Donor-Acceptor-Cyclopropanes: Versatile Starting Materials for the Synthesis of Cyclic Structures

Dissertation

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Der experimentelle Teil der vorliegenden Arbeit wurde in der Zeit von November 2020 bis Oktober 2023 unter der Leitung von Prof. Dr. Oliver Reiser am Lehrstuhl für organische Chemie der Universität Regensburg angefertigt. Von Januar 2022 bis Juni 2022 wurde die experimentelle Arbeit in Begleitung von Prof. Dr. Huw Davies an der Emory University, Atlanta, USA durchgeführt.

Herrn Prof. Dr. Oliver Reiser möchte ich herzlich für die Aufnahme in seinen Arbeitskreis, die Themenstellung, sowie für die anregenden Diskussionen und seine stete Unterstützung während der Durchführung dieser Arbeit danken.

To my Grandparents

Mein oberstes Prinzip: sich nicht unterkriegen lassen, nicht von den Menschen und nicht von den Ereignissen.

Marie Curie

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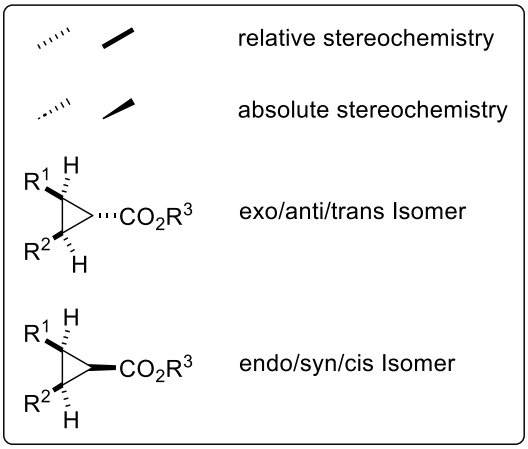
Abbreviations

°C	degrees centigrade
A	acceptor
Ac	acetyl
Acr	acridinium
AIBN	azobisbutyronitrile
APCI	atmospheric pressure chemical ionization
Ar	aryl
ASP	aspartic acid
ATRA	atom transfer radical addition
BHT	butylhydoxytoluene
BINOL	1,1'-Bi-2-napthol
Boc	*t*-butyl ester
bpy	bipyridine
bpz	bipyrazine
BVMO	Bayer-Villiger monooxygenases
Bz	benzyl
c	concentration
cat	catalyst
CPA	chiral phosphoric acid
c.r.m.	complex reaction mixture
CSA	camphor sulfonic acid
CT	charge transfer
D	donor
dap	2,9-dianisyl-1,10-phenanthroline
d.r.	diastereomeric ratio
DBU	1,8-diazabicyclo(5.4.0)undec-7-ene
DCA	9,10-dicyanoanthracene
DCM	dichloromethane
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzochinone
DFT	density functional theory
DIAD	diisopropyl azodicarboxylate
DIBAL	diisobutylaluminium hydride
DIPEA	diisopropylethylamin
dmb	3,5-dimethyl-4-benzaldehyde
DMC	dimethyl carbonate
DMF	dimethylformamide
dmp	dimethyl-1,10-phenanthroline
DMS	dimethyl sulfide
DMSO	dimethyl sulfoxide
DNP	2,4-dinitrophenol
dtbpy	4,4'-di-tert-butyl-2,2'-bipyridine
ee	enantiomeric excess
EI	electron ionization
equiv.	equivalent

ESI	electron spray ionization
Et	ethyl
et al.	et alia
EWG	electron-withdrawing group
FPT	Freeze-pump-thaw
g	gram
GDH	glutamate dehydrogenase
GP	general procedure
h	hour
HAT	hydrogen atom transfer
HEMA	2-hydroxyethyl methacrylate
HIV	human immunodeficiency virus
HMPT	hexamethylphosphoramide
HR-MS	high resolution mass spectrum
IR	infrared
ISC	intersystem crossing
kg	kilogram
KPi	potassium phosphate buffer
KRED	keto-reductase
L	liter
LHMDS	lithium bis(trimethylsilyl)amide
LDA	lithium diisopropyl amide
LE	locally excited
LED	light emitting diode
m	meter
M	molar
MB	methylene blue
m-CPBA	*meta*-chloroperbenzoic acid
Me	methyl
Mes	mesitylene
µg	microgram
mg	milligram
MHz	megahertz
min	minute
mL	milliliter
µm	micrometer
mm	millimeter
MO	molecular orbital
Moc	methoxy-ester
µ-TPSM	micro-total process system
MS	molecular sieves
MV	microwave
NADP	nicotinamide adenine dinucleotide phosphate
NBS	N-bromosuccinimide
n.c.	no conversion
NCS	N-chlorosuccinimide

NIS	N-iodosuccinimide
nm	nanometer
NMR	nuclear magnetic resonance
Nu	nucleophile
Oct	octanoate
ox	oxidation
p-ABSA	4-acetamidobenzenesulfonyl azide
PC	photocatalyst
PCC	pyridinium chlorochromate
PCET	proton-coupled electron transfer
PET	photoinduced electron transfer
PG	protecting group
Ph	phenyl
Pht	phtalimide
Piv	pivalate
ppy	2-phenylpyridine
p-TSA	*para*-toluenesulfonic acid
Pym	pyrimidine
pyr	pyridine
R	residue
Ra-Ni	Raney-nickel
RB	rose bengal
red	reduction
Rf	retention factor
rt	room temperature
SAMP	(*S*)-1-amino-2-methoxymethylpyrrolidine
SCE	standard calomel electrode
SET	single electron transfer
Sub	substrate
TBDMS	tert-butyldimethylsilyl
TEAMS	tetraethylammonium methanesulfonate
Tf	triflate
TFA	trifluoroacetic acid
TFEF	2,2,2-trifluoroethyl formate
THF	tetrahydrofuran
TLC	thin layer chromatography
TMS	trimethylsilane
TPAP	tetrapropylammonium perruthenate
TPP	tetraphenylporphyrin
Ts	tosyl
UV	ultraviolet
V	volt
W	watt
X	heteroatom


relative stereochemistry
absolute stereochemistry
R1
H
CO2R3
R2
H
exo/anti/trans Isomer
R1
H
CO2R3
R2
H
endo/syn/cis Isomer

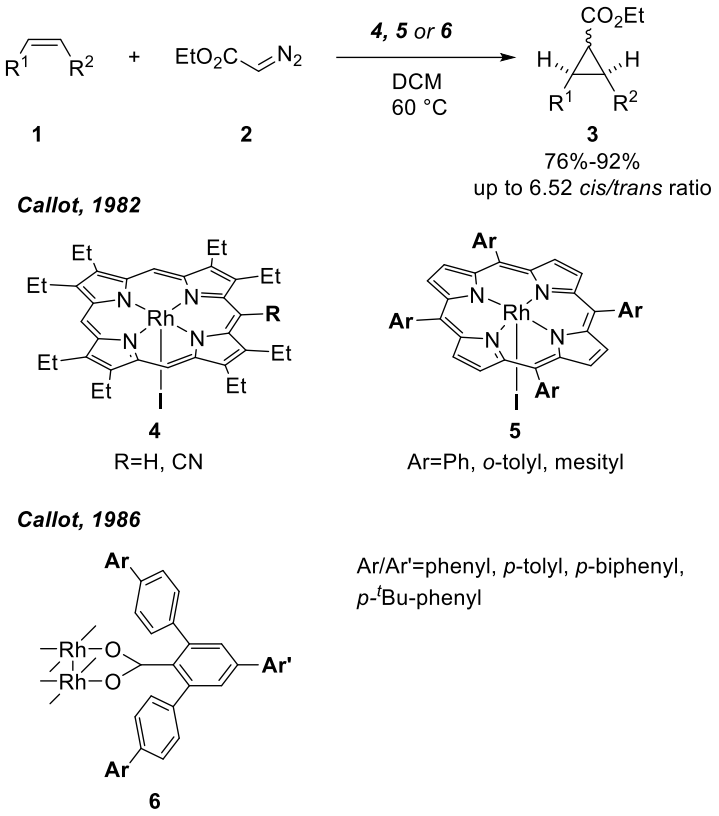
1 Introduction

Catalysis is one of the most important fields in chemical research, being widely applied in academia and industry.[1,2] Without it, many everyday items, plastics or other synthetic fibers, herbicides, pesticides, dyes, and pigments would not be easily accessible. The origin of catalysis lies in the 18th century: during this time, chemists were trying to gain deeper insights into reactions and stoichiometry, and Proust's Law of Constant Composition and Dalton's Law of Multiple Proportions were introduced.[3] Early research on catalysis and its meaning was carried out by many scientists. The term "catalysis" was defined by Jöns Jakob Berzelius in 1835 and originates from the Greek words *kata* (down) and *lyein* (to loosen),[3] which refers to the determination of the main feature of a catalyst as proposed by Ostwald: A substance which accelerates the reaction without being consumed in the process.[4,5] He later was awarded the Nobel Prize for this work,[6] and many more were granted for catalytic processes to different individuals, such as Haber (1918)[7], Bosch (1931)[8] and Ertl (2007)[9] for their contributions to the Haber-Bosch-process for the large scale production of ammonia or Ziegler and Natta (1963), whose polymerization catalysts made the plastic revolution possible.[10] Since the turn of the century, catalysis has often been the reason this prestigious award was given: to Knowles, Noyori and Sharpless (2001)[11] for asymmetrically catalyzed reduction and oxidation reactions, to Chauvin, Grubbs and Schrock (2005) for their metathesis catalysts,[12] to Heck, Negishi and Suzuki (2010)[13] for their palladium-catalyzed cross couplings and most recently, to List and MacMillan (2021) for their efforts in asymmetric organocatalysis.[14] This pursuit for new activation modes makes catalysis a constantly evolving field with tremendous potential, proven by the fact that newly developed areas are still emerging.[15,16] Catalysis also plays a crucial role for this work: not only are the donor-acceptor cyclopropane starting materials synthesized with the help of rhodium catalysis, but also the subsequent transformations heavily rely on catalytic procedures. The goal of this work was the development and investigation of catalytic, selective pathways for the synthesis of new compounds from donor-acceptor cyclopropanes.

1.1 Cyclopropanation with rhodium catalysts

1.1.1 Solving stereoselectivity issues

The cyclopropane ring is the 10th most abundant ring system in drugs.[17] It is present in protease inhibitors, antibacterial drugs and many more.[18] Unsurprisingly, the synthesis of cyclopropanes has long attracted the interest of organic chemists. One method which has been under investigation for quite some time is the addition of carbenes to olefins. Early reports focused on metals such as copper[19], palladium[20], chromium[21] or rhodium.[22] Carboxylate complexes of the latter were first introduced by Teyssie *et al.* in 1976 in the cyclopropanation of olefines with carbenes generated from diazo compounds and found them to be superior to copper and palladium species.[23] However, the major issue from the beginning was the diastereoselectivity of the reaction: usually, only a 1:1 mixture of the *exo*- and *endo*- or *trans*- and *cis*- isomers was obtained. Callot *et al.* were able to achieve some diastereoselectivity using rhodium(III)porphyrins **4** and **5** (**Scheme 1**).[24] They realized that the selectivity depended on the catalyst and the olefin employed and hypothesized that large residues R/Ar on the catalyst force the olefin substituents R^1 and R^2 and the ester group to point in the same direction with increasing size, away from the porphyrin cycle, increasing the *endo* or *cis* ratio. For example, for the cyclopropanation of cyclohexene with **2**, the *endo/exo* ratio increased from 0.67 when **5** was phenyl substituted to 1.17 when **5** was substituted with a mesityl group. The initial ratio was only 0.32 with $Rh_2(OPiv)_4$. This trend was observable with all employed olefins. When (*Z*)-4-methylpent-2-ene was cyclopropanated with **2** using mesityl-substituted **5** as a catalyst, the *cis/trans* ratio reached 6.52.



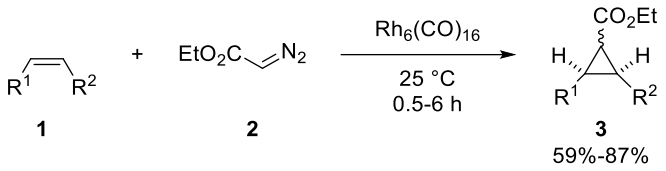
Scheme 1. Cyclopropanation of olefins with rhodium-porphyrin and triarylbenzoate catalysts.

The Callot group further developed this strategy with triaryl benzoate rhodium catalysts **6**, expanding the substrate scope and improving the *endo/exo* ratio.[25] The cyclopropanation of cyclohexene reached *endo/exo* ratios of up to 2.8, a drastic improvement from the porphyrin catalysts. Additionally, they found that highly crowded substituents on the aryl ring "plug" the active site of the catalysts, making them unstable and less reactive, but highly selective. Smaller substituents expose the reactive site more, increasing stability and reactivity but decreasing selectivity.

In the following years, rhodium catalyzed cyclopropanations were further researched, for example in the cyclopropanation of polyolefins or halogenated olefins, where rhodium catalysts outperformed their palladium- and copper analogues.[26,27]

Doyle *et al.* achieved a breakthrough when they employed the metal rhodium carbonyl cluster $Rh_6(CO)_{16}$ in the cyclopropanation of various alkenes **1**, including vinyl ethers, which were previously hard to access due to polymerization.[28] This new catalyst

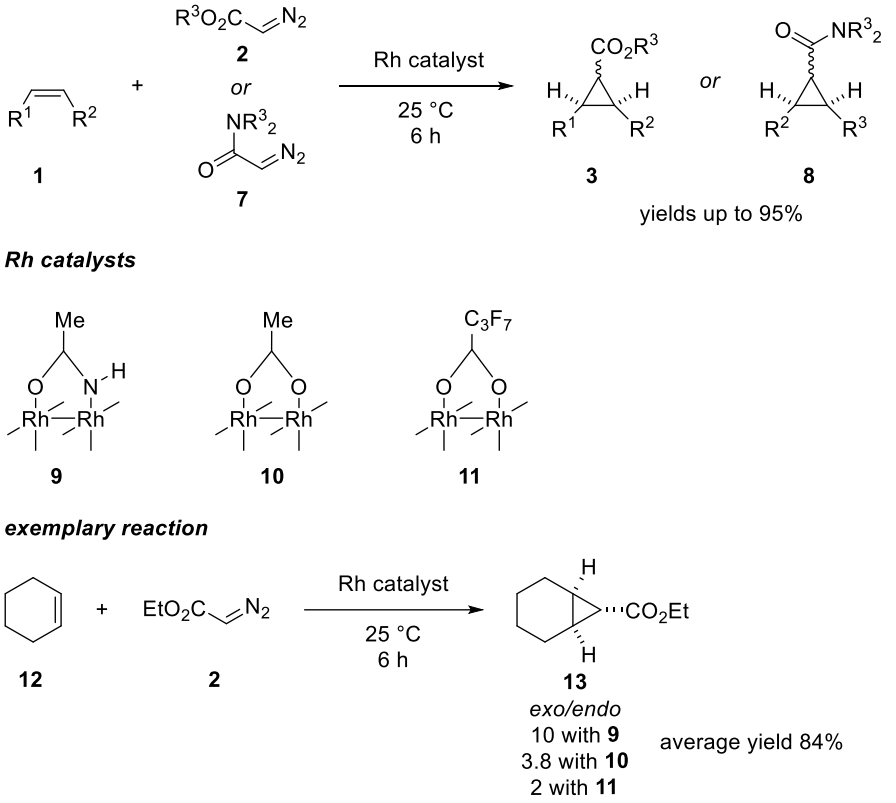
combined with a low addition speed resulted in consistently high yields, even when run under air (**Scheme 2**).



Scheme 2. Rhodium-carbonyl metal cluster catalyzed cyclopropanation.

After this initial report, the Doyle group standardized their reaction conditions and investigated whether they could employ equimolar amounts of alkene **1** by dropwise addition of diazo compound **2** and thus push back the dimerization of **2** to fumarate or maleate, a common side reaction in such cyclopropanations. They found that this is indeed possible and additionally, the catalyst loading can be lowered to 0.05 mol% if the addition rate of the diazo compound **2** is adjusted accordingly.[29]

Doyle *et al.* then focused their investigations on the influence of different parameters on the *cis/trans* and *endo/exo* selectivity of the cyclopropanation with different metal-centered catalysts.[30] They initially could not determine a correlation between olefin **1** structure, the metal center or the ligands of the catalysts developed at the time and the selectivity. In a later study, they compared not only the catalysts, but also of different diazo esters in respect to their ability to influence the *cis/trans* and *endo/exo* selectivity.[31] They found that increasing the size of the diazo esters and using acetamide catalyst **9** afforded the best *cis/trans* or *endo/exo* ratios (**Scheme 3**).



Scheme 3. Influence of catalyst structure on the stereoselectivity of cyclopropanation.

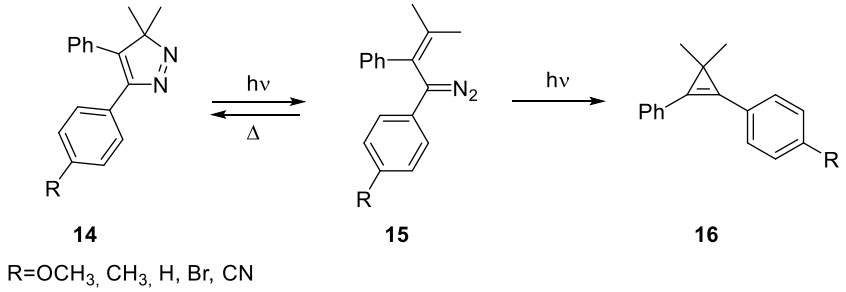
Aratani *et al.* further investigated the influence of the ester size of the diazoacetate, although they used a copper catalyst.[32] They found the size of the ester greatly influenced the selectivity: while an *cis/trans* ratio of 1:1 was observed with an ethyl reside , a menthyl residue showed almost exclusive *trans* selectivity. The Doyle group further broadened the scope and showed the applicability later on.[33]

Additionally, the catalyst the Aratani group employed is chiral. While this did not influence the *endo/exo* or *cis/trans* ratio, it did result in significant chiral induction on both isomers.[32]

1.1.2 The history of metal-catalyzed decomposition of vinyl diazo compounds

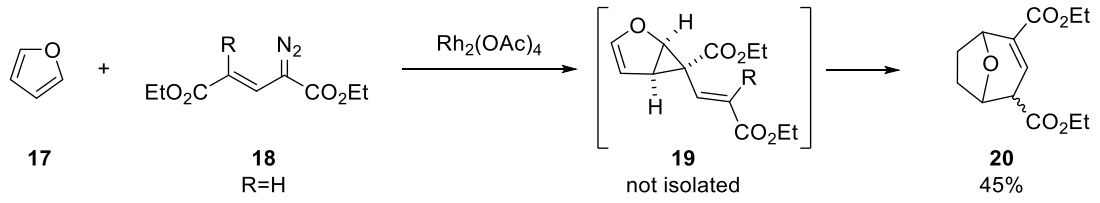
Vinyl diazo compounds **15** were first synthesized by Pincock *et al.* from the corresponding pyrazoles **14** by photolysis,[34,35] These diazo compounds **15** further reacted to the cyclopropenes **16** under the appropriate illumination conditions, or back to the pyrazole **14** under thermal conditions (**Scheme 4**). Mechanistically, the

intramolecular cyclopropanation takes place through carbene addition after extrusion of the diazo group.



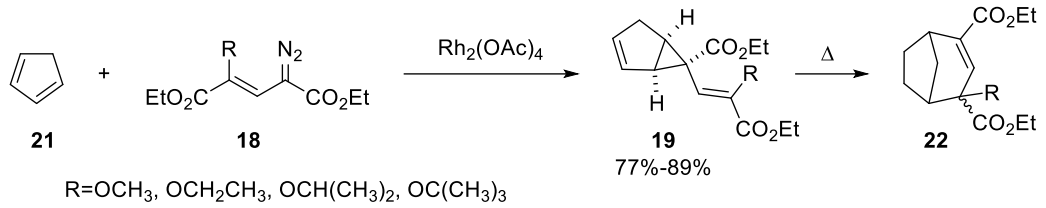
Scheme 4. Generation of vinyl diazo compounds by photolysis.

The Davies group was interested if they could stabilize the carbene generated after N_2 extrusion by displacing the diazo group with an appropriate metal, inhibiting intramolecular reactions and gaining control over the reactivity to enable intermolecular additions.[36] In order to suppress the thermal formation of the pyrazole , they chose **18**-H as their model substrate, based on previous research showing electron withdrawing groups inhibit the pyrazole pathway. The following decomposition of **18**-H mediated by $Rh_2(OAc)_4$ in the presence of furan was successful and formed the bridged product **20** (**Scheme 5**). They presumed cyclopropane intermediate **19** was involved and further investigated this idea.



Scheme 5. Synthesis of bridged bicycles **20**.

Switching to cyclopentadiene (**21**) instead of furan (**17**) and to vinyl diazo ester **18**-R (R≠H) slowed down the Cope rearrangement, allowing the isolation of **19**-R (R≠H) at room temperature, which subsequently could be rearranged to **22** at elevated temperature.[37]

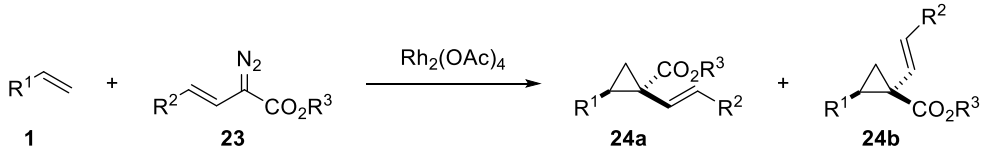


Scheme 6. Proof of mechanistic principle by synthesis of cyclopropanes **19** and subsequent rearrangement to **22**.

Besides intermolecular reactions, also intramolecular variants, combining the vinyl diazo unit and the acceptor alkene in one molecule, could be developed.[38–40]

Since the Cope rearrangement proceeded with remarkable diastereoselectivity, Davies *et al.* reasoned that the intermediate **19** obtained by the cyclopropanation of a cyclic alkene had formed with high diastereoselectivity. They subsequently found that also acyclic alkenes were cyclopropanated with high preference for **24a** (**Table 1**).[41]

Table 1. Stereoselectivity of cyclopropanation reactions.

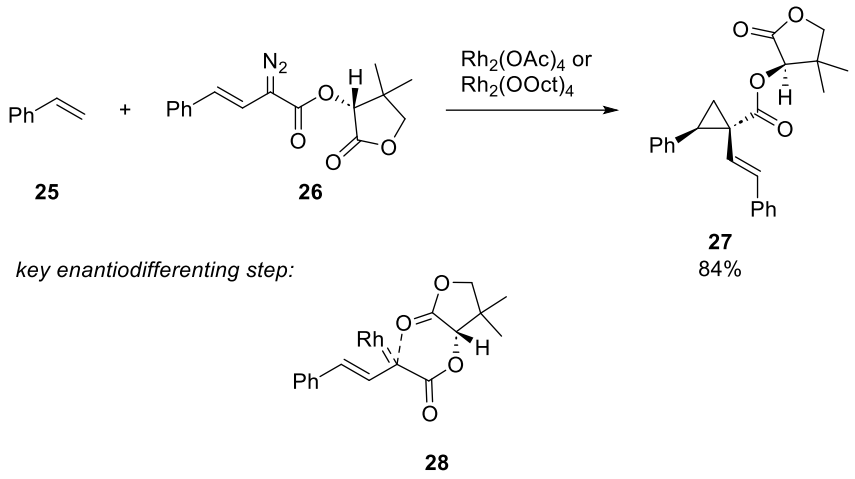


Entry	*R^1*	*R^2*	*R^3*	*yield*	*ratio a/b*
1	Ph	COOEt	Et	96%	>20:1
2	Ph	Ph	Me	94%	>20:1
3	AcO	COOEt	Et	79%	>20:1

In 1992, they expanded their methodology to cyclic ether systems: here, the oxygen moiety acts as an electron donor while the ester acts as an acceptor and therefore forming donor-acceptor cyclopropanes.[42] Simultaneously, since there is no second double bond present, the products do not undergo Cope rearrangements as seen with furan (**17**) or cyclopentene (**21**).

With the diastereoselectivity problem solved, attention was turned towards developing an enantioselective approach to cyclopropanations with vinyl diazo esters. The Davies group began their investigations into this topic by using previously developed chiral cyclopropanation catalysts, however, these did not form the desired compounds in the reaction between styrene and vinyl diazo esters.[43] As a first solution to this problem,

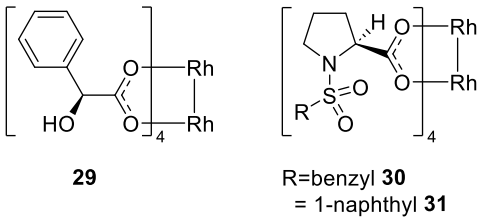
they wanted to modify the diazo ester with a chiral auxiliary. The use of these on the ester group of the diazo compound was previously explored with limited success,[44] however, remarkable enantioinduction was found when **26** was employed, with only little loss of yield. The enantiomeric purity could be increased by simple recrystallization. The rationale behind the enantioselectivity in this case is the presumed interaction in intermediate **28** between the oxygen of the chiral ester and the metal-bound carbene (**Scheme 7**).



Scheme 7. First enantioselective synthesis of **27** with chiral esters as auxiliary.

While these first results were promising, the ultimate goal in organic chemistry is to develop methods that are independent of the substrate: catalyst control is preferred over substrate control. The search for a way to induce enantioselectivity *via* the catalyst therefore continued.

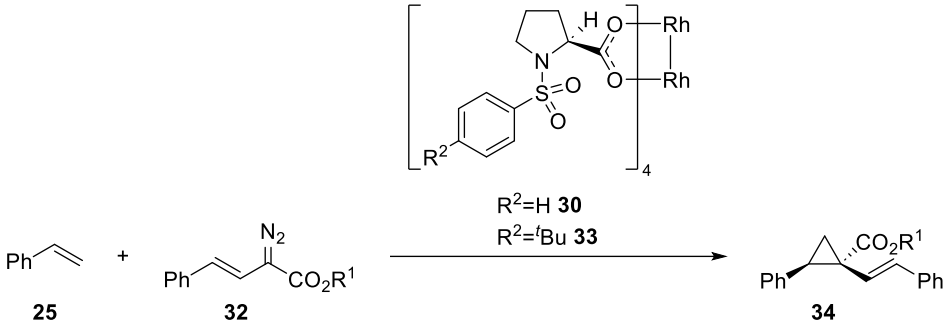
In 1990, the group of McKervey developed rhodium carboxylate catalysts **29**-**31** to catalyze C-H-insertion reactions and cyclopropanations of diazoketones (**Scheme 8**).[45]



Scheme 8. Rhodium catalysts used by McKervey for the decomposition of diazoketones.

They managed to obtain the intramolecular cyclopropanation products with an *ee* of 12%. When Davies *et al.* employed the McKervey prolinate catalyst **30** in their intermolecular cyclopropanation of different vinyl diazo esters **32** with styrene, they achieved high enantioselectivities in most cases:[46] In the initial experiment, the *ee* reached 74% (**Table 2**, Entry 1). They also found that decreasing polarity had a positive effect on the enantioinduction, especially with bulkier ester substitutions. They therefore synthesized Rh_2(*S*-TBSP)$_4$ **33**, since the solubility was expected to be higher in pentane, and this drastically increased the *ee* (**Table 2**).

Table 2. Catalyst performance for the enantioselective cyclopropanation of styrene.

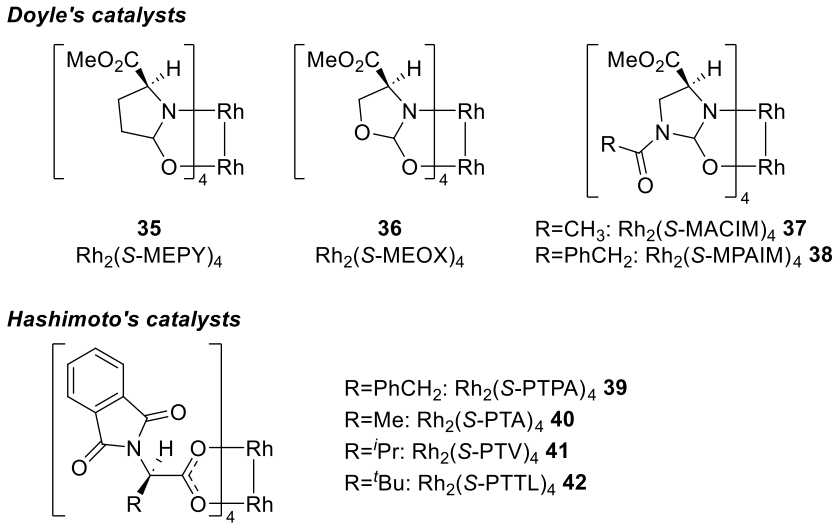


Entry	R^1	R^2	*solvent*	*ee*
1	Me	H	DCM	74%
2	^{t}Bu	H	DCM	9%
3	Me	H	benzene	87%
4	^{t}Bu	H	benzene	28%
5	Me	^{t}Bu	pentane	90%
6	^{t}Bu	^{t}Bu	pentane	50%

This system was applied to a variety of terminal alkenes, which gave *ee* values between 59% and >95% with yields between 40% and 91%.

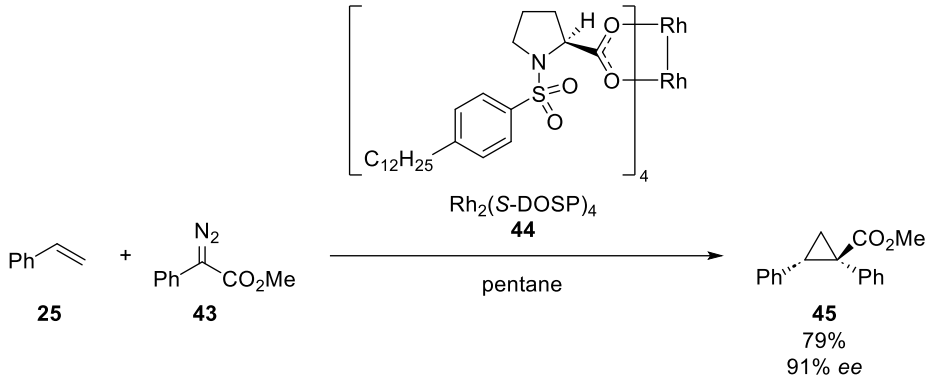
In the following years, many rhodium carboxylate catalysts were developed, for example Doyle's catalysts Rh_2(MEPY)$_4$ **35** or Rh_2(MACIM)$_4$ **37**,[47] or Hashimoto's Rhodium-phthaloyl-*tert*-leucinate catalysts (**Scheme 9**).[48] The breakthrough came in 1996, when Davies *et al.* published their investigations on prolinate catalysts. They found Rh_2(DOSP)$_4$ **44** catalyzed the transformation of alkenes with vinyl diazo compounds in high yields, with good diastereoselectivity and enantioselectivity. The main reasons for the high performance were believed to be the high solubility in hydrocarbon solvents mediated by the long alkyl chain and the combination with donor-acceptor systems,

since the diastereo- and enantioselectivities dropped considerably when these systems were not used.[49]



Scheme 9. Development of chiral rhodium catalysts.

This approach was extended to aryl diazoacetates as well and it was shown that donor-acceptor substitutions on the diazo compound are crucial for the cyclopropanations (**Scheme 10**). Using pure diazo acetate or phenyldiazomethane was unsuccessful.[50]

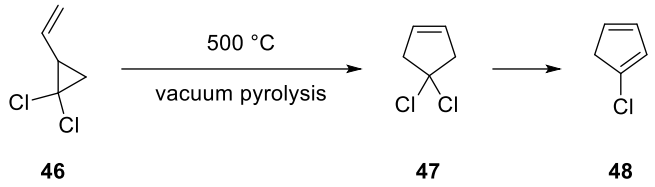


Scheme 10. Enantioselective donor-acceptor cyclopropane synthesis.

Since the development of $Rh_2(DOSP)_4$ **44** and the discovery of donor-acceptor diazo compounds in unison with rhodium carboxylate catalysts, Davies *et al.* and others have developed a wide variety of rhodium carboxylate catalysts for both cyclopropanation and C-H functionalization.[51,52] Their efforts have made cyclopropanes easily accessible, which fueled research on transformations and applications of these compounds.

1.2 Synthesis and use of cyclopentenes and the vinylcyclopropane-cyclopentene rearrangement

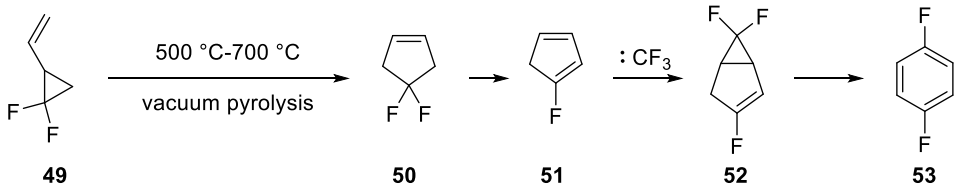
One of these reactions is the vinylcyclopropane-cyclopentene rearrangement, which has been of use in natural product synthesis for quite some time. It was first discovered by Neureiter in 1959 when he performed vacuum pyrolysis on 1,1-dichloro-2-vinylcyclopropane **46** (**Scheme 11**).[53] HCl can be eliminated from **47** to form **48**, fueled by increasing pyrolysis temperatures.



Scheme 11. First vinylcyclopropane-cyclopentene rearrangement of dichloro vinylcyclopropane.

Initially, a diradical mechanism for the transformation of **46** to **47** was proposed, occurring through a homolytic bond cleavage of the cyclopropane.

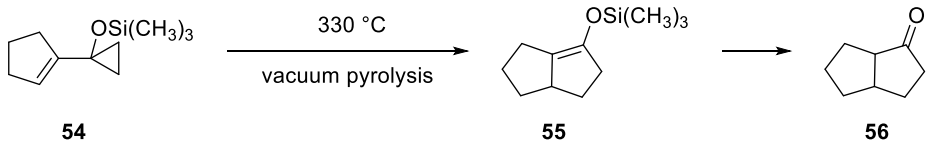
Nefedov and Ivashenko found the reaction shown in **Scheme 11** also proceeded with the difluoro derivative **49**. Cyclopentene **50** underwent the elimination of HF and the resulting cyclopentadiene **51** can be cyclopropanated with a CF_3 carbene. Subsequent elimination of HF gives difluoro benzene **53**, providing a new method of synthesis for these types of compounds (**Scheme 12**).[54]



Scheme 12. Vinylcyclopropane rearrangement with *gem*-difluroro vinylcyclopropane.

The potential of this rearrangement was quickly realized and further developed. Trost *et al.* utilized the reaction for the synthesis of carbonyls by performing the rearrangement on silyl enol ethers **54**. The reaction proceeded smoothly at only 330 °C

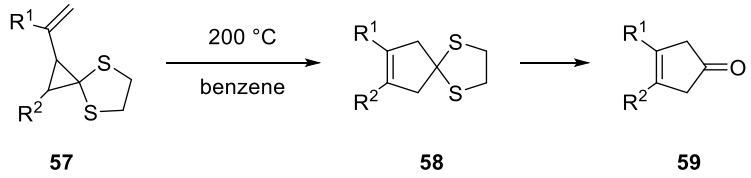
(**Scheme 13**), deprotection readily afforded carbonyl **56** and was a key step in their total synthesis of Aphidicolin.[55,56]



Scheme 13. Masked carbonyl strategy of the vinylcyclopropane rearrangement.

The same authors later replaced the silyl group with sulfides, which are easier to prepare and handle.[57]

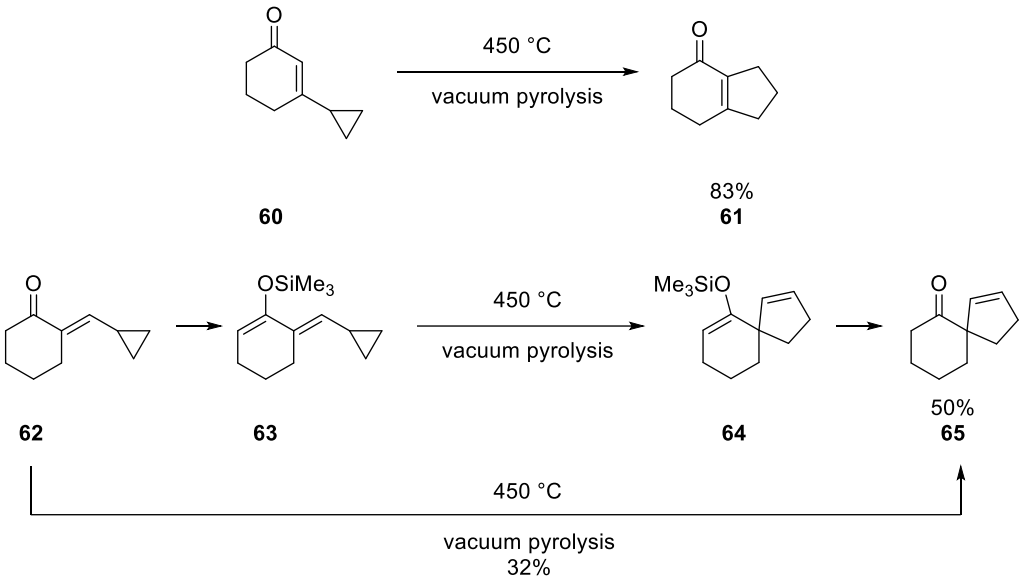
In order to mimic the addition of CO to dienes, Corey *et al.* developed a dithienium synthon approach. The spiro cyclopropanes **57** readily rearranged to the spiro cyclopentenes **58** upon heating, and were then unmasked to give the corresponding cyclopentenones (**Scheme 14**).[58]



Scheme 14. Dithienium-masked carbonyl strategy.

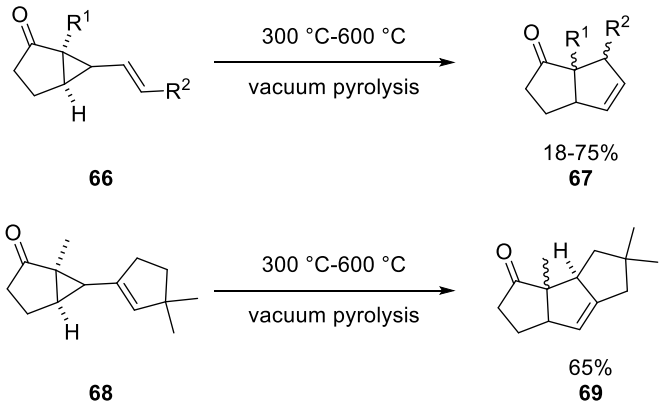
As shown by Piers *et al.*, unmasked cyclopropyl enones undergo the rearrangement as well. An example is shown in **Scheme 15**: the enone **60** undergoes direct conversion to **61** under pyrolysis at 450 °C in 83% yield. The group utilized this in their total synthesis of zizaene.[59]

However, for the synthesis of spiroannulated compounds **64**, masking the carbonyl first as a silyl ether provided better yields (32% with direct pyrolysis, 50% over 3 steps with TMS as protecting group, **Scheme 15**).[60]



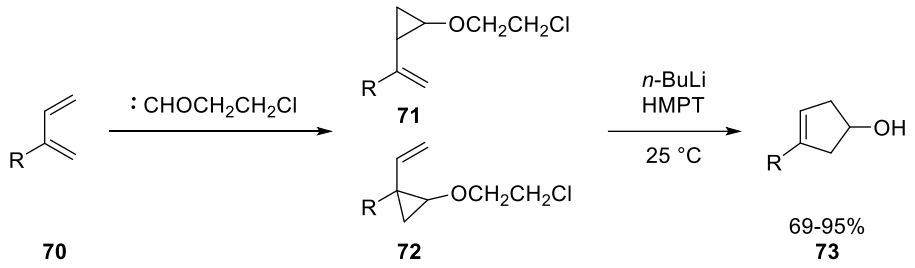
Scheme 15. Rearrangement of cyclopentenone vinylcyclopropanes.

The rearrangement with unprotected ketones also worked with cyclic cyclopropyl ketones, although mixtures of diastereomers were observed (**Scheme 16**).[61]



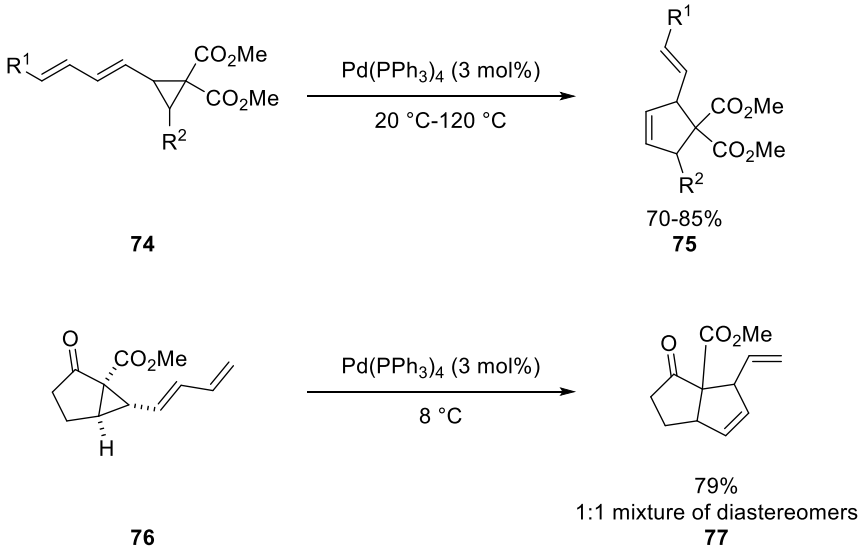
Scheme 16. Vinylcyclopropane rearrangement of fused vinylcyclopropanes.

The major drawback of all these strategies is the need for high temperatures. This was first circumvented by Danheiser *et al.*, who synthesized vinyl cyclopropyl ethers **71** and **72,** which they then subjected to *n*-BuLi at 25 °C (**Scheme 17**). **71** and **72** were cleaved to the corresponding lithium salts of the alcohols and rearranged in the same step to form cyclopentenes **73**.[62] They reasoned the alkoxy intermediate formed during the reaction process stabilizes the radical intermediates, which allows the low reaction temperatures.



Scheme 17. Room temperature vinylcyclopropane rearrangement of lithium salts.

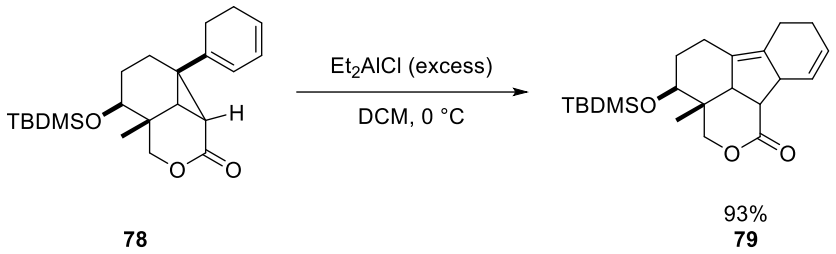
Other groups recognized the potential of room temperature rearrangements and sought to further modify the vinylcyclopropanes and reaction conditions to work towards this goal. Oshima *et al.* discovered that substituting the cyclopropane with two ester groups (**74**) provides the cyclopentene products **75** under Pd(0) catalysis at room temperature in most cases. Their conditions were also applicable to fused cyclopropanes **76** (**Scheme 18**) and were directly applied to the synthesis of Dolichodial and Iridodiol.[63] Enantiopurity was retained as well.[64] Metal-based procedures do not run through a radical mechanism, but rather a zwitterionic one where the metal coordinates to either the ester group or the double bond. The latter is the case for the transformation shown in **Scheme 18**.



Scheme 18. Pd-catalyzed rearrangement of diene-vinylcyclopropanes.

The method of using cyclopropanes with two ester substituents was considerably expanded by Trushkov *et al.,* who applied it to a variety of non-fused vinylcyclopropanes under Lewis acid catalysis.[65]

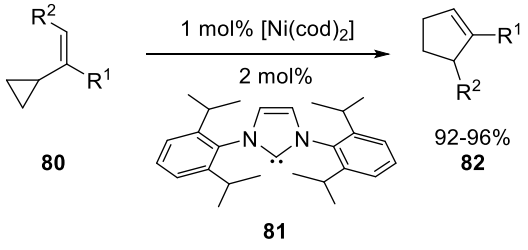
The development of reaction conditions utilizing metals and lower temperatures rather than pyrolysis was further advanced by Corey *et al.*, who elegantly synthesized the quadricycle **79** from **78**. The vinylcyclopropane rearrangement was initiated by Et_2AlCl and provided the desired compound in high yields and perfect diastereoselectivity (**Scheme 19**).[66,67]



Scheme 19. Corey's Et_2AlCl mediated vinylcyclopropane rearrangement.

There are numerous examples of this rearrangement utilized in natural product synthesis in literature.[68]

Louie *et al.* developed a nickel-catalyzed procedure for unactivated alkenes **80**. They were able to transform the vinylcyclopropanes to the corresponding cyclopentenes **82** in high yields at mild temperatures of only 60 °C (**Scheme 20**).[69]



Scheme 20. Ni-catalyzed vinylcyclopropane rearrangement of unactivated alkenes.

As mentioned previously (chapter 1.1.2), the synthesis of donor-acceptor vinylcyclopropanes by Davies *et al.* proceeded with excellent yields and diastereoselectivity. During their studies, they also discovered some of their

vinylcyclopropanes readily rearranged to the corresponding cyclopentenes. As shown in the previous examples, mild conditions for the catalysis of this transformation are less known, therefore, a catalytic strategy for the rearrangement of vinylcyclopropanes was developed, which will be discussed in chapter 2.2.[42,70]

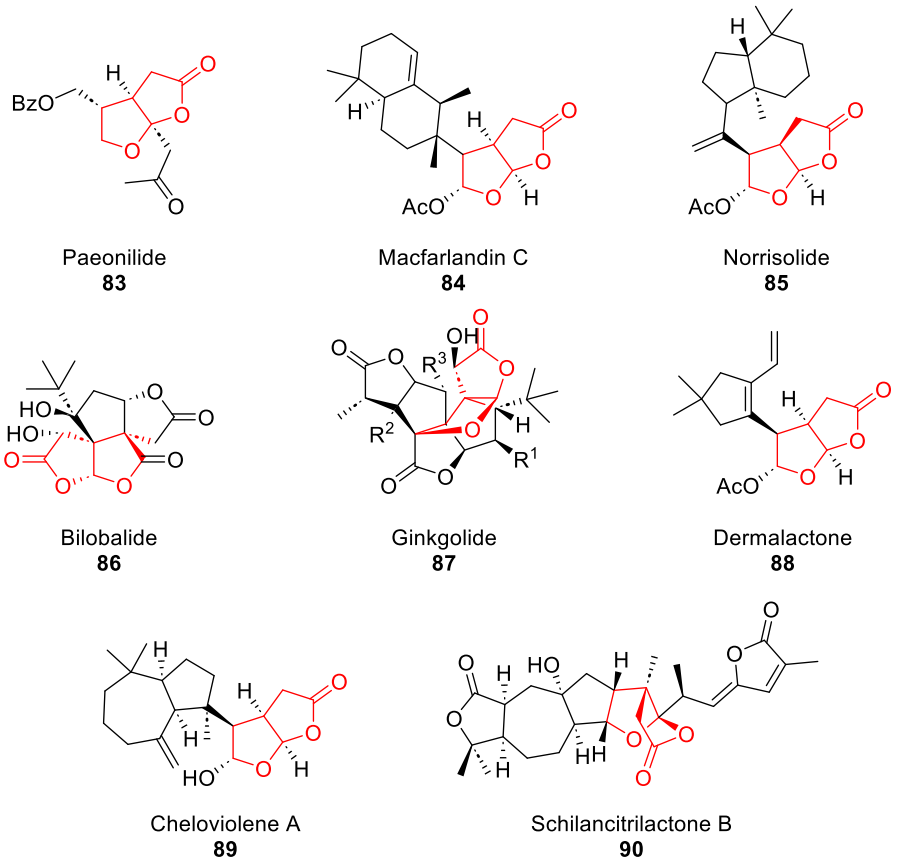
1.3 Tetrahydrofuran-fused lactones

Donor-acceptor cyclopropanes usually hold an ester functionality, which offers another point of attack for cyclopropane functionalization. This chapter will lead up to the transformation of tetrahydrofuran-fused cyclopropanes to the corresponding lactones, starting with the use of these compounds.

1.3.1 THF-fused lactones in natural products

Furofuranones, which consist of a THF ring fused to the gamma-butyrolactone, are often found in natural products. There are different types of these compounds, named depending on the position of the oxygen atom in the THF-ring: furo[2,3*b*]furanone, furo[2,3*c*]furanone and furo[3,2*b*]furanone. The focus in this work will lie on furo[2,3*b*]furanones. Some prominent examples for these types of natural products are shown in **Scheme 21**.

These compounds are found in plants,[71,72] marine sponges,[73] sea slugs,[74] fungi,[75] and others. Norrisolide-type structures can modify the Golgi-apparatus,[76] influencing protein synthesis, although the mode of activation is different for Norrisolide **85** and Macfarlandin C **84**. The mechanism is largely unexplored, however, it is known that the latter reacts readily with lysine side chains and other primary amines to form pyrroles, which may play a role.[77] Additionally, they have been shown to be active against cancer cell lines[78,79] or herpes simplex.[80] Other structures, such as Bilobalide **86** and Ginkgolide **87**, show neuroprotective effects.[81,82]



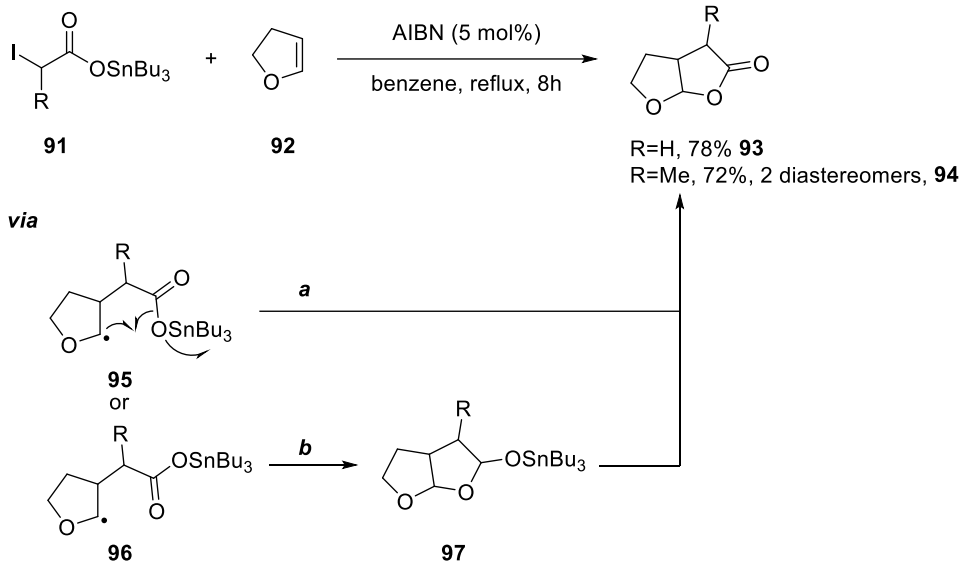
Scheme 21. Natural products containing the furo[2,3*b*]furanone core.

The synthesis of natural products has always been at the forefront of organic chemistry, as the isolation processes are often time consuming and difficult. Classic techniques include steam distillation, constant extraction, acid-base extraction or Soxhlet extraction.[83,84] These techniques however often require high temperatures or large solvent volumes and can have issues with reproducibility due to varying amounts of the natural product in the biological entity. Additionally, derivatization of the natural product is not always straightforward. Lots of work has therefore gone into the total synthesis of natural products, including furo[2,3*b*]furanones, as it allows easier scalability and derivatization options.

1.3.2 Synthesis of furo[2,3*b*]furanones

Bhat, Rashid and Mehta have recently provided a comprehensive overview of the synthesis of natural products containing the furo[2,3*b*]furanone core.[85]

An early synthesis by Kraus *et al.* utilized a radical approach starting from alkenes and α-iodo stannyl esters **91**. Thermal radical formation by using a catalytic amount of AIBN while refluxing in benzene gave the desired lactones in good yields. Their approach was applicable to cyclic alkenes as well, which formed the core furofuranones structures **93** and **94** (**Scheme 22**).[86]

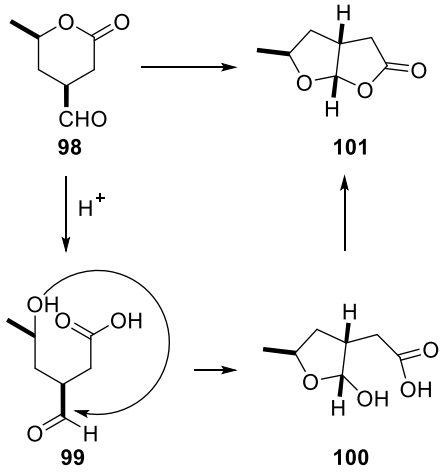


Scheme 22. Radical approach for the addition of α-iodo esters to alkenes.

Utilizing an α-substituted ester yielded a 1:1 mixture of diastereomers (**94**). Mechanistically, two pathways were proposed, one in which the radical formed on the alkene adds directly to the carbonyl-C, giving the product after $SnBu_3$ abstraction (**Scheme 22b**), and the Baldwin-forbidden pathway, in which the radical adds to the ester-oxygen, simultaneously abstracting the stannyl radical (**Scheme 22a**). Even though the latter is formally not possible, mechanistic evidence had been gathered by other groups showcasing the possibility.[87,88] Later, however, the groups of Kraus and Maillard showed that the mechanism actually proceeds through a homolytic radical addition followed by an ionic cyclization.[89] The synthesis with α-halo esters has been optimized for a variety of γ-lactones.[90–93]

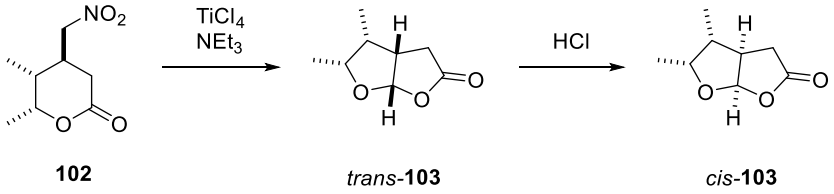
A different approach was investigated by the Yoshikoshi group, who made use of a the acyl-lactone rearrangement, previously discovered by Lange, Wamhoff and Korte.[94] The mechanism elucidated by Lange *et al.* is depicted in **Scheme 23**.[95] The reaction

starts with aldehyde **98**: The lactone is opened, and the formation of the 5-membered ring **100** is favored over the recyclization to the 6-membered ring. **100** then undergoes acid mediated lactonization to give the final product **101**.



Scheme 23. Acid mediated ring contraction of 6-membered lactones.

A similar approach was chosen by Nakata and Oishi *et al.* in their total synthesis of (+)-Pederin. The nitro-lactone **102** was converted into the corresponding aldehyde with the help of $TiCl_4$ and subsequently treated with NEt_3 to cleave the lactone and catalyze the recyclization. They also showed it is possible to transform diastereomer *trans*-**103** into the thermodynamically more stable *cis*-**103** by HCl treatment.[96]

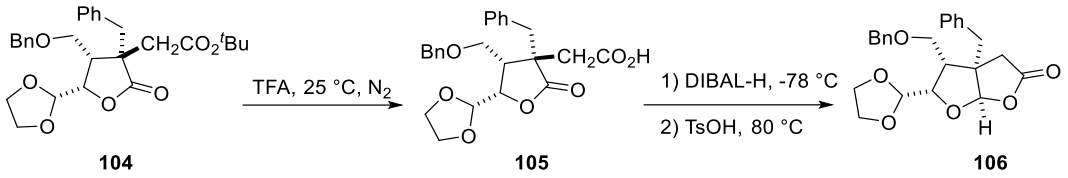


Scheme 24. Acyl-lactone rearrangement of **102**.

The acyl group can also be masked by a 1,3-diaxolane. Piva *et al.* synthesized the corresponding lactone *via* ring closing metathesis, followed by photochemical addition of 1,3-dioxolane. After hydrolysis of the group, the acyl readily underwent the transformation to the desired lactone.[97]

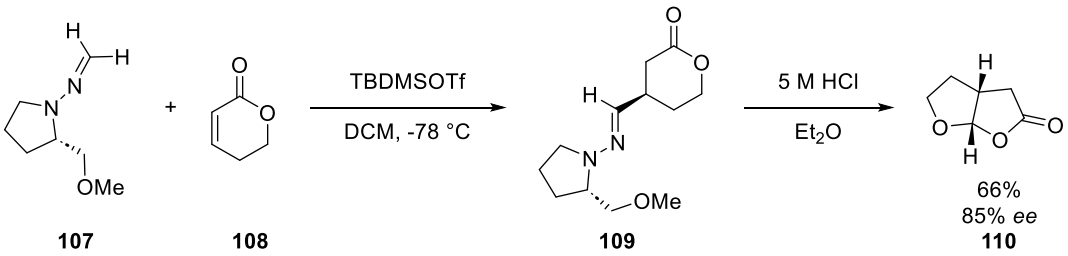
A similar strategy was reported by Anderson *et al.* during their synthesis of the ginkgolide ring system. After saponification of the *tert*-butyl ester with TFA to give

lactone **105**, they performed a DIBAL-H reduction of the lactone, which then underwent acid-mediated lactonization to give the final product **106** (**Scheme 25**).[98]



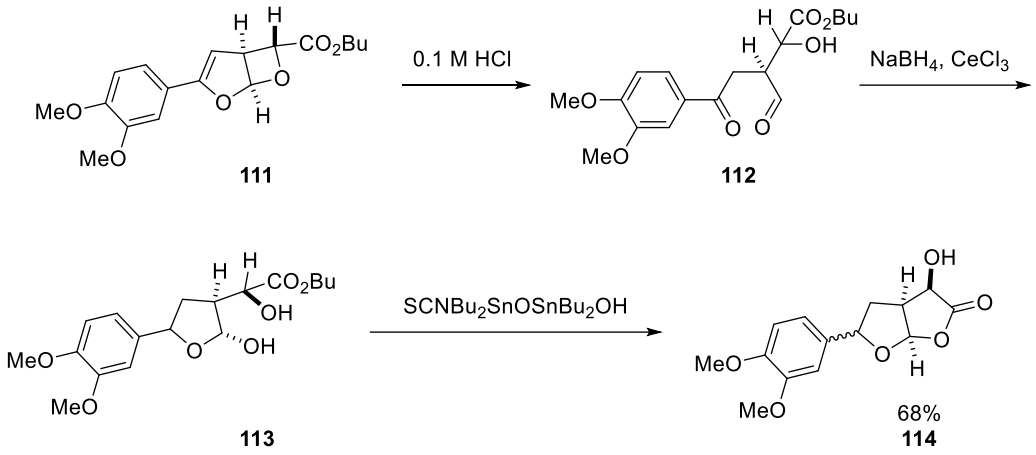
Scheme 25. Reduction-lactonization sequence of ginkgolide precursors.

One of the first enantioselective approaches relies on the acyl-lactone rearrangement as well. The SAMP-hydrazone **107** reaction developed by Corey and Enders[99] followed by hydrolysis of the imine **109** gives the acyl lactones needed to perform the dia-and enantioselective rearrangement to the chiral furofuranones **110**. If a substituent next to the carbonyl in **108** was needed, it could be introduced in another alkylation step with the help of LDA and HMPA. Starting from enantiopure reagents, this reaction provided products with an *ee* of up to 98% (**Scheme 26**).[100]



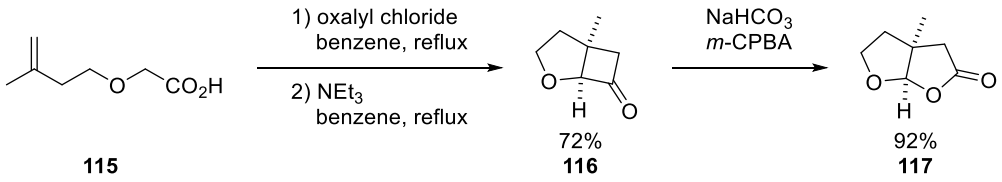
Scheme 26. Enantioselective SAMP-hydrazone mediated acyl lactone rearrangement.

Similarly, this approach can also be used in ring expansions of oxetanes with subsequent transesterification. Schreiber *et al.* synthesized oxetane **111** by [2+2] cycloaddition of butyl 2-oxoacetate and tributyl(furan-2-yl)stannane and subsequent displacement of the stannane with veratrole bromide.[101] They then hydrolyzed the acetal and performed a Luche reduction on **112** to give lactol **113**, which was closed to give the final product **114** using Otera's stannane transesterification catalyst (**Scheme 27**). Interestingly, this catalyst differentiated between the formation of the 5- and 6-membered lactone depending on the temperature.



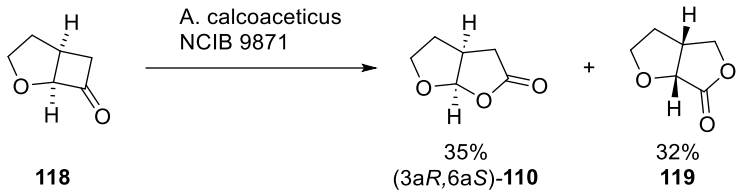
Scheme 27. Formal ring expansion of oxetanes.

The expansion of 4-membered rings is another viable pathway for the synthesis of furo[2,3*b*]furan cores: Bayer-Villiger reactions are ideal for this case, as the precursors needed can be synthesized by [2+2] cycloadditions. The first group to report a systematic intramolecular [2+2] cycloaddition of ketenes to alkenes was Snider *et al*., who investigated this transformation extensively.[102] Additionally, they showed the Bayer-Villiger oxidation on some model compounds, which proceed in high yields of 90-95% (**Scheme 28**).



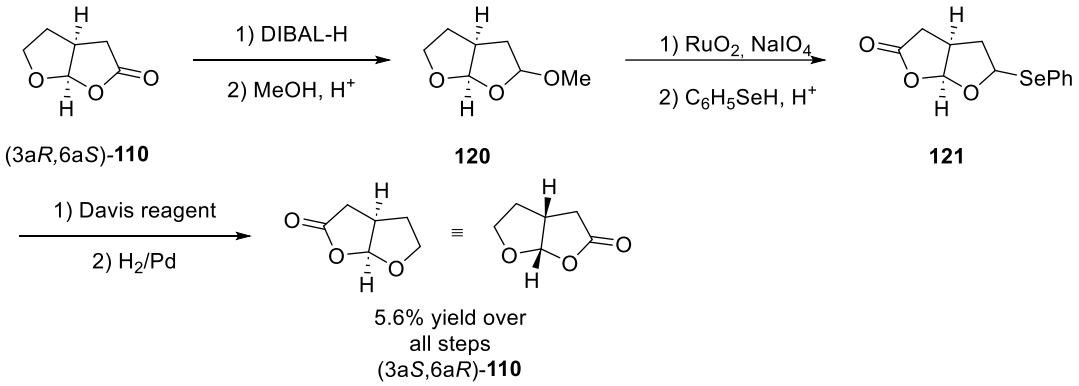
Scheme 28. Bayer-Villiger Oxidation following [2+2] cycloaddition of ketenes.

An enantioselective synthesis of the furofuranone core was also achieved by a Bayer-Villiger oxidation. Contrary to the classic method using *m*-CPBA, Furstoss *et al.* used the enzyme A. calcoaceticus to perform the reaction. Interestingly, they obtained not only the desired compound (3a*R*, 6a*S*)-**110**, but also its isomer **119** in a ratio of 1:1.[103] However, the obtained lactone **110** is the wrong enantiomer for the clerodane skeleton the group was trying to build (**Scheme 29**).



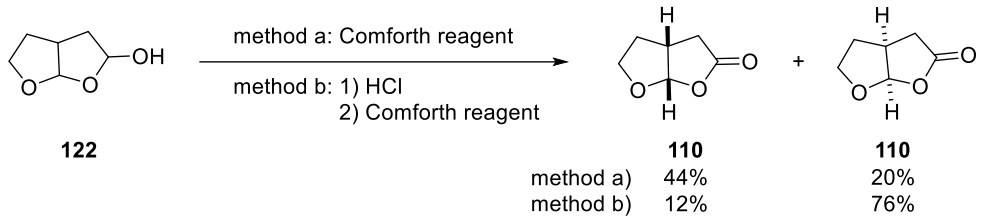
Scheme 29. Enzymatic Bayer-Villiger Oxidation.

The Furstoss group, who developed this chemistry, therefore sought to transform it into the correct enantiomer, which they achieved 2 years later (**Scheme 30**). Starting from (3a*R*,6a*S*)-**110**, they first reduced the lactone to the corresponding lactol. After esterification to **120**, the other α-oxygen position was oxidized, followed by the displacement of the methoxy group with a phenylselenyl moiety giving **121**. This was eliminated to give the alkene and the desired enantiomer (3a*S*,6a*R*)-**110** was formed after hydrogenation of the alkene with only minimal loss of *ee* (80% down from 86%).[104]



Scheme 30. Correction of the enantiomers.

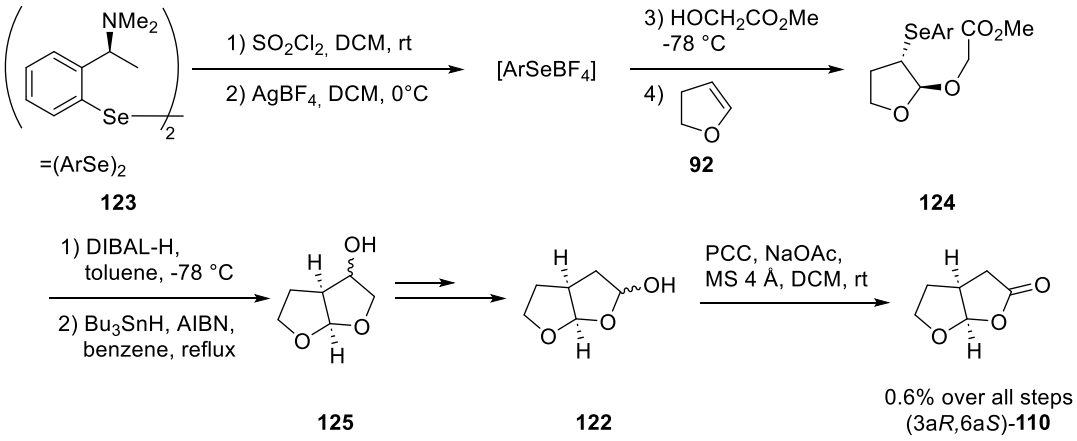
Aside from addition reactions with subsequent lactonization, the oxidation of alcohols **122** to ketones was also investigated. Using an acyl-lactone rearrangement, Groot *et al.* synthesized the alcohols **122** and subsequently oxidized them with pyridinium chlorochromate (Comforth reagent). Equilibration of the alcohol prior to the oxidation improves the yield of the obtained products (**Scheme 31**).[105]



Scheme 31. Oxidation of alcohol **122**.

The same route was followed by Kato *et al.* in multiple synthetic pathways as intermediates in the synthesis of perhydrofuro[2,3*b*]furans.[106,107]

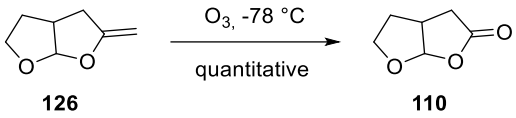
The Uchiyama group used this strategy as well, however, the buildup of the bicycle is distinctly different than previously mentioned procedures. They used their previously developed oxyselenenylation between the arylselenium compound **123** and dihydrofuran. The resulting compound **124** is reduced by DIBAL-H and cyclized with the help of the radical initiator AIBN and tributylstannane. 5 more steps lead to lactol **112** which is oxidized by PCC (**Scheme 32**).[108]



Scheme 32. Oxyselenenylation approach with subsequent PCC oxidation.

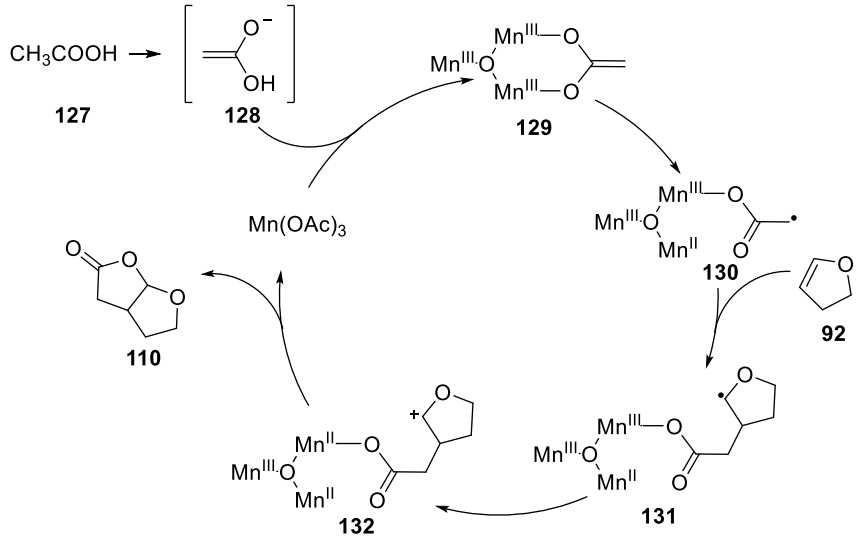
Similar routes have been followed in recent natural product syntheses, often also combined with previously mentioned rearrangements.[77,109,110]

A comparable reaction is the oxidation of alkene substituents α to one of the oxygens *via* ozonolysis, as demonstrated by the group of Lallemand (**Scheme 33**).[111,112]



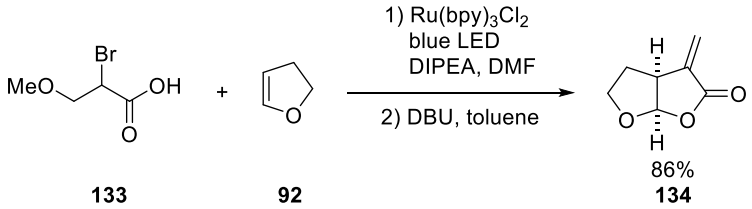
Scheme 33. Ozonolysis of alkene **126**.

Another approach utilizing radicals was developed by Trogolo *et al.*, who used $Mn(OAc)_3$ together with ultrasound irradiation. With easily enolizable compounds and enol ethers, high intensity ultrasound irradiation at low temperatures gave the corresponding lactones in excellent yields (**Scheme 34**).[113,114]



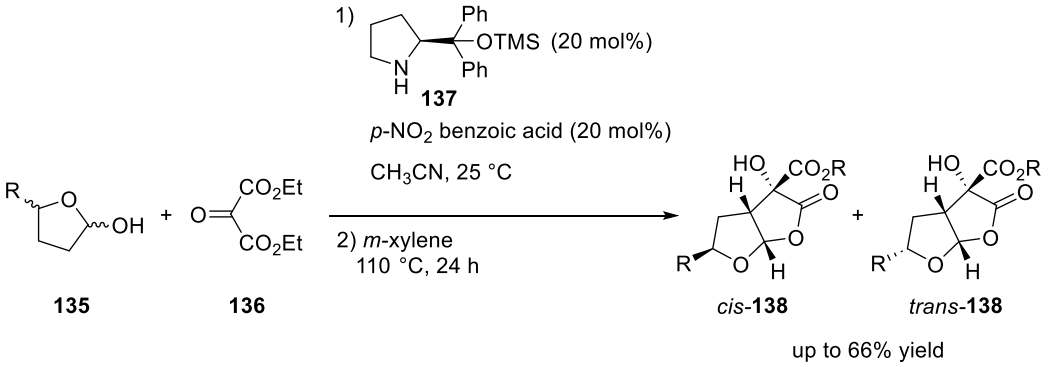
Scheme 34. Mechanism of the $Mn(OAc)_3$ mediated addition of enol ethers to acetic acid.

Yet another radical pathway was developed by Tang *et al*. in their photo [3+2] addition. Starting from 2,3-dihydrofuran (**92**) and **133**, they were able to synthesize lactone **134** after β-elimination (**Scheme 35**).[115]



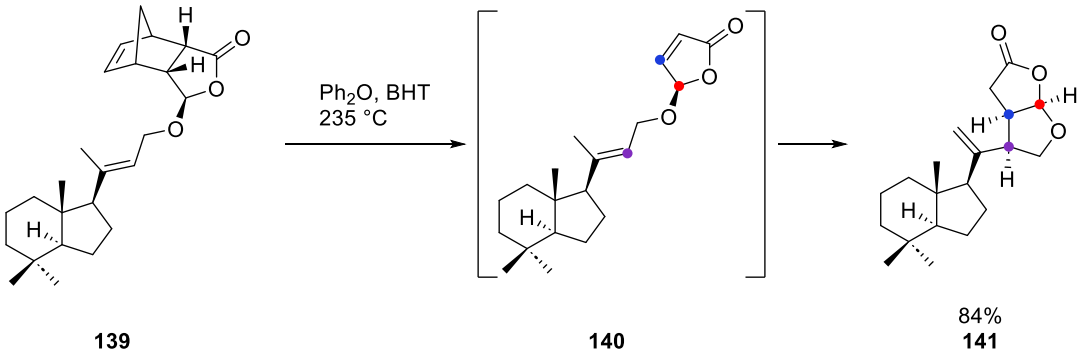
Scheme 35. Photoredox catalyzed [3+2] cycloaddition followed by β-elimination.

In recent years, there has been a larger focus on developing enantioselective tools for the catalytic synthesis of furo[2,3*b*]furanones without the need for enantiopure starting materials or additives. Liu *et al.* developed an enantioselective desymmetrizing aldol reaction between hemiacetals **135** and ketomalonate (**Scheme 36**). While the reaction produced 2 diastereomers, both were formed with high *ee* values mostly over 97%.[116]



Scheme 36. Desymmetrizing aldol reaction.

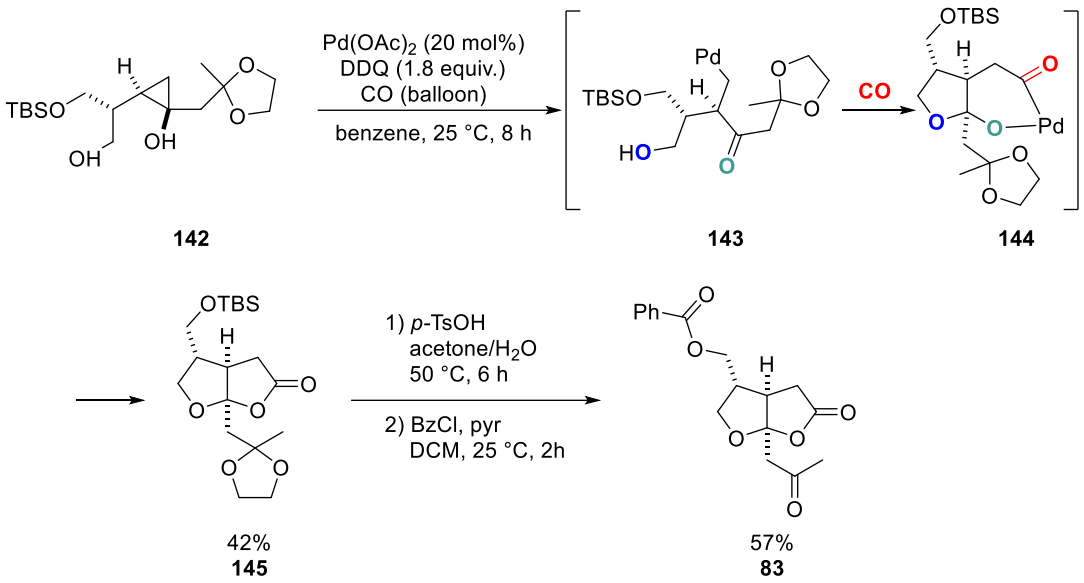
A formidable cascade which builds up a key intermediate in the synthesis of Norrisolide-type products is the ene-reaction of **139** developed by the group of Liang. After a retro Diels-Alder reaction, the intermediate **140** reacts smoothly to the key structure **141** (**Scheme 37**).[117]



Scheme 37. Cascade retro Diels-Alder-ene reaction.

A recently developed racemic synthesis of Paeonilide utilizes a palladium-catalyzed hydroxy cyclopropanol opening with CO addition as key step. The mechanism is illustrated in **Scheme 38**.[118] After Pd-assisted ring opening, the alcohol previously on the cyclopropyl moiety in **142** is oxidized by DDQ to the ketone **143**. The blue hydroxyl

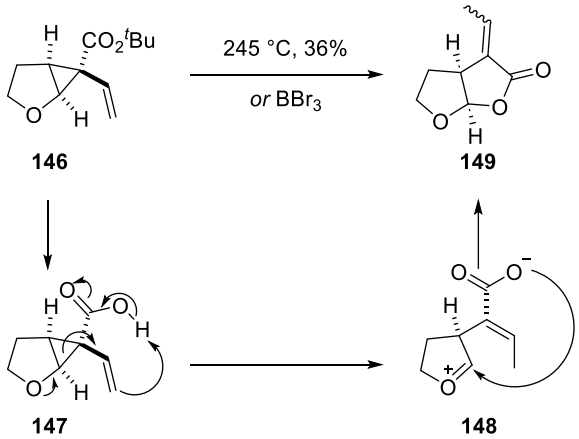
group then attacks the turquoise ketone to form the first THF-cycle, and palladium-assisted CO addition gives intermediate **144**. Pd is released to form **145**, which is finally transformed into racemic Paeonilide **83**.



142 **143** **144** **145** **83**

Scheme 38. Pd-catalyzed cyclopropanol ring opening synthesis of Paeonilide.

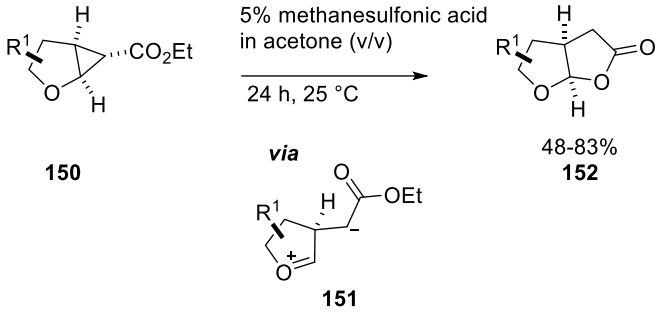
A very substrate dependent methodology is the ring expansion of *tert*-butyl vinylcyclopropane carboxylate to butyrolactones. Davies *et al.* showed the formation of lactone **148** when vinylcyclopropane **146** was treated with either high temperatures or BBr_3 (**Scheme 39**).[119] This transformation was only observed with the ^{t}Bu-ester, otherwise the vinylcyclopropane-cyclopentene rearrangement or fragmentation was observed.



146 **149** **147** **148**

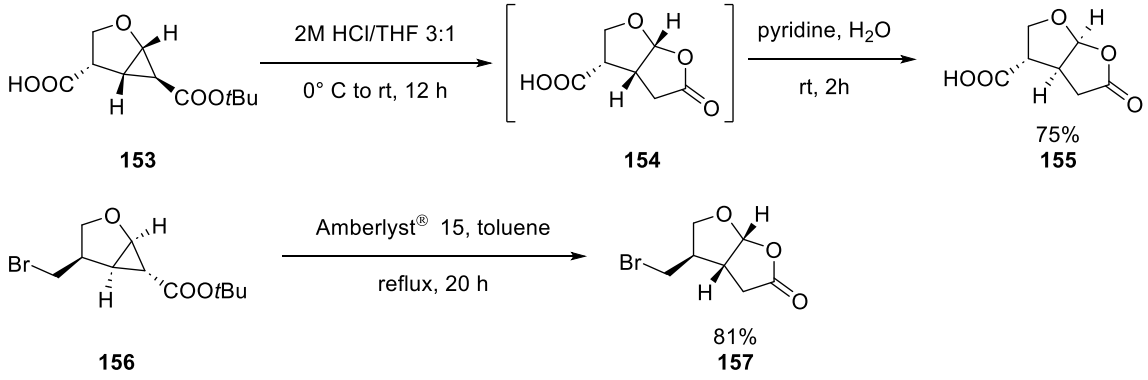
Scheme 39. Heat/Lewis acid catalyzed rearrangement of vinylcyclopropane **146**.

This reaction is similar to the well-known vinylcyclopropane-cyclopentene rearrangement, which is discussed in chapter 1.2. Cyclopropanes can also be opened to lactones with the help of Brønsted acid catalysis. Work on this transformation was pioneered by the group of Theodorakis *et al.* on their endeavors to synthesize Norrisolide **65**. The key feature of this transformation is the use of the oxygen in α-position to the cyclopropane as a donor and the ester moiety as the acceptor (**Scheme 40**).[120] This allows the cyclopropane ring to open and form **151** as the intermediate, which undergoes hydrolysis under acidic conditions to give the final product **152** as a single diastereomer. The strategy supports several substituents on the tetrahydrofuran ring, and non-cyclic substrates and protecting- and functional groups such as acetals, exocyclic ketones and silyl ethers were transformed as well with excellent chemoselectivity.



Scheme 40. Synthesis of γ-butyrolactones from cyclopropanes.

In a similar fashion, Reiser *et al*. have utilized this transformation in their endeavors to synthesize both enantiomers of Paeonilide **63** (**Scheme 41**).[71,121]



Scheme 41. Acid mediated ring expansion of cyclopropanes.

Although they needed slightly different acids to induce the transformation, it went smoothly. Additionally, they showed that the equilibration to the desired diastereomers was possible, either base-induced or by effectively tuning the reaction conditions to allow for ring opening and equilibration in one step. Neither Theodorakis nor Reiser observed significant loss of chiral information in their approaches. They laid the groundwork for the chemistry described in chapter 2.3.

1.4 Photoredox catalysis

As detailed in the introductory chapter, the field of catalysis has been undergoing accelerated development since the turn of the century, with rapidly emerging novel methodologies. This work incorporates innovative catalytic approaches, including a photoredox-catalyzed transformation. The following chapter establishes the fundamental knowledge required to comprehend this chemistry.

The idea to use light for chemical reactions was first raised in 1912. Giacomo Ciamician was the first chemist to address this possibility using sunlight, as it provides sufficient energy for plant processes and therefore should be applicable to chemical reactions as well.[122] Sunlight has a very broad emission spectrum consisting of 3% UV light, 44% visible light and 53% infrared, depicted in **Figure 1**.[123]

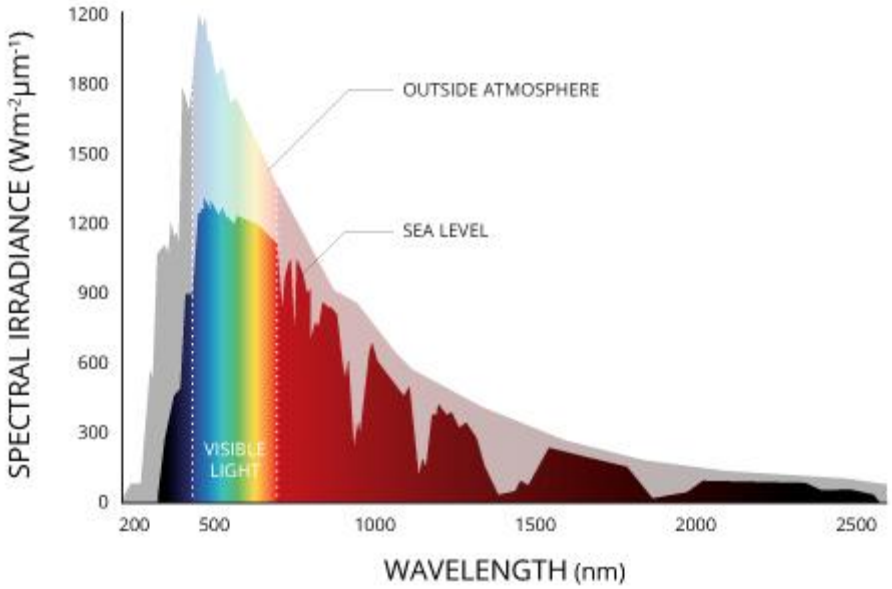
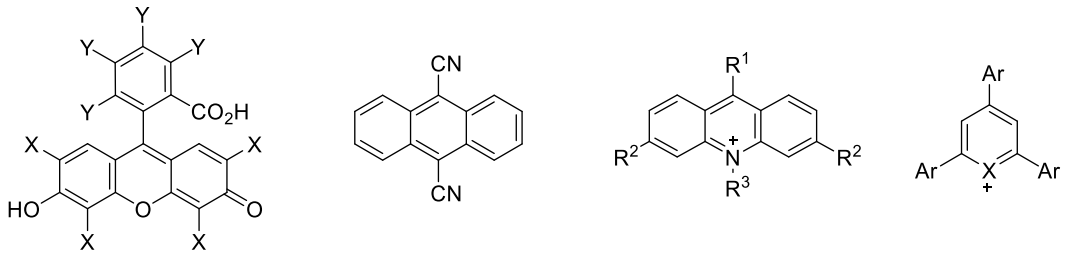


Figure 1. Spectrum of sunlight.[123]

Organic molecules excited by UV light can, amongst other reactions, undergo Norrish Type 1 and 2 reactions, Yang cyclizations or Paternó-Büchi reactions.[124] However, chemistry using UV light has some major drawbacks: First of all, UV light is highly energetic, which is a hazard for human health. Secondly, special quartz glassware, which is quite expensive, has to be used as most commonly used labware is made of borosilicate glass. It has a UV cutoff at approximately 300-320 nm, making the UV light unavailable for the reaction. Finally, chemoselectivity is significantly reduced because functional groups are often activated uncontrollably, going so far as to mediate complete decomposition of the molecule.[125] An ideal approach would therefore be to use more benign and longer wavelength visible light as method of excitation, as it minimizes safety concerns, does not interfere with a large number of substrates and tolerates the majority of different functional groups. This is where the field of photoredox catalysis has found its places in synthetic chemistry. The basic idea is to repurpose the transition metal complexes already used in solar panels as energy transfer reagents in synthetic organic chemistry.[126] These mostly ruthenium- and iridium-based complexes with polypyridyl ligands enabled many previously inaccessible transformations under comparably mild conditions.

However, these transition metal based complexes of platinum group metals (Ru, Rh, Pd, Os, Ir, Pt) have inherent toxicity issues and are expensive due to their rarity, which makes them problematic for industrial purposes.[127] These are the reasons why researchers have turned their attention to other, earth abundant metals. Especially 3d-metals have been explored in this regard, like $[Cu(dap)_2]^+$, a prominent 3d-transition metal catalyst established by the Reiser group.[128] Organic photoredoxcatalysts offer an alternative to metal complexes. Various structural motifs exist, some examples being rose bengal (**159**), 9,10 dicyanoanthracene (**160**), Eosin Y (**158**), pyryliums (**162**) and Acridinium salts (**161**) (**Scheme 42**).[129] Especially acridinium salts **161** and pyrylium catalysts **162** give access to highly oxidizing transition states unreachable by metal-based catalysts *(vide infra)*.



X=Br; Y=H: Eosin Y **158**
X=I; Y=Cl: Rose Bengal **159**

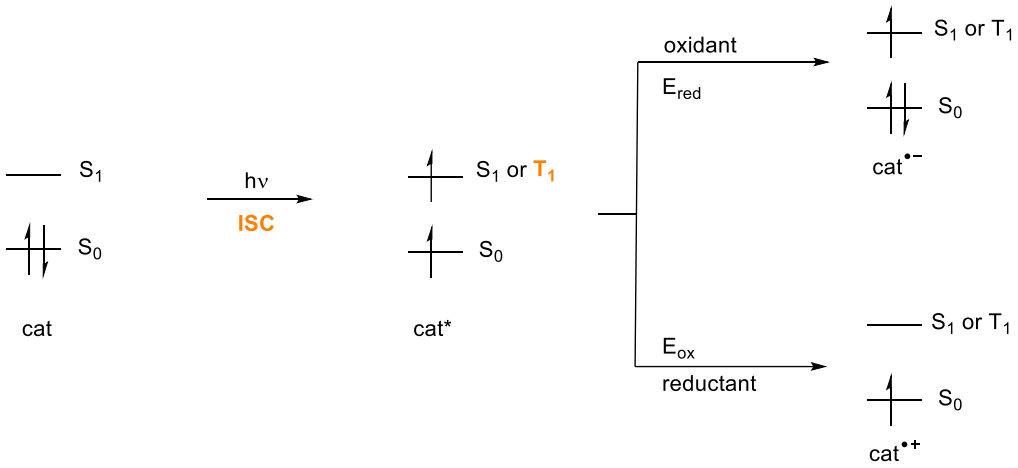
9,10-Dicyanoanthracene **160**

Acridinium salts **161**

Pyryliums
X=O,S **162**

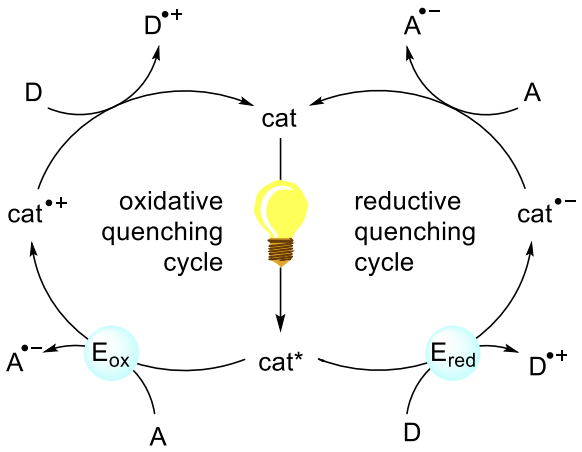
Scheme 42. Common organic photoredox catalysts.

The working principle is illustrated in **Scheme 43**. When the photocatalyst (cat) is excited by visible light, an electron from the ground singlet state S_0 transitions to higher excited singlet state. Excited states higher than S_1 quickly relax to the lowest energy excited S_1 state. This state can either relax back to S_0 by radiative or non-radiative processes, or it can undergo a non-radiative, spin-forbidden intersystem crossing (ISC) to the T_1 state. This is longer-lived than the S_1 state, as the decay to the ground state S_0 is spin-forbidden as well. These S_1 and T_1 excited state intermediates cat* are now good oxidants and reductants at the same time.[129] In contrast to metal-based photoredox catalysts, both the S_1 and the T_1 excited states can catalyze energy and electron transfer processes. Additionally, the loss of photoexcitation energy is lower in organic photoredox based catalysts, which allows for better use of the excitation energy.[130]



Scheme 43. Photophysical processes of organic photoredoxcatalysts.

A photoredox catalyzed reaction can proceed either *via* the oxidative or the reductive quenching cycle (**Scheme 44**). In the oxidative quenching cycle, the excited photocatalyst cat* is oxidized by giving an electron to an acceptor A, therefore reducing it. Typical examples for the latter are viologens, polyhalomethanes, dinitro- and dicyanobenzenes or aryldiazonium salts. This results in the oxidized catalyst, which now is oxidatively quenched by any type of electron donor. The reductive quenching cycle proceeds when the excited photocatalyst cat* is reduced by an electron donor D in the first step. This intermediate can donate an electron to an acceptor, thus regenerating the catalyst. Typical donors commonly used are tertiary amines.[131] Processes that do not need external donors or acceptors are net-redox neutral and preferred due to their excellent atom economy.[129]

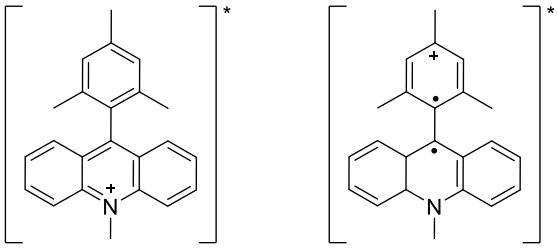


Scheme 44. Schematic overview of the oxidative and reductive quenching cycle.

Which cycle the reaction will proceed through can be estimated by comparing the potentials of the half reactions of the catalyst and the substrate, which are measured in Volts against the standard calomel electrode. As processes catalyzed by organic photoredox catalysts can proceed from both the S_1 and T_1 state, they are subscripted with the respective state, e.g. $E_{red}^{S_1}$.

Fukuzumi's catalyst, which is employed in this work, belongs to the class of acridinium ions which can form charge transfer or charge shift states if the aryl substituent is electron rich enough.[129] This means that there are four possible excited states: a locally

excited (LE) (**163**) and a charge transfer (CT) state (**164**) of the S_1 and T_1 states, respectively (**Scheme 45**).[132]



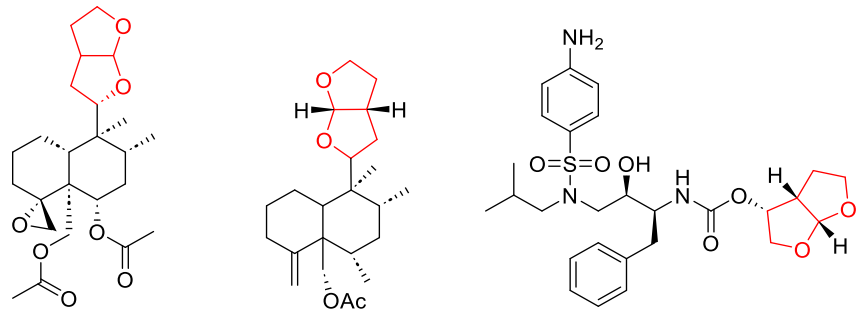
Scheme 45. Locally excited and charge transfer state of Fukuzumi's catalyst.

Which one of these states is the one participating in reactions is not fully understood. The triplet state is currently favored, although it is not clear if it is the LE state ($E_{red}^{T_1}$= +1.45 V vs. SCE) or the CT state ($E_{red}^{T_1}$= +1.88 V vs. SCE).[129] Nevertheless, this catalyst and other acridinium salt derivatives have been widely applied in various reactions.

Since photoredox catalysis is a young field, new methods based on it are ever-emerging. Acridinium salts, with their high oxidation potentials, make the activation of substrate classes possible which were previously inaccessible. This was exploited in the synthesis of fused THF-structures different to the ones mentioned in chapter 1.3. The donor-acceptor vinylcyclopropane functionalities result in an interplay crucial for the transformation. The structures and their methods of synthesis will be introduced in the next chapter.

1.5 Hexahydrofuro[2,3b]furans

Hexahydrofuro[2,3b]furans are bicyclic fused tetrahydrofurans. Some examples are lupulin C **166**, dihydroclerodin **165**, or the anti-HIV medication Darunavir **167** (**Scheme 46**). Among these compounds, also known as perhydrofurans, the dihydro-clerodins were discovered first, isolated from plants around 1972.[133]



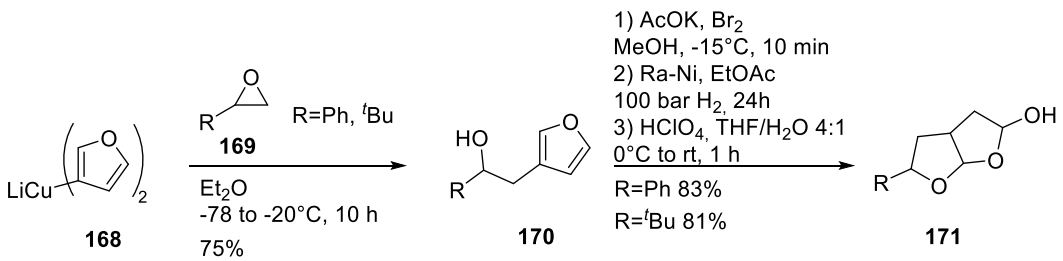
165 **166** **167**

Scheme 46. Examples of molecules with a hexahydrofuran core.

The fused tetrahydrofuran rings are the active structural motif for efficacy against insects and viruses due to its unique conformation. Although clerodanes have been synthesized, research on their extraction from plants outweighs investigations on their chemical synthesis.[134–136] Today's focus mainly lies on the synthesis of Darunavir, as it has shown remarkable activities against multidrug-resistant HIV strains.[137]

1.5.1 Investigations towards clerodane derivatives

After establishing the hexahydrofuran core as the important structure for antifeedant activity,[138,139] the synthesis of clerodanes was examined. The group of Kato was pioneering in this work, synthesizing simple perhydrofurans from their previously developed synthesis of substituted furans **170** with the help of lithiumcuprates (**Scheme 47**).[138]



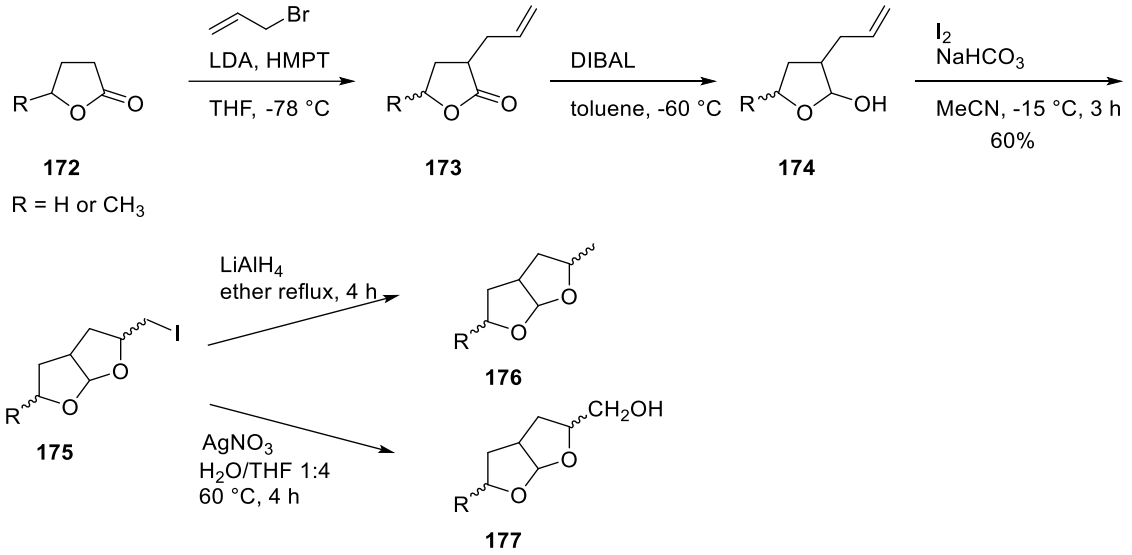
168 **170** **171**

Scheme 47. Pioneering synthesis by Kato *et al.*

Their initial synthesis provided good yields and the hexahydrofuran **171** was obtained as a diastereomeric mixture. When testing the newly synthesized compounds for their

activity against *spodoptera litura F*, a nocturnal moth which feeds on many economically important agricultural crops[140], they found the rigid conformation of the bis-THF ring is important for the antifeedant activity. Large substituents stabilize the conformation, and sterically demanding groups can easily be coupled *via* esterification reactions or substitutions on the alcohol moiety.

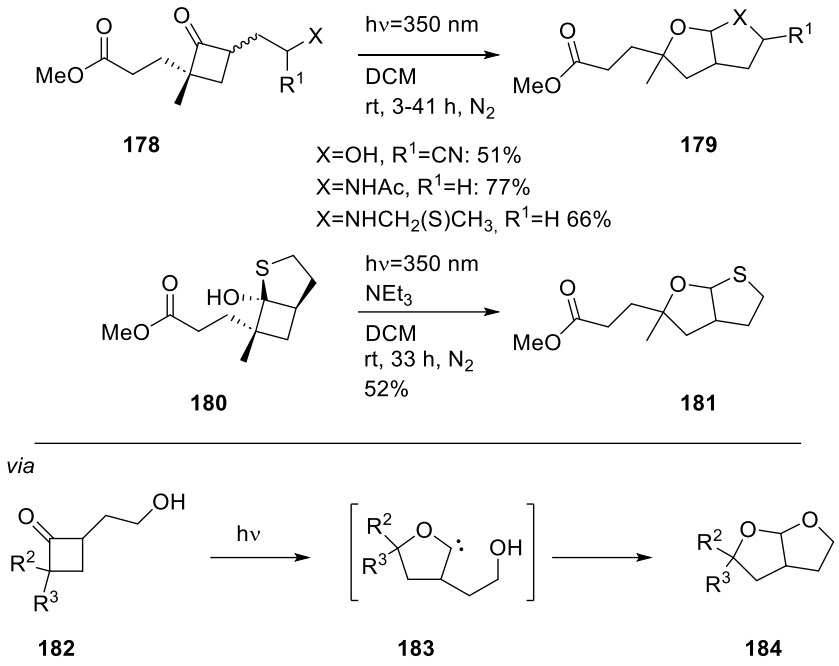
In 1982, Lallemand *et al.* reported a synthesis *via* iodo-lactonization starting from compound **172** (**Scheme 48**).[111]



Scheme 48. Iodo-lactonization by Lallemand *et al.*

Similar to the previously mentioned approach, toxic reagents such as HMPT in conjunction with a comparatively high number of reaction steps were found to be necessary.

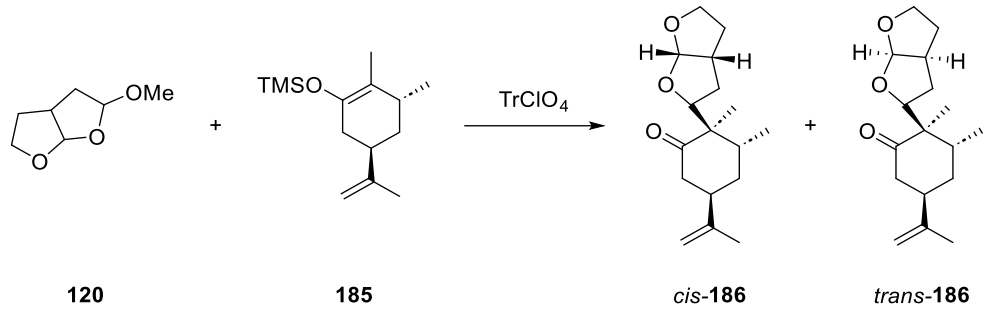
In sharp contrast, Pirrung *et al.* published a photochemical radical reaction starting from substituted cyclobutanones in 1989.[141] Irradiation of **178** and **180** with UV-A light in DCM provided the bis-THF structures in acceptable yields, and the method even enabled the production of compounds with N- and S- heterocycles (**Scheme 49**). The mechanism proceeds *via* a homolytic cleavage of the bond adjacent to the carbonyl group, followed by a C-X insertion to yield **179** and **181**.



Scheme 49. Pirrung's photochemical synthesis.

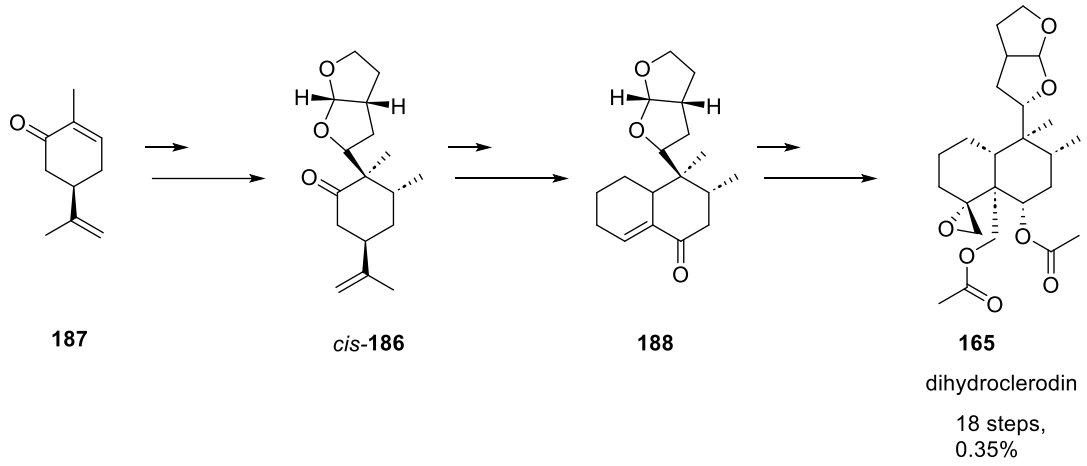
Although this reaction does not require any toxic reagents and can be performed under comparably mild conditions, the yields are considerably lower than the previous multi-step approaches. All these methods suffer from issues with diastereoselectivity, although in some cases they are separable by crystallization.

In the following years, clerodanes were isolated from plants, but no attempts were made at the synthesis of dihydroclerodin until 1999, when de Groot *et al.* reported the total synthesis starting from *R*-(-)-Carvone.[142] Key step for the desired configuration is a Mukiyama reaction between **120** and **185**. The hexahydrofuro[2,3b]furan was used as a racemic mixture, but attached itself to the Carvone derivative in remarkable diastereoselectivity. No yields are given for the diastereomers *cis*-**186** and *trans*-**186**, but the authors were satisfied enough with the yields to continue the synthesis with the desired diastereomer.



Scheme 50. Key step of the total synthesis of dihydroclerodin by de Groot *et al.*

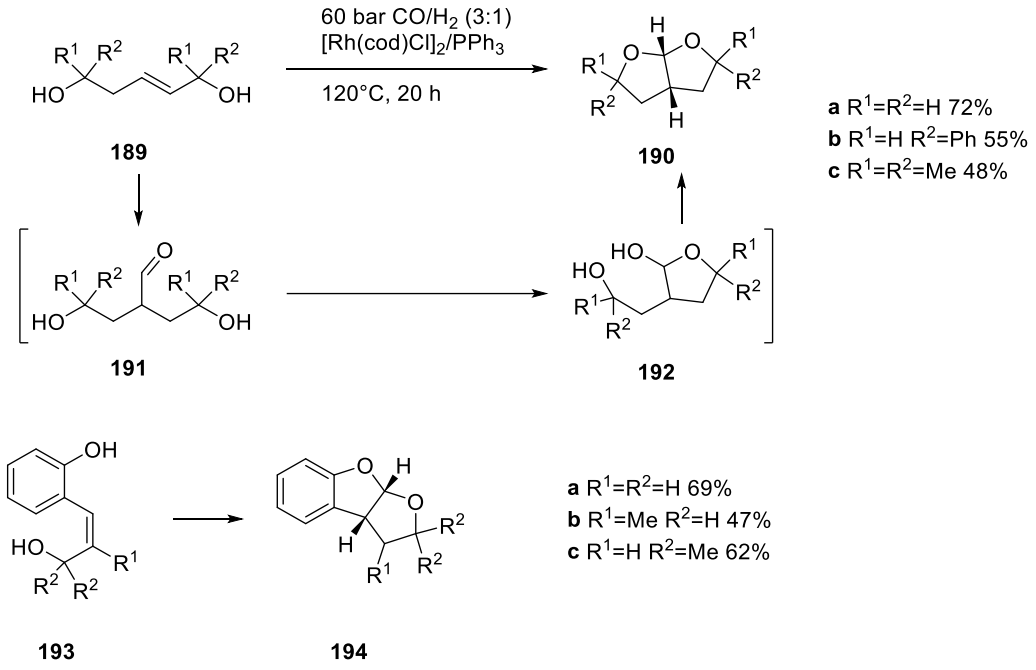
In total, 18 steps were needed to produce an overall yield of 0.35% (**Scheme 51**), however, the group showed with their early incorporation of **120** that the fused ring system is stable to a wide variety of reaction conditions, including reductions, ozone, metals, Grignard reactions, heat, basic and acidic milieus.



Scheme 51. Pathway overview of the de Groot synthesis.

The total synthesis of clerodanes remains a field difficult to navigate, which is why many groups focus on the synthesis of the bis-THF moiety instead of the complete natural products.

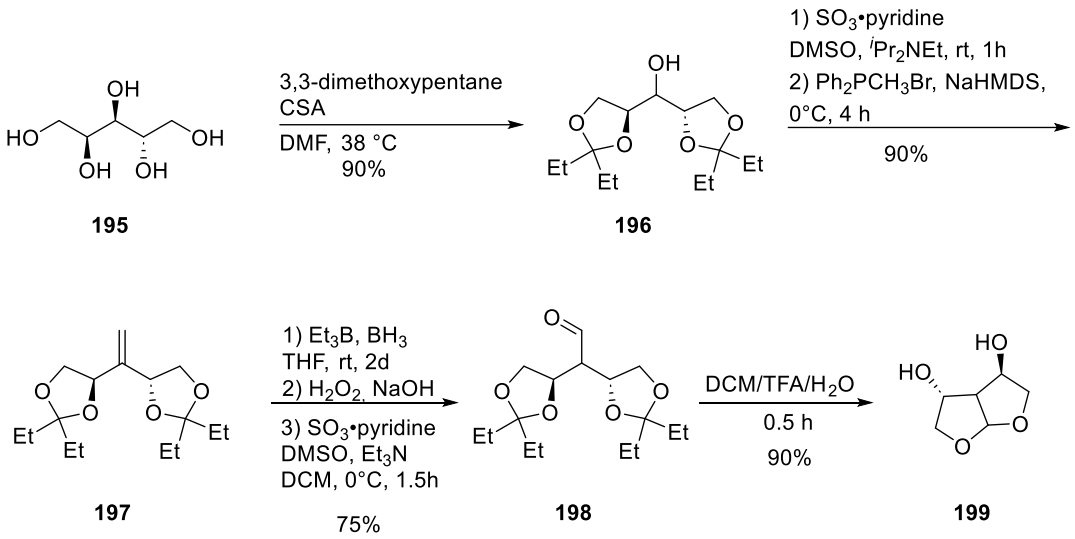
In 2002, the group of Eilbracht published a tandem hydroformylation/acetalization starting from alkenediols to furo[2,3*b*]furans.[143] The procedure also worked well for benzannulated substrates, with moderate to good yields (**Scheme 52**). The intermediate **191**, product of the initial hydroformylation reaction, cyclizes to the hemiacetal **192**, which undergoes another cyclization to the final product **190**.



Scheme 52. Tandem hydroformylation/acetalization by Eilbracht *et al.*

This is one of the most promising approaches, as hydroformylation is a well-employed process in industry and the incorporation into pre-existing reactors is easier than designing new ones. The authors only tested a limited scope of different molecules, but based on the fact that hydroformylation can be applied to molecules with a variety of functional groups,[144] they assume their reaction should fall under similar conditions as well. Another advantage of this reaction is the readily available starting material in comparison to, for example, the more complex cyclobutanes employed by Pirrung *et al.* (**Scheme 49**).

Starting material accessibility is another point of discussion in the context of total synthesis, especially when the product is to be produced on a multigram scale. Linclau *et al.* developed a synthesis of simple bis-THF systems from the sugar *L*-Arabitol **195**. After protection and hydroboration, a Parikh-Doering oxidation yields the precursor **197**, which can be converted into the final product **199** through a deprotection/cyclization cascade (**Scheme 53**).[145,146] This reaction, however, also is in need of many steps and harsh reagents, making it unsuitable for a larger scale synthesis needed for application.



Scheme 53. Synthesis of bis-THF from L-arabitol.

1.5.2 Application as core structure in anti-HIV medications

In 1998, Ghosh *et al.* demonstrated the high potential of the bis-THF moiety to inhibit a HIV-protease.[147] In 2005, different parameters were investigated towards the applicability as medication specifically for HIV-strains resistant to drugs already on the market, finding the molecule to be a very good candidate.[137] The drug was approved by the FDA for patients unresponsive to existing drugs in 2006 and for all patients in 2008.[148] The bis-THF moiety is a perfect fit for the cavity of the inhibition site of the HIV-protease, forming strong hydrogen bonds between the THF oxygens and protein side chains ASP 29 and ASP 30 (**Figure 2**).[149]

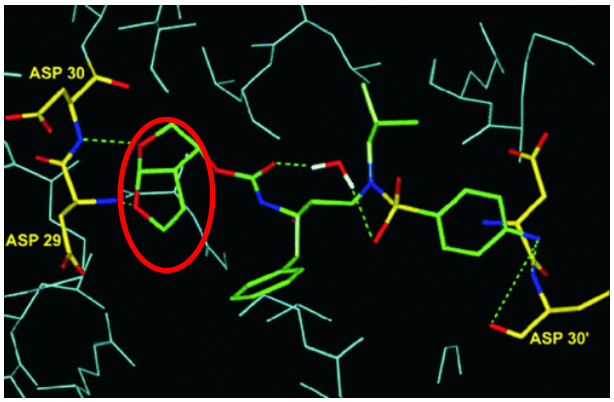
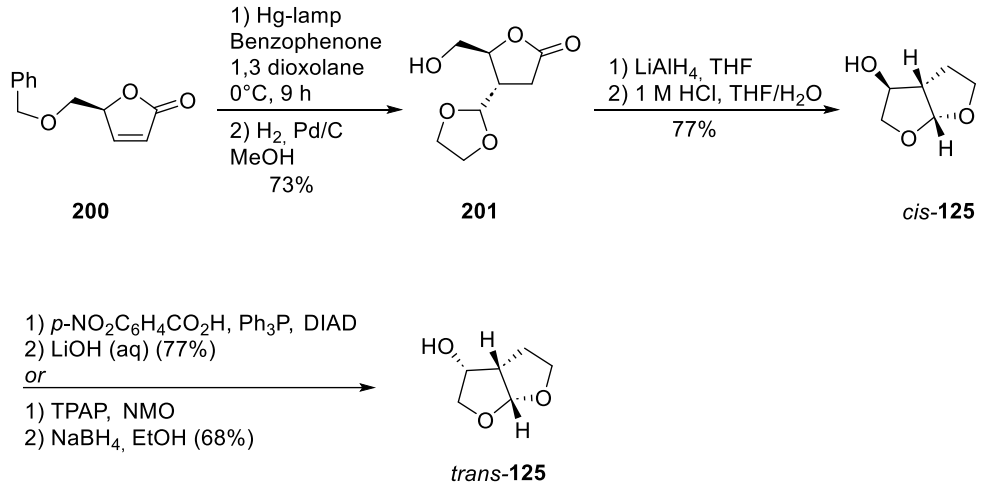


Figure 2. Interactions between bis-THF moiety and HIV-protease inhibitor site, marked in red.[†]

Needless to say, the drug is a success story. Many efforts have gone into the synthesis of the hexahydrofuro[2,3*b*]furan, as it serves as the core structure to be functionalized with the residual side chain, usually through an alcohol or the succinimide derivative.[150]

Ghosh *et al.* reported in 2004 a synthesis starting from **200** to achieve the optically active bis-THF in 38% overall yield. The attempt is similar to earlier ones at synthesizing the hexahydrofuro[2,3*b*]furan from above (**Scheme 54**).[151]

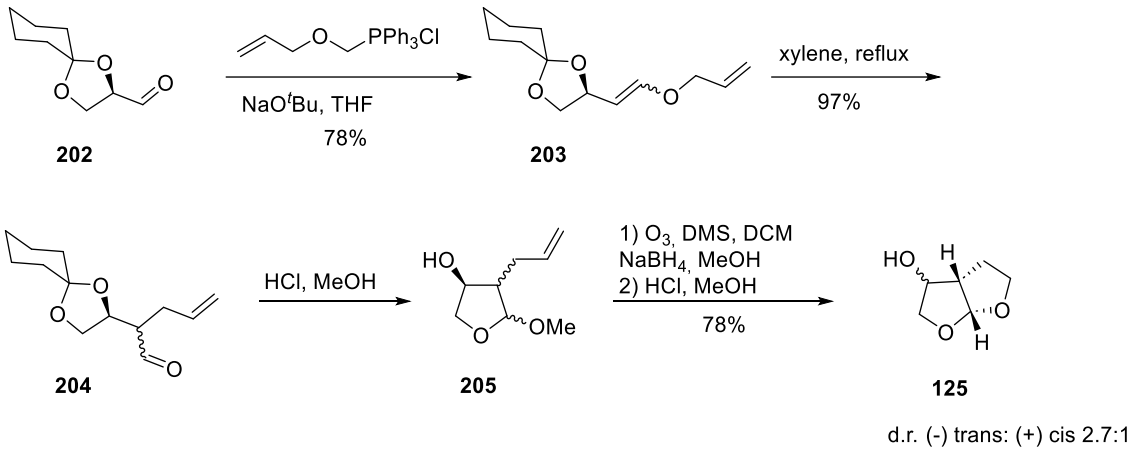


Scheme 54. Early synthesis of tetrahydrofuran moiety by Ghosh *et al.*

In another approach, published by Kulkarni *et al.* in 2010, the enantiopure compound was synthesized from 2,3-*O*-cyclohexylidene-D-gyceraldehyde **202** *via* a Wittig reaction,

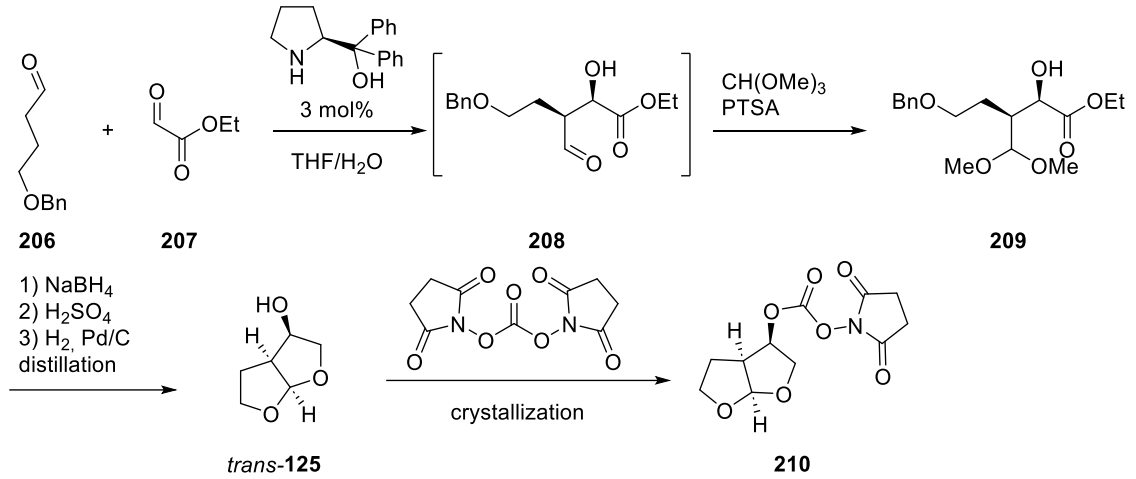
[†]Reprinted with permission from Ghosh, A. K.; Ramu Sridhar, P.; Kumaragurubaran, N.; Koh, Y.; Weber, I. T.; Mitsuya, H., *ChemMedChem* **2006**, *1*, 939–950. Copyright © 2006 John Wiley and Sons.

followed by a Claisen rearrangement. Ozonolysis was employed as the final step of this conversion (**Scheme 55**).[152]



Scheme 55. Synthesis of hexahydrofuro[2,3b]furan from 2,3-*O*-cyclohexylidene-D-gyceraldehyde.[152]

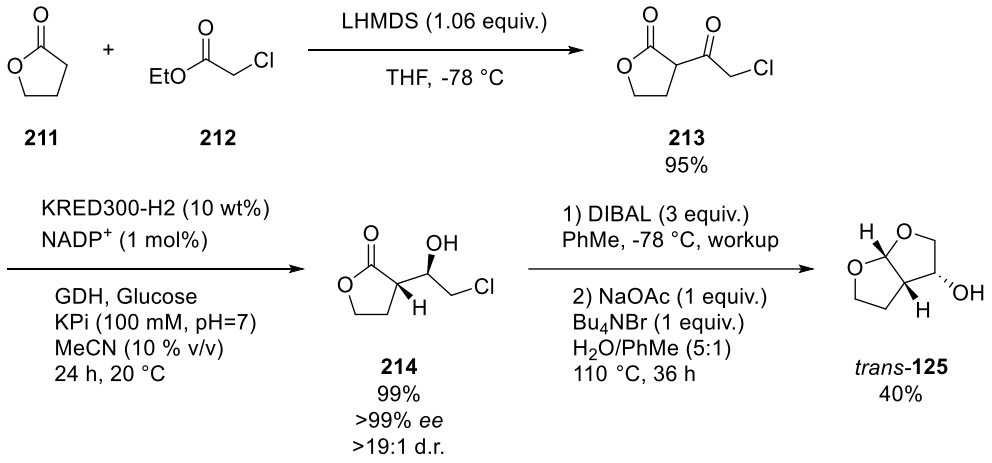
This reaction, however, suffers from low atom economy. Moreover, the final product **198** was converted to the corresponding enantiomers through a highly toxic Mitsunobu inversion. Therefore, while the reaction is interesting in its approach, is rather hard to scale up. In contrast, Ikemoto *et al.* have published a large-scale synthesis of the succinimide derivative **210**. They employed an organocatalytic procedure and a crystallization, yielding them a d.r. of more than 99:1 with 99% *ee* (**Scheme 56**).[153] This procedure does not require harsh conditions and more importantly, no purification is needed before **125**. The final step can be achieved in a single crystallization and the whole reaction can be performed on a 1.4 mol scale.



Scheme 56. Big Scale synthesis of succinimide derivative.

However, the synthesis of Darunavir is still very expensive, which means its availability in regions with few resources is low. The focus nowadays is therefore focused on reducing the cost of the synthesis of the drug.

Very recently, two promising syntheses of the hexahydrofuran core as well as the drug Darunavir itself have been published. In 2022, the group of Hyster *et al.* published the enzymatically catalyzed synthesis of the core using a ketoreductase as the key step (**Scheme 57**).[154]

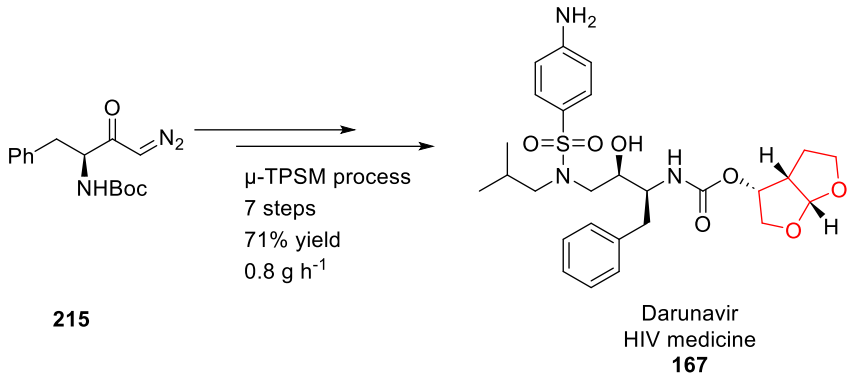


Scheme 57. Synthesis of hexahydrofuran core *via* enzymatic catalysis.

Previously reported strategies relied on enzymatic resolution of the racemic alcohol,[155,156] lowering the overall yield. The group of Hyster followed a different strategy: they wanted to reduce ketone **213** to the corresponding alcohol **214** with the use of a ketoreductase. They employed a high throughput screening approach, first screening 384 ketoreductases in their wild type and then searching the metagenome library for related homologues. This approach led them to ketoreductase KRED300-H2, which, after optimization of all reaction parameters, produced the desired halohydrin **214** in quantitative yield with >99% *ee* and >19:1 diastereomeric ratio. The final reduction and cyclization, however, only provided the product in 40% yield. Nevertheless, this method showcases the power of library-assisted screening methods.

Very recently, the group of Singh *et al.* published a micro-total process system (μ-TPSM) approach for the continuous flow synthesis of Darunavir.[157] After optimization of the

single reaction steps, they constructed a reactor which was able to produce the product in a continuous flow process with a yield of 0.8 g h^{-1} from start to finish.



Scheme 58. μ-TPSM process for the synthesis of Darunavir.

There is no isolation of the intermediates and separation of aqueous and organic phases is achieved directly on-line. The group even optimized a reactor system for their synthesis and additionally were able to replace expensive palladium hydrogenation reagents with cheaper Raney-Nickel.

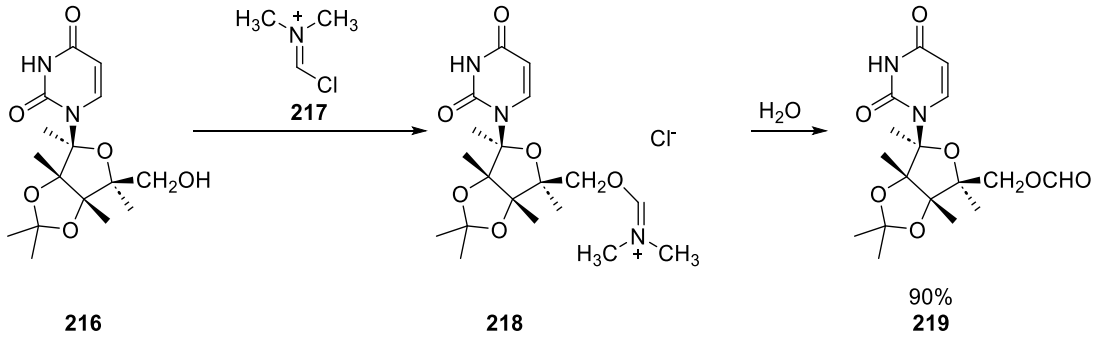
Overall, the need for inexpensive synthesis methods of the hexahydro[2,3*b*]furan cores is high and the field is fast-developing.

1.6 Synthesis of formyl esters

The photocatalytic activation of cyclopropanes is not new. Leading up to the past chapter, the structures obtained from the transformation of vinylcyclopropanes was discussed. However, aryl acetate cyclopropanes are known to undergo photocatalytic activation as well.[158] During the exploration of other activation methods for cyclopropanes, it was found aryl acetate cyclopropanes can open in a cascade to give formyl esters. These have a plethora of applications, especially in biocatalysis. Examples include the regeneration of NADH in enzymatic reactions[159] or use as a selective protecting groups for alcohols and other synthetic applications.[160–162]

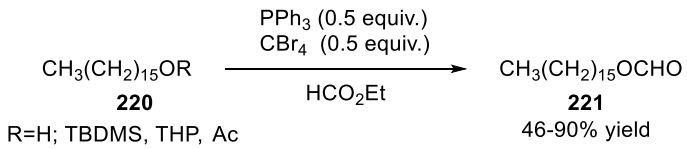
The synthesis of formyl esters in organic chemistry has gained attention as well, where the focus lies mostly on the esterification of alcohol groups with formic acid, although other uses are also of interest.

Žemlička *et al.* used the quaternary ammonium salt **217** which, after nucleophilic attack from the alcohol **216** then undergoes hydrolysis to the formyl ester **219**. In this approach, the heterocycle and ketal moieties present in the rather complex molecule were not affected, proving the great functional group tolerance of this approach (**Scheme 59**).[163]



Scheme 59. Formyl ester synthesis with quaternary ammonium salt.

Esterification of alcohols was also investigated by Hagiwara *et al.* who discovered their procedure of acetylating alcohols with PPh_3/CBr_4 produced the formyl esters **221** when methyl or ethyl formate were employed in the reaction. Triphenylphosphine and CBr_4 form a complex with water, which subsequently eliminates hydrobromic acid that then acts as the proton donor to facilitate the reaction. Even though similar yields were obtained with pure HBr, in the case of some diols, the reaction shut down. Although there was no comment from the authors, this suggests a further substrate coordination to the phosphine as well (**Scheme 60**).[164] This procedure is formidable, as it formylates protected alcohols as well in the same step, however cannot differentiate between primary and secondary alcohols.

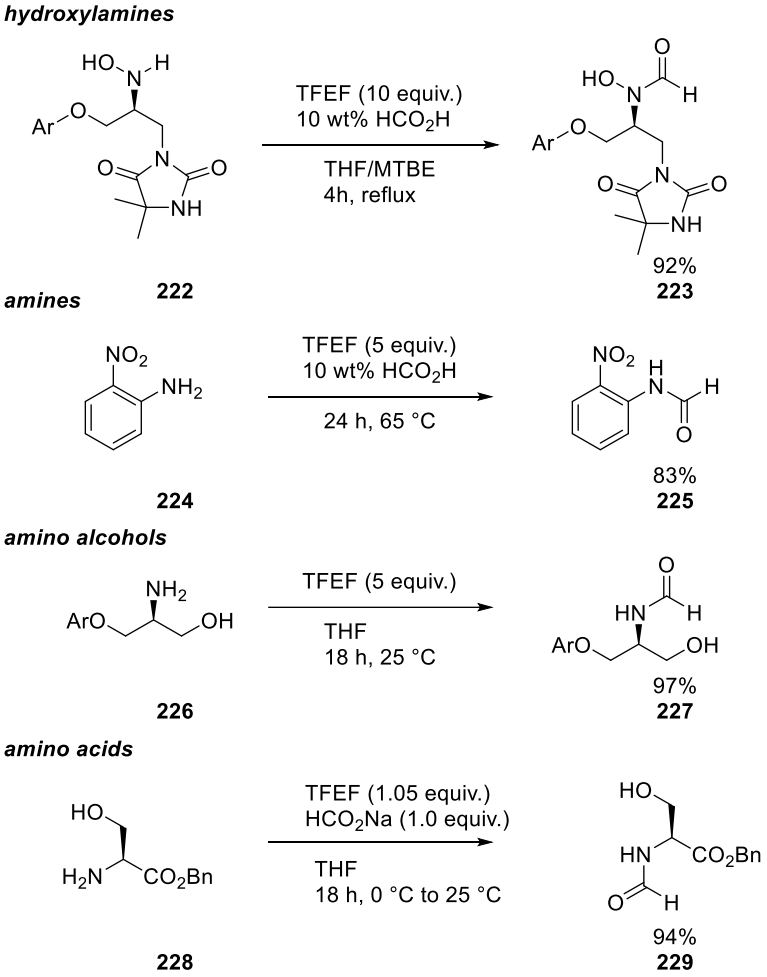


Scheme 60. PPh_3/CBr_4 formylation strategy.

A similar strategy was followed by Iranpoor *et al.* who discovered refluxing TMS-protected alcohols in the presence of $TiCl_4$ resulted in the formates. Their

procedure supported a variety of functionalities and structures, however, the tolerance of other protecting groups towards the method was not studied.[165] Other Lewis acids were not as efficient in catalyzing the transformation.

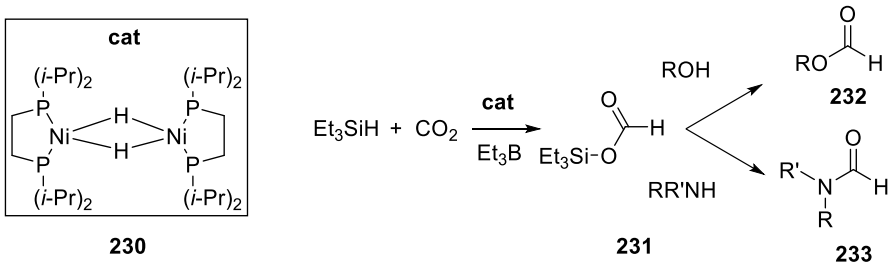
The Hill group developed a more generally applicable procedure for the formylation of *N*-hydroxylamines **222,** amines **224** and alcohols **226** using 2,2,2-trifluoroethyl formate (TFEF). This came with several advantages: The reagent is easy to prepare, handle and store and the procedure is selective towards amines when multiple functionalities are present.[166] Selected examples are presented in **Scheme 61**.



Scheme 61. TFEF catalyzed formylation of alcohols and amines.

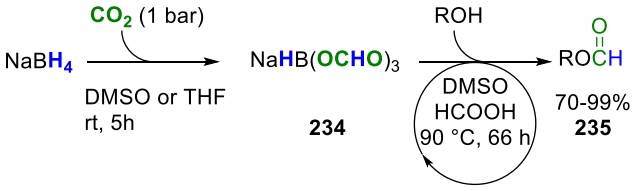
Further approaches of the formylation and acetylation of alcohols include the use of Cerium,[167] Magnesium,[168] or Iodine.[169] Additionally, another approach is the transesterification of formyl esters.[170,171]

Newer procedures for the formation of formyl esters include the hydrosilylation of CO_2 with nickel catalyst **230**. This produces a silyl formate **231** which can be trapped with alcohols or amines to form the corresponding *N*- and *O*-formates (**Scheme 62**).[172] Different alkyl and aryl *N*-and *O*-formates were synthesized with this methodology, although, again, its robustness against functional groups was not commented on.



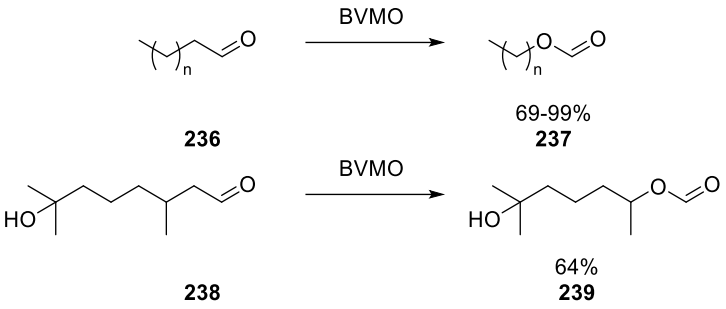
Scheme 62. Hydrosilylation of CO_2 with consecutive trapping.

Similar to this work is the approach by Uranga and Dyson. Alcohols were again the starting point; however, they chose a sustainable pathway, using CO_2 as the C1 source. With $NaBH_4$ as the reductant and DMSO as a green solvent, they were able to formylate a wide variety of alcohols, tolerating some functional groups such as nitro compounds and carboxylic esters or dienes (**Scheme 63**).[173]



Scheme 63. Autocatalytic formylation of alcohols using renewable resources.

Although Bayer-Villiger monooxygenases (BVMO) are usually used in ring expansions, they can also be used in the synthesis of formyl esters. Opperman *et al.* found that they catalyze the transformation of aldehydes to the formyl esters. This is especially interesting because usually, these enzymes catalyze the oxidation to the corresponding carboxylic acids.[174] The oxidation is also selective towards aldehyde groups: when an alcohol is present, it is not oxidized further (**Scheme 64**).



Scheme 64. Enzymatic oxidation of aldehydes **237** and **239**.

1.7 Aim of this work

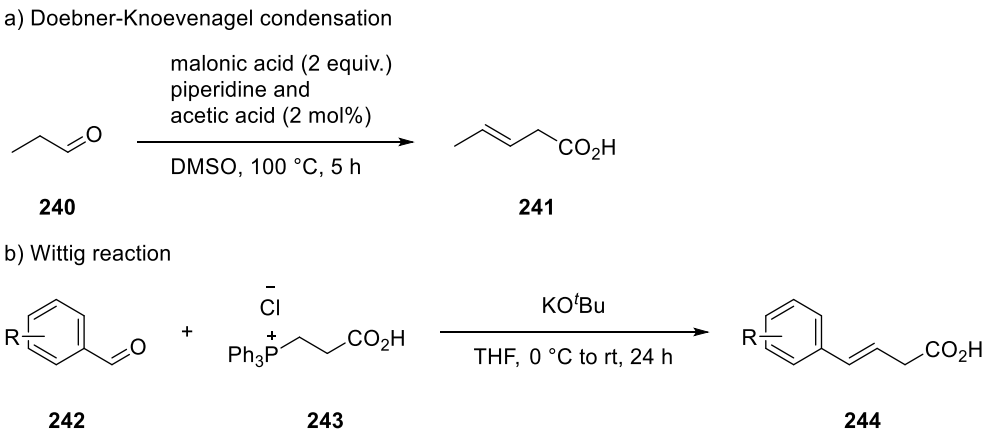
The development of catalytic methods to solve problems in modern chemistry is a highly achievable goal. These approaches should also tolerate many functionalities and side reactions are to be kept to a minimum. In this work, vinylcyclopropanes are transformed into three separate products entirely dependent on the reaction conditions, exploiting the interplay of functionalities all while breaking the same bond. Additionally, the previously developed chemistry on ring openings of aryl acetate cyclopropanes is expanded, showcasing the applicability of these structures in natural product synthesis.

2 Main Part

2.1 Synthesis of cyclopropanes

2.1.1 Synthesis of precursors

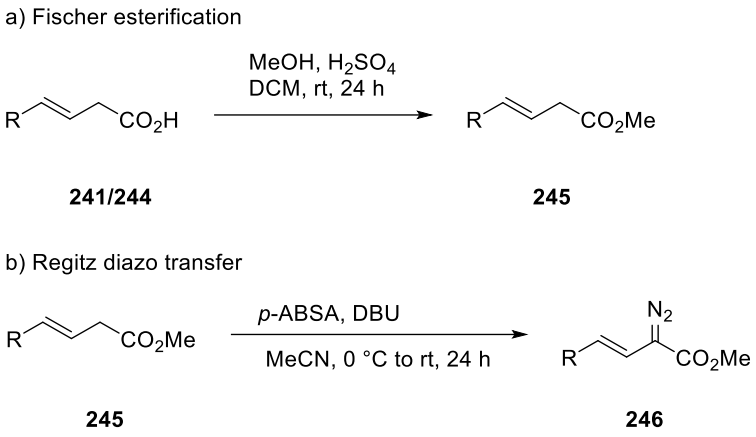
The vinylcyclopropane starting materials **250** were synthesized by rhodium-catalyzed decomposition of vinyl diazo compounds in the presence of a variety of alkenes. The diazo esters were obtained in a 3-step procedure starting from acids **241** and **244** which were synthesized either *via* a Doebner-Knoevenagel condensation following Ragoussis *et al.* or a Wittig reaction following Park *et al.* (**Scheme 65**). [175,176]



Scheme 65. Synthesis of acid starting materials.

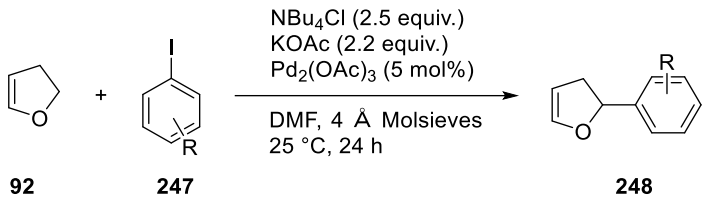
The obtained products were esterified through an acid catalyzed Fischer-esterification.

The final step was a Regitz diazo transfer using DBU and *p*-ABSA (**Scheme 66**).



Scheme 66. Esterification and diazo transfer.

Substituted 2,3-dihydrofuran starting materials **248** were synthesized *via* a Heck-type coupling developed by David *et al.* (**Scheme 67**).[177]



Scheme 67. Heck-type coupling of 2,3-dihydrofurans with iodo-arenes.

2.1.2 General synthetic procedure

Diazo esters **111** were utilized in rhodium-catalyzed cyclopropanations. These are well-known in literature, and photochemical alternatives have been developed as well.[49,178,179] Although the latter are preferable due to the high cost of rhodium, vinyl diazo compounds only form complex reaction mixtures under blue light irradiation . For the racemic cyclopropanes, the reaction relies on decomposition of **111** in the presence of Rh_2OOct_4 in pentane or Rh_2OAc_4 in DCM. The former works better since the metal-coordinated vinyl carbene is subject to dipolar reactions (see chapter 2.2). This can be circumvented using unpolar solvents.[180]

Davies *et al.* have shown remarkably low concentrations of rhodium catalysts are needed for the cyclopropanation to proceed in a speedy fashion.[181] Indeed, the cyclopropanation proceeded with only 1 mol% of catalyst and finished in 30 minutes. In

addition, the reaction proceeds with high diastereoselectivity, with only one diastereomer visible with 2,3-dihydrofuran and good diastereomeric ratios of roughly 4:1 for substituted 2,3-dihydrofurans. The minor diastereomer was readily separated by column chromatography. In the major diastereomer, the aryl group on the tetrahydrofuran core is *cis* to the H-atoms on the cyclopropane as proven by X-Ray crystallography (**Figure 3**).

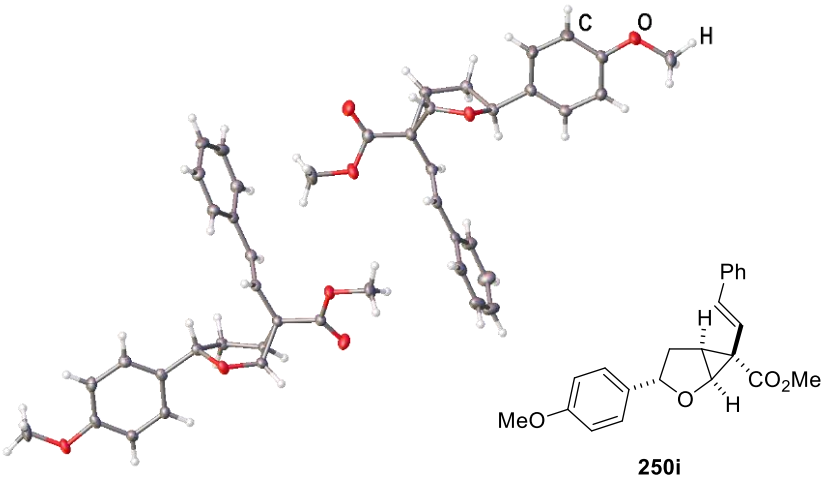


Figure 3. Crystal structure of cyclopropane **250i**.

Not only 2,3-dihydrofurans, but also styrene, vinyl ether, as well as oxetanes were cyclopropanated easily with high yields and easy purification. The oxetane cyclopropanes readily precipitated out of the reaction solution and were obtained as single diastereomers as well. X-Ray crystallography revealed the exact stereochemistry (**Figure 4**).

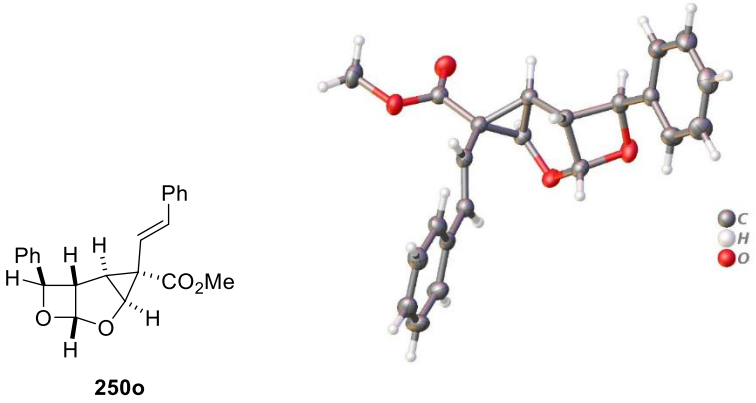
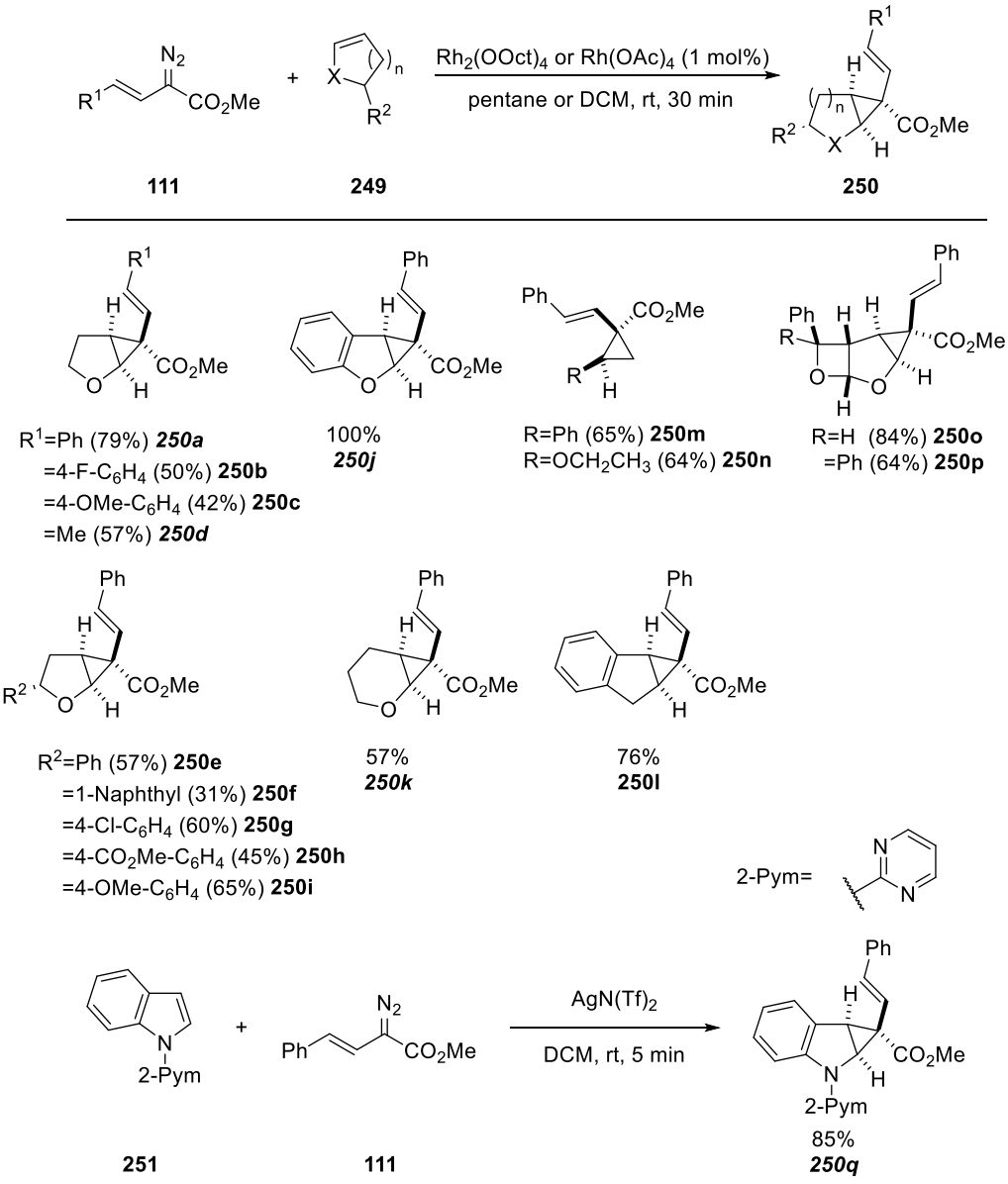


Figure 4. X-Ray structure of **250o**.

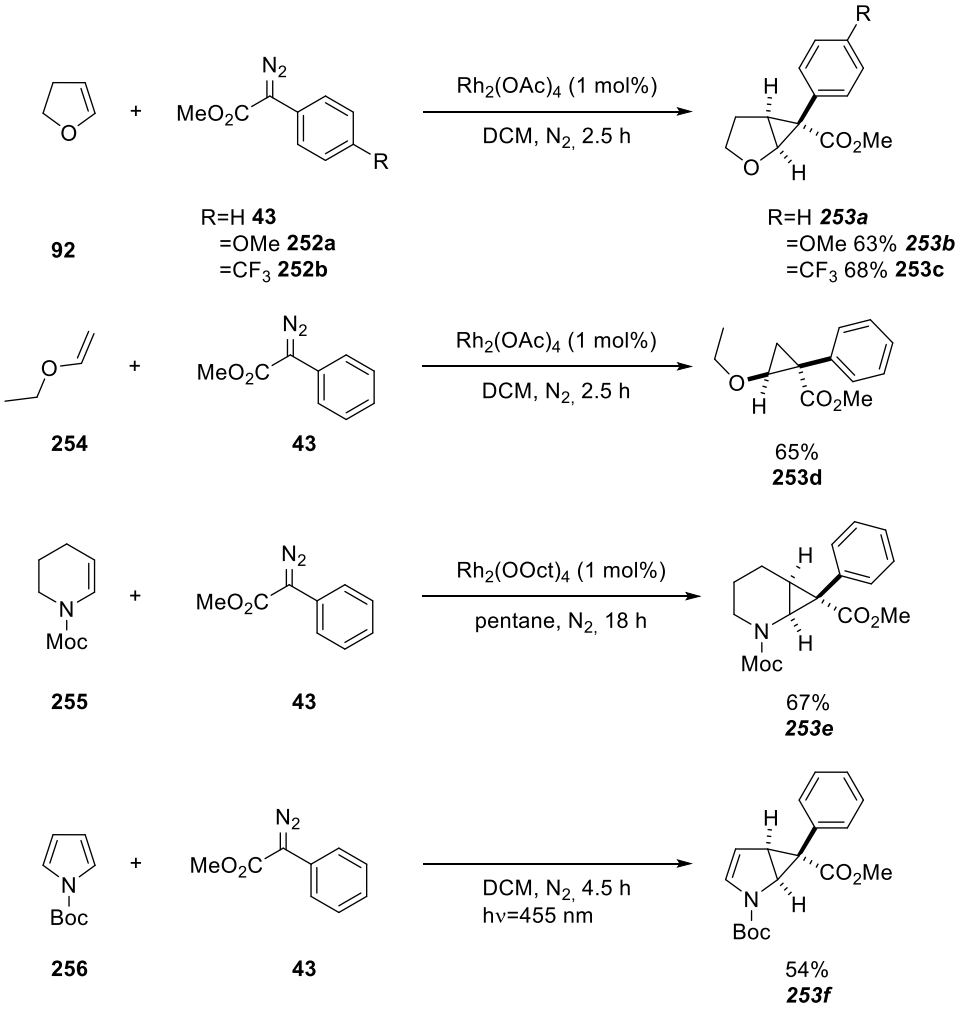
Finally, also the cyclopropanation of other cycles such as indene and protected indole **251** was achieved. However, the indole does not undergo cyclopropanation, but rather C-H insertion on the β-position with rhodium and instead has to be cyclopropanated with the help of a silver catalyst (**Scheme 68**).



Scheme 68. Vinylcyclopropane scope.

In addition to the vinylcyclopropanes, classic aryl acetate cyclopropanes **253** were synthesized. Both cyclopropanation with the help of rhodium and blue light were utilized in this case (**Scheme 69**). During the syntheses, it was found that often, more

polar cyclopropanes such as the Moc-protected 4*H*-pyridine **253e** precipitate readily when unpolar solvents such as pentane are used. They can then be collected by vacuum filtration, circumventing the column chromatography step usually needed. Overall, the substrate scope again proves the versatility of rhodium-catalyzed cyclopropanations. This prompted the investigation of the enantioselective variants of the cyclopropanation using chiral rhodium catalysts and vinyl diazo compounds.

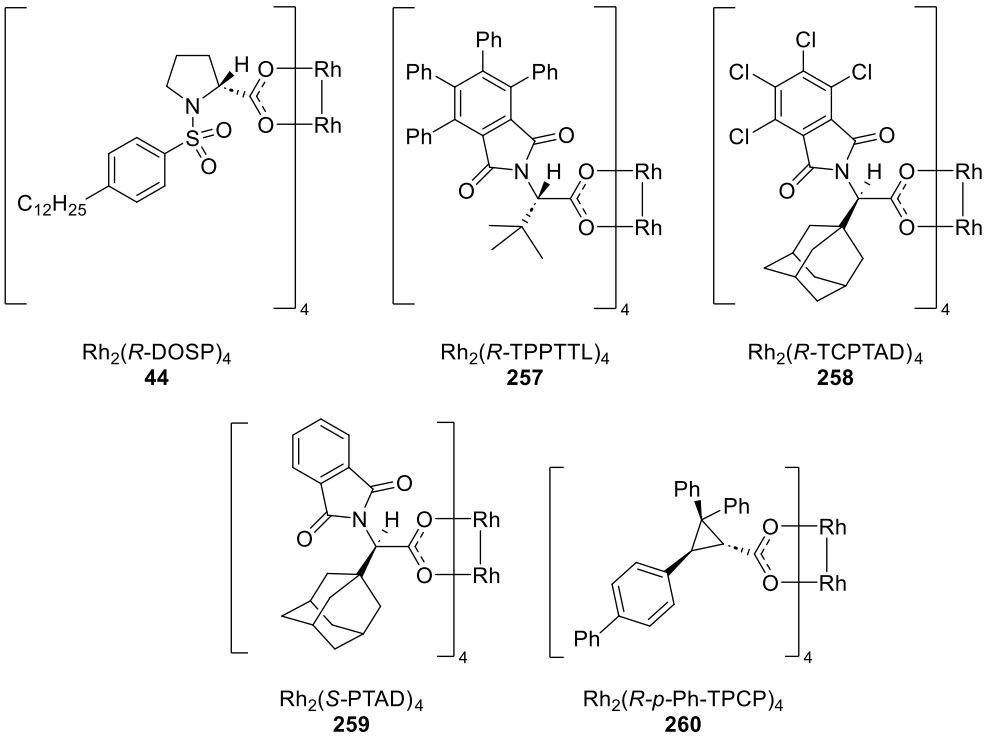


cursive products known in literature

Scheme 69. Synthesis of arylacetate cyclopropanes.

2.1.3 Development of an enantioselective synthesis of cyclopropanated substituted dihydrofurans[‡]

Chiral rhodium-catalyzed cyclopropanations have gained massive interest since the first report by Davies *et al.* in 1996 where they were searching for a catalyst for the transformation of vinyl diazo compounds.[49] Previously, only few examples of catalysts for chiral cyclopropanation (chapter 1.1.1) existed. Davies *et al.* showed $Rh_2(DOSP)_4$ **44** gave excellent control over diastereoselectivity and enantioselectivity in the cyclopropanation of vinyl diazo esters with a variety of alkenes. Since then, the Davies group has developed a wide range of Rhodium carboxylate catalysts, increasing their bulk size and reaching impressive enantiomeric excesses (**Scheme 70**)[182]



Scheme 70. Overview of chiral rhodium-catalysts.

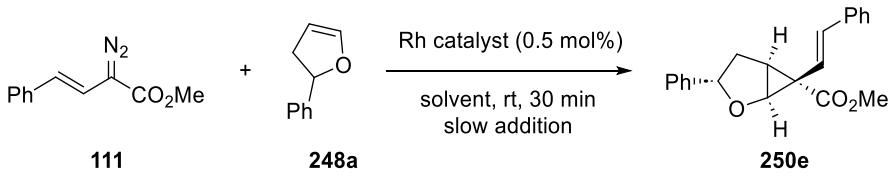
This previously developed methodology was expanded to substituted dihydrofurans **249** as already synthesized previously in a racemic fashion.

[‡] This work was performed under Prof. Dr. Huw Davies in his laboratory at Emory University, Atlanta, USA.

2.1.3.1 Catalyst screening

The screening was commenced with a screen of the catalysts shown in **Scheme 70**. Initial studies at room temperature showed good yields with moderate enantiomeric excesses (**Table 3**).

Table 3. Initial catalyst screen at room temperature.

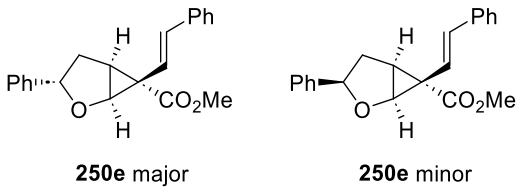


111 **248a** **250e**

Entry	*catalyst*	*solvent*	*yield*	*ee*	*d.r.*
1	*R*-DOSP	pentane	71%	69%	6:1
2	*R*-TCPTAD	DCM	81%	64%	>20:1

Conditions: 0.2 mmol scale, c(**248a**)=0.12 M, c(**111**)=0.08 M, 3 equiv. **248a**, 0.5 mol% catalyst, 25 °C, 30 min.

Rhodium-carboxylate catalyzed cyclopropanations are known to be extremely diastereoselective towards the formation of the *exo*-product.[42] As shown in the racemic transformation, the major product stems from the additional substituent on the dihydrofuran ring adjacent to the oxygen being on the same side as the cyclopropane hydrogens. The diastereomeric ratio therefore refers to this position (**Scheme 71**).



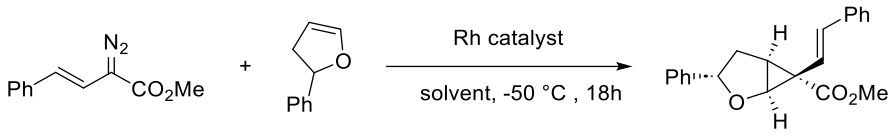
250e major **250e** minor

Scheme 71. Explanation of the two formed diastereomers.

This ratio makes sense, since the steric hindrance between the aryl group on the dihydrofuran ring and the vinyl substituent is minimized. However, the result still stands in contrast with results previously obtained by Reiser *et al.* with the non-vinyl aryl acetate diazo ester cyclopropanations, where no diastereomers were observed.[158] Presumably, the double bond moves the phenyl ring far away enough from the α-oxygen position to allow for a minor formation of the second diastereomer. When the sterically more demanding catalyst Rh_2(*R*-TCPTAD)$_4$ **258** is employed, the diastereomeric ratio is considerably better, with only trace amounts of the second diastereomer being formed

(**Table 3**, Entry 2). Since low temperatures have been shown to be beneficial for the enantioinduction process, the temperature was lowered before testing more catalysts.

Table 4. Catalyst screening at -50 °C.



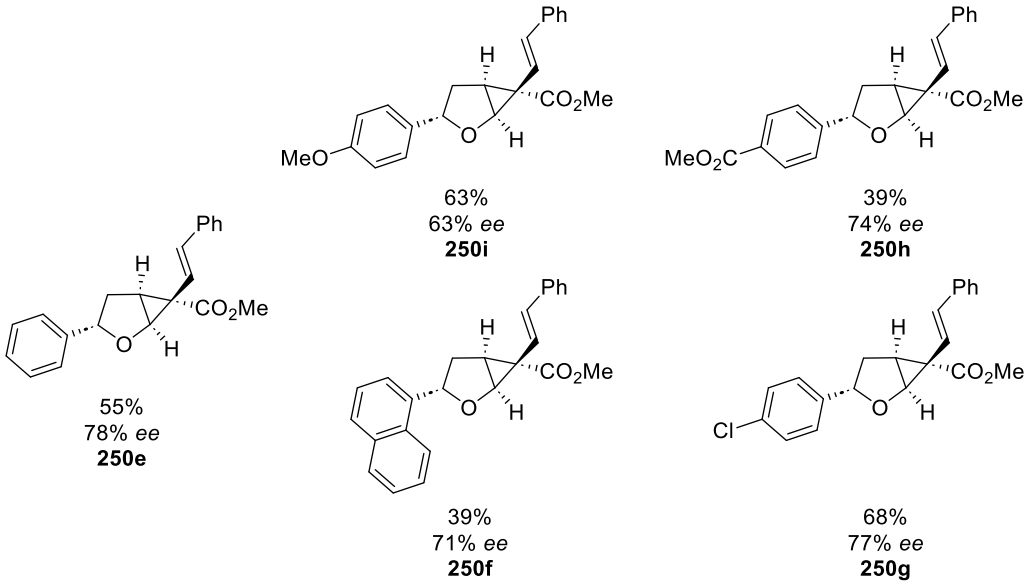
111 **248a** **250e**

Entry	***catalyst***	***solvent***	***yield***	***ee***	***d.r.***
1	*R*-DOSP	pentane	55%	78%	8:1
2[a]	*R*-DOSP	pentane	61%	77%	>20:1
3	*R*-TCPTAD	DCM	62%	34%	>20:1
4	*R*-p-Ph-TPCP	DCM	30%	n.d.	n.d.
5	*R*-TPPTTL	DCM	45%	62%	16:1
6	*R*-PTAD	DCM	37%	34%	>20:1

Conditions: 0.2 mmol scale, c(**248a**)=0.12 M, c(**111**)=0.08 M, 3 equiv. **248a**, 0.5 mol% catalyst, -50 °C, 18 . [a]5 equiv. of dihydrofuran **248a** were employed.

As can be seen in **Table 4**, the yields are comparable for both Rh_2(*R*-DOSP)$_4$ and Rh_2(*R*-TCPTAD)$_4$ (**Table 4**, entries 1 and 3). However, there is a considerable difference in the *ee*, with Rh_2(*R*-TCPTAD)$_4$ only giving 34% *ee* compared to 78% with Rh_2(*R*-DOSP)$_4$. The d.r. is considerably better with this newer-generation catalyst, as expected due to steric effects. All the other screened catalysts suffered from low yield an in most cases also from low *ee* values, although the *d.r.* values were higher compared to Rh_2(*R*-DOSP)$_4$ in most cases. Finally, the influence of the amount of 2,3-dihydrofuran **248a** was examined. When one enantiomer of the alkene starts to deplete during the reaction, the carbene more readily reacts with the other enantiomer, leading to a lower *ee*. A higher concentration of 2,3-dihydrofuran therefore means a higher concentration of the desired enantiomer during the whole course of the reaction. However, when 5 equivalents of the 2,3-dihydrofuran was employed, only a sharp increase in d.r. was seen, but no influence on the *ee* (**Table 4**, Entry 2).

2.1.3.2 Substrate Screening



Scheme 72. Substrate scope of the enantioselective cyclopropanation.

The developed conditions were subsequently tested on a variety of substrates. The results are shown in **Scheme 72**. Stereochemistry of the products was assigned according to the results previously obtained by Davies *et al.*[49] The yields are similar to the ones obtained in the racemic cyclopropanations, with electron-withdrawing groups such as the methyl ester (**250i**) diminishing the yield. The electronic effect of the *para*-substituent of the aryl on the double bond is arguably weak, and other effects such as interactions with the catalyst might play a bigger role here. This is also observed in C-H activation reactions with bowl-shaped rhodium carboxylates, where substituents cause a different orientation of the product, allowing for high selectivity.[183] The other cyclopropanations proceeded in moderate yields, except in the case of **250f**, again most likely owning to steric interactions hampering the transformation. A further explanation for lower yields compared to the racemic transformations is the cyclization of the vinyl diazo compounds to the corresponding pyrazoles, which is accelerated in solution.[184] This presents a problem as the reaction is very slow at the low temperatures. Even when employing the diazo compound directly after purification *via* column chromatography, the white precipitation indicating the pyrazole could be detected. Using an excess of vinyl diazo compound could possibly circumvent this problem, however, the influence

on the *ee* would need to be investigated in this case. Nevertheless, the obtained *ee* values are moderately good considering 4 stereocenters are formed in one reaction step and consistently between 63% and 77% *ee*. Both the yields and the *ee* values are similar to previously reported cyclopropanations on less sterically demanding systems.[46]

2.1.4 Conclusion and outlook

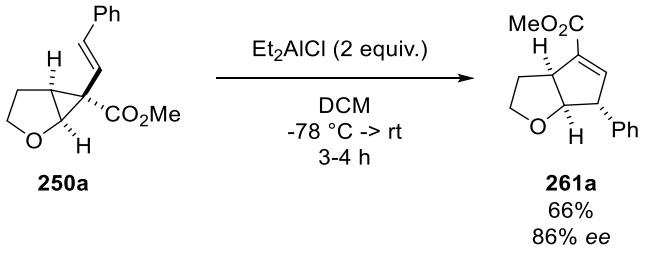
This chapter has shown the versatility of the cyclopropanation with vinyl diazo compounds **111**. Even though they are not the most stable, they readily cyclopropanate a wide variety of alkenes **249**. This work has only shown the beginning of possibilities of cyclopropanation with vinyl diazo compounds. Additionally, the enantioselective cyclopropanation of substituted 2,3-dihydrofurans **248** provides the corresponding cyclopropanes **250** in good yields and *ee* values, especially considering 4 stereocenters are formed. This substrate scope can be explored as well.

2.2 Vinylcyclopropane-Cyclopentene rearrangement

2.2.1 Screening of reaction conditions

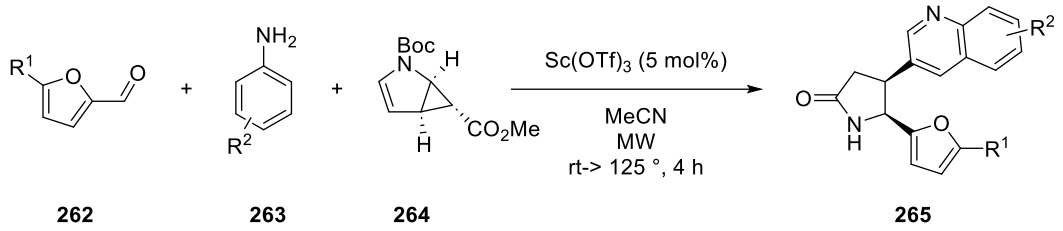
Once the synthesis of the vinylcyclopropanes **250** was complete, they were subjected to a variety of conditions to test their reactivity.

The vinylcyclopropane-cyclopentene rearrangement is well-known as described in chapter 1.2. In 1998, the Davies group applied the strategy from Corey *et al.* to fused vinylcyclopropane **250a**.[66,185] After treatment with 2 equivalents of Et_2AlCl at -78 °C, the cyclopentene **261a** was obtained in 84% yield. This chapter will show the further development of this transformation.



Scheme 73. Vinylcyclopropane-cyclopentene rearrangement of fused vinylcyclopropanes.

The group of Reiser *et al.* activated endocyclic vinylcyclopropanes with Lewis acids in their three-component reaction in **Scheme 74**. First, aniline **263** reacts with furan **262** to an imine. This adduct undergoes cycloaddition with the double bond of **264**. The ester on the cyclopropane is then activated by $Sc(OTf)_3$, and triggers the ring opening of the ring together with the free electron pair of the Boc-protected nitrogen. [186] This ring opening step was envisioned to work with vinylcyclopropanes **250** as well: Once the ester was activated, the cyclopropane would open, and the resulting intermediate recyclize to the cyclopentene.



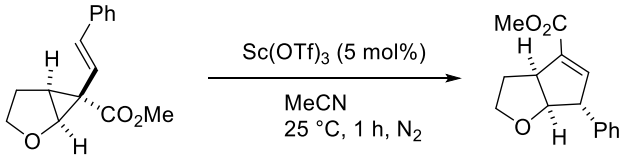
Scheme 74. Lewis acid mediated three component synthesis by Reiser *et al.*

However, when the starting material **250a** was employed using the conditions of Reiser *et al.*, it was consumed after only 1 hour as indicated by TLC and the cyclopentene was obtained in 41% yield (**Table 5**, Entry 1), proving the hypothesis.

The literature precedent on cyclopropane activation revealed that during the optimization of reaction conditions, the Reiser group initially employed 40 mol% of the triflate catalyst and achieved full conversion. When lowering the catalyst loading, the conversion and yield marginally decreased as well. To investigate the relationship between catalyst loading and yield, 40 mol% $Sc(OTf)_3$ were employed in the transformation. Subjecting vinyl cyclopropane **250a** to the transformation at room temperature with 40 mol% $Sc(OTf)_3$ gave 72% yield after 1 hour as determined by qNMR. With this promising result in hand, the next step was screening of a small variety of Lewis acids to determine the ideal candidate for the transformation. Scandium triflate is fairly hygroscopic and has to be kept under dry conditions, and as such is not the most desirable compound to catalyze the reaction.[187] Copper triflate is also very hygroscopic and moisture sensitive, but, in comparison, more reactive.[188] Compared with these

candidates, $Yb(OTf)_3$ is not moisture sensitive and cheap. $TiCl_4$ as a non-triflate Lewis-acid was tested as well. The result of the screening can be seen in **Table 5**.

Table 5. Screening of Lewis Acids.



250a **261a**

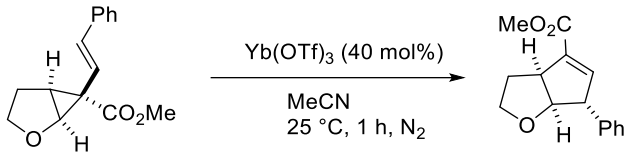
Entry	***variation***	***NMR yield[a]***
1	None	41%
2	40 mol% $Sc(OTf)_3$	72%
3	40 mol% $Cu(OTf)_2$	15%
4	40 mol% $TiCl_4$	19%
5	40 mol% $Yb(OTf)_3$	92%

Conditions: 0.2 mmol scale, c=0.1 M, catalyst, dry MeCN, MW, rt, 1h, N_2. [a]Determined with tetrachloroethane as internal standard.

Even though copper triflate is more reactive, employing 40 mol% gave a significantly lower yield of only 15% (**Table 5**, Entry 3). The crude NMR shows evidence of lactone **272a** in 29% yield. This is a surprising result, since lactonization occurs under Brønsted acidic rather than Lewis acidic conditions (see chapter 2.3). This indicates the presence of a Brønsted acid in the reaction mixture. Indeed, it has been shown that $Cu(OTf)_2$ can decompose to HOTf when a hydrogen donor is present.[189] This is in accordance with the results achieved in the study of the vinylcyclopropane-cyclopentene rearrangement.

Titanium (IV) tetrachloride was tested as well, however, only 19% yield were achieved, and numerous side products observed. Finally, with $Yb(OTf)_3$, the expected product was formed in 92% yield, a satisfying result, especially since $Yb(OTf)_3$ is significantly easier to handle and extract by aqueous workup. With an active catalyst in hand, the next step was further optimization of the reaction conditions (**Table 6**).

Table 6. Screening of reaction conditions for cyclopropane-cyclopentene rearrangement.



250a **261a**

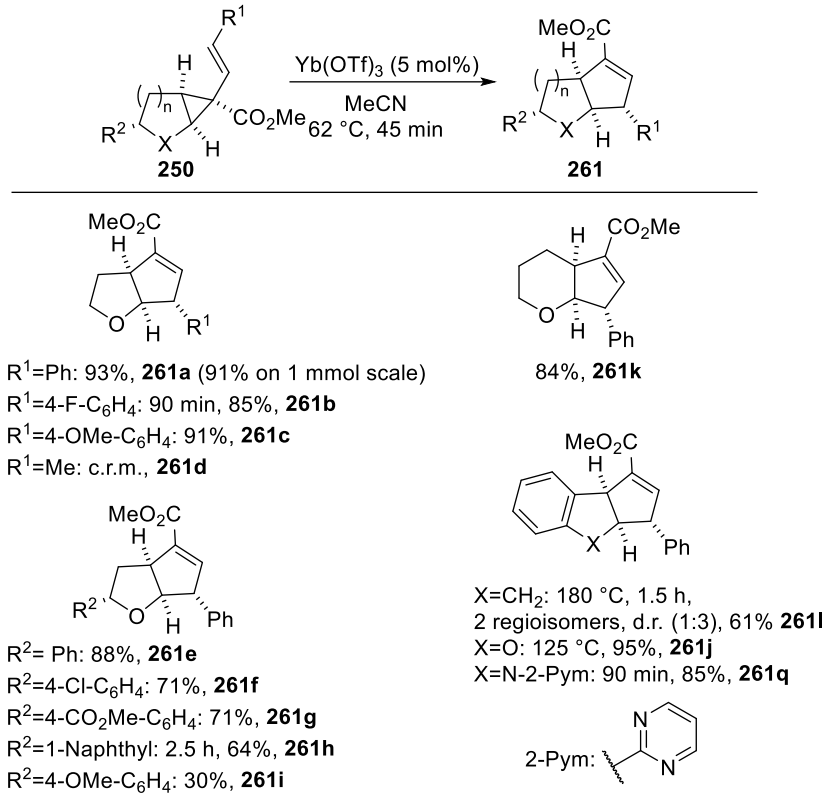
Entry	*variation*	*NMR yield*[a]
1	none	92%
2	5 mol% $Yb(OTf)_3$	44%
3	5 mol% $Yb(OTf)_3$ /125 °C	75%
4	5 mol% $Yb(OTf)_3$/62 °C	77%
5	5 mol% $Yb(OTf)_3$/62 °C/no MW	75%
6	5 mol% $Yb(OTf)_3$/62 °C/no MW/30 min	67%
7	5 mol% $Yb(OTf)_3$/62 °C/no MW/45 min	79%
8	No catalyst	20%
9	wet MeCN, no N_2, 5 mol% $Yb(OTf)_3$/62 °C/no MW/45 min	77%
10	c=0.2 M (+conditions Entry 9)	66%
11	c=0.05 M (+conditions Entry 9)	58%

Conditions: 0.2 mmol scale, c=0.1 M, 40 mol% $Yb(OTf)_3$, dry MeCN, MW, rt, 1h, N_2. [a]Determined with tetrachloroethane as internal standard.

Employing 40 mol% catalyst is not very sustainable. Consequently, the catalyst loading was reduced to 5 mol%, leading to a corresponding decrease in yield to 44% (**Table 6**, Entry 2). To compensate for this, different conditions such as temperature, time, microwave conditions and concentration were investigated. This showed that yields of up to 77% are obtained when the temperature is increased to 62 °C and the reaction time can be lowered to 45 minutes (**Table 6**, Entry 9). Considering these reactions usually require high temperatures or stoichiometric amounts of reagents, this result is quite remarkable.[53,56,62] During the screening, it was also found that the concentration had somewhat of an influence (**Table 6**, Entries 10 and 11). This is most likely based on the catalyst-substrate interaction which is shown in **Scheme 79**. With concentrations lower than 0.1 M, the likeliness of catalyst and substrate meeting is decreased, which can be circumvented with increased temperature and/or reaction time. With concentrations higher than 0.1 M, the coordination of the catalyst is less effective: instead of coordinating to just one molecule, unspecific coordination can occur, decreasing the efficacy of the reaction.

2.2.2 Substrate scope

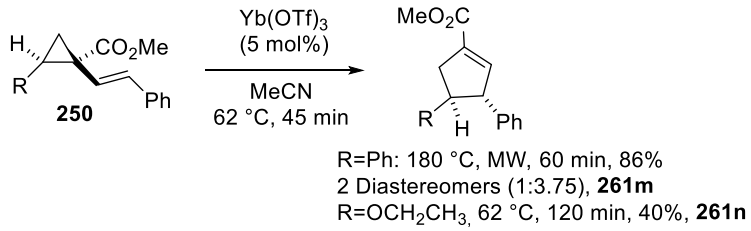
With the optimized conditions in hand, the scope of the reaction was tested. The results can be seen in **Scheme 75** and **Scheme 76**.



Scheme 75. Substrate Scope of Vinylcyclopropane-Cyclopentene rearrangement.

The substrate scope shows the reaction proceeds very well on a wide variety of cyclopropanated heterocycles. The initial NMR yield of 77% for **261a** when the reaction is run on a 0.2 mmol scale can be increased to an isolated yield of 93% when run on a 0.5 mmol scale. The reaction can be scaled up to 1 mmol easily with no decrease in yield. Substitutions on the vinyl moiety are tolerated well, with only a slight drop in yield for electron-withdrawing substituents. However, in stark contrast to the results achieved by Davies *et al.* when employing Et_2AlCl, methyl-substituted **250d** only gave a complex reaction mixture when subjected to the reaction conditions.[185] Substitutions on the dihydrofuran ring were tolerated well in most cases (**261e** to **261i**), although the time had to be increased for sterically more demanding substrates and yields dropped as well. It is noteworthy adding an electron-donating group such as *para*-methoxy on the phenyl

ring results in a considerable yield drop. Expansion to the 6-membered ring was tolerated as well (**261k**). Even the benzofuran and indole derivatives readily reacted to the corresponding products after increase of time and temperature, respectively. Overall, the method is very robust and tolerates a variety of functional groups.

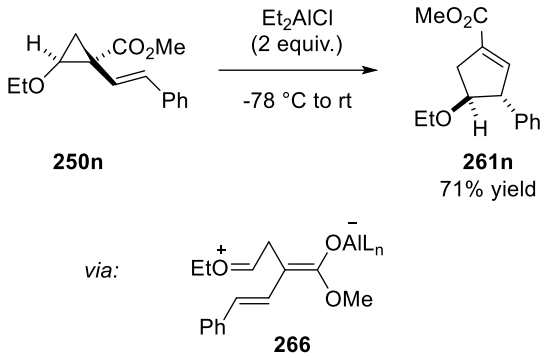


Scheme 76. Transformations of non-cyclic annulated cyclopropanes.

The substrate scope was broadened to include non-annulated substrates (**Scheme 76**). First, cyclopropanated ethyl vinyl ether **250n** was employed in the reaction. The yield dropped considerably, and the temperature had to be increased, but the reaction proceeded, nevertheless. In the published procedure, this compound was formed with 72% yield.[185]

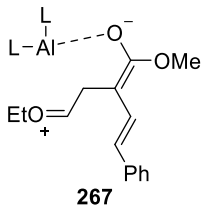
The most interesting results were obtained once the heteroatom was replaced by a carbon. Two substrates of this kind were synthesized and employed in the reaction: cyclopropanated styrene and cyclopropanated indene. Both substrates needed a considerable increase in temperature to 180 °C as well as a time increase to 1 hour (**Scheme 76**) and 1.5 hours (**Scheme 75**), respectively. Once the reaction was complete, the products were obtained as two stereoisomers. In the case of the styrene derivative, it was determined that the two stereoisomers were in fact two diastereomers. The ratio is about 1:3.75.

To understand the change in diastereoselectivity, one has to look at the zwitterionic intermediate **266** proposed by Davies *et al.* for the rearrangement to **261n.** The Lewis acid coordinates to the carbonyl function of the ester, which leads to opening of the cyclopropane (**Scheme 77**).[185] The ring closure to the *trans*-configured product is preferred for steric reasons.



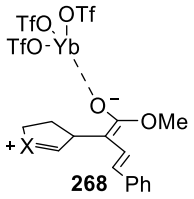
Scheme 77. Zwitterionic intermediate **266** proposed by Davies *et al.*

An alternative explanation is shown in **Scheme 78**.



Scheme 78. Alternative explanation for the diastereoselectivity.

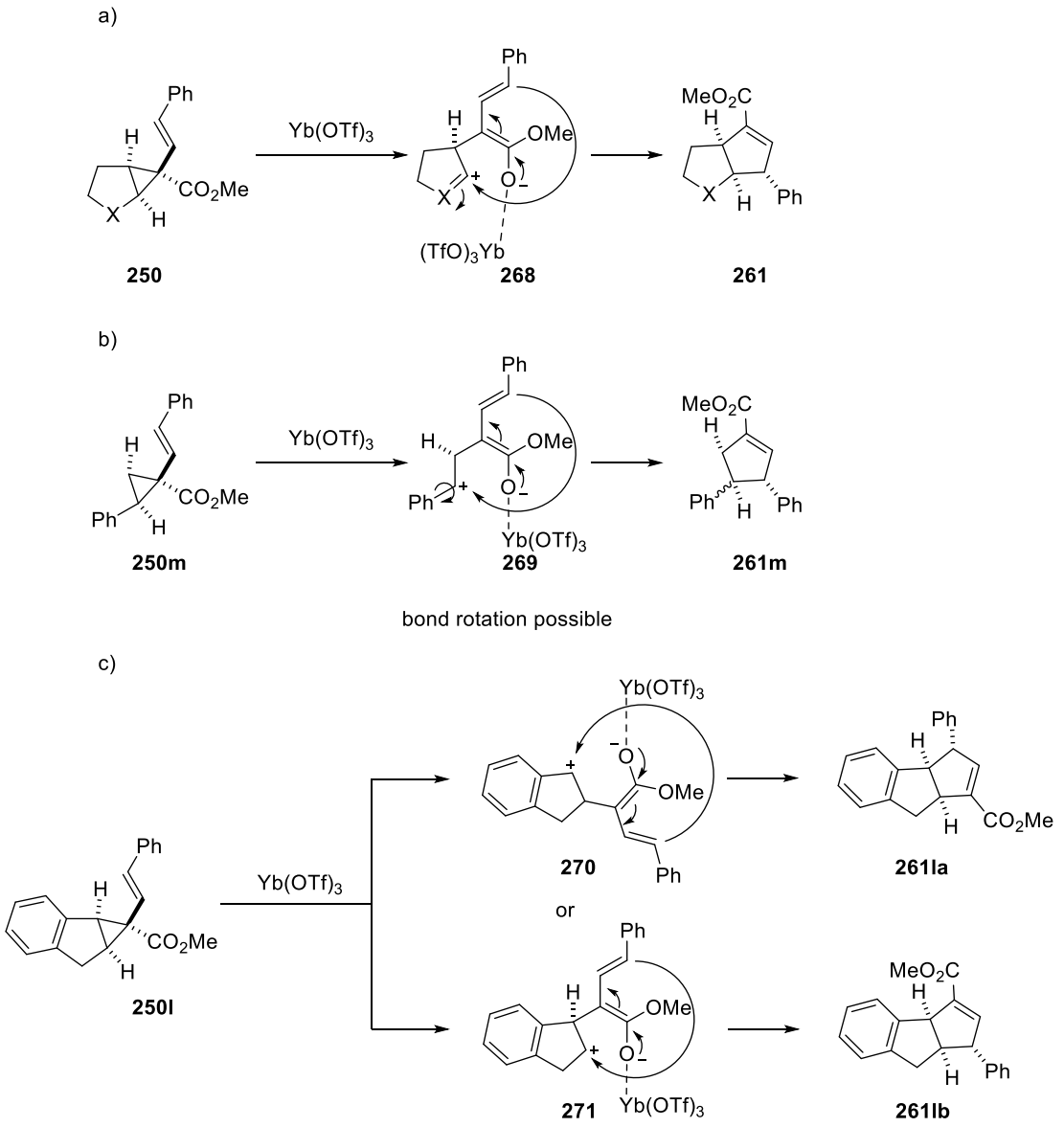
This model can be adapted to fit the rearrangement mediated by $Yb(OTf)_3$ (**Scheme 79**).



Scheme 79. Adapted model for diastereoselectivity.

Based on these results and the previously mentioned literature precedent, following mechanism is proposed: The Lewis acid coordinates to the carbonyl moiety of the ester, facilitating the ring opening of the cyclopropane. When a heteroatom is adjacent to the cyclopropane (**Scheme 80a**), only one diastereomer is formed. Once cyclopropanated styrene **250m** is employed, bond rotation is possible, as can be seen in **Scheme 80b**. The product is formed in 2 diastereomers. Finally, the cyclopropanated indene presents a special case (**Scheme 80c**). While the opening to **270** is favored because of the benzylic carbocation formed, **270** cannot be ruled out as an intermediate. This leads to two

possible products: **261la** and **261lb**. In principle, the *trans*-isomers of these compounds can be formed as well. The ^{1}H-NMR spectrum shows 2 compounds in a ratio of 3:1, however, the assignment not trivial. High-resolution mass spectrometry shows the products have the same mass, indicating the presence of stereoisomers rather than 2 completely different molecules. Additionally, the ^{13}C-NMR spectrum shows similar shifts for both compounds and no other coupling partners are added to the reaction mixture. The ^{1}H-NMR shifts differ greatly, which indicates the presence of stereoisomers **261la** and **261lb** rather than *cis/trans* isomers of **261la**. A definite identification however is not possible.



Scheme 80. Mechanistic rationale for product formation.

2.2.3 Conclusion and outlook

The known cyclopropane-cyclopentene rearrangement developed by Corey *et al*.[66] and applied to annulated vinylcyclopropanes by Davies *et al.* was further developed and expanded to a wide variety of vinylcyclopropanes. The transformation was achieved catalytically by employing 5 mol% $Yb(OTf)_3$. The most striking feature of this procedure is the fact that most products could be isolated in their pure form after aqueous workup of the reaction mixture. The transformation proceeded readily with a wide variety of substrates. In the cases of cyclopropanated styrene and indene, loss of diastereoselectivity and regioselectivity was observed, respectively.

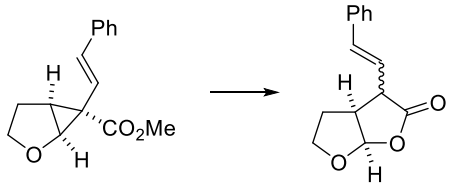
2.3 Lactonization

2.3.1 Lactonization of vinylcyclopropanes

2.3.1.1 Screening of reaction conditions

As described in chapter 1.3.2, cyclopropanes with an ester substituent are subject to hydrolysis with subsequent ring opening and lactonization. Although it has been tested on some acceptor-only substituted cyclopropanes, there are to this date no reports on reactions with donor-acceptor substituted cyclopropanes. This chapter will show the expansion of the methodology to cyclopropanes with di-substituted cyclopropanes.

Table 7. Screening of the lactonization reaction conditions.



250a **272a**

Entry	***conditions***	***yield***
1	H_2SO_4 (2 equiv.), H_2O/MeCN 1:1, 24 h, 25°C	50%
2	Amberlyst® 15, toluene, reflux, 20 h	21%
3	HCl (conc.)/Dioxane/H_2O, 1:1:1, 90°C, 4h	n.d.
4	5% methanesulfonic acid in acetone, 2 h, 60 °C	70%[a]
5	5% toluenesulfonic acid in acetone, 1 h, 60 °C	83%[a]

conditions: 0.2 mmol scale, c=0.1 M. [a]Determined *via* NMR with tetrachloroethane as internal standard.

Initially, the lactonization was attempted under typical acidic conditions using sulfuric acid in a mixture of water/acetonitrile. While this already yielded the product in acceptable 50% yield (**Table 7**, Entry 1), other options were explored. The conditions used by the Reiser[71,121,190] and Theodorakis[120] groups were tested in their applicability to the transformation of the vinylcyclopropane **250a**. Employing Amberlyst®15 only provided the product in 21% yield, switching to concentrated HCl in dioxane only yielded the product in trace amounts (**Table 7**, Entry 3). However, when the conditions of Theodorakis *et al.* were used, the product could be obtained in 70% yield (**Table 7**, Entry 4). In some cases, using methanesulfonic acid resulted in low yields and complex reaction mixtures. Switching to *para*-toluenesulfonic acid gave the product in 83% yield (**Table 7**, Entry 5) and proved to be the better acid for these substrates. In general, dehydrating acids such as sulfuric acid and methanesulfonic acid have a detrimental effect on the transformation. This is supported by discoloration of the mixture, which turns from colorless to brown during the reaction time. As will be explained in chapter 2.3.2, the postulated intermediate contains an alcohol group, which can be subject to reactions with harshly dehydrating agents. The switch to *para*-toluenesulfonic acid circumvents this problem. All methods yielded the product in a diastereomeric mixture with a *d.r.* of 1:1 (**Table 7**, Entry 5).

2.3.1.2 Substrate Scope

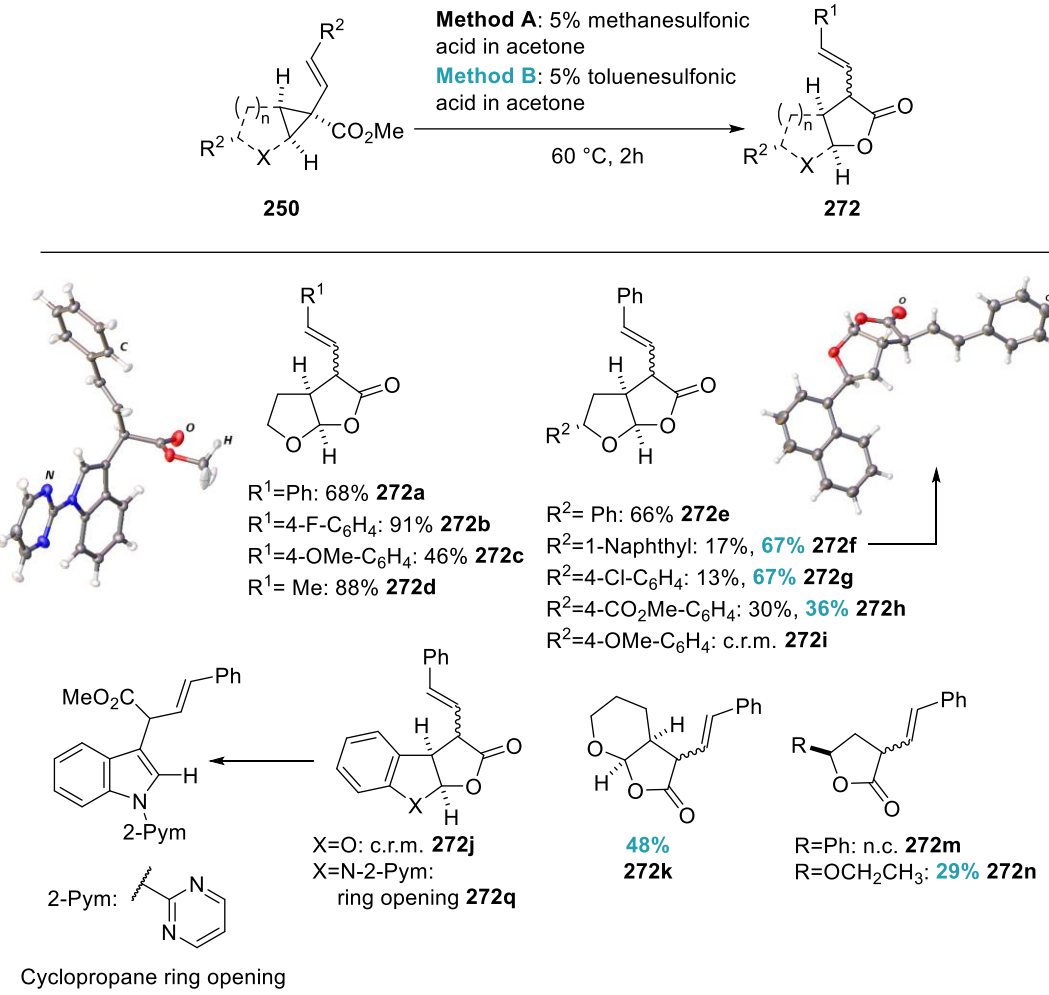
With the optimized conditions in hand, the substrate scope of the reaction was examined.

Substitutions on the vinyl moiety were well tolerated, from changing the electronic properties of the aryl substituent to changing it to a methyl substituent (**272d**). Substituting the THF ring showed the necessity of using *para*-toluenesulfonic acid: only then acceptable yields were produced in most cases, for example, the yield using *para*-chloro-phenyl substituted starting material **250g** increased from 13% to 67% (**272g**). *Para*-methoxy and *para*-methoxy ester substituted aryl substituents were tolerated less well (**272h** and **272i**) and not at all, respectively. In the case of the methoxy ester, hydrolysis of the ester on the aryl group is possible which could cause trouble with side

reactions occurring. The oxygen in general could cause problems-changing the acid to a non-sulfonic acid might be able to circumvent this problem.

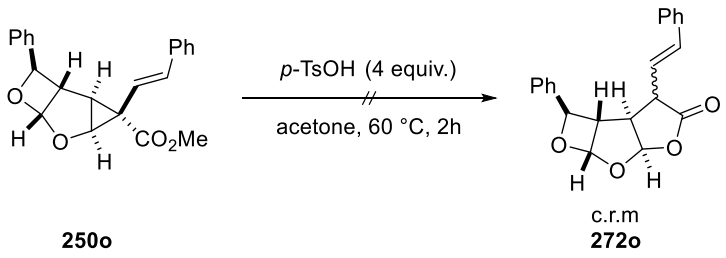
Expanding the ring system to a pyran only slightly diminished the yield (**272k**). Tricyclic ring systems are interesting subjects as well, however, employing cyclopropanated benzofuran only gave a complex reaction mixture. In an attempt to expand the substrate scope to other heterocycles, cyclopropanated 2-pyrimidine-protected indole was employed in the reaction. However, this only led to a ring opening of the cyclopropane which is known in literature as the product of the gold-catalyzed alkylation of indoles.[191]

Finally, cyclopropanated styrene and ethyl vinyl ether were explored as well. While the transformation proceeded with the latter, albeit at low yields, the former did not react, even when temperatures and reaction time were increased. This indicates a heteroatom adjacent to the cyclopropane is critical for the transformation to proceed.



Scheme 81. Substrate Scope.

Another attempt to synthesize more complex annulated ring systems was made in the transformation of cyclopropanated oxetane **250o**. However, decomposition could be observed in less than five minutes and only a complex reaction mixture was obtained (**Scheme 82**).



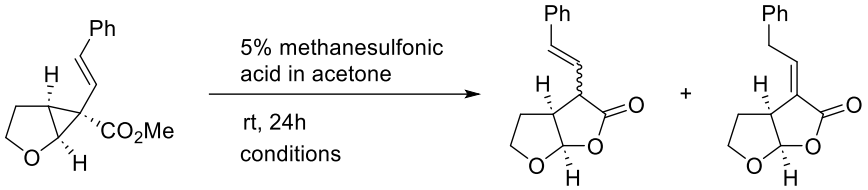
Scheme 82. Attempted lactonization of cyclopropanated oxetane **250o**.

2.3.1.3 Equilibration experiments

Aside from the substrate scope, another focus was on the fact that the reaction is not diastereoselective regarding the α-residue on the lactone. Previous work by the Reiser group in their endeavors to synthesize both enantiomers of Paeonilide encountered similar problems.[121,192] In their work, the substituent was located on the THF ring as opposed to the cyclopropane in this work. They developed various protocols depending on the enantiomer to solve this problem.

This strategy was seen as a possibility to apply to the newly synthesized lactones, which could undergo a similar process and equilibrate to one stereoisomer.

Table 8. Equilibration experiments.



250a **272a** **273a**

Entry	*conditions*	*ratio 272a/273a*
1	5 equiv. NEt_3, 30 min, rt	1:1.2
2	5 equiv. NEt_3. 30 min, 60 °C	1:1.6
3	5 equiv. DBU, 30 min, 80 °C	decomposition
4	20 mol% $Sc(OTf)_3$, 30 min, 60 °C	1:2.2
5	pyridine (c=1 M), H_2O, rt, 2 h	1:3

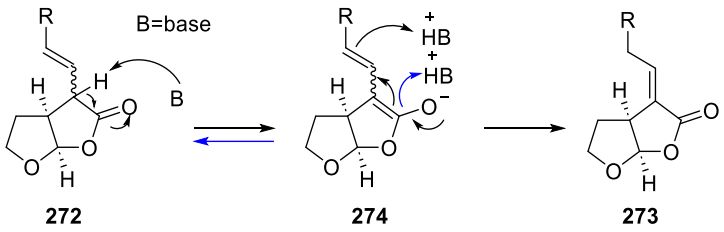
conditions: 0.2 mmol scale, c=0.2 M.

However, when the experiments were carried out, instead of equilibration of the two diastereomers, a third set of signals turned up in the ^{1}H-NMR. Investigations revealed they belonged to a regioisomer: the α,β unsaturated compound **273a**. This intriguing result prompted further investigations into whether the equilibration could be pushed completely to this compound. As a starting point, 5 equivalents of NEt_3 were employed at room temperature. However, only a 1:1 mixture of **272a** and **273a** was obtained. Increasing the temperature to 60 °C did not significantly change this result (**Table 8**, Entries 1 and 2). Using the stronger base DBU resulted in complete decomposition of the lactone (**Table 8**, Entry 3).

Another idea was to employ a Lewis acid, activating the ester and triggering the cascade to the desired compound. This produced somewhat higher ratios, was still however not successful (**Table 8**, Entry 4).

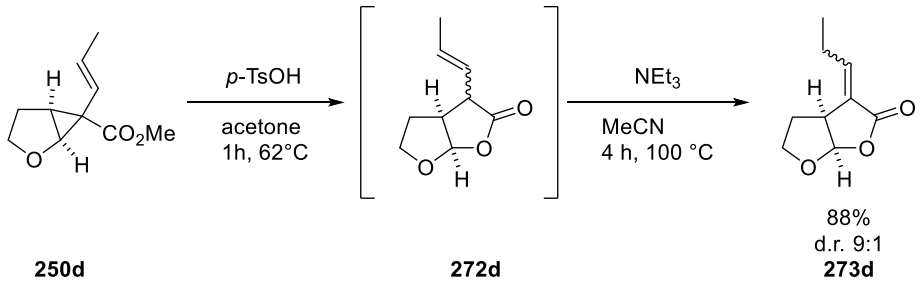
Finally, a procedure from the Reiser group was employed, where a 1 M solution of pyridine in water was used to equilibrate the diastereomers.[192] While this worked best out of all attempts, the thermodynamic equilibrium between **272a** and **273a** could not be overcome.

The mechanistic rationale for the equilibration is shown in **Scheme 83**. After deprotonation, the enolate intermediate can be reprotonated by the base either at the vinylic position, leading to the α,β-lactone **273**, or at the original abstraction position, leading to the original lactone **272** (**Scheme 83**, blue arrows). Structure **274** is highly stabilized due to the mesomeric effect when R=phenyl, meaning all structures are in equilibrium with each other.



Scheme 83. Mechanism of the equilibration to the α, β-lactone.

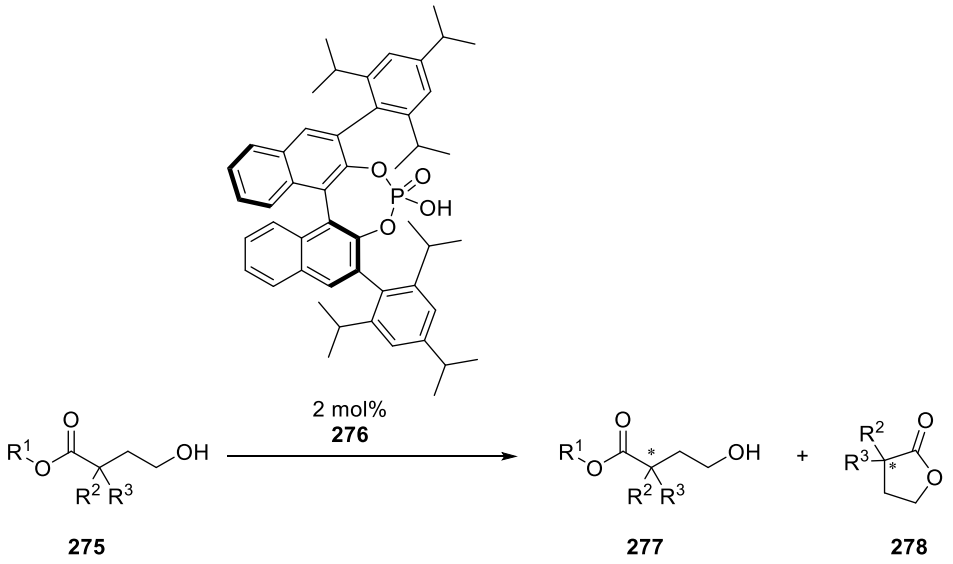
As mentioned above, it was impossible to push the reaction towards the desired α,β-lactone **273** in this case. However, the stabilization of **274** is somewhat smaller when the residue is non-aromatic. When R was changed to methyl, the equilibration with NEt_3 gave the α,β-lactone **273d** in quantitative yield and high diastereoselectivity with a *d.r.* of only 9:1.



Scheme 84. Equilibration of **250d**.

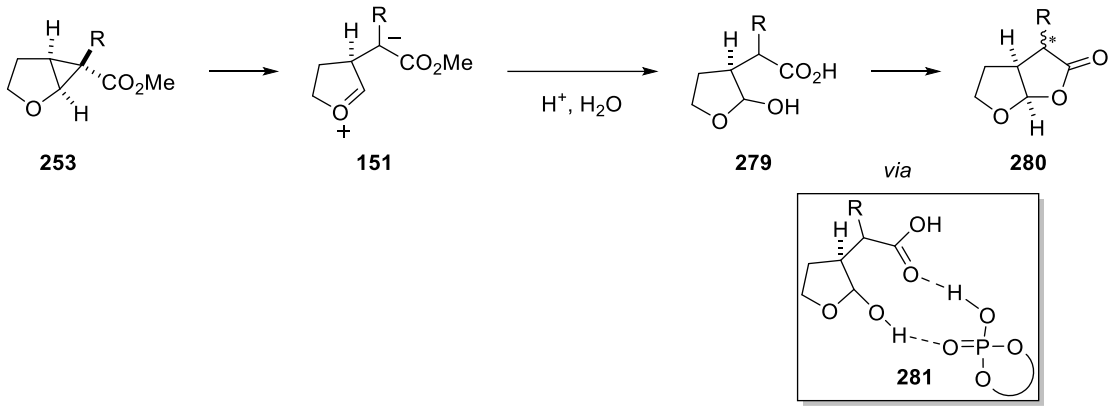
2.3.2 Studies towards chiral lactonization of aryl acetate cyclopropanes

In 2013, the group of Kimberly *et al.* showed a tandem deracemization/lactonization strategy of catalyzed by chiral phosphoric acids (CPAs) where they employed a racemic starting material **275**, obtaining the enantioenriched α-substituted γ-hydroxy esters **177** as well as the enantioenriched lactone **278** (**Scheme 85**).[193]



Scheme 85. Deracemization/lactonization of α-substituted γ-hydroxy esters.

This strategy was combined with the lactonization strategy developed in chapter 2.3.1 and applied to the aryl acetate cyclopropanated dihydrofuran **253**. The working model is described in **Scheme 86**.

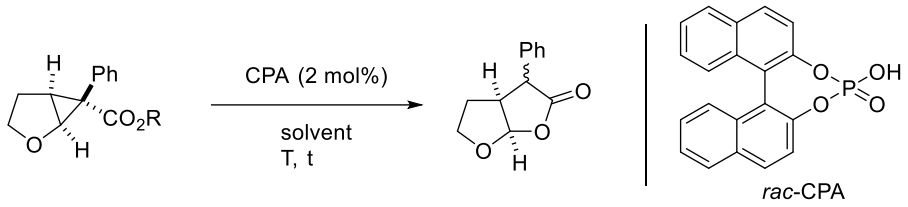


Scheme 86. Mechanistic model for the CPA-catalyzed lactonization of **253**.

2.3.2.1 Solvent screen

To test if the reaction could run on a catalytic scale, the reaction conditions were screened with the racemic catalyst. The results of the screening can be seen in **Table 9**. Using the conditions developed in chapter 2.3.1, but with 2 mol% catalyst instead of 4 equiv. *p*-TsOH, no conversion of the starting material was observed (**Table 9**, Entry 1). Different solvents were screened based on the literature:[193] In all cases, product formation was observed, however, there was no full conversion in any screened solvent (**Table 9**, entries 2 to 5). The hypothesis was that the hydrolysis of the ester was sluggish, hampering with the reaction. To test this, the ester was hydrolyzed, and the obtained carboxylic acid was employed in the reaction. The two best solvents, toluene and acetonitrile, were tested with the carboxylic acid and gave 87% and 81% NMR yield, respectively (**Table 9**, entries 6 and 7). When the temperature was increased to 92 °C, quantitative yield was obtained after 4 hours (**Table 9**, Entry 8).

Table 9. Screening of reaction conditions.



253 **280a** **282**

Entry	*R*	*solvent*	*T [°C]*	*t [h]*	*outcome*
1	Me	acetone	62	24	n.c.
2	Me	toluene	62	24	No full conversion
3	Me	DCM	62	24	No full conversion
4	Me	DMC	62	24	No full conversion
5	Me	MeCN	62	24	No full conversion
6	H	toluene	62	24	87 % NMR yield
7	H	MeCN	62	24	81% NMR yield
8	H	toluene	92	4	quantitative
9[a]	H	toluene	92	4	91%

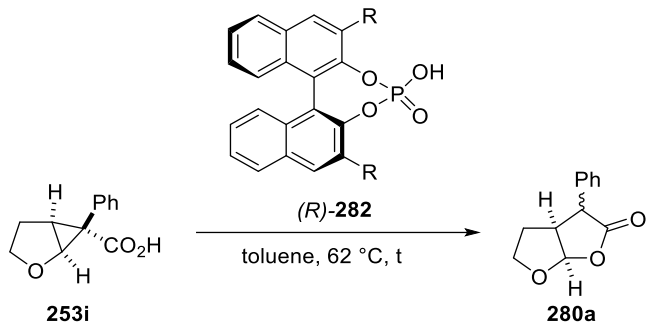
conditions: 0.2 mmol, c=0.2 M, 2 mol% CPA. Solvent, time and temperature as indicated. NMR yields measured using tetrachloroethane as internal standard. [a](*R*)-isomer was used.

2.3.2.2 Catalyst screen

With the optimized reaction conditions in hand, the *(R)*-isomer of the initial CPA was employed in the reaction. Similar to the chemistry by Kimberly *et al.*, one enantiomer of the starting material should react to the lactone in an enantiopure fashion while leaving the other enantiomer of the starting material untouched.[194,195]

The *(R)*-enantiomer of the catalyst gave 91% yield of the product (**Table 9**, Entry 9), and no enantioselectivity was observed. Kimberly *et al*. obtained similar results in their studies. They only observed enantioselectivity once they substituted the phosphoric acids in the 3, 3' positions. Since it was proven the reaction works with one enantiomer of the catalyst, different catalysts with 3, 3' substitutions were tested. These were synthesized by Dr. Andreas Hartl during his PhD thesis.[196]

Table 10. Screening of CPA catalysts.



Entry	*R*	*t [h]*	*yield*	*ee*
1	Ph	48	88%	0%
2	2,4,6-(*i*-Pr)$_3$-C$_6$H$_2$	48	60%, 26 % remaining starting material	16% ee with one diastereomer
3	SiPh$_3$	48	52%, 35% remaining starting material	-11% ee with one diastereomer

conditions: 0.2 mmol, c=0.2 M, 2 mol% CPA, toluene, 62 °C. Time as indicated. NMR yields measured using tetrachloroethane as internal standard.

With a phenyl substitution in the 3, 3' position, the yield was comparably high to the unsubstituted BINOL-phosphoric acid and no *ee* was observed (**Table 10**, Entry 1). With larger residues such as 2,4,6-(isopropyl)$_3$-C$_6$H$_2$, the yield dropped considerably and one of the diastereomers was obtained with an *ee* of 16% (**Table 10**, Entry 2). Similarly, when the size of the residue was increased even by a small increment to a triphenyl silane residue, the yield and conversion dropped even further (**Table 10**, Entry 3). Curiously, the *ee* was similar to the 2,4,6-(isopropyl)$_3$-C$_6$H$_2$ substituted CPA, however, the opposite enantiomer of the same diastereomer was obtained. This is unexpected since the size difference is not that large, however, the electronic effects and the orientation of the phenyl rings as well as the silane may play a special role in this case.

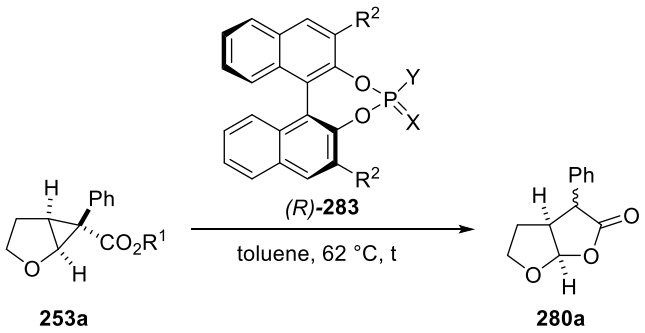
Since their emergence, a wide variety of chiral phosphoric acid derivatives have been developed, among them *N*-triflyl phosphoramides. These new catalysts have a higher Brønsted-acidity than the classic CPA catalysts.[197] With this in mind, a triflic amide catalyst was employed in the reaction with both the carboxylic acid as well as with the methyl ester, determining if the acidity was high enough to catalyze the hydrolysis of the ester and circumvent the lack of reactivity observed with the CPAs (see above). Indeed, employing the catalyst in the conversion of the carboxylic acid gave the product

280a in 94% yield after only 4 hours with no *ee.* When the ester cyclopropane was employed as starting material, the conversion was incomplete and the reaction very messy. No *ee* was determined in this case since the yield dropped considerably to just 17% and the product could not be cleanly separated from the reaction mixture.

Seleno-phosphoric acid catalysts are a completely new class recently developed by Johannes Eder and Dr. Alexander Antonov of the Gschwind group.[198] Their acidity is expected to be higher than traditional CPAs. The same experiments were performed with these catalysts; however, no conversion of the ester was observed (**Table 11**, Entry 4) and the reaction from the acid proceeded only in a very sluggish matter, forming 27% product with 63% starting material remaining and the isolation of the product from the reaction mixture being impossible.

The enantiomeric excess of the starting material could not be determined, as the carboxylic acid does not run on the available chiral columns and could not be separated from the CPA out of the reaction mixture.

Table 11. Investigations with new CPA catalysts.



253a **280a**

Entry	***R¹***	***R²***	***X***	***Y***	***t [h]***	***yield***	***ee***
1	H	3,5-CF_3-C_6H_3	O	NHTf	48	95%	0%
2	Me	3,5-CF_3-C_6H_3	O	NHTf	48	17%, 26 % remaining starting material	n.d.
3	H	H	Se	SeK	168	27%, 63% remaining starting material	n.d.
4	Me	H	Se	SeK	48	n.d.	n.d.

conditions: 0.2 mmol, c=0.2 M, 2 mol% catalyst, toluene, 62 °C. Time as indicated. NMR yields measured using tetrachloroethane as internal standard.

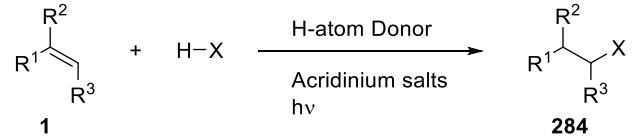
2.3.3 Conclusion and outlook

The previously developed lactonization procedure by Reiser *et al.* and Theodorakis *et al.* was expanded to vinylcyclopropanes. It proceeded readily with cyclopropanes with an oxygen atom in α-position to the cyclopropane. Indole derivatives and cyclopropanated styrene did not react to the corresponding lactones. Equilibration to the α,β-lactone was possible when the vinyl substituent was non-aromatic. First attempts showed the enantioselective transformation to the chiral lactones derived from the aryl acetate-cyclopropanes could be achieved with some selectivity for one diastereomer. Further investigation into the exact role and structure of potential ion pairs needs to be conducted for further understanding of this mechanism. Selenium- and triflic amide derivatives were unsuccessful in the reaction.

2.4 Visible light mediated synthesis of hexahydro[2,3*b*]furans

2.4.1 Prior investigations on styrene activation and anti-Markovnikov nucleophilic addition

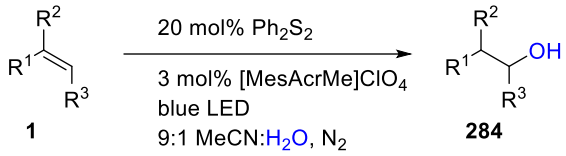
During the search for further ways to transform **250**, the styrene moiety gained interest. Styrenes have high oxidation potentials of over +1.5 V vs. SCE,[199] and not many metal-based photocatalysts have the electronic properties to reach these potentials.[200] Nicewicz *et al.* realized the potential of organic photoredox catalysts, which usually have the electronic properties to oxidize alkenes directly, and developed a general procedure for the *anti*-Markovnikov hydrofunctionalization of alkenes (**Scheme 87**).



Scheme 87. *Anti*-Markovnikov addition of nucleophiles to styrenes.

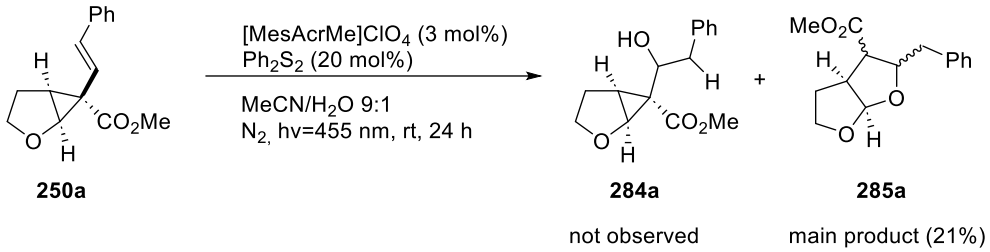
The group of Lei were able to synthesize alcohols from alkenes and water utilizing the Nicewicz chemistry. When they used [MesAcrMe]ClO_4 combined with Ph_2S_2 as hydrogen

atom catalyst under blue irradiation and solvent equivalents of water, they obtained the alcohols **284** in good yields (**Scheme 88**).



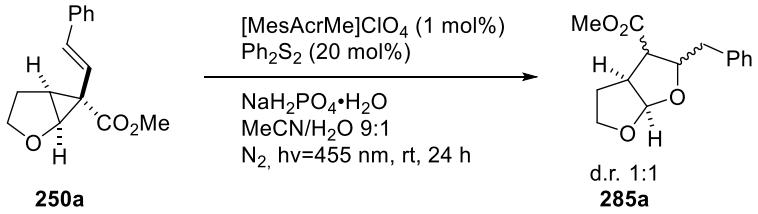
Scheme 88. Lei *et al*. synthesis of alcohols.

Vinylcyclopropane **250a** with its styrene moeity can be activated by the acridinium catalyst [MesAcrMe]ClO_4. Surprisingly, when **250a** was subjected to the conditions of the Lei group, bicycle **285a** was formed instead of the expected addition product **284a** (**Scheme 89**).



Scheme 89. Application of the activation of styrenes to vinylcyclopropane **250a**.

Previously to this work, the reaction was optimized, control experiments were performed, and a small substrate scope was evaluated.



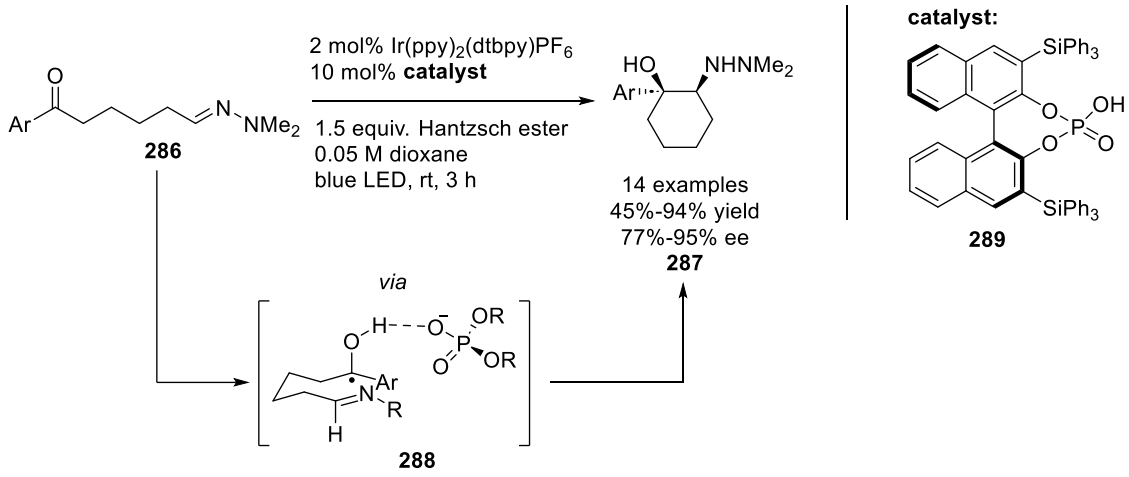
Scheme 90. Optimized reaction conditions for the transformation of **250a** to **285a**.

The main drawbacks of the reaction were found to be the moderate yields and the formation of diastereomers. In this chapter, both problems will be addressed, and the mechanism will be eluded.

2.4.2 Attempts at solving diastereoselectivity problems with chiral phosphoric acids

2.4.2.1 Chiral phosphoric acids in photocatalysis

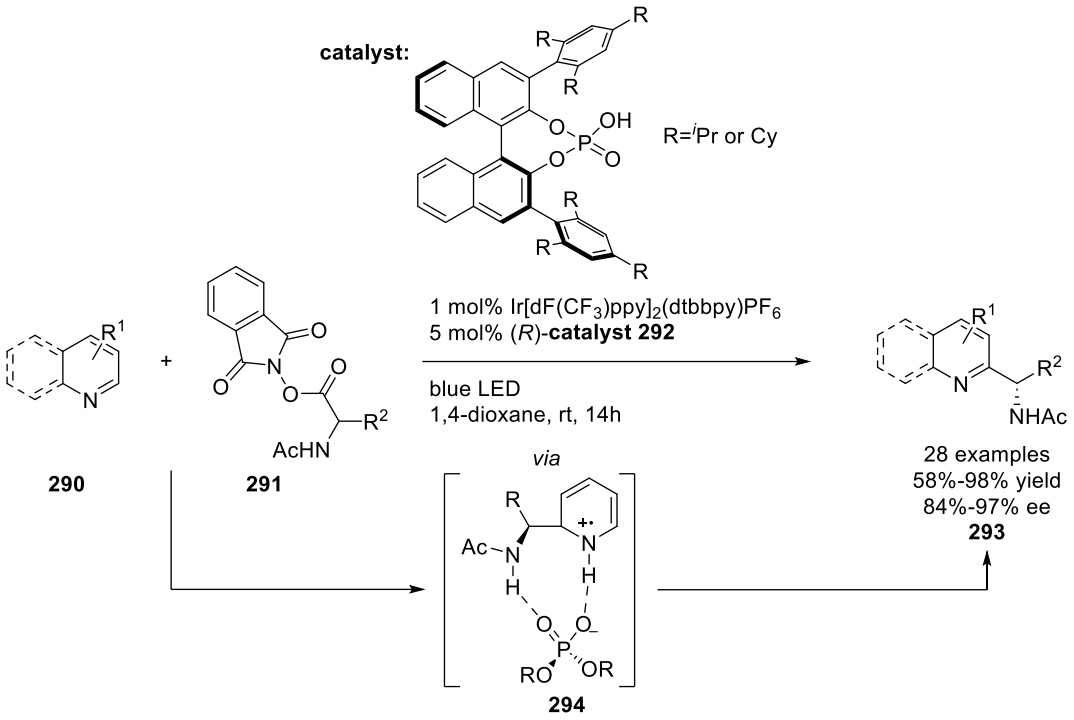
Only little is known on photocatalysis with chiral phosphoric acids (CPAs). The first account is a procedure by Knowles *et al.* where they employ a CPA in combination with iridium photocatalysis for the intramolecular cyclization of ketones (**Scheme 91**). After a proton-coupled electron transfer (PCET), an alcohol is formed, which interacts with the chiral phosphoric acid, locking it into a specific conformation determining which enantiomer is formed in the following C-C bond formation step. A nitrogen-centered radical is formed, and the CPA-radical complex is reduced by the help of the sacrificial electron donor Hantzsch dihydropyridine, and the reduction of the radical to the pyridine and subsequent proton transfer regenerates the catalysts (**Scheme 91**).[201]



Scheme 91. Asymmetric aza-pinacol rearrangement.

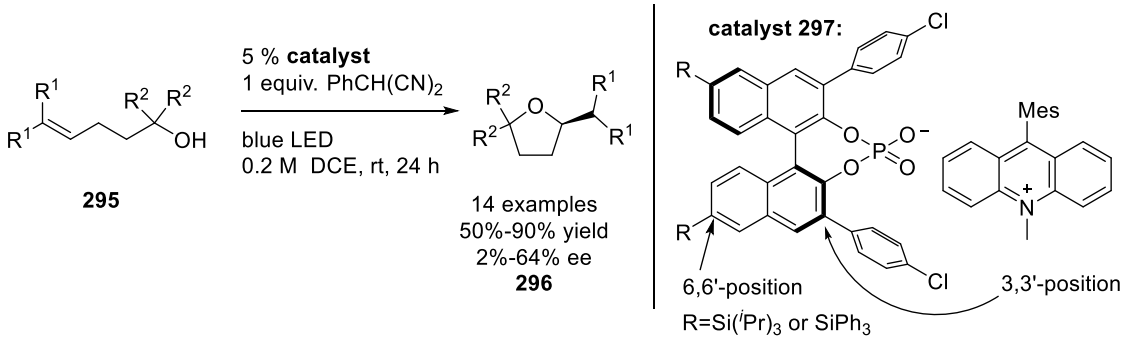
The method provided moderate to good yields with good enantiomeric excess in most cases.

In comparison, Phipps *et al.* developed an intermolecular Minisci-type addition to pyridines using redox active phthalimide esters and CPAs. After loss of the phthalimide and CO_2, the formed radical coordinates to the CPA along with the pyridine, followed by radical addition in an enantioselective fashion. The product is obtained after deprotonation and oxidation with full regeneration of the catalysts as above (**Scheme 92**).[202]



Scheme 92. Asymmetric intermolecular Minisci-type addition.

Both reactions have one major drawback: poor atom economy. Knowles *et al.* utilize a stoichiometric sacrificial proton donor, and the method of Phipps *et al.* produces phthalimide as a stoichiometric by-product. Nevertheless, these reactions are powerful examples of how well the combination of radical chemistry and ion-pair chemistry can work in synchrony to produce highly sought after compounds in high enantiomeric excesses.

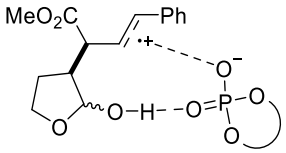


Scheme 93. Intramolecular *anti*-Markovnikov cyclization.

The synergy of photoredox activation and chiral ion pairing was further demonstrated in the work by Luo *et al.*, wherein they developed an enantioselective variant of the

cyclization-hydroetherification reaction of Nicewicz *et al.*[203,204] Contrary to the two previously described procedures, there was not a set of two catalysts, but a combination of the photoredoxcatalyst with the chiral ion-pairing catalyst (**Scheme 93**). While the enantiomeric excess was only moderate compared to Phipps and Knowles, it showcases the potential of combining two catalytic activation modes into one catalyst. Surprisingly, tuning the catalyst at the 6, 6'-position leads to a significant increase in enantioselectivity. This is in stark contrast with the usual trend that tuning the catalyst in 3, 3'-position leads to the biggest changes in enantioselectivity by changing the steric and electronic properties of the so-called "pocket" around the ion-binding sites.[205]

Since the last example utilizes the chemistry developed by Nicewicz applied to the synthesis of hexahydro[2,3*b*]-furans from vinylcyclopropanes, it provided the base for the first attempts at overcoming the issues with diastereoselectivity. The hypothetic idea of a core structure for the transformation is shown in **Scheme 94**: H-bonding to the hydroxyl group and electrostatic interactions between the negatively charged oxygen on the CPA and the radical cation are in theory possible. A similar structure was also proposed in Luo's hydroetherification reaction shown in **Scheme 93** .[204] For further details on the mechanism, refer to chapter 2.4.5.



298

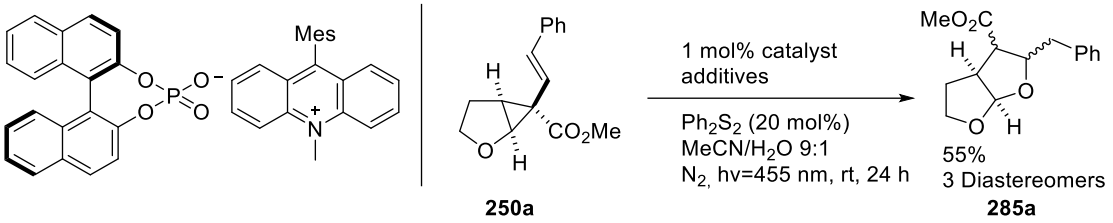
Scheme 94. Core structure and point of attack for the CPA.

2.4.2.2 Catalyst synthesis and evaluation

The first goal was to improve the diastereomeric ratio of the reaction by incorporating chiral phosphoric acids (CPAs). The steric bulk of the BINOL-backbone could block one side of the molecule, only allowing the water attack and ring closure from the other side. In addition, it was theorized that the CPA-Na-salt could be a viable alternative to $NaH_2PO_4 \cdot H_2O$. The salt was synthesized according to literature procedure by deprotonation with NaOMe.[206]

Table 12. Screening of chiral CPA additives.

chiral Fukuzumi catalyst 299:



Entry	*catalyst*	*additives*	*yield*[a]
1	Fukuzumi ClO_4 salt	(*R*)-CPA (10 mol%)	11%
2	Fukuzumi ClO_4 salt	(*R*)-CPA (10 mol%), $NaH_2PO_4{\cdot}H_2O$ (25 mol%)	45%
3[b]	Fukuzumi ClO_4 salt (5 mol%)	Sodium CPA salt (*rac*) (5 mol%)	44%
4[b]	Fukuzumi ClO_4 salt (5 mol%)	Sodium CPA salt (*rac*) (5 mol%), $NaH_2PO_4{\cdot}H_2O$	49%
5[b]	Fukuzumi CPA catalyst (*rac*)		34%
6[b]	Fukuzumi CPA catalyst (*rac*)	$NaH_2PO_4{\cdot}H_2O$	46%
7[b]	Fukuzumi CPA catalyst (*S*)		43%
8[b]	Fukuzumi CPA catalyst (*S*)	$NaH_2PO_4{\cdot}H_2O$	53%

conditions: 0.2 mmol scale, c=0.2 M, 20 mol% Ph_2S_2, N_2, hν=455 nm, rt, 24 h. [a] determined by ^{1}H-NMR with tetrachloroethane as internal standard. n.c.=no conversion. [b] 5 mol% catalyst used.

First, the reaction was tested under similar conditions developed by the Knowles group: 10 mol% of the chiral phosphoric acid was added as co-catalyst.[201] Without $NaH_2PO_4{\cdot}H_2O$, the yield diminished considerably (**Table 12**, Entry 1), which was in line with the discoveries made earlier. Accordingly, adding $NaH_2PO_4{\cdot}H_2O$ increased the yield again (**Table 12**, Entry 2), however, still considerably lower than the previously established yields. The next step was the evaluation of the ClO_4 salt of $[MesAcrMe]^+$ and the sodium salt of the CPA and increasing the catalyst loading to 5 mol% as in the procedure by the Luo group. The difference between the reaction with and without $NaH_2PO_4{\cdot}H_2O$ was by far the smallest, well within the error margin of the method used to determine NMR yields (**Table 12**, entries 3 and 4). This indicates the anion of the CPA plays a similar role as $NaH_2PO_4{\cdot}H_2O$. Addition of $NaH_2PO_4{\cdot}H_2O$ did not increase the yield significantly in this case. Finally, exchanging the catalyst and CPA for the synthesized chiral salt of Fukuzumi's catalyst **299** provided similar yields, even though the effect was not quite as stark between the reaction with and without $NaH_2PO_4{\cdot}H_2O$ (**Table 12**,

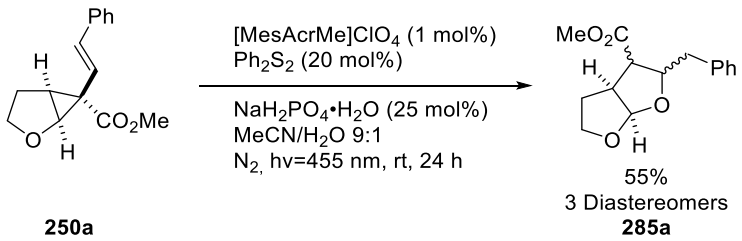
entries 5 and 6).[204] The *(S)*-isomer of the catalyst seemed to have a small effect, bringing the yield to the same level as with the previously developed conditions.

However, the main goal was to improve diastereoselectivity. Unfortunately, no change in diastereomeric ratio was observed in all cases. Whether the conditions, nor the use of enantiomerically pure reagents vs. the single enantiomers brought any change into the diastereomeric ratio.

2.4.3 Further optimization of the reaction conditions

Since the diastereoselectivity seemed to be a problem which could not be overcome at the time, attention was turned to further screening the reaction conditions to understand the reaction further and improve the yield. A wide variety of conditions were screened in the next step.

Table 13. Further screening of reaction conditions.



250a **285a**

Entry	*conditions*	*yield*[a]
1	3 equiv. water	44%
2	water-free conditions	c.r.m.
3	(*n*-Bu)$_4$NCl instead of $NaH_2PO_4 \cdot H_2O$	41%
4	LiH_2PO_4 instead of $NaH_2PO_4 \cdot H_2O$	50%
5	McIlvaine buffer instead of $NaH_2PO_4 \cdot H_2O$ and water (pH 4)	35%
6	pH 13 buffer	48%
7	pH 0.65 buffer	0%
8	48 h reaction time	50%
9	50 °C reaction temperature	52%
10	TEAMS ionic liquid/H_2O 9:1 instead of MeCN/H_2O 9:1	0%
11	40 mol% Thiophenol as HAT catalyst	87%
12	40 mol% Thiophenol as HAT catalyst, 0.5 mmol scale	79% (75%)[b]
13	40 mol% PhSNa as HAT catalyst	42%

conditions: 0.2 mmol scale, 0.2 mmol, c=0.2 M, 1 mol% [MesAcrMe]ClO_4, 20 mol% Ph_2S_2, 25 mol% additive, hv=455 nm, rt, 24 h. [a] determined by ^{1}H-NMR with tetrachloroethane as internal standard. [b]isolated yield. c.r.m.= complex reaction mixture.

First, the amount of water was examined. Up to this point, solvent equivalents of water had been used. Since water is a reagent in this reaction, using an overstoichiometric

amount could lead to side reactions or unwanted products. Defining an exact amount of water, limiting the number of contact options between the starting material and reagent, could prove beneficial to the reaction. In addition, having only a few equivalents of water in the reaction together with $NaH_2PO_4 \cdot H_2O$ could result in small water "pockets" by raising the polarity of the water so high it becomes immiscible with acetonitrile. However, reducing the amount of water to only 3 equivalents did not improve the yield (**Table 13**, Entry 1). Since the starting material is not soluble in water, using more equivalents did not seem fruitful and this pathway was not explored. In this context, however, the reaction was examined when no water was present. While the starting material was fully consumed, no meaningful products could be detected.

Following a similar thought process, the $NaH_2PO_4 \cdot H_2O$ was exchanged with $(n\text{-Bu})_4NCl$. In previous studies, NH_4Cl had proven to be almost as efficient as the sodium salt in co-catalyzing the reaction. This was an interesting find, as most salts screened were inefficient, save for the phosphate salts. Since alkyl ammonium salts are efficient phase transfer catalysts,[207] they can ease the addition of water, and, in addition, form small micelles in which the reaction could take place. However, also in this case the yield was diminished compared to the standard reaction conditions (**Table 13**, Entry 3).

In the next step, the influence of the cation was explored. Lithium has a different oxophilicity than sodium, which is why using LiH_2PO_4 instead of $NaH_2PO_4 \cdot H_2O$ held an appeal.[208,209] Cations are known to form π-complexes with aromatic rings and coordinate to alkenes and ether oxygens.[210,211] If the effect of the salt is coordination of the oxygen atoms, having a different oxophilicity could result in a change in the substrate binding and therefore better catalysis. However, as can be seen in **Table 13** (Entry 4), exchanging the salt did not increase the yield, even if it did not diminish it either. It was concluded that the cation had limited, if any, influence on the outcome of the reaction.

Since tuning the properties of the cation and anion did not have an influence on the reaction, attention was turned to other parameters.

One parameter is the pH of the reaction. The pH value of the reaction is dependent on a wealth of factors: The base, thiophenol and finally, the substrate itself can influence

the pH of the reaction, changing it during the runtime. To evaluate the effect, the reaction was buffered with a McIlvaine buffer, keeping it at the calculated pH of roughly 4. This is a phosphate buffer, mimicking the role of the sodium salt while keeping the pH constant. The buffer was used in place of the water. However, the use diminished the yield to just 35%.

Next, the pH was raised to 13 and buffered with the help of a KCl/NaOH buffer. While this did not have a positive influence on the reaction outcome, it did not significantly increase the yield of the reaction, in stark contrast to the buffer at pH 4.

Decreasing the pH to 0 with the help of a NaOAc/HCl buffer completely shut down the reaction. Only a complex reaction mixture could be observed.

It was determined that changes in pH value during the reaction had no impact on its outcome.

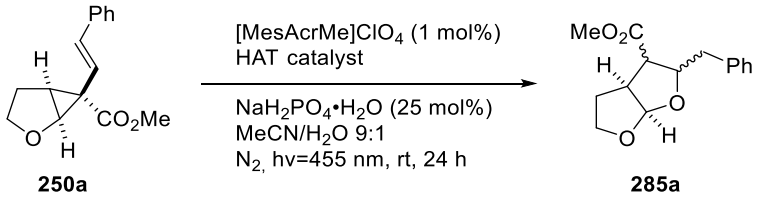
Even though the starting material was completely consumed after 24 hours, the reaction time was increased to 48 hours to determine if the product is prone to decomposition under the reaction conditions or non-isolable intermediates require more reaction time. Since there was never any observation of significant amounts of side products as well in the crude NMR and no other fractions could be isolated after column chromatography, there is a distinct possibility there might be ionic or polymer intermediates or side products which are either too small in quantity to be visible in the crude NMR or unable to run on the column even with highly polar mobile phases. However, after 48 hours there was neither an increase nor decrease in yield. Hence, it was possible to showcase product stability under irradiation with the standard reaction conditions, thus determining that the light source is not responsible for the low yields due to product decomposition. Therefore, attention could be shifted away from optimizing reaction times due to fear of product loss.

Based on previous work on photoredox catalysis at elevated temperatures, it was theorized that increasing the reaction temperature in conjunction with light irradiation can also have a beneficial impact on the yield. However, increasing the reaction temperature slightly to 50 °C did not better the yield either.

Finally, and despite the disclosure by Nicewcz *et. al.,* the decision was made to change the Ph_2S_2 for PhSH.[212] The general understanding is that the Ph_2S_2 reacts to two $PhS^{\cdot}$ radicals under irradiation with blue light, which is why no effect from a switch to PhSH was expected. However, the Nicewicz group has also disclosed that different thiophenols have a significant influence on the reaction yields, even it is not obvious form the proposed reaction mechanism and there has never been an explanation why this could be the case.[213] Indeed, employing PhSH as the HAT catalyst resulted in a significant increase in yield to 75% isolated yield, an increase by another 20% compared to the standard reaction conditions (**Table 12**,Entry 12). While this is an impressive result, thiophenol is extremely toxic and not trivial to handle, which is why the attempt was made to exchange PhSH for its sodium salt. However, the observed increase in yield remained exclusive to the use of PhSH (**Table 12**, Entry 13).

2.4.4 Screening of hydrogen atom transfer catalysts

Table 14. Screening of hydrogen atom transfer catalysts.



Entry	*conditions*	*yield[a]*
1	20 mol% Phenyldimalononitrile	0%
2	40 mol% Diethylmalonate	0%
3	40 mol% Tris(trimethylsilyl)silane	0%
4	20 mol% Ph_2Se_2	54%
5	40 mol% *p*-Nitrothiophenol	26%
6	40 mol% *o*-Aminothiophenol	38%
7	40 mol% *p*-Methoxythiophenol	83%

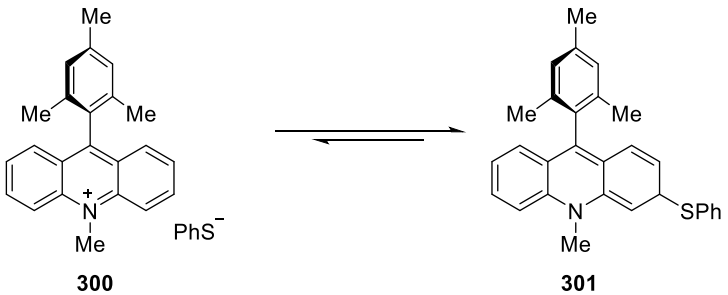
conditions: 0.2 mmol scale, 0.2 mmol, c=0.2 M, 1 mol% [MesAcrMe]ClO_4, 40 mol% Ph_2SH, 25 mol% additive, hv=455 nm, rt, 24 h. [a] determined by ^{1}H-NMR with tetrachloroethane as internal standard.

Since this previously thought irrelevant change from Ph_2S_2 to PhSH showed such drastic changes in the reactivity, it was deemed necessary to screen more hydrogen atom transfer (HAT) catalysts to analyze the impact of the hydrogen atom transfer step. During the development of the reaction, it was already determined the HAT catalyst is essential to the success of the reaction. In their first reports, Nicewicz *et al.* used

phenyldimalononitrile or diethyl malonate as HAT catalysts. Following this pioneering work, these were the first catalysts to be tested in the reaction. However, contra-intuitively, no isolable product was observed, even though the starting material was consumed completely (**Table 14**, Entries 1 and 2). The HAT catalyst tris(trimethylsilyl)silane[214,215] was tested next. With this catalyst, no consumption of the starting material was observed.

Ph_2Se_2 is also a known HAT catalyst. Interestingly, this catalyst yielded the product on the same scale as Ph_2S_2 (**Table 14**,Entry 4). Other thiophenols yielded the product in varying yields (**Table 14**, entries 5-7). Nitro- and amino groups on the thiophenol hampered the reaction. Especially *o*-aminothiophenol possesses two further nucleophilic functionalities, making it a possible inhibitor of the reaction.

This screening had a further very interesting result: The reaction, with one exception, appears to only work with thiophenols and derivatives thereof. This points towards a very specific and essential catalyst-cocatalyst interaction. Nicewicz *et al.* proposed a reversible addition of the PhS^- anion to the catalyst, with the continuous availability of the $[MesAcrMe]^+$ cation for excitation (**Scheme 95**).[212] However, it is unsure whether the same intermediate is formed in this reaction. The main reason against this hypothesis is that many reactions developed by Nicewicz *et al.* run with other cocatalysts. One example is the initially developed hydroetherification which utilizes phenyldimalononitrile as cocatalyst.[203] Secondly, the reactions are reported to also run with other photoredoxcatalysts, such as dicyanoanthracene. However, the ring opening of the cyclopropanes developed here completely shuts down when other catalysts than acridinium salts are used, even when using highly oxidizing pyrylium salts.

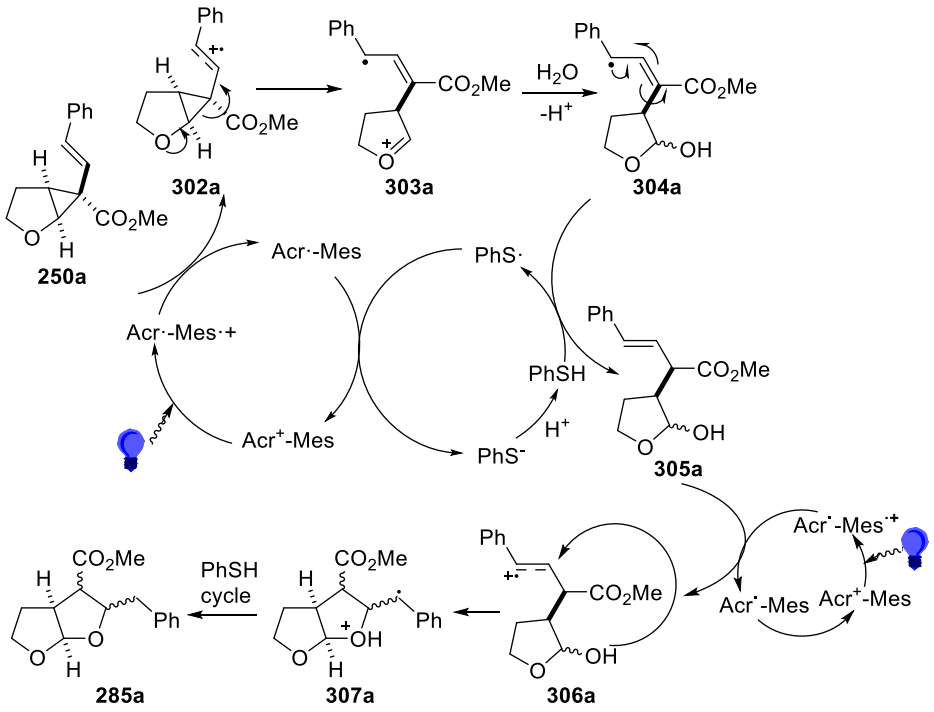


Scheme 95. Possible Interaction between acridinium salts and thiophenolate anion.

These facts indicate a very specific substrate-catalyst-cocatalyst interaction which apparently greatly influences the reaction.

In their mechanistic investigations, the Nicewicz group found the reaction mixture underwent photobleaching with the color reappearing after some time and when the light was turned off. This effect was observed in the transformation of the vinylcyclopropanes **250** as well. It was decided to further explore this effect with the help of UV-Vis measurements (see chapter 2.4.8) and delve deeper into the understanding of the possible mechanism.

2.4.5 Mechanistic proposal

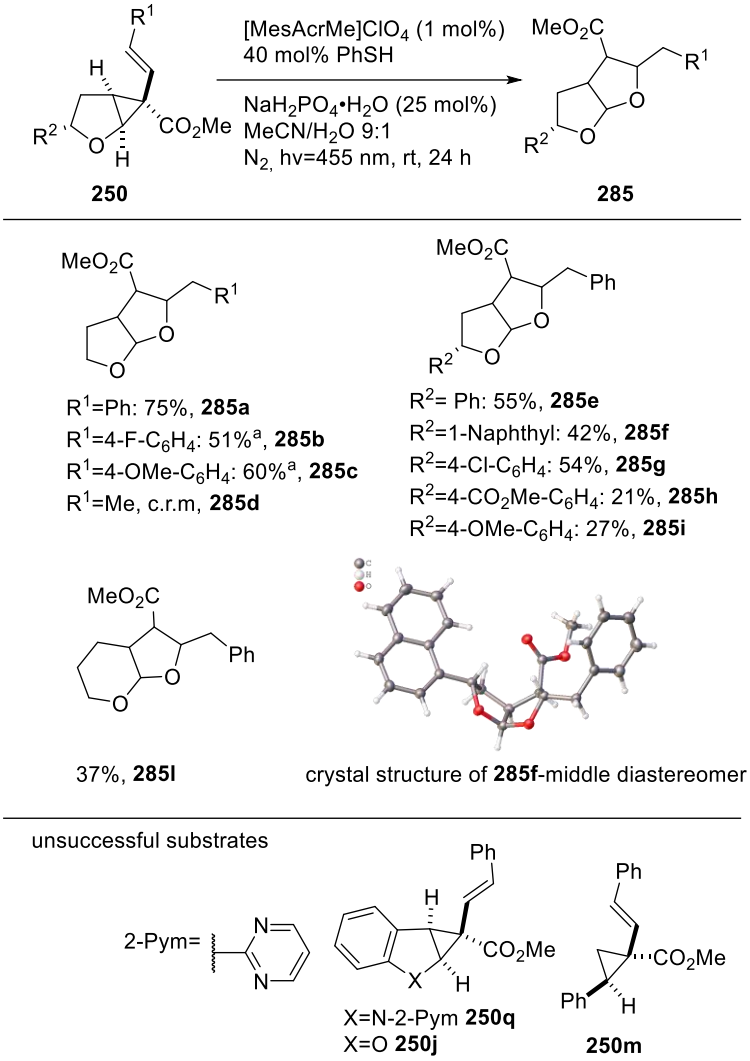


Scheme 96. Mechanistic proposal for the formation of hexahydro[2,3*b*]furans.

Based on the previously obtained results and the mechanistic proposal by Nicewicz *et al.*, a working mechanistic hypothesis was formed. After one-electron oxidation of the *exo*-vinyl on the cyclopropane by the excited photocatalyst, a ring opening cascade is triggered. The free electron pair of the oxygen is essential in this step, allowing for cation formation. The ring-opened charge separated radical cation **303a** then undergoes addition of water to the hemiacetal **304a**. This radical is extremely

stabilized as it is allylic, benzylic, and also tertiary. A hydrogen atom transfer from PhSH forms the intermediate **305a**, which again undergoes one-electron oxidation to form the radical cation. The reaction then proceeds in the typical *anti*-Markovnikov fashion and after a second HAT produces the final product **285a**.

2.4.6 Substrate scope



Scheme 97. Substrate scope of the photoredox catalyzed interrupted-Nicewicz-rearrangement.

After identifying suitable reaction conditions, the substrate scope was investigated to explore the limitations of the reaction. R^2 substituents change the electronic properties of the THF-oxygen and add steric bulk, R^1 substituents change the electronic properties

of the double bond. The substitution of the hydrogen adjacent to the oxygen on the tetrahydrofuran ring with a phenyl group gave sufficient yield of 55% (**285e**).

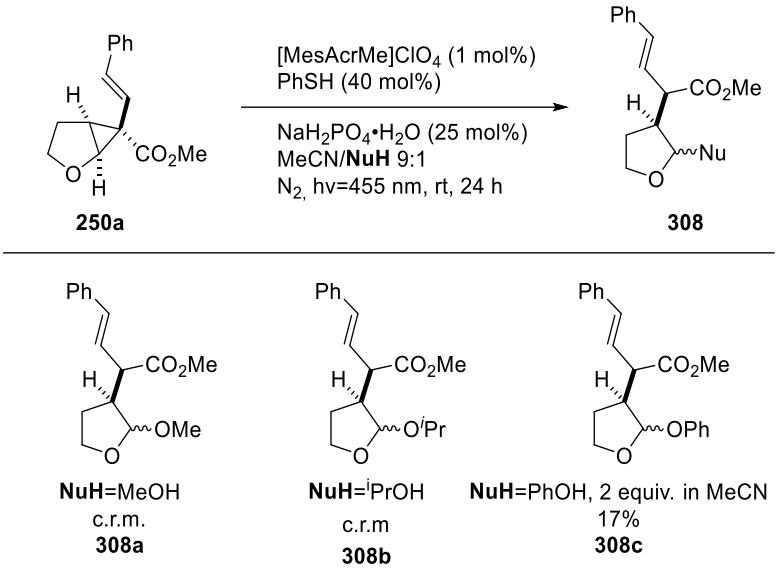
Expanding this to the sterically more demanding naphthyl substitution (**285f**) was met with only a slight reduction in yield to 42%. A para-chloro substitution on the phenyl ring (**285g**) gave comparable yield of 54%, whereas installing a para-methoxy or para-methoxy-ester substitution drastically decreased the yield (**285i** and **285**). The electron-withdrawing groups on the phenyl ring in R^2 reduce the ability of the THF oxygen to donate electrons into the cyclopropane, hindering its ability to stabilize the carbocation. Para-methoxy substitution on the alkene gave the best yields (**285c**), whereas a para-fluoro substitution (**285b**) gave slightly diminished but still acceptable yields, which can be explained through the donation of electrons into the aromatic ring and thus into the double bond by the para-methoxy group, thereby making it more electron-rich and more oxidizable than the para-fluorine substituted styrene. Non-arene alkenes could not be activated (**285d**), which can be explained by the oxidation potential of the double bond being too high to be activated by the photocatalyst.[199] Additionally, non-fused ring systems also failed to provide the substituted tetrahydrofuran ring systems. In the case of cyclopropanated styrene **250m**, it is assumed this is due to the missing oxygen atom adjacent to the cyclopropane ring. Employing the indole-derived cyclopropane **250q** in the reaction only gave the ring opening product previously observed in the Brønsted-acid mediated lactonization (chapter 2.3.1.2). Thiophenol is acidic (p_KA=6.6 at 25 °C) and can catalyze this transformation.[216]

2.4.7 Nucleophile screening

During the mechanistic investigations, the question arose as to where the nucleophilic attack takes place. If the mechanism proceeds in analogy with Nicewicz *et al.*, there would first be a one-electron oxidation of the double bond with a subsequent nucleophilic attack of H_2O, giving the *anti*-Markovnikov addition product subsequently cyclizing in the next step. However, the cyclopropane bond with the α-oxygen can also undergo exocyclic ring opening, forming a stabilized cation on the oxygen as well as a very stable benzylic-allylic-tertiary radical. The H_2O would attack at the carbon adjacent

to the oxygen and after HAT give the hemiacetal which cyclizes in the second step as well.

Substituting H_2O for an alcohol would make the second cyclization step impossible and give an acetal. It can be assumed the alcohol would attack at the same position as H_2O. Similarly, if the hemiacetal could be synthesized and employed in the photoreaction and give the hexahydro[2,3*b*]furan products, its existence in the reaction would be confirmed.



Scheme 98. Screening of nucleophile addition partners.

The first experiments were run by exchanging the water in the solvent system with MeOH and *i*-PrOH. However, in both cases, while the starting material was consumed, no identifiable products were obtained. This prompted the use of a larger residue which would also be more stable. Indeed, when phenol was employed as the nucleophile, the desired acetal **308c** could be obtained in 17% yield as a mixture of 2 diastereomers. The NMR indicated 2 olefinic protons, now as a doublet and a doublet of doublet (**Figure 5**, red boxes) in contrast to the doublets observed in the cyclopropane (**Figure 5**, blue boxes). At the same time, the cyclopropyl protons were not observed. This indicated that while the double bond was still present in the product, the cyclopropane ring was opened, disproving the theory that the nucleophile adds to the double bond as observed in the literature precedent by the Lei and Nicewicz groups.[212,217] In addition, a doublet

in the downfield region, away from the aliphatic region but too far upfield for olefinic protons, indicated a hydrogen between two heteroatoms (**Figure 5**, orange boxes).

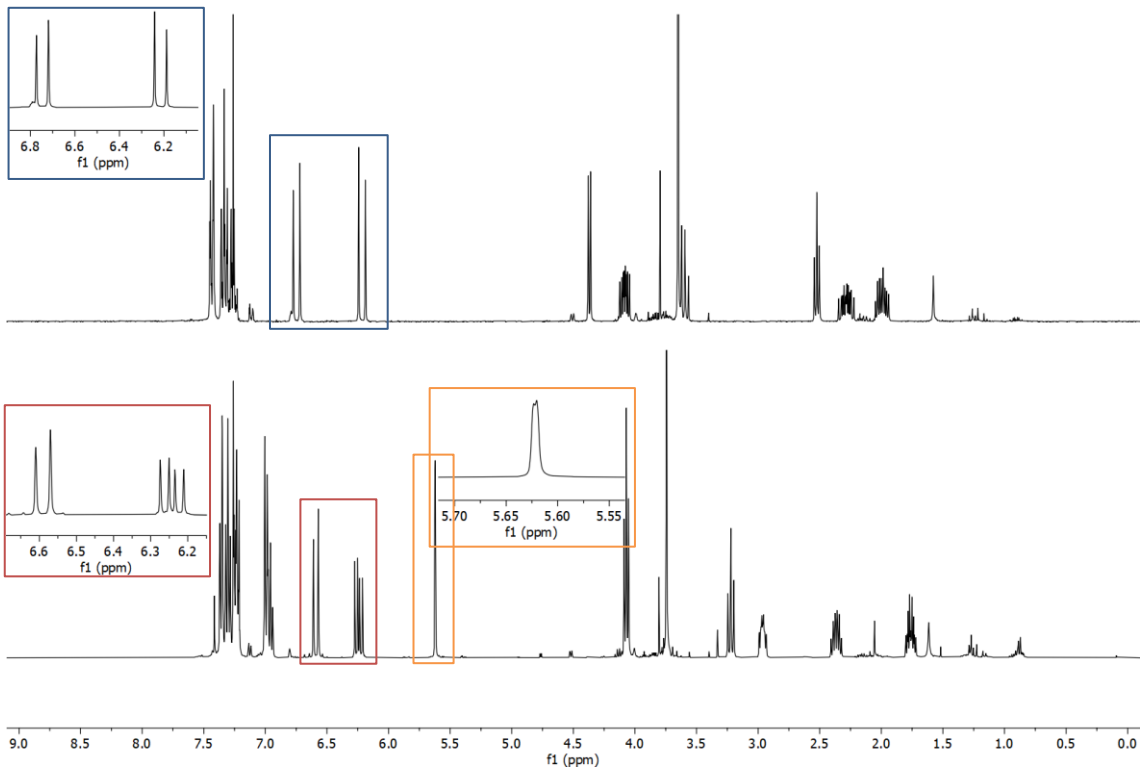
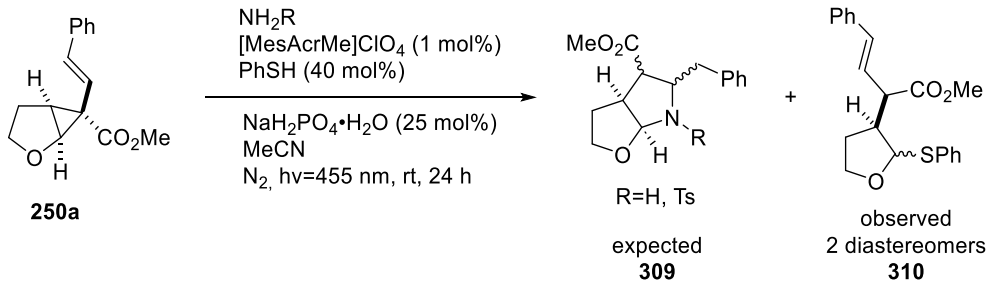


Figure 5. Comparison of the NMR spectra of the starting material **250a** (top) and the product **308c** (bottom).

Nitrogen-nucleophiles were tested as well. The benefit here is the possibility of the synthesis of protected and unprotected nitrogen cycles in one step (**Scheme 99**).



Scheme 99. Synthesis of nitrogen heterocycles.

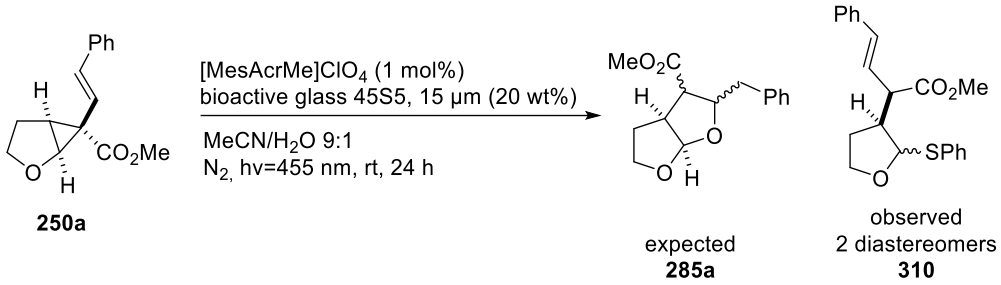
Surprisingly, the transformation with both tosyl amide and ammonia only gave the addition product with thiophenol. PhSH itself is a nucleophile which can participate in

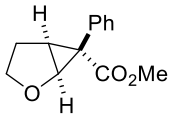
the reaction. However, no addition of PhSH was observed previously, even though 40 mol% is a considerable amount which should allow for some product formation if this was a viable pathway. However, when the reaction solution was basic enough as in the cases with the nitrogen precursors, the thiophenolate anion transforms into a viable nucleophile for the reaction, giving the observed addition product. This can even happen when water is present, under superbasic conditions which can be achieved with bioactive glass.

Bioactive glass differs from conventional glass in many ways, the main difference being it continuously releases ions when it comes into contact with aqueous media. This is used in many applications such as medicine and cosmetics.[218] These types of glasses are generally considered to be superbasic. The idea was to employ these glasses as a substitute for $NaH_2PO_4 \cdot H_2O$ to investigate the difference in the reaction. Bioactive glass 45S5 provided by Vanessa Rudolph from the Kunz group at the University of Regensburg was used. It is made up of 46.1 mol% SiO_2, 2.6 mol% P_2O_5, 24.4 mol% Na_2O and 26.9 mol% CaO and releases PO_4^{3-} ions into aqueous media. Surprisingly, no product was obtained, but instead the crude NMR indicated a structure similar to the one described previously with PhOH as nucleophile. Investigations revealed that instead of the addition of water to form **285a**, PhSH was added onto the molecule, forming **310** (**Table 15**). This is a very interesting result considering water was present in solvent equivalents and PhSH was only available in substoichiometric amounts. The hexahydro[2,3*b*]furan product was not observable even in traces.

A short screening revealed the water was essential to the success of the reaction, which proceeded with a lower yield and variety of byproducts in the absence of water (**Table 15**, entries 2 and 3). To rule out the possibility of an alternate addition pathway, donor-acceptor cyclopropane **253a** was used, but even after a reaction time of 7 days no conversion of the starting material was observed (**Table 15**, Entry 4), indicating the reaction runs according to the same mechanism as with the H_2O or PhOH addition.

Table 15. Screening of thiophenol addition.



Entry	*variation*	*yield[a]*
1	40 mol% PhSH	n.d.
2	1 equiv. PhSH	71%
3	1 equiv. PhSH, no water	46%, byproducts
4[b]	Starting material **253a** 	No conversion

conditions: 0.2 mmol, c=0.2 M, 1 mol% [MesAcrMe]ClO_4, 40 mol% PhSH, 20 wt% bioactive glass 45S5, hv=455 nm, rt, 2 h. [a]determined by ^{1}H-NMR with tetrachloroethane as internal standard. [b]reaction time 7 days.

The exact reaction pathway is unknown; however, the most likely possibility is the bioactive glass and its superbasicity making the PhSH a better nucleophile than water. This is supported by the fact that the reaction does not proceed to the thiophenol addition product without the bioactive glass 45S5, even when water is absent in the reaction.

2.4.8 UV-Vis measurements[§]

The easiest approach to determine if the previously mentioned photobleaching is in fact happening was to measure the UV-Vis spectra of the reaction solution before and after irradiation. In the blue (–) curve measured before irradiation, the absorption of the catalyst is clearly visible, especially at 455 nm where the irradiation takes place. After only 10 minutes of irradiation at 455 nm, the absorption of the acridinium catalyst has completely vanished (**Figure 6**).

[§] The time resolved UV-Vis measurements in this chapter were done by Svenja Wortmann from the group of Prof. Dr. Patrick Nürnberger.

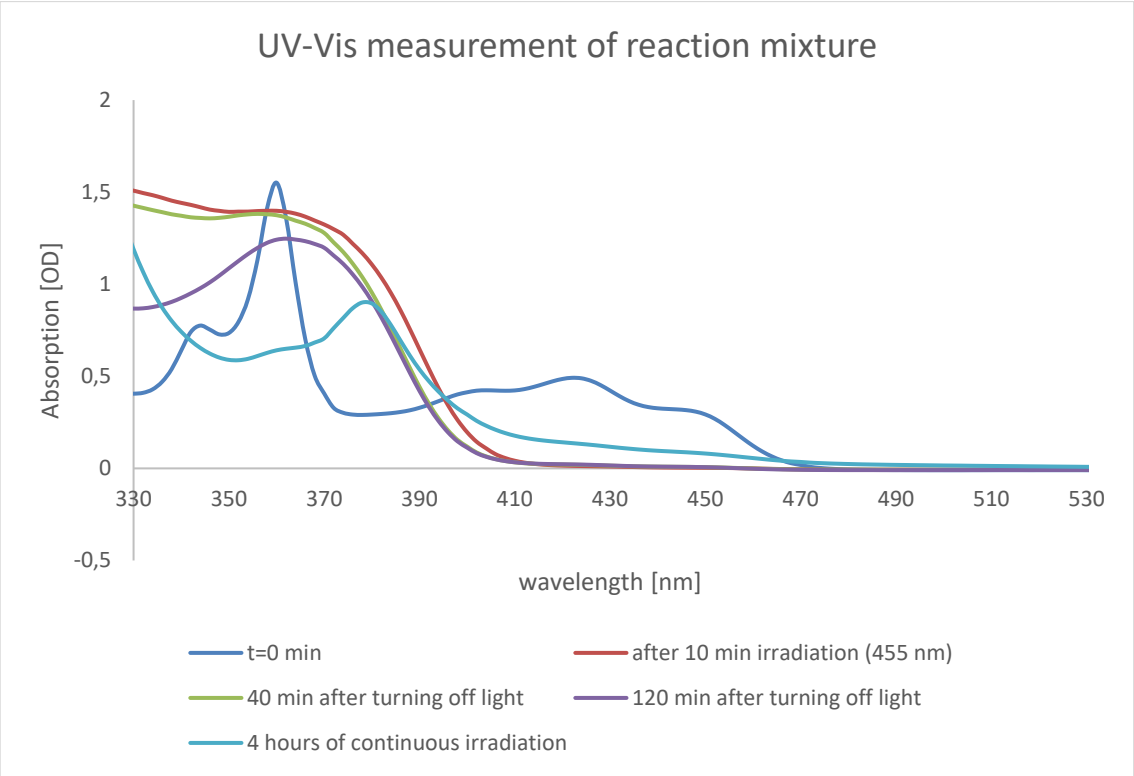


Figure 6. UV-Vis measurements of reaction mixture. Measurements were conducted in a solution of degassed MeCN/H_2O 9:1. c(MesAcrMeClO_4)=$5\cdot10^{-5}$ M. c(PhSH)=$2\cdot10^{-3}$ M. c($NaH_2PO_4\cdot H_2O$)=$1.25\cdot10^{-3}$ M. c(cyclopropane)=$5\cdot10^{-3}$ M.

In addition, a tremendous amount of scattering can be seen in the regions below 410 nm, showing quick degradation of the catalyst.

Experimentally, the yellowish color of the reaction solution reappears after about 4 hours of irradiation. After this time span, the solution was re-examined with UV-Vis measurements. The major absorption under 410 nm decreased, however, the defined spectrum of $[MesAcrMe]^+$ did not reappear (**Figure 6**, teal line). This is in line with Nicewicz *et al.,* who report a reappearance of the absorption of $[MesAcrMe]^+$ after ca. 6 h.[212]

When irradiation was turned off after 10 minutes and the reaction stirred in the dark, the absorption at 455 nm did not reappear even after 2 hours (**Figure 6**, purple line). No product formation was observed, the conversion was incomplete, and lactone **272a** was isolated as a side product, since thiophenol is acidic and can catalyze the lactonization.

These experiments led to following conclusions:

The photocatalyst degrades under the reaction conditions, even though some of the structure is retained. This is supported by the UV-Vis spectrum where semi-defined peaks can be seen after 4 hours of continuous irradiation (**Figure 6**). There is a second degradation process which can be observed in the first 10 minutes of the reaction, leading to complete loss of absorption of the reaction solution at 455 nm, which is the wavelength used for illumination. These processes are not the same, however. If the catalyst would degrade to a completely inactive compound which does not participate in the reaction after only 10 minutes, the reaction should be complete by this time, as the control experiments show the reaction needs the photocatalyst to proceed.

The possibility that the reaction could simply be a photoinitiated process versus a photocatalyzed process was considered. Photoinitiated and photocatalyzed processes are the same in regards to excitation and quenching, however, while the photocatalyst is restored to its ground state in photocatalyzed process (**Figure 7a**), this step is not needed in the case of photoinitiation (**Figure 7**b), and even missing in some cases.[219]

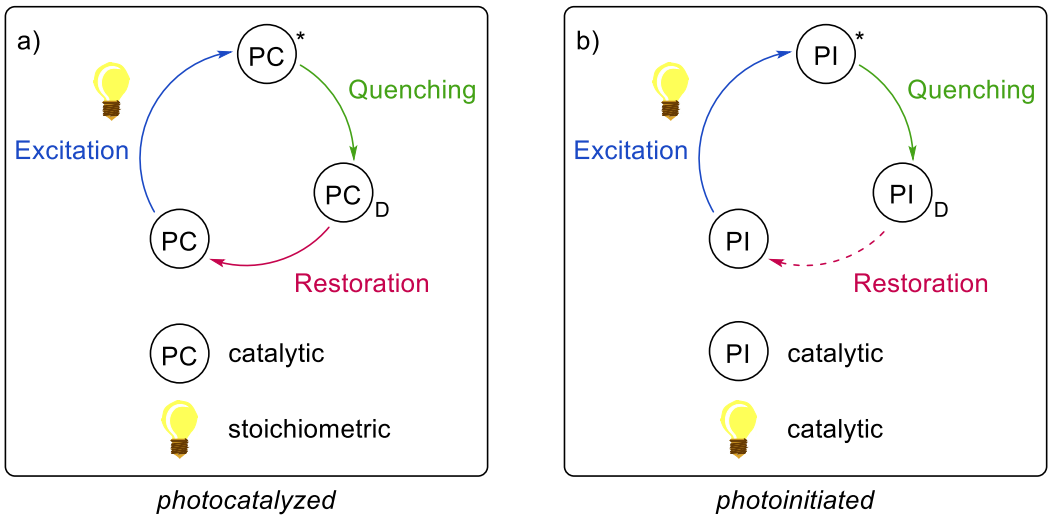


Figure 7. Photocatalyzed (a) versus photoinitiated (b) processes. PC=photocatalyst. PI=photoinitiator. D=deactivated.[219]

Photoinitiated processes are usually radical chain mechanisms such as polymerizations, and few true photoinitiation processes are known with acridinium salts.[220] Once these processes are initiated by the photoinitiator, they are self-catalyzed. If the transformation were photoinitiated, the reaction would be able to go to completion

even after the light were switched off. In this case, it would not matter if the catalyst would degrade after initiation. This hypothesis can be refuted since no product formation was observed after turning off the light.

This leaves complexation. Nicewicz *et al.* have shown the $[MesAcrMe]^+$ cation forms a complex with the alkenes employed in the reaction. The electron transfer step is much more efficient in the excited complex, increasing the overall efficiency of the reaction. Moreover, the excitation can occur from both the singlet and triplet excited state.[212] And, as previously mentioned, there is also the possibility of formation of a complex between the catalyst and thiol cocatalyst.

Another theory is the formation of a catalytically active species after excitation which does not absorb at 455 nm. It would form rather quickly but would need to be re-generated constantly. This would explain the photobleaching at least to some degree.

In order investigate this possibility, time-resolved UV-Vis measurements were performed by Svenja Wortmann from the group of Prof. Dr. Nürnberger.

2.4.8.1 Experimental setup

The experiments were performed on a Cary60 UV-Vis Spectrometer using a Quartz cuvette with an internal diameter of 2x10 mm from Starna. The absorption spectrum was detected over the 10 mm path length, while the LED (wavelength 455 nm, ThorLabs, M455L4, 0.7 A) was arranged perpendicular to illuminate the sample volume homogeneously over the 2 mm path length. 200 µL of the sample was used to ensure homogeneous illumination of the entire volume.

2.4.8.2 Time-resolved UV-Vis absorption spectroscopy

The time resolved spectra confirmed the findings previously described.

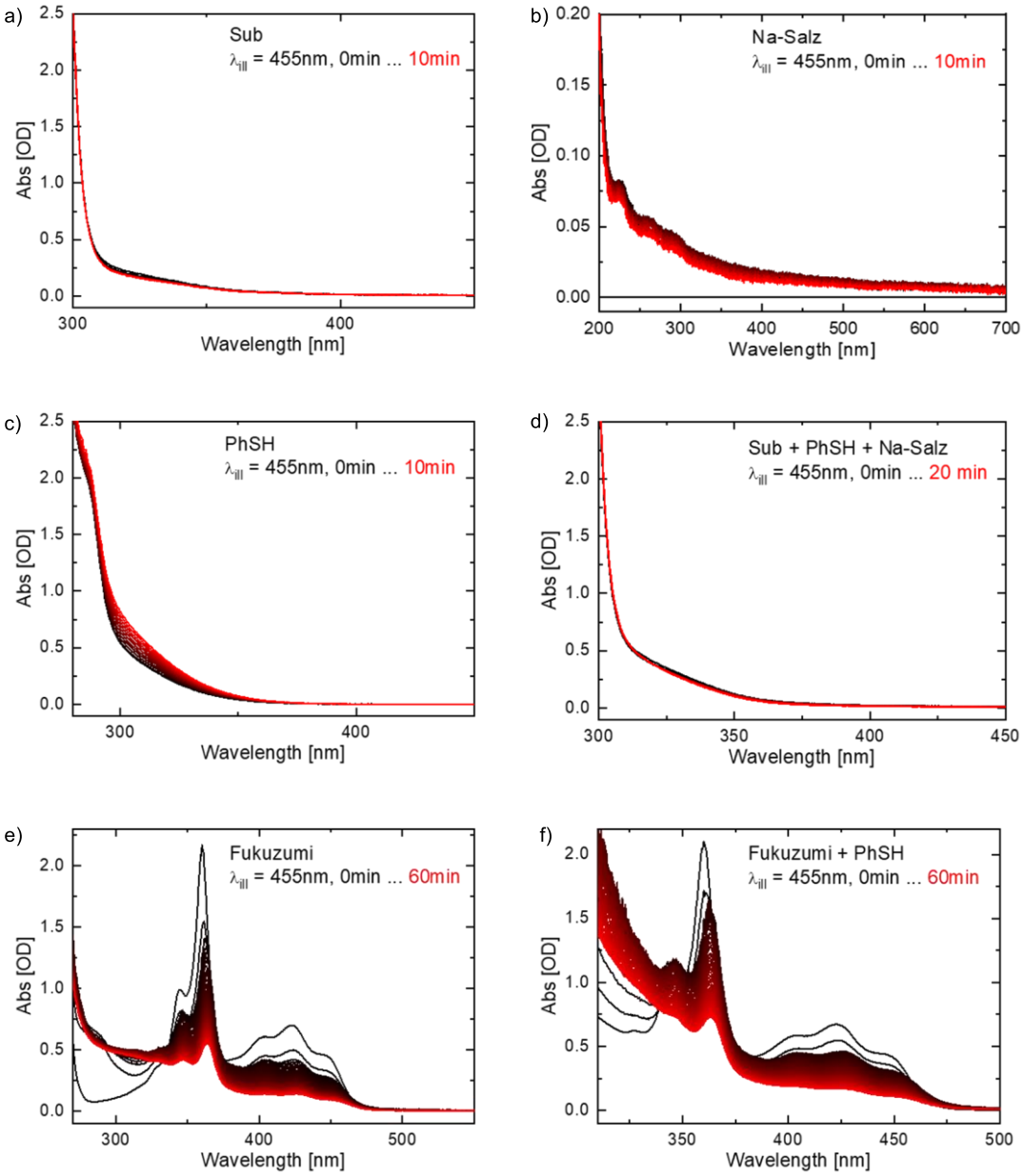


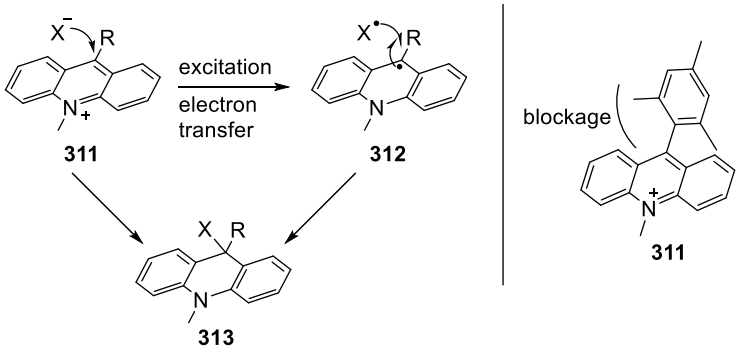
Figure 8. UV-Vis absorption spectra of reaction components recorded after illumination at 455 nm for distinct time intervals (each minute). Measurements were carried out in a solution of degassed MeCN/H_2O 9:1. c($MesAcrMeClO_4$)=$5\cdot10^{-5}$ M. c(PhSH)=$2\cdot10^{-3}$ M. c($NaH_2PO_4\cdot H_2O$)=$1.25\cdot10^{-3}$ M. c(cyclopropane)=$5\cdot10^{-3}$ M.

When examining the single components of the reaction by illumination with 455 m light for distinct times, no significant spectral changes could be observed (**Figure 8a-c**). The substrate and the Na-salt are slightly decomposing, resulting in a small decrease in absorption. In the case of PhSH, a small increase in absorption is observed, which might be caused either by evaporation of a minor amount of the solvent, or by increased scattering due to decomposition of the sample. When a reaction mixture containing these three components was illuminated, no spectral changes could be observed that would indicate any kind of complex formation in the visible spectral range after irradiation (**Figure 8d**). Only Fukuzumi's catalyst itself showed a decreasing absorption of the main bands around 435 nm and 360 nm within the first 5 minutes of illumination, while simultaneously an increased absorption intensity below 335 nm is detected, yielding an isosbestic point at 335 nm (**Figure 8e**). However, after 5 minutes of constant illumination with the 455 nm LED, the catalyst starts to decompose, which is indicated by a consistent decrease in absorption over the full spectral range. Exactly the same spectral behavious under illumination was also recorded for a mixture consisting of Fukuzumi's catalyst and PhSH (**Figure 8f**), meaning the adduct proposed by Nicewicz *et al*. is most likely not formed in the examined system (**Scheme 95**).[212] Finally, it can be concluded from these experiments that in all investigated cases after at least 5 minutes of illumination at 455 nm a decomposition without any product formation in the visible spectral range was observed.

Benniston *et al.* have shown Fukuzumi's catalyst can undergo oxidation to the corresponding aldehyde 3,5-dimethyl-4-(10-methylacridinium)-benzaldehyde dmb-Acr-Me$^+$.[221] They reported this reaction to take place fairly quickly, with significant amounts of the aldehyde present after only 12 hours of irradiation. However, the reaction requires oxygen, which is not present in this reaction.

Since the measurements were performed in a solution of 9:1 Acetonitrile/water, there is also the possibility of pseudobase formation. These compounds are colorless due to loss of the extensive conjugated ring system, which would be an explanation for the photobleaching effect observed. First reported by Hantzsch *et al.* in 1899, these compounds have been subject to investigation as photobases for the controlled release

of hydroxide anions. Bunting *et al.* studied the kinetics of the formation under different pH levels, showing that 9-phenyl substituted 10-methyl acridiniums are stabilized towards pseudobase formation, even though they exist in equilibrium in the appropriate solvents.[222] Ackmann *et al.* investigated the stability of the 9-phenyl-10-methyl acridinium in acetonitrile-water systems and was able to show stable turnover of the pseudobase to the acridinium cation once irradiated.[223] The investigated systems all have one major difference to Fukuzumi's catalyst: The substitutions in 10-position are either alkyl or phenyl with *para*-substitutions. These compounds are not suitable for photoredox-catalysis, as they are susceptible to deactivation by nucleophile or radical addition (**Scheme 100**).[129]



Scheme 100. Deactivation of acridiniums.[129]

Exchanging them with the mesityl residue leads to a blockage of the 9-position for deactivation, making them stable towards most deactivation modes, even though in some cases, the amino group can be subject to dealkylation.[224] Ultimately, it was concluded the deactivation does not proceed through either of these mechanisms.

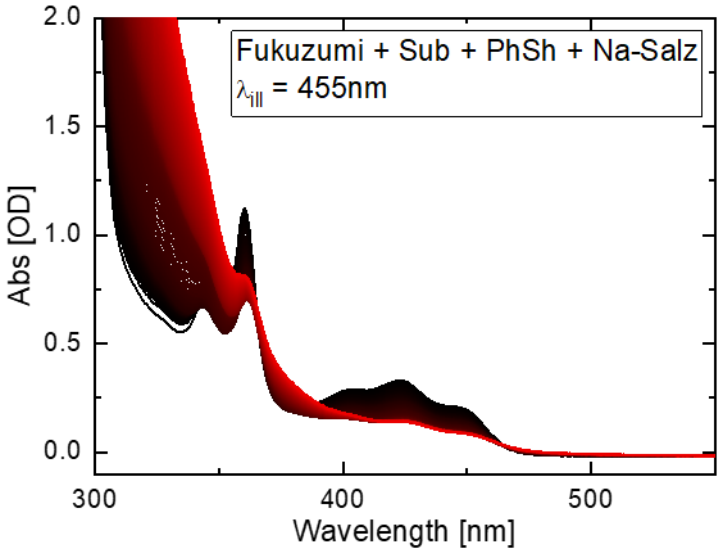


Figure 9. UV-Vis absorption spectra of the complete reaction mixture, detected each minute after illumination with 455 nm light. Measurements were conducted in a solution of degassed MeCN/H_2O 9:1. C(MesAcrMeClO$_4$)=5·10^{-5} M. c(PhSH)=2·10^{-3} M. c(NaH_2PO_4·H_2O)=1.25·10^{-3} M. c(cyclopropane)=5·10^{-3} M.

Finally, the complete reaction mixture was observed with time-resolved UV-Vis spectroscopy. The previously mentioned effects are even stronger, with large observable scattering effects.

Ultimately, the underlying mechanisms of the reaction could not be unveiled by the so far employed measurements, for which reason further time-resolved experiments could be carried out in future, e.g. by reducing the intensity of the illumination light source, or by fs-ns/ns-ms TA in order to observe the formed excited state species during the reaction instead of destroying the individual components. Nevertheless, the performed absorption measurements prove the photobleaching effect, even though they cannot explain it.

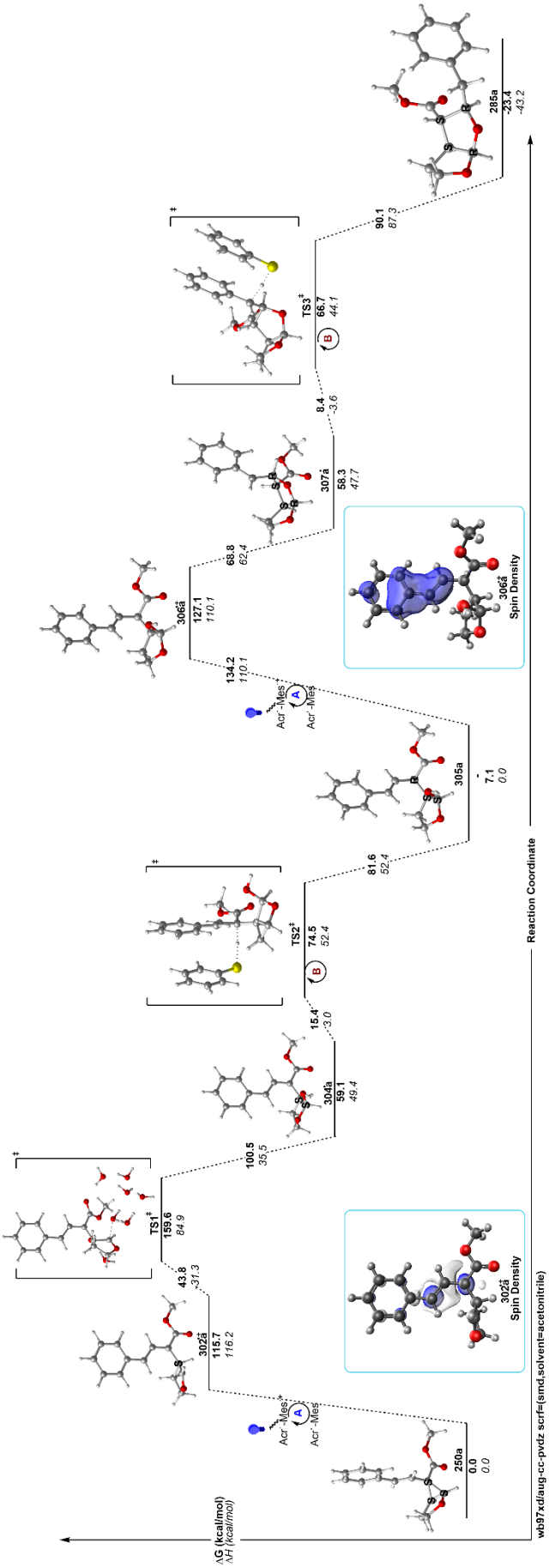
2.4.9 DFT calculations**

To support the mechanistic proposal (see chapter 2.4.5), DFT calculations were performed by Gülbahar Bozan in the group of Prof. Dr. Julia Rehbein. All calculations

** The calculations in this chapter were carried out by Gülbahar Bozan from the group of Prof. Dr. Julia Rehbein

were conducted using Gaussian16.[225] The DFT functional wB97XD functional was used including empirical dispersion correction.[226] The employed Dunning-type double zeta basis set was augmented with diffuse functions (aug-cc-pVDZ)[227] to allow for a suitable flexibility of constructing the wavefunction. All presented structures were fully optimized and conformed as stationary points by subsequent frequency analysis as either being local minima (no imaginary frequencies) or transition state structures (single imaginary frequency). Reported enthalpies and Gibb's free energies remained unscaled and are reported for standard conditions in kcal/mol. Solvent effect of acetonitrile were considered in an implicit manner using a SMD variation of the IEFPCM method.[228]

Scheme 101 illustrates the key steps of the reaction. The first step, the proposed 1 electron oxidation of the double bond, is very fast. This intermediate undergoes such fast opening to the cationic radical **302a** that it is not visible in the calculations, explaining the rather high energy difference of 115.7 kcal/mol. After addition of the water, an exergonic step, the radical intermediate **304** is formed, which coordinates the thiol in the transition state. The hydrogen transfer again is an endergonic step, followed by another 1 electron oxidation. The second cycle, a classic Nicewicz addition, proceeds with similar energy differences as the first step. The final product is lower in energy, making the whole process an exergonic reaction with a difference in enthalpy of 43.2 kcal/mol. This makes sense as the ring strain of the 3-membered cyclopropane is released to form the less strained THF-ring.



Scheme 101. Calculated Enthalpies and Energies

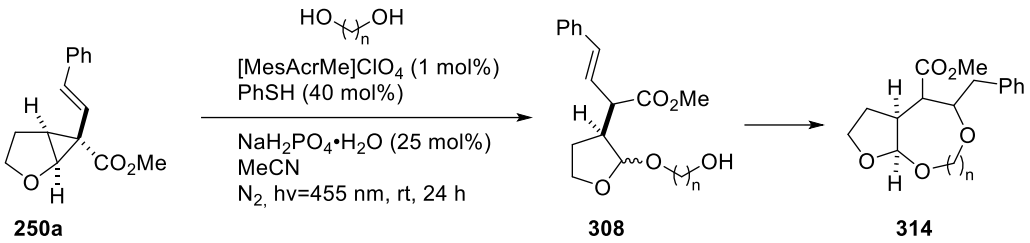
2.4.10 Conclusion and outlook

Extensive studies were conducted to understand the reaction and increase the yields. It was discovered that employing CPAs to influence the diastereoselectivity *via* counter-ion influence was not successful. Exchanging the HAT catalyst Ph_2S_2 for PhSH increased the yield considerably. Interestingly, the reaction only proceeds with thiols and Ph_2Se_2 and Fukuzumi's catalyst. No other HAT or photocatalyst provided the product. The reaction is limited to cyclopropanes fused to cyclic ethers with aryl functionalities in the vinyl position. Nitrogen heterocycles and cyclopropanated styrene did not provide any product. Exchanging the nucleophiles to form open-chained intermediates was only successful in the case of phenol. When trying to employ nitrogen nucleophiles, the addition product of PhSH was observed. This same result was achieved when bioactive glass 45S5 was employed instead of $NaH_2PO_4 \cdot H_2O$, even when water was present in the reaction. Notably, this result was not achieved when the reaction was performed under water-free conditions. The superbasic bioactive glass as well as NH_3 and $TsNH_2$ make the PhSH so basic it becomes a better nucleophile than water, allowing for its addition.

Additionally, DFT calculations were performed to further support the mechanistic hypothesis.

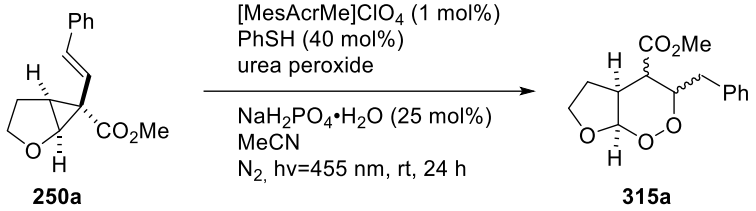
Photobleaching was observed during the reaction. After about 10 minutes, the reaction turned colorless and UV-Vis experiments confirmed the reaction did not absorb light at 455 nm. However, continuous irradiation was still needed for the reaction to proceed. This apparent paradox could not be solved.

Further mechanistic investigations to resolve this issue and understand the interplay between catalyst and cocatalyst should be performed in the future. This can also shed light onto the formation of the diastereomers, opening doors to solving this problem as well. Additionally, exploring the coupling of further alcohols can be explored. For example, if symmetrical alcohols are employed, larger cycles should be possible (**Scheme 102**).



Scheme 102. Synthesis of larger ether macrocycles.

Employing non-aqueous peroxides, such as the hydrogen peroxide equivalent urea peroxide, can allow access to 7-membered endoperoxide rings (**Scheme 103**).



Scheme 103. Synthesis of 6-membered endoperoxides.

2.5 Visible light mediated synthesis of formyl esters

2.5.1 Similarities between styrenes and aryl acetate cyclopropanes

The photochemical activation of styrenes in ATRA-type reactions using copper (I) and copper (II)-catalysts is well explored.[229,230] In 1979, de Meijere proposed that cyclopropanes and styrenes are, in fact, electronically very similar and therefore exhibit similar properties and reactivity.[231]

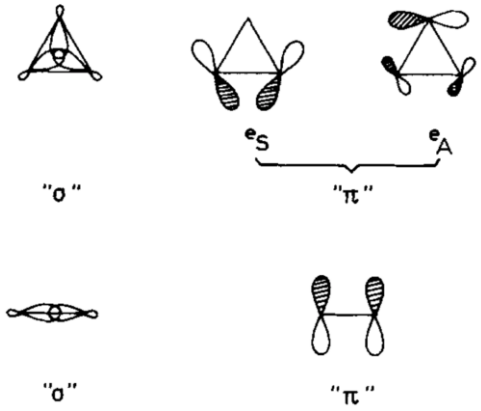
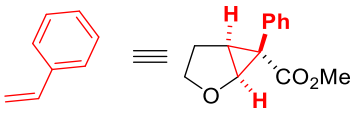


Figure 10. MO description of bonding in cyclopropane and ethylene.††

He describes it with the molecular orbital description from Walsh,[232] where the three p-orbitals are combined, with the only difference being the symmetry. These apparent similarities are shown in **Figure 10**.

Based on these two concepts, a new hypothesis was developed. Cyclopropanes **253a** substituted with an aryl group would be synthetic analogues to styrenes and should undergo similar reactions when subjected to ATRA-type reaction conditions. Predestined for this type of chemistry are aryl acetate-donor-acceptor-cyclopropanes as shown in **Scheme 104**, as their synthetic utility has been shown many times.[52,233]

††Reprinted with permission from Meijere, A. de, *Angew. Chem. Int. Ed. Engl.* **1979**, *18*, 809–826. Copyright © 2003 John Wiley and Sons.



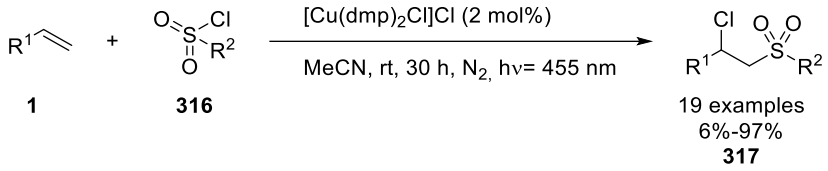
25 253a

Scheme 104. Visualization of the similarities between styrene and cyclopropane **253a**.

Three test reactions were chosen as models to test the theory: the classic chlorosulfonylation, which has been well-explored by the Reiser group,[234] the addition of iodoform,[235] and finally, a iodoamination.[236]

2.5.2 First test reactions

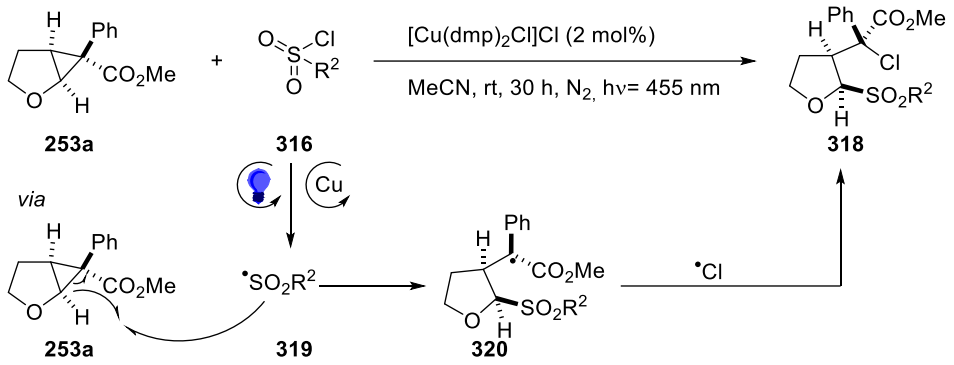
Chlorosulfonylation-ATRA-reactions are well-known in literature. The classic example by Reiser *et al.* gives the chlorosulfonylation products in high yields (**Scheme 105**).[234,237]



1 316 19 examples 6%-97% **317**

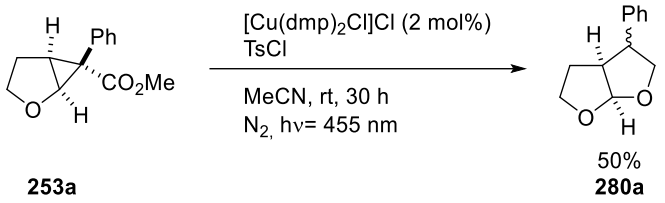
Scheme 105. Copper-catalyzed chlorosulfonylation of styrenes.

The ATRA reagent tosyl chloride **316** is cleaved by the excited catalyst and subsequently adds to the styrene, forming a radical, which then undergoes radical-radical recombination with the chlorine radical to give the final product **317**. When this is translated onto the cyclopropane **253a**, the mechanism is similar (**Scheme 106**). After cleavage of tosyl chloride, the tosyl radical adds to the cyclopropane α to the oxygen position, as it is a electrophilic radical[238] and the oxygen makes this position especially electron-rich through donation of the free electron pair. The radical **320** then undergoes radical-radical recombination with the Cl-radical to give the final product **318**.



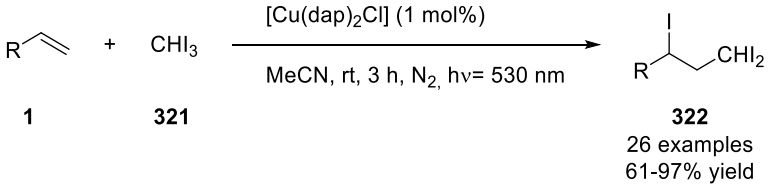
Scheme 106. Proposed reaction mechanism for the chlorosulfonylation of **253a**.

However, when the reaction was performed, only lactone **280a** could be isolated. The lactonization stems from the tosyl chloride, which is acidic enough to catalyze this reaction (**Scheme 107**).



Scheme 107. Outcome of the attempted chlorosulfonylation of **253a**.

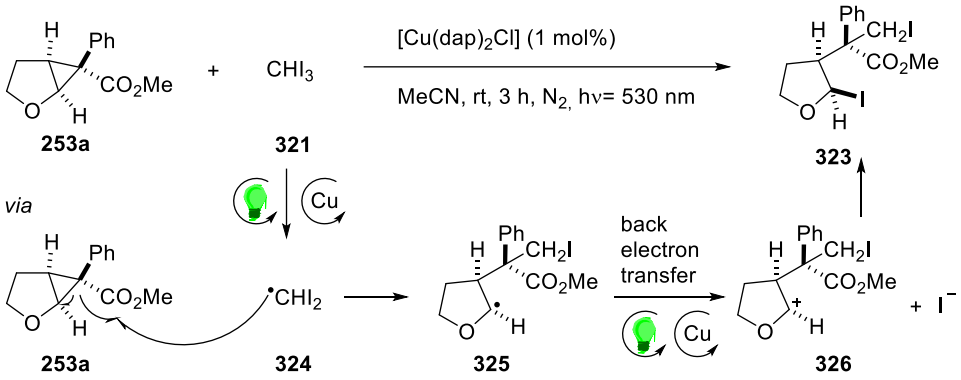
Next, the addition of iodoform to the cyclopropane was explored. The pioneering work was done by Reiser *et al.* in 2020, when they showed iodoform readily adds to styrene under catalysis with [Cu(dap)$_2$]Cl (**Scheme 108**).[235] Notably, this reaction only proceeds with copper as the catalyst, showcasing the crucial role it plays in this transformation.[229]



Scheme 108. Addition of iodoform to styrenes under copper catalysis.

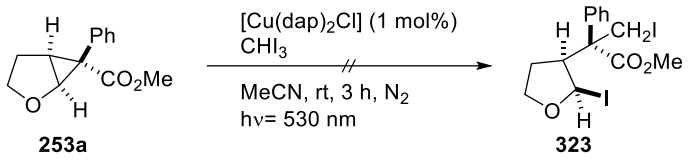
The first step of the mechanism is analogous to the chlorosulfonylation: cleavage of the ATRA reagent iodoform and subsequent addition of the iodoform radical to the

cyclopropane double bond under homolytic cleavage. However, the iodoform radical is nucleophilic, making it prone to attack the "other side" of the cyclopropane, forming the intermediate **325**. Then, instead of radical-radical recombination, a back electron transfer to close the copper-catalytic cycle forms a carbocation and iodine ion, which react to the proposed final product **323** (**Scheme 109**).



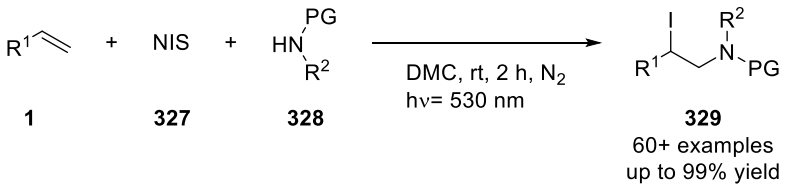
Scheme 109. Mechanism of iodoform addition to cyclopropane **253a**.

However, when the conditions were applied to cyclopropane **253a**, only decomposition of the starting material to a complex reaction mixture was observed (**Scheme 110**).



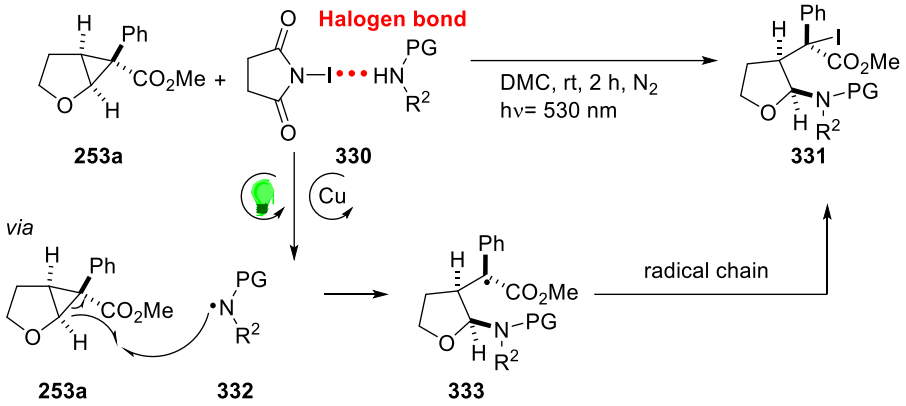
Scheme 110. Attempt at iodoform addition to cyclopropane **253a**.

Finally, the iodoamination conditions were applied to the cyclopropane analogue of styrene. In 2021, Reiser *et al.* showed the iodoamination of styrenes with the use of NIS and amines (**Scheme 111**).[236]



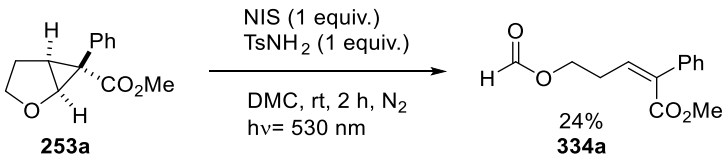
Scheme 111. Catalyst-free iodoamination of alkenes.

This concept is catalyst-free. The active species stems from the interaction between NIS and the amine as can be seen in **Scheme 112**. The formed complex absorbs in the visible light region[166] and subsequently is cleaved to the amidyl radical, which, as an electrophilic radical, attacks in the same fashion as in the chlorosulfonylation. A radical chain mechanism closes the cycle to the iodoaminated product.



Scheme 112. Mechanism of the proposed iodoamination of **253a**.

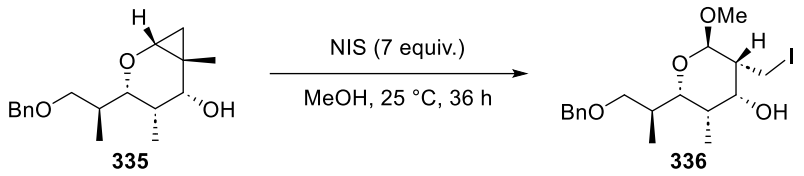
However, when cyclopropane **253a** was subjected to the reaction conditions, the crude NMR indicated not only the opening of the cyclopropane ring, but also of the THF ring it was fused to, as no diastereotopic protons were observed. The structure was revealed to be that of a formyl ester **334a** (**Scheme 113**).



Scheme 113. Formyl ester synthesis from cyclopropane **253a**.

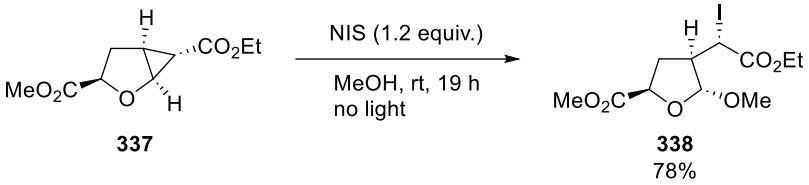
2.5.3 NIS-mediated cleavage of cyclopropanes

This result was quite unexpected and does not seem to follow the ATRA process since no amine was incorporated. The rearrangements of α-oxygen cyclopropanes with NIS has been previously explored in sugars.[239] Danishefsky *et al.* found that subjecting *C*-glycosides **335** to NIS in methanol gave the desired iodo-compounds **336**, which could be further functionalized (**Scheme 114**).



Scheme 114. NIS mediated cleavage of C-glycosides.

The groups of Nagarajan[240] and Chandrasekaran[241] further explored these ring openings with NIS, NBS and NCS. These types of ring openings were also found to work on cyclopropylamines.[242] Cyclopropanes fused with THF rings also undergo these types of transformations, as shown by Weisser *et al*. (**Scheme 115**).[243]



Scheme 115. Transformation of cyclopropanes fused to THF mediated by NIS.

The formed iodide is a versatile intermediate since it is a good leaving group, allowing for displacement by a variety of reagents such as TMS-azide, TMSCN or the formed succinimide itself.[242,243]

The transformation with cyclopropane **253a** obviously must undergo a similar pathway, but subsequently another reaction step must take place to give the final reaction product of the formyl ester **334a**.

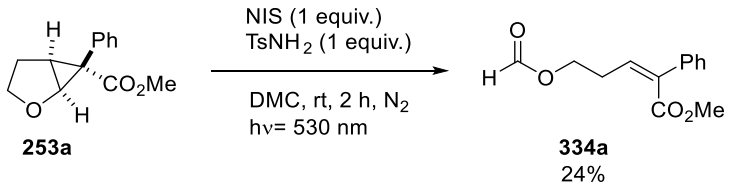
2.5.4 Screening of reaction conditions

In order to further evaluate the mechanism, a few screening experiments were conducted.

Since none of the aforementioned reactions were performed under light, the first experiment aimed to investigate the effect of the irradiation. Without light, the yield stayed roughly the same at 26%, indicating light is not crucial to the transformation (**Table 16**, Entry 1). Since tosyl amide was not incorporated into the product, it was left

out of the reaction. This increased the yield further to 38%, however, no tosyl amide and no light dropped the yield again to 10% (**Table 16**, Entries 2 and 3).

Table 16. Initial screening of reaction conditions.



253a **334a** 24%

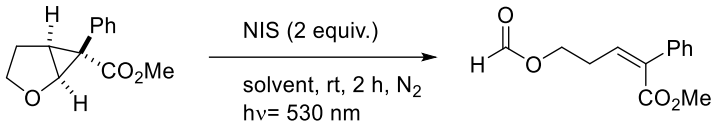
Entry	***variation***	***NMR yield***
1	No light	26%
2	No tosyl amide	38%
3	No tosyl amide, no light	10%
4[a]	O_2-atmosphere	14%
5[a]	2 equiv. NIS	54%
6[a]	1 equiv. I_2	c.r.m.
7[a]	2 equiv. ICl	c.r.m.
8[a]	455 nm LED, 2 equiv. NIS	34%

Conditions: cyclopropane (0.2 mmol), NIS (0.2 mmol), $TsNH_2$ (0.2 mmol), 1 mL DMC (0.2 M), 2 h, N_2, hν= 530 nm. Yields were determined using tetrachloroethane as internal standard. c.r.m= complex reaction mixture. [a]reaction was performed without tosyl amide.

Under oxygen atmosphere, the yield dropped to only 14%, but increased to 54% when 2 equivalents of NIS were added (**Table 16**, Entries 4 and 5). When analyzing these results, it seemed as though light was a crucial factor. This is surprising since NIS by itself does not absorb visible light.[244] In the literature reports, NIS forms a complex with the tosyl amide which in turn absorbs the visible light (*vide supra*). It seemed as if 2 equivalents of iodine reagent, either I^+, which can be formed through heterolytic cleavage, or iodine radicals $I^\bullet$, formed by homolytic cleavage, were necessary. Even though there is no literature precedent on the visible light mediated cleavage of iodine, the NIS was replaced with 1 equivalent of I_2 to investigate the role played. However, only a decomposition of the starting material was observable (**Table 16**, Entry 6). Finally, employing a rather harsh iodo-reagent such as ICl also decomposed the starting material. To further investigate the role of the light, 455 nm LEDs were employed, however, the yield depleted to 34%. These results showed no clear picture, which prompted a solvent screen (**Table 17**). This showed quite interesting results: no solvent aside from DMF provided any product, although the starting material was completely consumed (**Table 17**, entries 1-4). This result is quite surprising, especially since DCM

and DMC gave almost identical yields in the literature precedent.[236] However, DMF gave some yield, which shaped the theory that NIS was forming a complex with the solvent, in this case DMC, which in turn was excited and forming the corresponding radicals which enabled the transformation. To test this theory, 2 equivalents of tosyl amide were added in DCM, the literature best performing solvent. The yield could be increased to 36%, which, albeit better, was not as good as the previously obtained 54% (**Table 17**, Entry 5).

Table 17. Solvent screen of the formyl ester formation.



253a **334a** 54%

Entry	***solvent***	***NMR yield***
1	MeCN	c.r.m.
2	DCM	c.r.m.
3	acetone	c.r.m.
4	DMF	10%
5[a]	DCM, 2 equiv. tosyl amide	36%

Conditions: cyclopropane (0.2 mmol), NIS (0.4 mmol), 1 mL DMC (0.2 M), 2 h, N_2, hν= 530 nm. Yields were determined using tetrachloroethane as internal standard. c.r.m= complex reaction mixture.[a]2 equiv. tosyl amide were employed.

The possibility of a halogen bond between the NIS and the solvent was investigated with the help of UV-Vis spectroscopy. Surprisingly, however, no UV-Vis absorption could be detected for the mixture DMC-NIS (**Figure 11**). The spectra showed NIS behaves the same in MeCN and DMC. This is in contrast to the results obtained by the Li group, where clear complexation was observed.[244]

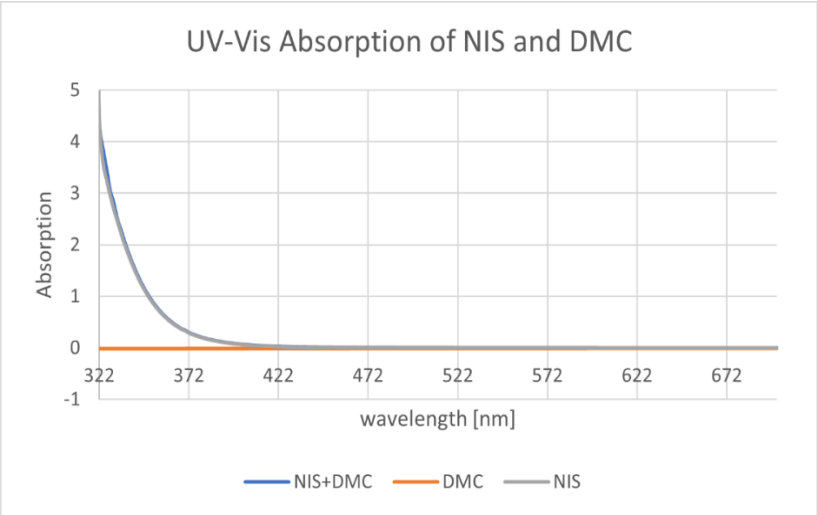
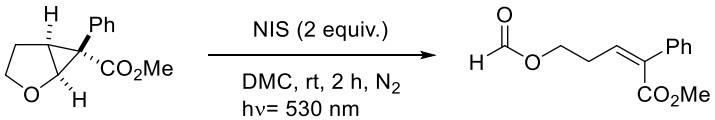


Figure 11. UV-Vis Absorption Spectra of NIS (blue), DMC (orange) and the mixture (gray). NIS absorption spectra measured in MeCN (c(NIS)=0.2 M).

Since the formation of a light absorbing NIS solvent complex was not found, further investigations were conducted aimed towards increasing the yield.

Table 18. Further yield optimization studies.



253a **334a** 54%

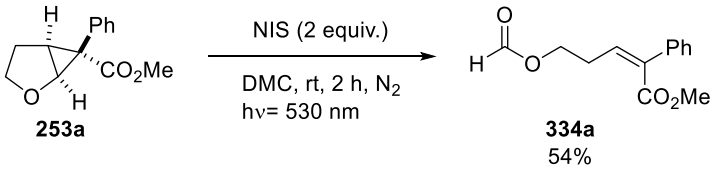
Entry	***variation***	***NMR yield***
1	3 equiv. NIS	49%
2	5 equiv. NIS	56%
3	2 equiv. NIS+2 equiv. TEMPO	c.r.m.
4	1 mol% $[Cu(dap)_2]Cl$	32%
5	2 equiv. NCS	c.r.m.
6	2 equiv. NBS	c.r.m.

Conditions: cyclopropane (0.2 mmol), NIS (0.4 mmol), 1 mL DMC (0.2 M), 2 h, N_2, hv= 530 nm. Yields were determined using tetrachloroethane as internal standard. c.r.m= complex reaction mixture.

Employing more equivalents of NIS was beneficiary to the yield in previous reports.[244] This strategy however did not prove fruitful in the described transformation (**Table 18**, Entries 1 and 2). Employing TEMPO in the reaction shut it down, indicating radicals being crucial to the transformation (**Table 18**, Entry 3). Since copper catalysts have proven themselves to catalyze transformations otherwise unavailable in photocatalytic systems, $[Cu(dap)_2]Cl$ was employed in the reaction, albeit unsuccessfully (**Table 18**,

Entry 4). Finally, transformations with NIS to form the iodo-analogues have been altered to form the bromo-and chloro-analogues as well. Examples again included the transformation of cyclopropane-fused tetrahydrofurans.[243,245,246] The use of N-bromo succinimide and its chloro-analogue did not provide any product, however (**Table 18**, Entries 5 and 6). These experiments show the transformation is dependent on NIS entirely, through a possible radical mechanism, is not catalytic and works better with light.

Table 19. Final screening of reaction conditions.



253a **334a** 54%

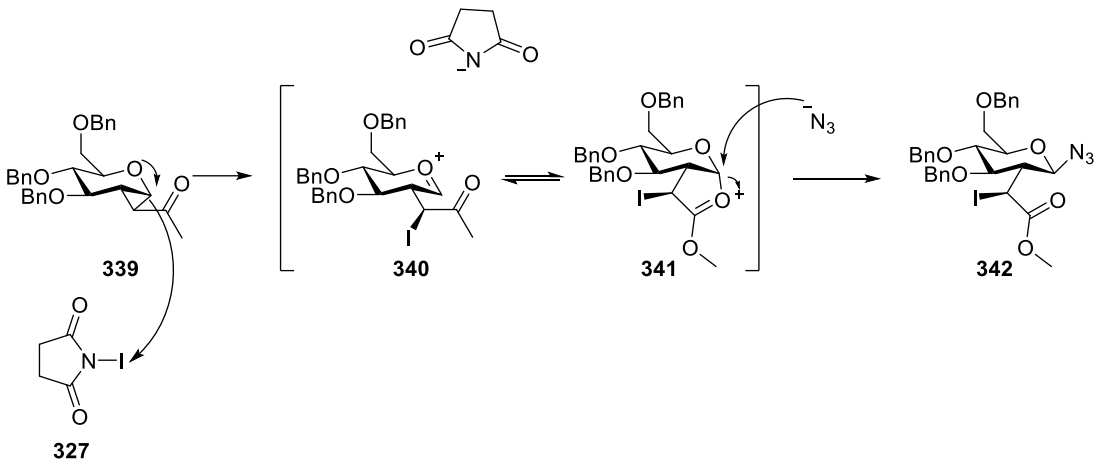
Entry	***variation***	***NMR yield***
1	1,2-propylene carbonate instead of DMC	47%
2	Super dry DMC	c.r.m.
3	DMC/H_2O 9:1	83%
4	H_2O-saturated DMC	70%
5	9:1 DMC/57% HI in H_2O	lactone formation
6	DMSO/H_2O 9:1	51%
7	DMF/H_2O 9:1	48%
8	MeCN/H_2O 9:1	50%

Conditions: cyclopropane (0.2 mmol), NIS (0.4 mmol), 1 mL DMC (0.2 M), 2 h, N_2, hν= 530 nm. Yields were determined using tetrachloroethane as internal standard. c.r.m= complex reaction mixture.

Going back to the drawing board, the solvent was re-examined. Using a cyclic carbonate with a more rigid backbone (**Table 19**, Entry 1) gave the product in a similar yield. Finally, attention was turned to the water content. DMC was used straight out of a bottle which was not dried before use. When freshly opened, sealed and extra-dry DMC was used, the reaction shut down and only delivered a complex reaction mixture (**Table 19**, Entry 2). Water was identified as a crucial player at this point. A 9:1 mixture of DMC with water increased the yield to 83% (**Table 19**, Entry 3). A substantial amount of water is needed, as DMC saturated with water (prepared by shaking DMC with water and then separating the phases) did not give quite the same amount of yield (**Table 19**, Entry 4). However, this is also a surprising result as NIS is not stable in water and decomposes to HI and N-hydroxysuccinimide. Therefore, a 9:1 solution of DMC and HI in water was tested in replacement of the NIS, however, only lactone **280a** was formed (**Table 19**,

Entry 5). It is quite surprising that even though HI is most likely formed in the reaction, the transformation to the formyl ester is more desired and no lactone is observed. Finally, a short solvent screen, this time as a 9:1 mixture of solvent/water was performed, however, no solvent outperformed DMC in this transformation (**Table 19**, Entries 6 to 8).

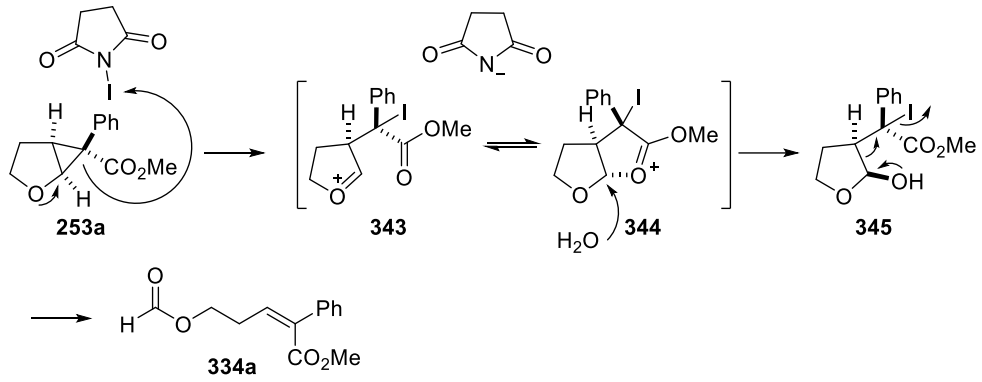
2.5.5 Mechanistic proposal



Scheme 116. Mechanistic proposal by Chandrasekaran *et al.*

From the results previously obtained in the screening as well as reported mechanisms, the next step was proposing a plausible mechanism. The NIS-mediated ring opening of cyclopropanes by Chandrasekaran *et al.* is proposed to run through a cascade: first the free electron pair of the oxygen triggers the ring opening of the cyclopropane **339** with the addition of an I^+-ion from the NIS. The resulting structure is in equilibrium as open-chained form **340** or as 5-membered cycle **341**. This is important, as it determines the exclusive stereoisomer since the azide can only attack in equatorial position, as the axial position is blocked by the ring (**Scheme 116**).

A similar mechanism can be proposed for the formyl ester formation.



Scheme 117. Mechanism for the formation of the formyl ester.

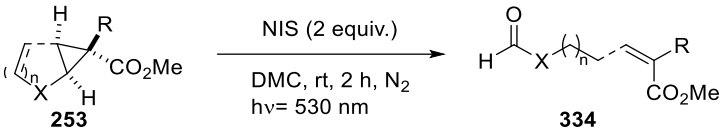
After ring opening of the cyclopropane **253a** with I^+-addition, the cationic intermediate **344** is attacked by the water to form the hemiacetal **345**. The second ring opening is triggered by formal loss of HI to give the final product **334a**. This is supported by the previous investigations: without water, there is no reagent to intercept the cationic intermediate. In addition, the heteroatom is crucial for the ring opening process. This can also be seen later in the substrate scope analysis (*vide supra*). The formation of iodine and the need for 2 equivalents of NIS can be explained by the trapping of the I^--Ion by I^+ from NIS, forming iodide. Why TEMPO shuts down the reaction and the role of light are still unknown.

2.5.6 Substrate scope

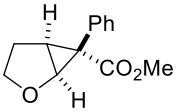
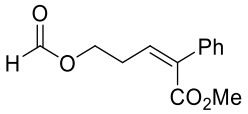
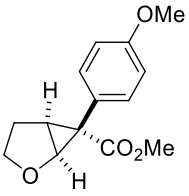
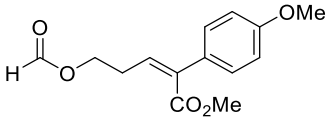
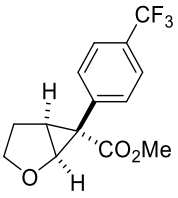
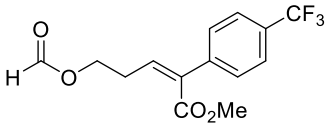
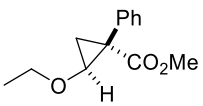
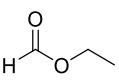
With the optimized reaction conditions in hand, the substrate scope was explored. The reaction suffers from problems with scale up, which could be observed when running the model reaction on scale. Since the reaction turns dark with the formation of iodine rather quickly, the main problem in this case was identified as the penetration of the light through the solution. Modifications with the photoreactor or perhaps longer reaction times could solve this problem. When modifying the phenyl ring with different *para*-substituents, strongly electron-withdrawing ones such as trifluoromethyl considerably lowered the yield (**Table 20**, Entry 2). They make the cyclopropane bond which is broken less electron dense and therefore less prone to attack the I^+. Also, the transition state proposed in chapter 2.5.5 is more stabilized in this case, although no lactone formation is observed. On the other hand, electron-donating groups were

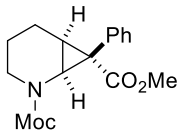
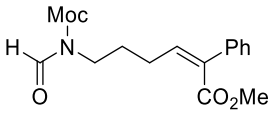
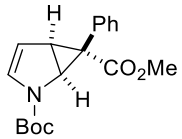
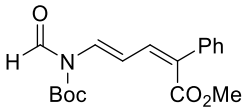
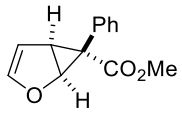
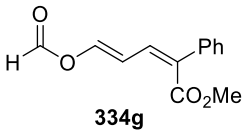
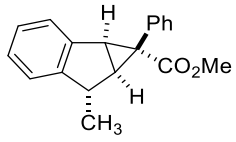
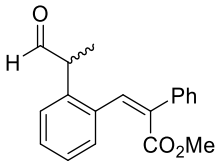
tolerated well and did not significantly impact the yield (**Table 20**, Entry 3). As a proof-of-concept molecule, cyclopropanated ethyl vinyl ether **253d** was employed in the reaction. As expected, it reacted to the α-methyl ester styrene and ethyl formate, which was proven by headspace GC-MS analysis (**Table 20**, Entry 4). The saturated heterocycle piperidine underwent clean conversion to the corresponding formamide (**Table 20**, Entry 5). Unsaturated heterocycles such as cyclopropanated pyrrole or furan only yielded complex reaction mixtures (**Table 20**, entries 6 and 7). Cyclopropanes without a heteroatom in α-position to the cyclopropanes did not convert at all (**Table 20**, Entry 8) due to the inability to form the cation **343** (*vide infra*).

Table 20. Substrate scope.



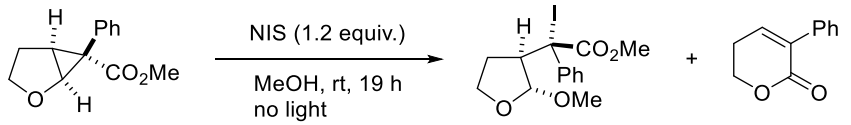
253 **334**

Entry	*starting material*	*product*
1	 **253a**	 **334a** 61%
2	 **253b**	 **253b** 55%
3	 **253c**	 **334c** 32%
4	 **253d**	 **346** detected by MS  **347** detected by NMR

5	 **253e**	 **334e** 56%
	Unsuccessful substrates	
6	 **253f**	 **334f** c.r.m.
7	 **253g**	 **334g** c.r.m.
8	 **253h**	 **334h** n.c.

2.5.7 Further transformations

The NIS-mediated transformations developed by Chandrasekaran *et al.*[241] and further utilized by Weisser *et al.*[243] were also tested on the geminal substituted cyclopropanes **253a** (**Scheme 118**). This process should yield different products, as there is no water involved and the reaction proceeds in the dark.



253a | **348** expected | **349** obtained, 36%

Scheme 118. Alkoxylation of **253a**.

This proved true, however, the expected iodo-alkoxylation to form product **348** did not take place. Instead, X-Ray analysis showed lactone **349** was formed (**Figure 12**).

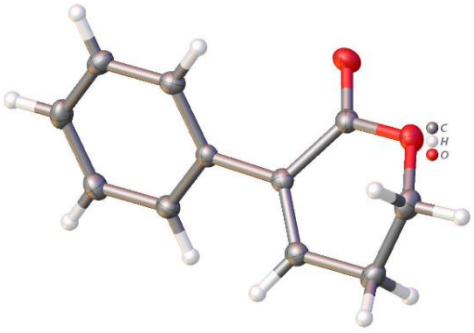
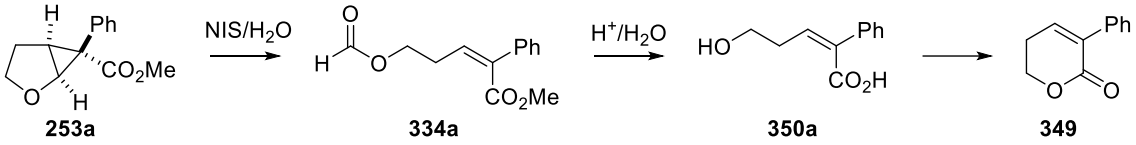


Figure 12. X-Ray structure of **349**.

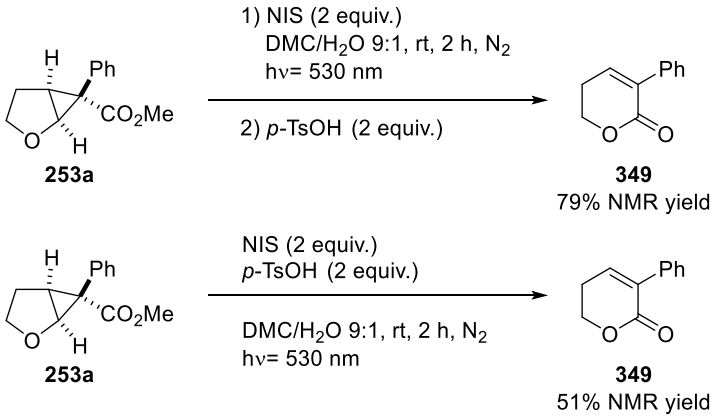
This lactone is the result of the acid mediated cleavage of the formyl and ethyl ester and subsequent lactonization. This is, however, surprising, since water is necessary for the formation of the formyl ester (**Scheme 119**).



253a **334a** **350a** **349**

Scheme 119. Mechanistic proposal for the formation of lactone **349**.

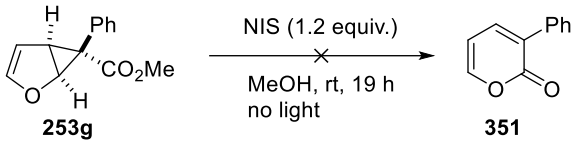
To test this hypothesis, two test reactions were run: one stepwise, where 2 equivalents of acid (*p*-TsOH) were added once the formyl ester synthesis was finished, and one where the acid was added directly in the beginning of the reaction. Both experiments showed clean conversion to the lactone **349**, proving the hypothesis that the formation goes through a formyl ester intermediate state (**Scheme 120**) and is more effective in a stepwise fashion. This may also be due to deactivation of the NIS through *p*-TsOH.



Scheme 120. Proof of concept for lactonization.

This experiment also proves the double bond configuration: the ester substituent has to be *Z* to the rest of the molecule for the cyclization to proceed.

With this in mind, the procedure developed by Weisser was extended to the cyclopropanated furans **253g**. This would allow access to substituted pyrones; however, the reaction only yielded a complex reaction mixture (**Scheme 121**).

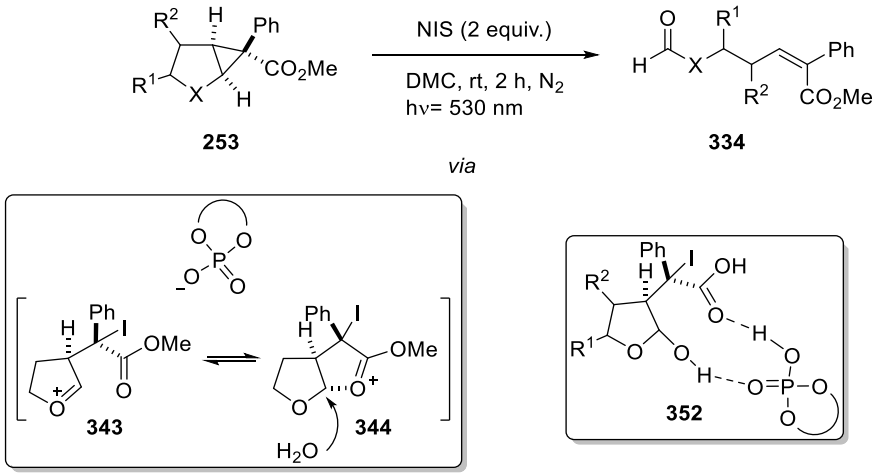


Scheme 121. Attempted reaction to form pyrones **351**.

2.5.8 Conclusion and outlook

The NIS-mediated ring opening of cyclopropanes **253** to the corresponding formyl esters **334** was developed. During the screening, water and 2 equivalents of NIS were determined to be the deciding factors on product formation. The mechanism is based on previous reports by Chandrasekaran *et al.*[241] and Weisser.[243] The resulting products can be further transformed into lactones **351**, which are also formed in the water-free transformation with methanol. The exact mechanism still has to be investigated. A small, preliminary substrate scope shows the versatility of the reaction with tolerance of both electron-donating and -withdrawing groups and heteroatoms. The reaction is limited to cyclopropanes with heteroatoms in α-position, as the ring opening otherwise is not possible.

In the future, the substrate scope can be expanded to more highly substituted cyclopropanes. This would be interesting also from a stereochemical standpoint: with substitutions on the other side of the cycles, which can already be synthesized enantioselectively, it would be interesting to see if this could be retained in the resulting formyl ester. Additionally, since an ion pair is present, the effect of chiral counterions could be investigated as well (**Scheme 122**).



Scheme 122. Possible further functionalizations and ion pair interactions.

3 Summary

The aim of this work was the development of ring opening reactions of fused cyclopropanes **250** and **253**. The substrate scope of the Rh-catalyzed cyclopropanation was expanded to include cyclic ethers, carbocycles, heterocycles and more. Additionally, the enantioselective cyclopropanation of substituted 2,3-dihydrofurans was developed, using the well-known catalyst Rh_2(*R*-DOSP)$_4$ and allowing for *ee* values of up to 78%. These vinylcyclopropanes are known to undergo the vinylcyclopropane rearrangement to give cyclopentenes **261**. Previously established procedures relied on harsh reaction conditions, whereas the developed procedure allowed for mild and facile rearrangement of a wide variety of vinylcyclopropanes **250** using only 5 mol% of $Yb(OTf)_3$ at 62 °C, with no chromatography needed in most cases. The method was shown to be versatile, catalyzing the transformation of vinylcyclopropanes fused to cyclic ethers, carbocycles and N-heterocycles, as well as non-cyclic systems in yields of up to 95%. The well-known lactonization was performed on closely related cyclopropanes by both Reiser *et al.* and Theodorakis *et al.* on monosubstituted cyclopropanes.[120,121,190] The conditions were optimized for the vinylcyclopropanes and the lactones could be obtained in yields of up to 91% as a mixture of 2 diastereomers. An oxygen atom in α-position to the cyclopropane is needed in this case. When the vinyl moiety was substituted with a methyl group, equilibration to the α,β-lactone was achieved with NEt_3. The attempted enantioselective lactonization of the geminal substituted cyclopropanes **253a** showed promising beginning results. Enantiomeric excess of up to 16% on one diastereomer could be obtained. Finally, the previously developed photoredox catalyzed reaction to hexahydro[2,3*b*]furans *via* an interrupted Nicewicz rearrangement was further developed and investigated. The yield was improved to up to 75%. The mechanistic proposal was supported by various experiments including isolation of intermediates, time-resolved UV-Vis spectroscopy and DFT calculations. The diastereoselectivity is low, and attempts to solve this by using CPAs was unfruitful. Finally, cyclopropanes **253** were subjected to an NIS-mediated rearrangement. This yielded formyl esters **334** in up to 61% yield, which could be further transformed to lactone **349**.

4 Zusammenfassung

Das Ziel dieser Arbeit war die Erforschung und Entwicklung von Ringöffnungsreaktionen von anellierten Cyclopropanen **250** und **253**, wobei der Schwerpunkt auf **250** lag. Die Rh-katalysierten Cyclopropanierung wurde um eine große Anzahl Substrate erweitert, um cyclische Ether, Carbocyclen, Heterocyclen und komplexere Bizyklen einzuschließen. Zusätzlich wurde die enantioselektive Cyclopropanierung von substituierten 2,3-Dihydrofuranen entwickelt, wobei der bekannte Katalysator Rh_2(*R*-DOSP)$_4$ in 0,5 mol% verwendet wurde und *ee*-Werte von bis zu 78% ermöglichte. Diese Vinylcyclopropane können in der sogenannten Vinylcyclopropan-Umlagerung Cyclopentene **261** bilden. Früher etablierte Verfahren beruhen auf harten Reaktionsbedingungen wie giftigen Reagenzien oder hohen Temperaturen. Das in dieser Arbeit entwickelte Verfahren ermöglichte eine milde und einfache Umlagerung einer Vielzahl von Vinylcyclopropanen **250** unter Verwendung von nur 5 mol% Yb(OTf)$_3$ bei 62 °C, wobei in den meisten Fällen keine Chromatographische Trennung erforderlich war. Die Methode erwies sich als vielseitig und katalysierte die Umwandlung von Vinylcyclopropanen, die mit cyclischen Ethern, Carbocyclen und N-Heterocyclen anelliert waren, sowie nicht-zyklischen Systemen in Ausbeuten von bis zu 95%. Eine weitere bekannte Reaktion von Cyclopropanen ist die Lactonisierung der Estergruppe. Diese Reaktion wurde an ähnlichen Cyclopropanen sowohl von Reiser *et al.* als auch von Theodorakis *et al.* an monosubstituierten Cyclopropanen durchgeführt.[120,121,190] Die Bedingungen wurden für die Vinylcyclopropane optimiert, und die Lactone konnten in Ausbeuten von bis zu 91% als Gemisch von 2 Diastereomeren erhalten werden. Ein Sauerstoffatom in α-Position zum Cyclopropan ist in diesem Fall erforderlich, und Stickstoffheterocyclen waren unreaktiv. Wenn die Vinylgruppe mit einer Methylgruppe substituiert war, konnte die Äquilibration zum α,β-Lacton mithilfe von NEt_3 erreicht werden. Gleichzeitig wurde versucht, geminal substituierte Cyclopropane **253** enantioselektiv zu lactonisieren, was vielversprechende Anfangsergebnisse zeigte. Ein *ee* von bis zu 16% bei einem Diastereomer konnte erzielt werden. Schließlich wurde die zuvor entwickelte photoredox-katalysierte Reaktion von **250** zu Hexahydro[2,3*b*]furanen über eine unterbrochene Nicewicz-Umlagerung

weiterentwickelt und untersucht. Die Ausbeute wurde auf bis zu 75% verbessert. Der vorgeschlagene Mechanismus wurde durch verschiedene Experimente unterstützt, einschließlich der Isolierung von Intermediaten, zeitaufgelöster UV-Vis-Spektroskopie und DFT-Berechnungen. Die Diastereoselektivität ist gering, und der Versuch, dies durch den Einsatz von CPAs zu lösen, war nicht erfolgreich. Schließlich wurden Cyclopropane **253** einer NIS-vermittelten Umlagerung unterzogen. Dies führte zu Formylestern **334** in einer Ausbeute von bis zu 61%, die weiter zu Lactonen **349** umgewandelt werden konnten.

5 Experimental Part

5.1 General information

Chemicals and solvents

Commercially available chemicals were of analytical grade and used without further purification. Technical grade hexanes and ethyl acetate were distilled prior to use.

Chromatography

Column Chromatography

Preparative column chromatography was performed with silica gel 60 from *Merck* (0.040-0.063 µm, 240-400 mesh). Conditioning of the column was performed by the "wet-packing" technique. In some cases, chromatography was performed using a Büchi Pure C-815 flash system with a generic 12 g silica column and a flow rate of 15 mL/min with the gradient specified.

Thin-layer chromatography (TLC)

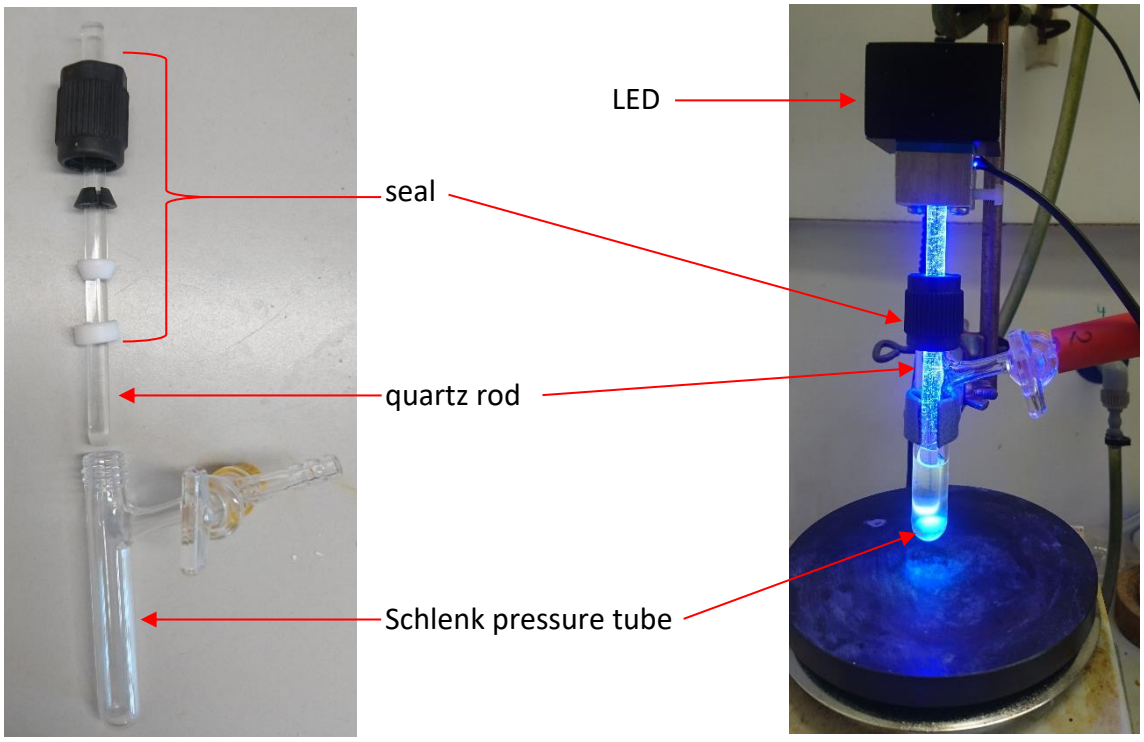
All reactions were monitored using precoated *TLC sheets ALUGRAM Xtra SIL G/UV254* from *Macherey-Nagel GmbH & Co. KG,* Düren. TLC sheets were coated with 0.2 mm silica gel 60 with fluorescent indicator UV254. UV active spots were detected at longwave UV (254 nm and 366 nm). Ethyl acetate and petroleum ether mixtures were used as mobile phase unless otherwise stated. Commonly used vanillin and DNP stains as well as Seebach's magic stain were employed for visualization.

^{1}H-NMR and ^{13}C-NMR spectroscopy

^{1}H-NMR spectra were recorded either on a Bruker Avance 300 (300 MHz) or a Bruker Avance 400 (400 MHz) at room temperature. ^{13}C-NMR spectra were recorded on a Bruker Avance 300 (75 MHz) or Bruker Avance 400 (101 MHz) at room temperature. Unless otherwise noted, all spectra were recorded in $CDCl_3$ and the chemical shifts refer to the singlet of $CHCl_3$ at 7.26 ppm and 77.36 ppm, respectively. The multiplicity of the signals is described as follows: s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet. The integrals represent the relative number of hydrogen atoms related to the

corresponding signals. Data is reported as follows: chemical shift, multiplicity, coupling constant *J* in Hz, integral. When multiple diastereomers are present, the number of hydrogen atoms was adjusted as if the ratio would be 1:1.

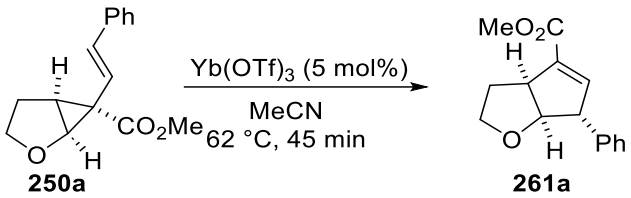
Photochemical setup



LED light source: Osram Oslon SSL80 LED, deep blue, wavelength 445 nm, radiant power Φ_E 0.8 W

5.2 Screening tables

5.2.1 Vinylcyclopropane-Cyclopentene rearrangement

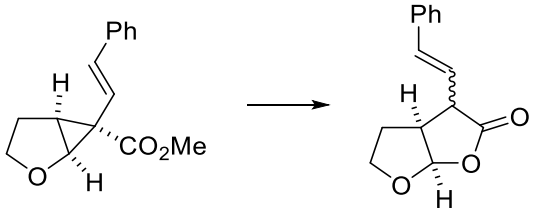


250a **261a**

Entry	*variation*	*NMR yield*[a]
1	40 mol% $Sc(OTf)_3$, N_2, 25 °C	72%
2	40 mol% $Cu(OTf)_2$, N_2, 25 °C	15%
3	40 mol% $TiCl_4$, N_2, 25 °C	19%
4	40 mol% $Yb(OTf)_3$, N_2, 25 °C	92%
5	5 mol% $Yb(OTf)_3$, N_2, 25 °C	44%
6	5 mol% $Yb(OTf)_3$, 125 °C, N_2	75%
7	5 mol% $Yb(OTf)_3$, 62 °C, N_2	77%
8	5 mol% $Yb(OTf)_3$, 62 °C, no MW, N_2	75%
9	5 mol% $Yb(OTf)_3$, 62 °C, no MW, 30 min, N_2	67%
10	5 mol% $Yb(OTf)_3$, 62 °C, no MW, 45 min, N_2	79%
11	Entry 10 + No catalyst	20%
12	Entry 10+Wet MeCN, no N_2	77%
13	Entry 10+c=0,2 M, wet MeCN, no N_2	66%
14	Entry 10+c=0,05M, wet MeCN, no N_2	59%

conditions: c=0.1 M, 0.2 mmol substrate, dry MeCN, 62 °C, 45 min. [a]determined with tetrachloroethane as internal standard.

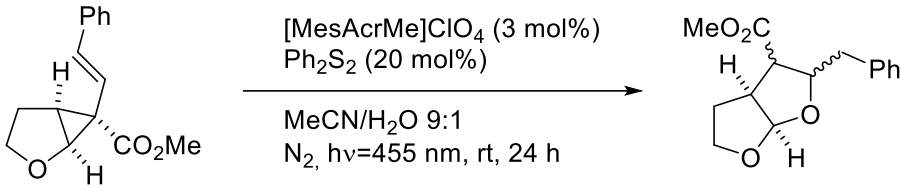
5.2.2 Lactonization



250a **272a**

Entry	*conditions*	*yield*
1	H_2SO_4 (2 equiv.), H_2O/MeCN 1:1, 24 h, 25°C	50%
2[121]	Amberlyst 15, toluene, reflux, 20 h	21%
3[243]	HCl (conc.)/Dioxane/H_2O, 1:1:1, 90°C, 4h	n.d.
4	5% methanesulfonic acid in acetone, 2 h, 60 °C	70%
5	5% toluenesulfonic acid in acetone, 1 h, 60 °C	83%

5.2.3 Photooxidation



250a **285a**

Entry	*variation*	*NMR yield[a]*
1	25 mol% 2,6-lutidine	24%
2	5 mol% p-TSA	5%
3	25 mol% K_2HPO_4	43%
4	25 mol% KOAc	0%
5	25 mol% $NaHSO_4$ H_2O	19%
6	25 mol% KH_2PO_4	66%
7	25 mol% H_3PO_4	44%
8	25 mol% $NaHCO_3$	0%
9	25 mol% NH_4Cl	54%
10	25 mol% NaH_2PO_4 H_2O	58%
11	25 mol% $NH_4H_2PO_4$	54%
12	100% KH_2PO_4	33%
13	5 mol% KH_2PO_4	42%
14[b]	3 mol% Fukuzumi BF_4 salt as catalyst	40%
15[b]	3 mol% Dicyanoanthracene as catalyst	0%
16[b]	3 mol% $Ru(bpz)_3(PF_6)_2$ as catalyst	0%
17[b]	3 mol% Pyrylium as catalyst	0%
18[b]	1 mol% Fukuzumi ClO_4	58%
19[b]	6 mol% Fukuzumi ClO_4	50%
20[b,c]	DMF instead of MeCN	0%
21[b,c]	DMSO instead of MeCN	0%
22[b,c]	No light	0%
23[b,c]	Under air	33%
24[b,c]	No catalyst	0%
25[b,c]	no Ph_2S_2	0%
26[b,c]	3 equiv. Water	44%
27[c]	25 mol% tetrabutylammoniumchloride	41%
28[c]	25 mol% lithium phosphate	50%
29[b,c]	pH 4 buffer (McIlvaine) instead of water and NaH_2PO_4 H_2O	35%
30[b,c]	48 h reaction time	50%
31[b,c]	50 °C reaction temperature	52%
32[b,c]	pH 13 buffer instead of water	48%
33[b,c]	pH 0,65 buffer instead of water	0%
34[b,c]	Thiphenol as HAT catalyst (40 mol%)	87%

35 [b,c]	PhSNa as HAT catalyst (40 mol%)	42%
36 [b,c]	PMO as HAT catalyst	0%
37 [b,c]	diethylmalonate as HAT cat	0%
38 [b,c]	Tris(trimethylsilyl)silane as HAT Kat	0%
39 [b,c]	TEAMS IL/H_2O 9:1 as solvent	13%
40 [b,c]	Ph_2Se_2 as HAT Kat	54%
41 [b,c]	p-Nitrothiophenol as HAT Kat	26%
42 [b,c]	o-aminothiophenol as HAT Kat	38%
43 [b,c]	p-Methoxythiophenol as HAT Kat	83%
44 [b,c,d]	365 nm LED	41%
45 [b,c,d]	c=0,008 M	18%
46 [b,c,d]	10 mol% AIBN, 365 nm LED	0%
47 [b,c,d]	Light off after 10 min	0%
48 [b,c,d]	No water, dry conditions	7%
49 [b,c,d]	Highly substituted catalyst	29%
50 [b,c,d]	HFIP/H_2O 9:1	0%

conditions: 0.2 mmol, c=0.2 M, 3 mol% [MesAcrMe]ClO4, 20 mol% Ph_2S_2, 25 mol% additive, hv=455 nm, rt, 24 h [a]determined with tetrachloroethane as internal standard.[b]addition of 25 mol% $NaH_2PO_4 \cdot H_2O$.[c]use of 1 mol% photocatalyst. [d]use of 40 mol% thiophenol as HAT catalyst.

5.2.4 Formyl ester synthesis

Entry	*variation*	*NMR yield*[a]
1	No light, 24 h reaction time	26%
2	No tosyl amine, 24 h reaction time	38%
3 [b]	1.5 h reaction time	31%
4 [b]	no light	10%
5 [b]	O_2-atmosphere	14%
6 [b]	2 equiv. NIS	54%
7 [b]	1 equiv. I_2	0%
8 [b,c]	455 nm LED, 2 equiv. NIS	34%
9 [b,c]	MeCN as solvent	0%
10 [b,c]	DCM as solvent	0%
11 [b,c]	Acetone as solvent	0%
12 [b,c]	DMF as solvent	10%
13 [c]	DCM as solvent, 2 equiv. Tosyl amine	36%
14 [b]	3 equiv. NIS	49%
15 [b]	5 equiv NIS	56%
16 [b,c]	2 equiv TEMPO	0%
17 [b,c]	1 mol% Cu[dap_2]Cl	32%
18[b]	2 equiv. NCS	0%
19[b]	2 equiv. NBS	0%
20 [b,c]	Propylene carbonate as solvent	47%
21 [b,c]	Superdry DMC as solvent	0%

22 [b,c]	9:1 DMC/H_2O as solvent	83%
23 [b,d]	2 equiv. ICl	0%
24 [b,c]	DMC saturated with H_2O as solvent	70%
25 [b]	9:1 DMC/HI-solution as solvent	0%
26 [b,c]	DMSO/H_2O 9:1 as solvent	51%
27 [b,c]	DMF/H_2O 9:1 as solvent	48%
28	MeCN/H_2O 9:1 as solvent	50%

conditions: 0.2 mmol, c=0.2 M, 1 equiv. tosyl amine, 1 equiv. NIS, hv=530 nm, rt, 2 h. [a]determined with tetrachloroethane as internal standard.[b]no tosyl amide was used.[c]2 equiv. NIS was used.[d]9:1 DMC/H_2O was used as solvent.

5.3 Synthesis of diazo esters

252a synthesized by Sebastian Fischer according to literature.[247] **253a** synthesized by Johannes Floß and Lucie Reitmeier according to literature.[248] Oxetanes synthesized by Tim Köglmeier according to literature.[249]

General Procedure A (GP A) [175]

A flame-dried round bottomed Schlenk flask was charged with (2-carboxyethyl)-triphenylphosphonium chloride (1.1 equiv.) and suspended in dry THF (0.5 M). To the stirred suspension was added the corresponding aldehyde (1.0 equiv.) and the flask was backfilled with N_2. The mixture was cooled to 0 °C and KO^{t}Bu (2.7 equiv.) in 50 mL dry THF (0.5 M) were slowly added over an hour at 0 °C. The reaction was stirred at 0 °C for 1 hour and allowed to warm to room temperature overnight. The reaction was quenched with saturated $NaHCO_3$ solution and extracted with diethyl ether. The remaining water phase was acidified with 6.0 M HCl and extracted with EtOAc. The combined organic phases were washed with water, dried with $MgSO_4$ and the solvent was evaporated under reduced pressure. The residue was dissolved in EtOAc and extracted with 2.0 M NaOH. The combined water phases were treated with 6.0 M HCl until pH 1 and extracted with EtOAc. The combined organic phases were washed with water, dried over $MgSO_4$ and the solvent was evaporated under reduced pressure.

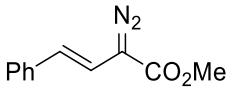
The crude product was used without further purification.

A round bottomed flask was charged with $MgSO_4$ (4.0 equiv.) in dry DCM (1 M) and concentrated H_2SO_4 was added (1.0 equiv.) and the slurry stirred for 30 minutes. The

corresponding unsaturated acid (1.0 equiv.) and dry methanol (5.0 equiv.) were added and the reaction mixture stirred overnight for 24 hours. The slurry was filtered and quenched with saturated $NaHCO_3$. The organic layer was washed with brine and dried over $MgSO_4$ and the solvent was evaporated under reduced pressure. The product was used without further purification.[250]

A round bottomed flask was charged with the unsaturated ester (1.0 equiv.) and *p*-ABSA (1.5 equiv.) in MeCN and cooled to 0 °C. DBU (2.0 equiv.) was slowly added, and the reaction mixture stirred at 0 °C for 30 minutes, warmed to room temperature and stirred an additional 2 hours. The reaction was quenched with saturated NH_4Cl and extracted with diethyl ether. The combined organic layers were washed with brine and dried over $MgSO_4$. The solvent was evaporated under reduced pressure at room temperature. The products were purified using column chromatography (SiO2, hexanes/ethyl acetate 19:1) to afford the final product. The unsaturated diazo compounds slowly decompose at -18 °C and need to be purified before use. Special care has to be used when handling diazo compounds due to their potential explosive behavior at room temperature.[251]

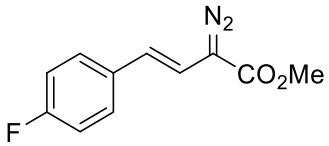
Methyl (E)-2-diazo-4-phenylbut-3-enoate 111a



The title compound was prepared according to GP A using benzaldehyde (1.00 mL, 9.80 mmol, 1 equiv.), (2-carboxyethyl)-triphenylphosphonium chloride (4.36 g, 11.8 mmol, 1.2 equiv.), KO^{t}Bu (2.97 g, 26.5 mmol, 2.7 equiv.), $MgSO_4$ (4.75 g, 39.5 mmol, 4 equiv.), H_2SO_4 (0.53 mL, 9.87 mmol, 1.0 equiv.), MeOH (2.00 mL, 49.3 mmol, 5.0 equiv.), *p*-ABSA (2.62, 10.9 mmol, 1.5 equiv.) and DBU (2.17 mL, 14.5 mmol, 2.0 equiv.) to yield methyl (E)-2-diazo-4-phenylbut-3-enoate (806 mg, 3.99 mmol, 41% yield over all steps) as a red solid. Analytical data is in accordance with literature.[185]

^{1}H NMR (300 MHz, $CDCl_3$) δ [ppm]= 7.46 – 7.28 (m, 4H), 7.22 (dd, *J* = 7.4, 1.4 Hz, 1H), 6.49 (d, *J* = 16.3 Hz, 1H), 6.20 (d, *J* = 16.3 Hz, 1H), 3.86 (s, 3H).

Methyl (E)-2-diazo-4-(4-fluorophenyl)but-3-enoate 111b

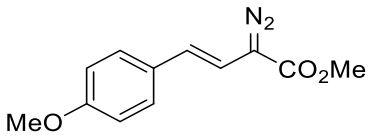


The title compound was prepared according to GP A using (2-carboxyethyl)-triphenylphosphonium chloride (4.11 g, 11.1 mmol, 1.1 equiv.), *p*-fluorobenzaldehyde (1.09 mL, 10 mmol, 1.0 equiv.), KO^{t}Bu (2.30 g, 20 mmol, 2.0 equiv.), $MgSO_4$ (4.10 g, 42 mmol, 4.0 equiv.), H_2SO_4 (0.5 mL, 10 mmol, 1.0 equiv.), MeOH (1.7 mL, 52 mmol, 5.0 equiv.), p-ABSA (3.96 g, 16.5 mmol, 1.5 equiv.) and DBU (3.28 mL, 22.0 mmol, 2.0 equiv.) to and purified by column chromatography (SiO_2, hexanes:ethyl acetate 9:1) to yield methyl (E)-2-diazo-4-(4-fluorophenyl)but-3-enoate (1.25 g, 5.68 mmol, 48% yield over all steps) as a red solid. Analytical data is in accordance with literature.[252]

^{1}H NMR (300 MHz, $CDCl_3$) δ [ppm]= 7.31 (ddd, *J* = 9.0, 5.3, 0.6 Hz, 2H), 7.01 (t, *J* = 8.7 Hz, 2H), 6.38 (dd, *J* = 16.3, 0.6 Hz, 1H), 6.16 (d, *J* = 16.3 Hz, 1H), 3.85 (s, 3H).

^{19}F NMR (282 MHz, $CDCl_3$) δ [ppm]= -115.40.

Methyl (E)-2-diazo-4-(4-methoxyphenyl)but-3-enoate 111c

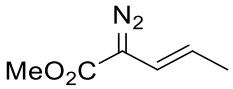


The title compound was prepared from according to GP A using (2-carboxyethyl)-triphenylphosphonium chloride (4.1 g, 11 mmol, 1.1 equiv.), anisaldehyde (1.2 mL, 10 mmol, 1.0 equiv.) and KO^{t}Bu (2.2 g, 20 mmol, 2.0 equiv.). For the esterification, the product from the first step was used directly. A 50 mL round bottomed flask was charged with the product, 7.5 mL MeOH (1.5 M) and 0.4 mL concentrated H_2SO_4 (0.3 mL/10 mmol). The reaction mixture was stirred for 12 hours at room temperature, slowly neutralized with saturated aqueous $NaHCO_3$ solution (careful! CO_2-evolution!) and extracted with DCM (3x 10 mL). The combined organic layers were washed with brine and dried over Na_2SO_4, filtered and concentrated *in* vacuo.[253] The crude product was

used directly in the next step without purification following GP A using *p*-ABSA (3.53 g, 14.7 mmol, 1.5 equiv.) and DBU (2.92 mL, 19.6 mmol, 2.0 equiv.) and purified by column chromatography (SiO_2, hexanes:ethyl acetate 9:1) to yield methyl (E)-2-diazo-4-(4-methoxyphenyl)but-3-enoate (1.34 g, 5.79 mmol, 52% yield over all steps) as a red solid. Analytical data is in accordance with literature.[254]

^{1}H NMR (400 MHz, $CDCl_3$) δ [ppm]= 7.33 – 7.26 (m, 2H), 6.90 – 6.83 (m, 2H), 6.30 (d, *J* = 16.3 Hz, 1H), 6.15 (d, *J* = 16.3 Hz, 1H), 3.85 (s, 3H), 3.81 (s, 3H).

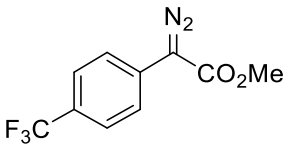
Methyl (E)-2-diazopent-3-enoate 111d



The title compound was prepared from the unsaturated ester (1.00 g, 8.76 mmol, 1 equiv.) using *p*-ABSA (3.16 g, 13.1 mmol, 1.5 equiv.) and DBU (2.62 mL, 17.5 mmol, 2.0 equiv.) to yield methyl (E)-2-diazopent-3-enoate (380 mg, 2.71 mmol, 31%) as an orange liquid. Caution: This compound is extremely volatile and should be used immediately after preparation as it decomposes quickly even at low temperatures. Analytical data is in accordance with literature.[185]

^{1}H NMR (300 MHz, $CDCl_3$) δ [ppm]= 5.81 – 5.66 (m, 1H), 5.33 (dq, *J* = 15.8, 6.7 Hz, 1H), 3.79 (s, 3H), 1.84 (dd, *J* = 6.7, 1.6 Hz, 3H).

Methyl 2-diazo-2-(4-(trifluoromethyl)phenyl)acetate 252b



The title compound was prepared according to literature procedure.[255] In a flame-dried 25 mL Schlenk round-bottomed, flask. 2-(4-(trifluoromethyl)phenyl)acetic acid (1.02 g, 5.00 mmol, 1.0 equiv.) was dissolved in 5 mL of anhydrous Methanol. The solution was cooled to 0 °C and acetyl chloride (0.50 mL, 7.00 mmol, 1.2 equiv.) was added dropwise. The reaction was allowed to warm to room temperature over night (18 h) and poured into a separation funnel containing 20 mL aqueous NH4Cl (sat.) and 10 mL diethyl ether. The phases were separated and the aqueous phase extracted twice with 10 mL of diethyl

ether. The combined organic phases were washed with brine (20 mL), dried over Na2SO4, filtered, and concentrated in vacuo. The crude product was directly used in the next step without purification.

In a 50 mL round-bottomed flask, the crude product was dissolved in 20 mL MeCN. *p*-ABSA (1.65 g, 6.88 mmol, 1.5 equiv.) was added and the solution cooled to 0 °C. DBU (1.37 mL, 9.17 mmol, 2.0 equiv.) was added dropwise and the reaction allowed to warm to room temperature over night (24 h). The reaction was quenched with aqueous NH4Cl (sat.) and extracted twice with 20 mL diethyl ether. The combined organic phases were washed with 20 mL brine, dried over MgSO4, filtered and concentrated *in vacuo*. The crude diazo compound was purified by column chromatography (SiO2, hexanes/diethyl ether 9:1) to yield methyl 2-diazo-2-(4-(trifluoromethyl)phenyl)acetate (0.99 g, 4.07 mmol, 81%) as a yellow solid. Analytical data is in accordance with literature.[248]

1H-NMR (300 MHz, CDCl3) δ [ppm]= 7.62 (s, 4H), 3.89 (s, 3H).

5.4 Cyclopropanation reactions

General Procedure B (GP B)

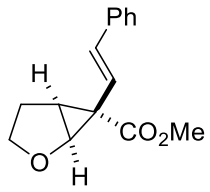
A flame-dried round bottomed Schlenk flask was charged with the corresponding dihydrofuran (1.5-3 equiv.) and $Rh_2(OAc)_4$ or $Rh_2(OOct)_4$ (0.01 equiv.) in dry DCM (when $Rh_2(OAC)_4$ was used; 0.25 M) or dry pentane (when $Rh_2(OOct)_4$ was used; 0.25 M). In a separate flame-dried round bottomed Schlenk flask, the corresponding diazo ester (1.0 equiv.) was dissolved in dry DCM or pentane. This solution was then drawn up into a syringe and added to the solution of dihydrofuran and catalyst *via* a syringe pump over the course of 30 minutes. After completed addition, the solution was stirred for an additional 5 minutes and the solvent was evaporated under reduced pressure. The crude product was purified by column chromatography (hexanes/ethyl acetate 19:1 to 9:1).

General Procedure EC

A flame-dried round bottomed Schlenk flask was charged with the corresponding dihydrofuran (3 equiv.) and Rh_2(*R*-DOSP)$_4$ in 5 mL dry pentane (0.25 M) and cooled to -78 °C with the help of a isopropanol/dry ice cooling bath. In a separate flame-dried round bottomed Schlenk flask, the corresponding diazo ester (1.0 equiv.) was dissolved

in 2.5 mL dry pentane. This solution was then drawn up into a syringe and added to the solution of dihydrofuran and catalyst *via* a syringe pump over the course of 30 minutes. After completed addition, the solution was stirred for 18 hours, and the solvent was evaporated under reduced pressure. The crude product was purified by column chromatography.

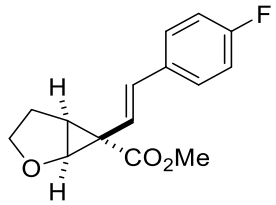
Methyl (E)-6-styryl-2-oxabicyclo[3.1.0]hexane-6-carboxylate 250a



The title compound was prepared according to GP B using 2,3-dihydrofuran (0.56 mL, 7.42 mmol, 1.5 equiv.), $Rh_2(OOct)_4$ (9.6 mg, 24.7 µmol, 0.01 equiv.) and methyl (E)-2-diazo-4-phenylbut-3-enoate **111a** (1.0 g, 4.95 mmol, 1.0 equiv.) and purified by column chromatography (hexanes/ethyl acetate 0 to 10%) to yield methyl (E)-6-styryl-2-oxabicyclo[3.1.0]hexane-6-carboxylate (957 mg, 3.92 mmol, 79%) as yellow oil. Analytical data is in accordance with literature.[49]

^{1}H NMR (300 MHz, $CDCl_3$) δ [ppm]= 7.46 – 7.14 (m, 5H), 6.49 (d, *J* = 16.3 Hz, 1H), 6.20 (d, *J* = 16.3 Hz, 1H), 3.86 (s, 3H).

Methyl (E)-6-(4-fluorostyryl)-2-oxabicyclo[3.1.0]hexane-6-carboxylate 250b



The title compound was prepared according to GP B using 2,3-dihydrofuran (114 µL, 1.5 mmol, 1.0 equiv.), $Rh_2(OAc)_4$ (6.8 mg, 15 µmol, 0.01 equiv.) and methyl (E)-2-diazo-4-(4-fluorophenyl)but-3-enoate **111b** (366 mg, 1.7 mmol, 1.1 equiv.) and purified by column chromatography (hexanes/ethyl acetate 9:1 to 4:1) to yield methyl (E)-6-(4-fluorostyryl)-2-oxabicyclo[3.1.0]hexane-6-carboxylate (200 mg, 0.8 mmol, 50%) as yellow solid.

R_f (SiO_2, hexanes:ethyl acetate 4:1) = 0.4 stains brown with Vanillin.

Melting point 52 °C.

^{1}H NMR (400 MHz, $CDCl_3$) δ [ppm]= 7.43 – 7.35 (m, 2H), 7.07 – 6.96 (m, 2H), 6.71 (d, J = 16.2 Hz, 1H), 6.12 (d, J = 16.2 Hz, 1H), 4.37 (d, J = 5.7 Hz, 1H), 4.12 – 4.05 (m, 1H), 3.65 (s, 3H), 3.59 (td, J = 8.8, 7.5 Hz, 1H), 2.52 (t, J = 6.0 Hz, 1H), 2.29 (dddd, J = 13.5, 10.3, 7.4, 6.4 Hz, 1H), 1.97 (ddd, J = 13.5, 9.0, 5.0 Hz, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) δ [ppm]= 171.53, 136.16, 127.87, 127.79, 118.59, 115.60, 115.39, 71.82, 70.20, 52.21, 35.09, 32.75, 25.52.

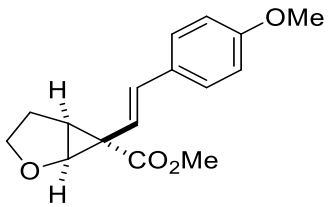
^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$) δ [ppm]= -114.72.

^{19}F NMR (376 MHz, $CDCl_3$) δ [ppm]= -114.73 (td, J = 8.7, 4.3 Hz).

IR (neat): 2952, 2903, 1707, 1599, 1505, 1442, 1293, 1222, 1159, 1114, 1066, 980, 943, 823, 775, 685 cm^{-1}.

HR-MS (EI-MS): m/z calc. for $C_{15}H_{15}FO_3$ [M+·] 262.09997, found 262.10016.

Methyl (E)-6-(4-methoxystyryl)-2-oxabicyclo[3.1.0]hexane-6-carboxylate 250c



The title compound was prepared according to GP B using 2,3-dihydrofuran (148 µL, 2.0 mmol, 1.0 equiv.), $Rh_2(OAc)_4$ (8.7 mg, 20 µmol, 0.01 equiv.) and methyl (E)-2-diazo-4-(4-methoxyphenyl)but-3-enoate **111c** and purified by column chromatography (hexanes/ethyl acetate 19:1 to 9:1) to yield methyl (E)-6-(4-methoxystyryl)-2-oxabicyclo[3.1.0]hexane-6-carboxylate (227 mg, 0.8 mmol, 42%) as yellow oil.

R_f (SiO_2, hexanes:ethyl acetate 9:1)=0.22 stains brown with Vanillin.

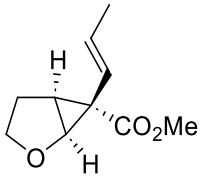
^{1}H NMR (300 MHz, $CDCl_3$) δ [ppm]= 7.42 – 7.34 (m, 2H), 6.94 – 6.83 (m, 2H), 6.68 (d, *J* = 16.2 Hz, 1H), 6.06 (d, *J* = 16.2 Hz, 1H), 4.35 (d, *J* = 5.7 Hz, 1H), 4.11 – 4.02 (m, 1H), 3.81 (s, 3H), 3.64 (s, 3H), 3.63 – 3.55 (m, 1H), 2.50 (t, *J* = 6.0 Hz, 1H), 2.27 (dddd, *J* = 13.0, 10.3, 7.6, 6.3 Hz, 1H), 1.98 (ddd, *J* = 13.4, 9.0, 4.9 Hz, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) δ [ppm]= 171.83, 159.41, 136.74, 130.06, 127.51, 116.45, 114.01, 71.72, 70.22, 55.35, 52.16, 35.07, 32.61, 25.54.

IR (neat): 2956, 2900, 2840, 1711, 1607, 1513, 1439, 1375, 1301, 1238, 1174, 1111, 1074, 1033, 969, 902, 820, 719 cm^{-1}.

HR-MS (EI-MS): m/z calc. for $C_{16}H_{18}O_4$ [M+·] 274.11996, found 274.11926.

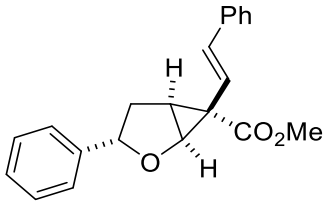
Methyl -6-((E)-prop-1-en-1-yl)-2-oxabicyclo[3.1.0]hexane-6-carboxylate 250d



The title compound was prepared according to GP B using 2,3-dihydrofuran (869 µL, 11.5 mmol, 5.0 equiv.), $Rh_2(OOct)_4$ (17.9 mg, 23.0 µmol, 0.01 equiv.) and methyl (E)-2-diazo-4-(4-methoxyphenyl)but-3-enoate (322 mg, 2.3 mmol, 1 equiv.) **111d** and purified by column chromatography (hexanes/ethyl acetate 19:1) to yield methyl (E)-6-(4-methoxystyryl)-2-oxabicyclo[3.1.0]hexane-6-carboxylate (237 mg, 1.3 mmol,57%) as yellow oil. Analytical data is in accordance with literature.[185]

^{1}H NMR (300 MHz, $CDCl_3$) δ [ppm]= 5.93 – 5.75 (m, 1H), 5.46 (dq, *J* = 15.6, 1.7 Hz, 1H), 4.25 (d, *J* = 5.7 Hz, 1H), 4.06 (ddd, *J* = 10.3, 8.4, 4.8 Hz, 1H), 3.63 (d, *J* = 0.5 Hz, 3H), 3.60 – 3.48 (m, 1H), 2.38 (t, *J* = 6.0 Hz, 1H), 2.23 (dddd, *J* = 12.9, 10.4, 7.6, 6.4 Hz, 1H), 1.96 – 1.85 (m, 1H), 1.78 (ddd, *J* = 6.5, 1.7, 0.5 Hz, 3H).

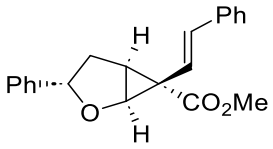
Methyl-3-phenyl-6-((E)-styryl)-2-oxabicyclo[3.1.0]hexane-6-carboxylate 250e



The title compound was prepared according to GP B using 2-phenyl-2,3-dihydrofuran (400 mg, 2.7 mmol, 1.0 equiv.), $Rh_2(OAc)_4$ (12 mg, 27 µmol, 0.01 equiv.) and methyl (E)-2-diazo-4-phenylbut-3-enoate (609 mg, 3.0 mmol, 1.1 equiv.) **111a** and purified by column chromatography (hexanes/ethyl acetate 19:1) to yield methyl-3-phenyl-6-((E)-

styryl)-2-oxabicyclo[3.1.0]hexane-6-carboxylate (498 mg, 1.55 mmol, 57%) as a yellow oil.

Methyl (1*S*,3*S*,5*S*,6*S*)-3-phenyl-6-((*E*)-styryl)-2-oxabicyclo[3.1.0]hexane-6-carboxylate



The title compound was prepared according to **General Procedure EC** using 2-phenyl-2,3-dihydrofuran (87.7 mg, 0.60 mmol, 3.0 equiv.), methyl (E)-2-diazo-4-phenylbut-3-enoate **111a** (40.4 mg, 0.2 mmol, 1.0 equiv.) and Rh_2(*R*-DOSP)$_4$ (1.1 mg, 1.0 µmol, 0.5 mol%) to yield methyl (1*S*,3*S*,5*S*,6*S*)-3-phenyl-6-((*E*)-styryl)-2-oxabicyclo[3.1.0]hexane-6-carboxylate (35.4 mg, 110 µmol, 55%) as a yellow oil.

$[\alpha]_D^{20}$= 8.468° (MeOH, c = 1 g/L)

HPLC: ADH column, 1 mL/min, 5% *i*-PrOH in hexane, 15 min, t_R major 9.696 min, minor 6.662 min, 79% *ee.*

R_f (SiO_2, hexanes:ethyl acetate 9:1) = 0.26, stains brown with Vanillin.

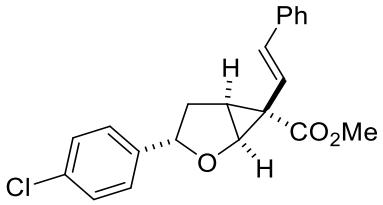
^{1}H NMR (300 MHz, $CDCl_3$) δ [ppm]= 7.54 – 7.46 (m, 2H), 7.41 – 7.28 (m, 6H), 7.26 – 7.20 (m, 2H), 6.84 (d, *J* = 16.2 Hz, 1H), 6.36 (d, *J* = 16.2 Hz, 1H), 4.83 (dd, *J* = 8.6, 7.1 Hz, 1H), 4.64 (d, *J* = 5.7 Hz, 1H), 3.68 (s, 3H), 2.66 – 2.45 (m, 2H), 2.22 (ddd, *J* = 13.5, 7.1, 6.4 Hz, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) δ [ppm]= 171.85, 142.83, 137.72, 137.20, 128.68, 128.49, 127.92, 127.56, 126.44, 125.42, 119.14, 84.58, 70.44, 52.28, 34.98, 34.49, 32.36.

IR (neat): 3060, 3027, 2952, 1778, 1715, 1603, 1495, 1450, 1293, 1241, 1066, 1021, 969, 872, 835, 753, 967 cm^{-1}.

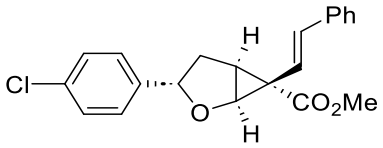
HR-MS (EI-MS): m/z calc. for $C_{21}H_{20}O_3$ [$M^{+\cdot}$], 320.14071 found 320.14028.

Methyl-3-(4-chlorophenyl)-6-((E)-styryl)-2-oxabicyclo[3.1.0]hexane-6-carboxylate 250g



The title compound was prepared according to GP B using 2-phenyl-2,3-dihydrofuran (547 mg, 3.0 mmol, 1.2 equiv.), $Rh_2(OAc)_4$ (11.2 mg, 25 µmol, 0.01 equiv.) and methyl (E)-2-diazo-4-phenylbut-3-enoate **111a** (500 mg, 2.47 mmol, 1.0 equiv.) and purified by column chromatography (hexanes/ethyl acetate 19:1) to yield methyl-3-(4-chlorophenyl)-6-((E)-styryl)-2-oxabicyclo[3.1.0]hexane-6-carboxylate (540 mg, 1.52 mmol, 60%) as a yellow oil.

Methyl (1*S*,3*S*,5*S*,6*S*)-3-(4-chlorophenyl)-6-((*E*)-styryl)-2-oxabicyclo[3.1.0]hexane-6-carboxylate



The title compound was prepared according to **General Procedure EC** using 2-(4-chlorophenyl)-2,3-dihydrofuran (108 mg, 0.60 mmol, 3.0 equiv.), methyl (E)-2-diazo-4-phenylbut-3-enoate (40.4 mg, 0.2 mmol, 1.0 equiv.) and Rh_2(*R*-DOSP)$_4$ (1.1 mg, 1.0 µmol, 0.5 mol%) to yield methyl (1*S*,3*S*,5*S*,6*S*)-3-(4-chlorophenyl)-6-((*E*)-styryl)-2-oxabicyclo[3.1.0]hexane-6-carboxylate (48.4 mg, 136 µmol, 68%) as a yellow oil.

$[\alpha]_D^{20}$= - 1.810 ° (MeOH, c = 1 g/L)

HPLC: Amylose-1 column, 1 mL/min, 10% *i*-PrOH in heptane, 20 min, t_R major 12.47 min, minor 7.59 min, 77% *ee.*

R_f (SiO_2, hexanes:ethyl acetate 9:1) = 0.26, stains brown with Vanillin.

^{1}H NMR (400 MHz, $CDCl_3$) δ [ppm]= 7.51 – 7.45 (m, 2H), 7.40 – 7.34 (m, 2H), 7.31 – 7.25 (m, 3H), 7.21 – 7.12 (m, 2H), 6.82 (d, *J* = 16.3 Hz, 1H), 6.34 (d, *J* = 16.3 Hz, 1H), 4.82 –

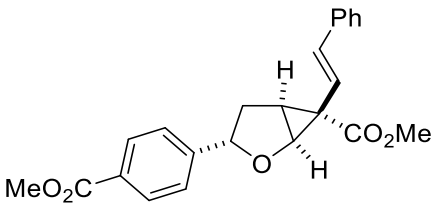
4.76 (m, 1H), 4.62 (d, *J* = 5.7 Hz, 1H), 3.67 (s, 3H), 2.58 (t, *J* = 6.0 Hz, 1H), 2.50 (dd, *J* = 13.5, 8.7 Hz, 1H), 2.15 (dt, *J* = 13.5, 6.7 Hz, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) δ [ppm]= 171.73, 141.33, 137.82, 137.07, 133.22, 128.69, 128.61, 127.99, 126.79, 126.43, 118.92, 83.78, 70.34, 52.31, 35.03, 34.43, 32.12.

IR (neat): 3056, 3027, 2952, 1711, 1599, 1491, 1435, 1297, 1241, 1070, 1014, 969, 921, 828, 734, 693 cm^{-1}.

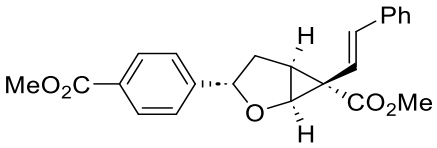
HR-MS (EI-MS): m/z calc. for $C_{21}H_{19}O_3Cl$ [M+·], 354.10172 found 354.10102.

Methyl-3-(4-(methoxycarbonyl)phenyl)-6-((E)-styryl)-2-oxabicyclo[3.1.0]hexane-6-carboxylate 250h



The title compound was prepared according to GP B using methyl 4-(2,3-dihydrofuran-2-yl)benzoate (757 mg, 3.7 mmol, 1.5 equiv.), $Rh_2(OAc)_4$ (10.9 mg, 24.7 µmol, 0.01 equiv.) and methyl (E)-2-diazo-4-phenylbut-3-enoate (500 mg, 2.47 mmol, 1.0 equiv.) **111a** and purified by column chromatography (hexanes/ethyl acetate 0 to 10%) to yield methyl -3-(4-(methoxycarbonyl)phenyl)-6-((E)-styryl)-2-oxabicyclo[3.1.0]hexane-6-carboxylate (417 mg, 1.1 mmol, 45%) as a yellow solid.

Methyl (1*S*,3*S*,5*S*,6*S*)-3-(4-(methoxycarbonyl)phenyl)-6-((*E*)-styryl)-2-oxabicyclo[3.1.0]hexane-6-carboxylate



The title compound was prepared according to **General Procedure EC** using methyl 4-(2,3-dihydrofuran-2-yl)benzoate (123 mg, 0.60 mmol, 3.0 equiv.), methyl (E)-2-diazo-4-phenylbut-3-enoate (40.4 mg, 0.2 mmol, 1.0 equiv.) and Rh_2(*R*-DOSP)$_4$ (1.1 mg, 1.0 µmol, 0.5 mol%) to yield Methyl (1*S*,3*S*,5*S*,6*S*)-3-(4-(methoxycarbonyl)phenyl)-6-

((*E*)-styryl)-2-oxabicyclo[3.1.0]hexane-6-carboxylate (29.5 mg, 78.0 µmol, 39%) as a yellow oil.

$[\alpha]_D^{20}$= 3.915 ° (MeOH, c = 1 g/L)

HPLC: Amylose-1 column, 1 mL/min, 20% *i*-PrOH in heptane, 25 min, t_R major 19.23 min, minor 8.48 min, 74% *ee.*

R_f (SiO_2, hexanes:ethyl acetate 9:1) = 0.13

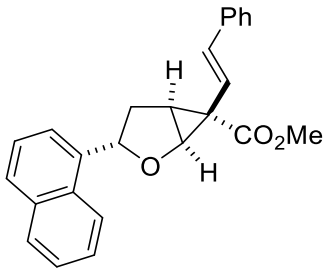
^{1}H NMR (400 MHz, $CDCl_3$) δ [ppm]= 8.02 – 7.94 (m, 2H), 7.52 – 7.45 (m, 2H), 7.41 – 7.32 (m, 2H), 7.34 – 7.26 (m, 3H), 6.84 (d, *J* = 16.2 Hz, 1H), 6.35 (d, *J* = 16.3 Hz, 1H), 4.91 – 4.82 (m, 1H), 4.66 (d, *J* = 5.7 Hz, 1H), 3.90 (s, 3H), 3.68 (s, 3H), 2.63 – 2.49 (m, 2H), 2.23 – 2.11 (m, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) δ [ppm]= 171.68, 166.85, 147.95, 137.89, 137.04, 129.86, 129.30, 128.69, 128.01, 126.43, 125.18, 118.85, 83.89, 70.46, 52.32, 52.10, 34.98, 34.49, 32.09.

IR (neat): 3056, 3001, 2952, 2113, 1923, 1707, 1613, 1580, 1491, 1431, 1342, 1275, 1241, 1185, 1144, 1107, 1066, 1018, 921, 850, 768, 686 cm^{-1}.

HR-MS (ESI-MS): m/z calc. for $C_{23}H_{23}O_5$ [M+H+], 379.154 found 379.1542.

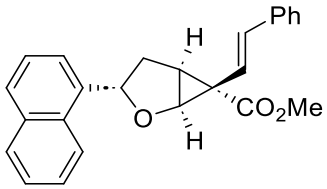
Methyl-3-(naphthalen-1-yl)-6-((E)-styryl)-2-oxabicyclo[3.1.0]hexane-6-carboxylate 250f



The title compound was prepared according to GP B using 2-(naphthalen-1-yl)-2,3-dihydrofuran (801 mg, 4.1 mmol, 1.5 equiv.), $Rh_2(OOct)_4$ (19.3 mg, 24.7 µmol, 0.01 equiv.) and methyl (E)-2-diazo-4-phenylbut-3-enoate (500 mg, 2.47 mmol, 1.0 equiv.) **111a** and purified by column chromatography (hexanes/ethyl acetate 19:1)

to yield methyl-3-(naphthalen-1-yl)-6-((E)-styryl)-2-oxabicyclo[3.1.0]hexane-6-carboxylate (280 mg, 754 µmol, 31%) as a yellow-white solid.

Methyl (1*S*,3*S*,5*S*,6*S*)-3-(naphthalen-1-yl)-6-((*E*)-styryl)-2-oxabicyclo[3.1.0]hexane-6-carboxylate



The title compound was prepared according to **General Procedure EC** using methyl 4-(2,3-dihydrofuran-2-yl)benzoate (123 mg, 0.60 mmol, 3.0 equiv.), methyl (E)-2-diazo-4-phenylbut-3-enoate (40.4 mg, 0.2 mmol, 1.0 equiv.) and Rh_2(*R*-DOSP)$_4$ (1.1 mg, 1.0 µmol, 0.5 mol%) to yield Methyl (1*S*,3*S*,5*S*,6*S*)-3-(4-(methoxycarbonyl)phenyl)-6-((*E*)-styryl)-2-oxabicyclo[3.1.0]hexane-6-carboxylate (29.5 mg, 78.0 µmol, 39%) as a yellow oil.

$[\alpha]_D^{20}$= 23.190 ° (MeOH, c = 0.7 g/L)

HPLC: Amylose-1 column, 1 mL/min, 10% *i*-PrOH in heptane, 25 min, t_R major 19.07 min, minor 9.93 min, 71% *ee.*

R_f (SiO_2, hexanes:ethyl acetate 9:1) = 0.23, stains brown with Vanillin.

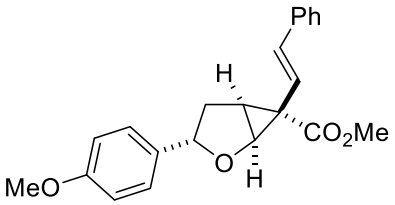
^{1}H NMR (300 MHz, $CDCl_3$) δ [ppm]= 7.85 (d, *J* = 9.6 Hz, 1H), 7.76 (d, *J* = 8.1 Hz, 1H), 7.70 – 7.65 (m, 1H), 7.61 (d, *J* = 6.1 Hz, 1H), 7.57 – 7.52 (m, 2H), 7.48 – 7.41 (m, 4H), 7.38 (d, *J* = 7.7 Hz, 1H), 7.31 (d, *J* = 7.2 Hz, 1H), 6.95 (d, *J* = 16.2 Hz, 1H), 6.45 (d, *J* = 16.3 Hz, 1H), 5.50 (dd, *J* = 8.8, 6.7 Hz, 1H), 4.78 (d, *J* = 5.8 Hz, 1H), 3.71 (s, 3H), 2.75 – 2.56 (m, 2H), 2.30 (dt, *J* = 13.3, 6.6 Hz, 1H).

^{13}C NMR (75 MHz, $CDCl_3$) δ [ppm]= 171.85, 138.20, 137.90, 137.22, 133.92, 129.56, 128.91, 128.73, 128.05, 127.97, 126.48, 126.07, 125.57, 125.43, 123.32, 122.29, 119.18, 83.27, 70.52, 52.35, 34.72, 34.25, 32.67.

IR (neat): 3056, 3027, 2952, 2363, 2207, 1718, 1599, 1495, 1435, 1238, 1074, 969, 779, 753, 693 cm^{-1}.

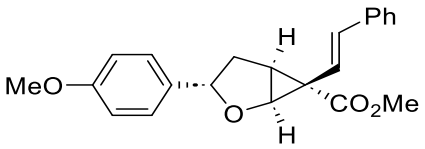
HR-MS (EI-MS): m/z calc. for $C_{25}H_{22}O_3$ [$M^{+\cdot}$] 370.15635, found 370.15671.

Methyl (E)-3-(4-methoxyphenyl)-6-styryl-2-oxabicyclo[3.1.0]hexane-6-carboxylate 250i



The title compound was prepared according to GP B using 2-(4-methoxyphenyl)-2,3-dihydrofuran (385 mg, 2.2 mmol, 1.0 equiv.), $Rh_2(OAc)_4$ (9.7 mg, 22 µmol, 0.01 equiv.) and methyl (E)-2-diazo-4-phenylbut-3-enoate **111a** (486 mg, 2.4 mmol, 1.1 equiv.) and purified by column chromatography (hexanes/ethyl acetate 19:1 to 9:1) to yield methyl (E)-3-(4-methoxyphenyl)-6-styryl-2-oxabicyclo[3.1.0]hexane-6-carboxylate (500 mg, 1.4 mmol, 65%) as yellow solid. Suitable crystals for X-ray structure analysis were obtained by vapor diffusion of 2-methylbutane into a ethylacetate solution.

Methyl (1*S*,3*S*,5*S*,6*S*)-3-(4-methoxyphenyl)-6-((*E*)-styryl)-2-oxabicyclo[3.1.0]hexane-6-carboxylate



The title compound was prepared according to **General Procedure EC** using 2-(4-methoxyphenyl)-2,3-dihydrofuran (106 mg, 0.60 mmol, 3.0 equiv.), methyl (E)-2-diazo-4-phenylbut-3-enoate (40.4 mg, 0.2 mmol, 1.0 equiv.) and Rh_2(*R*-DOSP)$_4$ (1.1 mg, 1.0 µmol, 0.5 mol%) to yield methyl (1*S*,3*S*,5*S*,6*S*)-3-(4-methoxyphenyl)-6-((*E*)-styryl)-2-oxabicyclo[3.1.0]hexane-6-carboxylate (44.4 mg, 127 µmol, 63%) as a yellow oil.

$[\alpha]_D^{20}$= 44.339 ° (MeOH, c = 1 g/L)

HPLC: Amylose-1 column, 1 mL/min, 10% *i*-PrOH in heptane, 25 min, t_R major 19.07 min, minor 9.93 min, 63% *ee.*

R_f (SiO_2, hexanes:ethyl acetate 9:1) = 0.14, stains brown with Vanillin.

Melting point: 89 °C.

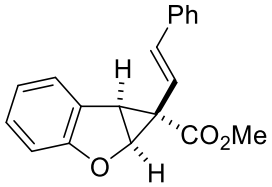
^{1}H NMR (300 MHz, $CDCl_3$) δ [ppm]= 7.54 – 7.44 (m, 2H), 7.41 – 7.27 (m, 3H), 7.22 – 7.11 (m, 2H), 6.87 – 6.78 (m, 3H), 6.34 (d, *J* = 16.2 Hz, 1H), 4.76 (t, *J* = 7.8 Hz, 1H), 4.60 (d, *J* = 5.7 Hz, 1H), 3.78 (s, 3H), 3.67 (s, 3H), 2.59 (t, *J* = 6.0 Hz, 1H), 2.46 (dd, *J* = 13.4, 8.5 Hz, 1H), 2.25 – 2.15 (m, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) δ [ppm]= 171.88, 159.11, 137.64, 137.22, 134.84, 128.66, 127.88, 126.91, 126.42, 119.19, 113.85, 84.38, 70.24, 55.31, 52.26, 34.92, 34.41, 32.41.

IR (neat): 3036, 3000, 2952, 2836, 1707, 1610, 1513, 1435, 1297, 1241, 1174, 1140, 1066, 1036, 969, 916, 872, 827, 749, 693 cm^{-1}.

HR-MS (APCI-MS): m/z calc. for $C_{22}H_{22}O_4$ [M+·] 351.1600, found 350.1525.

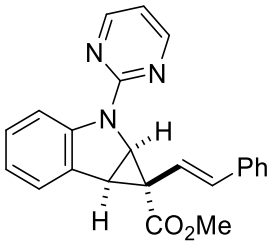
Methyl (E)-1-styryl-1a,6b-dihydro-1H-cyclopropa[b]benzofuran-1-carboxylate 250j



The title compound was prepared according to GP B using benzofuran (333 mg, 2.8 mmol, 1.0 equiv.), $Rh_2(OAc)_4$ (12.4 mg, 28 µmol, 0.01 equiv.) and methyl (E)-2-diazo-4-phenylbut-3-enoate (856 mg, 4.2 mmol, 1.5 equiv.) **111a** and purified by column chromatography (hexanes/ethyl acetate 19:1) to yield methyl (E)-1-styryl-1a,6b-dihydro-1H-cyclopropa[b]benzofuran-1-carboxylate (825 mg, 8.2 mmol, 100%) as yellow solid. Analytical data is in accordance with literature.[185]

^{1}H NMR (300 MHz, $CDCl_3$) δ [ppm]= 7.39 (dd, *J* = 7.4, 1.5 Hz, 2H), 7.25 – 7.01 (m, 6H), 6.91 (td, *J* = 7.5, 1.0 Hz, 1H), 6.81 – 6.72 (m, 1H), 6.47 (d, *J* = 16.2 Hz, 1H), 5.56 (dd, *J* = 16.2, 0.8 Hz, 1H), 5.25 (dd, *J* = 5.5, 0.8 Hz, 1H), 3.75 (s, 3H), 3.59 (d, *J* = 5.4 Hz, 1H).

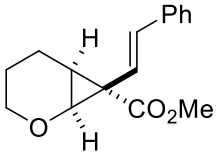
Methyl -2-(pyrimidin-2-yl)-1-((E)-styryl)-1,1a,2,6b-tetrahydrocyclopropa[b]indole-1-carboxylate 250q



The title compound was prepared according to literature.[191] A flame-dried 100 mL round-bottomed Schlenk flask was charged with the protected indole **251** (400 mg, 2.0 mmol, 1 equiv.) and silver(I) bis((trifluoromethyl)sulfonyl)amide (39.4 mg, 102 µmol, 0.05 equiv.). Methyl (E)-2-diazo-4-phenylbut-3-enoate (621 mg, 3.1 mmol, 1.5 equiv.) **111a** was dissolved in 40 mL dry and degassed DCM and added in one portion. The solution was stirred for 30 minutes under nitrogen atmosphere and the solvent evaporated under reduced pressure. The crude product was purified by column chromatography (hexanes:ethyl acetate 9:1 to 4:1) to yield methyl -2-(pyrimidin-2-yl)-1-((E)-styryl)-1,1a,2,6b-tetrahydrocyclopropa[b]indole-1-carboxylate (645 mg, 1.8 mmol, 85%) as a white solid. Analytical data is in accordance with literature.[191]

^{1}H NMR (300 MHz, $CDCl_3$) δ [ppm]= 8.58 (d, *J* = 4.8 Hz, 1H), 8.27 (d, *J* = 8.7 Hz, 1H), 7.50 – 7.44 (m, 1H), 7.24 – 7.20 (m, 1H), 7.14 – 7.06 (m, 3H), 7.03 (td, *J* = 7.5, 1.1 Hz, 1H), 6.89 – 6.81 (m, 3H), 6.18 (d, *J* = 16.2 Hz, 1H), 5.46 (d, *J* = 16.2 Hz, 1H), 5.29 (d, *J* = 6.7 Hz, 1H), 3.80 (s, 3H), 3.70 (d, *J* = 6.7 Hz, 1H).

Methyl (E)-7-styryl-2-oxabicyclo[4.1.0]heptane-7-carboxylate 250k

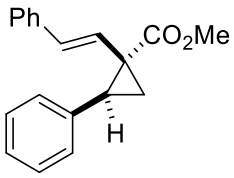


The title compound was prepared according to GP B using 3,4-dihydro-2*H*-pyran (255 µL, 2.8 mmol, 1.0 equiv.), $Rh_2(OAc)_4$ (12.4 mg, 28 µmol, 0.01 equiv.) and methyl (E)-2-diazo-4-phenylbut-3-enoate (626 mg, 3.09 mmol, 1.1 equiv.) **111a** and purified by column chromatography (hexanes/ethyl acetate 9:1) to yield methyl (E)-7-styryl-2-

oxabicyclo[4.1.0]heptane-7-carboxylate (414 mg, 1.6 mmol, 57%) as colorless oil. Analytical data is in accordance with literature.[42]

^{1}H NMR (300 MHz, $CDCl_3$) δ [ppm]= 7.50 – 7.14 (m, 5H), 6.74 (d, *J* = 16.5 Hz, 1H), 6.20 (d, *J* = 16.5 Hz, 1H), 4.05 (d, *J* = 7.0 Hz, 1H), 3.76 – 3.64 (m, 1H), 3.65 (s, 3H), 3.38 (td, *J* = 11.0, 3.3 Hz, 1H), 2.13 – 1.92 (m, 3H), 1.51 – 1.29 (m, 2H).

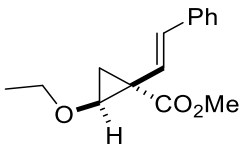
Methyl-2-phenyl-1-((E)-styryl)cyclopropane-1-carboxylate 250m



The title compound was prepared according to GP B using styrene (920 µL, 8.03 mmol, 5 equiv.), methyl (E)-2-diazo-4-phenylbut-3-enoate (325 mg, 1.61 mmol, 1.0 equiv.) **111a** and $Rh_2(OAc)_4$ (7.1 mg, 16.1 µmol, 0.01 equiv.) and purified by column chromatography (hexanes/ethyl acetate 0 to 10%) to yield methyl-2-phenyl-1-((E)-styryl)cyclopropane-1-carboxylate (291 mg, 1.04 mmol, 65%) as a white solid. Analytical data is in accordance with literature.[49]

^{1}H NMR (300 MHz, $CDCl_3$) δ [ppm]= 7.29 – 7.08 (m, 10H), 6.34 (d, *J* = 16.0 Hz, 1H), 6.13 (d, *J* = 16.0 Hz, 1H), 3.76 (s, 3H), 3.01 (dd, *J* = 9.2, 7.3 Hz, 1H), 2.08 – 1.97 (m, 1H), 1.83 (dd, *J* = 7.3, 5.0 Hz, 1H).

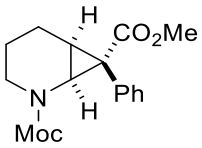
Methyl-2-ethoxy-1-((E)-styryl)cyclopropane-1-carboxylate 250n



The title compound was prepared according to GP B using ethylvinylether (144 µL, 1.5 mmol, 3 equiv.), methyl (E)-2-diazo-4-phenylbut-3-enoate (101 mg, 0.5 mmol, 1.0 equiv.) **111a** and $Rh_2(OOct)_4$ (3.89 mg, 5.00 µmol, 0.01 equiv.) and purified by column chromatography (hexanes/ethyl acetate 0 to 10%) to yield methyl-2-ethoxy-1-((E)-styryl)cyclopropane-1-carboxylate (79.1 mg, 0.32 mmol, 64%) as a yellow oil. Analytical data is in accordance with literature.[42]

^{1}H NMR (300 MHz, $CDCl_3$) δ [ppm]= 7.47 – 7.27 (m, 4H), 7.23 – 7.17 (m, 1H), 6.75 (d, *J* = 16.3 Hz, 1H), 6.44 (d, *J* = 16.3 Hz, 1H), 3.79 (dd, *J* = 7.0, 4.9 Hz, 1H), 3.74 (s, 3H), 3.64 – 3.44 (m, 1H), 3.44 – 3.30 (m, 1H), 1.88 (t, *J* = 6.6 Hz, 1H), 1.63 (dd, *J* = 6.2, 4.9 Hz, 1H).

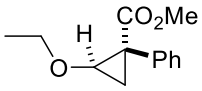
Dimethyl-7-phenyl-2-azabicyclo[4.1.0]heptane-2,7-dicarboxylate 253e



The title compound was prepared according to GP B using methyl 3,4-dihydropyridine-1(2H)-carboxylate (847 mg, 6.0 mmol, 2.0 equiv.), methyl 2-diazo-2-phenylacetate (529 mg, 3.0 mmol, 1.0 equiv.) and $Rh_2(OOct)_4$ (11.7 mg, 30.0 µmol, 0.01 equiv.). The formed white precipitate was collected by vacuum filtration and washed with cold pentane to yield dimethyl-7-phenyl-2-azabicyclo[4.1.0]heptane-2,7-dicarboxylate (577 mg, 2.0 mmol, 67%) as a white solid. Analytical data is in accordance with literature.[178]

^{1}H-NMR (300 MHz, CDCl3) δ[ppm]= 7.37 – 7.27 (m, 3H), 7.26 – 7.21 (m, 1H), 7.18 – 7.13 (m, 1H), 3.88 (s, 2H), 3.78 (d, J = 9.1 Hz, 1H), 3.77 (s, 1H), 3.60 (s, 2H), 3.57 (s, 1H), 3.32 – 3.07 (m, 1H), 2.82 – 2.68 (m, 1H), 2.43 – 2.27 (m, 1H), 2.03 – 1.74 (m, 2H), 1.21 (dt, J = 13.8, 4.0 Hz, 1H), 0.39 (qd, J = 11.3, 6.3 Hz, 1H).

Methyl 2-ethoxy-1-phenylcyclopropane-1-carboxylate 253d



The title compound was prepared according to GP B using ethyl vinyl ether (0.577 mL, 6.0 mmol, 3.0 equiv.), methyl 2-diazo-2-phenylacetate (352 mg, 2.0 mmol, 1.0 equiv.) and $Rh_2(OAc)_4$ (4.42 mg, 20.0 µmol, 0.01 equiv.) and purified by column chromatography (12 g SiO_2 column, 15 mL/min flowrate, hexanes/ethyl acetate 0% to 8% over 10 minutes, 5 minute hold) to yield methyl 2-ethoxy-1-phenylcyclopropane-1-carboxylate (286 mg, 1.3 mmol, 65%) as a colorless oil.

R_f (SiO_2, hexanes/ethyl acetate 9:1)=0.34

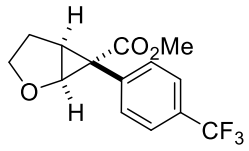
^{1}H-NMR (400 MHz, CDCl3) δ [ppm]= 7.38 – 7.26 (m, 5H), 3.93 (dd, J = 7.0, 4.6 Hz, 1H), 3.63 (s, 3H), 3.58 (qd, J = 7.0, 2.3 Hz, 2H), 1.79 (dd, J = 7.0, 5.7 Hz, 1H), 1.63 (dd, J = 5.8, 4.6 Hz, 1H), 1.00 (t, J = 7.0 Hz, 3H).

^{13}C-NMR (101 MHz, CDCl3) δ [ppm]= 173.62, 134.32, 131.47, 127.88, 127.21, 66.56, 64.82, 52.36, 35.08, 21.06, 14.88.

IR (neat)= 3060, 3030, 2978, 2878, 2363, 1882, 1715, 1603, 1498, 1435, 1346, 1260, 1189, 1118, 1088, 1029, 969, 910, 850, 816, 783, 701, 667 cm^{-1}.

HRMS (EI-MS) (M+) m/z calc. for $C_{13}H_{16}O_3$ 220.10940, found 220.10992.

Methyl-6-(4-(trifluoromethyl)phenyl)-2-oxabicyclo[3.1.0]hexane-6-carboxylate 253c



The title compound was prepared according to GP B using 2,3-dihydrofuran (0.34 mL, 4.5 mmol, 3.0 equiv.), methyl 2-diazo-2-(4-(trifluoromethyl)phenyl)acetate **AR-544** (366 mg, 1.5 mmol, 1.0 equiv.) and $Rh_2(OAc)_4$ (3.3 mg, 15.0 µmol, 0.01 equiv.) and purified by column chromatography (12 g SiO_2 column, 15 mL/min flowrate, hexanes/ethyl acetate 0% to 10% over 10 minutes, 5 minute hold) to yield methyl-6-(4-(trifluoromethyl)phenyl)-2-oxabicyclo[3.1.0]hexane-6-carboxylate (293 mg, 1.0 mmol, 68%) as a white solid.

R_f (SiO_2, ethyl acetate/hexanes 9:1)=0.29

Melting point 66.5 °C

^{1}H-NMR (400 MHz, CDCl3) δ [ppm]= 7.66 – 7.60 (m, 2H), 7.48 – 7.41 (m, 2H), 4.53 (d, J = 5.7 Hz, 1H), 3.81 (ddd, J = 10.1, 8.6, 3.8 Hz, 1H), 3.57 (s, 3H), 2.70 (t, J = 5.8 Hz, 1H), 2.39 (q, J = 8.6 Hz, 1H), 2.29 (dddd, J = 13.1, 10.4, 8.7, 6.0 Hz, 1H), 1.81 (ddd, J = 12.7, 8.5, 3.8 Hz, 1H).

^{13}C-NMR (101 MHz, CDCl3) δ [ppm]= 171.13, 136.41, 131.93, 125.39 (q, J (*C-F*) = 3.8 Hz), 70.24, 69.94, 52.42, 37.96, 32.63, 26.07.

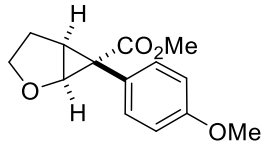
^{19}F{^{1}H}-NMR (377 MHz, CDCl3) δ [ppm]= -63.01.

^{19}F-NMR (377 MHz, CDCl3) δ [ppm]= -63.01.

IR (neat) = 2960, 2907, 1714, 1618, 1484, 1439, 1323, 1252, 1163, 1118, 1066, 1040, 969, 906, 872, 839, 734, 701 cm^{-1}.

HRMS (EI-MS) m/z calc. for C14H13F3O3 286.08113, found 286.08122.

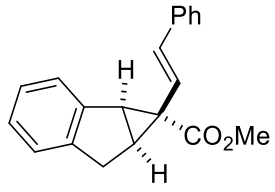
Methyl -6-(4-methoxyphenyl)-2-oxabicyclo[3.1.0]hexane-6-carboxylate 253b



The title compound was prepared according to GP B using 2,3-dihydrofuran (0.34 mL, 4.5 mmol, 3.0 equiv.), methyl 2-diazo-2-(4-methoxyphenyl)acetate (309 mg, 1.5 mmol, 1.0 equiv.) and $Rh_2(OAc)_4$ (3.3 mg, 15.0 µmol, 0.01 equiv.) and purified by column chromatography (12 g SiO_2 column, 15 mL/min flowrate, hexanes/ethyl acetate 0% to 10% over 10 minutes, 10 minute hold) to yield methyl -6-(4-methoxyphenyl)-2-oxabicyclo[3.1.0]hexane-6-carboxylate late (233 mg, 0.94 mmol, 63%) as a clear oil. Analytical data is in accordance with literature.[256]

^{1}H-NMR (300 MHz, CDCl3) δ [ppm]= 7.25 – 7.21 (m, 2H), 6.94 – 6.86 (m, 2H), 4.47 (d, J = 5.7 Hz, 1H), 3.81 (s, 3H), 3.81 – 3.73 (m, 1H), 3.57 (s, 3H), 2.61 (t, J = 5.9 Hz, 1H), 2.44 (q, J = 8.7 Hz, 1H), 2.24 (dddd, J = 12.9, 10.4, 8.8, 6.0 Hz, 1H), 1.83 (ddd, J = 12.6, 8.7, 3.7 Hz, 1H).

Methyl -1-((E)-styryl)-1,1a,6,6a-tetrahydrocyclopropa[a]indene-1-carboxylate 250l



The title compound was prepared according to GP B using indene (264 µL, 2.3 mmol, 1.0 equiv.), $Rh_2(OAc)_4$ (9.9 mg, 22 µmol, 0.01 equiv.) and methyl (E)-2-diazo-4-phenylbut-3-enoate **111a** (500 mg, 2.5 mmol, 1.1 equiv.) and purified by column chromatography (hexanes/ethyl acetate 4:1) to yield methyl -1-((E)-styryl)-1,1a,6,6a-

tetrahydrocyclopropa[a]indene-1-carboxylate (492.8 mg, 1.7 mmol, 76%) as a yellow oil.

R_f (SiO_2, hexanes:ethyl acetate 9:1) = 0.0.35, stains brown in Vanillin.

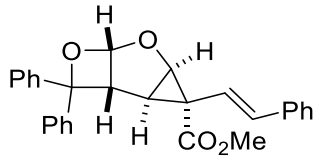
^{1}H NMR (300 MHz, $CDCl_3$) δ [ppm]= 7.44 – 7.32 (m, 1H), 7.22 – 7.07 (m, 5H), 7.04 – 6.94 (m, 3H), 6.28 (d, *J* = 16.3 Hz, 1H), 5.51 (d, *J* = 16.3 Hz, 1H), 3.72 (s, 3H), 3.33 – 3.16 (m, 2H), 2.86 (d, *J* = 17.9 Hz, 1H), 2.73 (t, *J* = 6.6 Hz, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) δ [ppm]= 173.75, 143.57, 140.91, 137.27, 136.90, 128.33, 127.33, 126.80, 126.35, 126.05, 124.92, 124.42, 119.63, 52.41, 40.47, 33.87, 32.82, 32.72.

IR (neat): 3027, 2952, 2907, 2363, 2341, 1718, 1603, 1476, 1435, 1293, 1245, 1088, 965, 738, 693 cm^{-1}.

HR-MS (EI-MS): m/z calc for $C_{20}H_{18}O_2$ [M+] 290.13013, found 290.12951.

Methyl-8,8-diphenyl-3-((*E*)-styryl)-5,7-dioxatricyclo[4.2.0.02,4]octane-3-carboxylate 250p



The title compound was prepared according to GP B using 6,6-diphenyl-2,7-dioxabicyclo[3.2.0]hept-3-ene (752 mg, 3.0 mmol, 1.5 equiv.), $Rh_2(OOct)_4$ (8.3 mg, 21.3 µmol, 0.01 equiv.) and methyl (E)-2-diazo-4-phenylbut-3-enoate **111a** (430 mg, 2.1 mmol, 1.0 equiv.). 10 mL dry toluene were added to enhance solubility. A white precipitate formed during the addition of the diazo compound, which was collected *via* vacuum filtration to yield methyl-8,8-diphenyl-3-((*E*)-styryl)-5,7-dioxatricyclo[4.2.0.02,4]octane-3-carboxylate (575 mg, 1.4 mmol, 65%) as a white solid.

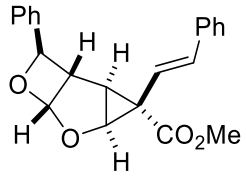
^{1}H-NMR (400 MHz, CDCl3) δ [ppm]= 7.50 – 7.41 (m, 4H), 7.41 – 7.31 (m, 8H), 7.30 – 7.27 (m, 1H), 7.25 – 7.22 (m, 2H), 6.71 (d, J = 16.4 Hz, 1H), 6.03 (d, J = 16.3 Hz, 1H), 5.56 (dd, J = 3.8, 0.8 Hz, 1H), 4.48 (d, J = 5.5 Hz, 1H), 3.83 (d, J = 3.7 Hz, 1H), 3.61 (s, 3H), 2.20 (d, J = 5.6 Hz, 1H).

^{13}C-NMR (101 MHz, CDCl3) δ [ppm]= 171.01, 145.21, 141.67, 138.51, 136.70, 129.07, 128.64, 128.39, 128.33, 128.26, 128.08, 127.51, 127.41, 126.34, 125.60, 118.26, 107.44, 84.96, 70.03, 52.40, 52.38, 35.76, 33.01.

IR (neat): 3056, 3027, 2956, 1715, 1491, 1439, 1364, 1290, 1241, 1118, 1070, 939, 872, 839, 749, 701 cm^{-1}.

HR-MS (ESI-MS), m/z calc. for $C_{28}H_{24}O_4$ [MH+] 425.1747, found 425.1746.

Methyl-8-phenyl-3-((*E*)-styryl)-5,7-dioxatricyclo[4.2.0.02,4]octane-3-carboxylate 250o



The title compound was prepared according to GP B using 6-phenyl-2,7-dioxabicyclo[3.2.0]hept-3-ene (265 mg, 1.5 mmol, 1.5 equiv.), $Rh_2(OOct)_4$ (7.9 mg, 10.1 µmol, 0.01 equiv.) and methyl (E)-2-diazo-4-phenylbut-3-enoate **111a** (205 mg, 1.0 mmol, 1.0 equiv.). 1 mL dry toluene was added to enhance solubility. A white precipitate formed during the addition of the diazo compound, which was collected *via* vacuum filtration to yield methyl-8-phenyl-3-((E)-styryl)-5,7-dioxatricyclo[4.2.0.02,4]octane-3-carboxylate (296 mg, 852 µmol, 84%) as a white solid. Suitable crystals for X-Ray diffraction were obtained from slow evaporation of *n*-heptane.

^{1}H-NMR (400 MHz, $CDCl_3$) δ [ppm]=7.42 – 7.23 (m, 10H), 6.65 (d, *J* = 16.3 Hz, 1H), 6.04 (d, *J* = 16.3 Hz, 1H), 5.71 (d, *J* = 3.8 Hz, 1H), 5.55 (d, *J* = 3.8 Hz, 1H), 4.83 (d, *J* = 5.5 Hz, 1H), 3.70 (s, 3H), 3.22 (t, *J* = 3.8 Hz, 1H), 2.92 (d, *J* = 5.6 Hz, 1H).

^{13}C-NMR (101 MHz, $CDCl_3$) δ[ppm]= 171.14, 140.97, 138.75, 136.60, 128.77, 128.66, 128.29, 128.15, 126.38, 125.26, 117.90, 109.86, 82.40, 69.75, 52.53, 50.53, 35.66, 34.34.

IR (neat)= 3027, 3064, 2986, 2952, 1730, 1603, 1491, 1431, 1364, 1334, 1290, 1230, 1122, 1066, 1033, 932, 839, 738, 693 cm^{-1}.

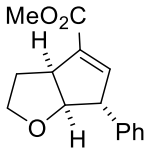
HRMS (APCI-MS), m/ calc. for $C_{22}H_{20}O_4$ 349.1434 (M+H)+, found 349.1436.

5.5 Lewis acid mediated rearrangements

General Procedure C (GP C)

A 5 mL Schlenk pressure tube was charged with the corresponding cyclopropane (500 µmol, 1 equiv.) and $Yb(OTf)_3$ (25 µmol, 0.05 equiv.) and dissolved in 5 mL MeCN. The reaction was stirred at the appropriate temperature until TLC indicated complete conversion. The solvent was evaporated under reduced pressure and the residue was redissolved in EtOAc and extracted with water (2x 10 mL) and brine (1x10 mL) and dried over $NaSO_4$. The solvent was evaporated under reduced pressure to yield the pure product.

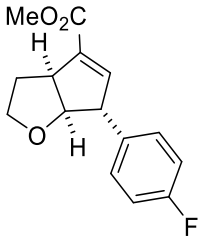
Methyl-6-phenyl-3,3a,6,6a-tetrahydro-2H-cyclopenta[b]furan-4-carboxylate 261a



The title compound was prepared according to GP C at 62 °C for 45 min using methyl (E)-6-styryl-2-oxabicyclo[3.1.0]hexane-6-carboxylate **250a** (122 mg, 0.5 mmol, 1 equiv.) and $Yb(OTf)_3$ (15.5 mg, 25 µmol, 0.05 equiv.) to yield methyl-6-phenyl-3,3a,6,6a-tetrahydro-2H-cyclopenta[b]furan-4-carboxylate (113 mg, 463 µmol, 93%) als yellow oil. Analytical data is in accordance with literature. [185]

^{1}H NMR (300 MHz, $CDCl_3$) δ [ppm]= 7.27 (ddt, *J* = 8.0, 6.5, 1.2 Hz, 2H), 7.20 – 7.16 (m, 1H), 7.10 – 7.03 (m, 2H), 6.74 (s, 1H), 4.46 (dt, *J* = 6.3, 1.3 Hz, 1H), 3.95 (q, *J* = 2.0 Hz, 1H), 3.80 (ddd, *J* = 8.6, 7.2, 4.3 Hz, 1H), 3.75 (s, 3H), 3.74 – 3.64 (m, 2H), 2.11 (dtd, *J* = 12.6, 8.5, 7.2 Hz, 1H), 1.97 (dddd, *J* = 12.9, 7.3, 5.3, 3.4 Hz, 1H).

Methyl-6-(4-fluorophenyl)-3,3a,6,6a-tetrahydro-2H-cyclopenta[b]furan-4-carboxylate 261b



The title compound was prepared according to GP C at 62 °C for 45 min using methyl (E)-6-(4-fluorostyryl)-2-oxabicyclo[3.1.0]hexane-6-carboxylate **250b** (131 mg, 0.5 mmol, 1 equiv.) and $Yb(OTf)_3$ (15.5 mg, 25 µmol, 0.05 equiv.) to yield methyl-6-(4-fluorophenyl)-3,3a,6,6a-tetrahydro-2H-cyclopenta[b]furan-4-carboxylate (112 mg, 427 µmol, 85%) as yellow solid.

mp: 47 °C

R_f (SiO2, hexanes: ethyl acetate 9:1)=0.19, stains brown in Vanillin.

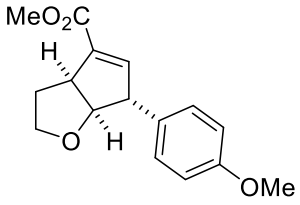
^{1}H NMR (300 MHz, $CDCl_3$) δ [ppm]= 7.12 – 6.95 (m, 4H), 6.81 – 6.69 (m, 1H), 4.48 – 4.43 (m, 1H), 3.97 (t, *J* = 2.2 Hz, 1H), 3.84 (ddd, *J* = 8.6, 7.1, 4.3 Hz, 1H), 3.80 (s, 3H), 3.78 – 3.68 (m, 2H), 2.23 – 2.07 (m, 1H), 2.06 – 1.95 (m, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) δ [ppm]= 165.01, 144.44, 137.16, 136.77, 136.74, 128.96, 128.88, 115.74, 115.53, 89.98, 67.25, 58.28, 51.70, 49.04, 30.98.

IR (neat): 2952, 2870, 2363, 2207, 2162, 1722, 1633, 1510, 1275, 1223, 1111, 1070, 835, 667 cm^{-1}.

HR-MS (EI-MS): m/z calc. for $C_{15}H_{15}O_3F$ 262.09997, found 262.09934.

Methyl-6-(4-methoxyphenyl)-3,3a,6,6a-tetrahydro-2*H*-cyclopenta[*b*]furan-4-carboxylate 261c



The title compound was prepared according to GP C at 62 °C for 60 min using methyl-6-((E)-4-methoxystyryl)-2-oxabicyclo[3.1.0]hexane-6-carboxylate **250c** (136 mg, 0.5 mmol, 1 equiv.) and $Yb(OTf)_3$ (15.5 mg, 25 µmol, 0.05 equiv.) to yield methyl-6-(4-methoxyphenyl)-3,3a,6,6a-tetrahydro-2*H*-cyclopenta[*b*]furan-4-carboxylate (124 mg, 452 µmol, 91%) as yellow oil.

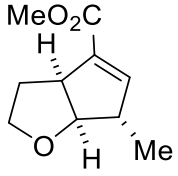
^{1}H NMR (300 MHz, $CDCl_3$) δ [ppm]= 7.04 – 6.97 (m, 2H), 6.86 – 6.79 (m, 2H), 6.77 – 6.74 (m, 1H), 4.45 (dt, *J* = 6.4, 1.2 Hz, 1H), 3.98 – 3.89 (m, 1H), 3.82 (ddd, *J* = 8.6, 7.2, 4.4 Hz, 1H), 3.77 (s, 3H), 3.76 (s, 3H), 3.75 – 3.66 (m, 2H), 2.21 – 1.93 (m, 2H).

^{13}C NMR (75 MHz, $CDCl_3$) δ [ppm]= 165.13, 158.62, 145.14, 136.61, 133.05, 128.45, 114.18, 90.11, 67.20, 58.21, 55.26, 51.62, 49.02, 30.99.

IR (neat): 2952, 2363, 1718, 1610, 1513, 1439, 1305, 1252, 1208, 1178, 1111, 1066, 1036, 936, 831, 872, 772 cm^{-1}.

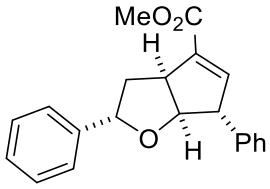
HR-MS (EI-MS): m/z calc. for $C_{16}H_{18}O_4$ 274.11996, found 274.12026.

Methyl 6-methyl-3,3a,6,6a-tetrahydro-2*H*-cyclopenta[*b*]furan-4-carboxylate 261d



Preparing the title compound according to **GP C** for 90 minutes at 60 °C using methyl (E)-6-(prop-1-en-1-yl)-2-oxabicyclo[3.1.0]hexane-6-carboxylate **250d** (88.0 mg, 483 µmol, 1 equiv.) and $Yb(OTf)_3$ (15.0 mg, 24.2 µmol, 0.05 equiv.) failed to yield the compound.

Methyl-2,6-diphenyl-3,3a,6,6a-tetrahydro-2H-cyclopenta[b]furan-4-carboxylate 261e



The title compound was prepared according to GP C at 62 °C for 45 min using methyl-3-phenyl-6-((E)-styryl)-2-oxabicyclo[3.1.0]hexane-6-carboxylate **250e** (160 mg, 0.5 mmol, 1 equiv.) and $Yb(OTf)_3$ (15.5 mg, 25 µmol, 0.05 equiv.) to yield methyl-2,6-diphenyl-3,3a,6,6a-tetrahydro-2H-cyclopenta[b]furan-4-carboxylate (141 mg, 441 µmol, 88%) als yellow oil.

R_f (SiO_2, hexanes:ethyl acetate 9:1)=0.29, stains purple with Vanillin.

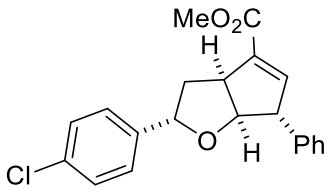
^{1}H NMR (300 MHz, $CDCl_3$) δ [ppm]= 7.38 – 7.33 (m, 4H), 7.33 – 7.29 (m, 3H), 7.29 – 7.27 (m, 1H), 7.16 – 7.11 (m, 2H), 6.93 (p, *J* = 1.3 Hz, 1H), 4.90 (dd, *J* = 10.5, 4.9 Hz, 1H), 4.82 (dd, *J* = 6.2, 1.3 Hz, 1H), 4.12 (t, *J* = 2.0 Hz, 1H), 3.90 (ddt, *J* = 8.1, 5.8, 1.8 Hz, 1H), 3.83 (s, 3H), 2.52 (ddd, *J* = 13.0, 5.0, 1.4 Hz, 1H), 2.12 – 1.98 (m, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) δ [ppm]= 165.03, 145.87, 141.10, 140.95, 136.55, 128.85, 128.42, 127.62, 127.47, 127.06, 126.01, 89.97, 79.66, 77.23, 59.91, 51.73, 50.09, 39.39.

IR (neat): 3060, 6027, 2948, 2863, 1715, 1629, 1495, 1450, 1361, 1334, 1290, 1264, 1200, 1163, 1103, 1059, 969, 902, 753, 701 cm^{-1}.

HR-MS (EI-MS): m/z calc for $C_{21}H_{20}O_3$ [M+] 320.14070, found 320.13978.

Methyl-2-(4-chlorophenyl)-6-phenyl-3,3a,6,6a-tetrahydro-2H-cyclopenta[b]furan-4-carboxylate 261g



The title compound was prepared according to GP C at 62 °C for 45 min using methyl-3-(4-chlorophenyl)-6-((E)-styryl)-2-oxabicyclo[3.1.0]hexane-6-carboxylate **250g** (177 mg, 0.5 mmol, 1 equiv.) and $Yb(OTf)_3$ (15.5 mg, 25 µmol, 0.05 equiv.) to yield methyl-2-(4-

chlorophenyl)-6-phenyl-3,3a,6,6a-tetrahydro-2H-cyclopenta[b]furan-4-carboxylate (118 mg, 332 µmol, 71%) als yellow oil.

R_f (SiO_2, hexanes:ethyl acetate 4:1)=0.44, stains brown with Vanillin.

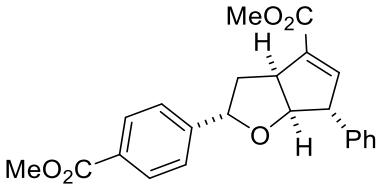
^{1}H NMR (300 MHz, $CDCl_3$) δ [ppm]= 7.37 – 7.29 (m, 6H), 7.27 (q, J = 1.4 Hz, 1H), 7.16 – 7.08 (m, 2H), 6.93 (p, J = 1.3 Hz, 1H), 4.92 – 4.78 (m, 2H), 4.10 (p, J = 1.6 Hz, 1H), 3.89 (ddt, J = 8.2, 5.8, 1.8 Hz, 1H), 3.82 (s, 3H), 2.58 – 2.45 (m, 1H), 2.08 – 1.89 (m, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) δ [ppm]= 164.95, 145.90, 140.78, 139.73, 136.37, 133.23, 128.88, 128.55, 127.44, 127.34, 127.13, 90.02, 78.99, 59.88, 51.75, 50.07, 39.45.

IR (neat): 3060, 3027, 2948, 2359, 1782, 1715, 1629, 1599, 1491, 1439, 1361, 1293, 1264, 1264, 1200, 1092, 1066, 969, 917, 828, 753, 701 cm^{-1}.

HR-MS (EI-MS): m/z calc. for $C_{21}H_{19}O_3Cl$ [M+] 354.10172, found 354.10087.

Methyl-2-(4-(methoxycarbonyl)phenyl)-6-phenyl-3,3a,6,6a-tetrahydro-2H-cyclopenta[b]furan-4-carboxylate 261h



The title compound was prepared according to GP C at 62 °C for 4.5 h using methyl -3-(4-(methoxycarbonyl)phenyl)-6-((E)-styryl)-2-oxabicyclo[3.1.0]hexane-6-carboxylate **250h** (189 mg, 0.5 mmol, 1 equiv.) and $Yb(OTf)_3$ (15.5 mg, 25 µmol, 0.05 equiv.) to yield methyl-2-(4-(methoxycarbonyl)phenyl)-6-phenyl-3,3a,6,6a-tetrahydro-2H-cyclopenta[b]furan-4-carboxylate (136 mg, 360 µmol, 72%) als yellow oil.

R_f (SiO_2, hexanes:ethyl acetate 4:1)= 0.38, stains purple in Vanillin.

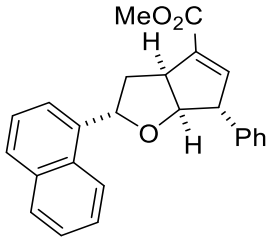
^{1}H NMR (300 MHz, $CDCl_3$) δ [ppm]= 8.04 – 7.98 (m, 2H), 7.46 – 7.39 (m, 2H), 7.37 – 7.27 (m, 3H), 7.17 – 7.10 (m, 2H), 6.97 – 6.91 (m, 1H), 4.94 (dd, *J* = 10.5, 5.0 Hz, 1H), 4.84 (dt, *J* = 6.2, 1.2 Hz, 1H), 4.12 (q, *J* = 2.0 Hz, 1H), 3.91 (s, 3H), 3.90 – 3.87 (m, 1H), 3.83 (s, 3H), 2.62 – 2.52 (m, 1H), 1.99 (ddd, *J* = 12.9, 10.5, 8.3 Hz, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) δ [ppm]= 166.97, 164.94, 146.62, 145.96, 140.71, 136.31, 129.77, 129.35, 128.90, 127.45, 127.16, 125.78, 90.17, 79.21, 59.87, 52.08, 51.78, 50.09, 39.50.

IR (neat): 3403, 3027, 2997, 2952, 1715, 1614, 1580, 1495, 1435, 1364, 1275, 1193, 1103, 1059, 1018, 165, 910, 857, 757, 701 cm^{-1}.

HR-MS (EI-MS): m/z calc. for $C_{23}H_{22}O_5$ [M+] 378.14618, found 378.14518.

Methyl-2-(naphthalen-1-yl)-6-phenyl-3,3a,6,6a-tetrahydro-2H-cyclopenta[b]furan-4-carboxylate 261f



The title compound was prepared according to GP C at 62 °C for 2.5 h using methyl-3-(naphthalen-1-yl)-6-((E)-styryl)-2-oxabicyclo[3.1.0]hexane-6-carboxylate **250f** (185 mg, 0.5 mmol, 1 equiv.) and $Yb(OTf)_3$ (15.5 mg, 25 µmol, 0.05 equiv.) to yield Methyl-2-(naphthalen-1-yl)-6-phenyl-3,3a,6,6a-tetrahydro-2H-cyclopenta[b]furan-4-carboxylate (169.2 mg, 457 µmol, 91%) als yellow oil.

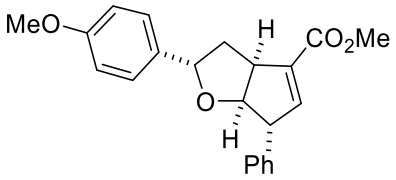
^{1}H NMR (300 MHz, $CDCl_3$) δ [ppm]= 8.06 – 7.92 (m, 1H), 7.92 – 7.82 (m, 1H), 7.81 – 7.75 (m, 1H), 7.72 – 7.63 (m, 1H), 7.56 – 7.42 (m, 3H), 7.41 – 7.27 (m, 3H), 7.24 – 7.13 (m, 2H), 7.04 – 6.96 (m, 1H), 5.66 (dd, *J* = 10.1, 5.2 Hz, 1H), 4.96 (dt, *J* = 6.2, 1.3 Hz, 1H), 4.24 (q, *J* = 1.9 Hz, 1H), 3.97 (tt, *J* = 6.4, 1.9 Hz, 1H), 3.86 (s, 3H), 2.78 (ddd, *J* = 13.0, 5.3, 1.6 Hz, 1H), 2.21 (ddd, *J* = 12.9, 10.1, 8.5 Hz, 1H).

^{13}C NMR (75 MHz, $CDCl_3$) δ [ppm]= 165.12, 145.94, 140.97, 136.96, 136.76, 133.77, 130.68, 128.92, 128.85, 128.00, 127.56, 127.15, 125.98, 125.56, 125.54, 123.42, 122.44, 89.88, 77.21, 59.91, 51.84, 50.16, 38.44.

IR (neat): 3056, 2948, 2251, 1711, 1629, 1599, 1491, 1439, 1394, 1361, 1290, 1260,1200, 1103, 1074, 910, 865, 779,730 cm^{-1}.

HR-MS (EI-MS): m/z calc. for $C_{25}H_{22}O_3$ [M+·] 370.15635, found 370.15546.

Methyl-2-(4-methoxyphenyl)-6-phenyl-3,3a,6,6a-tetrahydro-2*H*-cyclopenta[*b*]furan-4-carboxylate 261i



The title compound was prepared according to GP C at 62 °C for 1 h using methyl-3-(4-methoxyphenyl)-6-((E)-styryl)-2-oxabicyclo[3.1.0]hexane-6-carboxylate **250i** (105 mg, 0.301 mmol, 1 equiv.) and $Yb(OTf)_3$ (9.32 mg, 15.0 µmol, 0.05 equiv.) to yield methyl-2-(4-methoxyphenyl)-6-phenyl-3,3a,6,6a-tetrahydro-2H-cyclopenta[b]furan-4-carboxylate (32.1 mg, 91.6 µmol, 30%) als yellow oil.

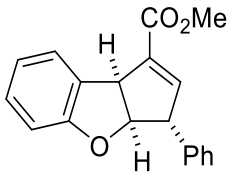
^{1}H NMR (400 MHz, $CDCl_3$) δ [ppm]= 7.34 – 7.27 (m, 5H), 7.17 – 7.10 (m, 2H), 6.92 (p, *J* = 1.2 Hz, 1H), 6.90 – 6.84 (m, 2H), 4.85 (dd, *J* = 10.5, 4.9 Hz, 1H), 4.79 (dd, *J* = 6.2, 1.3 Hz, 1H), 4.10 (p, *J* = 1.7 Hz, 1H), 3.92 – 3.86 (m, 1H), 3.82 (s, 3H), 3.80 (s, 3H), 2.51 – 2.42 (m, 1H), 2.03 (ddd, *J* = 12.8, 10.6, 8.4 Hz, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) δ [ppm]= 165.04, 159.19, 145.85, 141.02, 136.60, 132.95, 128.83, 127.46, 127.40, 127.04, 113.83, 89.79, 79.34, 59.93, 55.31, 51.72, 50.07, 39.22.

IR (neat): 3060, 3027, 3001, 2948, 2837, 1715,1614, 1513, 1439, 1361, 1290, 1245, 1200, 1178, cm^{-1}.

HR-MS (EI-MS): m/z calc. for $C_{22}H_{22}O_4$ [M] 350.15126, found 350.15101.

Methyl-3-phenyl-3a,8b-dihydro-3H-cyclopenta[b]benzofuran-1-carboxylate 261j

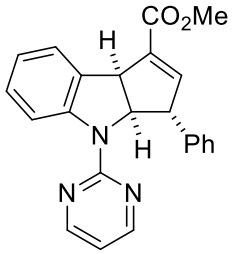


The title compound was prepared according to GP C at 125 °C for 45 min using methyl (E)-1-styryl-1a,6b-dihydro-1H-cyclopropa[b]benzofuran-1-carboxylate **250j** (146 mg, 0.5 mmol, 1 equiv.) and $Yb(OTf)_3$ (15.5 mg, 25 µmol, 0.05 equiv.) to yield methyl-3-

phenyl-3a,8b-dihydro-3H-cyclopenta[b]benzofuran-1-carboxylate (139 mg, 474 µmol, 95%) as yellow oil. Analytical data is in accordance with literature.[185]

^{1}H NMR (300 MHz, $CDCl_3$) δ [ppm]= 7.44 – 7.28 (m, 4H), 7.22 – 7.13 (m, 3H), 7.00 (dd, *J* = 2.6, 0.6 Hz, 1H), 6.97 – 6.85 (m, 2H), 6.21 (ddd, *J* = 8.2, 2.2, 0.6 Hz, 1H), 4.20 (q, *J* = 2.4 Hz, 1H), 4.16 – 4.07 (m, 1H), 3.87 (s, 3H).

Methyl-3-phenyl-4-(pyrimidin-2-yl)-3,3a,4,8b-tetrahydrocyclopenta[b]indole-1-carboxylate 261q



The title compound was prepared according to GP C at 62 °C for 1.5 h using methyl -2-(pyrimidin-2-yl)-1-((E)-styryl)-1,1a,2,6b-tetrahydrocyclopropa[b]indole-1-carboxylate **250q** (185 mg, 0.5 mmol, 1 equiv.) and $Yb(OTf)_3$ (15.5 mg, 25 µmol, 0.05 equiv.) to yield methyl-3-phenyl-4-(pyrimidin-2-yl)-3,3a,4,8b-tetrahydrocyclopenta[b]indole-1-carboxylate (159 mg, 430 µmol, 86%) als yellow solid.

R_f (SiO_2, hexanes:ethyl acetate 4:1) = 0.6, stains yellow in Ninhydrin.

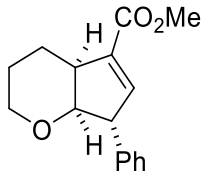
^{1}H NMR (300 MHz, $CDCl_3$) δ [ppm]= 8.59 – 8.40 (m, 3H), 7.66 (ddt, *J* = 7.5, 1.5, 0.6 Hz, 1H), 7.43 – 7.22 (m, 6H), 6.98 (td, *J* = 7.4, 1.1 Hz, 1H), 6.80 – 6.64 (m, 2H), 5.26 (ddd, *J* = 8.9, 2.2, 0.6 Hz, 1H), 5.01 (d, *J* = 8.9 Hz, 1H), 4.22 (q, *J* = 2.3 Hz, 1H), 3.83 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ [ppm]= 165.09, 159.00, 157.30, 145.49, 143.04, 142.25, 136.77, 131.41, 128.43, 128.16, 128.11, 126.94, 125.91, 121.83, 115.28, 112.16, 72.68, 59.99, 51.69, 50.49.

IR (neat): 3027, 2956, 2889, 2117, 1949, 1715, 1633, 1580, 1554, 1484, 1439, 1346, 1260, 1238, 1185, 1092, 1021, 988, 913, 783, 753, 701 cm^{-1}.

HR-MS (EI-MS): m/z calc. for $C_{23}H_{19}N_3O_2$ [M+] 369.148, found 370.1553.

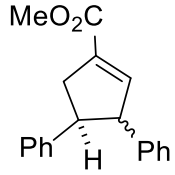
Methyl-7-phenyl-2,3,4,4a,7,7a-hexahydrocyclopenta[b]pyran-5-carboxylate 261k



The title compound was prepared according to GP C at 62 °C for 60 min using methyl-7-((E)-styryl)-2-oxabicyclo[4.1.0]heptane-7-carboxylate **250k** (178 mg, 0.59 mmol, 1 equiv.) and $Yb(OTf)_3$ (18.1 mg, 29.3 µmol, 0.05 equiv.) to yield methyl-7-phenyl-2,3,4,4a,7,7a-hexahydrocyclopenta[b]pyran-5-carboxylate (127 mg, 490 µmol, 84%) as yellow oil. Analytical data is in accordance with literature.[42]

^{1}H NMR (300 MHz, $CDCl_3$) δ [ppm]= 7.38 – 7.13 (m, 5H), 6.90 – 6.82 (m, 1H), 4.16 – 4.07 (m, 2H), 3.85 – 3.79 (m, 1H), 3.79 (s, 3H), 3.72 – 3.64 (m, 1H), 3.05 – 2.92 (m, 1H), 2.20 – 1.99 (m, 1H), 1.81 – 1.69 (m, 1H), 1.67 – 1.47 (m, 2H).

Methyl-3,4-diphenylcyclopent-1-ene-1-carboxylate 261m



The title compound was prepared according to GP C at 180 °C for 60 min using methyl-2-phenyl-1-((E)-styryl)cyclopropane-1-carboxylate **250m** (55.7 mg, 0.2 mmol, 1 equiv.) and $Yb(OTf)_3$ (6.20 mg, 10.0 µmol, 0.05 equiv.) to yield methyl-3,4-diphenylcyclopent-1-ene-1-carboxylate (47.7 mg, 171 µmol, 86%) as a mixture of 2 diastereomers (1:4) as a yellow oil.

Major: ^{1}H NMR (400 MHz, $CDCl_3$) δ [ppm]= 7.34 – 7.00 (m, 10H), 6.83 (td, *J* = 2.3, 1.5 Hz, 1H), 4.10 (dq, *J* = 7.7, 2.6 Hz, 1H), 3.82 (s, 3H), 3.44 (q, *J* = 8.2 Hz, 1H), 3.22 (dddd, *J* = 16.5, 8.9, 2.5, 1.5 Hz, 1H), 2.89 (ddt, *J* = 16.6, 8.0, 2.6 Hz, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) δ [ppm]= 165.51, 144.78, 144.10, 142.87, 135.90, 128.65, 128.60, 127.45, 127.32, 126.86, 126.57, 60.56, 54.48, 51.69, 40.02.

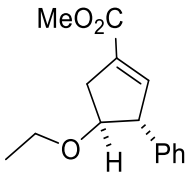
Minor: ^{1}H NMR (400 MHz, $CDCl_3$) δ [ppm]= 7.33 – 7.00 (m, 8H), 6.97 – 6.93 (m, 1H), 6.86 (dd, *J* = 7.5, 2.1 Hz, 2H), 6.81 – 6.77 (m, 2H), 4.33 (dq, *J* = 8.7, 2.1 Hz, 1H), 4.00 (q, *J* = 8.5 Hz, 1H), 3.85 (s, 3H), 3.04 (ddt, *J* = 8.4, 4.9, 1.8 Hz, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) δ [ppm]= 165.64, 144.80, 140.47, 138.47, 137.35, 128.71, 128.36, 127.92, 127.67, 126.52, 126.06, 56.69, 51.74, 49.83, 36.31.

IR (neat): 3373, 3060, 3027, 2952, 2855, 1715, 1633, 1495, 1439, 1249, 1193, 1096, 910, 865, 757 cm^{-1}.

HR-MS (EI-MS): m/z calc. for $C_{19}H_{18}O_2$ 278.131013, found 278.12994.

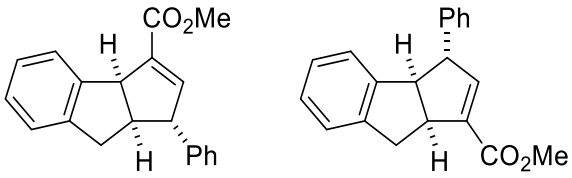
Methyl-4-ethoxy-3-phenylcyclopent-1-ene-1-carboxylate 261n



The title compound was prepared according to GP C at 62 °C for 2 h using methyl-2-ethoxy-1-((E)-styryl)cyclopropane-1-carboxylate **250n** (123 mg, 0.5 mmol, 1 equiv.) and $Yb(OTf)_3$ (15.5 mg, 25.0 µmol, 0.05 equiv.) and purified by column chromatography (hexanes/ethyl acetate 9:1-> 4:1) to yield methyl-4-ethoxy-3-phenylcyclopent-1-ene-1-carboxylate (49.8 mg, 202 µmol, 40%) as a yellow oil. Analytical data is in accordance with literature. [42]

^{1}H NMR (300 MHz, $CDCl_3$) δ [ppm]= 7.37 – 7.27 (m, 3H), 7.23 – 7.08 (m, 2H), 6.74 (q, *J* = 2.1 Hz, 1H), 4.06 – 3.99 (m, 2H), 3.77 (s, 3H), 3.03 (ddt, *J* = 16.9, 6.9, 2.0 Hz, 1H), 2.66 (ddt, *J* = 16.9, 3.9, 1.9 Hz, 1H).

Methyl-1-phenyl-1,3a,8,8a-tetrahydrocyclopenta[a]indene-3-carboxylate and methyl-3-phenyl-3,3a,8,8a-tetrahydrocyclopenta[a]indene-1-carboxylate 261l



The title compound was prepared according to GP C at 125 °C for 1.5 h using methyl-2-ethoxy-1-((E)-styryl)cyclopropane-1-carboxylate **250l** (123 mg, 0.5 mmol, 1 equiv.) and $Yb(OTf)_3$ (15.5 mg, 25.0 µmol, 0.05 equiv.) and purified by column chromatography (hexanes/ethyl acetate 9:1-> 4:1) to yield methyl-4-ethoxy-3-phenylcyclopent-1-ene-1-carboxylate (49.8 mg, 202 µmol, 40%) as a yellow oil.

major: **^{1}H-NMR** (300 MHz, CDCl3) δ [ppm]= [ppm]= 7.42 – 7.15 (m, 9H), 6.72 – 6.69 (m, 1H), 4.14 – 4.02 (m, 2H), 3.98 – 3.92 (m, 1H), 3.79 (s, 3H), 3.42 – 3.26 (m, 1H), 3.22 – 3.09 (m, 1H).

minor: **^{1}H-NMR** (300 MHz, CDCl3) δ [ppm]= 7.42 – 7.14 (m, 3H), 7.11 (d, J = 7.5 Hz, 1H), 7.00 (tt, J = 7.5, 1.0 Hz, 1H), 6.93 – 6.87 (m, 2H), 6.73 (t, J = 2.1 Hz, 1H), 6.67 (dd, J = 7.4, 1.1 Hz, 1H), 5.92 (d, J = 7.7 Hz, 1H), 4.56 (dt, J = 9.5, 2.3 Hz, 1H), 4.34 (t, J = 8.9 Hz, 1H), 3.94 – 3.92 (m, 1H), 3.81 (s, 3H), 3.44 – 3.27 (m, 1H), 3.21 – 3.10 (m, 1H).

major: **^{13}C-NMR** (101 MHz, CDCl3) δ [ppm]= 165.64, 145.90, 145.08, 143.70, 142.18, 138.85, 129.07, 127.52, 127.45, 127.03, 126.93, 125.32, 124.41, 59.95, 58.21, 51.68, 48.31, 37.22.

minor: **^{13}C-NMR** (101 MHz, CDCl3) δ [ppm]= 165.70, 145.21, 142.91, 141.73, 139.88, 139.66, 129.46, 128.06, 126.93, 126.86, 126.64, 125.34, 124.36, 55.42, 53.42, 51.68, 48.38, 37.76.

IR (neat)= 3403, 3027, 2952, 2922, 1711, 1629, 1603, 1491, 1439, 1353, 1286, 1256, 1096, 1025, 999, 921, 801, 749, 697 cm^{-1}.

minor: **HR-MS** (EI-MS): m/z calc for $C20H_{18}O_2$ [M+] 290.13013, found 290.12995.

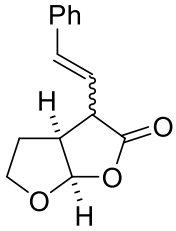
major: **HR-MS** (EI-MS): m/z calc for $C_{20}H_{18}O_2$ [M+] 290.13013, found 290.13051.

5.6 Synthesis of lactones

General Procedure D (GP D) for the synthesis of lactones

A 5 mL Schlenk pressure tube was charged with the corresponding cyclopropane (500 µmol, 1.0 equiv.) and dissolved in 2.5 mL of a freshly prepared 5% (vol./vol.) solution of methanesulfonic acid in acetone or charged with *p*-toluenesulfonic acid (344 mg, 4.0 equiv.) and dissolved in 2.5 mL acetone. The pressure tube was sealed with a Teflon sealed cap and heated to 60 °C for the specified time. The solvent was evaporated *in vacuo* and the crude product was purified by column chromatography.

3-Styryltetrahydrofuro[2,3-b]furan-2(3H)-one 272a



The title compound was prepared according to **GP C** for 60 minutes using ethyl (E)-6-styryl-2-oxabicyclo[3.1.0]hexane-6-carboxylate **250a** (264.5 mg, 1.1 mmol, 1 equiv.) and purified by column chromatography (hexanes:ethyl acetate 3% to 20%) to yield 3-styryltetrahydrofuro[2,3-b]furan-2(3H)-one (168.8 mg, 733 µmol, 68%) as a mixture of 2 diastereomers as a yellow oil.

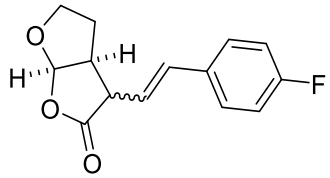
^{1}H-NMR (400 MHz, $CDCl_3$) δ [ppm]= 7.36 – 7.10 (m, 10H), 6.61 – 6.46 (m, 2H), 6.14 – 6.05 (m, 2H), 6.01 (d, *J* = 5.3 Hz, 1H), 5.97 (d, *J* = 4.8 Hz, 1H), 4.09 – 3.87 (m, 4H), 3.27 – 3.22 (m, 2H), 3.21 – 3.15 (m, 1H), 3.06 – 2.98 (m, 1H), 2.26 – 2.12 (m, 1H), 2.06 – 1.87 (m, 2H), 1.87 – 1.79 (m, 1H).

^{13}C-NMR (101 MHz, $CDCl_3$) δ [ppm]= 175.43, 174.33, 136.16, 135.93, 133.60, 128.70, 128.67, 128.20, 126.50, 126.48, 123.67, 121.08, 107.04, 106.65, 68.83, 67.76, 49.88, 46.97, 45.58, 44.69, 31.45, 25.99.

IR (neat)= 3448, 3027, 2982, 2885, 2359, 2087, 1890, 1767, 1495, 1450, 1357, 1319, 1271, 1170, 1085, 1040, 965, 936, 749, 963 cm^{-1}

HRMS (EI-MS): m/z calc. for $C_{14}H_{14}O_3$ [MH+] 231.1016, found 231.1018.

3-(4-Fluorostyryl)tetrahydrofuro[2,3-b]furan-2(3H)-one 272b



The title compound was prepared according to **GP D** for 60 minutes using methyl-6-((E)-4-fluorostyryl)-2-oxabicyclo[3.1.0]hexane-6-carboxylate (153.6 mg, 585 µmol, 1 equiv.) and purified by column chromatography (hexanes:ethyl acetate 3% to 25%) to yield 3-(4-fluorostyryl)tetrahydrofuro[2,3-b]furan-2(3H)-one (132 mg, 533 µmol, 91%) as a mixture of 2 diastereomers as a yellow oil.

^{1}H-NMR (400 MHz, $CDCl_3$) δ[ppm]= 7.39 – 7.29 (m, 4H), 7.01 (td, *J* = 8.7, 2.2 Hz, 4H), 6.61 (ddd, *J* = 20.9, 16.3, 1.4 Hz, 2H), 6.16 – 6.04 (m, 4H), 4.19 – 3.97 (m, 5H), 3.36 – 3.24 (m, 2H), 3.15 – 3.06 (m, 1H), 2.35 – 2.24 (m, 1H), 2.17 – 2.06 (m, 1H), 2.02 – 1.89 (m, 2H).

^{13}C-NMR (101 MHz, CDCl3) δ [ppm]=175.41, 174.32, 163.86, 161.40, 134.77, 132.47, 128.12, 128.10, 128.05, 128.02, 123.45, 123.43, 120.82, 120.80, 115.76, 115.73, 115.55, 115.51, 107.05, 106.68, 68.83, 67.75, 49.81, 46.95, 45.57, 44.66, 31.45, 25.95.

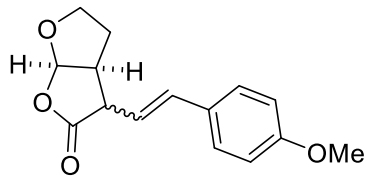
^{19}F-NMR (377 MHz, $CDCl_3$) δ[ppm]= -113.95 (ddt, *J* = 14.2, 11.0, 5.5 Hz).

^{19}F-NMR {^{1}H} (377 MHz, $CDCl_3$) δ[ppm]= -113.95, -113.99.

IR (neat)= 3373, 2960, 1771, 1674, 1603, 1510, 1361, 1323, 1226, 1178, 1096, 969, 839, 723 cm^{-1}

HRMS (EI-MS): m/z calc. for $C_{14}H_{13}FO_3$ [MH+] 249.0921, found 249.092.

3-(4-Methoxystyryl)tetrahydrofuro[2,3-*b*]furan-2(3*H*)-one 272c



The title compound was prepared according to **GP D** for 60 minutes using methyl-6-((E)-4-methoxystyryl)-2-oxabicyclo[3.1.0]hexane-6-carboxylate **250c** (138.2 mg, 504 µmol, 1 equiv.) and *para*-toluenesulfonic acid (383 mg, 2.02 mmol, 4 equiv.) and purified by

column chromatography (hexanes:ethyl acetate 0% to 100%) to yield 3-(4-methoxystyryl)tetrahydrofuro[2,3-b]furan-2(3*H*)-one (3.2 mg. 0.012 mmol, 2%) as a mixture of 2 diastereomers as a yellow oil.

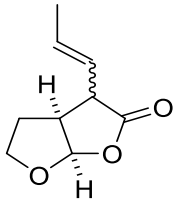
^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.39 – 7.21 (m, 4H), 6.86 (dd, *J*=8.9, 2.3, 4H), 6.58 (td, *J*=16.6, 1.4, 2H), 6.11 (d, *J*=5.4, 1H), 6.08 – 5.99 (m, 2H), 4.19 – 3.96 (m, 4H), 3.81 (s, 3H), 3.80 (s, 3H), 3.72 (ddd, *J*=8.7, 7.2, 1.4, 1H), 3.55 (d, *J*=7.7, 1H), 3.31 (ddd, *J*=7.2, 4.6, 1.5, 1H), 3.14 – 3.06 (m, 1H), 2.28 (dddd, *J*=12.9, 10.2, 8.8, 8.0, 2H), 2.15 – 1.98 (m, 1H), 1.96 – 1.88 (m, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) δ [ppm]= 175.67, 174.58, 159.64, 141.00, 135.39, 133.02, 129.37, 128.96, 128.70, 127.72, 127.71, 121.40, 118.71, 114.09, 114.06, 107.03, 106.60, 68.80, 67.75, 55.32, 49.92, 47.01, 45.69, 44.75, 31.43, 25.98.

IR (neat): 2960, 1767, 1607, 1577, 1513, 1461, 1357, 1297, 1245, 1174, 1111, 1085, 1029, 965, 936, 835, 760, 731, 671

HR-MS (EI-MS) m/z calc. for $C_{15}H_{16}O_4$ 260.10431, found 260.10425.

3-(Prop-1-en-1-yl)tetrahydrofuro[2,3-b]furan-2(3H)-one 272d



The title compound was prepared according to **GP D** for 60 minutes using methyl-6-((E)-prop-1-en-1-yl)-2-oxabicyclo[3.1.0]hexane-6-carboxylate **250d** (91.1 mg, 500 µmol, 1 equiv.) and purified by column chromatography (hexanes:ethyl acetate 3% to 40%) to yield 3-(Prop-1-en-1-yl)tetrahydrofuro[2,3-b]furan-(2(3H)-one (73.9 mg, 439 µmol, 88%) as a mixture of 2 diastereomers as a yellow oil.

^{1}H-NMR (300 MHz, $CDCl_3$) δ[ppm]= 6.04 (d, *J* = 5.4 Hz, 1H), 6.00 (d, *J* = 4.9 Hz, 1H), 5.86 – 5.66 (m, 2H), 5.48 (dp, *J* = 6.1, 1.6 Hz, 1H), 5.43 (ddt, *J* = 7.7, 3.0, 1.6 Hz, 1H), 4.16 – 4.03 (m, 2H), 4.02 – 3.91 (m, 2H), 3.52 (ddt, *J* = 8.6, 7.6, 1.0 Hz, 1H), 3.18 (ddd, *J* = 11.0, 5.8, 3.3 Hz, 1H), 3.11 (dddt, *J* = 7.1, 4.7, 2.4, 1.2 Hz, 1H), 2.97 (dtd, *J* = 8.5, 5.0, 2.6 Hz,

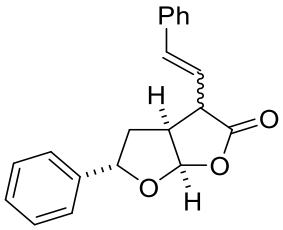
1H), 2.22 (dddd, *J* = 12.9, 10.3, 8.8, 8.1 Hz, 1H), 2.10 – 1.91 (m, 1H), 1.85 (ddt, *J* = 12.9, 5.5, 2.6 Hz, 2H), 1.80 – 1.76 (m, 3H), 1.74 (dt, *J* = 6.4, 1.3 Hz, 3H).

^{13}C-NMR (101 MHz, $CDCl_3$) δ[ppm]= 176.05, 175.02, 132.79, 129.99, 125.41, 122.61, 106.92, 106.52, 68.70, 67.68, 49.80, 46.88, 45.59, 44.54, 31.34, 25.85, 18.23, 17.93.

IR (neat)= 2967, 2885, 2356, 2132, 1767, 1681, 1454, 1361, 1297, 1260, 1178, 1085, 1044, 969, 936, 857, 798, 667 cm^{-1}.

HRMS (EI-MS): m/z calc. for $C_9H_{12}O_3$ [MH+] 169.0859, found 169.0856.

5-Phenyl-3-styryltetrahydrofuro[2,3-*b*]furan-2(3*H*)-one 272e



The title compound was prepared according to **GP D** for 60 minutes using methyl 3-phenyl-6-((E)-styryl)-2-oxabicyclo[3.1.0]hexane-6-carboxylate **250e** (128.2 mg, 400 µmol, 1 equiv.) and purified by column chromatography (hexanes:ethyl acetate 3% to 20%) to yield 5-phenyl-3-styryltetrahydrofuro[2,3-b]furan-2(3H)-one (81.2 mg, 265 µmol, 66%) as a yellow oil.

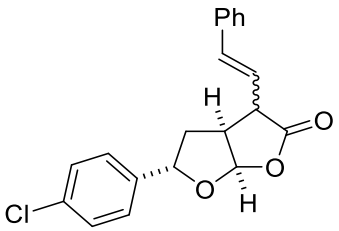
^{1}H-NMR (400 MHz, $CDCl_3$) δ[ppm]= 7.33 – 7.13 (m, 10H), 6.55 (dd, *J* = 15.9, 1.4 Hz, 1H), 6.20 (d, *J* = 5.5 Hz, 1H), 6.11 (dd, *J* = 15.9, 7.1 Hz, 1H), 5.14 (dd, *J* = 10.3, 5.4 Hz, 1H), 3.36 (ddd, *J* = 6.9, 5.1, 1.5 Hz, 1H), 3.22 – 3.14 (m, 1H), 2.23 (ddd, *J* = 13.1, 5.4, 2.0 Hz, 1H), 2.11 (ddd, *J* = 13.1, 10.3, 8.6 Hz, 1H).

^{13}C-NMR (101 MHz, $CDCl_3$) δ[ppm]= 175.56, 138.99, 135.92, 133.77, 128.71, 128.67, 128.35, 128.24, 126.52, 125.94, 123.67, 106.63, 80.57, 49.88, 46.12, 40.24.

IR (neat)= 2926, 2855, 1774, 1614, 1513, 1461, 1375, 1327, 1301, 1245, 1174, 1096, 1036, 969,902, 828, 779, 667 cm^{-1}.

HRMS (EI-MS): m/z calc. for $C_{20}H_{18}O_3$ [M+] 306.12466, found 306.12505.

5-(4-Chlorophenyl)-3-styryltetrahydrofuro[2,3-b]furan-2(3H)-one 272g



The title compound was prepared according to **GP D** for 2.5 h using methyl-3-(4-chlorophenyl)-6-((E)-styryl)-2-oxabicyclo[3.1.0]hexane-6-carboxylate **250g** (177 mg, 500 µmol, 1 equiv.) and *p*-toluenesulfonic acid (344 mg, 2.0 mmol, 4 equiv.) and purified by column chromatography (hexanes:ethyl acetate 0% to 15%) to yield 5-(4-chlorophenyl)-3-styryltetrahydrofuro[2,3-b]furan-2(3H)-one (114.7 mg, 337 µmol, 67%) as a yellow oil.

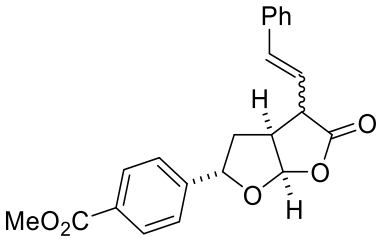
^{1}H-NMR (300 MHz, $CDCl_3$) δ [ppm]= 7.44 – 7.24 (m, 9H), 6.65 (dd, *J* = 15.9, 1.4 Hz, 1H), 6.32 – 6.16 (m, 2H), 5.22 (dd, *J* = 10.3, 5.3 Hz, 1H), 3.46 (ddd, *J* = 7.1, 5.2, 1.5 Hz, 1H), 3.29 (dtd, *J* = 8.7, 5.3, 1.9 Hz, 1H), 2.37 – 2.25 (m, 1H), 2.21 – 2.09 (m, 1H).

^{13}C-NMR (101 MHz, $CDCl_3$) δ [ppm]= 175.41, 137.55, 135.85, 134.10, 133.87, 128.86, 128.73, 128.29, 127.28, 126.52, 123.49, 106.49, 79.83, 49.79, 46.09, 40.29.

IR (neat)=2403, 3027, 2983, 2255, 21820, 1897, 1771, 1655, 1599, 1491, 1409, 1368, 1331, 1211, 1170, 1088, 969, 906, 820, 731 cm^{-1}.

HRMS (EI-MS): m/z calc. for $C_{20}H_{17}ClO_3$ [MH+] 341.0939, found 341.093.

Methyl 4-(5-oxo-4-styrylhexahydrofuro[2,3-b]furan-2-yl)benzoate 272h



The title compound was prepared according to **GP D** for 45 minutes using methyl-3-(4-(methoxycarbonyl)phenyl)-6-((E)-styryl)-2-oxabicyclo[3.1.0]hexane-6-carboxylate **250h** (189.2 mg, 500 µmol, 1 equiv.) and *p*-toluenesulfonic acid (344 mg, 2.0 mmol,

4.0 equiv.) and purified by column chromatography (hexanes:ethyl acetate 0% to 20%) to yield methyl 4-(5-oxo-4-styrylhexahydrofuro[2,3-b]furan-2-yl)benzoate (64.9 mg, 178 µmol, 36%) as a yellow oil.

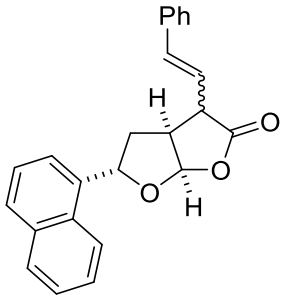
^{1}H-NMR (400 MHz, $CDCl_3$) δ[ppm]= 8.09 – 8.00 (m, 4H), 7.49 – 7.24 (m, 14H), 6.67 (ddd, *J* = 15.9, 11.4, 1.4 Hz, 2H), 6.32 (t, *J* = 5.2 Hz, 2H), 6.23 (ddd, *J* = 15.9, 10.2, 7.2 Hz, 2H), 5.34 – 5.25 (m, 2H), 3.92 (d, *J* = 4.0 Hz, 6H), 3.47 (ddd, *J* = 6.8, 5.1, 1.6 Hz, 2H), 3.34 – 3.27 (m, 2H), 2.49 (ddd, *J* = 13.5, 7.1, 4.9 Hz, 1H), 2.39 (ddd, *J* = 13.1, 5.5, 1.9 Hz, 1H), 2.18 (ddd, *J* = 13.1, 10.4, 8.6 Hz, 1H), 2.02 (ddd, *J* = 13.5, 10.0, 8.0 Hz, 1H).

^{13}C-NMR (101 MHz, $CDCl_3$) δ[ppm]= 175.31, 174.33, 166.69, 145.01, 144.19, 136.21, 136.03, 135.83, 133.91, 130.07, 129.98, 129.94, 129.90, 129.01, 128.72, 128.39, 128.32, 128.30, 126.52, 126.49, 125.82, 125.69, 125.51, 123.42, 120.74, 106.55, 106.41, 80.51, 79.99, 52.21, 49.78, 46.54, 46.07, 44.32, 40.25, 34.47.

IR (neat)= 3347, 2963, 2359, 2128, 1774, 1718, 1636, 1490, 1435, 1259, 1178, 1096, 1021, 798 cm^{-1}.

HRMS (EI-MS): m/z calc. for $C_{22}H_{20}O_5$ [M+H+], 365.1384 found 365.1384.

5-(Naphthalen-1-yl)-3-styryltetrahydrofuro[2,3-b]furan-2(3H)-one 272f



The title compound was prepared according to **GP D** for 60 minutes using methyl-3-(naphthalen-1-yl)-6-((E)-styryl)-2-oxabicyclo[3.1.0]hexane-6-carboxylate **250f** (185.2 mg, 500 µmol, 1 equiv.) and *p*-toluenesulfonic acid (344 mg, 2.0 mmol, 4 equiv.) and purified by column chromatography (hexanes:ethyl acetate 0% to 15%) to yield 5-(naphthalen-1-yl)-3-styryltetrahydrofuro[2,3-b]furan-2(3H)-one (118.8 mg, 333 µmol, 67%) as a yellow oil. X-Ray suitable crystals were obtained by vapor diffusion from ethyl acetate/hexane.

Diastereomer 1:

^{1}H-NMR (400 MHz, $CDCl_3$) δ [ppm]= 7.87 – 7.81 (m, 1H), 7.78 – 7.75 (m, 1H), 7.72 – 7.68 (m, 1H), 7.54 – 7.49 (m, 1H), 7.46 – 7.31 (m, 4H), 7.25 – 7.11 (m, 4H), 6.56 (dd, *J* = 15.9, 1.5 Hz, 1H), 6.30 (d, *J* = 5.5 Hz, 1H), 6.12 (dd, *J* = 15.9, 7.0 Hz, 1H), 5.85 (dd, *J* = 9.7, 5.6 Hz, 1H), 3.46 (ddd, *J* = 7.0, 4.5, 1.5 Hz, 1H), 3.23 – 3.16 (m, 1H), 2.41 (ddd, *J* = 13.1, 5.7, 2.6 Hz, 1H), 2.23 (ddd, *J* = 13.1, 9.7, 8.8 Hz, 1H).

^{13}C-NMR (101 MHz, $CDCl_3$) δ [ppm]= 175.57, 135.91, 134.74, 133.75, 130.35, 128.98, 128.73, 128.27, 126.55, 126.47, 125.89, 125.44, 123.61, 123.02, 122.41, 106.72, 78.10, 50.36, 46.03, 38.92.

Diastereomer 2:

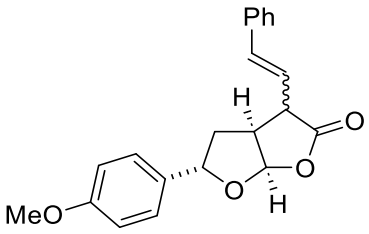
^{1}H-NMR (400 MHz, $CDCl_3$) δ [ppm]= 7.76 – 7.63 (m, 3H), 7.45 (d, *J* = 7.1 Hz, 1H), 7.38 – 7.31 (m, 3H), 7.30 – 7.27 (m, 1H), 7.23 – 7.11 (m, 4H), 6.55 (dd, *J* = 16.1, 1.4 Hz, 1H), 6.27 (d, *J* = 4.9 Hz, 1H), 6.16 (dd, *J* = 16.1, 6.9 Hz, 1H), 5.85 (t, *J* = 7.0 Hz, 1H), 3.69 (ddd, *J* = 8.6, 6.8, 1.5 Hz, 1H), 3.32 (tt, *J* = 9.1, 5.5 Hz, 1H), 2.48 (ddd, *J* = 13.2, 7.2, 5.9 Hz, 1H), 2.10 – 1.99 (m, 1H).

^{13}C-NMR (101 MHz, $CDCl_3$) δ [ppm]= 174.55, 136.11, 135.84, 135.71, 133.73, 128.95, 128.74, 128.72, 128.48, 128.27, 126.50, 126.44, 125.85, 125.34, 122.92, 121.87, 120.98, 106.61, 79.17, 46.76, 44.25, 33.84.

IR (neat)=3053, 2971, 2371, 2251, 2110, 1882, 1771, 1655, 1599, 1513, 1450, 1372, 1334, 1208, 1170, 1107, 1070, 969, 902, 783, 731 cm^{-1}.

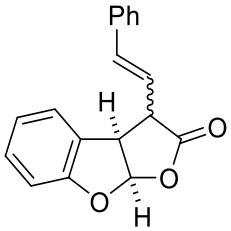
HRMS (EI-MS): m/z calc. for $C_{24}H_{20}O_3$ [M+] 356.43969, found 356.14070.

5-(4-Methoxyphenyl)-3-styryltetrahydrofuro[2,3-b]furan-2(3H)-one 272i



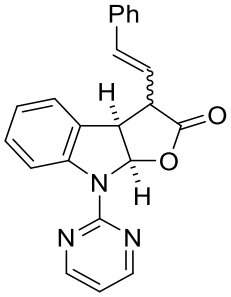
Preparing the title compound according to **GP D** for 60 minutes using methyl-3-(4-methoxyphenyl)-6-((E)-styryl)-2-oxabicyclo[3.1.0]hexane-6-carboxylate **250i** (175.1 mg, 500 µmol, 1 equiv.) failed to yield the compound.

3-Styryl-3a,8a-dihydrofuro[2,3-b]benzofuran-2(3H)-one 272j



Preparing the title compound according to **GP D** for 120 minutes at 60 °C and further 60 minutes at 120 °C using methyl-1-((E)-styryl)-1a,6b-dihydro-1H-cyclopropa[b]benzofuran-1-carboxylate **250j** (145.8 mg, 500 µmol, 1 equiv.) failed to yield the compound.

8-(Pyrimidin-2-yl)-3-styryl-3,3a,8,8a-tetrahydro-2H-furo[2,3-b]indol-2-one 272q

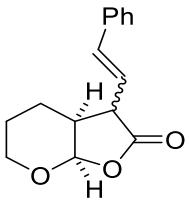


Preparing the title compound according to **GP D** for 60 minutes using methyl-2-(pyrimidin-2-yl)-1-((E)-styryl)-1,1a,2,6b-tetrahydrocyclopropa[b]indole-1-carboxylate (184.7 mg, 500 µmol, 1 equiv.) **250q** failed to yield the compound. Instead, methyl (E)-

4-phenyl-2-(1-(pyrimidin-2-yl)-1H-indol-3-yl)but-3-enoate (100.7 mg, 273 mmol, 55%) was formed. Analytical data is in accordance with literature.[191]

^{1}H NMR (400 MHz, $CDCl_3$) δ [ppm]= = 8.82 (dt, *J*=8.4, 0.9, 1H), 8.69 (d, *J*=4.8, 2H), 8.31 (d, *J*=0.9, 1H), 7.67 (ddd, *J*=7.8, 1.3, 0.7, 1H), 7.44 – 7.27 (m, 6H), 7.25 – 7.21 (m, 1H), 7.04 (t, *J*=4.8, 1H), 6.74 – 6.60 (m, 2H), 4.84 – 4.77 (m, 1H), 3.77 (s, 3H).

3-Styryltetrahydro-4H-furo[2,3-b]pyran-2(3H)-one 272k



The title compound was prepared according to **GP D** for 20 minutes using methyl-7-((E)-styryl)-2-oxabicyclo[4.1.0]heptane-7-carboxylate **250k** (129 mg, 500 µmol, 1 equiv.) and *p*-toluenesulfonic acid (344 mg, 2.0 mmol, 4.0 equiv.) and purified by column chromatography (hexanes:ethyl acetate 9:1 to 4:1) to yield 3-styryltetrahydro-4H-furo[2,3-b]pyran-2(3H)-one (58.8 mg, 241 µmol, 48%) as a mixture of diastereomers as a yellow oil.

Minor: ^{1}H-NMR (300 MHz, $CDCl_3$) δ [ppm] 7.43 – 7.12 (m, 5H), 6.65 (dd, *J* = 16.1, 1.2 Hz, 1H), 6.18 (dd, *J* = 16.1, 7.7 Hz, 1H), 5.76 (d, *J* = 3.9 Hz, 1H), 3.90 – 3.71 (m, 2H), 3.60 (ddd, *J* = 7.7, 6.5, 1.2 Hz, 1H), 2.70 – 2.55 (m, 1H), 2.01 – 1.86 (m, 1H), 1.77 – 1.60 (m, 2H), 1.53 – 1.33 (m, 1H).

^{13}C-NMR (75 MHz, $CDCl_3$) δ[ppm] 174.35, 136.29, 136.27, 128.64, 128.10, 126.47, 119.64, 99.97, 61.99, 50.08, 39.10, 22.55, 21.21.

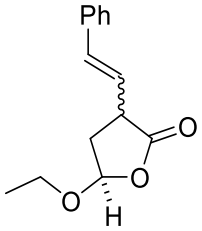
Major: ^{1}H-NMR (300 MHz, $CDCl_3$) δ[ppm] 7.41 – 7.24 (m, 5H), 6.58 (dd, *J* = 15.9, 1.2 Hz, 1H), 6.08 (dd, *J* = 15.9, 7.7 Hz, 1H), 5.58 (d, *J* = 4.0 Hz, 1H), 3.95 (dtd, *J* = 9.9, 4.3, 1.4 Hz, 1H), 3.60 (ddd, *J* = 11.8, 9.2, 2.8 Hz, 1H), 3.41 (ddd, *J* = 8.9, 7.5, 1.2 Hz, 1H), 2.41 (ddt, *J* = 8.7, 5.6, 4.3 Hz, 1H), 2.02 – 1.65 (m, 3H), 1.65 – 1.53 (m, 1H).

^{13}C-NMR (75 MHz, $CDCl_3$) δ[ppm] 175.92, 136.09, 135.04, 128.67, 128.13, 126.49, 122.44, 99.19, 64.08, 45.94, 40.39, 22.38, 20.19.

IR (neat): 2948, 2870, 1785, 1491, 1443, 1379, 1279, 1234, 11780, 1088, 1036, 988, 906, 824, 753, 701 cm^{-1}.

HRMS (EI-MS): m/z calc. for $C_{15}H_{16}O_3$ 244.10940, found 244.10913.

5-Ethoxy-3-styryldihydrofuran-2(3*H*)-one 272n



The title compound was prepared according to **GP D** for 45 minutes using methyl-2-ethoxy-1-((E)-styryl)cyclopropane-1-carboxylate **250n** (123 mg, 500 µmol, 1 equiv.) and *p*-toluenesulfonic acid (344 mg, 2.0 mmol, 4.0 equiv.) and purified by column chromatography (hexanes:ethyl acetate 9:1 to 4:1) to yield 5-ethoxy-3-styryldihydrofuran-2(3*H*)-one (34.2 mg, 147 µmol, 29%) as a mixture of diastereomers as a yellow oil.

Diastereomer 1:

^{1}H-NMR (300 MHz, $CDCl_3$) δ [ppm]= 7.42 – 7.21 (m, 5H), 6.55 (dd, *J* = 16.0, 1.5 Hz, 1H), 6.22 (dd, *J* = 15.9, 6.7 Hz, 1H), 5.54 (dd, *J* = 5.5, 1.0 Hz, 1H), 3.89 (dq, *J* = 9.5, 7.1 Hz, 1H), 3.75 – 3.54 (m, 2H), 2.49 (ddd, *J* = 13.2, 8.6, 1.0 Hz, 1H), 2.35 (ddd, *J* = 13.2, 10.8, 5.5 Hz, 1H), 1.25 (t, *J* = 7.1 Hz, 3H).

^{13}C-NMR (101 MHz, $CDCl_3$) δ [ppm]= 177.01, 136.42, 133.79, 128.74, 128.07, 126.56, 124.11, 102.08, 65.27, 41.49, 35.92, 15.09.

Diastereomer 2:

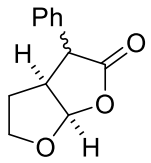
^{1}H-NMR (300 MHz, $CDCl_3$) δ [ppm]= 7.43 – 7.19 (m, 5H), 6.56 (ddd, *J* = 16.0, 9.7, 1.5 Hz, 1H), 6.27 (dd, *J* = 15.9, 7.4 Hz, 1H), 5.57 (dd, *J* = 5.7, 4.4 Hz, 1H), 3.94 (dq, *J* = 9.5, 7.1 Hz, 1H), 3.79 – 3.62 (m, 1H), 3.45 (dtd, *J* = 9.6, 7.4, 1.3 Hz, 1H), 2.72 (ddd, *J* = 13.6, 9.6, 5.7 Hz, 1H), 2.16 (ddd, *J* = 13.6, 7.3, 4.4 Hz, 1H), 1.27 (t, *J* = 7.1 Hz, 3H).

^{13}C-NMR (101 MHz, $CDCl_3$) δ [ppm]= 175.88, 136.47, 133.74, 128.77, 128.04, 126.62, 124.72, 103.32, 66.09, 43.56, 35.41, 15.18.

IR (neat): 3414, 3030, 2926, 2855, 2359, 1774, 1495, 1450, 1349, 1260, 1208, 1148, 1115, 1029, 969, 924, 854, 798, 149, 697 cm^{-1}.

HRMS (EI-MS): m/z calc. for $C_{14}H_{16}O_3$ 232.10940, found 232.10852.

3-Phenyltetrahydrofuro[2,3-b]furan-2(3H)-one 280a



The title compound was prepared according to **GP D** for 45 minutes using methyl-6-phenyl-2-oxabicyclo[3.1.0]hexane-6-carboxylate **280a** (43.6 mg, 0.5 mmol, 1.0 equiv.) and *p*-toluenesulfonic acid (344 mg, 2.0 mmol, 4.0 equiv.) and purified by column chromatography (12 g silica column, hexanes:ethyl acetate 0% to 30% over 20 minutes, 5 minute hold) to yield 3-phenyltetrahydrofuro[2,3-b]furan-2(3H)-one (37.9 mg, 362 µmol, 72%) as a mixture of diastereomers as a yellow oil.

For experiments with chiral phosphoric acids, **GP D** was modified using 6-henyl-2-oxabicyclo[3.1.0]hexane-6-carboxylic acid **253i** (40.1 mg, 0.2 mmol, 1 equiv.) and the corresponding CPA (4.0 µmol, 2.0 mol%) and 1 mL of solvent. To determine the NMR yield, the solvent was evaporated *in vacuo* and the crude mixture was redissolved in 1 mL $CDCl_3$ and 20 µL tetrachloroethane. After solubilization, 0.5 mL were taken from this solution and transferred to an NMR tube and the syringe washed with 0.2 mL $CDCl_3$.

^{1}H-NMR (300 MHz, CDCl3) δ [ppm]= 7.44 – 7.19 (m, 10H), 6.22 (d, J = 5.4 Hz, 1H), 6.14 (d, J = 5.1 Hz, 1H), 4.29 (d, J = 9.5 Hz, 1H), 4.22 – 3.87 (m, 4H), 3.72 (d, J = 4.4 Hz, 1H), 3.43 (tt, J = 9.8, 5.0 Hz, 1H), 3.27 – 3.18 (m, 1H), 2.31 (dddd, J = 12.9, 10.3, 8.9, 8.1 Hz, 1H), 2.00 (ddt, J = 13.0, 5.6, 2.9 Hz, 1H), 1.79 (ddt, J = 13.4, 10.1, 8.4 Hz, 1H), 1.65 – 1.51 (m, 1H).

Minor: **^{13}C-NMR** (101 MHz, CDCl3) δ [ppm]= 174.22, 134.15, 129.05, 127.95, 127.75, 106.12, 68.19, 49.33, 45.29, 26.45.

Major: **^{13}C-NMR** (101 MHz, CDCl3) δ 175.67, 137.26, 129.29, 128.91, 127.38, 107.18, 67.56, 53.18, 48.08, 32.05.

IR (neat)= 3064, 3030, 2982, 2885, 1767, 1603, 1498, 1454, 1357, 1331, 1252, 1170, 1088, 1044, 969, 924, 850, 753, 697 cm^{-1}

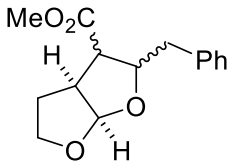
HR-MS (APCI-MS): m/z calc for $C_{12}H_{12}O_3$ 205.0859, found 205.0862.

5.7 Visible light mediated synthesis of hexahydro[2,3b]furans

General Procedure E (GP E)

A Schlenk pressure tube was charged with the corresponding cyclopropane (500 µmol, 1.0 equiv.), $[MesAcrMe]ClO_4$ (2.1 mg, 5.0 µmol, 0.01 equiv.), $NaH_2PO_4{\cdot}H_2O$ (17 mg, 125 µmol, 0.25 equiv.) and PhSH (20 µl, 200 µmol, 0.4 equiv.) in 9:1 MeCN/water and degassed by 3 FPT cycles. The pressure tube was sealed 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 was magnetically stirred from below. The mixture was stirred for 24 hours under N_2 atmosphere. The reaction mixture was quenched with sat. $NaHCO_3$ solution (aqueous), extracted with EtOAc and dried over $NaSO_4$. The solvent was evaporated *in vacuo* and the crude product purified by column chromatography.

Methyl-2-benzylhexahydrofuro[2,3-b]furan-3-carboxylate 285a



The title compound was prepared according to **GP E** using methyl (E)-6-styryl-2-oxabicyclo[3.1.0]hexane-6-carboxylate **250a** (92.2 mg, 377 µmol, 1 equiv.), $[MesAcrMe]ClO_4$ (1.5 mg, 3.8 µmol, 0.01 equiv.), $NaH_2PO_4{\cdot}H_2O$ (17.2 mg, 125 µmol, 0.25 equiv.) and PhSH (15.4 µl, 151 µmol, 0.4 equiv.) and purified by column chromatography (hexanes:ethyl acetate 9:1 to 1:1) to yield methyl-2-benzylhexahydrofuro[2,3-b]furan-3-carboxylate (74.1 mg, 282 µmol, 75%) as a mixture of 2 diastereomers as yellow oil.

R_f (SiO2, hexanes:ethyl acetate 9:1)=0.05, visualized with Seebach's magic stain.

^{1}H NMR (400 MHz, $CDCl_3$) δ [ppm]= 7.34 – 7.18 (m, 10H), 5.72 (d, *J* = 5.0 Hz, 1H), 5.68 (d, *J* = 5.5 Hz, 1H), 4.52 (ddd, *J* = 10.7, 6.0, 5.0 Hz, 1H), 4.22 (dt, *J* = 9.5, 5.6 Hz, 1H), 3.98

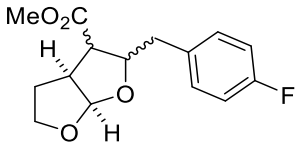
– 3.83 (m, 3H), 3.66 – 3.61 (m, 1H), 3.60 (s, 6H), 3.14 – 3.04 (m, 2H), 2.99 (d, *J* = 5.6 Hz, 2H), 2.92 (t, *J* = 5.7 Hz, 2H), 2.84 (dd, *J* = 10.4, 8.9 Hz, 1H), 2.40 (dd, *J* = 9.5, 8.3 Hz, 1H), 2.01 – 1.88 (m, 2H), 1.82 – 1.74 (m, 1H), 1.71 (dd, *J* = 12.8, 5.1 Hz, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) δ [ppm]= 172.68, 171.22, 137.05, 136.80, 129.83, 129.72, 128.25, 128.19, 126.58, 126.49, 108.22, 108.04, 81.00, 80.48, 68.83, 66.25, 53.14, 52.06, 51.93, 51.76, 47.98, 45.65, 40.12, 39.89, 32.03, 28.00.

IR (neat): 3064, 3027, 2952, 2878, 1730, 1603, 1498, 1439, 1361, 1260, 1197, 1167, 999, 924, 850, 753, 701 cm^{-1}.

HR-MS (EI-MS): m/z calc. for $C_{15}H_{18}O_4$ [M+·] 262.11996, found 262.11955.

Methyl (3aS,6aR)-2-(4-fluorobenzyl)hexahydrofuro[2,3-b]furan-3-carboxylate 285b



The title compound was prepared according to **GP E** using methyl (E)-6-(4-fluorostyryl)-2-oxabicyclo[3.1.0]hexane-6-carboxylate **250b** (131 mg, 0.5 mmol, 1 equiv.), $[MesAcrMe]ClO_4$ (2.1 mg, 5 µmol, 0.01 equiv.), $NaH_2PO_4{\cdot}H_2O$ (17.2 mg, 125 µmol, 0.25 equiv.) and PhSH (20.4 µl, 200 µmol, 0.4 equiv.) and purified by column chromatography with deactivated silica (hexanes:ethyl acetate 9:1) to yield methyl (3aS,6aR)-2-(4-fluorobenzyl)hexahydrofuro[2,3-b]furan-3-carboxylate (61,7 mg, 220 µmol, 44%) as a mixture of 2 diastereomers as yellow oil.

R_f (SiO_2, hexanes:ethyl acetate 9:1) = 0.08, visualized with Seebach's magic stain.

^{1}H NMR (400 MHz, $CDCl_3$) δ [ppm]= 7.25 – 7.15 (m, 4H), 7.01 – 6.93 (m, 4H), 5.71 (d, *J* = 5.0 Hz, 1H), 5.67 (d, *J* = 5.4 Hz, 1H), 4.47 (ddd, *J* = 10.7, 6.2, 4.6 Hz, 1H), 4.18 (ddd, *J* = 9.5, 6.1, 4.8 Hz, 1H), 3.97 – 3.85 (m, 3H), 3.64 (s, 3H), 3.64 (s, 3H), 3.63 – 3.56 (m, 1H), 3.09 (td, *J* = 8.7, 4.9 Hz, 2H), 3.04 – 2.90 (m, 3H), 2.88 – 2.77 (m, 2H), 2.37 (s, 1H), 1.94 (ddd, *J* = 12.6, 7.1, 4.6 Hz, 2H), 1.71 (dd, *J* = 12.7, 4.9 Hz, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) δ [ppm]= 172.57, 171.19, 162.99, 162.96, 160.56, 160.53, 132.82, 132.79, 132.52, 132.49, 131.39, 131.31, 131.19, 131.11, 115.13, 115.06, 114.92,

114.85, 108.20, 108.04, 80.82, 80.82, 80.31, 80.31, 68.82, 66.26, 52.87, 52.15, 51.84, 51.82, 47.86, 45.60, 40.85, 39.19, 38.88, 32.02, 27.98, 23.83, 20.79, 17.49, 17.30, 14.65.

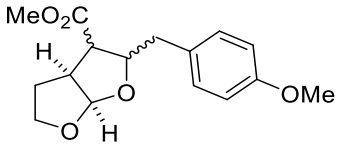
^{19}F NMR (377 MHz, $CDCl_3$) δ [ppm]= -117.11, -117.31.

^{19}F NMR (377 MHz, $CDCl_3$) δ [ppm]= -117.04 – -117.17 (m), -117.25 – -117.38 (m).

IR (neat): 2960, 2878, 1737, 1603, 1510, 1439, 1364, 1264, 1223, 1159, 1096, 1006, 924, 935, 760 cm^{-1}.

HR-MS (EI-MS): m/z calc. for $C_{15}H_{17}FO_4$ [M+·] 280.11054, found 280.11097.

Methyl 2-(4-methoxybenzyl)hexahydrofuro[2,3-b]furan-3-carboxylate 285c



The title compound was prepared according to **GP E** using methyl (E)-6-(4-methoxystyryl)-2-oxabicyclo[3.1.0]hexane-6-carboxylate **250c** (138 mg, 500 µmol, 1.0 equiv.), $[MesAcrMe]ClO_4$ (2.1 mg, 5.0 µmol, 0.01 equiv.), $NaH_2PO_4 \cdot H_2O$ (17 mg, 125 µmol, 0.25 equiv.) and PhSH (20.4 µl, 200 µmol, 0.4 equiv.) and purified by column chromatography (hexanes/ethyl acetate 9:1 to 4:1) to yield methyl 2-(4-methoxybenzyl)hexahydrofuro[2,3-b]furan-3-carboxylate (26.2 mg, 89.2 µmol, 18%) as a colorless oil.

R_f (SiO_2, hexanes:ethyl acetate 9:1) = 0.05, visualized with Seebach's magic stain.

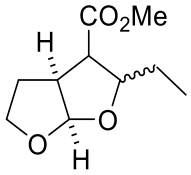
^{1}H-NMR (300 MHz, $CDCl_3$) δ [ppm]= 7.21 – 7.08 (m, 4H), 6.85 – 6.77 (m, 4H), 5.71 (d, *J* = 5.0 Hz, 1H), 5.67 (d, *J* = 5.4 Hz, 1H), 4.47 (ddd, *J* = 10.6, 5.9, 5.0 Hz, 1H), 4.17 (ddd, *J* = 9.5, 5.9, 5.1 Hz, 1H), 3.98 – 3.87 (m, 3H), 3.78 (s, 3H), 3.78 (s, 3H), 3.66 – 3.56 (m, 1H), 3.62 (s, 3H), 3.61 (s, 3H), 3.14 – 3.02 (m, 2H), 2.93 (dd, *J* = 5.5, 3.3 Hz, 2H), 2.90 – 2.84 (m, 2H), 2.84 – 2.77 (m, 1H), 2.39 (dd, *J* = 9.5, 8.4 Hz, 1H), 1.98 – 1.85 (m, 2H), 1.81 – 1.66 (m, 2H).

^{13}C-NMR (75 MHz, $CDCl_3$) δ [ppm]= 172.75, 171.31, 158.34, 158.30, 130.87, 130.74, 129.09, 128.86, 113.69, 113.60, 108.23, 108.05, 81.21, 80.66, 68.85, 66.28, 55.26, 52.95, 52.11, 51.81, 51.75, 47.96, 45.66, 39.09, 38.86, 32.06, 28.03.

IR (neat): 2956, 1733, 1614, 1513, 1439, 1364, 1301, 1245, 1178, 1111, 1033, 924, 835 cm^{-1}.

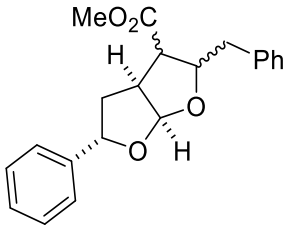
HR-MS (EI-MS): m/z calc. for $C_{16}H_{20}O_5$ [M+·] 292.13053, found 292.12973.

Methyl 2-ethylhexahydrofuro[2,3-b]furan-3-carboxylate 285d



Preparing the title compound according to **GP E** using methyl (E)-6-(prop-1-en-1-yl)-2-oxabicyclo[3.1.0]hexane-6-carboxylate **250d** (91.1 mg, 500 µmol, 1 equiv.) $[MesAcrMe]ClO_4$ (2.1 mg, 5.0 µmol, 0.01 equiv.), $NaH_2PO_4{\cdot}H_2O$ (17 mg, 125 µmol, 0.25 equiv.) and PhSH (20.4 µl, 200 µmol, 0.4 equiv.)failed to yield the compound.

Methyl-2-benzyl-5-phenylhexahydrofuro[2,3-b]furan-3-carboxylate 285e



The title compound was prepared according to **GP E** using methyl-3-phenyl-6-((E)-styryl)-2-oxabicyclo[3.1.0]hexane-6-carboxylate **250e** (160 mg, 500 µmol, 1 equiv.), $[MesAcrMe]ClO_4$ (2.1 mg, 5 µmol, 0.01 equiv.), $NaH_2PO_4{\cdot}H_2O$ (17.2 mg, 125 µmol, 0.25 equiv.) and PhSH (20.4 µl, 200 µmol, 0.4 equiv.) and purified by column chromatography (hexanes:ethyl acetate 9:1 to 2:1) to yield methyl-2-benzyl-5-phenylhexahydrofuro[2,3-b]furan-3-carboxylate (93.3 mg, 256 µmol, 55%) as a mixture of 3 diastereomers as yellow oil.

R_f (SiO2, hexanes:ethyl acetate 4:1)=0.37, visualized with Seebach's magic stain.

^{1}H NMR (300 MHz, $CDCl_3$), Diastereomer 1 δ [ppm]= 7.81 – 7.46 (m, 4H), 7.36 – 7.24 (m, 6H), 5.96 (d, *J* = 4.9 Hz, 1H), 5.19 (dd, *J* = 9.8, 5.9 Hz, 1H), 4.68 (dt, *J* = 10.8, 5.6 Hz, 1H), 3.59 (s, 3H), 3.25 (ddd, *J* = 9.4, 7.2, 4.8 Hz, 1H), 3.02 – 2.86 (m, 3H), 2.16 (ddd, *J* = 13.6, 5.9, 2.6 Hz, 1H), 1.96 – 1.82 (m, 1H).

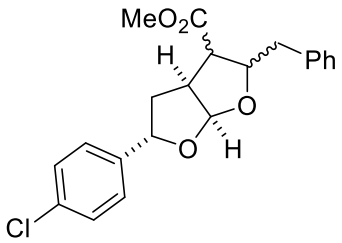
^{1}H NMR (400 MHz, $CDCl_3$), Diastereomers 2+3 δ [ppm]= 7.38 – 7.19 (m, 30H), 6.13 (d, *J* = 5.1 Hz, 1H), 5.96 (d, *J* = 5.0 Hz, 1H), 5.87 (d, *J* = 5.5 Hz, 1H), 5.19 (dd, *J* = 9.8, 5.9 Hz, 1H), 5.13 (dd, *J* = 9.7, 6.1 Hz, 1H), 4.74 (dd, *J* = 11.1, 4.6 Hz, 1H), 4.71 – 4.65 (m, 2H), 4.29 (dt, *J* = 9.5, 5.4 Hz, 1H), 3.74 (s, 3H), 3.62 (s, 3H), 3.59 (s, 3H), 3.37 (ddd, *J* = 11.9, 5.2, 2.7 Hz, 1H), 3.24 (td, *J* = 8.2, 5.3 Hz, 3H), 3.07 (dd, *J* = 5.5, 3.9 Hz, 2H), 3.05 – 2.81 (m, 4H), 2.59 (dd, *J* = 9.5, 8.5 Hz, 1H), 2.23 – 2.12 (m, 2H), 2.11 – 2.03 (m, 2H), 1.87 (ddt, *J* = 12.9, 11.1, 7.4 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ [ppm]= 172.67, 171.31, 141.31, 139.91, 136.99, 136.70, 130.09, 129.77, 129.19, 128.48, 128.44, 128.39, 128.32, 128.23, 127.81, 127.61, 126.68, 126.59, 126.11, 126.08, 125.67, 125.65, 109.09, 108.39, 107.89, 81.95, 81.71, 81.34, 81.02, 80.88, 78.98, 77.37, 77.25, 77.05, 76.73, 54.39, 53.25, 52.16, 52.14, 51.95, 51.83, 48.69, 47.11, 46.27, 40.82, 40.41, 40.18, 39.79, 38.02, 37.04.

IR (neat): 3064, 3030, 2952, 2359, 1733, 1602, 1498, 1439, 1361, 1223, 1163, 1100, 1036, 910, 798, 757, 701.

HR-MS (EI-MS): m/z calc. for $C_{21}H_{22}O_4$ [M+·] 339.1594, found 338.1521.

Methyl-2-benzyl-5-(4-chlorophenyl)hexahydrofuro[2,3-b]furan-3-carboxylate 285g



The title compound was prepared according to **GP E** using methyl-3-(4-chlorophenyl)-6-((E)-styryl)-2-oxabicyclo[3.1.0]hexane-6-carboxylate **250g** (177 mg, 500 µmol, 1 equiv.), $[MesAcrMe]ClO_4$ (2.1 mg, 5 µmol, 0.01 equiv.), $NaH_2PO_4{\cdot}H_2O$ (17.2 mg, 125 µmol, 0.25 equiv.) and PhSH (20.4 µl, 200 µmol, 0.4 equiv.) and purified by column chromatography (hexanes:ethyl acetate 9:1) to yield methyl-2-benzyl-5-(4-chlorophenyl)hexahydrofuro[2,3-b]furan-3-carboxylate (64.4 mg, 173 µmol, 35%) as a mixture of 2 diastereomers as yellow oil.

R_f (SiO_2, hexanes:ethyl acetate 4:1)=0.49

Diastereomer 1:

^{1}H NMR (400 MHz, $CDCl_3$) δ [ppm]= 7.32 – 7.17 (m, 9H), 5.95 (d, *J* = 4.9 Hz, 1H), 5.15 (dd, *J* = 9.9, 5.8 Hz, 1H), 4.72 – 4.62 (m, 1H), 3.59 (s, 3H), 3.32 – 3.20 (m, 1H), 3.12 – 3.00 (m, 1H), 2.99 – 2.87 (m, 2H), 2.15 (ddd, *J* = 13.6, 5.9, 2.3 Hz, 1H), 1.86 – 1.75 (m, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) δ [ppm]= 171.28, 139.87, 136.90, 133.28, 129.75, 128.54, 128.34, 127.04, 126.63, 108.39, 81.54, 81.01, 52.10, 51.88, 46.26, 40.43, 37.18.

Diastereomer 2:

^{1}H NMR (300 MHz, $CDCl_3$) δ [ppm]= 7.33 – 7.15 (m, 9H), 5.85 (d, *J* = 5.5 Hz, 1H), 4.67 (dd, *J* = 11.1, 4.6 Hz, 1H), 4.28 (dt, *J* = 9.6, 5.4 Hz, 1H), 3.62 (s, 3H), 3.24 (td, *J* = 8.2, 5.4 Hz, 1H), 3.06 (dd, *J* = 5.4, 4.1 Hz, 2H), 2.57 (dd, *J* = 9.6, 8.5 Hz, 1H), 2.05 (dd, *J* = 12.9, 4.6 Hz, 1H), 1.79 (ddd, *J* = 12.9, 11.1, 8.0 Hz, 1H).

^{13}C NMR (75 MHz, $CDCl_3$) δ [ppm]= 172.54, 138.48, 136.60, 133.49, 130.11, 128.56, 128.23, 127.43, 126.71, 107.85, 80.90, 78.26, 53.12, 52.21, 48.62, 40.92, 39.72.

Diasteromer 3:

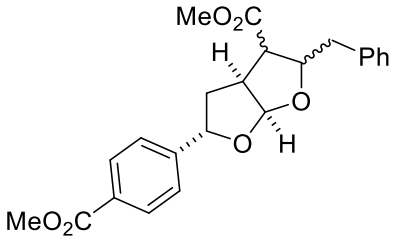
^{1}H NMR (300 MHz, $CDCl_3$) δ [ppm]= 7.37 – 7.18 (m, 9H), 6.11 (d, *J* = 5.1 Hz, 1H), 5.09 (dd, *J* = 9.8, 6.0 Hz, 1H), 4.66 (q, *J* = 6.5 Hz, 1H), 3.74 (s, 3H), 3.37 (ddd, *J* = 9.9, 5.1, 2.6 Hz, 1H), 3.07 (dd, *J* = 6.2, 2.7 Hz, 1H), 2.83 (d, *J* = 6.6 Hz, 2H), 2.18 (ddd, *J* = 13.3, 6.0, 2.4 Hz, 1H), 2.12 – 1.97 (m, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) δ [ppm]= 172.34, 139.69, 137.88, 133.35, 129.16, 128.58, 128.48, 127.00, 126.60, 109.07, 82.03, 80.29, 54.32, 51.97, 47.05, 40.21, 38.01.

IR (neat): 3064, 3030, 2952, 2356, 1733, 1495, 1439, 1357, 1267, 1200, 1088, 1036, 1014, 913, 829, 757, 701 cm^{-1}.

HR-MS (EI-MS): m/z calc. for $C_{21}H_{21}ClO_4$ [M+·] 372.11229, found 372.11130.

Methyl-2-benzyl-5-(4-(methoxycarbonyl)phenyl)hexahydrofuro[2,3-b]furan-3-carboxylate 285i



The title compound was prepared according to **GP E** using methyl-3-(4-(methoxycarbonyl)phenyl)-6-((E)-styryl)-2-oxabicyclo[3.1.0]hexane-6-carboxylate **250i** (189 mg, 0.5 mmol, 1 equiv.), $[MesAcrMe]ClO_4$ (2.1 mg, 5 µmol, 0.01 equiv.), $NaH_2PO_4 \cdot H_2O$ (17.2 mg, 125 µmol, 0.25 equiv.) and PhSH (20.4 µl, 200 µmol, 0.4 equiv.) and purified by column chromatography (hexanes:ethyl acetate 9:1) to yield methyl-2-benzyl-5-(4-(methoxycarbonyl)phenyl)hexahydrofuro[2,3-b]furan-3-carboxylate (42.5 mg, 107 µmol, 21%) as a mixture of 2 diastereomers as yellow oil.

R_f (SiO_2, hexanes:ethyl acetate 4:1)=0.25

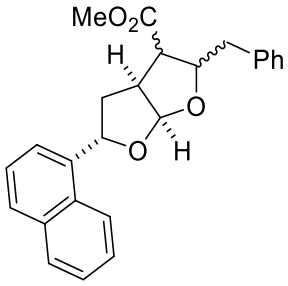
^{1}H NMR (400 MHz, $CDCl_3$) δ [ppm]= 8.10 – 7.86 (m, 4H), 7.40 – 7.18 (m, 14H), 5.97 (d, *J* = 4.9 Hz, 1H), 5.88 (d, *J* = 5.5 Hz, 1H), 5.23 (dd, *J* = 9.9, 5.9 Hz, 1H), 4.76 (dd, *J* = 11.1, 4.7 Hz, 1H), 4.67 (dt, *J* = 10.9, 5.7 Hz, 1H), 4.30 (dt, *J* = 9.5, 5.4 Hz, 1H), 3.91 (s, 3H), 3.90 (s, 3H), 3.63 (s, 3H), 3.60 (s, 3H), 3.25 (td, *J* = 8.2, 5.4 Hz, 2H), 3.13 – 2.85 (m, 4H), 2.59 (dd, *J* = 9.5, 8.4 Hz, 1H), 2.24 – 2.18 (m, 1H), 2.10 (dd, *J* = 12.9, 4.7 Hz, 1H), 1.89 – 1.74 (m, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) δ [ppm]= 172.50, 171.26, 166.91, 166.89, 146.57, 145.26, 136.89, 136.61, 130.09, 129.75, 129.56, 129.39, 128.35, 128.24, 126.72, 126.64, 125.85, 125.47, 108.49, 107.97, 81.56, 81.19, 80.99, 78.45, 53.13, 52.21, 52.12, 52.10, 51.90, 48.64, 46.23, 40.90, 40.41, 39.77, 37.11.

IR (neat): 3027, 2952, 2963, 2087, 1942, 1722, 1614, 1498, 1435, 1275, 1193, 1103, 1006, 913, 857, 760, 701 cm^{-1}.

HR-MS (EI-MS): m/z calc. for $C_{23}H_{24}O_6$ [M+·] 396.15647, found 396.15674.

Methyl-2-benzyl-5-(naphthalen-1-yl)hexahydrofuro[2,3-b]furan-3-carboxylate 285f



The title compound was prepared according to **GP E** using methyl-3-(naphthalen-1-yl)-6-((E)-styryl)-2-oxabicyclo[3.1.0]hexane-6-carboxylate **250f** (185 mg, 0.5 mmol, 1 equiv.), $[MesAcrMe]ClO_4$ (2.1 mg, 5 µmol, 0.01 equiv.), $NaH_2PO_4 \cdot H_2O$ (17.2 mg, 125 µmol, 0.25 equiv.) and PhSH (20.4 µl, 200 µmol, 0.4 equiv.) and purified by column chromatography with deactivated silica (hexanes:ethyl acetate 0 to 10%) to yield methyl-2-benzyl-5-(naphthalen-1-yl)hexahydrofuro[2,3-b]furan-3-carboxylate (80.8 mg, 208 µmol, 42%) as a mixture of 3 diastereomers. One diastereomer could be isolated separately and was recrystallized from heptane/ethyl acetate to give crystals suitable for X-Ray. The other 2 diastereomers were isolated as a mixture as a yellow oil.

$\mathbf{R_f}$ (SiO2, hexanes:ethyl acetate 4:1)= 0.32, visualized with Seebach's magic stain.

Diastereomer 1:

^{1}H NMR (400 MHz, $CDCl_3$) δ [ppm]= 7.94 (dd, *J* = 8.2, 1.4 Hz, 1H), 7.88 – 7.82 (m, 1H), 7.75 (d, *J* = 8.2 Hz, 1H), 7.61 (dt, *J* = 7.1, 1.1 Hz, 1H), 7.55 – 7.41 (m, 3H), 7.35 – 7.20 (m, 5H), 6.10 (d, *J* = 4.9 Hz, 1H), 5.94 (dd, *J* = 9.4, 5.9 Hz, 1H), 4.83 (dt, *J* = 10.3, 5.7 Hz, 1H), 3.61 (s, 3H), 3.29 (tdd, *J* = 9.4, 5.0, 2.8 Hz, 1H), 3.07 (dd, *J* = 13.9, 5.9 Hz, 1H), 3.02 – 2.91 (m, 2H), 2.43 (ddd, *J* = 13.6, 5.9, 2.8 Hz, 1H), 1.90 (dt, *J* = 13.5, 9.4 Hz, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) δ [ppm]= 171.51, 137.27, 136.93, 133.65, 130.20, 129.81, 128.78, 128.36, 127.86, 126.64, 126.10, 125.52, 123.22, 121.63, 108.30, 81.53, 79.27, 52.13, 51.91, 46.49, 40.55, 36.54.

Diastereomers 2+3:

^{1}H NMR (300 MHz, $CDCl_3$) δ [ppm]= 7.94 – 7.58 (m, 8H), 7.56 – 7.20 (m, 16H), 6.28 (d, *J* = 5.1 Hz, 1H, minor), 5.97 (d, *J* = 5.6 Hz, 1H, major), 5.86 (dd, *J* = 9.0, 6.3 Hz, 1H, minor),

5.40 (dd, *J* = 11.0, 4.6 Hz, 1H, major), 4.81 (q, *J* = 6.4 Hz, 1H, minor), 4.35 (dt, *J* = 9.8, 5.0 Hz, 1H, major), 3.77 (s, 3H, minor), 3.69 (s, 3H, major), 3.47 – 3.37 (m, 1H, minor), 3.32 (td, *J* = 8.1, 5.5 Hz, 1H, major), 3.23 (d, *J* = 4.8 Hz, 1H, minor), 3.20 – 3.14 (m, 1H, major), 3.08 (dd, *J* = 14.1, 5.3 Hz, 1H, major), 2.92 – 2.87 (m, 2H, minor), 2.72 (dd, *J* = 9.5, 8.2 Hz, 1H, major), 2.43 (ddd, *J* = 13.3, 6.3, 3.1 Hz, 1H, minor), 2.27 – 2.16 (m, 2H), 1.95 (ddd, *J* = 12.9, 11.0, 8.1 Hz, 1H, major).

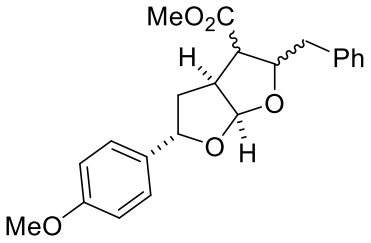
^{13}C NMR (major) (75 MHz, $CDCl_3$) δ [ppm]= 172.72, 136.51, 135.50, 133.59, 130.59, 130.38, 128.75, 128.27, 128.12, 126.80, 125.96, 125.58, 125.55, 123.33, 122.56, 107.54, 80.52, 75.95, 53.09, 52.27, 48.44, 40.00, 39.39.

^{13}C NMR (minor) (75 MHz, $CDCl_3$) δ [ppm]= 172.46, 137.98, 136.96, 133.72, 130.14, 129.23, 128.93, 128.53, 128.04, 126.62, 126.01, 125.58, 125.55, 123.14, 122.12, 109.06, 81.78, 78.60, 54.51, 52.01, 47.04, 39.13, 38.06.

IR (neat): 3056, 3030, 2948, 2251, 1938, 1733, 1599, 1498, 1434, 1379, 1349, 1267, 1200, 1081, 1006, 910, 783, 731, 701 cm^{-1}.

HR-MS (EI-MS): m/z calc. for $C_{25}H_{24}O_4$ [M+·] 389.1748, found 388.1673.

Methyl 2-benzyl-5-(4-methoxyphenyl)hexahydrofuro[2,3-b]furan-3-carboxylate 285i



The title compound was prepared according to **GP E** using methyl (E)-3-(4-methoxyphenyl)-6-styryl-2-oxabicyclo[3.1.0]hexane-6-carboxylate **250i** (175 mg, 500 µmol, 1.0 equiv.), $[MesAcrMe]ClO_4$ (2.1 mg, 5.0 µmol, 0.01 equiv.), $NaH_2PO_4 \cdot H_2O$ (17 mg, 125 µmol, 0.25 equiv.) and PhSH (20.4 µl, 200 µmol, 0.4 equiv.) and purified by column chromatography (hexanes/ethyl acetate 9:1 to 4:1) to yield methyl 2-benzyl-5-(4-methoxyphenyl)hexahydrofuro[2,3-b]furan-3-carboxylate as three inseparable diastereomers (49.8 mg, 135 µmol, 27%) as a colorless oil.

R_f (SiO_2, hexanes:ethyl acetate 9:1) = 0.12, visualized with Seebach's magic stain.

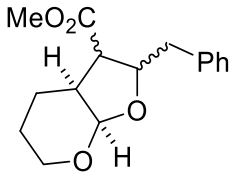
^{1}H NMR (400 MHz, $CDCl_3$) δ [ppm]= 7.34 – 7.19 (m, 21H), 6.90 – 6.82 (m, 6H), 6.10 (d, *J* = 5.1 Hz, 1H), 5.93 (d, *J* = 5.0 Hz, 1H), 5.84 (d, *J* = 5.5 Hz, 1H), 5.11 (ddd, *J* = 22.4, 9.8, 6.1 Hz, 2H), 4.72 – 4.64 (m, 3H), 4.27 (dt, *J* = 9.5, 5.4 Hz, 1H), 3.79 (d, *J* = 3.1 Hz, 9H), 3.74 (s, 3H), 3.62 (s, 3H), 3.58 (d, *J* = 1.4 Hz, 3H), 3.37 (ddt, *J* = 8.0, 5.4, 2.8 Hz, 2H), 3.27 – 3.19 (m, 3H), 3.07 (dd, *J* = 5.4, 3.0 Hz, 3H), 3.03 – 2.87 (m, 1H), 2.86 – 2.81 (m, 2H), 2.57 (dd, *J* = 9.5, 8.4 Hz, 1H), 2.16 – 2.07 (m, 2H), 2.06 – 1.99 (m, 2H), 1.86 (ddd, *J* = 12.9, 11.1, 8.0 Hz, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) δ [ppm]= 172.71, 172.51, 171.34, 159.33, 159.21, 137.98, 137.02, 136.73, 133.23, 133.05, 131.77, 130.10, 129.78, 129.20, 129.16, 128.48, 128.32, 128.22, 127.58, 127.13, 127.11, 126.67, 126.57, 113.83, 113.79, 113.77, 108.95, 108.25, 107.74, 81.96, 81.38, 80.80, 80.78, 78.72, 55.30, 54.41, 53.28, 52.18, 52.15, 51.94, 51.82, 48.68, 47.15, 46.33, 40.69, 40.46, 40.15, 39.78, 38.05, 37.00.

IR (neat): 3067, 3027, 2952, 1730, 1614, 1513, 1439, 1353, 1245, 1170, 1029, 1003, 910, 828, 701 cm^{-1}.

HR-MS (EI-MS): m/z calc. for $C_{22}H_{24}O_5$ [M+·] 368.16183, found 368.16105.

Methyl-2-benzylhexahydro-4H-furo[2,3-b]pyran-3-carboxylate 285k



The title compound was prepared according to **GP E** using methyl-7-((E)-styryl)-2-oxabicyclo[4.1.0]heptane-7-carboxylate **250k** (129 mg, 500 µmol, 1 equiv.), $[MesAcrMe]ClO_4$ (1.5 mg, 3.8 µmol, 0.01 equiv.), $NaH_2PO_4{\cdot}H_2O$ (17.2 mg, 125 µmol, 0.25 equiv.) and PhSH (15.4 µl, 151 µmol, 0.4 equiv.) and purified by column chromatography (hexanes:ethyl acetate 9:1 to 4:1) to yield methyl-2-benzylhexahydro-4H-furo[2,3-b]pyran-3-carboxylate (50.6 mg, 183 µmol, 37%) as a mixture of 2 diastereomers as yellow oil.

R_f (SiO2, hexanes:ethyl acetate 9:1)=0.29.

Diastereomer 1:

^{1}H NMR (300 MHz, $CDCl_3$) δ [ppm]= 7.36 – 7.17 (m, 5H), 5.18 (d, *J*=3.7, 1H), 4.79 (dt, *J*=9.2, 5.3, 1H), 3.84 – 3.73 (m, 1H), 3.67 – 3.57 (m, 1H), 3.62 (s, 3H), 3.04 – 2.80 (m, 3H), 2.25 (dt, *J*=6.8, 3.7, 1H), 1.65 – 1.49 (m, 4H).

Diastereomer 2:

^{1}H NMR (300 MHz, $CDCl_3$) δ [ppm]= 7.32 – 7.16 (m, 5H), 5.02 (d, *J*=3.6, 1H), 4.51 (ddd, *J*=8.6, 7.4, 6.3, 1H), 3.98 – 3.88 (m, 1H), 3.52 (s, 3H), 3.41 (td, *J*=11.5, 2.5, 1H), 3.16 (dd, *J*=13.5, 7.4, 1H), 3.03 – 2.86 (m, 3H), 2.47 (dq, *J*=11.2, 3.6, 1H), 1.84 (dt, *J*=8.8, 4.2, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) δ [ppm]= 172.68, 171.22, 137.05, 136.80, 129.83, 129.72, 128.25, 128.19, 126.58, 126.49, 108.22, 108.04, 81.00, 80.48, 77.34, 77.02, 76.70, 68.83, 66.25, 53.14, 52.06, 51.93, 51.76, 47.98, 45.65, 40.12, 39.89, 32.03, 28.00.

IR (neat): 3064, 3027, 2952, 2878, 1730, 1603, 1498, 1439, 1361, 1260, 1197, 1167, 999, 924, 850, 753, 701 cm^{-1}.

HR-MS (EI-MS): m/z calc. for $C_{16}H_{29}O_4$ [M+·] 276.13561, found 276.13543.

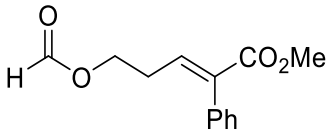
5.8 Visible light mediated synthesis of formyl esters

General Procedure F (GP F)

A 5 mL Schlenk tube was charged with the corresponding cyclopropane (0.50 mmol, 1.0 equiv.) and N-iodosuccinimide (NIS) (225 mg, 1.00 mmol, 2.0 equiv.), dissolved in 2.5 mL dimethyl carbonate/H_2O 9:1 and degassed *via* 3 FPT cycles. The pressure tube was sealed with a Teflon sealed inlet for a glass rod, through which irradiation with a 530 nm high power LED took place from above while the reaction was magnetically stirred from below. The mixture was stirred for 2 hours under N_2 atmosphere, during which it turned black. After the reaction was complete, the crude mixture was transferred to a separation funnel containing 10 mL ethyl acetate and 10 mL aqueous sodium thiosulfate solution (sat.). The phases were separated and the organic phase washed with another 10 mL of sodium thiosulfate solution. The combined aqueous phases were extracted once more with 10 mL ethyl acetate and the combined organic phases dried over Na_2SO_4, filtered and dried *in vacuo*. The crude reaction product was

purified by column chromatography (SiO_2, hexanes/ethyl acetate 0% to 10%) to afford the pure product.

Methyl (E)-5-(formyloxy)-2-phenylpent-2-enoate 334a



The title compound was prepared according to **GP F** using methyl-6-phenyl-2-oxabicyclo[3.1.0]hexane-6-carboxylate **253a** (218 mg, 1.0 mmol, 1.0 equiv.) and NIS (450 mg, 2.0 mmol, 2.0 equiv.) and purified by column chromatography (12 g silica column, flowrate 15 mL/min, hexanes:ethyl acetate 0% to 10% over 10 minutes, 5 minute hold) to yield methyl (E)-5-(formyloxy)-2-phenylpent-2-enoate (144 mg, 613 mmol, 61%) as a colorless liquid.

R_f (SiO2, 9:1 hexanes/ethyl acetate)=0.18

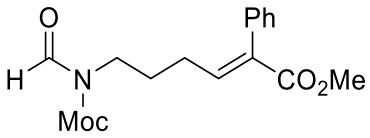
1H-NMR (400 MHz, CDCl3) δ [ppm]= 8.01 (s, 1H), 7.33 – 7.19 (m, 5H), 6.13 (t, J = 7.5 Hz, 1H), 4.28 (t, J = 6.4 Hz, 2H), 3.75 (s, 3H), 2.80 (q, J = 6.8 Hz, 2H).

13C-NMR (101 MHz, CDCl3) δ [ppm]=168.02, 160.94, 137.52, 136.95, 128.36, 127.96, 127.43, 62.82, 51.94, 29.47.

IR (neat)= 3027, 2952, 1715, 1636, 1599, 1495, 1435, 1275, 1204, 1156, 1118, 1029, 992, 924, 880, 835, 753, 967 cm^{-1}.

HR-MS (APCI-MS): m/z calc. for $C_{13}H_{15}O_4$ [MH+·] 235.0965, found 235.0964.

Methyl (E)-6-(N-(methoxycarbonyl)formamido)-2-phenylhex-2-enoate 334e



The title compound was prepared according to **GP F** using dimethyl-7-phenyl-2-azabicyclo[4.1.0]heptane-2,7-dicarboxylate **253e** (145 mg, 0.50 mmol, 1.0 equiv.) and NIS (225 mg, 1.0 mmol, 2.0 equiv.) and purified by column chromatography (12 g silica column, flowrate 15 mL/min, hexanes:ethyl acetate 0% to 20% over 10 minutes,

5 minute hold) to yield Methyl (E)-6-(N-(methoxycarbonyl)formamido)-2-phenylhex-2-enoate (86.1 mg, 282 µmol, 56%) as a colorless liquid.

R_f (SiO_2, hexanes/ethyl acetate 1:1)=0.56

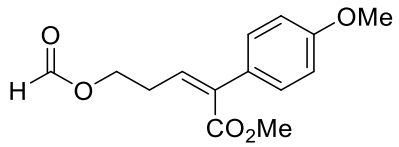
^{1}H-NMR (400 MHz, CDCl3) δ [ppm]= 9.22 (d, J = 0.7 Hz, 1H), 7.38 – 7.24 (m, 5H), 6.17 (t, J = 7.6 Hz, 1H), 3.90 (d, J = 0.8 Hz, 3H), 3.80 (d, J = 0.6 Hz, 3H), 3.75 – 3.66 (m, 2H), 2.47 (q, J = 7.5 Hz, 2H), 1.77 (p, J = 7.6 Hz, 2H).

^{13}C-NMR (101 MHz, CDCl3) δ [ppm]= 168.31, 162.70, 154.56, 139.18, 137.80, 135.32, 128.32, 127.71, 127.35, 53.97, 51.81, 40.39, 27.75, 27.33.

IR (neat)= 3027, 2956, 1685, 1495, 1443, 1402, 1334, 1286, 1200, 1174, 1092, 962, 895, 775, 697 cm^{-1}.

HR-MS (ESI-MS) (M+H+) m/z calc for $C_{16}H_{19}NO_5$ 306.1336, found 306.1343.

Methyl (*Z*)-5-(formyloxy)-2-(4-methoxyphenyl)pent-2-enoate 334b



The title compound was prepared according to **GP F** using methyl-6-(4-methoxyphenyl)-2-oxabicyclo[3.1.0]hexane-6-carboxylate **253b** (124 mg, 0.50 mmol, 1.0 equiv.) and NIS (225 mg, 1.0 mmol, 2.0 equiv.) and purified by column chromatography (12 g silica column, flowrate 15 mL/min, hexanes:ethyl acetate 0% to 15% over 13 minutes, 8 minute hold) to yield methyl (*Z*)-5-(formyloxy)-2-(4-methoxyphenyl)pent-2-enoate (72.3 mg, 274 µmol, 55%) as a colorless liquid.

R_f (SiO_2, hexanes/ethyl acetate 4:1)=0.24, visualized with permanganate.

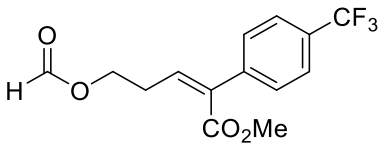
^{1}H-NMR (400 MHz, CDCl3) δ [ppm]= 8.12 – 8.05 (m, 1H), 7.29 – 7.23 (m, 2H), 6.93 – 6.84 (m, 2H), 6.13 (t, J = 7.5 Hz, 1H), 4.35 (td, J = 6.5, 0.8 Hz, 2H), 3.83 (s, 6H), 2.90 – 2.78 (m, 2H).

^{13}C-NMR (101 MHz, CDCl3) δ [ppm]= 168.30, 160.94, 159.45, 136.43, 133.43, 129.96, 128.56, 113.78, 62.90, 55.31, 51.90, 29.44.

IR (neat)= 2952, 2840, 1715, 1607, 1513, 1461, 1364, 1290, 1249, 1204, 1170, 1111, 1033, 992, 924, 880, 831 cm^{-1}.

HRMS (ESI-MS) (MH+) calc. for $C_{14}H_{15}O_5$ 265.1071, found 265.1072.

Methyl (*Z*)-5-(formyloxy)-2-(4-(trifluoromethyl)phenyl)pent-2-enoate 334c



The title compound was prepared according to **GP F** using methyl-6-(4-(trifluoromethyl)phenyl)-2-oxabicyclo[3.1.0]hexane-6-carboxylate **253c** (143 mg, 0.50 mmol, 1.0 equiv.) and NIS (225 mg, 1.0 mmol, 2.0 equiv.) and purified by column chromatography (12 g silica column, flowrate 15 mL/min, hexanes:ethyl acetate 0% to 15% over 10 minutes, 5 minute hold) to yield methyl (*Z*)-5-(formyloxy)-2-(4-(trifluoromethyl)phenyl)pent-2-enoate (48.4 mg, 160 µmol, 32%) as a yellow liquid.

R_f (SiO_2, hexanes/ethyl acetate 9:1)=0.18, visualized with permanganate.

^{1}H-NMR (400 MHz, CDCl3) δ[ppm]= 8.07 (s, 1H), 7.62 – 7.55 (m, 2H), 7.45 – 7.38 (m, 2H), 6.27 (t, J = 7.4 Hz, 1H), 4.35 (t, J = 6.4 Hz, 2H), 3.82 (s, 3H), 2.92 (q, J = 6.7 Hz, 2H).

^{13}C-NMR (101 MHz, CDCl3) δ [ppm]= 167.30, 161.00, 141.40, 138.53, 135.83, 128.16, 125.41 (q, J = 3.8 Hz), 62.74, 52.22, 29.69.

^{19}F{^{1}H}-NMR (376 MHz, CDCl3) δ [ppm]= -63.16.

^{19}F-NMR (376 MHz, CDCl3) δ [ppm]= -63.16.

IR (neat) = 2956, 1718, 1618, 1439, 1413, 1364, 1323, 1207, 1163, 1111, 1066, 1018, 932, 842, 794, 760, 678 cm^{-1}.

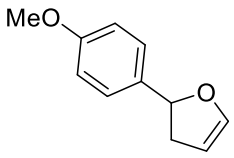
HRMS (ESI-MS) (H+) m/z calc for $C_{14}H_{13}F_3O_4$ 303.0839, found 303.0839.

5.9 Synthesis of substituted 2,3-dihydrofurans

General Procedure F (GP F)

Following literature procedure,[177] a 250 mL round-bottomed flask was charged with potassium acetate (4.6 g, 47 mmol, 2.2 equiv.), tetrabutylammoniumchloride (14.8 g, 53 mmol, 2.5 equiv.) and 4 Å molecular sieves (0.5 g/5 mL DMF) and suspended in 20 mL DMF. The corresponding aldehyde (21 mmol, 1.0 equiv.), 2,3-dihydrofuran (14.5 mL, 192 mmol, 9.0 equiv.) and palladium acetate (240 mg, 1.1 mmol, 0.05 equiv.) were added in this order. The mixture turned black and was stirred over night at room temperature. For workup, 10 mL diethyl ether per mmol anisole was added and the mixture was filtered over celite. The organic phase was washed twice with water, once with brine and dried over $MgSO_4$. The solvent was evaporated under reduced pressure and the resulting crude brown oil was purified by column chromatography (SiO_2, hexanes:ethyl acetate 19:1 to 9:1) to give the corresponding products.

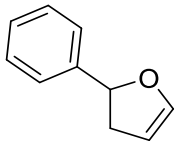
2-(4-Methoxyphenyl)-2,3-dihydrofuran 294e



The title compound was prepared according to **GP F** using potassium acetate (4.6 g, 47 mmol, 2.2 equiv.), tetrabutylammoniumchloride (14.8 g, 53 mmol, 2.5 equiv.), Iodoanisole (5.0 g, 21 mmol, 1.0 equiv.), 2,3-dihydrofuran (14.5 mL, 192 mmol, 9.0 equiv.), palladium acetate (240 mg, 1.1 mmol, 0.05 equiv.) in 20 mL DMF. The resulting crude brown oil was purified by column chromatography (SiO_2, hexanes:ethyl acetate 19:1 to 9:1) to give 2-(4-methoxyphenyl)-2,3-dihydrofuran (1.8 g, 10 mmol, 47%) as colorless oil. Analytical data is in accordance with literature.[177]

^{1}H NMR (300 MHz, $CDCl_3$) δ [ppm]= 7.43 – 7.22 (m, 2H), 7.00 – 6.82 (m, 2H), 6.43 (q, *J* = 2.4 Hz, 1H), 5.47 (dd, *J* = 10.6, 8.5 Hz, 1H), 4.96 (q, *J* = 2.6 Hz, 1H), 3.81 (s, 3H), 3.17 – 2.88 (m, 1H), 2.76 – 2.47 (m, 1H).

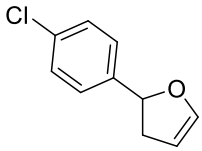
2-Phenyl-2,3-dihydrofuran 249a



The title compound was prepared according to **GP F** using potassium acetate (2.1 g, 22 mmol, 2.2 equiv.), tetrabutylammoniumchloride (6.8 g, 25 mmol, 2.5 equiv.), iodobenzene (1.1 mL, 9.8 mmol, 1.0 equiv.), 2,3-dihydrofuran (6.7 mL, 88 mmol, 9.0 equiv.), palladium acetate (110 mg, 0.5 mmol, 0.05 equiv.) in 10 mL DMF. The resulting crude brown oil was purified by column chromatography (SiO_2, hexanes:ethyl acetate 19:1 to 9:1) to give 2-phenyl-2,3-dihydrofuran (889 mg, 6.1 mmol, 62%) as colorless oil. Analytical data is in accordance with literature.[158]

^{1}H NMR (300 MHz, $CDCl_3$) δ [ppm]= 7.41 – 7.23 (m, 5H), 6.46 (q, *J* = 2.4 Hz, 1H), 5.52 (dd, *J* = 10.7, 8.4 Hz, 1H), 4.97 (q, *J* = 2.6 Hz, 1H), 3.09 (ddt, *J* = 15.4, 10.7, 2.4 Hz, 1H), 2.62 (ddt, *J* = 15.2, 8.4, 2.4 Hz, 1H).

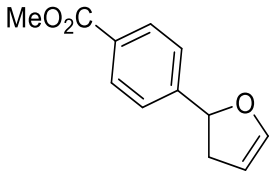
2-(4-Chlorophenyl)-2,3-dihydrofuran 249c



The title compound was prepared according to **GP F** using potassium acetate (1.8 g, 18.5 mmol, 2.2 equiv.), tetrabutylammoniumchloride (5.8 g, 21 mmol, 2.5 equiv.), 1-chloro-4-iodobenzene (1.1 mL, 8.4 mmol, 1.0 equiv.), 2,3-dihydrofuran (5.7 mL, 75 mmol, 9.0 equiv.), palladium acetate (94 mg, 0.4 mmol, 0.05 equiv.) in 10 mL DMF. The resulting crude brown oil was purified by column chromatography (SiO_2, hexanes:ethyl acetate 19:1) to give 2-(4-chlorophenyl)-2,3-dihydrofuran (738 mg, 4.1 mmol, 49%) as colorless oil. Analytical data is in accordance with literature.[158]

^{1}H NMR (300 MHz, $CDCl_3$) δ [ppm]= 7.44 – 7.24 (m, 4H), 6.44 (q, *J* = 2.4 Hz, 1H), 5.49 (dd, *J* = 10.7, 8.2 Hz, 1H), 4.96 (q, *J* = 2.6 Hz, 1H), 3.08 (ddt, *J* = 15.4, 10.7, 2.4 Hz, 1H), 2.55 (ddt, *J* = 15.2, 8.2, 2.4 Hz, 1H).

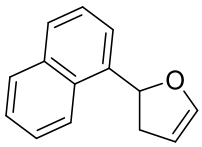
Methyl 4-(2,3-dihydrofuran-2-yl)benzoate 249d



The title compound was prepared according to **GP F** using potassium acetate (2.1 g, 21 mmol, 2.2 equiv.), tetrabutylammoniumchloride (6.6 g, 24 mmol, 2.5 equiv.), methyl 4-iodobenzoate (1.4 mL, 9.5 mmol, 1.0 equiv.), 2,3-dihydrofuran (6.5 mL, 86 mmol, 9.0 equiv.), palladium acetate (107 mg, 0.5 mmol, 0.05 equiv.) in 8 mL DMF. The resulting crude brown oil was purified by column chromatography (SiO_2, hexanes:ethyl acetate 19:1) to give methyl 4-(2,3-dihydrofuran-2-yl)benzoate (548 mg, 2.7 mmol, 28%) as colorless oil. Analytical data is in accordance with literature.[158]

^{1}H NMR (300 MHz, $CDCl_3$) δ [ppm]= 8.15 – 7.96 (m, 2H), 7.50 – 7.35 (m, 2H), 6.47 (q, *J* = 2.4 Hz, 1H), 5.57 (dd, *J* = 10.9, 8.2 Hz, 1H), 4.97 (q, *J* = 2.6 Hz, 1H), 3.92 (s, 3H), 3.13 (ddt, *J* = 15.5, 10.9, 2.4 Hz, 1H), 2.57 (dd, *J* = 15.2, 8.1 Hz, 1H).

2-(Naphthalen-1-yl)-2,3-dihydrofuran 249b

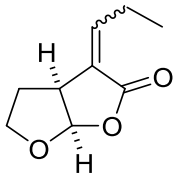


The title compound was prepared according to **GP F** using potassium acetate (2.3 g, 24 mmol, 2.2 equiv.), tetrabutylammoniumchloride (7.5 g, 27 mmol, 2.5 equiv.), 1-iodonaphthalene (1.6 mL, 11 mmol, 1.0 equiv.), 2,3-dihydrofuran (7.4 mL, 97 mmol, 9.0 equiv.), palladium acetate (122 mg, 0.5 mmol, 0.05 equiv.) in 10 mL DMF. The resulting crude brown oil was purified by column chromatography (SiO_2, hexanes:ethyl acetate 19:1) to give 2-(naphthalen-1-yl)-2,3-dihydrofuran (1.0 g, 5.1 mmol, 47%) as colorless oil. Analytical data is in accordance with literature.[158]

^{1}H NMR (300 MHz, $CDCl_3$) δ [ppm]= 7.97 – 7.87 (m, 2H), 7.80 (dt, *J* = 8.2, 1.1 Hz, 1H), 7.65 – 7.44 (m, 4H), 6.59 (q, *J* = 2.4 Hz, 1H), 6.18 (dd, *J* = 11.0, 8.5 Hz, 1H), 5.04 (q, *J* = 2.6 Hz, 1H), 3.30 (ddt, *J* = 15.2, 11.0, 2.4 Hz, 1H), 2.67 (ddt, *J* = 15.2, 8.5, 2.4 Hz, 1H).

5.10 Other reactions

Lactone 273d



A 100 mL 2-necked round bottom flask was charged with methyl -6-((*E*)-prop-1-en-1-yl)-2-oxabicyclo[3.1.0]hexane-6-carboxylate **250d** (1.00 g, 5.49 mmol, 1.0 equiv.) and *p*-toluenesulfonic acid (3.78 g, 22.0 mmol, 4.0 equiv.) and dissolved in 30 mL acetone (c=0.2 M). The reaction was stirred for 20 minutes at 60 °C until a brown discoloration was observed. Full conversion of the starting material was determined *via* TLC. The solvent was removed *in vacuo*, the crude mixture redissolved in 30 mL MeCN and NEt_3 (3.64 mL, 27.4 mmol, 5.0 equiv.) was added. The mixture was stirred at 76 °C for 3 h. The reaction was extracted with EtOAc (3x10 mL) and the organic phases washed with brine, dried over Na2SO4. The solvent was evaporated under reduced pressure to give 3-Propylidenetetrahydrofuro[2,3-*b*]furan-2(3*H*)-one (809 mg, 4.8 mmol, 88%) as a mixture of 2 diastereomers as a yellow oil.

Major:

^{1}H NMR (400 MHz, $CDCl_3$) δ [ppm]= 6.71 (tdd, *J* = 7.7, 2.5, 1.2 Hz, 1H), 6.01 (d, *J* = 5.6 Hz, 1H), 4.01 (ddd, *J* = 9.1, 8.0, 1.4 Hz, 1H), 3.76 – 3.65 (m, 1H), 3.56 (dddt, *J* = 8.1, 5.6, 2.6, 1.4 Hz, 1H), 2.32 – 2.16 (m, 3H), 1.79 (ddt, *J* = 12.4, 5.6, 1.5 Hz, 1H), 1.14 – 1.00 (m, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ [ppm]= 169.57, 144.42, 128.86, 105.58, 66.85, 41.53, 32.70, 23.35, 12.71.

Minor

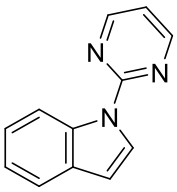
^{1}H NMR (400 MHz, $CDCl_3$) δ [ppm]= 6.26 (td, *J* = 7.7, 2.1 Hz, 1H), 5.93 (d, *J* = 5.6 Hz, 1H), 3.98 – 3.94 (m, 1H), 3.63 – 3.60 (m, 1H), 3.25 – 3.18 (m, 1H), 2.75 – 2.59 (m, 2H), 1.71 – 1.58 (m, 2H), 0.99 (t, *J* = 7.6 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ [ppm]= 168.60, 148.69, 127.31, 104.84, 66.67, 44.44, 34.78, 21.35, 13.39.

IR (neat): 2971, 2876, 1752, 1674, 1454, 1349, 1305, 1252, 1215, 1185, 1152, 1103, 1010, 958, 865, 753, 671 cm^{-1}.

HR-MS (EI-MS): m/z calc. for $C_9H_{12}O_3$ [M+·] 168.07810, found 168.07766.

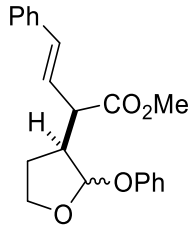
1-(Pyrimidin-2-yl)-1H-indole 251



A flame-dried 50 mL round-bottomed Schlenk flask was charged with indene (1.17 g, 10.0 mmol, 1 equiv.) in 10 mL of dry DMF and cooled to 0 °C. Sodium hydride (60% suspension in oil, 360 mg, 15.0 mmol, 1.5 equiv.) was added in portions. The solution was stirred for 1 hour at 0 °C, during which a white precipitate formed. 2-Chloropyrimidine (1.72 g, 15.0 mmol, 1.5 equiv.) was added, upon which the precipitate re-dissolved. The reaction was heated to 150 °C for 16 hours. After cooling to room temperature, the reaction mixture was poured onto a mixture of 150 mL saturated NaCl-solution and 150 mL ethyl acetate. The aqueous phase was extracted twice with ethyl acetate (150 mL), the combined organic phases dried over $MgSO_4$ and the solvent evaporated *in vacuo*. The crude product was purified *via* column chromatography (SiO2, hexanes/ethyl acetate 19:1 to 9:1) to give 1-(pyrimidin-2-yl)-1H-indole (826.1 mg, 4.23 mmol, 42%) as a white solid. Analytical data is in accordance with literature.[257]

^{1}H-NMR (300 MHz, $CDCl_3$) δ [ppm]= 8.85 – 8.78 (m, 1H), 8.75 – 8.68 (m, 2H), 8.29 (d, *J* = 3.5 Hz, 1H), 7.63 (dt, *J* = 7.7, 1.0 Hz, 1H), 7.35 (ddd, *J* = 8.4, 7.1, 1.4 Hz, 1H), 7.28 – 7.21 (m, 1H), 7.06 (t, *J* = 4.9 Hz, 1H), 6.71 (dd, *J* = 3.7, 0.8 Hz, 1H).

Methyl (*E*)-2-(2-phenoxytetrahydrofuran-3-yl)-4-phenylbut-3-enoate 308c



A Schlenk pressure tube was charged with methyl (E)-6-styryl-2-oxabicyclo[3.1.0]hexane-6-carboxylate **250a** (122 mg, 500 µmol, 1.0 equiv.), $[MesAcrMe]ClO_4$ (2.1 mg, 5.0 µmol, 0.01 equiv.), $NaH_2PO_4 \cdot H_2O$ (17 mg, 125 µmol, 0.25 equiv.), phenol (47.0 mg, 500 µmol, 1 equiv.) and PhSH (20 µl, 200 µmol, 0.4 equiv.) in dry MeCN and degassed by 3 FPT cycles. The pressure tube was sealed 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 was magnetically stirred from below. The mixture was stirred for 3 hours under N_2 atmosphere. The reaction mixture was quenched with 1 M aqueous NaOH solution and extracted with 5 mL EtOAc. The combined organic phases were washed 5 times with 1 M aqueous NaOH and dried over $NaSO_4$. The solvent was evaporated *in vacuo* and the crude product purified by column chromatography.

R_f (SiO2, 95:4:1 toluene/DCM/EtOAc)=0.4

^{1}H-NMR (minor) (300 MHz, CDCl3) δ[ppm]= 7.42 – 7.27 (m, 7H), 7.06 – 6.95 (m, 3H), 6.55 (d, J = 15.8 Hz, 1H), 6.19 (dd, J = 15.8, 9.5 Hz, 1H), 5.58 (d, J = 2.0 Hz, 1H), 4.07 – 4.00 (m, 2H), 3.69 (s, 3H), 3.24 – 3.15 (m, 1H), 2.99 – 2.87 (m, 1H), 2.30 – 2.17 (m, 1H), 1.89 – 1.76 (m, 1H).

^{1}H-NMR (major) (300 MHz, CDCl3) δ[ppm]= 7.43 – 7.19 (m, 7H), 7.02 – 6.91 (m, 3H), 6.59 (d, J = 15.8 Hz, 1H), 6.24 (dd, J = 15.8, 9.4 Hz, 1H), 5.62 (d, J = 1.5 Hz, 1H), 4.07 (t, J = 7.1 Hz, 2H), 3.74 (s, 3H), 3.27 – 3.14 (m, 1H), 2.96 (dddd, J = 9.8, 7.9, 4.8, 1.5 Hz, 1H), 2.36 (ddt, J = 12.9, 7.9, 6.6 Hz, 1H), 1.75 (dtd, J = 12.4, 7.5, 4.7 Hz, 1H).

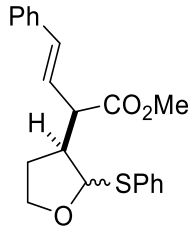
^{13}C-NMR (minor) (101 MHz, CDCl3) δ[ppm]= 173.08, 157.10, 136.32, 134.23, 129.41, 128.65, 128.00, 126.50, 124.88, 121.85, 116.80, 104.99, 67.32, 52.19, 51.31, 48.17, 27.94.

^{13}C-NMR (major) (101 MHz, CDCl3) δ[ppm]= 173.05, 156.99, 136.35, 134.42, 129.49, 128.71, 128.09, 126.63, 125.23, 121.96, 117.02, 104.58, 67.49, 52.31, 52.13, 48.09, 28.63.

HR-MS (ESI-MS) m/z calc. for C21H22O4 361.141, found 361.1416.

IR (neat)= 3027, 2952, 2892, 1733, 1595, 1491, 1435, 1364, 1264, 1223, 1159, 1070, 965, 869, 835, 753, 693 cm^{-1}

Methyl (*E*)-4-phenyl-2-(-2-(phenylthio)tetrahydrofuran-3-yl)but-3-enoate 310



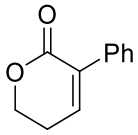
A Schlenk pressure tube was charged with methyl (E)-6-styryl-2-oxabicyclo[3.1.0]hexane-6-carboxylate **250a** (48.9 mg, 200 µmol, 1.0 equiv.), [MesAcrMe]ClO_4 (0.8 mg, 2.0 µmol, 0.01 equiv.), bioactive glass 45S5 (9.8 mg, 20 wt%) and PhSH (20 µl, 200 µmol, 1.0 equiv.) in 9:1 MeCN/H_2O and degassed by 3 FPT cycles. The pressure tube was sealed 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 was magnetically stirred from below. The mixture was stirred for 2 hours under N_2 atmosphere. The reaction mixture was quenched with 1 M aqueous NaOH solution and extracted with 5 mL EtOAc. The solvent was evaporated *in vacuo* and the residue mixed with 28 mg of tetrachloroethane. The mixture was dissolved in 1.0 mL $CDCl_3$, of which 0.5 mL was taken and diluted to 0.7 mL for NMR measurement. The NMR yield was determined to be 71%. Because of machine malfunction, NMRs are not completely clean, however, it was determined the important signals for structure analysis were legible and therefore the structure can be seen as reliable.

Diastereomer 1: **^{1}H-NMR** (300 MHz, CDCl3) δ[ppm]= 7.58 – 7.47 (m, 2H), 7.42 – 7.18 (m, 8H), 6.51 (d, J = 15.8 Hz, 1H), 6.20 (dd, J = 15.8, 9.6 Hz, 1H), 5.37 (d, J = 5.0 Hz, 1H), 4.06 – 3.94 (m, 2H), 3.73 (s, 3H), 3.25 (t, J = 9.2 Hz, 1H), 2.69 (qd, J = 8.1, 5.0 Hz, 1H), 2.19 – 2.02 (m, 1H), 1.82 – 1.66 (m, 1H).

^{13}C-NMR (101 MHz, CDCl3) δ[ppm]0 171.82, 135.28, 134.04, 133.20, 130.58, 127.84, 127.59, 126.95, 126.12, 125.46, 123.44, 89.21, 65.77, 51.60, 51.12, 47.14, 28.50.

HRMS (ESI-MS); m/z calc. for $C_{21}H_{22}O_3S$ 355.1362, found 355.1361.

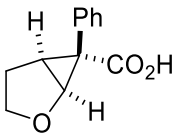
3-Phenyl-5,6-dihydro-2H-pyran-2-one 249



A flame-dried 25 mL Schlenk round bottomed flask was charged with methyl-6-phenyl-2-oxabicyclo[3.1.0]hexane-6-carboxylate **253a** (437 mg, 2.0 mmol, 1.0 equiv.) and NIS (540 mg, 2.4 mmol, 1.2 equiv.) and dissolved in 10 mL dry MeOH. The flask was covered in aluminum foil to ensure dark conditions and the reaction stirred for 19 hours at 25 °C. The mixture was transferred to a separation funnel and DCM (15 mL) and aqueous Na2SO3 (sat) (10 mL) were added. The layers were separated and the aqueous layer extracted twice with DCM (15 mL). The reaction was dried over Na2SO4 and concentrated *in vacuo* and the crude product purified by column chromatography (12 g silica column, flowrate 15 mL/min, hexanes:ethyl acetate 0% to 10% over 15 minutes, 10 minute hold) to yield 3-phenyl-5,6-dihydro-2H-pyran-2-one (127 mg, 729 µmol, 26%) as a white solid. Suitable crystals for X-Ray crystallography were obtained from evaporation of *n*-heptane. Analytical data is in accordance with literature.[258]

^{1}H-NMR (400 MHz, $CDCl_3$) δ [ppm]= 7.52 – 7.43 (m, 2H), 7.41 – 7.31 (m, 3H), 7.00 (t, *J* = 4.4 Hz, 1H), 4.53 – 4.45 (m, 2H), 2.63 (td, *J* = 6.2, 4.5 Hz, 2H).

6-Phenyl-2-oxabicyclo[3.1.0]hexane-6-carboxylic acid 253i



A 25 mL round bottomed flask was charged with methyl-6-phenyl-2-oxabicyclo[3.1.0]hexane-6-carboxylate **253a** (437 mg, 2.0 mmol, 1.0 equiv.) and dissolved in 10 mL of THF/H2O 1:1 and cooled to 0 °C. LiOH (191 mg, 8.0 mmol, 4 equiv.) were added, the mixture stirred for 5 minutes at 0 °C and then warmed to room

temperature and stirred for 4 hours. The THF was evaporated, and the reaction mixture extracted three times with EtOAc (10 mL). The aqueous phase was acidified with 6 M HCl and extracted with EtOAc (3x5 mL). After drying over Na2SO4, the solvent was evaporated to give 6-phenyl-2-oxabicyclo[3.1.0]hexane-6-carboxylic acid (346 mg, 1.7 mmol, 85%) as white solid.

^{1}H-NMR (300 MHz, CDCl3) δ [ppm]= 7.42 – 7.28 (m, 5H), 4.54 (d, J = 5.7 Hz, 1H), 3.78 (ddd, J = 10.3, 8.5, 3.6 Hz, 1H), 2.67 (t, J = 5.8 Hz, 1H), 2.41 (q, J = 8.7 Hz, 1H), 2.31 – 2.17 (m, 1H), 1.86 (ddd, J = 12.6, 8.6, 3.6 Hz, 1H).

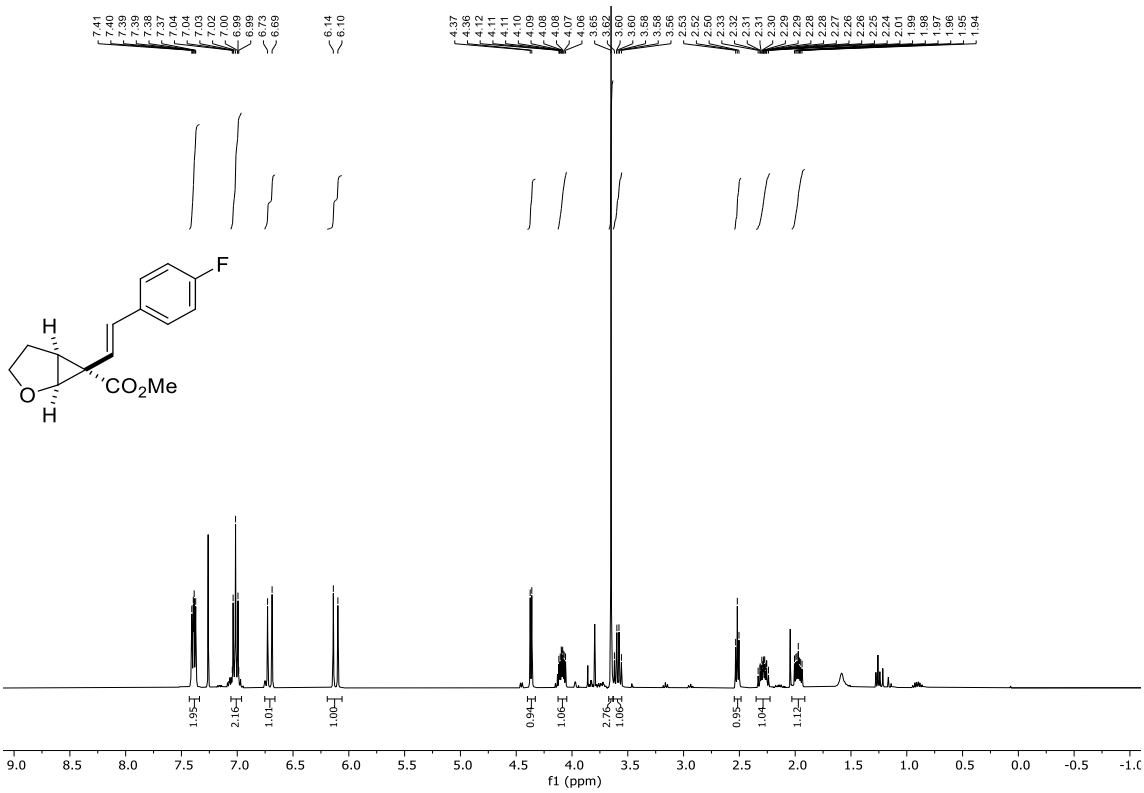
^{13}C-NMR (75 MHz, CDCl3) δ [ppm]= 176.77, 131.58, 131.41, 128.60, 127.81, 70.59, 70.06, 37.82, 32.98, 26.18.

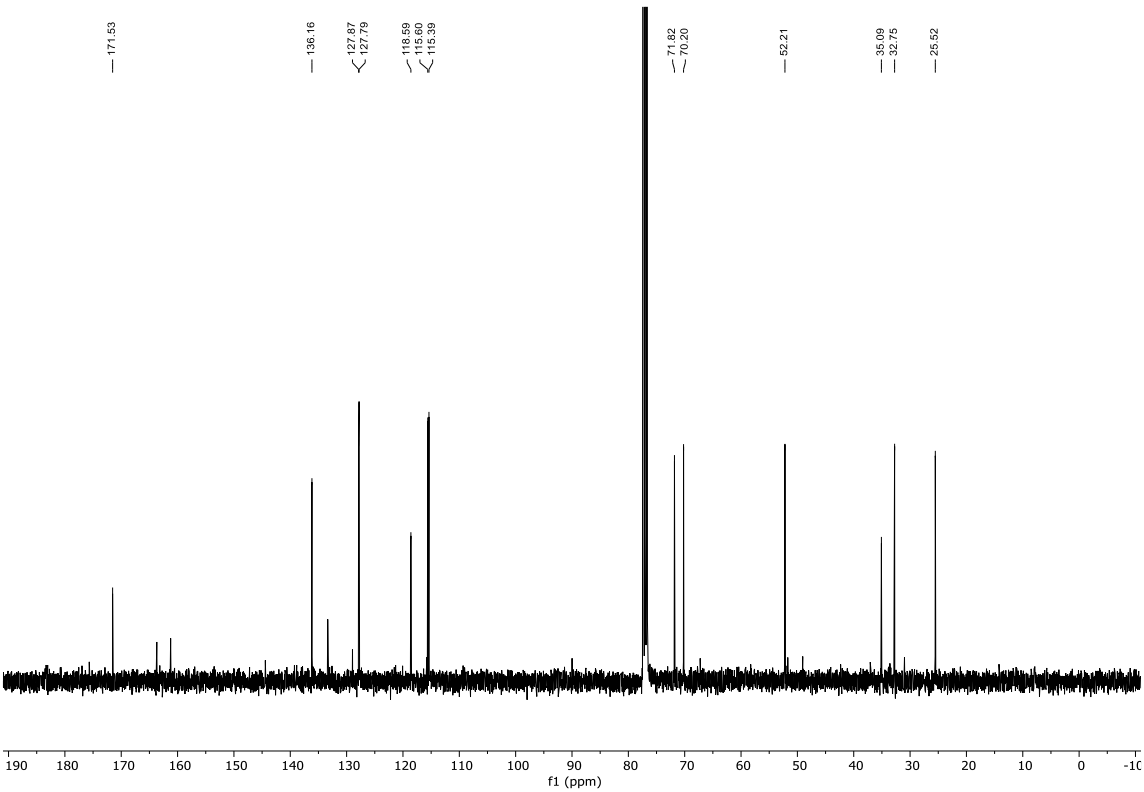
IR (neat): 3027, 2956, 2896, 2825, 2643, 2576, 2497, 1670, 1495, 1424, 1334, 1267, 1200, 1155, 1118, 1070, 1036, 917, 872, 697 cm^{-1}.

HR-MS (EI-MS) m/z calc. for $C_{12}H_{12}O_3$ 204.07810, found 204.07777.

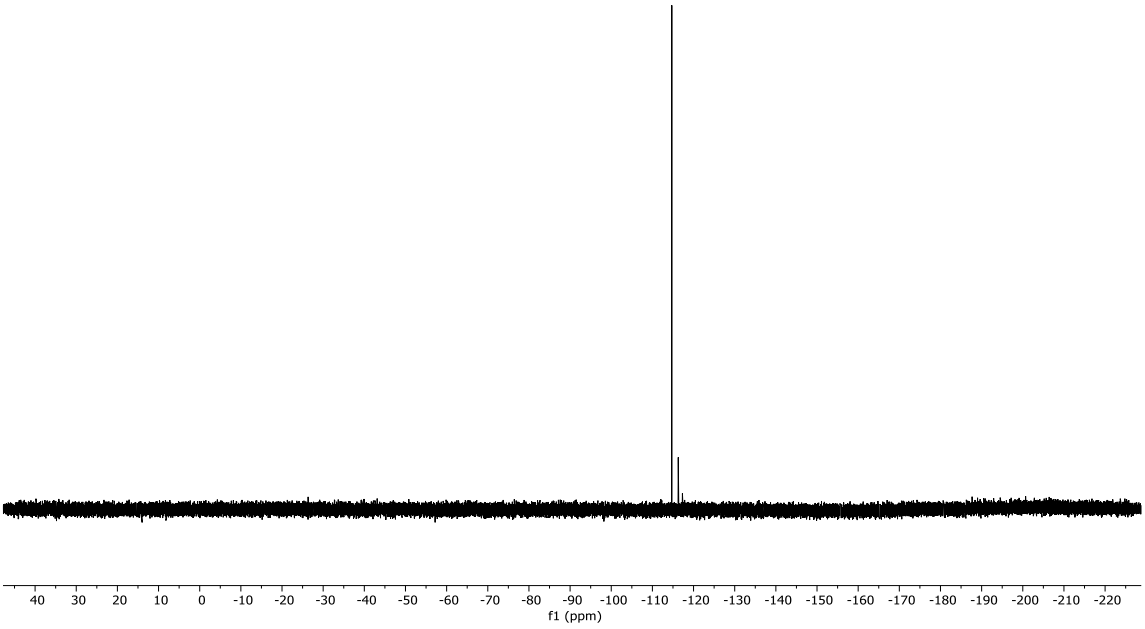
6 NMR Spectra

Methyl (E)-6-(4-fluorostyryl)-2-oxabicyclo[3.1.0]hexane-6-carboxylate 250b

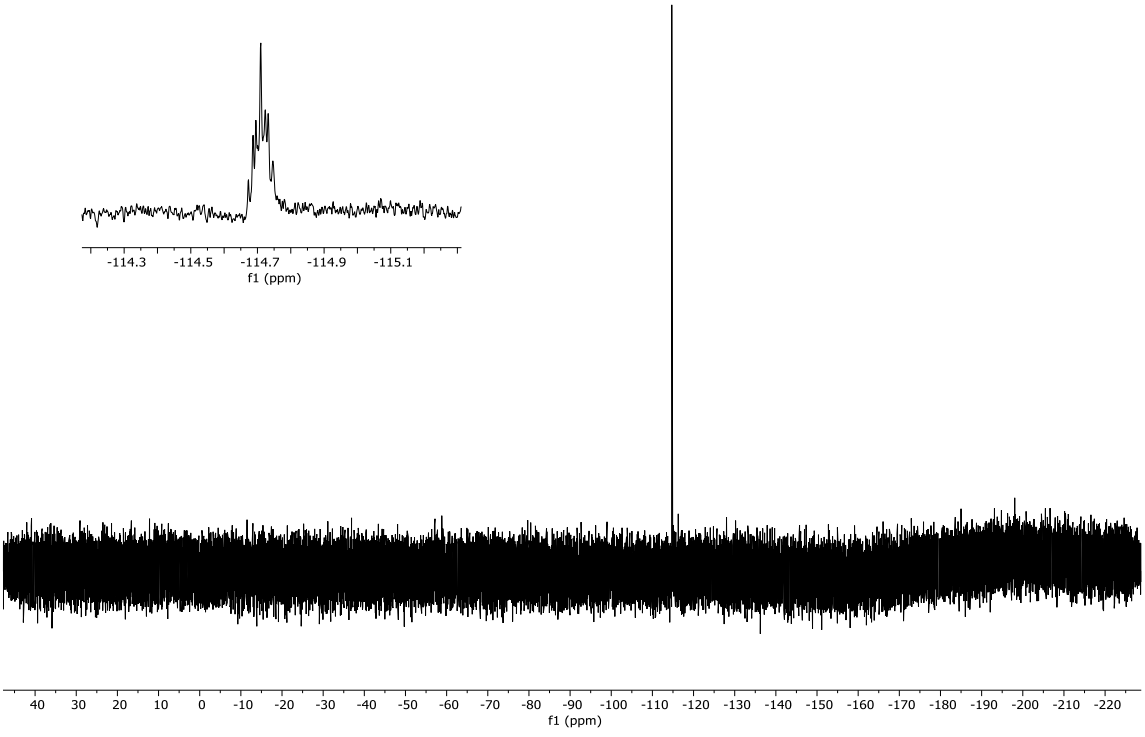




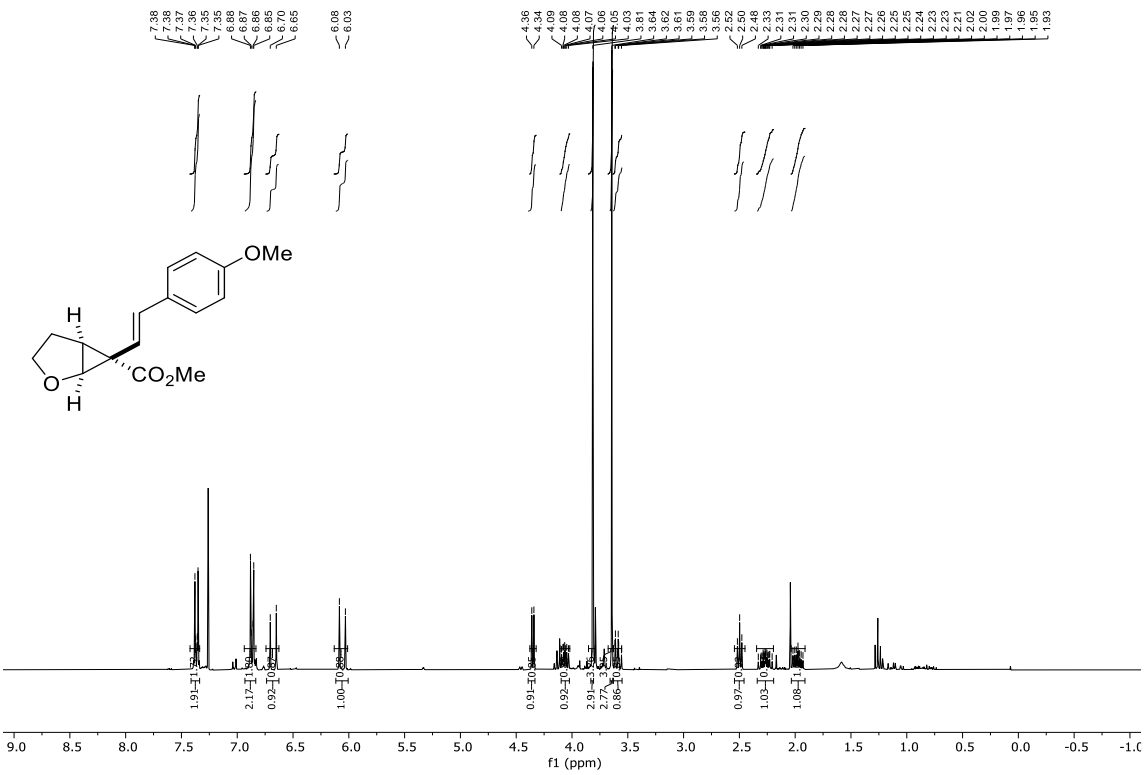
$^{19}F\{^{1}H\}$-NMR

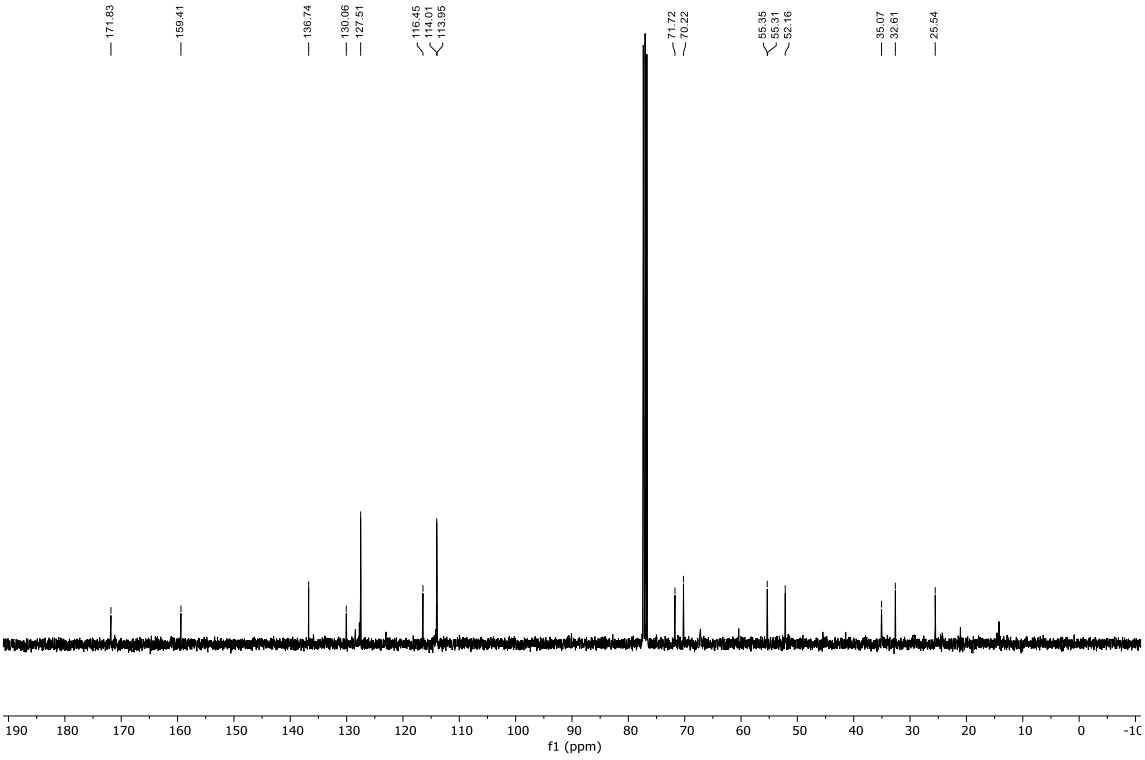


^{19}F-NMR

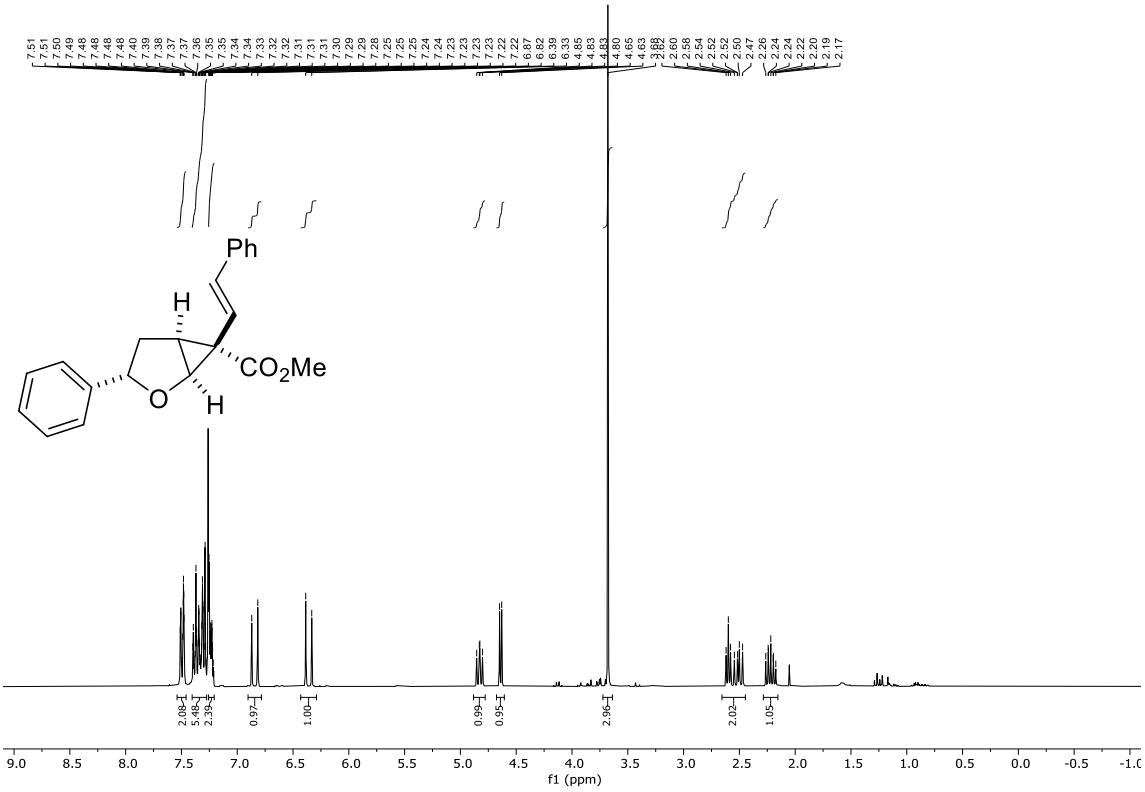


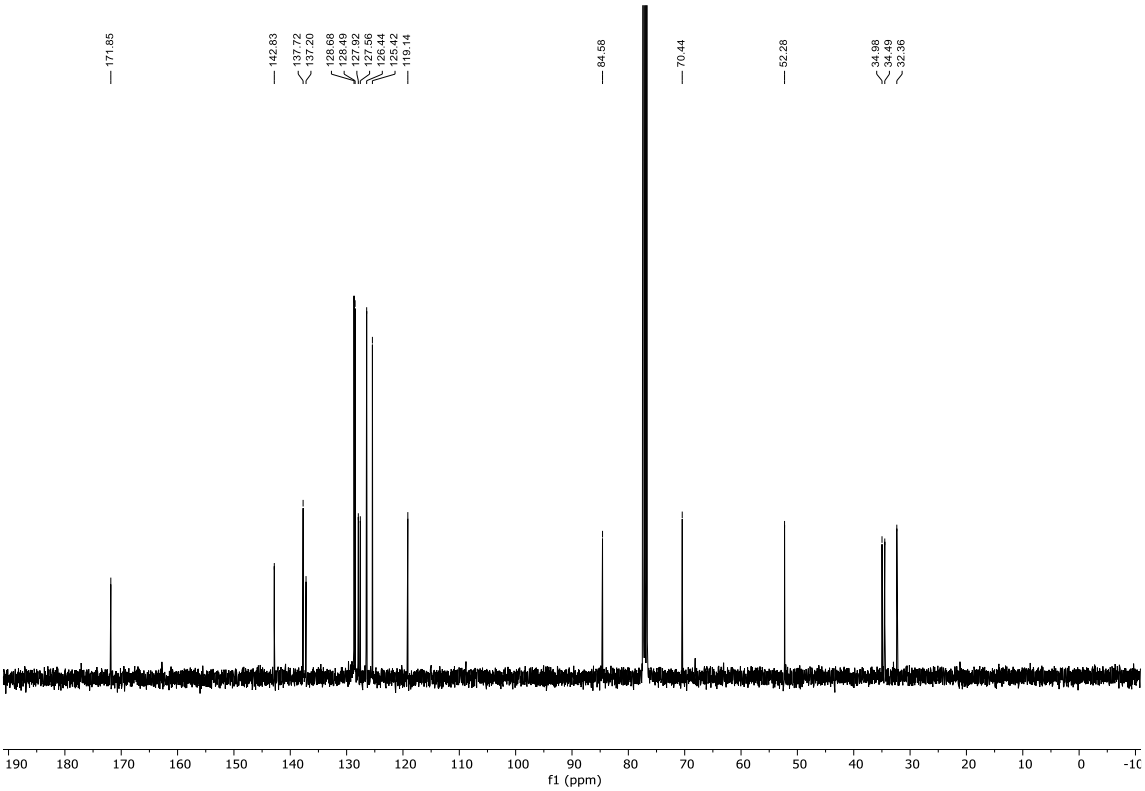
Methyl (E)-6-(4-methoxystyryl)-2-oxabicyclo[3.1.0]hexane-6-carboxylate 250c





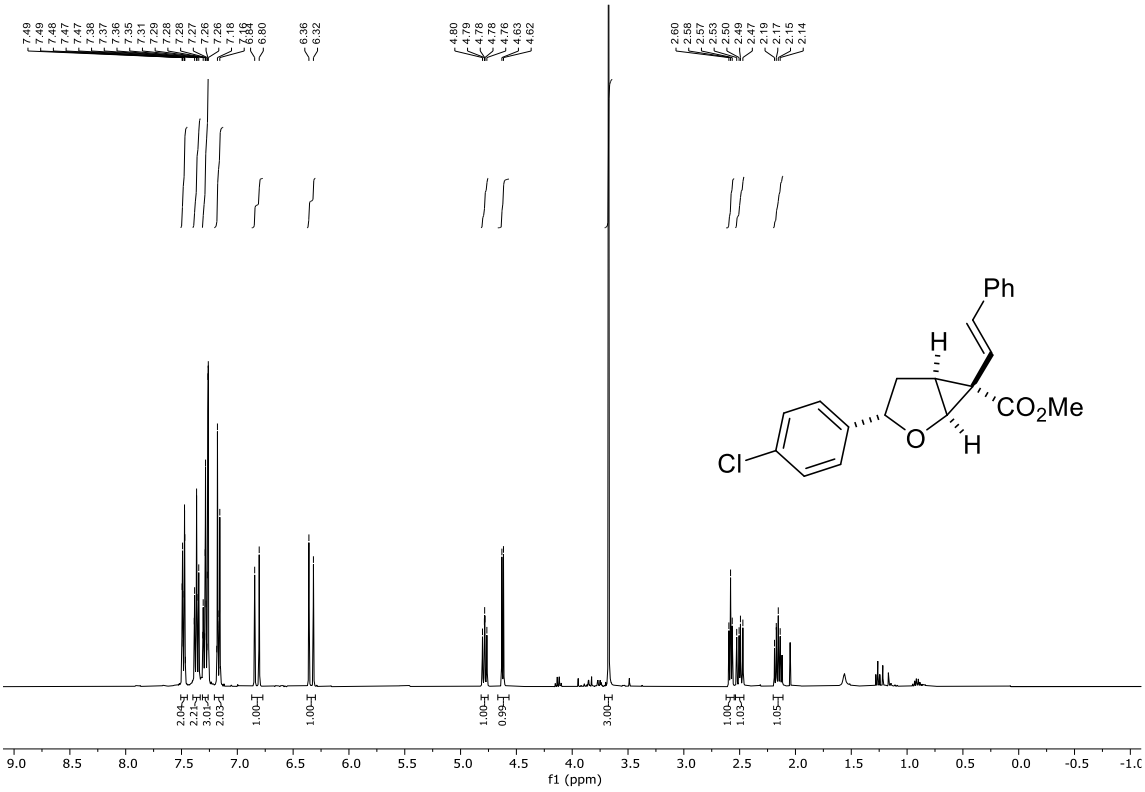
Methyl-3-phenyl-6-((E)-styryl)-2-oxabicyclo[3.1.0]hexane-6-carboxylate 250e

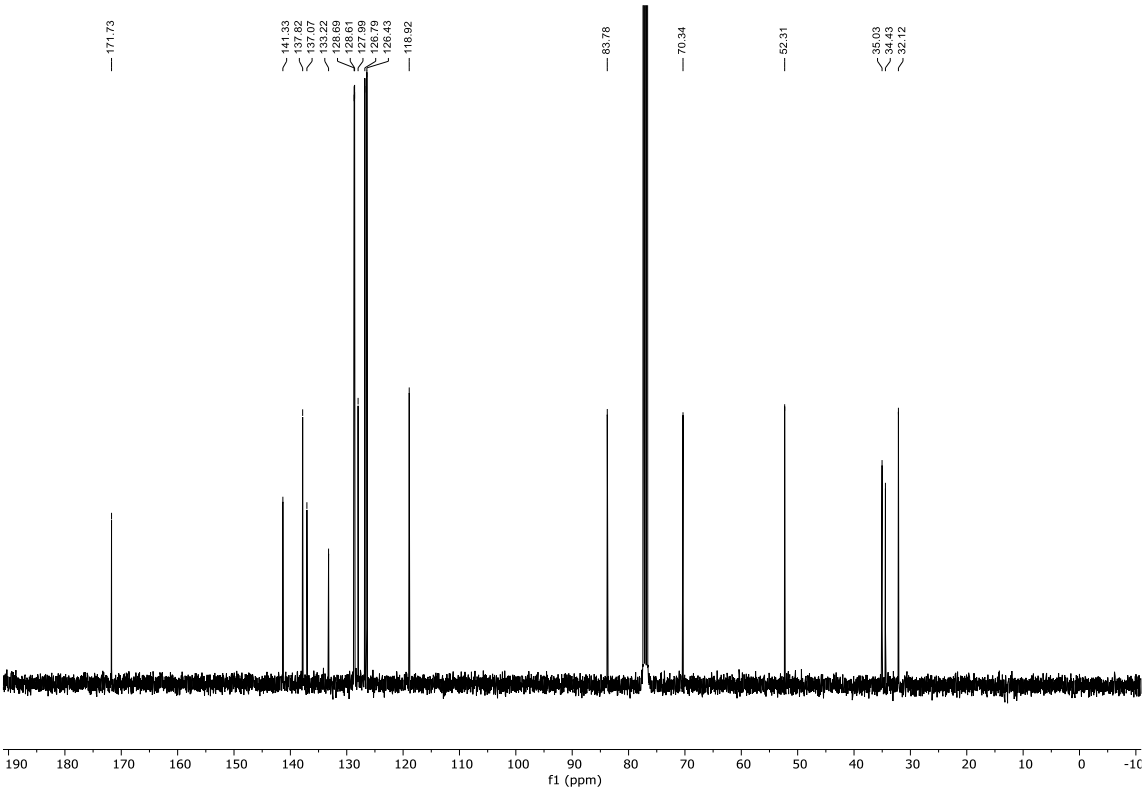




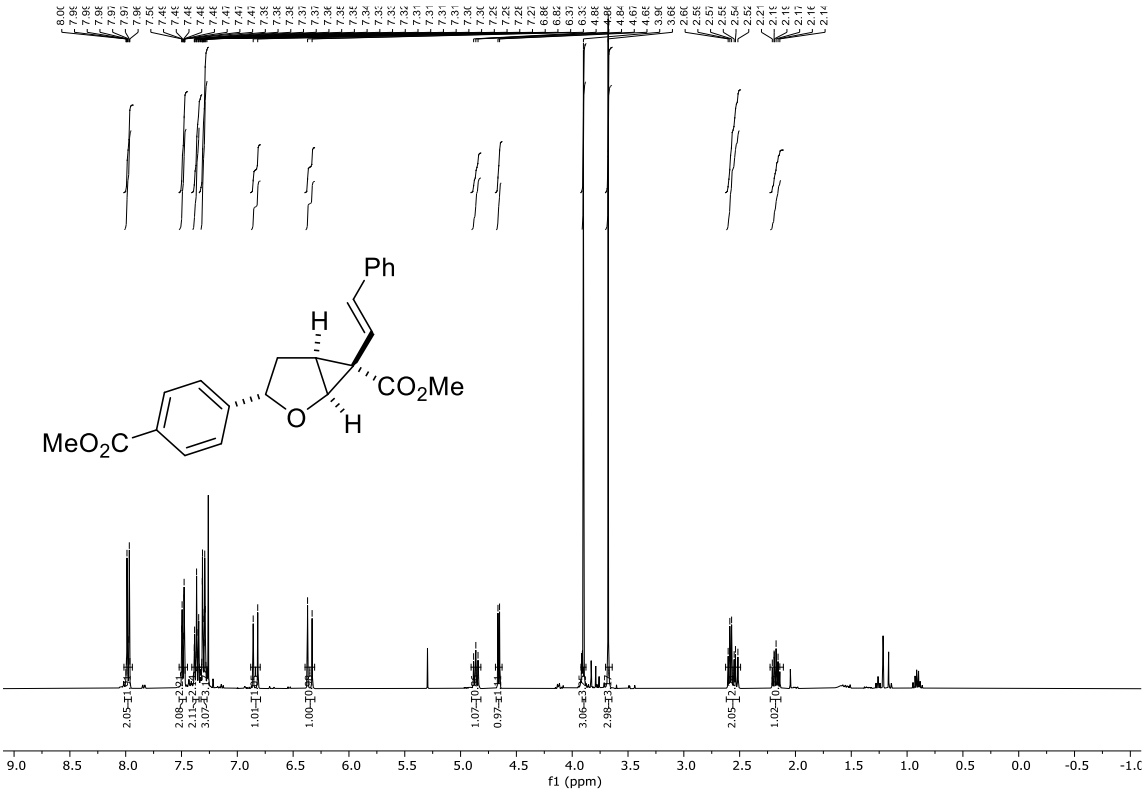
Methyl-3-(4-chlorophenyl)-6-((E)-styryl)-2-oxabicyclo[3.1.0]hexane-6-carboxylate

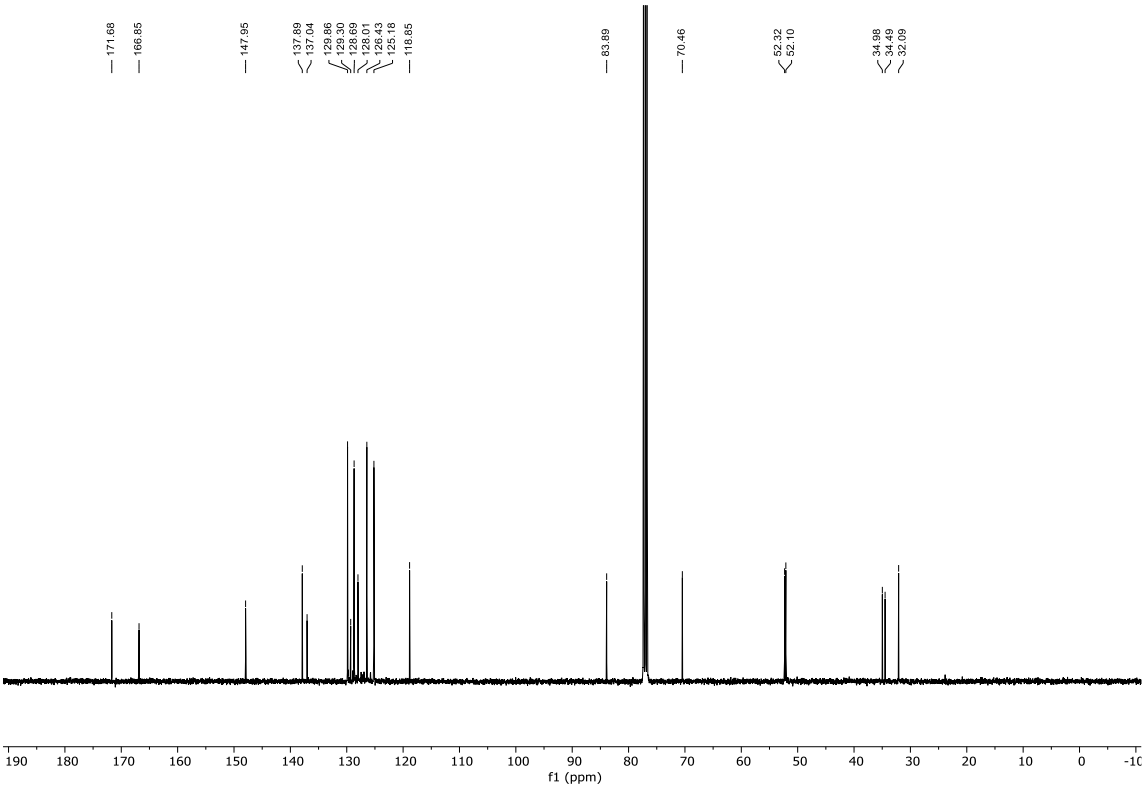
250f





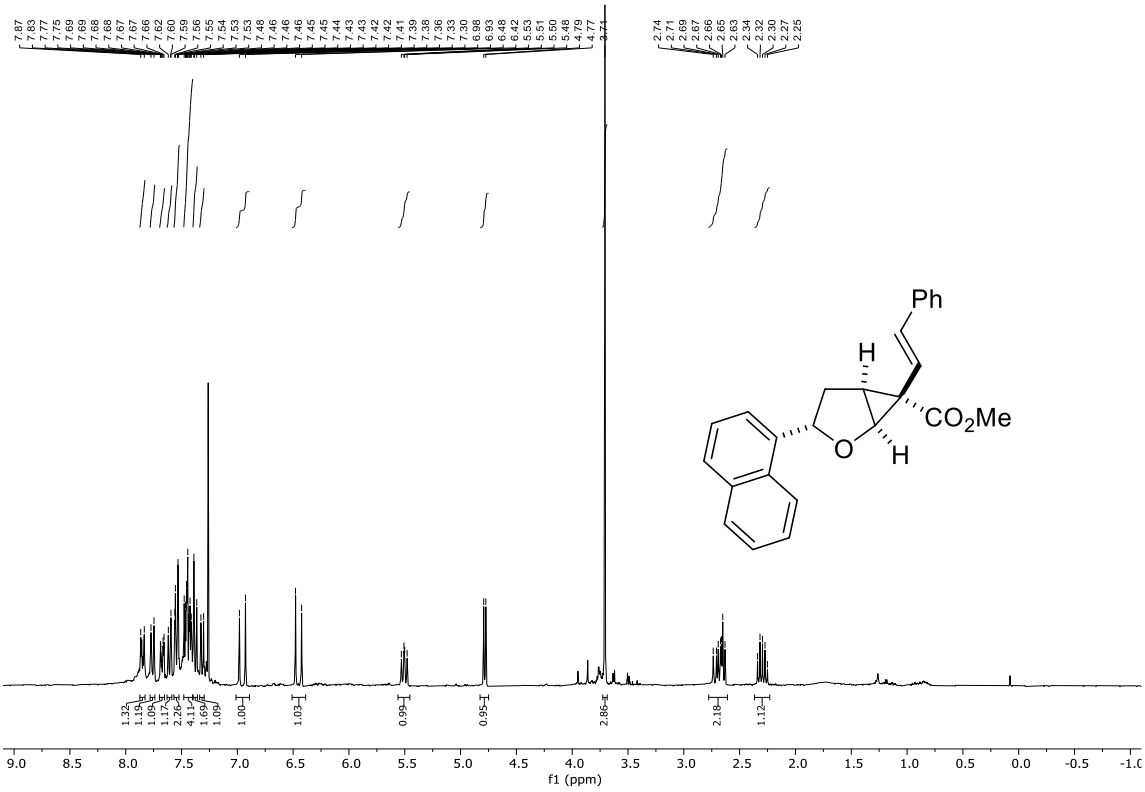
Methyl-3-(4-(methoxycarbonyl)phenyl)-6-((E)-styryl)-2-oxabicyclo[3.1.0]hexane-6-carboxylate 250g

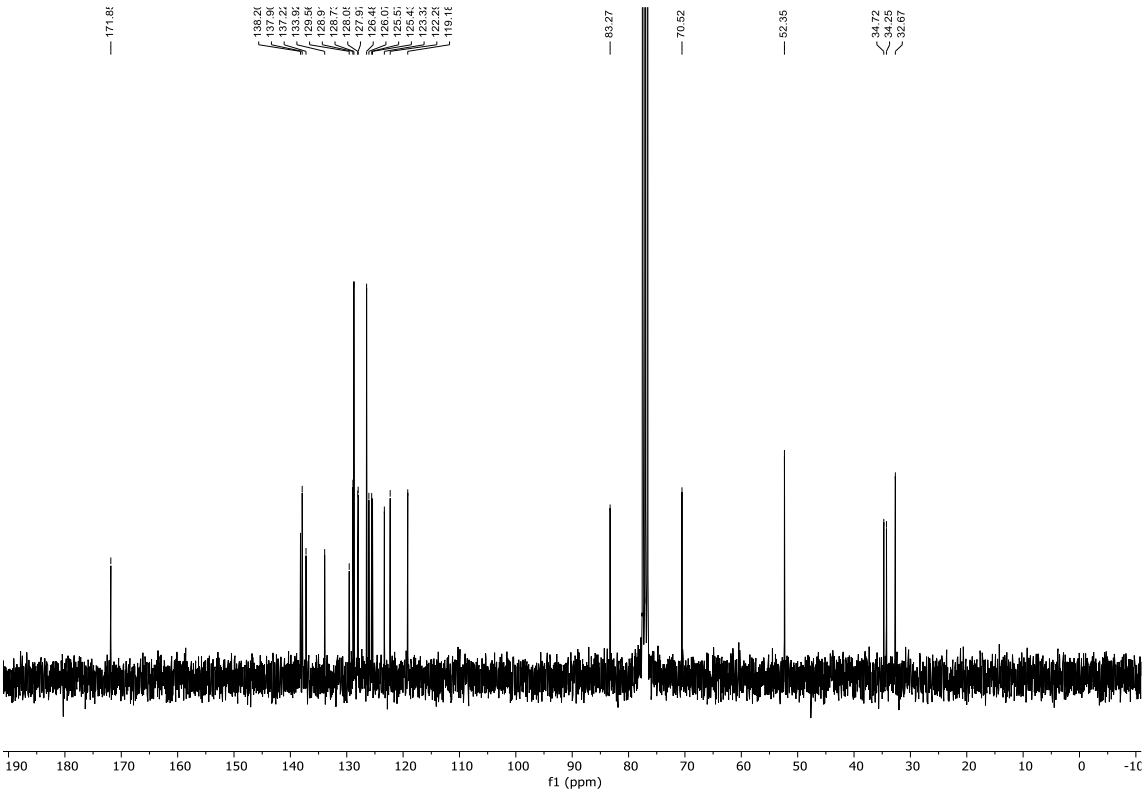




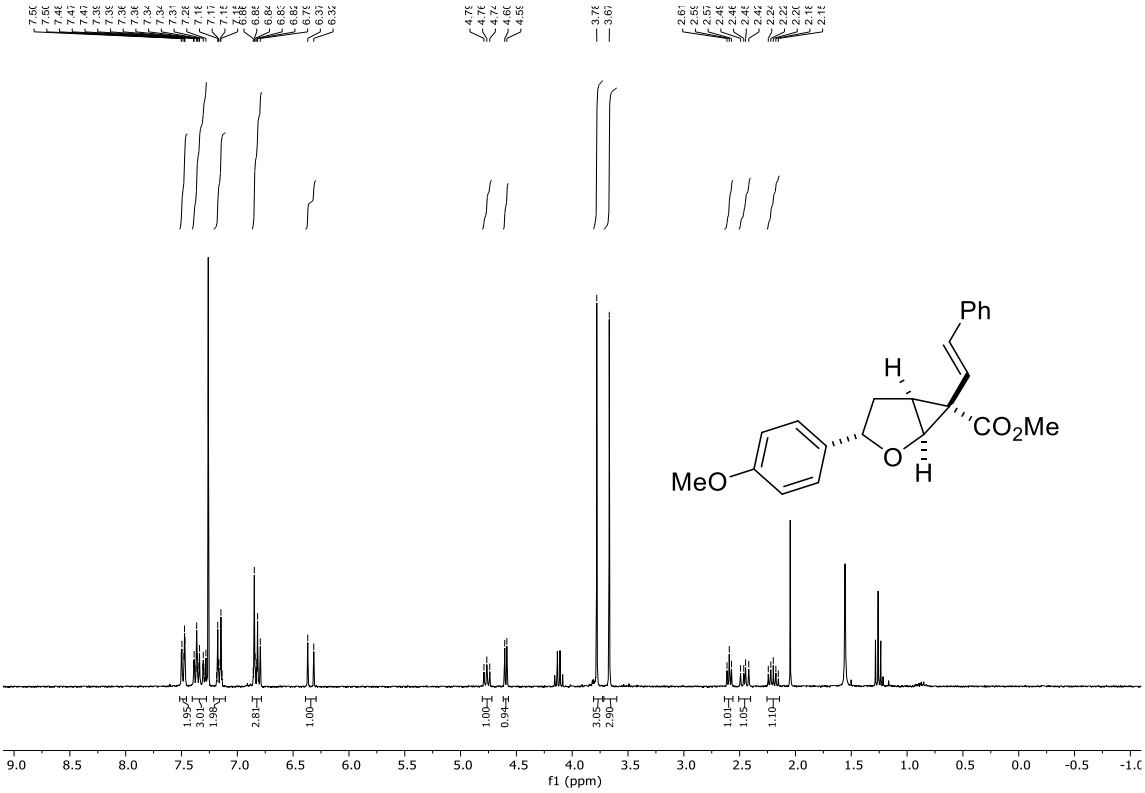
Methyl-3-(naphthalen-1-yl)-6-((E)-styryl)-2-oxabicyclo[3.1.0]hexane-6-carboxylate

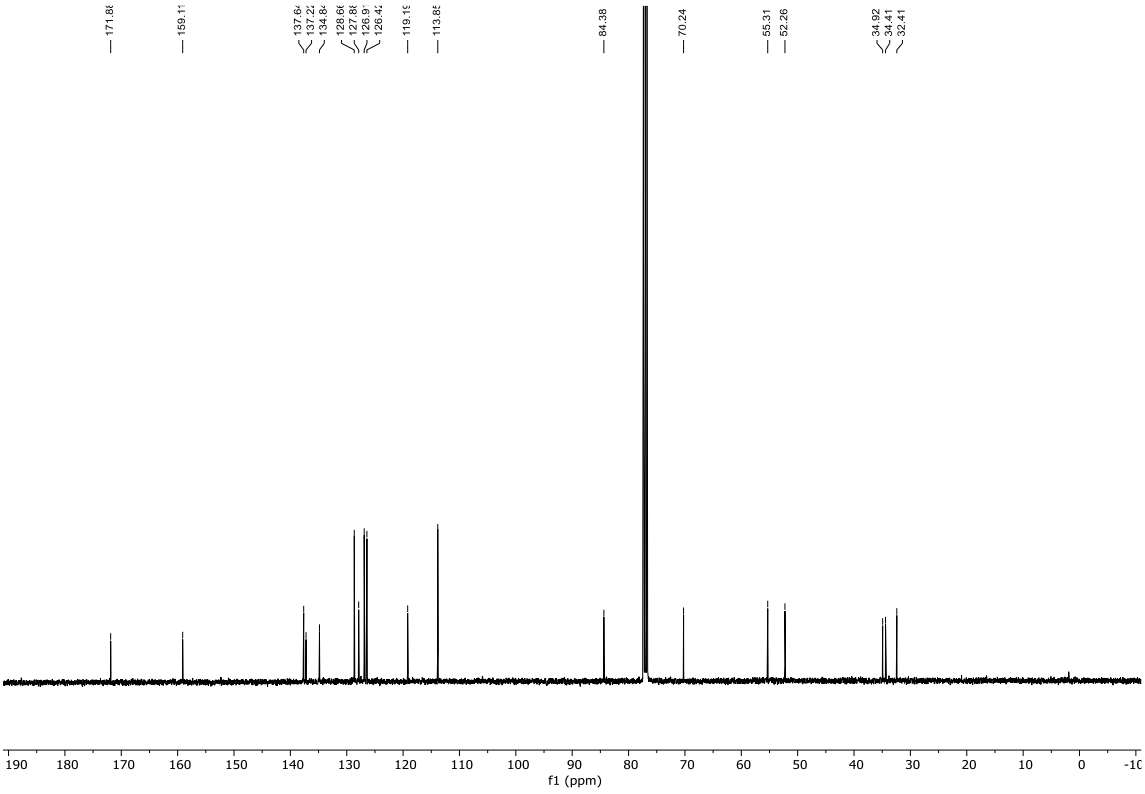
250h



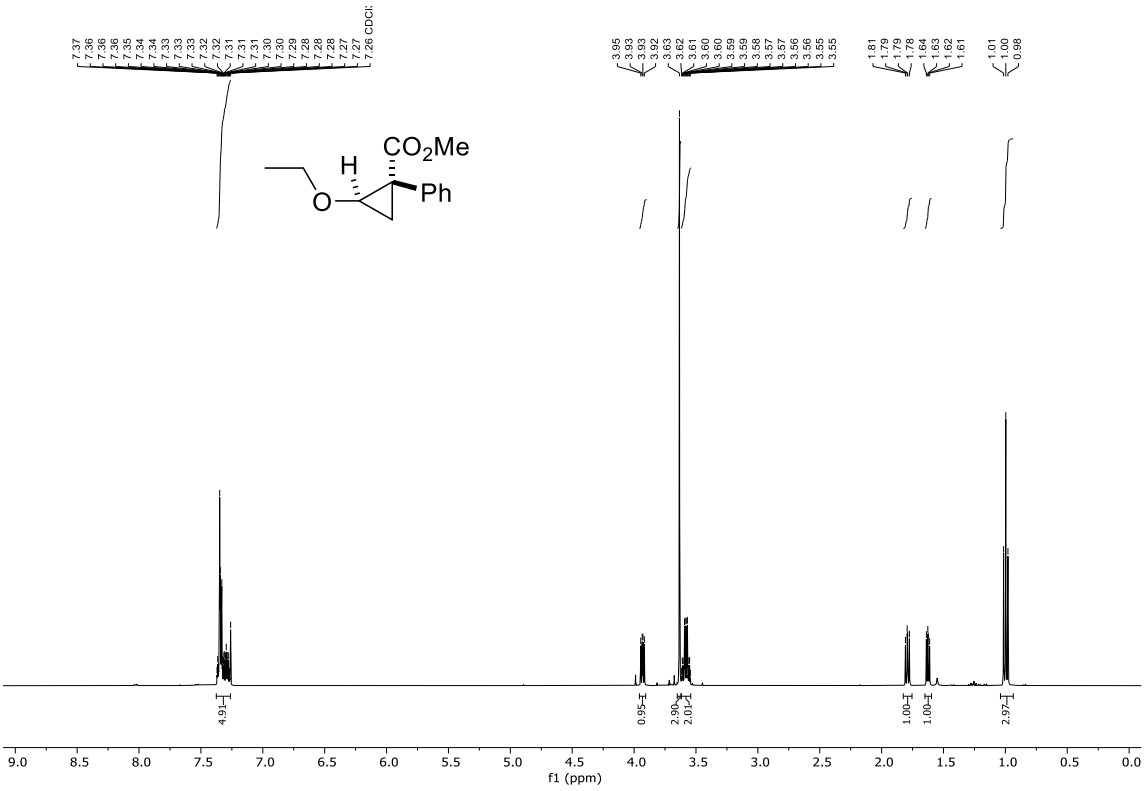


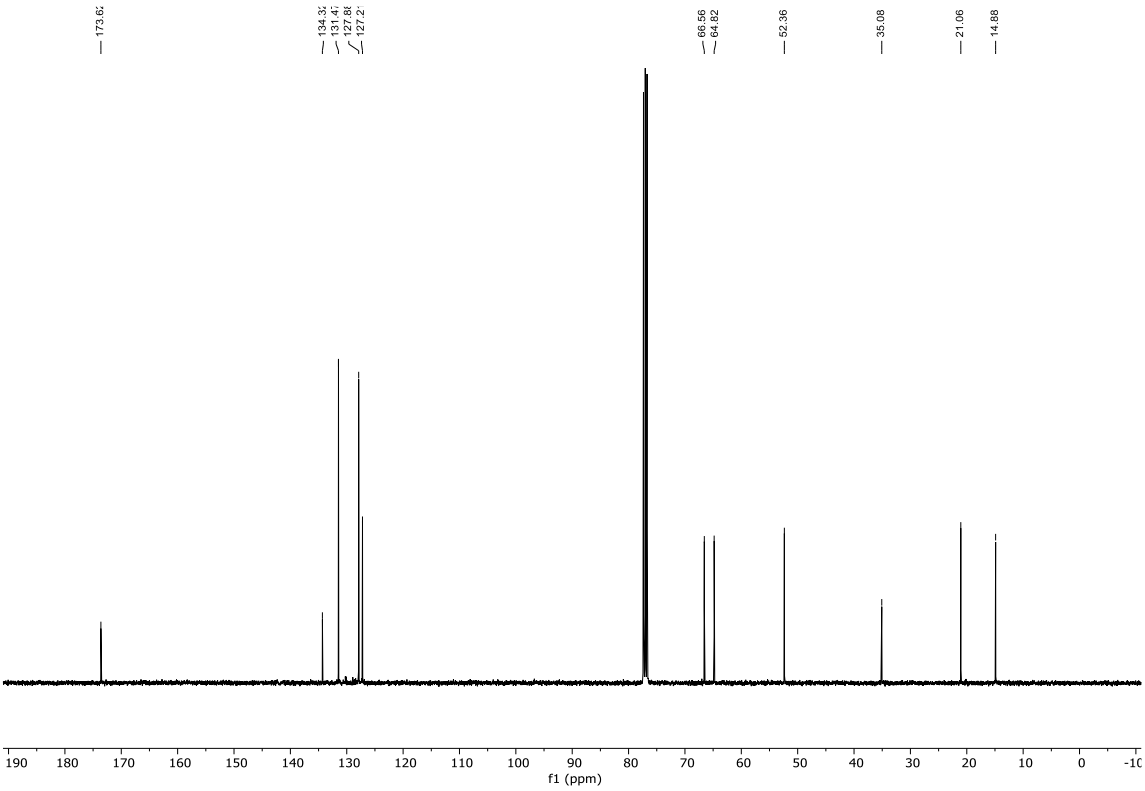
Methyl (E)-3-(4-methoxyphenyl)-6-styryl-2-oxabicyclo[3.1.0]hexane-6-carboxylate 250i



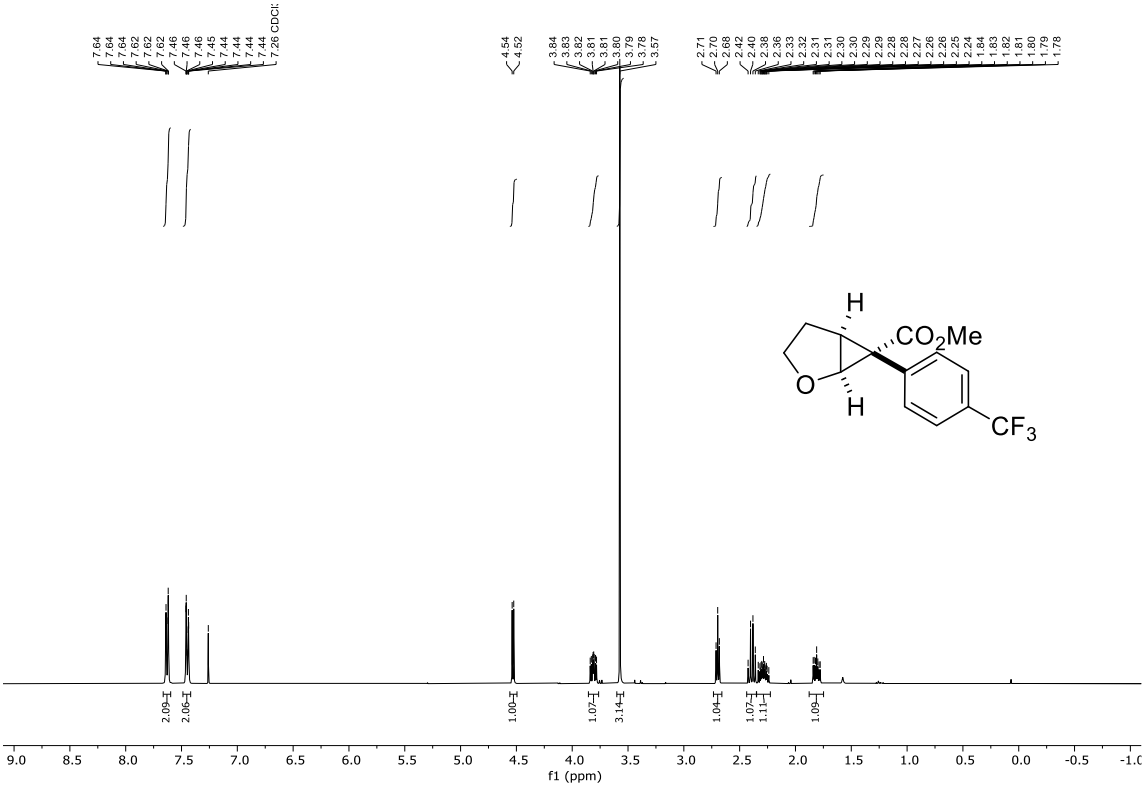


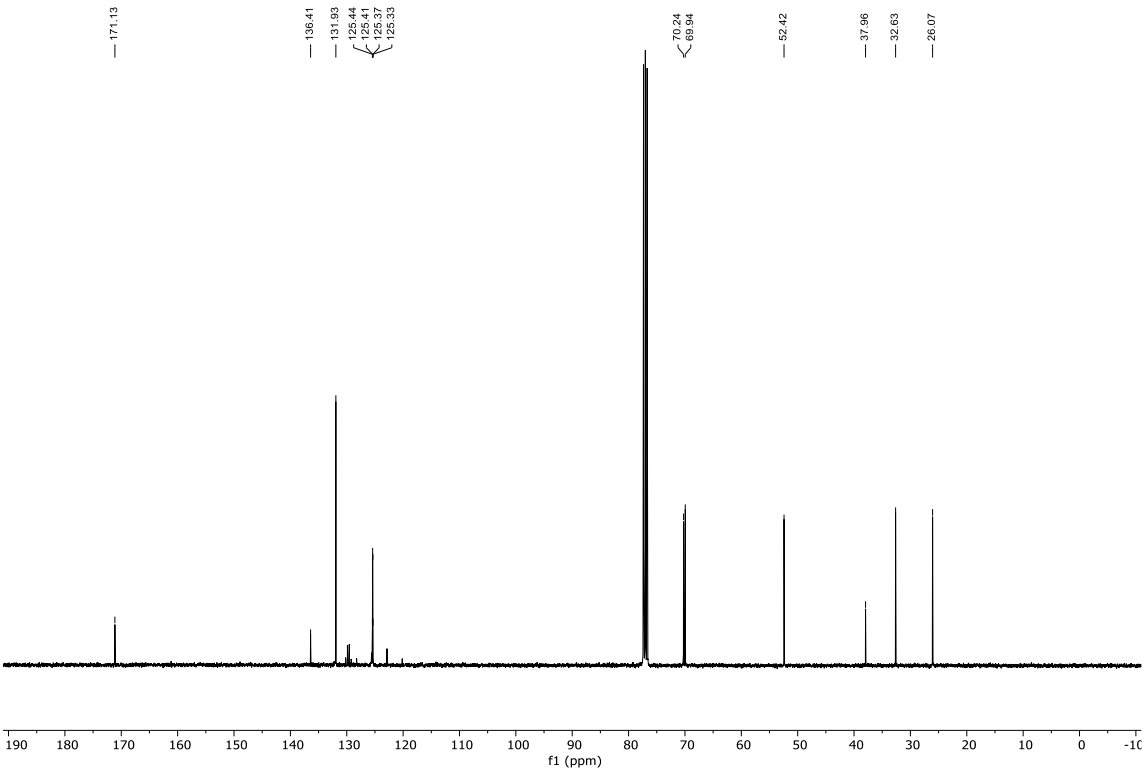
Methyl 2-ethoxy-1-phenylcyclopropane-1-carboxylate 253d



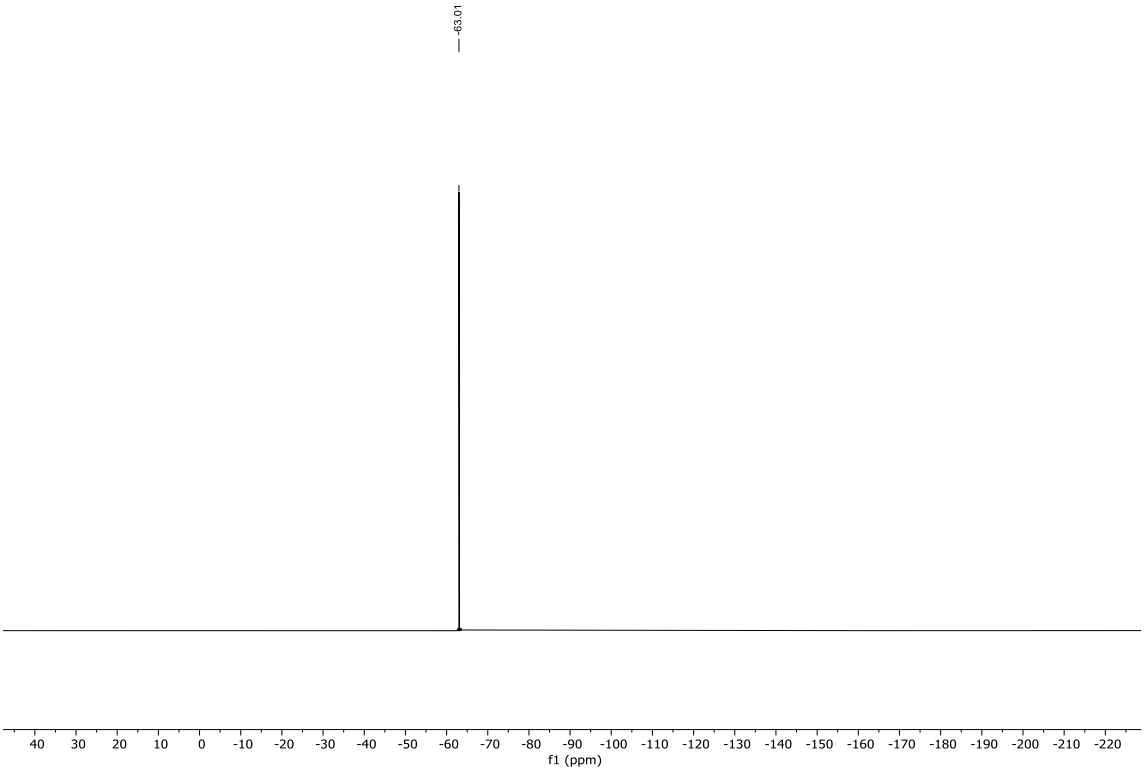


Methyl-6-(4-(trifluoromethyl)phenyl)-2-oxabicyclo[3.1.0]hexane-6-carboxylate 253c

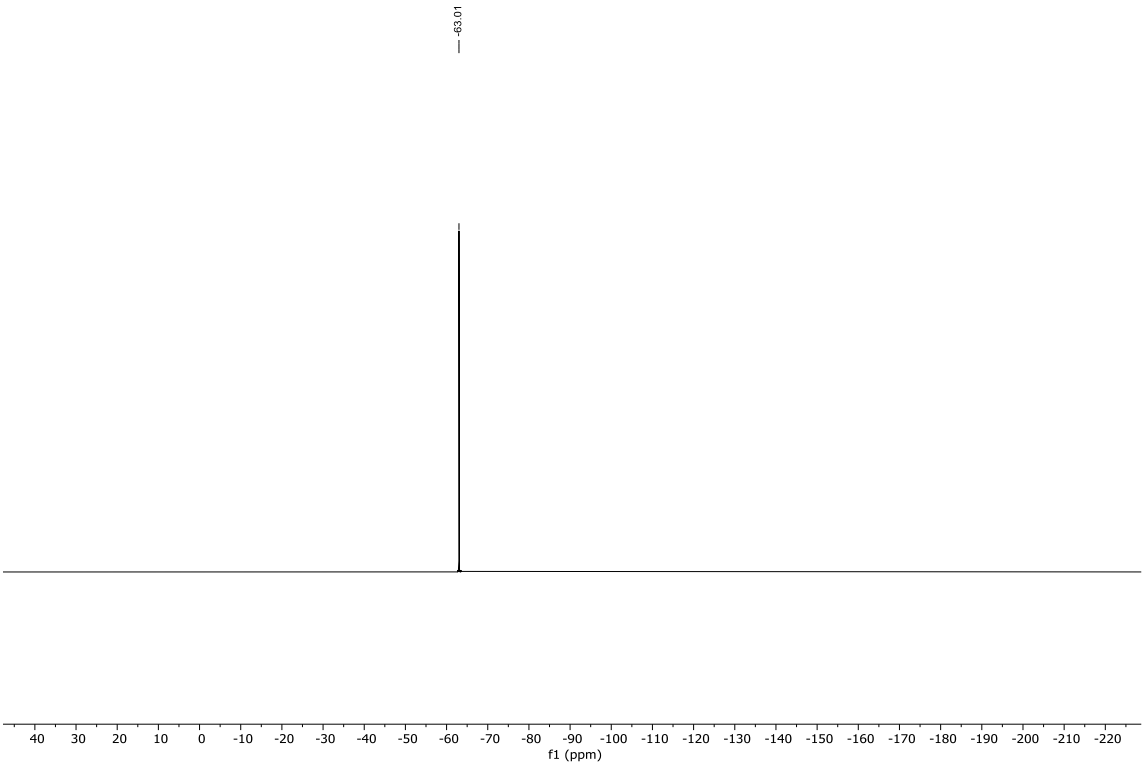




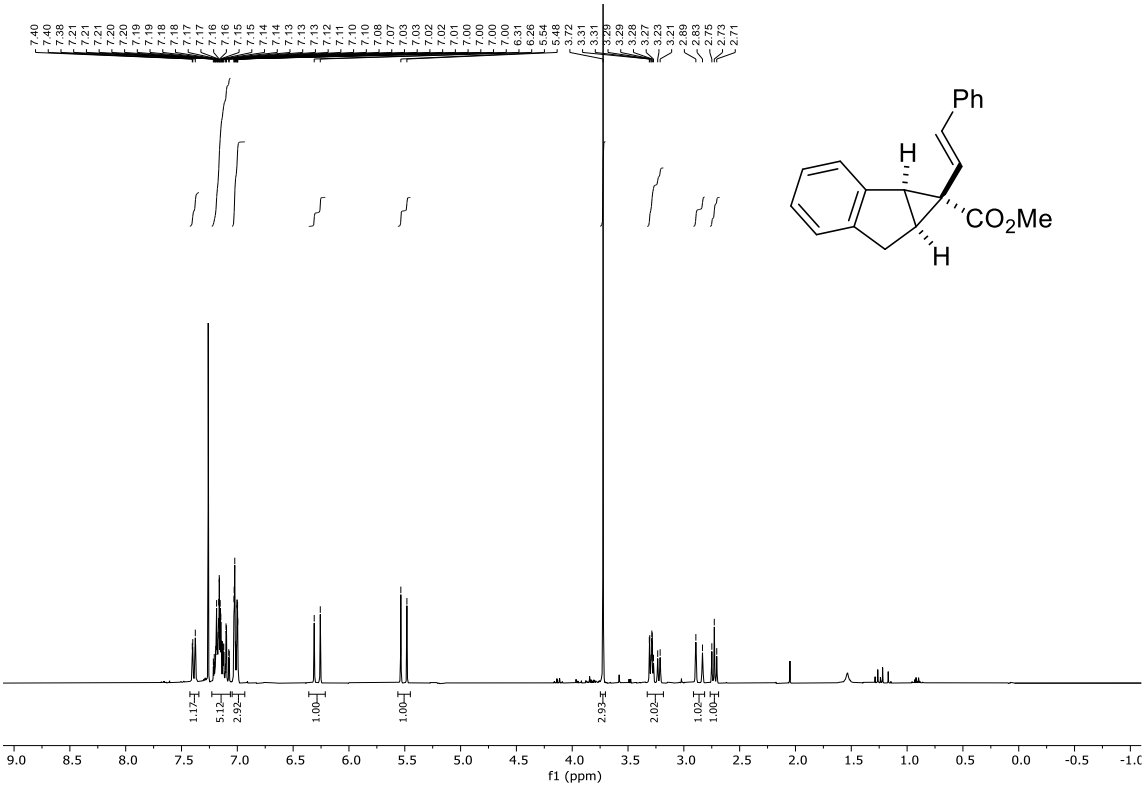
$^{19}F\{^{1}H\}$-NMR

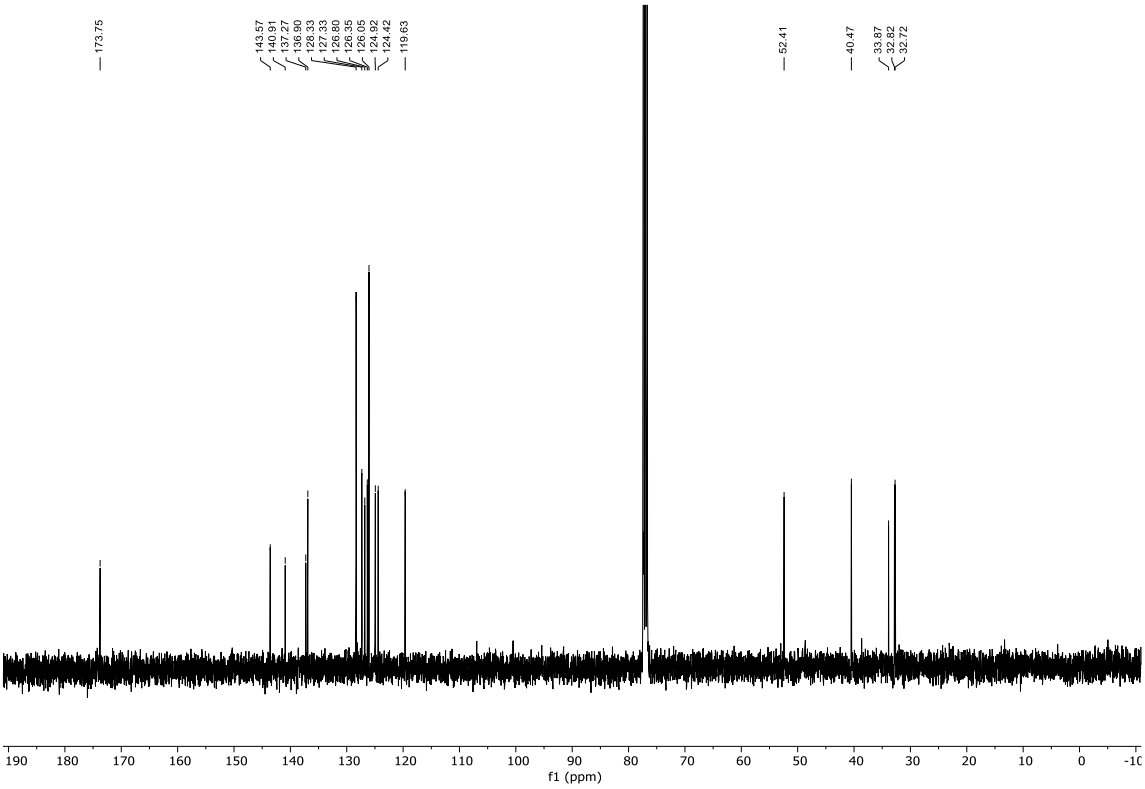


^{19}F-NMR

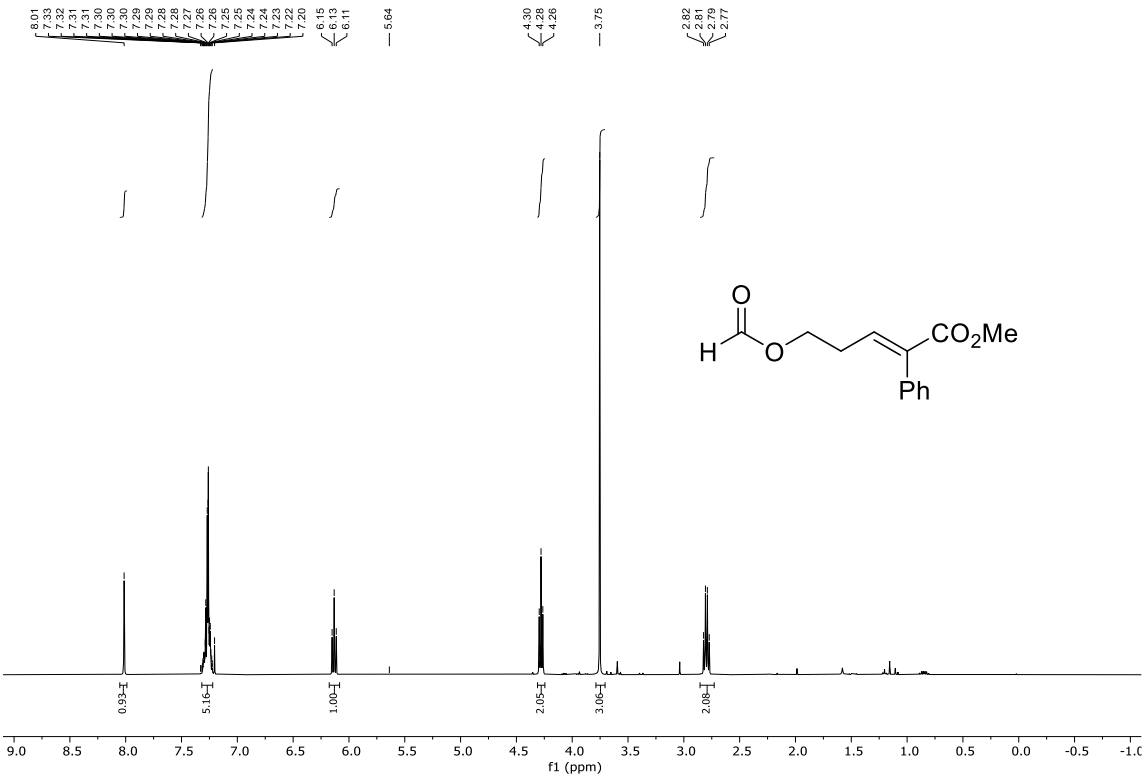


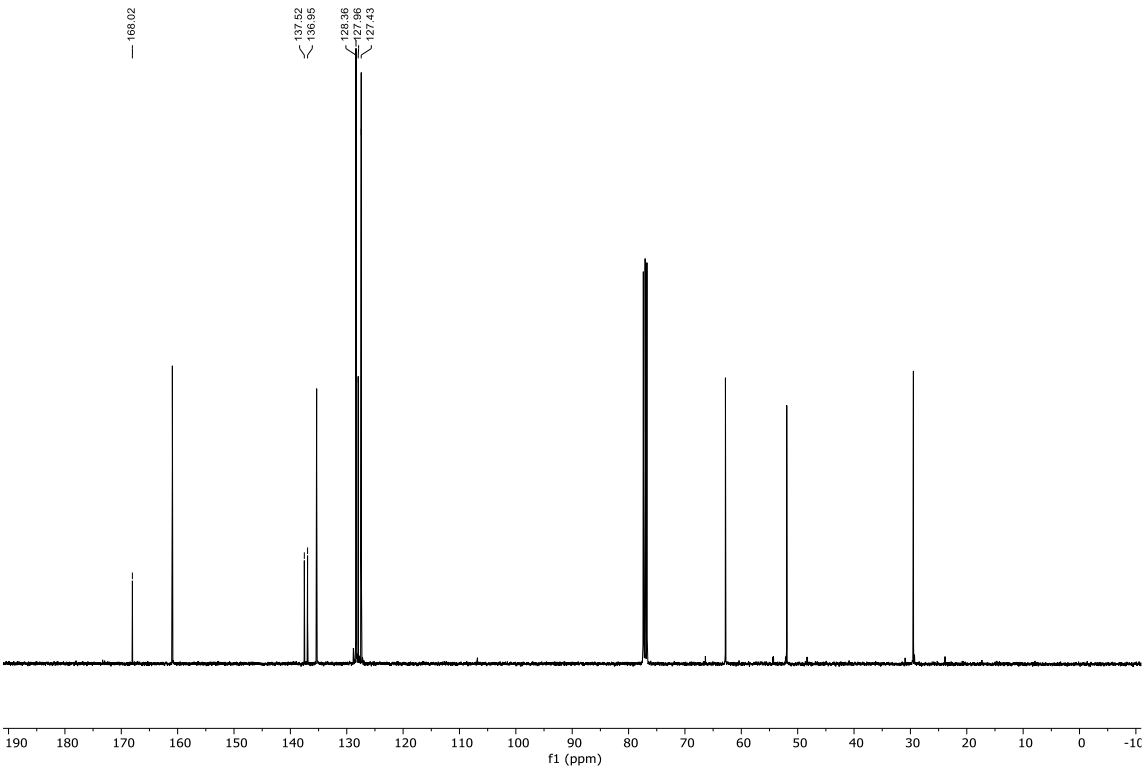
Methyl -1-((E)-styryl)-1,1a,6,6a-tetrahydrocyclopropa[a]indene-1-carboxylate 250l



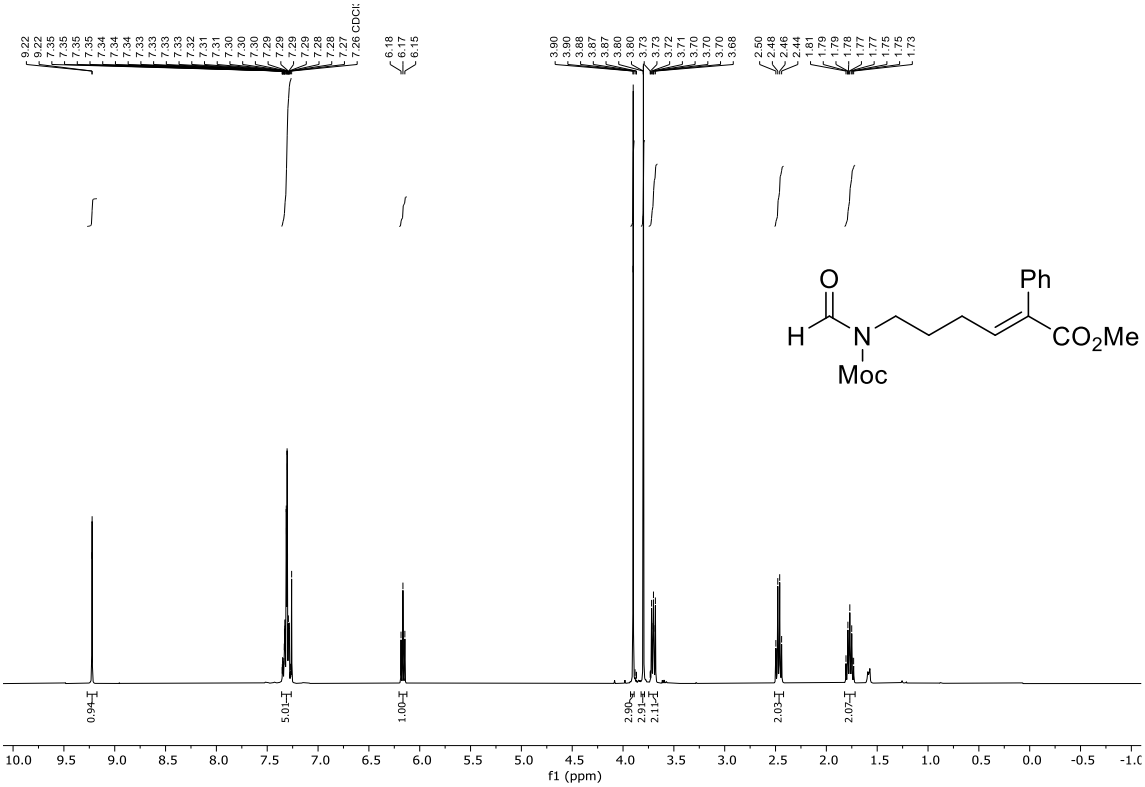


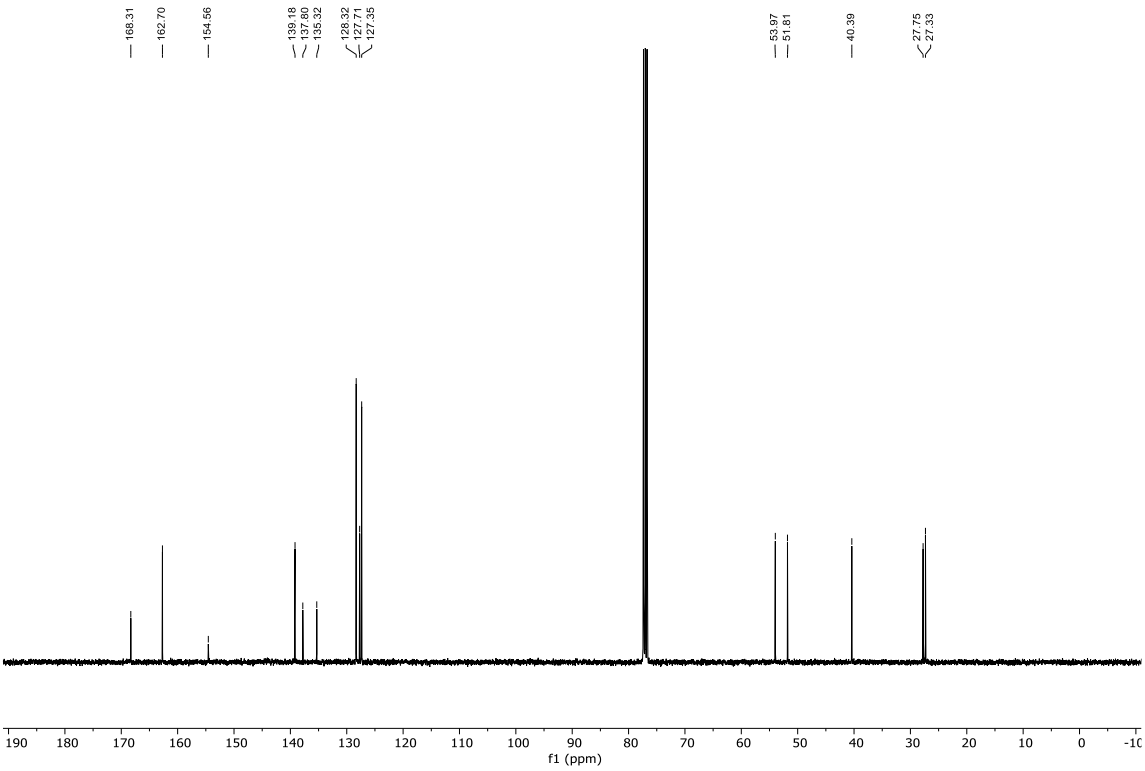
Methyl (*E*)-5-(formyloxy)-2-phenylpent-2-enoate 334a



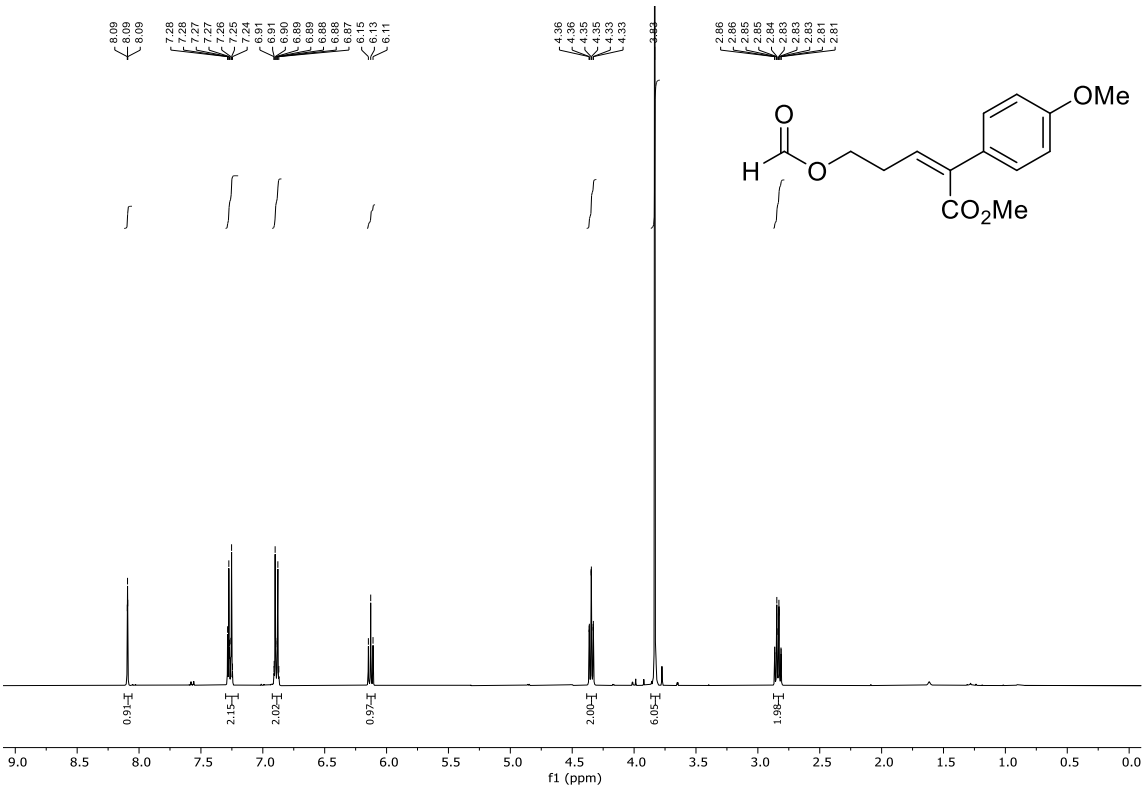


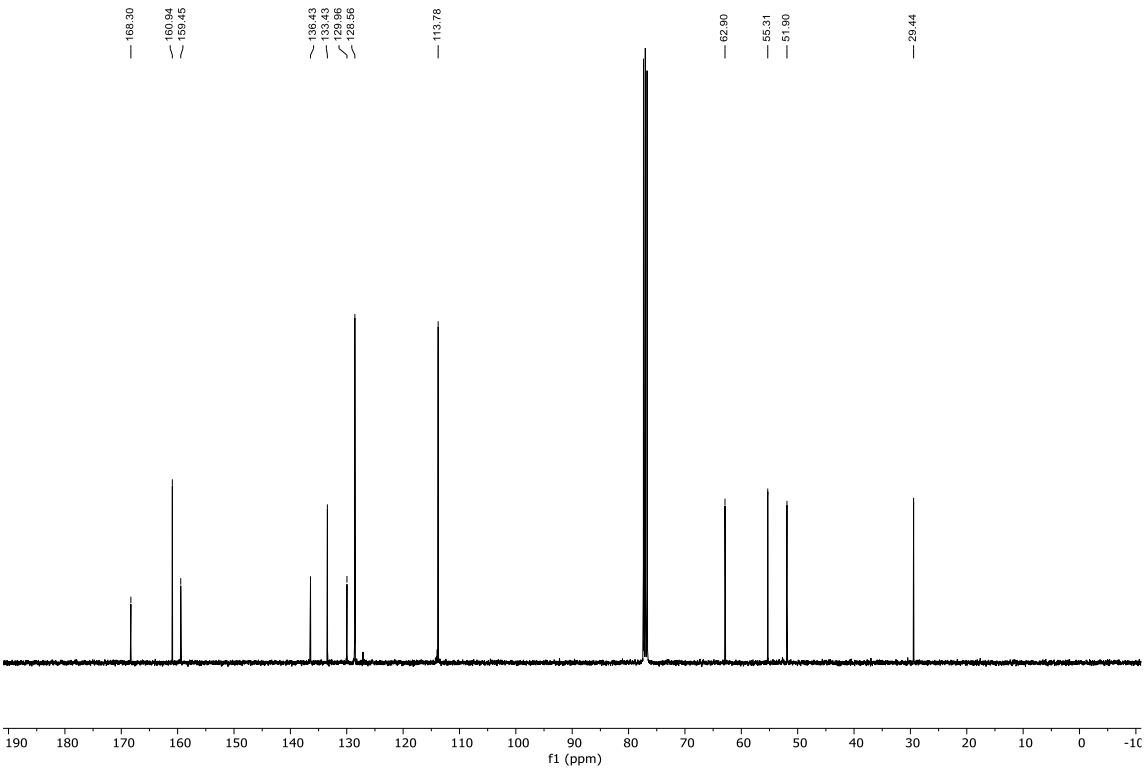
Methyl (E)-6-(N-(methoxycarbonyl)formamido)-2-phenylhex-2-enoate 334e



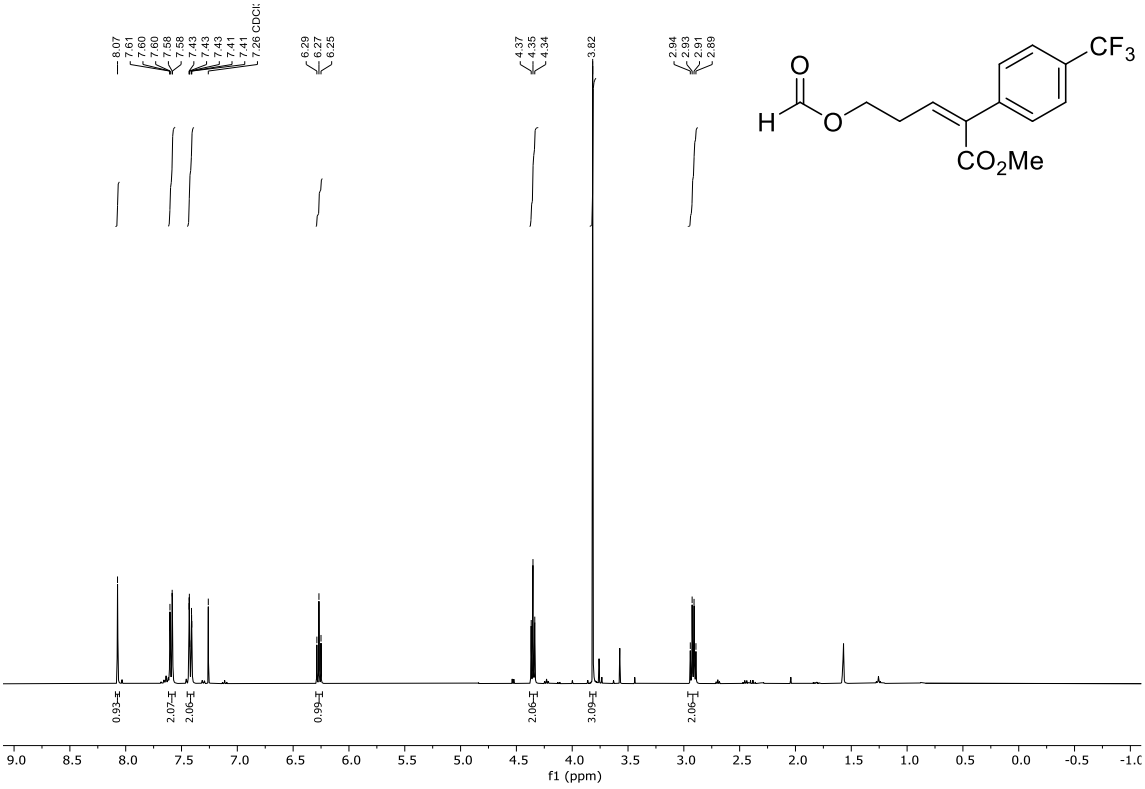


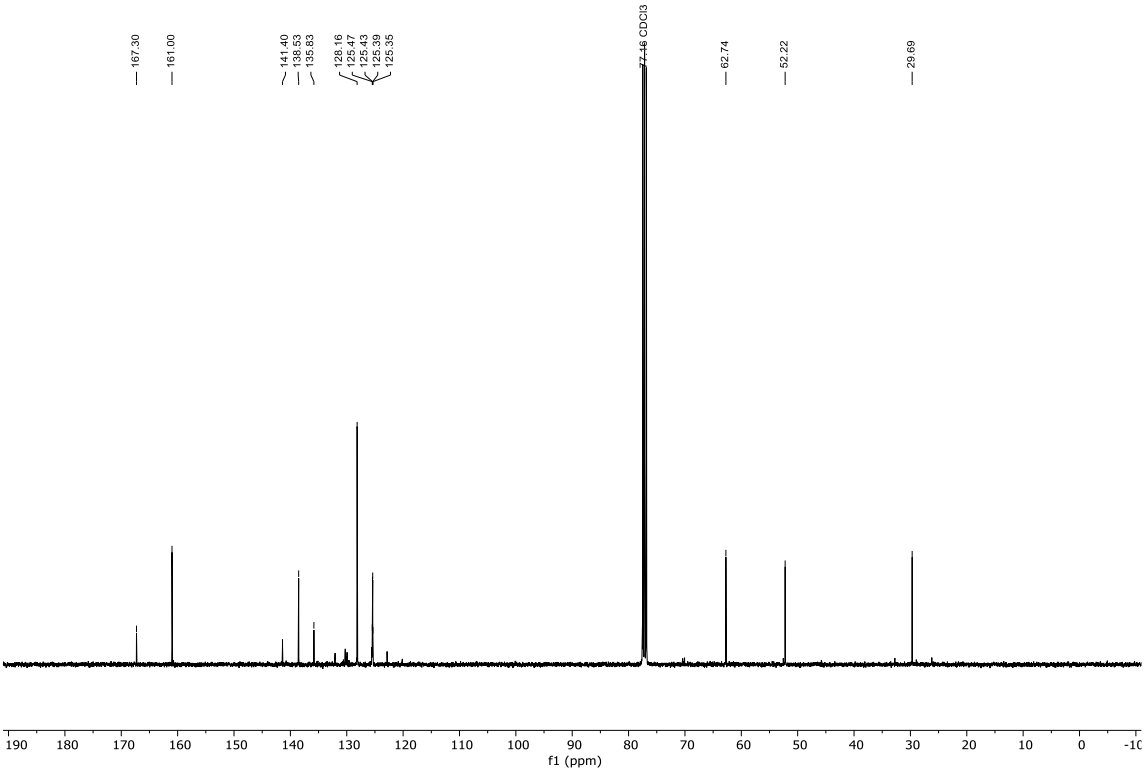
Methyl (*Z*)-5-(formyloxy)-2-(4-methoxyphenyl)pent-2-enoate 334b



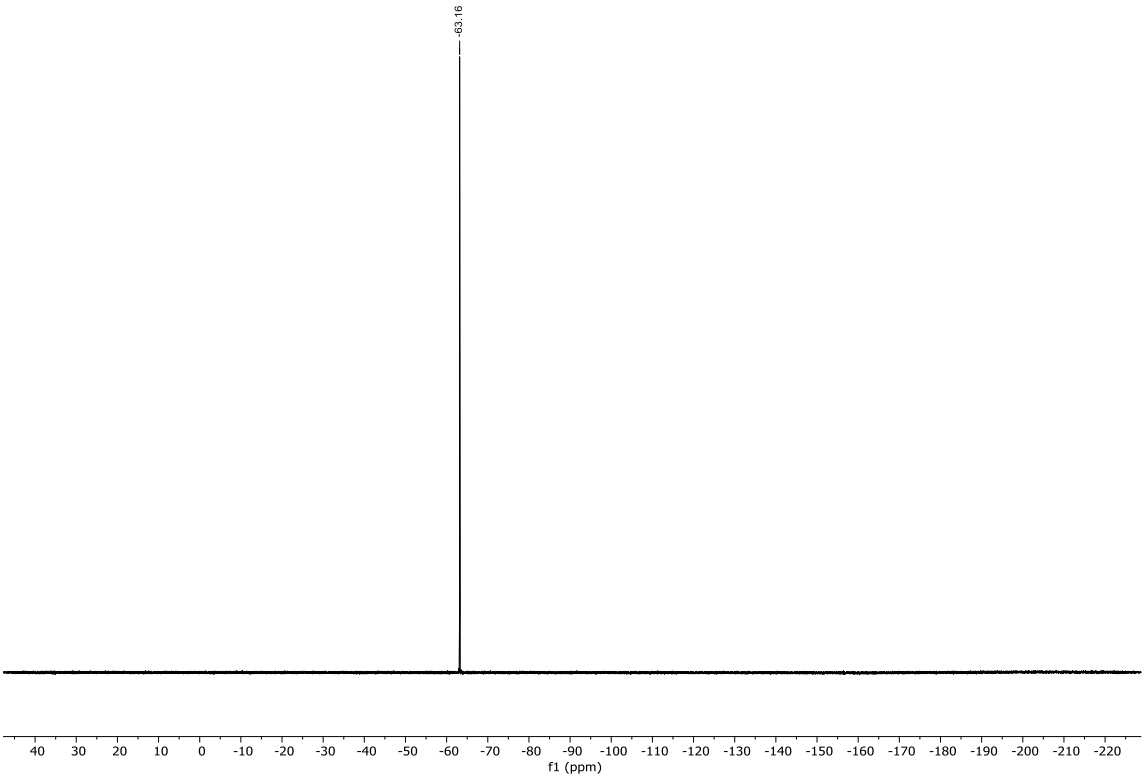


Methyl (*Z*)-5-(formyloxy)-2-(4-(trifluoromethyl)phenyl)pent-2-enoate 334c

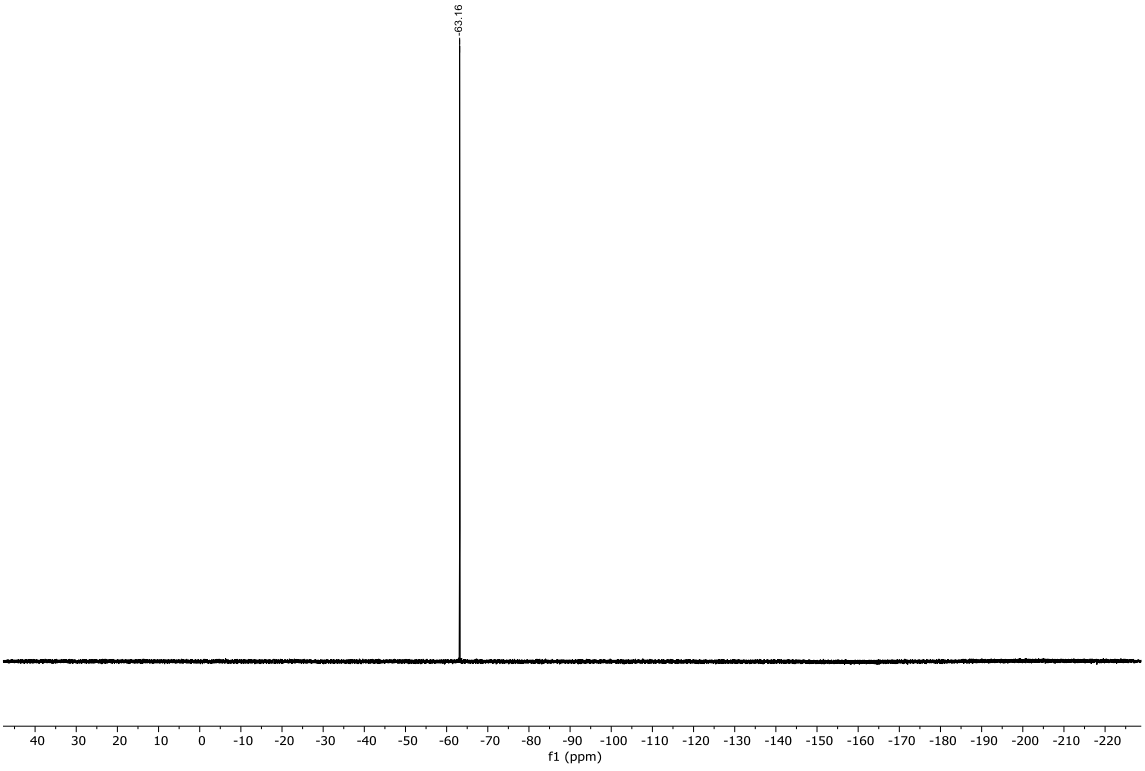




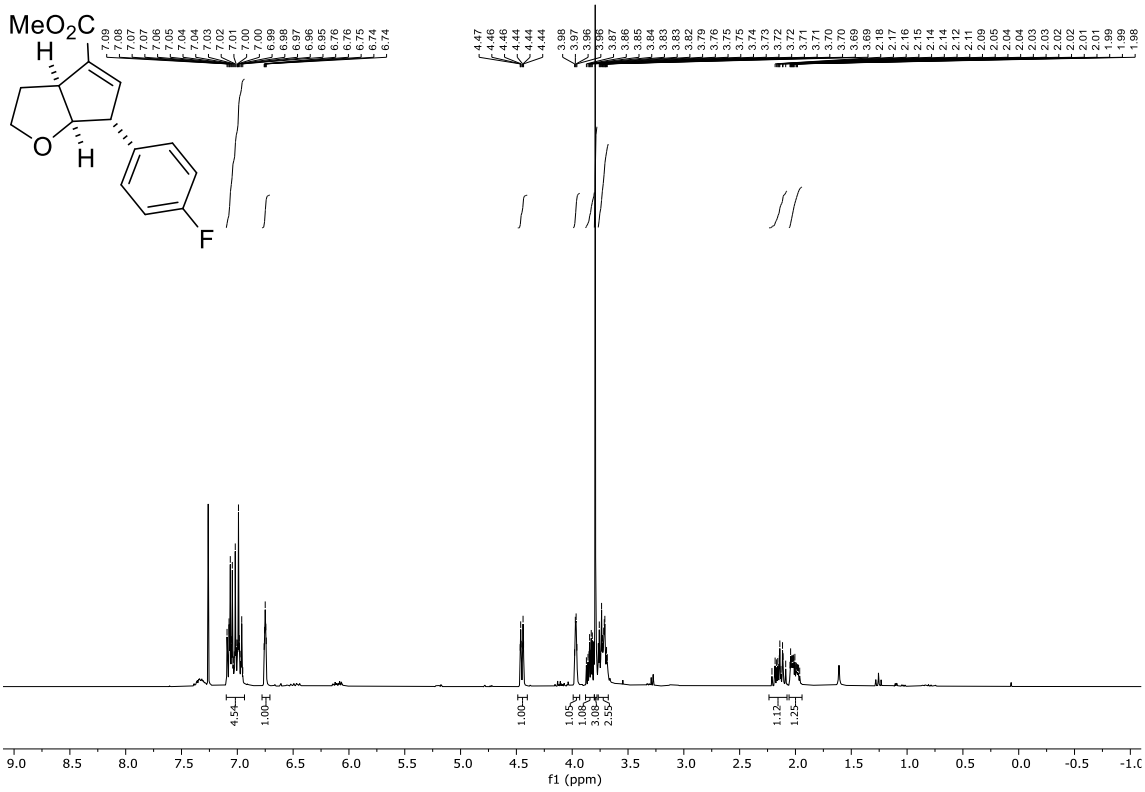
$^{19}F\{^{1}H\}$-NMR

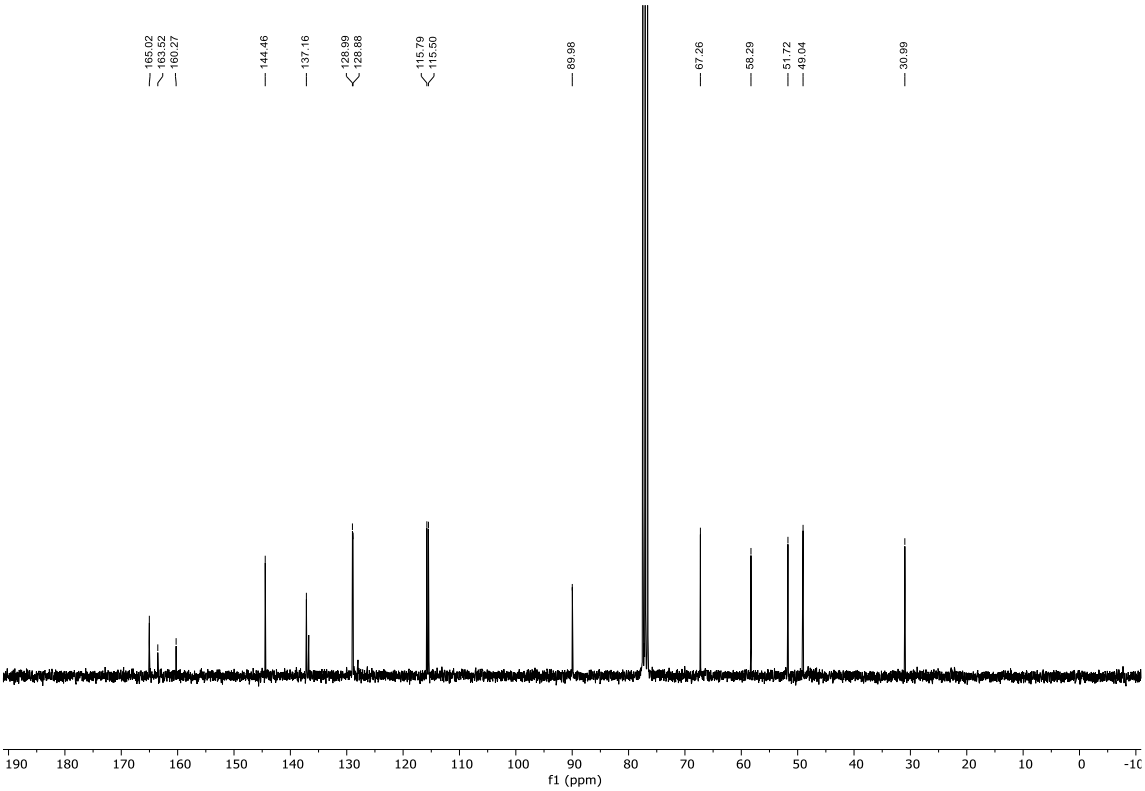


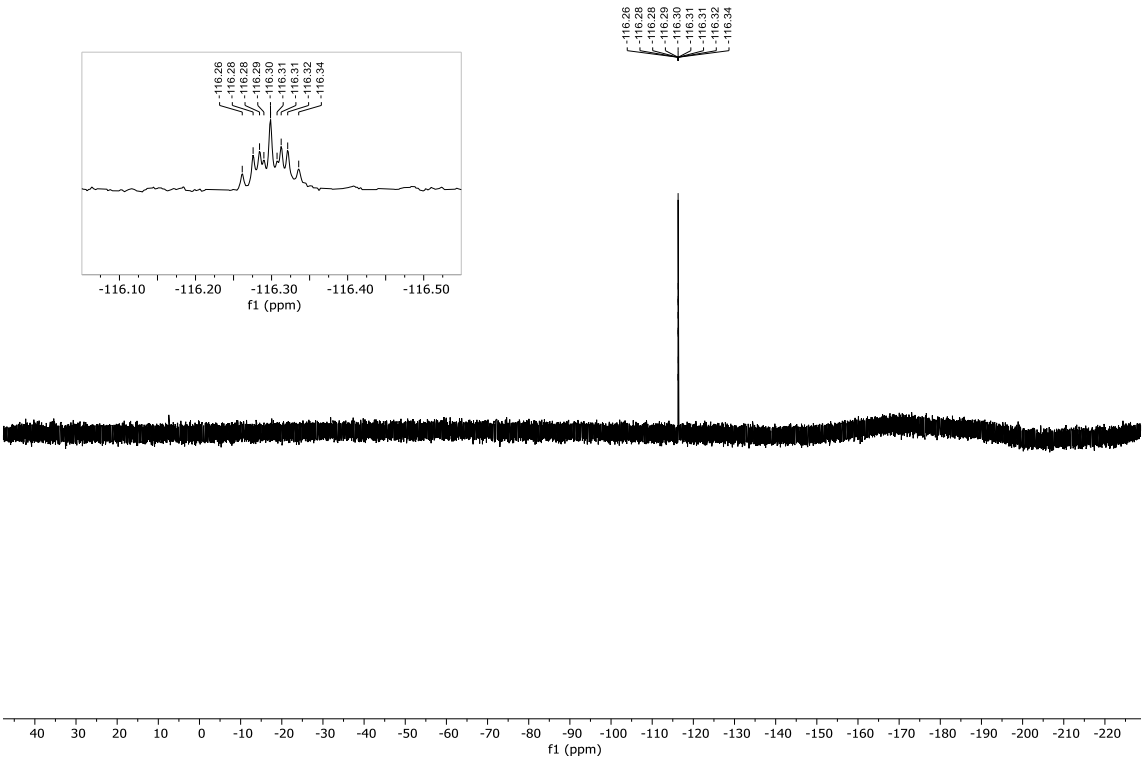
^{19}F-NMR

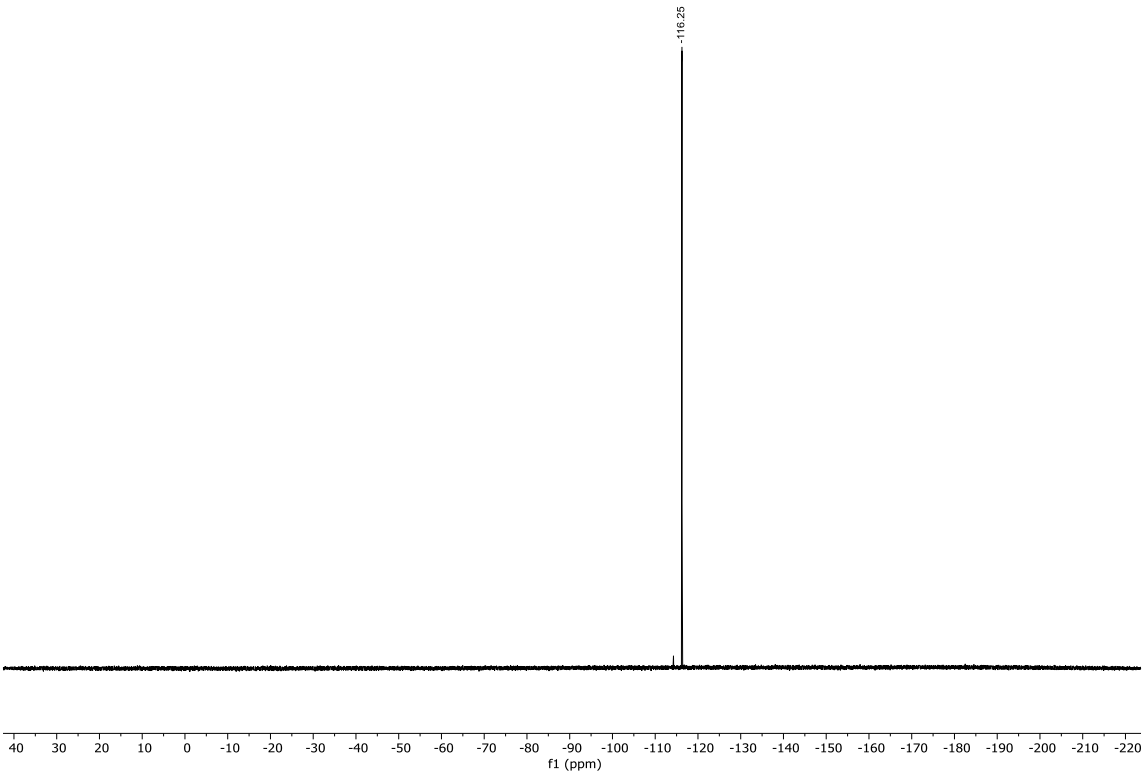


Methyl-6-(4-fluorophenyl)-3,3a,6,6a-tetrahydro-2H-cyclopenta[b]furan-4-carboxylate 261b

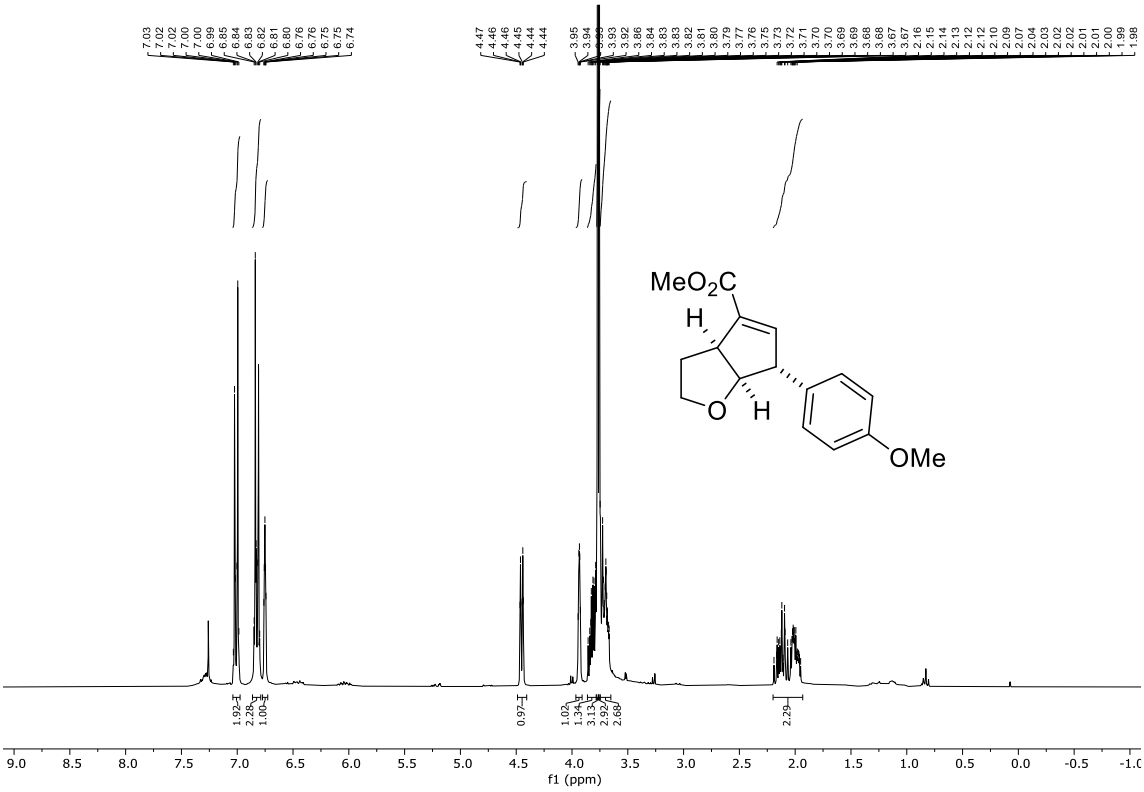


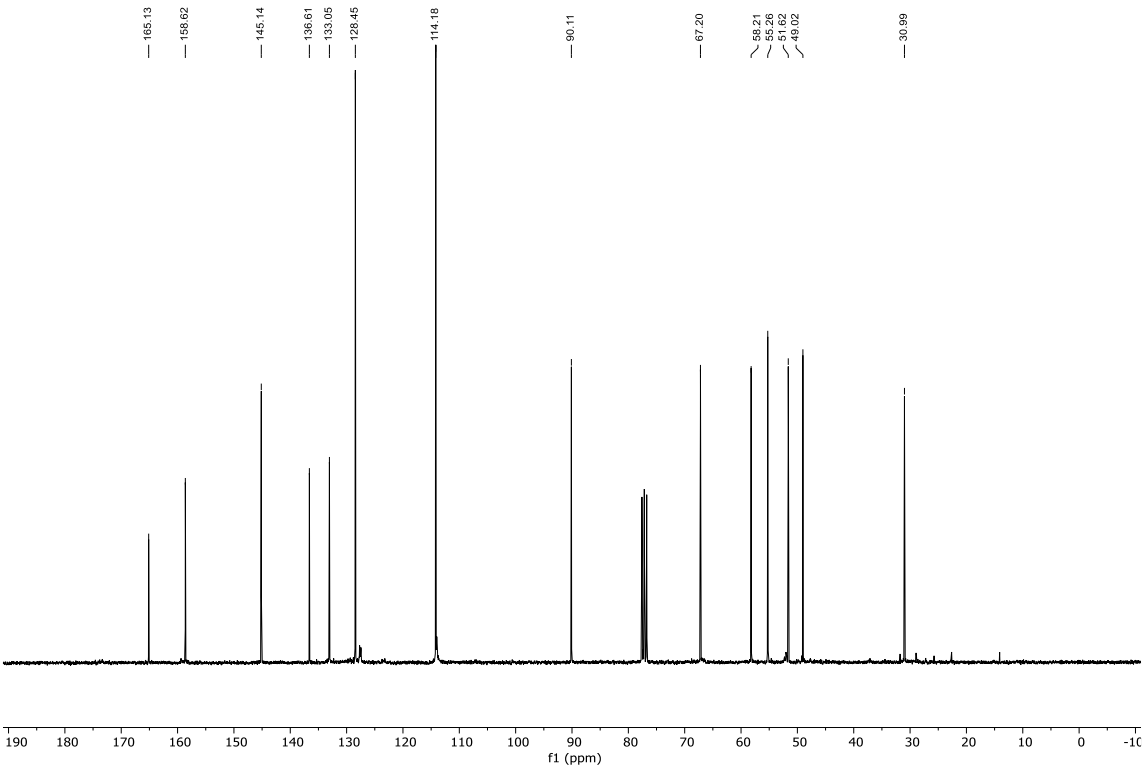



-116.26
-116.28
-116.28
-116.29
-116.30
-116.31
-116.32
-116.34
-116.10
-116.20
-116.30
-116.40
-116.50
f1 (ppm)
40 30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210 -220
f1 (ppm)

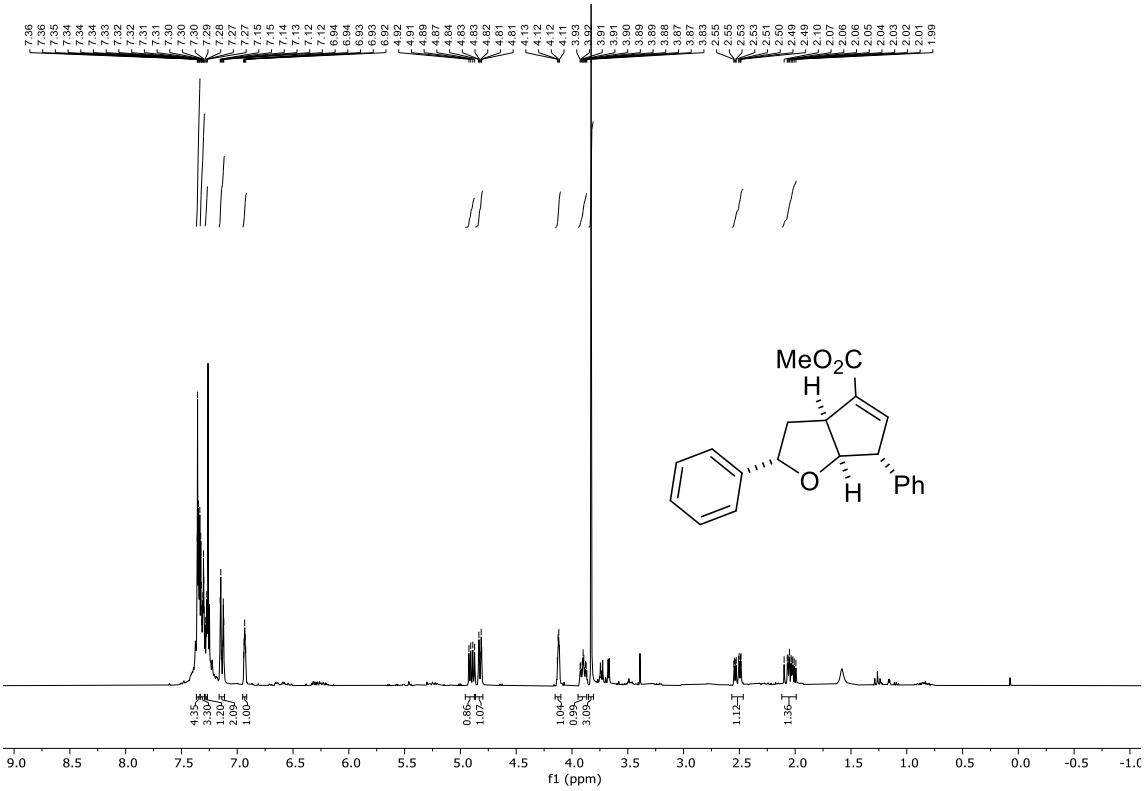

-116.25
40 30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210 -220
f1 (ppm)

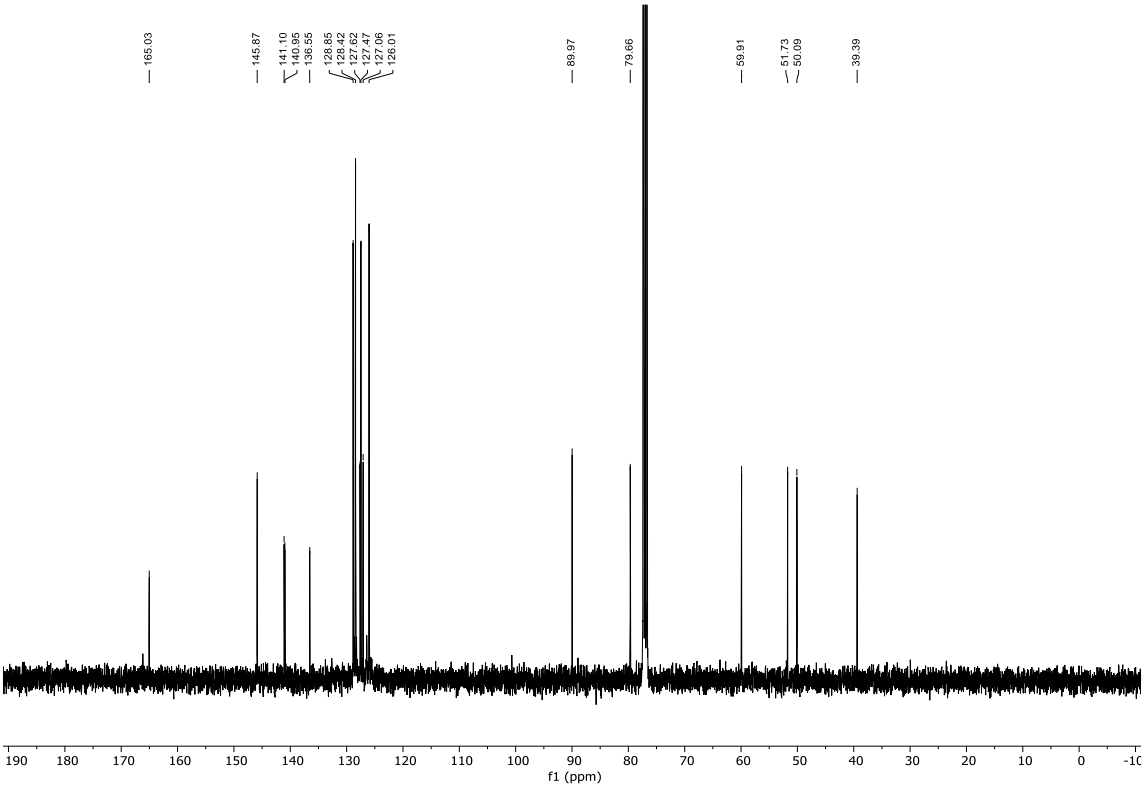
Methyl-6-(4-methoxyphenyl)-3,3a,6,6a-tetrahydro-2*H*-cyclopenta[*b*]furan-4-carboxylate 261c



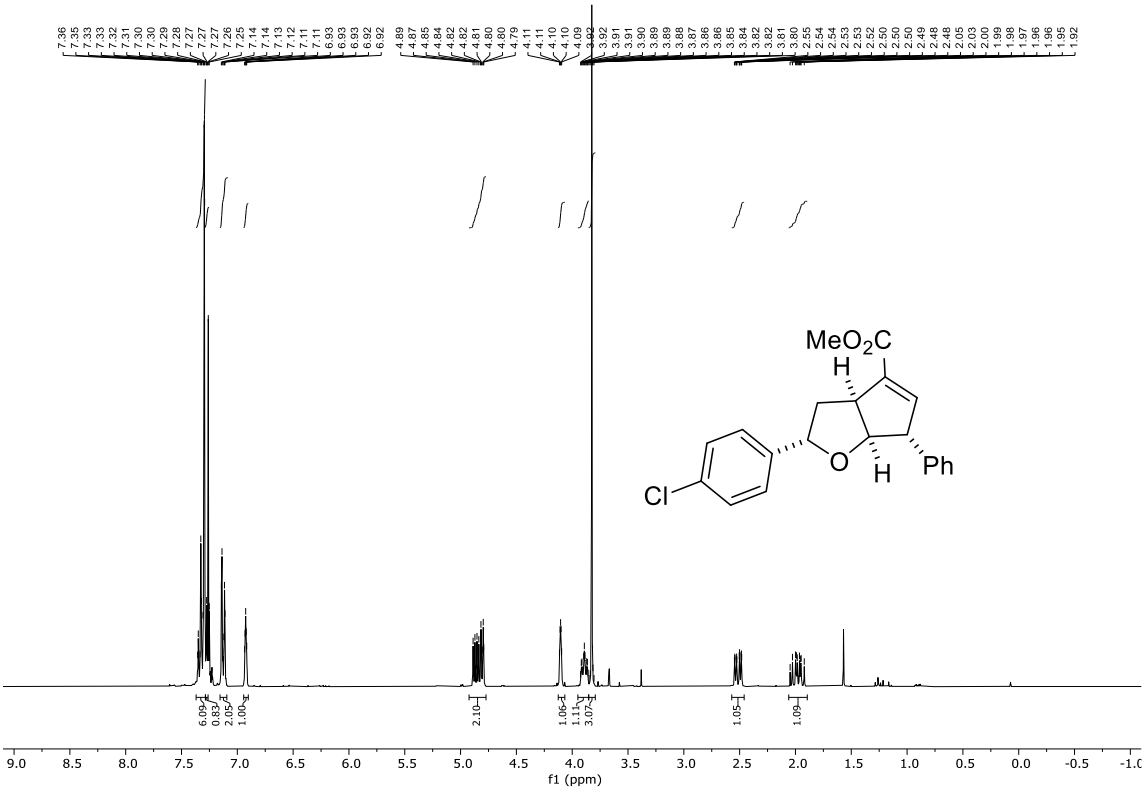


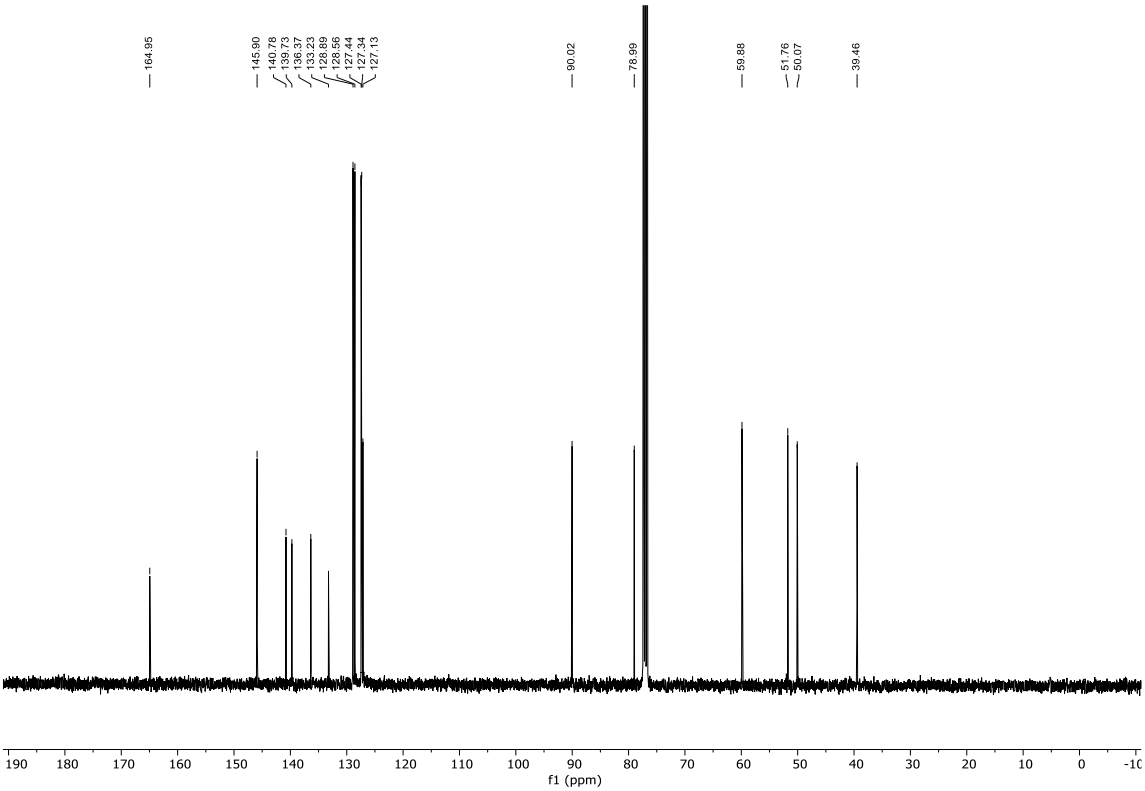
Methyl-2,6-diphenyl-3,3a,6,6a-tetrahydro-2H-cyclopenta[b]furan-4-carboxylate 261e



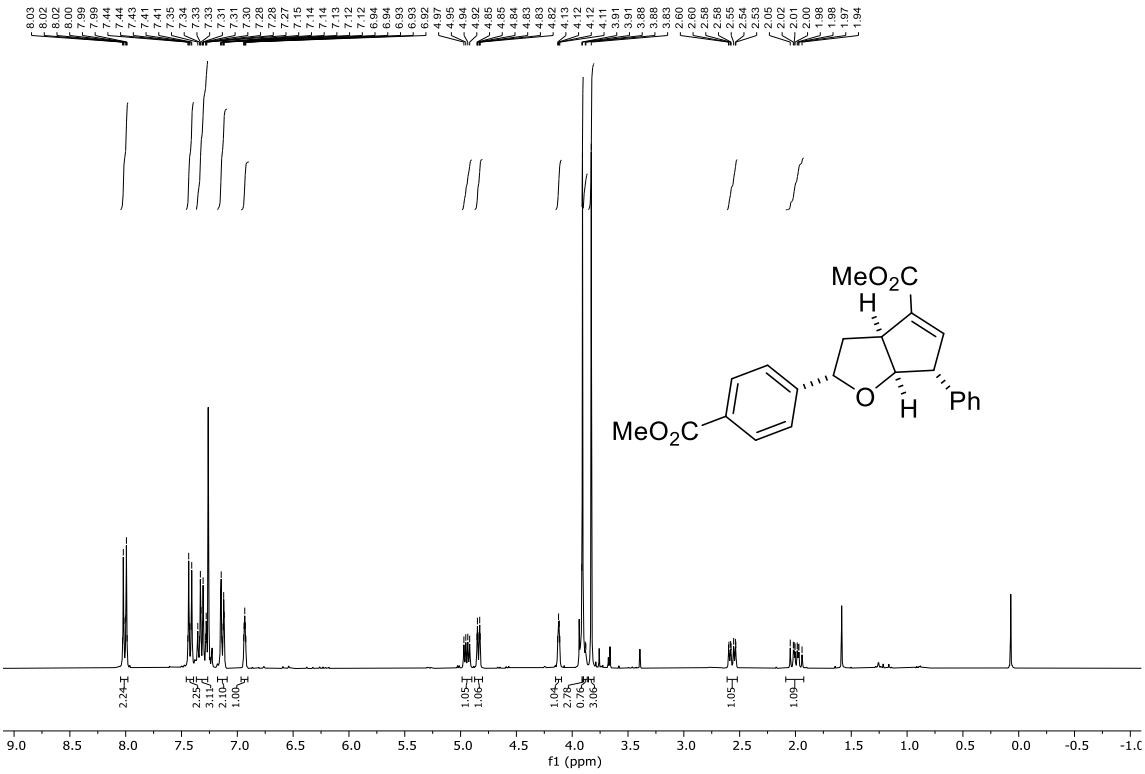


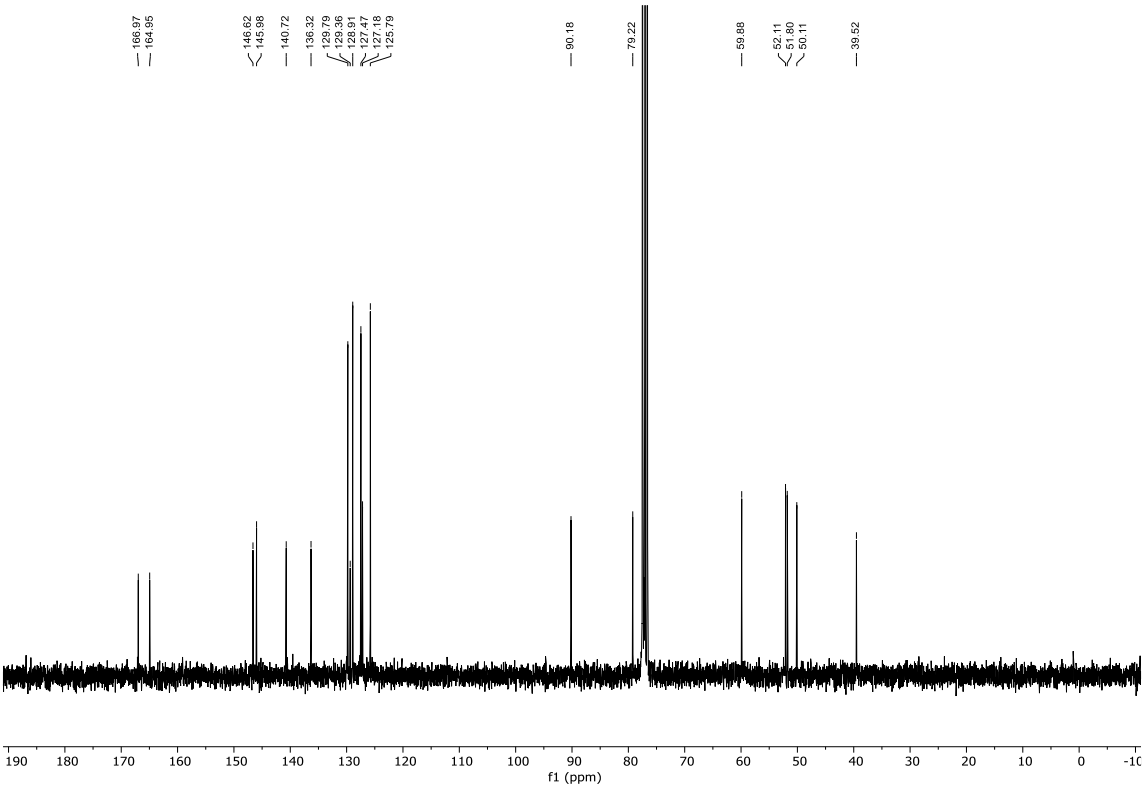
Methyl-2-(4-chlorophenyl)-6-phenyl-3,3a,6,6a-tetrahydro-2H-cyclopenta[b]furan-4-carboxylate 261g



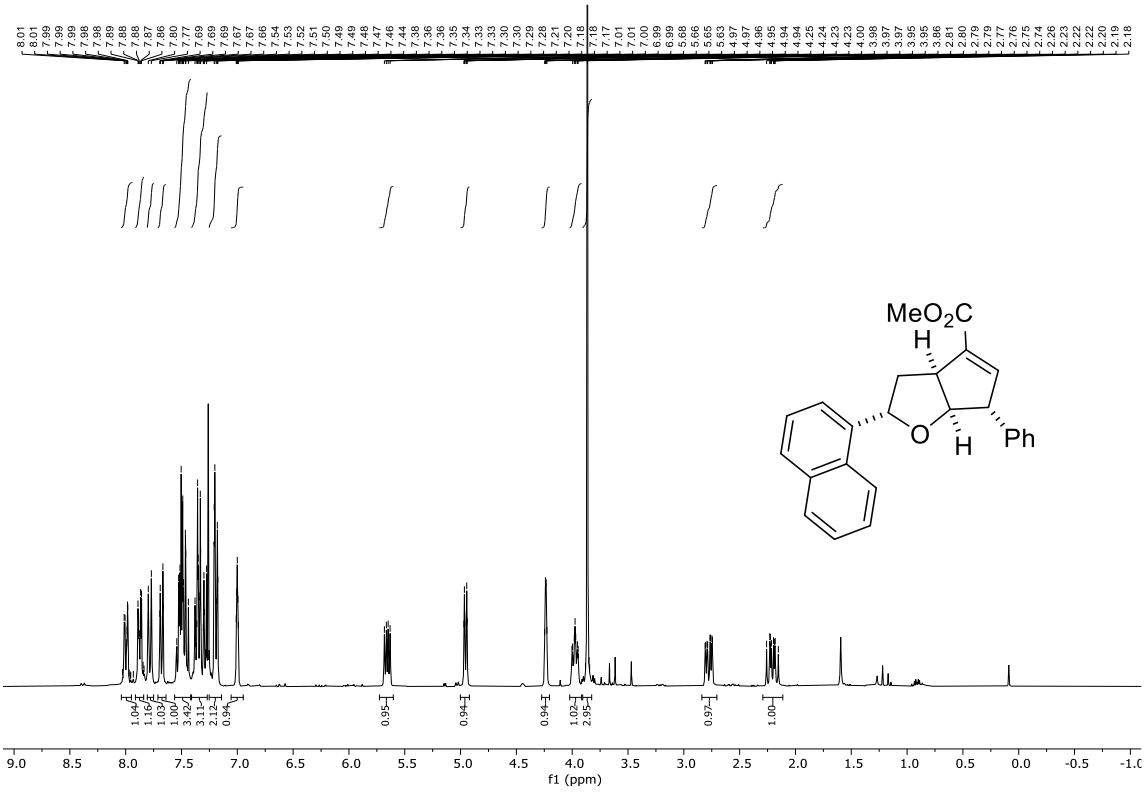


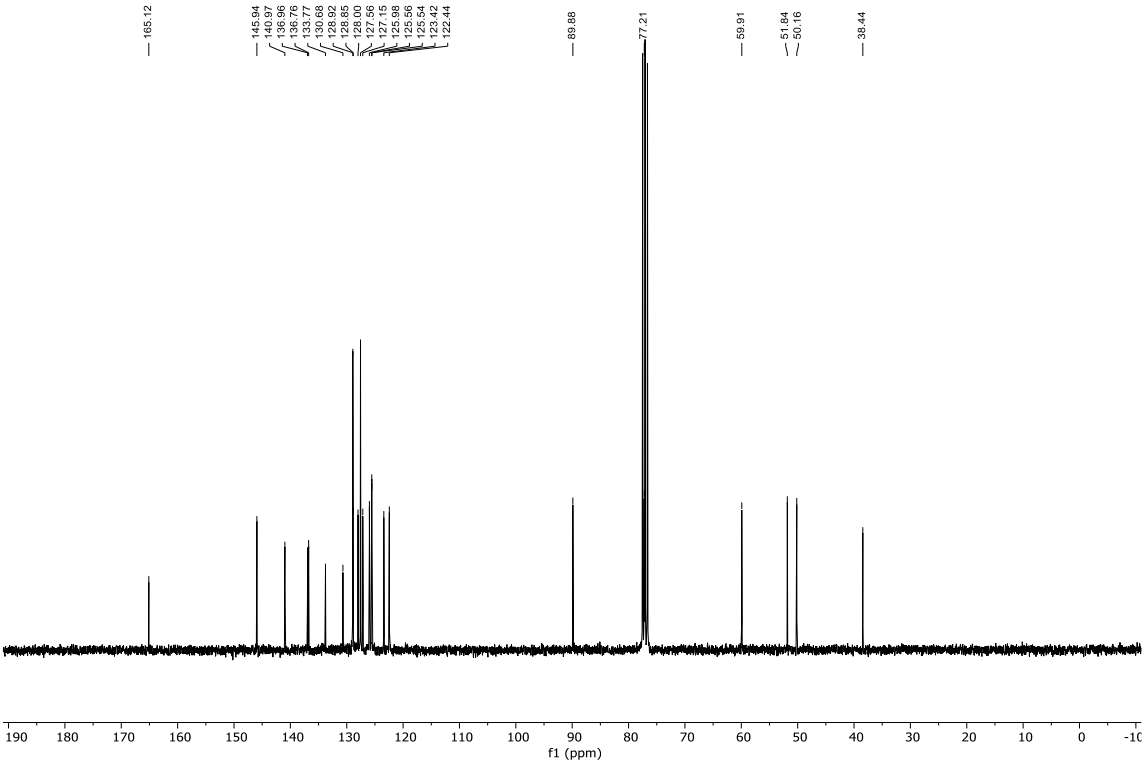
Methyl-2-(4-(methoxycarbonyl)phenyl)-6-phenyl-3,3a,6,6a-tetrahydro-2H-cyclopenta[b]furan-4-carboxylate 261h



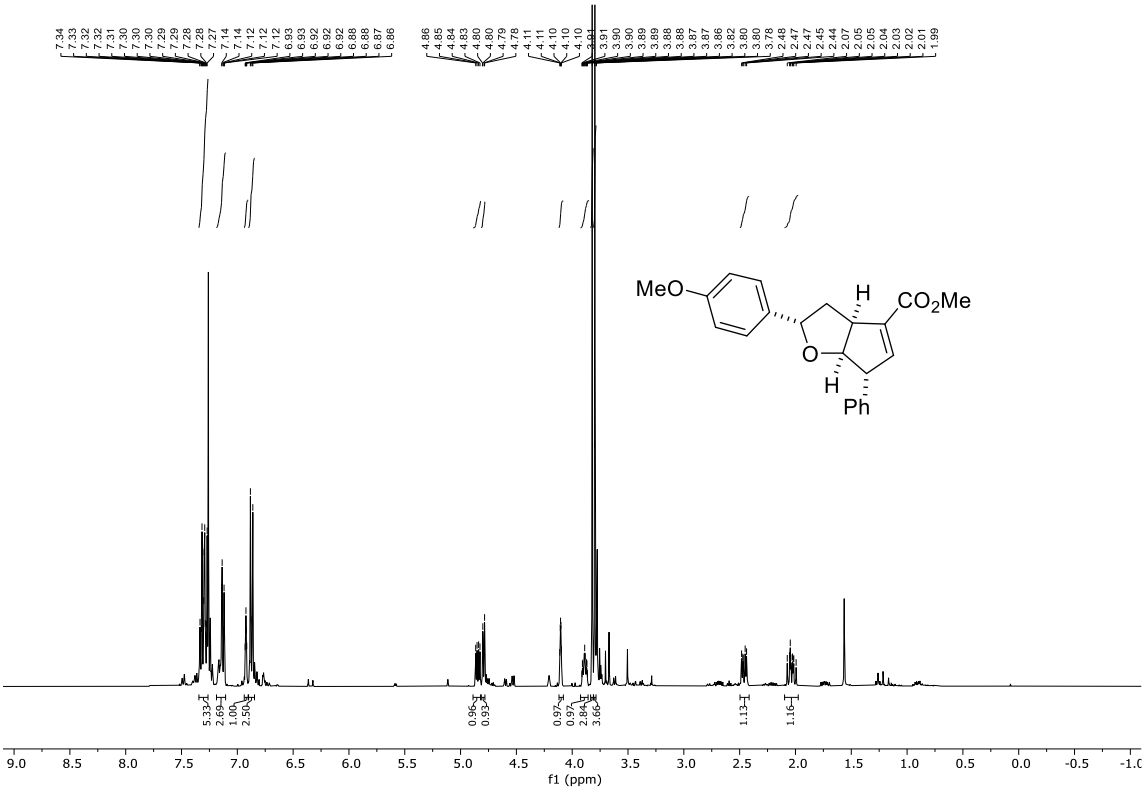


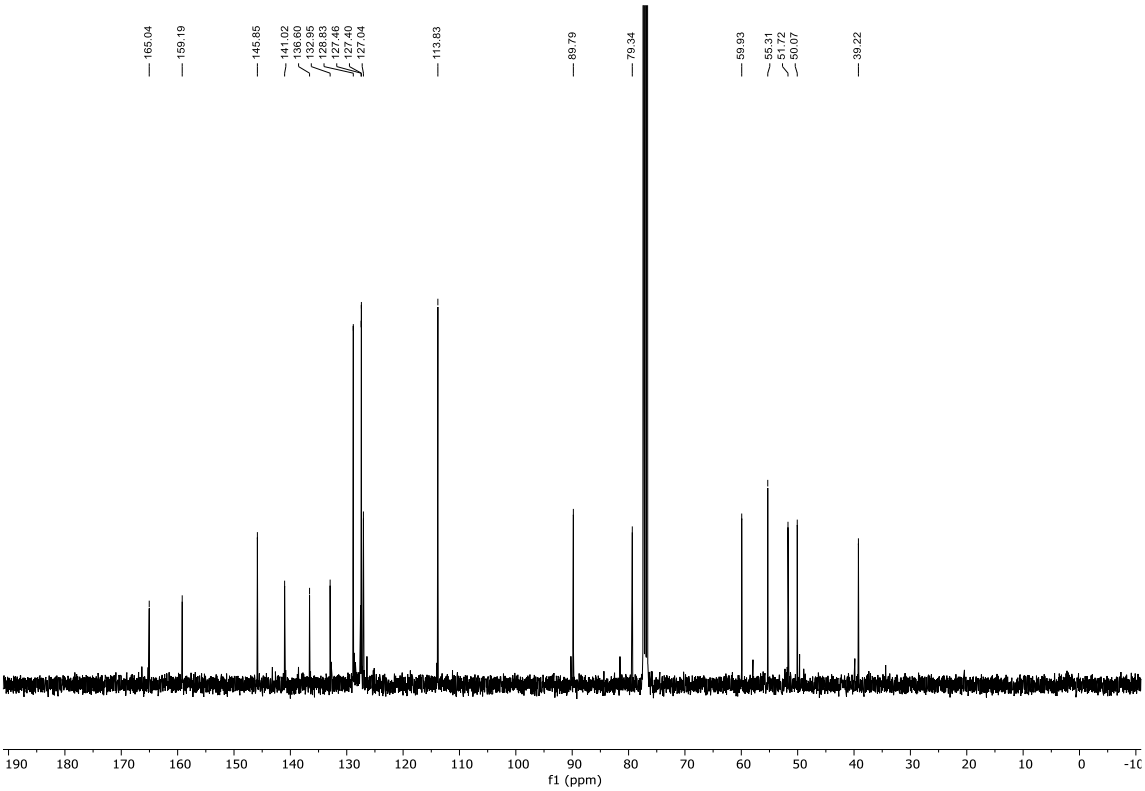
Methyl-2-(naphthalen-1-yl)-6-phenyl-3,3a,6,6a-tetrahydro-2H-cyclopenta[b]furan-4-carboxylate 261f



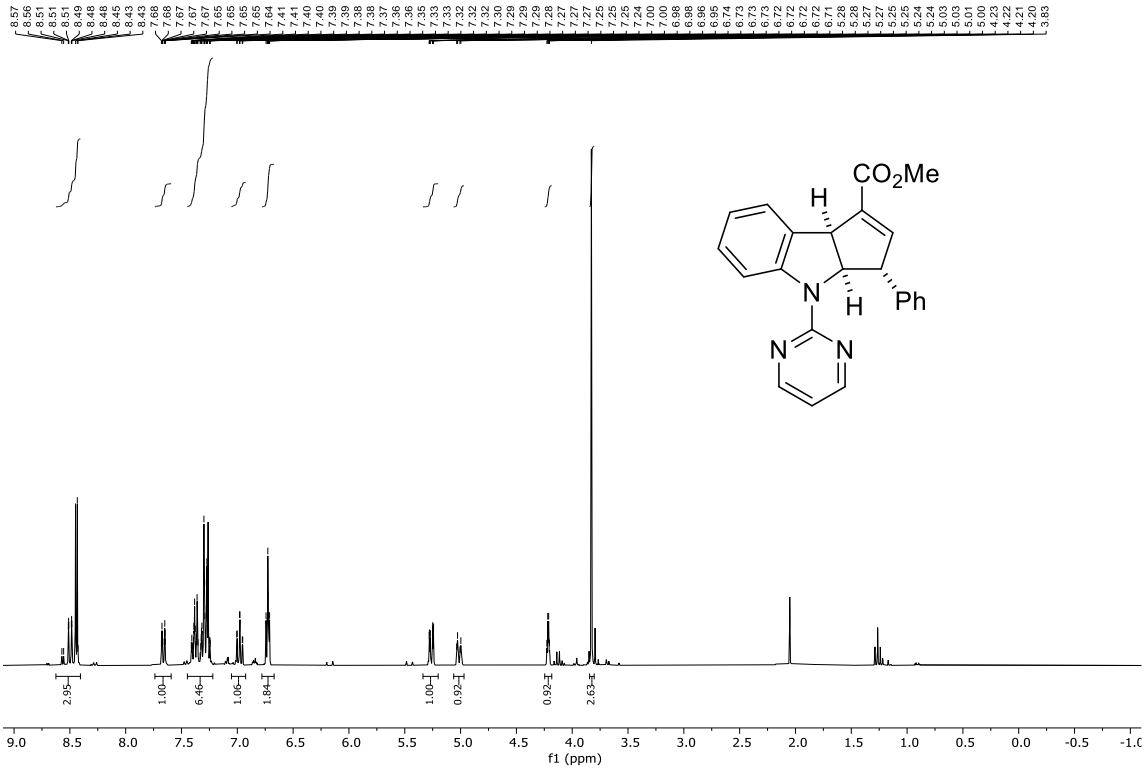


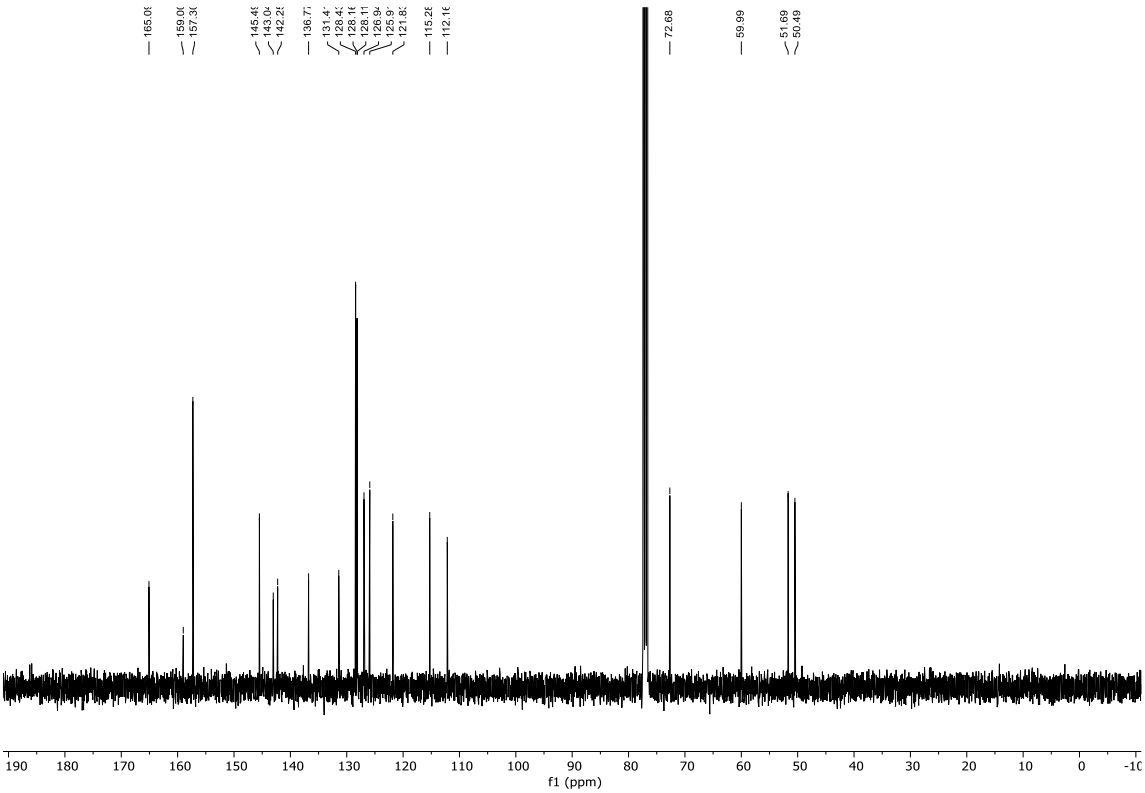
Methyl-2-(4-methoxyphenyl)-6-phenyl-3,3a,6,6a-tetrahydro-2*H*-cyclopenta[*b*]furan-4-carboxylate 261i





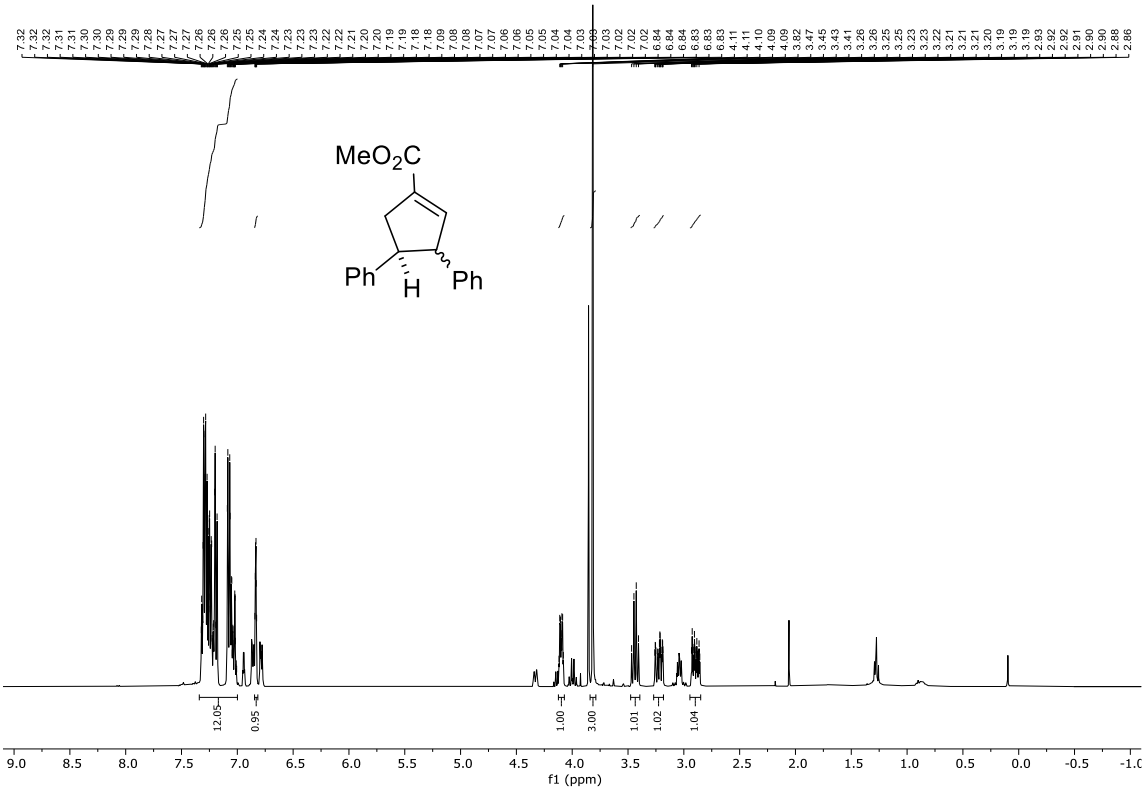
Methyl-3-phenyl-4-(pyrimidin-2-yl)-3,3a,4,8b-tetrahydrocyclopenta[b]indole-1-carboxylate 261q

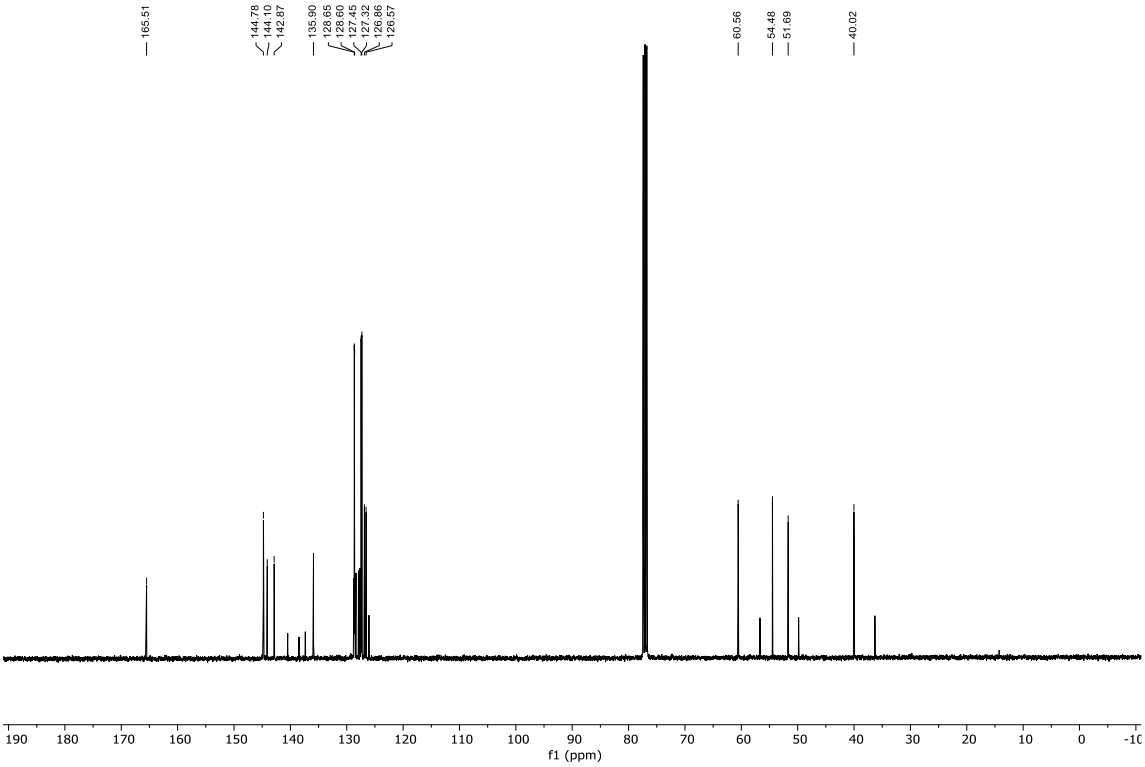




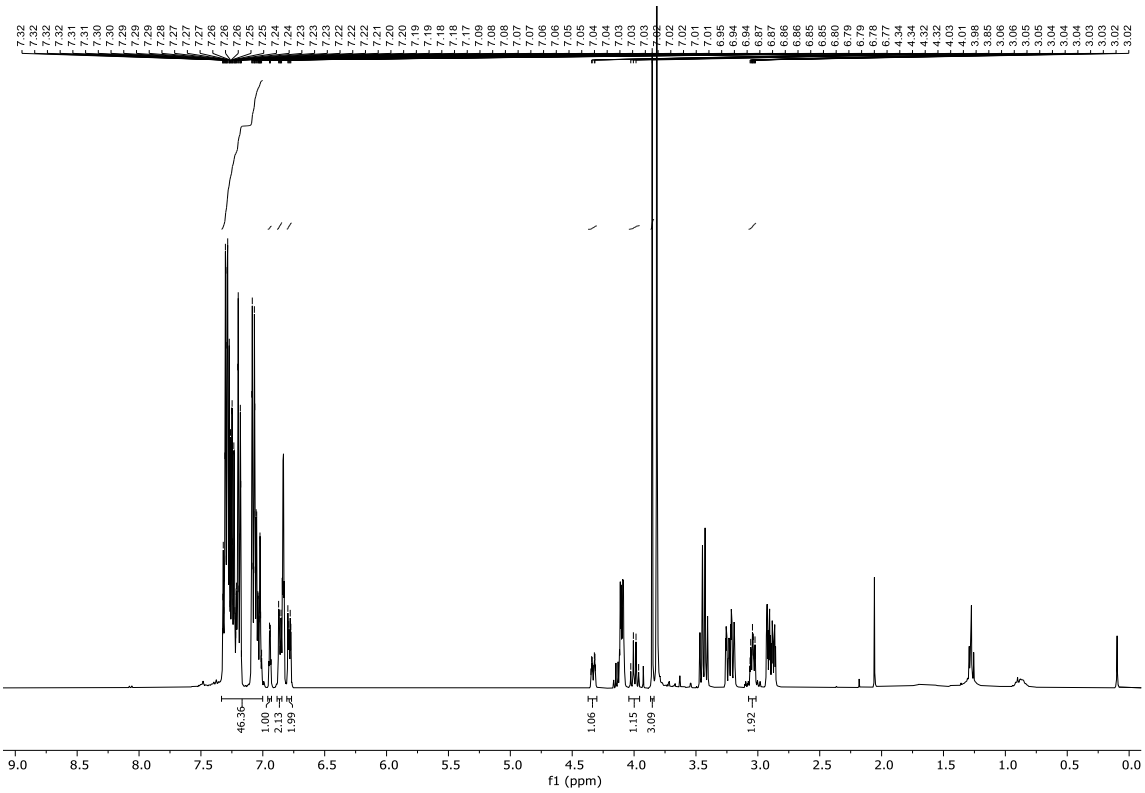
Methyl-3,4-diphenylcyclopent-1-ene-1-carboxylate 261m

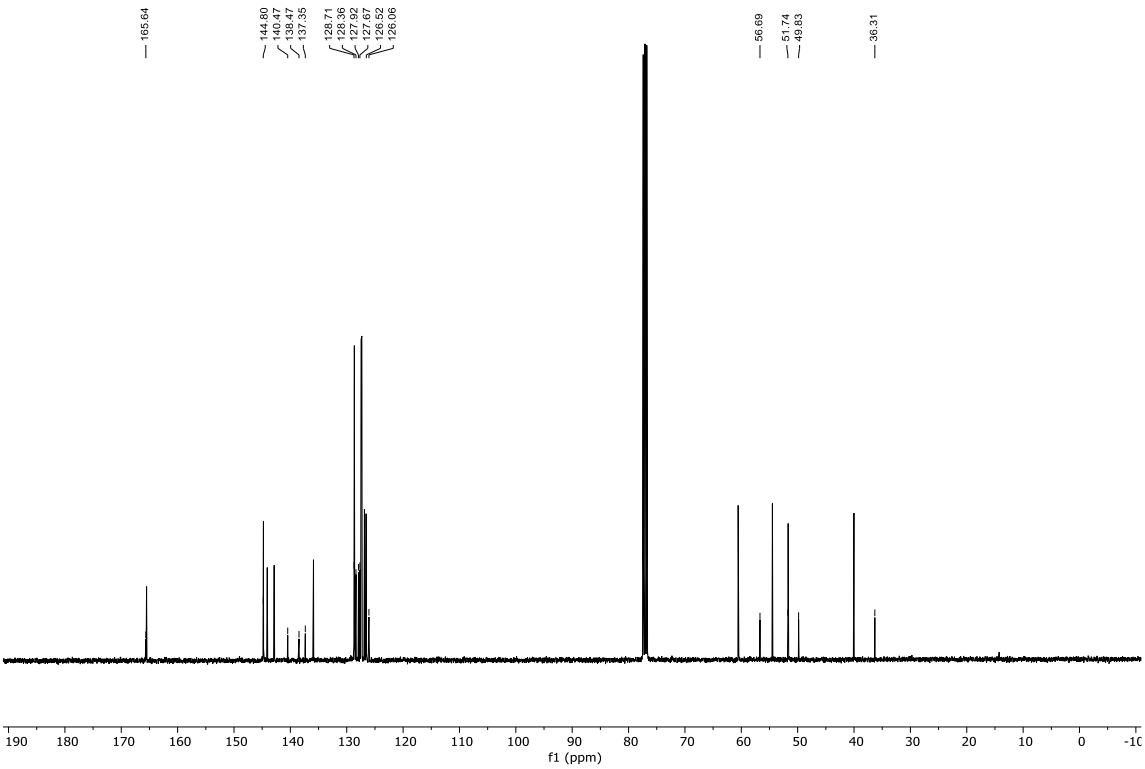
Major:





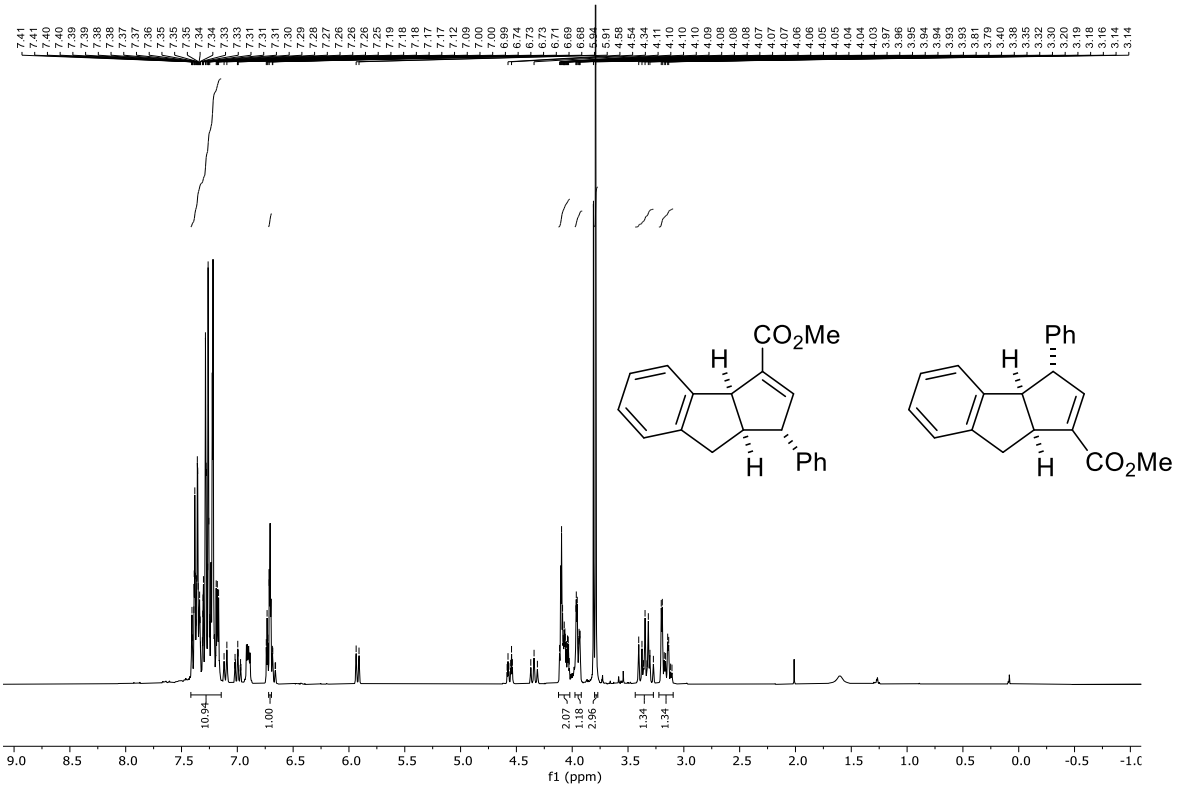
Minor:

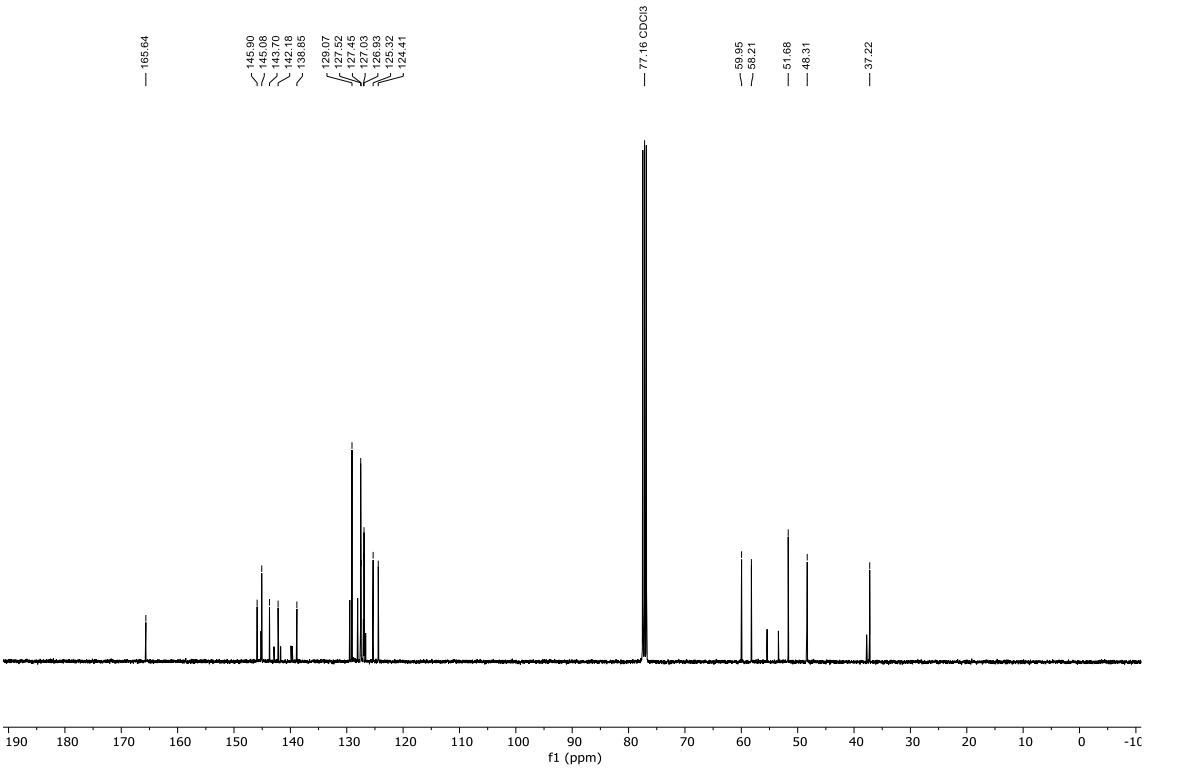

7.32 7.32 7.32 7.32 7.31 7.31 7.30 7.30 7.29 7.29 7.29 7.28 7.27 7.27 7.27 7.26 7.26 7.26 7.25 7.25 7.24 7.24 7.24 7.23 7.23 7.23 7.22 7.22 7.22 7.21 7.20 7.20 7.19 7.19 7.18 7.18 7.17 7.09 7.08 7.08 7.07 7.07 7.06 7.06 7.05 7.05 7.04 7.04 7.03 7.03 7.02 7.02 7.02 7.01 7.01 6.95 6.94 6.94 6.87 6.87 6.86 6.86 6.85 6.85 6.80 6.79 6.79 6.78 6.77 4.34 4.34 4.32 4.32 4.03 4.01 3.98 3.85 3.06 3.06 3.05 3.05 3.04 3.04 3.04 3.03 3.03 3.02 3.02
46.36
1.00
2.13
1.99
1.06
1.15
3.09
1.92
f1 (ppm)


165.64
144.80
140.47
138.47
137.35
128.71
128.36
127.92
127.67
126.52
126.06
56.69
51.74
49.83
36.31
f1 (ppm)

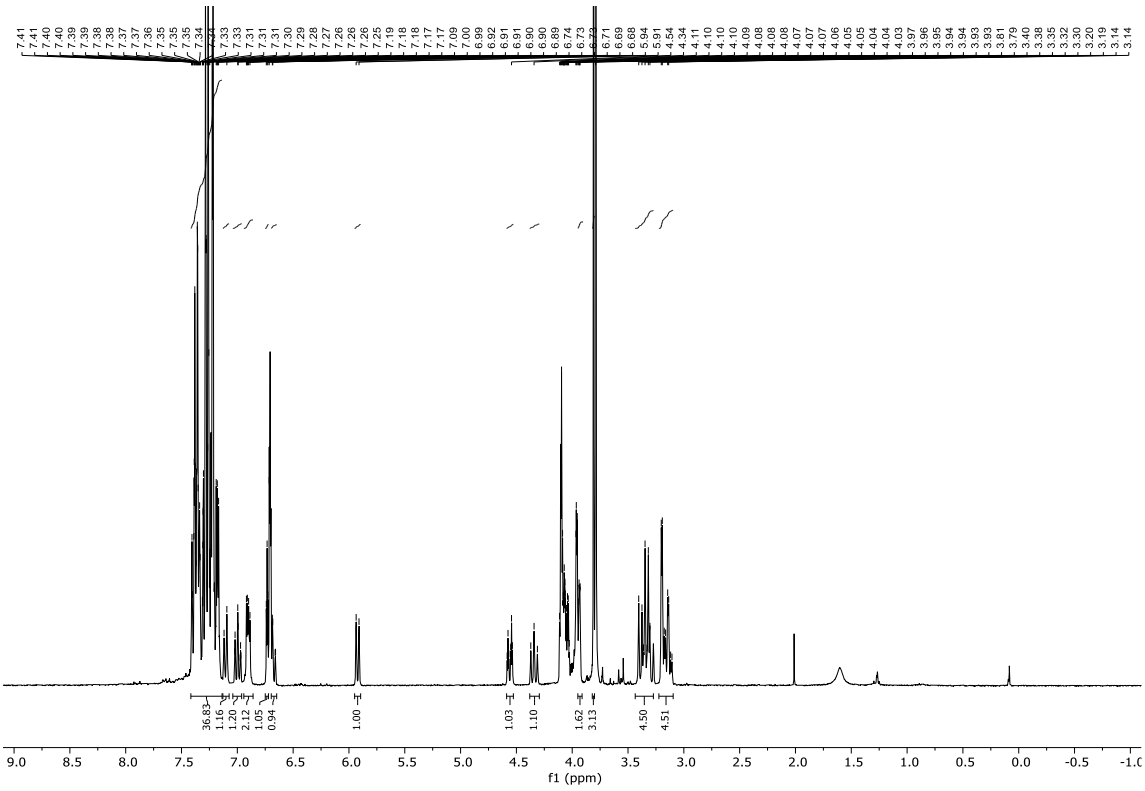
Methyl-1-phenyl-1,3a,8,8a-tetrahydrocyclopenta[a]indene-3-carboxylate and methyl-3-phenyl-3,3a,8,8a-tetrahydrocyclopenta[a]indene-1-carboxylate 261l

major:





Minor: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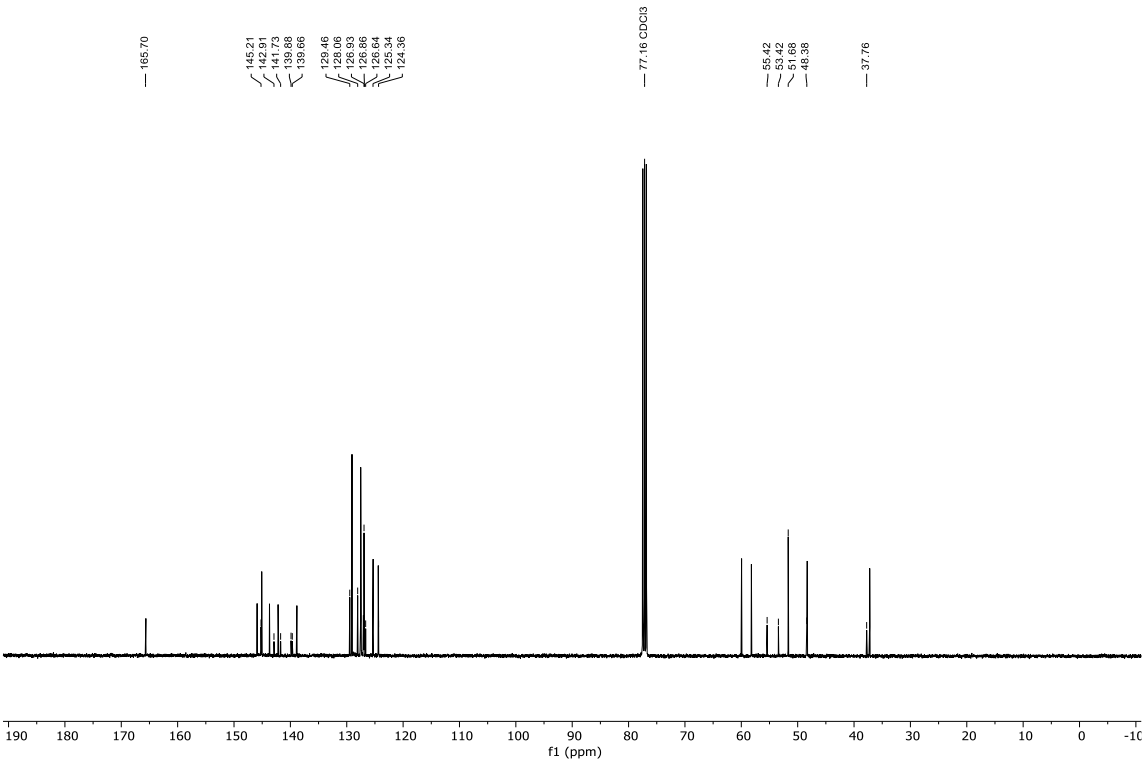
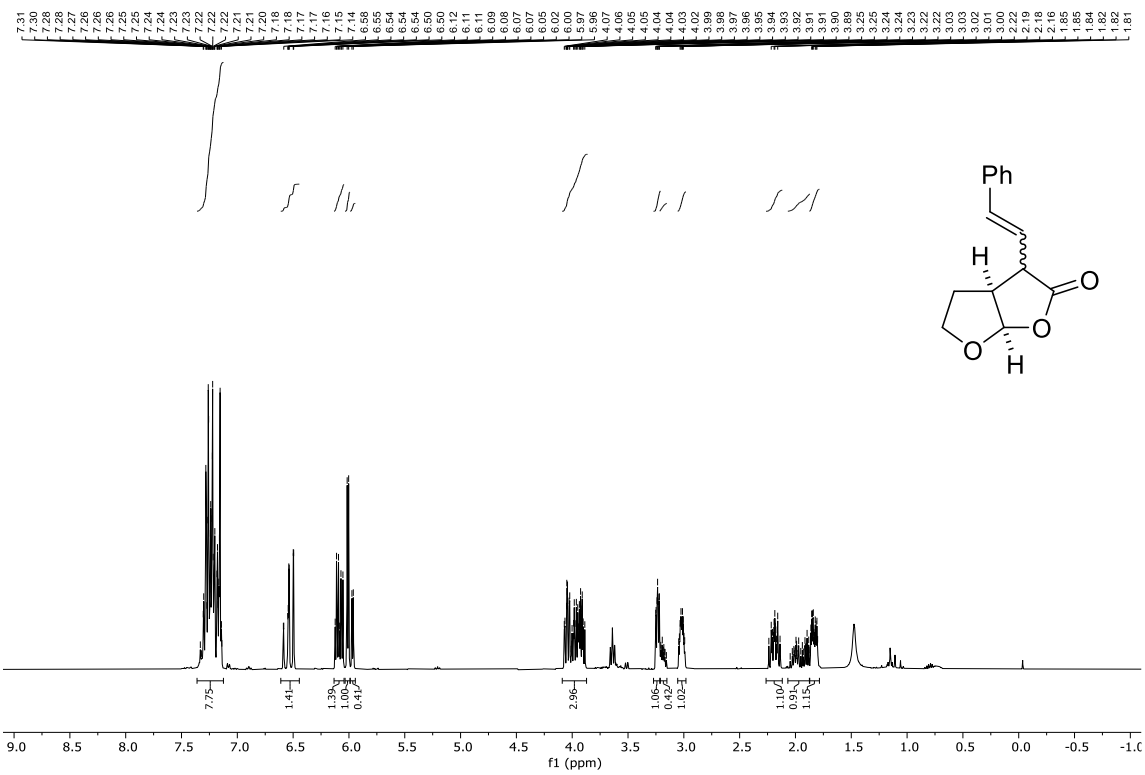
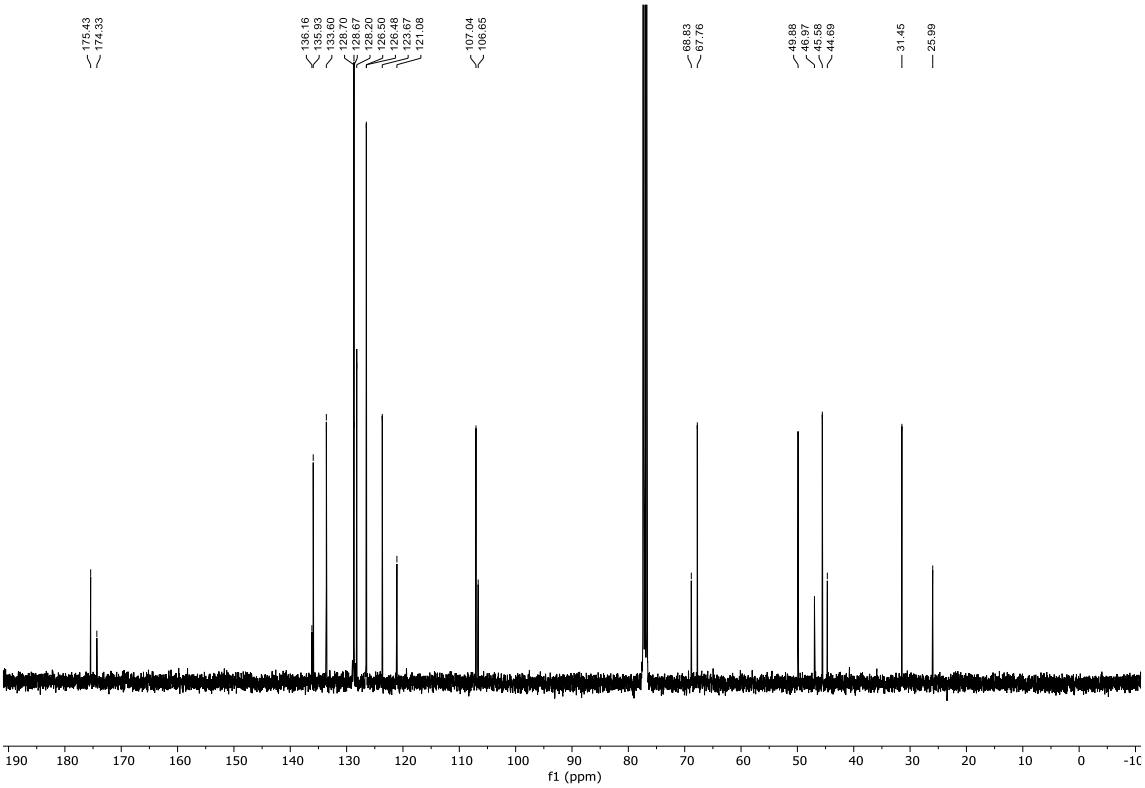
36.83 1.16 1.20 2.12 1.05 0.94 1.00 1.03 1.10 1.62 3.13 4.50 4.51
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0
f1 (ppm)

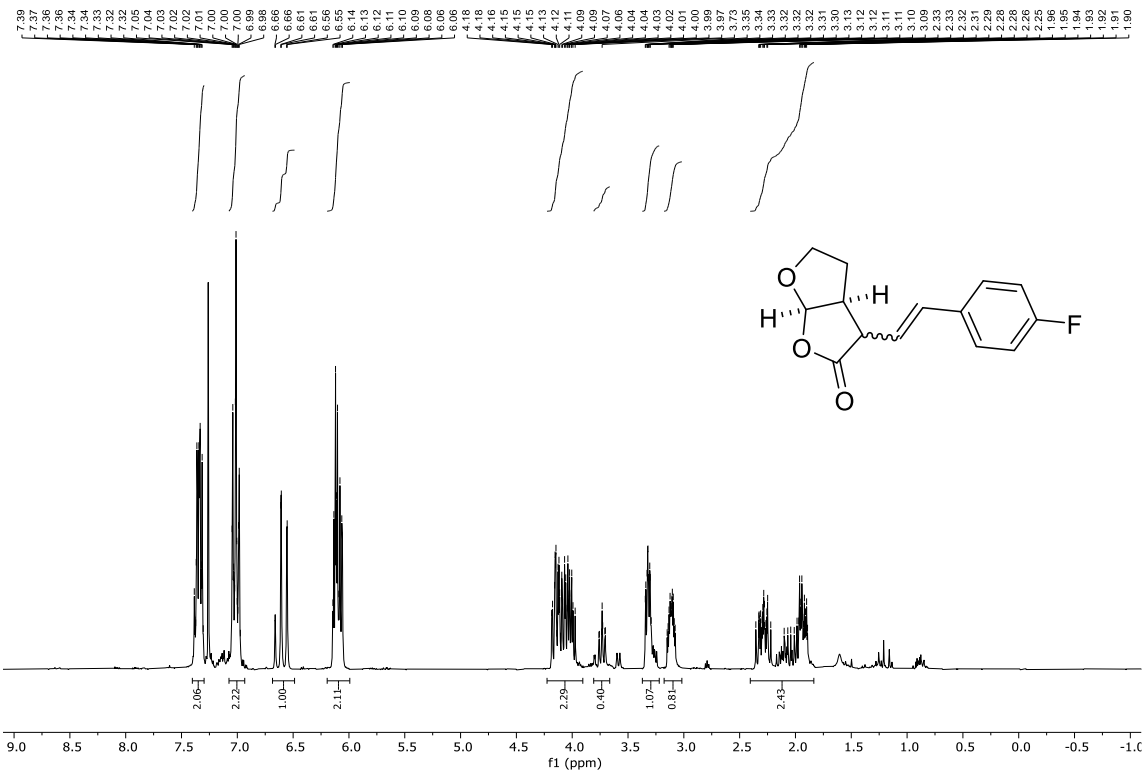

165.70
145.21 142.91 141.73 139.88 139.66 129.46 128.06 126.93 126.86 126.64 125.34 124.36
77.16 CDCl3
55.42 53.42 51.68 48.38
37.76
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

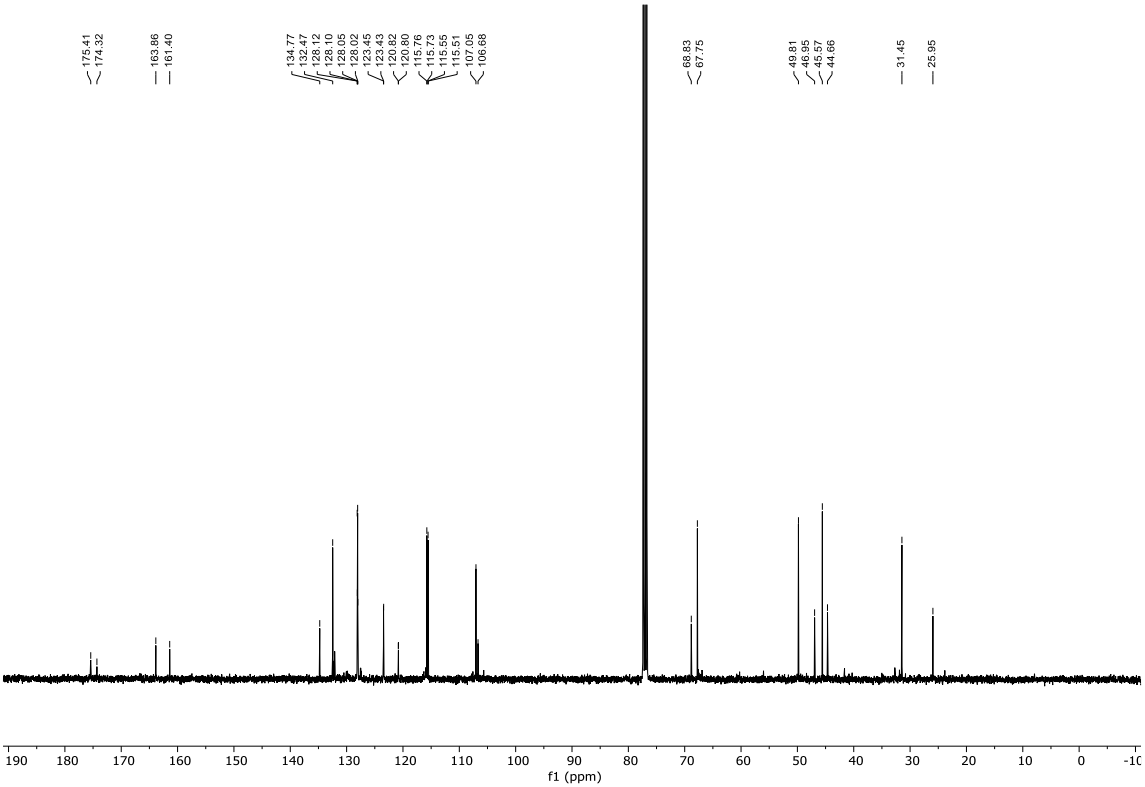
3-Styryltetrahydrofuro[2,3-b]furan-2(3H)-one 272a

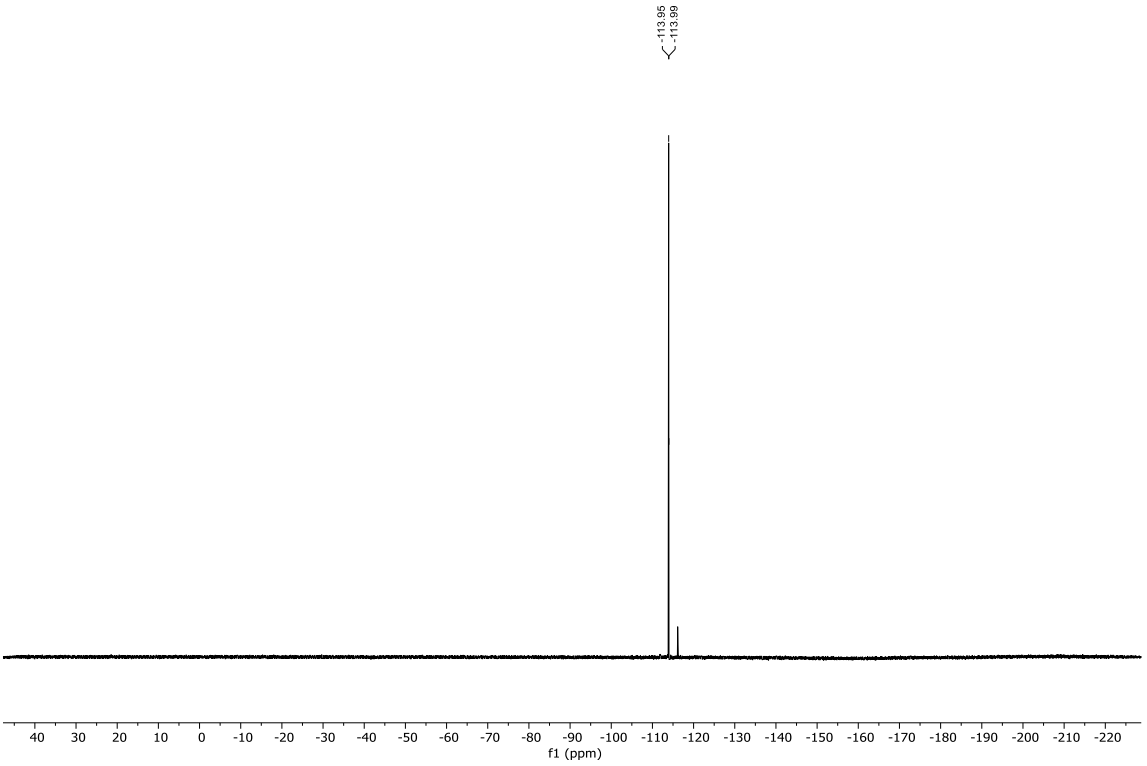


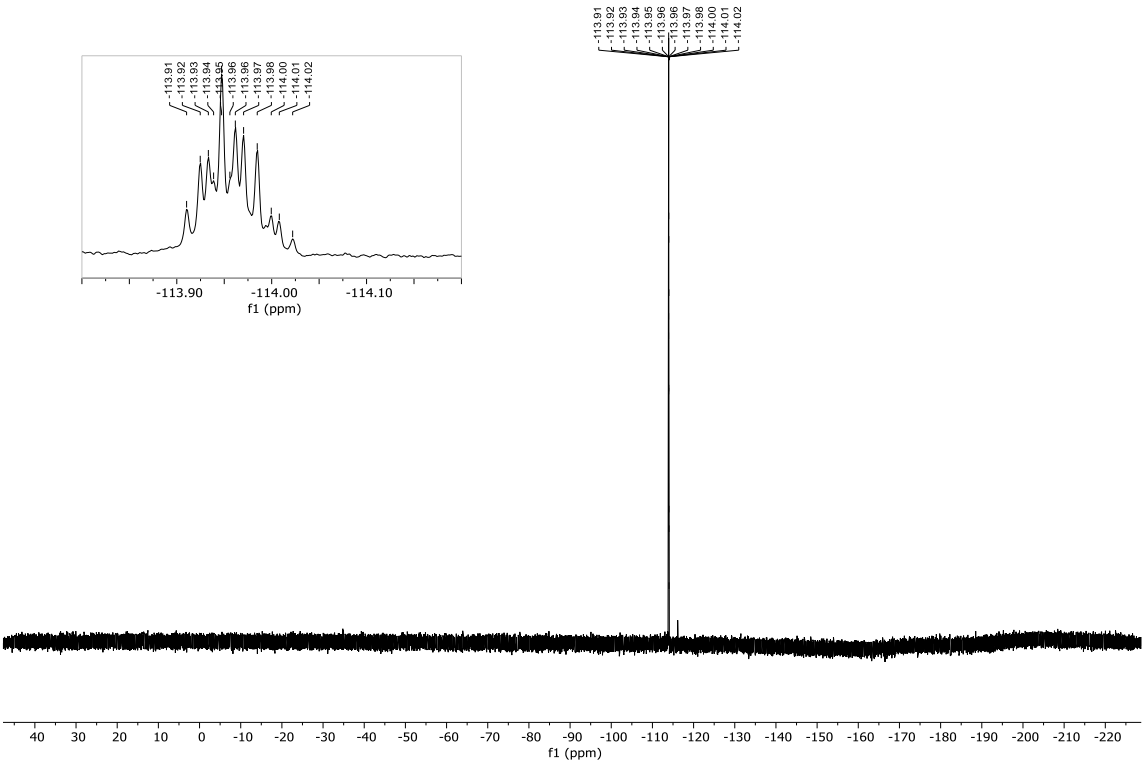


3-(4-Fluorostyryl)tetrahydrofuro[2,3-*b*]furan-2(3*H*)-one 272b

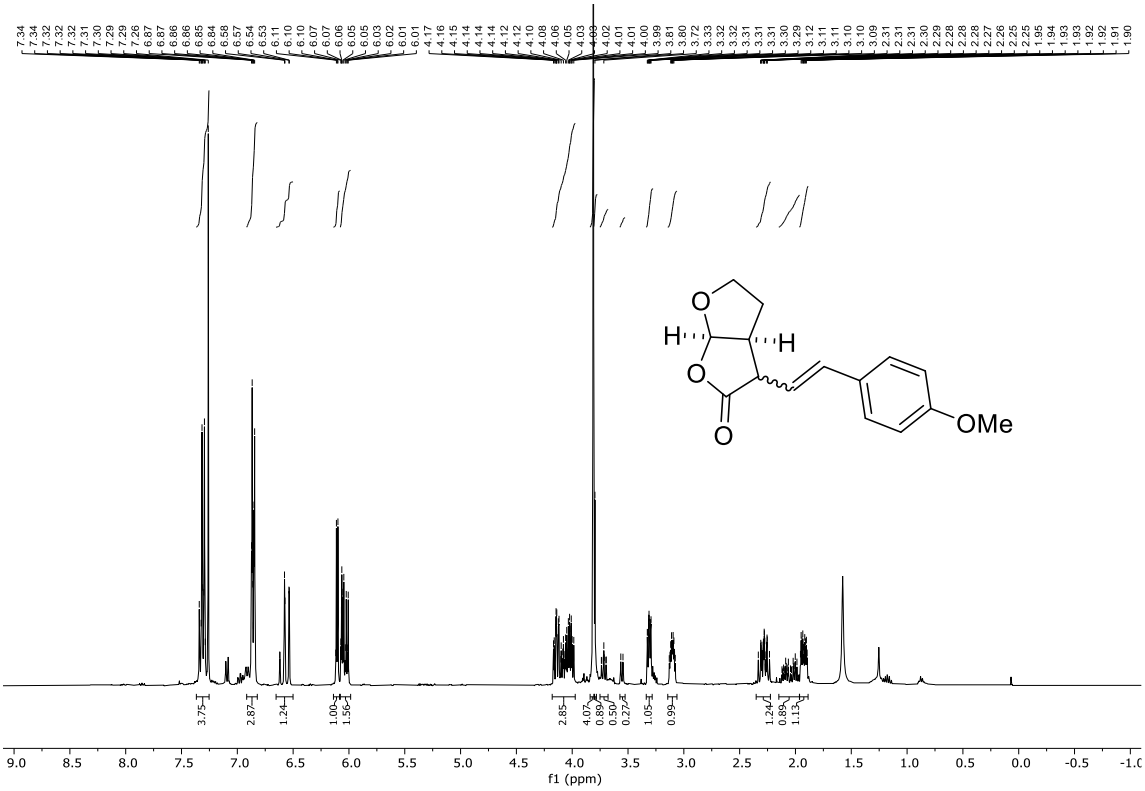


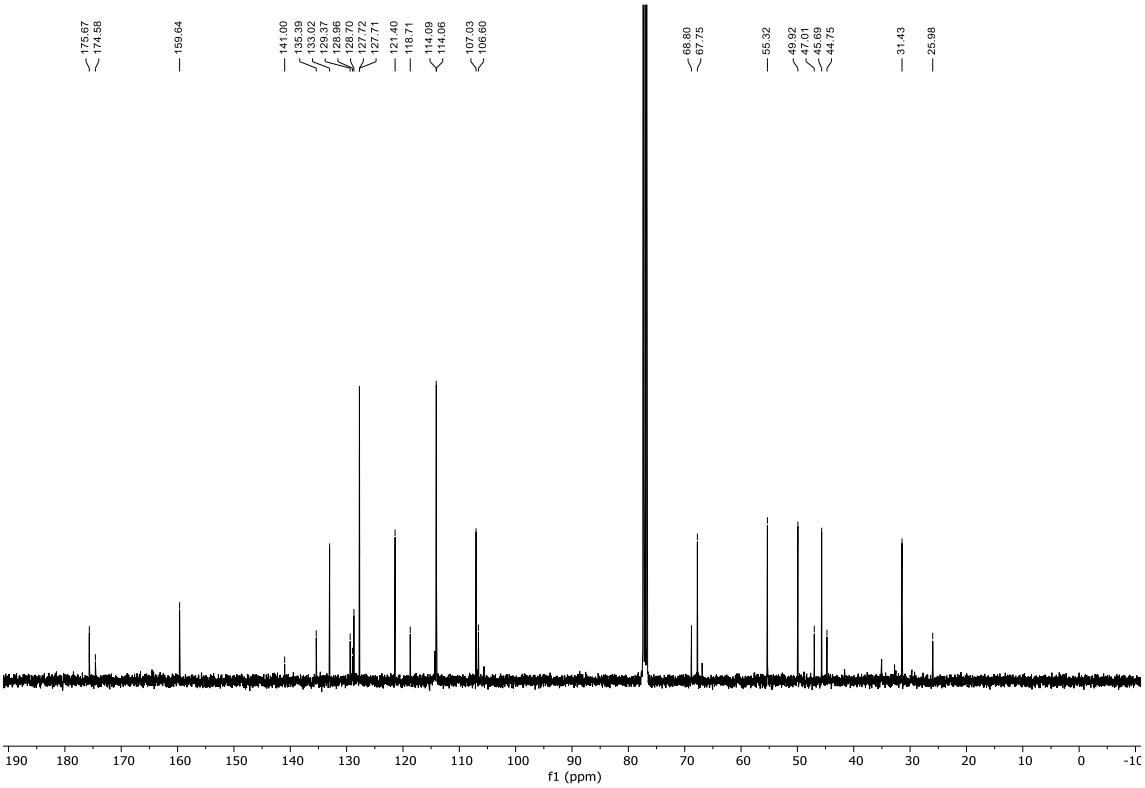



-113.95
-113.99
40 30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210 -220
f1 (ppm)

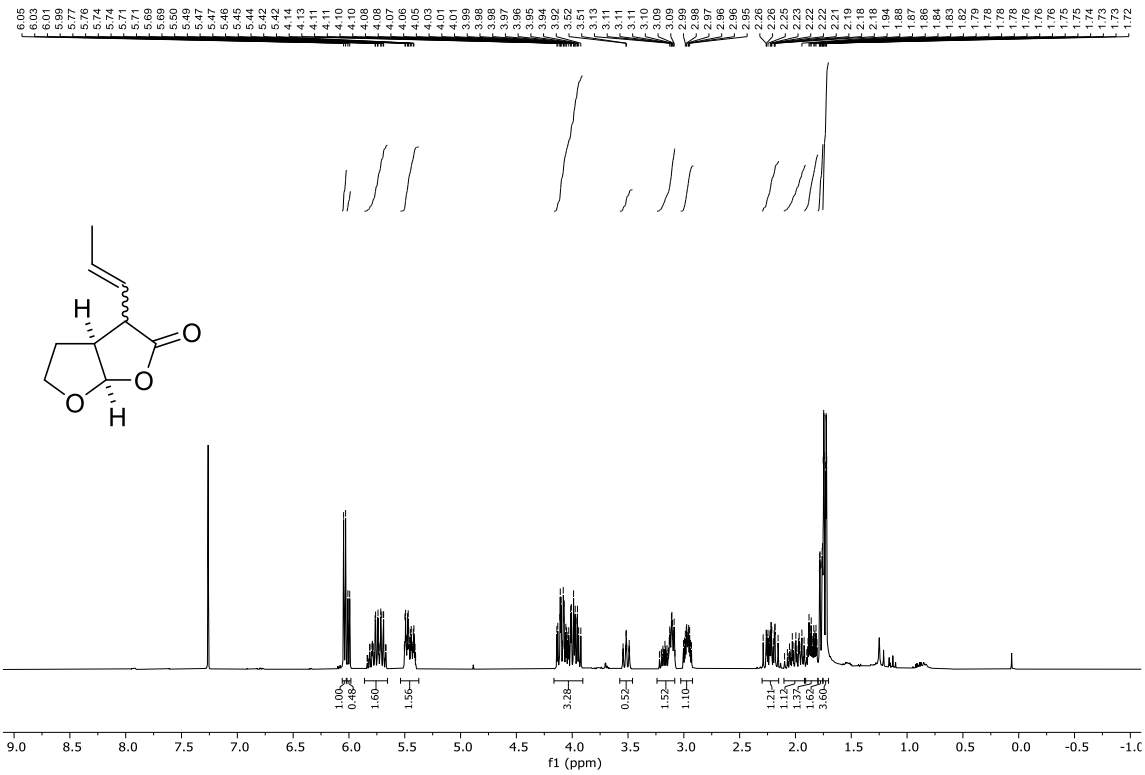

-113.91
-113.92
-113.93
-113.94
-113.95
-113.96
-113.97
-113.98
-114.00
-114.01
-114.02
-113.90
-114.00
-114.10
f1 (ppm)
40 30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210 -220
f1 (ppm)

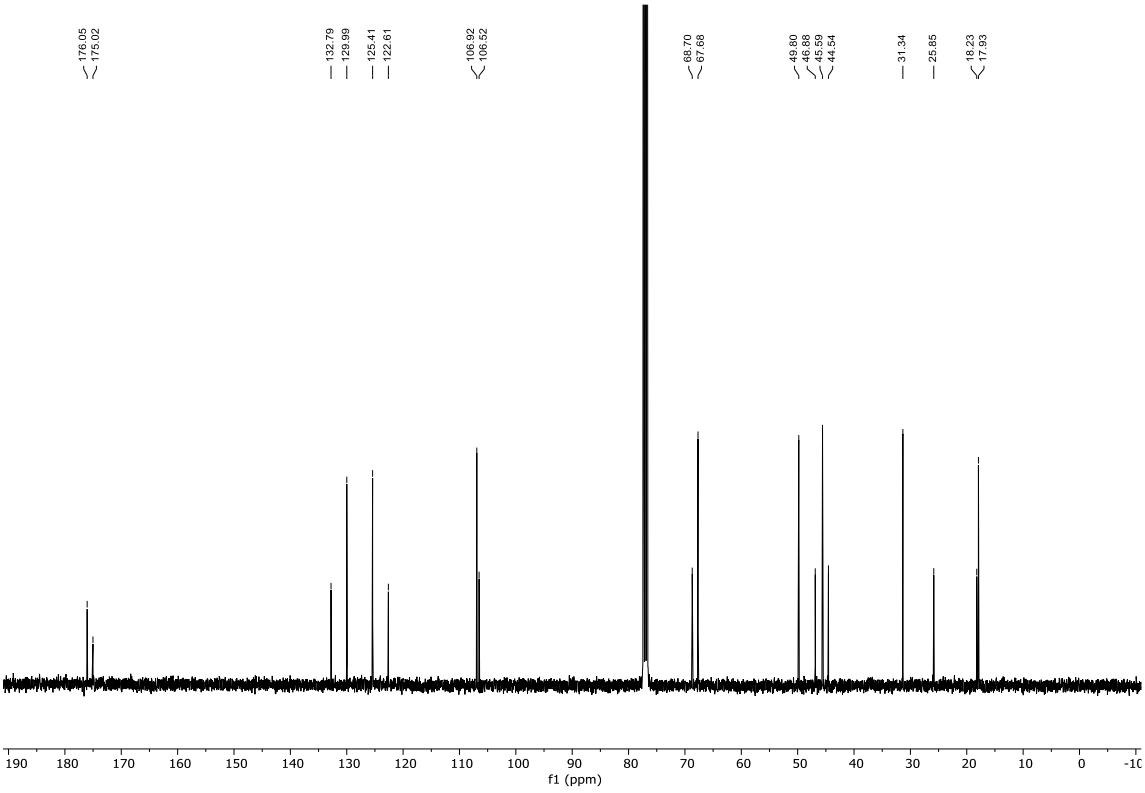
3-(4-Methoxystyryl)tetrahydrofuro[2,3-*b*]furan-2(3*H*)-one 272c



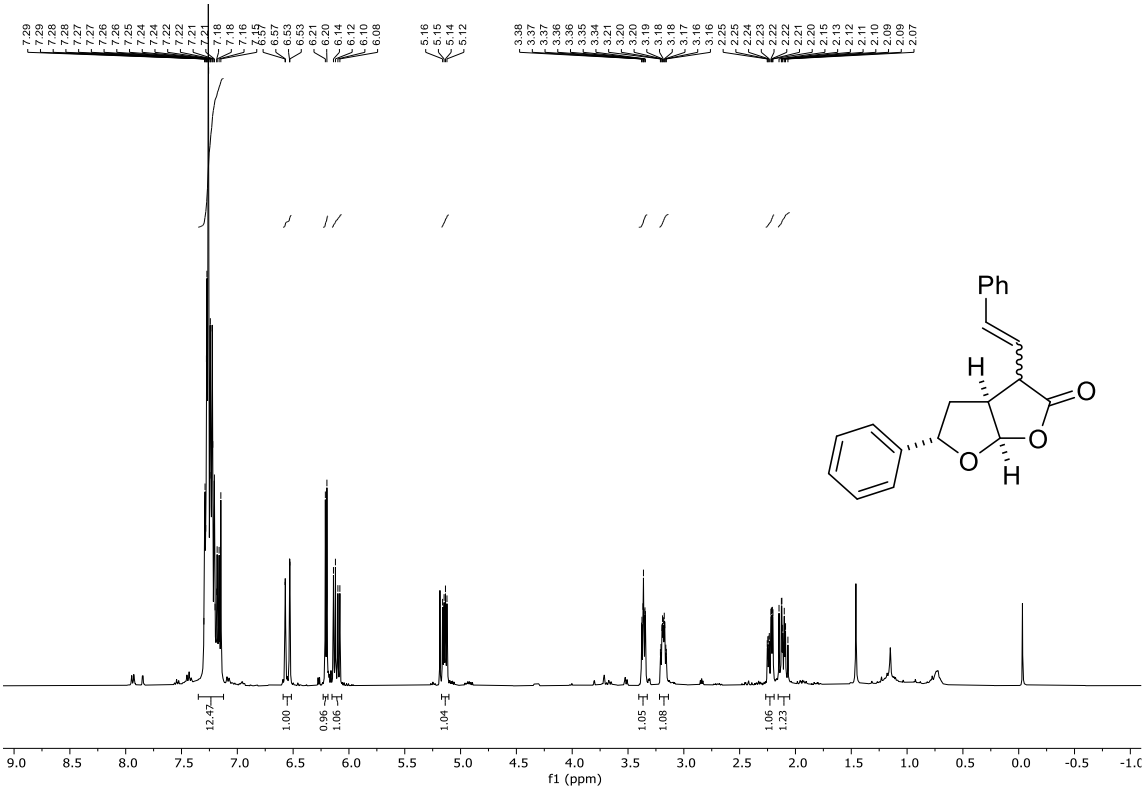


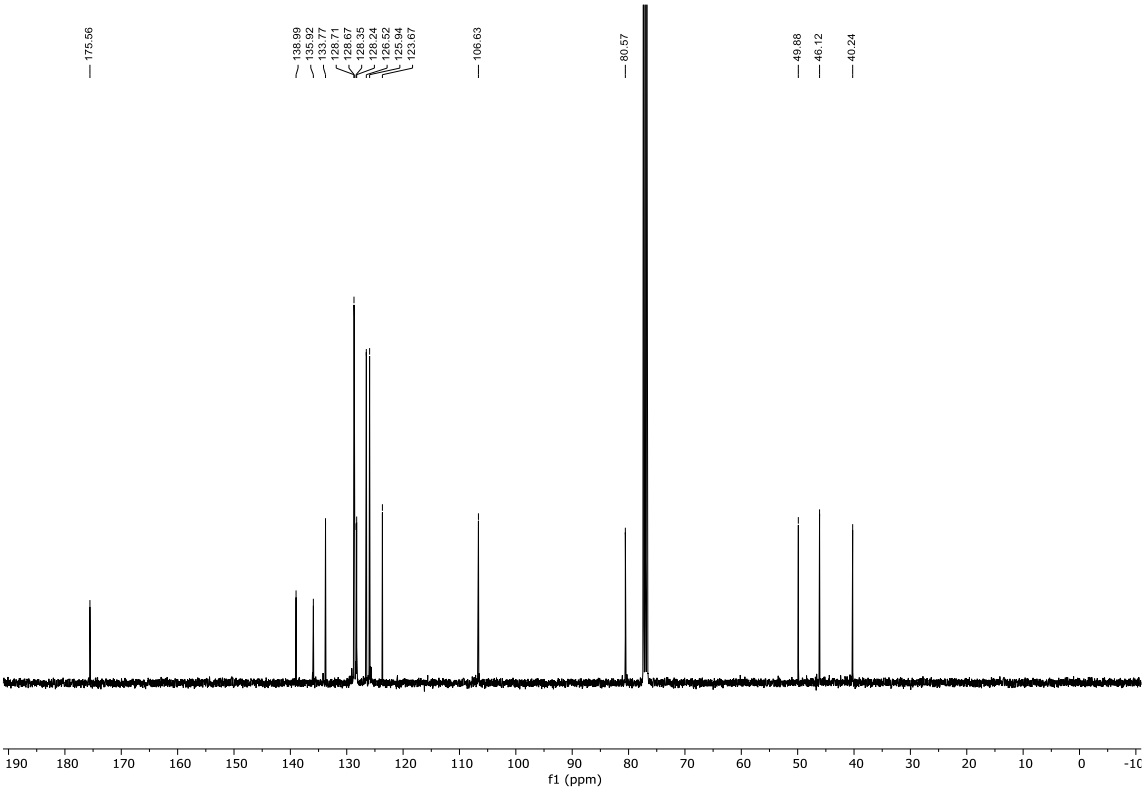
3-(Prop-1-en-1-yl)tetrahydrofuro[2,3-b]furan-2(3H)-one 272d



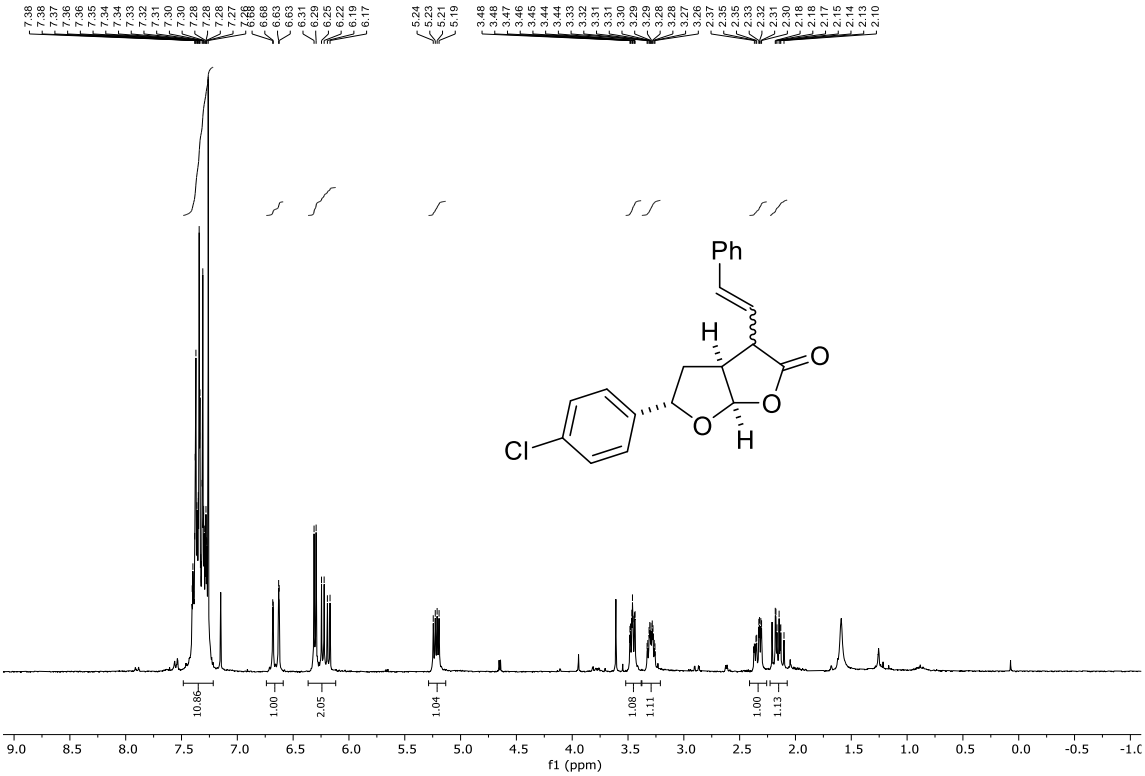


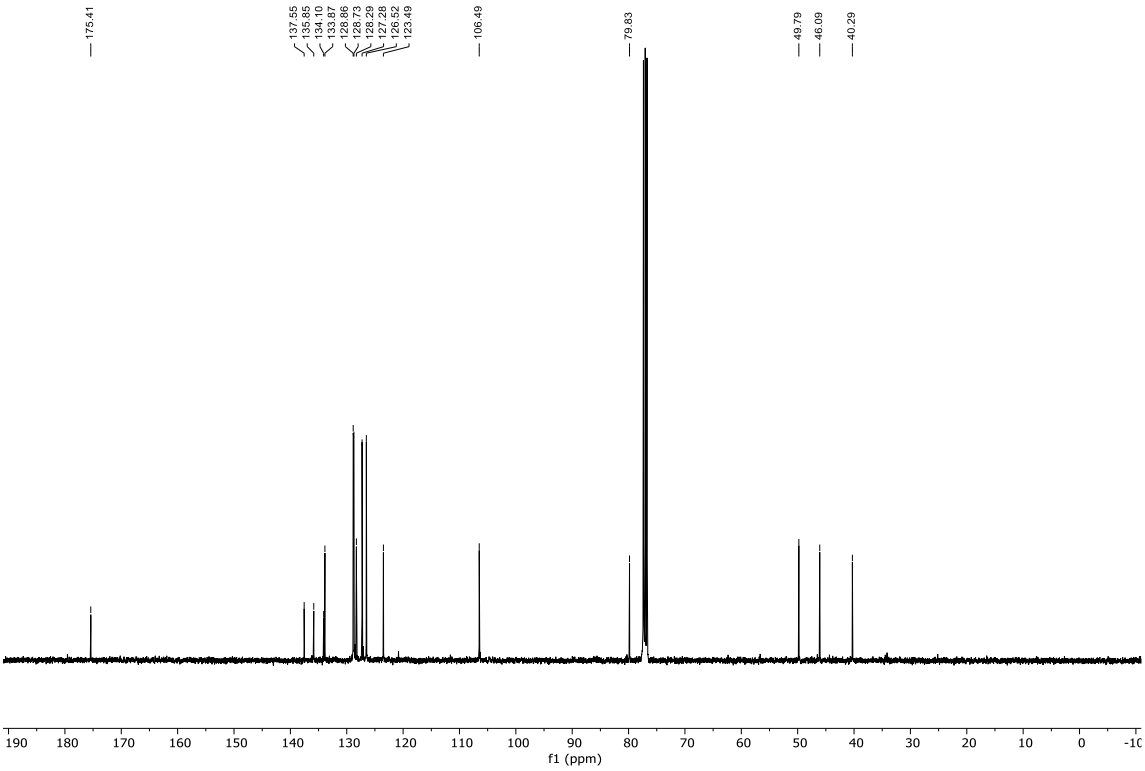
5-Phenyl-3-styryltetrahydrofuro[2,3-*b*]furan-2(3*H*)-one 272e



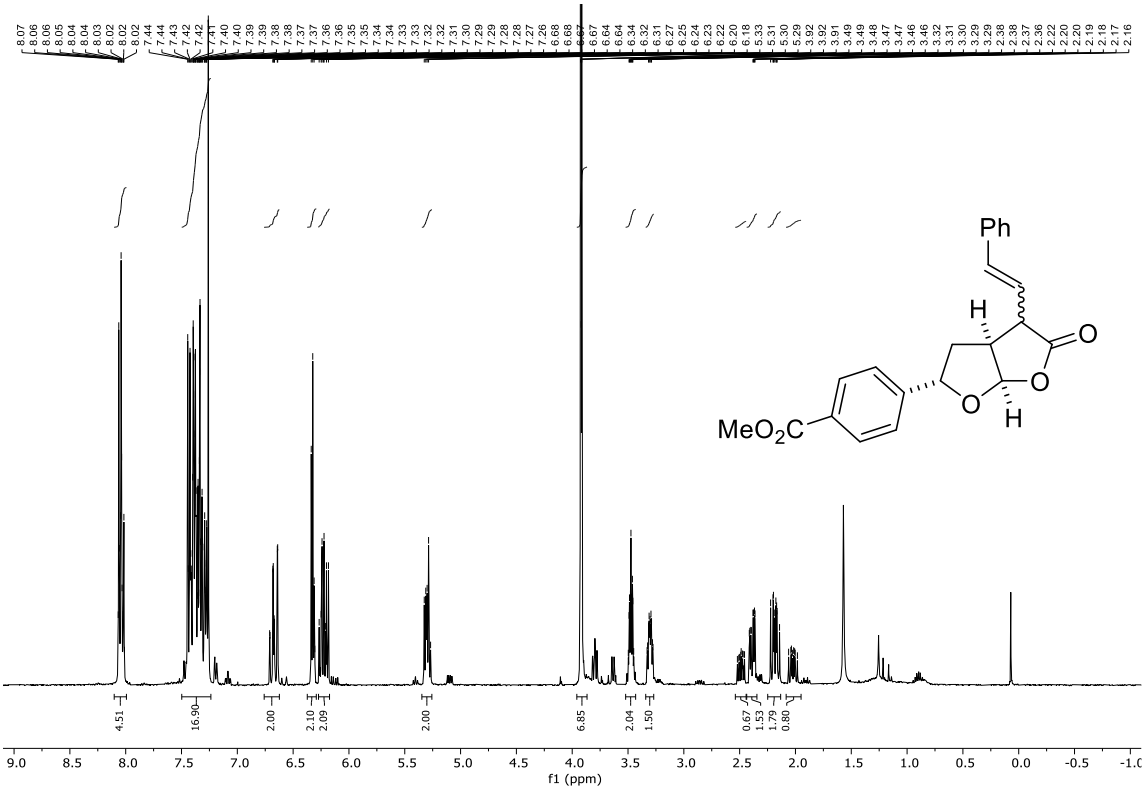


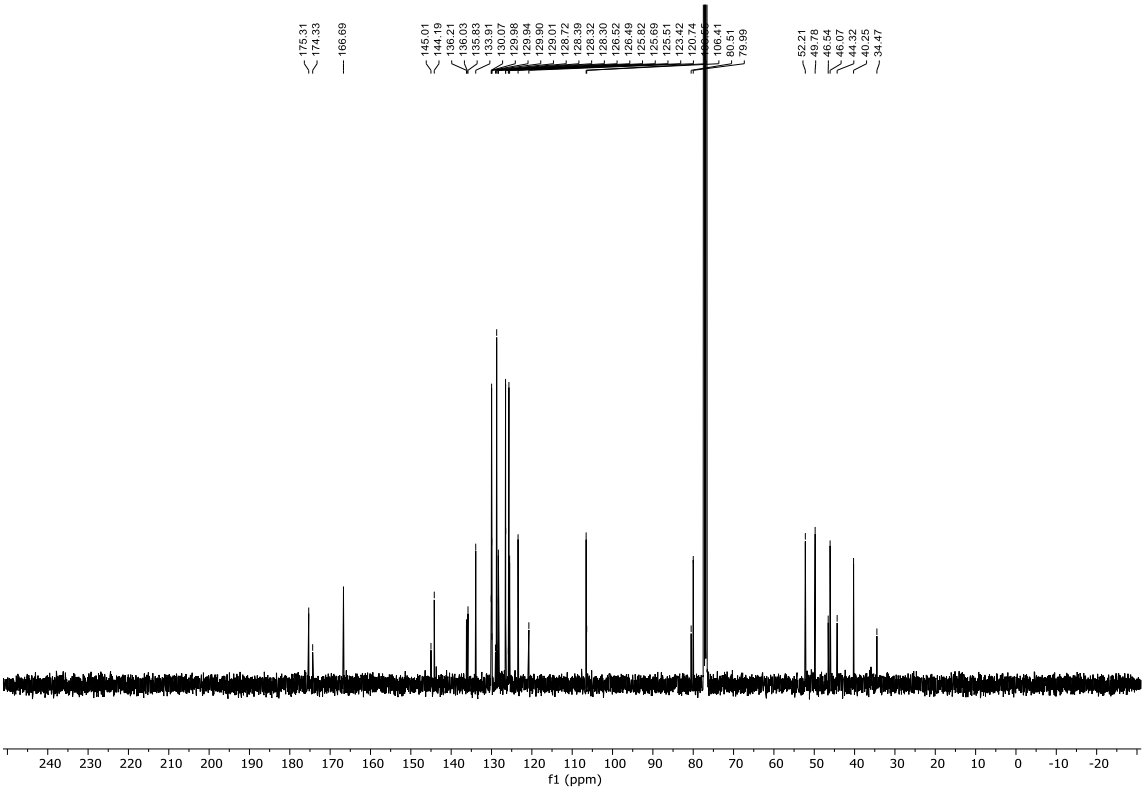
5-(4-Chlorophenyl)-3-styryltetrahydrofuro[2,3-b]furan-2(3H)-one 272g





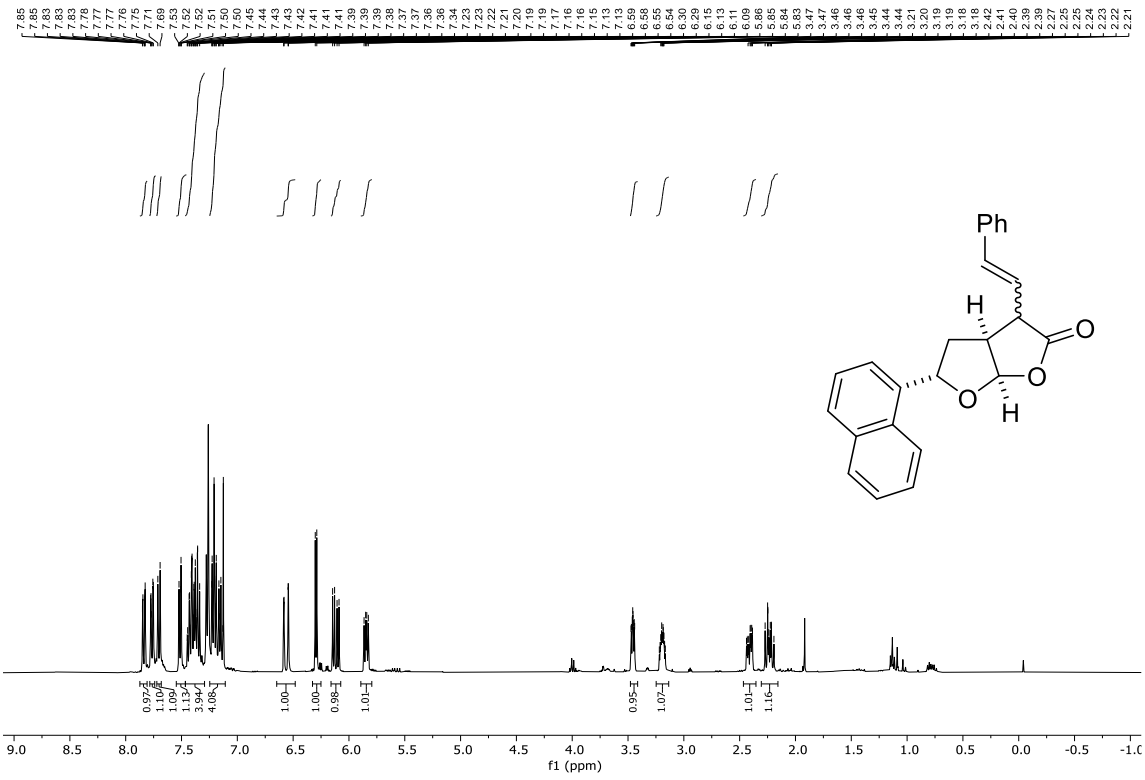
Methyl 4-(5-oxo-4-styrylhexahydrofuro[2,3-b]furan-2-yl)benzoate 272h

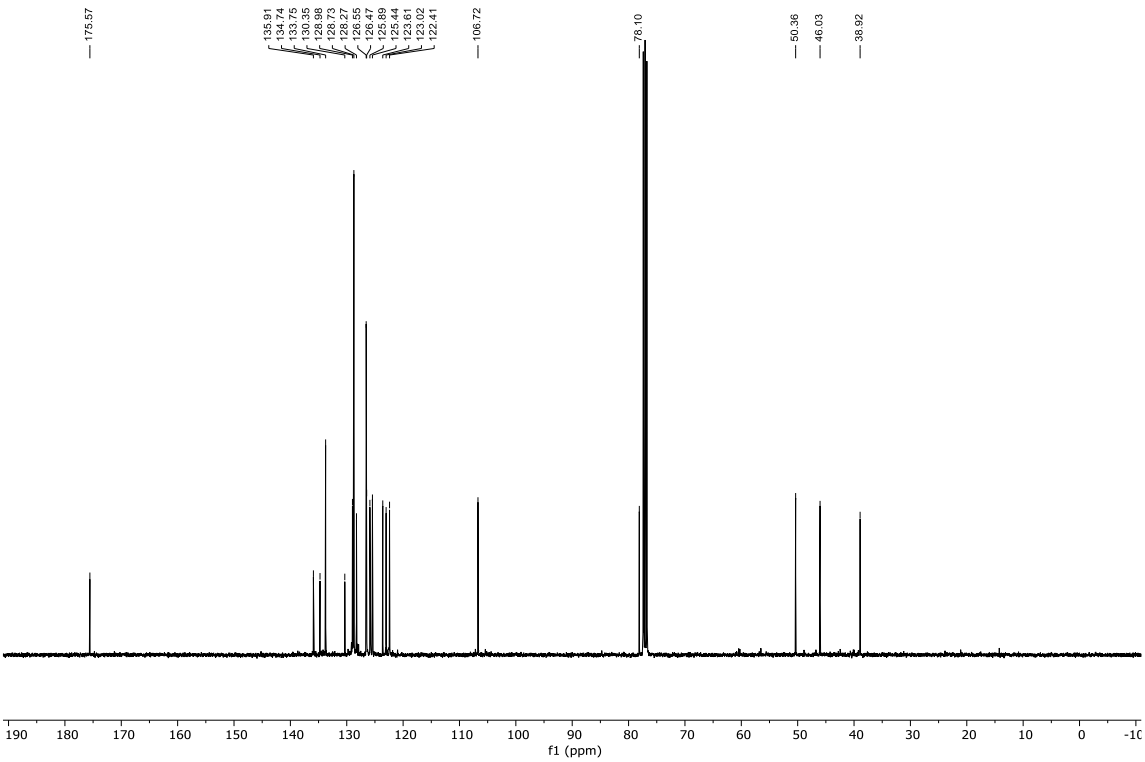




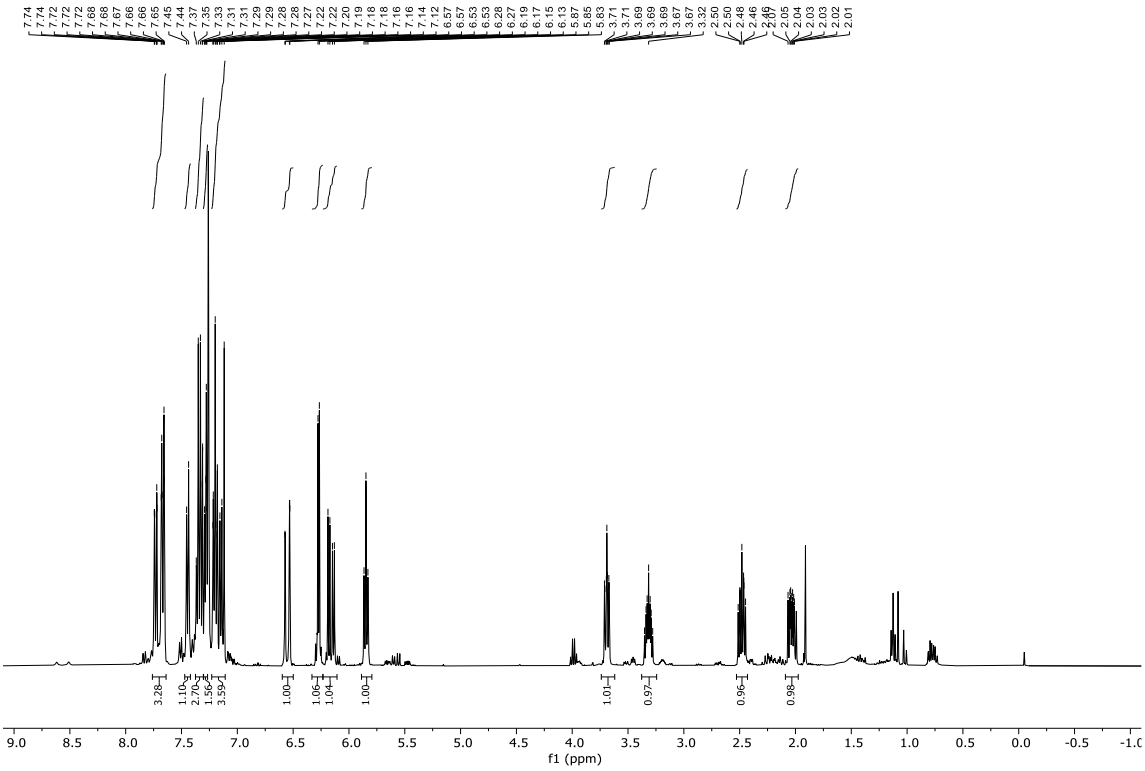
5-(Naphthalen-1-yl)-3-styryltetrahydrofuro[2,3-b]furan-2(3H)-one 272f

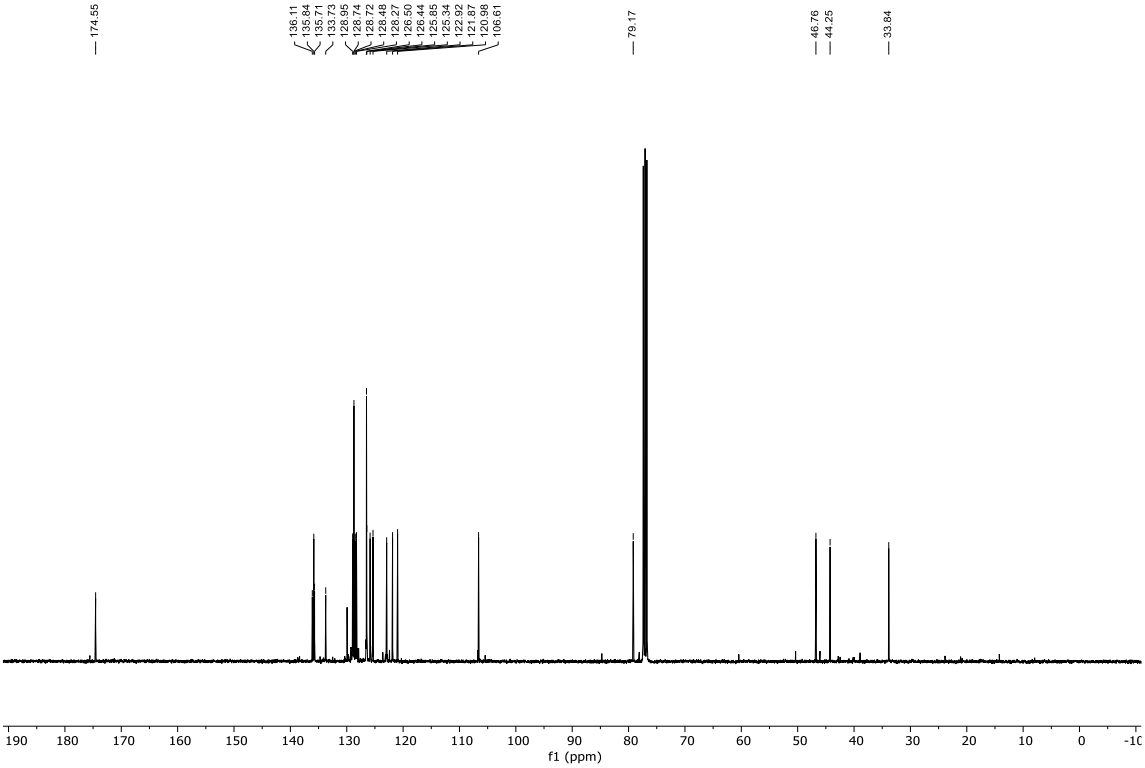
Diastereomer 1





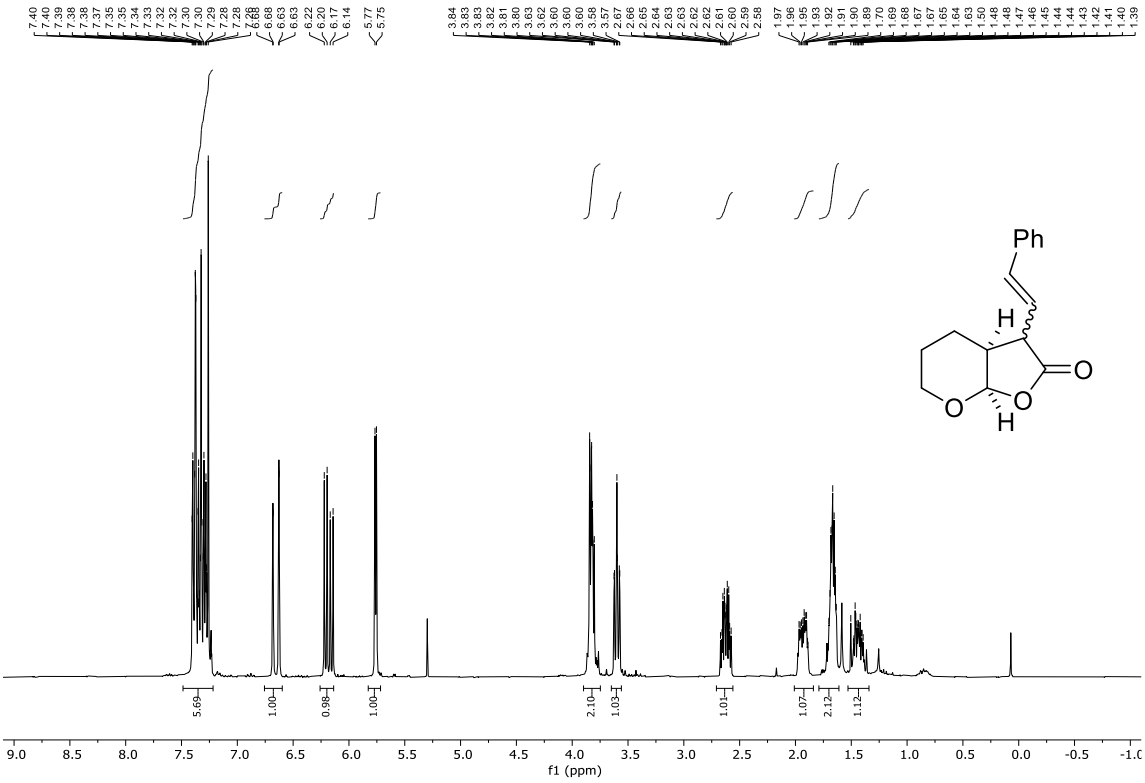
Diastereomer 2:

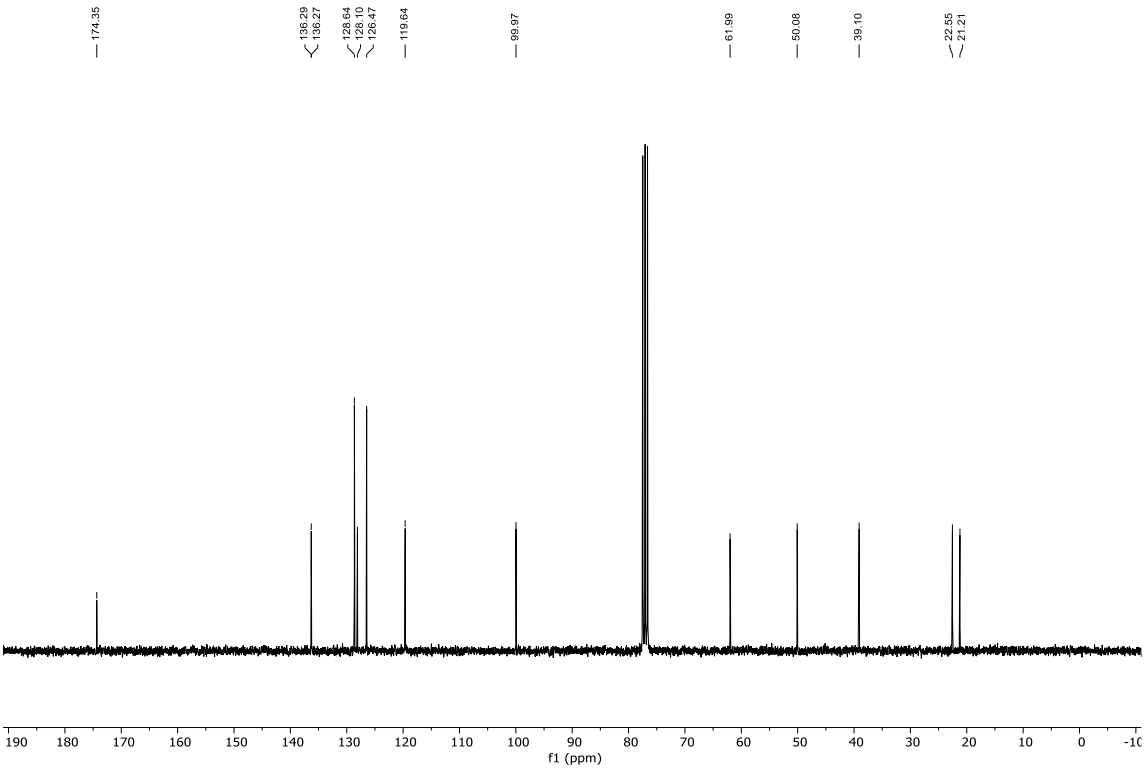




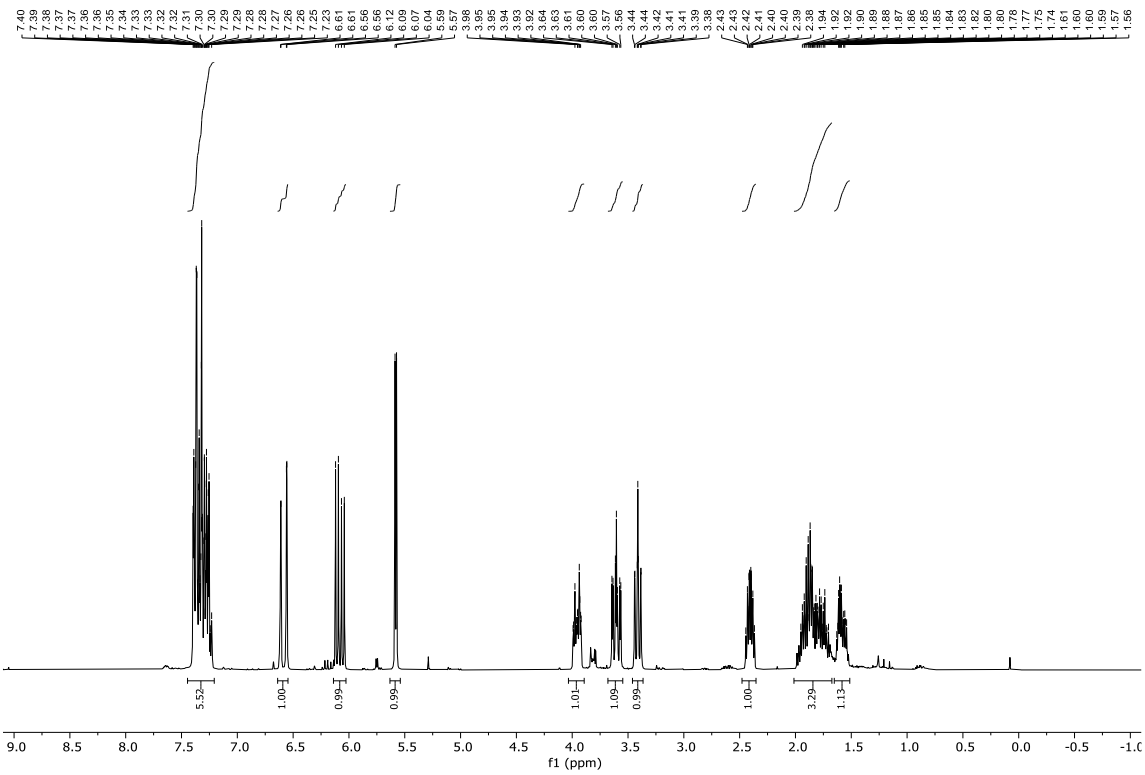
3-Styryltetrahydro-4H-furo[2,3-b]pyran-2(3H)-one 272k

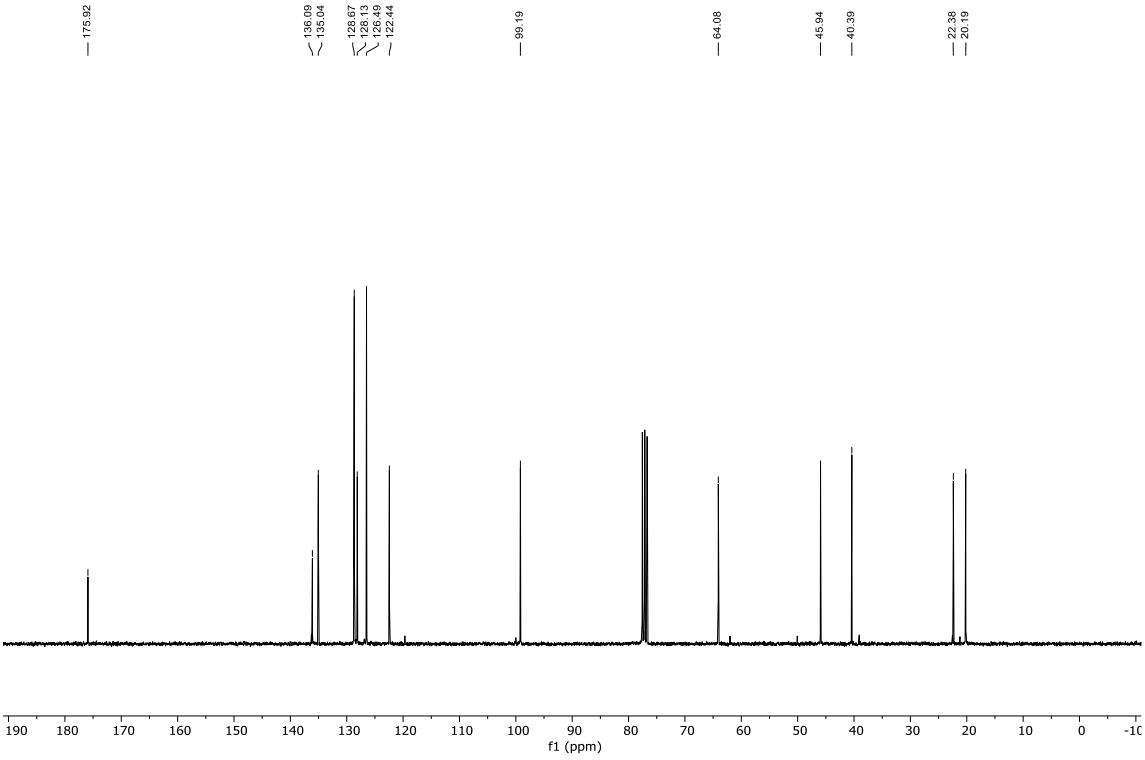
Minor:





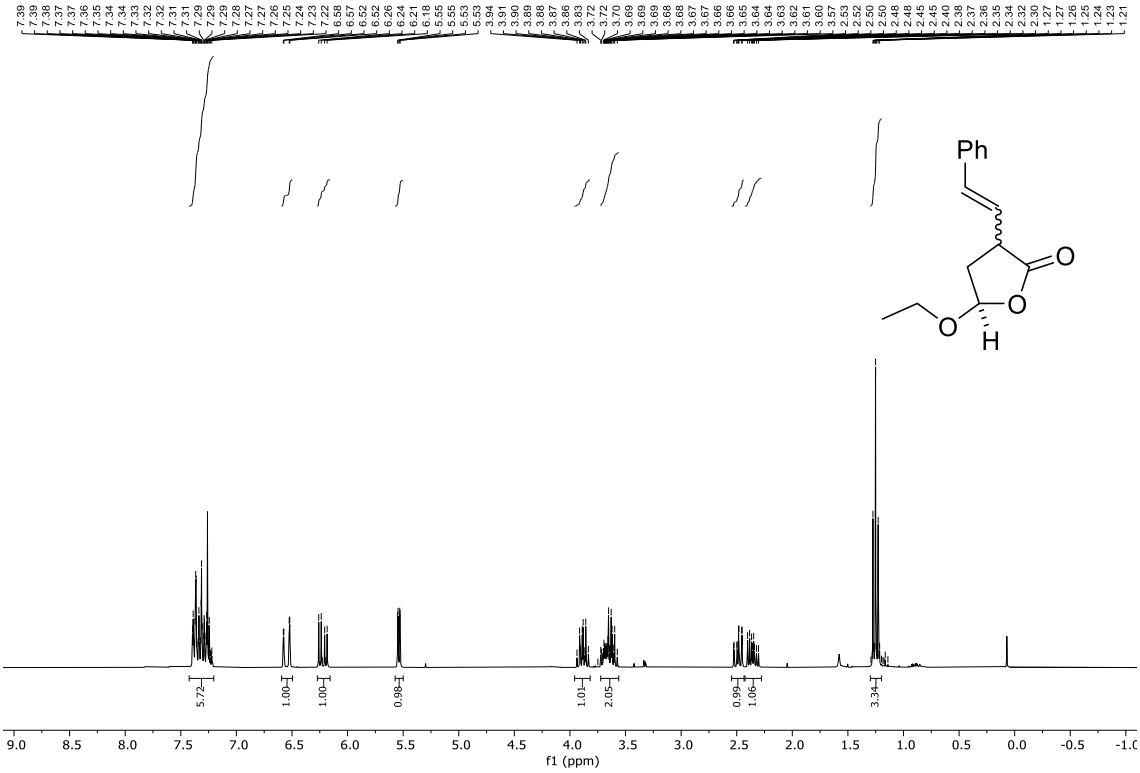
Major:

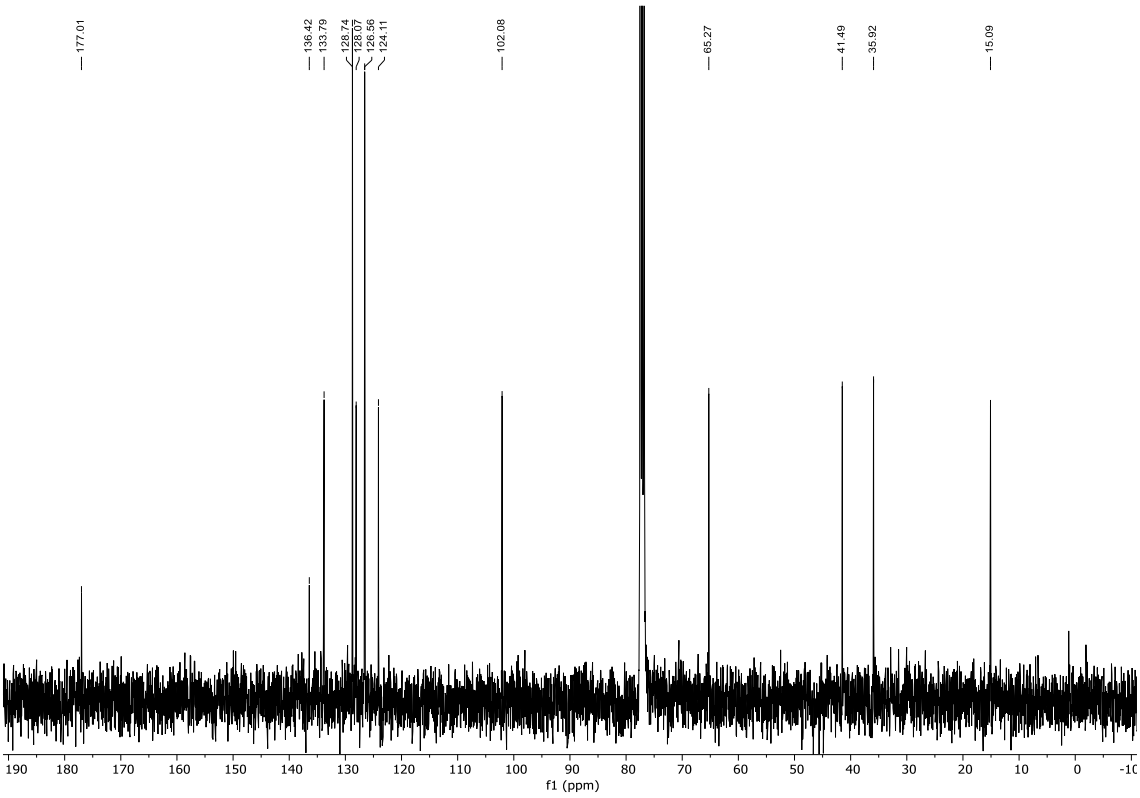

7.40 7.39 7.38 7.37 7.37 7.36 7.36 7.35 7.34 7.33 7.33 7.32 7.32 7.31 7.30 7.30 7.29 7.29 7.28 7.28 7.27 7.26 7.26 7.25 7.23 6.61 6.61 6.56 6.56 6.12 6.09 6.07 6.04 5.59 5.57 3.98 3.96 3.95 3.94 3.93 3.92 3.64 3.63 3.61 3.60 3.60 3.57 3.56 3.44 3.44 3.42 3.41 3.41 3.39 3.38 2.43 2.43 2.42 2.41 2.40 2.40 2.39 2.38 1.94 1.92 1.92 1.90 1.89 1.88 1.87 1.86 1.85 1.85 1.84 1.83 1.82 1.80 1.80 1.78 1.77 1.75 1.74 1.61 1.60 1.60 1.59 1.57 1.56
5.52 1.00 0.99 0.99 1.01 1.09 0.99 1.00 3.29 1.13
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 -0.5 -1.0
f1 (ppm)


175.92
136.09 135.04 128.67 128.13 126.49 122.44
99.19
64.08
45.94
40.39
22.38 20.19
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

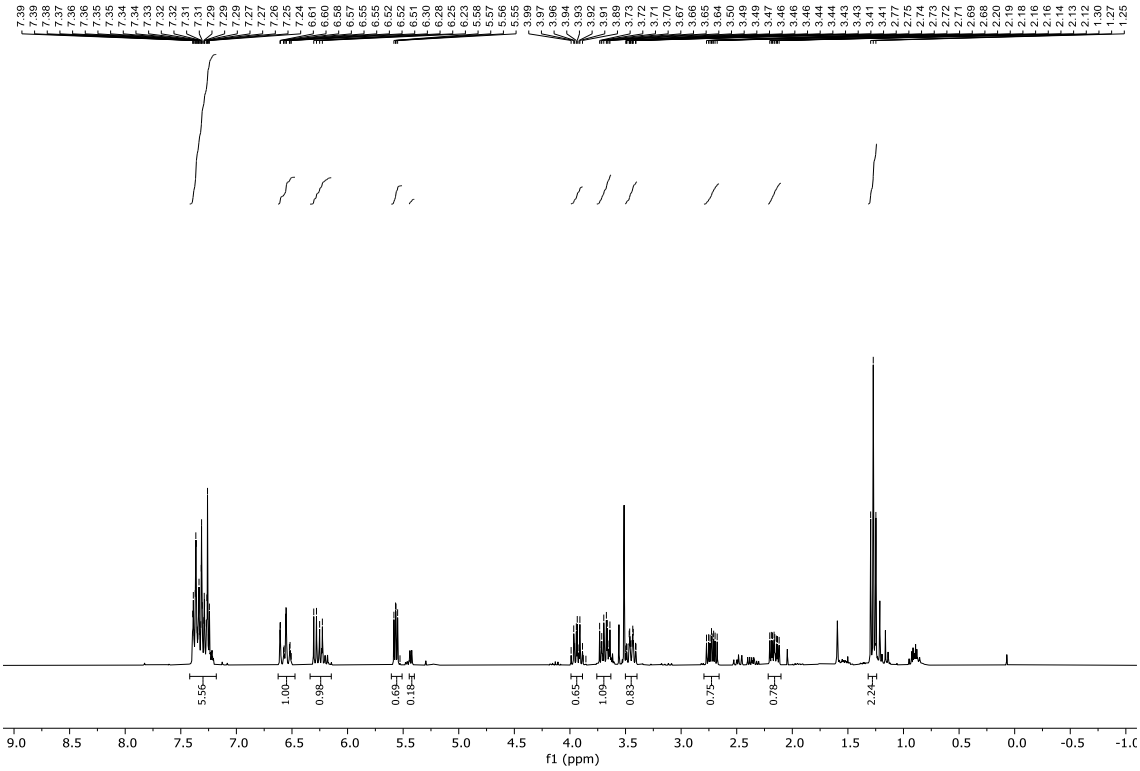
5-Ethoxy-3-styryldihydrofuran-2(3*H*)-one 272n

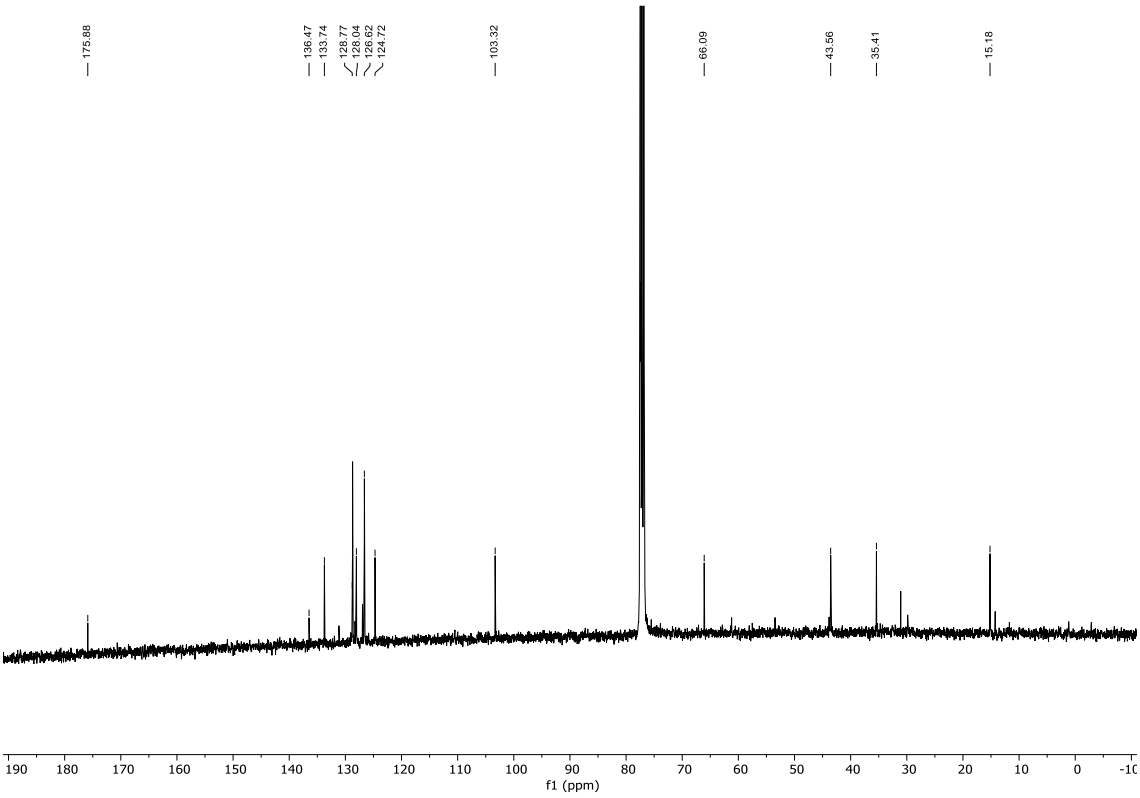
Diastereomer 1



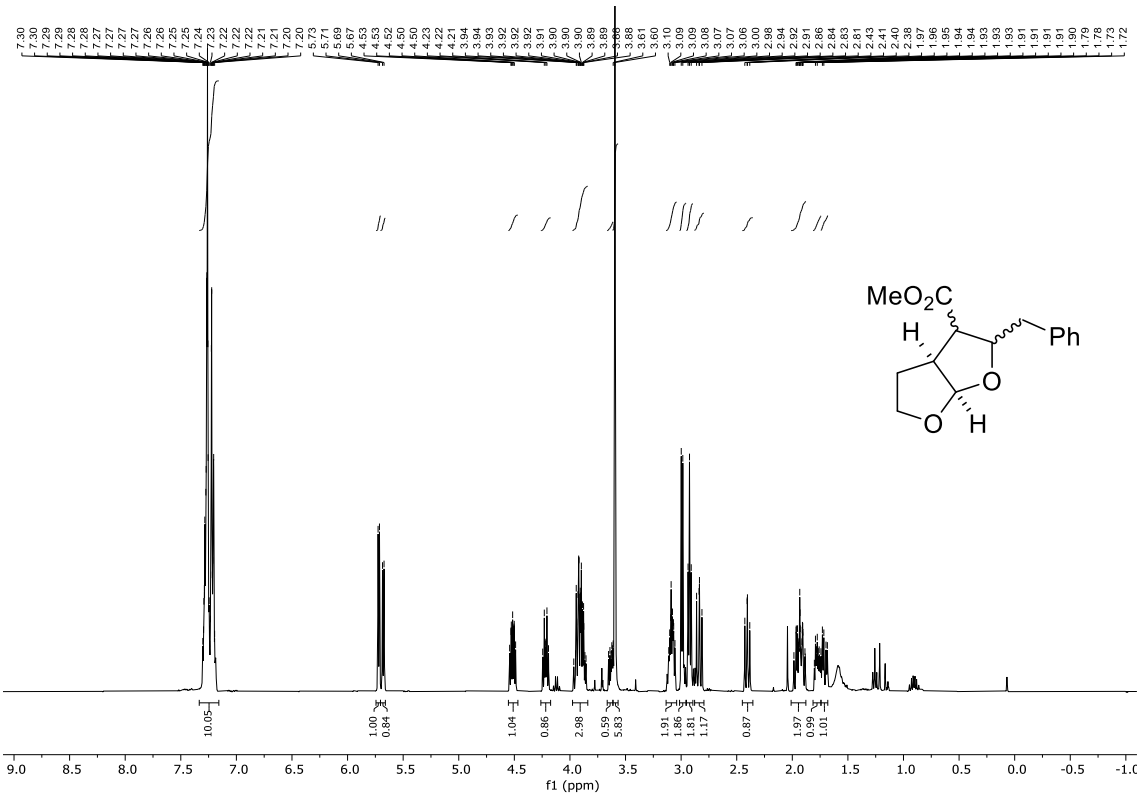


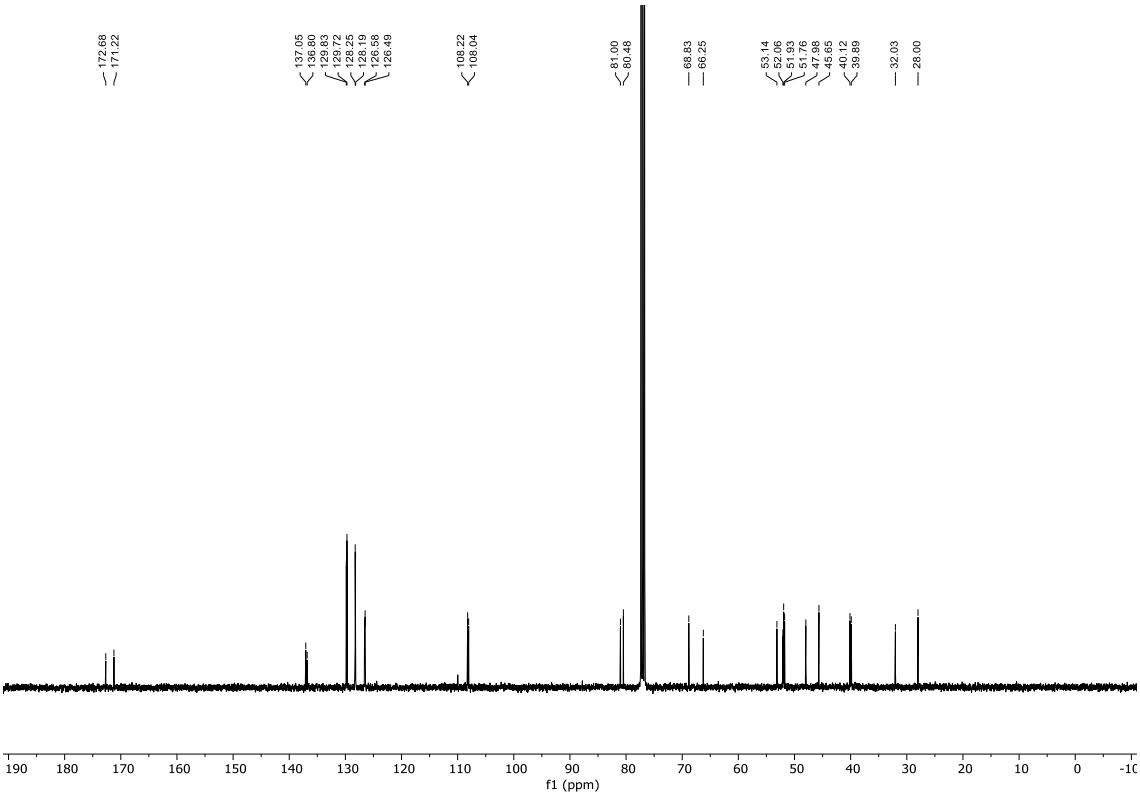
Diastereomer 2



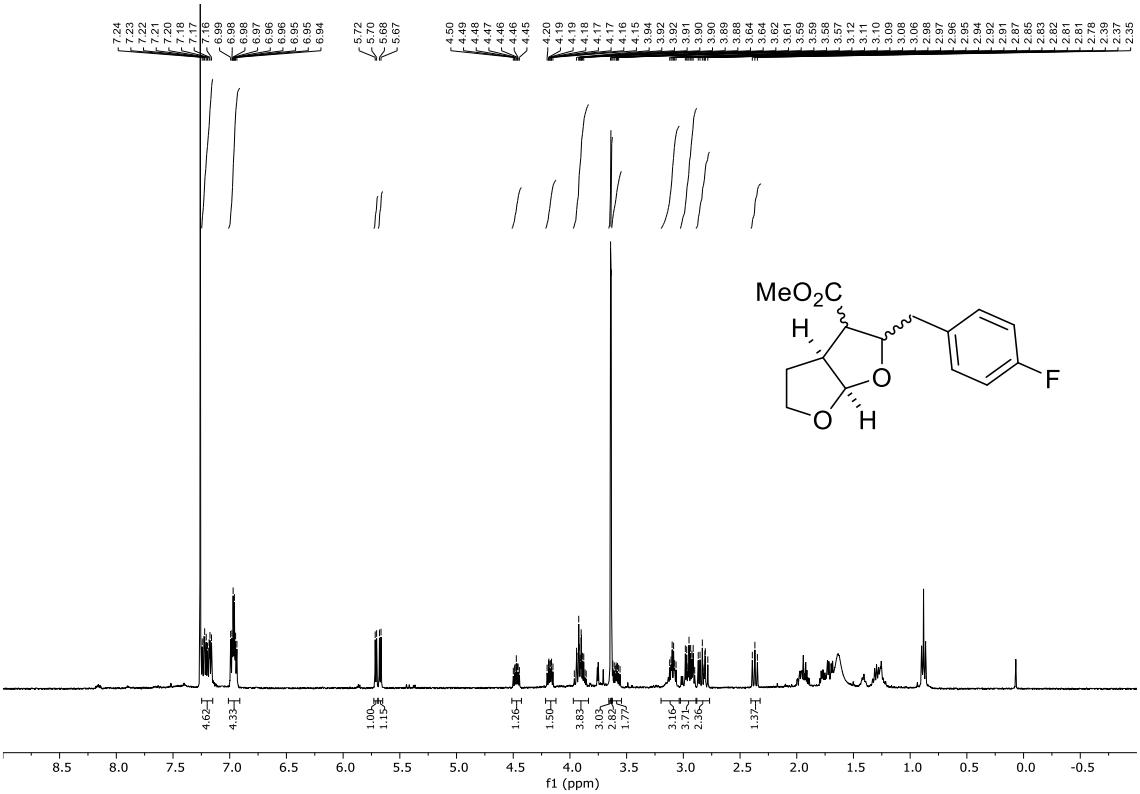


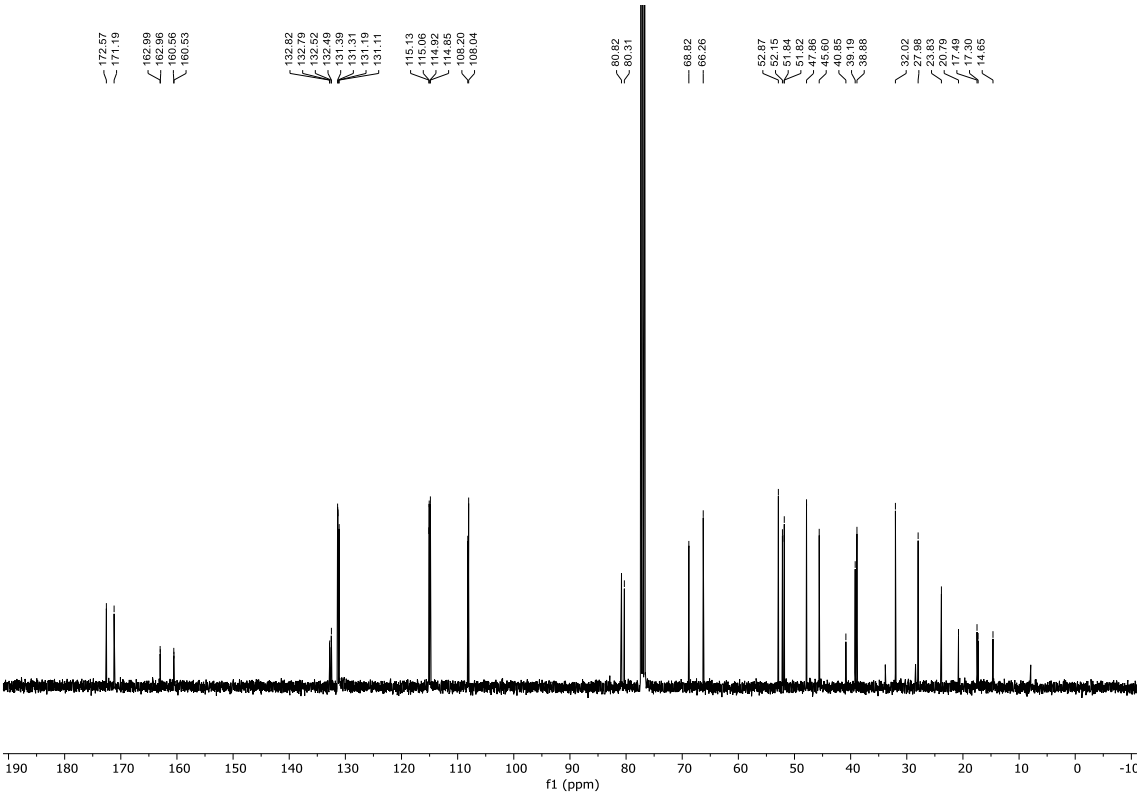
Methyl-2-benzylhexahydrofuro[2,3-b]furan-3-carboxylate 285a

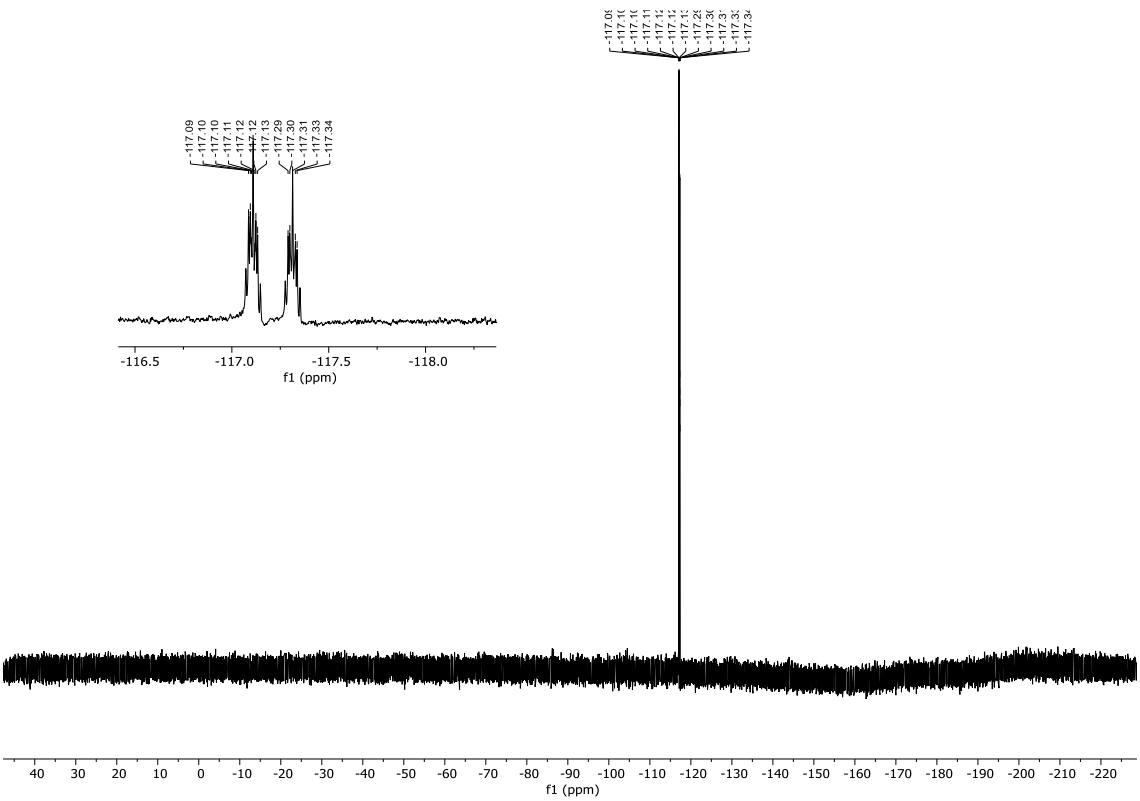


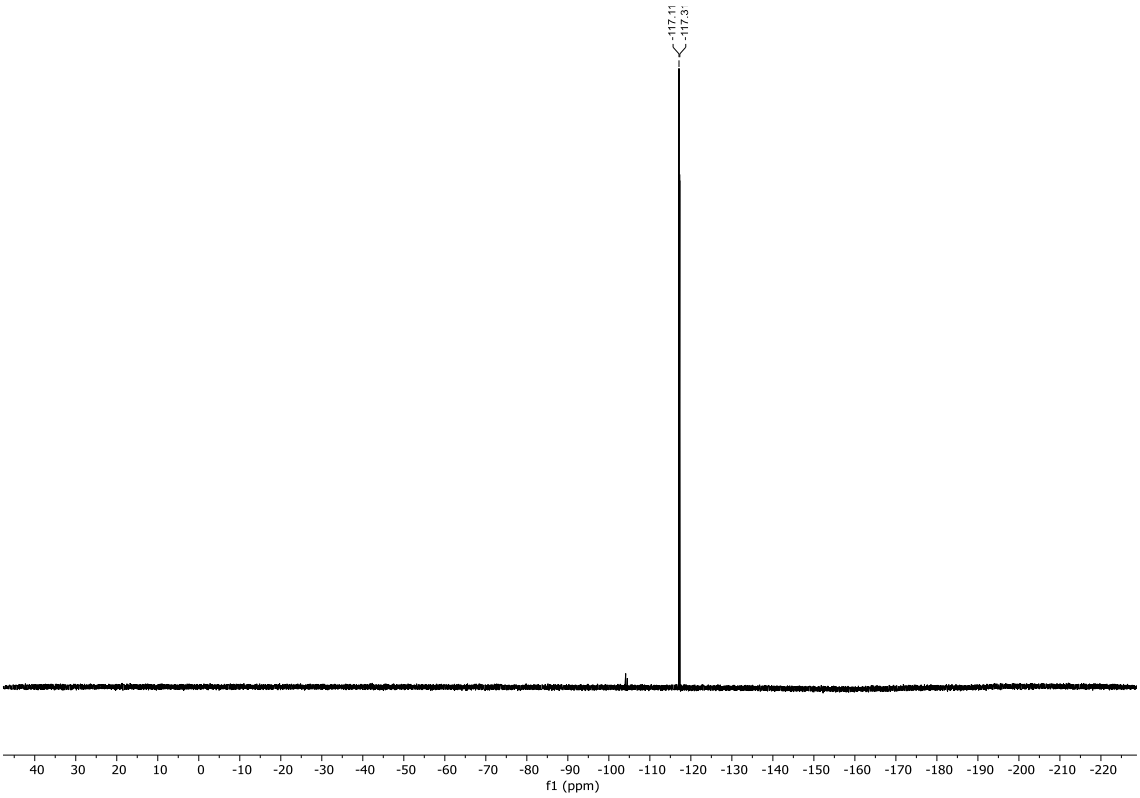


Methyl (3aS,6aR)-2-(4-fluorobenzyl)hexahydrofuro[2,3-b]furan-3-carboxylate 285b

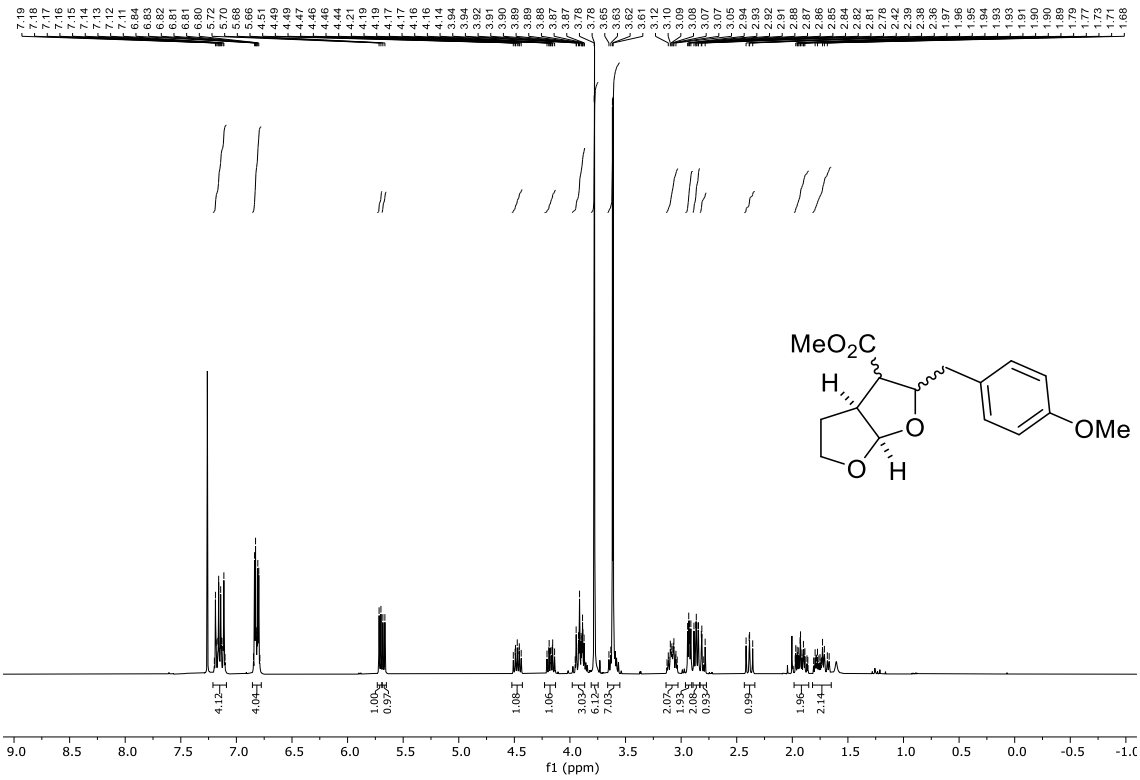


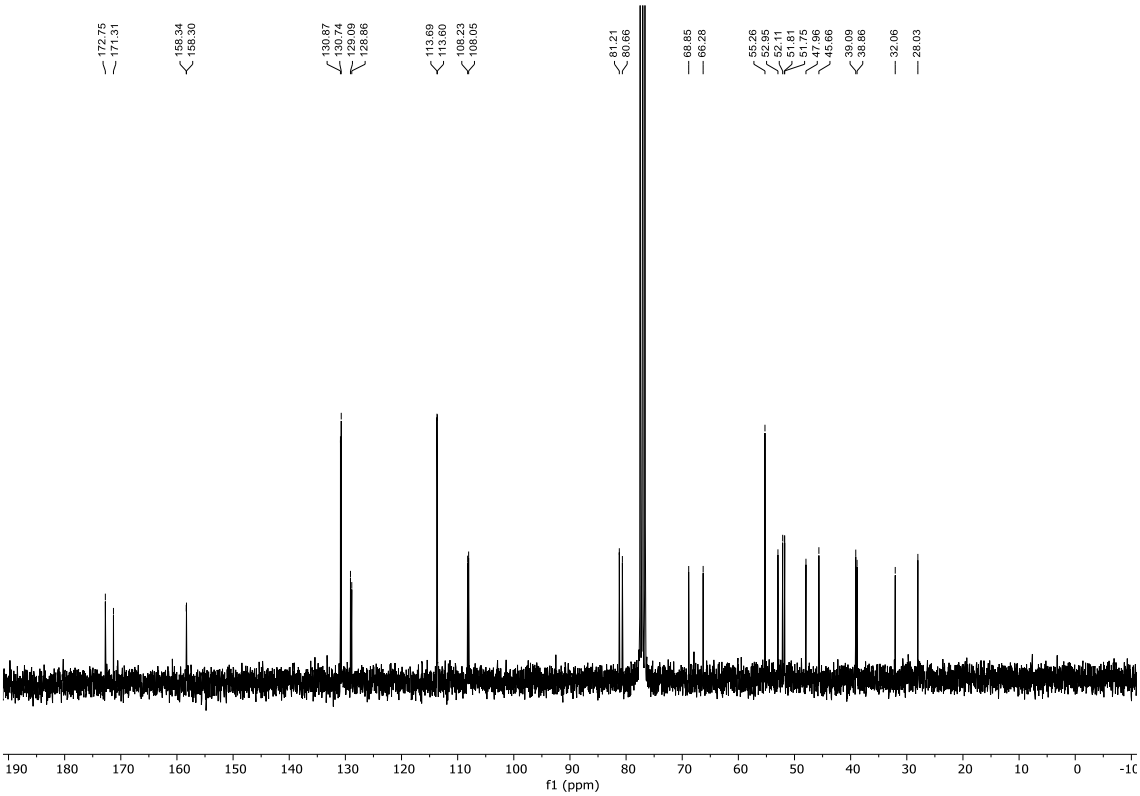



-117.09
-117.10
-117.10
-117.11
-117.12
-117.12
-117.13
-117.29
-117.30
-117.31
-117.33
-117.34
-116.5
-117.0
-117.5
-118.0
f1 (ppm)
40 30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210 -220
f1 (ppm)


-117.11
-117.31
40 30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210 -220
f1 (ppm)

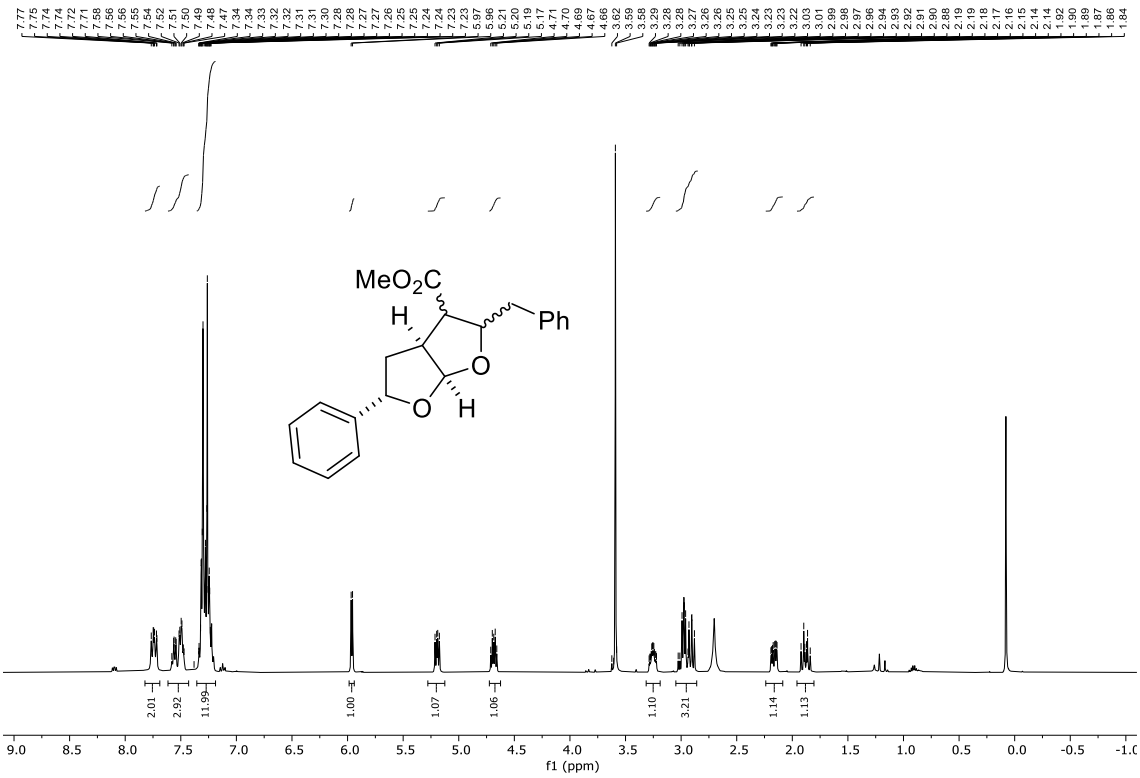
Methyl 2-(4-methoxybenzyl)hexahydrofuro[2,3-b]furan-3-carboxylate 285c

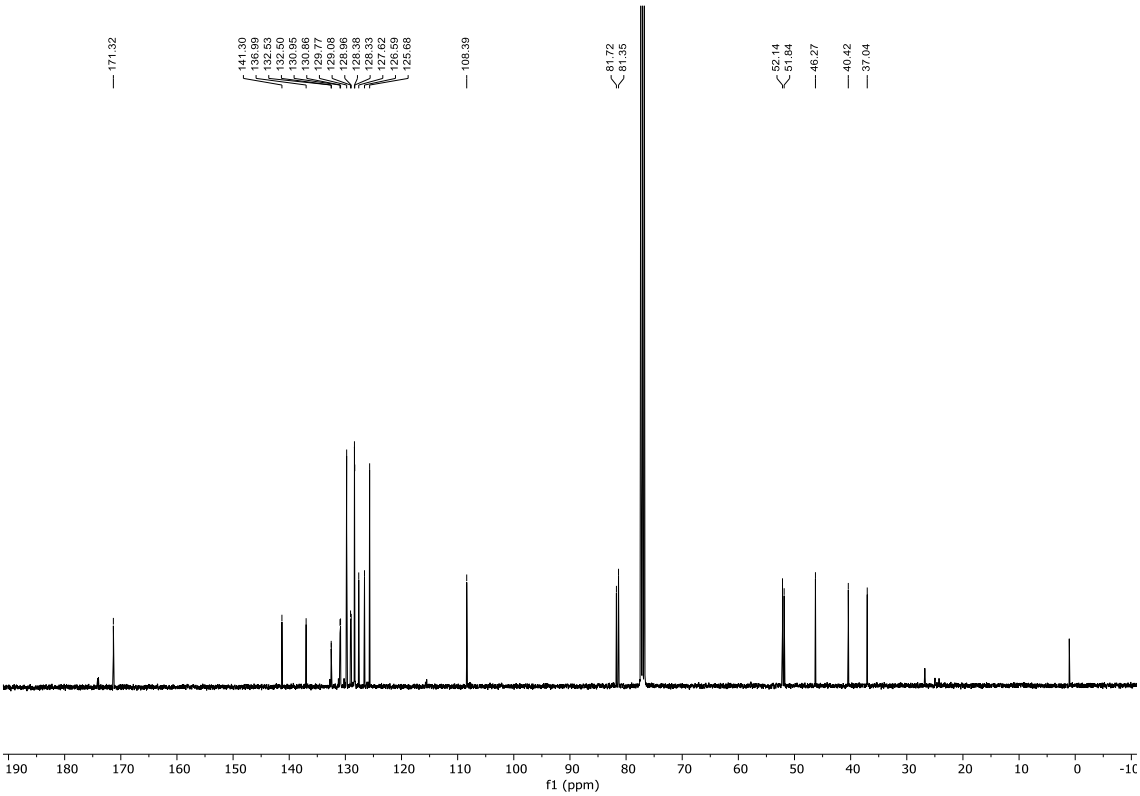




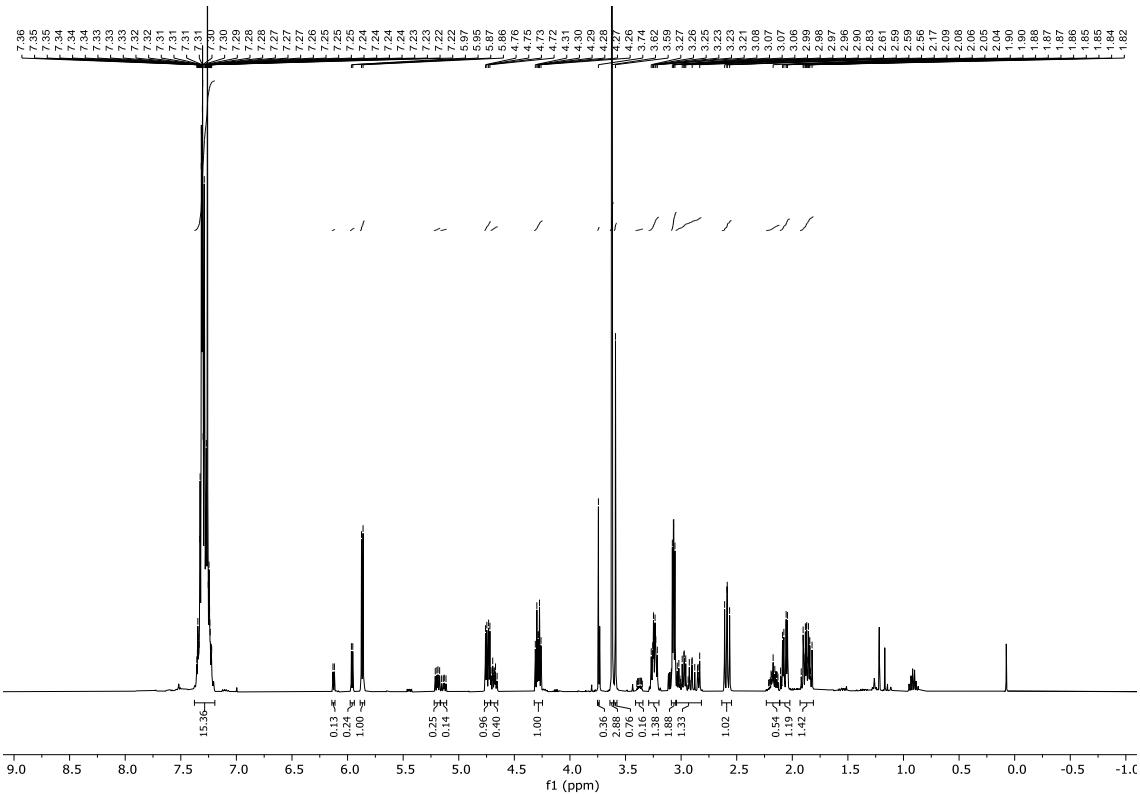
Methyl-2-benzyl-5-phenylhexahydrofuro[2,3-b]furan-3-carboxylate 285e

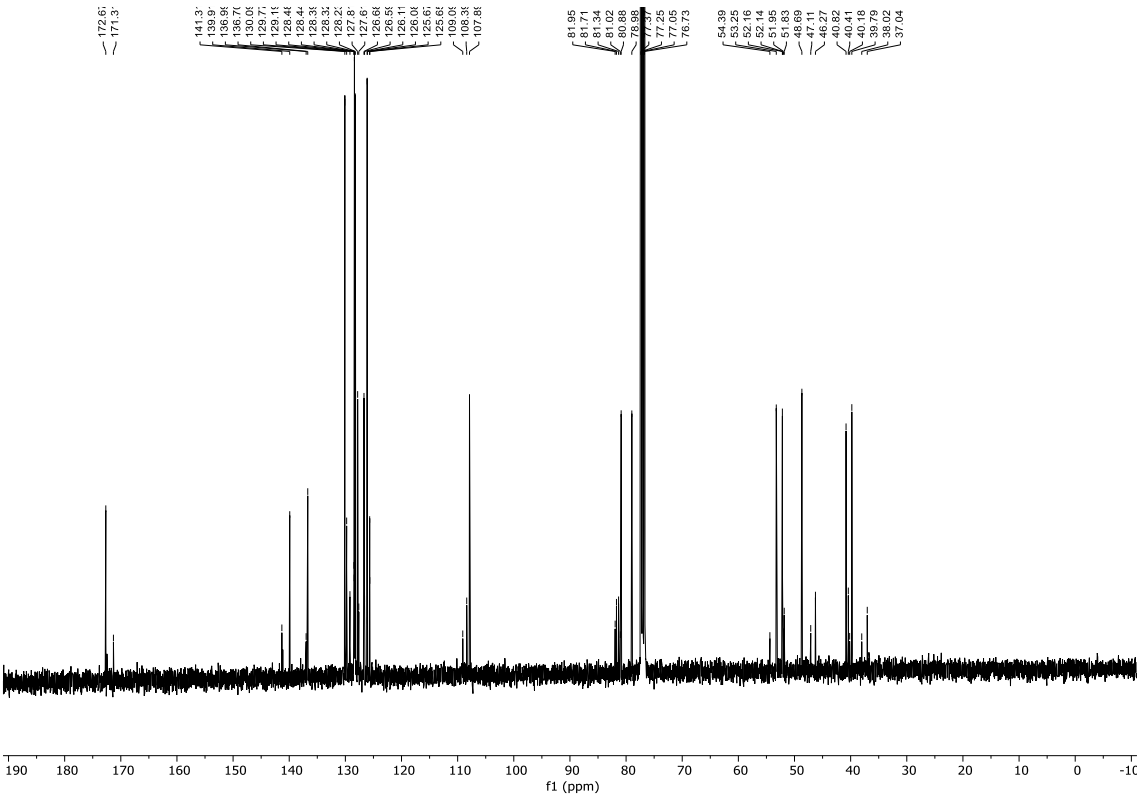
Diastereomer 1:





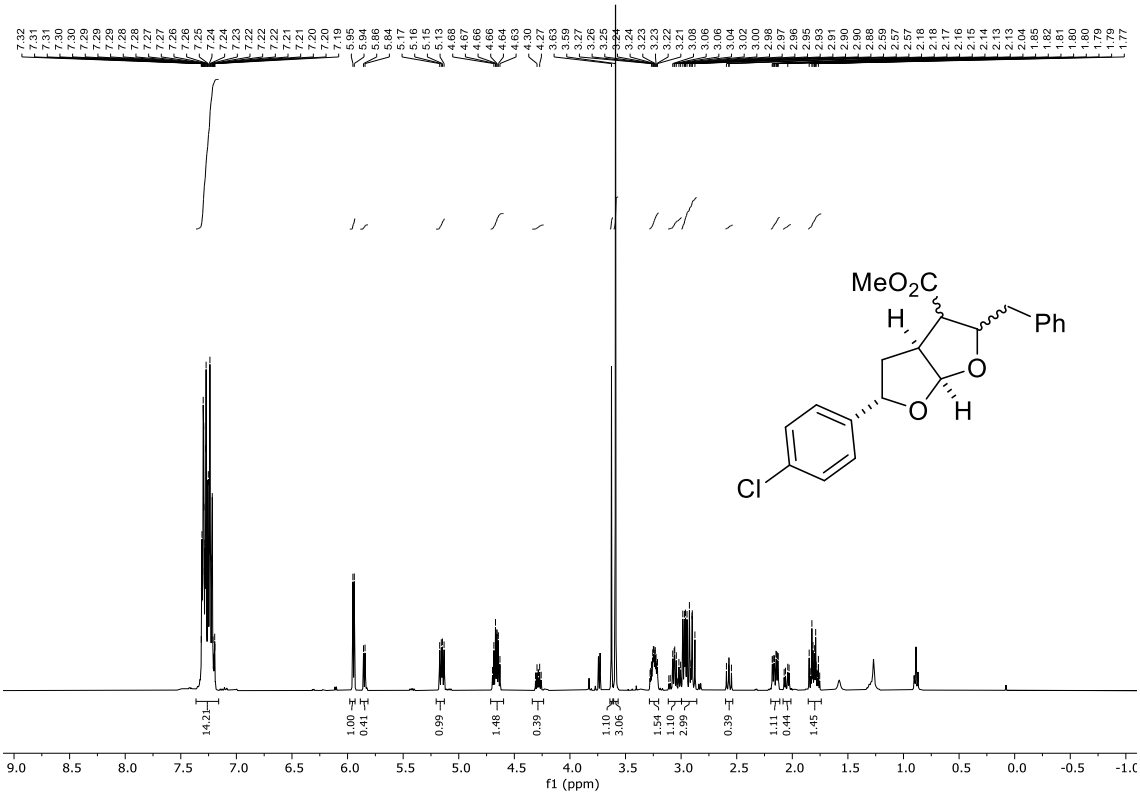
Diastereomers 2+3:

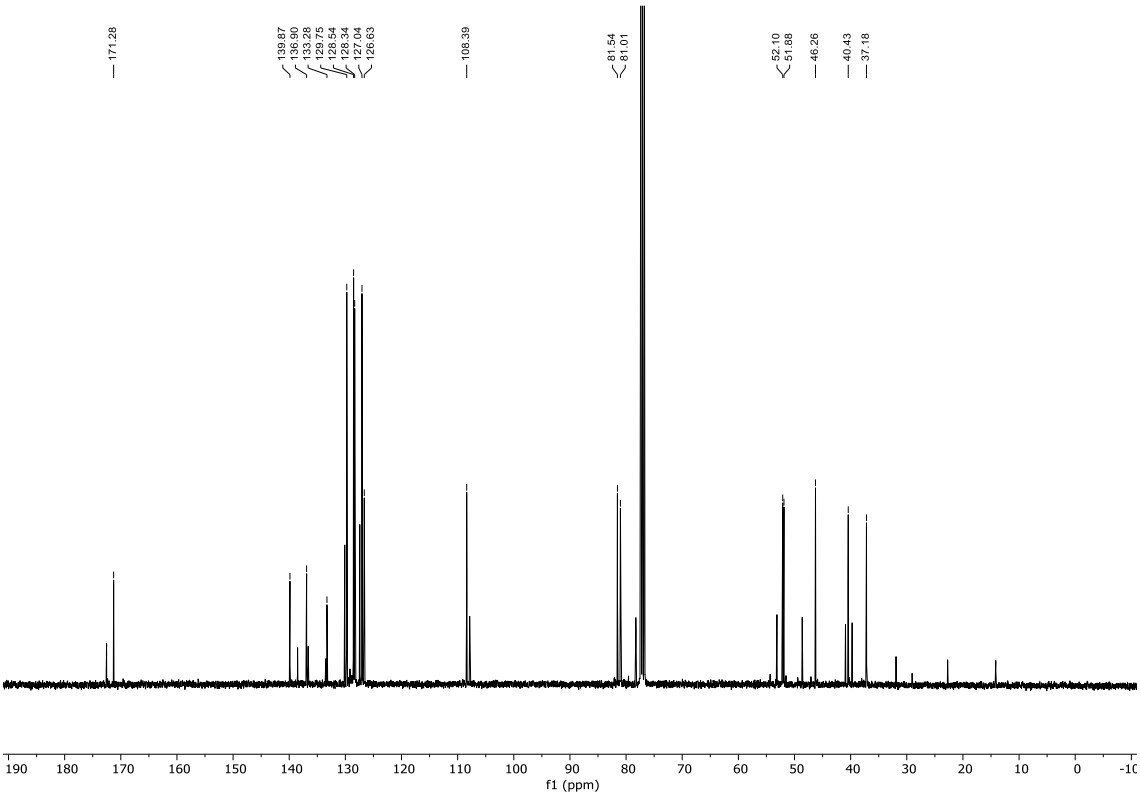




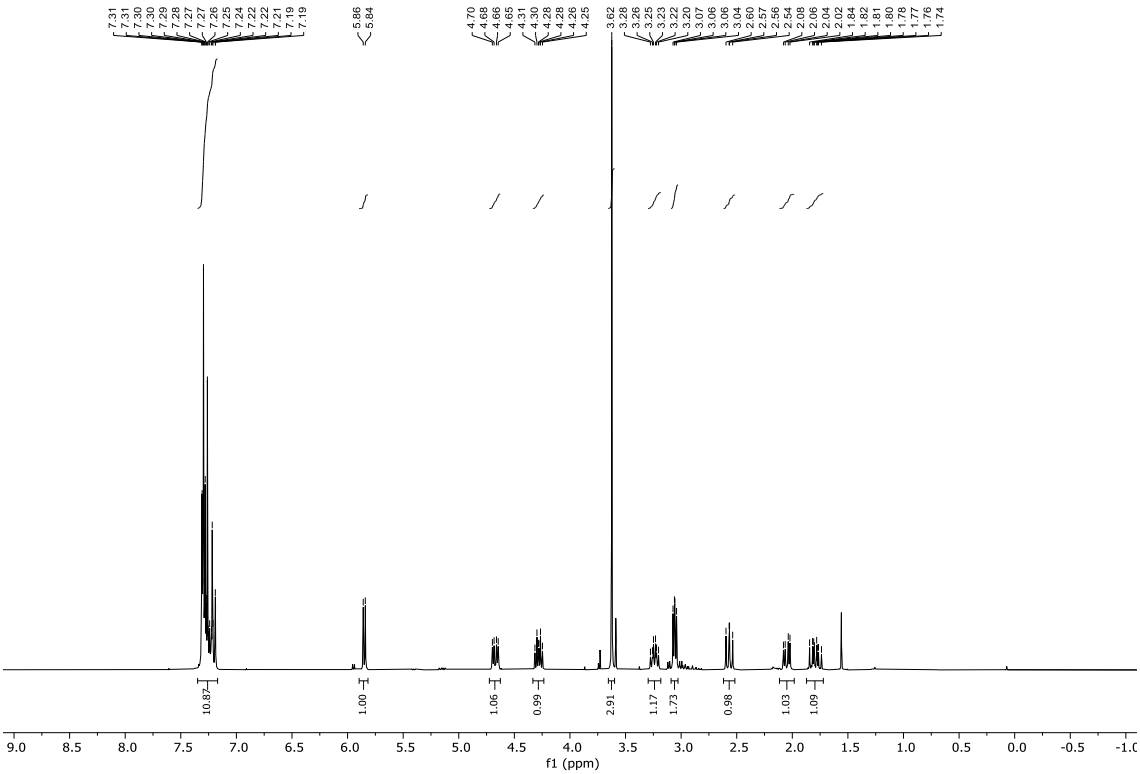
Methyl-2-benzyl-5-(4-chlorophenyl)hexahydrofuro[2,3-b]furan-3-carboxylate 285g

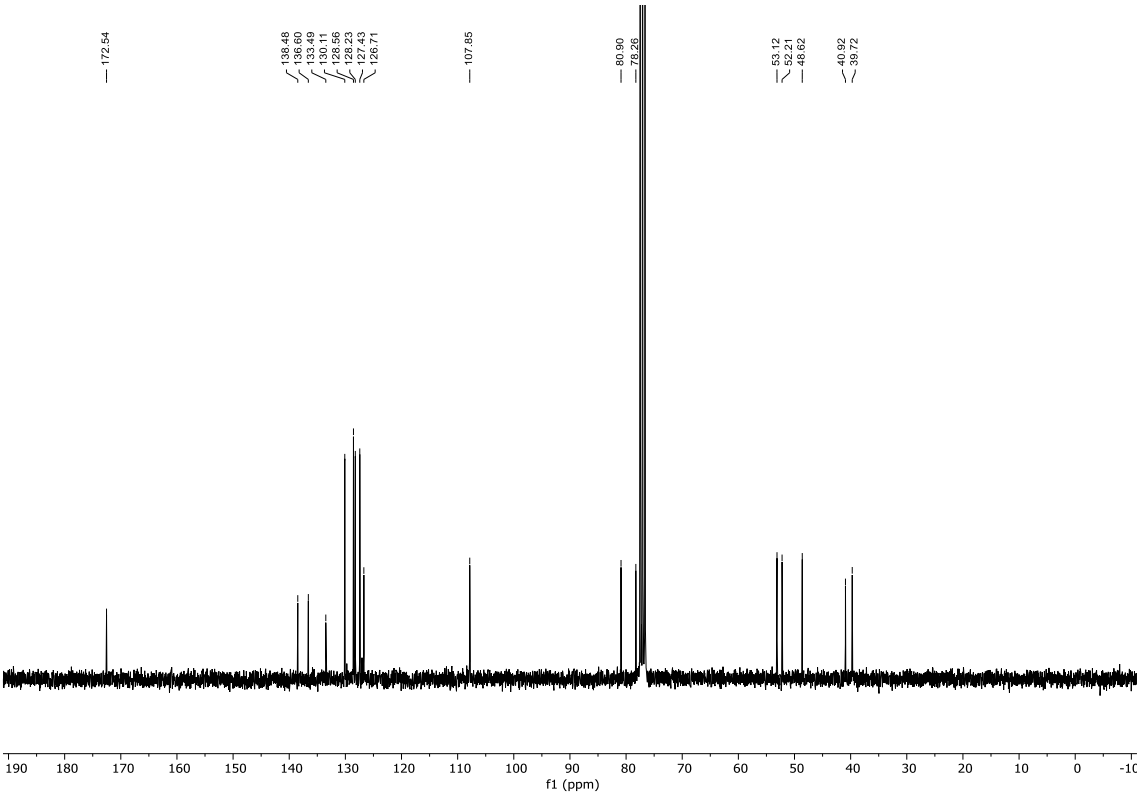
Diastereomer 1:



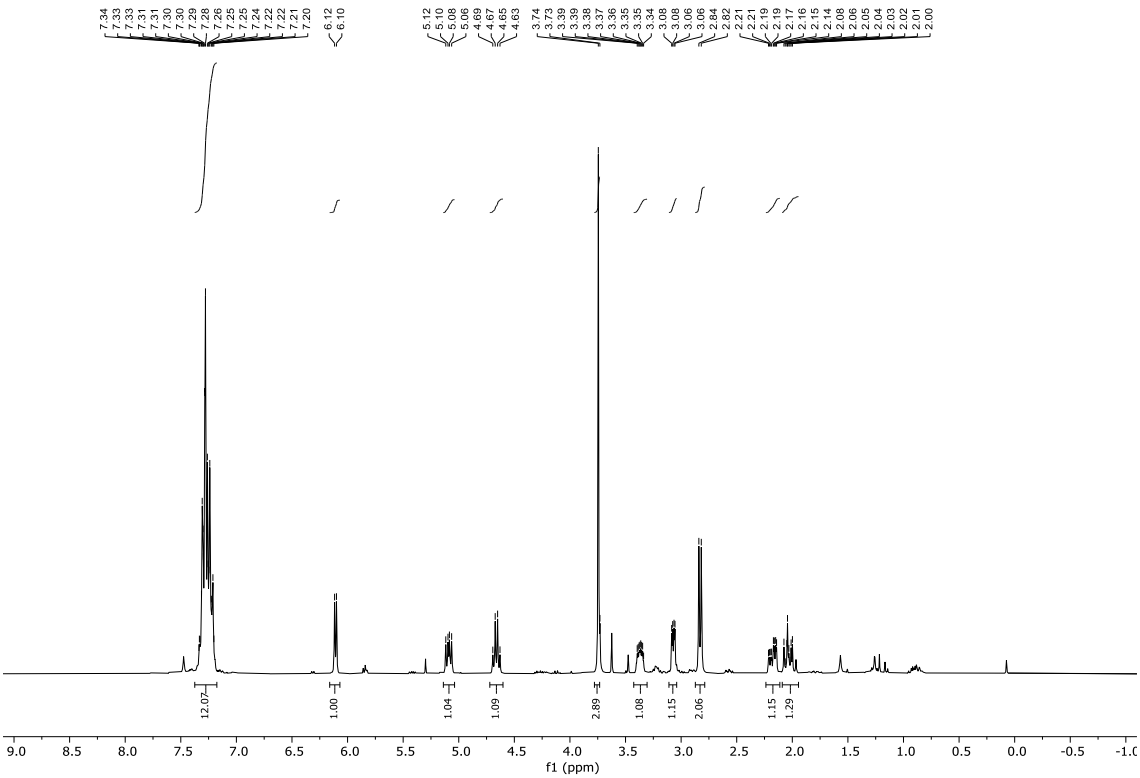


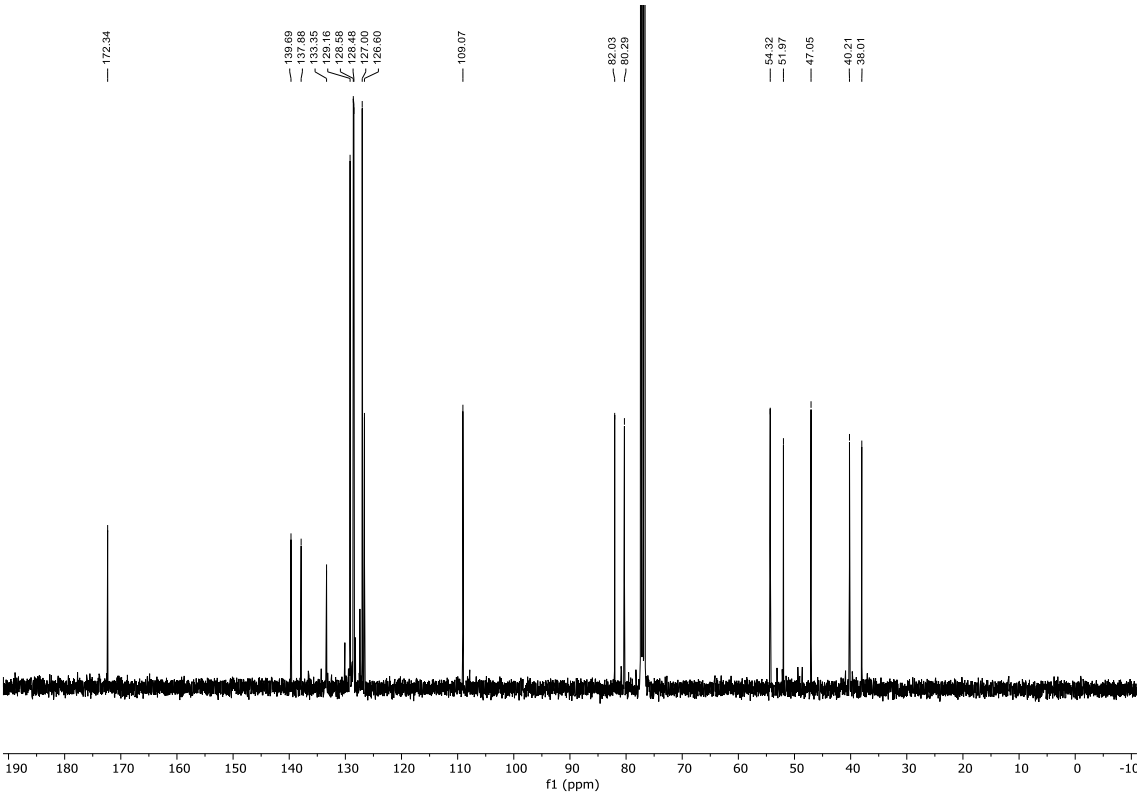
Diastereomer 2:



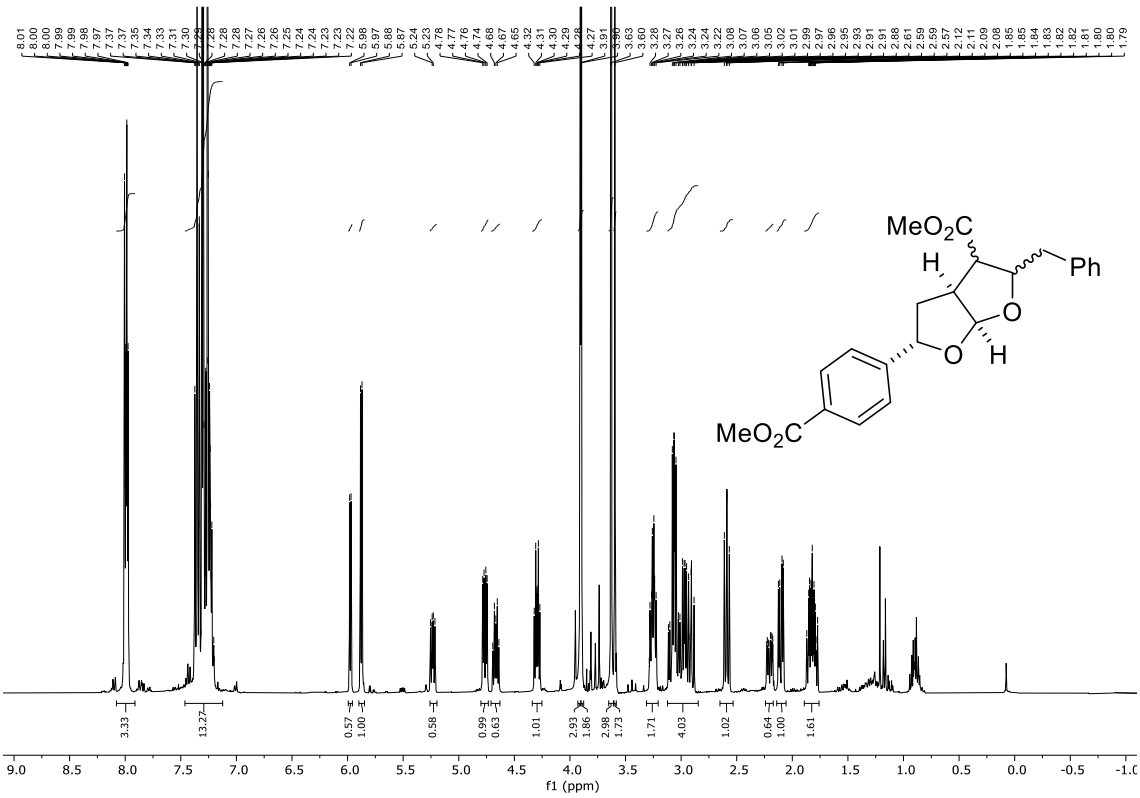


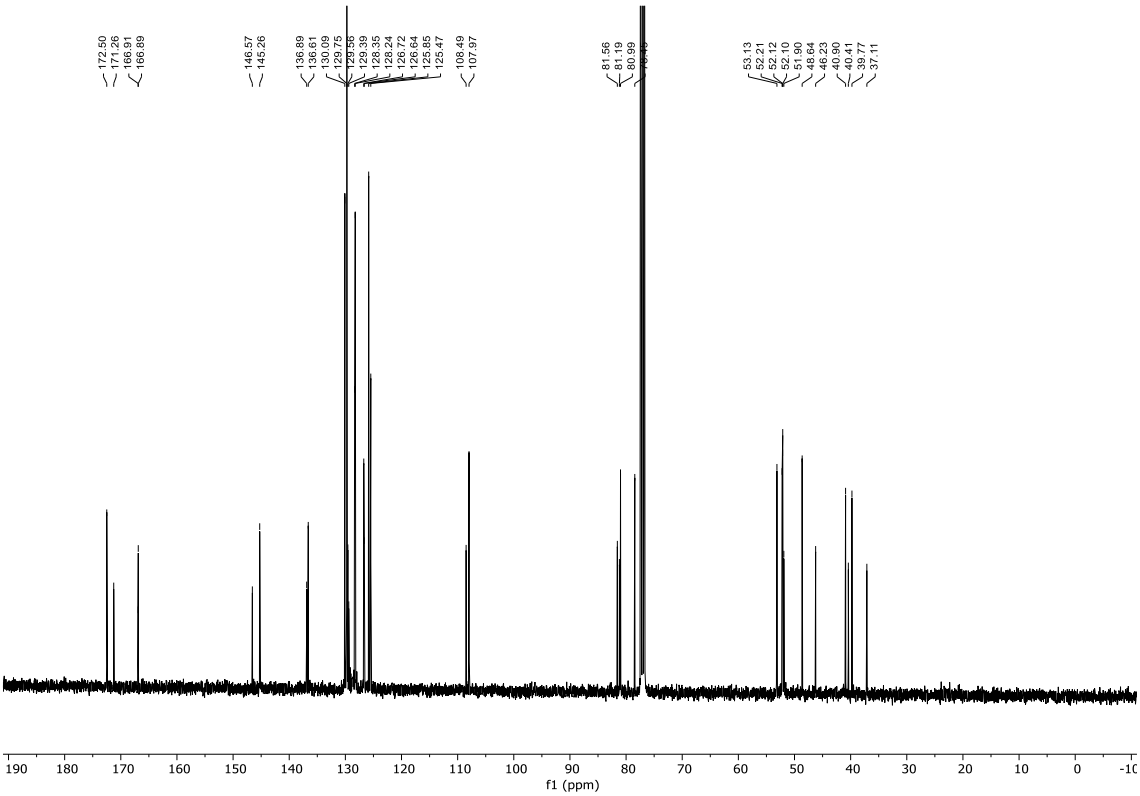
Diastereomer 3:





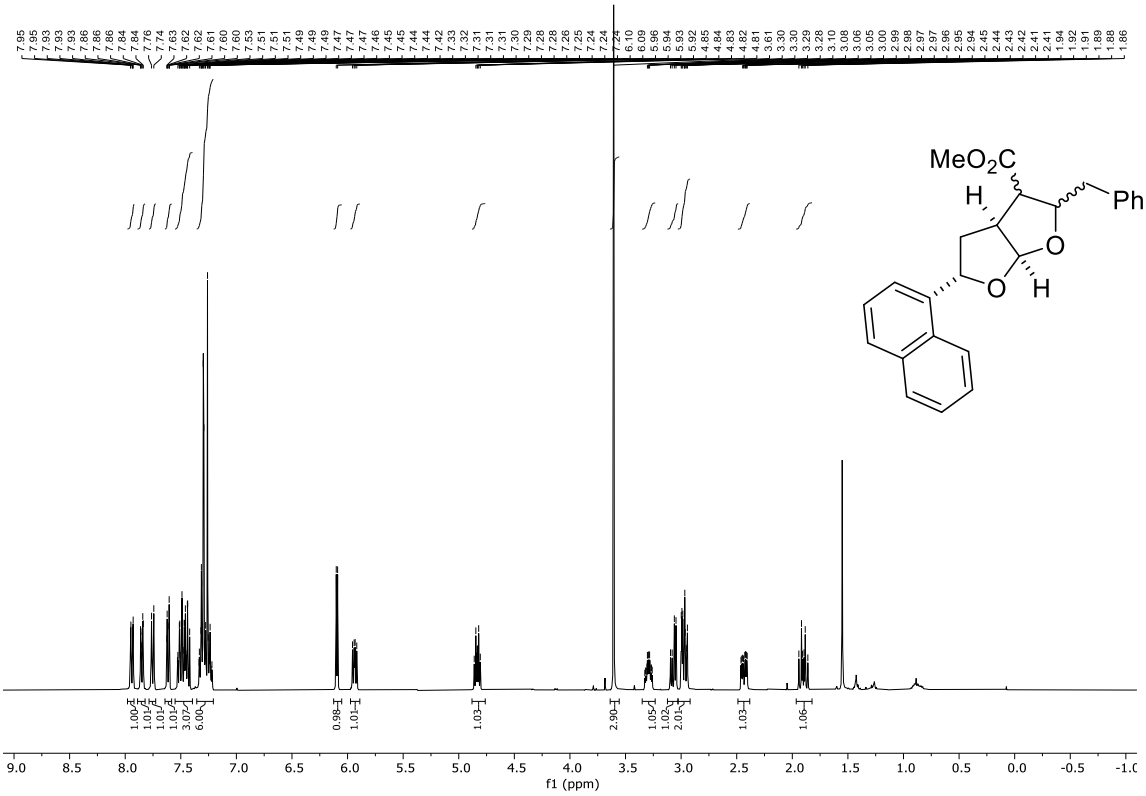
Methyl-2-benzyl-5-(4-(methoxycarbonyl)phenyl)hexahydrofuro[2,3-b]furan-3-carboxylate 285h

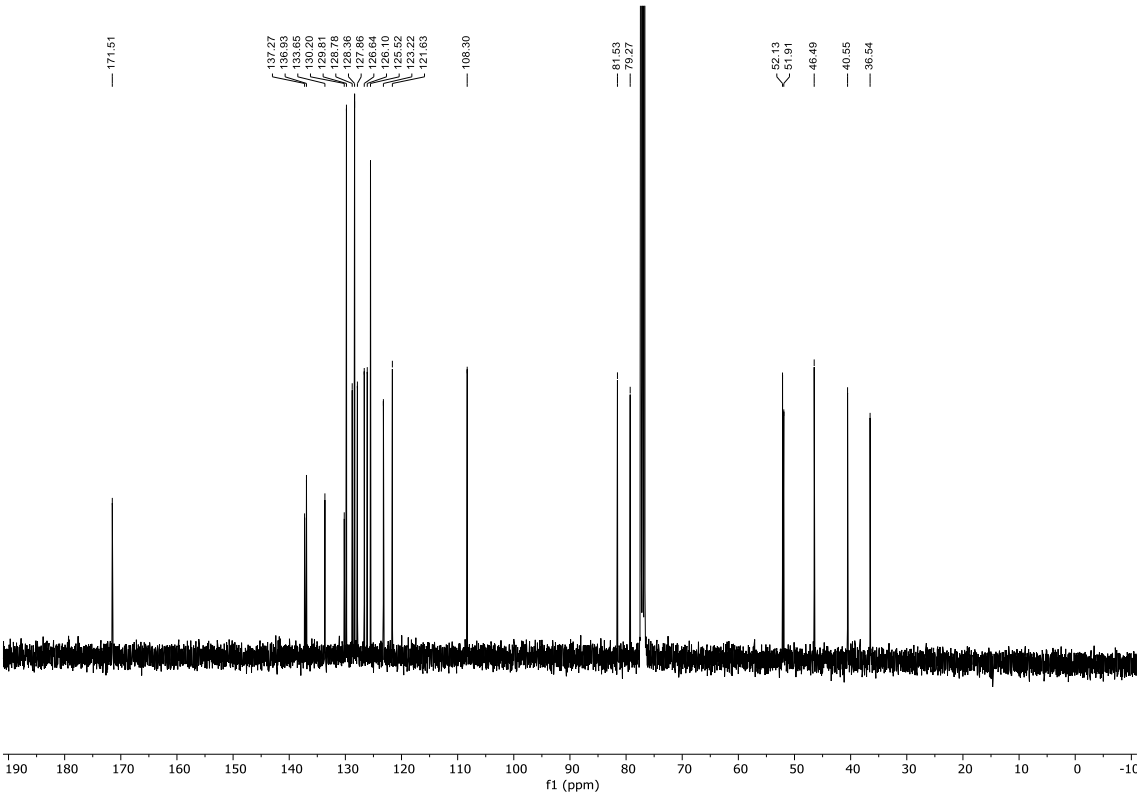




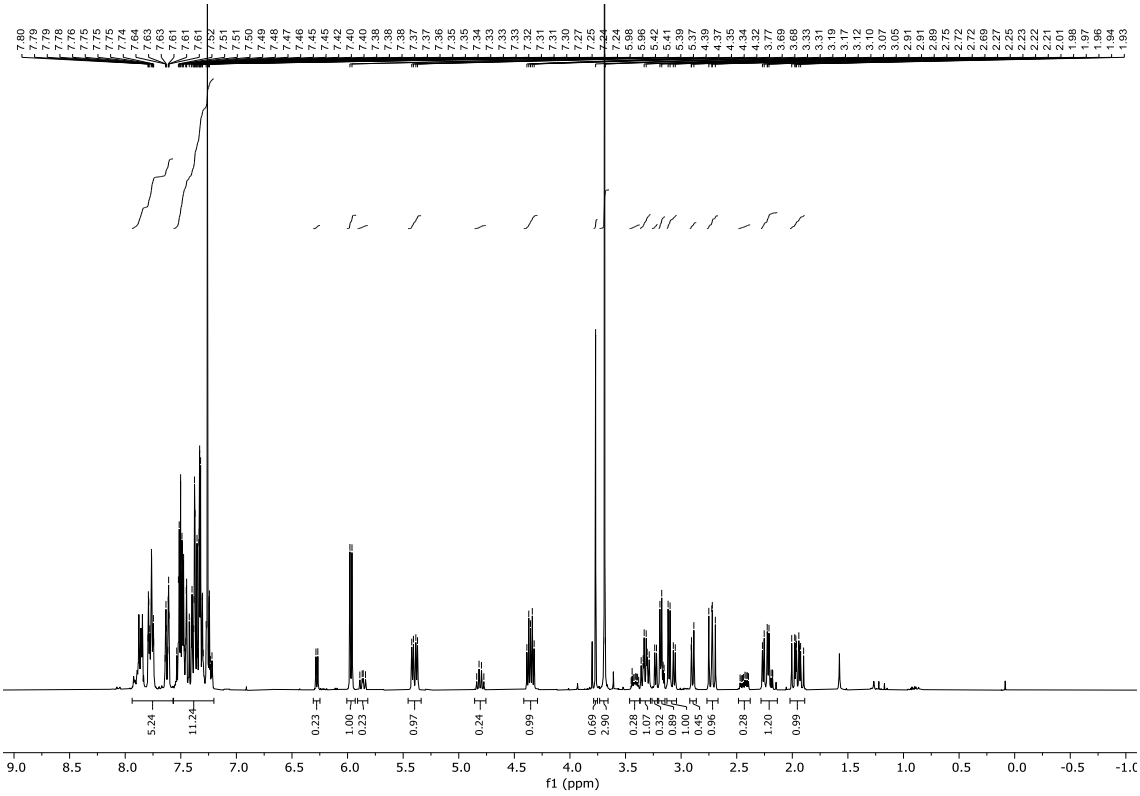
Methyl-2-benzyl-5-(naphthalen-1-yl)hexahydrofuro[2,3-b]furan-3-carboxylate 285f

Diastereomer 1:

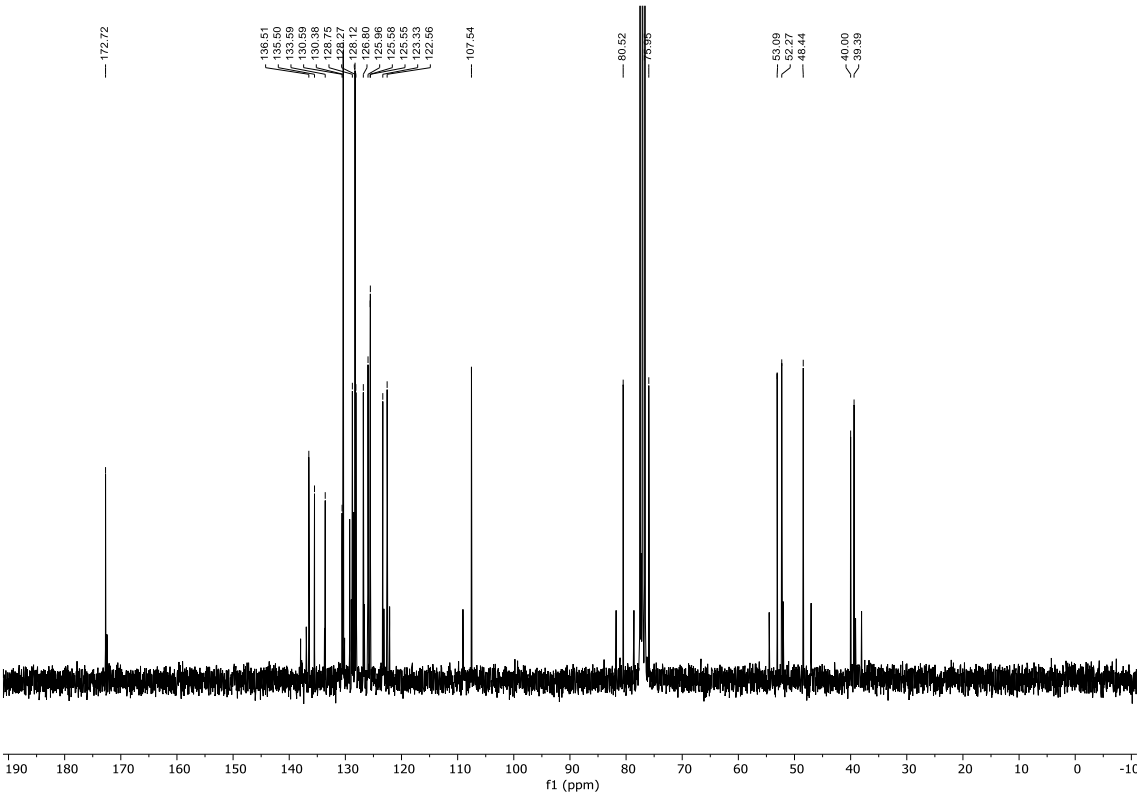




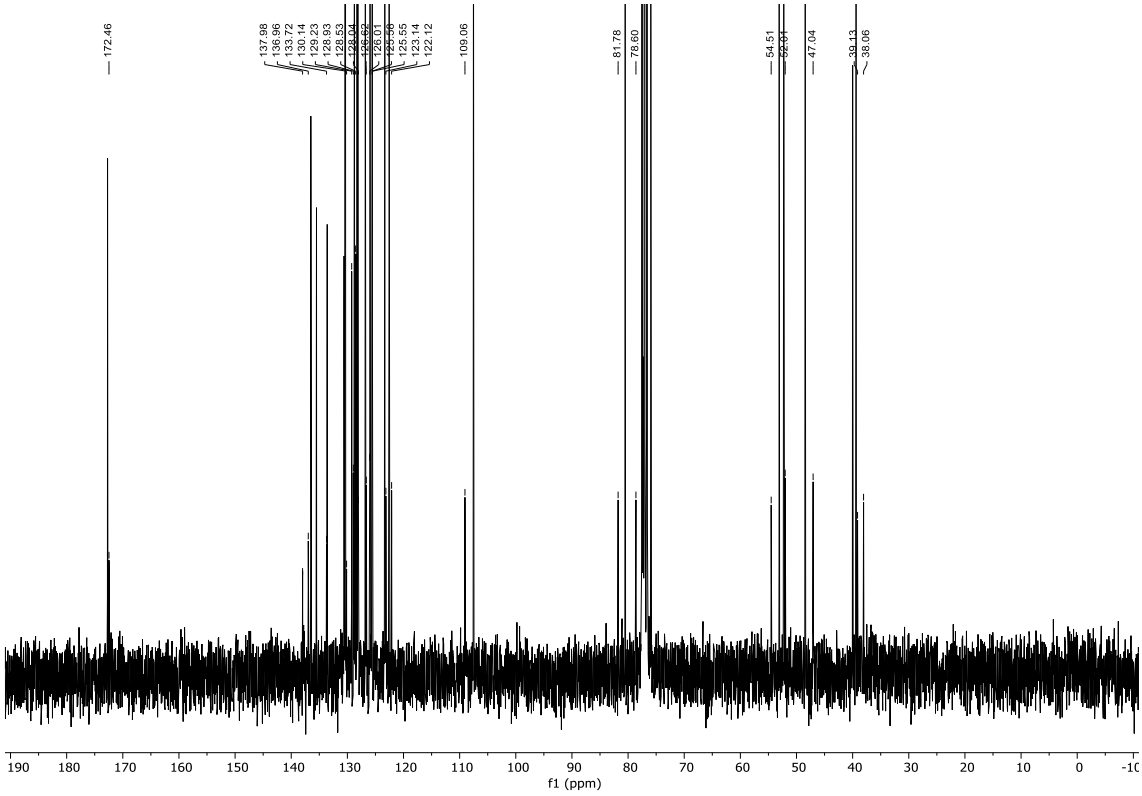
Diastereomers 2+3:



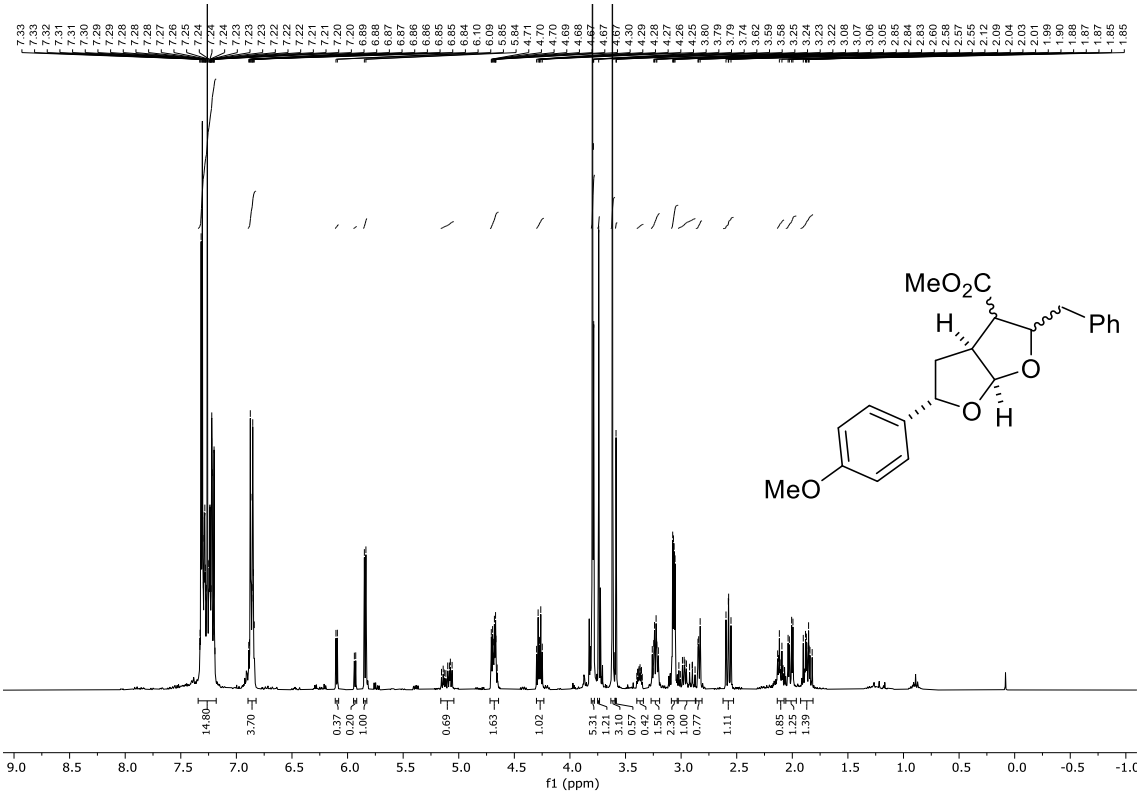
Major:

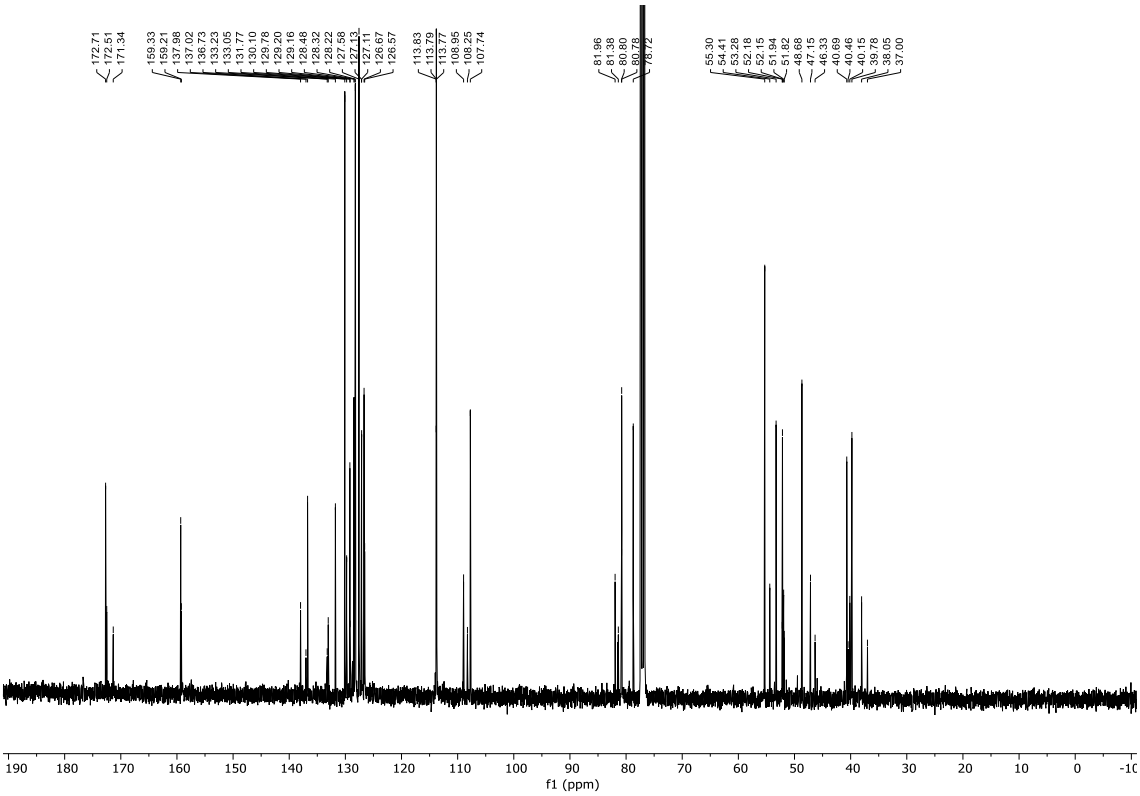


Minor:


172.46
137.98
136.96
133.72
130.14
129.23
128.83
128.53
128.04
126.62
126.01
125.56
125.55
123.14
122.12
109.06
81.78
78.60
54.51
52.81
47.04
39.13
38.06
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

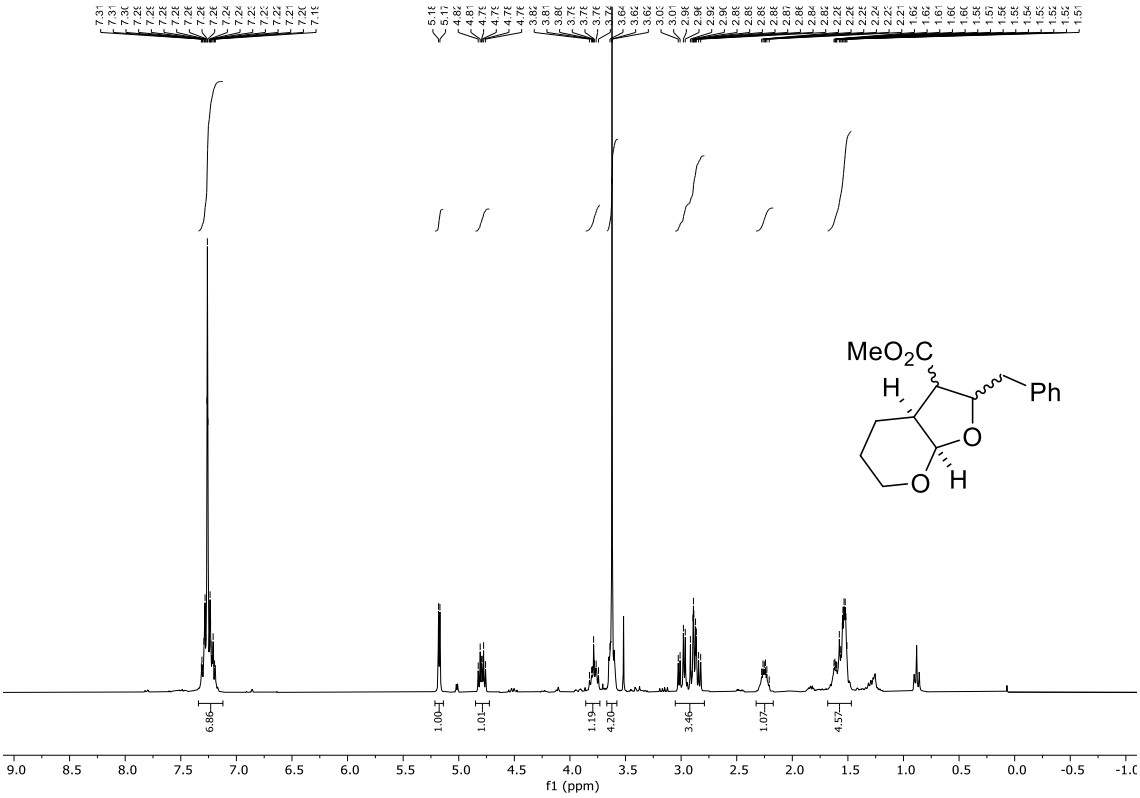
Methyl 2-benzyl-5-(4-methoxyphenyl)hexahydrofuro[2,3-b]furan-3-carboxylate 285i

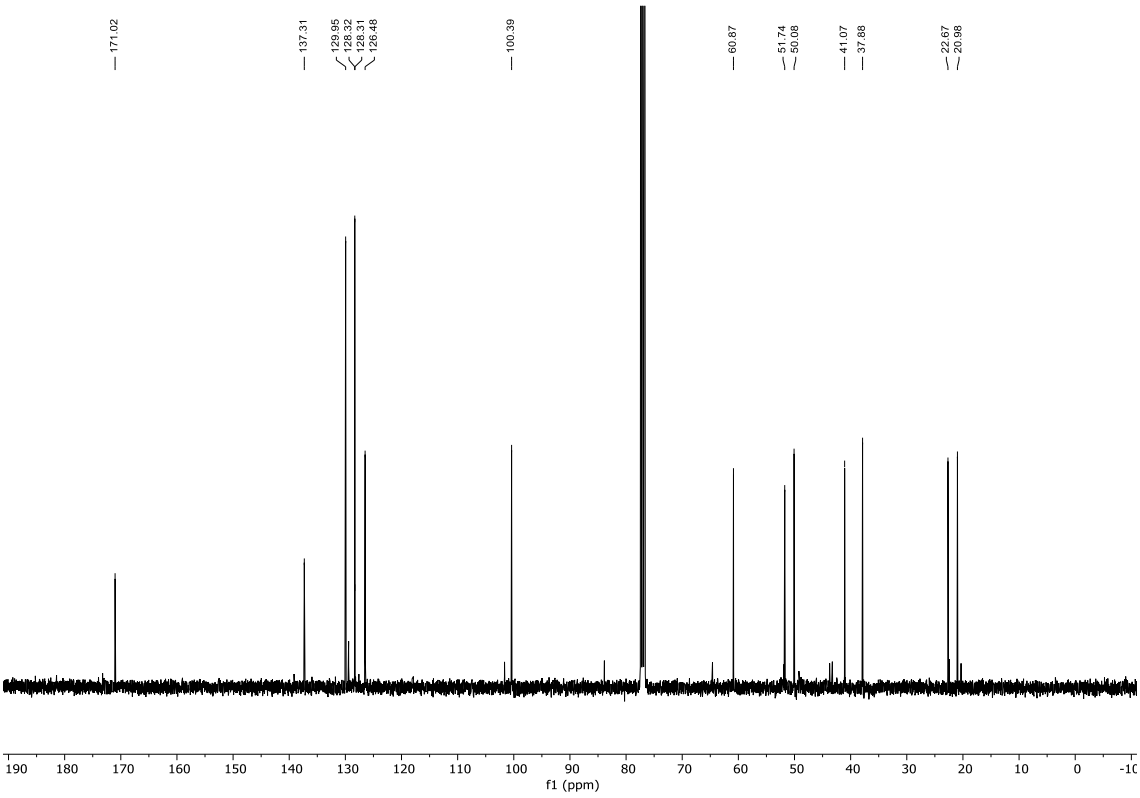




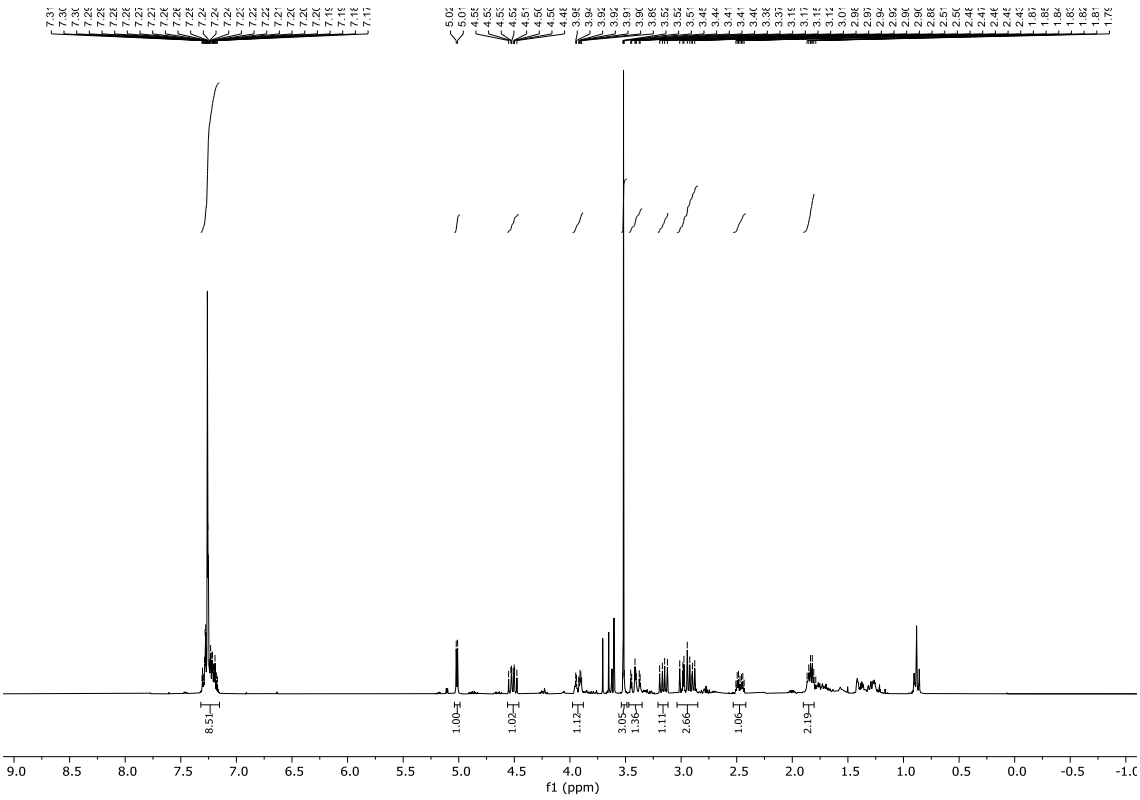
Methyl-2-benzylhexahydro-4H-furo[2,3-b]pyran-3-carboxylate 285k

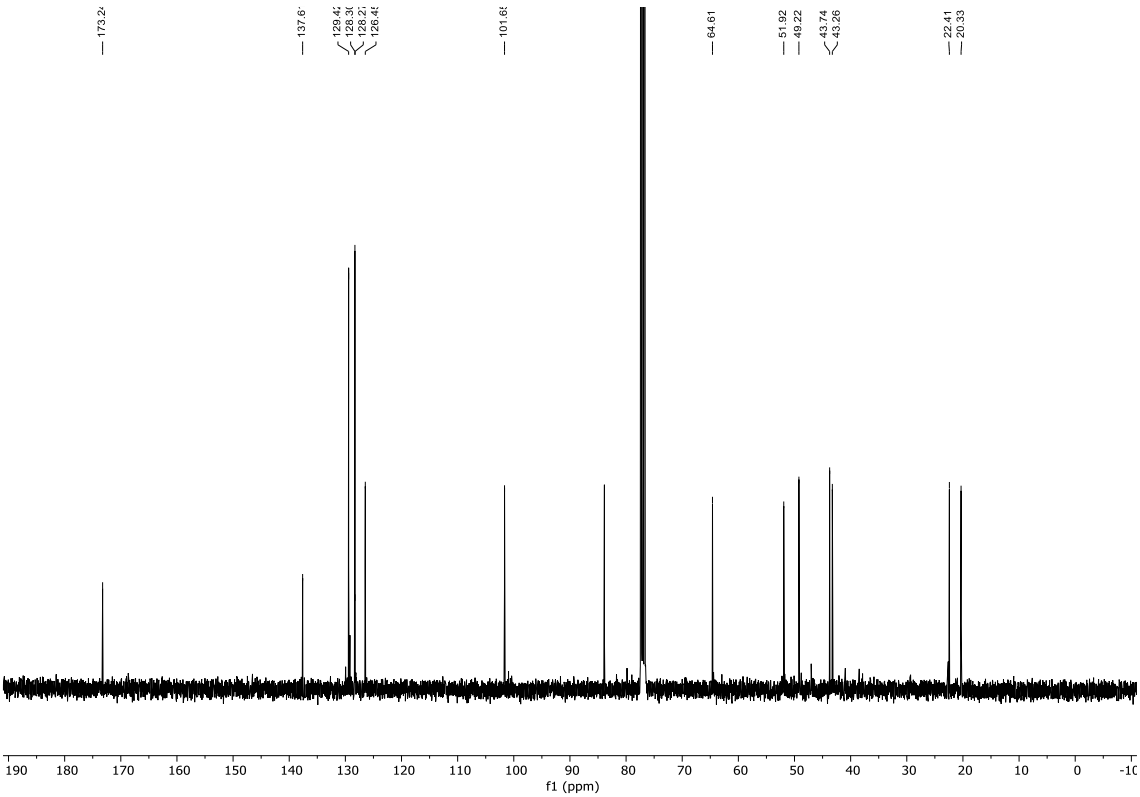
Diastereomer 1





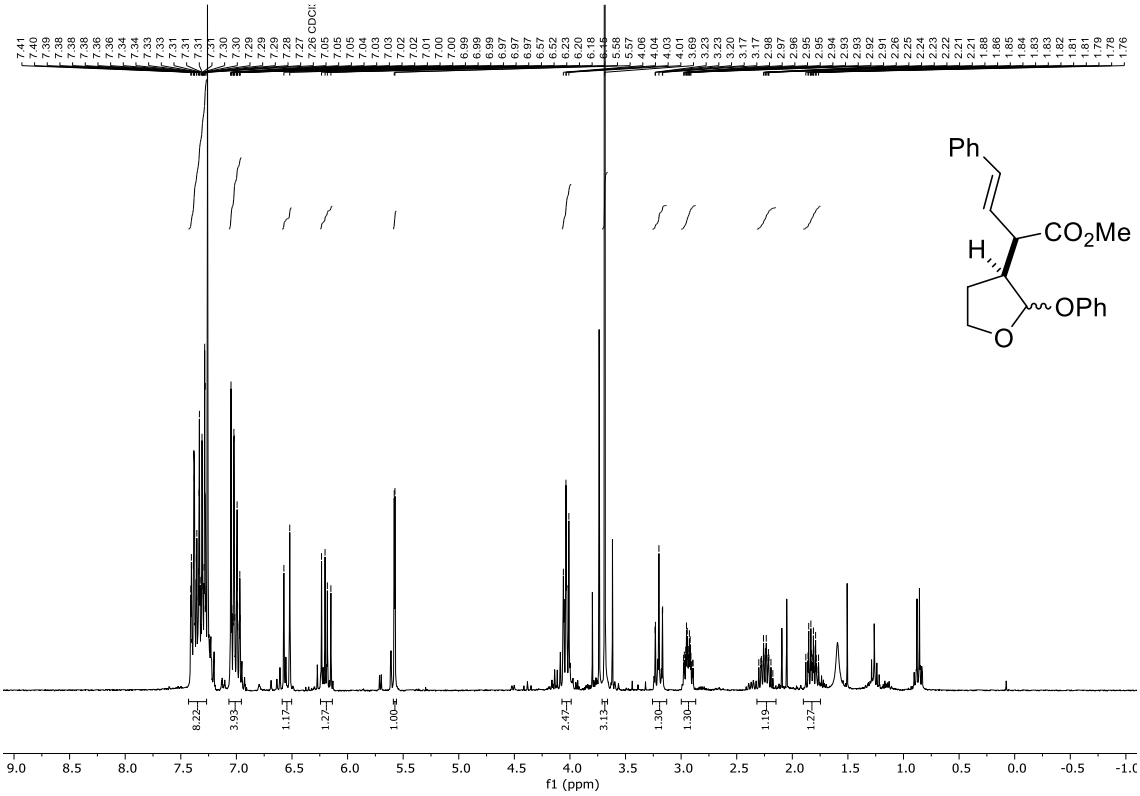
Diastereomer 2

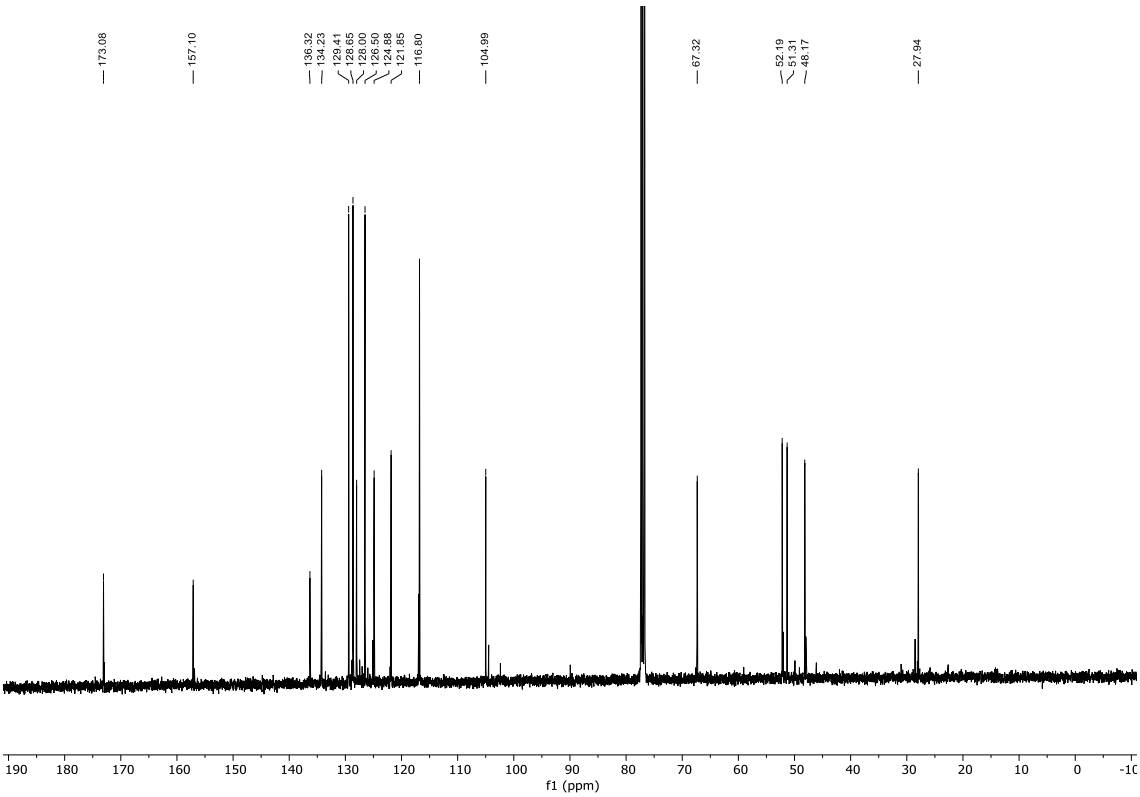




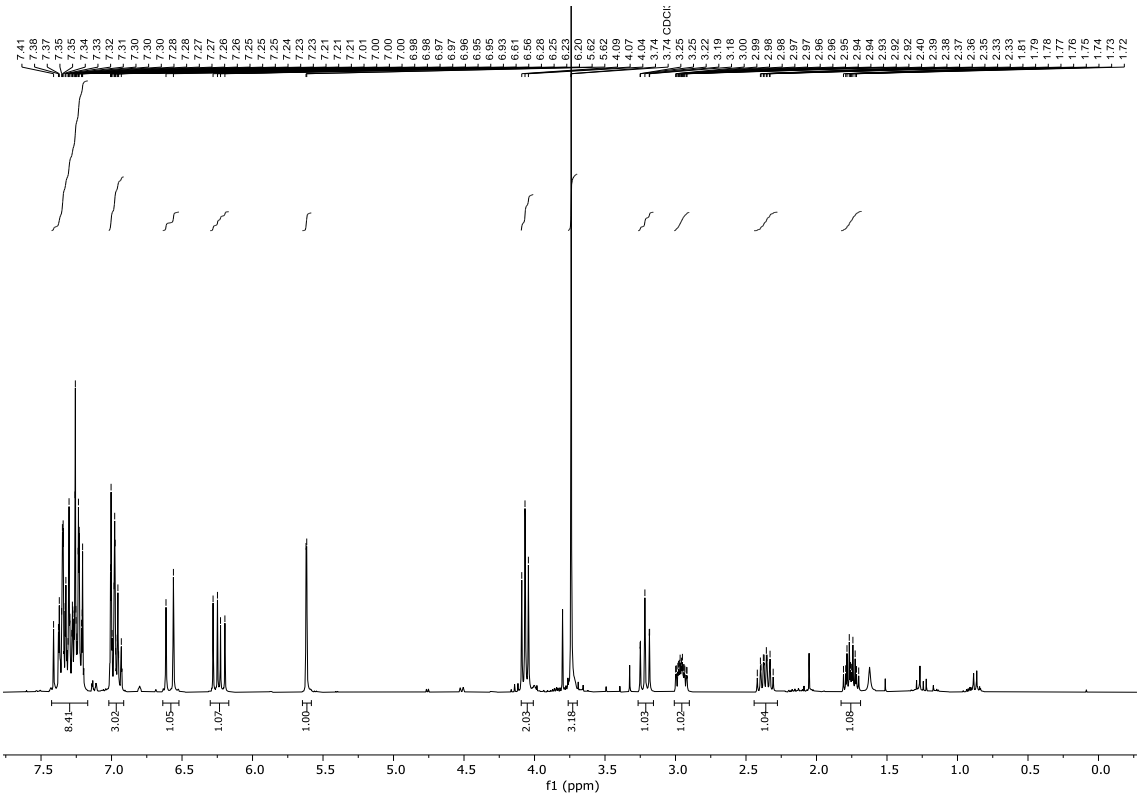
Methyl (*E*)-2-(2-phenoxytetrahydrofuran-3-yl)-4-phenylbut-3-enoate 308c

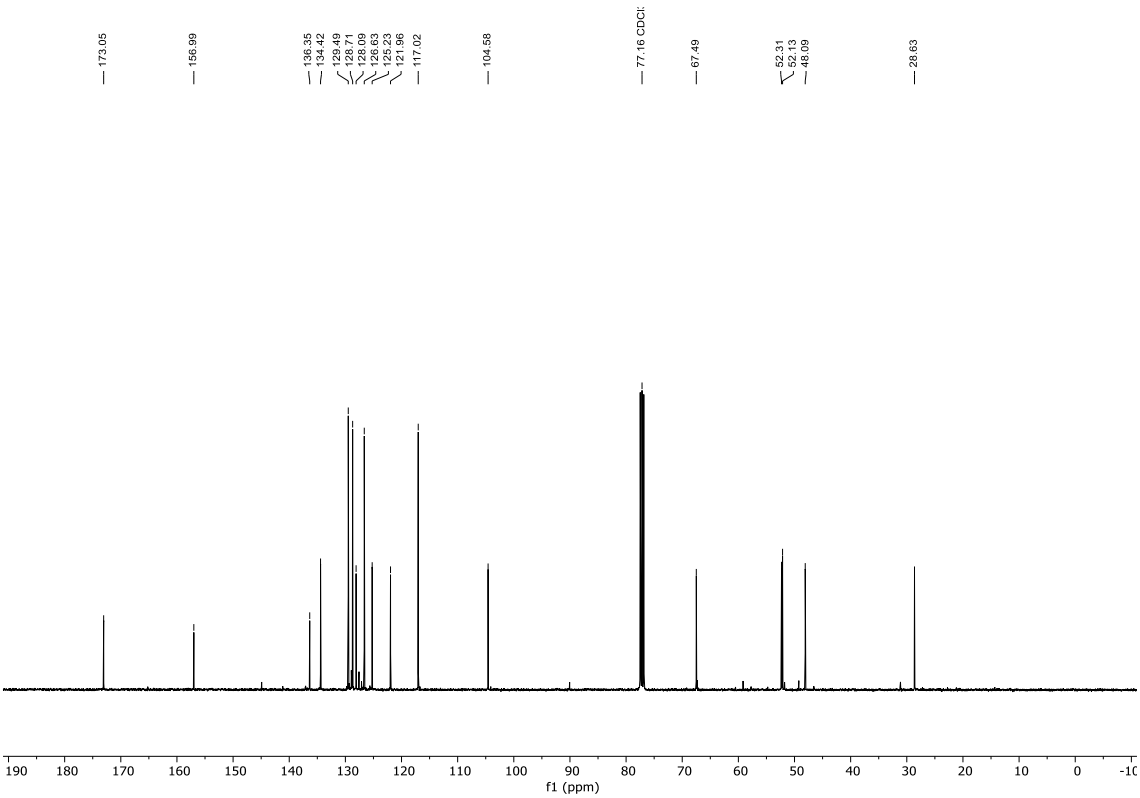
minor





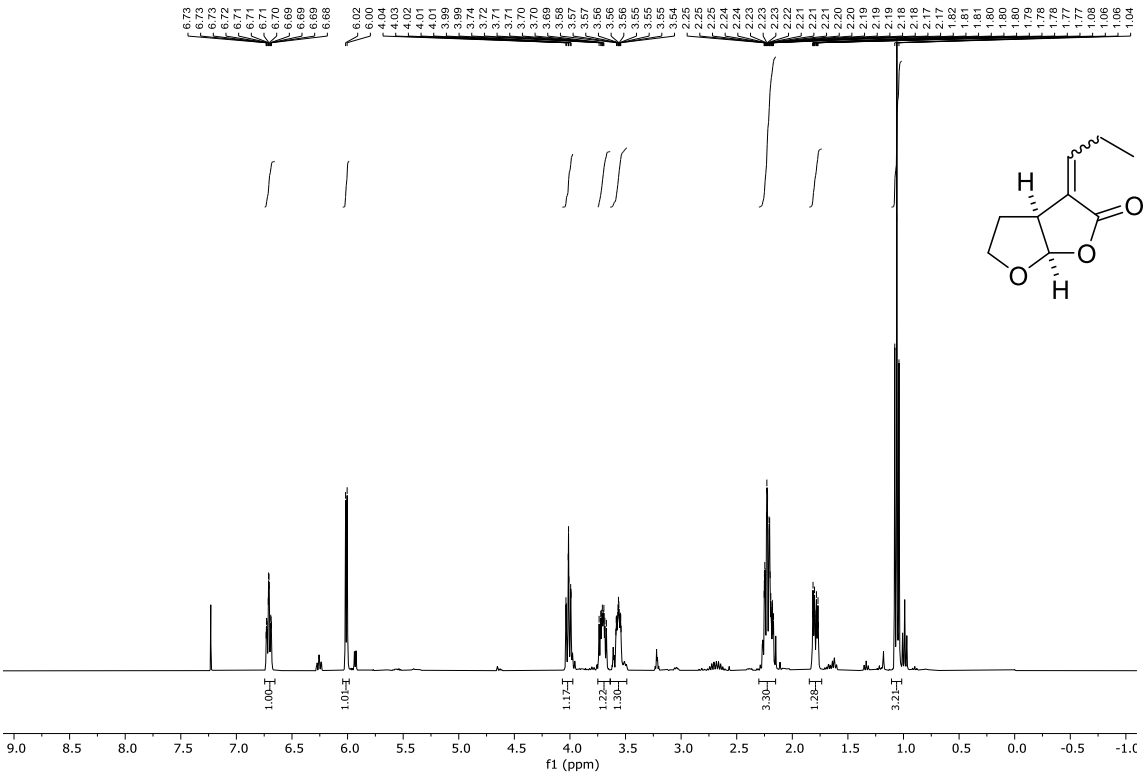
Major

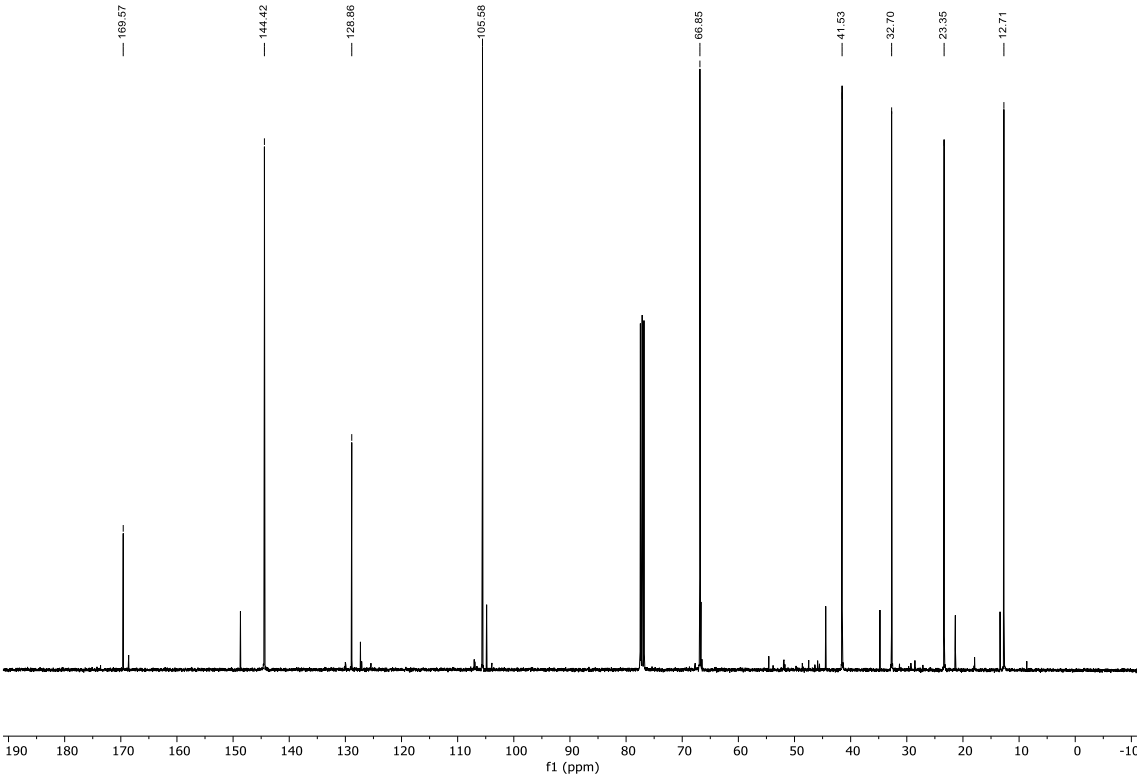

7.41 7.38 7.37 7.36 7.35 7.34 7.33 7.32 7.31 7.30 7.30 7.30 7.28 7.28 7.27 7.27 7.26 7.26 7.25 7.25 7.25 7.24 7.23 7.23 7.21 7.21 7.21 7.01 7.00 7.00 7.00 6.98 6.98 6.97 6.97 6.96 6.95 6.95 6.93 6.61 6.56 6.28 6.25 6.23 6.20 5.62 5.62 4.09 4.07 4.04 3.74 3.74 CDCl3 3.25 3.25 3.22 3.19 3.18 3.00 2.99 2.98 2.98 2.97 2.97 2.96 2.96 2.95 2.95 2.94 2.93 2.92 2.92 2.40 2.39 2.38 2.37 2.36 2.35 2.33 1.81 1.79 1.78 1.77 1.76 1.75 1.74 1.73 1.72
8.41 3.02 1.05 1.07 1.00 2.03 3.18 1.03 1.02 1.04 1.08
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
f1 (ppm)


173.05 156.99 136.35 134.42 129.49 128.71 128.09 126.63 125.23 121.96 117.02 104.58 77.16 CDCl3 67.49 52.31 52.13 48.09 28.63
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

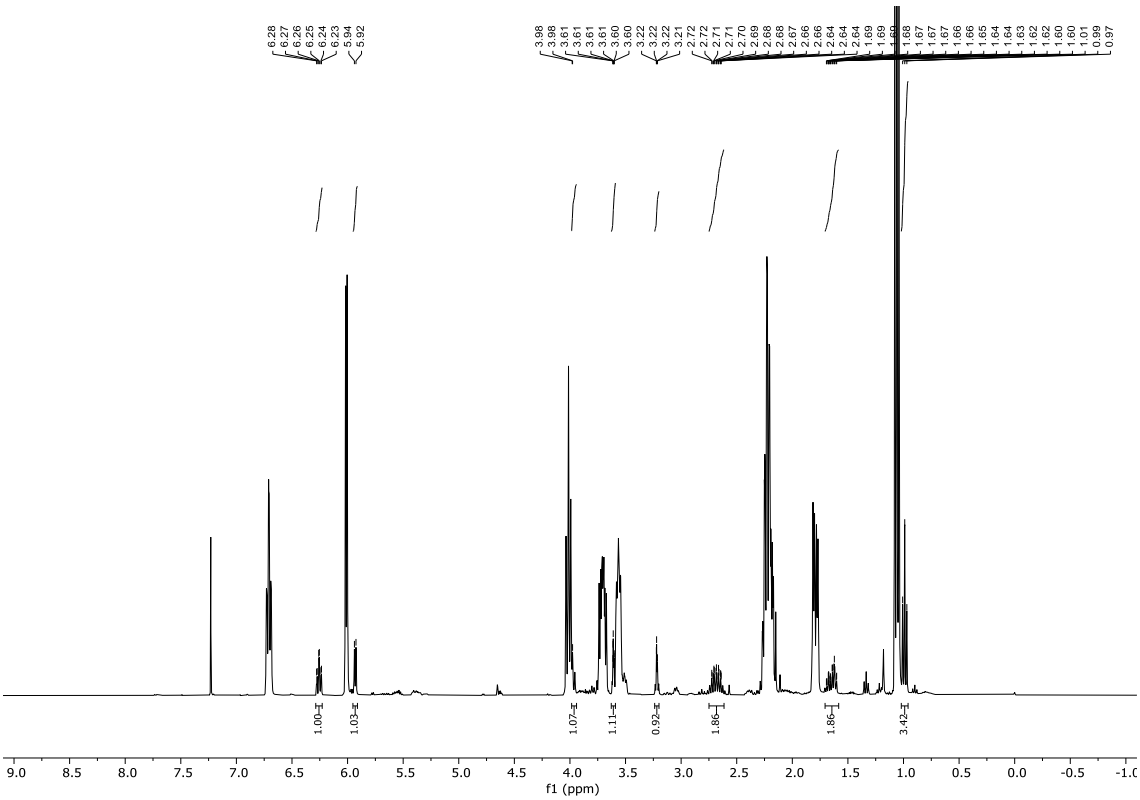
Lactone 273d

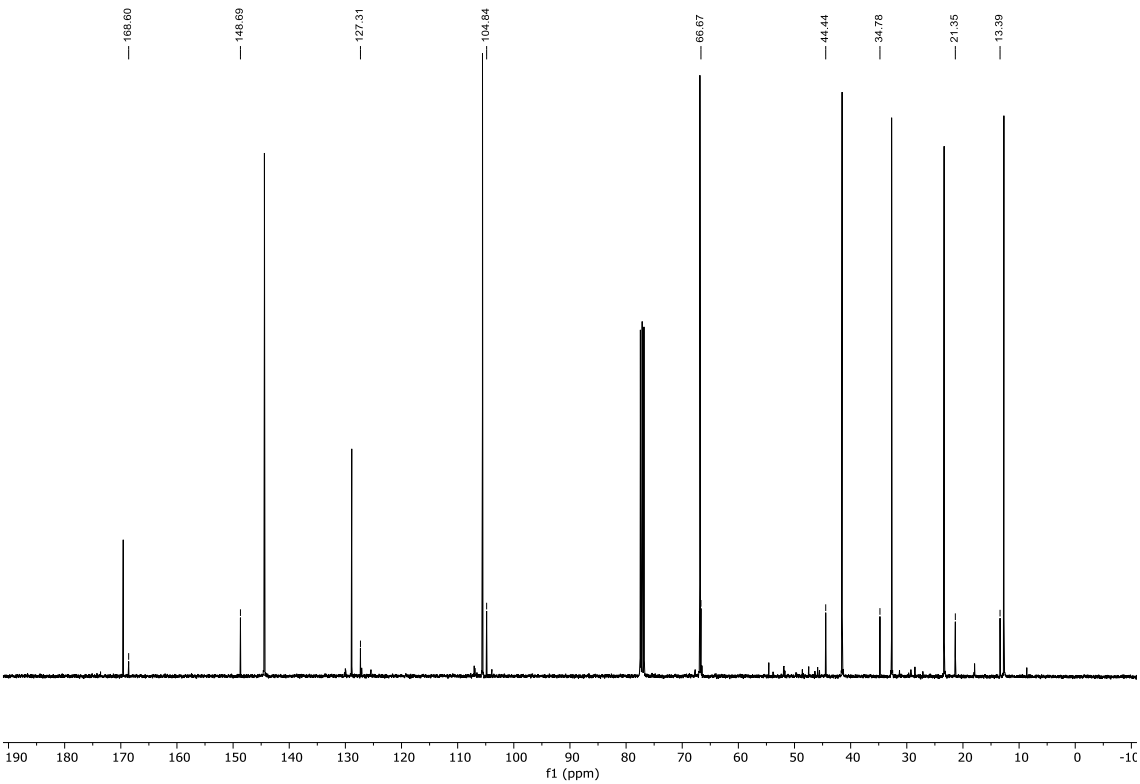
major





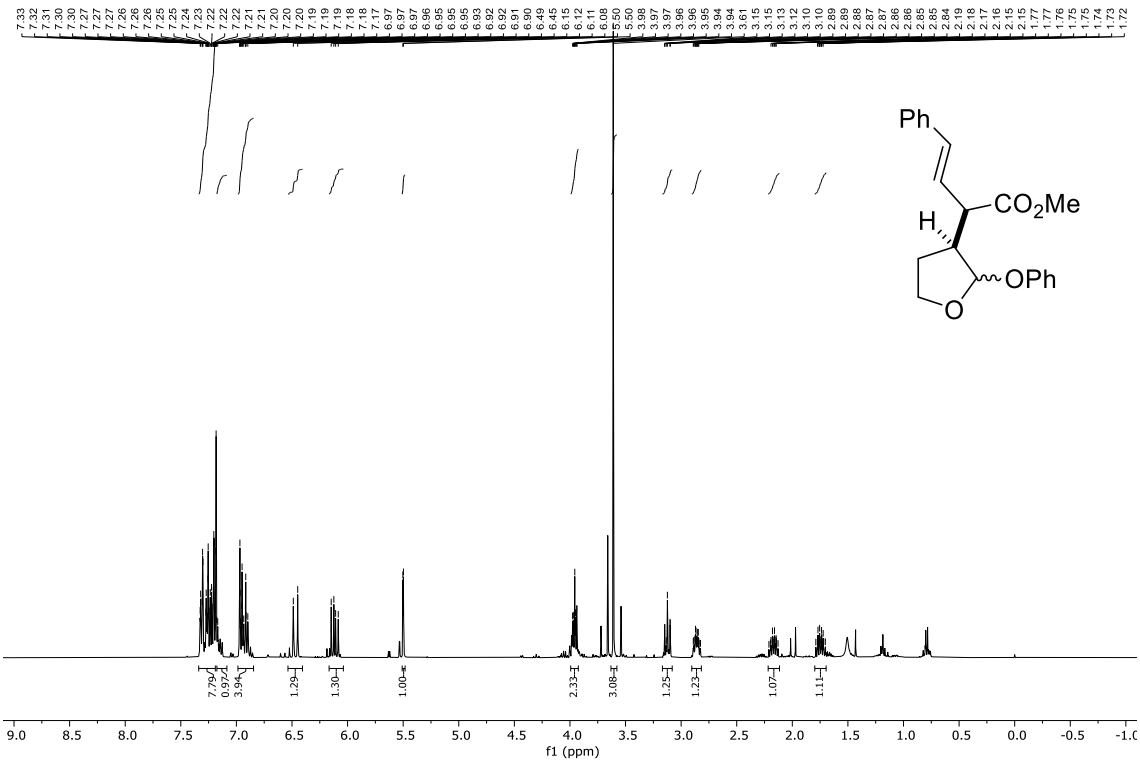
Minor

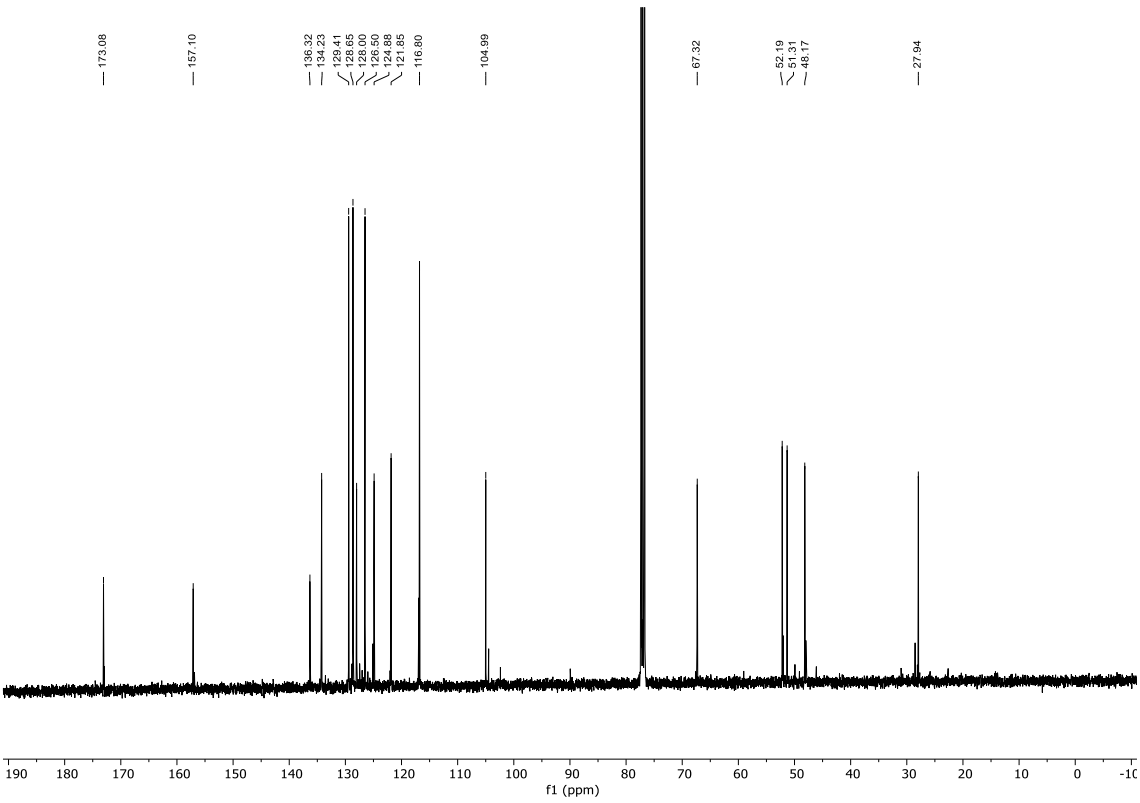

6.28
6.27
6.26
6.25
6.24
6.23
5.94
5.92
3.98
3.96
3.61
3.61
3.61
3.60
3.60
3.22
3.22
3.22
3.21
2.72
2.71
2.71
2.70
2.69
2.68
2.68
2.67
2.66
2.66
2.64
2.64
2.64
1.69
1.69
1.68
1.67
1.67
1.67
1.66
1.66
1.65
1.64
1.64
1.63
1.62
1.62
1.60
1.60
1.01
0.99
0.97
1.00
1.03
1.07
1.11
0.92
1.86
1.86
3.42
9.0 8.5 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 -0.5
f1 (ppm)


168.60
148.69
127.31
104.84
66.67
44.44
34.78
21.35
13.39
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

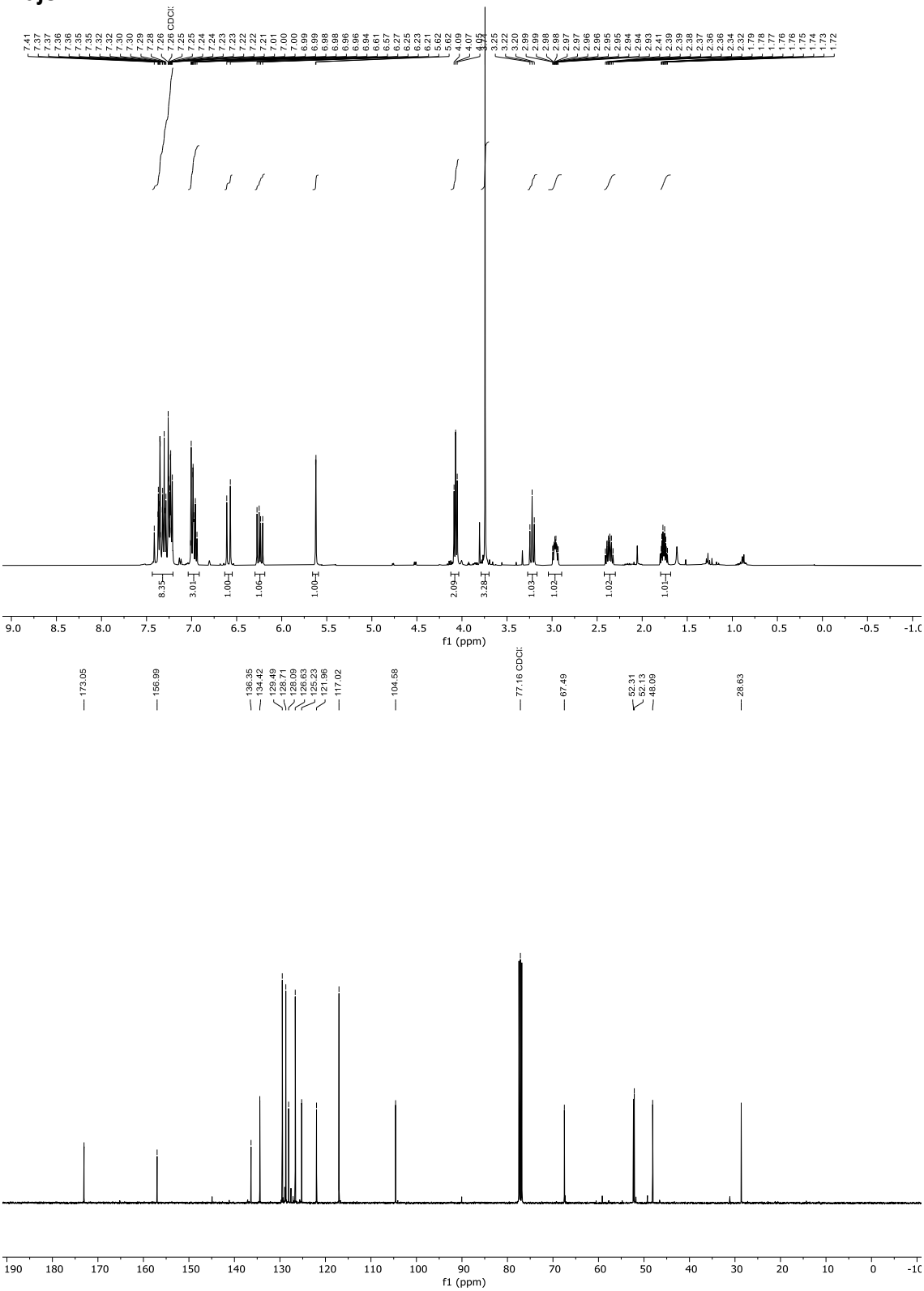
Methyl (*E*)-2-(2-phenoxytetrahydrofuran-3-yl)-4-phenylbut-3-enoate 308c

Minor:



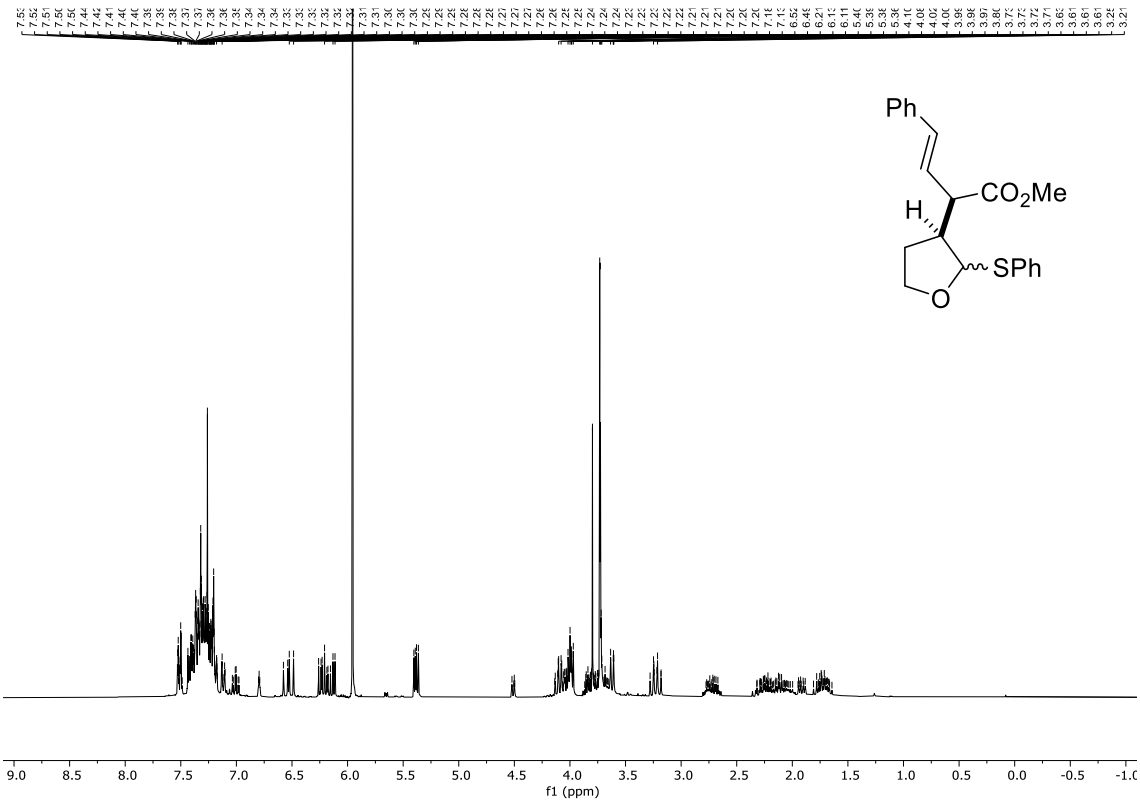


Major

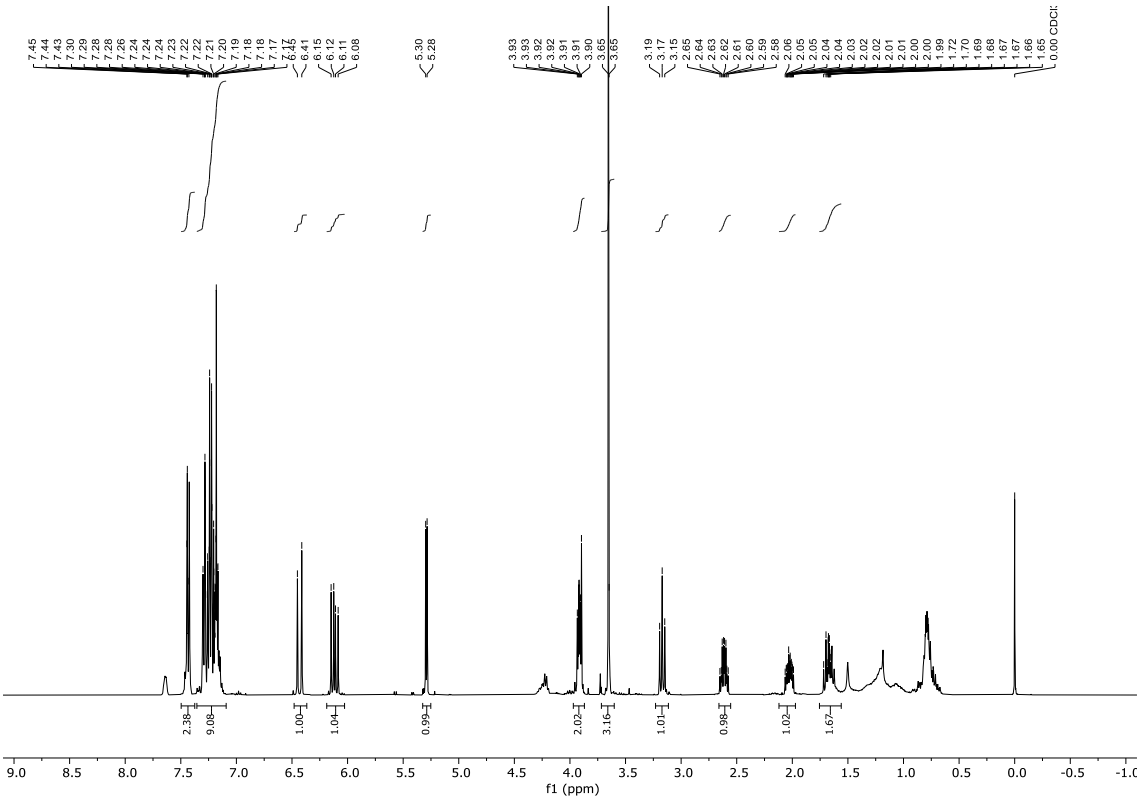

7.41 7.37 7.37 7.36 7.36 7.35 7.35 7.32 7.32 7.30 7.30 7.29 7.28 7.26 CDCl3 7.25 7.25 7.24 7.24 7.23 7.23 7.22 7.22 7.21 7.21 7.01 7.00 7.00 6.99 6.99 6.98 6.98 6.96 6.96 6.94 6.94 6.61 6.57 6.27 6.25 6.23 6.21 5.62 4.09 4.07 4.05 3.25 3.22 3.20 3.00 2.99 2.98 2.98 2.97 2.97 2.96 2.96 2.95 2.95 2.94 2.94 2.93 2.41 2.39 2.39 2.38 2.37 2.36 2.36 2.34 2.32 1.79 1.78 1.77 1.76 1.76 1.75 1.74 1.73 1.72
8.35 3.01 1.00 1.06 1.00 2.09 3.28 1.03 1.02 1.02 1.01
f1 (ppm)
173.05 156.99 136.35 134.42 129.49 128.71 128.09 126.63 125.23 121.96 117.02 104.58 77.16 CDCl3 67.49 52.31 52.13 48.09 28.63
f1 (ppm)

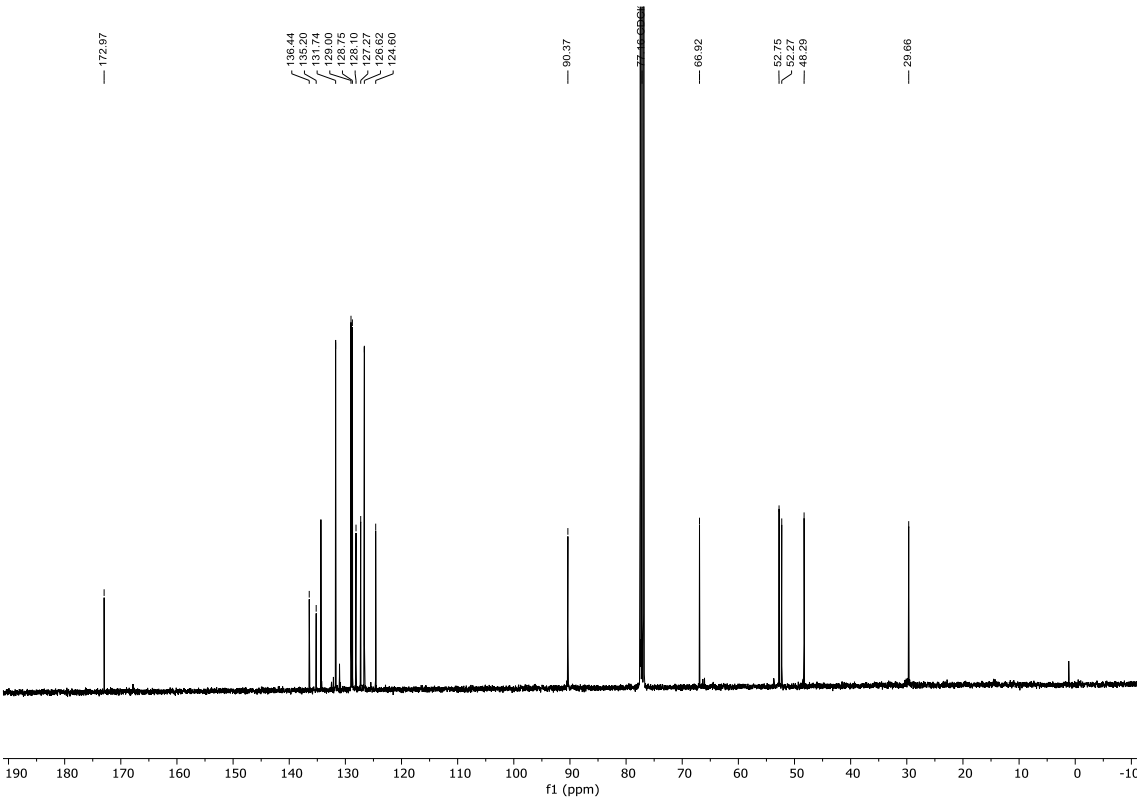
Methyl (*E*)-4-phenyl-2-(-2-(phenylthio)tetrahydrofuran-3-yl)but-3-enoate 310

Crude spectrum with evidence of 2 Diastereomers and internal standard:



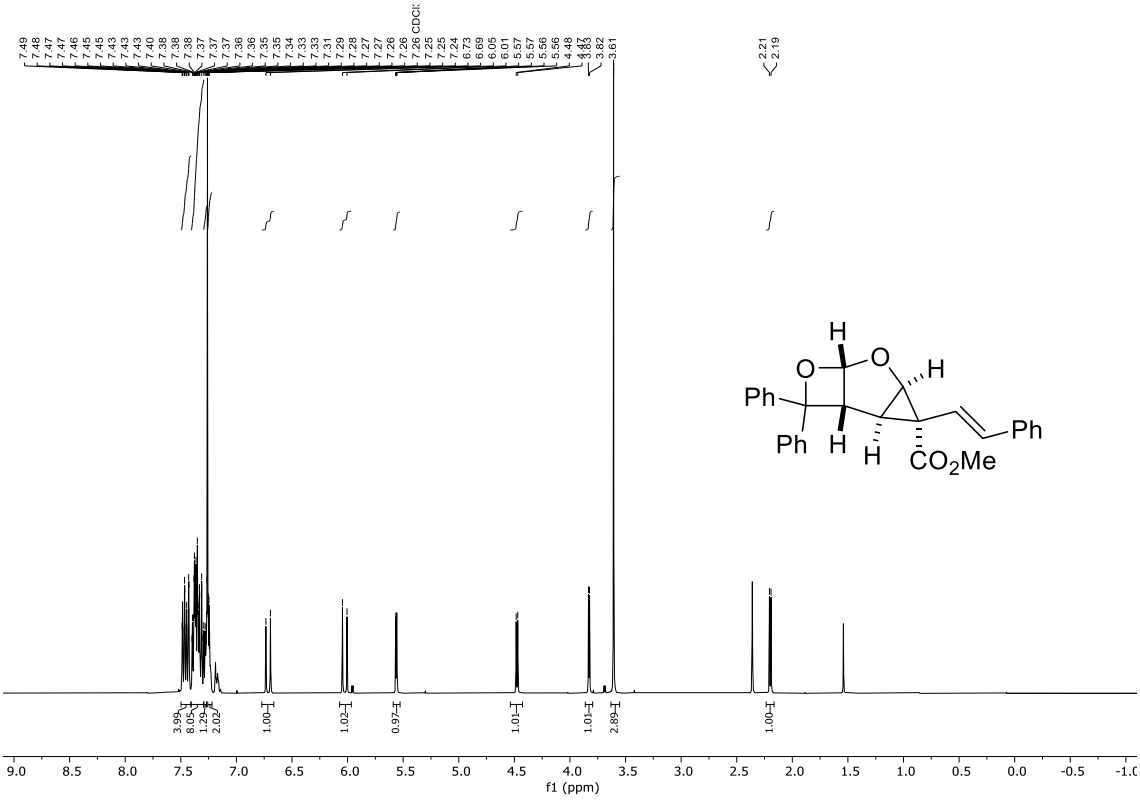
1 Diastereomer:

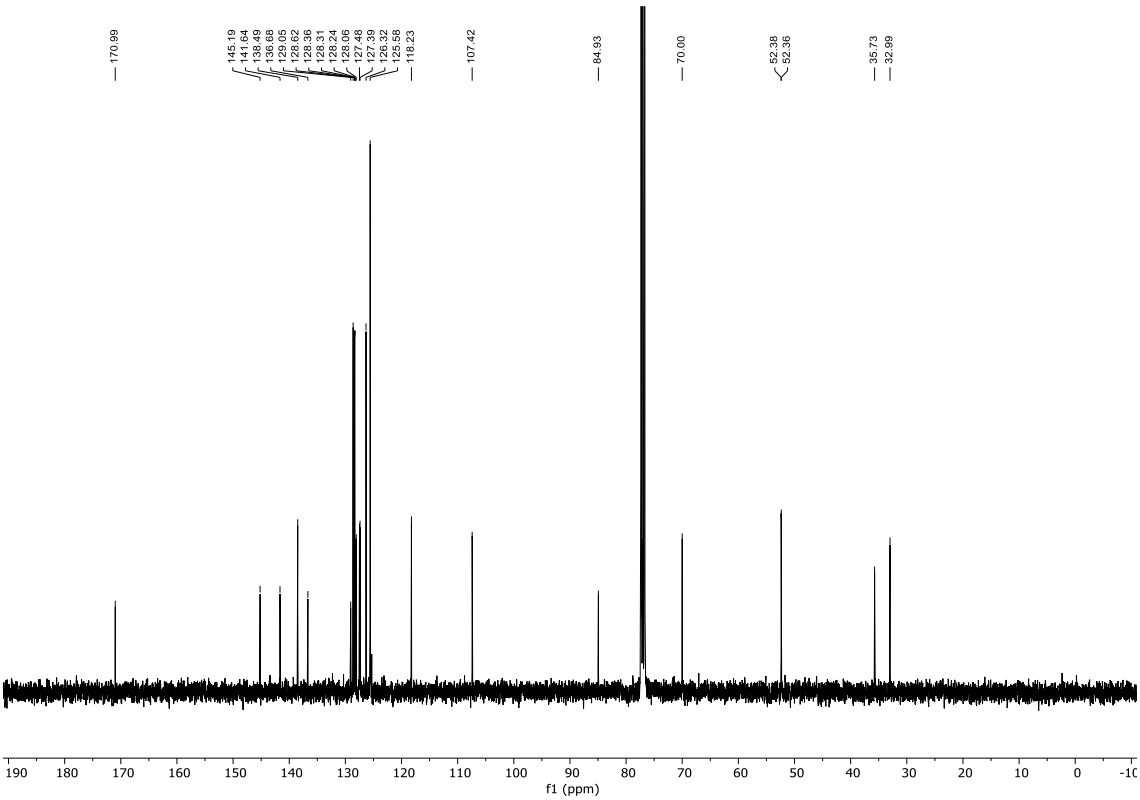




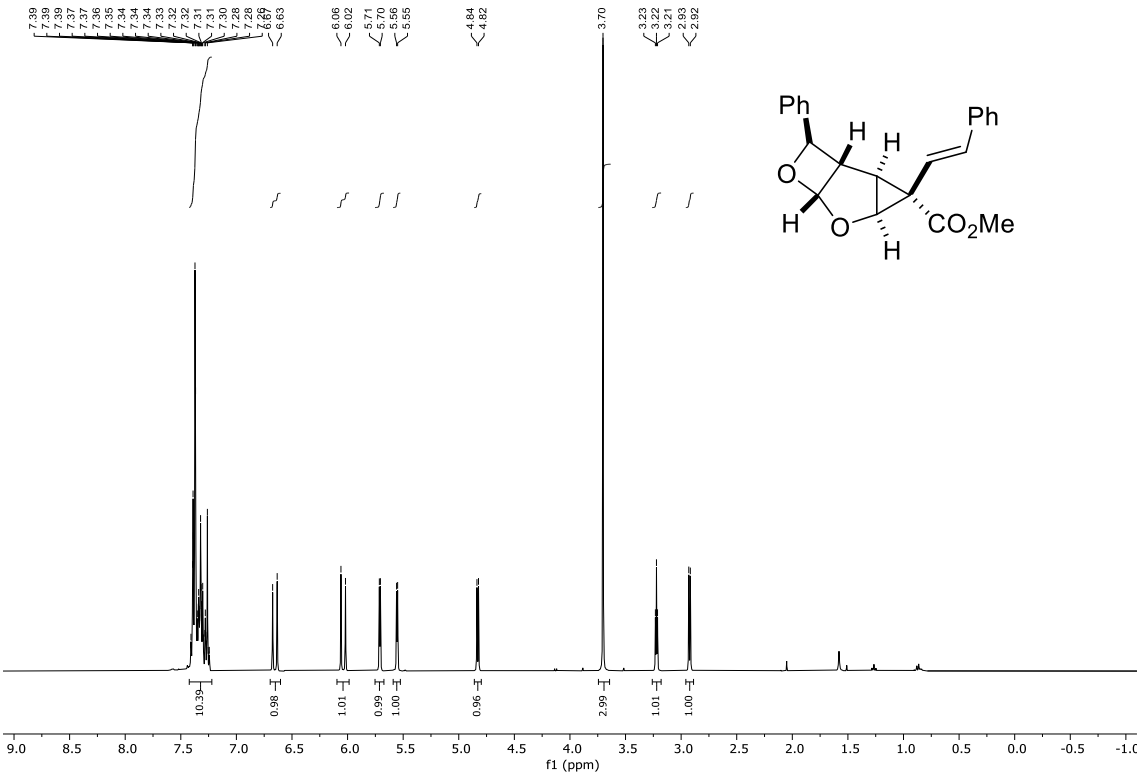
Methyl-8,8-diphenyl-3-((*E*)-styryl)-5,7-dioxatricyclo[4.2.0.02,4]octane-3-carboxylate

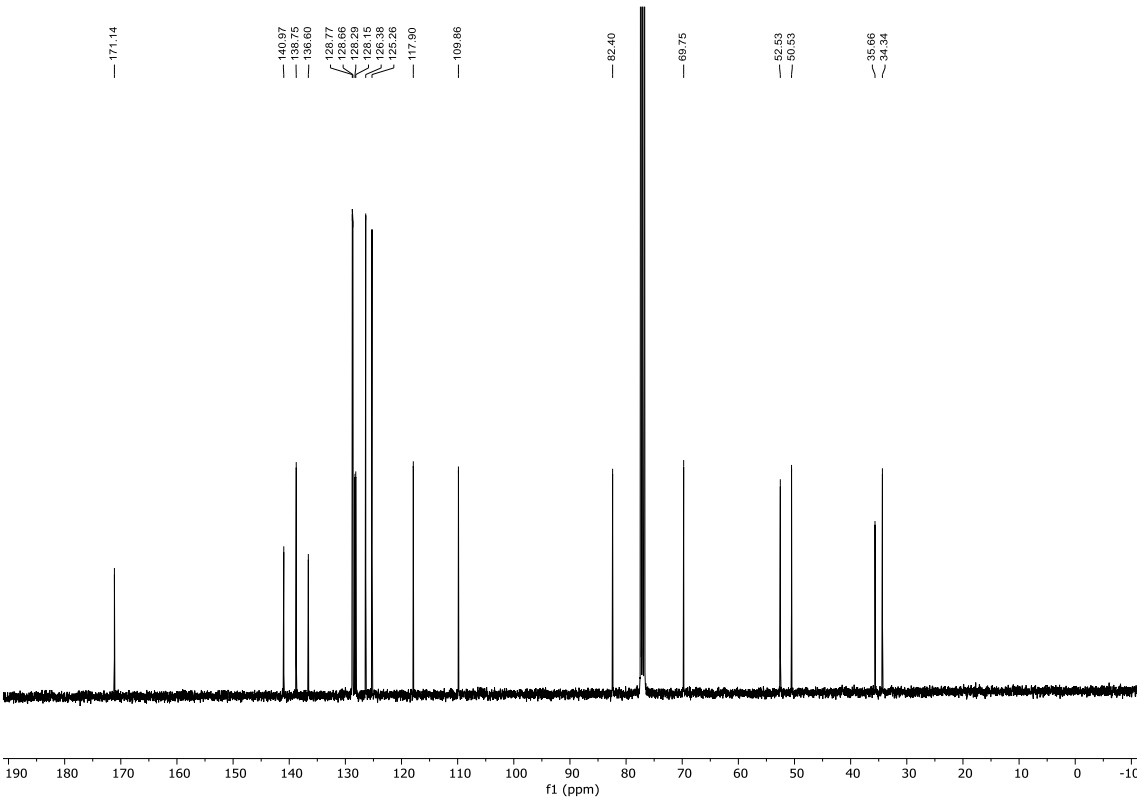
250p





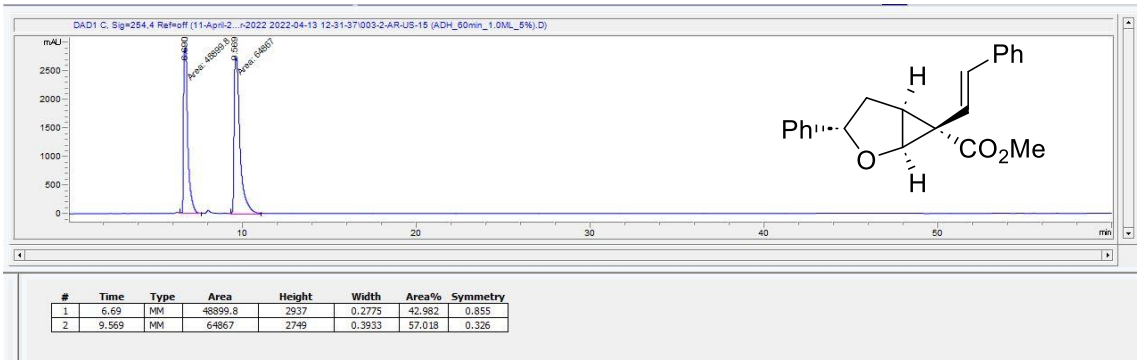
Methyl-8-phenyl-3-((*E*)-styryl)-5,7-dioxatricyclo[4.2.0.02,4]octane-3-carboxylate 250o



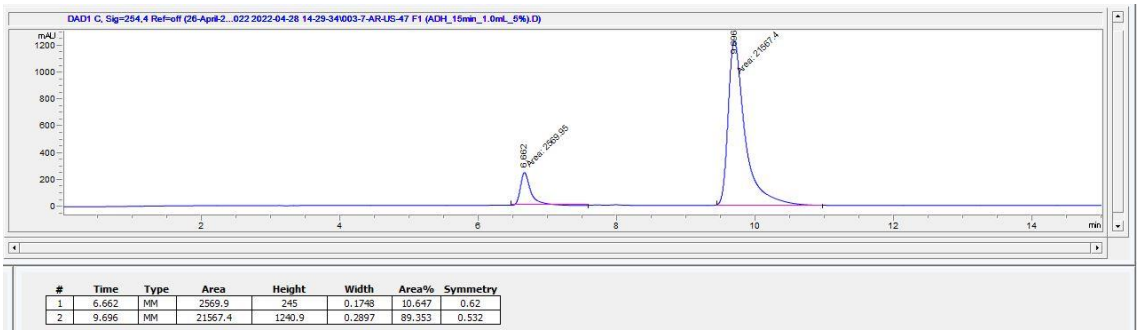


7 HPLC chromatograms

Methyl (1*S*,3*S*,5*S*,6*S*)-3-phenyl-6-((*E*)-styryl)-2-oxabicyclo[3.1.0]hexane-6-carboxylate 250e

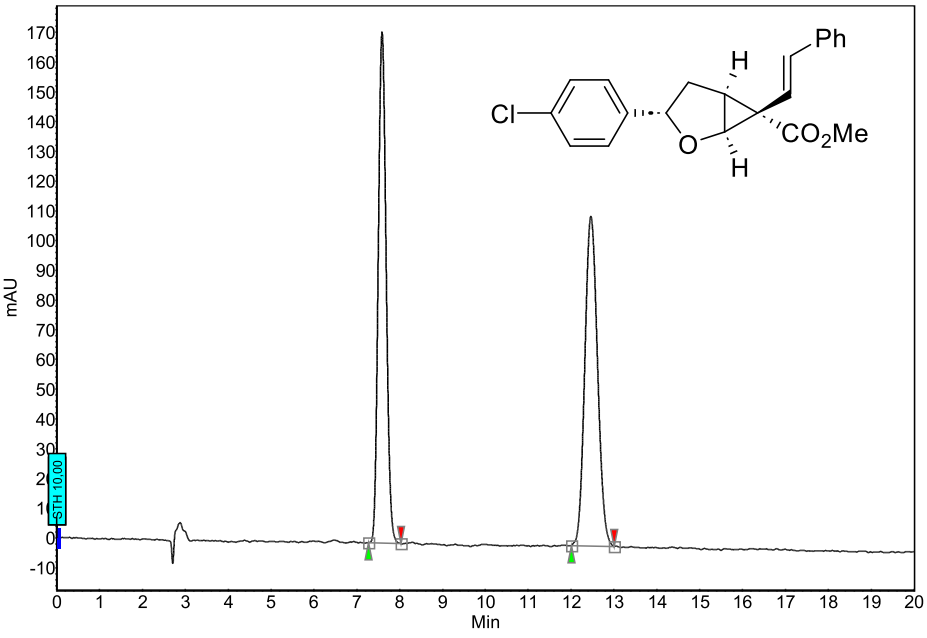


#	Time	Type	Area	Height	Width	Area%	Symmetry
1	6.69	MM	48899.8	2937	0.2775	42.982	0.855
2	9.569	MM	64867	2749	0.3933	57.018	0.326

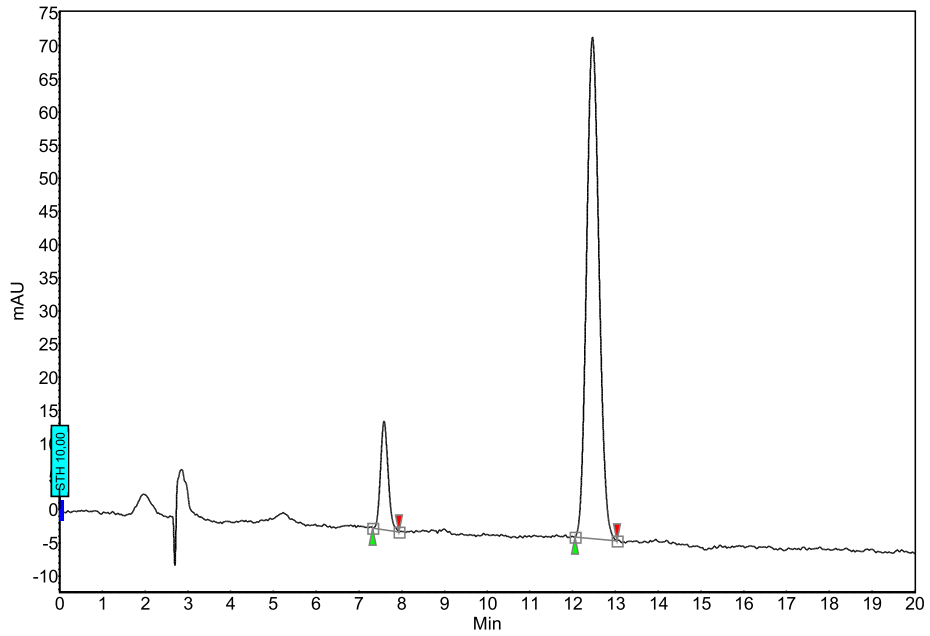


#	Time	Type	Area	Height	Width	Area%	Symmetry
1	6.662	MM	2569.9	245	0.1748	10.647	0.62
2	9.696	MM	21567.4	1240.9	0.2897	89.353	0.532

Methyl (1*S*,3*S*,5*S*,6*S*)-3-(4-chlorophenyl)-6-((*E*)-styryl)-2-oxabicyclo[3.1.0]hexane-6-carboxylate 250g

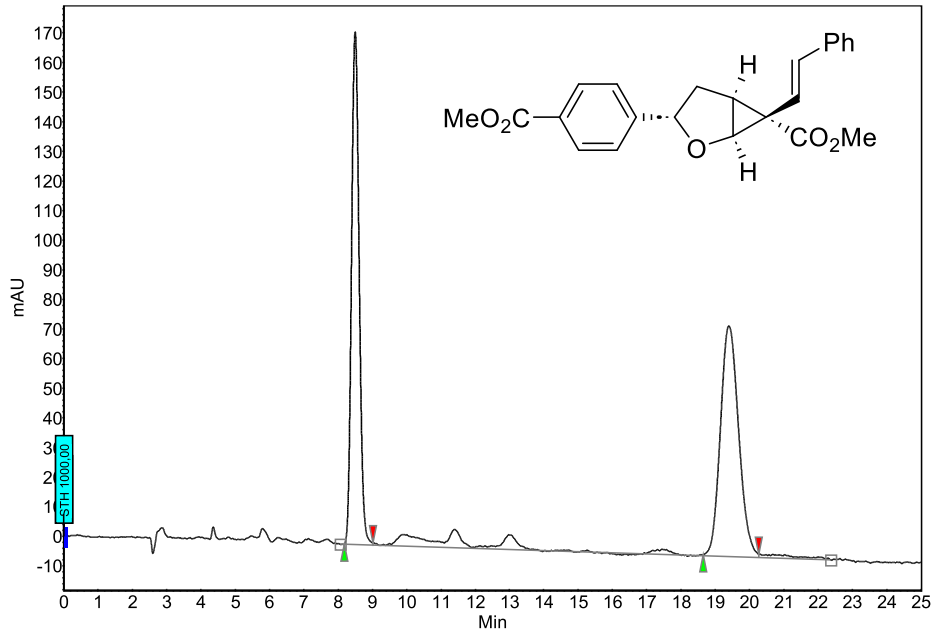


Index	Name	Time [Min]	Quantity [% Area]	Height [mAU]	Area [mAU.Min]	Area % [%]
1	UNKNOWN	7,59	49,02	171,8	36,6	49,023
2	UNKNOWN	12,47	50,98	110,9	38,0	50,977
Total			100,00	282,7	74,6	100,000

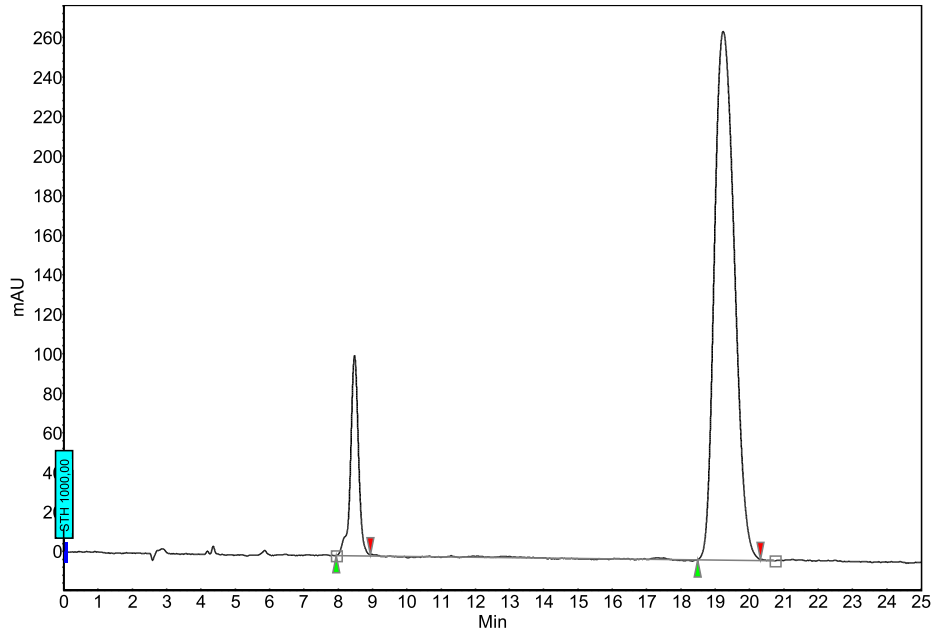


Index	Name	Time [Min]	Quantity [% Area]	Height [mAU]	Area [mAU.Min]	Area % [%]
1	UNKNOWN	7,59	11,63	16,4	3,4	11,631
2	UNKNOWN	12,47	88,37	75,6	25,5	88,369
Total			100,00	92,0	28,9	100,000

Methyl (1*S*,3*S*,5*S*,6*S*)-3-(4-(methoxycarbonyl)phenyl)-6-((*E*)-styryl)-2-oxabicyclo[3.1.0]hexane-6-carboxylate 250h

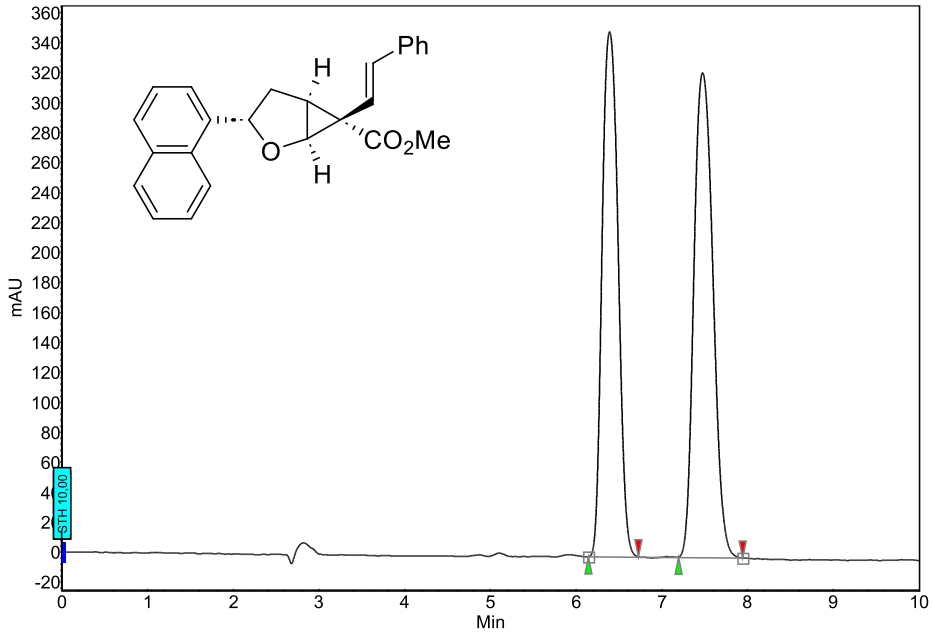


Index	Name	Time [Min]	Quantity [% Area]	Height [mAU]	Area [mAU.Min]	Area % [%]
1	UNKNOWN	8,50	48,20	173,1	44,6	48,197
2	UNKNOWN	19,39	51,80	77,8	47,9	51,803
Total			100,00	251,0	92,5	100,000

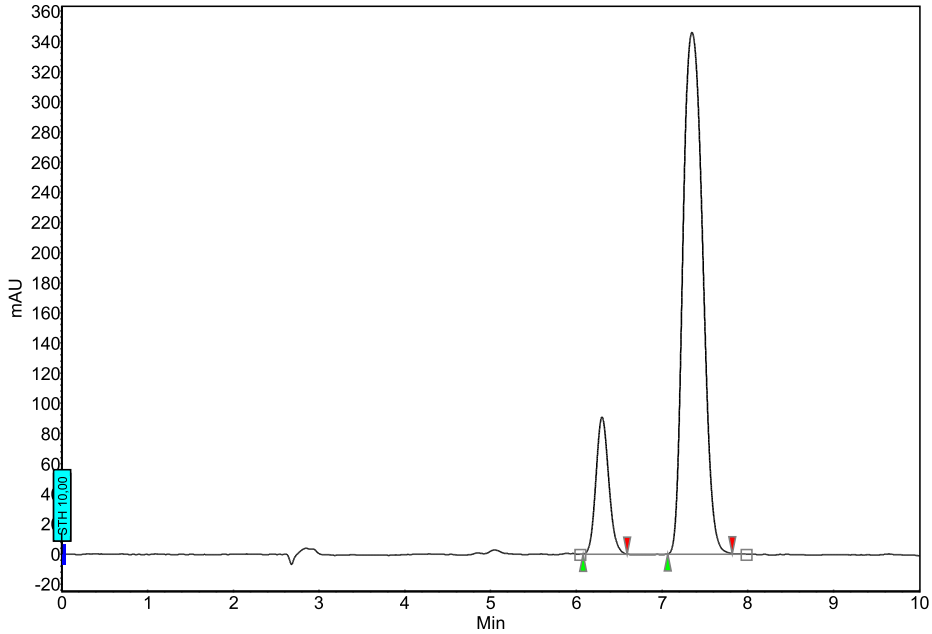


Index	Name	Time [Min]	Quantity [% Area]	Height [mAU]	Area [mAU.Min]	Area % [%]
1	UNKNOWN	8,48	13,10	101,3	27,2	13,098
2	UNKNOWN	19,23	86,90	267,3	180,6	86,902
Total			100,00	368,6	207,9	100,000

Methyl (1*S*,3*S*,5*S*,6*S*)-3-(naphthalen-1-yl)-6-((*E*)-styryl)-2-oxabicyclo[3.1.0]hexane-6-carboxylate 250f

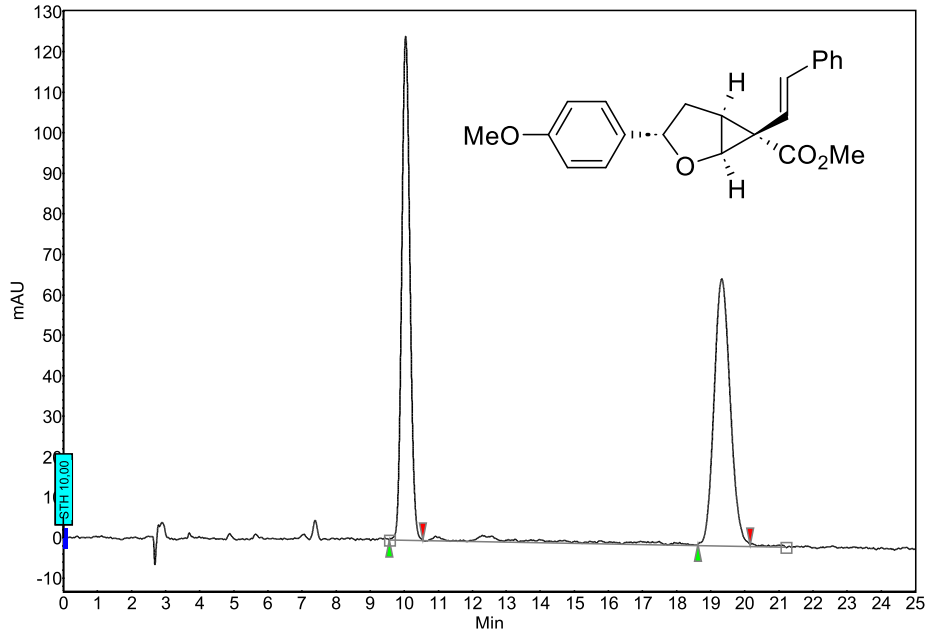


Index	Name	Time [Min]	Quantity [% Area]	Height [mAU]	Area [mAU.Min]	Area % [%]
1	UNKNOWN	6,39	47,49	350,2	75,5	47,492
2	UNKNOWN	7,48	52,51	323,5	83,5	52,508
Total			100,00	673,7	159,0	100,000

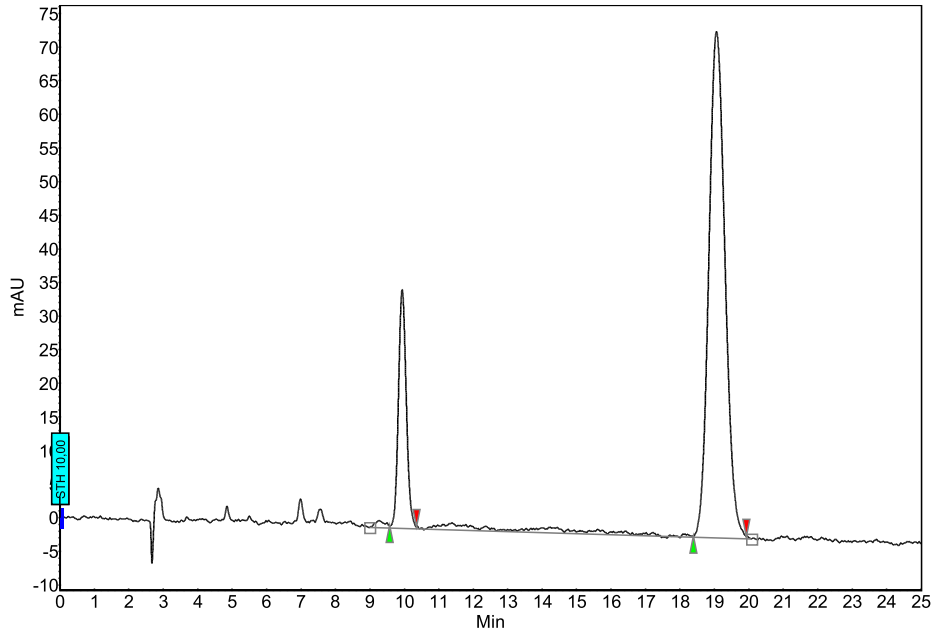


Index	Name	Time [Min]	Quantity [% Area]	Height [mAU]	Area [mAU.Min]	Area % [%]
1	UNKNOWN	6,30	14,72	91,0	15,8	14,721
2	UNKNOWN	7,35	85,28	345,9	91,7	85,279
Total			100,00	436,9	107,5	100,000

Methyl (1*S*,3*S*,5*S*,6*S*)-3-(4-methoxyphenyl)-6-((*E*)-styryl)-2-oxabicyclo[3.1.0]hexane-6-carboxylate 250i



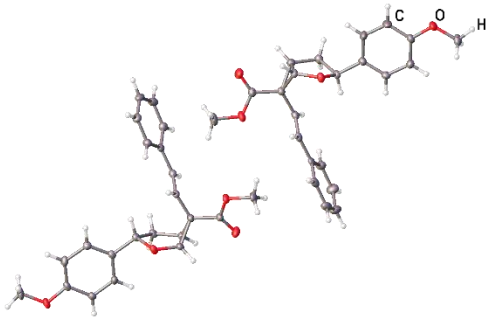
Index	Name	Time [Min]	Quantity [% Area]	Height [mAU]	Area [mAU.Min]	Area % [%]
1	UNKNOWN	10,04	48,84	124,4	34,7	48,835
2	UNKNOWN	19,33	51,16	66,1	36,3	51,165
Total			100,00	190,5	71,0	100,000



Index	Name	Time [Min]	Quantity [% Area]	Height [mAU]	Area [mAU.Min]	Area % [%]
1	UNKNOWN	9,93	18,69	35,5	9,4	18,688
2	UNKNOWN	19,07	81,31	75,3	41,0	81,312
Total			100,00	110,8	50,4	100,000

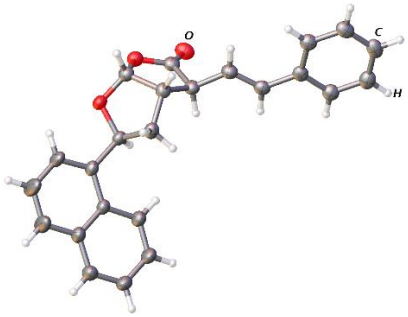
8 X-Ray Data

Methyl (E)-3-(4-methoxyphenyl)-6-styryl-2-oxabicyclo[3.1.0]hexane-6-carboxylate 250i



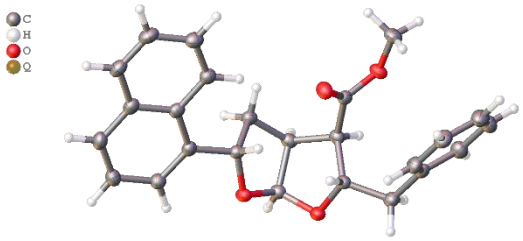
Formula	C88H88O16
Dcalc./ g cm-3	1.280
□/mm-1	0.706
Formula Weight	1401.58
Colour	clear colourless
Shape	block
Size/mm3	? ×? ×?
T/K	123.00(10)
Crystal System	monoclinic
Space Group	P21/c
a/Å	17.7050(4)
b/Å	8.6277(2)
c/Å	24.1396(4)
□/°	90
□/°	99.596(2)
□/°	90
V/Å3	3635.81(13)
Z	2
Z'	0.5
Wavelength/Å	1.54184
Radiation type	Cu K□
□min/°	3.714
□max/°	72.775
Measured Refl's.	17179
Indep't Refl's	6659
Refl's I≥2 □(I)	5609
Rint	0.0290
Parameters	473
Restraints	0
Largest Peak	0.240
Deepest Hole	-0.262
GooF	1.020
wR2 (all data)	0.1056
wR2	0.0998
R1 (all data)	0.0493
R1	0.0402

5-(Naphthalen-1-yl)-3-styryltetrahydrofuro[2,3-b]furan-2(3H)-one 272f



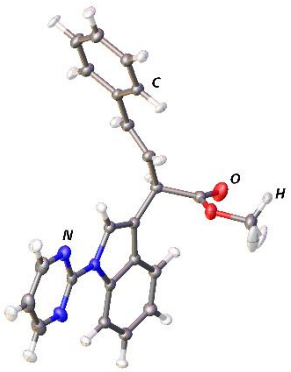
Formula	$C_{24}H_{20}O_3$
$D_{calc.}$/ g cm^{-3}	1.312
μ/mm^{-1}	0.683
Formula Weight	356.40
Colour	clear colourless
Shape	plate-shaped
Size/mm^3	0.24×0.07×0.05
T/K	100.01(10)
Crystal System	monoclinic
Space Group	$P2_1/c$
a/Å	5.39170(10)
b/Å	10.8542(2)
c/Å	30.8472(5)
α/°	90
β/°	91.742(2)
γ/°	90
V/Å^3	1804.42(6)
Z	4
Z'	1
Wavelength/Å	1.54184
Radiation type	Cu K_α
Θ_{min}/°	2.866
Θ_{max}/°	75.365
Measured Refl's.	44213
Indep't Refl's	3676
Refl's I≥2 σ(I)	3086
R_{int}	0.0438
Parameters	244
Restraints	0
Largest Peak	0.216
Deepest Hole	-0.270
GooF	1.058
wR_2 (all data)	0.1208
wR_2	0.1158
R_1 (all data)	0.0577
R_1	0.0489

Methyl-2-benzyl-5-(naphthalen-1-yl)hexahydrofuro[2,3-b]furan-3-carboxylate 285f



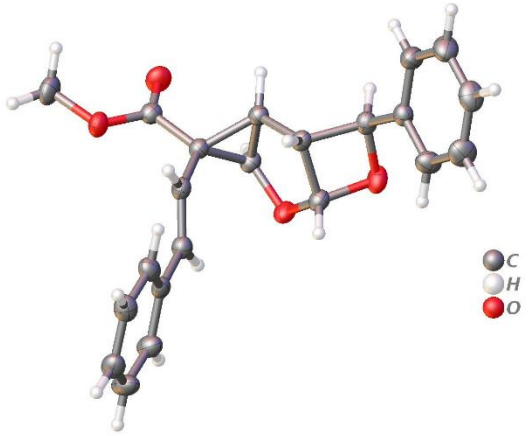
Formula	$C_{25}H_{24}O_4$
$D_{calc.}$/ g cm^{-3}	1.314
μ/mm^{-1}	0.709
Formula Weight	388.44
Colour	clear colourless
Shape	prism-shaped
Size/mm^3	0.16×0.07×0.01
T/K	122.99(10)
Crystal System	monoclinic
Space Group	$P2_1/c$
a/Å	7.58550(10)
b/Å	25.1655(2)
c/Å	10.28420(10)
α/°	90
β/°	90.9950(10)
γ/°	90
V/Å^3	1962.88(4)
Z	4
Z'	1
Wavelength/Å	1.54184
Radiation type	Cu K$_\alpha$
Θ_{min}/°	3.513
Θ_{max}/°	75.688
Measured Refl's.	34908
Indep't Refl's	4047
Refl's I≥2 σ(I)	3556
R_{int}	0.0305
Parameters	358
Restraints	0
Largest Peak	0.242
Deepest Hole	-0.256
GooF	1.055
wR_2 (all data)	0.0883
wR_2	0.0851
R_1 (all data)	0.0377
R_1	0.0328

Methyl (E)-4-phenyl-2-(1-(pyrimidin-2-yl)-1H-indol-3-yl)but-3-enoate



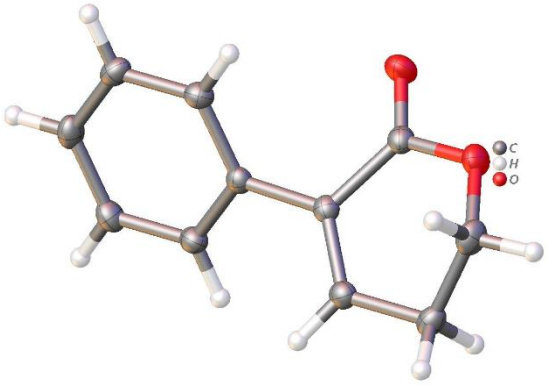
Formula	*C23H19N3O2*
Dcalc./ g cm-3	*1.338*
□/mm-1	*0.700*
Formula Weight	*369.426*
Colour	*clear colourless*
Shape	*prism-shaped*
Size/mm3	*0.18×0.07×0.06*
T/K	*123.00(10)*
Crystal System	*triclinic*
Space Group	*P-1*
a/Å	*9.1882(2)*
b/Å	*9.8389(2)*
c/Å	*11.1612(3)*
□/°	*72.243(2)*
□/°	*73.291(2)*
□/°	*89.623(2)*
V/Å3	*916.70(4)*
Z	*2*
Z'	*1*
Wavelength/Å	*1.54184*
Radiation type	*Cu K□*
□min/°	*4.36*
□max/°	*75.16*
Measured Refl's.	*32390*
Indep't Refl's	*3690*
Refl's I≥2 □(I)	*3425*
Rint	*0.0205*
Parameters	*424*
Restraints	*0*
Largest Peak	*0.0784*
Deepest Hole	*-0.1064*
GooF	*1.2137*
wR2 (all data)	*0.0297*
wR2	*0.0292*
R1 (all data)	*0.0161*
R1	*0.0142*

Methyl-8-phenyl-3-((*E*)-styryl)-5,7-dioxatricyclo[4.2.0.02,4]octane-3-carboxylate 250o



Formula	*C22H20O4*
Dcalc./ g cm-3	*1.316*
□/mm-1	*0.730*
Formula Weight	*348.38*
Colour	*clear colourless*
Shape	*plate-shaped*
Size/mm3	*0.22×0.07×0.03*
T/K	*123.00(10)*
Crystal System	*monoclinic*
Space Group	*P21/c*
a/Å	*12.34040(10)*
b/Å	*5.50040(10)*
c/Å	*26.0543(2)*
□/°	*90*
□/°	*96.3250(10)*
□/°	*90*
V/Å3	*1757.73(4)*
Z	*4*
Z'	*1*
Wavelength/Å	*1.54184*
Radiation type	*Cu K□*
□min/°	*3.413*
□max/°	*75.491*
Measured Refl's.	*38498*
Indep't Refl's	*3598*
Refl's I≥2 □(I)	*3241*
Rint	*0.0338*
Parameters	*236*
Restraints	*0*
Largest Peak	*0.250*
Deepest Hole	*-0.213*
GooF	*1.064*
wR2 (all data)	*0.1000*
wR2	*0.0974*
R1 (all data)	*0.0408*
R1	*0.0371*

3-Phenyl-5,6-dihydro-2H-pyran-2-one 249



Formula	*C11H10O2*
Dcalc./ g cm-3	*1.358*
□/mm-1	*0.753*
Formula Weight	*174.201*
Colour	*clear colourless*
Shape	*prism-shaped*
Size/mm3	*0.14×0.07×0.05*
T/K	*123.02(10)*
Crystal System	*monoclinic*
Space Group	*P21/c*
a/Å	*10.1567(3)*
b/Å	*7.4123(2)*
c/Å	*12.3988(4)*
□/°	*90*
□/°	*114.099(4)*
□/°	*90*
V/Å3	*852.08(5)*
Z	*4*
Z'	*1*
Wavelength/Å	*1.54184*
Radiation type	*Cu K□*
□min/°	*4.77*
□max/°	*75.46*
Measured Refl's.	*18779*
Indep't Refl's	*1738*
Refl's I≥2 □(I)	*1604*
Rint	*0.0202*
Parameters	*118*
Restraints	*0*
Largest Peak	*0.2587*
Deepest Hole	*-0.1918*
GooF	*1.0675*
wR2 (all data)	*0.0801*
wR2	*0.0788*
R1 (all data)	*0.0332*
R1	*0.0310*

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11 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 acknowledgement of collaborative research.

Regensburg, 17.04.2024

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Anna Rustler