHz, CDCl$_3$) and ^{13}C NMR (101 MHz, CDCl$_3$):

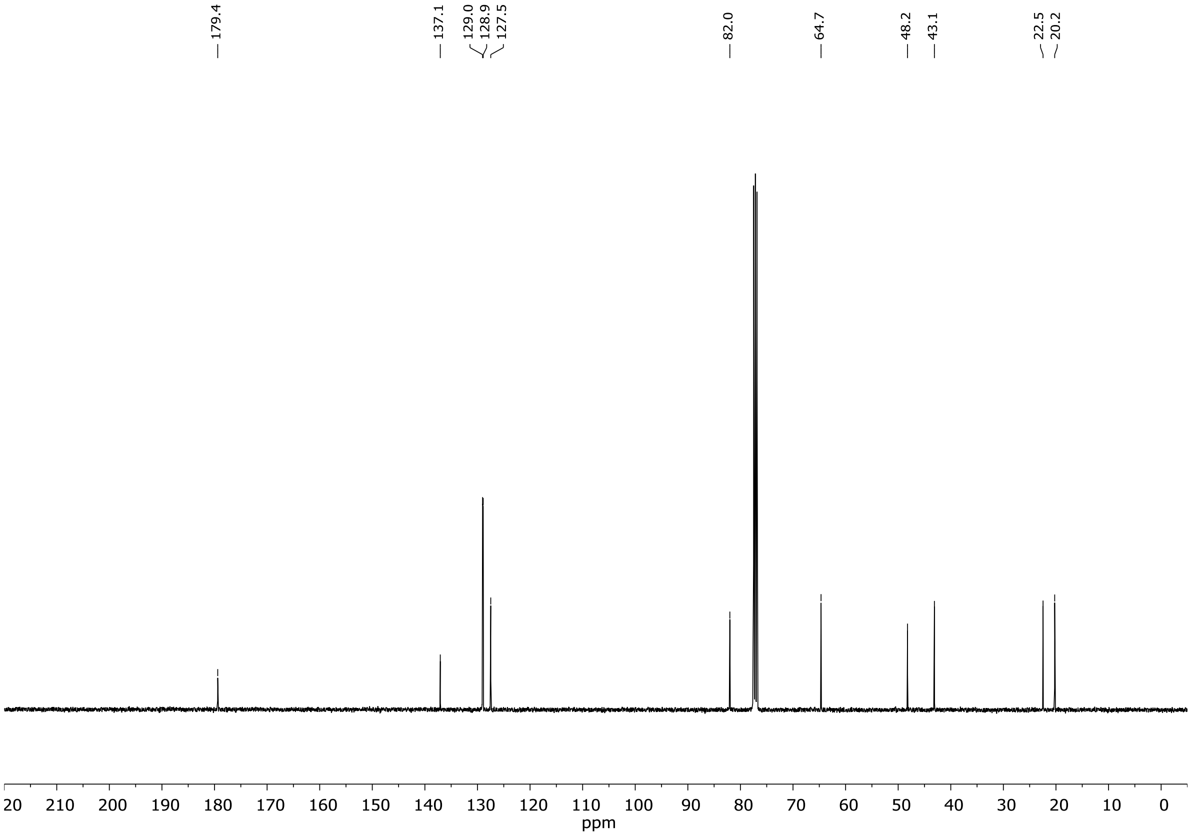




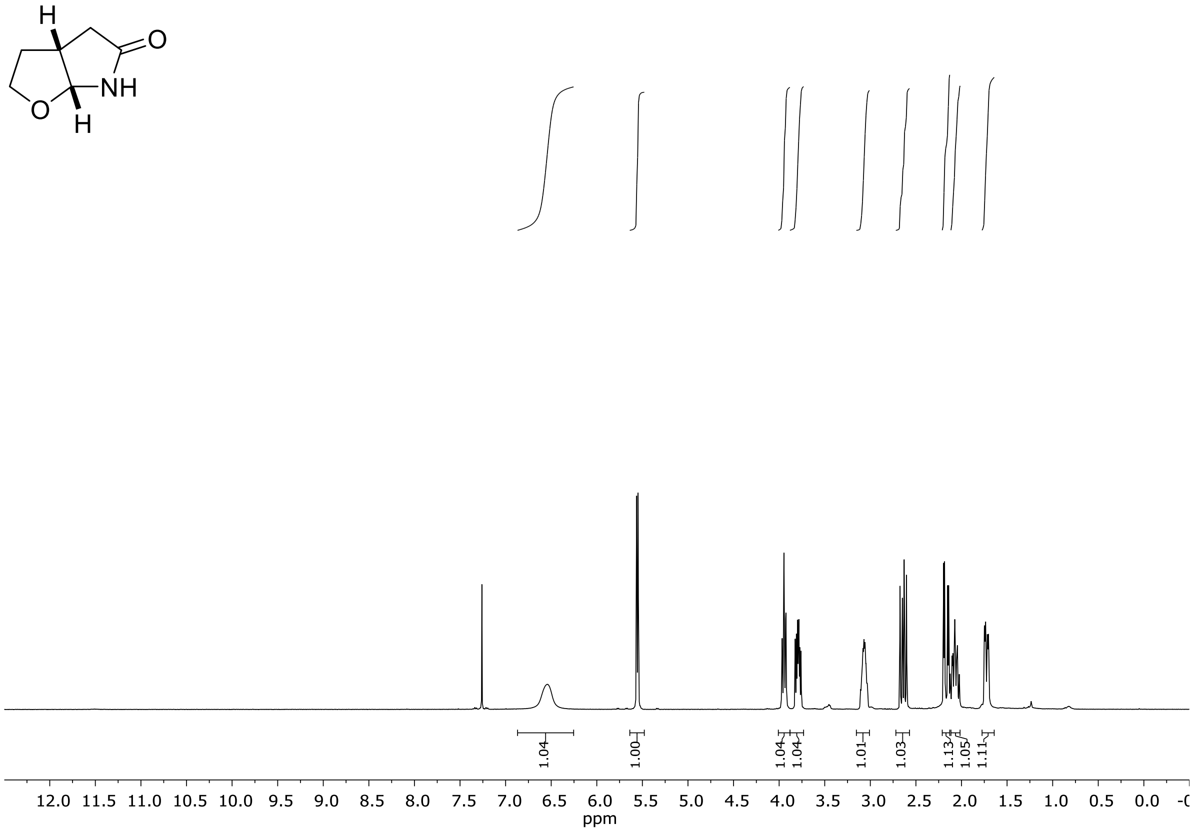
Compound **179c**: ^{1}H NMR (400 MHz, CDCl$_3$) and ^{13}C NMR (101 MHz, CDCl$_3$):

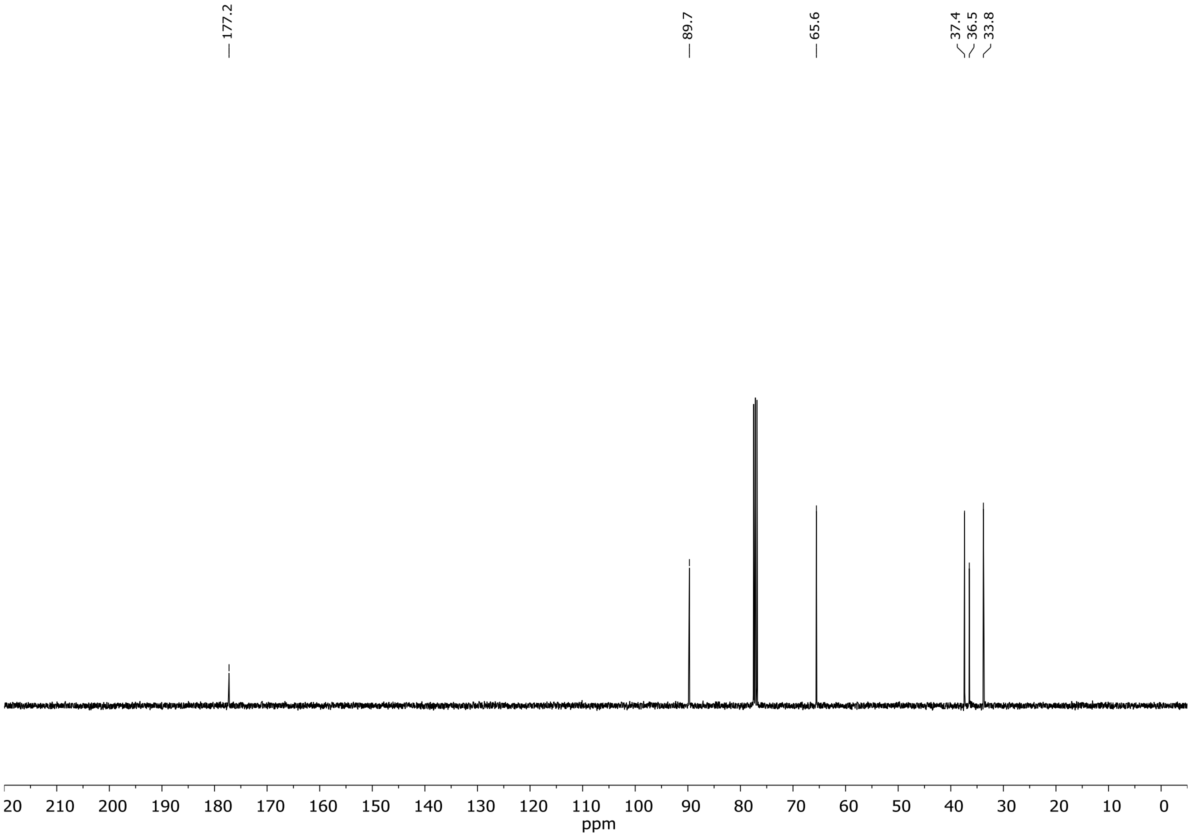




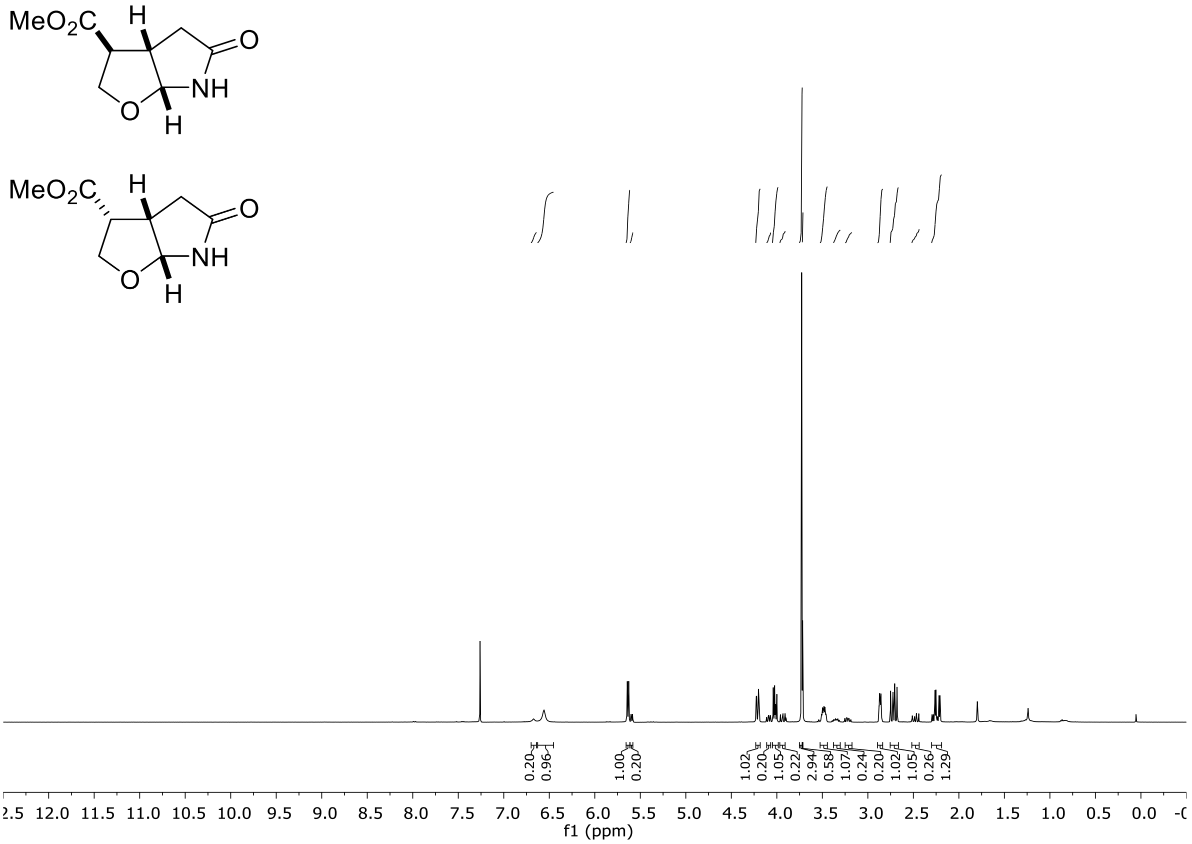


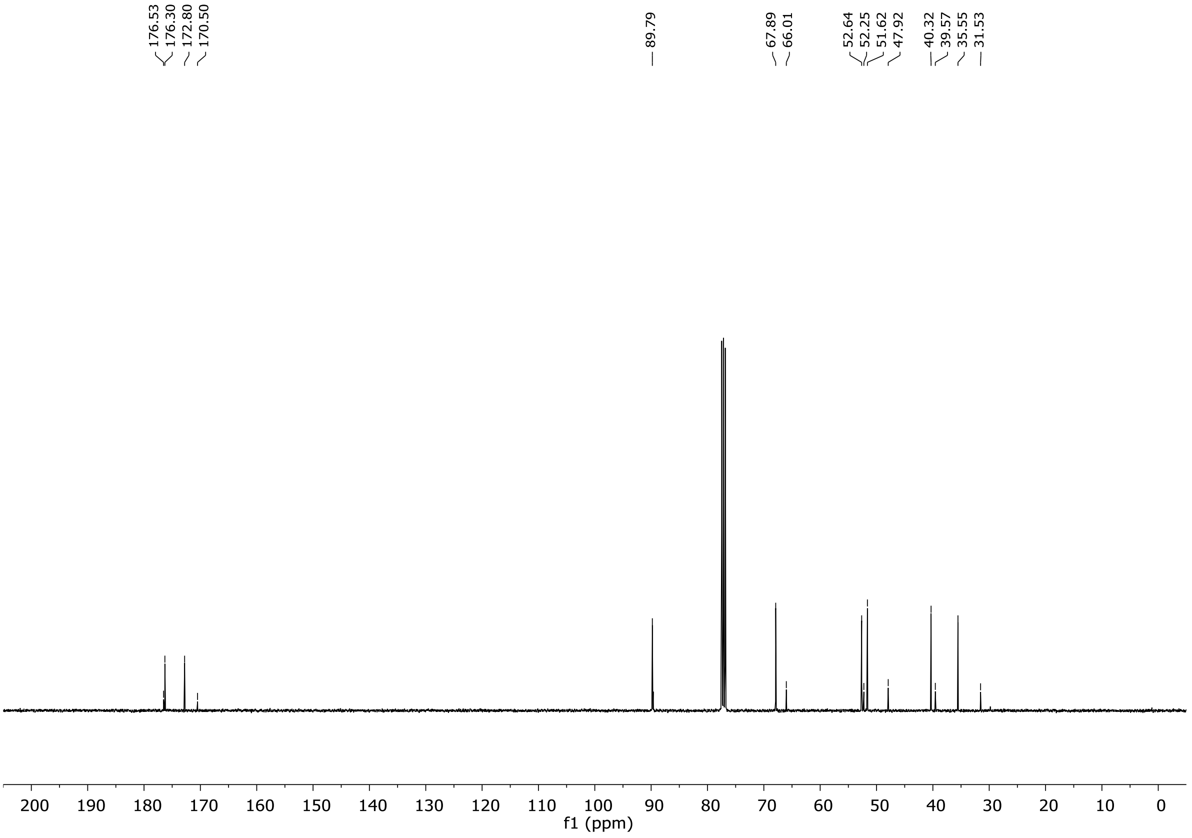
Compound **179d**: ^{1}H NMR (400 MHz, $CDCl_3$) and ^{13}C NMR (101 MHz, $CDCl_3$):



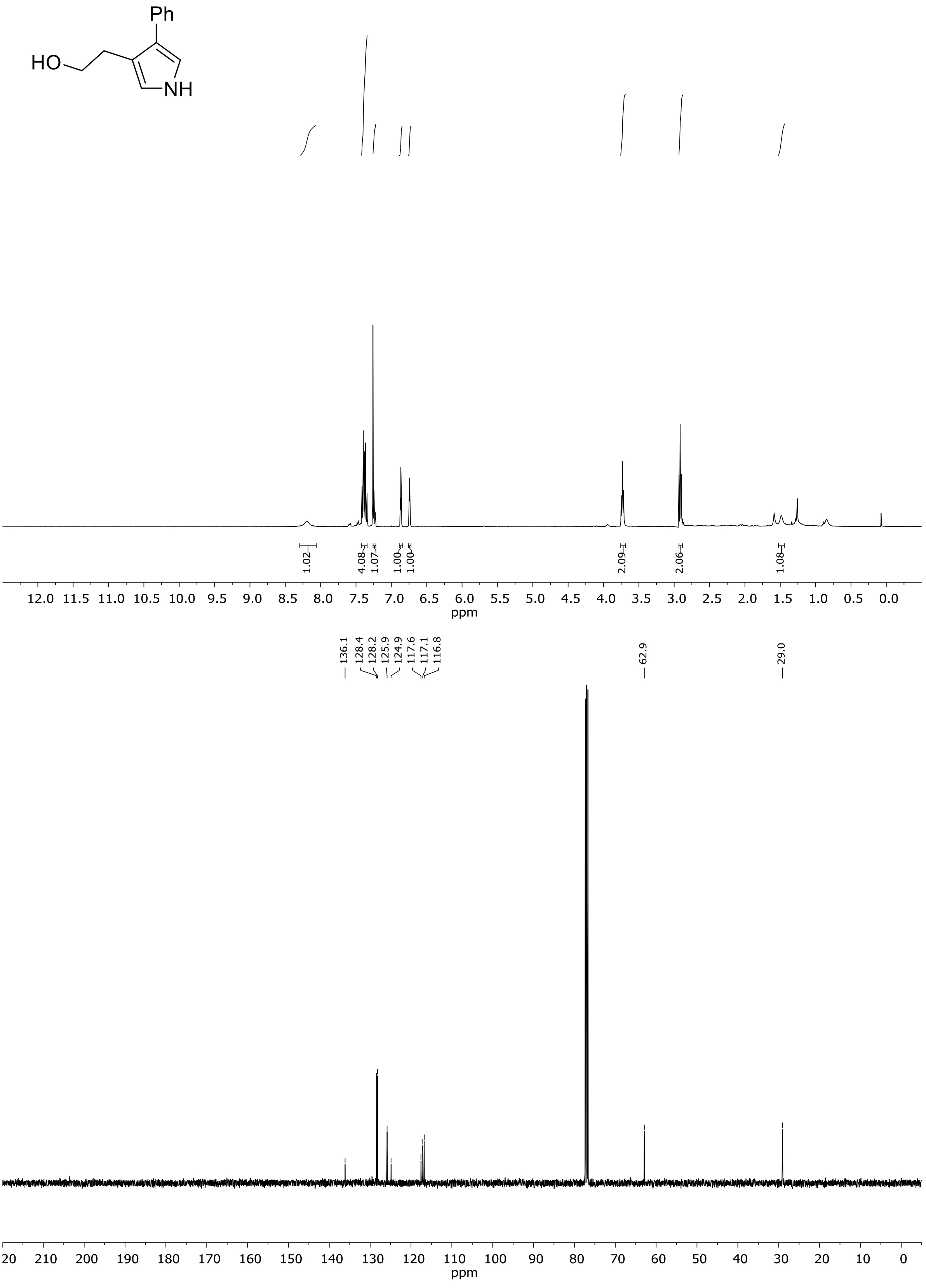


Compound **179e** and **179ee**: ^{1}H NMR (400 MHz, CDCl$_3$) and ^{13}C NMR (101 MHz, CDCl$_3$):

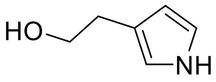


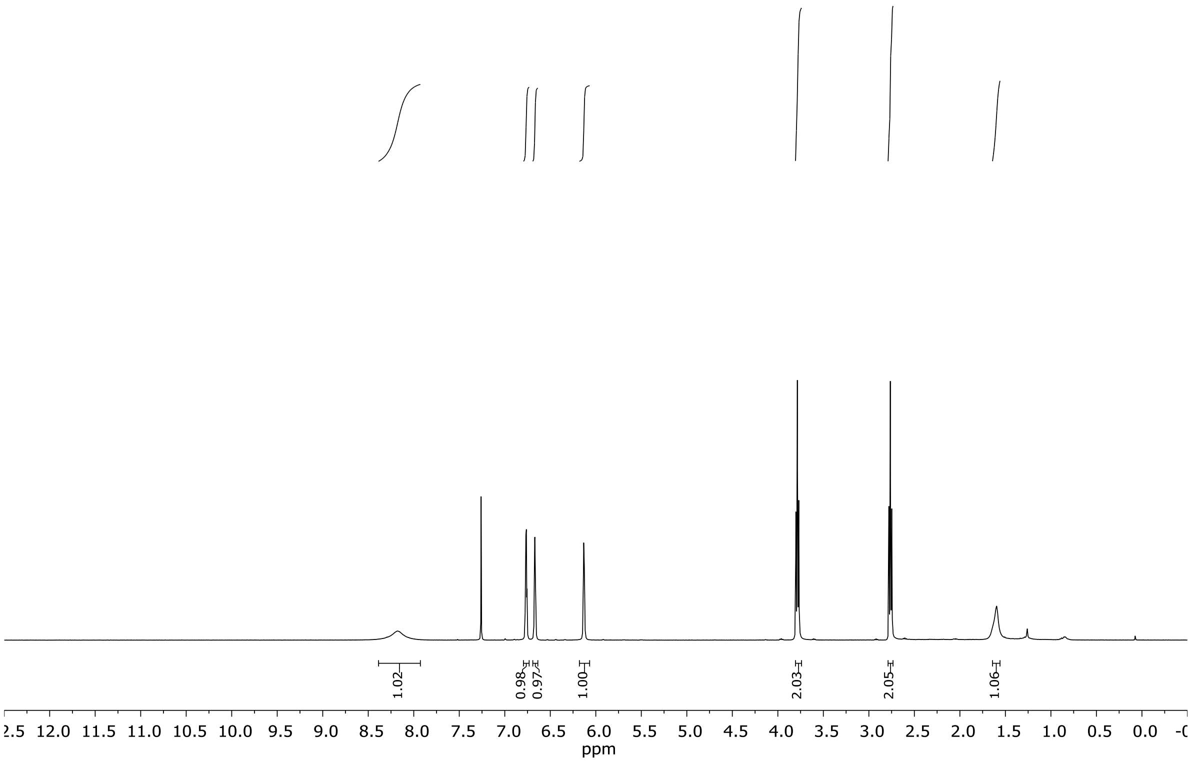


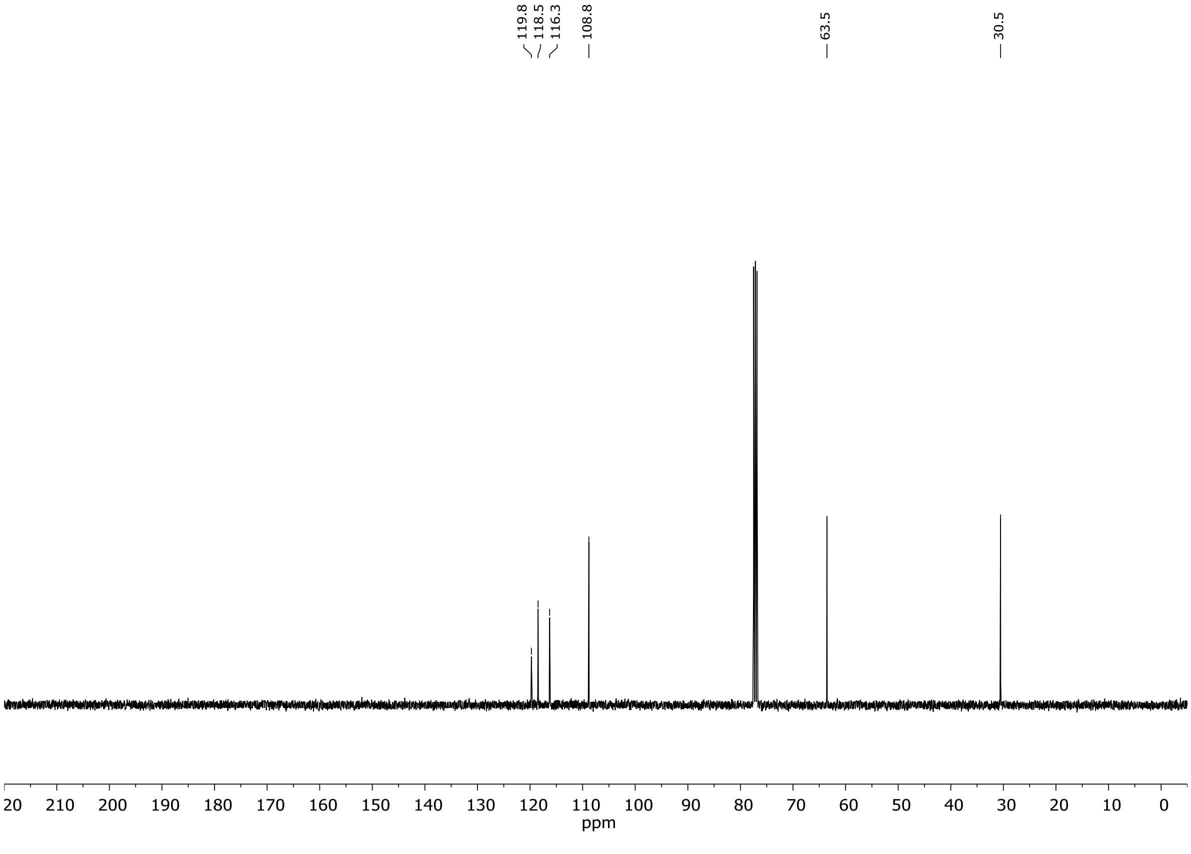
Compound **186a**: ^{1}H NMR (400 MHz, CDCl$_3$) and ^{13}C NMR (101 MHz, CDCl$_3$):



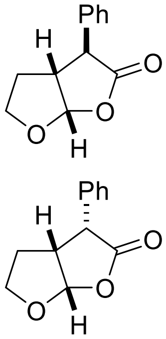
Compound **186b**: ^{1}H NMR (400 MHz, $CDCl_3$) and ^{13}C NMR (101 MHz, $CDCl_3$):

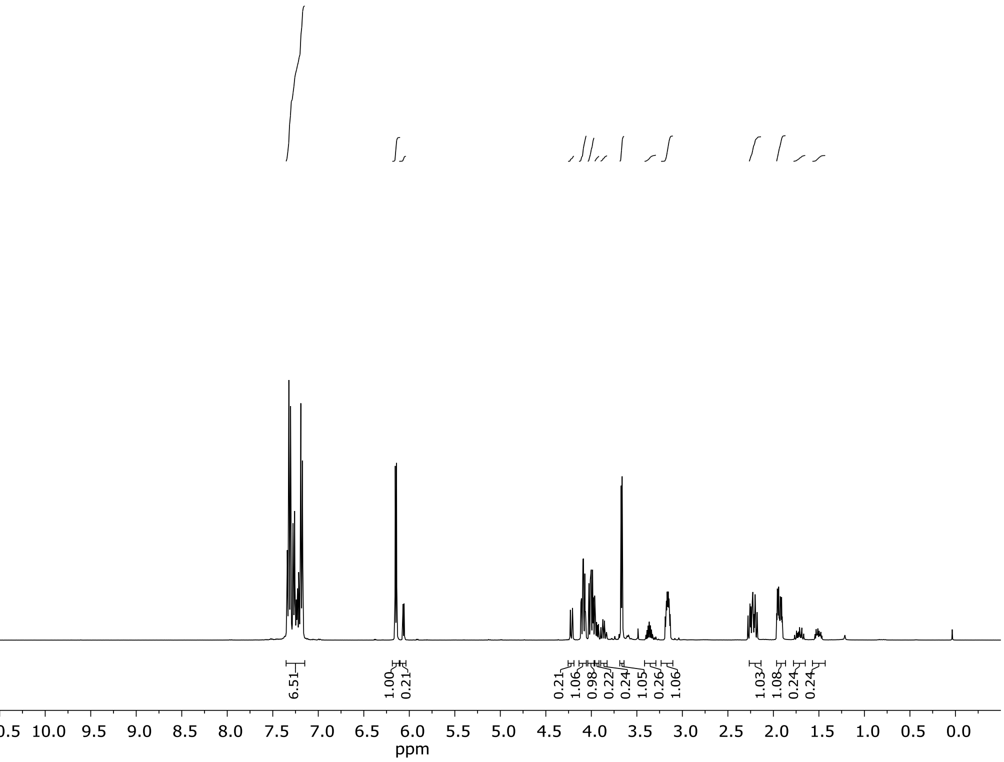


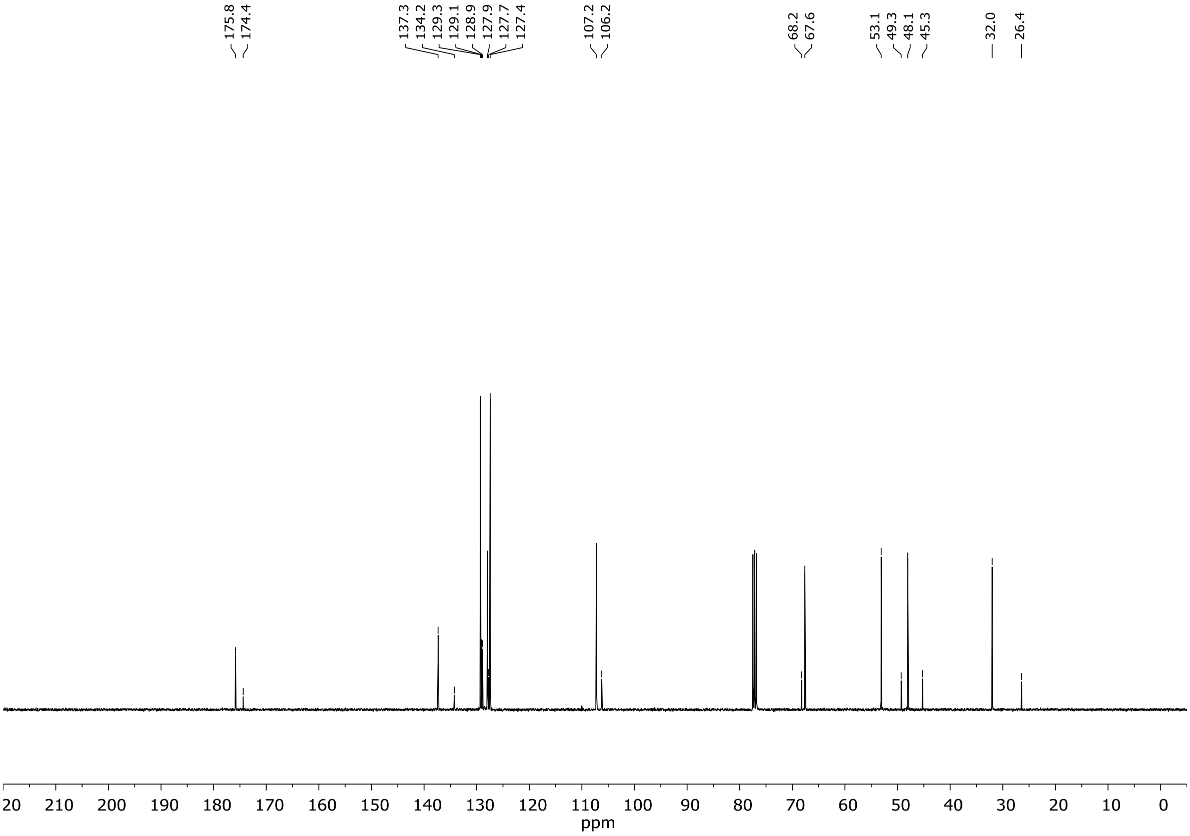




Compound **173a** and **173aa**: ^{1}H NMR (400 MHz, CDCl$_3$) and ^{13}C NMR (101 MHz, CDCl$_3$):







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D. Curriculum Vitae

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Education

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Conferences & Presentations

[redacted]

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List of Publications

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E. Acknowledgement

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F. Declaration

Herewith I declare that this present thesis is a presentation of my original work prepared single-handed. Wherever contributions from others are involved, all of them are marked, clearly, with reference to the literature, license, and acknowledgment of collaborative research.

Regensburg, 2025

Andreas Ratzenböck